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Advancing precision medicine in acute stroke care: personalized treatment strategies and outcomes

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Advancing precision medicine in acute stroke care: personalized treatment strategies and outcomes

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Table of contents

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Editorial: Advancing precision medicine in acute stroke care: personalized treatment strategies and outcomes

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Editorial on the Research Topic
Advancing precision medicine in acute stroke care: personalized treatment strategies and outcomes

Introduction

Precision medicine in acute stroke care has matured from a visionary concept into an operational framework. The articles in this Research Topic, spanning molecular biomarkers, imaging phenotypes, therapeutic optimization, neuro-recovery science, and health-system engineering, all converge on a single imperative of individualizing decisions at the speed and scale required by cerebrovascular emergencies. Below, we summarize the cross-cutting insights, highlighting how this body of work collectively reframes the concept of "time is brain" as "the right treatment for this brain now."

Biology that stratifies risk and reveals targets

Routine, low-cost laboratory tests can carry disproportionate prognostic value and a huge return on investment, presenting an opportunity for risk stratification and decoding prognosis. For instance, Wang et al. reported on a large ischemic stroke cohort of 11,405 patients and found that baseline alkaline phosphatase (ALP) was associated with 3-month and 1-year mortality, poor functional outcomes, and increased disability. Marked variability was noted among subtypes representing different etiologies. These results may suggest potential links between mineral metabolism, vascular calcification, and neurorepair while arguing for the validation of ALP as a triage signal for follow-up intensity. Similarly, a retrospective study of 200 patients with aneurysmal subarachnoid hemorrhage (aSAH) reported by Min et al. showed that, on postoperative day 7, the neutrophil count, neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory response index (SIRI), and systemic immune-inflammation index (SII) were significantly higher

in patients with poor outcomes vs. those with good outcomes. In multivariate analysis, cerebrospinal fluid (CSF) red blood cell (RBC) count on day 1 ($\geq$177 $\times$ 10^9/L; OR 7.227, 95% CI: 1.160–45.050, $P = 0.034$), surgical duration ($\geq$169 min), Fisher grade (III–IV), hypertension, and infections were associated with poor outcomes. On day 7, a CSF RBC count ($\geq$54 $\times$ 10^9/L; OR 39.787, 95% CI: 6.799–232.836, $P < 0.001$) and an NLR ($\geq$8.16; OR 6.362, 95% CI: 1.424–28.428, $P = 0.015$) remained independent predictors. NLR ($r = 0.297$, $P = 0.007$) and SIRI ($r = 0.325$, $P = 0.003$) correlated with CSF RBC count. Overall, elevated NLR and CSF RBC count were strongly associated with poor prognosis in aSAH. These findings suggest that neuroinflammation may be both a marker and a modifiable pathway.

Building on this idea, renal indices do not reflect a mere comorbid noise. In a cohort of 230 patients with acute large vessel occlusion (LVO) stroke, Rocha et al. showed that nearly one-third of the patients exhibited a fast progressor phenotype, characterized by higher serum creatinine, lower estimated glomerular filtration rate (eGFR), and substantially worse clinical outcomes. Elevated creatinine levels ($\geq$1.2 mg/dl) independently predicted fast progression, poor 90-day functional recovery, and mortality, while reduced eGFR ($<$60 ml/min/1.73 m^2) was associated with fast progression but not with longer-term outcomes. These findings suggest that simple, routinely available creatinine-based biomarkers of renal dysfunction may serve as early indicators of aggressive infarct dynamics, helping clinicians identify high-risk patients during emergency evaluations and prioritize them for expedited endovascular therapy.

Two contributions extend this biological lens even further. First, a systematic review performed by Al-Jehani et al. positioned microRNAs as plausible tools for stratifying risk and forecasting outcomes in ischemic stroke, spanning signatures of endothelial dysfunction, inflammation, and thrombus biology. In contrast, a study of 317 patients of whole-blood viscosity (WBV) after thrombectomy reported by Thapa et al. found no association with discharge disability; however, this finding may be influenced by limitations in the formula used to estimate shear rates. While this report suggests that WBV alone does not directly impact prognosis, other determinants of blood viscosity may still meaningfully influence outcomes after thrombectomy and warrant further investigation.

Finally, an interpretable machine learning model incorporating the platelet distribution width-to-platelet count ratio (PPR) to predict hemorrhagic transformation (HT) after reperfusion was developed by Li, Lei, et al. Among AIS patients treated with IVT, six features—age, diabetes, malignancy, onset-to-treatment time, baseline NIHSS score, and PPR—were identified via LASSO regression. Logistic regression (LR) outperformed other models, achieving an AUC of 0.919, with accuracy, sensitivity, and specificity around 0.83. Feature importance ranked baseline NIHSS, diabetes, and PPR highest. The LR-based model offers a rapid, accurate tool to predict HT risk and support clinical decision-making in AIS patients receiving thrombolysis.

Imaging phenotypes that individualize decisions

Several studies clarify which images matter when the stakes are highest. In a study by Yeo et al., including 325 consecutive patients with anterior circulation LVO, multiphase CTA collateral grade strongly discriminated 3-month outcomes among EVT candidates, reinforcing the importance of collateral-aware selection and expectation-setting beyond "time alone." Li, Gao. et al., on the other hand, showed that high-resolution vessel-wall MRI features (intraplaque hemorrhage and normalized wall index) combined with clinical scores effectively predict recurrence risk in patients with high-risk, non-disabling ischemic cerebrovascular events, and the resulting nomogram offers a practical tool for identifying high-risk individuals.

Beyond occlusion-centric selection, covert substrate matters. Abdulsalam et al. reported that silent brain infarcts and leukoaraiosis co-occurred in middle-aged adults and were associated with each other in a cohort of 50 patients, arguing that the burden of small-vessel disease should inform cognitive surveillance and counseling after apparently "minor" strokes.

Two articles deepen physiologic precision. A prospective, serial-MRI study by Carbó et al. quantified impaired microvascular reperfusion (IMR) in one-quarter of "successfully reperfused" patients; larger IMR volumes correlated with worse early neurological status, highlighting evidence that tissue-level heterogeneity persists despite angiographic success and that IMR is a plausible target and imaging surrogate for adjuvant therapies. A radiomics approach reported by Yang et al. that fused DSC-PWI "critical-moment" features with conventional parameter maps achieved superior outcome prediction (AUC ~0.92), illustrating the value of richer spatiotemporal signatures. This approach has the potential to improve AIS prognosis assessment and aid clinicians in selecting optimal treatments.

Imaging also refines our ability to identify etiology. A meta-analysis by Xu et al. showed that cardiac CT angiography (CCTA) detects intracardiac thrombus in ~8% of AIS within 1 month, including many patients without documented AF, supporting the use of early CCTA when TEE is delayed or poorly tolerated, as it can accelerate secondary prevention.

Optimizing reperfusion and adjuncts

Therapeutic precision spans drugs, devices, and dosing. A network meta-analysis by Sun et al. across randomized trials suggested that reteplase may increase the odds of an excellent 90-day outcome compared to alteplase. Tenecteplase at a dose of 0.25 mg/kg was found to be the most effective in achieving good outcomes with a similar safety profile, encouraging phenotype- and dose-specific trials. In an MRI-selected mild stroke (NIHSS $\leq$ 5) study reported by Li, Chen, et al., dual antiplatelet pretreatment plus low-dose rt-PA (0.6 mg/kg) yielded higher early neurological improvement and better 90-day function than standard-dose rt-PA or DAPT alone, without an increased risk of hemorrhage. This is hypothesis-generating evidence that a

biology- and imaging-guided approach to tailoring doses may benefit mild phenotypes.

Adjunctive strategies are moving from theory to plausible practice. In a propensity-matched cohort by ElBassiouny et al., early cerebrolysin administration after thrombectomy for cardioembolic LVO was associated with greater independence and less hemorrhagic transformation—results that now demand randomized confirmation, ideally with IMR-type tissue metrics as mechanistic endpoints. For intracerebral hemorrhage, minimally invasive evacuation using a YL-1 hematoma crushing needle was associated with faster resolution and improved short-term function compared to conservative care in a retrospective series reported by Chen et al.. Their findings support MIS pathways where craniotomy risk or delay is prohibitive, pending controlled trials.

Posterior circulation epidemiology reminds us that case mix dominates. A U.S. National Inpatient Sample analysis conducted by Saha et al., focusing on vertebrobasilar occlusion (VBAO), showed that younger patients (18–64 years) tended to receive EVT more frequently than older patients, with no significant differences observed between sexes, likely reflecting selection and severity. Cancer-related stroke exemplifies uncertainty where precision is needed most. Kielkopf et al. showed that, in patients with active cancer and AIS, anticoagulation vs. antiplatelet therapy at discharge yielded similar adjusted risks for 1-year mortality and recurrent stroke, highlighting the need for randomized, biology-anchored selection.

Systems that compress time and align care with phenotype

Operational precision is where biomarkers and images become minutes saved. A Hybrid Emergency Room System (HERS) reported by Kashiura et al. shaved ∼30–40 min off door-to-puncture and door-to-recanalization times for EVT—an implementation signal that invites multicenter, phenotype-enriched evaluations where time sensitivity is greatest. Population-level lenses ensure that translation is equitable and context-aware. In Jordan, the 1-year stroke incidence in AF was 3.4%, with diabetes and prior stroke conferring ≈2.6-fold higher odds, as reported by Al-Shatanawi et al.. This can inform the tailoring of anticoagulation strategies to local comorbidity profiles. In China, Tang et al. reported that the burden of ischemic stroke attributable to high fasting plasma glucose increased in absolute terms from 1990 to 2019, with projections suggesting future decline under current trends, reinforcing glycemic control as a population lever for precision prevention.

Recovery science that personalizes rehabilitation

Precision extends to neurorecovery. A systematic review of sensorimotor network (SMN) alterations across fMRI studies by Sahrizan et al. documented early disruptions with progressive reintegration through compensatory reorganization; lesion topology was found to modulate trajectories, advocating for network-aware rehabilitation that adapts to time since stroke and structural substrate.

A practical synthesis for the bedside

Collectively, these studies outline a layered, workflow-embedded model:

1) Baseline biology, such as ALP, creatinine/eGFR, microRNAs, and inflammatory signals, flags trajectories (e.g., fast progression, poor repair) and informs hemodynamic goals, nephro-pharmacologic caution, and surveillance intensity.
2) Imaging phenotypes, such as collaterals, vessel-wall features, IMR, radiomics, and covert SVD, personalize EVT candidacy, adjuvant choices, and cognitive follow-up.
3) Etiologic precision, such as early CCTA to detect thrombus even without known AF, accelerates anticoagulation in selected patients.
4) Therapeutic tailoring, i.e., dose- and phenotype-aware thrombolysis, candidate neuroprotective adjuncts (e.g., cerebrolysin), and MIS for ICH, where feasible, should be tested with tissue-level surrogates (e.g., IMR) and patient-centered endpoints.
5) Operational precision, such as HERS-like infrastructures and collateral/fast-progressor-triggered fast tracks, must prove their ability to convert minutes into disability-free days, especially in the posterior circulation and in cancer-related phenotypes, where equipoise persists.

Conclusion

This Research Topic offers a coherent, actionable blueprint for precision stroke care: measure what matters, when it matters, for the patient in front of you. By combining accessible biomarkers (e.g., ALP, renal indices, microRNAs), richer imaging phenotypes (e.g., collaterals, vessel-wall features, IMR, radiomics, covert SVD), optimized reperfusion and adjunct strategies (e.g., dose-tuned thrombolysis, neuroprotection, MIS), and systems engineering (e.g., HERS, phenotype-triggered pathways), the field is poised to transform variability into value. The next phase hinges on rigorous external validation, workflow-embedded trials, and equitable deployment so that personalization augments, rather than replaces, clinical judgment for every patient we serve.

Author contributions

MD: Conceptualization, Writing – original draft, Writing – review & editing. NB: Writing – review & editing. AA-B: Writing – review & editing. J-CB: Writing – review & editing. JA: Conceptualization, Writing – original draft, Writing – review & editing.

Conflict of interest

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Impact of alkaline phosphatase on clinical outcomes in patients with ischemic stroke: a nationwide registry analysis

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Background: Data on the association between serum alkaline phosphatase (ALP) levels and clinical outcomes in patients with ischemic stroke (IS) are inconsistent and limited. Therefore, this study aimed to investigate the correlation between ALP and prognosis in patients with IS.

Methods: Patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA) from the Third China National Stroke Registry were divided into four groups according to the quartiles of serum ALP levels on admission. Cox proportional hazards and logistic regression models were used to evaluate the correlation between ALP and the risk of all-cause mortality, disability (modified Rankin Scale (mRS) score 3–5), and poor functional outcomes (mRS score 3–6).

Results: A total of 11,405 patients were included in the study. Higher levels of ALP were associated with all-cause mortality at 3 months (adjusted hazard ratio [HR] per standard deviation [SD]: 1.16; 95% confidence interval (CI): 1.07–1.27; $p = 0.001$) and 1 year (adjusted HR: 1.11; 95% CI: 1.03–1.20; $p = 0.010$). At the 3-month follow-up, each SD increase of ALP was associated with a 12 and 14% higher risk of disability (adjusted odds ratio (OR): 1.12; 95% CI: 1.06–1.18; $p < 0.001$) and poor functional outcomes (adjusted OR: 1.14; 95% CI: 1.08–1.20; $p < 0.001$). Similar results were observed at the 1-year follow-up. Higher ALP levels were associated with an increased risk of all-cause mortality, disability, and poor functional outcomes in patients with "others" subtypes (including other determined etiology and undetermined etiology) ($p < 0.05$).

Conclusion: Elevated ALP levels were associated with an increased risk of all-cause mortality, disability, and poor function outcomes in patients with IS. Heterogeneity was observed among the subtypes of different etiologies.

KEYWORDS

alkaline phosphatase, mortality, disability, poor functional outcomes, stroke

1 Introduction

Stroke is the second leading cause of death and the third leading cause of disability worldwide (1, 2). Globally, China faces the most significant stroke burden, with ischemic stroke (IS) accounting for over 82% of all stroke cases (3). Therefore, identifying reliable blood markers for stroke prognosis is crucial for optimizing healthcare resource allocation (4).

Alkaline phosphatase (ALP), a widely expressed enzyme in human tissues, has been implicated in vascular calcification and the development of atherosclerosis (5–7). Inhibition of ALP has been shown to prevent the formation of vascular atherosclerosis (8). Traditionally recognized as a marker for skeletal or hepatobiliary dysfunction (9, 10), ALP is now considered indicative of atherosclerosis and inflammatory responses (6, 11). Studies have indicated that elevated serum ALP levels are linked to increased atherosclerosis in coronary and peripheral arteries and that higher ALP levels are independently associated with the risk of cardiovascular disease (CVD) and mortality events (12–14). However, conflicting findings exist among epidemiological investigations regarding the association between higher serum ALP levels and adverse clinical outcomes in stroke patients. Multiple studies have suggested that high serum ALP levels are associated with an increased incidence of stroke, higher post-stroke mortality rates, and poor functional outcomes (15–19). However, other studies have concluded that there was no significant association between increased ALP levels and poor functional outcomes (18, 20). Therefore, at present, there is no research consensus on the association between ALP levels and clinical outcomes in patients with stroke, and studies on this topic have been limited. Furthermore, the different etiologies of stroke have not yet been examined.

Therefore, this study aims to utilize a large sample from the China National Stroke Registry III (CNSR-III) to investigate the correlation between serum ALP levels and clinical outcomes (mortality, disability, and poor functional outcomes) in patients with acute ischemic stroke (AIS) and transient ischemic attack (TIA), analyze the association between serum ALP levels and stroke subtypes, and further explore the underlying mechanism of ALP.

2 Methods

2.1 Study population

CNSR-III is a nationwide prospective registry of consecutive patients with AIS or TIA. Patients were enrolled from 201 hospitals between August 2015 and March 2018. The detailed design and description of the CNSR-III have been published previously (21). The inclusion criteria were as follows: (1) age 18 years or older and (2) diagnosis of ischemic stroke or TIA within 7 days from the onset of symptoms to enrollment. The exclusion criteria were as follows: (1) silent cerebral infarction with no manifestation of symptoms and signs, and (2) refusal to participate in the registry.

The CNSR-III study was approved by the ethics committee of Beijing Tiantan Hospital (NO. KY2015-001-01), and written informed consent was obtained from patients or their legally authorized representatives. The study complied with the principles of the Declaration of Helsinki.

2.2 Data collection and management

After admission, the participants were collected by a trained neurologist in the hospital and the following baseline data were recorded: age, sex, body mass index (BMI, calculated as kg/m^2), smoking and alcohol consumption status, medical history (previous diabetes, hypertension, dyslipidemia, coronary heart disease, and stroke), treatment during hospitalization (intravenous thrombolysis, mechanical thrombectomy, antiplatelet aggregation therapy, anticoagulation therapy, and lipid-lowering therapy), National Institutes of Health Stroke Scale (NIHSS) score on admission, and pre-stroke modified Rankin Scale (mRS) score. In addition, serum ALP, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were obtained through venous puncture within 24 h. Total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), estimated glomerular filtration rate (eGFR), and high-sensitivity C-reactive protein (hs-CRP) samples were transported to the central laboratory of Beijing Tiantan Hospital for centralized testing through the cold chain.

All imaging data were collected on disks in the DICOM format, analyzed by two professional neurologists, and classified by etiological TOAST (Org10172 trial in the treatment of acute stroke). As there were a few patients with a stroke of other determined etiology, these patients were combined as a stroke of undetermined etiology and defined together as the "others." Hence, patients in this study were classified into four subtypes: large-artery atherosclerosis (LAA), cardioembolism, small-vessel occlusion, and others (including other determined etiology and undetermined etiology).

2.3 Patient follow-up and clinical outcome assessment

The clinical outcomes were obtained by trained research coordinators who were unaware of the participants' baseline characteristics, through a face-to-face interview at 3 months and via the telephone at 1 year after the onset of symptoms. Clinical outcomes included all-cause mortality, disability, and poor functional outcomes at the 3-month and 1-year follow-up. All-cause mortality was either confirmed by a death certification from the attended hospital or the local citizen registry, and the mRS score ranged from 0 (no symptoms) to 6 (death); poor functional outcome was determined by an mRS score of 3–6, while major disability was determined by an mRS score of 3–5.

2.4 Statistical analysis

This study's population characteristics were presented as medians (interquartile ranges, IQRs) or numbers (proportions) by quartiles of serum ALP levels. The associations of ALP with all-cause mortality, disability, and poor functional outcomes at 3 months and 1 year were assessed. For all-cause mortality, we used the Kaplan–Meier method to estimate the cumulative incidence in the ALP quartile groups, and the difference across groups was compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards models. The proportional hazards assumption was checked using Schoenfeld

residuals over time, and no deviations from the assumption were found. For disability and poor functional outcomes, odds ratios (ORs) with 95% CIs were estimated using logistic regression models. Serum ALP was included in the models, both as a categorized variable (in quartiles) and as a continuous variable.

Based on the clinical experience and relevant literature (16–18), we selected covariates and fitted three adjusted models. Model 1 was adjusted for age and gender. Model 2 was further adjusted for BMI, current smoking, heavy drinking, pre-stroke mRS score, TOAST classification, hypertension, diabetes, dyslipidemia, coronary heart disease, and previous stroke. Model 3 was further adjusted for antiplatelet agents, anticoagulant agents, estimated glomerular filtration rate, and high-sensitivity C-reactive protein. To visualize the potential non-linear associations of serum ALP with death, disability, and poor functional outcomes, we constructed restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles. Stratified analyzes were performed in the subgroups of TOAST types. All statistical analyzes were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) and R software version 4.1.3 (R Foundation for Statistical Computing). The statistical significance was determined as two-sided *p*-values of <0.05.

3 Results

3.1 Baseline characteristics

We excluded 3,761 patients from the initial 15,166 patients due to underlying conditions, such as liver disease ($n = 100$), kidney disease ($n = 131$), arthritis ($n = 329$), cancer ($n = 134$), infection within 2 weeks before admission ($n = 450$), or missing ALP values ($n = 2,337$), as well as mRS scores at the 1-year ($n = 349$) or 3-month ($n = 170$) follow-up (Supplementary Figure S1). The final analysis encompassed 11,405 patients. The baseline characteristics of both included and excluded patients are presented in Supplementary Table S1, demonstrating a balanced distribution between the two groups. Table 1 summarizes the baseline characteristics of the included patients, with a median age of 63 (54.0–70.0) years. Among the included patients, 10,525 (92.3%) were diagnosed with AIS, 7,784 (68.3%) were male patients, 3,605 (31.6%) were current smokers, 1,628 (14.3%) were heavy drinkers, 949 (8.3%) received intravenous thrombolysis, and 32 (0.3%) of them underwent mechanical thrombectomy. The median NIHSS score was 3 (1.0, 6.0). In the higher quartile ALP groups, patients were more likely to have a history of hypertension, coronary heart disease, and stroke, while they were less likely to have diabetes, be smokers, and consume alcohol. In TOAST classification, all ALP quartile groups had a relatively higher number of LAA and undetermined etiology stroke patients. The levels of hs-CRP increased with the increase in serum ALP levels (Table 1).

3.2 All-cause mortality

A total of 160 (1.4%) and 355 (3.1%) patients died during the 3-month and 1-year follow-up, respectively. The Kaplan–Meier curves showed that the cumulative incidence of all-cause mortality increased in patients with higher serum ALP levels within 3-month (log-rank $p = 0.015$) and 1-year (log-rank $p = 0.058$) follow-up (Figure 1). Higher levels of ALP were associated with all-cause mortality at 3 months (adjusted HR per standard deviation [SD]: 1.16; 95% CI: 1.07–1.27; $p = 0.001$) and 1 year (adjusted HR: 1.11; 95% CI: 1.03–1.20; $p = 0.010$) (Table 2). In addition, there was a linear correlation between the increase in ALP and all-cause mortality ($p < 0.001$; Figures 2A,D).

3.3 Functional outcome

In total, 1,354 patients (12.0%) had an mRS score of 3–5, and 1,514 patients (13.3%) had an mRS score of 3–6 at 3 months. At the 1-year assessment, 1,108 patients (10.0%) had an mRS score of 3–5, and 1,463 patients (12.8%) had an mRS score of 3–6. The higher the level of ALP grouping, the higher the proportion of patients with high mRS scores (Supplementary Figure S2).

At the 3-month follow-up, compared with the lowest quartile, patients in the highest quartile had a 28 and 33% greater risk of disability and poor functional outcomes, respectively (adjusted OR: 1.28; 95% CI: 1.09–1.52; $p = 0.004$ and 1.33; 95% CI: 1.13–1.57; $p = 0.001$). Similarly, at the 1-year follow-up, the risk of poor functional outcomes was found to increase in the highest quartile compared with the lowest quartile, with adjusted OR 1.24 (95% CI: 1.05–1.46; $p = 0.011$) (Table 2).

At the 3-month follow-up, each SD increase of ALP levels was associated with 12 and 14% higher risk of disability (adjusted OR: 1.12; 95% CI: 1.06–1.18; $p < 0.001$) and poor functional outcomes (adjusted OR: 1.14; 95% CI: 1.08–1.20; $p < 0.001$) in the fully adjusted model, respectively. Similar results were found at the 1-year follow-up (Table 2). In addition, the restricted cubic spline regression analysis showed a linear and positive correlation between serum ALP and functional poor outcomes at 3 months and 1 year (Figures 2B,C,E,F).

3.4 TOAST classification

As for TOAST etiologies, for each 1 SD increase of ALP in the "others" subtype, the risk of death at 3 months increased by 19% (adjusted HR: 1.19; 95% CI: 1.04–1.36; $p = 0.014$). Similarly, the risk of death at 1 year increased by 16% (adjusted HR: 1.16; 95% CI: 1.04–1.30; $p = 0.008$) (Supplementary Table S2). However, no correlation with mortality was found among LAA, SVO, and CE subtypes.

After adjusting for potential confounding factors (Model 3), in the "others" subtype, higher levels of ALP were associated with poor functional outcomes at 3 months (OR per SD: 1.15 [95% CI: 1.06–1.24; $p = 0.001$]) and 1 year (OR per SD: 1.16; 95% CI: 1.07–1.26, $p < 0.001$). Similar results were found for disability. In LAA and SVO subtypes, elevated ALP levels were associated with an increased risk of poor functional outcomes at 3 months, with ORs were 1.11 (95% CI: 1.01–1.22, $p = 0.023$) and 1.18 (95% CI: 1.04–1.34, $p = 0.010$), respectively. Similar trends were observed for disability. Furthermore, compared to the lowest quartile, higher levels of ALP were associated with an increased risk of disability and poor functional outcomes in patients with LAA at 3 months ($p < 0.05$), and there was also an increased risk of poor functional outcomes in patients with the "others" subtype at 3 months and 1 year ($p < 0.05$) (Figure 3; Supplementary Table S2). However, no correlation between disability and poor functional prognosis was found in the SVO and CE subtypes.

TABLE 1 Baseline characteristics by alkaline phosphatase quartile.

Characteristics	Quartiles of ALP					*p*-value
	Overall	Q1 (<62)	Q2 (62–75)	Q3 (75–91)	Q4 (≥91)	
n	11,405	2,794	2,864	2,894	2,853	
AIS	10,525 (92.3)	2,531 (90.6)	2,637 (92.1)	2,687 (92.8)	2,670 (93.6)	<0.001
Age, years	63.0 [54.0, 70.0]	62.0 [54.0, 71.0]	62.0 [54.0, 69.0]	62.0 [54.0, 70.0]	63.0 [55.0, 70.0]	0.111
Men, *n* (%)	7,784 (68.3)	2080 (74.4)	2065 (72.1)	1991 (68.8)	1,648 (57.8)	<0.001
Body mass index, kg/m^2	24.5 [22.6, 26.5]	24.5 [22.6, 26.4]	24.5 [22.6, 26.4]	24.5 [22.6, 26.6]	24.5 [22.5, 26.6]	0.920
Current smoking, *n* (%)	3,605 (31.6)	863 (30.9)	926 (32.3)	970 (33.5)	846 (29.7)	0.010
Heavy drinking, *n* (%)	1,628 (14.3)	487 (17.4)	426 (14.9)	417 (14.4)	298 (10.4)	<0.001
Prestroke mRS score	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.008
NIHSS score at admission	3.0 [1.0, 6.0]	3.0 [1.0, 5.0]	3.0 [1.0, 5.0]	3.0 [1.0, 6.0]	4.0 [1.0, 6.0]	<0.001
TOAST classification, *n* (%)						0.605
Large-artery atherosclerosis	2,898 (25.4)	699 (25.0)	701 (24.5)	737 (25.5)	761 (26.7)	
Cardioembolism	691 (6.1)	188 (6.7)	170 (5.9)	168 (5.8)	165 (5.8)	
Small-vessel occlusion	2,392 (21.0)	579 (20.7)	604 (21.1)	628 (21.7)	581 (20.4)	
Other determined etiology	147 (1.3)	38 (1.4)	42 (1.5)	38 (1.3)	29 (1.0)	
Undetermined etiology	5,277 (46.3)	1,290 (46.2)	1,347 (47.0)	1,323 (45.7)	1,317 (46.2)	
Medical history, *n* (%)						
Hypertension	7,123 (62.5)	1,695 (60.7)	1778 (62.1)	1810 (62.5)	1840 (64.5)	0.029
Diabetes mellitus	2,662 (23.3)	661 (23.7)	659 (23.0)	687 (23.7)	655 (23.0)	0.844
Dyslipidemia	861 (7.5)	233 (8.3)	184 (6.4)	230 (7.9)	214 (7.5)	0.039
Previous stroke	2,527 (22.2)	592 (21.2)	643 (22.5)	636 (22.0)	656 (23.0)	0.411
Coronary heart disease	1,189 (10.4)	283 (10.1)	281 (9.8)	290 (10.0)	335 (11.7)	0.065
Treatment in hospital, *n* (%)						
Intravenous thrombolysis	949 (8.3)	296 (10.6)	229 (8.0)	231 (8.0)	193 (6.8)	<0.001
Mechanical thrombectomy	32 (0.3)	12 (0.4)	9 (0.3)	5 (0.2)	6 (0.2)	0.258
Antiplatelet agents	11,002 (96.5)	2,682 (96.0)	2,743 (95.8)	2,804 (96.9)	2,773 (97.2)	0.010
Anticoagulant agents	1,191 (10.4)	307 (11.0)	275 (9.6)	289 (10.0)	320 (11.2)	0.138
Lipid-lowering agents	10,889 (95.5)	2,663 (95.3)	2,726 (95.2)	2,760 (95.4)	2,740 (96.0)	0.434
Laboratory tests						
TC, mmol/L	4.2 [3.4, 4.9]	4.1 [3.4, 4.8]	4.1 [3.4, 4.8]	4.2 [3.4, 5.0]	4.2 [3.5, 5.0]	<0.001
HDL-C, mmol/L	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	0.006
LDL-C, mmol/L	2.5 [1.9, 3.1]	2.4 [1.8, 3.1]	2.4 [1.9, 3.1]	2.5 [1.9, 3.1]	2.5 [1.9, 3.2]	0.004
TG, mmol/L	1.4 [1.0, 1.9]	1.3 [1.0, 1.8]	1.4 [1.0, 1.9]	1.4 [1.0, 2.0]	1.4 [1.1, 2.0]	<0.001
ALT, U/L	18.0 [13.0, 25.0]	17.0 [12.0, 23.0]	17.7 [13.0, 25.0]	18.0 [13.0, 25.0]	19.0 [14.0, 28.0]	<0.001
AST, U/L	19.0 [16.0, 24.0]	18.0 [15.0, 22.6]	19.0 [15.3, 23.9]	19.0 [16.0, 24.0]	20.0 [16.0, 26.0]	<0.001
eGFR, mL/min/1.73 m^2	93.2 [82.0, 101.8]	93.0 [81.4, 102.0]	93.5 [82.8, 102.0]	93.5 [82.5, 101.7]	93.0 [81.4, 101.8]	0.465
hs-CRP, mg/L	1.8 [0.8, 4.6]	1.3 [0.7, 3.5]	1.6 [0.8, 4.2]	1.9 [0.9, 4.7]	2.3 [1.0, 5.7]	<0.001

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as frequency (%). AIS, acute ischemic stroke; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TC, total cholesterol; TG, triglycerides; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

4 Discussion

This study revealed a positive association between elevated ALP levels and an increased risk of mortality, disability, and poor functional outcomes in patients with AIS. Specifically, elevated ALP levels were linked to adverse clinical outcomes in the others subtype and were correlated with an increased risk of disability and poor functional outcomes in the LAA and SVO subtypes at 3 months. These findings offer new insights into the role of ALP levels in the AIS prediction. The Chinese Stroke Registry II and the Xi'an multicenter study reported

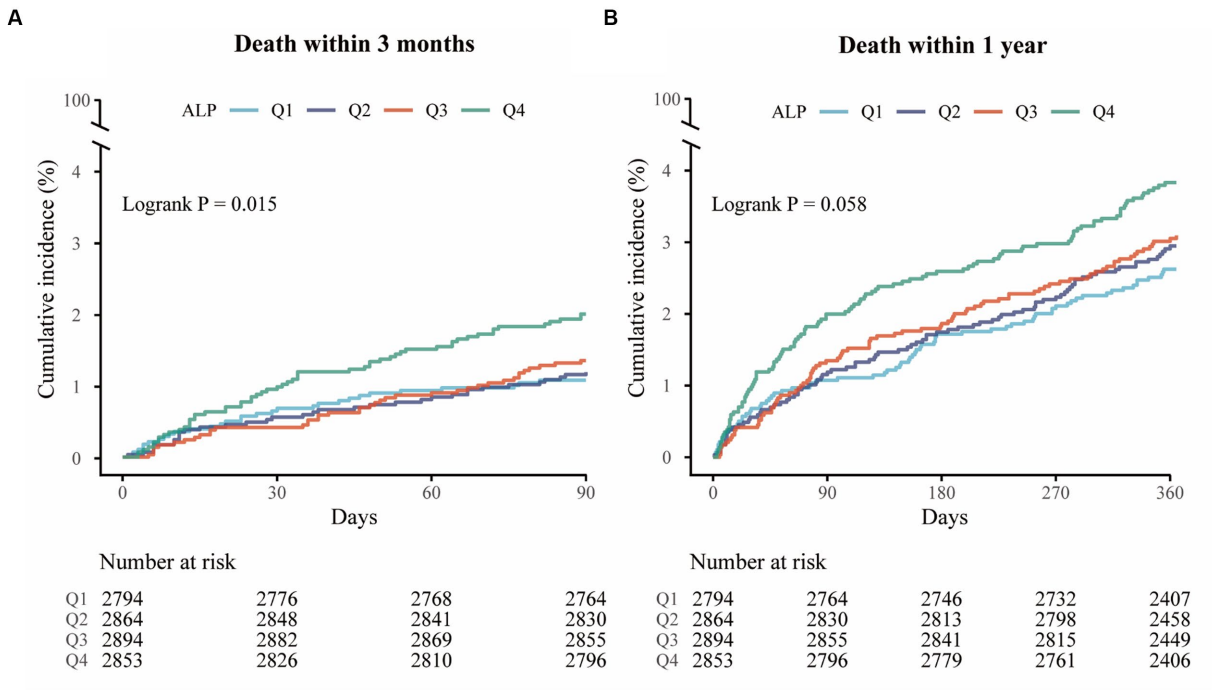

FIGURE 1
Kaplan–Meier curves for all-cause mortality. **(A)** Kaplan–Meier curves for all-cause mortality within 3 months (log-rank test; $p = 0.015$). **(B)** Kaplan–Meier curves for all-cause mortality within 1 year (log-rank test; $p = 0.058$).

that higher ALP levels were associated with increased patient mortality, without identifying a linear correlation (17, 18). Conversely, a Korean single-center study indicated a positive linear correlation between elevated ALP levels and mortality (16). In line with these findings, our study indicated that elevated ALP levels were associated with an increased risk of all-cause mortality, with a linear correlation observed. The differences in the studies primarily resulted from the included populations. The linear correlation study focused on IS patients, while the non-linear correlation studies included mixed stroke (including ischemic stroke and hemorrhagic stroke) patients. Ryu et al. also revealed that hemorrhagic stroke patients in the elevated ALP group had a higher risk of death than ischemic patients, which may affect the linear and non-linear relationships (16). Furthermore, Zhong et al. (22) observed similar results in their study of 2,944 enrolled AIS patients. We also performed an analysis of poor functional outcomes, and similar to Zhu et al. and Kim et al., we found that higher ALP levels were associated with an increased risk of poor functional outcomes (11, 19). However, Guo et al. and Liu et al. found that elevated ALP levels were not associated with poor functional outcomes in stroke patients (18, 20). The difference in conclusions may be related to the participant characteristics and sample size. Furthermore, we analyzed the disability and discovered that elevated levels of ALP could serve as a predictor for disability in patients with AIS and TIA.

In CVD studies, the elevated mortality associated with increased ALP levels was related to atherosclerosis (23). Unlike CVD, IS is a heterogeneous disease with a distinct pathogenesis. The mechanism between elevated serum ALP and prognosis in patients with IS remains unclear; no studies have investigated the role of ALP in different subtypes of IS. However, in this study, an increase in ALP was not found to be associated with all-cause mortality in patients with the LAA subtype, and only LAA and SVO subtypes were associated with poor functional outcomes and disability during the short-term follow-up. Kim et al. also found that higher ALP levels were not associated with cerebral atherosclerosis (19). Therefore, the association between higher ALP levels and an increased risk of adverse outcomes in stroke patients might be unrelated to the mechanism of atherosclerosis. This study discovered a significant association between elevated levels of ALP and the prognosis of patients with an undetermined etiology stroke subtype. Furthermore, it revealed that patients with a history of coronary heart disease exhibited elevated serum ALP levels. The occurrence of adverse clinical outcomes may be related to unstable and easy detachment of calcified plaques or cardioembolism (24, 25), which requires further research.

Systemic inflammation has been recognized as a significant factor influencing the short-term and long-term outcomes of patients with stroke (26, 27). The pathophysiological mechanisms underlying the adverse clinical outcomes in patients with elevated ALP levels may be associated with the interplay between elevated ALP, neuroinflammation, blood–brain barrier (BBB) permeability, and vascular homeostasis (28). The immune rescue mechanism of neuroinflammation was reported to be activated after cerebral ischemia (29), resulting in an increase in ALP (7, 30, 31), which was consistent with the current proposal that peripheral immunity is involved in complex brain immune networks (32). Furthermore, tissue-non-specific alkaline phosphatase (TNAP), the isoenzyme of ALP, is abundant in brain endothelial cells and neurons (33) and regulates neuroinflammatory responses (34, 35). After the breakdown of the BBB, TNAP is lost to the periphery, and the decrease in TNAP levels further exacerbates brain damage (36, 37). Thus,

TABLE 2 Associations of alkaline phosphatase with all-cause mortality, disability, and poor functional outcomes.

	Events, *n* (%)	Unadjusted	*p*	Model 1	*p*	Model 2	*p*	Model 3	*p*
At 3 months									
Death									
Per SD increase	160 (1.4)	1.19 (1.10, 1.28)	<0.001	1.16 (1.07, 1.26)	<0.001	1.16 (1.07, 1.25)	<0.001	1.16 (1.07, 1.27)	0.001
Q1	30 (1.1)	Reference		Reference		Reference		Reference	
Q2	34 (1.2)	1.11 (0.68, 1.81)	0.690	1.16 (0.71, 1.89)	0.564	1.10 (0.67, 1.80)	0.697	1.10 (0.67, 1.80)	0.699
Q3	39 (1.4)	1.25 (0.78, 2.02)	0.350	1.27 (0.79, 2.04)	0.334	1.23 (0.76, 1.98)	0.403	1.23 (0.77, 1.99)	0.388
Q4	57 (2.0)	1.87 (1.20, 2.91)	0.006	1.83 (1.17, 2.87)	0.008	1.73 (1.11, 2.72)	0.016	1.63 (1.03, 2.56)	0.036
mRS score 3–5									
Per SD increase	1,354 (12.0)	1.15 (1.10, 1.21)	<0.001	1.13 (1.07, 1.19)	<0.001	1.13 (1.07, 1.19)	<0.001	1.12 (1.06, 1.18)	<0.001
Q1	290 (10.5)	Reference		Reference		Reference		Reference	
Q2	316 (11.2)	1.07 (0.91, 1.27)	0.418	1.08 (0.91, 1.28)	0.374	1.06 (0.89, 1.26)	0.504	1.06 (0.89, 1.26)	0.495
Q3	351 (12.3)	1.20 (1.01, 1.41)	0.034	1.19 (1.00, 1.40)	0.046	1.16 (0.98, 1.37)	0.086	1.17 (0.99, 1.39)	0.067
Q4	397 (14.2)	1.41 (1.20, 1.66)	<0.001	1.35 (1.14, 1.59)	<0.001	1.29 (1.09, 1.53)	0.003	1.28 (1.09, 1.52)	0.004
mRS score 3–6									
Per SD increase	1,514 (13.3)	1.17 (1.11, 1.23)	<0.001	1.14 (1.09, 1.2)	<0.001	1.14 (1.09, 1.20)	<0.001	1.14 (1.08, 1.20)	<0.001
Q1	320 (11.5)	Reference		Reference		Reference		Reference	
Q2	350 (12.2)	1.08 (0.92, 1.26)	0.372	1.09 (0.92, 1.28)	0.316	1.06 (0.90, 1.26)	0.469	1.06 (0.90, 1.26)	0.482
Q3	390 (13.5)	1.20 (1.03, 1.41)	0.021	1.19 (1.02, 1.40)	0.032	1.16 (0.99, 1.37)	0.067	1.18 (1.00, 1.39)	0.052
Q4	454 (15.9)	1.46 (1.25, 1.71)	<0.001	1.40 (1.20, 1.64)	<0.001	1.34 (1.14, 1.58)	<0.001	1.33 (1.13, 1.57)	0.001
At 1 year									
Death									
Per SD increase	355 (3.1)	1.13 (1.05, 1.21)	0.001	1.11 (1.04, 1.20)	0.003	1.11 (1.03, 1.19)	0.005	1.11 (1.03, 1.20)	0.010
Q1	73 (2.6)	Reference		Reference		Reference		Reference	
Q2	84 (2.9)	1.12 (0.82, 1.54)	0.469	1.18 (0.86, 1.62)	0.297	1.12 (0.82, 1.54)	0.473	1.13 (0.82, 1.55)	0.448
Q3	89 (3.1)	1.18 (0.87, 1.61)	0.296	1.21 (0.89, 1.65)	0.230	1.15 (0.85, 1.57)	0.367	1.17 (0.86, 1.60)	0.312
Q4	109 (3.8)	1.47 (1.10, 1.98)	0.010	1.50 (1.11, 2.03)	0.008	1.39 (1.03, 1.88)	0.033	1.33 (0.98, 1.80)	0.069
mRS score 3–5									
Per SD increase	1,108 (10.0)	1.13 (1.07, 1.19)	<0.001	1.11 (1.05, 1.17)	<0.001	1.11 (1.05, 1.17)	0.001	1.11 (1.05, 1.17)	0.001
Q1	261 (9.6)	Reference		Reference		Reference		Reference	
Q2	239 (8.6)	0.89 (0.74, 1.07)	0.200	0.90 (0.75, 1.08)	0.265	0.88 (0.73, 1.06)	0.188	0.88 (0.73, 1.07)	0.200
Q3	282 (10.1)	1.05 (0.88, 1.26)	0.565	1.05 (0.88, 1.26)	0.580	1.03 (0.86, 1.23)	0.767	1.04 (0.87, 1.25)	0.680
Q4	326 (11.9)	1.27 (1.07, 1.51)	0.006	1.24 (1.04, 1.48)	0.018	1.19 (0.99, 1.42)	0.057	1.19 (0.99, 1.42)	0.061
mRS score 3–6									
Per SD increase	1,463 (12.8)	1.14 (1.08, 1.20)	<0.001	1.12 (1.07, 1.18)	<0.001	1.12 (1.06, 1.18)	<0.001	1.11 (1.06, 1.17)	<0.001
Q1	334 (12.0)	Reference		Reference		Reference		Reference	
Q2	323 (11.3)	0.94 (0.80, 1.10)	0.427	0.95 (0.81, 1.13)	0.580	0.93 (0.78, 1.10)	0.371	0.92 (0.78, 1.09)	0.340
Q3	371 (12.8)	1.08 (0.92, 1.27)	0.322	1.08 (0.92, 1.27)	0.325	1.06 (0.90, 1.24)	0.518	1.06 (0.90, 1.26)	0.458
Q4	435 (15.3)	1.33 (1.14, 1.54)	<0.001	1.30 (1.11, 1.53)	0.001	1.24 (1.06, 1.46)	0.008	1.24 (1.05, 1.46)	0.011

Hazard ratios were used for death; Odds ratios were used for an mRS score of 3–5 and an mRS score of 3–6. Model 1 was adjusted for age and sex. Model 2 was further adjusted for body mass index, current smoking, heavy drinking, pre-stroke mRS score, TOAST classification, and hypertension, diabetes mellitus, dyslipidemia, previous stroke, and coronary heart disease. Model 3 was further adjusted for antiplatelet agents, anticoagulant agents, estimated glomerular filtration rate, and high-sensitivity C-reactive protein. mRS, modified Rankin Scale. SD, standard deviation; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

we hypothesized that elevated serum ALP levels in the acute phase could indicate a significant depletion of ALP in the brain, reflecting the extent of neurological impairment and ultimately leading to a poor prognosis. The potential of oral ALP or TNAP administration for the treatment of nerve damage following IS presents a compelling area for future investigation.

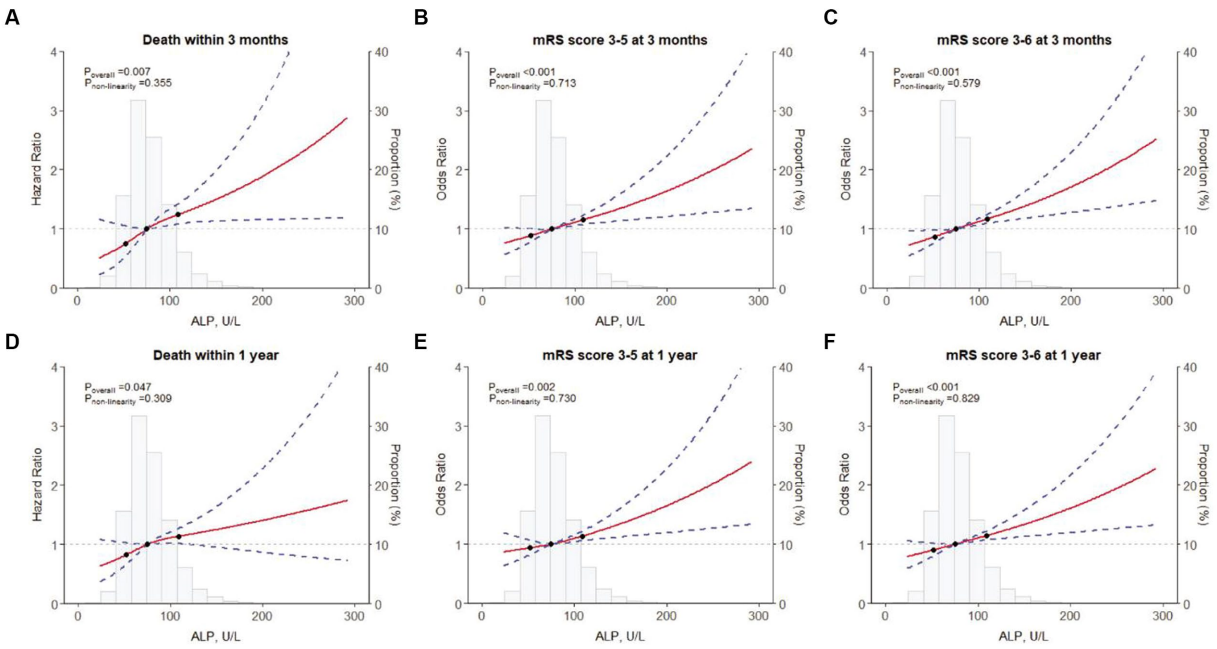

FIGURE 2
Restricted cubic spline for associations between ALP and clinical outcomes. **(A)** Death within 3 months; **(B)** an mRS score of 3–5 at 3 months; **(C)** an mRS score of 3–6 at 3 months; **(D)** Death within 1 year; **(E)** an mRS score of 3–5 at 1 year; **(F)** an mRS score of 3–6 at 1 year. ALP, alkaline phosphatase; mRS, modified Rankin Scale.

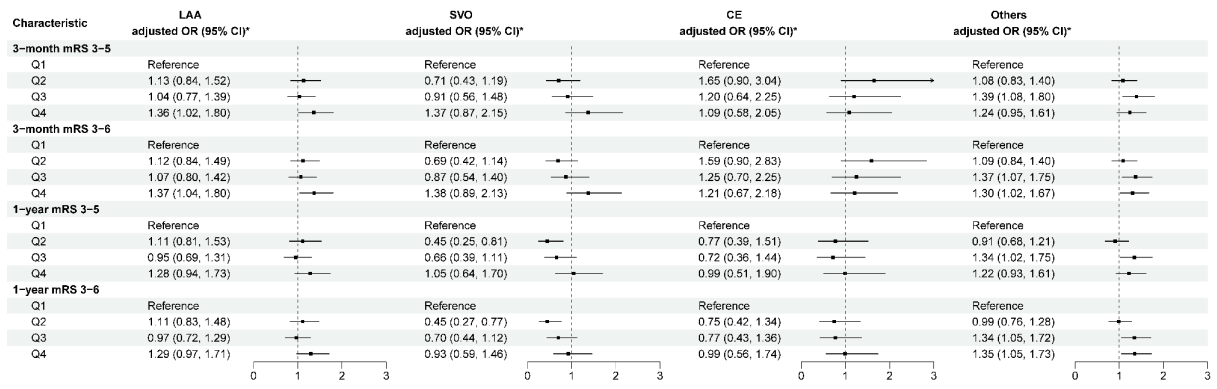

FIGURE 3
Multivariable analysis of disability and poor functional outcomes according to TOAST classification. *Model 3 is adjusted for age, sex, body mass index, current smoking, heavy drinking, pre-stroke mRS score, TOAST classification, hypertension, diabetes, dyslipidemia, coronary heart disease, previous stroke, antiplatelet agents, anticoagulant agents, estimated glomerular filtration rate, and high-sensitivity C-reactive protein. CE, cardioembolism; LAA, large-artery atherosclerosis; mRS, modified Rankin Scale; others, other determined etiology and undetermined etiology; SVO, small-vessel occlusion; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

This study is a large-scale, multicenter prospective study with a substantial sample size, including patients from 201 hospitals, which enhances the generalizability of the research findings. This study explores, for the first time, the impact of ALP on various TOAST subtypes. However, the study also has some limitations. First, this was an observational study, controlling for some important potential confounding factors in the multivariable adjustment model; however, it is still difficult to entirely eliminate the possibility of residual confounding. Second, we did not collect information on vitamin D deficiency in our study, despite the known impact of vitamin D on serum ALP levels. To minimize the potential confounding effects, we collected blood samples at a predetermined time (the next morning after the admission with overnight fasting). Third, our study only examined ALP levels in the acute phase and did not assess their continuity over time. Therefore, it remains unclear whether changes in ALP levels may in turn impact the outcomes of IS. Fourth, the types of ALP isoenzymes have not been evaluated, and it was not possible to assess which types of ALP are associated with adverse stroke outcomes. Further studies are needed to confirm the role of isoenzymes in AIS and TIA, which might provide more valuable information for understanding the mechanism of ALP on clinical

outcomes. Additionally, since all participants in the study were Chinese, the generalizability to other races and ethnicities may be limited.

5 Conclusion

In summary, this study showed that elevated ALP levels were associated with an increased risk of all-cause mortality, disability, and poor function outcomes in patients with IS. Furthermore, heterogeneity was observed among the subtypes of different stroke etiologies.

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.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Beijing Tiantan Hospital (No. KY2015-001-01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZW: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. JLi: Methodology, Writing – original draft, Writing – review & editing. JJ: Data curation, Project administration, Supervision, Writing – review & editing. ZZ: Data curation, Project administration, Supervision, Writing – review & editing. QX: Data curation, Formal analysis, Writing – review & editing. TL: Data curation, Project administration, Supervision, Writing – review & editing. JLin: Data curation, Formal analysis, Investigation, Writing – review & editing. YJ: Data curation, Methodology, Writing – review & editing. YW: Conceptualization, Supervision, Writing – review & editing. AW: Conceptualization, Methodology, Supervision, Writing – review & editing. XM: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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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.2024.1336069/full#supplementary-material

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Red blood cell count in cerebrospinal fluid was correlated with inflammatory markers on the seventh postoperative day and all associated with the outcome of aneurysmal subarachnoid hemorrhage patients

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Background: Exploring factors associated with the outcome of patients with aneurysmal subarachnoid hemorrhage (aSAH) has become a hot focus in research. We sought to investigate the associations of inflammatory markers and blood cell count in cerebrospinal fluid with the outcome of aSAH patients.

Methods: We carried a retrospective study including 200 patients with aSAH and surgeries. The associations of neutrophil, lymphocyte, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune inflammation index (SII), system inflammation response index (SIRI), and blood cell count in cerebrospinal fluid on the 1st and 7th postoperative days with the outcome of aSAH patients were investigated by univariate analysis and multivariate logistic regression model.

Results: According to the modified Rankin scale (mRS) score, there were 147 patients with good outcome and 53 patients with poor outcome. The neutrophil, NLR, SIRI, and SII levels on the seventh postoperative day in patients with poor outcome were all significantly higher than patients with good outcome, $P < 0.05$. The multivariate logistic regression model including inflammatory markers and blood cell counts in cerebrospinal fluid on the 1st postoperative day confirmed that red blood cell count in cerebrospinal fluid ($\geq 177 \times 10^9$/L; OR: 7.227, 95% CI: 1.160–45.050, $P = 0.034$) was possibly associated with poor outcome of aSAH patients, surgical duration (≥169 min), Fisher grade (III–IV), hypertension, and infections were also possibly associated with the poor outcome. The model including inflammatory markers and blood cell counts in cerebrospinal fluid on the 7th postoperative day confirmed that red blood cell count in cerebrospinal fluid ($\geq 54 \times 10^9$/L; OR: 39.787, 95% CI: 6.799–232.836, $P < 0.001$) and neutrophil-lymphocyte ratio (≥8.16; OR: 6.362, 95% CI: 1.424–28.428, $P = 0.015$) were all possibly associated with poor outcome of aSAH patients. The NLR ($r = 0.297$, $P = 0.007$) and SIRI ($r = 0.325$, $P = 0.003$) levels were all correlated with the count of red blood cells in cerebrospinal fluid.

Discussion: Higher neutrophil-lymphocyte ratio and higher red blood cell count in cerebrospinal fluid were all possibly associated with poor outcome of

patients with aneurysmal subarachnoid hemorrhage. However, we need a larger sample study.

KEYWORDS

aneurysmal subarachnoid hemorrhage, systemic immune inflammation index, system inflammation response index, neutrophil-lymphocyte ratio, cerebrospinal fluid

Introduction

Stroke is one of the leading causes of disability and death worldwide, of which aneurysmal subarachnoid hemorrhage is more common. A community study on deaths and recurrent vascular events among 500,000 Chinese adults who experienced their first stroke showed that subarachnoid hemorrhage accounted for 2% of strokes (1). Among them, the mortality and disability rate of aneurysmal subarachnoid hemorrhage were relatively high. The mortality of 4,506 patients with higher Hunt-Hess grade aneurysmal subarachnoid hemorrhage (aSAH) from 85 clinical studies was 34% (2). Exploring the prognostic factors of patients with aSAH is a hot research direction. But there is limited research on the association of neutrophil to lymphocyte ratio (NLR), and red blood cell count in cerebrospinal fluid with the outcome of patients. A few studies confirmed the association of NLR with the outcome of aSAH patients. Patients with higher NLR at admission had poorer clinical outcome (3, 4). On the other hand, cerebral vasospasm induced by hemoglobin released from dissolved red blood cells after hemorrhage possibly played an important role in delayed ischemia and poor outcome (5). Our study aimed to explore the associations of neutrophil to lymphocyte ratio and red blood cell count in cerebrospinal fluid with clinical outcome in patients with aSAH, and further investigate whether there was an association between red blood cell count in cerebrospinal fluid and NLR level.

Methods

Study design and participants

There were 200 surgical patients with aSAH from the Neurointensive Care Unit in the First Affiliated Hospital of Yangtze University from 2020 to 2023 included in this retrospective study. Inclusion criteria: (1) age $\geq$30 years old; (2) with subarachnoid hemorrhage caused by ruptured aneurysms confirmed by Computed Tomographic Angiography (CTA) and/or Digital Subtraction Angiography (DSA); (3) received endovascular embolization or craniotomy within 48 h of admission. Exclusion criteria: (1) had subarachnoid hemorrhage caused by trauma or unexplained; (2) suffered from serious systemic diseases before admission, such as liver and kidney dysfunction, hematological tumors; (3) with modified Rankin scale (mRS) score before admission more than 2; (4) unable to complete follow-up. This research has been reviewed and approved by the Ethics Committee of hospital. The clinical outcome was determined by the mRS results from 90-day follow-up. The patients with mRS score of 0–2 were determined to have a good outcome, and patients with mRS score of 3–6 were determined to have a poor outcome (6). The flowchart was showed in Figure 1.

Data collection

Baseline characteristics included age, gender, and comorbidities (hypertension and diabetes), surgical method, surgical duration, Hunt Hess grade, and Fisher grade were also recorded. Blood cells counts including neutrophils, lymphocytes and platelets on the first and seventh postoperative days, and counts of cells in cerebrospinal fluid were extracted from the hospital information system. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were calculated. Systemic immune inflammation index (SII) and system inflammation response index (SIRI) were also calculated. SII = platelet count $\times$ NLR. SIRI = monocyte count $\times$ NLR.

Statistical analysis

SPSS 23.0 and GraphPad Prism 6.0 were used for data analysis and graphics. The receiver operating characteristic curve (ROC) was used for the cut-off value analysis. The qualitative variables were compared by Pearson chi-square test, Continuity correction or Fisher exact tests. The quantitative variables were compared by independent-sample t-test, corrected t-test, or Mann-Whitney U-test. The multivariate logistic regression model was constructed for factors associated with the 90-d outcome of patients with aneurysmal subarachnoid hemorrhage. Covariates that had a P-value < 0.05 in the univariate analysis were added to the multivariate logistic regression model. All P-values were 2-sided and the statistical significance was set at $P < 0.05$.

Results

Among the 200 patients included, there were 78 males and 122 females. The average age was 60 years old. There were 35 patients with GCS score <11, 88 patients with intraventricular hemorrhage, 67 patients with Hunt-Hess grade III-V, and 72 patients with Fisher grade III-IV. There were 165 patients with embolization surgeries and 35 patients with craniotomy surgeries. The median surgical duration was 170 min. There were 107 patients with hypertension and 26 patients with diabetes (Table 1).

Among all included aSAH patients, the neutrophil level on the first postoperative day was 9.28 $\pm$ 5.00 $\times$ 10^9/L, the lymphocyte level was 0.90 $\pm$ 0.57 $\times$ 10^9/L, the SIRI level was 7.18 $\pm$ 8.44

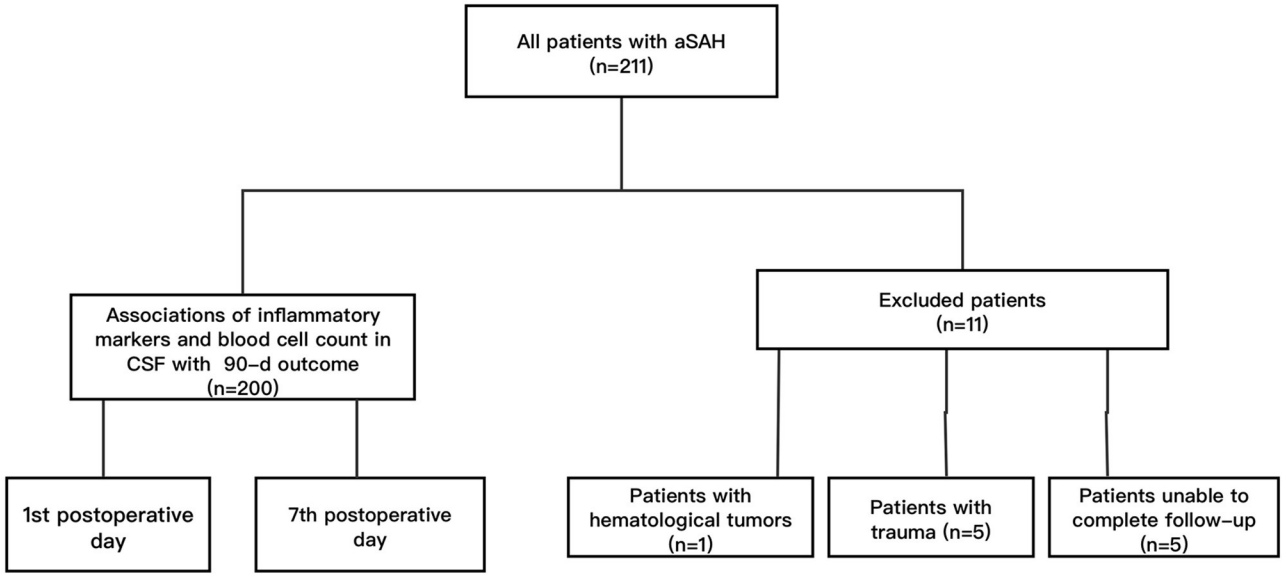

FIGURE 1
The flow chart of the study. Among 200 included patients, there were 147 patients with good outcome and 53 patients with poor outcome according to the mRS score.

$\times 10^9$/L, and the NLR level was 10.72 ± 8.24. On the seventh postoperative day, the neutrophil level was 7.49 ± 4.45 $\times 10^9$/L, the lymphocyte level was 1.26 ± 0.71 $\times 10^9$/L, the SIRI level was 4.17 ± 4.23 $\times 10^9$/L, and the NLR level was 5.81 ± 4.50. The red blood cell count in cerebrospinal fluid on the first postoperative day was 129 ± 253 $\times 10^9$/L, and was 34.5 ± 77.3 $\times 10^9$/L on the seventh postoperative day. The white blood cell count in cerebrospinal fluid on the first postoperative day and seventh postoperative day were 0.146 ± 0.323 $\times 10^9$/L and 0.243 ± 0.493 $\times 10^9$/L, respectively (Table 2).

According to the mRS score, there were 147 patients with good outcome and 53 patients with poor outcome. The average age in patients with poor outcome was 62 years old, older than patients with good outcome (59 years), $P = 0.019$. Among patients with poor outcome, there were 66.0% cases with hypertension, more than patients with good outcome (49.0%), $P < 0.001$. The proportions of cases with GCS score <11 (43.4 vs. 8.2%, $P < 0.001$), with ventricular hemorrhage (67.9 vs. 35.4%, $P < 0.001$), with Hunt-Hess grade III–V (66.0 vs. 21.8%, $P < 0.001$), and with Fisher grade III–IV (71.7 vs. 23.1%, $P < 0.001$) in patients with poor outcome were all significantly higher than patients with good outcome. Among patients with poor outcome, there were 19 (35.8%) cases undergoing craniotomy surgeries, which was also significantly higher than patients with good outcome (10.9%), $P < 0.001$. Patients with poor outcome also had higher proportion of infections (88.7 vs. 61.9%, $P < 0.001$). The surgical duration in patients with poor outcome was 180 ± 95 min, significantly longer than patients with good outcome (160 ± 70 min), $P = 0.019$. There were no significant differences in the proportions of males ($P = 0.080$), cases with posterior circulation aneurysms ($P = 0.312$), diabetes ($P = 0.672$), and coronary atherosclerotic heart disease ($P = 0.574$) between patients with good outcome and poor outcome (Table 1).

On the first postoperative day, the neutrophil level in patients with poor outcome was 11.34 ± 5.55 $\times 10^9$/L, significantly higher than patients with good outcome (8.82 ± 4.49 $\times 10^9$/L), $P < 0.001$. The NLR level in patients with poor outcome was 14.05 ± 11.59, significantly higher than patients with good outcome (9.94 ± 7.57), $P < 0.001$. The SIRI level (10.21 ± 8.83 $\times 10^9$/L vs. 5.87 ± 6.56 $\times 10^9$/L, $P < 0.001$) and SII level (2,385.61 ± 1,788.81 $\times 10^9$/L vs. 1,787.56 ± 1,564.96 $\times 10^9$/L, $P = 0.001$) in patients with poor outcome were all significantly higher than patients with good outcome. The red blood cell count in cerebrospinal fluid among patients with poor outcome was 311 ± 221 $\times 10^9$/L, significantly higher than patients with good outcome (103 ± 200 $\times 10^9$/L), $P < 0.001$. The white blood cell count in cerebrospinal fluid among patients with poor outcome was 0.400 ± 0.607 $\times 10^9$/L, significantly higher than patients with good outcome (0.119 ± 0.260 $\times 10^9$/L), $P < 0.001$ (Table 2).

On the seventh postoperative day, the neutrophil level in patients with poor outcome was 10.66 ± 4.59 $\times 10^9$/L, significantly higher than patients with good outcome (6.95 ± 3.33 $\times 10^9$/L), $P < 0.001$. The lymphocyte level was 1.09 ± 0.68 $\times 10^9$/L, lower than patients with good outcome (1.30 ± 0.67 $\times 10^9$/L), $P = 0.017$. The NLR level in patients with poor outcome was 9.48 ± 9.30, significantly higher than patients with good outcome (5.51 ± 3.48), $P < 0.001$. The SIRI level (7.28 ± 8.78 $\times 10^9$/L vs. 3.64 ± 3.08 $\times 10^9$/L, $P < 0.001$) and SII level (1,977.70 ± 1,762.96 $\times 10^9$/L vs. 1,212.70 ± 938.36 $\times 10^9$/L, $P < 0.001$) in patients with poor outcome were all significantly higher than patients with good outcome. The red blood cell count in cerebrospinal fluid among patients with poor outcome was 86.5 ± 202.8 $\times 10^9$/L, significantly higher than patients with good outcome (26.0 ± 35.8 $\times 10^9$/L), $P < 0.001$. The white blood cell count in cerebrospinal fluid among patients with poor outcome was 0.451 ± 0.866 ×

TABLE 1 Baseline characteristics data in included patients with aneurysmal subarachnoid hemorrhage.

Characteristics	Total ($n = 200$)	Good outcome ($n = 147$)	Poor outcome ($n = 53$)	*P*-value
Gender [*n* (%)]				
Male	78 (39.0%)	52 (35.4%)	26 (49.1%)	0.080
Female	122 (61.0%)	95 (64.6%)	27 (50.9%)	
Age (years)	60 ± 10	59 ± 10	62 ± 9	0.019
Surgical duration (minutes)	170 ± 80	160 ± 70	180 ± 95	0.019
Glasgow coma scale score [*n* (%)]				
<11	35 (17.5%)	12 (8.2%)	23 (43.4%)	<0.001
≥11	165 (82.5%)	135 (91.8%)	30 (56.6%)	
With intraventricular hemorrhage [*n* (%)]				
No	112 (56.0%)	95 (64.6%)	17 (32.1%)	<0.001
Yes	88 (44.0%)	52 (35.4%)	36 (67.9%)	
Hunt-Hess grade [*n* (%)]				
I–II	133 (66.5%)	115 (78.2%)	18 (34.0%)	<0.001
III–V	67 (33.5%)	32 (21.8%)	35 (66.0%)	
Fisher grade [*n* (%)]				
I–II	128 (64.0%)	113 (76.9%)	15 (28.3%)	<0.001
III–IV	72 (36.0%)	34 (23.1%)	38 (71.7%)	
Surgical mode [*n* (%)]				
Embolization	165 (82.5%)	131 (89.1%)	34 (64.2%)	<0.001
Craniotomy	35 (17.5%)	16 (10.9%)	19 (35.8%)	
Hypertension				
No	93 (46.5%)	75 (51.0%)	18 (34.0%)	<0.001
Yes	107 (53.5%)	72 (49.0%)	35 (66.0%)	
Diabetes				
No	174 (87.0%)	127(86.4%)	47 (88.7%)	0.672
Yes	26 (13.0%)	20(13.6%)	6 (11.3%)	
Location of aneurysm				
Anterior circulation aneurysms [*n* (%)]	187 (93.5%)	139 (94.6%)	48 (90.6%)	0.312
Posterior circulation aneurysms [*n* (%)]	13 (6.5%)	8 (5.4%)	5 (9.4%)	
Coronary atherosclerotic heart disease [*n* (%)]				
No	193 (96.5%)	143 (97.3%)	50 (94.3%)	0.574
Yes	7 (3.5%)	4 (2.7%)	3 (5.7%)	
Infections [*n* (%)]				
No	62 (31.0%)	56 (38.1%)	6 (11.3%)	<0.001
Yes	138 (69.0%)	91 (61.9%)	47 (88.7%)	

10^9/L, significantly higher than patients with good outcome (0.133 ± 0.348 × 10^9/L), $P = 0.001$ (Table 2).

We used the receiver operating characteristic curve for the cut-off value. The cut-off value of surgery duration was 169 min (AUC = 0.608, 95% CI: 0.516–0.701, Youden index = 0.282, $P = 0.019$). The cut-off value of red blood cell count in cerebrospinal fluid on the first postoperative day was 177 × 10^9/L (AUC = 0.733, 95% CI: 0.629–0.837, Youden index = 0.493, $P < 0.001$), with sensitivity of 82.6% and specificity of 66.7%. The cut-off value of NLR level on the seventh postoperative day was 8.16 (AUC = 0.756, 95% CI: 0.670–0.843, Youden index = 0.481, $P < 0.001$), with sensitivity of 63.6% and specificity of 84.5%. The cut-off value of red blood cell count in cerebrospinal fluid was 54 × 10^9/L (AUC = 0.779, 95% CI: 0.671–0.887, Youden index = 0.527, $P < 0.001$), with sensitivity of 66.7% and specificity of 86.0% (Table 3).

The multivariate logistic regression model including inflammatory markers and blood cell counts in cerebrospinal fluid on the 1st postoperative day confirmed that red blood cell count in cerebrospinal fluid (≥177 × 10^9/L; OR: 7.227, 95% CI: 1.160–45.050, $P = 0.034$) was possibly associated with poor

TABLE 2 Inflammatory markers and blood cell counts in cerebrospinal fluid in all included patients.

	Total ($n = 200$)	Good outcome ($n = 147$)	Poor outcome ($n = 53$)	*P*-value
Peripheral blood cell counts and inflammatory markers				
Neutrophil on the 1st postoperative day ($\times 10^9$/L)	9.28 ± 5.00	8.82 ± 4.49	11.34 ± 5.55	<0.001
Lymphocyte on the 1st postoperative day ($\times 10^9$/L)	0.90 ± 0.57	0.95 ± 0.60	0.82 ± 0.43	0.081
System inflammation response index on the 1st postoperative day ($\times 10^9$/L)	7.18 ± 8.44	5.87 ± 6.56	10.21 ± 8.83	<0.001
Systemic immune inflammation index on the 1st postoperative day ($\times 10^9$/L)	1,891.87 ± 1,652.47	1,787.56 ± 1,564.96	2,385.61 ± 1,788.81	0.001
Neutrophil-lymphocyte ratio on the 1st postoperative day	10.72 ± 8.24	9.94 ± 7.57	14.05 ± 11.59	<0.001
Platelet-lymphocyte ratio on the 1st postoperative day	200.04 ± 126.24	196.55 ± 116.43	212.20 ± 167.06	0.275
Neutrophil on the 7th postoperative day ($\times 10^9$/L)	7.49 ± 4.45	6.95 ± 3.33	10.66 ± 4.59	<0.001
Lymphocyte on the 7th postoperative day ($\times 10^9$/L)	1.26 ± 0.71	1.30 ± 0.67	1.09 ± 0.68	0.017
System inflammation response index on the 7th postoperative day ($\times 10^9$/L)	4.17 ± 4.23	3.64 ± 3.08	7.28 ± 8.78	<0.001
Systemic immune inflammation index on the 7th postoperative day ($\times 10^9$/L)	1,272.53 ± 1,136.51	1,212.70 ± 938.36	1,977.70 ± 1,762.96	<0.001
Neutrophil-lymphocyte ratio on the 7th postoperative day	5.81 ± 4.50	6.95 ± 3.33	9.48 ± 9.30	<0.001
Platelet-lymphocyte ratio on the 7th postoperative day	171.05 ± 102.84	167.46 ± 94.80	192.12 ± 138.35	0.416
Blood cell counts in cerebrospinal fluid				
White blood cell count in cerebrospinal fluid on the 1st postoperative day ($\times 10^9$/L)	0.146 ± 0.323	0.119 ± 0.260	0.400 ± 0.607	<0.001
Red blood cell count in cerebrospinal fluid on the 1st postoperative day ($\times 10^9$/L)	129 ± 253	103 ± 200	311 ± 221	<0.001
White blood cell count in cerebrospinal fluid on the 7th postoperative day ($\times 10^9$/L)	0.243 ± 0.493	0.133 ± 0.348	0.451 ± 0.866	0.001
Red blood cell count in cerebrospinal fluid on the 7th postoperative day ($\times 10^9$/L)	34.5 ± 77.3	26.0 ± 35.8	86.5 ± 202.8	<0.001

outcome of aSAH patients. Surgical duration (≥169 min), Fisher grade (III–IV), hypertension, and infections were also possibly associated with poor outcome of aSAH patients (Table 4). The sensitivity and specificity of the model were 91.3 and 88.3%, respectively (AUC = 0.951, 95% CI: 0.909–0.992, Youden index = 0.796, $P < 0.001$; Figure 2A). The model including inflammatory markers and blood cell counts in cerebrospinal fluid on the 7th postoperative day confirmed that red blood cell count in cerebrospinal fluid (≥54 × 10^9/L; OR: 39.787, 95% CI: 6.799–232.836, $P < 0.001$) and neutrophil-lymphocyte ratio (≥8.16; OR: 6.362, 95% CI: 1.424–28.428, $P = 0.015$) were all possibly associated with poor outcome of aSAH patients (Table 4). The sensitivity and specificity of this model were 90.0 and 80.0%, respectively (AUC = 0.921, 95% CI: 0.857–0.984, Youden index = 0.700, $P < 0.001$; Figure 2B).

We conducted a correlation analysis between inflammatory marker and blood cell count in cerebrospinal fluid respectively on the first postoperative day and seventh postoperative day. The results on the 7th postoperative day showed that the NLR ($r = 0.297$, $P = 0.007$) and SIRI ($r = 0.325$, $P = 0.003$) levels were all correlated with the count of red blood cells in cerebrospinal fluid (Figure 3). The results on the 1st postoperative day showed that NLR level ($r = 0.173$, $P = 0.039$) was correlated with the count of white blood cells in cerebrospinal fluid. The SIRI level ($r = 0.337$, $P = 0.002$) was also correlated with the count of white blood cells in cerebrospinal fluid on the 7th postoperative day. No correlations were found between other inflammatory markers and cell count in cerebrospinal fluid (Table 5).

Discussion

Aneurysmal subarachnoid hemorrhage is a highly complex and fatal disease. Although significant progression has been made in the treatment of aSAH in recent years, the outcome of some patients is still poor. In recent years, many studies found that neuroinflammation played an important role in the progression of subarachnoid hemorrhage (7, 8). Therefore, many studies have begun to explore the associations between inflammatory markers and clinical outcome of patients.

NLR is the ratio of neutrophil to lymphocyte, which has become a research focus due to its ability to reflect the changes of neutrophil and lymphocyte. The NLR level was shown to be associated with the 90-d outcome in patients with cerebral hemorrhage, and also

TABLE 3 The results of area under the curve and cut-off values by the receiver operating characteristic curves.

	Cut-off value	Area under the curve (95% CI)	Youden index	*P*-value	Sensitivity	Specificity
On the 1st postoperative day						
Neutrophil ($\times 10^9$/L)	10.40	0.705 (0.622–0.788)	0.366	<0.001	67.9%	68.7%
System inflammation response index ($\times 10^9$/L)	5.9	0.678 (0.594–0.762)	0.315	<0.001	81.10%	50.3%
Systemic immune inflammation index ($\times 10^9$/L)	2,054.51	0.659 (0.576–0.743)	0.279	0.001	66.00%	61.9%
Neutrophil-lymphocyte ratio	11.24	0.678 (0.597–0.759)	0.305	<0.001	67.90%	62.6%
RBCs in cerebrospinal fluid ($\times 10^9$/L)	177	0.733 (0.629–0.837)	0.493	<0.001	82.60%	66.7%
WBCs in cerebrospinal fluid ($\times 10^9$/L)	0.180	0.761 (0.664–0.857)	0.511	<0.001	87.00%	64.2%
On the 7th postoperative day						
Neutrophil ($\times 10^9$/L)	9.96	0.755 (0.670–0.841)	0.490	<0.001	65.9%	83.1%
lymphocyte ($\times 10^9$/L)	1.11	0.619 (0.524–0.715)	0.207	0.017	66.2%	54.5%
System inflammation response index ($\times 10^9$/L)	5.89	0.779 (0.698–0.860)	0.507	<0.001	70.50%	80.3%
Systemic immune inflammation index ($\times 10^9$/L)	1,894.37	0.688 (0.593–0.783)	0.347	<0.001	52.30%	82.4%
Neutrophil-lymphocyte ratio	8.16	0.756 (0.670–0.843)	0.481	<0.001	63.60%	84.5%
RBCs in cerebrospinal fluid ($\times 10^9$/L)	54	0.779 (0.671–0.887)	0.527	<0.001	66.70%	86.0%
WBCs in cerebrospinal fluid ($\times 10^9$/L)	0.192	0.715 (0.599–0.831)	0.347	0.001	76.70%	58.0%

associated with GCS score and amount of hemorrhage (9). Higher NLR level was also a risk factor for 90-d mortality in patients with cerebral hemorrhage (4). In patients with aSAH, cases with poor outcome had significantly higher NLR level at admission, which was an important factor associated with poor outcome in these patients (3). Different from this study, we found a significant increase of NLR level on the first and seventh postoperative days. Moreover, the multivariate logistic regression model also showed that NLR $\geq$ 8.16 on the seventh postoperative day was associated with poor outcome of aSAH patients.

In our study, we also explored the associations between other inflammatory markers and the 90-d outcome of patients. PLR is the ratio of platelet to lymphocyte. It was not only associated with the outcome of many tumor patients, but also associated with the response of tumor patients to anti-tumor therapy (10, 11). Among patients with acute ischemic stroke, higher PLR was possibly associated with poor outcome, reperfusion insufficiency, and infarct size (12). The SII marker integrates platelet, neutrophil, and lymphocyte. It was possibly associated with the severity of some diseases and the outcome of cancer patients (13–15). A meta-analysis including 19 studies and 18,609 stroke patients showed that higher SII was possibly associated with poor outcome of stroke patients (16). SIRS integrates neutrophil, monocyte, and lymphocyte. Some studies also supported the association between SIRI level and the survival of cancer patients (17, 18). In our study, all multivariate logistic regression models did not confirm the associations of PLR, SII, SIRI, and lymphocyte with poor outcome of aSAH patients.

As many studies have shown, hemoglobin released by red blood cells possibly induced cerebral vasospasm, further affected the outcome of cerebral hemorrhage patients. Nozaki et al. detected the spasmodic activity of various blood components in dogs and showed that red blood cells were possibly required for late and prolonged arterial spasms after subarachnoid hemorrhage (19). Moreover, patients with delayed cerebral ischemia showed a significant increase of red blood cells in cerebrospinal fluid (20). Our study analyzed the associations of red blood cells and white blood cells in cerebrospinal fluid on the first and seventh postoperative days with clinical outcome. The multivariate model including inflammatory markers and blood cell count in cerebrospinal fluid on the first and seventh postoperative days all showed that higher red blood cell count in cerebrospinal fluid was possibly associated with poor outcome of aSAH patients.

We also conducted the correlation analysis between red blood cell count in cerebrospinal fluid and inflammatory markers (including NLR, SIRI, PLR, and SII) on the first

TABLE 4 Factors associated with poor outcome in aneurysmal subarachnoid hemorrhage patients by multivariate logistic regression models.

Models	Variable	B	S.E.	Wald	*P*-value	Adjusted odds ratio (95% CI)
Multivariate logistic regression model including inflammatory markers and blood cell counts in cerebrospinal fluid on the 1st postoperative day						
1	Surgical duration (≥169 min)	2.097	0.810	6.703	0.010	8.144 (1.665–39.845)
	Fisher grade (III–IV)	2.991	0.838	12.749	<0.001	19.904 (3.854–102.794)
	Hypertension	2.437	0.912	7.150	0.007	11.443 (1.917–68.302)
	Infections	2.719	1.057	6.620	0.010	15.160 (1.911–120.253)
	White blood cell count in cerebrospinal fluid (≥0.180 × 10^9/L)	1.910	0.976	3.826	0.050	6.753(0.996–45.776)
	Red blood cell count in cerebrospinal fluid (≥177 × 10^9/L)	1.978	0.934	4.488	0.034	7.227 (1.160–45.050)
Multivariate logistic regression model including inflammatory markers and blood cell counts in cerebrospinal fluid on the 7th postoperative day						
2	Neutrophil (≥9.96× 10^9/L)	2.496	0.842	8.786	0.003	12.135 (2.329–63.218)
	Neutrophil-lymphocyte ratio (≥8.16)	1.850	0.764	5.869	0.015	6.362 (1.424–28.428)
	Red blood cell count (≥54 × 10^9/L)	3.684	0.901	16.698	<0.001	39.787(6.799–232.836)

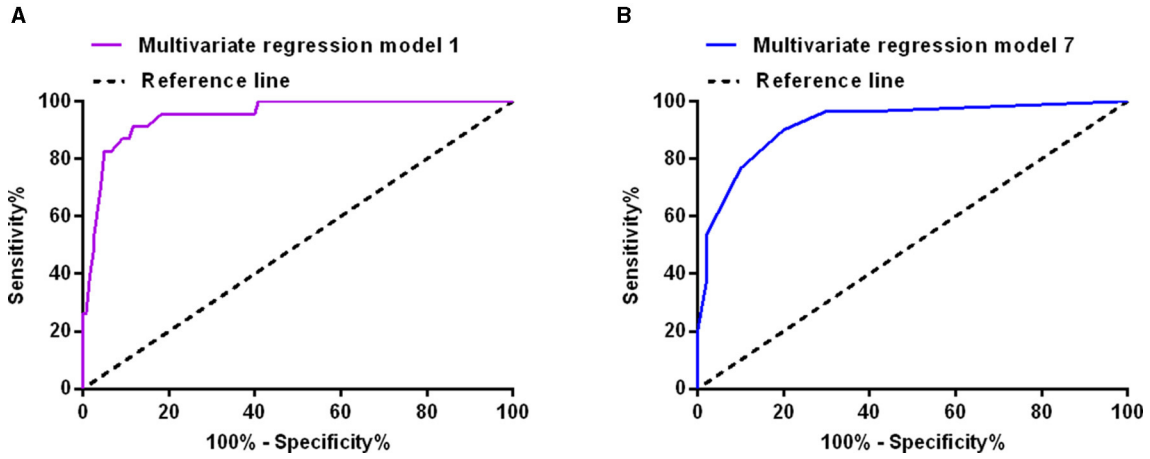

FIGURE 2
The receiver operating characteristic curves of the multivariate logistic regression model including inflammation markers and blood cell count in cerebrospinal fluid on the first postoperative day **(A)**, and on the seventh postoperative day **(B)**.

and seventh postoperative days. The results showed a mild correlation of red blood cell count in cerebrospinal fluid with NLR and SIRI levels on the seventh postoperative day. We speculated that red blood cell count in cerebrospinal fluid could reflect the inflammatory response status in aSAH patients. Systemic inflammation after hemorrhagic stroke possibly played an important role in inducing intracranial and extracranial tissue damage (21–23). After occurrence of aneurysmal subarachnoid hemorrhage, the blood accumulated in the subarachnoid space, and then red blood cells underwent hemolysis and degradation.

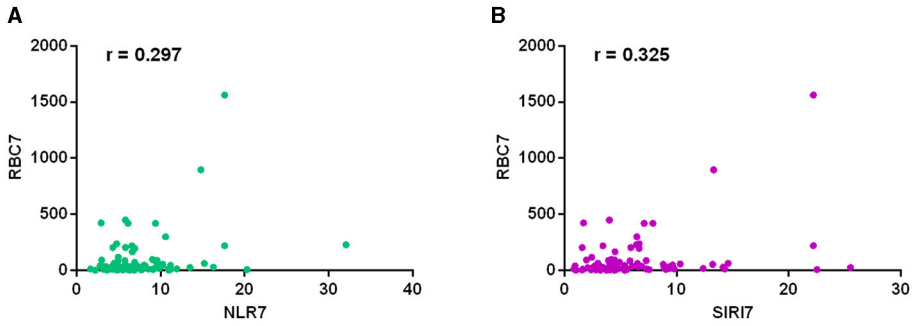

FIGURE 3
The correlation analysis between inflammatory marker and cell count in cerebrospinal fluid on the seventh postoperative day. The results showed that the NLR ($r = 0.297$, $P = 0.007$) **(A)** and SIRI ($r = 0.325$, $P = 0.003$) **(B)** levels were all correlated with the count of red blood cells in cerebrospinal fluid.

TABLE 5 **The results of correlation analysis between inflammatory marker and blood cell count in cerebrospinal fluid.**

On the 7th postoperative day							
		N	L	NLR	SIRI	SII	PLR
Red blood cell count in CSF	*r*	0.091	−0.199	0.297	0.325	0.193	0.141
	P-value	0.422	0.077	0.007	0.003	0.087	0.211
White blood cell count in CSF	*r*	0.116	−0.101	0.215	0.337	0.114	0.049
	P-value	0.306	0.373	0.056	0.002	0.313	0.664
On the 1st postoperative day							
		N	L	NLR	SIRI	SII	PLR
Red blood cell count in CSF	*r*	0.088	−0.063	0.109	0.064	0.001	−0.048
White blood cell count in CSF	*P*-value	0.295	0.454	0.196	0.448	0.991	0.569
Red blood cell count in CSF	*r*	0.139	−0.077	0.173	0.11	0.053	−0.027
White blood cell count in CSF	*P*-value	0.099	0.362	0.039	0.191	0.526	0.752

CSF, cerebrospinal fluid; N, neutrophil; L, lymphocyte; NLR, neutrophil-lymphocyte ratio; SIRI, system inflammation response index; SII, systemic immune inflammation index.

Oxidized hemoglobin induced systemic inflammation through a series of cytokines and multiple signaling pathways, leading to the contraction of vascular smooth muscle, further cerebral vasospasm and ultimately delayed brain injury (24–29).

In our study, patient with poor outcome had more surgical craniotomy, longer surgical duration and higher systemic inflammatory response, we speculated that the surgical approach was possibly associated with longer operation time, more intracerebral bleeding, or more infections. We also speculated that a less invasive approach might correlate with few complications and a weak pro-inflammatory response. Other important message of our study was the beneficial effects of the less invasive approach, compared with craniotomy.

Our study had several limitations. Firstly, due to the limitation of retrospective nature, cerebrospinal fluid sample on the seventh postoperative day was relatively small, which could lead to some bias. We will expand the sample size in the future study. Secondly, we only collected cerebrospinal fluid data on the first and seventh postoperative day, did not study the dynamic changes of inflammatory markers. We will explore the associations of dynamic inflammatory marker and blood cell count in cerebrospinal fluid with the outcome of aSAH patients. Due to the limitation of laboratory condition in the hospital, we were unable to detect hemoglobin levels in cerebrospinal fluid, which was also one limitation. An important limitation was the lack of any cytokine data including IL-6, IL-10, and TNF alfa in cerebrospinal fluid, which would have added insights to the study.

Higher neutrophil-lymphocyte ratio and higher red blood cell count in cerebrospinal fluid were all possibly associated with poor outcome of patients with aneurysmal subarachnoid hemorrhage. It is very important to conduct a study on reducing blood stimulation to the subarachnoid space and inflammatory response to improve clinical outcome of aneurysmal subarachnoid hemorrhage patients. We also need a larger sample study.

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 humans were approved by the First Affiliated Hospital of Yangtze University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. 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

JM: Conceptualization, Supervision, Writing – original draft. YZ: Data curation, Software, Writing – review & editing. CL: Data curation, Writing – review & editing. HH: Data curation, Writing – review & editing.

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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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Pre-treatment radiological factors associated with poor functional outcome in an Asian cohort of large vessel occlusion acute ischemic stroke patients undergoing mechanical thrombectomy

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Background and aims: Endovascular thrombectomy (EVT) is the current standard of care for large vessel occlusion (LVO) acute ischemic stroke (AIS); however, up to two-thirds of EVT patients have poor functional outcomes despite successful reperfusion. Many radiological markers have been studied as predictive biomarkers for patient outcomes in AIS. This study seeks to determine which clinico-radiological factors are associated with outcomes of interest to aid selection of patients for EVT for LVO AIS.

Methods: A retrospective study of patients who underwent EVT from 2016 to 2020 was performed. Data on various radiological variables, such as anatomical parameters, clot characteristics, collateral status, and infarct size, were collected alongside traditional demographic and clinical variables. Univariate and multivariate analysis was performed for the primary outcomes of functional independence at 3 months post-stroke (modified Rankin Scale 0–2) and secondary outcomes of in-hospital mortality and symptomatic intracranial hemorrhage.

Results: The study cohort comprised 325 consecutive patients with anterior circulation LVO AIS (54.5% male) with a median age of 68 years (interquartile range 57–76). The median NIHSS was 19. Age, hypertension, hyperlipidaemia, National Institutes of Health Stroke Scale (NIHSS), Alberta mCTA score, ASPECTS, clot length, thrombus HU and mTICI score and the angle between ICA and CCA were associated with functional outcomes at 3 months on univariate analysis. On multivariate analysis, age, Alberta mCTA collaterals and NIHSS were significantly associated with functional outcomes, while ASPECTS approached significance.

Conclusion: Among the many proposed radiological markers for patients in the hyperacute setting undergoing EVT, the existing well-validated clinico-radiological measures remain strongly associated with functional status.

KEYWORDS

stroke, acute ischemic stroke, prognosis, symptomatic intracranial haemorrhage, endovascular thrombectomy

Highlights

- **What is already known on this topic:** There are numerous proposed radiological markers related to outcomes for mechanical thrombectomy in the literature such as clot length, surface phenotype and vascular tortuosity.
- **What this study adds:** In our cohort, these signs were not significantly associated with functional outcomes or risk of procedural complications. Existing well-validated signs remain the most closely associated with post-procedural outcomes.
- **How this study might affect research, practice or policy:** Amidst the widening indications for endovascular thrombectomy in acute ischaemic stroke with large vessel occlusion, patient selection should be guided by existing well-validated markers.

Introduction

Endovascular thrombectomy (EVT) has emerged as the standard of care for patients with large vessel occlusion (LVO) acute ischemic stroke (AIS), which has led to its increasing adoption in stroke centers worldwide. When treated within 24 h of symptom onset, endovascular thrombectomy increases patients' chances of survival and good functional outcomes (1).

However, approximately 10–20% of patients who undergo EVT do not achieve successful recanalization (2), and up to two-thirds of patients who undergo EVT do not achieve functional independence despite successful recanalization (3). Furthermore, the procedure itself is not without risk; complications of EVT include access site complications, device-related complications, arterial perforation, dissection, and intracranial hemorrhage (4). It is therefore germane to pre-procedurally identify clinico-radiological factors that may portend a more favorable outcome.

Radiological signs that are readily available on a patient's index CT scan have generated interest as predictors for patients undergoing EVT for LVO AIS. For example, poor baseline collateral flow status and Alberta Stroke Program Early CT Score (ASPECTS), assessed via CT angiography, are associated with a larger ischemic core and worse functional outcomes (5, 6). Other radiological variables which have been investigated include clot characteristics including clot length, density, surface phenotype, truncal versus branch-type occlusions and the presence of a meniscus sign (7–11). Further radiological variables that have been studied pertain to vascular anatomy and include parameters that quantify vascular tortuosity such as the aortic arch type (12, 13).

In this study, we sought to determine associations between clinico-radiological factors and outcomes of interest in LVO AIS to determine which factors have the best predictive capability in guiding patient selection for EVT.

Methods

Study design

This was an observational cohort study of consecutive patients who underwent EVT for LVO AIS from a single comprehensive stroke center over a five-year period from 2016 to 2020. Patients underwent non-enhanced CT and high-resolution CT angiogram (CTA) as part of their hyperacute stroke assessment. The CT scans were performed on a 128-slice multidetector helical scanner (Philips Inc.) with a 60-70-mL bolus injection of iohexol contrast. Scan parameters were: source axial thickness of 0.625 mm, matrix 512 × 512, and 120 kV. The scan coverage was from the aortic arch to the vertex, and the source images were reformatted into 10×2.5 mm axial, coronal, and sagittal maximum intensity projection images. The initiation of the multiphasic CTA (mCTA) was triggered by the technician upon the initial visibility of contrast in the aortic arch. Subsequently, CTA images were captured with a 2 mm slice thickness, starting from the aortic arch, proceeding through the circle of Willis, and extending to the vertex. Axial, coronal, and sagittal projections were obtained. The pre-treatment mCTA included immediate (peak arterial), first (peak venous), and second (late venous) phases. The delayed scans occurred 10 and 12 s later.

All patients above the age of 18 who underwent EVT for ischaemic stroke secondary to large vessel occlusion identified on multidetector CT angiogram (CTA) were included. The selection criteria for patients for patients undergoing EVT were in accordance with the American Heart Association/American Stroke Association guidelines for the early management of patients with AIS (14). Patients that had hemorrhagic stroke at presentation or patients who were ultimately deemed not to have LVO AIS were excluded. Patients who did not have an adequate field of imaging to include the aortic arch to the vertex or had poor quality imaging were also excluded.

The study was approved by an institutional ethics committee and research board (NHG Domain Specific Review Board Reference Number 2022/00109).

Data collection

Clinical variables including age, sex, comorbidities, mRS score, NIHSS, and tPA administration, as well as data relevant to the EVT

procedure - onset-to-puncture time, thrombolysis in cerebral infarction (TICI) score, thrombus characteristics (irregular surface, presence of meniscus sign or calcified) - were collected from patients' electronic medical records. Radiological variables collected included: ASPECTS, clot length, thrombus Hounsfield Units, aortic arch type, truncal occlusion, meniscus sign, irregular clot surface, angle of internal carotid artery (ICA) and common carotid artery (CCA), and Alberta multiphase CT angiography (mCTA) score. Aortic arch type was defined using Madhwal's classification (15). Truncal occlusions were defined as large vessel occlusions where all major branches and bifurcation sites were clearly visible beyond the occlusion segment. The meniscus sign was defined as a clot with a concave appearance on angiography. The data were collected independently by 2 residents; differences between the datasets were resolved by a senior consultant neurologist.

Outcome measures

The primary outcome measure was functional independence (FI), defined as a Modified Rankin Scale (mRS) score of 0–2 at 3 months post-stroke. Secondary outcome measures were in-hospital mortality and symptomatic intracranial hemorrhage (sICH), as defined by ECASS2 consensus criteria (16). Other procedural complications that were observed included groin hematomas and distal emboli.

Statistical analyses

Clinically relevant variables were incorporated into the analysis. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as percentages. We employed the Pearson $\chi 2$ test (or Fisher exact test when applicable) for categorical variables and Student's t-test for normally distributed continuous variables. Univariate regression was performed to identify significant covariates with the primary and secondary outcomes.

Multivariate binary logistic regression models were constructed using baseline covariates with statistically significant ($p < 0.05$) associations to identify independent predictors of the primary and secondary outcomes. Adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs) and p-values were calculated for all statistical analyses.

Statistical analyses were conducted using IBM SPSS Statistics version 26. A statistically significant finding was indicated by a two-sided p value of <0.05.

Results

The demographic and clinical characteristics of the study cohort are shown in Table 1. A total of 484 patients (45.5% women) of median age 68 that underwent EVT for LVO AIS were included. 150 patients were excluded due to factors such as poor-quality scans or insufficient coverage up to the aortic arch. (Figure 1) while 9 patients had missing 90-day mRS data with a cohort of 325 for analysis. 132 patients (42.2%) attained FI at 3 months post-stroke. In hospital mortality was 10.2%, and 32 (9.6%) patients developed sICH post-EVT.

On univariate analysis, the radiological variables which were associated with FI at 3 months post-stroke were Alberta mCTA score, ASPECTS, clot length, thrombus Hounsfield Units (HU), angle between ICA and CCA, as well as the modified TICI score (Table 2). On multivariate analysis, the radiological variables that were significantly associated with FI was the Alberta mCTA score (OR 13.4 95% CI 1.39–130, $p = 0.025$), with the ASPECTS approaching significance (OR 0.693, 95% CI 0.473–1.01, $p = 0.059$).

The clinical variables significantly associated with FI in the multivariate analysis was younger age (OR 1.062, 95% CI 1.01–1.12, $p = 0.021$), the presence of diabetes (OR 4.14 95%CI 1.01–16.9, $p = 0.048$), and higher NIHSS (OR 1.13 95%CI 1.02–1.25, $p = 0.0160$). This model demonstrated an AUROC 0.87 (Figure 2) with a Brier's score of 0.14. The absolute magnitude of their coefficients in the logistic regression is shown in Figure 3.

For the radiological variables, Alberta mCTA score, aortic arch type, and TICI recanalisation status were associated with in-hospital mortality on univariate analysis. ASPECTS remained significantly associated with in-hospital mortality post EVT on multivariate analysis (OR 0.720 95%CI 0.522–0.993, $p = 0.045$) (Supplementary Table S1). The model had a Brier's score of 0.060 and an AUROC of 0.816 (Supplementary Figure S1).

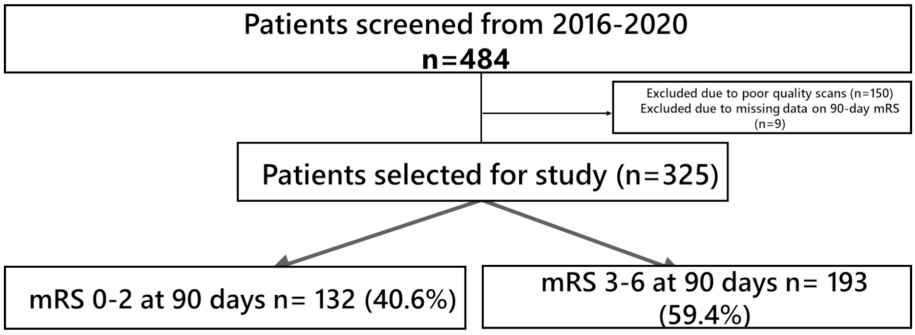

FIGURE 1
Patient selection.

TABLE 1 Baseline characteristics of the study cohort ($n = 325$).

		FI	No FI
n	325	132	193
Age, median [IQR]	68 [57–76]	63 [53–70.3]	72 [63–79]
Race			
Chinese	220 (65.9)	88 (66.7)	127 (65.8)
Indian	29 (8.7)	29 (22.0)	42 (21.8)
Malay	71 (21.3)	9 (6.8)	18 (9.3)
Others	14 (4.2)	6 (4.5)	6 (3.1)
Sex (female)	152 (45.5)	56 (42.4)	92 (47.6)
Hypertension	239 (71.6)	83 (63.0)	150 (77.7)
Diabetes mellitus	94 (28.1)	26 (19.7)	67 (34.7)
Hyperlipidemia	185 (55.4)	64 (48.5)	117 (60.6)
Ischemic heart disease	76 (22.8)	26 (19.7)	50 (25.9)
Congestive cardiac failure	41 (12.3)	14 (10.6)	27 (14.0)
Smoking	63 (18.9)	29 (22.5)	33 (17.8)
Atrial fibrillation	164 (49.1)	59 (45.0)	101 (52.3)
Previous stroke	49 (14.5)	18 (13.6)	31 (16.0)
SBP on arrival (mmHg), median [IQR]	149 [133–168]	148 [131–165]	149 [135–168]
DBP on arrival (mmHg), median [IQR]	82 [71–95]	82 [71.5–91.5]	82 [70.5–96.5]
NIHSS, median [IQR]	19 [10–27]	15 [11–20]	20 [17–23]
Thrombolysis with rTPA	215 (64.4)	84 (64.1)	126 (65.3)
Onset to puncture time (mean, mins)	272.2	273.0	273.4
TOAST classification*			
Large artery atherosclerosis	99	41	58
Cardioembolic	180	65	115
Other determined cause	3	1	2
Cryptogenic	46	25	21
Occlusion site			
ICA (including terminal ICA)	88	22	64
MCA (M1, M2)	218	102	116
ACA (A1)	2	1	1
Tandem occlusion	26	8	17
Baseline mRS			
0	279	125	147
1	13	5	8
2	14	2	11
mRS at 3 months post-stroke			
0	55	53	-
1	40	39	-
2	41	40	-
3	54	-	52
4	78	-	73
5	25	-	24
6	45	-	44
In-hospital mortality	35 (10.5)	-	35
Symptomatic intracranial hemorrhage	32 (9.6)	2	29

ACA, anterior cerebral artery; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; rTPA, recombinant tissue plasminogen activator; SBP, systolic blood pressure; DBP, diastolic blood pressure. Categorical variables presented as *n* (%) unless otherwise stated. *The TOAST classification denotes five subtypes of ischemic stroke: (1) large-artery atherosclerosis, (2) cardioembolic, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology.

ASPECTS and clot length were significantly associated with the development of SICH post-EVT on univariate and multivariate analyses. Favorable aortic arch types also showed a trend to significance with SICH (OR 0.433 95% CI 0.186–1.007, $p = 0.052$) on multivariate analysis (Supplementary Table S2). The model had a Brier's score of 0.077 and an AUROC of 0.82 (Supplementary Figure S2).

Discussion

In this cohort of patients, the radiological variables which were associated with FI at 3 months post-EVT were the Alberta mCTA score, ASPECTS, clot length, thrombus Hounsfield Units (HU), angle between ICA and CCA, as well as the achievement of first-pass TICI 2B or 3 recanalisation. On multivariate analysis, only the Alberta mCTA score was significantly associated with FI, with the ASPECTS approaching significance. With respect to secondary outcomes, the ASPECTS was significantly associated with the development of post-EVT SICH on both univariate and multivariate analyses. Thrombus clot length was also found to be predictive of post-EVT SICH on multivariate analysis.

The most widely-studied radiological markers that predict endovascular or functional outcomes in stroke include the ASPECTS (17) or multiphasic CT-angiogram score (18). In this study cohort, patients who achieved FI at 3 months post-EVT had a higher median ASPECTS and higher percentages of possessing a good collateral circulation as compared to patients who did not attain FI. Both mCTA collateral status and ASPECTS remained associated with FI post-EVT on multivariable analysis. A lower ASPECTS was also associated with the development of SICH. Our study validates findings from previous studies done in Western cohorts which have identified the ASPECTS and mCTA as prognostic neuroimaging markers for functional outcomes (6, 18). Other studies have also shown the association between a low ASPECTS score as a predictor of post-EVT SICH (19). In particular, newer, more recent trials have attempted to demonstrate the efficacy of EVT in large ischemic-core volume infarcts with an ASPECTS score of 3–5 or a core volume of greater than 50 mL on perfusion imaging, with a tendency towards greater rates of functional independence (20).

Radiological clot characteristics (clot length, density, truncal type occlusions and surface characteristics) have also generated interest as potential biomarkers that may predict functional outcomes in EVT and LVO AIS. For example, thrombus lengths greater than 8 mm were

TABLE 2 Analysis of variables associated with 90-day functional independence.

		Univariate analysis				Multivariate analysis	
		FI	No FI	*p*-value	OR (95%CI)	Adjusted OR (95% CI)	*p*-value
Age (mean)		61.2	69.5	**<0.001**	**1.05 (1.03–1.07)**	1.056 (1.00–1.11)	**0.036**
Female		56 (42.4%)	92 (47.6%)	0.366			
Race							
Chinese		88	127	0.793			
Malay		29	42				
Indian		9	18				
Others		6	6				
Clinical factors							
Hypertension		83 (62.95%)	150 (77.7%)	**0.004**	**2.06 (1.26–3.36)**	0.983 (0.237–4.079)	0.981
Diabetes Mellitus		26 (19.7%)	67 (34.7%)	**0.004**	**2.17 (1.29–3.65)**	4.23 (1.02–17.5)	**0.047**
Hyperlipidemia		64 (48.5%)	117 (60.6%)	**0.032**	**1.64 (1.05–2.56)**	1.62 (0.483–5.40)	0.436
Smoking		29 (22.5)	33 (17.8%)	0.317			
Ischaemic heart disease		26 (19.7%)	50 (25.9%)	0.23			
Congestive cardiac failure		14 (11.6%)	27 (15.0%)	0.494			
Pre-admission mRS 0–2		132 (100%)	166 (86.0%)	**<0.001**	**N.A.**	32.5 *10^7	0.999
TOAST	Large artery atherosclerosis	41 (32.0%)	56 (28.9%)	0.152			
	Cardioembolic	61 (47.6%)	115 (59.3%)				
	Small vessel disease	0	0				
	Other determined cause	1 (0.78%)	2 (1.03%)				
	Cryptogenic	25 (19.5%)	21 (10.82%)				
Prior stroke		17 (12.9%)	31 (16.2%)	0.500			
Atrial fibrillation		59 (45.0%)	101 (52.3%)	0.214			
Systolic Blood Pressure on arrival (mean)		149	152	0.297			
Diastolic Blood Pressure on arrival (mean)		84.3	86.1	0.408			
Thrombolysis with rTPA		84 (64.1%)	126 (65.3%)	0.906			
Onset-to-puncture (mean, mins)		283.7	280.3	0.88			
NIHSS (median)		15	20	**<0.001**	**1.08 (1.04–1.13)**	1.12 (1.02–1.24)	**0.021**
Radiological factors							
Alberta mCTA <3		86 (95.6%)	79 (70.5%)	**<0.001**	**8.98 (3.05–26.5)**	13.1 (1.35–127)	**0.026**
MCA Top-to-bottom distance (mean, cm)		0.689	0.704	0.627			
Aortic arch type (median)		2	2	0.871			
Angle between ICA and CCA (mean)		34	38	**0.039**	**1.01 (1.00–1.03)**	0.99 (0.96–1.03)	0.78
Meniscus sign present		35 (30.7%)	60 (36.6%)	0.368			
Irregular surface of clot		43 (37.7%)	47 (28.5%)	0.119			
Occlusion location:		43 (62.3%)	78 (66.7%)	0.633			
Truncal							
Bifurcation		26 (37.7%)	39 (33.3%)				
Clot burden score (median)		4	4	0.174			
ASPECTS (median)		9	7	**<0.001**	**0.709 (0.603–0.833)**	0.69 (0.47–1.00)	0.052

(Continued)

TABLE 2 (Continued)

	Univariate analysis				Multivariate analysis	
	FI	No FI	*p*-value	OR (95%CI)	Adjusted OR (95% CI)	*p*-value
MCA-hyperdensity	70 (59.3%)	118 (67.4%)	0.173			
Clot length (mean, cm)	1.26	1.54	**0.014**	**1.71 (1.11–2.66)**	1.01 (0.43–2.35)	0.981
Thrombus HU (non-contrasted CT)	117 (39.1)	170 (41.6)	**0.04**	**1.03 (1.00–1.05)**	1.05 (0.99–1.12)	0.126
TICI 2B/3	116 (92.1%)	137 (71.7%)	**< 0.001**	**0.219 (0.107–0.449)**	0.50 (0.065–3.76)	0.50

P-values < 0.05 are bolded.

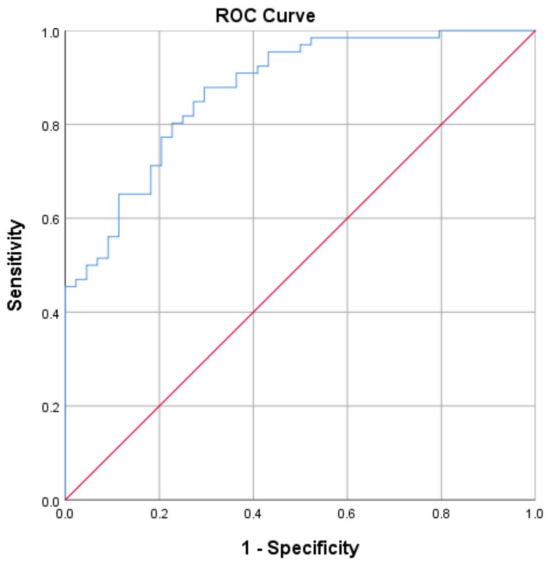

FIGURE 2
ROC curve for the logistic regression model.

associated with failure of recanalization following intravenous thrombolysis (21), and shorter thrombus lengths were found to be associated with better functional outcomes following EVT for LVO AIS (22). In our study, clot length was associated with post-EVT SICH. Clot density was previously identified to be predictive of successful recanalization on EVT (23, 24). However, our study corroborates other studies in the literature which did not identify a significant association between clot density and better outcomes post-EVT (25).

Truncal-type occlusions have been regarded as a surrogate marker for LVO from intracranial atherosclerosis (11) and were found to be less amenable to mechanical thrombectomy using a stent-retriever approach (26) but the presence of the sign was not reported to be predictive of the recanalization rate or clinical outcomes post-EVT (27). In this study population, there was no significant association identified between truncal-type occlusions and the outcomes of interest.

Other clot-related signs that may aid in prognosticating post-EVT outcomes is the meniscus sign (28). It has been postulated that clots with a meniscus sign may be rich in red blood cells and break down easily compared to a fibrin clot. Supporting this are studies which identified a higher recanalization rate and better functional outcomes in patients who received direct aspiration as opposed to stent retriever for LVO AIS presenting with a meniscus sign (10). However, a more recent multicentric study involving prospective local registries of high-volume centres subsequently demonstrated little prognostic significance for the meniscus sign, consistent with what was found in our center (26). One possible explanation is that modern neurointerventional techniques apply a combined approach utilizing both stenting and direct aspiration, negating the individual effects of either approach. Furthermore, new thrombectomy devices are becoming more effective as the technology progresses and are able to handle a wider variety of occlusive clots that were previously refractory to earlier techniques.

Further radiological variables that have been studied relate to vascular anatomy and the technical aspects of performing mechanical thrombectomy. For instance, Shirakawa et al. (29) found that the MCA tortuosity, measured using the top-bottom distance of the proximal M1 segment on angiography, was significantly associated with the incidence of post-EVT hemorrhage. Carotid artery tortuosity measured using the angle between the CCA and ICA was previously found to be an independent predictor of achieving first-pass recanalization in endovascular thrombectomy (30). In this study, carotid artery tortuosity was associated with functional independence at 3 months post-EVT on univariate analysis and the aortic arch type was associated with in-hospital mortality and SICH post-EVT.

Limitations

The limitations of this study include recruitment of the cohort from a single stroke center. While reflective of a heterogenous Southeast Asian population, the results of this study may not be fully generalizable to other populations. Distinct risk factor profiles have emerged from population studies, with Asians displaying a higher susceptibility to intracranial stenosis, while Caucasians exhibit a higher prevalence of atrial fibrillation or extracranial stenosis (31). This study also focused on patients with anterior circulation occlusions, and the findings may not be generalizable to patients who present with posterior circulation LVO. Finally, our cohort is derived from a single study and is of a moderate size. It may not be adequately powered to perform subgroup analysis. Future studies involving multi-center collaboration may yet identify other prognostic radiological biomarkers within patient subgroups.

A further limitation arises from incomplete data owing to re-identification losses and data cleaning. To avoid introducing any biases into the multivariate model, imputation was not performed. As a result, not all of the patients were included in the analysis, and may limit the value of the model as a predictor. Despite this limitation, the mean squared difference between the predicted probabilities and actual was 0.14 with a good AUROC of 0.87. Future studies with larger cohorts would help to ascertain the generalizability of our findings.

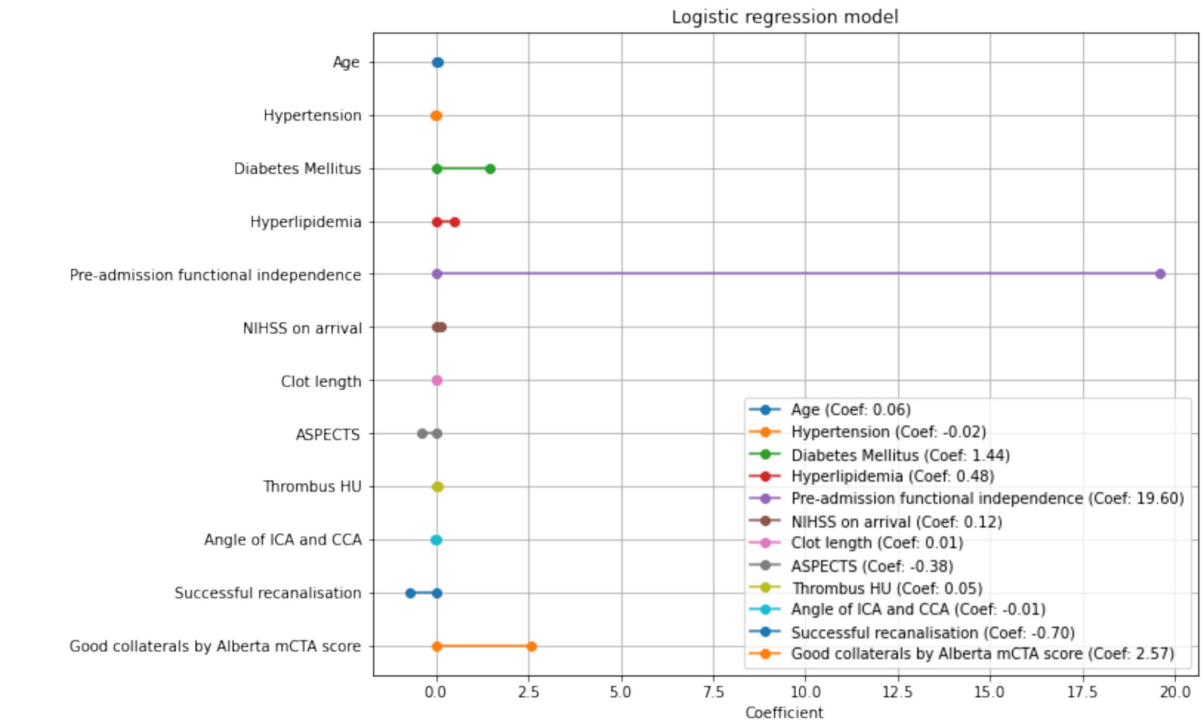

FIGURE 3
Coefficients in the logistic regression model.

Our study shows that despite the interest in intra-and pre-procedural angiographic signs, well-validated clinico-radiological variables remain the most valuable in terms of prognostic value. In particular, older age, NIHSS, diabetes mellitus and the Alberta mCTA score was associated with functional independence while thrombus clot length was associated with SICH. Clinicians may choose to review these markers in assessing the likelihood of a patient to benefit from mechanical thrombectomy for large vessel occlusion strokes.

Conclusion

Among the proposed radiological markers for patients in the hyperacute setting, existing well-validated clinico-radiological measures such as the ASPECTS and Alberta mCTA grading remain strongly associated with functional status. Thrombus clot length demonstrates an association with functional status and risk of SICH post-EVT. Future studies involving multi-center collaboration may yet identify other prognostic radiological biomarkers within patient subgroups.

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 humans were approved by NHG Domain Specific Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JY: Writing – original draft, Writing – review & editing. KT: Writing – original draft, Writing – review & editing. ET: Validation, Writing – review & editing. CY: Data curation, Writing – review & editing. HH: Data curation, Writing – review & editing. HL: Data curation, Writing – review & editing. BN: Data curation, Writing – review & editing. YW: Data curation, Writing – review & editing. CS: Data curation, Writing – review & editing. AM: Data curation, Writing – review & editing. WH: Writing – review & editing. MC: Writing – review & editing. C-HS: Writing – review & editing. MJ: Methodology, Supervision, Writing – review & editing. BT: Resources, Supervision, Writing – review & editing. DT: Resources, Supervision, Writing – review & editing. LY: Formal analysis, Methodology, Resources, Supervision, Writing – review & editing.

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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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1415233/full#supplementary-material

SUPPLEMENTARY FIGURE 1
ROC curve for prediction of SICH.

SUPPLEMENTARY FIGURE 2
ROC curve for prediction of mortality.

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HR-MRI-based nomogram network calculator to predict stroke recurrence in high-risk non-disabling ischemic cerebrovascular events patients

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Background and objective: To investigate the use of high-resolution magnetic resonance imaging (HR-MRI) to identify the characteristics of culprit plaques in intracranial arteries, and to evaluate the predictive value of the characteristics of culprit plaques combined with the modified Essen score for the recurrence risk of high-risk non-disabling ischemic cerebrovascular events (HR-NICE) patients.

Methods: A retrospective analysis was conducted on 180 patients with HR-NICE at the First Affiliated Hospital of Xinxiang Medical University, including 128 patients with no recurrence (non-recurrence group) and 52 patients with recurrence (recurrence group). A total of 65 patients with HR-NICE were collected from the Sixth Affiliated Hospital of Shanghai Jiaotong University as a validation group, and their modified Essen scores, high-resolution magnetic resonance vessel wall images, and clinical data were collected. The culprit plaques were analyzed using VesselExplorer2 software. Univariate and multivariate logistic regression analyses were used to identify independent risk factors for recurrence, and a nomogram was constructed using R software to evaluate the discrimination of the model. The area under the curve (AUC) of the receiver operating characteristic curve (ROC) was used to evaluate the model performance. Calibration curves and Decision Curve Analysis (DCA) were used to evaluate the model efficacy.

Results: Intra-plaque hemorrhage (OR = 3.592, 95% CI = 1.474–9.104, $p = 0.006$), homocysteine (OR = 1.098, 95% CI = 1.025–1.179, $p = 0.007$), and normalized wall index (OR = 1.114, 95% CI = 1.027–1.222, $p = 0.015$) were significantly higher in the recurrent stroke group than in the non-recurrent stroke group, and were independent risk factors for recurrent stroke. The performance of the nomogram model (AUC = 0.830, 95% CI: 0.769–0.891; PR-AUC = 0.628) was better than that of the modified Essen scoring model (AUC = 0.660, 95% CI: 0.583–0.738) and the independent risk factor combination model (AUC = 0.827, 95% CI: 0.765–0.889). The nomogram model still had good model performance in the validation group (AUC = 0.785, 95% CI: 0.671–0.899), with a well-fitting calibration curve and a DCA curve indicating good net benefit efficacy for patients.

Conclusion: High-resolution vessel wall imaging combined with a modified Essen score can effectively assess the recurrence risk of HR-NICE patients, and the nomogram model can provide a reference for identifying high-risk populations with good clinical application prospects.

KEYWORDS

stroke recurrence, high-resolution vessel wall imaging, nomogram, plaque, high-risk non-disabling ischemic cerebrovascular events

1 Introduction

China has one of the highest numbers of stroke patients globally, with stroke being the leading cause of death and disability among adults (1). Up to 80% of ischemic stroke patients may initially present with transient mild symptoms, like minor ischemic stroke and transient ischemic attack, without residual disability. However, many of these patients face stroke recurrence or progression due to unstable conditions, leading to severe clinical outcomes. This situation is termed high-risk non-disabling ischemic cerebrovascular events (HR-NICE). China has a large population of HR-NICE patients, and considering the national conditions and healthcare levels, they should be prioritized for cerebrovascular disease prevention and treatment (2). High-resolution magnetic resonance imaging (HR-MRI) has recently become crucial for assessing atherosclerosis. HR-MRI can identify various plaque components and pathological changes, providing a comprehensive evaluation of plaque vulnerability, stroke recurrence risk, and prognosis (3). The Essen Stroke Risk Score (ESRS) is one of the few effective tools for predicting recurrence risk in ischemic stroke patients. However, ESRS is relatively simple and does not incorporate significant risk factors like imaging features, limiting its predictive value. A prospective study in China showed that a modified ESRS, incorporating history of hypertension, diabetes mellitus, and TOAST classification of large artery atherosclerosis, better predicts recurrent cardiovascular events than the original ESRS. Yet, this modified score still has limitations, as it does not include critical risk factors like wall morphology and plaque characteristics prone to stroke recurrence (4). The nomogram, a data visualization tool, can visually display relationships between multiple variables, offering more comprehensive data analysis. It can directly calculate and show each variable's contribution to outcomes, aiding in evaluating their importance and influence. This study aims to identify independent imaging risk factors associated with stroke recurrence using HR-MRI and construct a nomogram model that combines these factors with the modified Essen score. This will provide a more convenient and efficient reference for predicting stroke recurrence risk in HR-NICE patients.

2 Materials and methods

2.1 General information

Retrospectively collected data from patients with HR-NICE who were treated at the First Affiliated Hospital of Xinxiang Medical University from January 2020 to December 2022 as the training group, and retrospectively collected data from patients with HR-NICE who were treated at the Sixth Affiliated Hospital of Shanghai Jiaotong University from January 2022 to December 2022 as the validation group. The inclusion criteria were: (1) HR-NICE patients who met the diagnostic criteria of the "Guidelines for the Diagnosis and Treatment of High-Risk Non-Disabling Ischemic Cerebrovascular Events" (2); (2) Age $\geq$ 18 years old; (3) MRA, CTA or digital subtraction angiography has confirmed the presence of at least one stenosis ($\geq$30%) in the intracranial artery that controls the symptomatic limb; (4) At least one risk of atherosclerosis factors, such as hypertension, diabetes, dyslipidemia, smoking, etc.; (5) The patient has completed the HR-MRI examination, the image is clear, and the clinical data required for this study are complete. Exclusion criteria: (1) Non-atherosclerotic vascular diseases, such as moyamoya disease or vasculitis; (2) Obvious moderate to severe disease in cervical arteries (common carotid artery, extracranial segment of internal carotid artery or vertebral artery) Patients with stenosis (stenosis >50%); (3) Patients with cardiogenic or hemorrhagic stroke; (4) HR-MRI examination image quality is poor or cannot tolerate magnetic resonance examination; (5) Patients' clinical data are not recorded whole. Follow-up visits were conducted on the included patients for 1 year to determine whether they had a recurrence of ischemic cerebrovascular events. This study complies with the Helsinki Declaration and has obtained ethical approval from the two hospitals mentioned above, exempting participants from informed consent.

2.2 Imaging method

All patients were examined using a 16-channel combined head and neck coil and 3.0 T magnetic resonance equipment. Each patient first underwent diffusion-weighted imaging (DWI), three-dimension time-of-flight magnetic resonance angiography (3D-TOF MRA), T1-weighted imaging, T2-weighted imaging and T2 fluid attenuated inversion recovery (T2 Flair). After that, a 3D HR-MRI scan was performed. After the imaging was completed, gadobutrol (Gadavist, Bayer, 0.1 mmol/kg) was injected, followed by another 3D HR-MRI scan. The scanning parameters for each sequence are shown in Supplementary Table 1.

2.3 Image post-processing and analysis

All images were analyzed by two senior neuroimaging experts according to the patient's clinical presentation, 3D-TOF MRA, and DWI results. Each detected plaque was classified as a "culprit" or

"non-culprit "plaque. The definition of culprit plaque was the lesion appearing on the same side of the fresh infarction on the DWI image. If there were more than one plaque in the same vessel distribution area, the narrowest lesion was selected for analysis. The collected 3D HR-MRI data were normalized and reconstructed using VesselExplorer2 (Qingying Huakang Technology Co., Ltd., Beijing) post-processing workstation according to the American Society of Neuroradiology Vessel Wall Imaging Guidelines (5). Images were obtained in coronal, sagittal, and axial views to better display the state of plaques and vessel walls, and image quality was scored (1 point for poor image quality affecting observation; 2 points for most of the image being clear with only a small portion of the vessel wall being slightly blurred; 3 points for clear vessel wall outline). After excluding images with a quality score of 1, the software was used to analyze plaque characteristics, including plaque identification and delineation, intra-plaque hemorrhage (IPH), plaque enhancement, and stenosis rate. First, HR-MRI data were imported into the post-processing software and images were reconstructed perpendicular to the long axis of the vessel where the culprit plaque was located. The section where the culprit plaque was located was enlarged by 400%, and the outer contour of the vessel wall and intraluminal contour were manually delineated. The software automatically measured the corresponding vessel area, luminal area, and maximum wall thickness. The reference level of vessel area (VA) and lumen area (LA) preferentially selects the level of no significant stenosis at the proximal end of the corresponding lumen, followed by the level of no significant stenosis at the distal end of the corresponding lumen. The degree of vessel stenosis is calculated using the following method: stenosis rate = (1-LAmin/LAreference) × 100%; wall area (WA) = VA-LA; plaque area (PA) = WAmin-WAreference; remodeling index (RI) = VAmin/VAreference, RI ≥ 1.05 is positive remodeling, RI ≤ 0.95 is negative remodeling. Normalized wall index (NWI) = WA/VA. The stenosis rate less than 50% is grade 0, the stenosis rate between 50 and 69% is grade 1, and the stenosis rate between 70 and 99% is grade 2. Based on the signal intensity of the pituitary in the enhanced T1WI image, the plaque signal remains unchanged in grade 0; there is enhancement, but the degree of enhancement is lower than that of the pituitary enhancement in grade 1; the plaque enhancement degree is similar to that of normal pituitary enhancement is grade 2. Intraplaque hemorrhage (IPH) is defined as a T1WI signal higher than 150% of the adjacent muscle tissue signal (6–9).

2.4 Statistical analysis

SPSS 27.0 software was used for statistical analysis. Measurement data that were normally distributed were expressed as mean ± standard deviation ($\bar{x}$ ± s). Two independent sample t-tests were used for comparison. Measurement data that did not conform to normal distribution were expressed as median [M (Q25, Q75)], the Mann–Whitney U test was used for comparison, the count data was expressed as the number of cases [*n* (%)], and the chi-square test or Fisher's exact probability method was used for comparison. Single-factor and multi-factor Logistics regression analysis were used to screen out independent risk factors affecting stroke recurrence, R software (version 4.3.1) was used to draw a nomogram, using ROC curves and Precision-Recall (PR) curve to analyze the model's ability, drawing calibration curves to evaluate the consistency of the model, and using DCA curves to evaluate the clinical efficacy of the nomogram model, $p < 0.05$ was considered statistically significant.

3 Results

3.1 Clinical characteristics of patients in the training group

The patients in this study with an average age of (58.1 ± 10.8) years. Among them, 52 (28.89%) patients had stroke recurrence and 128 (71.11%) patients did not have stroke recurrence. Age, gender, BMI, history of atrial fibrillation, history of myocardial infarction, history of diabetes, history of hypertension, history of cerebrovascular disease, history of alcohol consumption, admission NIHSS score, total cholesterol, triglycerides, and low-density lipoprotein of patients in the recurrence group and the non-recurrence group There was no statistical significance in protein cholesterol, high-density lipoprotein cholesterol, apolipoprotein A, apolipoprotein B, fibrinogen, blood glucose, and D-dimer ($p > 0.05$). There were statistically significant differences in smoking history and homocysteine (Hcy) between the two groups of patients ($p < 0.05$; Table 1).

3.2 Analysis of patients' HR-MRI data in the training group

There was no statistical significance in the plaque location distribution and maximum wall thickness between the recurrence group and the non-recurrence group ($p > 0.05$), but the plaque stenosis grade, plaque enhancement level, intra-plaque hemorrhage, positive reconstruction and normalized wall index were statistically significant ($p < 0.05$), see Table 1. Typical HR-MRI image data of patients in the recurrence group and non-recurrence group are shown in Figure 1.

3.3 Screening of risk factors for stroke recurrence and construction of combination models

The results of univariate analysis of all baseline data in the training group showed that normalized wall index, homocysteine, maximum wall thickness, stenosis grade, enhancement level, intraplaque hemorrhage, positive reconstruction, and smoking history were associated with recurrence of stroke in HR-NICE patients (Table 2). The risk factors with $p < 0.1$ in univariate analysis were included in multivariate binary logistic regression analysis. The results showed that normalized wall index (OR: 1.114; 95% CI: 1.027–1.222), homocysteine (OR: 1.098; 95% CI: 1.025–1.179), intra-plaque hemorrhage (OR: 3.592; 95% CI: 1.474–9.104) were independent risk factors for recurrence of stroke in HR-NICE patients (Table 2). Using the modified Essen score to construct a prediction model (AUC = 0.660, 95%CI: 0.583–0.738), using the independent risk factors screened in multivariate logistic regression analysis to construct a model (AUC = 0.827, 95%CI: 0.765–0.889), and using the modified Essen score and the risk factors in multivariate logistic regression to construct a prediction model (AUC = 0.830, 95%CI: 0.769–0.891) to predict the recurrence risk of HR-NICE

TABLE 1 Clinical characteristics and imaging data of the non-recurrent group and recurrence group in the training group.

project	Non-recurrence group (n = 128)	Recurrence group (n = 52)	t/Z/χ^2 value	p-value
Age [years, M (Q25, Q75)]	60 (51,67)	59 (50,66)	0.567	0.572
Male[n(%)]	85 (66.406)	37 (71.154)	0.382	0.537
BMI[kg/m^2, M(Q25,Q75)]	24.1 (22.4,27.0)	25.3 (22.9,27.2)	−0.911	0.363
Smoking history[n(%)]	44 (34.375)	27 (51.923)	4.767	0.029
Drinking history[n(%)]	30 (23.438)	18 (34.615)	2.363	0.124
Hypertension [n(%)]	70 (54.688)	24 (46.154)	1.079	0.299
Diabetes[n(%)]	25 (19.531)	12 (23.077)	0.285	0.594
Previous myocardial infarction [n(%)]	7 (5.469)	4 (7.692)	0.319	0.572
Admission NIHSS score [M (Q25, Q75)]	1 (0,4)	2 (0,4)	−0.881	0.355
Total cholesterol [mmol/L, M(Q25, Q75)]	3.6 (3.1,4.6)	4.0 (3.4,4.5)	−1.329	0.184
Triglycerides [mmol/L, M(Q25, Q75)]	1.2 (0.9,1.6)	1.3 (0.9,2.1)	−1.225	0.221
LDL[mmol/L, M(Q25, Q75)]	2.2 (1.7,2.9)	2.4 (2.0,2.8)	−1.043	0.298
HDL[mmol/L, M(Q25, Q75)]	0.9 (0.8,1.2)	1.0 (0.8,1.2)	0.642	0.522
Apo A [mmol/L, M(Q25, Q75)]	1.1 (1.0,1.3)	1.1 (1.0,1.3)	−0.727	0.468
Apo B [mmol/L, M(Q25, Q75)]	0.8 (0.7,1.0)	0.9 (0.7,1.0)	−1.270	0.204
Fibrinogen [mg/dL, M(Q25, Q75)]	284 (256,331)	295 (257,345)	−0.858	0.391
Blood sugar [mmol/L, M(Q25, Q75)]	5.2 (4.7,6.3)	5.3 (4.8,6.1)	−0.825	0.410
D-dimer [mg/L, M(Q25, Q75)]	0.6 (0.5,0.8)	0.7 (0.5,0.8)	−0.368	0.711
Homocysteine [mmol/L, M(Q25, Q75)]	16.1 (13.0,20.2)	19.9 (17.7,21.3)	−4.097	<0.001
Imaging data				
Anterior circulation [n(%)]	70 (54.688)	25 (48.077)	0.648	0.421
Maximum wall thickness [mm, M (Q25, Q75)]	1.5 (1.2,1.8)	1.6 (1.3,1.8)	−1.365	0.173
NWI [M(Q25, Q75)]	75.4 (68.5,81.3)	82.0 (80.8,83.2)	−5.889	<0.001
Stenosis grade [n(%)]				
Level 0	54 (42.188)	9 (17.308)	16.086	<0.001
Level 1	52 (40.625)	21 (40.385)		
Level 2	22 (17.188)	22 (42.308)		
Enhancement level [n(%)]				
Level 0	55 (42.969)	11 (21.154)	9.713	0.008
Level 1	52 (40.625)	24 (46.154)		
Level 2	21 (16.406)	17 (32.692)		
Intra-plaque hemorrhage [n(%)]	21 (16.406)	31 (59.615)	33.607	<0.001
Positive reconstruction [n(%)]	37 (28.906)	24 (46.154)	4.910	0.027

BMI, body mass index; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; NWI, normalized wall index.

patients. In our study, there was an imbalance between the stroke recurrence group and the non-recurrence group. When facing imbalanced datasets, PR-AUC better reflects the performance improvement of the model, so we evaluated the model using PR curves. The PR curve also showed that the combined prediction model constructed using the modified Essen score and the risk factors in multivariate logistic regression achieved good performance in the training group (PR-AUC = 0.627), as shown in Figure 2. Finally, we used R software to construct a nomogram model to predict the recurrence risk of HR-NICE patients by improving the Essen score, Normalized Wall Index, homocysteine, and intraplaque hemorrhage (Figure 3). The calibration curve showed that the nomogram model fitted well with the 45° diagonal line, indicating that the prediction of stroke recurrence probability by the nomogram model was highly consistent with the actual observed probability. The DCA curve showed that timely intervention using the nomogram model for HR-NICE patients could achieve good net benefits (Supplementary Figure 1). To demonstrate the better generalization of the model, we validated the constructed nomogram model in the validation group (AUC = 0.785, 95%CI: 0.671–0.899). The results showed that the model still had good diagnostic performance in the validation group. The calibration curve and DCA decision curve showed that the model could predict the recurrence risk of HR-NICE patients well (Figure 4).

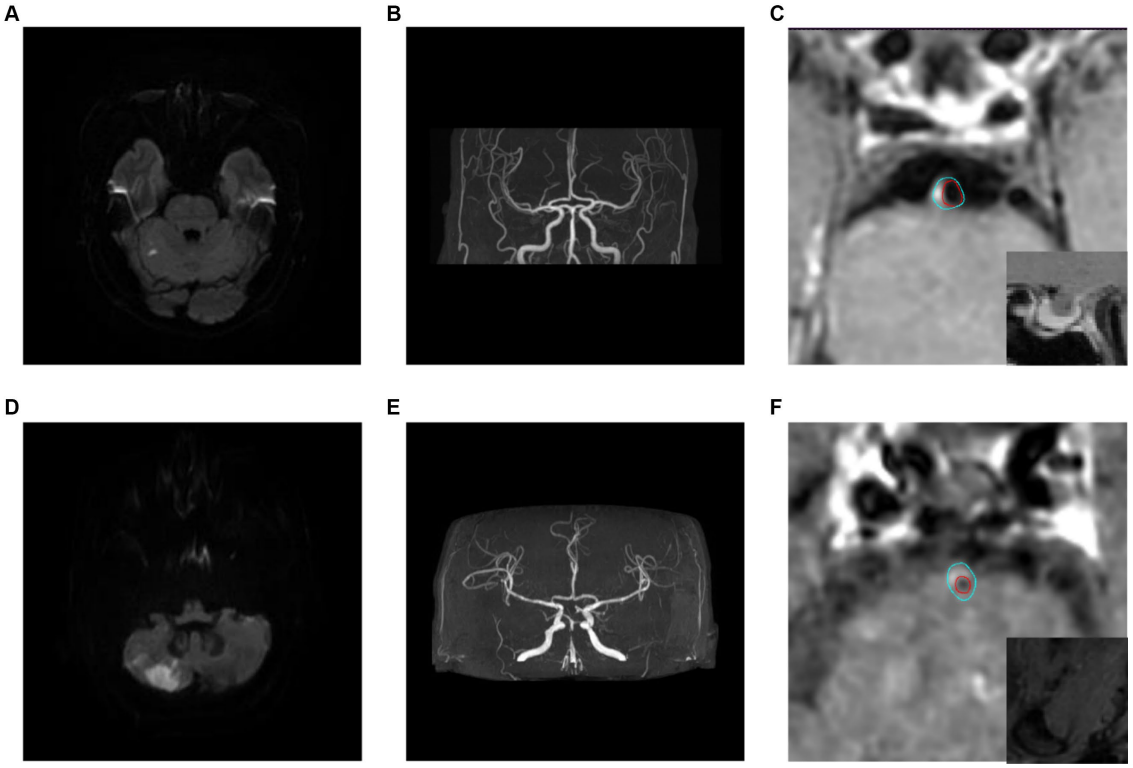

FIGURE 1
Typical HR-MRI images of patients in the recurrence group and non-recurrence group. **(A–C)** Male, 58 years old, with unsteady walking for 1 day. DWI showed acute cerebral infarction in the right cerebellar hemisphere **(A)**; MRA showed mild stenosis in the distal lumen of the basilar artery **(B)**; HR-MRI enhanced images show eccentric plaques in the basal artery with mild narrowing of the lumen, and the degree of plaque enhancement is higher than that of pituitary enhancement **(C)**; The blue line outlined the area of the wall, and the red line outlined the area of the lumen. **(D–F)** Male, 57 years old, with transient dizziness for more than 10 days. DWI showed acute cerebral infarction in the right cerebellar hemisphere **(D)**; MRA showed local severe stenosis in the basilar artery **(E)**; The HR-MRI image shows eccentric plaques in the basal artery, with severe narrowing of the lumen. The plaque signal is significantly higher than that of the adjacent medial pterygoid muscle, indicating the presence of Intra-plaque hemorrhage **(F)**.

TABLE 2 **Logistic regression results of risk factors for recurrence group in HR-NICE patients in the training group.**

Project	Univariate binary logistic regression			Multivariate binary logistic regression		
	OR	95%CI	*P*	OR	95%CI	*P*
NWI	1.193	1.112–1.28	0.000	1.114	1.027–1.222	0.015
Homocysteine	1.087	1.021–1.157	0.009	1.098	1.025–1.179	0.007
Maximum wall thickness	2.129	0.897–5.052	0.086			
Stenosis grade						
0						
1	2.423	1.016–5.777	0.046			
2	6.000	2.390–15.062	0.000			
Intra-plaque hemorrhage	7.522	3.643–15.530	0.000	3.592	1.474–9.104	0.006
Positive reconstruction	2.108	1.083–4.102	0.028			
Enhancement level						
0						
1	2.308	1.029–5.178	0.043			
2	4.048	1.629–10.055	0.003			
Smoking history	2.062	1.071–3.969	0.030			

NWI, Normalized Wall Index.

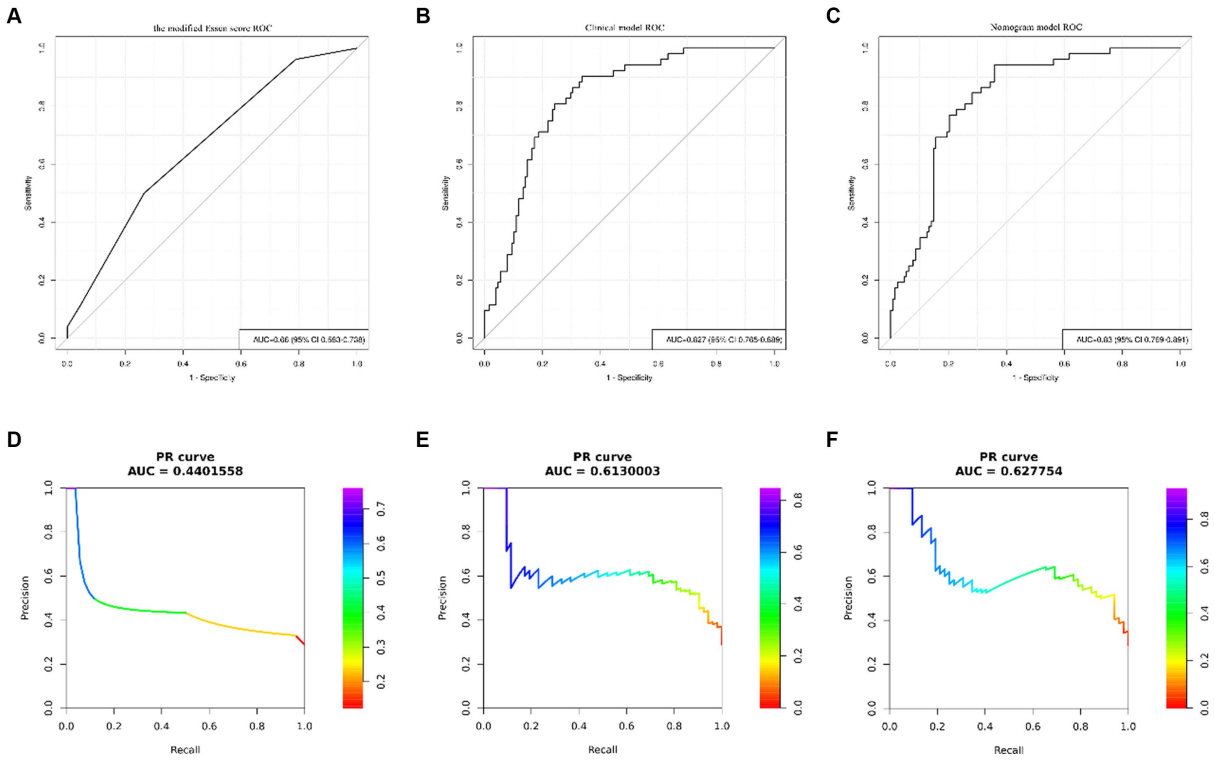

FIGURE 2
ROC curves and PR curves of different models in the training group. Panels **(A–C)** show the ROC curve of the modified Essen score, the ROC curve of the clinical model of independent risk factors screened by multivariate binary logistic regression, and the ROC curve of the nomogram model, respectively. Panels **(D–F)** show the PR curve of the modified Essen score, the PR curve of the clinical model of independent risk factors screened by multivariate binary logistic regression, and the PR curve of the nomogram model, respectively.

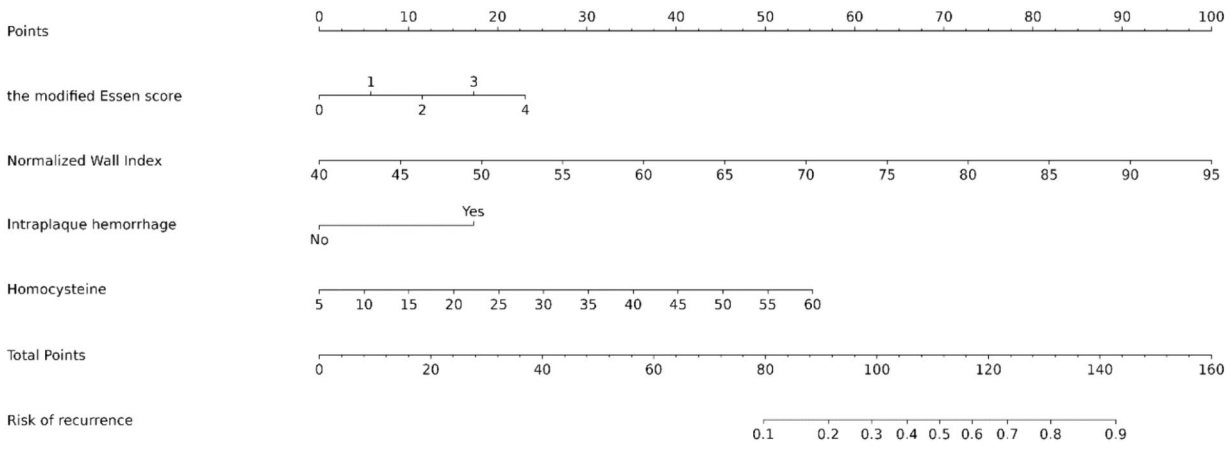

FIGURE 3
Nomogram predicting the risk of recurrence in HR-NICE patients. To obtain the probability of recurrent stroke risk for each HR-NICE patient, the "Total Points" is calculated by adding the respective "Points" values for each variable. Based on the corresponding total points, a vertical line can be drawn downward to obtain the probability of recurrence risk for each patient.

3.4 Online network calculator based on nomogram

The joint model represented by the nomogram has good performance in predicting the risk of recurrence in HR-NICE patients, so we have built an online network calculator based on the network[1] (Figure 5) to facilitate the better use of this model in clinical practice.

1 https://lza864545601.shinyapps.io/dynnomapp/

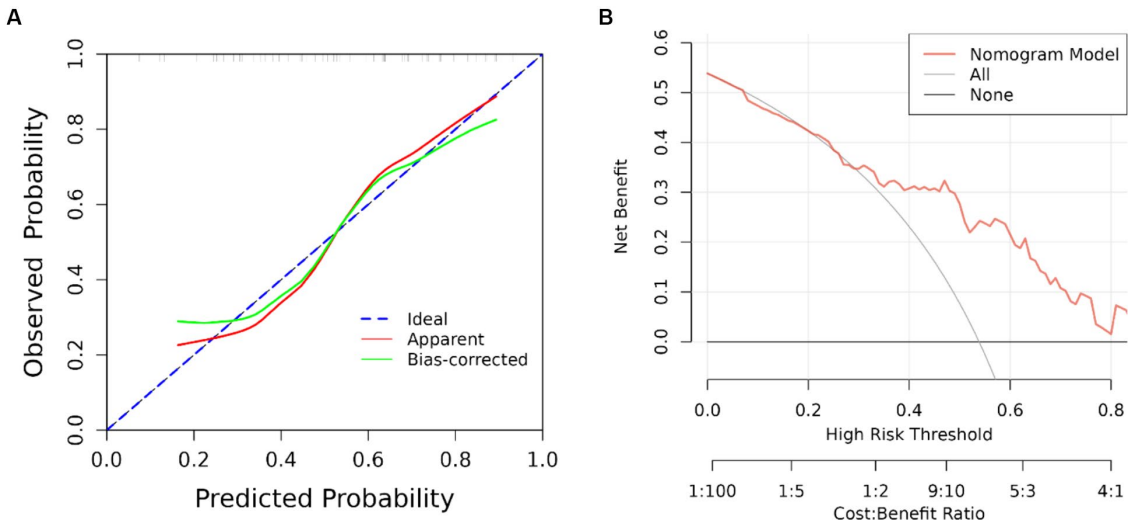

FIGURE 4
ROC curve, calibration curve and DCA curve of the validation group. **(A)** Calibration curve of the validation group and **(B)** clinical decision curve. The black straight line assumes all non-relapse patients, the gray curve assumes all relapse patients, and the red curve represents the nomogram model. The vertical axis is the net benefit rate, and the horizontal axis is the threshold probability.

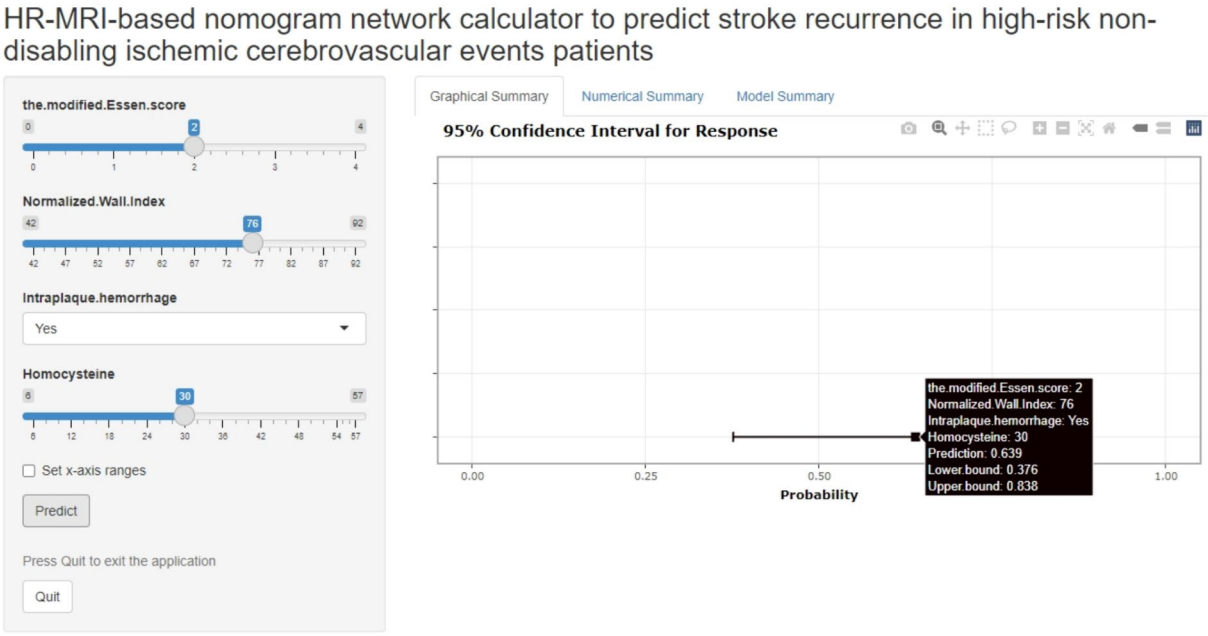

FIGURE 5
The picture above is a network calculator based on the nomogram model. The patient's Normalized Wall Index is 76, Intra-plaque hemorrhage is present, the blood homocysteine level is 30 mmol/L, the modified Essen score is 2 points, and the prediction probability of the model is 0.639 (95%CI: 0.376–0.838).

4 Discussion

China is currently one of the countries with the highest burden of stroke, and for ischemic stroke, some patients can maintain a stable state for a long time after onset, with a good prognosis, but more patients are in a sub-stable or unstable state, which often has a high recurrence rate in a short period of time and may lead to adverse outcomes such as disability or death, seriously affecting the quality of life of patients. Related studies have shown that approximately 65% of patients with ischemic cerebrovascular diseases are of this type. HR-NICE patients have the highest risk of stroke recurrence at 3 months, and once recurrence occurs, it usually leads to further deterioration or even death of the remaining neurological function (10–12). Therefore, it is necessary to identify the recurrence factors of stroke in HR-NICE patients in a timely and effective manner, which can

provide timely clinical intervention for patients with unstable conditions, reduce the risk of recurrence, and guide clinical prevention. This study used HR-MRI to conduct a more detailed study of the responsible plaques in intracranial arteries in HR-NICE patients. Through the evaluation of patient imaging data, we further screened the risk factors associated with ischemic event recurrence and combined them with the modified Essen score to perform timely and effective risk stratification for patients.

4.1 Correlation between clinical characteristics and stroke recurrence

Many previous studies have confirmed that serum homocysteine levels are related to the occurrence of various vascular events. The study by Del et al. (13) confirmed that the increase in Hcy levels after cerebral infarction is a predictor of recurrence of various vascular events. The increase in Hcy is often caused by a variety of factors, including insufficient intake or absorption of vitamin B6, lack of folic acid or vitamin B12, drug factors, and lifestyle factors (such as smoking, drinking, etc.) (14). The results of multiple animal experiments show that the increase in Hcy often leads to complex changes in the blood vessel wall, such as increased oxidative stress, pro-inflammatory effects, and endothelial dysfunction. This indicates that the increase in Hcy levels is related to the oxidative stress in the blood vessel wall, including pro-inflammatory effect and endothelial dysfunction (15, 16). The study by Holmen et al. (17) showed that when Hcy increases by five μmol/L, the risk of stroke increases by 43%. Therefore, we should pay more attention to the importance of Hcy in the examination of stroke patients. In the Chinese Adult Stroke Primary Prevention Trial (18), it was shown that patients in the folic acid treatment group had lower Hcy levels than the control group, and the probability of recurrent ischemic stroke was reduced by 24%. A review by Marti-Carvajal et al. (19) also found that patients receiving B12, folic acid, and B6 vitamins had a reduced risk of recurrent stroke compared with patients receiving placebo. This shows that for patients with high Hcy levels, timely and effective dietary control, can be of guiding significance in reducing the recurrence rate of ischemic cerebrovascular disease in the future. In addition, there was a statistical difference between smoking history and the recurrence of stroke events in univariate analysis. Smoking is an important risk factor for cardiovascular and cerebrovascular diseases, but we can avoid this risk factor by correcting our behavioral habits. Smoking causes endothelial dysfunction and atherosclerosis, including oxidative stress, reduced nitric oxide availability, increased monocyte adhesion, and the cytotoxic effects of nicotine, and increases coronary artery disease, myocardial infarction, and Risk of serious clinical complications such as stroke and peripheral arterial disease. Recent studies have also shown that there is a strong direct dose–response relationship between the number of cigarettes smoked and ischemic stroke. Although complete smoking cessation is a public health goal, reducing the number of cigarettes smoked can reduce the risk of ischemic stroke (20). There was no statistical difference in smoking history in the multivariate analysis. This may be due to the small sample size of this study, or it may be due to the fact that patients quit smoking promptly after experiencing TIA or minor stroke.

4.2 Correlation between plaque characteristics and stroke recurrence

The results of this study suggest that imaging characteristics of plaques, such as intraplaque hemorrhage and normalized wall index, are independent risk factors for recurrent ischemic cerebrovascular events in patients with HR-NICE. In recent years, studies have shown that the unstable characteristics of culprit plaques can predict the recurrence of future ischemic cerebrovascular events, and IPH has been proven to be a factor in plaque instability (21). In the process of plaque formation and organization, IPH is often caused by the unstable and immature vascular endothelium of new blood vessels, which causes the rupture of the capillary wall under the stimulation of hypoxia and inflammatory factors of the body, thus causing extravasation of blood (22). From a hemodynamic perspective, ruptured neovascular endothelium often leads to an increase in plaque volume and slope. The greater the slope of the lesion, the greater the longitudinal lumen curvature and the greater the stress. Larger slopes also disrupt local flow patterns, increasing wall shear stress and oscillatory shear index. The upstream plaque will bear the huge impact load caused by the accelerated blood flow, thus generating large wall shear stress. Larger wall shear stress may also exacerbate plaque vulnerability by accelerating endothelial dysfunction, weakening the plaque surface, and increasing the necrotic core (23). Physiologically and pathologically, IPH may destabilize atherosclerotic plaques by rapidly expanding the necrotic core and further promoting free cholesterol deposition through red blood cell membrane accumulation (21, 24). In addition, oxidative, proteolytic and inflammatory processes triggered by IPH, including leukocytes, platelets and plasma proteins, are also related to recurrent stroke events (25). The normalized wall index normalizes wall area to total vessel area and takes into account the inherent differences in wall area of vessels of different diameters, such as the basilar and middle cerebral arteries, providing a measure of lesion burden. In addition, considering that there are various ways of remodeling the lumen during plaque formation, simply measuring the stenosis area often cannot accurately reflect the stenosis of the responsible blood vessel, and NWI can well judge the current status of the blood vessel. A larger NWI often means that the patient has a greater plaque burden. An increase in the plaque burden may mean that the plaque becomes more stable, but it will also lead to the above-mentioned hemodynamic problems, thereby exacerbating the risk of plaque rupture and increasing the risk of plaque rupture. Leading to recurrence of stroke (26). The study by Ran et al. (27) showed that plaque burden is an independent risk factor for stroke recurrence in the middle cerebral artery blood supply area. For every 10% increase in plaque burden, the risk of stroke recurrence will increase by 2.26 times. The study by CX et al. also proved that when the patient's culprit plaque has the same or close NWI, the occurrence of intra-plaque hemorrhage can often provide a more effective predictive value for stroke recurrence (28). However, the maximum wall thickness, stenosis grade, positive remodeling and

enhancement grade that did not have statistical significance in the multiple binary logistic regression may be because the inclusion criteria of this study are the HR-NICE patient population, which are mostly TIA and mild cases. In patients with stroke, the clinical symptoms and imaging features may not be typical.

4.3 Correlation between modified Essen score and stroke recurrence

Individualized and customized prevention and treatment for HR-NICE patients often require timely prediction of potential stroke events before the patient occurs, which also relies on clinical data and predictive analysis. Choosing an appropriate and effective predictive score is an important tool for assessing patients' risk of future ischemic cerebrovascular events, stratifying patients, and selecting preventive treatments. Chen et al. (29) prospectively collected data from a total of 3,316 ischemic stroke patients in multiple centers in China to evaluate the accuracy of ESRS in predicting stroke recurrence and combined vascular events in patients with different categories of ischemic stroke within 1 year. The results showed that the accuracy of ESRS in predicting stroke recurrence was approximately 0.63 (95% CI, 0.57 ± 0.69), demonstrating the ability of ESRS to risk stratify patients. Ling et al. (4) modified the ESRS based on the characteristics of stroke in the Chinese population by adding the duration of hypertension, duration of diabetes, and stroke subtypes classified by etiology to the ESRS and deleting evaluation factors that were not efficient in the Chinese population. The modified Essen score was obtained, which constitutes a 4-point clinical index scale and was confirmed in a prospective cohort study based on the Chinese population to have an excellent ability to predict recurrent ischemic stroke and cardiovascular events. It is superior to ESRS in terms of clinical practicability and ease of rapid assessment. Although the modified Essen score has shown higher accuracy in predicting recurrence, this scale still fails to incorporate imaging features that are prone to the recurrence of cerebrovascular events. Therefore, this study proposes to combine the improved Essen score with the imaging features provided by HR-MRI to further optimize the recurrence prediction performance of the HR-NICE patient population and guide clinicians to better risk stratify patients.

4.4 Innovation and clinical practicality of online network calculators

At present, nomograms have been widely used in various clinical prediction models. This study constructed nomograms using the selected independent risk factors to assist clinical doctors in further decision-making analysis. Considering that the use of nomograms is still quite cumbersome, we have further developed a network calculator, which is the first online network calculator designed for the HR-NICE patient population. In addition, doctors can still use network calculators to dynamically monitor the recurrence risk of patients and provide more accurate personalized treatment by recalculating their clinical indicators after corresponding treatment for high-risk patients.

This study has the following limitations. Firstly, although this study is a dual-center study, the sample size is still small, and the coverage of patients in different regions is limited. The results may be affected by different ethnic groups and lifestyle habits, and a more detailed classification of clinical risk factors for patients has not been achieved. In the future, more center and large sample size trials are needed to further improve. Secondly, this study is a retrospective study, and it is more reasonable to use prospective studies to study the risk of patient recurrence. Clinical data and HR-MRI imaging features can be collected in a timely manner when patients experience recurrence. In future research, we will prospectively recruit more HR-NICE patients from multiple centers and establish a database to include more comprehensive risk factors for stroke recurrence. We will further deepen the research of HR-MRI technology, extract imaging omics features of responsible plaques and vascular walls, and conduct more detailed imaging omics, machine learning, and deep learning, aiming to further improve the predictive efficiency of the risk of recurrent ischemic cerebrovascular disease in the HR-NICE patient population.

5 Conclusion

In summary, this study found that modified Essen score, homocysteine, intra-plaque hemorrhage and normalized wall index are independent risk factors for recurrent ischemic cerebrovascular events in HR-NICE patients. The nomogram constructed by combining the modified Essen score with clinical and imaging features can improve the prediction performance of recurrent ischemic cerebrovascular events in HR-NICE patients. Based on this nomogram, we have created an online network calculator to help doctors stratify the risk of HR-NICE patients and develop personalized treatment plans.

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 humans were approved by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because this study complies with the Helsinki Declaration and has obtained ethical approval, exempting participants from informed consent.

Author contributions

Z-aL: Conceptualization, Writing – original draft, Writing – review & editing. YG: Conceptualization, Methodology,

Writing – review & editing, Writing – original draft. LH: Data curation, Writing – review & editing. B-cX: Data curation, Writing – review & editing. Y-cS: Data curation, Writing – review & editing. X-yZ: Software, Writing – review & editing. PZ: Methodology, Writing – review & editing. Y-dL: Methodology, Writing – review & editing. J-yY: Methodology, Writing – review & editing. R-fY: Methodology, Project administration, Writing – review & editing. H-KC: Project administration, Supervision, Writing – review & editing.

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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.2024.1407516/full#supplementary-material

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Effectiveness of a hybrid emergency room system in the management of acute ischemic stroke: a single-center experience

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Introduction: Hybrid emergency room systems (HERSs) have shown promise for the management of severe trauma by reducing mortality. However, the effectiveness of HERSs in the treatment of acute ischemic stroke (AIS) remains unclear. This study aimed to evaluate the impact of HERSs on treatment duration and neurological outcomes in patients with AIS undergoing endovascular therapy.

Materials and methods: This single-center retrospective study included 83 patients with AIS who were directly transported to our emergency department and underwent endovascular treatment between June 2017 and December 2023. Patients were divided into the HERS and conventional groups based on the utilization of HERSs. The primary outcome was the proportion of patients achieving a favorable neurological outcome (modified Rankin Scale score 0–2) at 30 days. The secondary outcomes included door-to-puncture and door-to-recanalization times. Univariate analysis was performed using the Mann–Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate.

Results: Of the 83 eligible patients, 50 (60.2%) were assigned to the HERS group and 33 (39.8%) to the conventional group. The median door-to-puncture time was significantly shorter in the HERS group than in the conventional group (99.5 vs. 131 min; $p = 0.001$). Similarly, the median door-to-recanalization time was significantly shorter in the HERS group (162.5 vs. 201.5 min, $p = 0.018$). Favorable neurological outcomes were achieved in 16/50 (32.0%) patients in the HERS group and 6/33 (18.2%) in the conventional group. The HERS and conventional groups showed no significant difference in the proportion of patients achieving favorable neurological outcomes ($p = 0.21$).

Conclusion: Implementation of the HERS significantly reduced the door-to-puncture and door-to-recanalization times in patients with AIS undergoing endovascular therapy. Despite these reductions in treatment duration, no significant improvement in neurological outcomes was observed. Further research is required to optimize patient selection and treatment strategies to maximize the benefits of the HERS in AIS management.

KEYWORDS

cerebral infarction, endovascular procedures, intracranial embolism and thrombosis, radiographic image enhancement, thrombectomy

1 Introduction

Acute ischemic stroke (AIS) caused by large-vessel occlusion is associated with poor outcomes. In cases of ischemic stroke, mortality within 3–6 months was higher after large-vessel occlusion than after non-large-vessel occlusion (26.2% vs. 1.3%, odds ratio: 4.1, 95% confidence interval: 2.5–6.7) (1). The penumbra, the tissue surrounding the infarction area that is at risk of cell death, can be salvaged by prompt recanalization (2). Numerous randomized trials have demonstrated the advantages of endovascular treatment, including thrombectomy following intravenous thrombolysis with a tissue plasminogen activator (tPA), in achieving recanalization and favorable neurological outcomes (3). Early successful recanalization after symptom onset remains a critical factor for optimal outcomes (4).

The implementation of hybrid emergency room (ER) systems (HERSs) in Japan has shown promising results in the management of cases involving severe trauma. An HERS is equipped with advanced diagnostic modalities, such as X-ray fluoroscopy and computed tomography (CT), enabling complete diagnosis and immediate treatment without the need for patient transfer (5, 6). The consequent elimination of transfer time has led to a decrease in mortality rates in patients with trauma (7). Timely reperfusion is crucial in AIS caused by large-vessel occlusion (8). Given the critical importance of time in both severe trauma and AIS management, the HERS could plausibly provide similar benefits for stroke care (9). However, the effectiveness of the HERS in the management of AIS remains unclear.

Therefore, this study aimed to retrospectively analyze patients who underwent endovascular treatment for AIS at our institution and evaluate the effectiveness of the HERS in this context. We hypothesized that the use of the HERS, which enables immediate CT diagnosis and rapid endovascular intervention without patient transfer, would result in shorter time intervals from hospital arrival to recanalization and, consequently, yield improved neurological outcomes in comparison with conventional stroke management. By addressing this gap in the current understanding of HERS applications, we aimed to contribute to the advancement of stroke care and potentially offer insights into the optimization of ER systems for the management of AIS.

2 Materials and methods

2.1 Study design and setting

This retrospective study was conducted at a single academic medical center located in an urban area of Kanto, Japan. The HERS, which was equipped with a sliding CT scanner system featuring interventional radiology capabilities, was established adjacent to the conventional ER in 2016 (Figure 1). The distance from the ambulance parking lot to the conventional ER and the hybrid ER was approximately 50 m. Acute AIS management using the HERS commenced in 2017, following the assignment of neuroendovascular specialists.

The HERS was preferentially employed when a patient with suspected stroke was transported within 6 h of symptom onset. All patients who were transported to our emergency department with suspected acute stroke underwent an initial evaluation by an emergency physician; if the hybrid ER was available, the patients were treated using the hybrid ER immediately after transport, and if the hybrid ER was being used to treat other patients, the patients were treated in the conventional ER. AIS was diagnosed using head CT, including perfusion imaging, or head magnetic resonance imaging in patients with renal dysfunction. Thrombolytic therapy was administered by the emergency physicians in consultation with a stroke specialist. Endovascular treatment was administered to patients with onset within 6 h or an unknown onset time showing occlusion of the internal carotid artery, M1 or M2 portion of the middle cerebral artery, or basilar artery along with a relatively large penumbra compared to the ischemic core, as judged by the emergency physician. An endovascular physician performed all endovascular treatments.

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplementary material File 1) (10). This study was approved by the Institutional Review Board of Jichi Medical University Saitama Medical Center. Participants were provided with the opportunity to opt out of the study at any time by withdrawing permission to use their data.

2.2 Patient selection and grouping

This investigation included a cohort of patients with AIS who were directly transported from prehospital locations to our emergency department by emergency medical service personnel and received endovascular treatment between June 2017 and December 2023. Patients who developed AIS at our hospital or who were transferred from other hospitals or clinics were excluded.

The study population was divided into two groups: the HERS group, in which patients received continuous care from initial evaluation to endovascular treatment using the HERS, and the conventional group, in which the HERS was not used.

2.3 Data collection

The following data were collected from electronic medical records: age, sex, modified Rankin Scale (mRS) score before admission (11), onset-to-door time (interval from symptom onset to hospital arrival), National Institutes of Health Stroke Scale (NIHSS) score on admission (12), door-to-picture time (interval from hospital arrival to CT imaging), Alberta Stroke Program Early Computed Tomography Score (ASPECTS) on admission (13), etiology of AIS (atrial fibrillation, atherothrombotic, left-to-right shunt, or cryptogenic), culprit lesion (M1 or M2 segment of middle cerebral artery, internal

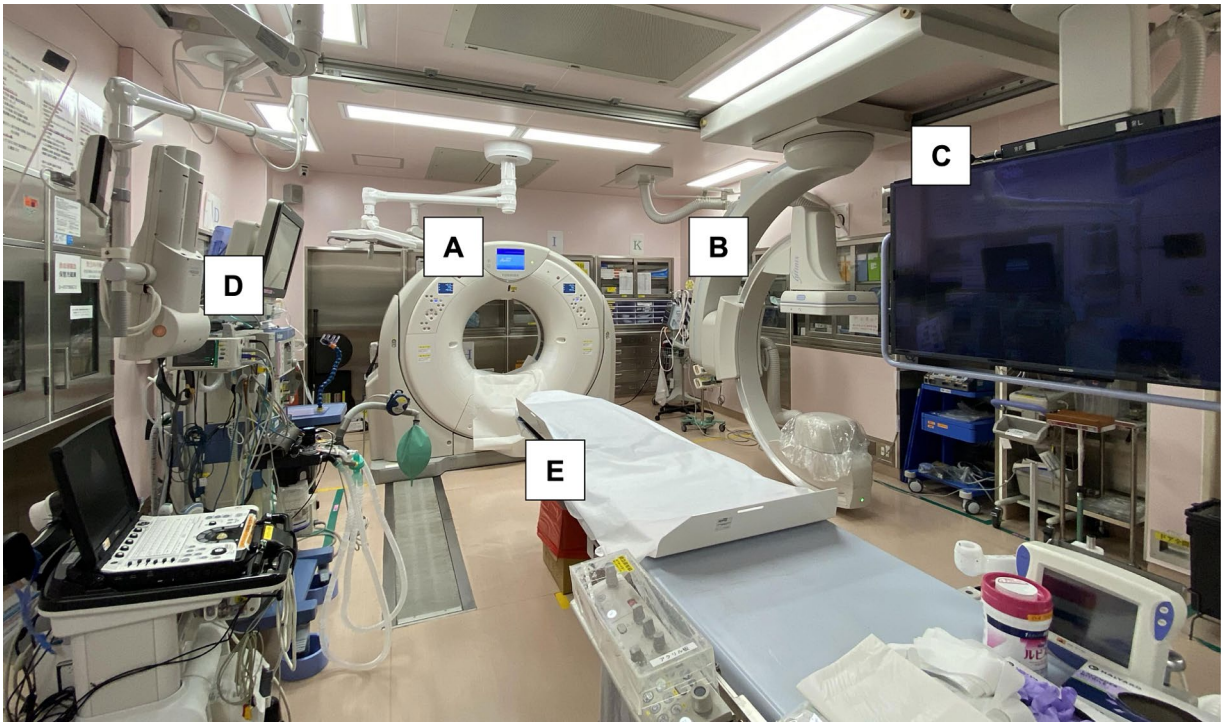

FIGURE 1
Photograph showing a sliding computed tomography scanner system with interventional radiology features in the emergency room. Acute procedures for ischemic stroke, including airway management, and angiography can be performed on the table without transferring the patient. **(A)** Sliding computed tomography (CT) scan device, **(B)** movable C-arm, **(C)** monitoring screen, **(D)** mechanical ventilator with anesthesia apparatus, and **(E)** CT examination and intervention table.

carotid artery, basilar artery), presence of tandem lesions, tPA administration, door-to-needle time (interval from hospital arrival to tPA administration), endovascular treatment procedure (fragmentation, mechanical thrombectomy, or carotid artery stenting and mechanical thrombectomy), door-to-puncture time (interval from hospital arrival to arterial puncture), door-to-recanalization time (interval from hospital arrival to recanalization), onset-to-recanalization time (interval from symptom onset to recanalization), Thrombolysis in Cerebral Infarction (TICI) grade, intracranial hemorrhage after procedure (symptomatic or asymptomatic), ASPECTS 30 days after admission, length of hospital stay, NIHSS score 30 days after admission, and mRS score 30 days after admission.

2.4 Outcome measures

The primary outcome was a favorable neurological outcome at 30 days, defined as an mRS score of 0–2. The secondary outcomes were door-to-puncture and door-to-recanalization times as direct measures of time reduction using the HERS, in addition to the distribution of the mRS score at 30 days.

2.5 Statistical analyses

Descriptive statistics were calculated for all the variables of interest. Continuous variables were presented as median and interquartile range (IQR), whereas categorical variables were presented as count and percentage. Univariate analysis was performed using the Mann–Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate.

All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. Statistical analyses were performed using R Statistical Software.

3 Results

3.1 Patient enrollment and grouping of eligible patients

During the study period, 115 patients with AIS underwent endovascular treatment. Of these, 14 patients (12.2%) were transferred from other hospitals, and 18 (15.7%) developed AIS at our hospital (Figure 2). After excluding these patients, 83 patients with AIS who were directly transported from prehospital locations to the emergency department and underwent endovascular treatment were included in the study. Of these, 50 patients (60.2%) were treated with the HERS (HERS group), whereas 33 (39.8%) were treated in the conventional ER (conventional group).

3.2 Patient characteristics

There were no missing data. The patient demographics, clinical characteristics, and outcomes are summarized in Table 1. The median age of the study population was 79 years (IQR: 73–85 years), and

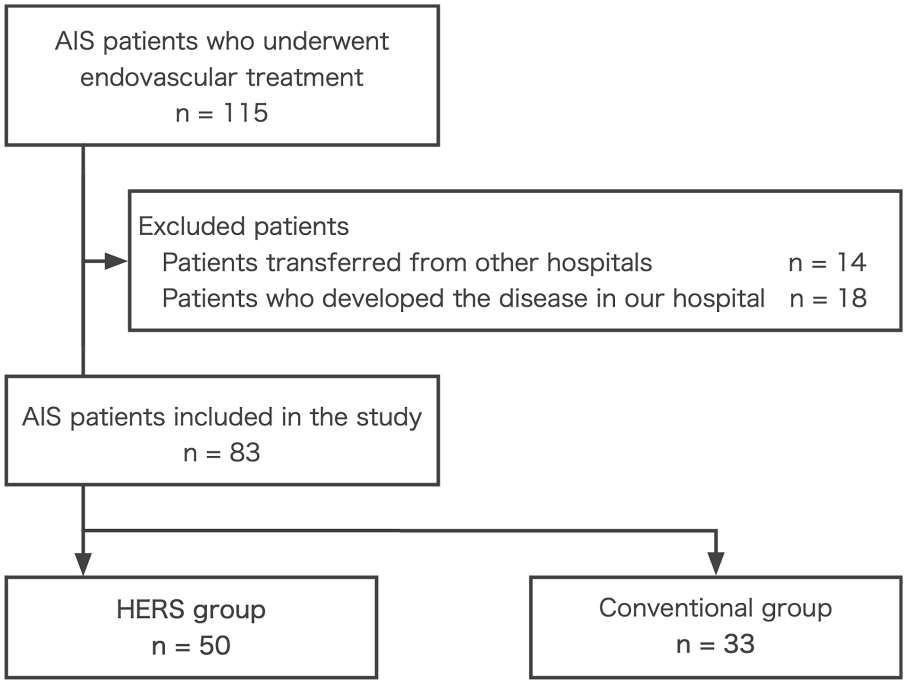

FIGURE 2
Patient selection flowchart. AIS, acute ischemic stroke; HERS, hybrid emergency room system.

62.7% of the patients were male. The median onset-to-door time was 55 min (IQR, 41–111 min), and the median NIHSS score at admission was 20 (IQR: 13.5–28). The most common etiology of AIS was atrial fibrillation (67.5%), and the culprit lesions were most frequently present in the M1 segment of the middle cerebral artery (53.0%). Tandem lesions were present in 4.8% of the patients. tPA was administered in 67.5% of the cases.

3.3 Patient outcomes

The median door-to-puncture time was significantly shorter in the HERS group than in the conventional group (99.5 [IQR: 75.75–117.5] min vs. 131 [IQR: 98–166] min, $p = 0.001$). Similarly, the median door-to-recanalization time was significantly shorter in the HERS group (162.5 [IQR: 141.75–184.5] min vs. 201.5 [IQR: 154–251] min, $p = 0.018$). However, the onset-to-recanalization time was not significantly different between the two groups (225 [IQR: 188.25–269.75] min vs. 274 [201–369] min, $p = 0.10$).

The primary outcome, i.e., an mRS score of 0–2 at 30 days after admission, was achieved in 32.0% of the patients in the HERS group and 18.2% of those in the conventional group; however, this difference was not statistically significant ($p = 0.21$). The distribution of the mRS scores 30 days after admission is shown in Figure 3.

4 Discussion

This retrospective study aimed to evaluate the efficacy of the HERS in managing patients with AIS undergoing endovascular treatment. Our findings demonstrate that the implementation of the HERS significantly reduced the median door-to-puncture and door-to-recanalization times in comparison with the conventional approach. However, despite the observed reduction in treatment times, the HERS and conventional groups showed no significant difference in the proportion of patients achieving favorable neurological outcomes. The significant reduction in door-to-puncture and door-to-recanalization times associated with the HERS highlights the potential of this novel system for streamlining the care pathway for patients with AIS.

By enabling rapid diagnosis and treatment initiation without the need for patient transfer, the HERS can minimize the delays that often compromise the effectiveness of endovascular therapy (9). The significant reduction in the treatment time observed in the HERS group in this study was consistent with the findings of previous studies demonstrating the benefits of the HERS in the management of acute conditions (14, 15). Kinoshita et al. found that the use of a hybrid ER significantly reduced the time required for CT examinations and emergency surgery in patients with severe traumatic brain injury (16). These findings support the notion that the integrated imaging and intervention capabilities of the HERS can streamline the care pathway for acute conditions and eliminate delays associated with patient transfer (6). Because early successful recanalization is a critical factor for favorable outcomes in AIS (2), the time savings afforded by the HERS may have important implications for patient prognosis.

However, the lack of a significant difference in favorable neurological outcomes between the HERS and conventional groups warrants further discussion. Although the use of the HERS significantly reduced treatment time, it did not translate into improved neurological outcomes in our study population. Expanding the application of the HERS to a broader range of patients with AIS may lead to improved outcomes; however, this

TABLE 1 Patient demographics, characteristics, and outcomes.

Factor	Overall (*n* = 83)	HERS group (*n* = 50)	Conventional group (*n* = 33)	*p* value
Age, years	79 [73–85]	78.5 [72.5–84]	79 [73–86]	0.62
Male (%)	52 (62.7)	31 (62.0)	21 (63.6)	1
mRS score before admission	0 [0–1]	0 [0–1]	0 [0–1]	0.74
Onset-to-door time, min	55 [41–111]	55 [41.5–80]	56 [41–157]	0.53
NIHSS score at admission	20 [13.5–28]	20 [11.5–29]	21 [14–26]	0.87
Door-to-picture time, min	20 [15.5–28]	19 [13–23]	28 [17–40]	<0.001
ASPECTS at admission	9 [8–10]	9 [8–10]	9 [8–10]	0.64
Etiology (%)				
Cryptogenic	20 (24.1)	8 (16.0)	12 (36.4)	0.13
Atrial fibrillation	56 (67.5)	38 (76.0)	18 (54.5)	
Arteriosclerotic disease	5 (6.0)	3 (6.0)	2 (6.1)	
Right-to-left shunt	2 (2.4)	1 (2.0)	1 (3.0)	
Culprit lesion (%)				
M1 segment of middle cerebral artery	44 (53.0)	29 (58.0)	15 (45.5)	0.51
M2 segment of middle cerebral artery	12 (14.5)	6 (12.0)	6 (18.2)	
Internal carotid artery	20 (24.1)	10 (20.0)	10 (30.3)	
Basilar artery	7 (8.4)	5 (10.0)	2 (6.1)	
Tandem lesions (%)	4 (4.8)	2 (4.0)	2 (6.1)	1
Tissue plasminogen activator administration (%)	56 (67.5)	37 (74.0)	19 (57.6)	0.15
Door-to-needle time, min	77 [66.5–100.5]	74 [64–84]	100 [78–107]	0.007
Procedures (%)				
Fragmentation	2 (2.4)	0 (0.0)	2 (6.1)	0.16
Mechanical thrombectomy	80 (96.4)	49 (98.0)	31 (93.9)	
Carotid artery stenting and mechanical thrombectomy	1 (1.2)	1 (2.0)	0 (0.0)	
Door-to-puncture time, min	107 [83–132]	99.5 [75.75–117.5]	131 [98–166]	0.001
Door-to-recanalization time, min	170 [142–216.5]	162.5 [141.75–184.5]	201.5 [154–251]	0.018
Onset-to-recanalization time, min	239 [190.5–318]	225 [188.25–269.75]	274 [201–369]	0.10
Thrombolysis in cerebral infarction grade (%)				
0	2 (2.4)	2 (4.0)	0 (0.0)	0.34
1	2 (2.4)	0 (0.0)	2 (6.1)	
2a	10 (12.0)	6 (12.0)	4 (12.1)	
2b	24 (28.9)	13 (26.0)	11 (33.3)	
3	45 (54.2)	29 (58.0)	16 (48.5)	
Intracranial cerebral hemorrhage (%)	16 (19.3)	9 (18.0)	7 (21.2)	0.78
Symptomatic intracranial cerebral hemorrhage (%)	11 (13.3)	6 (12.0)	5 (15.2)	0.75
ASPECTS 30 days after admission	7 [5–8.5]	6 [5–8]	7 [4–9]	0.77
Length of hospital stay, days	23 [14.5–31]	22.5 [14.5–30.5]	23 [15–31]	0.71

(Continued)

TABLE 1 (Continued)

Factor	Overall (*n* = 83)	HERS group (*n* = 50)	Conventional group (*n* = 33)	*p* value
NIHSS score 30 days after admission	16 [8.5–27]	16 [9–27]	18 [7–26]	0.94
mRS score 30 days after admission	4 [2–5]	4 [2–5]	4 [3–5]	0.22
Favorable neurological outcome 30 days after admission (%)	22 (26.5)	16 (32.0)	6 (18.2)	0.21

Continuous variables are presented as median [interquartile range]. Categorical variables were presented as count (percentage). ASPECTS, Alberta Stroke Program Early Computed Tomography Score; HERS, hybrid emergency room system; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

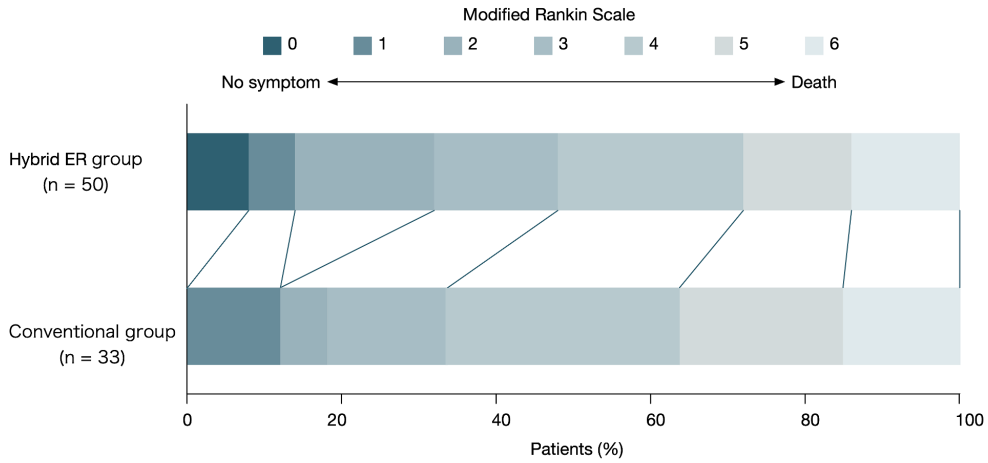

FIGURE 3
Distribution of modified Rankin Scale (mRS) scores at 30 days.

requires careful consideration and further research to identify optimal patient selection criteria. Furthermore, the median difference in the door-to-recanalization time to reperfusion was <40 min, and the onset-to-recanalization time was not significantly different, suggesting that the prognostic impact may be limited.

Current trends and future directions in AIS treatment emphasize the importance of reducing door-to-groin time and improving outcomes by employing a direct-to-angiography suite approach in the early time window for selected patients with large-vessel occlusions (17). Although our study demonstrated the effectiveness of the HERS in reducing treatment time, the lack of improvement in neurological outcomes highlights the need for further optimization of HERS-based treatment strategies. This may involve refining patient selection criteria, improving device selection and technical aspects of the procedure, and ensuring seamless coordination among multidisciplinary stroke teams.

This study had several limitations. First, the door-to-puncture time was delayed even in the HERS group. Such delays can be attributed to several reasons, including determination of the indications for endovascular treatment by emergency physicians, administration of tPA intravenously before endovascular treatment, and the on-call availability of endovascular physicians at night and on holidays. Second, this was a single-center observational study with a small number of cases and no adjustments for confounding factors. Prospective multicenter studies incorporating a large number of patients will be important to expand the coverage of the HERS and optimize treatment strategies for patients with AIS.

In conclusion, our study demonstrates the potential of the HERS in reducing the treatment time for patients with AIS undergoing endovascular therapy. Although the lack of improvement in neurological outcomes highlights the need for further research and optimization of treatment strategies, the significant reduction in door-to-puncture and door-to-recanalization times suggests that the HERS could be a valuable tool for the management of AIS. As the field of AIS treatment continues to evolve, investigating the effectiveness of the HERS in various patient subgroups and developing comprehensive stroke care protocols that maximize the benefits of this innovative system will become more important.

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 humans were approved by the Institutional Review Board of Jichi Medical University Saitama Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/Institutional Review Board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the requirement for informed consent was waived because of the observational study design, which posed minimal risk to the patients and preserved their anonymity. Patients and their respective families were provided with an opportunity to opt out of the study.

Author contributions

MK: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. CN: Data curation, Formal analysis, Supervision, Visualization, Writing – review & editing. YK: Supervision, Writing – review & editing. KT: Writing – review & editing. HT: Supervision, Writing – review & editing. HY: Conceptualization, Supervision, Writing – review & editing. MI: Supervision, Writing – review & editing. KY: Supervision, Writing – review & editing. YY: Supervision, Writing – review & editing. TM: Supervision, Writing – review & editing.

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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/fmed.2024.1420951/full#supplementary-material

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The one-year incidence of stroke in patients with atrial fibrillation in Jordan and its associated factors

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Background: An elevated risk of stroke is linked to atrial fibrillation (AF). Effective care and prevention measures for individuals with AF require an understanding of the factors impacting the incidence of stroke in this population. Evidence regarding the incidence of stroke among patients with AF is insufficient in Jordan. This study aimed to determine the incidence of stroke and its associated factors among patients with AF in Jordan.

Methods: The Jordan Atrial Fibrillation Registry JoFib was used to identify a total of 2020 AF patients meeting the study inclusion and exclusion criteria. Demographics, clinical characteristics, and the CHA2DS2-VASc score-based evaluation of stroke risk were extracted from the registry.

Results: This study encompassed 2020 participants diagnosed with AF, with 925 (45.8%) being men and 1,095 (54.2%) women. The one-year stroke incidence among the 2020 AF patients was 3.4%. Notably, stroke incidence significantly increased with age (p = 0.04) and was associated with the history of stroke (7.4% vs. 2.7%), hypertension (3.9% vs. 1.9%), and diabetes (5.1% vs. 2.1%). In the multivariate analysis, diabetes (OR = 2.6, 95% CI: 1.5–4.4, p = 0.001) and history of stroke (OR = 2.6, 95% CI: 1.5–4.6, p = 0.001) were significantly associated with stroke incidence.

Conclusion: This study emphasizes Jordan's high stroke rate among AF patients. Diabetes and prior stroke history are associated with increased odds of stroke, like all stroke patients. These results highlight the necessity for specialized management strategies among AF patients and highlight the significance of thorough risk assessment and focused interventions to reduce stroke risk in AF patients.

KEYWORDS

atrial fibrillation, metabolic abnormalities, stroke risk, diabetes, Jordan

Introduction

The most prevalent persistent cardiac arrhythmia, atrial fibrillation (AF), is linked to higher rates of morbidity, increased use of medical resources, and mortality. With an estimated 2–4 percent prevalence, AF affects approximately 33 million persons worldwide (1, 2). Given that a sizable percentage of patients go undetected, it is anticipated that this estimate will be underestimated (3). According to epidemiological research, more than 5.6 million Americans are likely to get AF by 2050, and by 2060, there will be 17.9 million AF patients in Europe who are older than 55 (4, 5).

A number of conditions, including coronary artery disease, heart failure, diabetes, obesity, and hypertension, are linked to an increased risk of AF (5). Likewise, these variables are linked to a higher chance of stroke and death in AF patients (3, 5, 6). Hemorrhagic strokes are caused by abrupt bleeding in the brain, while ischemic strokes are caused by obstructed blood flow to the brain. Stroke is attributed to many etiologies like atherosclerosis, cardioembolism (mainly associated with AF), small vessel disease, hypertension, aneurysm rupture, and others (7). Recent research addressed services for stroke patients in Jordan and the region with identified improvements strategies like accreditation, specialized training, and quality registries (8, 9). Patients with AF have a nearly five-fold increased risk of stroke compared to those without AF (2, 10), which accounts for around 25% of all stroke types (11). The main components of CHADS2-VASc score, which are used to assess the risk of stroke in patients with AF (12), include metabolic abnormalities linked to an elevated risk of stroke in patients with AF, the scoring items include established history of stroke/transient ischemic attack/thromboembolic event, in addition to congestive heart failure, hypertension, Age ≥ 75 years, diabetes mellitus, vascular disease (prior myocardial infarction MI, peripheral artery disease PAD, or aortic plaque), age 65 to 74 years, and sex category (female sex) (13, 14).

When compared to other forms of strokes, AF-related strokes are more deadly and cause greater death rates (11). Patients who get a stroke due to AF are twice as likely to end up bedridden as those who experience a stroke from another cause, which can be attributed to known AF before stroke (15, 16). Because of the nature of these occurrences, stroke linked to AF eventually results in a significant financial burden due to an increase in readmissions (11).

There is a lack of prior research on the incidence of stroke among patients with AF and its related variables in the Middle East, namely in Jordan. The usage of oral anticoagulants and the clinical characteristics of AF were the primary topics of the scant investigations conducted in the Middle East (17–19). Determining the incidence of stroke and the factors that contribute to it is crucial for comprehensive therapy of AF. Thus, the purpose of this study was to determine the incidence of stroke and its associated factors among patients with AF in Jordan.

Materials and methods

Study population

The Jordan Atrial Fibrillation (JoFIB) registry is a prospective, multicenter observational registry that, from May 2019 to January 2021, included consecutive AF patients who were over the age of eighteen in 19 hospitals and 11 outpatient clinics throughout Jordan. The methodology was already released in print (20). As an overview, data were gathered at enrollment and one, six, and 12 months following the initial examination utilizing a standardized clinical data form. A 12-lead electrocardiogram (EKG) rhythm strip lasting more than 30 s, more than one episode of AF on an ambulatory EKG monitor, or a previous diagnosis made by a treating cardiologist were used to confirm the diagnosis of AF. The usage of OACs and other pharmaceutical drugs, laboratory results, EKG, clinical and demographic profiles, and transthoracic echocardiographic features were all included in the baseline data. The classification of AF kinds, such as paroxysmal, persistent, long-standing, and permanent, and the computation of each patient's CHA2DS2-VASc and HAS-BLED scores were done using standard definitions (12, 21). The 2019 focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation was used to analyze eligibility for oral anticoagulant medicines (22).

Inclusion criteria and baseline data collection

Patients with AF who were above 18 years old and had been diagnosed with the condition with a 12-lead EKG rhythm strip lasting more than 30 s or an ambulatory EKG monitor displaying more than one episode of AF met the inclusion criteria. Demographics (age, gender, smoking history), clinical traits body mass index [BMI], self-reported comorbidities (ischemic heart disease, hypertension, diabetes, and dyslipidemia), and the CHA2DS2-VASc score were used to estimate the risk of stroke with no cut-off value for inclusion in the study (12, 23, 24).

Ethical considerations

The study's participating hospitals, which included Amman Surgical Hospital, Arab Medical Center, Essra Hospital, Ibn Haitham Hospital, Islamic Hospital, Istishari Hospital, Jordan Hospital, Khalidi Medical Center, King Abdullah University Hospital, King Hussein Medical Center, Prince Hamza Hospital, Prince Hashem Hospital, Queen Alia Cardiac Center, Salt Medical Center, and Specialist Hospital, all received ethical approval (approval number 10/2021/415). Written informed permission was acquired by each subject. The study was registered with the unique identifier NCT03917992 on clinicaltrials.gov. There was no patient or public participation in the planning, execution, reporting, or distribution of this study.

Statistical analysis

Data analysis was done with IBM SPSS version 20. Continuous variables (means and standard deviation [SD]) and categorical variables (percentages) were described via descriptive statistics. The chi-square test was used to compare the incidence of stroke among different variable categories. To identify the factors associated with stroke, binary logistic regression was conducted. A $p < 0.05$ was considered statistically significant.

Results

Characteristics of participants

Our study encompassed 2020 participants diagnosed with AF, with 925 (45.8%) being men and 1,095 (54.2%) women. A total of 752 (37.2%) patients were aged 70–79 years old, and 348 (17.2%) were aged 80 or older. Among participants, 280 (13.9%) were smokers and 1,136 (76.8%) had a BMI of 25 kg/m^2 or higher. Ischemic heart disease was present in 243 (12.0%) participants, while 310 (15.4%) had a history of stroke. Utilizing the CHA2DS2VAS score, stroke risk assessment categorized 815 (40.4%) patients as high risk and 1,205 (59.6%) as low risk. Hypertension was the most common comorbidity, affecting 1,506 (74.6%) patients, followed by diabetes in 881 (43.6%) and dyslipidemia in 909 (45.0%). Detailed patient characteristics specific to Jordanian AF patients are outlined in Table 1.

One-year incidence of stroke among AF patients

Table 2 delineates the one-year stroke incidence among the 2020 AF patients, indicating an overall incidence of 3.4%. Notably, stroke incidence significantly increased with age ($p = 0.04$) and was associated with the history of stroke (7.4% vs. 2.7%), hypertension (3.9% vs. 1.9%), and diabetes (5.1% vs. 2.1%).

TABLE 1 Demographic and clinical characteristics of patients with atrial fibrillation, $N = 2020$.

Variable	*N* (%)
Gender	
Male	925 (45.8)
Female	1,095 (54.2)
Age in years	
<50	184 (9.1)
50–59	275 (13.6)
60–69	461 (22.8)
70–79	752 (37.2)
≥80	348 (17.2)
Current smoking	
Non-smoker	1740 (86.1)
Smoker	280 (13.9)
Body Mass Index (Kg/m^2)	
<25	436 (21.6)
25–29.9	660 (32.7)
≥30	766 (37.9)
Ischemic heart disease	243 (12.0)
History of stroke	310 (15.4)
Strok risk (CHA2DS2-VASc score)	
Low risk	1,205 (59.6)
High risk	815 (40.4)
Hypertension	1,506 (74.6)
Diabetes	881 (43.6)
Dyslipidemia	909 (45.0)

Stroke incidence in relation to prescribed medications

No statistically significant associations were found between oral anticoagulant usage or antiplatelet drugs and stroke risk ($p > 0.05$). However, a noteworthy correlation ($p < 0.001$) was observed between ticagrelor usage and stroke occurrence. Additionally, correlations were found between stroke incidence and beta blockers ($p = 0.040$), amiodarone ($p = 0.035$), calcium channel blockers (CCBs) ($p < 0.001$), and statins ($p = 0.035$). No significant correlations were found with other medications. The association of stroke with prescribed medications are provided in Table 3.

Factors associated with one-year stroke incidence among AF patients

Multivariate analysis (Table 4) identified risk factors for stroke in AF patients after adjusting for variables including age, BMI, hypertension, and anticoagulant use. Diabetes (OR = 2.6, 95% CI: 1.5–4.4, $p = 0.001$) and history of stroke (OR = 2.6, 95% CI: 1.5–4.6, $p = 0.001$) were significantly associated with stroke incidence.

Discussion

In the present study, relevant data of AF patients were extracted from a national clinical trial, the Jordan Atrial Fibrillation Registry, and were assessed for stroke incidence and trends regarding associated factors to stroke burden in Jordan. This study serves as a continuum of efforts to better understand AF status and its associated comorbidities, including stroke. This is the largest study reporting stroke incidence in AF patients among Jordanian population.

According to our study's findings, 3.4% of individuals with AF had a stroke within a year. Interestingly, the likelihood of stroke in this cohort was found to be significantly increased by the presence of diabetes or a history of prior stroke. Our observed rate of stroke incidence is in line with earlier studies carried out in Jordan, which found that patients with AF had a 4.5% one-year risk of stroke/systemic embolization (17). Furthermore, our results are consistent with regional and international research that reports stroke incidence rates in people with AF ranging from 2 to 10% (25–27).

Regionally, fragmented evidence has reported incidence of stroke among AF patients (28). Stroke in AF patients was reported to be 6.4% in Qatar (29), 9.8% in Iraq (30), 10.8% in Egypt (31), 13.5% in Saudi Arabia (32), and 14.0% in Palestine (33). A study by Zubaid. et al. (34) reported 9.0% stroke prevalence among AF patients at an extensive survey of 23 hospitals in six middle-east gulf countries (Bahrain, Kuwait, Qatar, Oman, United Arab Emirates, and Yemen).

It is in line with previous research to identify diabetes as a major risk factor for stroke in patients with AF. Diabetes mellitus is known to raise the risk of thromboembolism by a number of pathological processes, such as impaired fibrinolysis,

10.3389/fmed.2024.1408249

TABLE 2 One-year stroke incidence among patients with atrial fibrillation according to demographic and clinical characteristics, *N* = 2020.

	Stroke		Total, *N*	*p*-value
	No, *N* (%)	Yes, *N* (%)		
Age				0.049
<50	182 (98.9)	2 (1.1)	184	
50–59	270 (98.2)	5 (1.8)	275	
60–69	448 (97.2)	13 (2.8)	461	
70–79	717 (95.3)	35 (4.7)	752	
≥80	334 (96.0)	14 (4.0)	348	
Gender				0.555
Male	891 (96.3)	34 (3.7)	925	
Female	1,060 (96.8)	35 (3.2)	1,095	
Body mass index (Kg/m^2)				0.796
<25	422 (96.8)	14 (3.2)	436	
25–29.9	640 (97.0)	20 (3.0)	660	
≥30	738 (96.3)	28 (3.7)	766	
Current smoking				0.106
No	1,676 (96.3)	64 (3.7)	1740	
Yes	275 (98.2)	5 (1.8)	280	
Use of anticoagulant				0.626
No use	356 (97)	11 (3.0)	367	
Use of oral anticoagulant	1,595 (96.5)	58 (3.5)	1,653	
History of stroke				<0.001
No	1,662 (97.3)	46 (2.7)	1708	
Yes	287 (92.6)	23 (7.4)	310	
Hypertension				0.034
No	504 (98.1)	10 (1.9)	514	
Yes	1,447 (96.1)	59 (3.9)	1,506	
Diabetes				<0.001
No	1,115 (97.9)	24 (2.1)	1,139	
Yes	836 (94.9)	45 (5.1)	881	
Dyslipidemia				0.087
No	1,080 (97.2)	31 (2.8)	1,111	
Yes	871 (95.8)	38 (4.2)	909	
Cancer				0.669
No	1834 (96.6)	64 (3.4)	1898	
Yes	117 (95.9)	5 (4.1)	122	
Heart failure				0.432
No	1,440 (96.8)	48 (3.2)	1,488	
Yes	511 (96.1)	21 (3.9)	532	

hypercoagulability, and endothelial dysfunction (35). Patients diagnosed with diabetes had significantly higher hazard ratios for both ischemic and hemorrhagic strokes, according to research from the Emerging Risk Factors Collaboration (35, 36). As a result, it is especially important to manage AF patients who also have diabetes, with anticoagulant therapy being essential in preventing strokes, according to new guidelines from the American Heart Association (24). Furthermore, concomitant conditions such hypertension, diabetes, congestive heart failure, dyslipidemia, coronary heart disease, sleep apnea, tobacco use, and obesity that are linked to an elevated risk of AF have also been linked to an increased risk of stroke (37–40). These systemic vascular risk factors lead to atrial cardiomyopathy, which can induce AF and thromboembolism. Following the beginning of AF, the atrial contractile function and

10.3389/fmed.2024.1408249

TABLE 3 The one-year incidence of stroke among patients with atrial fibrillation according to prescribed medications, *N* = 2020.

	Stroke		Total, *N*	*p-value*
	No, *N* (%)	Yes, *N* (%)		
Oral anticoagulation				0.442
None	356 (97)	11 (3)	367	
Warfarin	628 (96.3)	24 (3.7)	652	
Dabigatran	111 (98.2)	2 (1.8)	113	
Rivaroxaban	462 (96.9)	15 (3.1)	477	
Apixaban	349 (96.1)	14 (3.9)	363	
Enoxaparin	44 (93.6)	3 (6.4)	47	
Edoxaban	1 (100)	0 (0)	1	
Antiplatelet				
Aspirin				0.209
No	1,220 (97)	38 (3)	1,258	
Yes	731 (95.9)	31 (4.1)	762	
Clopidogrel				0.711
No	1,698 (96.6)	59 (3.4)	1757	
Yes	253 (96.2)	10 (3.8)	263	
Ticagrelor				<0.001
No	1939 (96.7)	66 (3.3)	2005	
Yes	12 (80)	3 (20)	15	
Prasugrel				0.079
No	1946 (96.6)	68 (3.4)	2014	
Yes	5 (83.3)	1 (16.7)	6	
Any antiplatelet				0.208
No	1,193 (97)	37 (3)	1,230	
Yes	758 (95.9)	32 (4.1)	790	
Two antiplatelets				0.364
No	1833 (96.7)	62 (3.3)	1895	
Yes	118 (94.4)	7 (5.6)	125	
Other medications				
Beta Blocker				0.040
No	394 (98.3)	7 (1.7)	401	
Yes	1,557 (96.2)	62 (3.8)	1,619	
Amiodarone				0.035
No	1,584 (97)	49 (3)	1,633	
Yes	367 (94.8)	20 (5.2)	387	
CCBs				<0.001
No	1735 (96.4)	65 (3.6)	1800	
Yes	216 (98.2)	4 (1.8)	220	
Digoxin				0.972
No	1,643 (96.6)	58 (3.4)	1701	
Yes	308 (96.6)	11 (3.4)	319	
Flecainide, tambocor or encainide				0.248
No	1914 (96.5)	69 (3.5)	1983	
Yes	37 (100)	0 (0)	37	
RAAS				0.559

(Continued)

TABLE 3 (Continued)

	Stroke		Total, *N*	*p-value*
	No, *N* (%)	Yes, *N* (%)		
No	1,199 (96.8)	40 (3.2)	1,239	
Yes	752 (96.3)	29 (3.7)	781	
Statin				0.035
No	1,233 (97.2)	35 (2.8)	1,268	
Yes	718 (95.5)	34 (4.5)	752	
Diuretic				0.322
No	1,190 (96.9)	38 (3.1)	1,228	
Yes	761 (96.1)	31 (3.9)	792	

CCBs, Calcium channel blockers (diltiazem or verapamil), RAAS, renin-angiotensin-aldosterone system inhibitors (including Angiotensin-converting-enzyme inhibitors and Angiotensin receptor blockers).

TABLE 4 Multivariate analysis of factors associated with stroke among patients with atrial fibrillation, *N* = 2020.

Variable	OR	95% confidence interval	*p*-value
Diabetes (yes vs. no)	2.6	(1.5–4.4)	0.001
History of stroke (yes vs. no)	2.6	(1.5–4.6)	0.001

the underlying atrial cardiomyopathy deteriorate, raising the risk of thromboembolism and providing an explanation for the rise in stroke risk (41).

Despite the scope of our study, it's worth mentioning other perspectives for the mechanism attributing the cause of AF to stroke itself (42). Associations between abnormal autonomic innervation and AF have been established, with insults to the central nervous system, such as stroke, believed to play a significant role in AF's pathogenesis (43). AF is diagnosed in about 7% of acute ischemic stroke patients within the first 3–5 days post-stroke, increasing to 25% with prolonged monitoring, a condition termed AF diagnosed after stroke (AFDAS) (16, 44, 45). AFDAS has been classified into ECG-detected AF and AF detected on a prolonged cardiac monitor (PCM-detected AF), with ECG-detected AF associated with a higher risk of recurrent ischemic stroke (46). Several mechanisms, including cardiac autonomic nervous system imbalances and stroke location within the brain, have been proposed for AF development post-stroke (47, 48). Additionally, the 'catecholamine surge hypothesis' and Stroke-Heart syndrome have been identified as potential contributors (44). Nevertheless, until further evidence is available, patients with AFDAS should receive anticoagulation as per current clinical practice.

Our results highlight the significance of a comprehensive care strategy for patients with AF, encompassing the timely identification, evaluation, and treatment of coexisting metabolic disorders like diabetes to reduce the risk of stroke and avoid unfavorable health consequences. It may be possible to improve the overall cardiovascular prognosis of AF patients with diabetes by teaching them about the significance of medication adherence, dietary changes, and timely medical treatment (49, 50).

Likewise, a history of stroke was found to be an additional independent risk factor that was substantially linked to an elevated risk of stroke in individuals with AF. People who have had a prior stroke are known to have a higher chance of having another one; recurrence rates range from about 30 to 43% (51–53). One of the strongest independent risk factors linked to the occurrence of strokes was a prior history of stroke, which is consistent with earlier studies conducted in Jordan (17).

These results emphasize how important it is to implement focused interventions to improve stroke preventive methods in AF patients who have previously experienced a stroke. In this high-risk subgroup, improving adherence to anticoagulant therapy and lifestyle adjustments ought to be prioritized. Furthermore, it is critical to improve public understanding and awareness of stroke risk factors and management, especially in areas like Jordan where the stroke burden is still high (54–58). Raising awareness and gaining information can help identify stroke symptoms early and get patients access to timely care, which will ultimately improve patient outcomes and lessen the burden of stroke-related morbidity and mortality in the general community.

Our study is strong in two areas. It is the first study of its kind on AF conducted in the Middle East today. The majority of earlier research on AF was carried out five to 10 years ago. Second, the study is the first multi-center investigation of the warfarin population in the area.

To ensure transparency and scientific validity, this study does come with limitations. Observational studies may introduce bias which is mainly sampling bias. Not every research subject has been enrolled in the study in order. Additionally, while other patients in the nation may be managed by their family medicine physicians, internists, or general physicians, all study participants had their AF managed by cardiologists at health facilities. Moreover, extensive associations related to variations in exact treatment regimens with incidence of stroke among AF patients cannot be concluded. Also, the study did not specify sub-types of stroke nor the types of AF and included all types of both conditions in the final analysis.

Conclusion

In line with earlier studies conducted in the area, the 1-year stroke incidence among patients with AF in Jordan was determined to be roughly 3%. Aligned with their influence on stroke population, our

research highlights the importance of diabetes and prior stroke as important risk factors for stroke incidence in patients with AF. Nevertheless, more long-term studies are necessary to fully stratify the risk of diabetes, prior strokes, and their corresponding correlations with stroke in AF patients. Further research may also examine the possible influence of therapies aimed at these risk factors on reducing the incidence of stroke and enhancing the prognosis of individuals with AF. Improved knowledge of these correlations may help develop specialized treatment plans meant to lessen the impact of stroke morbidity and mortality among individuals with AF.

Data availability statement

Data supporting the findings of this research are available upon reasonable request from the corresponding author.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of the following participating healthcare settings: King Abdullah University Hospital, Amman Surgical Hospital, Arab Medical Center, Essra Hospital, Salt Medical Center, Islamic Hospital, Jordan Hospital, Khalidi Medical Center, King Hussein Medical Center, Prince Hamza Hospital, Istishari Hospital, Prince Hashem Hospital, Queen Alia Cardiac Center, Specialist Hospital, and Ibn Haitham Hospital. The participants provided their written informed consent to participate in this study.

Author contributions

TA-S: Conceptualization, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. OA: Data curation, Formal analysis, Methodology, Resources, Software, Writing – original draft, Writing – review & editing. YK: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. HA: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. OQ: Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. MJ: Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. AA: Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. RA-A: Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. TZ: Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. AH: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing.

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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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Temporal trends of ischemic stroke attributable to high fasting plasma glucose in China from the global burden of disease study 2019

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Background: Currently ischemic stroke poses a serious disease burden globally, and high fasting plasma glucose is one of the important risk factors. The aim of this study was to investigate the disease burden of ischemic stroke due to fasting glucose during 1990-2019 in China, to estimate the effect of age, period, and cohort on the trend of ischemic stroke disease burden, and to predict the disease burden of ischemic stroke in 2020-2030.

Methods: Ischemic stroke burden data were obtained by screening from the Global Burden of Disease Study 2019 (GBD 2019) database for high-risk populations in China. Annual average percentage change (AAPC) was calculated using the Joinpoint regression model to assess the trend of ischemic stroke burden between 1990 and 2019. Age-period-cohort models were introduced to estimate the independent effects of age, period, and cohort on ischemic stroke burden, and to predict the ischemic stroke burden in 2020-2030 based on Bayesian age-period-cohort models.

Results: From 1990 to 2019, the number of ischemic stroke deaths due to high fasting plasma glucose in China continued to increase with an AAPC of 3.61. Trends in age-standardized incidence rates did not show statistical significance. In the age-period-cohort analysis, the age effect of ischemic stroke burden showed a continuously increasing trend over the study period. The period effect showed an overall favorable trend over the study period. The overall and cohort effects for males showed an overall increasing trend, whereas the cohort effect for females showed a decreasing trend after a decreasing trend for the 1945 birth cohort.

Conclusions: This study found that ischemic stroke due to high fasting plasma glucose in China has generally fluctuated between 1990 and 2019, with a decreasing trend in recent years, and projections also suggest that it will continue to show a decreasing trend in the future. Age and period of birth were the main elements influencing the burden of disease, especially among the elderly and men. Policies should be used to promote the prevention of known risk factors and to strengthen health management for key populations.

KEYWORDS

ischemic stroke, high fasting plasma glucose, disease burden, age-period-cohort analyses, China

Introduction

Ischemic stroke is a disease caused by necrosis of brain tissue due to narrowing or occlusion of the arteries supplying blood to the brain and insufficient blood supply to the brain (1). Globally, China has the highest estimated risk of stroke and the risk continues to rise. In China, more than 70% of stroke cases are ischemic stroke (2). World Health Organization reports that ischemic stroke is the second leading cause of death in the world and the third leading cause of death in China (3). Diabetes and ischemic stroke are common conditions that often occur together. Additionally, diabetes is a serious public health problem in China. According to the International Diabetes Federation, there were about 140 million people with diabetes in China in 2021, and it is expected to reach 160 million by 2030 (4). Studies have shown that cardiovascular disease is the leading cause of death in diabetic patients. Ischemic stroke caused by hyperglycemia is a challenge for chronic disease management in China.

The Global Burden of Disease Study 2019 (GBD 2019) reported that stroke ranked third in both age-standardized mortality and disability-adjusted life years (DALYs) rates for all 204 diseases attributable to high fasting plasma glucose (5). High fasting plasma glucose leads to approximately 1/5 deaths and DALYs of cardiovascular disease. High fasting plasma glucose, as a risk factor for several chronic non-communicable diseases, such as diabetes, cardiovascular diseases, and tumors, has been shown to affect the organism through multiple pathways (6). Studies have shown that elevated glycemic can cause endothelial damage, increased blood viscosity, development of atherosclerosis, and increased lipids in plaques (7, 8). However, there is still a gap in research on the prevalence of ischemic stroke due to hyperglycemia in the Chinese population. Therefore, we leveraged the data from the GBD 2019, an updated global descriptive epidemiologic assessment of the disease, to systematically estimate and predict the trend in the burden of ischemic stroke attributable to high fasting plasma glucose in China from 1990 to 2030.

Methods

Data resource

The data for this study were derived from the Global Burden of Disease Study 2019 (GBD 2019), a study initiated by the Institute for Health Metrics and Evaluation (IHME) to estimate the global burden of different diseases and injuries. The GBD 2019 database includes data on 369 diseases, injuries, and their 87 risk factors for 204 countries and territories in 7 super-regions and 21 regions, covering the period 1990-2019 (3). More detailed information can be found on the official website (https://ghdx.healthdata.org/). In this study, data on the disease burden of ischemic stroke attributable to high fasting plasma glucose in China were retrieved from the database as the study population. The GBD 2019 study defines ischemic stroke based on the International Classification of Diseases, version 10 (ICD10) codes, which are coded as I63.0-I63.9. The GBD 2019 study defines a serum fasting glucose measurement of 4.8-8.4 mmol/L as high fasting plasma glucose (9). All the data were classified into 13 age groups (25-29, 30-34, …, 80-84, 85+), and age-standardized rates were calculated based on the GBD 2019 standard population.

Analysis of temporal trend

The analysis of the temporal trend of the ischemic stroke burden attributable to high fasting plasma glucose in China was based on a Joinpoint regression model (10). The Joinpoint regression model divides trends over a long time period into several sub-segments by identifying inflection points (Joinpoints) in the trend data. It then evaluates the overall trend after assessing the trend of each segment separately, using the annual percent change (APC) for each sub-segment trend and the average annual percent change (AAPC) for the overall trend. An APC and AAPC greater than 0 indicate an upward trend, while an APC and AAPC

less than 0 indicate a downward trend. In this study, we used the Joinpoint software (version 4.9.1.0; National Cancer Institute, Rockville, MD, US) to calculate the temporal trend of the ischemic stroke burden attributable to high fasting plasma glucose in China from 1990 to 2019, with a P-value of less than 0.05 considered statistically significant.

Age-period-cohort analysis and projection

The age-period cohort model (APC model) differs from traditional linear models in that it considers three dimensions simultaneously, estimating the effects of age, period, and birth cohort on the burden of ischemic stroke attributable to high fasting plasma glucose (11). The age effect describes the changes in an individual's life cycle as they age; the period effect reflects the trend of change in the society as a whole or the impact of events on the population; and the cohort effect emphasizes the role of the birth cohort to which an individual belongs on their disease burden (12). In this study, we conducted an APC analysis of ischemic stroke disease burden attributable to high fasting plasma glucose in China from 1990 to 2019 using a web tool (https://analysistools.cancer.gov/apc/) (13). In this study, the relative risks of age, period, and cohort effects were estimated for the 25-29 age group, the 2000-2004 burden of disease, and the 1945 birth cohort, respectively, as the reference group.

Next, we fitted the available data based on the Bayesian age-period-cohort model (BAPC model) to predict the burden of ischemic stroke attributable to high fasting plasma glucose in China in 2020-2030, and the BAPC model was able to better resolve the linear dependence among the three effects compared with the traditional APC model (14). The population data for 1990-2019 in this study were obtained from the GBD 2019 estimates, the population data for 2020-2030 were obtained from the projections for population data in the GBD study, and the calibration for the mortality and DALY rates were calculated based on the GBD 2019 standard population. Projections in this study were based on past trends and did not take into account changes in risk factors and interventions. BAPC modeling was performed using the BAPC package in the R 4.3.1.

Result

Temporal trend in the burden of ischemic stroke attributable to high fasting plasma glucose by sex in China

Table 1 shows the disease burden of ischemic stroke attributable to high fasting plasma glucose in China in 1990 and 2019. Overall, the cases of deaths increased from 60,400 in 1990 to 174,200 in 2019 (AAPC=3.61, $P<0.001$). In addition, ASMR increased from 9.94/100,000 in 1990 to 10.18/100,000 and ASDR increased from 182.62/100,000 to 192.34/100,000, but neither ASMR nor ASDR showed statistically significant changes, fluctuating upward and then downward fluctuations between 1990 and 2019 trend (Supplementary Table 1).

TABLE 1 Burden of ischemic stroke attributable to high fasting plasma glucose in China, 1990 and 2019.

	1990	2019	AAPC	*t*	*P*
Male					
Deaths (ten thousand)	3.01	10.28	4.19	11.01	<0.001
ASMR (per 100,000)	11.63	14.08	0.43	1.04	0.299
ASDR (per 100,000)	198.01	239.17	0.54	1.45	0.148
Female					
Deaths (ten thousand)	3.03	7.15	2.93	12.40	<0.001
ASMR (per 100,000)	8.91	7.51	-0.71	-3.22	0.001
ASDR (per 100,000)	172.08	155.46	-0.38	-1.43	0.152
Both					
Deaths (ten thousand)	6.04	17.42	3.61	11.43	<0.001
ASMR (per 100,000)	9.94	10.18	-0.02	-0.06	0.949
ASDR (per 100,000)	182.62	192.34	0.08	0.28	0.782

The burden of ischemic stroke attributable to high fasting plasma glucose across different age groups in China

Figure 1 shows the burden of ischemic stroke attributable to high fasting plasma glucose among different age groups in China in 1990 and 2019. In general, the disease burden of ischemic stroke was concentrated in people aged 70 years or older. Compared with 1990, both the number of deaths and the number of DALY person-years increased substantially in 2019, especially in the older age groups. However, this trend did not appear in the mortality and DALY rates. In 2019, ischemic stroke mortality rates were lower than in 1990 for both the under-75 age group and higher than in 1990 for the over-75 age group, and similarly, DALY rates for ischemic stroke were lower than in 1990 for both the under-70 age group and higher than in 1990 for the over-70 age group in 2019.

Age, period and cohort effects on the burden of ischemic stroke between 1990 to 2019

Figure 2 shows the estimated age, period, and cohort effects for ischemic stroke mortality and DALY rates. The age effects of mortality and DALY rates increase linearly and peak in later years. The overall period effect for ischemic stroke mortality in 1990-2019 is favorable. However, the period effect for males shows an unfavorable trend over the period 2005-2014. The DALY rates

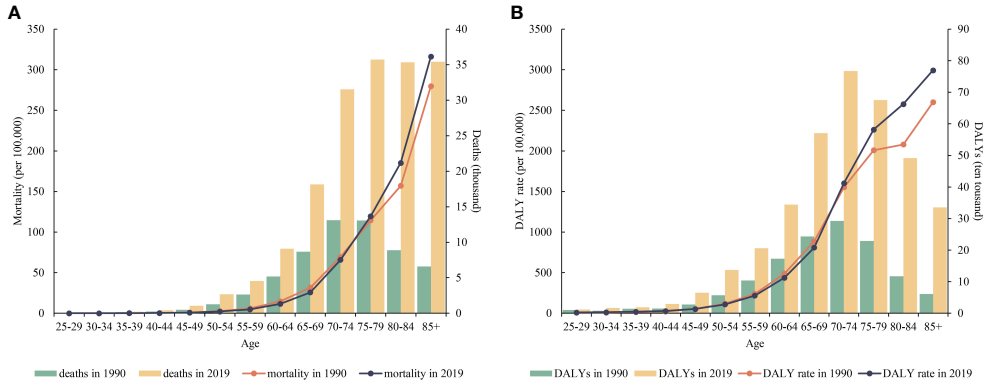

FIGURE 1
Burden of ischemic stroke attributable to high fasting plasma glucose in China, by age group, 1990 and 2019. **(A)** mortality (per 100,000) and deaths (thousand); **(B)**: DALYs rate (per 100,000) and DALYs (ten thousand).

for ischemic stroke show an overall favorable period effect from 1990-2019. However, the period effects both overall and for females showed unfavorable trends during 2005-2009, and for males during 2005-2014. The cohort effects for mortality and DALY rates showed fluctuating upward trends overall during 1990-2019. However, male and female burden cohort effects showed different trends. The disease burden for the male cohort effect showed a fluctuating increase and a surge among those born after 1945. For females, the disease burden cohort effect shows a fluctuating downward trend. Detailed information is shown in Supplementary Tables 2-4.

The projected burden of ischemic stroke attributable to high fasting plasma glucose, 2020-2030

According to the projections, the ASMR and ASDR for ischemic stroke attributable to high fasting plasma glucose in China are projected to show a similar and continuous decreasing trend from 2020 to 2030, as shown in Figure 3. Specifically, the ASMR is projected to decline from 10.26 per 100000 (with a 95% confidence interval of 9.52 to 11.00 per 100000) in 2020 to 8.66 per 100000

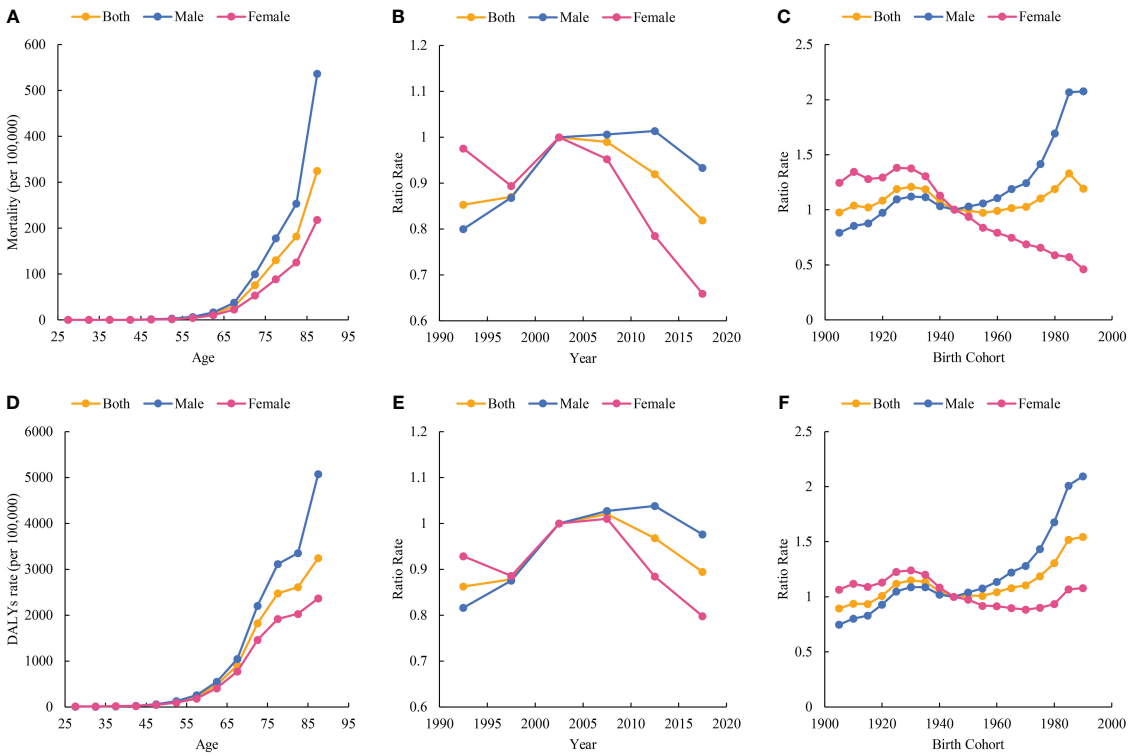

FIGURE 2
Parameter estimates of age, period, and cohort effects on burden of ischemic stroke attributable to high fasting plasma glucose and sex difference. **(A)** Age effect on mortality (per 100,000); **(B)** Period effects on mortality; **(C)** Cohort effects on mortality; **(D)** Age effect on DALYs rate (per 100,000); **(E)**: Period effects on DALYs rate; **(F)** Cohort effects on DALYs rate.

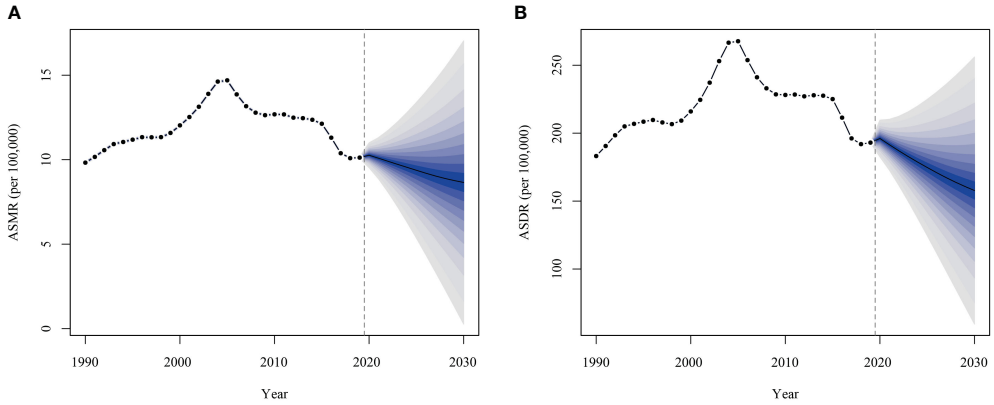

FIGURE 3
Projected burden of ischemic stroke attributable to high fasting plasma glucose in China, 2020-2030. **(A)** age-standardized mortality rate; **(B)** age-standardized DALYs rate.

(with a 95% CI of 0.26 to 17.05 per 100000) and the ASDR from 196.07 per 100000 (with a 95% CI of 182.56 to 209.57 per 100000) to 157.68 per 100000 (with a 95% CI of 60.41 to 254.95 per 100000) in 2020, as detailed in Supplementary Table 5.

Discussion

This study comprehensively analyzed the long-term disease burden of ischemic stroke attributable to high fasting plasma glucose in China from 1990 to 2019. We found that the number of deaths due to hyperglycemia-associated ischemic stroke decreased over 30 years, and age-standardized mortality and DALYs rates remained fluctuant. Notably, the burden rises sharply into old age, especially after age 70. The disease burden for females has shown the most significant decline in the last decade, while males show a more recent response. Predictions from the BAPC model suggested that the disease burden from hyperglycemia will continue to decline over the next 10 years. Against the background of an increasingly serious chronic disease management situation, stroke prevention as well as glycemic control are critical, particularly as the number of patients with diabetes continues to rise in China.

The AAPC analysis showed that age-standardized mortality and DALYs rate for ischemic stroke attributable to hyperglycemia remains stable over 30 years, which was in line with the temporal trend in the total burden of ischemic stroke (15). Compared with other major risk factors, high systolic blood pressure and ambient particulate matter pollution are the top 2 risk factors contributing to the burden and tend to be rising (15). This suggested that current diabetes management strategies in China were effective. A meta-analysis of 102 prospective studies showed that diabetes causes a twofold increase in the risk of multiple vascular diseases (16). Hyperglycemia induces an increase in inflammatory cytokines as well as monocytes and macrophages adhering to the endothelium, initiating oxidative stress and leading to endothelial dysfunction, sustained vascular injury, and ultimately atherosclerosis (17). High fasting glucose had also been demonstrated to cause pancreatic β-cell apoptosis, which reduced the effectiveness of glycemic control, leading to the development of diabetic complications (18). Given the huge burden of ischemic stroke in China, stroke care has become a national priority.

The China National Stroke Registry, initiated in 2007, completed a nationally representative stroke epidemiologic survey for 500,000 people in 2013. Additionally, the Phase 3 Stroke Survey Project, a multicenter, prospective, continuous, hospital-based registry study, began operations in 2015 to explore accurate early warning models for ischemic stroke and to assess healthcare delivery (19). The registry's purpose is to develop strategies for continuous improvement of stroke care in China, using real-time data. The results indicate that China's stroke incidence and mortality rates are among the highest in the world. Established in 2015, the National Stroke Center aims to have 3,000 hospitals join its network to promote stroke center construction and establish a regional emergency transport system for acute stroke (20). Studies have shown that the burden of stroke appears to grow more in rural areas (21), which may be related to differences in stroke awareness, quality of primary prevention, and socioeconomic status of the population. Improving stroke care and emergency transport capacity in rural hospitals is essential to reduce mortality from acute stroke attacks effectively. Considerable progress has been made in stroke care in China over the past decade, which corresponded to the declining trend in burden after 2010 in the period analysis. Prevention and control of ischemic stroke was a multifaceted and comprehensive collaborative process. China has emphasized the importance of glycemic control in both the investigation and treatment of stroke. However, significant gaps remain between guideline recommendations and clinical practice. Further emphasizing the role of glycemic control in stroke prevention could be beneficial.

Sex-based analysis showed a higher burden of ischemic stroke attributable to hyperglycemia in males than in females. Additionally, cohort effects analyses suggested an increasing trend of burden in males among individuals born after 1945, while the opposite trend was observed for burden in females. The burden attributed to hyperglycemia in males was often related to poor

lifestyle habits, such as higher frequency of smoking and unhealthy diet. Some studies suggested that gender differences in ischemic stroke depend on the patient's age, with the incidence of ischemic stroke being higher in males than in females during youth and middle age, and the incidence of ischemic stroke in females continued to increase after menopause (22). Although not identical to the findings of the present study, there is evidence that female patients have a worse functional prognosis for ischemic stroke and a reduced quality of life (23–25). National Health Interview Survey showed that the risk of diabetics suffering from cardiovascular disease was particularly acute in females (26). Another cohort study suggested that females with diabetes had a 27% higher risk of stroke than people with diabetes (27). Women tend to have a higher level of health consciousness (28), but diabetes seems to diminish or eliminate the female advantage and reveals that the burden on women should not be underestimated. Estrogen plays a protective role in many tissues, including the heart, brain, adipose tissue, and vascular system (29). With the onset of menopause and loss of estrogen, females should be aware of the risks for hyperglycemia-related ischemic stroke. Although the effects of diagnosis delay, inadequate treatment, and mechanisms of endothelial dysfunction linked to diabetes have been proposed (24), the drivers behind this gender difference remain largely unknown. Our study showed that males were still the main burden carriers, but the protection of females was also important. Recognition of the sex-specificity of stroke risk factors is an important way to move toward more effective and targeted stroke prevention strategies.

Age effects analysis indicated that the age-standardized mortality and DALYs rates increased rapidly with aging. As the aging population expands, the number of patients suffering from ischemic stroke will rise further (15). Age itself was an immutable and important risk factor for ischemic stroke, with differences in the effect of gender and diabetes mellitus (28). Diabetes serves as an independent risk factor for cardiovascular disease, and diabetes and ischemic stroke are two conditions that complement each other in terms of their cardiovascular risk implications. Both diseases cause inflammation, activate oxidative stress, induce endothelial damage, and promote cellular dysfunction and atherogenesis (17). Elderly stroke patients were long-term exposed to diabetes, which can cause chronic damage to the cerebral vasculature. Experimental stroke models also showed that chronic hyperglycemia led to cerebrovascular structural and functional defects (30). The elderly population was a heavily burden population, therefore early and ongoing screening for stroke and diabetes is essential.

Despite China's tireless efforts in the care and prevention of ischemic stroke over the past decade, the epidemic has not been halted In contrast, the disease and economic burden of diabetes in China has risen rapidly over the same period (31, 32). However, the BAPC model showed burden of ischemic stroke attributable to high fasting plasma glucose declined consistently over the next 10 years. These phenomena suggested that current stroke and diabetes management strategies in China were working. Over the last 30 years, China has undergone significant changes in industrialization, demographics, and healthcare. There is already a general consensus among national health organizations and widespread public support for reducing the burden of stroke and diabetes. Early detection of the course of chronic disease, patient education, and regular checkups are effective measures for burden mitigation and inform public health practitioners and policymakers.

Although GBD 2019 has used rigorous algorithms for data estimation, this study still has some limitations. First, the data used in GBD 2019 were based on estimates and not on real observations. As a result, the estimates derived from these data modeling methods may be biased. Moreover, given the limited evidence available, there may still be potential risk factors that affect the available results. Second, the present study analyzed data at the national level and lacked data reflecting provincial and urban-rural differences. Using more disaggregated data would enable the identification of region-specific differences. Third, age-period-cohort analyses were conducted over multiple five-year periods, which may have obscured some of the subtle variations in age, period, and cohort effects. Finally, BAPC analyses do not account for possible variations in factors such as interventions and the environment, which can lead to some bias in the prediction results.

Conclusion

In summary, we observed that ischemic stroke attributable to high fasting plasma glucose in China fluctuated overall from 1990-2019 and showed a decreasing trend in recent years and is projected to continue. Elderly people and men are the main groups affected by hyperglycemia. To reduce the burden of hyperglycemia-related ischemic stroke, the Chinese government should develop effective chronic disease management public health measures and policies to protect specific population groups.

Data availability statement

The data that support the findings of this study are available from the Global Burden of Disease 2019 database, which is publicly available. Requests to access the database should be directed to https://ghdx.healthdata.org/gbd-2019.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

LT: Conceptualization, Data curation, Methodology, Writing – original draft. LX: Data curation, Methodology, Writing – original draft. YL: Conceptualization, Writing – review & editing.

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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/fendo.2024.1408691/full#supplementary-material

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Correlation of silent brain infarcts and leukoaraiosis in middle-aged ischemic stroke patients: a retrospective study

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Background: Cerebrovascular diseases of the brain are usually defined by transient ischemic attacks and strokes. However, they can also cause brain injuries without neurological events. Silent brain infarcts (SBI) and leukoaraiosis are symptoms of both vascular and neurological abnormalities. This study aims to investigate the association between SBI, leukoaraiosis, and middle-aged patients with ischemic stroke.

Methods: A single-center retrospective study of 50 middle-aged, ischemic stroke patients were studied from November 2022 and May 2023. The patients were divided into two groups based on the presence or absence of leukoaraiosis. History taking, physical examination, brain CT scan, and MRI were all part of the diagnostic process. Metabolic syndrome (MetS) was also assessed through various factors. The statistical analysis included descriptive statistics, logistic regression analysis, and chi-square test.

Results: Out of the cohort comprising 50 patients, characterized by a mean age of 52.26 years (SD 5.29), 32 were male, constituting 64% of the sample. Among these patients, 26 individuals exhibited leukoaraiosis, with 17 of them (65.4%) also presenting with SBI. Moreover, within this cohort, 22 patients were diagnosed with MetS, representing 84.6% of those affected. The Multivariate logistic regression analysis showed a strong and independent association between leukoaraiosis and SBI. Individuals with leukoaraiosis were nearly five times more likely to have SBI compared to those without leukoaraiosis.

Conclusion: The study highlights leukoaraiosis as a significant risk factor for SBI, alongside MetS. Advanced imaging techniques have facilitated their detection, revealing a higher prevalence among stroke patients, particularly associated with age and hypertension. Further research is needed to fully understand their complex relationship and develop better management strategies for cerebrovascular diseases, ultimately improving patient outcomes.

KEYWORDS

cerebrovascular disease, ischemic stroke, leukoaraiosis, silent brain infarcts, silent lacunar infarcts, metabolic syndrome

Introduction

Historically, cerebrovascular disease of the brain has been defined by the symptoms and signs of transient ischemic attack or stroke. However, neuropathological studies in highly selected populations have revealed that vascular disease can cause brain injury in the absence of these acute neurological events. The advent of advanced brain-imaging techniques, such as computerized tomography (CT) and Magnetic resonance imaging (MRI), has allowed similar observations to be made in patient groups and healthy individuals, necessitating a reconsideration of the definition of cerebrovascular disease (1, 2). Signs of cerebral small vessel disease on conventional MRI include leukoaraiosis, recent subcortical lacunar infarcts (clinically symptomatic), lacunes (clinically silent), cerebral microbleeds, prominent perivascular spaces, and cerebral atrophy (3). These brain infarcts, while often asymptomatic, demand increased attention to mitigate the deleterious effects of vascular disease in the brain. Silent brain infarctions (SBIs) comprise two subtypes: lacunar and non-lacunar, resulting from small perforating artery occlusion and embolism or athero-sclerotic stenosis, respectively. The advancement of MRI technology enables the distinction between these subtypes (4–6). Therefore, exploring the distinct risk factors between the two subtypes, especially in the case of SBI, could lead to the development of specific prevention strategies, particularly for middle-aged individuals. Hypertension (HTN), apart from age, is the most widely accepted risk factor associated with SBI. Furthermore, the consistent correlation between hypertension and these infarcts suggests a critical role for hypertensive small-vessel disease in their pathogenesis (7). However, further research is necessary to better define the association between hypertension and brain infarcts, particularly in terms of preventing SBI through effective hypertension control. SBI and leukoaraiosis (LA) are intricate cerebral manifestations that have garnered considerable attention due to their association with diverse vascular and metabolic abnormalities. Hence, comprehending the intricate relationship between these cerebral alterations and MetS is of paramount importance for elucidating their underlying mechanisms and devising effective prevention and management strategies. Leukoaraiosis was observed through MRI and manifests as increased signal intensity in the white matter, often attributed to small vessel disease and pathological processes such as demyelination, gliosis, and vessel lipo hyalinosis (8). Conversely, SBIs denote brain tissue damage resulting from inadequate blood supply without acute neurological symptoms. Though often asymptomatic, SBIs pose a substantial risk for future stroke and cognitive decline (9). MetS plays a pivotal role in the development of LA and SBIs, operating through mechanisms such as vascular dysfunction, inflammation, insulin resistance, and dyslipidemia (10). The diagnosis of LA and SBIs primarily relies on MRI techniques, with fluid-attenuated inversion recovery (FLAIR) imaging sequences commonly employed to detect and assess the extent of white matter changes (11). Epidemiological data indicate a higher prevalence of LA and SBIs with advancing age, affecting a significant proportion of individuals over 65 years. This research aims to investigate the association between LA, SBIs, and middle-aged patients with ischemic stroke. The study focuses on middle-aged stroke patients to address the critical period in stroke epidemiology, capture a substantial portion of stroke cases in a relatively younger age group, identify early risk factors and pathophysiological mechanisms, and provide clinically relevant insights for healthcare providers in terms of risk stratification, diagnostics, and treatment strategies.

Methodology

Study design and setting

We conducted a retrospective single-center cohort study involving middle-aged ischemic stroke patients admitted to our university hospitals or followed up in our outpatient clinic between November 2022 and May 2023.

Participants selection

The study included middle-aged (35–64 years) (12) patients with ischemic stroke, who were divided into two groups. Group 1 consisted of patients with ischemic stroke associated with leukoaraiosis, while Group 2 consisted of patients with ischemic stroke not associated with leukoaraiosis.

The patients were diagnosed with ischemic stroke through a comprehensive process involving history taking, physical examination (including general and neurological examination), and a radiologic study using a brain CT scan.

To further evaluate the patients, the brain's magnetic resonance imaging (MRI) was performed to diagnose and grade leukoaraiosis. The MRI examinations were carried out using a 1.5 Tesla superconducting magnet system. The imaging protocol included T2-weighted, T1-weighted, and fluid-attenuated inversion recovery (FLAIR) images. Leukoaraiosis was defined as a white matter lesion showing hyperintensity on T2-weighted and FLAIR images without prominent hypointensity on TI-weighted images. The grading of leukoaraiosis was done according to the Atherosclerosis Risk in Communities Study (ARIC) criteria (13–15).

MetS assessment involves the evaluation of various factors, including impaired fasting glucose (IFG), elevated blood pressure (BP), hypertriglyceridemia (hyper-TG), low high-density lipoprotein cholesterol (HDL-C), and waist circumference. IFG was defined as a fasting glucose level of 110 mg/dL or higher, and elevated BP was determined by systolic BP of 130 mm Hg or higher and diastolic BP of 85 mm Hg or higher. Hyper-TG was identified based on serum triglyceride levels of 150 mg/dL or higher, while low HDL-C was defined as serum HDL-C levels below 40 mg/dL for men and below 50 mg/dL for women. Waist circumference was measured at a specific anatomical point (16).

Data collection

The data collected for this study included: (1) Demographics: Age and gender of the participants. (2) Medical Conditions: Presence of SBI and leukoaraiosis (3) Metabolic Syndrome (MetS): Presence or absence of MetS, as well as its individual components including Elevated blood pressure (BP), Impaired fasting glucose (IFG), Low high-density lipoprotein cholesterol (HDL-C), Hypertriglyceridemia (Hyper-TG), Large waist circumference (WC) 4. Atherosclerosis

Risk in Communities (ARIC) Grades: The severity of atherosclerosis was graded as none, minimal, mild, moderate, or severe.

Statistical analysis

The statistical analysis of the study involved the use of descriptive statistics, such as mean, standard deviation (SD), frequencies (N), and percentages (%), to summarize the data. MetS component conditions were treated as dichotomous variables based on NCEP/ATP III-defined cut points. The three grades of leukoaraiosis (severe, moderate, and mild) were combined due to a small number of subjects with those specific grades. The chi-square test examined statistically significant relationships between different qualitative data. Logistic regression analysis was performed to estimate the association between each variable and leukoaraiosis while controlling for other variables; it was expressed using odds ratio (OR) and 95% CI. A p-value of less than 0.05 was considered significant, while a p-value of less than 0.01 was considered highly significant. R (version 4.3.1)was used for all analyses.

Sample size

The study included 50 middle-aged ischemic stroke patients. This sample size was determined based on the availability of data from our hospital records during the study period. A post-hoc power analysis was performed to assess the study's power to detect a statistically significant association between leukoaraiosis and silent brain infarcts (SBI) given the observed effect size.

Results

Participant characteristics

The study included 50 ischemic stroke patients with a mean age of 52.26 (± 5.29) years with 32 (64%) male patients. The participants were divided into two groups: a control group (26 participants) without leukoaraiosis and an experimental group (24 participants) with leukoaraiosis. The median age was higher in patients with SBI compared to the SBI-negative group (p =0.149), with males' predominance in the SBI group (75%, p =0.207).

Association of silent brain infarcts with leukoaraiosis and other risk factors

MetS was significantly more common in the SBI-positive group (87.5%) compared to the negative group (38.5%, p =0.001). HTN and impaired fasting glucose (IFG) were also significantly more common in the SBI-positive group (p =0.001 and p <0.001, respectively). The population shows that 65.4% of those without SBI had no atherosclerosis (grade None) compared to only 29.2% of those with SBI. The presence of elevated blood pressure (BP), IFG, hypertriglyceridemia (hyper-TG), large waist circumference (WC), leukoaraiosis, and SBI were all significantly higher in individuals with MetS than those without MetS. Regarding the ARIC grade, individuals with MetS had a higher prevalence of leukoaraiosis than those without MetS (p =0.002). The median age of those with leukoaraiosis (55 years) was significantly higher than those without (50 years); (p =0.001). In addition, the percentage of individuals with MetS, HTN, IFG, and SBI was significantly higher in the group with leukoaraiosis compared to the group without leukoaraiosis. The demographics of the included participants are shown in Table 1.

The study found that 48% of patients had SBI, and 52% had leukoaraiosis. The chi-square test revealed that the association between leukoaraiosis and SBI was not statistically significant (p =0.13). In terms of sex, 36% of patients were female, and 64% were male. The chi-square test revealed a significant association between sex and SBI (p =0.013), with a higher percentage of male patients having silent brain infarction than female patients (Table 2).

Association of leukoaraiosis with MetS and its components

In terms of MetS, 62% of patients had MetS, and the chi-square test revealed a significant association between MetS and SBI (p =0.000). Patients with MetS had a higher percentage of SBI than patients without MetS. Similarly, MetS components, including elevated blood pressure, impaired fasting glucose, and large waist circumference, were significantly associated with silent brain infarction. The ARIC grades also showed a significant association with SBI (p =0.019), with patients in higher ARIC grades having a higher percentage of silent brain infarction. Overall, the study found that SBI was significantly associated with sex, MetS, MetS components, and the ARIC grades. However, there was no significant association between leukoaraiosis and SBI.

The results indicate that there was a significant association between MetS and leukoaraiosis (p =0.001), as well as between some of its components (elevated BP and IFG) and leukoaraiosis (p =0.004 and p =0.010, respectively). However, there was no significant association between sex or large WC and leukoaraiosis (Table 2).

Severity of leukoaraiosis and MetS

The severity of leukoaraiosis was significantly associated with the presence of MetS, as well as its components, with a higher proportion of participants with more severe leukoaraiosis having MetS or elevated BP or IFG (Table 2).

Multivariable analysis of SBI and leukoaraiosis

The results of the analysis showed that leukoaraiosis is significantly associated with SBI with an unadjusted odds ratio (OR) of 4.587 (p =0.012). The adjusted OR for the other predictors does not change the significance of the association between leukoaraiosis and SBI, indicating that this association is independent of the other predictors in the model. Therefore, the results emphasize the importance of considering SBI as a risk factor for leukoaraiosis. The results suggest that MetS, elevated BP, IFG, and leukoaraiosis are significantly associated with an

TABLE 1 Demographics of the included participants.

		Frequency (*n*[a])	Percentage (%[b])
Characteristics (n = 50)			
Age, Mean (SD)		52.26 (5.29)	
Gender	Male	32	64
	Female	18	36
SBI		24	48
Leukoaraiosis		26	52
MetS		31	62
MetS Components	Elevated BP[c]	31	62
	IFG[d]	28	56
	Low HDL-C[e]	25	50
	Hyper-TG[f]	17	34
	Large WC[g]	24	48
The ARIC grades[h]			
None		24	48
Minimal		10	20
Mild		6	12
Moderate		6	12
Severe		4	8
SBI			
	Negative	**Positive**	**P-value**
N	26	24	
Age, Median [IQR]	51.50 [49.25, 54.75]	55.00 [48.75, 58.25]	0.149
Gender (M), *N* (%)	14 (53.8)	18 (75.0)	0.207
MetS, *N* (%)	10 (38.5)	21 (87.5)	0.001*
Elevated BP[c]	8 (30.8)	20 (83.3)	0.001*
IFG[d]	6 (23.1)	19 (79.2)	<0.001*
Low HDL-C[e]	9 (34.6)	8 (33.3)	1
Hyper-TG[f]	11 (42.3)	13 (54.2)	0.579
Large WC[g]	16 (61.5)	19 (79.2)	0.294
The ARIC grades[h], *N* (%)			0.019*
None	17 (65.4)	7 (29.2)	-
Minimal	6 (23.1)	4 (16.7)	-
Mild	2 (7.7)	4 (16.7)	-
Moderate	1 (3.8)	5 (20.8)	-
Severe	0 (0.0)	4 (16.7)	-
Leukoaraiosis, *N* (%)	9 (34.6)	17 (70.8)	0.023*
MetS			
	Negative	**Positive**	**P-value**
N	19	31	
Age, Median [IQR]	51.00 [49.00, 54.50]	54.00 [49.50, 58.00]	0.182
Gender (M), *N* (%)	10 (52.6)	22 (71.0)	0.314
Elevated BP[c]	4 (21.1)	24 (77.4)	<0.001*
IFG[d]	4 (21.1)	21 (67.7)	0.004*
Low HDL-C[e]	3 (15.8)	14 (45.2)	0.069
Hyper-TG[f]	3 (15.8)	21 (67.7)	0.001*

(Continued)

TABLE 1 (Continued)

		Frequency (n^a)	Percentage (%[b])
Large WC[g]	10 (52.6)	25 (80.6)	0.075
The ARIC grades[h], *N* (%)			0.013*
None	15 (78.9)	9 (29.0)	-
Minimal	2 (10.5)	8 (25.8)	-
Mild	1 (5.3)	5 (16.1)	-
Moderate	0 (0.0)	6 (19.4)	-
Severe	1 (5.3)	3 (9.7)	-
Leukoaraiosis, *N* (%)	4 (21.1)	22 (71.0)	0.002*
SBI	3 (15.8)	21 (67.7)	0.001*
Leukoaraiosis			
	Negative	**Positive**	**P-value**
N	24	26	
Age, Median [IQR]	50.00 [47.00, 53.00]	55.00 [51.50, 58.75]	0.001*
Gender (M), *N* (%)	14 (58.3)	18 (69.2)	0.612
MetS, *N* (%)	9 (37.5)	22 (84.6)	0.002*
Elevated BP[c]	8 (33.3)	20 (76.9)	0.005*
IFG[d]	7 (29.2)	18 (69.2)	0.011*
Low HDL-C[e]	7 (29.2)	10 (38.5)	0.693
Hyper-TG[f]	9 (37.5)	15 (57.7)	0.252
Large WC[g]	16 (66.7)	19 (73.1)	0.853
SBI	7 (29.2)	17 (65.4)	0.023*

[a]Frequency, [b]Percentage, [c]Blood Pressure, [d]Impaired Fasting Glucose, [e]High-density lipoprotein-cholesterol, [f]Triglyceride, [g]Waist Circumflex, [h]Atherosclerosis Risk in Communities grades, SBI, Silent brain infarct; MetS, Metabolic syndrome.

increased risk of SBI (OR = 4.587 [0.985–8.190]; $p = 0.012$). Therefore, these findings suggest that individuals with leukoaraiosis may be at an increased risk for SBI and may benefit from closer monitoring and potential interventions to reduce their risk. The OR and 95% confidence intervals for the association between various risk factors of SBI and leukoaraiosis are shown in Table 3.

Discussion

The principal finding of the study is the significant association between leukoaraiosis and SBI, indicating that leukoaraiosis should be considered a significant risk factor for SBI. Additionally, MetS, particularly its components such as elevated blood pressure and impaired fasting glucose, showed a strong association with both leukoaraiosis and SBI. These findings underscore the importance of recognizing and managing these risk factors to potentially reduce the incidence of SBI and their associated complications.

SBIs and leukoaraiosis are common findings in patients with stroke. Several studies aimed at estimating the percentage of patients with SBIs or leukoaraiosis that presented with stroke. Putaala et al. found that in patients between the ages of 15–49 with first-ever ischemic stroke, 13% had one or more SBIs. The study also found that 5% presented with leukoaraiosis and 3% presented with both. However, these numbers seem to increase with age. In the previously mentioned study, those between the ages of 15 and 24 did not present with SBIs or leukoaraiosis. The highest percentage of patients with SBIs or leukoaraiosis were those aged 45–49. Approximately 27% of patients had SBIs or leukoaraiosis, or both (17). Several studies also noticed an increase in the occurrence of SBIs and leukoaraiosis with age. A study conducted in Japan found that 57% of stroke patients with a mean age of 69, had SBIs (18). Similarly, our study found that patients with leukoaraiosis had a higher age, 55, compared to those without leukoaraiosis, 50. This is consistent was previously published studies which found that leukoaraiosis incidence increases with age (19, 20). Patients with SBIs also had a higher age when compared to those without.

Previous studies have shown various results regarding the incidence of SBIs in men compared to women. Generally, results of previous studies have shown that females were more likely to suffer from SBIs when compared to males (21). Two studies have found that females were 30%–40% more likely to suffer from SBIs than males (2, 11, 21).

Our study found that a higher percentage of males were more likely to have SBIs. A comparative study examined the relationship between sex differences in the risk profile and SBIs. It states that both brain infarction and SBIs were more common in males. However, after adjusting other cofounders, they found a difference in the occurrence of SBI occurrence males and females disappeared. Our study has also found no difference in the occupancy of leukoaraiosis between men and women. However, previous studies

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TABLE 2 Summary of the association between leukoaraiosis and silent brain infarction with respect to demographic and metabolic variables, metabolic syndrome components, and ARIC grades.

Leukoaraiosis		**SBI**					
		Negative		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		17	34	7	14	24	48
Positive		9	18	17	34	26	52
Total		26	52	24	48	50	100
Chi-square	X^2	2.424					
	P-value	0.149					
Sex		**SBI**					
		Negative		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Female		12	24	6	12	18	36
Male		14	28	18	36	32	64
Total		26	52	24	48	50	100
Chi-square	X^2	6.559					
	P-value	0.013*					
MetS		**SBI**					
		Negative		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		16	32	3	6	9	38
Positive		10	20	21	42	31	62
Total		26	52	24	48	50	100
Chi-square	X^2	12.738					
	P-value	0.000*					
MetS Components		**SBI**					
Elevated BP[c]		**Negative**		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		18	36	4	8	22	44
Positive		8	16	20	40	28	56
Total		26	52	24	48	50	100
Chi-square	X^2	13.994					
	P-value	0.000*					
IFG[d]		**Negative**		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		20	40	5	10	25	50
Positive		6	12	19	38	25	50
Total		26	52	24	48	50	100
Chi-square	X^2	15.705					
	P-value	0.000*					
Low HDL-C[e]		**Negative**		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		17	34	16	32	33	66
Positive		9	18	8	16	17	34
Total		26	52	24	48	50	100

(Continued)

TABLE 2 (Continued)

Chi-square	X^2	0.009					
	P-value	1.000					
Hyper-TG[f]		**Negative**		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		15	30	11	22	26	52
Positive		11	22	13	26	24	48
Total		26	52	24	48	50	100
Chi-square	X^2	0.703					
	P-value	0.572					
Large WC[g]		**Negative**		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		10	20	5	10	15	30
Positive		16	32	19	38	35	70
Total		26	52	24	48	50	100
Chi-square	X^2	1.847					
	P-value	9.224					
The ARIC[h] **grades**		**SBI**					
		Negative		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
None		17	34	7	14	24	48
Minimal		6	12	4	8	10	20
Mild		2	4	4	8	6	12
Moderate		1	2	5	10	6	12
Severe		0	0	4	8	4	8
Total		26	52	24	48	50	100
Chi-square	X^2	11.839					
	P-value	0.019*					
SBI		**Leukoaraiosis**					
		Negative		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Negative		17	34	9	18	26	52
Positive		70	14	17	34	24	48
Total		24	48	26	52	50	100
Chi-square	X^2	6.559					
	P-value	0.13					
Sex		**Leukoaraiosis**					
		Negative		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]
Female		10	20	8	16	18	36
Male		14	28	18	36	32	64
Total		24	48	26	52	50	100
Chi-square	X^2	0.643					
	P-value	0.557					
MetS		**Leukoaraiosis**					
		Negative		**Positive**		**Total**	
		N[a]	**%**[b]	**N**[a]	**%**[b]	**N**[a]	**%**[b]

(Continued)

TABLE 2 (Continued)

Negative		15	30	4	8	19	38
Positive		9	18	22	44	31	62
Total		24	48	26	52	50	100
Chi-square	X^2	11.759					
	P-value	0.001*					
MetS Components		**Leukoaraiosis**					
Elevated BP[c]		**Negative**		**Positive**		**Total**	
		N[a]	**%[b]**	**N[a]**	**%[b]**	**N[a]**	**%[b]**
Negative		16	32	6	12	22	44
Positive		8	16	20	40	28	56
Total		24	48	26	52	50	100
Chi-square	X^2	9.624					
	P-value	0.004*					
IFG[d]		**Negative**		**Positive**		**Total**	
		N[a]	**%[b]**	**N[a]**	**%[b]**	**N[a]**	**%[b]**
Negative		17	34	8	16	25	50
Positive		7	14	18	36	25	50
Total		24	48	26	52	50	100
Chi-square	X^2	8.013					
	P-value	0.010*					
Low HDL-C[e]		**Negative**		**Positive**		**Total**	
		N[a]	**%[b]**	**N[a]**	**%[b]**	**N[a]**	**%[b]**
Negative		17	34	16	32	33	66
Positive		7	14	10	20	17	34
Total		24	48	26	52	50	100
Chi-square	X^2	0.480					
	P-value	0.559					
Hyper-TG[f]		**Negative**		**Positive**		**Total**	
		N[a]	**%[b]**	**N[a]**	**%[b]**	**N[a]**	**%[b]**
Negative		15	30	11	22	26	52
Positive		9	18	15	30	24	48
Total		24	48	26	52	50	100
Chi-square	X^2	2.039					
	P-value	0.171					
Large WC[g]		**Negative**		**Positive**		**Total**	
		N[a]	**%[b]**	**N[a]**	**%[b]**	**N[a]**	**%[b]**
Negative		8	16	7	14	15	30
Positive		16	32	19	38	35	70
Total		24	48	26	52	50	100
Chi-square	X^2	0.244					
	P-value	0.760					
The ARIC[h] grades		**Leukoaraiosis**					
		Negative		**Positive**		**Total**	
		N[a]	**%[b]**	**N[a]**	**%[b]**	**N[a]**	**%[b]**
None		24	48	0	0	24	48
Minimal		0	0	10	20	10	20

(Continued)

TABLE 2 (Continued)

Mild		0	0	6	12	6	12
Moderate		0	0	6	12	6	12
Severe		0	0	4	8	4	8
Total		24	48	26	52	50	100
Chi-square	X^2	50.000					
	P-value	0.000*					

*$p < 0.05$. [a]Frequency, [b]Percentage, [c]Blood Pressure, [d]Impaired Fasting Glucose, [e]High-density lipoprotein-cholesterol, [f]Triglyceride, [g]Waist Circumflex, [h] Atherosclerosis Risk in Communities grades. SBI, Silent brain infarct; MetS, Metabolic syndrome.

TABLE 3 Multivariate logistic regression analysis showing predictors of (A) Silent Brain Infarcts, (B) MetS, and (C) Leukoaraiosis.

Dependent variable	Independent variable	Unadjusted OR[a]	95% confidence interval (CI)	*p*-value
A				
SBI	Age	1.081	(−1.003, 3.165)	0.171
	Gender	2.571	(−0.064, 5.206)	0.124
	MetS[b]	11.200	(7.108, 15.292)	0.001*
	Elevated BP[c]	11.250	(7.336, 15.164)	0.000*
	IFG[d]	12.667	(8.761, 16.573)	0.000*
	Low HDL-C[e]	0.944	(−2.624, 4.512)	0.924
	Hyper-TG[f]	1.612	(−1.861, 5.084)	0.403
	Large WC[g]	2.375	(−0.389, 5.139)	0.179
	Leukoaraiosis	4.587	(0.985, 8.190)	0.012*
B				
MetS[b]	Age	1.25944	(0.207227, 7.654423)	0.002*
	Gender	1.607143	(0.208937, 12.358964)	0.42
	MetS[b]	9.166667	(2.297217, 36.614768)	0.001*
	Elevated BP[c]	6.666667	(1.930124, 22.978844)	0.002*
	IFG[d]	5.464286	(1.465766, 20.441014)	0.006*
	Low HDL-C[e]	1.517857	(0.312961, 7.364701)	0.489
	Hyper-TG[f]	2.272727	(0.506725, 10.178785)	0.156
	Large WC[g]	1.357143	(0.324471, 5.679855)	0.621
	Silent Lacunar Infarcts	4.587302	(1.329704, 15.810814)	0.01*
C				
Leukoaraiosis	Age	1.25944	(0.181007, 2.337873)	0.002*
	Gender	1.607143	(−2.862666, 6.076952)	0.423
	MetS[b]	9.166667	(5.281997, 13.05134)	0.001*
	Elevated BP[c]	6.666667	(2.962831, 10.3705)	0.002*
	IFG[d]	5.464286	(1.853614, 9.074957)	0.006*
	Low HDL-C[e]	1.517857	(−2.125023, 5.160737)	0.489
	Hyper-TG[f]	2.272727	(−0.774381, 5.319834)	0.156
	Large WC[g]	1.357143	(−2.428864, 5.14315)	0.621
	Silent Lacunar Infarcts	4.587302	(0.812214, 8.36239)	0.01*

*$p < 0.05$. [a]Odds Ratio, [b]Metabolic Syndrome, [c]Blood Pressure, [d]Impaired Fasting Glucose, [e]High-density lipoprotein-cholesterol, [f]Triglyceride, [g]Waist Circumflex, [h]Atherosclerosis Risk in Communities grades. SBI, Silent brain infarct; MetS, Metabolic syndrome.

have shown that in stroke patients, women were more likely to have leukoaraiosis. In non-stoke patients, the difference was not established (22).

MetS refers to the combination of hypertension, diabetes, and obesity. Previous studies have shown that MetS is associated with both SBIs and leukoaraiosis (23–26). Our study has confirmed

these results. 62% of the stroke patients included in the study suffered from MetS. Hypertension was found to be the most dominant component. The percentage was greater in patients with SBIs and leukoaraiosis. MetS was present in 87.5% of patients was SBIs and was also found in patients with leukoaraiosis at higher levels. Impaired fasting glucose and large waist circumference were also significantly associated with silent brain infarction. However, no association was found between large waist circumference and leukoaraiosis. This is consistent with other studies in the region, which showed that an association exists between MetS and leukoaraiosis. Elevated blood pressure and impaired fasting glucose were also independently associated. However, the large waste circumference was not (27). This study emphasizes the association between MetS and two specific conditions: leukoaraiosis and SBI. These conditions are likely caused by a common underlying vascular issue, namely atherosclerosis, which leads to small vessel disease (28). SBI was also found to be associated with a greater degree of leukoaraiosis.

SBIs and leukoaraiosis were also present in the general population but at fewer levels. A systematic review of published cohorts found that most studies have shown that SBIs occur between 10% and 20% in the general population (29). Similarly, it was found that the incidence of SBIs increases with age, with 35% of those over the age of 80 suffering from SBIs. The study also evaluated the effect of hypertension, dyslipidemia, and diabetes mellitus on the occurrence of SBIs. Hypertension was shown to impact the occurrence of SBIs and is considered one of the two most important risk factors. However, dyslipidemia and diabetes mellitus have shown various results. Leukoaraiosis incidence was also studied in the general population. It was found that 50.9% of healthy individuals between 44 and 48 had leukoaraiosis (30). The incidence also increases with age. Leukoaraiosis was found in 95% of people between the ages of 60–90. Although the pathogenesis of leukoaraiosis is unclear, it is known to be associated with dementia, stroke, abnormal gait, and disability (31). Leukoaraiosis is also used as an MRI marker for small vessel disease progression and is associated with worse stroke outcomes (32).

We recommend conducting longitudinal studies to explore the progression of SBI and leukoaraiosis over time in middle-aged stroke patients. Additionally, investigating the effectiveness of various treatment approaches, including lifestyle interventions and pharmacotherapy, in preventing or slowing down the development of these silent brain lesions would be valuable. Furthermore, assessing the association between silent brain lesions and long-term clinical outcomes, such as cognitive decline and recurrent stroke risk, is crucial for informing patient management strategies.

Limitations

This study is subject to several limitations. Firstly, the sample size is relatively small, consisting of only 50 patients from a single center, which may limit the generalizability of the findings to larger populations. Another limitation is the potential oversight of clinically silent lacunes' impact on cognitive performance, despite their significance in cerebral small vessel disease. Patients with a first-ever lacunar stroke often exhibit minor neuropsychological alterations related to these silent lacunar infarcts (33). Furthermore, this study employs a retrospective cohort design, which hinders the establishment of causal associations between variables. Future research should consider prospective study designs to better elucidate the relationships between various factors.

Conclusion

SBI and leukoaraiosis observation have been made easier by developing newer imaging techniques, such as more advanced CT and MRI modalities. SBIs and leukoaraiosis were found to be associated with age and hypertension. They were also found in higher percentages in stroke patients compared to the general population. The relationship between SBIs, leukoaraiosis, and MetS is a complex relationship that requires further study in order to understand the underlying mechanism and provide better management, prevention, and treatment options. Through a better understanding of the underlying mechanisms of cerebrovascular disease, better clinical practices can be achieved which will provide better outcomes to all patients.

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 humans were approved by Ethics Committee of Al-Azhar Faculty of Medicine (approval number: Near-Med-0079). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. NS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YA: Writing – original draft, Writing – review & editing. AR: Writing –

original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. FM: Writing – original draft, Writing – review & editing. EA: Writing – original draft, Writing – review & editing. A-GF: Writing – original draft, Writing – review & editing. MZ: Writing – original draft, Writing – review & editing. AE-A: Writing – original draft, Writing – review & editing. OF: Writing – original draft, Writing – review & editing. MH: Writing – original draft, Writing – review & editing.

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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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Cardiac thrombus detected by cardiac computed tomography angiography in patients with acute ischemic stroke: a meta-analysis

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Background: Detecting cardiac thrombus in patients with acute ischemic stroke is crucial in determine stroke etiology and predict prognosis. However, the prevalence of cardiac thrombus in patients with acute ischemic stroke is unclear.

Object: This study aimed to evaluate the prevalence of cardiac thrombus detected by cardiac computed tomography angiography (CCTA) in patients with acute ischemic stroke through a meta-analysis.

Methods: Embase, Web of Science, MEDLINE, and CENTRAL were searched from January 1, 2000, to May 1, 2024. We included observational studies enrolling patients who underwent CCTA within 1 month following acute ischemic stroke, and reporting the incidence of cardiac thrombi on CCTA. Meta-analysis was performed using random effects models.

Results: Twenty-six studies involving 4,516 patients were identified. The pooled prevalence of cardiac thrombus detected on CCTA in patients with acute ischemic stroke was 0.08 (95% confidence interval [CI]: 0.06–0.11). Inter-study heterogeneity was high (I^2 = 88%). Among stroke type, the prevalence of atrial fibrillation, timing of CCTA and CCTA technology, the prevalence of atrial fibrillation was the only factor associated with cardiac thrombi prevalence detected by CCTA. However, atrial fibrillation was not documented in 41.5% of the patients with cardiac thrombi.

Conclusion: CCTA is a useful non-invasive imaging approach for detecting cardiac thrombus in patients with acute ischemic stroke, which might be helpful to determine the stroke etiology.

KEYWORDS

atrial fibrillation, cardiac computed tomography angiography, stroke, thrombus, cardioembolism

1 Introduction

Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality worldwide. Identifying the etiology of stroke is crucial for preventing recurrence (1). However, in approximately one-third of AIS cases, the cause remains unknown after a systemic evaluation, classifying these as cryptogenic strokes (1). Cardioembolism might explain some cryptogenic strokes; these patients may require anticoagulant therapy instead of antiplatelet therapy. Evaluating cardiac thrombosis is essential for identifying the etiology of stroke (2). Furthermore, cardiac thrombus detected by imaging modality is a major contributor to poor prognosis in patients with cardioembolic stroke (3, 4). Therefore, detecting cardiac thrombosis is crucial in the acute stroke setting.

Traditionally, echocardiography (both transthoracic and transesophageal) has been the primary imaging modality for evaluating cardiac thrombosis. Although transthoracic echocardiography (TTE) is convenient, its sensitivity in detecting cardiac thrombosis, especially left atrial appendage (LAA) thrombosis, is low (5). Due to its proximity to the left atrial appendage, transesophageal echocardiography (TEE) is the standard method for evaluating thrombus in the left atrium (LA) and LAA (5). However, TEE is often performed days after the onset of AIS, typically following intravenous thrombolysis and anti-thrombosis treatment, which may reduce the likelihood of detecting cardiac thrombus. Moreover, TEE is a semi-invasive, time-consuming, and patient-unfriendly procedure.

Cardiac computed tomography angiography (CCTA) provides a non-invasive alternative, allowing for a detailed assessment of potential embolic sources, and can be performed in the hyperacute period (6, 7). However, the use of CCTA in the acute stroke setting remains controversial. This meta-analysis aimed to evaluate the prevalence of intracardiac thrombi detected by CCTA in patients with AIS and to offer insights into its integration into clinical protocols for the management of AIS.

2 Methods

The study was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (8). Detailed PRISMA reporting is shown in Supplementary Table S1.

2.1 Search strategy and eligibility criteria

We systematically searched Embase, Web of Science, MEDLINE, and CENTRAL for studies reported from January 1, 2000, to May 1, 2024, using various permutations of ischemic stroke and cardiac CT angiography. Supplementary Table S2 provides the detailed search strategy. No language restrictions were imposed. Additionally, we checked the reference lists of all the key articles for further eligible studies.

Studies were included if they met the following criteria: (1) enrolled patients with AIS (2), the patients underwent CCTA during the AIS admission, and (3) reported the incidence of cardiac thrombi on CCTA. Duplicate reports were excluded from analysis. For studies that contained overlapping populations, the largest study was considered for analysis. Abstracts of meeting proceedings were excluded unless full texts were published in a peer-reviewed journal. Eligible articles were selected independently by two investigators, with disparities resolved through discussion.

2.2 Data extraction and quality assessment

Two independent authors extracted following data from each eligible study: the year of publication, sample size, study design, patient characteristics, CT technology, interval between stroke and CCTA and incidence and the location of cardiac thrombus on CCTA.

Two independent reviewers evaluated the risk of bias in the included studies, utilizing the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data (9). This checklist is a nine-item tool where each question was rated as 1 for "Yes" and 0 for "No" or "Unclear." Detailed information on this tool is provided in Supplementary Table S3. Studies with scores of 0–5, 6–7, and 8–9 were considered to have a high, medium, and low risk of bias, respectively. All results were cross-checked, and any disagreements were resolved through discussion.

2.3 Statistical analysis

Owing to the clinical heterogeneity of the included study populations, all analyses were conducted using random-effects models. Generalized linear mixed models were used to pool data across the studies, and cardiac thrombus prevalence was reported with 95% confidence intervals (CIs). Inter-study heterogeneity was assessed using Cochran's Q test and expressed with the I^2 statistic, with significant heterogeneity presumed when $p < 0.05$ and/or $I^2 > 50\%$.

Sensitivity analyses were performed to evaluate the robustness of the pooled prevalence estimates and examine the influence of individual studies on the pooled results and inter-study heterogeneity. Sensitivity analyses excluded studies with: (1) a medium or high risk of bias (score < 8), (2) a study sample with <100 patients, (3) studies conducted before 2020, and (4) retrospective studies. The *p*-values were determined by testing the homogeneity of cardiac thrombus prevalence detected by CCTA between the included and excluded studies. In addition, to evaluate the effect of individual studies on the results, sensitivity analyses were performed by removing each study one at a time.

Subgroup analyses were conducted to identify factors related to the prevalence of cardiac thrombus detected by CCTA. These subgroups were based on: (1) stroke type (embolic stroke/cardioembolic stroke vs. unclassified stroke/transient ischemic attack [TIA]), (2) prevalence of atrial fibrillation among the study population (≥30% vs. <30%), (3) time interval from symptom onset to CCTA (within 24 h vs. after 24 h), and (4) CT technology (single-phase vs. double-phase and ECG-gated vs. non-ECG-gated). The *p*-values for the subgroup analysis were determined by testing homogeneity. Publication bias was qualitatively assessed using a funnel plot.

A two-sided *p*-value of <0.05 was considered significant. Statistical analyses were performed using the meta/metafor package in R statistical software (Version 4.0.1, Vienna, Austria).

3 Results

3.1 Characteristics of studies and quality assessment

The study selection process is illustrated in Figure 1. Initially, 3,100 references were identified through database searches. After screening the titles and abstracts, 2,864 articles were excluded. Subsequently, a total of 236 full-text articles were evaluated for eligibility. Ultimately, 25 studies involving 4,516 patients were included in the meta-analysis (2, 3, 6, 10–31).

The characteristics of the patients in the included studies are summarized in Table 1. All studies were single-center, and 16 studies employed a prospective design. Fourteen studies enrolled patients who had experienced a stroke or TIA, regardless of the stroke classification. The remaining 11 studies focused on patients with embolic stroke, with five studies specifically including patients classified as having cardioembolic stroke according to the TOAST classification. The time interval from stroke onset to CCTA scan was reported in 17 studies and CCTA was performed within 24 h in 10 studies. Dual-phase CCTA was used in 12 studies, and most studies used CT scanners with ≥64 slices.

Risk-of-bias assessment showed that 12, 11, and two studies had a low, medium and high risk of bias, respectively. Thirteen studies utilized single-phase CCTA to detect cardiac thrombi, which is considered less accurate than dual-phase CCTA (32). Other significant sources of bias included small sample sizes and a low number of patients with cardiac thrombi. Additionally, several studies lacked crucial patient information in their reports, such as the incidence of atrial fibrillation and age. Furthermore, seven studies had a response rate less than 90%. Supplementary Table S4 summarizes the details of the risk of bias assessment.

3.2 Prevalence of cardiac thrombus detected by CCTA

A meta-analysis of 25 studies indicated that CCTA identified intra-cardiac thrombi in 8% of patients with AIS (95% CI, 6–11%), with high interstudy heterogeneity (I^2: 88%) (Figure 2). Sensitivity analyses (Figure 3) revealed that excluding studies with a medium or high risk of bias, studies conducted before 2020, studies with small sample sizes, or retrospective studies had no significant impact on the results ($p > 0.05$ for all comparisons). Furthermore, the removal of any individual trial did not substantially impact outcomes.

Subgroup analyses revealed that a higher prevalence of atrial fibrillation significantly increased the detection rate of cardiac thrombi by CCTA (0.14; 95% CI, 0.08–0.21 vs. 0.07; 95% CI, 0.05–0.10; $p = 0.03$). Conversely, stroke type, interval from symptom onset to CCTA, and CCTA technology did not significantly influence the detection rate of cardiac thrombi. Details of these subgroup analyses are presented in Figure 4.

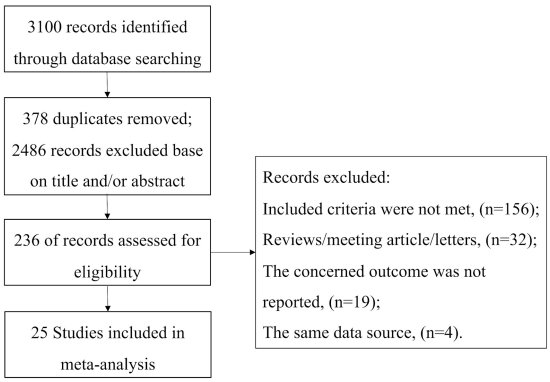

FIGURE 1
Flow diagram of the selection process of eligible articles.

3.3 Atrial fibrillation and cardiac thrombus

Given that atrial fibrillation is a major contributor to cardioembolic stroke, we examined the prevalence of atrial fibrillation in patients with cardiac thrombi detected by CCTA. Fifteen studies reported the incidence of atrial fibrillation in patients with cardiac thrombus, encompassing a total of 318 patients. Notably, 41.5% (132/318) of the patients did not have documented atrial fibrillation (Table 2).

3.4 Location of cardiac thrombus

Twenty-two studies provided data on the location of cardiac thrombi, revealing that 86.1% (285/331) of the thrombi were located in the LAA, followed by 14.5% (48/331) in the ventricles. Only three patients had thrombi in the right atrium (Table 2).

3.5 Publication bias

Visual assessment of the funnel plot (Supplementary Figure S1) did not indicate significant publication bias.

4 Discussion

To our knowledge, this is the first meta-analysis study to evaluate the prevalence of intracardiac thrombi detected by CCTA in patients with AIS. Our study suggests that cardiac thrombi can be detected on CCTA in approximately 8% of patients with AIS. Among stroke type, the prevalence of atrial fibrillation, timing of CCTA and CCTA technology, the prevalence of atrial fibrillation is the only factor associated with cardiac thrombi prevalence detected by CCTA. However, notably, almost half of the patients with cardiac thrombi detected by CCTA had no documented atrial fibrillation. The LAA and LA were the most common cardiac thrombus location, followed by the left ventricle.

Determining the etiology of a stroke is crucial for secondary prevention. Nevertheless, even after systematic evaluation, approximated one-third of strokes remain cryptogenic (1). In such cases, cardioembolic events may play a significant role, such as in patients with occult atrial fibrillation (1). Evaluating intracardiac thrombus during the acute phase of stroke may help identify the

TABLE 1 Characteristics of the included studies.

Study	N	Study type	Stroke type[a]	Age[b]	Male (%)	AF (%)	CT slice	CT technology	Timing of CCTA
Ajlan et al. (10)	47	Retrospective	CE	52 ± 11	53.2	4.2	128 s	Single-phase; ECG-gated	NR
Bernard et al. (11)	324	Retrospective	Stroke	With thrombus:82 ± 12; Without thrombus:74 ± 14	51.9	21.0	320 s	Single-phase; ECG-gated	Following emergency head CT
Philippe et al. (12)	415	Retrospective	Stroke	77 (60–86)	53.0	NR	320 s	Single-phase; ECG-gated	Following emergency head CT
Austein et al. (13)	60	Retrospective	CE	76 (72–82)	43.3	43.3	64 s	Two-phase; ECG-gated	Following emergency head CT
Kauw et al. (2)	353	Prospective	Stroke +TIA	67 ± 14	60.9	16.4	192 s	Single-phase; non-gated	Within 9 h
Holswilder et al. (14)	67	NR	Stroke +TIA	68 (51–89)	68.7	3.0	320 s	Single-phase; ECG-gated	Median interval: 2 days
Hur et al. (15)	55	Prospective	Stroke	With thrombus: 63 ± 10; Without thrombus:59 ± 14	65.5	60.0	64 s	Two-phase; ECG-gated	NR
Hur et al. (16)	137	Prospective	Stroke	61 ± 13	69.3	41.6	64 s	Two-phase; ECG-gated	Within 1 week after stroke
Hur et al. (17)	83	Prospective	Stroke[c]	63 ± 11	67.5	4.8	256 s	Single-phase; ECG-gated	NR
Lee et al. (18)	374	Prospective	Stroke	63 ± 13	67.9	12.0	128 s	Single-phase; ECG-gated	Within 1 week after stroke
Iwasaki et al. (19)	184	NR	ES	69 ± 13	66.3	14.1	64 s	Two-phase; ECG-gated	NR
Boussel et al. (20)	46	Prospective	Stroke	63 ± 11	82.6	6.5	40s	Two-phase; ECG-gated	NR
Yeo et al. (21)	20	Prospective	Stroke	64 ± 12	65.0	20.0	64 s	Single-phase; non-gated	Following emergency head CT
Rinkel et al. (22)	452	Prospective	Stroke	With thrombus: 76 (63–87); Without thrombus: 72 (62–80)	59.3	17.0	128 s	Single-phase; ECG-gated	Median interval: 32 min
Lee et al. (23)	120	Prospective	Stroke +TIA + SMS	73 (63–81)	55.0	26.7	64 s	Single-phase; non-gated	Following emergency head CT
Sipola et al. (24)	140	Prospective	CE	60 ± 10	67.9	NR	16 s and 64 s	Single-phase; ECG-gated	NR
Barnea et al. (25)	129	Retrospective	ESUS	74 ± 10	55.0	0.0%	256 s	Two-phase; ECG-gated	NR
Kawada et al. (26)	57	Prospective	ES	Median: 73; minmun:38; maximum: 93	68.4	NR	NR	Two-phase; ECG-gated	NR
Kim et al. (27)	314	Prospective	ES	65 ± 13	59.2	22.9	64 s	Two-phase; ECG-gated	Within 1 week after stroke
Ko et al. (28)	124	Prospective	ES	CCTA only: 76 (66–80); CCTA and TEE: 67 (58–72)	54.0	31.5	64 s	Two-phase; ECG-gated	Median interval: 2 days

(Continued)

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TABLE 1 (Continued)

Study	N	Study type	Stroke type[a]	Age[b]	Male (%)	AF (%)	CT slice	CT technology	Timing of CCTA
Popkirow et al. (29)	21	Retrospective	ESUS+CE	CE: 78 ± 8; ESUS: 80 ± 3	52.4	81.0	NR	Single-phase; non-gated	Following emergency head CT
Senadeera et al. (30)	303	Retrospective	Stroke +TIA	74 (66–84)	51.5	33.0	64 s and 128 s	Single-phase; ECG-gated	Within 24 h
Tomari et al. (6)	314	Prospective	Stroke +TIA + SMS	70 (56–79)	61.1	23.9	384 s	Two-phase; non-gated	Median interval: 2.8 h
Yan et al. (31)	74	Prospective	ESUS	62 ± 14	62.2	0.0	64 s	Two-phase; ECG-gated	Within 1 week after stroke
Zhang et al. (3)	303	Prospective	CE	73 (65–80)	52.5	66.7	64 s	Two-phase; ECG-gated	Within 1 week after stroke

[a]The stroke type was defined based on information that excluded results of CCTA.
[b]Age was expressed as mean ± SD or median (low quartile, high quartile).
[c]Stroke patients with risk factors for cardiac thrombus.
AF, atrial fibrillation; CCTA, cardiac computed tomography angiography; CE, cardioembolic stroke; ES, embolic stroke; ESUS, embolic stroke of undetermined source; NR, not reported; SMS, stroke-mimicking syndromes; TEE, transesophageal echocardiography; TIA, transient ischemic attacks.

thrombus source and guide treatment decisions. Furthermore, current classification of cardioembolic stroke mainly relies on medical history and indirect examination results, such as the presence of atrial fibrillation, valvular heart disease, or ventricular aneurysm (1). In patients with stroke presenting risk factors for cardioembolism, atherosclerotic risk factors often co-exist, making the exact mechanism of stroke difficult to pinpoint. Additionally, the presence of an intracardiac thrombus is an important prognostic risk factor, associated with worse functional outcomes and longer hospital stay (4). In summary, acute phase assessment of intracardiac thrombus formation aids in the long-term secondary prevention for patients and help predict prognosis.

Nowadays, TEE is the gold-standard imaging modality for identifying intracardiac thrombi. When using intraoperative thrombus detection as the reference standard, TEE demonstrated a sensitivity of 93–100% and a specificity of 99–100% for detecting LAA thrombi. However, TEE is a semi-invasive and time-consuming procedure, and is not routinely performed in the acute period, potentially reducing the likelihood of detecting cardiac thrombus after intravenous thrombolysis and anti-thrombosis treatment. CCTA provides a non-invasive approach to detect cardiac thrombus and can be performed during the hyperacute period of AIS without significantly increasing additional scan time (22). A recent meta-analysis found that the prevalence of cardiac detected by CCTA was significantly higher than that detected by TEE in patients with AIS (33). However, the diagnostic accuracy of CCTA largely depends on the CT technology applied. Using TEE as the gold standard, dual-phase CCTA has shown high accuracy in diagnosing intracardiac thrombi, whereas single-phase CCTA is less accurate (32). Many studies on hyperacute CCTA in patients with AIS have adopted a single-phase scanning strategy to reduce scan time, potentially increasing the thrombus detection rate (2, 22). However, it is noteworthy that recent studies have found that filling defects (blood stasis) in single-phase CT scans, which might be misdiagnosed as thrombi, are also significantly associated with stroke recurrence, indicating that the etiology of stroke is probably cardiogenic thromboembolism (34). In addition, our study found that the timing of the scan had no significant impact on thrombus detection rates. Therefore, in the acute period of AIS, particularly in the hyperacute period, using single-phase scanning to reduce the scan time may be a reasonable choice.

To evaluate the proportion of cardiogenic thrombi detected by CCTA in patients with AIS, we pooled results from 25 studies and found that nearly 8% of patients with AIS had detectable thrombi on CCTA. The results showed considerable heterogeneity among the studies (Figure 2), which could be attributed to differences in study design, criteria for thrombus detection, patient characteristics, timing of CCTA, and technical variations in CCTA. To address this, we conducted sensitivity analyses and subgroup analyses based on study design and patient characteristics. However, following these analyses, the heterogeneity was not entirely explained by probable study biases. Thus, heterogeneity was likely attributed to patient-level factors and the heterogeneous nature of stroke etiology. Moreover, the included studies were not sufficiently high, with only about half being judged as high quality, which might induce heterogeneity among the studies. Interestingly, although it was speculated that factors such as stroke type, prevalence of atrial fibrillation among the study population, timing of CCTA, and CCTA scanning techniques could significantly influence thrombus detection rates, subgroup analysis revealed that the prevalence of atrial fibrillation among the study population was the sole risk factor affecting thrombus detection rates.

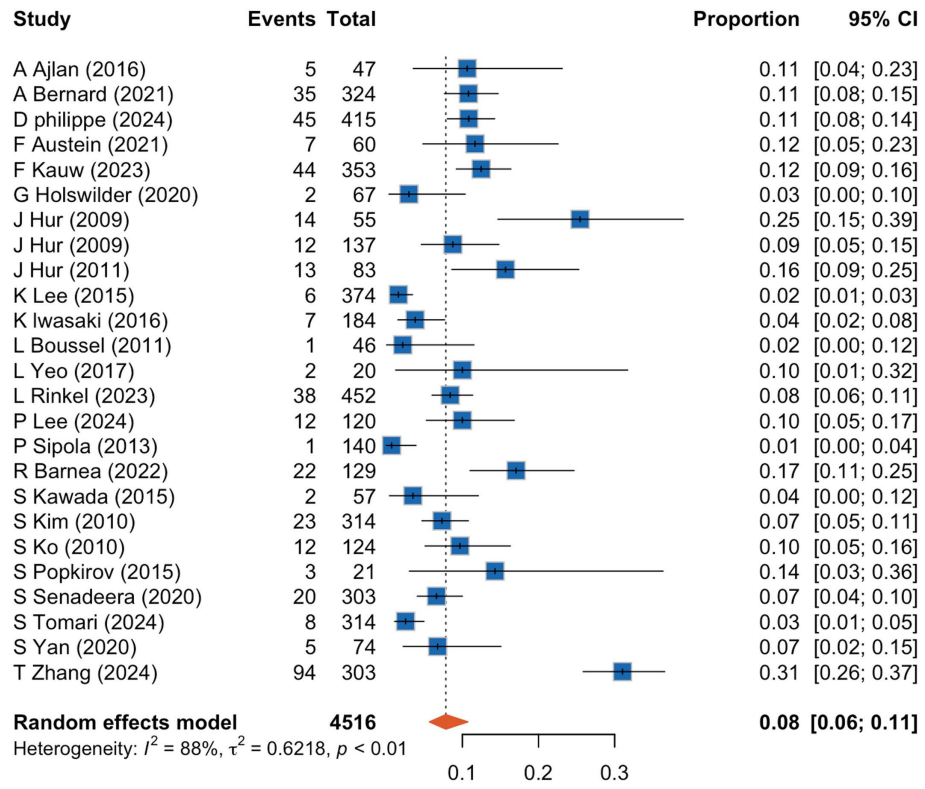

FIGURE 2
Forrest plot showing prevalence of cardiac thrombus detected by cardiac computed tomography angiography in acute ischemic stroke patients. CI, confidence interval.

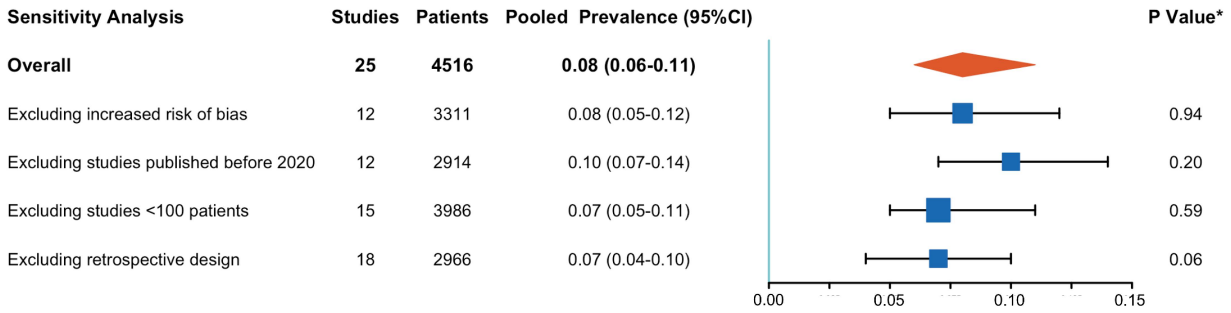

FIGURE 3
Results of sensitivity analysis. CI, confidence interval. *p-value for testing the null-hypothesis of homogeneity of cardiac thrombus prevalence between the included and excluded studies.

Among the 25 included studies, there was notable diversity in the types of strokes among the participants. Fourteen studies included all stroke types, including cases of TIA or stroke-mimicking symptoms. Conversely, some studies specifically focused on patients with cardioembolic or embolic stroke (Table 1). In the subgroup analysis, we did not observe a higher thrombus detection rate among cardioembolic or embolic stroke populations than general patients with stroke, and significant heterogeneity was evident within these groups. These confusing results likely stem from substantial inconsistencies in the clinical classification of stroke across different centers. It has been reported that the inter-center agreement regarding cardioembolic stroke was 38.7% (35). Furthermore, all included studies were observational single-center studies. There might be significant variations among the studies regarding the decision to perform CCTA in patients with AIS. In studies involving patients with unclassified stroke, those with cardioembolic stroke were still more likely to undergo CCTA examination, potentially introducing selection bias.

Among the enrolled 25 studies, only 10 studies conducted CCTA within 24 h of stroke onset, and only six studies provided precise timing details for CCTA. Our results did not support our hypothesis that earlier CCTA examinations would yield higher thrombus detection rates. Whether emergency CCTA scanning is warranted still requires further head-to-head comparison studies.

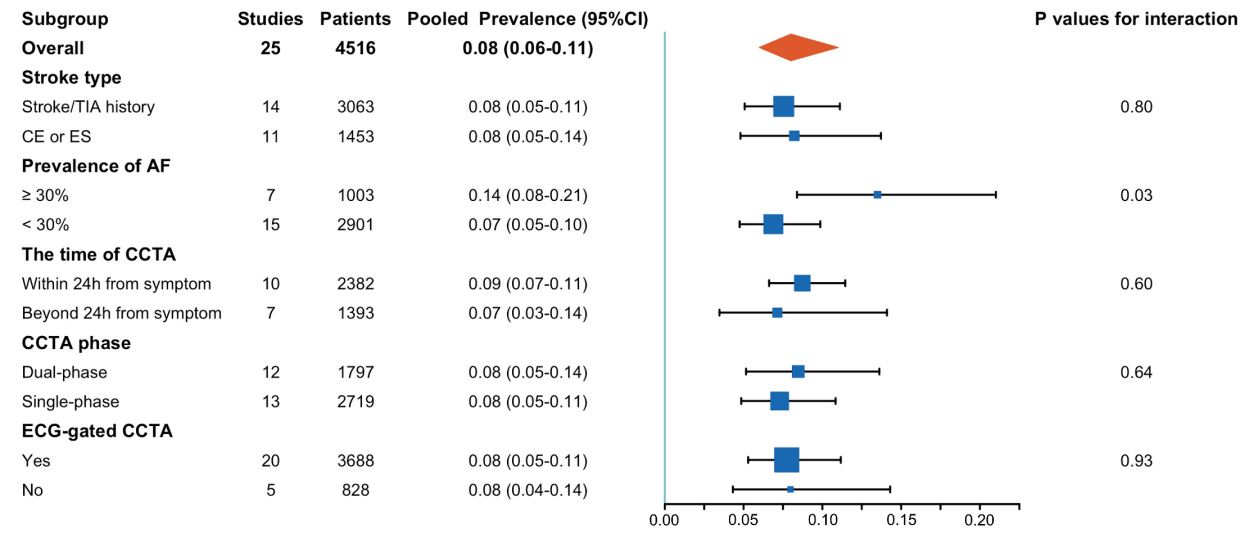

FIGURE 4
Results of subgroup analysis. AF, atrial fibrillation; CCTA, cardiac computed tomography angiography; CE, cardioembolic stroke; ES, embolic stroke.

TABLE 2 Prevalence of atrial fibrillation in patients with cardiac thrombus and cardiac thrombus location.

Study	N	AF (N)	Location of cardiac thrombus		
			LAA/LA(N)	V(N)	RA(N)
Ajlan et al. (10)	5	NR	3	2	0
Bernard et al. (11)	35	22	35	0	0
Philippe et al. (12)	45	NR	41	3	1
Austein et al. (13)	7	NR	6	1	0
Kauw et al. (2)	44	19	35	14	0
Holswilder et al. (14)	2	NR	NR	NR	NR
Hur et al. (15)	14	10	14	0	0
Hur et al. (16)	12	NR	11	1	0
Hur et al. (17)	13	4	13	0	0
Lee et al. (18)	6	NR	NR	NR	NR
Iwasaki et al. (19)	7	3	6	1	0
Boussel et al. (20)	1	NR	0	1	0
Yeo et al. (21)	2	NR	1	1	0
Rinkel et al. (22)	38	15	33	5	0
Lee et al. (23)	12	NR	11	1	0
Sipola et al. (24)	1	0	0	1	0
Barnea et al. (25)	22	0	9	13	0
Kawada rt al. (26)	2	1	2	0	0
Kim et al. (27)	23	NR	23	0	0
Ko et al. (28)	12	11	11	1	0
Popkirov et al. (29)	3	3	2	0	1
Senadeera et al. (30)	20	15	20	0	0
Tomari et al. (6)	8	6	4	3	1
Yan et al. (31)	5	0	5	0	0
Zhang et al. (3)	94	77	NR	NR	NR

AF, atrial fibrillation; LA, left atrium; LAA, left atrial appendage; NR, not reported; RA, right atrium; V, ventricle.

The prevalence of atrial fibrillation among the study participants was the sole risk factor associated with thrombus detection rates in our study. Although detecting cardioembolic thrombi may not significantly alter antithrombotic treatment decisions in patients with atrial fibrillation, thrombus detection can aid in prognosis prediction. Moreover, it is noteworthy that more than 40% of patients with detected thrombi did not have a history of atrial fibrillation. In these patients, thrombus detection holds significant implications for antithrombotic treatment decisions. This conclusion was recently validated by the ENCLOSE study, which demonstrated that CCTA-based thrombus detection significantly improved the diagnostic accuracy of cardioembolic stroke (2).

Finally, as expected, our study found that the LAA is a common site for thrombus formation; however, a significant proportion, approximately 14%, of thrombi can also be found in the ventricle. In rare cases, thrombi can occur in the right atrium. Due to their anatomical location away from the esophagus, thrombi in these areas can easily be missed during TEE, emphasizing the necessity of CCTA.

4.1 Limitation

This study had some limitations, including the great heterogeneity between studies, missing data, and low quality of the included studies, which might reduce the reliability of our results. Future high-quality prospective multicenter studies are warranted. Second, treatment decision changes and prognostic improvements resulting from CCTA findings are of great concern, however, few studies have reported on these outcomes. Future studies are needed to further establish the role of CCTA in improving the prognosis of AIS patients. Third, 11 studies focused on patients with embolic stroke, which might induce selection bias. However, in subgroup analysis, we did not demonstrate a significant impact of stroke type on the outcomes. Finally, various factors were associated with the incidence of intracardiac thrombus, such as age, heart failure, and left atrial size (36), which might influence the detection rate of cardiac thrombus on CCTA. However, due to missing data or a lack of significant differences among studies (e.g., age), we did not conduct subgroup analyses based on these factors.

5 Conclusion

CCTA might be a useful non-invasive imaging approach for evaluating cardiac embolism sources with cardiac thrombus being detected in approximately 8% of patients with AIS on CCTA. Atrial fibrillation was associated with an increased prevalence of cardiac thrombosis. However, the heterogeneity between studies necessitates future high-quality, large, multicenter prospective studies. Moreover, the optimal timing and technology aspects of CCTA require further studies.

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

BX: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. YD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. ZY: Data curation, Investigation, Methodology, Validation, Writing – review & editing. YS: Investigation, Methodology, Validation, Writing – review & editing. MX: Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing.

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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.2024.1453683/full#supplementary-material

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Association of renal biomarkers with fast progressor phenotype and related outcomes in anterior circulation large vessel occlusion stroke

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Background: Renal dysfunction is a known predictor of long-term functional dependency after anterior circulation large vessel occlusion (ACLVO) stroke. However, the impact of renal dysfunction on early infarct growth rate (IGR) has not been previously demonstrated. The objective of this study was to define the association of creatinine-based renal biomarkers with fast or slow progressor phenotypes and related clinical outcomes in ACLVO stroke.

Methods: This retrospective study examined patients with acute intracranial internal carotid artery or middle cerebral artery-M1 occlusions admitted between 2014 and 2019. Patients were included if they received baseline CT perfusion (CTP) or MRI on presentation within 24 h of estimated stroke onset. Infarct growth rate (IGR) was determined by ischemic core volume on CTP or MRI divided by time from stroke onset to imaging. IGR was used to stratify fast progressor (IGR ≥10 mL/h) and slow progressor (IGR < 10 mL/h) status. Renal dysfunction was assessed based on serum creatinine and estimated glomerular filtration rate (eGFR) on presenting laboratories. Logistic regression models, adjusted for significant covariates, identified independent associations between renal dysfunction biomarkers, progressor status, and clinical outcomes based on modified Rankin Scale (mRS) at 90 days.

Results: Among 230 patients with ACLVO, 29% were fast progressors, with median serum creatinine levels higher than slow progressors (1.1 vs. 0.9 mg/dL, $p < 0.05$) and lower median eGFR (66.2 vs. 69.0 mL/min/1.73m^2, $p < 0.05$). Elevated creatinine (≥1.2 mg/dL) was independently associated with fast progressor status (adjusted OR 2.37, 95% CI 1.18–4.77), worse 90-day mRS (adjusted OR 1.88, 95% CI 1.01–3.51) and mortality (adjusted OR 2.57, 95% CI 1.14–5.79). Reduced eGFR (<60 mL/min/1.73m^2) was independently associated with fast progressor status (adjusted OR 2.38, 95% CI 1.14–4.94), but not with 90-day mRS or mortality.

Conclusion: Serum creatinine-based biomarkers of renal dysfunction were associated with fast progressor phenotype of ACLVO stroke, and worse clinical outcomes, which may help identify such patients earlier during emergency

evaluation for expedited access to EVT. Future prospective studies are warranted to confirm and test implementation of these findings.

KEYWORDS

ischemic tolerance, large vessel occlusion, anterior circulation, renal function, stroke outcomes

Introduction

The systemic determinants of early infarct growth rate (IGR) and fast versus slow progressor phenotypes in large vessel occlusion (LVO) stroke are incompletely defined. Collateral blood flow is a key predictor of IGR in acute LVO, being modulated by native arteriolar anatomy and hemodynamic factors which vary widely across individuals (1). Age, metabolic syndrome, baseline atherosclerosis, and anemia have also been associated with modulation of collateral capacity and IGR (2–5). Good collateral capacity is strongly associated with slower IGR and improved clinical outcomes (6, 7). Systemic co-morbidities such as hypertension and diabetes are associated with a higher risk of stroke and worse outcomes (8, 9), potentially due to microvascular disease mediated by inflammation and impaired endothelial function (10, 11), representing potential additional mechanisms to early ischemic penumbra loss and core growth in LVO stroke.

Chronic kidney disease (CKD) is an important systemic condition that is prevalent in individuals with hypertension and diabetes due to end-organ damage from microvascular injury (11, 12). Previous research indicates that serum biomarkers of renal dysfunction have also been associated with cerebral microvascular injury and greater incidence of stroke (13, 14). Serum creatinine and estimated glomerular filtration rate (eGFR) are established laboratory indicators of renal insufficiency or prediction of CKD (9, 15). Numerous studies have demonstrated that renal dysfunction, indicated by elevated creatinine and reduced eGFR, is associated with higher stroke severity (16, 17), and worse long-term morbidity and mortality (18). Renal function is often assessed during acute evaluation of stroke patients, particularly those being considered for time-sensitive reperfusion therapies, such as anterior circulation LVO (ACLVO) patients.

Renal dysfunction has been previously associated with cerebral microangiopathy (13), poor collateral flow (19) and higher risk of mortality after endovascular therapy (EVT) for ACLVO (20). This study aimed to determine whether renal dysfunction biomarkers are independently associated with fast or slow progressor phenotypes of ACLVO stroke and related clinical outcomes. Determining whether renal function is associated with early infarct growth during acute ACLVO stroke presentation has the potential to help identify fast progressors on the field and provide novel insight into the pathophysiology of individual tolerance to focal cerebral ischemia.

Materials and methods

Population and study design

This was a chart review-based retrospective study of patients with acute intracranial internal carotid artery (ICA) or middle cerebral artery (MCA) M1 segment occlusion who were admitted between 2014 and 2019 at two academic comprehensive stroke centers (Supplementary Figure 1). Patients were included if they underwent baseline magnetic resonance imaging (MRI) or computed tomography perfusion (CTP) on presentation within 24 h after stroke onset, irrespective of subsequent EVT or medical management alone. Patients with missing advanced imaging or serum creatinine data were excluded.

Data collection and management

Demographics, medical history, National Institutes of Health Stroke Scale (NIHSS) score, basic metabolic laboratories, neuroimaging, treatment, and outcome data were collected by trained stroke researchers. The serum creatinine was obtained upon arrival to the comprehensive stroke center where advanced imaging was performed. The cutoff for abnormally elevated serum creatinine was arbitrarily set at 1.2 mg/dL based on an average threshold for standard female and male laboratory values (15, 21). The creatinine-based eGFR was calculated using the 2021 CKD-EPI equation, which has been extensively validated (22–24). The predictor group for lower glomerular function was defined as eGFR <60 mL/min/1.73m^2, since it is the main criteria for Stage 3 CKD according to international guidelines (9).

Progressor phenotypes and key clinical variables

Ischemic core volume was measured using automated RAPID software (iSchemaView; Menlo Park), with thresholds set for CTP (regional cerebral blood flow <30%) or MRI (apparent diffusion coefficient < 620 μm^2/s). The documented time of last known well was used as a surrogate for time of stroke onset. The IGR was determined by dividing the ischemic core volume (mL) by the time from estimated stroke onset to imaging acquisition (hours). Fast and slow progressor groups were stratified using an IGR cutoff of 10 mL/h as previously determined (6). Patients with IGR ≥10 mL/h were defined as fast progressors, and those with IGR <10 mL/h were defined as slow progressors. Chi-square analysis assessed if witnessed or unwitnessed stroke onset would affect the proportions of fast and slow progressors. The modified Rankin Scale (mRS) was used to measure functional outcomes on discharge and at 90 days post-stroke. Functional independence was defined as mRS 0–2 after stroke. Missing mRS scores at 90 days were imputed from the discharge mRS scores (14% of observations).

Statistical analysis

All statistical analyses were conducted using STATA 18.5 (StataCorp, College Station, TX). Baseline characteristics between groups were compared using chi-square and Mann–Whitney U tests

where appropriate. The model assumptions were verified using the Ramsey RESET test, the Breusch-Pagan test, and the Shapiro–Wilk test, leading to the selection of non-linear models accordingly. Bivariate and multivariate logistic regression modeling was used to identify associations with outcome variables of fast progressor status, functional independence (mRS 0–2) or mortality. Ordinal logistic regression was used for analyses of shift in mRS outcome. Additional regression analyses were conducted to explore the association of BUN-Creatinine ratio greater than 20 (BCr ratio > 20) with progressor status. All multivariate regression models were adjusted for age, sex, NIHSS and covariates with a *p*-value <0.1 in unadjusted group comparisons. An alpha level of 0.05 was considered statistically significant.

Results

There were 230 patients with acute intracranial ICA or MCA occlusion who met pre-defined inclusion criteria, including 163 (71%) slow progressors and 67 (29%) fast progressors. Demographic, clinical, imaging, and basic metabolic laboratory in the overall population, slow and fast progressor groups are presented in Table 1. In the overall population, the median age was 73 years, 57% were female, 12% were black, and the median body mass index (BMI) was 27.1 kg/m^2. The median time of last known well to advanced imaging was 6.4 h in the overall cohort, and a sensitivity analysis showed that the prevalence of slow and fast progressors was similar irrespective of witnessed or unwitnessed stroke onset (Supplementary Table 1).

Race, diabetes, hyperlipidemia, atrial fibrillation, smoking, and BMI were similarly distributed across fast and slow progressor groups, except for known hypertension which was numerically more prevalent in slow progressors (79%) than fast progressors (67%). In comparison to slow progressors, fast progressors had higher baseline NIHSS (median: 20 vs. 16), larger core volume (median: 99 mL vs. 6 mL) and higher IGR (median: 24.3 mL/h vs. 0.74 mL/h). Serum creatinine was higher in fast progressors (median, 1.1 mg/dL) compared to slow progressors (median, 0.9 mg/dL), with a greater proportion of fast

TABLE 1 Baseline patient characteristics per fast and slow progressor status.

Characteristic	All patients *N* = 230	Slow progressor (IGR ≤ 10 mL/h) *N* = 163	Fast progressor (IGR > 10 mL/h) *N* = 67	*p*
Demographics and medical history				
Age, years median (IQR)	73 (62–85)	73 (64–85)	69 (58–81)	0.060
Female Sex N (%)	132 (57%)	94 (57%)	38 (56%)	0.894
Black race N (%)	27 (12%)	18 (11%)	15 (14%)	0.070
Hypertension N (%)	173 (75%)	128 (79%)	45 (67%)	0.908
Diabetes N (%)	64 (28%)	45 (28%)	19 (28%)	0.337
Hyperlipidemia N (%)	104 (45%)	77 (47%)	27 (40%)	0.918
CHF / CAD N (%)	65 (28%)	46 (28%)	19 (28%)	0.878
Atrial Fibrillation N (%)	87 (38%)	62 (38%)	25 (37%)	0.325
Smoking N (%)	50 (22%)	35 (22%)	15 (22%)	0.060
BMI* median (IQR)	27.1 (23.6–31.6)	27.1 (23.4–31.7)	27.0 (23.8–31.5)	0.894
Clinical and imaging profile				
Baseline NIHSS median (IQR)	17 (12–21)	16 (11–20)	20 (15–24)	<0.001
Core volume, mL median (IQR)	14.05 (0–68)	6 (0–24)	99 (41–156)	<0.001
IGR, mL/h median (IQR)	2.60 (0–11.94)	0.74 (0–2.92)	24.26 (14.17–39.53)	<0.001
Basic metabolic laboratories				
Sodium, mM median (IQR)	138 (135–140)	138 (136–140)	137 (135–140)	0.229
Potassium, mM median (IQR)	4.05 (3.7–4.4)	4.00 (3.7–4.3)	4.16 (3.6–4.6)	0.059
Chloride, mM median (IQR)	104 (101–106)	104 (101–106)	103 (99–106)	0.279
Bicarbonate, mM median (IQR)	24.6 (22–27)	24 (22–26)	25 (23–27)	0.069
Glucose*, mg/dL median (IQR)	125 (106–154)	125 (106–154)	125 (107–159)	0.836
BUN, mg/dL median (IQR)	18 (13–24)	18 (14–24)	18 (13–25)	0.674
Creatinine, mg/dL median (IQR)	0.9 (0.8–1.2)	0.9 (0.8–1.1)	1.1 (0.8–1.3)	0.012
Creatinine ≥1.2 mg/dL N (%)	60 (26%)	35 (21%)	25 (37%)	0.013
eGFR, mL/min/1.73m^2 median (IQR)	67.9 (53.0–86.7)	68.4 (56.2–86.9)	63.8 (44.1–85.0)	0.118
eGFR <60 mL/min/1.73m^2 N (%)	86 (37%)	55 (34%)	31 (46%)	0.074

CHF/CAD, congestive heart failure and/or coronary artery disease; BMI, Body mass index; NIHSS, National Institutes of Health Stroke Scale; IGR, infarct growth rate; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate. *Missing data in three patients for BMI and two patients for Glucose.

progressors having creatinine levels ≥1.2 (37% vs. 21%, $p < 0.05$). Estimated GFR was numerically lower in fast compared to slow progressors (median: 63.8 vs. 68.4 mL/min/1.73m^2), with greater prevalence of fast progressors having reduced eGFR (46% vs. 34%, $p = 0.07$). Median potassium and bicarbonate levels were numerically higher in fast progressors (4.2 and 25 mM) than slow progressors (4.0 and 24 mM).

In regression analysis, elevated serum creatinine (≥1.2 mg/dL) was independently associated with fast progressor status (OR 2.18, 95% CI 1.17–4.05, and adjusted OR 2.37, 95% CI 1.18–4.77; Table 2). The association was adjusted for age, sex, hypertension, baseline NIHSS, potassium, and bicarbonate levels. Similarly, reduced eGFR (< 60 mL/min/1.73m^2) was independently associated with fast progressor status (OR 1.69, 95% CI 0.95–3.02; adjusted OR 2.38, 95% CI 1.14–4.94; Table 3). These data support the independent relationship between creatinine-based markers of renal dysfunction and fast progressor status.

In exploratory analysis, we tested whether the observed association between renal dysfunction markers and fast progressor status was driven by pre-renal acute kidney injury which is typically observed with a serum BCr ratio > 20. The analyses (Supplementary Table 2) showed that elevated creatinine remained significantly associated with fast progressor status (adjusted OR 2.33, 95% CI, 1.15–4.69), independently of serum BCr ratio > 20 (OR 0.79, 95% CI, 0.39–1.57). Similarly, eGFR <60 (Supplementary Table 3) remained significantly associated with fast progressor status (adjusted OR 2.32, 95% CI, 1.11–4.84), independently of BCr ratio > 20 (OR 0.80, 95% CI, 0.40–1.59).

In terms of treatments and outcomes, EVT was performed more frequently in slow progressors (65% vs. 40%, $p < 0.01$), while intravenous tPA was more commonly administered in fast progressors (49% vs. 29%, $p < 0.01$; Supplementary Table 4). At 90 days, fast progressors had a higher mRS score than slow progressors (median: 6 vs. 3, $p < 0.001$). In addition (Table 4), patients with creatinine ≥1.2 had a higher 90-day mRS score than those with creatinine <1.2 (median: 6 vs. 4, $p < 0.01$), and patients with eGFR <60 had a higher mRS score than those with eGFR ≥60 (median: 5 vs. 4, $p < 0.01$). Overall, patients with elevated serum creatinine (Figure 1) or lower eGFR (Figure 2) exhibited a higher proportion of severe disability and mortality compared to those with normal renal function. This trend was similarly observed in both fast and slow progressor groups suggesting an additive effect of renal dysfunction on long-term outcomes. Notably, the proportion of mortality in the fast progressor groups with preserved renal function (creatinine <1.2 or eGFR ≥60) was comparable to the percentage of patients with impaired renal function (creatinine ≥1.2 or eGFR <60) in slow progressor groups.

The independent association of serum creatinine and eGFR with clinical outcomes at 90 days was further evaluated. Overall, patients with either creatinine ≥1.2 or eGFR <60 were also older, had greater prevalence of hypertension, diabetes, hyperlipidemia, heart disease, atrial fibrillation, and smoking. After adjusting for significant demographic and vascular risk factors (Table 5), serum creatinine ≥1.2 mg/dL remained associated with worse mRS at 90 days (OR 2.57, 95% CI 1.47–4.47; adjusted OR 1.88, 95% CI 1.01–3.51). Additionally, elevated creatinine was associated with higher mortality (OR 2.99, 95% CI 1.63–5.50; adjusted OR 2.57, 95% CI 1.14–5.79) but not with functional independence (OR 0.51, 95% CI 0.25–1.06; adjusted OR 0.93, 95% CI 0.36–2.39). Lower glomerular filtration (eGFR <60) was similarly associated with worse ordinal mRS scores at 90 days (OR 2.30, 95% CI 1.40–3.76), although it was not significant after adjustment (adjusted OR 1.09, 95% CI 0.60–1.98). Additionally, patients with eGFR <60 had higher mortality (OR 2.76, 95% CI, 1.57–4.85) and lower functional independence (OR 0.52, 95% CI 0.28–0.99). However, these associations did not reach statistical significance after

TABLE 2 Association of elevated serum creatinine (≥ 1.2) with fast progressor status.

	OR (95% CI)	*p* value	aOR* (95% CI)	*p* value
Creatinine ≥1.2	2.18 (1.17–4.05)	<0.05	2.37 (1.18–4.77)	0.015
Age	–		0.98 (0.95–0.99)	0.034
Sex (Female)	–		1.28 (0.66–2.46)	0.464
Hypertension	–		0.58 (0.28–1.23)	0.157
Baseline NIHSS	–		1.12 (1.06–1.18)	<0.001
Potassium	–		1.22 (0.68–2.19)	0.513
Bicarbonate	–		1.10 (1.00–1.20)	0.048

*aOR: adjusted OR for co-variables displayed on the table.

TABLE 3 Association of lower glomerular filtration (eGFR <60) with fast progressor status.

	OR (95% CI)	*p* value	aOR* (95% CI)	*p* value
eGFR <60	1.69 (0.95–3.02)	0.077	2.38 (1.14–4.94)	0.020
Age	–	–	0.97 (0.95–0.99)	0.011
Sex (Female)	–	–	1.01 (0.53–1.93)	0.982
Hypertension	–	–	0.56 (0.27–1.19)	0.134
Baseline NIHSS	–	–	1.12 (1.06–1.18)	0.000
Potassium	–	–	1.17 (0.64–2.13)	0.607
Bicarbonate	–	–	1.08 (0.99–1.19)	0.080

*aOR: adjusted OR for co-variables displayed on the table.

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TABLE 4 Characteristics, treatment and outcome profiles per renal function.

Characteristic	Creatinine < 1.2 N = 170	Creatinine ≥ 1.2 N = 60	p	eGFR ≥ 60 N = 146	eGFR < 60 N = 84	p
Demographics and medical history						
Age, years median (IQR)	73 (62–83)	77 (64–87)	0.218	67 (57–79)	82 (72–87)	<0.001
Female Sex N (%)	104 (61%)	28 (47%)	0.051	72 (50%)	60 (70%)	0.003
Black race N (%)	17 (10%)	10 (17%)	0.168	18 (13%)	9 (10%)	0.643
Hypertension N (%)	125 (74%)	48 (80%)	0.318	98 (68%)	75 (87%)	0.001
Diabetes N (%)	39 (23%)	25 (42%)	0.005	36 (25%)	28 (33%)	0.216
Hyperlipidemia N (%)	71 (42%)	33 (55%)	0.077	59 (41%)	45 (52%)	0.094
CHF / CAD N (%)	42 (25%)	23 (38%)	0.044	32 (22%)	33 (38%)	0.008
Atrial Fibrillation N (%)	59 (35%)	28 (47%)	0.100	44 (31%)	43 (50%)	0.003
Smoking N (%)	39 (23%)	11 (18%)	0.457	41 (28%)	9 (10%)	0.001
BMI* median (IQR)	26.83 (23.6–31.6)	27.4 (23.8–31.7)	0.745	26.8 (23.6–31.6)	27.3 (23.7–32.9)	0.849
Clinical and imaging profile						
Baseline NIHSS median (IQR)	17 (12–21)	19 (15–22)	0.058	16 (12–20)	18 (13–22)	0.045
Core volume, mL median (IQR)	13 (0–64)	27 (4.5–99.5)	0.154	14 (3–71)	15 (0–63)	0.927
IGR, mL/h median (IQR)	2.42 (0–9.86)	4.42 (0.27–22.44)	0.102	2.54 (0.16–10.01)	2.66 (0–16.77)	0.563
Fast Progressors N (%)	42 (25%)	25 (42%)	0.013	36 (25%)	31 (36%)	0.074
Basic metabolic laboratories						
Sodium, mM median (IQR)	138 (136–140)	138 (135–140)	0.799	138 (136–141)	137.4 (135–139)	0.413
Potassium, mM median (IQR)	4 (3.6–4.3)	4.3 (3.9–4.6)	0.004	4.0 (3.6–4.3)	4.2 (3.9–4.5)	0.005
Chloride, mM median (IQR)	104 (101–106)	103 (99.5–106)	0.616	104 (101–106)	104 (99–106)	0.207
Bicarbonate, mM median (IQR)	25 (23–27)	24 (21–26.5)	0.342	24 (22–26)	25 (22–27)	0.500
Glucose*, mg/dL median (IQR)	122 (106–151.5)	132 (107.5–166.5)	0.115	125 (106–155)	125 (106–152)	0.884
BUN, mg/dL median (IQR)	16 (13–21)	25 (21–37)	<0.001	15 (12–19)	24 (20–32)	<0.001
Creatinine, mg/dL median (IQR)	0.9 (0.7–1)	1.4 (1.2–1.6)	<0.001	0.8 (0.7–0.9)	1.2 (1.0–1.5)	<0.001
eGFR, mL/min/1.73m^2 median (IQR)	76.9 (63.2–90.6)	41.7 (33.2–53.1)	<0.001	80.9 (69.6–95.5)	46.24 (38.1–54.6)	<0.001
Treatment and outcomes						
EVT N (%)	103 (61%)	30 (50%)	0.153	87 (60%)	46 (53%)	0.303
Intravenous tPA N (%)	60 (35%)	20 (33%)	0.784	46 (32%)	34 (40%)	0.242
Symptomatic ICH N (%)	12 (7%)	2 (3%)	0.295	11 (8%)	3 (3%)	0.198
Pre-stroke mRS median (IQR)	0 (0–1)	1 (0–3)	0.022	0 (0–1)	1 (0–2)	0.010
Discharge mRS median (IQR)	4 (3–5)	5 (4–6)	<0.001	4 (3–5)	4 (4–6)	0.001
90-Day mRS* median (IQR)	4 (2–6)	6 (3–6)	0.001	4 (2–6)	5 (3–6)	0.001
Functional independence at 90 days (mRS 0–2) N (%)	52 (31%)	11 (18%)	0.067	46 (32%)	17 (20%)	0.045
Mortality N (%)	47 (28%)	32 (53%)	<0.001	37 (26%)	42 (49%)	<0.001

*Missing data in three patients for BMI and two patients for Glucose. CHF/CAD, congestive heart failure and/or coronary artery disease; BMI, Body mass index; NIHSS, National Institutes of Health Stroke Scale; IGR, infarct growth rate; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate, EVT, endovascular thrombectomy, tPA, tissue plasminogen activator, ICH, intracerebral hemorrhage, mRS, modified Rankin Scale.

adjustment for other co-variables (adjusted OR 1.46, 95% CI 0.67–3.17 for mortality; adjusted OR 1.16, 95% CI 0.47–2.88, respectively).

Discussion

The main finding of our study is that creatine-based biomarkers of renal dysfunction are independently associated with the fast progressor phenotype and worse clinical outcomes in acute ACLVO stroke. In the overall study cohort, approximately 1 in 3 ACLVO patients presented with impaired eGFR (< 60 mL/min/1.73 m^2), similar to data reported in other LVO stroke cohorts (25, 26). The relationship between reduced eGFR and worse clinical outcomes in ACLVO patients after EVT has been previously well demonstrated in a recent meta-analysis of 11 international studies (27). Our data support and extend these earlier findings by indicating a novel

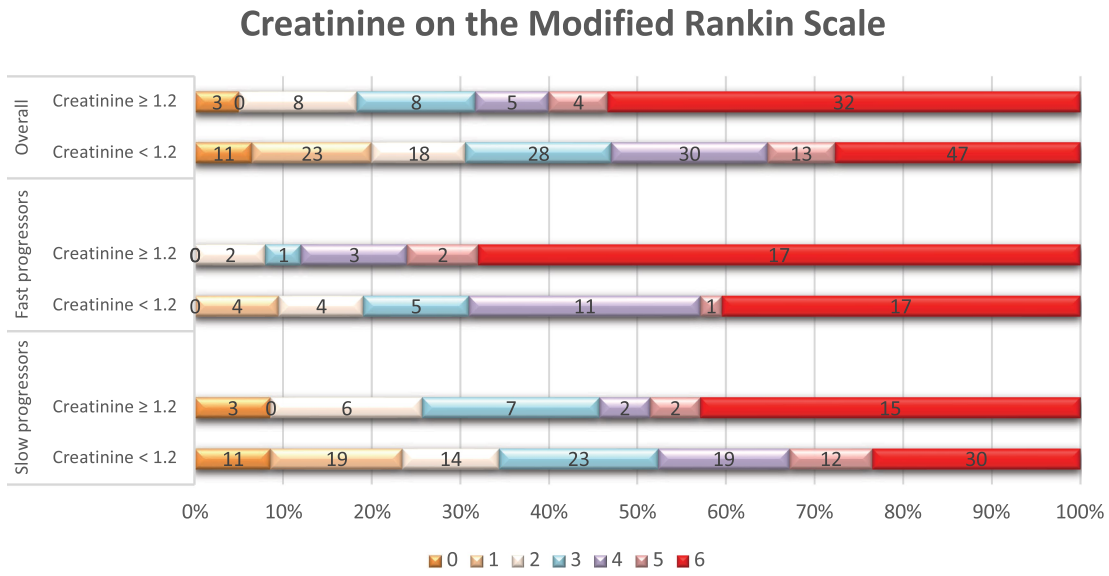

FIGURE 1
Distribution of scores on the modified Rankin scale at 90 days per serum creatinine status. Shown is the distribution of scores for disability on the modified Rankin scale (mRS) at 90 days among patients with elevated serum creatinine levels (≥ 1.2 mg/dL) and those with normal creatinine levels (< 1.2 mg/dL), in the overall population, fast, and slow progressor strata. The mRS ranges from 0 to 6, with higher scores indicating more severe disability. The numbers in the bars represent the absolute number of patients who had each score; the vertical lines represent percentages at the bottom of the figure.

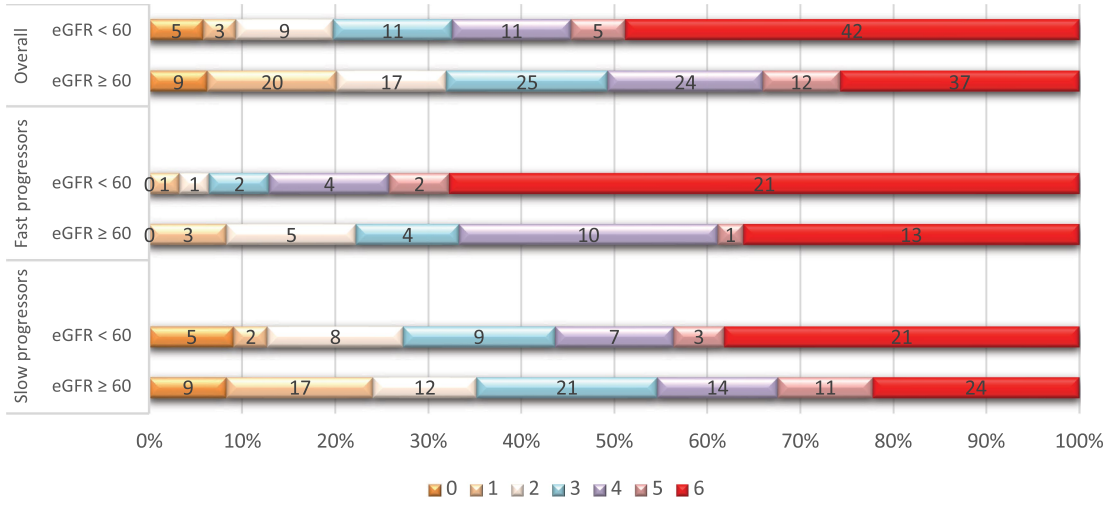

FIGURE 2
Distribution of scores on the modified Rankin scale at 90 days per eGFR status. Shown is the distribution of scores for disability on the modified Rankin scale (mRS) at 90 days among patients with reduced eGFR (< 60 mL/min/1.73m^2) and those with normal eGFR (≥ 60 mL/min/1.73m^2), in the overall population, fast, and slow progressor strata. The mRS ranges from 0 to 6, with higher scores indicating more severe disability. The numbers in the bars represent the absolute number of patients who had each score; the vertical lines represent percentages at the bottom of the figure.

association between creatinine-based biomarkers of renal dysfunction with rapid early ischemic core growth during ACLVO stroke, which is a known predictor of worse clinical outcomes in this population (6).

Since emergency point-of-care determination of serum creatinine is commonly performed during acute stroke evaluation before contrast-based CT studies, biomarkers of renal dysfunction could potentially aid in the early identification of ACLVO patients with fast progressor phenotype before advanced imaging is available. Therefore, serum creatinine-based biomarkers may have practical implications in the pre-hospital or primary stroke center when hemodynamic management and time-sensitive transfers of fast progressors directly to the neuro-angiography suite may have significant benefit. Early recognition of fast progressors may also have potential use to help enrollment in future clinical trials of hyper-acute neuroprotection

TABLE 5 Association of renal dysfunction markers with clinical outcomes at 90 days.

	OR (95% CI)	*p* value	aOR* (95% CI)	*p* value
Serum Creatinine ≥1.2				
Ordinal mRS	2.57 (1.47–4.47)	0.001	1.88 (1.01–3.51)	0.047
Functional independence	0.51 (0.25–1.06)	0.070	0.93 (0.36–2.39)	0.877
Mortality	2.99 (1.63–5.50)	<0.001	2.57 (1.14–5.79)	0.022
Stage 3 CKD (eGFR <60)				
Ordinal mRS	2.30 (1.40–3.76)	0.001	1.09 (0.60–1.98)	0.771
Functional independence	0.52 (0.28–0.99)	0.047	1.16 (0.47–2.88)	0.751
Mortality	2.76 (1.57–4.85)	<0.001	1.46 (0.67–3.17)	0.336

*All models were adjusted for age, sex, race, baseline NIHSS, progressor status, potassium, pre-stroke mRS, EVT, and IV tPA. Creatinine-based models were also adjusted for history of diabetes, hyperlipidemia, and CHF/CAD; eGFR-based models were also adjusted for history of hypertension, hyperlipidemia, CHF/CAD, atrial fibrillation, and smoking.

targeting patients with large ischemic core. However, data from our study is limited to serum creatinine levels available at the comprehensive stroke center where advanced imaging was obtained, and future studies examining renal dysfunction in the pre-hospital or primary stroke center setting are needed to confirm these contentions.

Possible explanations for the association between renal dysfunction and faster early IGR include CKD-related white matter microangiopathy (11) and reduced leptomeningeal collateral recruitment during ACLVO stroke (28). Castro et al. (13) also found that acute MCA territory stroke patients with CKD had significant impairment in dynamic cerebral autoregulation and increased burden of white matter hyperintensities relative to non-CKD controls. Therefore, patients with renal dysfunction could be potentially more vulnerable to faster early infarct growth due to impaired cerebral autoregulation causing reduced collateral capacity (19) and lower tolerance to acute ischemia due to baseline white matter disease burden (11). Further investigation is needed to elucidate the pathophysiological mechanisms linking renal dysfunction, early infarct growth rate, and individual ischemic tolerance to ACLVO stroke.

In support of previous reports, our data also demonstrated that lower renal function was associated with higher mortality and worse functional outcomes independently of reperfusion therapies. Notably, patients with markers of renal dysfunction consistently experienced worse outcomes in studies that did not consider baseline fast or slow progressor status (18, 27). In our unadjusted analysis, we found that baseline renal dysfunction markers and fast progressor status may have an incrementally worse effect on functional dependency and mortality after ACLVO stroke (Figures 1, 2). It is possible that renal dysfunction also reduces odds of longer-term stroke recovery due to association with pre-morbid burden of microvascular dysfunction and white matter hyperintensities (11, 28). However, our study was not designed to study these potential mechanisms which will need further investigation.

Age and common vascular risk factors such as hypertension and diabetes are also known predictors of worse functional outcomes after EVT for ACLVO stroke (29). Dawod et al. (12) argued that the presence of CKD may be a biomarker of end-organ vascular injury in stroke populations due to underlying hypertension or diabetes, rather than an independent stroke risk factor. Our study found older age and increased prevalence of hypertension, diabetes, hyperlipidemia, coronary disease, and atrial fibrillation in patients with creatinine, eGFR or both criteria for renal dysfunction on hospital presentation. However, abnormally elevated serum creatine conferred a 2-fold increase in odds of worse mRS at 90 days and a 2.5-fold increase in odds of mortality despite adjustment for age and significant vascular risk factors in our cohort. These findings are consistent with other studies demonstrating that renal dysfunction at the time of ACLVO stroke is an independent predictor of worse long-term functional outcomes via yet poorly defined mechanisms (27).

Other studies have further compared the impact of AKI and CKD on long-term outcomes after EVT. In particular, Fandler-Hofler et al. found that development of AKI during the hospitalization rather than pre-morbid CKD was a significant predictor of unfavorable prognosis after EVT (26). Moreover, acute hypovolemic renal insufficiency measured by a high BUN-creatine ratio has been weakly associated with poor outcomes in ischemic stroke (30, 31). In contrast to these previous reports, our supplementary analysis showed that elevated serum creatinine and reduced eGFR remained associated with fast progressor status after adjustment for BUN-Creatinine ratio > 20 (Supplementary Tables 2, 3). Therefore, we stipulate that the observed association between renal dysfunction markers and early rapid infarct growth in ACLVO stroke is more likely due to intrinsic renal impairment rather than acute prerenal azotemia from hypovolemia. In addition to hypovolemia, contrast induced nephropathy is a common contributor to acute renal insufficiency in stroke patients undergoing EVT (32, 33). Future studies are needed to clarify whether the association of creatine-based markers of renal dysfunction on hospital presentation and fast progressor phenotypes are due to acute, chronic, or acute on chronic nephropathy.

Our study has limitations. First, its retrospective design is intrinsically prone to selection bias. Some ACLVO stroke patients were excluded over the study period due to the absence of advanced imaging or laboratory data for serum creatinine measurement on hospital presentation. Second, we used a pre-specified laboratory cut-off point for serum creatinine of 1.2 mg/dL as an acceptable indicator of impaired renal function as previously determined (15, 21, 32). However, serum creatinine and eGFR can vary according to biological sex, race (23), and BMI, particularly in patients with higher muscle mass (9). To control for these potential confounders, our regression models were adjusted for sex and race, but not for BMI since it was similarly distributed across progressor status, creatine, and eGFR strata. Third, recorded serum creatinine values were only available at a single time point rather than over a prolonged period

which would have been necessary to confirm CKD (9) and chart diagnosis of pre-morbid CKD were not available. However, the prevalence of patients with eGFR <60 mL/min/1.73 m^2 in our population is similar to that from other similar cohorts that used alternative formulas for GFR calculation (27), supporting the validity of our estimates of renal dysfunction during acute stroke presentation.

Conclusion

This study found that biomarkers of renal dysfunction (serum creatinine ≥1.2 mg/dL or eGFR <60 mL/min/1.73m^2) were associated with a faster progressor phenotype of ACLVO stroke, and worse clinical outcomes, suggesting that serum creatinine could serve as an adjunct in early identification of higher risk ACLVO patients. These findings have potential implications in early management and prioritized transfer of fast progressor ACLVO patients to EVT, and for enrollment in future clinical trials of bridge neuroprotective therapies. Future prospective studies are required in larger and more diverse populations to confirm and test implementation of these findings.

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 humans were approved by University of Pittsburgh Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

LR: Writing – original draft, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. MK: Data curation, Formal analysis, Writing – review & editing. BM: Data curation, Writing – review & editing. AA-Q: Data curation, Writing – review & editing, Methodology. MD: Methodology, Writing – review & editing. AA-B: Writing – review & editing. NB: Methodology, Writing – review & editing. MS: Writing – review & editing, Methodology. SS: Data curation, Writing – review & editing, Methodology. RN: Writing – review & editing, Methodology. MR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

RGN reports consulting fees for advisory roles with Anaconda, Biogen, Cerenovus, Genentech, Philips, Hybernia, Imperative Care, Medtronic, Phenox, Philips, Prolong Pharmaceuticals, Stryker Neurovascular, Shanghai Wallaby, Synchron, and stock options for advisory roles with Astrocyte, Brainomix, Cerebrotech, Ceretrieve, Corindus Vascular Robotics, Vesalio, Viz-AI, RapidPulse, and Perfuze. RGN is one of the principal investigators of the "Endovascular Therapy for Low NIHSS Ischemic Strokes (ENDOLOW)" trial. Funding for this project is provided by Cerenovus. RGN is the principal investigator of the "Combined Thrombectomy for Distal MediUm Vessel Occlusion StroKe (DUSK)" trial. Funding for this project is provided by Stryker Neurovascular. RGN is an investor in Viz-AI, Perfuze, Cerebrotech, Reist/Q'Apel Medical, Truvic, Vastrax, and Viseon.

The remaining author 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. The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1475135/full#supplementary-material

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Thrombolytic therapy for patients with acute ischemic stroke: systematic review and network meta-analysis of randomized trials

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Objective: To systematically compare the benefits and risks of all thrombolytic agents (tenecteplase, reteplase, and alteplase) at different doses for thrombolytic therapy in patients with acute ischemic stroke (AIS).

Background: Alteplase is the cornerstone treatment for AIS, but alternative thrombolytic agents are needed. The efficacy and safety of tenecteplase and reteplase, compared to alteplase, remain unclear, as does the optimal dosing for these treatments.

Method: A systematic search was conducted in PubMed, Web of Science, SCOPUS, and the Cochrane Central Register of Controlled Trials (CENTRAL) for relevant English-language studies up to July 5, 2024. Randomized controlled trials (RCTs) comparing standard-dose alteplase with varying doses of tenecteplase or reteplase in AIS patients were included. Primary outcomes were functional outcome at 90 days, symptomatic intracranial hemorrhage, death within 90 days, and serious adverse events. Data on study characteristics, patient demographics, interventions, and outcomes were extracted, and bias risk assessed. A multivariate random-effects model was used for network meta-analysis to derive odds ratios (OR) and 95% confidence intervals (CI).

Result: Twelve RCTs were included (10 with tenecteplase, 2 with reteplase) involving 6,633 patients, all compared against 0.9 mg/kg alteplase. In comparison with alteplase, tenecteplase demonstrated OR of 1.08 for achieving an excellent functional outcome at 90 days (95% CI: 0.97 to 1.22, $P = 0.17$). Reteplase, on the other hand, showed a significantly higher OR of 1.55 for the same outcome (95% CI: 1.23 to 1.95, $P = 0.0002$). Reteplase at 18 mg + 18 mg (OR 1.6, 95% CI: 0.91–2.5) showed a higher probability of achieving an excellent functional outcome at 90 days compared to alteplase. When considering a good functional outcome at 90 days, tenecteplase had an OR of 1.03 (95% CI: 0.81 to 1.3, $P = 0.82$), while reteplase had an OR of 1.15 (95% CI: 0.61 to 2.19, $P = 0.66$). Tenecteplase at 0.25 mg/kg (OR 1.3, 95% CI: 0.79–2.5) had the highest probability of achieving a good functional outcome at 90 days. For safety outcomes, 0.25 mg/kg tenecteplase had lower incidences of symptomatic intracranial hemorrhage (OR 0.88, 95% CI: 0.35–1.8), death within 90 days (OR 0.91, 95% CI: 0.54–1.4), and serious adverse events (OR 1.0, 95% CI:

0.47–2.3) compared to alteplase, though differences were not statistically significant. Reteplase at 18 mg + 18 mg had higher incidences of death within 90 days (OR 1.2, 95% CI: 0.48–3) and serious adverse events (OR 1.4, 95% CI: 0.4–5.0) compared to alteplase, without significant differences. Subgroup analysis showed better efficacy with 0.25 mg/kg tenecteplase in Asians (OR 1.18, 95% CI 0.96–1.45, $P = 0.12$) than in Caucasians (OR 1.08, 95% CI 0.9–1.3, $P = 0.39$).

Conclusion: This study suggests that tenecteplase and reteplase are viable alternatives to alteplase for thrombolysis in AIS. Tenecteplase at 0.25 mg/kg and reteplase at 18 mg + 18 mg may offer better efficacy compared to standard-dose alteplase, although the risk of adverse events with reteplase should be considered. Tenecteplase at 0.25 mg/kg appears to provide the best benefit-risk profile based on current evidence. Further head-to-head trials of tenecteplase and reteplase are needed to determine the optimal thrombolytic agent and dosing.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, PROSPERO CRD42024566146.

KEYWORDS

acute ischemic stroke, alteplase, tenecteplase, reteplase, network meta-analysis

1 Introduction

AIS is among the most common and life-threatening cerebrovascular diseases worldwide. Intravenous thrombolysis with alteplase within 4.5 h of symptom onset is the globally recognized cornerstone of AIS treatment. However, due to its short half-life, alteplase requires continuous infusion, increasing the complexity of patient care and limiting its clinical use (1–3). Tenecteplase, a genetically modified version of alteplase with a longer half-life, can be administered as a single bolus injection, offering similar clinical benefits to alteplase and has been frequently recommended by the European Stroke Organization (ESO) guidelines (4, 5). Similarly, reteplase, a recombinant plasminogen activator given in a double-bolus regimen (two injections 30 min apart with a fixed dose), has shown a higher likelihood of achieving excellent functional outcomes compared to alteplase (6, 7). However, due to a lack of direct comparative evidence, the relative advantages of alteplase, tenecteplase, and reteplase for intravenous thrombolysis in AIS patients remain unclear.

Previous meta-analyses on thrombolytic therapy for AIS have yielded conflicting results, often limited by the lack of high-quality data from randomized trials (8, 9). This study addresses these limitations by exclusively including RCTs and overcoming other constraints: (1) We expanded the outcome measures to include death within 90 days and serious adverse events as safety indicators. (2) We conducted a network meta-analysis of different doses of tenecteplase and reteplase. (3) We performed subgroup analyses based on race and age.

The objectives of this systematic review and meta-analysis are: (1) To assess the efficacy and safety of alteplase, tenecteplase, and reteplase in the treatment of AIS. (2) To determine the optimal doses of tenecteplase and reteplase for AIS treatment. (3) To explore the impact of race and age on intravenous thrombolysis outcomes in AIS patients.

2 Method

2.1 Registration

This review follows the pre-specified protocol registered with PROSPERO (CRD42024566146). Differences between this review and the original PROSPERO protocol are detailed in Supplementary Table S1. This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for network meta-analyses (10). Ethical approval was not required as this study was primarily analyzed using data from existing RCTS in the database.

2.2 Eligibility criteria

Inclusion criteria for this network meta-analysis:

1. Studies utilizing all thrombolytic drugs for intravenous thrombolysis.
2. Large-scale phase 2/3 RCTs.
3. Studies involving adult patients (aged 18 years and above) undergoing intravenous thrombolysis who meet the standard criteria for thrombolysis.
4. Studies reporting at least one outcome measure of interest for this meta-analysis.

Exclusion criteria for this network meta-analysis:

1. Studies combining antiplatelet therapy with thrombolysis.
2. Studies involving mechanical thrombectomy.
3. Studies not published in English.
4. Studies classified as fundamental experimental research, conference abstracts, case reports, or reviews.
5. Studies lacking a comparison group.
6. Studies presenting overlapping participant data.

2.3 Outcomes

The interventions of interest included different doses of tenecteplase (0.1 mg/kg, 0.25 mg/kg, 0.4 mg/kg) and reteplase (12 mg+12 mg, 18 mg+18 mg), compared to the standard dose of alteplase (0.9 mg/kg). Studies comparing these interventions against each other or against alteplase were included. Exclusion criteria are detailed in the Supplementary Table S2. Primary outcomes included functional outcomes at 90 days, determined by the modified Rankin Scale (mRS), including excellent functional outcome (mRS 0-1, or no change from baseline) and good functional outcome (mRS 0-2, or no change from baseline). Safety outcomes included symptomatic intracranial hemorrhage (sICH), death within 90 days, and serious adverse events (SAEs). Additional outcomes such as any parenchymal hemorrhage, any intracranial hemorrhage (ICH), asymptomatic ICH, and major neurological improvement within 72 h were initially considered but ultimately excluded due to insufficient data.

2.4 Data sources and searches

Two authors (Li-chao-yue Sun and Wen-shu Li) conducted a comprehensive search of PubMed, Web of Science, SCOPUS, and the Cochrane CENTRAL for relevant English-language studies up to July 2024. The search strategy included terms such as "stroke," "tenecteplase," "reteplase," "alteplase," and "randomized." Additional eligible trials were identified from two published systematic reviews (11, 12). Detailed search strategies are provided in the Supplementary Table S3.

2.5 Data extraction and quality assessment

Two authors independently screened titles, abstracts, and full texts for eligibility, with discrepancies resolved by a third reviewer (Li-chao-yue Sun, Wen-shu Li, Wei Chen). Four researchers (Ze Jiang, Li-chao-yue Sun, Wen-shu Li, Wei Chen) independently extracted data using standardized forms, including study characteristics, patient demographics, intervention details, and outcomes of interest. Any disagreements were resolved through consensus with a third evaluator. The risk of bias for eligible RCTs was independently assessed using the Cochrane Collaboration's risk of bias tool (13). Each study was evaluated for low, unclear, or high risk of bias across multiple domains.

2.6 Data synthesis and analysis

For each outcome, we first conducted pairwise meta-analyses using fixed/random effects models to estimate pooled OR and 95% CI. Heterogeneity was assessed using the I^2 statistic. For efficacy and safety outcomes, we ranked the probabilities of each treatment (alteplase, two doses of reteplase, and three doses of tenecteplase) using surface under the cumulative ranking (SUCRA) curves. Data analysis and bias assessments were performed using Review Manager Version 5.3, Stata 16 (mvmeta command and network routine), and the "rjags" and "gemtc" packages in R software (version 4.4) (14).

2.7 Sensitivity and subgroup analyses

The Supplementary material describes the methods for assessing consistency and publication bias (funnel plots and Egger's regression test). We examined potential sources of heterogeneity, including geographic regions (Caucasians and Asians), mean age differences (dichotomized at 65 years), baseline National Institutes of Health Stroke Scale (NIHSS) scores (0–5: low/minor stroke, 6–15: moderate, 15–20: moderate-high, >21: high), and gender. Subgroup analyses were performed for overall tenecteplase, reteplase, and alteplase (regardless of dose), as well as specific doses of tenecteplase (0.25 mg/kg) and reteplase (18 mg+18 mg) compared to the standard dose of alteplase.

3 Result

3.1 Systematic review and characteristics

Among the 4,220 non-duplicate studies screened, 12 RCTs (involving 6,633 acute stroke patients) met the inclusion criteria for this study (Figure 1) (15–26). These RCTs provided at least one outcome included in our network meta-analysis. Detailed reasons for exclusion are available in the Supplementary material, and Table 1 documents the basic characteristics and outcomes of the included RCTs.

Of the 12 RCTs included in the network meta-analysis, 10 (83.33%) directly compared the efficacy and safety of tenecteplase with alteplase for treating acute stroke, while 2 compared reteplase with alteplase (25, 26). Based on dosage, 8 RCTs reported comparisons between 0.25 mg/kg tenecteplase and alteplase, 3 reported on 0.1 mg/kg tenecteplase, 3 on 0.4 mg/kg tenecteplase, 2 on 18 mg + 18 mg reteplase, and 1 on 12 mg + 12 mg reteplase. The outcome measures in RCTs exhibit variations in their definitions. In assessing excellent functional outcomes at 90 days, Campbell et al. (17), TASTE-A (16), and NOR-TEST2 (PARTA) (24) define it as a mRS score of 0–1 or a return to baseline, whereas nine other RCTs define it as an mRS score of 0–1 at 90 days. Regarding sICH, ATTEST (18), Campbell et al. (17), TASTE-A (16), and Li2024 (26) define it according to the SITS-MOST criteria; NOR-TEST (20), TRACE (19), NOR-TEST2 (PARTA) (24), AcT (21), TRACE-2 (23), and RAISE (25) define it based on the ECASS III criteria. For details on the definitions of efficacy and safety outcomes, refer to Supplementary Table S5. All RCTs employed a parallel control design with the control group receiving 0.9 mg/kg alteplase; 8 trials had two groups, 3 had three groups, and 1 had four groups (Figure 2). The network map for different outcomes is shown in Supplementary Figure S1.

3.2 Quality assessment

Due to the lack of blinding for participants and personnel, most studies were deemed to have a high risk of bias (Figure 3). Green

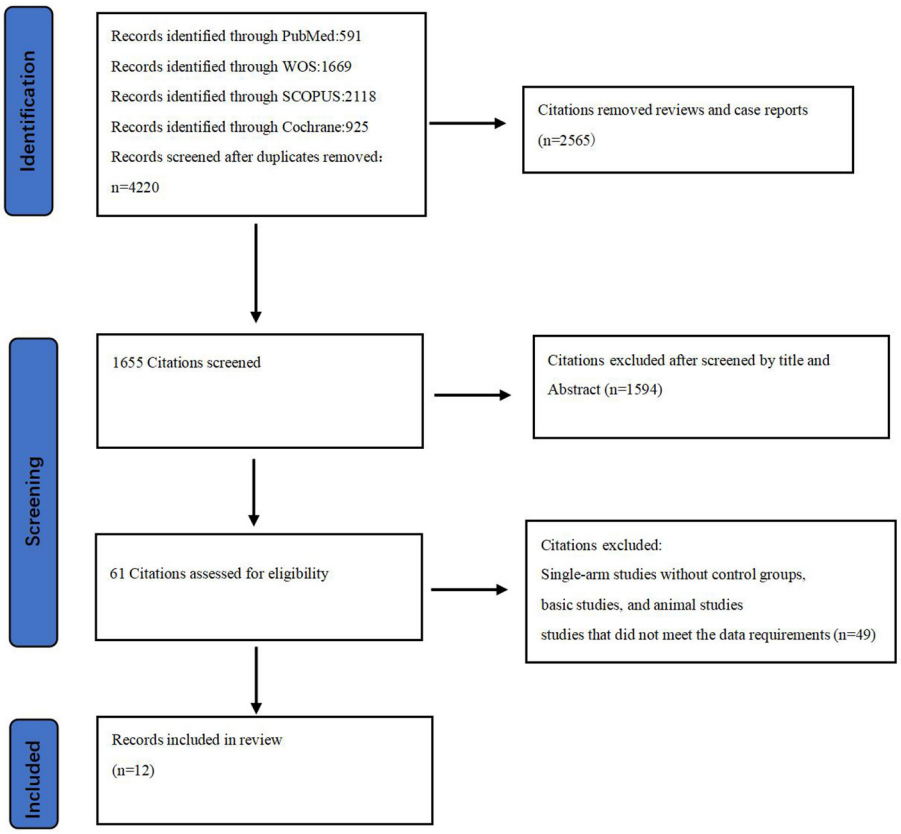

FIGURE 1
Study flow diagram for evidence source and selection.

represents low risk, yellow indicates unclear risk, and red denotes high risk. The direct comparisons between 0.25 mg/kg tenecteplase and 18 mg + 18 mg reteplase with alteplase contributed significantly to the network (Supplementary Figure S2). The RAISE trial did not provide blinding details, and the TRACE trial did not describe the allocation method, resulting in an unclear risk assessment.

3.3 Benefits

Compared to alteplase, tenecteplase showed no significant difference (excellent: OR 1.08, 95% CI: 0.97–1.22, $I^2 = 27\%$). However, patients treated with reteplase had better outcomes (excellent: OR 1.55, 95% CI: 1.23–1.95, $I^2 = 34\%$, $P = 0.0002$) (Figure 4). For good functional outcome at 90 days, neither tenecteplase (OR 1.03, 95% CI: 0.81–1.3, $I^2 = 60\%$) nor reteplase (OR 1.15, 95% CI: 0.61–2.19, $I^2 = 62\%$) showed significant differences compared to alteplase (Figure 5).

A network meta-analysis of different doses of tenecteplase and reteplase was conducted. For excellent functional outcome at 90 days, the efficacy ranking was: 18 mg + 18 mg reteplase > 0.25 mg/kg tenecteplase > 0.9 mg/kg alteplase > 0.4 mg/kg tenecteplase > 0.1 mg/kg tenecteplase > 12 mg + 12 mg reteplase. For good functional outcome at 90 days, the ranking was: 0.25 mg/kg tenecteplase > 18 mg + 18 mg reteplase > 0.9 mg/kg alteplase > 0.1 mg/kg tenecteplase > 12 mg + 12 mg reteplase > 0.4 mg/kg tenecteplase (Figure 6). Compared to 0.9 mg/kg alteplase, patients treated with 0.25 mg/kg tenecteplase (excellent: OR 1.2, 95% CI: 0.94–1.7; good: OR 1.3, 95% CI: 0.79–2.5) and 18 mg + 18 mg reteplase (excellent: OR 1.6, 95% CI: 0.91–2.5; good: OR 1.2, 95% CI: 0.42–3.5) had better functional outcomes at 90 days (Supplementary Figures S3, S4).

3.4 Harms

All RCTs reported sICH and death within 90 days, although no sICH cases occurred in the TASTE-A trial. Eight RCTs reported SAEs. The risk of sICH ranked from lowest to highest as follows: 0.1 mg/kg tenecteplase > 0.25 mg/kg tenecteplase > 0.9 mg/kg alteplase > 18 mg + 18 mg reteplase > 12 mg + 12 mg reteplase > 0.4 mg/kg tenecteplase (Figure 7A). Both 0.1 mg/kg tenecteplase (OR 0.78, 95% CI: 0.15–3.2) and 0.25 mg/kg tenecteplase (OR 0.88, 95% CI: 0.35–1.8) had lower risks compared to alteplase, as shown in Supplementary Figure S5.

The risk of death within 90 days ranked as follows: 0.1 mg/kg tenecteplase > 12 mg + 12 mg reteplase > 0.25 mg/kg tenecteplase > 0.9 mg/kg alteplase > 18 mg + 18 mg reteplase > 0.4 mg/kg tenecteplase (Figure 7B). Here, 0.1 mg/kg tenecteplase

TABLE 1 The characteristics of included RCTs.

References	Recruitment time	Country	Publication date	RCT number	Intervention	No. patients	Age, mean (SD)	Male sex (%)	Time of onset to treatment	Baseline NIHSS	Outcomes
Haley et al. (15)	2006–2008	United States	2010	NA	TNK (0.1/0.25/0.4 mg/kg)	31:31:19:31	TNK0.1:67 ± 16; TNK0.25:69 ± 15; TNK0.4:68 ± 16; rt–PA:72 ± 16	TNK0.1: 39; TNK0.25: 52; TNK0.4: 68; rt-PA:16	NA	TNK 0.1: 8 (5–11); TNK 0.25: 10 (6–15); TNK 0.4: 9; (5–17) rt-PA: 13 (5–17)	mRS at 90 days, sICH, death within 90 days,
Parsons et al. (22)	2008–2011	Australia	2012	ACTRN12608000466347	TNK (0.1/0.25mg/kg)	25:25:25	TNK0.1:72 ± 6.9; TNK0.25:68 ± 9.4; rt–PA:70 ± 8.4	TNK0.1:52; TNK0.25:52; rt-PA:48	TNK0.1:3.1 ± 0.9; TNK0.25:3.0 ± 0.7; rt-PA:12.7 ± 0.8	TNK0.1:14.5 ± 2.3 TNK0.25:14.6 ± 2.3; rt-PA:14 ± 2.3	mRS at 90 days, sICH, death within 90 days,
ATTEST; Huang et al. (18)	2012–2013	Scotland	2015	NCT01472926	TNK (0.25mg/kg)	47:49	TNK0.25:71 ± 13; rt–PA:71 ± 12	TNK0.25:64; rt-PA:63	TNK0.25:184 ± 44; rt-PA:192 ± 54	TNK0.25: 12 (9–18); rt-PA: 11(8–16)	mRS at 90 days, sICH, death within 90 days, SAE
NOR-TEST; Logallo et al. (20)	2012–2016	Norway	2017	NCT01949948	TNK (0.4mg/kg)	549:541	TNK0.4:70.8 ± 14.4; rt–PA:71.2 ± 13.2	TNK0.4:58; rt-PA:62	TNK0.4:118(79-180); rt-PA: 111(80-174)	TNK0.4:4(2-7); rt-PA: 4(2-8)	mRS at 90 days, sICH, death within 90 days, SAE
Campbell et al. (17)	2015–2017	Australia and New Zealand	2018	NCT02388061	TNK (0.25mg/kg)	101:101	TNK0.25:70.4 ± 15.1; rt–PA:71.9 ± 13.7	TNK0.25:57; rt-PA:51	TNK0.25:125(105-156); rt-PA:134(104-176)	TNK0.25:17(12-22); rt-PA:17(12-22)	mRS at 90 days, sICH, death within 90 days, SAE
TRACE; Li et al. (19)	2018–2020	China	2022	NCT04676659	TNK (0.1/0.25/0.32 mg/kg)	60:57:60:59	TNK0.1:62.4 ± 11.1; TNK0.25:64.3 ± 12.8; TNK0.4:64.8 ± 12.1; rt–PA:66.5 ± 12.6	TNK 0.1: 80; TNK 0.25: 74; TNK 0.32: 70; rt-PA: 64	TNK 0.1: 154 (56–195); TNK 0.25: 149 (80–179); TNK 0.32: 147 (69–220); rt-PA: 153 (18–187)	TNK 0.1: 7.0 (5–10); TNK 0.25: 8 (5–12); TNK 0.32: 7.5 (6–12); rt-PA: 8 (5–12)	mRS at 90 days, sICH, death within 90 days, SAE
TASTE-A; Bivard et al. (16)	2019–2021	Australia	2022	NCT04071613	TNK (0.25mg/kg)	55:49	TNK0.25:76 (60–84) rt–PA:73(61–80)	TNK0.25:60; rt-PA:61	TNK0.25: 97 (68–157) rt-PA: 92 (66–31)	TNK: 8 (5–14); rt-PA: 8 (5–17)	mRS at 90 days, death within 90 days,
NOR-TEST2 (PARTA); Kvistad et al. (24)	2019–2021	Norway	2022	NCT03854500	TNK (0.4mg/kg)	96:101	TNK0.4: 73.2 ± 12.6; rt–PA: 68.6 ± 15.6	TNK0.4: 45; rt-PA: 51	TNK0.4: 92.5 (74–143); rt-PA: 99 (73–143)	TNK0.4: 11.5 (8–17); rt-PA: 11 (8–17.6)	mRS at 90 days, sICH, death within 90 days,
AcT; Menon et al. (21)	NA	Canada	2022	NCT03889249	TNK (0.25mg/kg)	806:711	TNK0.25:74 (63–83) ;rt–PA:73 (62–83)	TNK0.25:52.6;rt-PA:51.6	TNK0.25:128 (93–186) ;rt-PA:131 (95–188)	TNK0.25:9 (6–16) rt-PA:10 (6–17)	mRS at 90 days, sICH, death within 90 days, SAE
TRACE-2; Wang et al. (23)	2021–2022	China	2023	NCT04797013	TNK (0.25mg/kg)	705:696	TNK0.25:67 (58–73) rt–PA:65 (58–72)	TNK0.25:69; rt-PA:68	TNK0.25:180(135-222); rt-PA:178.5(135-230)	TNK0.25:7(5-10); rt-PA:7(6-10)	mRS at 90 days, sICH, death within 90 days, SAE

(Continued)

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TABLE 1 (Continued)

References	Recruitment time	Country	Publication date	RCT number	Intervention	No. patients	Age, mean (SD)	Male sex (%)	Time of onset to treatment	Baseline NIHSS	Outcomes
Li et al. (26)	2019–2021	China	2024	NCT04028518	Reteplase (18mg+18mg); Reteplase (12mg+12mg)	66:60:50	Ret12:62.8(10.1) Ret18:61.9(9.5) rt–PA:63.3(9.5)	Ret12:76.7 Ret18:69.7 rt-PA:76	Ret12:213.5 (162-241.5); Ret18:212.0 (163.0-235.0); rt-PA:215(162-244)	Ret12:6.0(5-8.5); Ret18:6(5-8); rt-PA:8(5-10)	mRS at 90 days, sICH, death within 90 days, SAE
RAISE; Li et al. (25)	2022–2023	China	2024	NCT05295173	Reteplase (18mg+18mg)	707:705	Ret18:63 (56–70); rt–PA:63 (56–70)	Ret18:71.9; rt-PA:69.2	Ret18:180 (131–221); rt-PA:183 (139–222)	Ret18:6(5-8); rt-PA:6(5-8)	mRS at 90 days, sICH, death within 90 days, SAE

1. RCT, randomized controlled trials; TNK, tenecteplase; ALT/rt-PA, alteplase; Ret, reteplase; sICH, symptomatic intracranial haemorrhage; SAE, serious adverse event.
TNK0.1: 0.1 mg/kg tenecteplase, TNK0.25: 0.25mg/kg tenecteplase, TNK0.4: 0.4mg/kg tenecteplase, Ret12: 12mg+12mg reteplase, Ret18: 18mg+18mg reteplase.
2. Time of onset to treatment is usually measured in minutes/min.

(OR 0.59, 95% CI: 0.21–1.5), 12 mg + 12 mg reteplase (OR 0.66, 95% CI: 0.13–3.9), and 0.25 mg/kg tenecteplase (OR 0.91, 95% CI: 0.54–1.4) had lower risks compared to alteplase, as shown in Supplementary Figure S6.

The risk of SAEs ranked as follows: 12 mg + 12 mg reteplase > 0.25 mg/kg tenecteplase > 0.4 mg/kg tenecteplase > 0.9 mg/kg alteplase > 0.1 mg/kg tenecteplase > 18 mg + 18 mg reteplase (Figure 7C). The risks for 12 mg + 12 mg reteplase (OR 0.99, 95% CI: 0.17–1.9), 0.25 mg/kg tenecteplase (OR 1.0, 95% CI: 0.47–2.3), and 0.4 mg/kg tenecteplase (OR 1.0, 95% CI: 0.19–5.5) were as shown in Supplementary Figure S7.

3.5 Sensitivity and subgroup analyses

We performed subgroup analyses based on different patient baselines in the included RCTs. All RCTs had a higher proportion of male patients (>50%), showing no gender-based differences. Regarding mean age, only the TRACE trial (64.5 years) for tenecteplase had a mean participant age <65 years. For reteplase, both the RAISE (63 years) and Li2024 (62.5 years) trials had mean participant ages <65 years. Based on race, the TRACE and TRACE-2 trials, RAISE, and Li2024 (conducted in China) included Asian patients, while other RCTs predominantly included Caucasians. Stratifying by NHISS baseline, the NOR-TEST trial had a low NHISS score (<5), the Campbell2018 trial had a moderate-high NHISS score (15–20), and other RCTs had moderate NHISS scores (5–15). Due to limitations in the number of RCTs and lack of data, we conducted subgroup analyses only for race and mean age, including tenecteplase (not dose-stratified, Supplementary Tables S5, S6), 0.25 mg/kg tenecteplase, and 18 mg + 18 mg reteplase (the most effective doses in previous analyses, Supplementary Tables S7, S8).

3.5.1 Type of age

We stratified by a threshold mean age of 65 years, dividing into <65 years and ≥65 years groups. For patients with a mean age <65 years, tenecteplase showed no significant difference compared to alteplase (excellent: OR 0.98, 95% CI: 0.54–1.78, $P = 0.98$; good: OR 0.87, 95% CI: 0.45–1.68, $P = 0.68$). For patients with a mean age ≥65 years, tenecteplase also showed no significant difference compared to alteplase (excellent: OR 1.05, 95% CI: 0.93–1.18, P=0.44; good: OR 1.04, 95% CI: 0.81–1.34, $P = 0.74$) (Supplementary Table S5). Comparing 0.25 mg/kg tenecteplase to 0.9 mg/kg alteplase: for patients with a mean age <65 years (excellent: OR 1.09, 95% CI: 0.52–2.3, $P = 0.82$; good: OR 1.04, 95% CI: 0.46–2.37, $P = 0.92$), and for patients with a mean age ≥65 years (excellent: OR 1.12, 95% CI: 0.98–1.29, $P = 0.1$; good: OR 1.23, 95% CI: 0.88–1.77, $P = 0.22$) (Supplementary Table S7). Regardless of average age, 0.25 mg/kg tenecteplase was the most effective tenecteplase dose, and 18 mg + 18 mg reteplase was the most effective reteplase dose (Supplementary Tables S5, S7).

3.5.2 Type of ethnicity

Due to the inclusion of only Asian patients in reteplase-related RCTs, we conducted subgroup analysis for tenecteplase

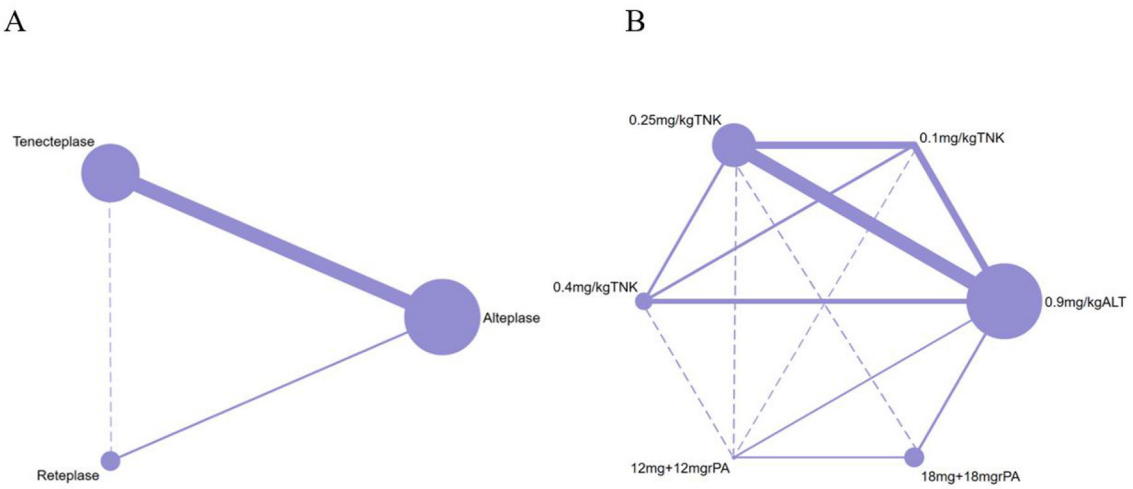

FIGURE 2
Network plot of studies included in network meta-analysis. **(A)** The network of included studies by type of thrombolytic drug. **(B)** The network of included studies by type and dose of thrombolytic drugs. ALT, Alteplase; TNK, Tenecteplase; rPA, Reteplase. Each node represents a treatment modality, with its size proportional to the number of patients receiving that treatment. The lines connecting two nodes indicate direct comparisons between the two treatment modalities, with the thickness of each line proportional to the number of trials comparing those two treatments. Dashed lines indicate that no direct comparison exists between the two thrombolytic treatments.

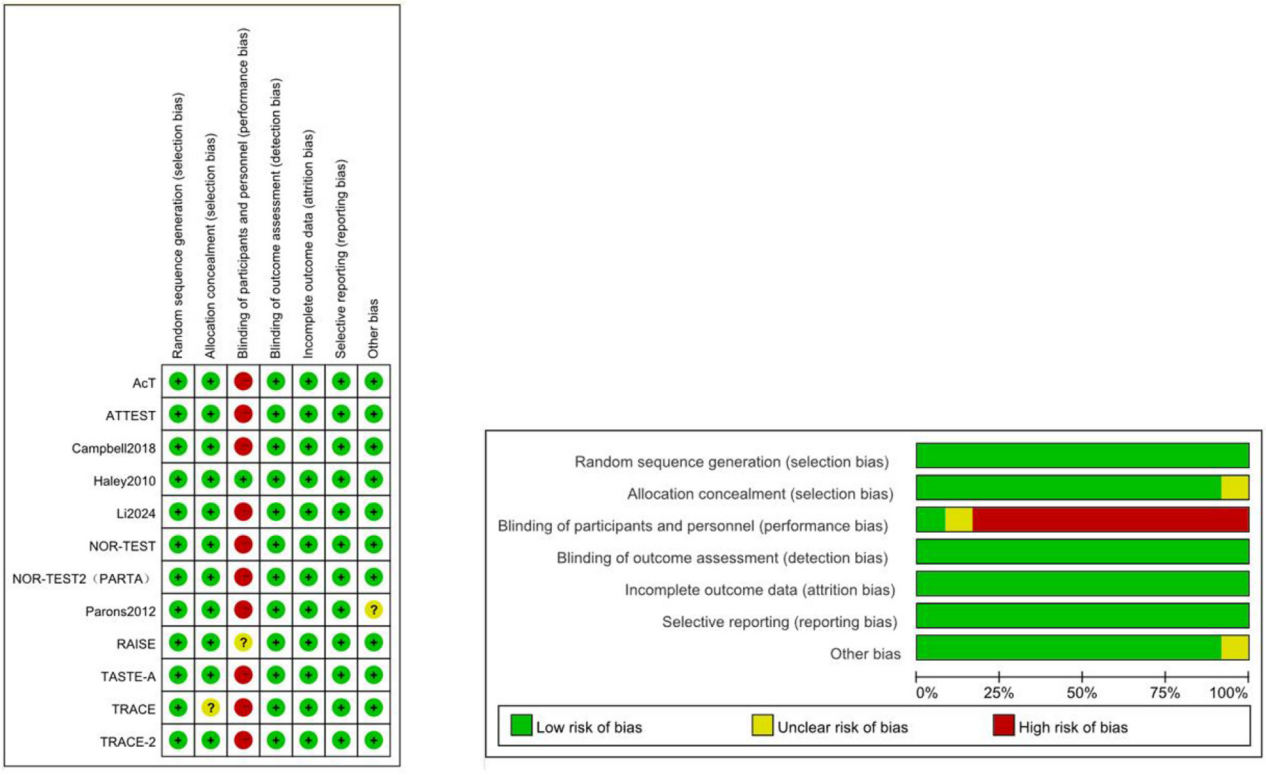

FIGURE 3
Cochrane risk of bias tool.

vs. alteplase based on ethnicity. For excellent functional outcome at 90 days, tenecteplase in Asian (OR 1.16, 95% CI: 0.95–1.42, $P = 0.15$) and in Caucasian (OR 0.99, 95% CI: 0.86–1.44, $P = 0.93$); 0.25 mg/kg tenecteplase in Asian (OR 1.18, 95% CI: 0.96–1.45, $P = 0.12$) and in Caucasian (OR 1.08, 95% CI: 0.9–1.3, $P = 0.39$) (Supplementary Tables S5, S7). These results indicate

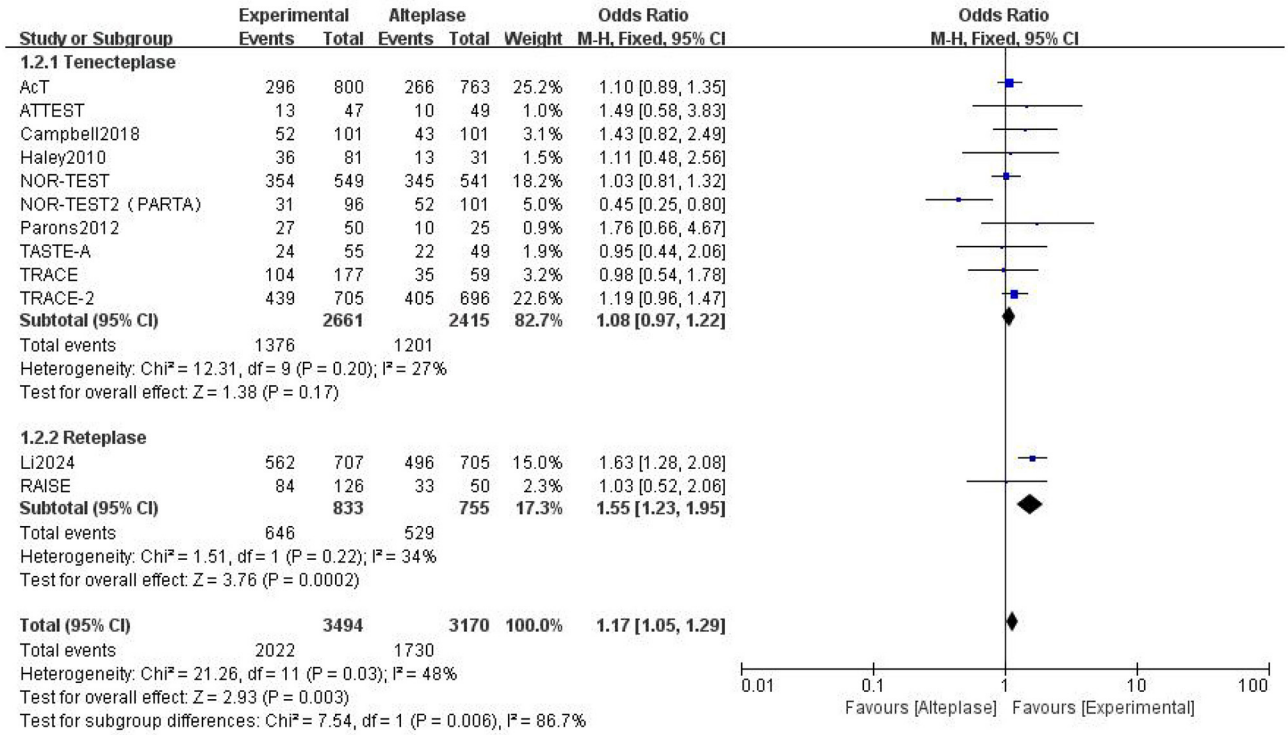

FIGURE 4
Forest plot for the tenecteplase and reteplase on excellent functional outcome at 90 days.

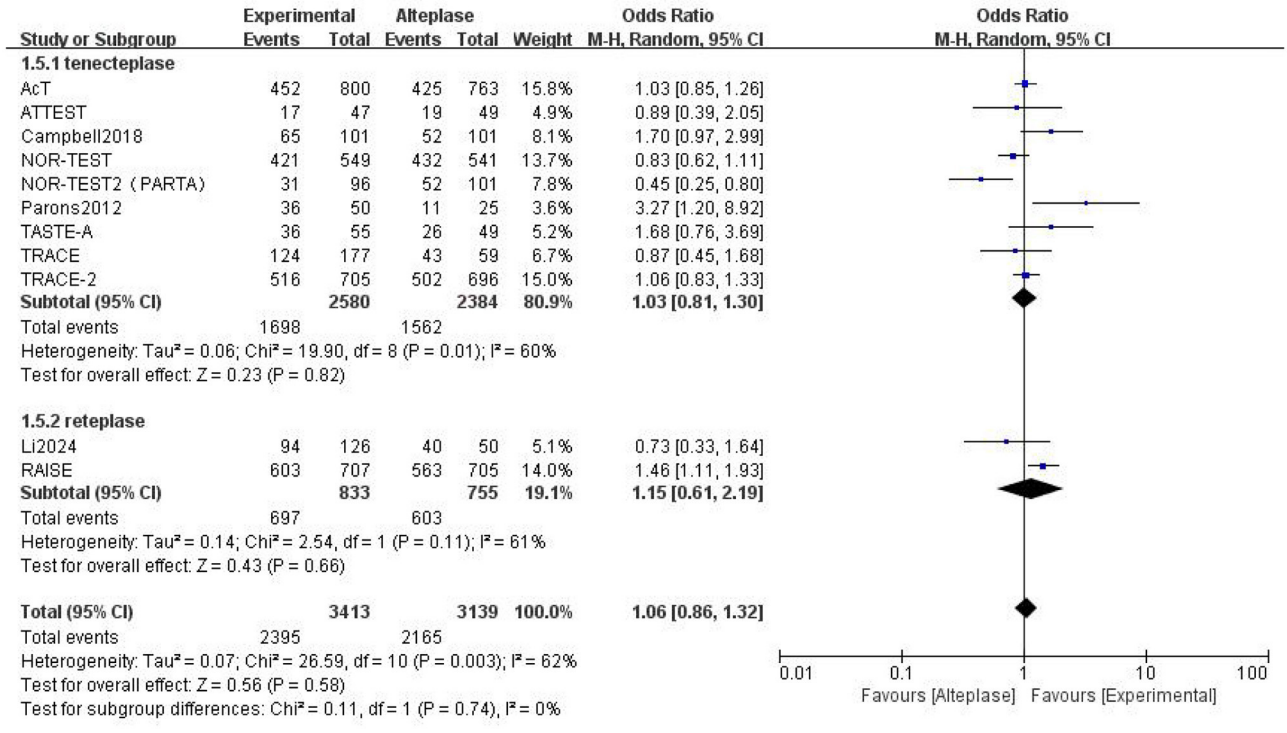

FIGURE 5
Forest plot for the tenecteplase and reteplase on good functional outcome at 90 days.

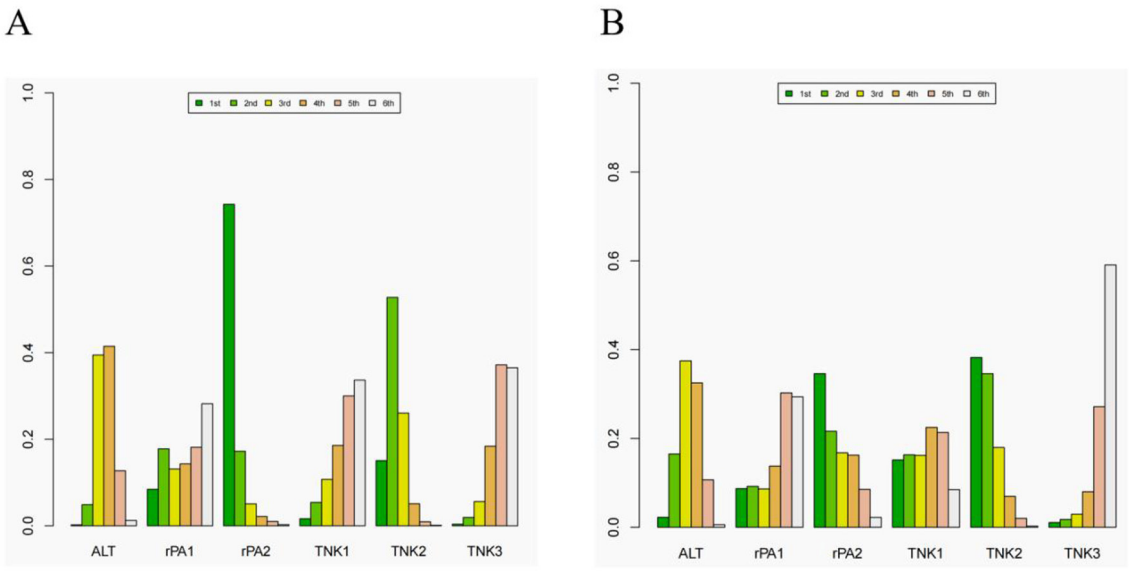

FIGURE 6
The rank of different dose of the tenecteplase and reteplase on excellent and good functional outcome at 90 days. **(A)** the rank of thrombolytic therapy on excellent functional outcome at 90 days. **(B)** the rank of thrombolytic therapy on good functional outcome at 90 days. ALT= 0.9 mg/kg alteplase, rPA1= 12 mg + 12 mg reteplase, rPA2= 18 mg + 18 mg reteplase, TNK1, 0.25 mg/kg tenecteplase; TNK2, 0.25 mg/kg tenecteplase; TNK3, 0.4 mg/kg tenecteplase.

that tenecteplase is more effective in treating Asian AIS patients compared to Caucasians, and 0.25 mg/kg tenecteplase is more effective than other doses and the standard dose of alteplase across ethnicities.

3.5.3 Type of NIHSS score

We stratified patients based on the average baseline NIHSS score, following the criteria of the AcT and TRACE-2 studies (21, 23), into three groups: scores below 8, between 8 and 15, and above 15. There were 3 RCTs using tenecteplase in the group with scores below 8; 6 RCTs in the group with scores between 8 and 15; and only 1 RCT in the group with scores above 15. All RCTs involving reteplase had patients with baseline NIHSS scores below 8. Regardless of the average NIHSS score, tenecteplase showed no intergroup differences in efficacy and safety outcomes compared to alteplase across all score ranges, as detailed in Supplementary Table S11.

3.5.4 Other outcomes and heterogeneity analyses

This study also provided detailed subgroup analyses of the safety outcomes for tenecteplase and reteplase based on age and ethnicity (Supplementary Tables S6, S8). Additionally, we presented the publication bias of this network meta-analysis for different outcomes using funnel plots (Supplementary Figures S8–S12). Other patient stratifications (NHISS baseline, onset-to-treatment time) and outcome indicators (major neurological improvement, any intracranial hemorrhage, any parenchymal hemorrhage) were not analyzed due to insufficient data. No adjustments for other potential sources of heterogeneity were made due to a lack of power.

4 Discussion

This study represents the first network meta-analysis to simultaneously compare the efficacy and safety of reteplase, alteplase, and tenecteplase for treating acute ischemic stroke. By including 12 RCTs encompassing 6,633 patients (2,661 tenecteplase, 833 reteplase, and 3,139 alteplase), we assessed the benefits and risks of thrombolytic treatment with different doses of these agents. Preliminary analysis indicates that reteplase outperforms alteplase in achieving excellent functional outcomes at 90 days, while tenecteplase and alteplase show no significant differences. For other outcomes, including good functional outcomes at 90 days, symptomatic intracranial hemorrhage, death within 90 days, and serious adverse events, reteplase and tenecteplase demonstrated no significant differences compared to alteplase. Dose-specific analysis revealed that 18 mg + 18 mg reteplase and 0.25 mg/kg tenecteplase provided higher probabilities of achieving excellent/good functional outcomes at 90 days compared to 0.9 mg/kg alteplase, with 0.25 mg/kg tenecteplase showing lower risks of sICH, death within 90 days, and SAEs. Subgroup analysis by mean age and ethnicity confirmed the superior efficacy of 0.25 mg/kg tenecteplase regardless of race or age.

Despite the current lack of consensus on the optimal dose of tenecteplase for AIS, previous meta-analyses have supported 0.25 mg/kg as the most effective dose, aligning with our findings (9, 12, 27). Two RCTs demonstrated that 0.4 mg/kg tenecteplase provided no additional benefits over 0.9 mg/kg alteplase but increased the

A

0.1mg/kg tenecteplase	1.1 (0.24, 5.48)	1.19 (0.14, 9.21)	1.27 (0.3, 6.33)	2.57 (0.17, 41.6)	2.95 (0.6, 24.35)
●RANK 1st	0.25mg/kg tenecteplase	1.07 (0.19, 5.06)	1.13 (0.55, 2.84)	2.28 (0.21, 28.12)	2.58 (0.85, 15.16)
	○RANK 2nd	18mg+18mg reteplase	1.06 (0.3, 5.3)	2.13 (0.23, 24.91)	2.4 (0.55, 25.4)
●RANK 1st		●RANK 3th	0.9mg/kg alteplase	1.99 (0.2, 20.38)	2.27 (0.87, 10.03)
0.1mg/kg tenecteplase	○RANK 2nd		○RANK 4th	12mg+12mg reteplase	1.16 (0.1, 19.32)
0.91 (0.18, 4.18)	0.25mg/kg tenecteplase	●RANK 3th		●RANK 5th	0.4mg/kg tenecteplase
0.84 (0.11, 7.1)	0.94 (0.2, 5.14)	18mg+18mg reteplase	○RANK 4th		○RANK 6th
0.79 (0.16, 3.29)	0.88 (0.35, 1.81)	0.94 (0.19, 3.32)	0.9mg/kg alteplase	●RANK 5th	
0.39 (0.02, 5.96)	0.44 (0.04, 4.85)	0.47 (0.04, 4.31)	0.5 (0.05, 5.05)	12mg+12mg reteplase	○RANK 6th
0.34 (0.04, 1.67)	0.39 (0.07, 1.17)	0.42 (0.04, 1.83)	0.44 (0.1, 1.16)	0.86 (0.05, 9.96)	0.4mg/kg tenecteplase

B

0.1mg/kg tenecteplase	1.11 (0.17, 6.89)	1.53 (0.59, 4.28)	1.69 (0.68, 4.76)	2.05 (0.57, 7.96)	2.32 (0.77, 7.83)
●RANK 1st	12mg+12mg reteplase	1.37 (0.28, 7.44)	1.52 (0.34, 7.84)	1.84 (0.42, 9.07)	2.09 (0.39, 12.67)
	○RANK 2nd	0.25mg/kg tenecteplase	1.1 (0.71, 1.84)	1.33 (0.49, 3.78)	1.51 (0.67, 3.69)
●RANK 1st		●RANK 3th	0.9mg/kg alteplase	1.21 (0.48, 2.95)	1.37 (0.66, 2.91)
0.1mg/kg tenecteplase	○RANK 2nd		○RANK 4th	18mg+18mg reteplase	1.13 (0.36, 3.74)
0.9 (0.15, 5.76)	12mg+12mg reteplase	●RANK 3th		●RANK 5th	0.4mg/kg tenecteplase
0.65 (0.23, 1.69)	0.73 (0.13, 3.56)	0.25mg/kg tenecteplase	○RANK 4th		○RANK 6th
0.59 (0.21, 1.47)	0.66 (0.13, 2.94)	0.91 (0.54, 1.41)	0.9mg/kg alteplase	●RANK 5th	
0.49 (0.13, 1.75)	0.54 (0.11, 2.36)	0.75 (0.26, 2.03)	0.82 (0.34, 2.07)	18mg+18mg reteplase	○RANK 6th
0.43 (0.13, 1.3)	0.48 (0.08, 2.53)	0.66 (0.27, 1.49)	0.73 (0.34, 1.53)	0.88 (0.27, 2.79)	0.4mg/kg tenecteplase

C

12mg+12mg reteplase	1.01 (0.17, 5.94)	1.02 (0.19, 5.54)	1.03 (0.16, 6.63)	1.13 (0.21, 6.15)	1.19 (0.15, 9.67)
●RANK 1st	0.9mg/kg alteplase	1.03 (0.09, 11.74)	1.05 (0.47, 2.31)	1.16 (0.11, 12.64)	1.34 (0.31, 6.04)
	○RANK 2nd	0.4mg/kg tenecteplase	1.06 (0.15, 7.32)	1.18 (0.22, 6.35)	1.38 (0.17, 11.5)
●RANK 1st		●RANK 3th	0.25mg/kg tenecteplase	1.2 (0.1, 13.77)	1.4 (0.4, 5.02)
12mg+12mg reteplase	○RANK 2nd		○RANK 4th	0.1mg/kg tenecteplase	1.42 (0.25, 8.2)
0.99 (0.17, 5.89)	0.9mg/kg alteplase	●RANK 3th		●RANK 5th	18mg+18mg reteplase
0.97 (0.09, 11.26)	0.98 (0.18, 5.32)	0.4mg/kg tenecteplase	○RANK 4th		○RANK 6th
0.94 (0.14, 6.65)	0.95 (0.43, 2.12)	0.97 (0.15, 6.36)	0.25mg/kg tenecteplase	●RANK 5th	
0.83 (0.07, 9.53)	0.84 (0.16, 4.49)	0.86 (0.08, 9.21)	0.88 (0.16, 4.72)	0.1mg/kg tenecteplase	○RANK 6th
0.7 (0.12, 3.99)	0.71 (0.2, 2.48)	0.73 (0.09, 5.95)	0.75 (0.17, 3.25)	0.84 (0.1, 6.82)	18mg+18mg reteplase

FIGURE 7
Summary of target safety outcomes by bayesian network meta-analysis, including **(A)** symptomatic intracranial haemorrhage, **(B)** death within 90 days and **(C)** serious adverse events.

incidence of mortality and hemorrhagic events (16, 28). Our study found that 0.1 mg/kg tenecteplase was less effective than 0.9 mg/kg alteplase for 90-day functional outcomes, likely due to underdosing (29). Reteplase, traditionally used for acute myocardial infarction, has shown efficacy comparable to alteplase in trials such as GUSTO III and RAPID II (30, 31). Li's RCTs have extended the use of reteplase to AIS, suggesting that 18 mg + 18 mg reteplase is a suitable dose (25, 26). Further high-quality trials are needed to determine the optimal reteplase dose and its efficacy relative to alteplase.

Simultaneously, the thrombolytic time window for alteplase has been extensively investigated. A recent TRACE-III study indicated that the treatment time window for tenecteplase could be extended to 24 h, which resulted in an increased risk of bleeding but did not elevate the incidence of serious clinical adverse events (32). For tenecteplase and reteplase, most evidence suggests optimal thrombolysis occurs within 4.5 h; however, further research is required to ascertain whether these thrombolytic agents possess longer therapeutic windows.

Key indicators for evaluating thrombolytic efficacy include the rate of complete or partial recanalization within 24 h and major neurological improvement at 24 h (33). Previous meta-analyses have shown higher rates of successful recanalization with tenecteplase compared to alteplase (34, 35). Tenecteplase has demonstrated comparable or superior outcomes for major neurological improvement at 24 h. Some RCTs have introduced new metrics such as the Barthel Index score at 90 days to assess patient recovery, providing alternative perspectives on thrombolysis results in AIS patients (23, 24, 36). Additionally, the high cost of alteplase may limit its clinical use, whereas tenecteplase offers a cost advantage (37, 38). However, there is currently a lack of cost-effectiveness analysis comparing reteplase and alteplase for AIS treatment.

5 Strength and limitation

1. The two RCTs involving reteplase exclusively included Chinese stroke patients, which may introduce racial bias. Further trials focusing on Caucasian and African populations are necessary.
2. The primary patient population in RCTs conducted in Western countries is predominantly Caucasian (though not exclusively), while the majority of RCTs conducted in Asian regions involve Asian populations. This demographic difference may introduce a certain degree of bias in the description of our results. Furthermore, we believe that including an analysis by ethnicity in future RCTs could help mitigate this bias and enhance the generalizability of the study findings.
3. The small number of studies and limited sample sizes in some trials may introduce errors in our results, highlighting the need for larger-scale RCTs.
4. There are no direct comparison trials between tenecteplase and reteplase. Due to heterogeneity in the trial populations, the results from indirect comparisons have inherent limitations.
5. Different RCTs used varying scales for outcome measures, such as SITS-MOS and ECASS II for sICH, potentially introducing bias.

6 Conclusion

Using systematic review and meta-analysis, this study investigated the effectiveness of different thrombolytic agents in improving functional outcomes in AIS patients. We compared the efficacy of alteplase, tenecteplase, and reteplase, incorporating dose-specific and subgroup analyses. The findings indicate that tenecteplase and reteplase, in addition to alteplase, are effective treatment options for AIS. Specifically, 0.25 mg/kg tenecteplase and 18 mg + 18 mg reteplase demonstrated higher probabilities of achieving excellent/good functional outcomes at 90 days compared to 0.9 mg/kg alteplase. Furthermore, 0.25 mg/kg tenecteplase showed superior safety compared to alteplase and 18 mg + 18 mg reteplase. These results provide valuable guidance for clinicians in selecting thrombolytic agents for AIS treatment.

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

L-C-YS: Writing – original draft, Writing – review & editing. W-SL: Investigation, Writing – original draft, Writing – review & editing. QX: Conceptualization, Investigation, Writing – review & editing. WC: Writing – review & editing. ZR: Data curation, Methodology, Writing – review & editing. C-XL: Methodology, Software, Writing – review & editing. ZJ: Conceptualization, Supervision, Writing – original draft. LW: Data curation, Investigation, Writing – review & editing. D-LW: Methodology, Writing – review & editing.

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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

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Role of microRNA in the risk stratification of ischemic strokes

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Background: Ischemic stroke is a major cause of death and morbidity, and risk classification is essential for predicting therapeutic outcomes. MicroRNAs may be useful indicators for risk stratification, as they control gene expression and influence physiological and pathological processes.

Methodology: A systematic strategy was developed to search relevant material using databases like PubMed, Scopus, and Web of Science. Selection criteria included human research, a certain date, or categories of studies. Data extraction, synthesis, and analysis were carried out to find trends, similarities, and differences among the chosen studies. The study's design, sample size, methodology, statistical analysis, and any potential biases or restrictions from the selected reference papers were also taken into account.

Results and findings: MicroRNA is an important biomarker for risk stratification in Ischemic Strokes. It can be used to identify Stroke-Specific microRNA Signatures, identify diagnostic and prognostic values, and regulate Vascular Inflammation, Endothelial Dysfunction, and Thrombus Formation and Resolution. It also has potential therapeutic applications.

Conclusion: MicroRNAs have emerged as promising biomarkers for predicting stroke risk, severity of strokes, and clinical outcomes. They can be used to predict the severity of a stroke and aid clinicians in making treatment decisions.

KEYWORDS

ischemic stroke, microRNAs, inflammatory response, neuronal death, vascular inflammation, endothelial dysfunction, thrombus formation

Introduction

Ischemic stroke are frequent cerebrovascular events defined as an abrupt reduction in blood flow to the brain, which causes tissue damage and neurological impairments. It is a major contributor to death and morbidity on a global scale. For patients with ischemic stroke, effective risk classification is essential for predicting outcomes and directing therapy choices. A number of variables, including age, sex, medical history, and imaging results, are generally considered to determine further risk classification, have been studied extensively. Most of the work up done is

after the event happens and fails to identify the individual's specific risk of stroke occurrence or recurrence. MicroRNAs (miRNAs) may be useful indicators for ischemic stroke risk stratification, according to recently published research papers (1, 2).

MicroRNAs are tiny, non-coding RNA molecules that control gene expression by attaching to and degrading or inhibiting the translation of their target messenger RNAs (mRNAs). Numerous physiological and pathological processes, such as neuronal growth, synaptic plasticity, and neuroinflammation, are influenced by miRNAs. Dysregulation of some miRNAs has been connected to the etiology of ischemic stroke and may provide important clues for stroke risk assessment (3–5).

Numerous studies have shown that ischemic stroke patients' miRNA expression patterns are different from those of healthy controls. The molecular processes implicated in the pathogenesis of stroke, including as inflammation, oxidative stress, apoptosis, angiogenesis, and neuroplasticity, are influenced by these differentially expressed miRNAs. Notably, several miRNAs have consistently displayed dysregulation in many investigations, suggesting their potential as accurate biomarkers for predicting the risk of stroke (6, 7).

In a variety of biofluids, such as blood, cerebrospinal fluid, and saliva, miRNAs may be found and measured. They make good candidates for clinical applications because of their non-invasive nature. The discovery of certain miRNA signatures linked to various stroke subtypes, severity, and prognosis has also been made easier because to developments in high-throughput technologies like microarray analysis and next-generation sequencing (8).

It is very promising to employ miRNAs as biomarkers for ischemic stroke risk stratification. MiRNA profiling may improve the accuracy of current risk prediction methods and enable individualized treatment approaches. Additionally, miRNAs may be used as therapeutic targets for stroke since altering their expression may be able to affect pathways linked to stroke and aid in neuroprotection and recovery (9).

In nutshell research into the role of miRNAs in the risk assessment of ischemic strokes is still in its infancy. MiRNAs have distinctive patterns of expression in stroke patients and are engaged in a number of molecular processes that contribute to the pathophysiology of stroke. MiRNA profiles may enhance the predictive accuracy of current risk prediction algorithms and help to individualized stroke therapy. To confirm the clinical usefulness of miRNAs and investigate their potential therapeutic uses in ischemic stroke, more research is necessary. It could be able to create risk stratification models for ischemic strokes that are more precise by combining miRNA profiling with conventional risk factors including age, sex, hypertension, diabetes, and smoking history. In turn, this can aid in locating stroke-at-risk people who may benefit from proactive measures and specialized treatment plans to lower their risk. Present review article focuses on the role of microRNA in the risk stratification of Ischemic Strokes. MicroRNAs (miRNAs) are promising indicators for ischemic stroke risk stratification due to their stability in biofluids, dynamic expression changes in response to stroke-related pathophysiological processes, and role in regulating gene expression. Unlike DNA or mRNA, miRNAs provide a more sensitive and minimally invasive means to assess stroke risk and progression. Their ability to reflect inflammation, endothelial dysfunction, and neuronal injury makes them uniquely relevant for personalized risk assessment and monitoring.

Objectives

- To review the current knowledge on the association between microRNAs and ischemic strokes.
- To identify the gaps in knowledge and highlight the areas that require further research to establish the utility of microRNAs as risk stratification biomarkers in ischemic strokes.

Methodology

- Research question: Role of microRNA in the risk stratification of ischemic strokes?
- Study Design: Narrative Review.
- Search strategy: A review of the relevant literature was framed by identifying appropriate databases such as PubMed, Scopus, and Web of Science using relevant keywords, including "microRNA," "risk stratification," and "ischemic stroke." Variations of these keywords and synonyms were also considered. Additionally, the reference lists of relevant articles was reviewed to identify additional sources.
- Selection criteria: Proper criteria for selecting relevant studies were established. These criteria may include the inclusion of human studies, a specific timeframe, or specific types of studies (e.g., clinical trials, observational studies). It was also ensured that the studies selected are directly related to the role of microRNA in risk stratification of ischemic strokes.
- Data extraction: Relevant data from the selected studies was extracted. This may include study characteristics (e.g., study design, sample size), microRNA-related information (e.g., microRNA types, expression levels), stroke-related information (e.g., stroke subtype, risk factors), and any other relevant findings or outcomes.
- Data synthesis and analysis: the extracted data was organized into meaningful categories or themes by identifying patterns, similarities, and differences across the selected studies. The findings in the context of the research question were analyzed looking for consistencies or discrepancies in the role of microRNA in risk stratification of ischemic strokes.
- Critical evaluation: the quality and reliability of the selected studies was assessed considering the study design, sample size, methodology, statistical analysis, and any potential biases or limitations and discussing the strengths and weaknesses of the evidence presented in each study.

Results and important findings

Role of microRNA in ischemic strokes

Dysregulation of microRNA in ischemic strokes

Small non-coding RNA molecules called microRNAs (miRNAs) are essential for the post-transcriptional control of gene expression. They participate in several biological processes, such as cellular differentiation, disease etiology, and development. MiRNA dysregulation has been linked to a number of illnesses, including ischemic strokes (7, 8, 10).

Ischemic stroke happens when the blood flow to the brain is interrupted, which causes the brain cells to perish from a lack of oxygen and nutrition. MiRNA dysregulation in ischemic strokes can take place on several levels and affect the pathophysiology of the disease (Table 1).

Gaining knowledge of the dysregulation of miRNAs in ischemic strokes might help identify possible treatment targets as well as the underlying biological causes. It's crucial to remember that the area of miRNA research is still developing, and more study is required to understand the intricate relationships and pinpoint individual miRNA candidates for use in ischemic stroke diagnosis and treatment.

Impact of microRNA on ischemic stroke pathophysiology

The involvement of miRNAs in ischemic stroke has been extensively studied, and their dysregulation has been implicated in several aspects of stroke pathophysiology (Table 2).

Discovering new therapeutic targets for stroke treatment may be possible by better understanding the precise functions of miRNAs in the pathogenesis of ischemic stroke. To develop miRNA-based therapy strategies for stroke patients, more studies are required to clarify the intricate regulatory networks involving miRNAs and their target genes in the setting of ischemic stroke.

MicroRNA as biomarkers for risk stratification

Identification of stroke-specific microRNA signatures

Small non-coding RNA molecules called microRNAs (miRNAs) are essential for controlling the expression of genes. They have been recognized as possible stroke biomarkers among other disorders. To aid in the early detection, diagnosis, and risk stratification of stroke, researchers have been looking into the identification of miRNA signatures that are unique to stroke (11).

Studies have compared the miRNA expression patterns of stroke patients and healthy people to find miRNAs that are differently expressed and linked to stroke. MiRNA expression patterns in blood, cerebrospinal fluid, and brain tissue from stroke patients have been examined using high-throughput methods such microarray analysis and next-generation sequencing (12, 13).

Specific miRNA signatures that are connected to stroke have been found by comparing the miRNA profiles of stroke patients and healthy controls. Depending on the kind and severity of the stroke, these stroke-specific miRNA signatures may include upregulated or downregulated miRNAs, and their expression levels may change (9).

Diagnostic and prognostic value of microRNA in ischemic strokes

The most frequent form of stroke, an ischemic stroke, is brought on by a blockage in a blood artery feeding the brain. In ischemic strokes, microRNAs have demonstrated encouraging diagnostic and prognostic usefulness. Specific miRNAs that can identify ischemic stroke patients from healthy people or those who have had other types of strokes have been found in several studies (2, 14).

Diagnostic value

It has been reported that a number of miRNAs, including miR-124, miR-125b, miR-133a, and miR-210, are increased in the blood or cerebrospinal fluid of people who have had ischemic strokes. These miRNAs may be used as possible diagnostic biomarkers to help identify and classify ischemic strokes earlier.

Prognostic value

The severity of ischemic strokes and their clinical consequences have been linked to the expression levels of certain miRNAs. In individuals with ischemic stroke, increasing levels of miR-23a and miR-221 have been linked to poorer neurological outcomes and higher mortality. Decisions about therapy and prognosis may be aided by tracking the expression of these miRNAs.

TABLE 1 Levels of dysregulation of microRNA in ischemic stroke (7, 10).

Study number	Levels of dysregulation	Pathophysiology
1	Modulation of the inflammatory response	Ischemic stroke causes a sophisticated inflammatory response in the brain. Dysregulated miRNAs can affect the expression of pro- or anti-inflammatory genes, which can influence this response. By targeting anti-inflammatory molecules, miR-155, for instance, has been demonstrated to enhance neuroinflammation, whereas miR-146a functions as a negative regulator of the inflammatory response.
2	Neuronal cell death	After an ischemic stroke, miRNAs can affect whether neurons survive or die. MiRNAs that target anti-apoptotic or genes involved in cell survival pathways, such miR-21 and miR-29a, have been reported to be increased in ischemic stroke. These miRNAs may accelerate neuronal cell death.
3	Blood–brain barrier integrity	The blood–brain barrier (BBB) is crucial for preserving brain homeostasis and safeguarding it from potentially hazardous chemicals. During an ischemic stroke, miRNA dysregulation can impact the integrity of the BBB. For instance, it has been demonstrated that the tight junction protein essential in maintaining the BBB, miR-132, targets it, potentially increasing permeability.
4.	Neurogenesis and angiogenesis	An ischemic stroke sets off a series of processes, including angiogenesis and neurogenesis, aimed at tissue healing. By altering the expression of genes involved in vascular expansion and neural differentiation, miRNAs can control these processes. MiR-126 and miR-210, for instance, have been linked to angiogenesis, whilst miR-124 and miR-137 have been linked to neurogenesis.

TABLE 2 Pathophysiology and role of miRNAs in ischemic stroke (16, 22, 23).

Study number	Pathophysiology	Role of miRNAs
1	Neuronal cell death	Neuronal cell death brought on by an ischemic stroke is regulated by miRNAs, which have been linked to controlling apoptosis, or planned cell death, in neurons. By targeting anti-apoptotic genes or fostering pro-apoptotic signaling pathways, certain miRNAs, including miR-21, miR-29a, miR-34a, and miR-210, have been found to be increased in ischemic stroke and contribute to neuronal apoptosis.
2	Inflammation and immune response	The development of an ischemic stroke is significantly influenced by the inflammatory response. Following a stroke, miRNAs have been linked to the control of inflammatory and immunological responses. By targeting important genes involved in immune cell activation and cytokine production, for instance, miR-155, miR-146a, and miR-223 are involved in controlling the inflammatory response.
3	Blood–brain barrier (BBB) disruption	The breakdown of the BBB, which aids in keeping the brain microenvironment in a state of homeostasis, advances the course of an ischemic stroke. Matrix metalloproteinases (MMPs), which break down the extracellular matrix, and endothelial cell tight junction proteins are the targets of miRNAs, which have been demonstrated to modulate the integrity of the BBB. The BBB is regulated during a stroke by miRNAs such miR-155, miR-126, and miR-132.
4	Angiogenesis and neurovascular remodeling	Angiogenesis, the development of new blood vessels, and neurovascular remodeling are brought on by ischemic stroke. By focusing on genes involved in endothelial cell proliferation, migration, and vessel stability, miRNAs have been shown to regulate angiogenesis. It is known that miR-210, miR-132, and miR-126 contribute to angiogenesis and neurovascular remodeling after stroke.
5	Neuroplasticity and recovery	Long-term functional losses from ischemic stroke are common, yet the brain is capable of reorganization and rehabilitation. Numerous neuroplasticity-related processes, such as synaptic plasticity, neuronal differentiation, and axonal regeneration, have been revealed to be regulated by miRNAs. Examples of miRNAs that are involved in controlling neuroplasticity during stroke recovery include miR-134, miR-124, and miR-9.

Association of microRNA with stroke subtypes and severity

Stroke is a diverse disorder with several subgroups, including stroke of other determined or unexplained origin, cardio embolism, small vessel disease, and stroke of big artery atherosclerosis. MicroRNAs have been linked to various stroke subtypes and can shed light on the pathophysiology and underlying causes (2, 12, 15).

It has been discovered that distinct miRNAs are connected with particular subtypes of stroke. For instance, miR-125a-5p and miR-150 have both been linked to cardioembolic strokes and major artery atherosclerosis, respectively. These subtype-specific miRNAs may help with individualized treatment plans by acting as biomarkers for subtype categorization.

Furthermore, there is a link between the magnitude of a stroke and miRNA expression levels. For example, higher levels of miR-424 and miR-320a have been linked to more severe strokes. It may be possible to forecast the severity of a stroke and customize the right treatment approaches by evaluating the expression levels of these miRNAs.

Thus, microRNAs have demonstrated potential as biomarkers for stroke risk assessment. Finding stroke-specific miRNA signatures, comprehending their diagnostic and prognostic value in ischemic strokes, and investigating their associations with stroke subtypes and severity can aid in the development of novel therapeutic targets, more individualized treatment plans, and better stroke management.

Mechanisms of microRNA-mediated risk stratification

Regulation of vascular inflammation by microRNA

Small non-coding RNA molecules called microRNAs (miRNAs) are essential for post-transcriptional gene control. In addition to controlling vascular inflammation, they are engaged in a number of physiological and pathological processes. Vascular inflammation has a significant role in the onset and development of cardiovascular disorders including atherosclerosis (16–18).

A number of miRNAs have been shown to control vascular inflammation. These miRNAs have the ability to target particular genes implicated in inflammatory pathways, which affects how vascular cells respond to inflammation. For instance, miR-155, a key regulator of inflammation, has been demonstrated to enhance vascular inflammation by inhibiting the nuclear factor-kappa B (NF-B) pathway. On the other side, miR-146a targets important components in the toll-like receptor (TLR) signaling pathway and functions as a negative regulator of inflammation (15).

Dysregulation of miRNA expression may promote chronic inflammation and the development of vascular disorders by causing an imbalance in the inflammatory response. In order to reduce vascular inflammation, miRNAs have become viable therapeutic targets as well as indicators for risk assessment.

MicroRNA-mediated effects on endothelial dysfunction

Cardiac failure, hypertension, and atherosclerosis are just a few of the several cardiovascular illnesses that frequently exhibit endothelial dysfunction. By controlling vascular tone, inflammation, and thrombosis, the endothelium is essential in preserving vascular homeostasis. Vasodilation is reduced, oxidative stress is elevated, and inflammatory reactions are amplified in endothelial cells that are dysfunctional (18).

The modulation of endothelial function and dysfunction has been linked to miRNAs. They can specifically target genes related to nitric oxide synthesis, endothelial cell adhesion molecules, and endothelial cell survival pathways, among other genes. For instance, it has been demonstrated that miR-155 and miR-221/222 target eNOS, lowering

nitric oxide generation and compromising endothelium-dependent vasodilation.

Endothelial dysfunction and the development of cardiovascular illnesses can be attributed to altered expression of certain miRNAs in endothelial cells. Insights into disease causes and prospects for therapeutic treatments may be gained from the discovery and characterization of miRNAs implicated in endothelial dysfunction.

Role of microRNA in thrombus formation and resolution

In hemostasis and the response to vascular damage, thrombus development and resolution are closely controlled processes. Deep vein thrombosis, pulmonary embolism, and stroke are thrombotic diseases that can be caused by the dysregulation of these mechanisms (4, 14).

It has been discovered that miRNAs have a role in the control of thrombus development and resolution. They have the ability to affect platelet activation, coagulation, and fibrinolysis, among other elements of thrombus formation. Adenosine diphosphate receptor P2Y12, which is involved in platelet aggregation, has been revealed to be a target of miR-223, which has been proven to decrease platelet activation.

Additionally, miRNAs have a role in the dissolution of thrombi. They have the ability to alter the expression of fibrinolysis-related genes such as tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1). MiR-30c and miR-223 have been demonstrated to control the expression of tPA and PAI-1, respectively, affecting fibrinolysis and thrombus resolution.

The development of novel therapeutic approaches for the prevention and treatment of thrombotic diseases may be facilitated by a better understanding of the function of miRNAs in the generation and resolution of thrombi (14).

Potential therapeutic applications

Targeting microRNA for stroke prevention and treatment

Targeting certain miRNAs that have been found to be dysregulated in stroke patients shows promise for stroke therapy and prevention. It could be able to modify the expression of genes implicated in stroke etiology and possibly lessen the damage caused by stroke by adjusting the amounts of these miRNAs.

Targeting miRNAs for stroke treatment has been investigated using a variety of strategies. Antisense oligonucleotides (ASOs), also known as antagomirs, are one strategy and are created to attach to certain miRNAs and suppress their action. These compounds may be able to offer neuroprotection and enhance stroke outcomes by preventing the negative effects of dysregulated miRNAs (19).

Another strategy is to utilize synthetic miRNAs called miRNA mimics, which may be delivered into cells to raise the levels of a particular miRNA. By promoting neuronal survival and recovery, this strategy seeks to make up for the decreased expression of protective miRNAs in stroke victims.

The area of miRNA-based treatments is still in its infancy, and additional studies are required to fully comprehend the intricate functions that miRNAs play in stroke pathophysiology and to create efficient and secure therapeutic approaches. Clinical studies are being conducted to assess the effectiveness and safety of therapies based on miRNA in stroke patients.

Challenges and future directions in microRNA-based therapeutics

While targeting miRNAs for therapeutic purposes shows promise, there are several challenges and future directions that need to be addressed (Table 3).

Future perspectives

Although microRNAs are crucial in ischemic strokes, further study is required to confirm and standardize their signatures. The predictive power of microRNAs for stroke recurrence and long-term outcomes must be determined by longitudinal investigations. Prospective studies can shed light on how the expression of microRNAs varies over time and how that affects the risk of stroke (20, 21).

The precision of risk stratification models can be increased by combining microRNA signatures with other biomarkers, such as imaging characteristics or clinical risk scores. Genomic, transcriptomic, and proteomic data can provide us a more complete knowledge of the pathogenesis of stroke. To gain insight into underlying processes and prospective treatment targets, more research is required to clarify the precise targets and pathways controlled by stroke-associated microRNAs.

Extensive preclinical and clinical investigations are needed for microRNA-based treatments in order to optimize delivery strategies, evaluate off-target effects, and ensure safety and effectiveness. MicroRNAs show significant potential as useful tools for ischemic stroke risk stratification, opening up new opportunities for enhancing stroke therapy and patient outcomes. To fully use the therapeutic potential of microRNAs in ischemic stroke risk assessment and customized treatment, more study is required.

MicroRNAs (miRNAs) offer significant potential in improving the clinical management of ischemic strokes by serving as reliable biomarkers for risk stratification. Their incorporation into clinical workflows could enhance early detection, enable personalized treatment plans, and provide tools for monitoring therapeutic responses. Developing non-invasive diagnostic assays, such as blood-based miRNA panels, could further bridge the gap between laboratory findings and real-world applications, facilitating more precise and proactive patient care.

Conclusion

With several studies demonstrating their potential for predicting stroke risk, determining the severity of strokes, and predicting clinical outcomes, microRNAs have emerged as promising biomarkers for the risk stratification of ischemic strokes. These tiny non-coding RNAs participate in a number of biological processes, including apoptosis, angiogenesis, and inflammation, all of which are important in the pathophysiology of ischemic strokes. Researchers have discovered distinctive fingerprints connected to various stroke subtypes and risk

TABLE 3 Challenges and future directions in microRNAs- based therapeutics (16, 20).

Sr. no	Challenges	Description
1	Delivery	MiRNA-based therapies are difficult to deliver to the target tissues or cells. The delivery method must be effective, secure, and capable of getting to the intended location of action, which in a stroke situation would be the brain. There is ongoing research into creating efficient delivery systems, including those that utilize viral vectors or nanoparticles.
2	Specificity	To prevent off-target impacts and unforeseen consequences, target specificity must be attained. It is crucial to make sure that miRNA-based treatments regulate the targeted miRNA only, with no adverse effects on associated miRNAs or disruption of regular cellular processes.
3	Pharmacokinetics and stability	To achieve the intended effects, miRNA-based treatments must have sufficient stability and half-life in the body. MiRNA mimics or inhibitors can have their chemical structure or chemical backbone altered to increase their stability and improve their pharmacokinetic characteristics.
4	Safety and off-target effects	It is essential to carefully evaluate any potential off-target effects and safety profiles. MiRNA-based therapies have a lot of potential, but they might have unanticipated negative consequences if they interact with other biological functions. In-depth preclinical and clinical research is required to assess the effectiveness and safety of miRNA-based therapies.
5	Biomarker discovery and validation	For patient screening and treatment efficacy monitoring, it is crucial to identify reliable biomarkers linked to particular illnesses and treatment response. The implementation of miRNA-based treatments into clinical practice will be aided by the validation of miRNA biomarkers and the development of reliable diagnostic assays.
6	Combination therapies	MiRNA-based treatments may be more successful when combined with other treatment methods, such as conventional pharmacotherapy or physical therapy, because disorders like stroke are multifactorial in nature. Future studies might examine combinatorial methods and synergistic interactions.

levels by examining the expression patterns of certain microRNAs. Additionally, microRNAs can be used to predict the severity of a stroke and assist clinicians make treatment decisions, improving patient care and outcomes. Finally, altering the expression levels of certain microRNAs with antagonists or mimics has shown promise in animal models, demonstrating the value of microRNAs as therapeutic targets. This creates new opportunities for targeted medicines and customized therapeutic approach.

Data availability statement

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

Author contributions

HA-J: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MA: Writing – original draft, Writing – review & editing. FA-M: Conceptualization, Writing – original draft, Writing – review & editing.

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Cerebrolysin as an adjuvant therapy after mechanical thrombectomy in large vessel occlusion cardioembolic stroke: a propensity score matching analysis

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Introduction: Endovascular recanalization therapy has demonstrated considerable efficacy in the treatment of acute ischemic stroke (AIS). However, not all patients appear to benefit on the long term from this therapy. No studies have assessed the role of Cerebrolysin following mechanical thrombectomy (MT). The present study was conducted to evaluate the safety and efficacy of Cerebrolysin as add-on treatment to MT in patients with cardioembolic AIS.

Methods: This study evaluated 150 patients admitted to the stroke unit. Data were prospectively collected from 75 patients with cardioembolic AIS and National Institutes of Health Stroke Scale (NIHSS) $\geq$10, who underwent successful MT $\pm$ recombinant tissue plasminogen activator (rt-PA). Patients fulfilling inclusion criteria were consecutively enrolled and treated with Cerebrolysin at a daily dose of 30 ml for 14 days, with treatment initiated within 8 h following MT. Patients were compared with a historical control group of 75 well-matched patients who underwent MT $\pm$ rt-PA but did not receive Cerebrolysin. The primary outcome measure was a favorable modified Rankin Scale (mRS = 0–2) at day 90. Secondary parameters included the NIHSS, the Montreal Cognitive Assessment (MoCA), the rate of hemorrhagic transformation, mortality, and adverse events. Propensity score matching was performed to match the variables between the compared groups.

Results and discussion: The overall results demonstrated that patients treated with Cerebrolysin exhibited a significantly higher proportion of mRS scores of 0–2 at day 90 (64% vs. 34.7%) in comparison to the control group. This finding was consistent with lower NIHSS and mRS scores at all study visits, and a lower any hemorrhagic transformation rate (20% vs. 57.3%). Furthermore, the logistic regression analysis revealed that patients with favorable mRS scores were less likely to undergo hemorrhagic transformation (odds ratio = 2.75, 95% confidence interval = 1.17, 6.45; $p = 0.002$). The administration of Cerebrolysin as an add-on treatment resulted in a significant benefit for AIS patients following MT, characterized by an improvement in mRS and NIHSS scores, along with a reduced rate of hemorrhagic transformation. The administration of Cerebrolysin was safe and well tolerated. Further studies are required to confirm these results.

KEYWORDS

Cerebrolysin, mechanical thrombectomy, cardioembolic ischemic stroke, cerebroprotection, endovascular recanalization

1 Introduction

Acute ischemic stroke (AIS) is a significant global health concern, given its high morbidity and mortality rates worldwide (1). In 2015, a major advancement in the treatment of AIS was observed following the publication of groundbreaking randomized controlled trials (RCTs) that compared medical and endovascular treatments. These studies demonstrated the efficacy of mechanical thrombectomy (MT) for large vessel occlusion (LVO) in reducing mortality and improving outcomes (2–4). Of particular note is the finding that the number needed to treat fell within the range of 3–7 individuals (5). The positive outcomes following MT can be attributed to technical advancements and refined patient selection criteria, including perfusion and collateral status assessment (6).

Despite the advancement in MT, a marked discrepancy persists between effective recanalization and the restoration of pre-stroke functional abilities. The mortality rate of 15.3% remains a cause for concern. Furthermore, within a 3-month period, only 46% of individuals with anterior circulation AIS who underwent endovascular therapy attained functional independence (7). In addition, studies have demonstrated significant variability in the long-term follow-up outcomes of thrombectomy, with certain aspects of this treatment, such as the optimal time window, yet to be fully optimized (8).

In view of the aforementioned uncertainties, it is imperative to concentrate not only on advancements in vascular recanalization, but also on cerebroprotection, which refers to strategies to protect viable brain tissue in the acute phase of stroke to minimize infarct growth and preserve neurological function. Consequently, exploring rapid and effective cerebroprotection strategies to complement MT will be crucial in enhancing the prognosis of post-stroke patients (9, 10).

Research in the field of cerebroprotection and neurorecovery in stroke has yielded encouraging results in both preclinical and clinical settings. Despite the promising experiences with various agents, their translation into human application has been challenging due to several factors, such as the absence of continuous reopening of the blocked vessel, delayed intervention, insufficient dosage, and inconsistencies in research methodologies. Consequently, there is necessity for a paradigm shift in modern stroke treatment from pure neuroprotection to neurovascular protection, with the recognition of the critical roles of neurovascular unit elements (11, 12).

Cerebrolysin, a neurotrophic peptidergic preparation, has been demonstrated to exert multifactorial cerebroprotective effects. It enhances cellular survival, and it has been shown to inhibit glutamate excitotoxicity and to counter the formation of free radicals and pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, and NF-κB (11). While the literature consistently demonstrates the pleiotropic and multimodal activity of Cerebrolysin in both *in vitro* and animal studies, there is a paucity of research exploring its efficacy as an adjunct therapy to reperfusion therapy in AIS (12). In an experimental rat model with temporary occlusion of the middle cerebral artery, the administration of Cerebrolysin 3 h following ischemia substantially decreased the volume of tissue damage. This reduction was attributed to the inhibition of neuroinflammation *via* the activation of the CREB/PGC-1α pathway and the suppression of free radical formation, promoting long-term functional recovery (13). A previous pilot trial involving 44 severe stroke patients (NIHSS > 8) treated with futile reperfusion therapy found that those receiving Cerebrolysin (30 mL/day for 14–21 days) showed a trend toward better outcomes (mRS 0–3) at 12 months compared to controls (70% vs. 48%; $p = 0.1$) (14). Another recent clinical trial reported that Cerebrolysin significantly reduced the rate of symptomatic hemorrhagic transformation (OR 0.248, 95% CI 0.072–0.851; $p = 0.019$) (15).

The hypothesis of this study was that the administration of Cerebrolysin within 8 h following the onset of stroke, in subjects who met specific clinical and radiological criteria, had the potential to enhance the efficacy of MT. The initiation of cerebroprotective effects and the prevention of reperfusion injury by this multimodal approach is expected to facilitate post-stroke recovery. The selection of Cerebrolysin was based on its recognized pharmacological attributes, its capacity to penetrate the blood-brain barrier (BBB), its established safety profile, and the encouraging outcomes observed in preclinical studies and clinical trials. The present study assessed the efficacy and safety of Cerebrolysin as a supplementary therapy to MT in both the acute and subacute recovery stages among individuals with cardioembolic AIS.

2 Materials and methods

2.1 Ethics statement

The present study was granted approval by the Ethical Committee at Ain Shams University in Cairo, Egypt (approval number: FAMASU R85/2024). The study was conducted in strict accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (16) (Supplementary material) and followed the principles of the Declaration of Helsinki. Written informed consent was obtained from patients in the Cerebrolysin group prior to MT. For participants lacking decision-making capacity, consent was obtained from a legal representative. For the historical control arm, a waiver of consent was granted since the data were anonymized and de-identified prior to analysis, posing no risk to patients, ensuring no impact on participants' rights, involving no additional interventions or contact, and avoiding potential distress to the patients or their family members (17).

2.2 Study design and setting

This study was a prospective cohort study with a historical control group. Patients with cardioembolic AIS, which accounts for at least 20% of all ischemic strokes (18), and large vessel occlusion (LVO) who underwent MT were admitted to the stroke unit at Ain Shams University Hospital between October 2021 and January 2024.

2.2.1 Patient population

Patients diagnosed with cardioembolic stroke met the following criteria: at least one cardiac source identified for the embolus and no significant vascular abnormality such as severe atherosclerosis or stenosis in the large ipsilateral arteries associated with the cerebral infarction. Of the 150 patients included in the analysis, 75 patients in the study group received Cerebrolysin within 8 h of the MT, while 75 patients in the control group underwent MT only (identified from medical records between June 2017 and February 2021). Cerebrolysin was administered within 8 h of MT. It is crucial to initiate cerebroprotective measures in the early phase after an AIS while the salvageable brain tissue (penumbra) is still viable (19). Both groups were matched by the occlusion location, age (within ±5 years), co-morbidities, baseline mRS (0–2 or 3–5), initial NIHSS ≥10, initial ASPECT ≥6 (before MT), onset to reperfusion time (within ±2 h), and employing bridging therapy with rt-PA.

The inclusion criteria involved: (1) patients with cardioembolic AIS demonstrating evidence of LVO, (2) patients who received Cerebrolysin infusion within 8 h after successful MT (defined as substantial reperfusion of the affected territory, with a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3 at the end of the procedure) with or without IV rt-PA administration, (3) age between 18 and 80 years, and (4) a baseline NIHSS score of ≥10, as this is indicative of moderate-to-severe stroke severity, often associated with LVO and higher hemorrhagic transformation. Exclusion criteria encompassed: (1) patients older than 80 years, (2) individuals with epilepsy, (3) pregnant or lactating women, (4) patients with terminal illnesses, or a life expectancy of ≤ 6 months, and (5) individuals with premorbid cognitive impairment, and (6) patients with incomplete medical records.

2.3 Treatment

Patients in the study group received an intravenous infusion of 30 ml of Cerebrolysin diluted with 100 ml of 0.9% normal saline. This was administered promptly after thrombectomy, within 8 h of completion of MT. It was then given once daily for a duration of 14 days. This specified dose of Cerebrolysin was administered routinely according to the stroke unit guidelines (15, 20). All patients received standard stroke treatments, which encompassed antiplatelet or anticoagulation medications and control for hypertension, hyperlipidemia, and hyperglycemia. The treatment of patients qualifying for MT followed international guidelines (21, 22). MT was performed using stent retrievers, aspiration, or a combination of these techniques (23), *via* groin access by experienced operators familiar with the MT procedures. The choice of anesthesia, whether local or general, was at the operator's discretion. The MT procedures were consistent across the Cerebrolysin and historical control groups. The mTICI score was used to evaluate reperfusion following thrombectomy. The scale ranges from 0 (no reperfusion) to 3 (complete reperfusion of the previously occluded target artery, with no visible occlusion in distal branches). Intermediate scores include: 1 (limited distal branch filling with slow or minimal reperfusion beyond the initial occlusion) and 2a (reperfusion of less than half of the affected artery territory, such as two major divisions of the MCA and their branches). Bridging therapy with rt-PA followed current guidelines (0.9 mg/kg) (24).

2.4 Outcome parameters

The primary outcome parameter was the mRS (score of 0–2) at day 90. Secondary outcome parameters included the mRS and NIHSS at days 14, 30, and 90, the Montreal Cognitive Assessment (MoCA) at day 90, and the symptomatic and asymptomatic hemorrhagic transformation and mortality. The MoCA was used to establish a baseline cognitive profile of the patients, ensuring that any cognitive changes observed later could be attributed to the treatment and recovery process rather than pre-existing conditions or procedural effects. Safety parameters assessed lab values and adverse events.

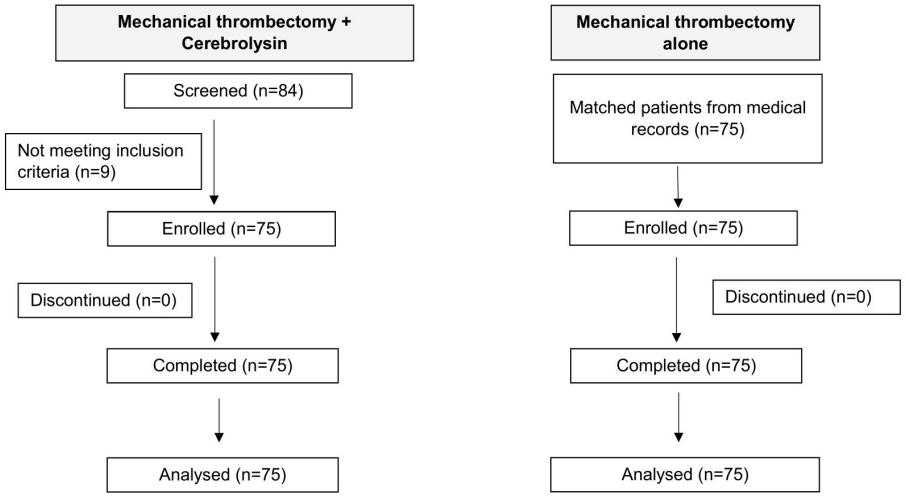

FIGURE 1
Flowchart of the study.

TABLE 1 Baseline characteristics and risk factors before and after PSM.

Variables	All patients			Propensity score-matched patients			SMD
	MT + Cerebrolysin ($n = 75$)	MT alone ($n = 75$)	p-value	MT + Cerebrolysin ($n = 51$)	MT alone ($n = 51$)	p-value	
Sex, no. (%)							
Male	31 (41.3)	45 (60)	**0.02***	23 (45)	25 (49.0)	0.84	−0.08
Female	44 (58.7)	30 (40)	**0.02***	28 (55)	26 (51)	0.08	0.08
Age, mean ± SD	59.27 ± 15.48	61.76 ± 11.40	0.26	59.45 ± 15.99	60.76 ± 11.95	0.64	−0.04
Risk factors, no. (%)							
Smoking	26 (34.7)	25 (33.3)	0.86	18 (35.3)	21 (41.2)	0.54	−0.06
Diabetes mellitus	27 (36)	36 (48)	0.14	20 (39.2)	21 (41.2)	0.84	−0.04
Hypertension	45 (60)	38 (50.7)	0.25	30 (58.8)	28 (54.9)	0.69	0.08
Hyperlipidemia	24 (32)	14 (18.7)	0.06	10 (19.6)	11 (21.6)	0.81	−0.04
Ischemic heart disease	22 (29.3)	21 (28)	0.86	14 (27.5)	14 (27.5)	1	<0.001
Previous ischemic stroke	9 (12)	9 (12)	1	6 (11.8)	5 (9.8)	0.81	0.06
Peripheral artery disease	9 (12)	0 (0)	**0.002***	0 (0.0)	0 (0.0)	NA	<0.001
Causes of cardioembolic stroke							
Atrial fibrillation	30 (40)	29 (38.7)	0.87	22 (43.1)	21 (41.2)	0.84	0.04
Mechanical prosthetic valve	10 (13.3)	10 (13.3)	1	5 (9.8)	6 (11.8)	0.75	−0.06
Left ventricle thrombus	7 (9.3)	5 (6.7)	0.76	5 (9.8)	3 (5.9)	0.46	0.09
Dilalted cardiomyopathy	19 (25.3)	18 (24.0)	1	12 (23.5)	12 (23.5)	1	<0.001
Recent myocardial infarction	3 (4.0)	5 (6.7)	0.72	3 (5.9)	4 (7.8)	0.70	−0.02
Rheumatic heart disease	6 (8)	10 (13.3)	0.07	4 (7.8)	5 (9.8)	0.73	−0.07
Initial NIHSS, median (range)	16 (10–25)	16 (11–25)	0.37	16 (10–25)	16 (11–25)	0.41	−0.25
Initial mRS, median (range)	5 (4–5)	5 (4–5)	0.85	5 (4–5)	5 (4–5)	0.64	−0.09
Initial MoCA, median (range)	23 (21–30)	23 (21–30)	0.11	23 (21–29)	23 (21–29)	0.09	0.02
Location of occlusion, no. (%)							
ICA	22 (29.3)	22 (29.3)	0.99	17 (33.3)	13 (25.5)	0.38	0.53
MCA (M1 segment)	46 (65.7)	53 (70.7)	0.23	29 (56.9)	38 (74.5)	0.06	
Basilar and PCA	2 (2.7)	0 (0)	0.16	1 (2)	0 (0.)	0.31	
ASPECTS							
6–7	14 (18.7)	14 (18.7)	1	8 (16)	9 (18)	0.79	−0.05
8–10	61 (81.3)	61 (81.3)	1	43 (84)	42 (8)	0.79	0.05
IV thrombolysis	30 (40)	21 (28)	0.12	17 (33.3)	16 (31.4)	0.82	0.02
Onset to recanalization in minutes, median (range)	410 (150–780)	420 (210–910)	0.74	420 (170–780)	420 (210–800)	0.86	0.08
Number of retrieval attempts ≤3	58 (77.3)	54 (72)	0.45	38 (74.5)	37 (72.5)	0.82	0.04
TICI ≥2b	66 (88)	61 (81.3)	0.26	44 (86.3)	42 (82.4)	0.91	0.06

SMD, standardized mean difference; ASPECTS, Alberta Stroke Program Early CT Score; mRS, modified Rankin Scale; MT, Mechanical thrombectomy; TICI, Treatment in Cerebral Ischemia; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; SD, standard deviation; NA, not applicable, Chi square test was used when comparing dichotomous data, Mean (±SD) and Student's t-test was used for normally distributed variables, Median (range) and Mann Whitney test was used for not normally distributed variables, bold values and *p-value <0.05 was considered statistically significant.

2.5 Neuroimaging

Cardioembolic stroke, defined according to the TOAST criteria (25), has a higher bleeding risk (26). Therefore, this study also aimed to assess the impact of Cerebrolysin on specific subtypes of hemorrhagic transformation: hemorrhagic infarction (HI) and parenchymal hematoma (PH). On a computed tomography (CT) scan, HI appears as a heterogeneous hyperdensity within the ischemic infarct zone, whereas PH is a more homogeneous and dense hematoma with a mass effect. Both HI and PH have two subtypes: HI type 1 (HI1) presents as small, scattered hyperdense petechiae, and HI type 2 (HI2) shows confluent hyperdensity throughout the infarct zone without mass effect. PH type 1 (PH1) is defined as a homogeneous hyperdensity occupying <30% of the infarct zone with some mass effect, while PH type 2 (PH2) occupies more than 30% of the infarct zone and causes significant mass effect (27, 28). Symptomatic hemorrhagic transformation was defined as the presence of hemorrhage on a CT scan, along with neurological deterioration, indicated by an increase of more than 4 points in the NIHSS (29). Asymptomatic hemorrhagic transformation was defined as radiological evidence of hemorrhage detected on follow-up imaging that was not associated with any new or worsening neurological symptoms. The neuroradiological acute stroke protocol mandates brain non-contrast CT (NCCT) for hemorrhage exclusion, magnetic resonance imaging, magnetic resonance angiography, followed by CT angiography to identify LVO status in eligible patients. We evaluated NCCT images at 24 h (all patients), 1 week, and 2 weeks after MT. Early ischemic indicators were assessed using the Alberta Stroke Program Early CT Score (ASPECTS) on baseline (30). Intracranial hemorrhages were diagnosed *via* control NCCT at 24 h or later for neurological deterioration (a ≥4-point NIHSS score increase from baseline and PH2).

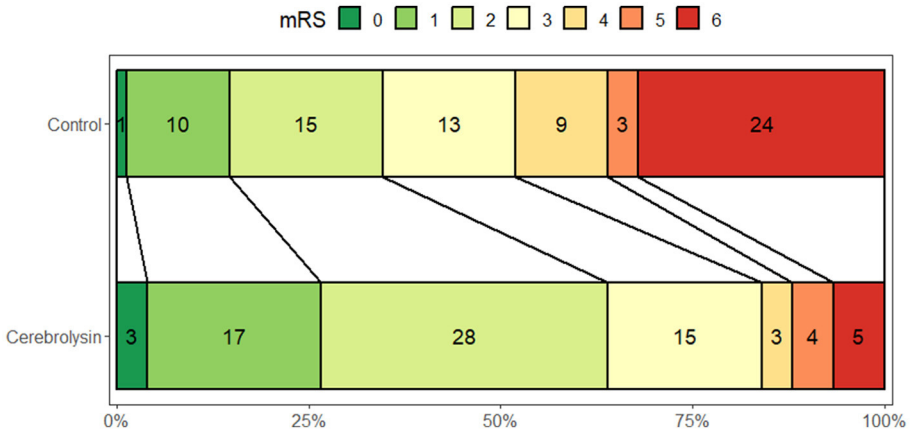

FIGURE 2
Distribution of the mRS scores at day 90 ($n = 75$ per group).

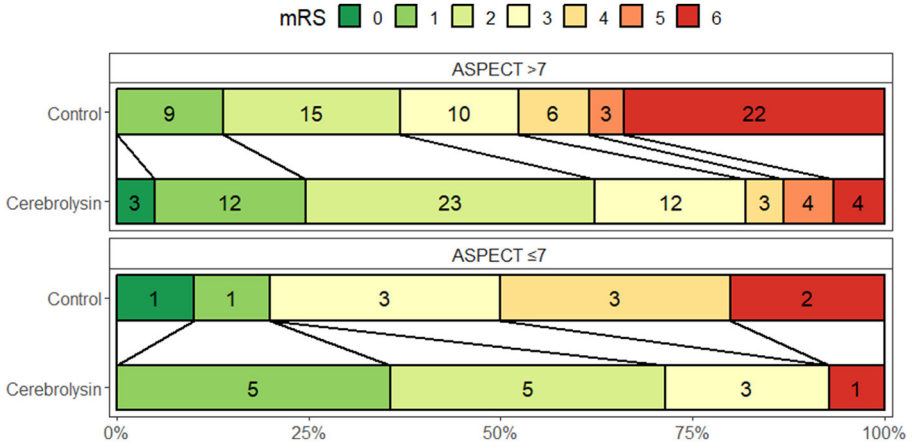

FIGURE 3
Distribution of the mRS scores at day 90 ($n = 75$ per group) stratified by ASPECTS 8–10 and 6–7.

2.6 Sample size

The sample size was calculated using G*Power 3.1.9.7 software. The favorable primary outcome rate was assumed to be 85% for the Cerebrolysin group and 60% for the control group, based on the findings of previous MT trials (3, 4, 31). With an alpha level of 5%, a total of 150 patients, 75 per group, was required to achieve 80% power to detect a significant difference in the primary outcome.

2.7 Statistical analysis

Normally distributed continuous variables were expressed as the mean ± standard deviation or otherwise as the median with range. Categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test was used to assess normality. Student's *t*-test was used to compare continuous variables with a normal distribution, and for non-normally distributed data Mann-Whitney U was used. The chi-square test was used to analyze categorical data. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with binary logistic regression analysis to assess predictors of favorable mRS and hemorrhagic transformation. Propensity score matching (PSM) was conducted using a one-to-one nearest neighbor method without replacement with a caliper width of 0.2, with Cerebrolysin and control as the exposures. The matching covariates included sex, age, risk factors, causes of cardioembolic stroke, baseline NIHSS, mRS, ASPECTS, onset-to-recanalization time, and IV thrombolysis. Following matching, the balance of the sample was evaluated using standardized mean differences (SMD) for included covariates, with acceptable balance defined as a SMD of ≤0.1 (32). Additionally, an *E*-value analysis was conducted to evaluate the extent of unmeasured confounding that could potentially nullify our estimates (33). A *p*-value <0.05 was determined as statistically significant. The analysis was performed using SPSS 27.0 and R software version 4.4.2 (MatchIt and rankinPlot packages, https://www.r-project.org/).

3 Results

Of 84 patients who received Cerebrolysin, five cases were excluded due to incomplete data on key variables and four cases due to non-cardioembolic stroke etiology. The final analysis included 75 patients treated with Cerebrolysin after MT, which were well matched with 75 historic controls from the hospital's medical records. The matching criteria included similar occlusion location, age (within ±5 years), co-morbidities, baseline mRS (0–2 or 3–5), initial NIHSS ≥10, ASPECT ≥6, onset to reperfusion time (within ±2 h), and rt-PA administration. Overall, data of 150 patients were analyzed in this study. A flowchart illustrating the patient enrolment is presented in Figure 1.

At baseline, there was a significantly higher proportion of males in the control group ($n = 45$, 60%) compared to the Cerebrolysin group ($n = 31$, 41.3%). The mean age was comparable between both groups, with 59.3 ± 15.5 years in the Cerebrolysin group and 61.8 ± 11.4 years in the control group. Both groups were comparable regarding risk factors, causes of cardioembolic stroke, initial NIHSS, mRS, MoCA, location of occlusion, ASPECT scores, IV thrombolysis, onset to recanalization time, number of retrieval attempts, and TICI ≥2b rates. Peripheral artery diseases were found to be significantly higher in the Cerebrolysin group (12% vs. 0%, $p = 0.002$). After PSM, 51 patients in the Cerebrolysin group were matched with 51 patients in the control group and all covariates demonstrated no statistically significant differences between the two groups. The distribution of propensity scores is shown in Supplementary Figures S1, S2. A summary of baseline characteristics before and after PSM is presented in Table 1.

TABLE 2 Functional outcomes at different follow up points before and after PSM.

Functional outcomes	All patients			Propensity score-matched patients		
	MT + Cerebrolysin ($n = 75$)	MT alone ($n = 75$)	*p*-value	MT + Cerebrolysin ($n = 51$)	MT alone ($n = 51$)	*p*-value
Favorable mRS at 90 days, *n* (%)	48 (64)	26 (34.7)	**<0.001***	33 (65)	16 (31)	**<0.001***
mRS at 14 days, median (range)	3 (1–6)	4 (1–6)	**0.02***	3 (1–6)	4 (1–6)	**0.044***
mRS at 30 days, median (range)	2 (0–5)	3 (1–6)	**<0.001***	3 (0–5)	3 (1–6)	**0.004***
mRS at 90 days, median (range)	2 (0–6)	3 (0–6)	**<0.001***	2 (0–6)	4 (0–6)	**<0.001***
NIHSS at 14 days, median (range)	7 (2–19)	10 (2–28)	**<0.001***	7 (2–18)	10 (2–28)	**<0.001***
NIHSS at 30 days, median (range)	5 (0–17)	8 (1–20)	**0.01***	5.5 (1–16)	8 (1–20)	**0.02***
NIHSS at 90 days, median (range)	5 (0–16)	6 (1–16)	**0.02***	5 (1–15)	6 (1–16)	0.08
MoCA at 90 days, median (range)	30 (23–30)	29.5 (17–30)	0.13	30 (23–30)	30 (17–30)	0.20

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MoCA, Montreal Cognitive Assessment; MT, mechanical thrombectomy; Median (range) and Mann Whitney test was used for not normally distributed data, bold values and *p-value <0.05 was considered statistically significant.

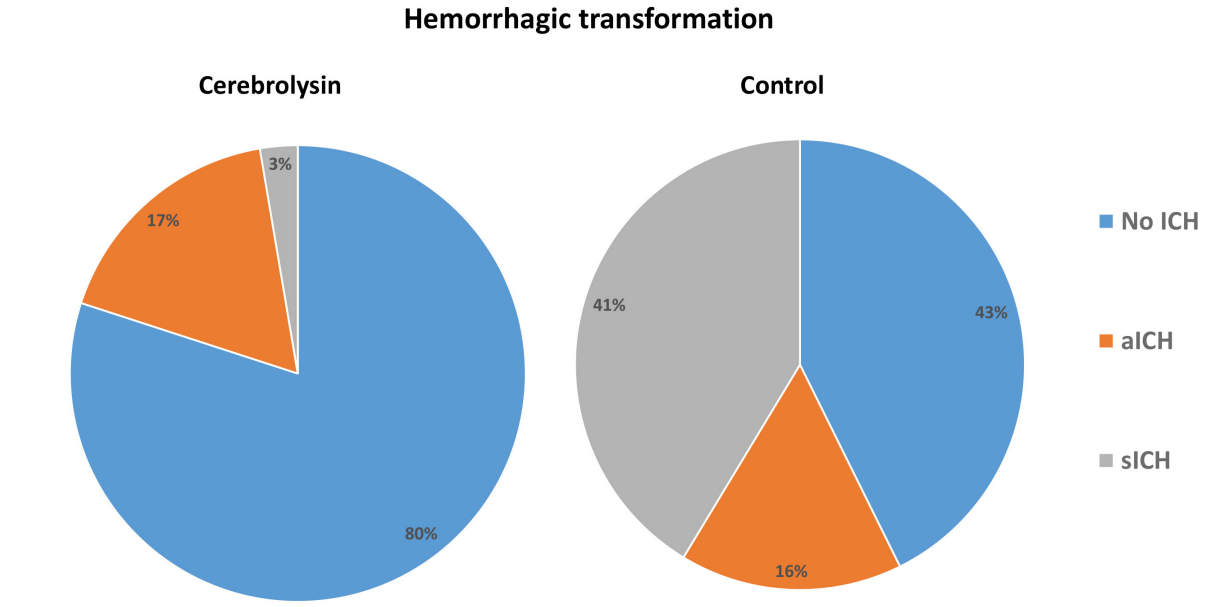

FIGURE 4
Hemorrhagic transformation rates in the compared groups.

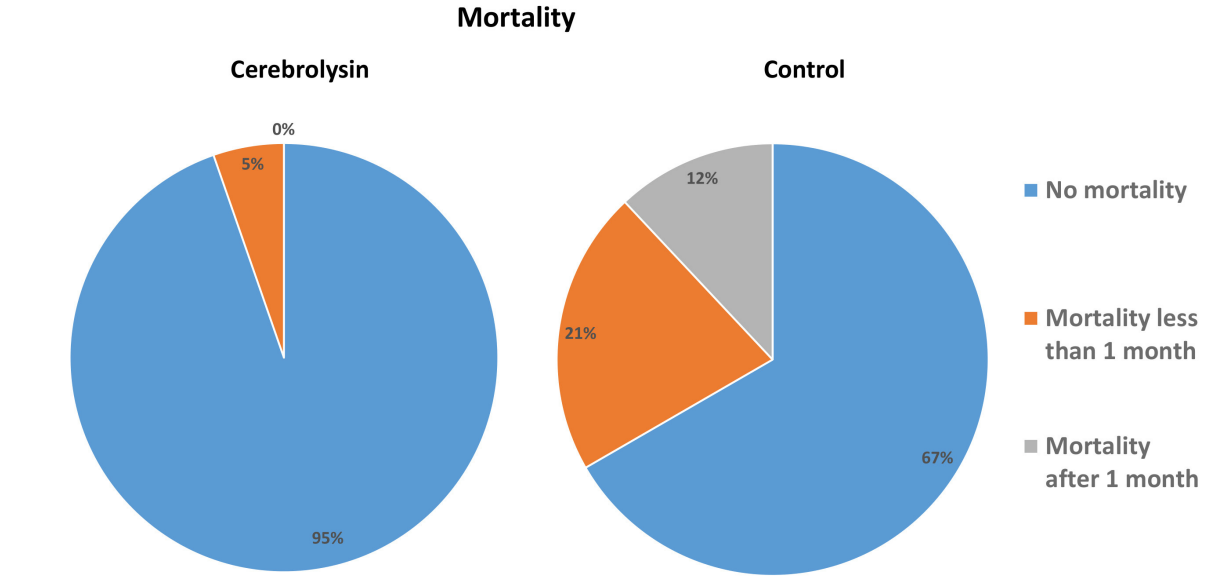

FIGURE 5
Mortality rates in the compared groups.

3.1 Primary outcome

At day 90, a significantly higher percentage of patients in the Cerebrolysin group achieved a favorable outcome (mRS = 0–2) as compared to the control group (64% vs. 34.7%, $p < 0.001$; Figure 2).

Subgroup analyses showed that in the Cerebrolysin group 50.7% of patients with ASPECTS of 8–10 achieved a favorable outcome compared to 32% in the control group. In the subgroup of patients with ASPECTS of 6–7, 13.3% of patients in the Cerebrolysin group achieved a favorable outcome as compared to 2.7% in the control group (Figure 3). The results after PSM are consistent with the results of all patients included before PSM, Table 2.

3.2 Secondary outcomes

The median mRS scores demonstrated a significant decrease in the Cerebrolysin group at the 2-week, 1 and 3-month time points. Similarly, the median NIHSS scores showed a significant

decrease in the Cerebrolysin group at the 2-week, 1 and 3-month time points. However, the MoCA scores at month 3 did not show significant group differences. The results obtained after PSM are consistent with the results of all patients before PSM, except for NIHSS score at 3 months, where no significant difference was observed, Table 2.

The incidences of any hemorrhagic transformation (57.3% vs. 20%) and symptomatic hemorrhage (41.3% vs. 2.7%) were higher in the control group than in the Cerebrolysin group (Figure 4). Furthermore, patients in the control group suffered from higher incidences of PH1 after 24 h, HI2 at day 7, and HI1 and HI2 at day 14. Moreover, the mortality was found to be higher in the control group (32% vs. 5.3%) as was the mortality within the first month (20% vs. 5.3%) and beyond 1 month (12% vs. 0%) (Figure 5). These results were consistent with the findings following PSM analysis, Table 3.

The most prevalent causes of mortality were identified as hemorrhagic transformation and sepsis, with a significantly higher prevalence observed in the control group (Table 3).

3.3 Adverse events

The percentages of sepsis (4% vs. 13.3%, $p = 0.045$) and acute kidney injury (0% vs. 5.3%, $p = 0.043$) were significantly less frequent in the MT plus Cerebrolysin group. Following the implementation of the PSM analysis, both groups were found to be comparable with respect to sepsis and acute kidney injury. The occurrence of pneumonia, cardiac ischemia, stroke, infection, hyponatremia, hypernatremia, anemia, deep venous thrombosis, or hypokalemia was comparable in the two groups in the pre- and post-PSM analysis (Table 4).

TABLE 3 Hemorrhagic transformation and mortality rates before and after PSM.

Variables, no. (%)	All patients			Propensity score-matched patients		
	MT + Cerebrolysin ($n = 75$)	MT alone ($n = 75$)	*p*-value	MT + Cerebrolysin ($n = 51$)	MT alone ($n = 51$)	*p*-value
Any hemorrhagic transformation	15 (20)	43 (57.3)	**<0.001***	13 (25.5)	29 (56.9)	**0.001***
Symptomatic hemorrhagic transformation	2 (2.7)	31 (41.3)	**<0.001***	2 (3.9)	22 (43.1)	**<0.001***
Hemorrhagic transformation after 24 h						
HI1	4 (5.3)	10 (13.3)	0.09	2 (3.9)	6 (11.8)	0.14
HI2	9 (12)	8 (10.7)	0.80	9 (17.6)	5 (9.8)	0.25
PH1	1 (1.3)	21 (28)	**<0.001***	1 (2)	16 (31.4)	**<0.001***
PH2	1 (1.3)	4 (5.3)	0.17	1 (2)	2 (3.9)	0.56
Hemorrhagic transformation at day 7						
HI1	10 (13.3)	14 (18.7)	0.38	10 (19.6)	8 (15.7)	0.60
HI2	1 (1.3)	22 (29.3)	**<0.001***	1 (2)	14 (27.5)	**<0.001***
PH1	1 (1.3)	3 (4)	0.31	1 (2)	3 (5.9)	0.31
Hemorrhagic transformation at day 14						
HI1	0 (0)	6 (8)	**0.048***	0 (0)	3 (5.9)	0.09
HI2	1 (1.3)	9 (12)	**0.008***	1 (2)	6 (11.8)	**0.050***
PH1	0 (0)	2 (2.7)	0.54	0 (0)	2 (3.9)	0.15
Overall mortality	4 (5.3)	24 (32)	**<0.001***	3 (5.9)	12 (24)	**<0.001***
Mortality <1 month	4 (5.3)	16 (21.3)	**0.004***	3 (5.9)	5 (9.8)	0.46
Mortality after 1 month	0 (9)	9 (12)	**0.008***	0 (0)	7 (13.7)	**0.006***
Causes of mortality						
Hemorrhagic transformation	1 (1.3)	7 (9.3)	**0.03***	1	7 (13.7)	**0.03***
Chest infection	2 (2.7)	5 (6.7)	0.25	2 (3.9)	4 (7.8)	0.4
Sepsis	0 (0)	6 (8)	**0.01***	0 (0)	3 (5.9)	0.09
Sudden death	0 (0)	1 (1.3)	0.32	0 (0)	1 (2)	0.31
Myocardial infarction	1 (1.3)	0 (0)	0.32	0 (0)	0 (0)	NA
Unknown causes	0 (0)	3 (4)	0.08	0 (0)	2 (3.9)	0.15

HI, hemorrhagic infarct; PH, Parenchymal hemorrhage; MT, Mechanical thrombectomy; NA, not applicable. Chi square test was used; Bold values and *p-value <0.05 was considered statistically significant.

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3.4 Subgroup and sensitivity analyses

In the present study, a multifaceted approach was employed to identify predictors of favorable mRS outcomes and the risk of hemorrhagic transformation. To this end, a binary logistic regression analysis was conducted, with the following stratifications: gender (male vs. female), age (≥70 vs. <70), baseline ASPECTS (6–7 vs. 8–10), and baseline NIHSS (≤17 vs. >17). The results of the logistic regression analysis showed that patients aged 70 and above had a lower likelihood of a favorable mRS and patients with an initial NIHSS scores ≤17 had a higher likelihood of a favorable mRS. However, the analysis did not identify age or NIHSS as predictors of a favorable mRS following the PSM analysis. Furthermore, factors such as sex, the use of IV thrombolysis, ASPECTS, and stenting were not identified as predictors for a favorable mRS in either the pre- and post-PSM analyses, as shown in Table 5.

The application of a logistic regression analysis to the cohort of patients receiving Cerebrolysin showed the presence of predictors of hemorrhagic transformation. Patients exhibiting a favorable mRS were found to be less prone to the development of any such transformation. In the context of the present sample, factors such as sex, age, IV thrombolysis, ASPECT scores, initial NIHSS scores, and stenting were not identified as predictors of hemorrhagic transformation. These findings were consistent with the results following the PSM analysis, as shown in Table 6.

E-values were calculated in order to assess the robustness of the findings to unmeasured confounding. For the association between Cerebrolysin and mRS, an *E*-value of 6.16 suggests that only a confounder with an extremely strong association (OR ≥ 6.16) with both Cerebrolysin use and mRS could fully explain the observed effect (Figure 3, Supplementary material). A similarly observation was made in the analysis of the association between Cerebrolysin and hemorrhagic transformation, which showed an *E*-value of 10.0, suggesting an even greater degree of robustness (Figure 4, Supplementary material). These results suggest that the findings are unlikely to be nullified by unmeasured confounding.

TABLE 4 Adverse events before and after PSM.

Adverse events, no. of patients (%)	All patients			Propensity score-matched patients		
	Cerebrolysin ($n = 75$)	Control ($n = 75$)	*p*-value	Cerebrolysin ($n = 51$)	Control ($n = 51$)	*p*-value
Pneumonia	13 (17.3)	16 (21.3)	0.51	11 (21.6)	9 (17.6)	0.62
Sepsis	3 (4.0)	10 (13.3)	**0.045***	2 (3.9)	6 (11.8)	0.14
Cardiac ischemia	1 (1.3)	1 (1.3)	1	0 (0)	1 (2.0)	0.31
Stroke	1 (1.3)	3 (4.0)	0.31	1 (2.0)	2 (3.9)	0.56
Infection	2 (2.7)	6 (8.0)	0.15	2 (3.9)	5 (9.8)	0.24
Acute kidney injury	0 (1.3)	4 (5.3)	**0.043***	0 (0)	3 (5.9)	0.08
Hyponatremia	0 (0)	1 (1.3)	0.32	0 (0)	1 (2.0)	0.31
Hypernatremia	1 (1.3)	0 (0)	0.32	1 (2.0)	0 (0)	0.31
Anemia	1 (1.3)	0 (0)	0.32	1 (2.0)	0 (0)	0.31
Deep venous thrombosis	0 (0)	2 (2.7)	0.16	0 (0)	1 (2.0)	0.31
Superficial vein thrombosis	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Hypokalemia	0 (0)	1 (1.3)	0.32	0 (0)	1 (2.0)	0.31

NA, not applicable. Chi-Square test was used to compare both groups, bold values and **p*-value <0.05 was considered statistically significant.

TABLE 5 Adjusted binary logistic regression analysis of factors associated with favorable mRS in the Cerebrolysin group before and after PSM.

Factors	All patients		Propensity score-matched patients	
	Odds ratio (95% CI)		Odds ratio (95% CI)	*p*-value
Sex (Female vs. male)	0.60 (0.36, 1.01)	0.06	0.16 (0.02, 1.27)	0.08
Age (≥ 70 vs. <70)	0.48 (0.26, 0.89)	**0.02***	0.37 (0.07, 2.09)	0.26
IV thrombolysis (yes vs. no)	1.08 (0.60, 1.96)	0.79	1.19 (0.16, 8.70)	0.86
ASPECT (6-7 vs. 8-10)	1.41 (0.49, 4.06)	0.52	6.52 (0.37, 115.64)	0.20
Initial NIHSS (≤17 vs. >17)	1.49 (1.002, 2.21)	**0.03***	5.44 (0.79, 37.67)	0.09
Stenting (yes vs. no)	0.95 (0.69, 1.30)	0.74	0.40 (0.07, 2.20)	0.29

ASPECTS, Alberta Stroke Program Early CT Score; mRS, modified Rankin Scale; MT, Mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; Bold values and **p*-value <0.05 was considered statistically significant.

TABLE 6 Adjusted binary logistic regression analysis of factors associated with hemorrhagic transformation in the Cerebrolysin group before and after PSM.

Factors	All patients		Propensity score-matched patients	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Gender (Female vs. male)	1.32 (0.74, 2.35)	0.29	0.23 (0.21, 2.57)	0.23
Age (≥ 70 vs. <70)	0.56 (0.31, 1.04)	0.09	5.47 (0.62, 47.98)	0.13
IV thrombolysis (yes vs. no)	0.64 (0.37, 1.13)	0.16	0.14 (0.02, 1.35)	0.09
ASPECT (6–7 vs. 8–10)	0.92 (0.29, 2.88)	0.89	6.97 (0.33, 146.25)	0.21
NIHSS (≤17 vs. >17)	1.17 (0.75, 1.82)	0.46	0.45 (0.05, 4.48)	0.51
Favorable vs. unfavorable mRS	2.75 (1.17, 6.45)	**<0.001***	0.009 (0.0001, 0.17)	**0.002***
Stenting (yes vs. no)	1.34 (0.82, 2.21)	0.17	0.31 (0.04, 2.46)	0.27

ASPECTS, Alberta Stroke Program Early CT Score; mRS, modified Rankin Scale; MT, Mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; CI, confidence interval; Bold values and **p*-value <0.05 was considered statistically significant.

4 Discussion

The development of effective treatment strategies for AIS beyond recanalization is of critical importance. Given that ∼80% of strokes are attributable to arterial occlusion, recanalization therapy is imperative for restoring blood flow and reducing stroke-related disability. Nevertheless, it is important to note that only a subset of patients benefits from endovascular therapy (EVT), underscoring the necessity for the development of additional cerebroprotective treatments.

The present study showed a significant improvement in functional outcomes in patients treated with MT ± rt-PA plus Cerebrolysin as compared to MT ± rt-PA alone. The results of the study showed that a higher percentage of patients in the Cerebrolysin group achieved a favorable mRS at day 90, with early recovery evident as early as 2 weeks after stroke.

A novel treatment target for cerebroprotective agents is the enhancement of BBB integrity. As shown in Teng et al. (34), Cerebrolysin has anti-inflammatory effects, reducing the release of pro-inflammatory cytokines, and, consequently, stabilizing the BBB. The present study demonstrates that early administration of Cerebrolysin as an adjunct to MT yielded beneficial outcomes for the rate of symptomatic hemorrhagic transformation. However, it is important to note that Cerebrolysin reduced also the rate of asymptomatic hemorrhagic transformation, a complication that is associated with worse neurological outcome (35). Furthermore, this therapeutic strategy significantly reduced the mortality rate.

The present findings are consistent with the results of the study by Poljakovic et al. in AIS patients with unsuccessful recanalization post-rt-PA. Patients treated with Cerebrolysin (30 ml/day for 14–21 days) showed a notable reduction in hemorrhagic transformation rates and achieved a more favorable outcome (mRS 0–3) at month 12 compared to the control group (70% vs. 48%, $p = 0.1$) (14).

The findings of this study are also consistent with those of the CEREHETIS study by Khasanova (15), which showed that the early administration of Cerebrolysin as an add-on to reperfusion therapy significantly reduced the incidence of symptomatic hemorrhagic transformation and early neurological deficits.

The prolonged and sustained positive effects of Cerebrolysin observed in the patient cohort under investigation are likely due to its neurotrophic and neuroplastic properties, which stimulate neurogenesis and oligodendrogenesis, protecting the neurovascular unit even in the absence of recanalization (12, 36).

With regard to the occurrence of hemorrhagic transformation, the results of the logistic regression analysis indicated that patients exhibiting favorable mRS outcomes were less likely to experience any such transformation. This finding supports the hypothesis that initial recovery outcomes that are more favorable are associated with a reduced risk of post-thrombectomy hemorrhage (37).

With regard to safety and tolerability, the adverse events observed in this study were consistent with those reported in previous Cerebrolysin trials. The types and frequency of symptoms were similar. This finding indicates that Cerebrolysin can be safely administered in conjunction with MT. A meta-analysis of 12 RCTs further confirmed the excellent safety profile of Cerebrolysin (38). An ongoing clinical trial evaluates the efficacy of Cerebrolysin as an adjunct therapy to MT for large vessel occlusion in AIS patients, with symptomatic hemorrhagic transformation and functional outcomes serving as the study endpoints (39).

4.1 Strengths

To the best of our knowledge, this research is the first to assess the administration of Cerebrolysin following MT, complemented by a comprehensive assessment of both clinical outcomes and brain imaging. There is a paucity of investigations exploring cerebroprotective substances in combination with MT in cardioembolic AIS. Furthermore, both groups received standard medical care and a PSM was conducted to achieve a more precise estimation of treatment effects, reduce a greater portion of bias, and balance the dataset, enabling direct and effective comparison of baseline covariates between treated and untreated patients (40).

4.2 Limitations

The proposed study is subject to several limitations. Firstly, the study incorporates data from the control group, obtained from medical records, which may be subject to selection bias. Secondly, the study was conducted at a single center and included a small sample size. These factors may limit the generalizability

of the study's results. Thirdly, the study exhibited limited ethnic and racial diversity, with all participants being of Egyptian origin. Consequently, there is a necessity for additional large-scale clinical studies. Furthermore, although PSM was employed to reduce confounding, it is important to note that retrospective matching is inherently limited in its ability to account for all potential confounding variables. Unmatched or unmeasured variables, such as pre-hospital delays, socioeconomic factors, or operator expertise, could introduce residual bias. Furthermore, temporal differences in clinical practices and diagnostic tools between the historical and treatment groups may also have influenced outcomes.

5 Conclusion

The safety of adding Cerebrolysin early to reperfusion therapy was confirmed, and it was found to be associated with significantly improved functional outcomes and reduced symptomatic hemorrhagic transformation and mortality rates. Further prospective studies with larger sample sizes are required to confirm these findings and explore whether extending the treatment period with Cerebrolysin could yield further improvements.

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 humans were approved by the Ethical Committee at Ain Shams University, Cairo, Egypt. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AE: Conceptualization, Investigation, Methodology, Project administration, Validation, Writing – original draft, Resources. MS: Conceptualization, Formal analysis, Methodology, Writing – original draft. AZ: Data curation, Formal analysis, Methodology, Resources, Validation, Writing – review & editing. RB: Data curation, Investigation, Resources, Validation, Writing – review & editing. AE-S: Data curation, Methodology, Supervision, Validation, Investigation, Resources, Visualization, Writing – review & editing. AN: Conceptualization, Investigation, Supervision, Writing – review & editing.

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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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Efficacy of YL-1 hematoma crushing needle combined with hematoma drainage in intracerebral hemorrhage treatment

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Objective: Early craniotomy evacuation in hematoma surgery does not significantly improve the prognosis of patients with spontaneous intracerebral hemorrhage (ICH). The YL-1 hematoma crushing puncture needle, specifically designed for ICH evacuation, has an uncertain therapeutic efficacy. This study aimed to evaluate its clinical effectiveness.

Materials and methods: We retrospectively reviewed medical records of patients with ICH who underwent twist intraosseous drill needle (TIDN) surgery at our institution between September 2016 and March 2023. Clinical outcomes were analyzed.

Results: The surgical group demonstrated a significantly shorter hematoma resolution time, averaging 14.71 days less than the conservative group ($p < 0.001$). The Barthel Index improved more in the surgical group, with an average increase of 8.214 points ($p < 0.001$). Seven days post-admission, the increase in Glasgow Coma Scale (GCS) scores was significantly higher in the surgical group, with an average improvement of 1.471 points ($p < 0.001$). Additionally, the duration of mannitol administration was significantly reduced in the surgical group ($p < 0.001$).

Conclusion: TIDN surgery combined with hematoma drainage may serve as a viable surgical alternative for basal ganglia hemorrhage patients. This approach appears to reduce mannitol usage, mitigate craniotomy-associated risks, and promote short-term improvements in GCS scores and Barthel Index, highlighting its potential clinical benefits.

KEYWORDS

intracerebral hemorrhage, YL-1 hematoma crushing needle, hematoma drainage, craniotomy, urokinase, minimally invasive surgery

Introduction

Spontaneous intracerebral hemorrhage (ICH) is a common neurological condition associated with high mortality (1). Surgical interventions for ICH include craniotomy for hematoma evacuation, neuroendoscope-assisted hematoma removal, and stereotactic minimally invasive hematoma puncture with drainage (2). However, early craniotomy evacuation has shown limited improvement in patient prognosis (2, 3). With the increasing adoption of minimally invasive techniques, there is a growing preference for such approaches in ICH management (4–6). The YL-1 hematoma crushing needle, also known as the twist intraosseous drill needle (TIDN), is a specialized device designed for intracranial hematoma evacuation (7, 8). TIDN surgery is minimally invasive, technically simple, and may offer a viable option for patients unable to tolerate craniotomy (9). While it has been used in the treatment of chronic subdural hematomas (10–12), its efficacy in ICH treatment remains uncertain. To evaluate the effectiveness of TIDN surgery using the YL-1 hematoma crushing needle in ICH management, we conducted a retrospective analysis of 51 patients with spontaneous ICH admitted to our institution between September 2016 and March 2023.

Materials and methods

The diagnosis of ICH was confirmed through head CT imaging. Additionally, Computed Tomography Angiography (CTA) or Digital Subtraction Angiography (DSA) scans were performed to exclude vascular abnormalities such as intracranial aneurysms and arteriovenous malformations. All patients were diagnosed and treated in strict accordance with stroke treatment guidelines and underwent minimally invasive puncture combined with hematoma drainage. TIDN surgery was performed only after obtaining written informed consent from the patient' s legal guardian or next of kin, including specific consent for urokinase administration. This study was approved by the institutional ethics committee (approval number: 2025001), and informed consent was obtained from all participants in accordance with ethical guidelines.

Inclusion criteria

(1) Age $\geq$ 40 years. (2) Diagnosis of hypertensive intracerebral hemorrhage (ICH) confirmed by head CT scan, with symptom onset within 24 h. (3) The hematoma must be located in the basal ganglia, with or without intraventricular hemorrhage. (4) Hematoma volume $>$ 25 mL without signs of brain herniation. (5) CTA or DSA performed to exclude vascular abnormalities such as intracranial aneurysms and arteriovenous malformations.

Exclusion criteria

(1) Intracerebral hemorrhage caused by intracranial aneurysms, arteriovenous malformations, tumors, infarction, or trauma. (2) Severe coagulopathies (e.g., thrombocytopenia, hepatitis) or severe dysfunction of the heart, liver, kidneys, or lungs. (3) History of stroke leading to neurological deficits, discontinuation of treatment, or death after admission. (4) Refusal to sign the informed consent form.

Clinical data

Baseline clinical data included age, sex, Glasgow Coma Scale (GCS) scores at admission and on the seventh day of hospitalization, Barthel Index scores at admission and discharge, hematoma volume at admission, hematoma resolution time, mannitol usage, and length of hospital stay. Additionally, potential prognostic factors were considered, including comorbidities, complications, personal medical history, past medical history, and anticoagulant use. TIDN surgery was performed only after obtaining written informed consent from the patient's legal agent or authorized representative, specifically including consent for urokinase administration. The procedure utilizing the YL-1 hematoma crushing needle kit has been comprehensively detailed in our previous report (8). The general surgical steps were as follows.

Surgical steps

Fixation of the YL-1 Hematoma Crushing Needle: The YL-1 hematoma crushing needle was securely attached to a handheld electric drill (Figure 1a).

Localization: Anatomical landmarks near the hematoma site and CT-based markers were used to determine the hematoma plane (Figure 1b). The scalp overlying the largest layer of the hematoma, as identified on CT scans, was selected as the puncture site, ensuring the avoidance of the Sylvian fissure. The intracranial and extracranial distance from the hematoma center to the puncture point was measured using CT imaging, and a 5.0 cm or 7.0 cm YL-1 hematoma crushing needle kit (Beijing Wantefu Medical Equipment Co., Ltd.) was selected accordingly.

Puncture and Aspiration: The patient was placed in a supine position, and the surgical field was disinfected with 2% iodine tincture, followed by deiodination with 75% alcohol after 2–3 min, before applying a sterile drape. After administering local anesthesia with 5 mL of 2% lidocaine to the scalp and periosteum, an assistant stabilized the patient's head. The needle was inserted perpendicularly to the cranial surface at the preselected puncture site without making a skin incision (Figure 1c). A distinct breakthrough sensation was felt upon penetrating the inner table of the skull. At this point, the YL-1 puncture needle was detached from the drill and automatically fixed onto the skull. Next, the depth of the YL-1 puncture needle was adjusted. The drill cap was removed, and a plastic sleeve needle was manually inserted, advancing the entire assembly slowly until reaching the predetermined depth. This ensured that the front end of the hematoma crushing needle was positioned at the center of the hematoma cavity. The plastic inner needle was then removed, and the three-way needle body was sealed with a cap and gasket. A drainage tube was connected, and hematoma aspiration was performed using a 5-mL syringe (Figure 1d). After aspirating the liquid portion of the hematoma, a drainage device was connected

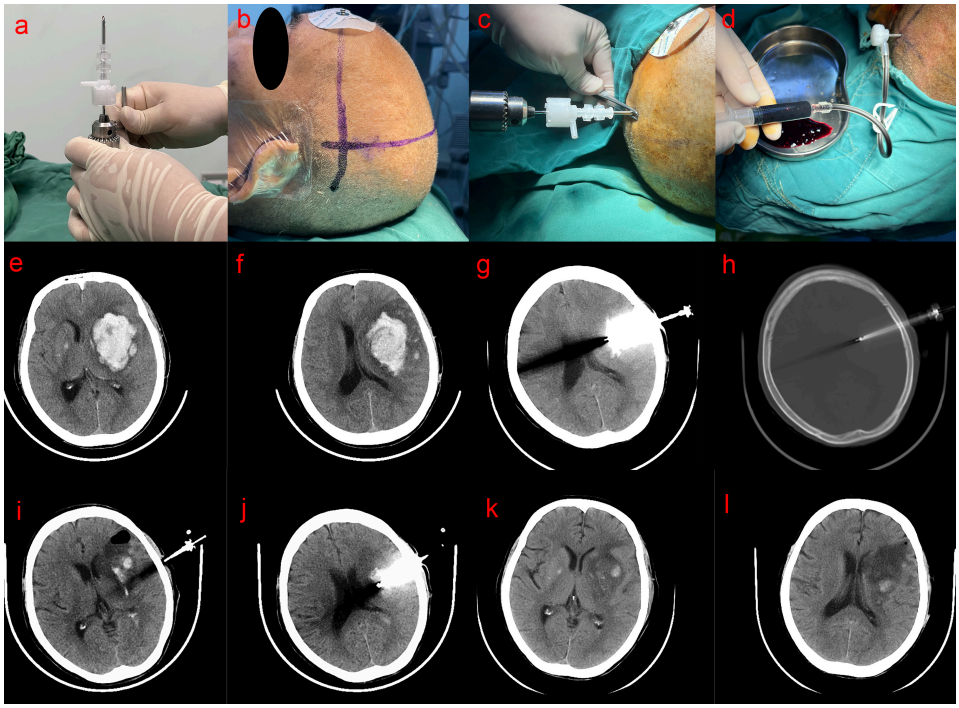

FIGURE 1
(a) Mounting of the YL-1 hematoma crushing needle on the drill; **(b)** positioning puncture point; **(c)** perpendicular drilling **(d)** aspirated; **(e,f)** preoperative head CT scan showed the hematoma volume about 45 mL; **(g,h)** CT scan on the first day after operation showed that the YL-1 puncture needle penetrated the skull into the hematoma cavity; **(i,j)** CT scan on the 4th day after operation showed that hematoma was almost evacuated; **(k,l)** 10 days after the operation, head CT showed that the hematoma was completely evacuated.

to the tubing. Since hematomas often contain solid components, complete aspiration was not always achieved during the initial attempt.

Postoperative Management and Urokinase Administration: Drainage volume was recorded, and a follow-up head CT scan was performed within 24 h postoperatively to assess the need for urokinase injection for hematoma liquefaction and drainage. The urokinase dosage was determined based on the method described by Liu et al. (13): 20,000 IU of urokinase (Tianjin Biochemical Pharmaceutical Co., Ltd.) diluted in 5 mL of normal saline. Following urokinase injection, the drainage tube was clamped for 2–4 h before reopening. Depending on the drainage volume, urokinase was administered continuously for up to 3 days. On postoperative day 3, a follow-up head CT scan was conducted. If significant hematoma remained, bedside aspiration or continued urokinase perfusion was considered. To minimize the risk of intracranial infection, urokinase administration did not exceed 5 days.

Figures 1e–l illustrate preoperative and postoperative CT scans of a representative case.

Primary endpoint

Hematoma Volume Calculation:

Hematoma volumes were calculated using the Tada formula (14):

Hematoma volume = $\frac{\pi}{6}$ × length diameter (cm) × width diameter (cm) × layer thickness (cm) × number of layers.

Hematoma Disappearance Assessment:

Hematoma disappearance was defined as follows: if the ratio of residual hematoma volume to initial hematoma volume, multiplied by 100%, was <5%, it was considered that the hematoma had disappeared.

Activities of Daily Living (ADL) Assessment:

The patient's activities of daily living (ADL) were assessed using the Barthel index for ADL scale (15). ADL improvement amplitude (Δ ADL) was calculated as:

Δ ADL = Barthel index at discharge - Barthel index at admission

A negative value indicated a decrease in ADL.

Increase in Glasgow Coma Scale (GCS) Score After 7 Days:

The increase in GCS score after 7 days of admission (Δ GCS) was calculated as:

Δ GCS = GCS score on the 7th day after admission – GCS score at admission

A negative value indicated a decrease in the GCS score.

Mannitol Administration:

Mannitol was administered in accordance with the manufacturer's instructions. The dose of mannitol was calculated based on the standard of 1.5 g·kg-1·d-1, which is equivalent to 125 mL of 20% mannitol intravenous drip per day for adults weighing 50 kg, administered once every 8 h. Mannitol duration (in days) was calculated as:

Mannitol Duration (days) = (Total Mannitol Use)/(1.5 g·kg-1·d-1))

Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 23.0, IBM; Armonk, NY, USA). Descriptive statistics were expressed as mean ± standard deviation ($\bar{x} \pm s$) for continuous variables and percentage (%) for categorical variables.

The normality of continuous variables was assessed using the Shapiro-Wilk test. If the data followed a normal distribution, independent *t*-tests were used to compare means between two groups. For non-normally distributed data, the Mann-Whitney *U* test was applied for comparisons between two independent samples. Categorical variables were analyzed using the chi-square test. Statistical significance was set at $p < 0.05$.

Results

From September 2016 to April 2023, a total of 420 patients with intracerebral hemorrhage (ICH) were admitted to our institution, including 352 patients with hematomas located in the basal ganglia. Of these, 153 patients underwent surgical treatment: 47 received craniotomy, 45 underwent surgery using the YL-1 hematoma crushing needle, and 61 had nerve endoscope-assisted hematoma evacuation or other minimally invasive hematoma drainage surgeries. A total of 51 patients met the inclusion criteria, with 30 receiving surgical treatment using the YL-1 hematoma crushing needle and 21 undergoing conservative treatment.

In the surgical group, there was one case each of mild pulmonary dysfunction (bronchiectasis), hypertensive heart disease, and senile heart valve disease. In the conservative treatment group, four patients had mild pulmonary dysfunction (all due to senile emphysema), one patient had hypertensive heart disease, and one had atrial fibrillation.

Imaging Characteristics: All patients underwent head CT scans upon admission. Hematomas were located in the basal ganglia in all cases. In the surgical group, four cases had intraventricular hemorrhage, while two cases in the conservative treatment group had intraventricular hemorrhage.

Medical History: In the surgical group, two patients had a history of anticoagulant use, while no patients in the conservative group had such a history. Patient information is summarized in Table 1.

Regarding the average age, the surgical group had an average age of 60.97 ± 9.96 years, while the conservative group had an average age of 61.10 ± 10.23 years. The independent sample *t*-test yielded $t = -0.045$, $p > 0.05$, indicating no statistically significant difference.

When comparing the sex distribution between the surgical and conservative groups, the surgical group consisted of 17 males (56.7%) and 13 females (43.3%), while the conservative group included 13 males (61.9%) and 8 females (38.1%). The chi-square test results revealed $\chi^2 = 0.140$, $p > 0.05$, indicating no statistically significant difference.

When comparing the distribution of comorbidities between the surgical and conservative groups, 3 patients (10.0%) in the surgical group had comorbidities, while 5 patients (23.8%) in the conservative group had comorbidities. The chi-square test results

TABLE 1 Comparison of data between the surgical group and the conservative group.

	Surgical group (n = 30)	Conservative group (n = 21)	Mean value difference	Difference 95 % confidence interval		F	t/χ^2	P
				Lower	Upper			
Age (y)	60.967 ± 9.960	61.095 ± 10.227	−0.129	−5.886	5.629	0.000	−0.045	0.964
Males	17 (56.7%)	13 (61.9%)					0.140	0.778
Females	13 (43.3%)	8 (38.1%)					0.140	0.778
Comorbidities	3 (10.0%)	5 (23.8%)					1.781	0.182
Smoking history	3 (10.0%)	1 (4.8%)					0.469	0.493
Initial GCS	10.133 ± 2.70	11.667 ± 2.887	−1.533	−3.122	0.055	0.194	−1.940	0.058
Initial ICH volume (mL)	44.443 ± 14.329	38.000 ± 9.813	6.443	−0.808	13.694	2.879	1.786	0.080
ΔGCS	1.567 ± 1.716	0.095 ± 1.179	1.471	0.60247	2.340	4.301	3.403	0.001
Time of hematoma disappearance (d)	9.100 ± 3.871	23.810 ± 3.803	−14.710	−16.907	−12.512	0.070	−13.450	<0.001
ΔADL	25.833 ± 10.755	17.619 ± 13.098	8.214	1.486	14.943	2.822	2.453	0.018
Hospitalization days (d)	33.467 ± 12.760	33.000 ± 12.857	0.467	−6.852	7.785	0.165	0.128	0.899
Complications	22 (73.3%)	11 (52.4%)					2.375	0.123

GCS, Glasgow Coma Scale score; ICH, intracerebral hemorrhage; ADL, Activities of Daily Living.

showed $\chi^2 = 1.781$, $p > 0.05$, indicating that the difference was not statistically significant.

When comparing the distribution of smoking history between the surgical and conservative groups, 3 patients (10.0%) in the surgical group had a smoking history, while 1 patient (4.8%) in the conservative group had a smoking history. The chi-square test results showed $\chi^2 = 0.469$, $p > 0.05$, indicating that the difference was not statistically significant.

For the average hematoma volume at admission, the surgical group had an average volume of 44.44 ± 14.33 mL, while the conservative group had an average volume of 38.00 ± 9.81 mL. The independent sample *t*-test showed $t = 1.786$, $p > 0.05$, indicating no statistically significant difference.

In terms of Glasgow Coma Scale (GCS) scores at admission, the surgical group had an average GCS score of 10.13 ± 2.70, while the conservative group had an average GCS score of 11.67 ± 2.89. The independent sample *t*-test revealed $t = -1.940$, $p > 0.05$, suggesting no statistically significant difference.

When comparing the average ΔADL between the surgical and conservative groups, the results indicated that the surgical group had a significantly higher ΔADL (25.83 ± 10.76) compared to the conservative group (17.62 ± 13.10), with an average increase of 8.21 (95% CI 1.49 – 14.94). The independent sample *t*-test results revealed $t = 2.453$, $p = 0.018 < 0.05$, indicating a statistically significant difference.

Regarding the average ΔGCS, the surgical group showed a significantly higher ΔGCS (1.57 ± 1.72) compared to the conservative group (0.10 ± 1.18), with an average increase of 1.47 (95% CI 0.60–2.34). The independent sample *t*-test results showed $t = 3.403$, $p = 0.001 < 0.05$, indicating a statistically significant difference.

For the average hospitalization duration, the surgical group had a mean length of stay of 33.47 ± 12.76 days, while the conservative group had a mean of 33.00 ± 12.86 days. The independent sample *t*-test results showed $t = 0.128$, $p > 0.05$, indicating no statistically significant difference between the two groups.

When comparing the average time for hematoma disappearance, the surgical group (9.10 ± 3.87 days) had a significantly shorter duration than the conservative group (23.81 ± 3.80 days), with an average reduction of 14.71 days (95% CI 12.51–16.91). The independent sample *t*-test results showed $t = -13.45$, $p < 0.001$, indicating a statistically significant difference.

The Mann–Whitney U test was used to assess the difference in the duration of mannitol administration between the surgical and conservative groups. The average rank for mannitol duration in the surgical group was 19.170, while the conservative group had an average rank of 35.760. The Mann-Whitney U test results indicated a statistically significant difference in the duration of mannitol between the two groups ($U = 110.00$, $p < 0.001$).

When comparing the distribution of complications between the surgical and conservative groups, 22 patients (73.3%) in the surgical group experienced complications, including 21 cases of lung infection and 1 case of stress ulcer. In the conservative group, 11 patients (52.4%) had complications, all of which were lung infections. The chi-square test results showed $\chi^2 = 2.375$, $p > 0.05$, indicating that the difference was not statistically significant.

Discussion

This study compared the baseline characteristics between the surgical and conservative groups, including age, sex, comorbidities, medical history, GCS score at admission, and initial hematoma volume. No significant differences were observed between the groups ($p > 0.05$).

The surgical group demonstrated a significantly shorter hematoma resolution time compared to the conservative group, with an average reduction of 14.71 days ($p < 0.001$). Additionally, the surgical group showed a greater increase in the Barthel index (ΔADL), with an average improvement of 8.21 points ($p < 0.001$). After 7 days of admission, the increase in GCS scores was also significantly higher in the surgical group, with an average improvement of 1.47 points ($p < 0.001$). Furthermore, the amount of mannitol administered in the surgical group was significantly lower than in the conservative group ($p < 0.001$).

However, there were no significant differences in the length of hospital stay between the two groups ($p > 0.05$), and surgery did not significantly increase the incidence of complications ($p > 0.05$).

TIDN surgery is a simple and cost-effective procedure that requires only local anesthesia at the puncture site, resulting in a short surgical duration and minimal bleeding. The procedure utilizes a YL-1 hematoma crushing needle and does not require a scalp incision. Instead, a small bone hole, approximately 2 mm in diameter, is drilled into the skull, allowing for self-fixation (8). This approach is particularly advantageous for older patients or those with varying severities of underlying conditions who may not tolerate a craniotomy. The use of the YL-1 hematoma crushing needle for puncture and drainage reduces surgical trauma (9, 16). Additionally, older individuals often experience varying degrees of brain atrophy, which leads to relatively larger cranial spaces (17). Compared to younger patients, older individuals have a larger intracranial buffer space when their brain tissue is compressed by the same hematoma volume, providing favorable conditions for minimally invasive puncture and drainage surgery.

Urokinase is a promising fibrinolytic agent known for its safety and efficacy (18). It not only enhances the clot dissolution rate but also reduces the adverse outcomes associated with fibrinolysis following ICH (19, 20). Recent studies report that the risk of rebleeding associated with urokinase ranges from 4.4 to 19.4% (18, 21, 22). Consistent with previous findings (8), the urokinase dose administered in this study was 20,000 UI/d. Following 3 days of urokinase treatment, a follow-up head CT scan was conducted. Based on the residual hematoma volume, a decision was made whether to proceed with secondary aspiration or to re-administer urokinase for further hematoma liquefaction. Most intracranial hematomas were evacuated after 5 days of minimally invasive puncture and drainage; thus, urokinase is typically used for no more than 5 days (13). In our experience, after 3 days of urokinase treatment, the hematoma becomes gelatinous and can be easily aspirated. If the head CT scan shows a significant residual hematoma, a 5-mL syringe can be used to aspirate the hematoma twice through the drainage tube. After the second aspiration, most hematomas can be successfully evacuated. It is crucial to note that excessive aspiration may lead to rebleeding.

Following intracerebral hemorrhage (ICH), in addition to the destruction of neurons at the lesion site, secondary neuronal

injury around the lesion begins in the early stages of the disease. Inflammation, thrombin activation, and erythrocyte dissolution resulting from hematoma formation can promote the development of cerebral edema (23, 24). Early hematoma evacuation is crucial to alleviate the compression on adjacent brain tissue, potentially reducing secondary neuronal injury (25, 26). In this study, the hematoma resolution time in the surgical group was shorter than in the conservative group. Early evacuation of some hematomas in the surgical group facilitated partial decompression, allowing patients to pass the peak of the intracranial pressure-volume curve earlier and preventing progression to cerebral herniation. After 7 days of treatment, the increase in GCS scores in the surgical group was 1.471 points higher than in the conservative group. This improvement may be attributed to the reduction of secondary neuroinflammation following hematoma evacuation, thereby shortening the duration of cerebral edema and enhancing neurological recovery in ICH patients.

Perihematomal edema (PHE) can develop following intracerebral hemorrhage (ICH). PHE gradually increases within the first 24 h and intensifies rapidly 3 days after disease onset. It typically reaches its initial peak between the 7th and 11th day, followed by a slow, sustained increase (27). Twenty percent mannitol is the preferred hypertonic agent for clinical management of elevated intracranial pressure (28, 29). In patients without contraindications to mannitol, this treatment alone may suffice to surpass the peak of the intracranial pressure-volume curve. However, some patients may have underlying cardiac or renal dysfunction, and a rapid increase in blood volume following mannitol administration could lead to congestive heart failure. Consequently, excessive fluid intake must be avoided, and patients with severe renal insufficiency should restrict fluid intake to prevent exacerbation of PHE (30). In such cases, the limitation of dehydrating agents may impair PHE resolution and worsen the prognosis. In this study, the duration of mannitol use was reduced in the surgical group, with some patients not requiring mannitol for PHE treatment post-surgery. Given that the majority of ICH patients are older adults with varying degrees of cardiopulmonary insufficiency and other comorbidities, the risks associated with craniotomy and the size of the surgical wound are increased (31). The YL-1 hematoma crushing needle, which requires only local anesthesia, enables hematoma puncture and drainage with a smaller surgical wound, less bleeding, and a shorter operation time (8, 9). Therefore, the use of the YL-1 hematoma crushing needle for hematoma puncture and drainage represents a surgical method worth considering.

TIDN surgery is convenient, quick, and more cost-effective than traditional craniotomy. Conventional hematoma drainage surgery involves making an incision in the scalp and drilling a hole in the skull to create a puncture channel (32, 33). In contrast, TIDN surgery eliminates the need for a scalp incision, allowing for direct drilling through both the skull and dura mater, which facilitates rapid puncture to the target site. This approach minimizes trauma, reduces blood loss, and streamlines the surgical procedure. It enables effective removal of intracranial hematomas while avoiding craniotomy, which can reduce the financial burden on patients. For those undergoing anticoagulant therapy, the risk associated with craniotomy is significantly increased. Our preliminary experience supports the use of TIDN in patients on anticoagulants, as it offers potential benefits for these individuals (9). In this study, two patients receiving anticoagulant therapy showed positive treatment outcomes following TIDN surgery. Although the sample size is small, these preliminary results suggest that TIDN surgery may have potential applications in patients undergoing anticoagulant therapy. However, these findings require validation through larger-scale studies to confirm their efficacy and safety in clinical practice.

Limitations

Our study has several limitations. First, we did not compare TIDN with other surgical approaches such as craniotomy hematoma evacuation, nerve endoscope-assisted hematoma evacuation, or stereotactic hematoma puncture drainage. Therefore, a large-scale, multicenter, randomized controlled trial (RCT) is necessary to further evaluate these methods. Second, this study focused exclusively on patients with basal ganglia hemorrhage. Future research should explore the efficacy of TIDN in treating intracerebral hemorrhage (ICH) in other brain regions to better understand its broader applicability and potential benefits. Third, as a single-center retrospective study, our findings are subject to inherent biases and limitations associated with retrospective analyses and single-center samples. Multi-center prospective studies or RCTs would provide more robust evidence, and future research should consider adopting these designs to validate our results. Finally, the lack of long-term follow-up data and information on surgical complications limits the comprehensiveness of our analysis. Future studies should incorporate these data to fully assess the long-term efficacy and safety of the YL-1 hematoma crushing needle.

Conclusion

The combination of TIDN puncture with hematoma drainage offers a safe, effective, and minimally invasive surgical alternative for older patients with basal ganglia hemorrhage who are unsuitable for craniotomy. The use of a YL-1 hematoma crushing needle in TIDN treatment appears to reduce the need for mannitol administration while avoiding craniotomy. Additionally, this approach may lead to short-term improvements in patients' GCS scores and Barthel index.

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 humans were approved by Ethics Committee of Hui'an County Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. 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

XC: Data curation, Methodology, Supervision, Writing – review and editing. DC: Conceptualization, Writing – review and editing. SS: Data curation, Writing – original draft, Resources. ZH: Data curation, Writing – original draft, Conceptualization, Investigation. WH: Supervision, Writing – review and editing. QZ: Data curation, Investigation, Writing – review and editing, Conceptualization.

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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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Relevance of persistent perfusion deficits on clinical outcomes after successful endovascular treatment: a prospective serial magnetic resonance study

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Background: Half of the patients who undergo successful recanalization after endovascular treatment (EVT) experience poor clinical outcomes. Impaired microvascular reperfusion (IMR) may explain this lack of improvement, but its frequency and clinical significance remain unclear. The study aims to describe the frequency and associated factors of IMR.

Materials and methods: We conducted a study on a cohort of patients with anterior large artery occlusion, treated with EVT at a single center, who achieved mTICI ≥2C. Perfusion MRI was obtained at arrival, up to 2 h after EVT (post-EVT MRI), and on day 5. IMR was observed only on the post-EVT relative cerebral blood volume (rCBV) maps as voxels within the follow-up ischemic lesion, exhibiting a > 15% asymmetry compared to a mirror homolog, in the absence of internal carotid occlusion, hemorrhagic transformation, or arterial reocclusion. Patients with an IMR volume greater than 5 mL were defined as having significant IMR. IMR was analyzed as a binary variable (presence/absence using the 5 mL cut-off) and by total and relative volume.

Results: IMR was present in 8 out of 33 patients (24.2%), with 4 out of 11 (36.4%) having mTICI 2C, and 4 out of 22 (18.2%) having mTICI 3. After adjustment for relevant variables, absolute and relative IMR volumes were associated with higher National Institutes of Health Stroke Scale (NIHSS) scores at 5 days (adjusted beta =0.50 [0.05, 0.96], p = 0.03) and at 24 h (adjusted beta = 0.11 [0.02, 0.19], p = 0.01). No independent associations were found between IMR and the 90-day modified Rankin Scale (mRS).

Conclusion: IMR is present in one-quarter of patients and is associated with worse early neurological outcomes.

KEYWORDS
no-reflow, perfusion imaging, MRI, ischemic stroke, reperfusion

Introduction

The no-reflow (NR) phenomenon (1) has been defined as the absence of microvascular filling after endovascular treatment (EVT). Initially identified in preclinical models of the nervous system, NR is attributed to the obstruction of arterioles and capillaries resulting from microthrombi, endothelial swelling, and pericyte contraction (2, 3). Early *in vivo* descriptions of NR highlighted the absence of capillary blush in selective angiograms distal to the occlusion site after EVT (4). While microthrombi and pericyte contraction are central to the NR phenomenon, other factors—such as circulatory failure or vasogenic edema—may also play a role beyond its primary scope (5). To address these broader mechanisms, the term *impaired microvascular reperfusion* (IMR) *despite complete recanalization* is currently preferred. Unlike the NR concept, IMR offers a more pragmatic framework, including all forms of persistent hypoperfusion, regardless of the underlying cause.

The earlier studies on IMR utilized digital subtraction angiography (DSA), which was performed immediately after EVT. Despite the lack of validation in preclinical models (5), perfusion imaging techniques have become the preferred method for identifying IMR, relying on persistent hypoperfusion as a surrogate marker (6). The perfusion maps used, the inclusion criteria applied, and the definition of IMR on these maps have all varied. Some studies have focused on persistent hypoperfusion in relative cerebral blood volume (rCBV) or relative cerebral blood flow rCBF maps within the infarcted area (7), while others have evaluated it as persistent regions of Tmax>6 s outside or within the infarcted tissue (8). This variability across studies helps to explain the differences in reported prevalence (0–42.9%) and its impact on functional outcomes (7–9). Recently, ter Schiphorst's review (5) proposed a set of inclusion criteria to establish a baseline quality standard.

This study aimed to investigate the prevalence and prognostic significance of impaired microvascular perfusion in a sample of patients achieving successful angiographic recanalization after acute ischemic stroke. We hypothesized that brain perfusion abnormalities after successful EVT are common and contribute to adverse clinical outcomes in stroke patients.

Materials and methods

This study is a part of the prospective project Futile Reperfusion in Ischemic Acute Stroke (FURIAS). The clinical and radiological protocol of the FURIAS project was detailed in a previous study (10). The comparison of the characteristics of the eligible cohort can be found in Supplementary Table 2. The Research Ethics Committee of the Germans Trias I Pujol Hospital approved the study. All the patients or their relatives provided written informed consent. We recruited consecutive patients with anterior large vessel occlusion who underwent EVT. In this group of patients, we performed MRI at three time points: at hospital arrival (MRI pre-EVT), less than 2 h after endovascular treatment (MRI post-EVT), and 5 days after the stroke (MRI on day 5). All patients had an mRS score of less than 2 before the stroke and an NIHSS score of ≥6 upon admission. Additionally, they had time from onset to admission of ≤6 h, until the publication of the DAWN trial (11). After January 2018, we recruited patients with the DAWN criteria (11).

Inclusion criteria: For this sub-study, we included patients achieving final mTICI2c or mTICI3, with adequate perfusion imaging at arrival and post-EVT. Exclusion criteria: we excluded patients with an extracranial internal carotid artery (ICA) occlusion and those who presented a hemorrhagic transformation (parenchymal hematoma; PH or hemorrhagic infarct; IH) or an arterial reocclusion on the post-EVT MRI. Patients with ICA occlusion, patients with mTICI <2C, and patients presenting reocclusion in the magnetic resonance angiogram (MRA) post-EVT were excluded because some perfusion deficit is expected in such situations. Furthermore, patients showing any hemorrhagic transformation in the post-EVT MRI were excluded because blood can produce artifacts in the perfusion sequences.

MRI protocol

All images were performed using a 3 Tesla Siemens Magnetom Verio (Siemens, Erlangen, Germany), except for nine MRIs at 5 days that were acquired on a 1.5 Tesla Philips (Philips Healthcare, Best, Netherlands). The MRI protocol included diffusion-weighted imaging (DWI), susceptibility-weighted imaging, fluid-attenuated inversion recovery (FLAIR), Time of flight MRA, and perfusion-weighted imaging (PWI). PWI was not performed at 5 days. Further information about the imaging protocol can be found elsewhere (10).

Image analysis and post-processing

All the images were securely stored and pseudonymized for analysis. PWI images pre- and post-EVT were processed using Olea Sphere 3.0 – SP22 software (Olea Medical, La Ciotat, France) to obtain rCBV, rCBF, Tmax, and time-to-peak maps. FMRIB's Linear Image Registration Tool (FLIRT) was used to perform a 6-degree corregistration of the post-EVT DWI (including the segmentations above) to the PWI post-EVT maps. We used mutual information as the evaluation metric during the registration process, and all the registrations were reviewed by an expert in neuroimaging (MH).

The pre-EVT MRI was utilized to assess penumbra volumes, while the post-EVT MRI enabled the application of the definition for IMR. Additionally, the 5-day MRI was used to evaluate outcomes, including final infarct volume and hemorrhagic transformation.

A stroke neurologist expert in neuroimaging (MH) manually segmented hyperintensities on DWI pre-EVT, post-EVT, and at day 5, creating lesion masks (12). Infarct volume (mm3) at each time point was calculated from the DWI masks, and hemorrhagic transformation was assessed on the MRI at 5 days according to the European Cooperative Acute Stroke Study II (ECASS-II) classification.

We obtained pre-EVT Tmax>6 s and Tmax>10s masks by applying the corresponding thresholds (6 and 10 s) to the pre-EVT

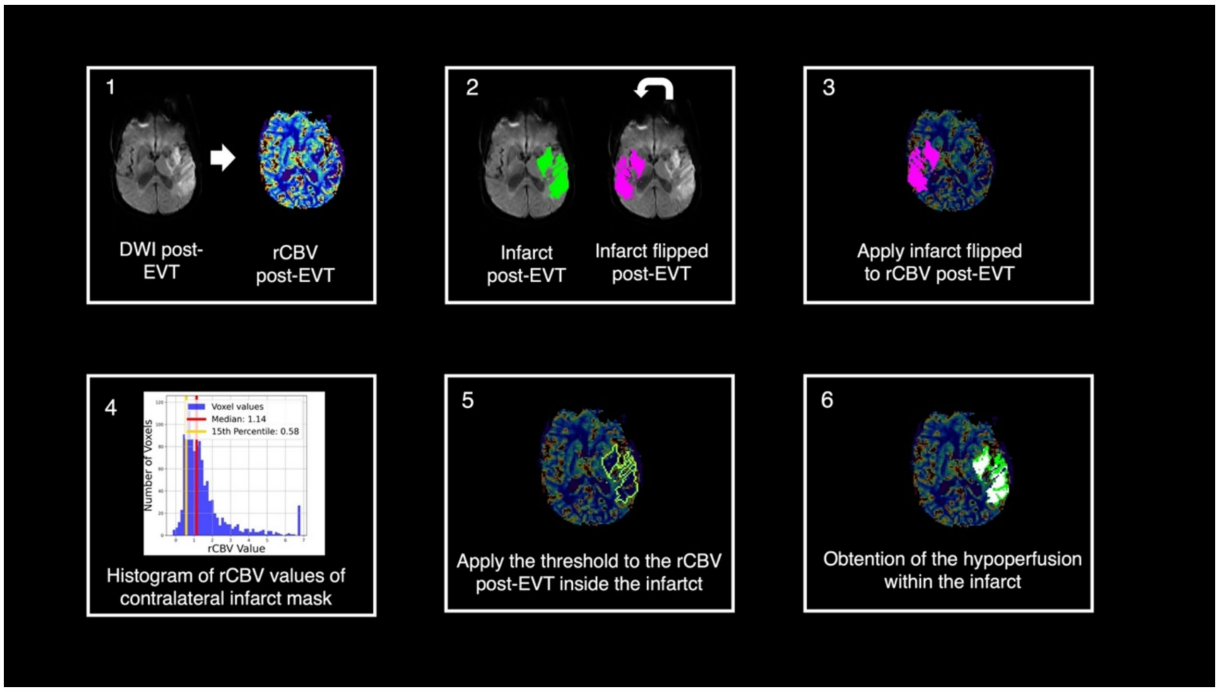

FIGURE 1
Pipeline of the post-processing. (1) Rigid registration of the DWI post-EVT and its infarct segmentation to the rCBV post-EVT. (2) Post-EVT Infarct flip. (3 and 4) Obtention of the voxel values of the rCBV post-EVT in the contralateral flipped infarct and determination of the 15% threshold. (5) Threshold application within the infarct segmentation. (6) Obtention of the infarct microvascular impairment segmentation. DWI, diffusion-weighted image; EVT, endovascular treatment, rCBV, relative cerebral blood volume.

Tmax maps. Hypoperfusion intensity ratio (HIR) was calculated on the pre-EVT maps by dividing the volume of tissue with Tmax >10s by the Tmax>6 s volume.

An experienced interventional neuroradiologist (MW) blinded to the clinical and radiological data evaluated all the angiographies and recorded the final arterial revascularization status according to the mTICI scale with 2c grades (12).

Impaired microvascular reperfusion definition

Figure 1 shows the pipeline of the imaging post-processing. We obtained a specular mask of the post-EVT infarct volume in the contralateral hemisphere and calculated the median value of rCBV excluding cerebrospinal fluid. Voxels within the post-EVT infarct volume that exhibited at least a 15% reduction in the rCBV value relative to the mirrored mask volume's median value were considered to have post-EVT hypoperfusion (7). Only clusters of more than 10 contiguous voxels with hypoperfusion were considered significant (5). All the final masks were reviewed by a vascular neurologist to discard artifacts and ensure the quality of the masks. We calculated the total volume of IMR and the median value of rCBV within IMR. Significant IMR was defined when a patient had an IMR volume beyond 5 mL. This cut-off was established based on previous literature, which suggested establishing a significant threshold (5) to evaluate perfusion deficits. All the images and masks were visually reviewed to exclude potential sequelae lesions associated with hypoperfusion.

Despite the comparability of rCBV and CBF maps in terms of IMR (13), rCBV was preferred due to its consistency in our cohort and its stronger association with capillary density and microvascular integrity, as demonstrated in other neurological conditions such as gliomas (14).

Statistical analysis

The study described variables by mean (standard deviation), median (interquartile range, IQR), or absolute frequencies and percentages as appropriate. We used a paired Wilcoxon signed-rank test to compare the rCBV values in regions of interest with the contralateral side. Baseline characteristics were compared between patients with and without IMR using the chi-square, Fisher exact, or Mann–Whitney test. A Spearman's rank correlation was conducted when evaluating associations between two quantitative variables.

We conducted multiple regression analyses to study the association between IMR (evaluated as a binary variable and as volumes) and clinical and radiological outcomes. Variables and models employed are found in Supplementary Table 1.

Statistical analysis was performed with R (22), with two-sided p-values <0.05 considered statistically significant.

All data are available upon reasonable request.

Results

Between April 2015 and October 2018, we recruited 99 patients, out of which 33 patients were selected for analysis. Figure 2 reveals reasons

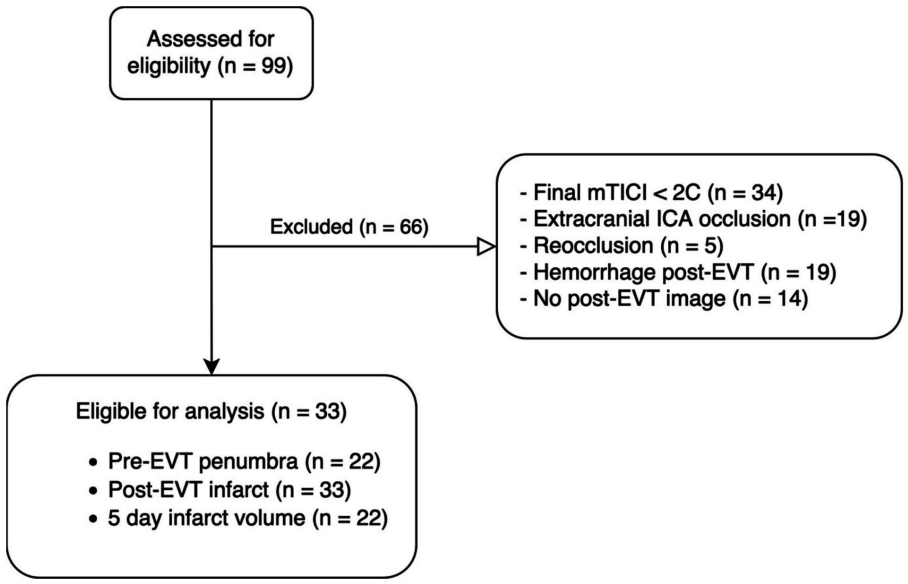

FIGURE 2
Consort diagram. EVT, Endovascular treatment; ICA, intracranial carotid artery; mTICI, modified Thrombolysis in Cerebral Infarction.

for exclusion. The median (IQR) volume of infarct post-EVT and saved penumbra were 15.8 [6.23; 20.1] ml and 99.4 [50.7; 191], respectively. Infarcted and saved penumbra areas in post-EVT exhibited similar median rCBV values to their specular ROIs in the healthy hemisphere. Specifically, the infarcted region had an rCBV value of 1.54 [1.19–2.31] mL/100 g compared to 1.34 [0.96–1.79] mL/100 g for its specular ROI, $p = 0.147$. Similarly, the saved penumbra region had an rCBV value of 1.61 [1.10–2.05] mL/100 g, compared to 1.37 [1.13–2.00] mL/100 g for its specular ROI, with a p-value of 0.84.

IMR and perfusion values within the infarct

Out of 33 patients analyzed, only 8 displayed significant IMR areas, which accounted for 24.2% of the patients. Figure 3 displays some representative cases. A significant IMR was present in 4 out of 11 (36.4%) patients achieving mTICI2c and in 4 out of 22 (18.2%) achieving mTICI3 ($p = 0.39$). In the patients with significant IMR, the median (IQR) IMR volume was 14.5 [11.4; 21.5] mL, with an area that represented 43 [34; 54] % of the infarcted tissue. Moreover, the IMR voxels had a median rCBV value of 0.58 [0.13; 0.86] mL/100 g.

Table 1 summarizes the baseline characteristics of the cohort and patients with significant IMR. The presence of significant IMR was associated with larger pre-EVT DWI lesions. In the adjusted analysis, the presence of significant IMR was not found to be associated with any outcome (Table 2).

When evaluated quantitatively, IMR volume was associated with post-EVT infarct volume (rho = 0.82, $p < 0.01$), infarct volume at day 5 (rho = 0.63, $p < 0.01$), NIHSS scores at 24 h (rho = 0.57, $p < 0.01$) and 5 days (rho = 0.63, $p < 0.01$), and mRS scores at 90 days (common OR = 1.09 [1.01; 1.18], $p = 0.03$). In the adjusted analysis, absolute and relative IMR volume remained significantly associated with the NIHSS scores at 5 days and 24 h, respectively (Table 2).

Post-EVT rCBV values within the infarct were not linked with final mTICI, NIHSS, hemorrhagic transformation, infarct growth, use of rTPA, or functional outcome at 3 months. The IMR frequency was similar in rTPA-treated and untreated patients (5/18 (27.8%) and 3/15 (20%) $p = 0.699$, respectively).

Discussion

Our data reveal that significant IMR is present in approximately one-quarter of patients following successful EVT. While a larger IMR volume was initially associated with a worse prognosis, this relationship did not persist after adjustment for confounding factors.

The prevalence of persistent perfusion deficits is debated; our study reported a 24.2% occurrence (18.2% in patients with final mTICI 3), contrasting with other rates ranging from 0 to 42.5% (6, 7, 15, 16). Discrepancies may arise from different imaging techniques, perfusion thresholds, timing of imaging, and inclusion criteria. Using definitions and exclusion criteria similar to previous studies (7), IMR rates in our cohort were comparable (25–29%) despite earlier imaging after recanalization.

Studies performing imaging within 30 min after EVT showed a delay exceeding Tmax >6 s in 42.5% of mTICI3 patients (6). However, these studies applied less stringent criteria, including patients with ICA occlusions (17% had tandem lesions) and post-EVT hematomas, potentially inflating IMR prevalence. In contrast, other studies using a more similar methodology than ours (7), but without excluding hemorrhagic areas, reported IMR in 25.3% of patients when imaging was acquired up to 24 h after complete recanalization. When researchers included mTICI 2c-3 patients and excluded the three possible causes of apparent persistent hypoperfusion (ICA stenosis, intracranial reocclusion, or areas of hemorrhage), the prevalence of IMR was dramatically reduced to 3.33% (16) or 0% (17).

Compared to those with similar selection criteria, our higher prevalence may be attributed to the shorter imaging acquisition time (<2 h vs. up to 24 h), the longer onset-to-recanalization time

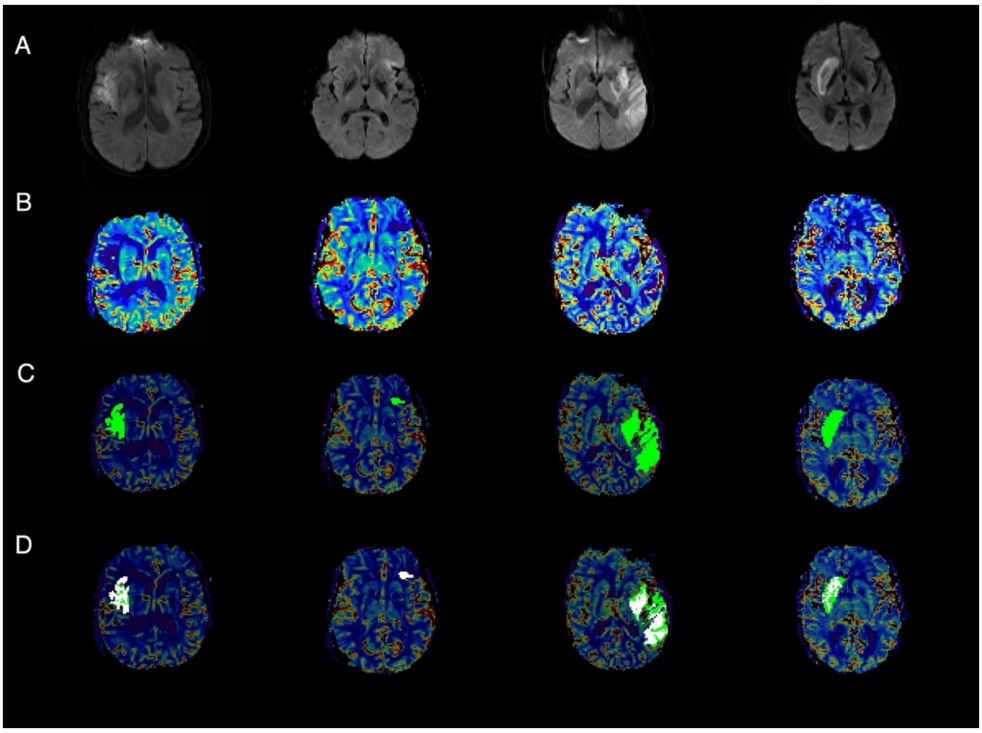

FIGURE 3
Representative cases of infarct microvascular impairment (IMR). **(A)** Post-EVT diffusion-weighted imaging (DWI); **(B)** Post-EVT relative cerebral blood volume (rCBV); **(C)** Post-EVT rCBV with overlaid infarct area (light green); **(D)** Post-EVT rCBV showing the infarct area (green) and regions of IMR (white).

TABLE 1 Baseline characteristics of the patients.

	All *N* = 33	No significant IMR *N* = 25	Significant IMR patients *N* = 8	*p*-value
Age (years), (median, IQR)	72.0 [69.0; 78.0]	72.0 [68.0; 81.0]	71.5 [70.8; 75.0]	0.659
Female sex (*n*, %)	17 (51.5%)	13 (52.0%)	4 (50.0%)	1.000
NIHSS score at admission (median IQR)	17.0 [12.0; 22.0]	16.0 [12.0; 21.0]	21.0 [16.8; 22.0]	0.302
Glycemia (mg/dl), (median IQR)	110 [99.5; 132]	110 [99.0; 130]	130 [104; 141]	0.372
Tmax>6 s volume at admission (ml), (median IQR)	103 [67.0; 140]	96.0 [46.0; 137]	126 [98.2; 214]	0.153
Saved penumbra volume (ml), (median IQR)	99.4 [50.7; 191]	155 [50.7; 201]	77.6 [54.5; 92.4]	0.268
Pre EVT infarct volume (ml), (median IQR)	10.1 [6.70; 15.7]	6.87 [6.05; 12.8]	35.9 [15.8; 61.5]	0.001
HIR (mean, SD)	0.41 [0.28; 0.55]	0.41 [0.24; 0.53]	0.48 [0.38; 0.72]	0.180
Time to treatment				1
<6 h	23 (69.7%)	17 (68.0%)	6 (75.0%)	
6-24 h	10 (30.3%)	8 (32.0%)	2 (25.0%)	
Time from symptom-onset-to-angiographic-reperfusion (minutes), (median IQR)	365 [255; 547]	335 [255; 565]	378 [287; 502]	0.900
Time to image (minutes), (median IQR)	270 [165; 448]	270 [165; 448]	273 [206; 379]	0.785
Treatment (*n*, %)				0.699
rTPA + EVT	15 (45.5%)	12 (48.0%)	3 (37.5%)	
Primary EVT	18 (54.5%)	13 (52.0%)	5 (62.5%)	
Final mTICI *n* (*n*, %)				0.391
mTICI 2c	11 (33.3%)	7 (28.0%)	4 (50.0%)	
mTICI 3	22 (66.7%)	18 (72.0%)	4 (50.0%)	

IMR, impaired microvascular reperfusion; HIR, Hypoperfusion intensity ratio; IQR, interquartile range; SD, standard deviation; rTPA, recombinant tissue plasminogen activator; EVT, endovascular treatment; mTICI, modified Thrombolysis in cerebral infarction; NIHSS, National Institute of Health Stroke Scale.

TABLE 2 Multiple regression analysis of IMR.

	Significant IMR	IMR volume	% of IMR volume within the infarct
NIHSS score at 24 h (β, 95% CI)	5.03 [−3.04, 13.10], $p = 0.21$	0.15 [−0.07, 0.36], $p = 0.17$	0.11 [0.02, 0.19], $p = 0.01$
NIHSS score 5 days or discharge (β, 95% CI)	6.81 [−4.79, 18.41], $p = 0.24$	0.50 [0.05, 0.96], $p = 0.03$	0.12 [−0.05, 0.28], $p = 0.17$
mRS score at 3 months (aOR, 95% CI)	0.72 [0.08, 5.97], $p = 0.77$	1.02 [0.90, 1.14], $p = 0.76$	1.00 [0.97, 1.04], $p = 0.92$
Functional independence (acOR, 95% CI)	1.30 [0.02, 68.19], $p = 0.89$	1.11 [0.78, 1.55], $p = 0.55$	1.02 [0.94, 1.11], $p = 0.58$
Any hemorrhagic transformation (aOR, 95% CI)	2.12 [0.42, 12.34], $p = 0.37$	1.05 [0.99, 1.19], $p = 0.29$	1.00 [0.96, 1.03], $p = 0.91$
Growth >10 mL at 5 days (aOR, 95% CI)	2.03 [0.11, 77.79], $p = 0.65$	1.05 [0.84, 1.36], $p = 0.69$	1.01 [0.96, 1.09], $p = 0.62$
Infarct volume at 5 days (β, 95% CI)	1.91 [−24.63, 28.45], $p = 0.88$	0.15 [−2.64, 2.94], $p = 0.91$	0.03 [−0.42, 0.48], $p = 0.90$

Betas of the covariates can be found in Supplementary Table 3.
IMR, impaired microvascular reperfusion; EVT, endovascular treatment; aOR, adjusted odds ratio; acOR, adjusted common odds ratio; CI, confidence interval; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

([255–547 min] vs. [61–367 min]), and the use of a less stringent method for assessing hypoperfusion (15% reduction compared to the mirror region vs. 40% of the mirror region or visual assessment). Recent research (13) has explored the optimal methodology for evaluating IMR by comparing four different definitions (6, 7, 16, 18) in a common cohort of 131 patients. Although the reported prevalence of IMR varied widely (0.8–22.1%), the definition employed in our study (7) proved to be the most effective in predicting functional outcomes at 3 months. While we assumed a 5-mL volume threshold (5) to determine significant IMR, it has not been validated, highlighting the need to establish a volume cut-off to determine relevant IMR. Additionally, the 15% difference compared to the mirror region is supported by limited evidence (side-to-side variations of 14.5% on SPECT between healthy hemispheres are considered normal (19, 20)), emphasizing the necessity for thresholds derived from preclinical studies that also account for distinctions between white and gray matter.

Consistent with previous literature (7), we found that IMR volume was associated with higher NIHSS scores at 5 days (absolute) and 24 h (relative). Still, we could not find any significant association between other outcomes and IMR in its current definition. Other studies have shown that persistent Tmax>6 s, either inside or outside the infarct, is associated with perfusion derangement and functional outcomes (8, 18), and in a previous study of our cohort, including patients with any final mTICI, post-EVT Tmax>6 s volume was associated with infarct growth (10).

Our analysis was possibly underpowered due to the small sample size; thus, the lack of association of IMR with outcomes could be a type II error. Given the stringent exclusion criteria (with 66% of our sample being excluded) and the intrinsic complexity of conducting repeated image studies with stroke patients shortly after revascularization, overcoming this obstacle will require the implementation of a well-designed multicentric study. While the prevalence of IMR is lower than what is typically observed in clinical practice after excluding all potential causes, it is still more common than earlier studies have suggested (16, 17). The strict selection criteria inherently limit the sample size [$n = 27$ and $n = 33$ in (16, 17)], making it challenging to identify statistically significant associations. Therefore, we call for the collaboration of other centers to continue this line of research.

Our study offers several strengths. We exclusively used MRI perfusion imaging, yielding unique data on perfusion values post-EVT. Unlike previous studies (6, 7, 9) that incorporate both CT and MRI, this approach helps reduce variability. In addition, our computational approach provides precise quantification of perfusion abnormalities and infarct characteristics, minimizing subjectivity and enhancing reproducibility compared to traditional visual assessment methods. Compared to other methods that consider the whole infarct as either affected or unaffected, our approach permits the segmentation of IMR, delimiting its extent to certain areas of the infarct, which allows its quantification.

However, like other methods, this approach struggles to differentiate distinct IMR thresholds between gray and white matter. Given the lower rCBV levels in white matter, particularly in infarcts affecting both gray and white matter, our method may be less sensitive in segmenting IMR voxels in the gray matter and less specific in identifying affected voxels in the white matter. In such cases, determining a separate threshold for each tissue type would be necessary. However, due to the disruption of tissue integrity following an infarct, applying such thresholds in the infarcted area would likely be challenging.

Additionally, we defined infarct based on DWI volume within 2 h after EVT, potentially underestimating the accurate infarct volume due to partial DWI's reversibility. Despite this, we found no differences in the presence of IMR among mTICI2c and mTICI3 grades. While we did not apply p-value corrections due to ongoing debates on their utility (21), our findings align with existing literature.

Our results emphasize the prognostic importance of post-EVT perfusion yet highlight the need for a consistent IMR definition. The dynamic nature of cerebral perfusion after reperfusion therapies complicates this effort, requiring consideration of imaging timing and thresholds. Radiological definitions should align with anatomopathological criteria, necessitating further radiological-pathological studies to establish a unified IMR concept, identify contributing factors, and develop therapeutic strategies.

In summary, IMR volume is significantly and independently associated with poor outcomes in ischemic stroke patients. However, additional research is required to validate these findings and investigate optimal timing and definitions of IMR.

Author's note

This article was presented as a poster at the ESOC (European Stroke Organization Conference) 2023.

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 humans were approved by the Research Ethics Committee of the Germans Trias I Pujol Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. AP: Data curation, Investigation, Writing – review & editing. CL: Data curation, Investigation, Writing – review & editing. MW: Writing – review & editing. LD: Writing – review & editing. SR: Writing – review & editing. JM: Writing – review & editing. JP: Writing – review & editing. YS: Writing – review & editing. NP: Writing – review & editing. MG: Writing – review & editing. AB: Writing – review & editing. CC: Writing – review & editing. LM: Funding acquisition, Project administration, Resources, Writing – review & editing. SD: Writing – review & editing. MT: Writing – review & editing. MM: Funding acquisition, Writing – review & editing. MH-P: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

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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.

Generative AI statement

The authors declare that Generative AI was used in the creation of this manuscript. The authors used ChatGPT 4.0 to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1478240/full#supplementary-material

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A study of the safety and efficacy of multi-mode NMR-guided double-antiplatelet pretreatment combined with low-dose rtPA in the treatment of acute mild ischemic stroke

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Objective: The objective of this study was to evaluate the safety and efficacy of dual antiplatelet pretreatment combined with low-dose rtPA therapy in patients with acute mild ischemic stroke, guided by multimodal MRI.

Methods: In this study, 383 patients with acute mild ischemic stroke (NIHSS ≤ 5) who had symptom onset within 4.5 hours of MRI screening were selected. Patients in the dual antiplatelet pretreatment plus low-dose rtPA group (164 cases) received dual antiplatelet therapy combined with low-dose (0.6 mg/kg) rtPA intravenous thrombolysis. Patients in the standard-dose group (112 cases) received conventional-dose (0.9 mg/kg) rtPA intravenous thrombolysis. Additionally, patients in the dual antiplatelet group who did not receive intravenous thrombolysis (107 cases) underwent 21 days of oral dual antiplatelet treatment.

Results: There was no significant difference in the baseline NIHSS scores among the three groups before treatment ($p > 0.05$). The proportion of early neurological improvement within 24 hours and within 7 days was significantly higher in the DAPT plus low-dose group compared to both the standard-dose group and the DAPT group, with statistical significance ($p < 0.05$). After 90 days of follow-up, the proportion of good functional outcomes in the DAPT plus low-dose group was significantly higher than in both the standard-dose group and the DAPT group ($p < 0.05$), but there was no significant difference between the standard-dose group and the DAPT group. Safety studies indicated that, under MRI guidance, the DAPT plus low-dose group and the standard-dose group had lower incidences of intracranial hemorrhage transformation and symptomatic intracranial hemorrhage, with no statistical difference among the three groups ($p > 0.05$). Mortality rates were also similar across the three groups ($p > 0.05$), with only one patient passing away in the standard-dose group.

Conclusion: After dual antiplatelet pretreatment combined with low-dose rtPA intravenous thrombolysis for acute mild stroke under multimodal MRI guidance, the proportion of patients with good functional outcomes within 90 days was higher compared to the DAPT group and the standard-dose group, with statistical significance. There was no significant increase in the risk of

cerebral hemorrhage compared to the standard-dose group and the DAPT group.

KEYWORDS

magnetic resonance imaging, mild stroke, ischemic stroke, alteplase, aspirin, clopidogrel, dual antiplatelet, recombinant tissue-type plasminogen activator

1 Introduction

Worldwide, mild strokes are quite common. Statistics show that more than 50% of individuals with acute ischemic stroke also experience mild ischemic stroke (1, 2). For acute ischemic stroke within 4.5 h of onset, intravenous thrombolysis with alteplase is the most well-supported pharmacological therapy according to evidence-based medicine. However, there is controversy regarding the use of intravenous thrombolysis for patients with mild strokes (3–6). Most experts agree that acute reperfusion therapy may pose more risks than benefits for those with mild strokes, who generally have a good prognosis. Nevertheless, the prognosis and clinical outcomes for these patients could still be improved. The MaRISS study found that 37% of patients with mild ischemic stroke (NIHSS ≤5) had functional disability at 90 days (mRS score of 2–6) (5). The administration of intravenous thrombolysis, as well as the dose of alteplase (recombinant tissue-type plasminogen activator, rt-PA), affects the prognosis of ischemic stroke patients. The ENCHANTED study (7) showed that low-dose rt-PA (0.6 mg/kg) can reduce mortality and disability after 90 days, but it did not establish that this treatment is superior to standard-dose intravenous thrombolysis. However, the incidence of symptomatic intracerebral hemorrhage (sICH) was lower in the low-dose group. A meta-analysis comparing the effects of standard-dose and low-dose rt-PA intravenous thrombolysis (8) showed that both doses were equally effective. However, the incidence of intracranial hemorrhage increased with the dose of rt-PA (9). Multimodal MRI examinations can effectively reflect the condition of the responsible blood vessels and aid in assessing the risk of disease progression. MRI-guided thrombolytic therapy appears to be both safe and effective for patients with low NIHSS scores or no disability (10).

This study examined the safety and efficacy of dual antiplatelet pretreatment combined with low-dose rtPA intravenous thrombolysis therapy in patients with acute mild ischemic stroke under MRI guidance. The goal was to provide a theoretical basis for using this combined approach in patients with mild ischemic stroke.

2 Materials and methods

2.1 Research subjects

A retrospective study was conducted involving 383 patients with mild stroke who visited Tianjin Huanhu Hospital from May 2021 to March 2024 and completed multimodal MRI examinations (including T1WI, T2WI, DWI, T2-FLAIR, GRE-T2*, and MRA) before treatment (Figure 1). The cohort consisted of 269 males and 114 females, aged 28–85 years. They were divided into three groups based on treatment: the DAPT plus low-dose thrombolysis group (164 cases), which received dual antiplatelet pretreatment combined with rt-PA (0.60 mg/kg) intravenous thrombolysis; the standard-dose thrombolysis group (112 cases), which received rt-PA (0.90 mg/kg) intravenous thrombolysis; and the DAPT group (107 cases), which refused intravenous thrombolysis.

2.1.1 Inclusion criteria

1. Patients met the indications for intravenous thrombolysis as outlined in the "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China 2018" (11) and the "2019 American Heart Association/American Stroke Association Guidelines for Early Treatment of Acute Ischemic Stroke" (12). 2. NIHSS score ≤ 5 points (0 points for awareness item) at admission. 3. Onset time ≤ 4.5 h. 4. Patients underwent a multimodal MRI examination (including T1WI, T2WI, DWI, T2-FLAIR, GRE-T2*, MRA) before intravenous thrombolysis, and acute ischemic cerebral infarction lesions were confirmed by DWI (with reference to the ADC map).

2.1.2 Exclusion criteria

1. Patients with contraindications to intravenous thrombolysis as specified in the "2018 Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China" and the "2019 American Heart Association/American Stroke Association Guidelines for the Early Treatment of Acute Ischemic Stroke." 2. Patients with a modified Rankin Scale (mRS) score ≥ 2 points. 3. Patients who received endovascular treatment. 4. Patients who did not receive dual antiplatelet therapy (except for those with contraindications due to bleeding from thrombolytic therapy).

Patients or their relatives were fully informed of the treatment plan and provided signed informed consent (Ethics Committee Approval No.: 2022–047).

2.2 Methods

2.2.1 DAPT plus low-dose thrombolysis group

DAPT plus low-dose thrombolysis group: Patients received 100 mg of aspirin orally before thrombolysis, within 4.5 h of onset, combined with 75 mg of clopidogrel pretreatment. They were then administered alteplase rt-PA (Boehringer Ingelheim, Germany, Aileton; specifications: 20 mg and 50 mg, S20110051) at a dosage of 0.60 mg/kg for intravenous thrombolysis (with a maximum dose not exceeding 60 mg). Treatment Method: Fifteen percent of the rt-PA dose was administered intravenously within 1 min, while the remaining 85% was infused intravenously at a constant rate over 60 min. During thrombolysis, the patient's neurological symptoms and bleeding were closely monitored, and a head CT was reviewed as needed. If the patient's condition was stable, a multimodal MRI

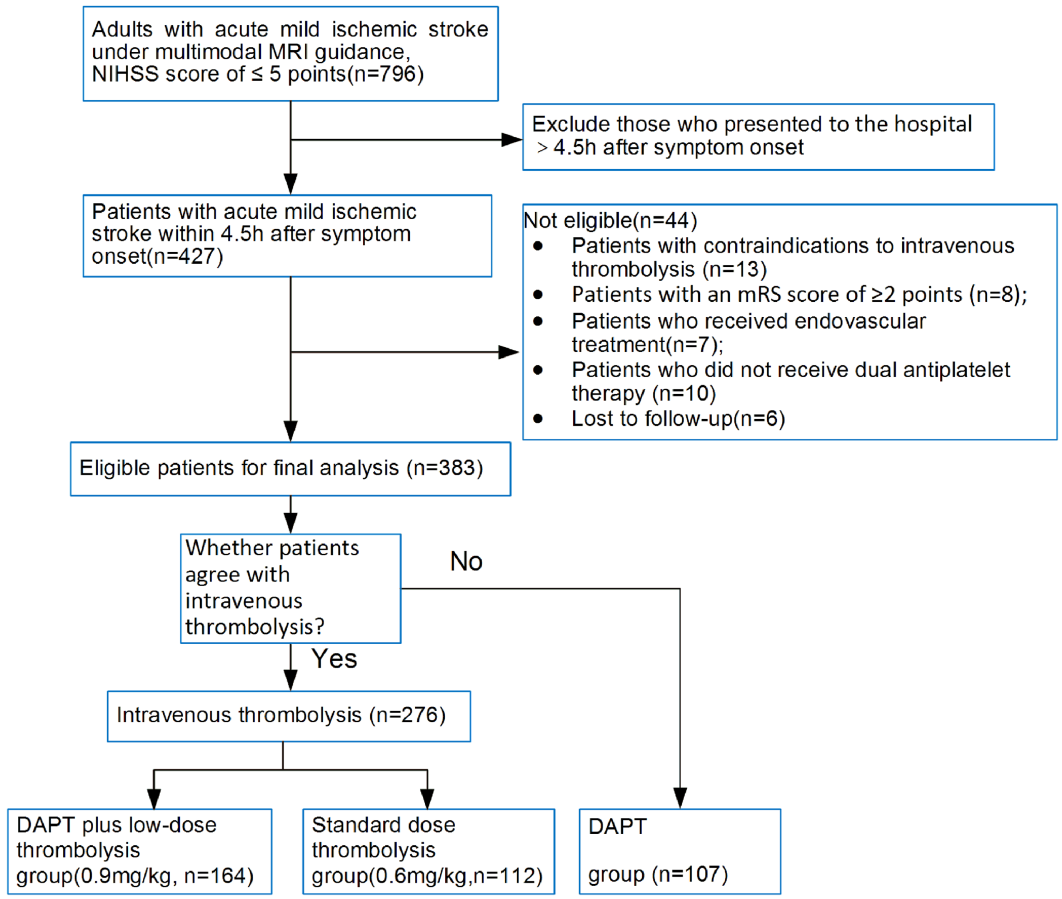

FIGURE 1
Flowchart of patient selection.

of the head was performed 24 h after thrombolysis. If there was a need to exclude bleeding, a head CT was conducted. Imaging examinations were used to rule out intracranial hemorrhage or bleeding in other critical organs, and the patient was prescribed dual antiplatelet therapy: aspirin 100 mg daily and clopidogrel 75 mg daily for 21 days.

2.2.2 Standard dose thrombolysis group

Standard dose thrombolysis group: Patients were administered alteplase rt-PA (Boehringer Ingelheim, Germany, Alite, specifications: 20 mg and 50 mg, S20110051) within 4.5 h of onset, with a dosage of 0.90 mg/kg for intravenous thrombolysis (maximum dose not exceeding 90 mg). Ten percent of the rt-PA dose was injected intravenously within 1 min, and the remaining 90% was infused at a constant rate over 60 min. During the thrombolysis process, the patient's neurological symptoms and bleeding were closely monitored, and a head CT was reviewed as necessary. If stable, a multimodal MRI of the head was performed 24 h after thrombolysis. If there was a concern about bleeding, a head CT was conducted. Imaging examinations were used to rule out intracranial hemorrhage or bleeding in other critical organs, and dual antiplatelet therapy was given with aspirin 100 mg daily and clopidogrel 75 mg daily for 21 days.

2.2.3 DAPT group

After completing the multimodal MRI examination, dual antiplatelet therapy was initiated, with aspirin 100 mg daily and clopidogrel 75 mg daily for 21 days.

2.3 Evaluation of efficacy

According to the NINDS clinical trial and evaluation criteria (13), NIHSS scores were assessed at admission, 24 h, and 7 days after treatment. Short-term prognosis was considered good if the neurological impairment score improved by ≥ 4 points or if clinical symptoms completely resolved, resulting in an NIHSS score of 0. A poor prognosis was indicated by a decrease in the NIHSS score of less than 4 points at 24 h and 7 days after treatment. Neurological prognosis was further evaluated using the mRS score at 90 days of follow-up, with scores of 0 to 2 indicating a good functional outcome.

2.4 Safety evaluation

According to the criteria of the European Collaborative Acute Stroke Study II (ECASS II) (14), symptomatic intracerebral

hemorrhage (sICH) is defined as bleeding in any part of the brain identified by CT scan, which directly exacerbates the patient's clinical symptoms or indicates a poor prognosis, such as increased lethargy, worsening hemiplegia, or an increase in the NIHSS score by more than 4 points.

2.5 Statistical analysis

All data were analyzed using IBM SPSS Statistics 29.0. Measurement data that conformed to a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), with comparisons between groups performed using the independent sample t-test for two groups or one-way analysis of variance for three or more groups. Data that did not conform to a normal distribution were expressed as the median and interquartile range (M [P25, P75]), with the Mann–Whitney U test and Kruskal-Wallis test applied. Count data were expressed as frequency (n) and percentage (%). Comparisons between count data groups were performed using the chi-square test or Fisher's exact test, depending on the conditions, with $p < 0.05$ considered statistically significant.

3 Results

3.1 General clinical data of patients with mild ischemic stroke

There were no statistically significant differences in gender, age, hypertension, diabetes mellitus, stroke history, coronary artery disease, atrial fibrillation, smoking status, alcohol use, random blood glucose, systolic blood pressure, diastolic blood pressure, white blood cell count, triglycerides, total cholesterol, low-density lipoprotein, high-density lipoprotein, fibrinogen (FIB), time from onset to medication, proportion of mRS score 0–1 before onset, baseline NIHSS score, proportion of each stroke type in the TOAST classification, proportion of responsible large artery occlusion, and proportion of anterior and posterior circulation among the three patient groups ($p > 0.05$). See Table 1.

3.2 Efficacy and safety analysis

Patients with acute mild ischemic stroke were treated using three methods: the DAPT low-dose group received dual antiplatelet pretreatment combined with (0.6 mg/kg) rtPA intravenous thrombolysis; the standard-dose group received (0.9 mg/kg) rtPA intravenous; and the DAPT group received aspirin and clopidogrel dual antiplatelet therapy. Short-term prognosis was assessed by comparing early neurological improvement within 24 h and 7 days after treatment, while long-term neurological function was evaluated based on good functional outcomes at a 90-day follow-up (see Table 2).

Recent neurological function evaluations showed that NIHSS scores at 24 h and 7 days post-treatment were lower than those before treatment (Table 3). For early neurological improvement within 24 h, the difference between the DAPT plus low-dose group and the standard-dose group was significant ($^{a1}P < 0.05$). Significant differences were also observed between the standard-dose group and the DAPT group ($^{b1}P < 0.05$), and between the DAPT plus low-dose group and the DAPT group ($^{c1}P < 0.05$). For early neurological improvement at 7 days, the difference between the DAPT plus low-dose group and the standard-dose group was significant ($^{a2}P < 0.05$). Significant differences were found between the DAPT plus low-dose group and the DAPT group ($^{c2}P < 0.05$), while the difference between the standard-dose group and the DAPT group was not statistically significant ($^{b2}P > 0.05$).

In terms of long-term neurological prognosis, the results from the 90-day follow-up of the three groups showed the following proportions of good functional outcomes: 153 cases (93.3%) in the DAPT plus low-dose group, 93 cases (83.0%) in the standard-dose group, and 90 cases (84.1%) in the DAPT group. Compared to the standard-dose and DAPT groups, the DAPT plus low-dose group showed a statistically significant difference ($^{a3,c3}P < 0.05$), while the difference between the standard-dose group and the DAPT group was not statistically significant ($^{b3}P > 0.05$). The good functional outcomes in the DAPT plus low-dose group were more pronounced, with significant differences among the three groups ($p = 0.016$). Results are shown in Table 2, and the distribution of 90-day mRS scores is illustrated in Figure 2.

Safety studies revealed that the incidence of bleeding, including intracranial hemorrhage transformation and symptomatic intracranial hemorrhage during intravenous thrombolysis under MRI guidance, was lower in the low-dose and standard-dose groups compared to the DAPT group. However, no significant differences among the three groups were observed ($p > 0.05$). Except for bleeding, there were no serious adverse events related to thrombolysis (such as severe laryngeal edema, allergic reactions, liver and kidney function damage, cytopenias, etc.) in the Standard dose group, the DAPT group, the DAPT plus low-dose group. Regarding mortality, only one patient died in the standard-dose group, and there were no significant differences among the three groups ($p > 0.05$). See Table 4.

4 Discussion

Current guidelines recommend administering alteplase intravenously to patients with acute ischemic stroke (AIS) who seek medical attention within 4.5 h of symptom onset (11, 12). However, there is controversy regarding intravenous thrombolytic therapy for mild cases (3–5). The "Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China 2018" states (11): For mild non-disabling strokes and strokes with rapid symptom improvement, intravenous thrombolytic therapy can be considered, provided a full evaluation and communication are conducted. The "2019 American Heart Association/American Stroke Association Guidelines for Early Treatment of Acute Ischemic Stroke" (12) recommends intravenous thrombolytic therapy for disabling mild ischemic strokes (NIHSS score 0–5) but not for non-disabling strokes. The definition of disability generally refers to the impact on the patient's daily life and work, though standards may vary among different patients.

Analysis of a subgroup of patients with mild ischemic stroke in the IST-3 randomized trial demonstrated that intravenous alteplase was superior to standard medical treatment (15). An observational

TABLE 1 Baseline characteristics of acute mild ischemic stroke patients in the three groups.

Characteristics	DAPT plus low dose group (*n* = 164)	Standard dose group (*n* = 112)	DAPT group (*n* = 107)	*P*
Male Sex [*n* (%)]	118 (72.0)	82 (73.2)	69 (64.5)	0.301
Age (years)	62.3 ± 9.6	60.4 ± 12.1	62.8 ± 9.3	0.115
Hypertension [*n* (%)]	122 (74.4)	72 (64.3)	80 (76.5)	0.138
Diabetes mellitus [*n* (%)]	44 (26.8)	35 (31.3)	36 (33.6)	0.462
Any stroke [*n* (%)]	35 (21.3)	22 (19.6)	31 (29.0)	0.210
Coronary artery disease [*n* (%)]	26 (15.9)	21 (18.8)	14 (13.1)	0.519
Atrial fibrillation [*n* (%)]	8 (4.9)	9 (8.0)	5 (4.7)	0.463
Current smoker [*n* (%)]	60 (36.6)	38 (33.9)	37 (34.6)	0.889
Alcohol use [*n* (%)]	38 (23.5)	21 (18.8)	20 (18.7)	0.530
Baseline blood pressure (mmHg)				
Systolic blood pressure	151.9 ± 19.5	152.1 ± 16.5	153.6 ± 24.0	0.781
Diastolic blood pressure	88.0 ± 11.6	87.5 ± 11.2	87.1 ± 16.3	0.856
Random blood glucose (mmol/L)	7.3 ± 2.4	7.6 ± 2.2	7.1 ± 2.4	0.276
WBC ($\times 10^9$/L)	7.5 ± 2.0	7.9 ± 2.1	7.5 ± 2.2	0.160
Total cholesterol (mmol/L)	5.0 ± 1.1	5.2 ± 1.1	5.0 ± 1.3	0.412
Triglycerides (mmol/L)	1. 6 ± 1.0	1.8 ± 1.3	1.6 ± 1.1	0.399
LDL cholesterol (mmol/L)	3.1 ± 0.9	3.3 ± 0.8	3.2 ± 1.0	0.187
Fibrinogen FIB	2.9 ± 0.9	2.8 ± 0.7	2.9 ± 0.7	0.253
Baseline NIHSS score	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	0.441
OTT time (minutes)	216.6 ± 35.1	208.1 ± 42.6	213.6 ± 44.2	0.226
mRS score before symptom onset: 0–1 [*n* (%)]				0.218
mRS score 0	156 (95.1)	110 (98.2)	100 (93.5)	
mRS score 1	8 (4.9)	2 (1.8)	7 (6.5)	
TOAST classification [*n* (%)]				0.733
Large artery atherosclerosis	82 (50.0)	46 (41.1)	55 (51.4)	
Small artery occlusion	50 (30.5)	44 (39.3)	31 (29.0)	
Cardioembolism	5 (3)	5 (4.5)	3 (2.8)	
Other determined cause	6 (3.7)	6 (5.4)	5 (4.7)	
Undetermined cause	21 (12.8)	11 (9.8)	13 (12.1)	
Microbleeds ≤ 10 [*n* (%)]	5 (3.0)	6 (5.4)	4 (3.7)	0.620
Intracranial aneurysm <10 mm [*n* (%)]	18 (11.1)	7 (6.3)	5 (4.7)	0.119
Circulation classification [*n* (%)]				0.994
Anterior circulation	97 (59.15)	64 (57.14)	63 (58.88)	
Posterior circulation	65 (39.63)	47 (41.96)	43 (40.19)	
Anterior and posterior circulation	2 (1.22)	1 (0.89)	1 (0.93)	
Occlusion of the responsible large artery [*n* (%)]	34 (20.7)	32 (28.6)	21 (19.6)	0.208

Data are presented as *n* (%), mean ± standard deviation, or *M* (P25,P75), and *p* values were compared among the three groups.

study (16) including 1,386 patients with NIHSS scores of ≤5 found that 194 (14.0%) received intravenous thrombolysis therapy. Results indicated that the thrombolysis group was more effective than the control group, with a statistically nonsignificant risk of symptomatic hemorrhagic transformation.

Multiple international meta-analyses have shown that intravenous thrombolysis is safe and effective in patients who are taking antiplatelet agents in the early stages (17, 18).

Because the half-life of rt-PA in plasma is very short, it is quickly eliminated from the blood after intravenous injection, and only 10% is left after 20 min of medication. With the gradual dissolution of thrombosis, the rupture of unstable plaque and the damaged intima can be exposed again. Thereby inducing and promoting local platelet activation and aggregation. It is easier to form thrombosis in the short term, and even some patients will have arterial re-occlusion, and the symptoms are repeated or aggravated.

TABLE 2 Comparison of therapeutic effectiveness among the three groups [*n* (%)].

Outcome	DAPT plus low dose group (*n* = 164)	Standard dose group (*n* = 112)	DAPT group (*n* = 107)	*P*
Early neurological improvement within 24 h	117 (71.3)[a1]	44 (39.3)[b1]	25 (23.4)[c1]	<0.01*
Early neurological improvement within 7 d	142 (86.6)[a2]	61 (54.5)[b2]	46 (43.0)[c2]	<0.01*
mRS score 0–2 within 90 d	153 (93.3)[a3]	93 (83.0)[b3]	90 (84.1)[c3]	0.016*

Data are presented as *n* (%), and *p* values were compared among the three groups. * indicates $p < 0.05$, indicating that the difference was statistically significant. [a1]: Comparison of neurological improvement within 24 h between the DAPT plus low-dose group and the standard-dose group; [b1]: Comparison between the standard-dose group and the DAPT group within 24 h; [c1]: Comparison between the DAPT plus low-dose group and the DAPT group within 24 h. [a2]: Comparison of neurological improvement between the DAPT plus low-dose group and the standard-dose group within 7 d; [b2]: Comparison between the standard-dose group and the DAPT group within 7 d; [c2]: Comparison between the low-dose group and the DAPT group within 7 d; [a3]: Comparison of the proportion of good functional outcomes between the DAPT plus low-dose group and the standard-dose group within 90-d mRS score 0–2; [b3]: Comparison between the standard-dose group and the DAPT group within 90 days; [c3]: Comparison between the DAPT plus low-dose group and the DAPT group within 90 d.

TABLE 3 Comparison of baseline NIHSS scores and 24 h, 7-d NIHSS scores in the three groups.

NIHSS score	DAPT plus low dose group (*n* = 164)	Standard dose group (*n* = 112)	DAPT group (*n* = 107)	*p*
Baseline NIHSS score	3 (1–4)	3 (1–4)	3 (1–4)	0.441
24-h NIHSS score	0 (0–1)	2 (0–4)	2 (1–4)	<0.001
7-d NIHSS score	0 (0–0)	1 (0–3)	1 (0–4)	<0.001

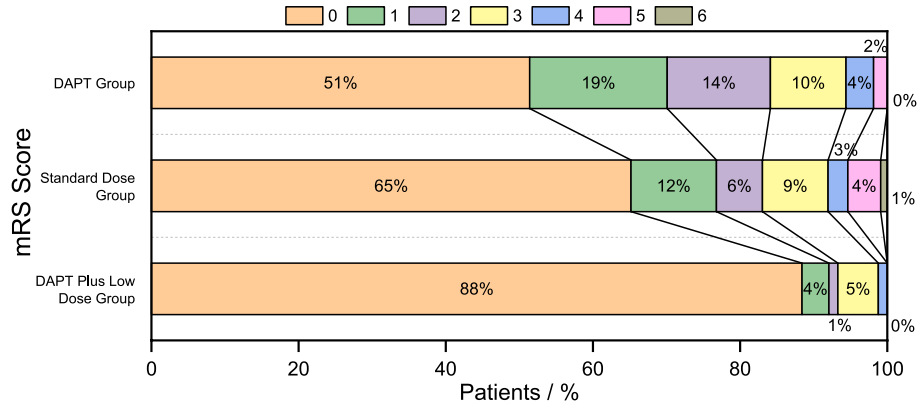

FIGURE 2
90-days mRS score displacement.

Aspirin and Clopidogrel are commonly used antiplatelet aggregation drugs in clinical practice, and their mechanisms of action are different: Aspirin effectively inhibits thromboxane A2 production by acting on cyclooxygenase, thereby inhibiting platelet aggregation (19). While Clopidogrel inhibits platelet aggregation by selectively inhibiting adenosine diphosphate (20). Early antiplatelet therapy after intravenous thrombolysis can reduce early neurological deterioration by preventing vascular re-occlusion and stroke progression (21). In a single-center clinical study from the Netherlands, antiplatelet agents prior to intravenous thrombolysis were shown to be independently associated with a favorable outcome (22).

Recently, meta-analyses of the efficacy of antiplatelet conditioning prior to intravenous thrombolysis have shown that antiplatelet conditioning prior to intravenous thrombolysis reduces the risk of long-term neurological deterioration (18). Low-dose Alteplase has also been shown to improve outcomes in patients with acute ischemic stroke who have received prior antiplatelet therapy with thrombolysis (23).

The study also showed that the proportion of patients with good functional outcomes at 90 days of follow-up was higher in the DAPT plus low-dose group than in both the standard-dose group and the DAPT group, with significant differences ($p < 0.05$). No significant difference was found between the standard-dose group and the DAPT group ($p > 0.05$). These findings suggest that dual antiplatelet pretreatment combined with low-dose rtPA intravenous thrombolysis is more effective for treating acute mild ischemic stroke than traditional dual antiplatelet therapy and standard-dose rtPA thrombolysis. Additionally, the proportion of patients showing early neurological improvement within 7 days was significantly higher in the DAPT plus low-dose group compared to the standard-dose group and the DAPT group ($p < 0.05$), while the difference between the standard-dose group and the DAPT group was not significant ($p > 0.05$). This suggests that dual antiplatelet pretreatment combined with low-dose rtPA therapy provides a faster onset of effect and significantly improves early neurological function.

The SITS registry reported that 25% of mild strokes were complicated by intracranial and extracranial large vessel occlusions,

TABLE 4 Comparison of treatment safety among the three groups [*n* (%)].

Safety indicators	DAPT plus low dose group (*n* = 164)	Standard dose group (*n* = 112)	DAPT group (*n* = 107)	*P*
Intracranial hemorrhage	2 (1.2)	3 (2.7)	0 (0)	0.216
sICH	0 (0)	1 (0.9)	0 (0)	0.314
Non-sICH	2 (1.2)	2 (1.8)	0 (0)	0.648
Death	0 (0)	1 (0.9)	0 (0)	0.302

Data are presented as *n* (%) and *p* values were compared among the three groups.

consistent with the findings of this paper (24). Studies have indicated that intravenous thrombolytic therapy is an independent predictor of good functional prognosis at 90 days for patients with mild non-disabling stroke and severe large vessel stenosis/occlusion (25). Several studies have also shown that patients with acute ischemic mild stroke and large artery occlusion are at high risk of progressive neurological deterioration, particularly those with posterior circulation cerebral infarction, who are critically ill and progress rapidly. Conventional doses of antiplatelet therapy, cerebral circulation improvement, and statin therapy for atherosclerosis are not optimal. Arterial thrombolysis is limited by technology, equipment, and its time-consuming nature, making it difficult to implement widely. Intravascular stent therapy for the posterior circulation system is also risky and challenging. Studies from the German Stroke Registry-Endovascular Treatment (GSR-ET) and the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) databases indicate that for patients with acute mild stroke (NIHSS score ≤ 5) and large vessel occlusion, intravenous thrombolysis results in a 2.16-fold improvement in 90-day functional outcomes compared to bridging therapy or direct mechanical thrombectomy (26). Antiplatelet therapy has been shown to be effective in acute ischemic stroke with macrovascular disease in recent studies (27, 28).

All patients in this study underwent multimodal MRI examinations before treatment. Multimodal MRI can detect ischemic lesions within minutes of symptom onset, providing early information on lesion size, location, and timing. It is more sensitive than conventional MRI for detecting small infarct lesions. Magnetic Resonance Angiography (MRA) can reveal occlusion or stenosis of large blood vessels in the head. Multimodal MRI and MRA examinations provide a clear view of the condition of the responsible blood vessels and support early treatment decisions for patients with mild ischemic stroke (17). This safety study found that, compared to the DAPT group, both the DAPT plus low-dose group and the standard-dose group under MRI guidance had lower rates of intracranial hemorrhage transformation and symptomatic intracranial hemorrhage, with no significant statistical difference among the three groups ($p > 0.05$). Mortality rates were not statistically different among the groups ($p > 0.05$), with only one patient passing away in the standard-dose group. The study concludes that intravenous thrombolysis guided by multimodal MRI can be beneficial and safe for patients with cerebral infarction, large vessel occlusion, and posterior circulation infarction.

In summary, for patients with mild stroke, opting for dual antiplatelet pretreatment guided by multimodal MRI and combined with low-dose rt-PA intravenous thrombolysis may reduce the risk of bleeding associated with intravenous thrombolysis and enhance patient prognosis. Future multicenter, long-term studies with large sample sizes are needed to further validate these findings and provide more individualized treatment options for acute mild ischemic stroke (MIS) patients.

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 humans were approved by the Tianjin Huanhu Hospital Ethics Committee (Approval number: 2022-047). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

XL: Conceptualization, Data curation, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. YC: Writing – review & editing. ZD: Writing – review & editing. FZ: Writing – review & editing. PC: Writing – review & editing. PZ: Funding acquisition, Project administration, Resources, Writing – review & editing.

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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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The correlation of whole blood viscosity and outcome in mechanical thrombectomy for acute ischemic stroke

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Introduction: Whole blood viscosity (WBV), reflecting the intrinsic resistance of blood flow, is an established predictor of stroke events in individuals. This study aims to correlate the WBV at different shear rates with the outcome of mechanical thrombectomy, known to be an effective treatment for large vessel occlusion (LVO) stroke.

Method: This is a single-center retrospective study conducted at our comprehensive stroke center. The charts of 317 patients who underwent mechanical thrombectomy within 6 h of LVO stroke presentation were reviewed. The modified Rankin score (mRS) at discharge was used as the outcome measure, with individuals categorized as low (0–2) or high (3–6). WBV at different shear rates was calculated using De Simone's Formula. The *T*-test and Chi-square test were used to compare baseline continuous and categorical data, respectively, amongst the mRS study groups. We utilized multivariable logistic regression analyses to identify the independent risk factors associated with the outcome of interest following mechanical thrombectomy. In addition, Spearman rank order correlation was used to assess for r value between mRS and WBV at different shear rates.

Results: Baseline group characteristics, including demographics and medical history, were similar among the two study groups. Of note, our study found no significant differences in clinical outcomes between the two groups with WBV at high shear rate (OR 0.969, 95% CI 0.77–1.204, $p = 0.780$) and low shear rate (OR 0.998, 95% CI 0.988–1.008, $p = 0.779$) following mechanical thrombectomy. Spearman rank order correlation between mRS at discharge with WBV at high shear rate ($r = 0.058$, $p = 0.123$) and low shear rate ($r = 0.048$, $p = 0.128$) was non-significant.

Discussion: There is limited information of the effect of WBV at high and low shear rates on the clinical outcome following mechanical thrombectomy in patients with LVO. Our results revealed that WBV at high and low shear rates did not impact the functional outcome of mechanical thrombectomy. This result might be affected by the potential limitation of the formula used to derive the given shear rates. Despite this lack of association observed in our study, other contributors of viscosity may still potentially play a significant role in outcome following mechanical thrombectomy.

KEYWORDS

stroke, ischemia, thrombectomy, viscosity, large vessel occlusion, modified Rankin score

Introduction

Whole blood viscosity (WBV) is a measure of resistance of blood to flow, resulting from friction between adjacent layers of blood (Pop et al., 2002). As a non-Newtonian fluid, the viscosity of blood is dependent on a variable range of shear rates or shear stress. Moreover, blood is a tissue composed of different cell types (e.g., RBCs, WBCs platelets, and plasma; Baskurt and Meiselman, 2003). Thus, the determinants of blood viscosity can be postulated as hematocrit, plasma viscosity (itself determined by lipoproteins and plasma fibrinogen), red cell aggregations, and red cell deformation (Lowe et al., 1997). In 1989, Simone et al. identified the hematocrit as the most important contributor to blood viscosity and derived an equation to calculate WBV using hematocrit and total plasma protein level, the latter an indicator of plasma viscosity (De Simone et al., 1990).

Disorders in the hemorheological variables, including blood viscosity, have been shown to constitute a significant risk factor in both the development and exacerbation of cardiovascular disorders (Tekin Tak et al., 2020; Cecchi et al., 2009). Prior studies have suggested the role of elevated blood viscosity to be a stronger predictor of stroke, and its recurrence, than more conventional risk factors (Lowe et al., 1997; Velcheva et al., 2008).

Mechanical thrombectomy (MT) has revolutionized the approach to acute stroke due to LVO (Berkhemer et al., 2015). Following the introduction of MT, further studies have continued to demonstrate its therapeutic efficacy for patients with LVO (Ghozy et al., 2022), in the context of improving degree of disability and early neurologic recovery with better functional outcomes (Saver et al., 2016). However, excellent outcomes are not routine, and prognosis presumably reflects coexistent factors such as age and timing of the procedure; additionally, intrinsic factors such as hemorheological status also play a role in the clinical outcome of patients with acute ischemic stroke (Costalat et al., 2012; O'Connor et al., 2020). The modified Rankin scale (mRS) is a well established outcome measure for stroke patients, which grades a patient's disability from 0 (no symptoms) to 6 (death; Powers et al., 2019; Banks and Marotta, 2007).

In our study, we assessed for a potential correlation between WBV at two different shear rates with the outcome following MT based on mRS scores at discharge in patients with LVO. It was proposed that our findings might provide relevant information about the effect of WBV on successful endovascular intervention in strokes secondary to LVO.

Methods

This was a single center retrospective study conducted at our comprehensive stroke center from January 2018 to July 2023, with inclusion of 317 consecutive patients in total. These were patients aged 18 years to 89 years who had undergone MT for LVO, with or without intravenous thrombolytics, within 6 h of stroke onset. Patients with any cancer, severe anemia, and those with incomplete information from the database were excluded. The study was approved by the local Institutional Review Board (IRB) of the medical center.

Per conventional outcome measures employed in analyses of patients with strokes, the study population was divided into two groups based on mRS score at discharge following MT. Group 1 is comprised of patients with mRS score 0–2 (favorable outcome) and Group 2 with mRS score 3–6 (unfavorable outcome). The WBV for each patient at high shear rates (HSR) and low shear rates (LSR) was calculated using De Simone's Formula: (De Simone et al., 1990).

$$WBV\ at\ HSR\ (208/sec\text{-}1) = (0.12 \times HcT) + 0.17\ (TP - 2.07)$$

$$WBV\ at\ LSR\ (0.5/sec\text{-}1) = (1.89 \times HcT) + 3.76\ (TP + 78.42)$$

where TP is total protein in g/L, HcT is hematocrit in %

Data analysis was performed using R software. For the comparison of continuous data across two groups, the *t*-test was chosen as the most appropriate statistical test. Similarly, given that categorical data were being compared across $n = 2$ groups, the Chi-square test was deemed appropriate for this purpose.

Given a binary outcome variable, that of two mRS score groups (i.e., 0–2 vs. 3–6), logistic regression was selected as the most appropriate statistical methodology for model analysis. Importantly, this was performed in both a univariate and more rigorous multivariable fashion. Per convention, a p-value <0.05 was used as statistically significant. Finally, given the underlying non-parametric distribution of the data, Spearman rank order correlation was used to assess for r between mRS and WBV at different shear rates, as opposed to a more traditional Pearson's r.

Results

We analyzed the data of 317 patients from the database. The mean age + SD in group 1 was 66.8 ± 13.7; in group 2, this was 66.7 ± 14.4. In group 1, the female population was 41%, whereas in group 2, this was 47%. There was no significant difference in age ($p = 0.97$) and gender ($p = 0.38$) between the two groups. Fifty-seven percentage were found to have a smoking history in group 1, greater than those found in group 2, 44%; this difference was statistically significant ($p = 0.046$). Time from door to puncture site was less in group 1 compared to group 2 (101 min vs. 121 min, $p = 0.01$). There were no significant differences between the two groups in terms of NIHSS at presentation, pre-existing diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, or laboratory findings of hematocrit, platelet, total protein, and lipid profile (Table 1).

Our study found no significant differences for a positive clinical outcome (mRS at discharge of 0–2) with WBV at HSR (OR 0.969, 95% CI 0.77–1.204, $p = 0.780$) and LSR (OR 0.998, 95% CI 0.988–1.008, $p = 0.779$) following mechanical thrombectomy.

Spearman rank order correlation between mRS at discharge with WBV at HSR ($r = 0.058$, $p = 0.123$) and LSR ($r = 0.048$, $p = 0.128$) was also non-significant (Figures 1, 2).

Discussion

Based on the analysis conducted using the present dataset, we did not find any correlation between WBV at high vs. low

TABLE 1 Demographic and medical history summary.

Variables	mRS 0–2 (88)	mRS 3-6 (229)	p-value
Age (years)	66.8 ± 13.7	66.7 ± 14.4	0.97
Gender (%)			0.38
Female	41	47	
Male	59	53	
NIHSS at presentation	13.2 ± 6.76	17.1 ± 6.69	0
Prior stroke (%)	16	17	1
BMI	31.2 ± 7.69	30.2 ± 8.09	0.33
Hypertension (%)	79	86	0.17
DM (%)	21	32	0.62
Coronary artery disease	15	20	0.40
Atrial fibrillation	30	27	0.75
Smoking	57	44	0.04
Hematocrit	0.39 ± 0.06	0.39 ± 0.07	0.79
Platelet	236 ± 82.6	247 ± 84.3	0.29
Total protein	67.9 ± 7.03	68 ± 7.45	0.9
Total cholesterol	154 ± 38.5	160 ± 44.8	0.24
TG	108 ± 60.8	118 ± 84.2	0.3
HDL	44.6 ± 13.3	45.9 ± 16.6	0.46
LDL	89.2 ± 32	93.4 ± 39.0	0.36
Door to puncture site	101 ± 51.6	121 ± 84.6	0.01
Reperfusion injury after MT(%)	12	21	0.11
WBV at HSR	11.2+-1.2	11.2+-1.25	0.97
WBV at LSR	−38.8+-26.5	−38.6+-27.7	0.97

NIHSS, National Institutes of Health Stroke scale; BMI, Body mass index; DM, Diabetes mellitus; TG, Triglycerides; HDL, high density lipid; LDL, Low density lipid; mRS, modified Rankin scale; MT, mechanical thrombectomy; WBV, whole blood viscosity; HSR, high shear rate; LSR, low shear rate.

shear rates and clinical outcomes following MT. This result is in concordance with a study conducted by Hashem et al., where significant correlation between an indicator of blood viscosity and stroke outcomes based on NIHSS and mRS scores was not observed. However, they reported relationship between both hematocrit and albumin, and stroke outcome in their study (Hashem et al., 2018).

Several other hematological factors have been shown to be associated with clinical and functional outcomes following acute ischemic stroke. Endothelial shear stress, proportional to blood viscosity, is a potent local stimulus for the formation and progression of atherosclerotic plaque (Chatzizisis et al., 2007). Studies conducted by Lowe et al. (1997) revealed a well-established association between endothelial sheer stress and a majority of cardiovascular events, including stroke and ischemic heart disease. WBV at both HSR and LSR is also associated with acute arterial occlusion, triggering a sudden decrease of blood flow to the area supplied by the affected artery (Erdogan et al., 2020; Çekici et al., 2019; Li et al., 2015). Increased fibrinogen, a determinant of plasma viscosity, and blood viscosity have also been shown to significantly contribute to the clinical outcome in patients who suffered from stroke (Resch et al., 1992).

The effects of MT on clinical outcomes is well-established in the literature. However, certain studies have also shown that successful reperfusion following MT appears to not necessarily correlate with positive clinical outcomes. The gap is well demonstrated in the literature in the difference in percentage of patients achieving successful reperfusion and the percentage of those achieving mRS 0–2 scores by 15–28%(Grotta and Hacke, 2015). Other different predictors of poor outcome that have been demonstrated, in the literature include age, site of occlusion, NIHSS score, history of diabetes mellitus, TICI score, number of passes, use of tPA, hematocrit, and serum albumin (Hashem et al., 2018; Linfante et al., 2016; Gordon et al., 2018).

Hemorheological abnormalities such as increases in WBV and plasma viscosity were demonstrated in the development of acute cerebral ischemia in study conducted by Fisher and Meiselman (1991). High blood viscosity is associated with increased thromboembolic risk and correlated with systemic inflammation as well (Pop et al., 2002).

Given the above, one would expect a relationship between WBV and clinical and functional stroke outcome. However, WBV, which directly and indirectly affects stroke incidence and outcomes, has rarely been identified as a predictor of thrombectomy outcome. In a study, Yenerçag et al. looked at the association of WBV with clinical outcome following MT in patients with acute ischemic stroke (Yenerçag et al., 2021), the authors reported that an increased WBV is an independent risk factor and is correlated with poor clinical outcomes in acute ischemic stroke patients treated with MT (Yenerçag et al., 2021). This is in contrast with the findings of our study. Despite a relatively large patient population, the retrospective nature of the study introduces the possibility of selection bias, where the included patients may not accurately represent the broader population. Variations in blood collection times across patients can significantly impact laboratory values. They might also be affected due to preexisting comorbidities with medication history in most of the patients as the retrospective design hindered the accurate determination of diagnosis timing for these factors. Most studies have used viscometer which provide an accurate estimate of blood viscosity compared to the formula we used in our study (Kensey, 2003; Cowan et al., 2012). Additionally, although objective measures were assed, any errors in mRS adjudication may introduce errors of outcome misclassification into the analysis as well. Finally, in using traditional logistic regression, although per prevailing convention in stroke analyses, more granular information is not discerned compared to, for example, the use of an ordered logit model.

Taking into account our findings, the relationship between functional outcome and WBV following MT requires further study. We believe that our attempt to study the correlation between a complex biomarker and stroke and the limitations provides valuable insights and lays the groundwork for

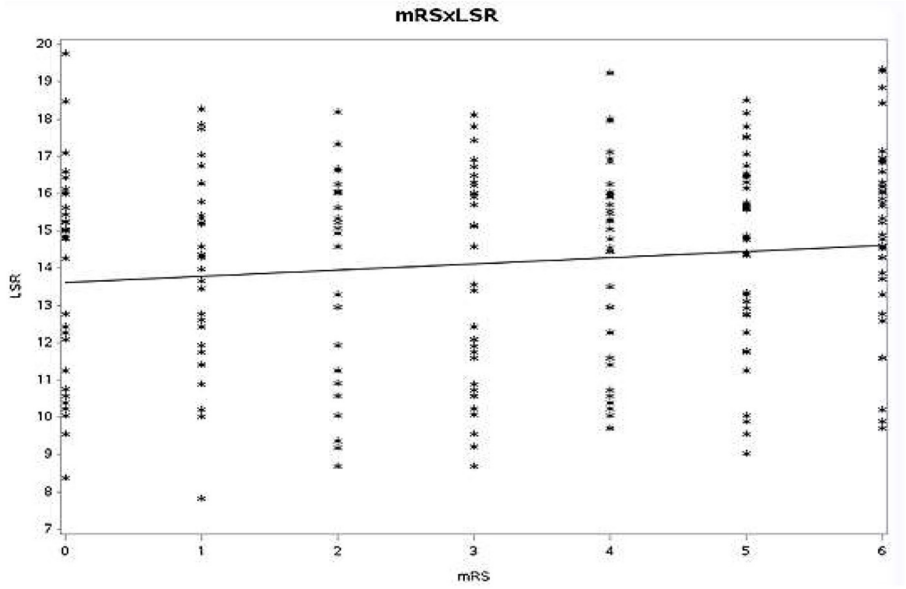

FIGURE 1
Spearman rank-order correlation between mRS and LSR (mRS, modified Rankin scale; LSR, low shear rate).

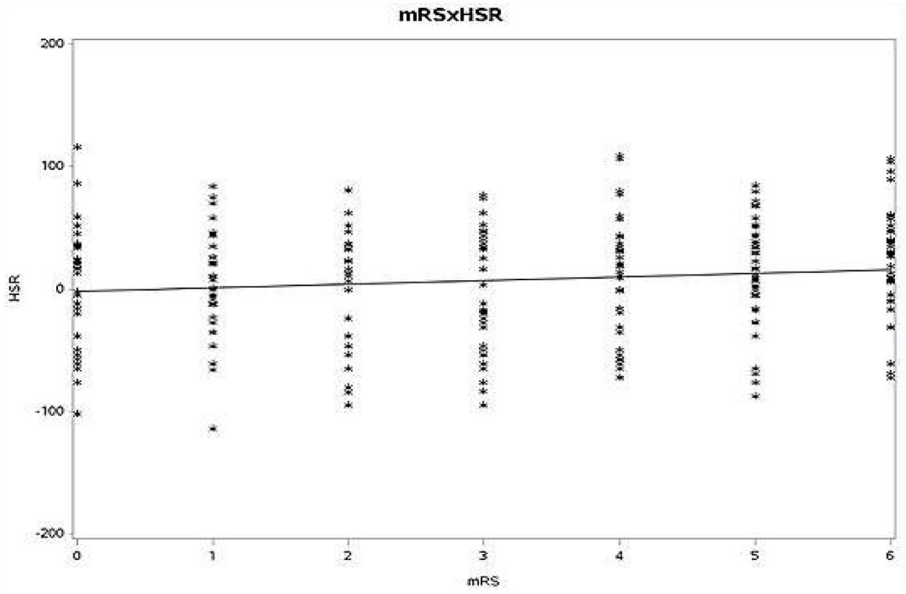

FIGURE 2
Spearman rank-order correlation between mRS and HSR (mRS, modified Rankin scale; HSR, high shear rate).

future research with improved methodologies and a more robust design.

Conclusion

Though a prior study has demonstrated the role of WBV on stroke outcomes, the evidence for an effect on clinical and functional outcomes following MT has been less robust. The present study did not find an association between WBV at HSR and LSR and mRS at discharge, in agreement with most previous work exploring this association. However, the presence of underlying associations between WBV and stroke outcomes, as well as work by Yenerçag et al., suggests that further study is needed to more thoroughly explore these potential associations.

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 humans were approved by LSU Health Sciences Center—Shreveport Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MT: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. JC: Writing – original draft, Writing – review & editing. RL: Writing – original draft, Writing – review & editing. PB: Writing – original draft, Writing – review & editing. MS: Writing – original draft, Writing – review & editing, Formal analysis, Methodology. RS: Writing – original draft, Writing – review & editing. PR: Writing – original draft, Writing – review & editing. HC: Writing – original draft, Writing – review & editing. MH: Writing – original draft, Writing – review & editing, Formal analysis, Methodology. MB: Writing – original draft, Writing – review & editing, Formal analysis, Methodology. JJ: Writing – original draft, Writing – review & editing. RK: Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Optimizing acute ischemic stroke outcome prediction by integrating radiomics features of DSC-PWI and perfusion parameter maps

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Introduction: Accurate prediction of the prognostic outcomes for patients with ischemic stroke can contribute to personalized treatment decisions and improve life-saving outcomes. This study focuses on the performance of critical moments DSC-PWI in the prognostic prediction of acute ischemic stroke (AIS). It aims to integrate this with perfusion parameters to enhance prediction accuracy.

Methods: Firstly, The radiomics technique employed to extract DSC-PWI features of critical moments and perfusion parameter features. Following this, a T-test and Lasso algorithm was used to select features associated with the prognosis. Subsequently, machine learning techniques were applied to predict the predictive outcomes of AIS patients.

Results: The experimental results showed that DSC-PWI sequences at three critical time points—the first moment after contrast injection, the moment of minimum mean time intensity, and the last moment, collectively referred to as 3PWI, had better prognostic prediction than a single perfusion parameter, achieving an optimal model AUC of 0.863. The performance improved by 23.9, 19.6, 6, and 24% compared with CBV, CBF, MTT, and Tmax parameters. The best prognostic prediction for AIS was obtained by integrating the radiomic features from both 3PWI and perfusion parameters, resulting in the highest AUC of 0.915.

Discussion: Integrating the radiomics features of DSC-PWI sequences of three critical scan time points with those from perfusion parameters can further improve the accuracy of prognostic prediction for AIS patients. This approach may provide new insights into the prognostic evaluation of AIS and provide clinicians with valuable support in making treatment decisions.

KEYWORDS

acute ischemic stroke, DSC-PWI sequence, perfusion parameters, radiomics, prognosis prediction

1 Introduction

Acute Ischemic Stroke (AIS) is a sudden blockage in the intracranial blood vessels that disrupts the brain's blood circulation. This disruption leads to varying degrees of tissue damage and necrosis in the affected area, forming two key regions: the infarct core and the ischemic penumbra (1). The infarct core causes brain tissue necrosis due to prolonged ischemia and hypoxia, resulting in irreversible damage (2). In the ischemic penumbra, brain cells retain partial function due to limited blood flow supplied by collateral vessels. However, if the blood supply continues to be insufficient, the cells may gradually die. Therefore, timely reperfusion of the blood vessels in the ischemic penumbra is crucial and is expected to improve patient outcomes. However, there may be a certain degree of prognostic risk such as hemorrhage (3). Therefore, individualized treatment strategies are necessary for patient recovery. Accurately predicting a patient's prognosis can help physicians more accurately evaluate the treatment effect, make individualized treatment decisions for patients, and reduce the risk of poor treatment outcomes.

In clinical analysis, the modified Rankin scale (mRS) is clinicians' most commonly used metric to report overall disability in stroke patients. It has been formally recommended for use in acute stroke clinical trials by regulatory agencies and clinical trial methodology consensus groups (4). The scale was adapted by Charles Warlow and others from the Rankin Scale in the 1980s (5). It measures a patient's ability to live independently, encompassing physical function, mobility, and participation in daily life. A score of 0–2 is often considered a good prognosis; a score of 3–6 is a poor prognosis (6, 7). Although there are clear definitions for each level, the specific scores are derived from the physician's experience by asking the patient through telephone follow-up, which is highly subjective, and the telephone questioning needs to rely on the patient's self-representation, which may be subject to bias. These potential factors can affect physicians' assessment of the prognosis of AIS patients. Thus, a more objective means of analyzing the prognosis of AIS is needed.

In terms of examination cost and scanning time, computed tomography perfusion (CTP) has long been considered the most suitable choice for patients with acute stroke. However, with advancements in MRI speed, concerns about radiation exposure and the use of iodinated contrast agents (which are contraindicated in patients with a history of allergic reactions or renal insufficiency) have prompted considerations of alternative imaging methods (8). Dynamic Susceptibility Contrast-Perfusion Weighted Imaging (DSC-PWI) is currently one of the most commonly used PWI techniques for assessing cerebral perfusion (9). Its fundamental principle relies on the local magnetic field inhomogeneity induced by a paramagnetic contrast agent as it passes through cerebral vasculature after intravenous injection. This leads to varying degrees of T2* signal attenuation proportional to the concentration of the contrast agent, allowing dynamic monitoring of signal intensity to reflect cerebral blood flow changes. DSC-PWI offers a temporal resolution of approximately 0.5–2 s, which is significantly higher than that of Arterial Spin Labeling (ASL), typically ranging from 1 to 4 s. This higher temporal resolution enables real-time, detailed recording of the T2* signal decay process and facilitates the capture of rapid cerebral blood flow changes. By applying mathematical modeling to signal variations allows obtaining the perfusion parameter maps, including Cerebral Blood Volume (CBV), Cerebral Blood Flow (CBF), Mean Transit Time (MTT), Time to Peak (TTP), and Time to Peak of Residual Function (Tmax). These parameters provide information about cerebral blood supply and perfusion, which is critical for understanding brain function, disease diagnosis, and therapeutic regimens development. Many current studies have explored the correlation between perfusion parameter maps and prognostic outcomes in AIS. For example, Park et al. (10) demonstrated that a reduction in rCBV ratio was associated with a poor prognosis in AIS in 58 patients undergoing intravenous thrombolysis, and Schaefer et al. (11) found that an MTT lesion of less than 50 mL had a better performance in predicting a good prognosis for patients. The results of these studies confirm the potential of perfusion parameters in the prognostic prediction of AIS. However, they have analyzed prognosis through statistical methods, with few studies utilizing radiomics features of perfusion parameters to construct prognostic models.

In addition to perfusion parameter maps, numerous studies have utilized information from CT and MRI images to construct prognostic prediction models for AIS through machine learning (ML) and deep learning (DL) methods (12–14). However, few studies have analyzed the ability of 4D perfusion sequences for AIS prognostic prediction. Meng et al. (15) generated four perfusion parameters (CBV, CBF, MTT, and TTP) from PWI to predict the prognosis of AIS patients with or without hemorrhage. After combining the clinical factors, the prediction accuracy reached 89.4%. The generated perfusion parameter maps are more targeted to utilize the cerebral hemodynamic information but ignore the time-dimensional and rich anatomical information of the 4D perfusion sequence. Some researchers have also used spatiotemporal convolutional networks to obtain the time-dimensional features of the 4D CTP (16). However, the features obtained with DL techniques cannot provide the corresponding meanings and will suffer from the problem of poor interpretability. Guo et al. (17) extracted whole-brain Radiomics features for all sequences of DSC-PWI to prognostic prediction of AIS, and the best Area Under the Curve (AUC) obtained was 82.8%. Although this way of analyzing all sequence features ensured comprehensive information, it also brought about problems of high computational volume and tedious tasks. In summary, to ensure the preservation of some temporal information while reducing the computational cost, the present study took radiomics technology to feature quantification of the DSC-PWI sequences at three representative time points as well as the perfusion parameters obtained by post-processing and then constructed a prognostic prediction model for AIS using the ML model, which is expected to become a new clinical auxiliary tool.

In conclusion, this study investigated the roles of DSC-PWI sequences at different scanning time points. It also assessed the impact of individual perfusion parameters (Cerebral Blood Volume [CBV], Cerebral Blood Flow [CBF], Mean Transit Time [MTT], and Time to Peak [Tmax]) as well as their combinations on the prognostic prediction of Acute Ischemic Stroke (AIS). Our findings aim to assist clinicians in making informed treatment decisions, developing personalized treatment plans for patients, and providing new ideas for clinical research. The main contributions of the research fall in the following three key areas.

(1) Six groups of radiomics features of DSC-PWI images at different key time points were used to construct different prediction models. The impact of time point selection on the prediction effect was compared. Ultimately, it was confirmed

that the selection of radiomics features of DSC-PWI sequences at three key time points has better prediction performance, which can reduce the computational complexity while ensuring accuracy.

(2) To explore the performance of the four perfusion parameters (CBV, CBF, MTT, and Tmax) obtained by post-processing on the prediction aspect of AIS results, the prediction performance of a single parameter and the prediction performance of the combination of the four parameters were explicitly analyzed. The results confirmed that combining these parameters can effectively improve prediction accuracy.

(3) The best prediction model was constructed by integrating source features derived from DSC-PWI sequences at three key time points and parameter features obtained from four perfusion parameter maps. The approach confirmed that the information on DSC-PWI sequences and perfusion parameters was complementary, highlighting the significant prognostic value inherent in the DSC-PWI sequences.

2 Materials

The dataset for this study was provided by the neurology department of the Shanghai Fourth People's Hospital, affiliated with the Tongji University School of Medicine, China. The dataset was retrospectively analyzed and included DSC-PWI images of 537 AIS patients from 2013 to 2019. All DSC-PWI sequences were approved by the Hospital Ethics Committee for ethical certification. For MR perfusion imaging, the contrast agent Gd-DTPA (Gadopentetate Dimeglumine, Shanghai Pharmaceutical Company, China) was infused intravenously at a rate of 4 mL/s at a dose of 0.2 mmol/kg according to the patient's body weight, and a saline flush of 30 mL was given at the same flow rate. The patient's inclusion and exclusion criteria were as follows (Figure 1): (1) The MR examinations were conducted within 24 h of symptom onset; (2) the presence of the middle cerebral artery (M1 segment) occlusion; (3) availability of complete clinical report including mRS score; (4) and availability of complete MR imaging sequences (DSC-PWI, CBV, CBF, MTT, and Tmax). A total of 72 AIS patients' DSC-PWI images were selected for this study. Based on the 90-day mRS score obtained through telephone follow-up, the patients were categorized into two groups: 39 with a good prognosis (mRS $\leq$ 2) and 33 with a poor prognosis (mRS > 2).

Further statistical information of the patients and the scanning parameters of the DSC-PWI sequence are provided in Table 1. All DSC-PWI sequences were scanned on a 1.5-Tesla MR scanner (Siemens, Munich, Germany). The matrix size of each scan was 256 × 256, the number of slices was 19 or 20, the slice thickness was 5 mm, the slice spacing was 6.5 mm, the echo time (TE) was set to 32 ms, and the repetition time (TR) was 1,590 ms. The pixel bandwidth was 1,347 Hz/pixel, and the field of view (FOV) was 230 × 230 square millimeters to capture medium-sized regions of interest. Each sequence had a temporal resolution of 1.59 s, with a total of 50

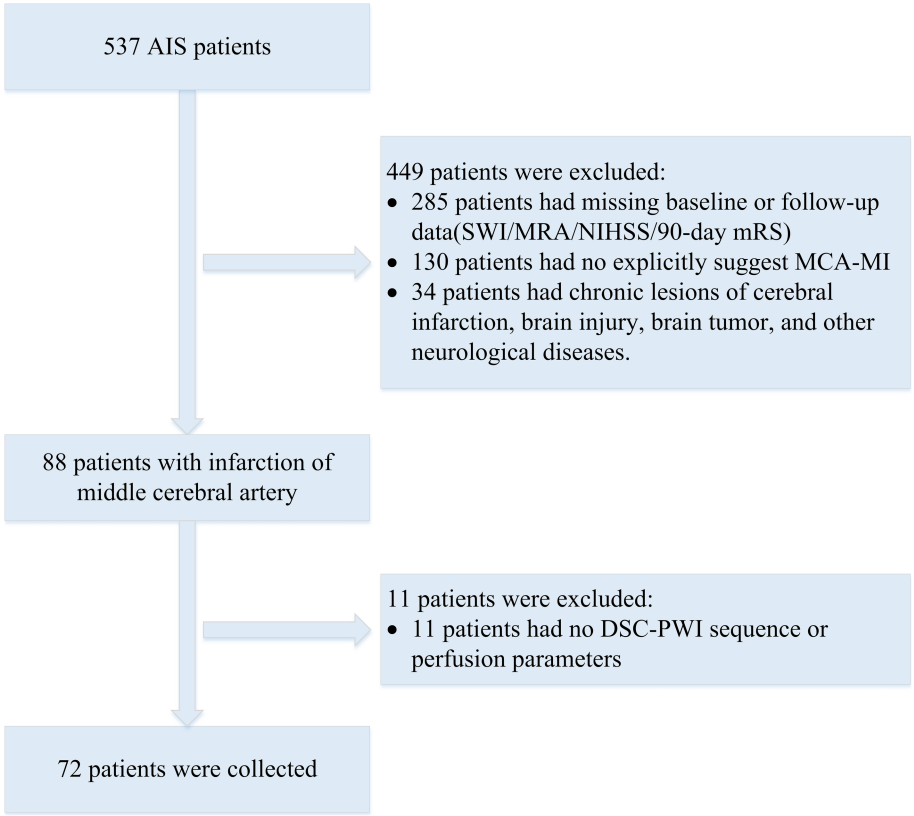

FIGURE 1
Flowchart of exclusion and inclusion of patients in our study. SWI, susceptibility weighted imaging; MRA, magnetic resonance angiography; NIHSS, National Institute of Health stroke scale.

TABLE 1 Scanning parameters of DSC-PWI images and patient information.

Scanning parameters of DSC-PWI images		Patient information	
Matrix	256 × 256	Patients	72
Number of slices	19 ± 1	Female (%)	16 (22.2%)
Spacing between slices	6.5 mm	Age (Mean ± Std)	71.32 ± 10.26
Number of measurements	50	90-day mRS (Mean ± Std)	2.60 ± 2.37
Thickness	5 mm	Onset time (Mean ± Std)	5.24 ± 4.15
TE/TR	32/1,590 ms	Hypertension	54
Pixel bandwidth	1,347 Hz/pixel	Diabetes	22
FOV	230 × 230 mm^2	Atrial fibrillation	25
Temporal resolution	1.59 s	rt-PA therapy	19
		Thrombectomy	11
		rt-PA + Thrombolytic	10
		rt-PA + intraarterial stent	1

sequences acquired. The study included 72 patients with a mean age of (71.32 ± 10.26) years and 22.2% of the participants were female. The patients' functional outcomes were measured using the 90-day modified Rankine Scale (mRS) with a Mean–Variance of 2.60 ± 2.37.

Among the 72 patients, 54 had hypertension, 22 had diabetes, and 25 had atrial fibrillation. Reperfusion of the ischemic penumbra was primarily achieved through thrombolysis and thrombectomy. The thrombolytic agent used was recombinant tissue plasminogen activator (rt-PA). A total of 30 patients underwent thrombolysis, and 21 patients underwent thrombectomy. Specifically:

- 12 patients received intravenous rt-PA (IV rt-PA).
- 3 patients received intraarterial rt-PA (IA rt-PA).
- 4 patients received both IV rt-PA and IA rt-PA.
- 11 patients underwent thrombectomy.
- 6 patients received IV rt-PA and thrombectomy.
- 2 patients received IA rt-PA and thrombectomy.
- 2 patients received IV rt-PA, IA rt-PA, and thrombectomy.
- 1 patient received IV rt-PA and intraarterial stenting.

3 Methods

The proposed framework of our conducted research is depicted in Figure 2, which consists of four main parts: (1) Data preprocessing; (2) Region of interest (ROI) segmentation and time of interest (TOI) computation; (3) Feature extraction and selection; (4) Prognosis prediction model construction. The data processing includes cleaning and registration of the input data to ensure consistency and improve the dataset's quality, further generating new parameters. The ROI phase is intended to identify the areas of the brain affected mainly by ischemia, known as regions of interest (ROI). Following this, key time points, referred to as times of interest (TOI), are selected, which are essential for understanding stroke progression. The feature extraction part extracts meaningful features from the imaging data, including DSC-PWI sequences and perfusion parameters like CBV, CBF, MTT, and TTP. Further, feature selection techniques are applied to retain the most relevant features, minimize dimensionality, and enhance model efficiency. A machine learning-based prediction model is constructed using the selected features in the prognosis prediction model construction part. The proposed model is trained to predict patient outcomes, helping to guide clinical decision-making. The overall framework of our study is shown in Figure 2. Each section of the proposed framework has been described in detail.

3.1 Data preprocessing

The data preprocessing in this study mainly involved several key steps: registration of position, segmenting brain tissue regions, denoising of images, and generation of perfusion parameters, as outlined in Figure 3. First, the spatial position of the multi-temporal DSC-PWI sequences was registered using the neuroimaging software package FSL (18). This step was taken to eliminate the positional deviation caused by head movement that might exist during scanning. At the same time, non-brain tissues were removed using the BET method in FSL, and brain tissue regions were preserved for further feature parameter analysis. Then, the DSC-PWI sequences were denoised by processing the DSC-PWI sequences using three-shift panning with a window of 3 × 3 and a step size of 1 to improve the data quality. Finally, four perfusion parameter maps, CBV, CBF, MTT, and Tmax, were generated by back-convolution of the arterial input function. This process was fully automated using the RAPID Perfusion and Diffusion Processing software (19), which calculated the perfusion parameters directly from the DSC-PWI sequences.

3.2 ROI segmentation and TOI calculation

DSC-PWI enables the visualization of blood flow within brain tissue by capturing the perfusion process, making it suitable for identifying areas of ischemic penumbra and infarct core (20, 21). The threshold of the quantitative perfusion parameter Tmax > 6 s obtained through DSC-PWI post-processing is commonly used to identify the ischemic penumbra region (22–24). This has emerged as a novel strategy to identify patients most likely to benefit from treatment by targeting salvageable penumbra tissue (25). Therefore, in this study, the ischemic penumbra region was used as the ROI for feature extraction, and the segmentation of ROI was performed using the commercial software RAPID (19).

DSC-PWI images usually contain dozens of time sequences, extracting features for each sequence increases computational complexity. Thus, to avoid repeated extraction of anatomical information from the images while effectively retaining temporal information about the dynamic changes in blood flow, we chose DSC-PWI sequences at specific scanning time points to obtain the information. DSC-PWI reflects intracranial blood flow status by inducing changes in tissue signal intensity through the contrast agent. When the contrast agent reaches poorly perfused brain tissues, it is reflected in the DSC-PWI sequence as a small or unchanged signal

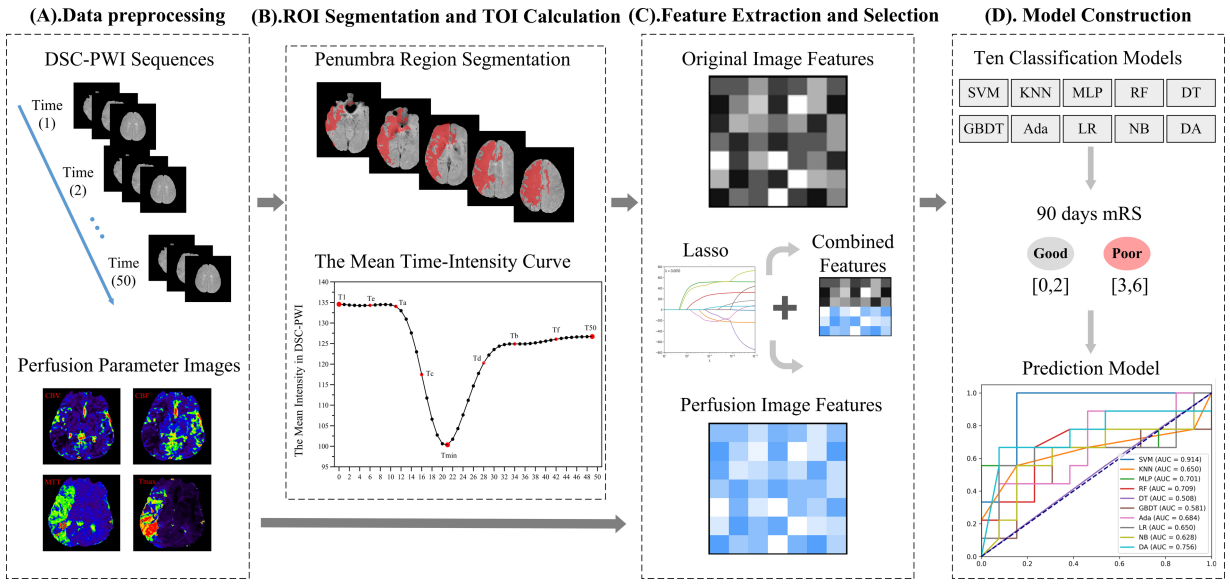

FIGURE 2
The framework of our method. **(A)** Data preprocessing. **(B)** Region of interest (ROI) segmentation and time of interest (TOI) calculation. **(C)** Feature extraction and selection. **(D)** Model construction.

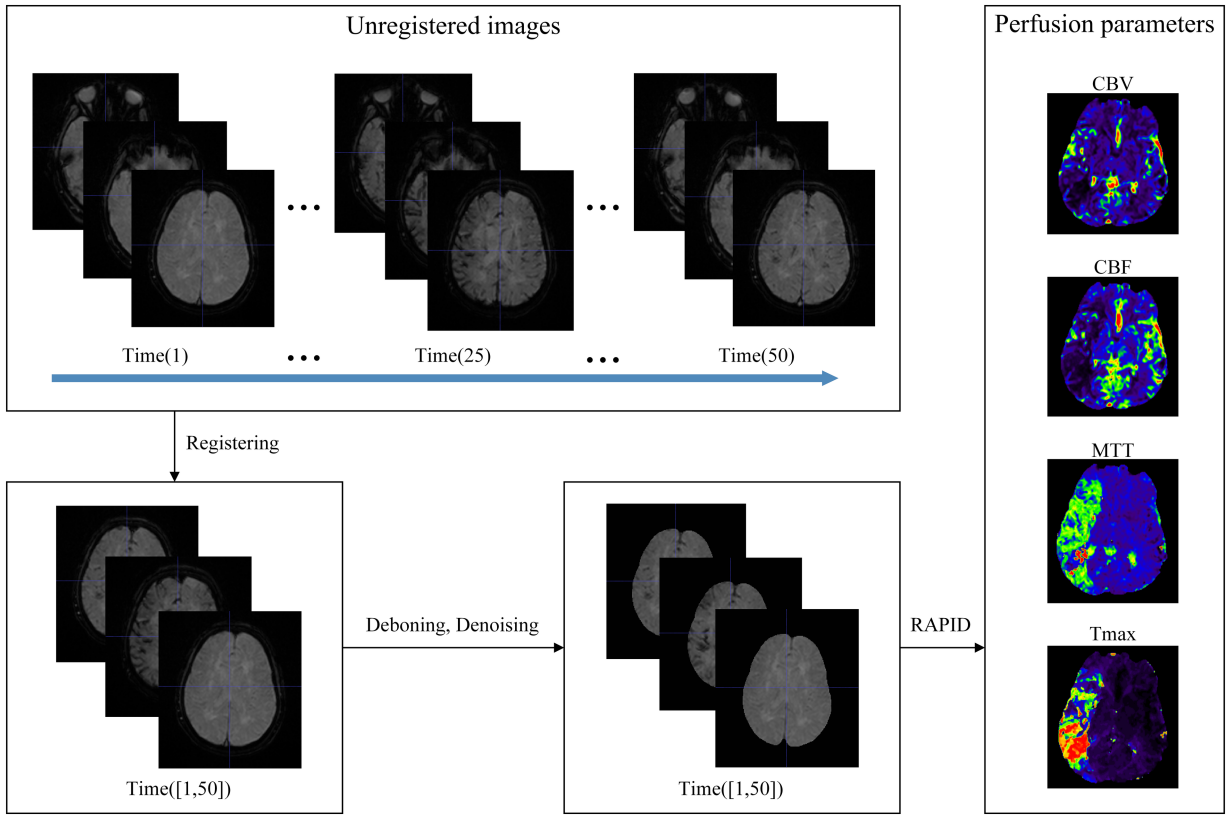

FIGURE 3
Data preprocessing. The unregistered multi-temporal DSC-PWI was registered, deboned, and denoised to generate perfusion parameters by specialized software.

intensity value (26). By analyzing the signal intensity within the brain tissue over time in the DSC-PWI sequence following contrast injection, Figure 4A shows the mean time-intensity curve for all pixel points within the brain tissue of a particular patient, measured across 50 time points. This curve illustrates a distinct pattern of decreasing and increasing signal intensity in the brain tissue.

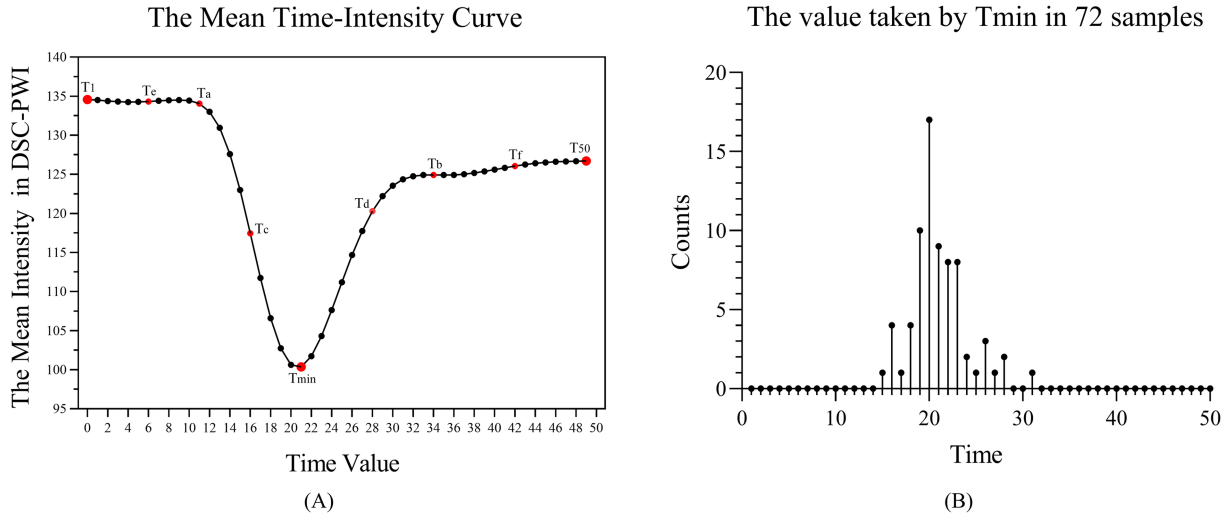

FIGURE 4
(A) Mean-time intensity curve of brain tissue at 50-time points of the DSC-PWI sequence. **(B)** The number of samples at 50-time points for the time value taken by Tmin, where Tmin is the time with the smallest mean intensity among the 50 times of the DSC-PWI sequence.

To consider the influence of the time-dimensional information and the number of selected time points on the prediction results, we identified nine key time points, referred to as Times of Interest (TOI). These include the first moment (T1), the moment with the lowest average intensity (Tmin), the last moment (T50), the midpoint between T1 and Tmin (Ta), between Tmin and T50 (Tb), between Ta and Tmin (Tc), between Tmin and Tb (Td), between Ta and T1 (Te), and between Tb and T50 (Tf). Figure 4B shows the number distribution of samples at 50-time points for the time values taken for Tmin. We found that the Tmin of the 72 samples is mainly concentrated at time points 19–23, with the largest number of samples taken at the 20th time point.

Eventually, five experimental groups were formed based on nine selected TOIs, namely Tmin, T1 + Tmin + T50, T1 + Ta + Tmin + Tb + T50, T1 + Ta + Tc + Tmin + Td + Tb + T50, and T1 + Te + Ta + Tc + Tmin + Td + Tb + Tf + T50. The DSC-PWI sequences for these five groups were labeled as 1PWI, 3PWI, 5PWI, 7PWI, and 9PWI, respectively. We will mainly focus on extracting the cerebral blood flow features associated with changes in the cerebral blood flow states from the DSC-PWI sequences at these selected time points and explore the associations of these features with the prediction of short-term prognosis of AIS. In addition, to investigate whether features from all scanned time points are essential, we also extracted features for all 50 moments of DSC-PWI sequences (50PWI) for prognostic prediction.

3.3 Feature extraction and selection

3.3.1 Radiomics features extraction of DSC-PWI sequences at critical time points and perfusion parameter maps

We used the Pyradiomics toolkit on Python 3.7 to extract radiomics features from ROIs (27). The extracted feature classes were divided into six classes: (1) 18 First-order statistics features (First-order); (2) 24 Gray Level Co-occurrence Matrix features (GLCM); (3) 16 Gray Level Run Length Matrix features (GLRLM); (4) 16 Gray Level Size Zone Matrix features (GLSZM); (5) 5 Neighboring Gray Tone Difference Matrix features (NGTDM); and (6) 14 Gray Level Dependence Matrix features (GLDM). Table 2 provides the specific feature terms associated with each class.

To capture the feature information of the image in different frequency domains, we used six filters to transform the image type, supplementing the six classes of feature information extracted from the original image. These filters included Laplacian of Gaussian (Log) with the sigma values {1.0, 2.0, 3.0, 4.0, 5.0}, as well as square, square root, logarithmic, exponential, and eight combinations of wavelet transform in three dimensions generated by high-pass and low-pass filters (LLH, LHL, LHH, HLL, HLH, HHL, HHH, LLL). So, for each image, we extracted 1,674 grouped features calculated as $(18 \times (18 + 24 + 16 + 16 + 5 + 14) = 1{,}674)$. Since the perfusion parameters CBV, CBF, MTT, and Tmax were generated by post-processing the DSC-PWI sequences, we refer to the features obtained from the six DSC-PWI sequences as the source features and denote them as 1PWI_F, 3PWI_F, 5PWI_F, 7PWI_F, 9PWI_F, and 50PWI_F. Features derived from the CBV, CBF, MTT, and Tmax are parametric features labeled as CBV_F, CBF_F, MTT_F, and Tmax_F, respectively. In addition, the radiomics feature is named according to its source image, filter type, feature class, and the specific feature name connected by underscores, such as "CBV_ logarithm_firstorder_ Kurtosis," which denotes the Kurtosis radiomics feature in the first_ order class extracted from the CBV that passed through the logarithm filter.

3.3.2 Radiomics features selection and combination

Since radiomics features extracted from images are diverse and have different scales, these different scale features have been assigned different weights in the feature selection and classification process, thus affecting the outcomes (28, 29). Research has also shown that the model constructed with normalized features has better prediction performance than the model built without normalized features (30).

TABLE 2 A summary of the high-throughput radiomics features extracted.

Feature classes	Feature names
First_order	10Percentile, 90Percentile, Energy, Entropy, Interquartile Range, Kurtosis, Maximum, Mean Absolute Deviation, Mean, Median, Minimum, Range, Robust Mean Absolute Deviation, Root Mean Squared, Skewness, Total Energy, Uniformity, Variance
GLCM	Autocorrelation, Joint Average, Cluster Prominence, Cluster Shade, Cluster Tendency, Contrast, Correlation, Difference Average, Difference Entropy, Difference Variance, Joint Energy, Joint Entropy, Informational Measure of Correlation 1, Informational Measure of Correlation 2, Inverse Difference Moment, Maximal Correlation Coefficient, Inverse Difference Moment Normalized, Inverse Difference, Inverse Difference Normalized, Inverse Variance, Maximum Probability, Sum Average, Sum Entropy, Sum of Squares
GLRLM	Short Run Emphasis, Long Run Emphasis, Gray Level Non-Uniformity, Gray Level Non-Uniformity Normalized, Run Length Non-Uniformity, Run Length Non-Uniformity Normalized, Run Percentage, Gray Level Variance, Run Variance, Run Entropy, Low Gray Level Run Emphasis, High Gray Level Run Emphasis, Short Run Low Gray Level Emphasis, Short Run High Gray Level Emphasis, Long Run Low Gray Level Emphasis, Long Run High Gray Level Emphasis
GLSZM	Small Area Emphasis, Large Area Emphasis, Gray Level Non-Uniformity, Gray Level Non-Uniformity Normalized, Size-Zone Non-Uniformity, Size-Zone Non-Uniformity Normalized, Zone Percentage, Gray Level Variance, Zone Variance, Zone Entropy, Low Gray Level Zone Emphasis, High Gray Level Zone Emphasis, Small Area Low Gray Level Emphasis, Small Area High Gray Level Emphasis, Large Area Low Gray Level Emphasis, Large Area High Gray Level Emphasis
NGTDM	Coarseness, Contrast, Busyness, Complexity, Strength
GLDM	Small Dependence Emphasis, Large Dependence Emphasis, Gray Level Non-Uniformity, Dependence Non-Uniformity, Dependence Non-Uniformity Normalized, Gray Level Variance, Dependence Variance, Dependence Entropy, Low Gray Level Emphasis, High Gray Level Emphasis, Small Dependence Low Gray Level Emphasis, Small Dependence High Gray Level Emphasis, Large Dependence Low Gray Level Emphasis, Large Dependence High Gray Level Emphasis

Therefore, in this study, after extracting radiomics features from the DSC-PWI sequences and perfusion parameters, we first applied mean normalization on the features to achieve the compression of all feature terms in the interval [−1, 1].

Then, since we extracted features from multiple DSC-PWI sequences with the same anatomical structure, redundant information and increased noise can arise. To address this, we followed the approach of many studies by using a combination of T-test and Least Absolute Shrinkage and Selection Operator (Lasso) for feature selection (31–33). The T-test is used to select and retain the significant features with $p < 0.05$ that can significantly differentiate between the two categories, achieving an initial dimensionality reduction of the features. The goal was to minimize the influence of redundant features on the Lasso algorithm, thereby reducing the risk of unstable selection results and also lowering computational complexity and the risk of overfitting for Lasso select features. The Lasso algorithm, commonly employed to identify relevant features for robust classification models (34). However, in high-dimensional datasets where the number of features far exceeds the number of samples, traditional Lasso regression may fail to effectively identify the truly important features, leading to false positive features. To overcome this, we adopted a threshold Lasso algorithm (35), which adds an extra thresholding step after Lasso's L1 regularization. The purpose is to set a threshold after Lasso regression has provided the coefficient estimates, further removing features with small coefficients that contribute little to the prediction, thus improving the model's accuracy and stability. We retained features with weight coefficients greater than 0.02, which are more predictive for the target task category. This method helps by "thresholding" non-significant coefficients to zero, effectively removing unnecessary features and reducing noise interference.

Specifically, we first extracted all six categories of radiomics features from the entire dataset, then normalized the data and divided it into a training set and a validation set. Next, we applied the T-test and Lasso algorithm sequentially to the features in the training set to select the relevant features, which were then used to construct the prognostic model. Thus, we constructed six source feature models with six source features (1PWI_F, 3PWI_F, 5PWI_F, 7PWI_F, 9PWI_F, and 50PWI_F) and four parametric feature models with four perfusion parameter features (CBV_F, CBF_F, MTT_F, and Tmax_F). Finally, selected relevant feature terms were identified in all radiomics of the validation set and used in the constructed prognostic model for outcome prediction of the validation set data.

Since different perfusion parameter maps characterize different hemodynamic information, so relying on a single parameter alone would lead to incomplete information. To address this, we combined the relevant features obtained from the four sets of parameter maps and noted the perfusion parameter combination feature as PerfusionF. In addition, the complementary nature of critical time-point DSC-PWI images, which provide visual image information about the cerebrovascular perfusion situation and anatomical structures, alongside the perfusion parameter maps, which provide detailed, quantitative hemodynamic information. Thus, we combined the obtained source features and PerfusionF to construct a thoroughly combined feature (CombinedF) model that can accurately predict good and poor prognosis in AIS patients. This CombinedF model is also the primary recommendation in our study.

3.4 Prognosis prediction model construction

The dataset split and model training process is shown in Figure 5. A total of 72 cases were collected in this study, which were categorized into 39 cases with good prognosis and 33 cases with poor prognosis based on the mRS score. Prior to model training, we used the train_test_split() function to divide the dataset into a training group ($n = 50$)

and a validation group ($n = 22$) with a 7:3 ratio. Additionally, the StratifiedKFold (n_splits = K) function has been employed, where $K = 5$, to perform a five-fold cross-validation for evaluating the training model. Finally, the trained model was tested on an independent validation set to obtain the final classification results.

Considering that the performance of the same features can differ across various models, to select models that are more sensitive to the radiomics features of this study and more effective for the classification task, we constructed the prognostic models by using 10 ML models with different classification principles, precisely: Support Vector Machines (SVM), K-nearest Neighbor (KNN), Multi-layer perceptual neural networks (MLP), Random forest (RF), Decision Tree (DT), Gradient Boosting Decision Tree (GBDT), Adaptive boosting (Ada), Logistic Regression (LR), Gaussian NB (NB), and Discriminant Analysis (DA).

All the predictive models were trained in the same training cohort and tested in the same validation cohort. The classification performance of the prediction models was evaluated by five classification metrics, including Accuracy (Acc), Precision (Pre), Recall, F1-score (F1), and Area Under the Curve (AUC). The Area Under the Curve (AUC) is derived from the Receiver Operating Characteristic (ROC) curve and serves as the primary metric for assessing the predictive performance in this study. Moreover, the model's stability is quantified by the coefficient of variation of the AUC values from the training set, referred to as the Relative Standard Deviation (RSD) (36). Equation 1 presents the RSD formula, where a lower RSD indicates a more stable model.

$$RSD = \frac{S_{AUC}}{\overline{AUC}} \times 100\% \quad (1)$$

where S_{AUC} denotes the standard deviation of the AUC value and $\overline{AUC}$ denotes the mean of five-fold cross-validated AUC value.

3.5 Comparative experimental design

3.5.1 Comparative experiments based on six sets of source features

DSC-PWI enables real-time monitoring of the perfusion status of brain tissue by rapidly acquiring multiple sequences of images regarding changes in the contrast agent. We identify three crucial time points by analyzing the mean time-intensity curve in Figure 4A. The curve's starting point indicates the basal signal intensity without the contrast agent; the lowest point of the curve suggests the peak of the contrast agent concentration, which reflects the maximum concentration of the contrast agent within the blood flow channel. The endpoint indicates the intensity of the contrast agent remaining after the contrast agent is washed out of the blood vessel and partially absorbed within the tissue. This endpoint reflects the vascular clearance of the blood flow and the cellular metabolism ability within the tissue. Consequently, the prediction model based on DSC-PWI sequence features of these three key time points is a recommended method in this study. Moreover, different time points were selected for comparison experiments to validate the advantages of these three critical times, as illustrated in Figure 6A.

3.5.2 Comparative experiments based on four sets of single-parameter features and one set of parameters combined feature

CBV indicates the cerebral blood volume of a certain amount of brain tissue, which can reflect the expansion and contraction of blood vessels. CBF measures the volume of blood passing through a given tissue per unit of time, indicating local vascular resistance. MTT is the average duration for a contrast agent to move through brain tissue, while Tmax denotes the time to peak contrast agent concentration. Prolonged MTT and Tmax both can reflect delayed blood flow or vascular obstruction. These four perfusion parameters contain different information and have

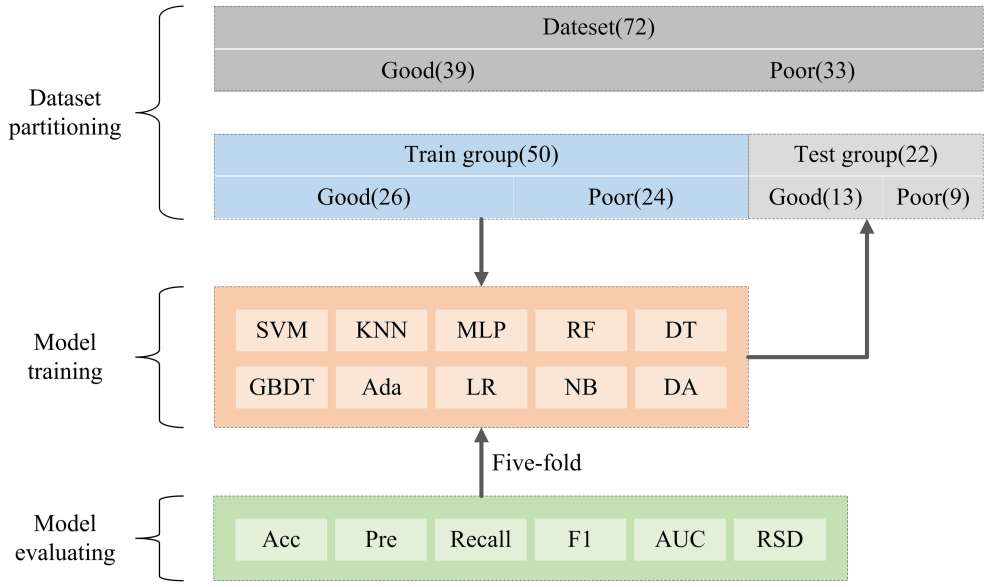

FIGURE 5
The data partitioning process and model training.

important clinical implications in diagnosing and treating ischemic stroke. To explore the most relevant parameters among these four parameters to AIS prognosis, four single-parameter prediction models were developed for comparison to determine the predictive ability of different perfusion parameters in AIS prognosis. In addition, since the four parameters may contain complementary information relevant to AIS prognostic prediction, we also combined the four single-parameter features. We assessed their predictive capability against that of the individual parameters, as illustrated in Figure 6B.

4 Results

4.1 Selected radiomics features

We applied the T-test and Lasso algorithm to select relevant features, finally identifying 9, 15, 15, 18, 13, and 14 features from the six groups of source features (1PWI_F, 3PWI_F, 5PWI_F, 7PWI_F, 9PWI_F, and 50PWI_F) and 11, 7, 5, and 10 relevant features from four groups of perfusion parameter features (CBV_F, CBF_F, MTT_F, and Tmax_F), respectively. We then compared the performance of the predictive models constructed from the six groups of source features and selected the best-performing set, combined with the perfusion parameter combined feature (PerfusionF) to create a fully combined feature set (CombinedF) consisting of 48 radiomics features. Figure 7 depicts the number of features across different feature classes, revealing that GLDM features were excluded from all sequences, and only one NGTDM feature, "logarithm_ngtdm_Contrast," was selected in the CBF.

4.2 Performance of CombinedF prediction model

In this study, radiomics features of DSC-PWI sequences at three key time points were combined with radiomics features of perfusion parameters generated by their post-processing. This combined feature (CombinedF) set was used to train 10 ML models, followed by testing the classification performance of these models on a validation cohort for predicting AIS prognostic outcomes. The results are summarized in Table 3, indicating the SVM-based model has the best predictive ability, with AUC, Acc, Pre, Recall, and F1 of 0.915, 0.818, 0.778, 0.778, and 0.778, respectively, and the RSD of the model is <6%, underscoring its robustness. In addition, the DA model performed well with an AUC, Acc, Pre, Recall, and F1 of 0.846, 0.818, 0.692, 1.000, and 0.818, respectively, and the RSD < 9%. We found that on RF, DT, GBDT, and Ada models, the RSD of the training process is >10%, and the developed prediction models are not stable enough. Among the 10 models tested, SVM and DA models outperformed the others, which shows that the performance of the constructed prediction models may differ depending on the classifiers chosen.

Furthermore, to investigate whether the clinical baseline data of enrolled patients had a potential impact on the model, we analyzed the statistical differences between these baseline variables and the two prognostic groups (good and bad prognostic). The analyzed variables included sex, age, hypertension, diabetes, atrial fibrillation, and onset time. Among them, sex, hypertension, diabetes, and atrial fibrillation were categorical variables, for which we performed chi-square tests to assess statistical differences between the two prognostic groups. Age and onset time were continuous variables, for which we conducted independent sample t-tests to evaluate statistical differences. The

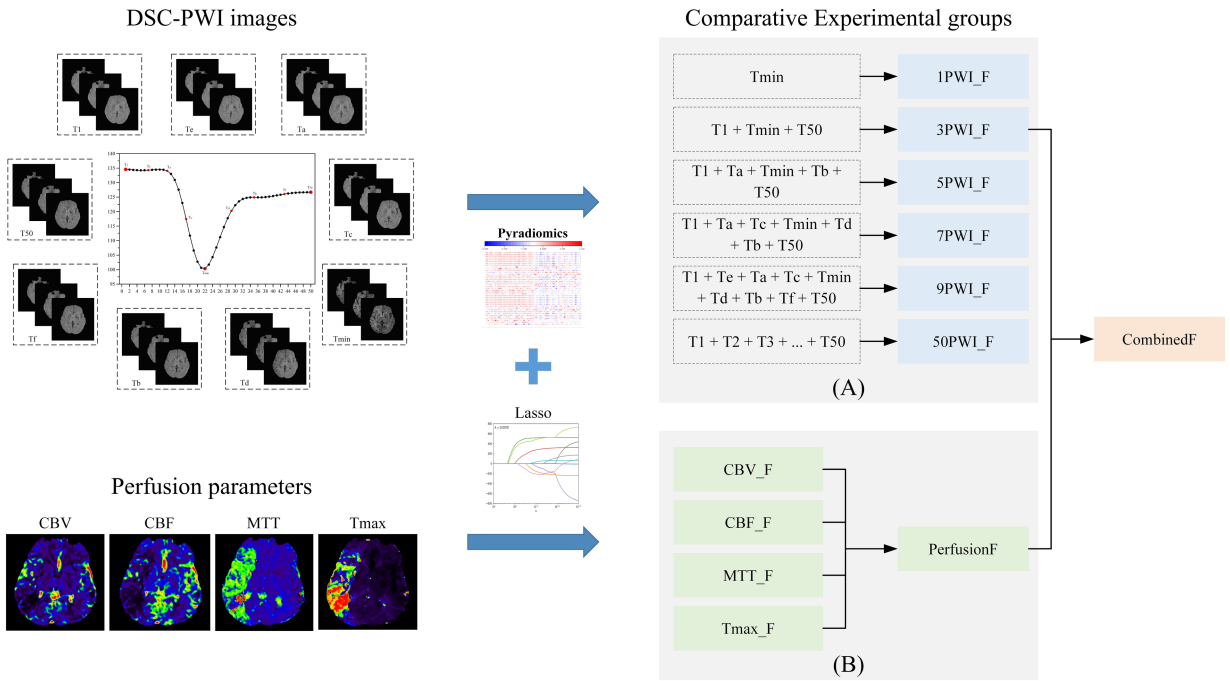

FIGURE 6
The overall experimental framework in this study consists of **(A)** comparative experimental groups based on six sets of source features and **(B)** comparative experimental groups based on four sets of parametric features and parameter combined features.

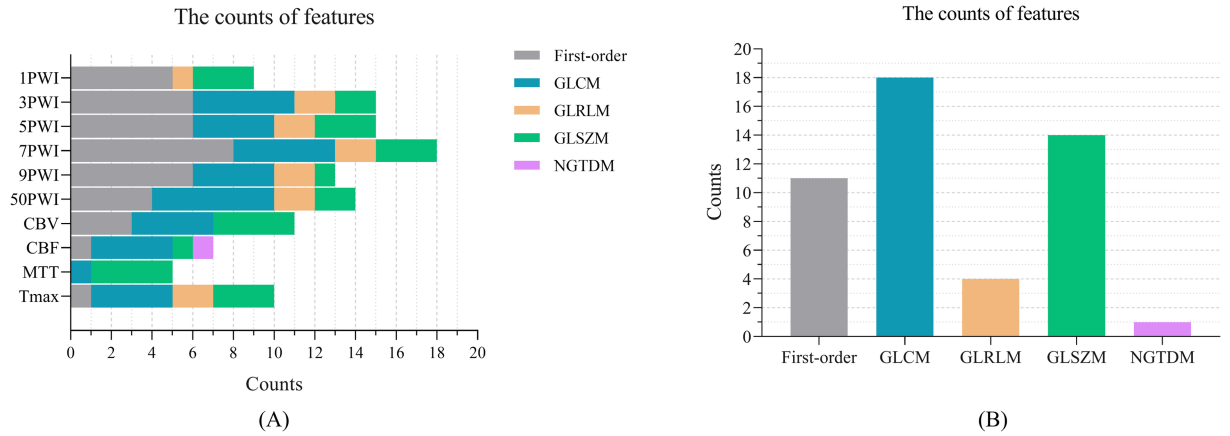

FIGURE 7
The number of features selected across different feature categories: **(A)** The relevant features selected by Lasso in the 10 feature groups, organized by feature category, and **(B)** the features within the CombinedF group, categorized by feature type.

results of our analysis are presented in Table 4. Except for diabetes, no other baseline clinical variables showed significant differences. Given the small sample size, the statistical significance of diabetes may be due to random factors. Therefore, its potential impact on the predictive model can be disregarded.

4.3 Performance of comparative experimental groups

4.3.1 Performance of six sets of source features

Six groups of source features (1PWI_F, 3PWI_F, 5PWI_F, 7PWI_F, 9PWI_F, and 50PWI_F) at different time points were used to construct prediction models, and the performance of models was assessed using six evaluation metrics. Table 5 shows the top three models (MLP, LR, and DA) and the Mean–Variance for all 10 ML models. Performance ranking for the models using these feature groups is as follows: 3PWI > 9PWI > 5PWI > 50PWI > 7PWI > 1PWI, among which the 3PWI feature group performs the best on the MLP model, with the AUC, Acc, Pre, Recall, and F1 of 0.863, 0.818, 0.778, 0.778, and 0.778, respectively, and the RSD < 10%. It could be noted that the prediction results of the model developed by the 50PWI feature group are not the best, but the model constructed by it shows better stability overall. This stability may be brought about by the large amount of computational data. In the future, adding more cases will eliminate this discrepancy.

4.3.2 Performance of four sets of single-parameter features and one set of parameters combined feature

Four groups of single-parameter features (CBV_F, CBF_F, MTT_F, and Tmax_F) obtained with different perfusion parameters were used to develop prediction models, and their performance was evaluated across six metrics. Table 6 shows the scores of the best three models (MLP, NB, and DA) and the Mean–Variance of the 10 ML models. The results indicate that the MTT feature group performs significantly better than the other three. The order of the four groups is MTT > CBV > CBF > Tmax, in which the MTT feature group performs the best on the DA model, with the best AUC, Acc, Pre, Recall, and F1 of 0.821, 0.727, 0.714, 0.556, and 0.625, respectively, in which the prediction model constructed by CBV feature group showed more stable performance.

Considering the existence of complementary prognostic information contained in different single parameters, we developed a PerfusionF model by integrating features selected from four single-parameter features. The prediction performance of the PerfusionF model is detailed in Table 7. To compare the results between single-parameter features and the combined features, the results of the six metrics of the single-parameter features on the 10 ML models are illustrated in Figure 8. Analyzing Table 7 and Figure 8, we find that the PerfusionF model achieved the best performance on the SVM model. It surpassed the single-parameter features with AUC, Acc, Pre, Recall, and F1 of 0.889, 0.864, 0.800, 0.889, and 0.842. This represents an improvement over the CBV of 18.8, 13.7, 16.4, 11.1, and 14.2%. The improvement over the CBF is 19.7, 22.8, 26.2, 11.1, and 20.6%, respectively. Then, over the MTT, it is 12.0, 13.7, 13.3, 22.2, and 17.5%, respectively. Lastly, the improvement over the Tmax is 28.2, 31.9, 35.6, 44.5, and 39.8%, respectively. However, in some cases, the performance of the combined parametric features was lower than the single-parameter features on certain models. This inconsistency may be because of the inconsistent sensitivity of the different models to the features, resulting in a large difference in the final classification performance.

According to Tables 3, 7, the AUC achieved by the CombinedF group across all models is higher than that of the PerfusionF group, except for the NB model. Conversely, the RSD achieved by the CombinedF group across other models is lower than that of the PerfusionF group, except for the RF and Ada models. For the remaining four metrics (Acc, Pre, Recall, and F1), the CombinedF group generally outperformed the PerfusionF group with some exceptions in specific models. The Mean–Variance values in the last column support this, with the CombinedF group achieving Acc, Pre, Recall, and F1 scores of 0.686 ± 0.118, 0.630 ± 0.145, 0.645 ± 0.155, and 0.628 ± 0.123, respectively, outperforming the PerfusionF group's scores of 0.609 ± 0.123, 0.524 ± 0.143, 0.556 ± 0.182, and 0.533 ± 0.155. This suggests that the prediction performance of

TABLE 3 Performance of CombinedF prediction model.

	Classifier	Train_RSD↓	Test_AUC↑	Test_Acc↑	Test_Pre↑	Test_Recall↑	Test_F1↑
CombinedF model	SVM	0.055	0.915	0.818	0.778	0.778	0.778
	KNN	0.056	0.714	0.773	0.750	0.667	0.706
	MLP	0.023	0.726	0.818	0.857	0.667	0.750
	RF	0.194	0.731	0.682	0.667	0.444	0.533
	DT	0.123	0.564	0.545	0.462	0.667	0.545
	GBDT	0.235	0.556	0.500	0.417	0.556	0.476
	Ada	0.125	0.684	0.591	0.500	0.556	0.526
	LR	0.031	0.684	0.682	0.625	0.556	0.588
	NB	0.038	0.662	0.636	0.556	0.556	0.556
	DA	0.082	0.846	0.818	0.692	1.000	0.818
	Mean ± Std	0.096 ± 0.072	0.708 ± 0.110	0.686 ± 0.118	0.630 ± 0.145	0.645 ± 0.155	0.628 ± 0.123

TABLE 4 Results of the statistical difference analysis between the clinical baseline data and the two prognostic groups.

Clinical datas	Good prognosis (n = 39)	Bad prognosis (n = 33)	p-value
Sex	7 (Female)	9 (Female)	0.343
Hypertension	30	24	0.682
Diabetes	7	15	0.032*
Atrial fibrillation	14	11	0.820
Age	69.69 ± 9.06	73.24 ± 11.22	0.157
Onset time	5.58 ± 4.96	4.80 ± 2.76	0.373

*p-value < 0.05.

perfusion parameter features with the addition of the source features is significantly improved.

Figure 8 illustrates the results of the six metrics for the source features across 10 models. The results highlight that models developed with the 3PWI and MTT feature groups achieved the best predictive performance. The 3PWI feature group attained the highest AUC of 0.863, outperforming all the single-parameter features. This AUC shows an improvement of 16.2, 17.1, 4.2, and 20.9% over the best AUCs for CBV, CBF, MTT, and Tmax, respectively. The AUC values of 3PWI were better than the CBV, CBF, and Tmax groups except on the DT model. The AUC values of 3PWI were superior to the MTT group except on the KNN, DT, and NB models. The other four indices (Acc, Pre, Recall, and F1) had similar patterns. It concluded that the radiomics features of DSC-PWI sequences at the three key time points might be superior to those of individual perfusion parameters in predicting AIS prognosis.

5 Discussion

Radiomics technology is a powerful tool for extracting high-throughput quantitative feature information from images, which can extract complex information that is difficult to recognize and quantify by the human eye (37). Using this information, potential prognostic indicators can be identified to construct a prediction model for AIS prognostic outcomes, which can be realized to accurately predict a patient's prognosis. A prognostic prediction model ultimately helps doctors' understanding of patients' prognostic risks and provides an objective basis for assisted decision-making to develop personalized patient treatment plans. In some studies, the prediction of prognostic outcomes has been realized by analyzing medical images (CT, DWI, SWI, PWI, CTP, and others) through radiomics techniques (38–40). Research in Tang et al. (41) has focused on predicting outcomes for AIS by extracting radiomics features based on images post-processed from perfusion sequences. However, there is a lack of studies directly processing the perfusion sequences using radiomics techniques. Another study Guo et al. (17) focused on time-dependent information in the perfusion sequences and analyzed the sequences for all scan times. Still, this approach has led to issues with feature redundancy and excessive computational demands. In this study, we focused on several key time points within DSC-PWI sequences and constructed predictive models using features obtained by radiomics techniques. The final results showed that the radiomics features at three key time points (3PWI) were the most effective for AIS prognostic prediction. In addition, we explored the performance of radiomics features of perfusion parameter maps in predicting AIS outcomes, including single perfusion parameters (CBV, CBF, MTT, and Tmax) and combined perfusion parameters (PerfusionF). The results showed that PerfusionF had an AUC score of 0.889, superior to the single perfusion parameter. In contrast, MTT had the best predictive performance among the four perfusion parameters, with an AUC score of 0.821. Additionally, by combining 3PWI_F and PerfusionF, we developed a CombinedF prediction model that attained an AUC score of 0.915, improving its prediction accuracy. This research confirms that the DSC-PWI sequence contains valuable prognostic-related information and suggests that analyzing only the perfusion parameters obtained by post-processing may lose some essential prognosis-related information.

5.1 The DSC-PWI sequences at three key time points provide greater predictive value

DSC-PWI imaging injects a magnetic contrast agent intravenously, altering the blood's sensitivity to the magnetic field. This causes a

TABLE 5 Performance of prediction models constructed by six source feature groups.

Feature Group	Classifier	Train_RSD↓	Test_AUC↑	Test_Acc↑	Test_Pre↑	Test_Recall↑	Test_F1↑
1PWI_F	MLP	0.280	0.590	0.545	0.444	0.444	0.444
	LR	0.259	0.709	0.682	0.600	0.667	0.632
	DA	0.241	0.744	0.727	0.667	0.667	0.667
	Mean ± Std	0.245 ± 0.040	0.649 ± 0.078	0.609 ± 0.081	0.523 ± 0.088	0.589 ± 0.118	0.551 ± 0.093
3PWI_F	MLP	0.096	0.863	0.818	0.778	0.778	0.778
	LR	0.137	0.829	0.727	0.667	0.667	0.667
	DA	0.057	0.821	0.773	0.667	0.889	0.762
	Mean ± Std	0.166 ± 0.098	0.762 ± 0.134	0.714 ± 0.134	0.646 ± 0.133	0.756 ± 0.102	0.691 ± 0.107
5PWI_F	MLP	0.141	0.692	0.591	0.500	0.667	0.571
	LR	0.110	0.761	0.773	0.700	0.778	0.737
	DA	0.123	0.786	0.773	0.750	0.667	0.706
	Mean ± Std	0.149 ± 0.066	0.713 ± 0.074	0.673 ± 0.085	0.589 ± 0.103	0.667 ± 0.139	0.622 ± 0.112
7PWI_F	MLP	0.135	0.795	0.727	0.636	0.778	0.700
	LR	0.137	0.701	0.682	0.571	0.889	0.696
	DA	0.046	0.744	0.727	0.615	0.889	0.727
	Mean ± Std	0.138 ± 0.036	0.701 ± 0.121	0.645 ± 0.113	0.544 ± 0.135	0.622 ± 0.241	0.574 ± 0.178
9PWI_F	MLP	0.096	0.701	0.682	0.600	0.667	0.632
	LR	0.131	0.641	0.727	0.714	0.556	0.625
	DA	0.122	0.692	0.727	0.667	0.667	0.667
	Mean ± Std	0.126 ± 0.028	0.741 ± 0.077	0.718 ± 0.064	0.662 ± 0.073	0.667 ± 0.128	0.656 ± 0.077
50PWI_F	MLP	0.049	0.632	0.500	0.400	0.444	0.421
	LR	0.049	0.675	0.636	0.545	0.667	0.600
	DA	0.033	0.709	0.591	0.500	0.667	0.571
	Mean ± Std	0.100 ± 0.100	0.709 ± 0.043	0.627 ± 0.060	0.532 ± 0.061	0.689 ± 0.115	0.599 ± 0.079

TABLE 6 Performance of predictive models constructed by four single-parameter feature groups.

Feature group	Classifier	Train_RSD↓	Test_AUC↑	Test_Acc↑	Test_Pre↑	Test_Recall↑	Test_F1↑
CBV_F	MLP	0.091	0.624	0.591	0.500	0.667	0.571
	NB	0.125	0.598	0.636	0.556	0.556	0.556
	DA	0.062	0.624	0.636	0.545	0.667	0.600
	Mean ± Std	0.143 ± 0.081	0.598 ± 0.062	0.586 ± 0.066	0.49 ± 0.075	0.533 ± 0.147	0.507 ± 0.105
CBF_F	MLP	0.222	0.667	0.727	0.667	0.667	0.667
	NB	0.210	0.615	0.636	0.556	0.556	0.556
	DA	0.173	0.607	0.545	0.455	0.556	0.500
	Mean ± Std	0.225 ± 0.033	0.622 ± 0.035	0.623 ± 0.071	0.537 ± 0.080	0.611 ± 0.095	0.570 ± 0.078
MTT_F	MLP	0.144	0.795	0.727	0.636	0.778	0.700
	NB	0.142	0.812	0.727	0.800	0.444	0.571
	DA	0.171	0.821	0.727	0.714	0.556	0.625
	Mean ± Std	0.162 ± 0.032	0.775 ± 0.042	0.704 ± 0.039	0.649 ± 0.083	0.689 ± 0.137	0.653 ± 0.039
Tmax_F	MLP	0.146	0.615	0.545	0.444	0.444	0.444
	NB	0.166	0.573	0.636	0.556	0.556	0.556
	DA	0.132	0.650	0.682	0.625	0.556	0.588
	Mean ± Std	0.153 ± 0.053	0.572 ± 0.079	0.577 ± 0.107	0.486 ± 0.144	0.433 ± 0.123	0.457 ± 0.130

TABLE 7 Performance of PerfusionF prediction model.

	Classifier	Train_RSD↓	Test_AUC↑	Test_Acc↑	Test_Pre↑	Test_Recall↑	Test_F1↑
PerfusionF model	SVM	0.084	0.889	0.864	0.800	0.889	0.842
	KNN	0.082	0.611	0.682	0.600	0.667	0.632
	MLP	0.044	0.590	0.591	0.500	0.556	0.526
	RF	0.059	0.573	0.636	0.600	0.333	0.429
	DT	0.123	0.380	0.409	0.250	0.222	0.235
	GBDT	0.299	0.436	0.591	0.500	0.556	0.526
	Ada	0.047	0.641	0.636	0.545	0.667	0.600
	LR	0.048	0.641	0.591	0.500	0.556	0.526
	NB	0.141	0.675	0.636	0.556	0.556	0.556
	DA	0.282	0.462	0.455	0.385	0.556	0.455
	Mean ± Std	0.121 ± 0.095	0.590 ± 0.144	0.609 ± 0.123	0.524 ± 0.143	0.556 ± 0.182	0.533 ± 0.155

change in the intensity of the magnetic resonance signal, which in turn modifies the grayscale of the voxels in the resulting images. In AIS, perfusion is severely affected in areas of insufficient blood flow due to cerebral vascular obstruction, characterized by reduced blood flow and delayed reperfusion. In DSC-PWI sequences, these regions typically display a lower intensity with reduced magnitude and slower response than normal tissue (26). The DSC-PWI sequence provides valuable information about blood flow status and is closely linked to AIS prognosis. However, DSC-PWI images usually contain dozens of time series, each with multiple slices, making feature extraction computationally intensive. Moreover, dozens of DSC-PWI sequences from the same patient contain consistent anatomical information; whether all sequences are necessary for analysis remains an important problem for further investigation. Therefore, multiple critical moments occur when the contrast agent enters and exits these regions; our study explores sequences with one critical time (1PWI), sequences with three critical times (3PWI), sequences with five critical times (5PWI), sequences with seven critical times (7PWI), sequences with nine critical times (9PWI), and all sequences with 50 critical times (50PWI) in assessing their impact on radiomics features for predicting AIS prognosis. The final experiment revealed that the average AUC scores of the six groups across the 10 ML models were ranked as follows: 3PWI > 9PWI > 5PWI > 50PWI > 7PWI > 1PWI, and the best AUC score was obtained by 3PWI on MLP as 0.863, which is a 9.4% improvement over the best AUC score obtained by 50PWI.

The results indicate that the three selected time points—baseline time, peak enhancement time, and perfusion washout time—provide the highest predictive value for AIS prognosis, whereas incorporating additional time points may be counterproductive. In terms of feature extraction and selection, using only three time points significantly reduces computational complexity, by an order of magnitude compared to utilizing all 50 time points. Moreover, all DSC-PWI sequences from the same patient share identical anatomical structures. Repeatedly extracting the same features across multiple time points introduces redundant information. During feature selection, redundant features may be retained along with other correlated features, even if their contribution to prediction is negligible. This not only reduces the efficiency of feature selection algorithms but also degrades the overall performance of the final model. This is because strong correlations may exist among redundant features, potentially leading to collinearity issues. Collinearity can make the coefficient estimates in regression models unstable, resulting in inaccurate predictions (42). Additionally, each sequence contains some level of noise, and incorporating more time-series features may amplify this noise. As a result, the likelihood of retaining noisy features during selection increases, ultimately degrading the performance of the final model. In current literature (43–45), these three time periods of the perfusion curve are highlighted, and several important parameters (Tmax and others) are also derived from the values of these three time periods. The baseline time indicates the moment before the contrast agent arrives and can be used as a benchmark. The peak enhancement time indicates when the contrast agent is actively circulating, which can provide more information about cerebral vascular circulation, and the perfusion washout time indicates that the contrast agent has passed through and is partially absorbed by the tissue, providing valuable information about brain tissue metabolism. Therefore, these three key time points may capture more dynamic changes that are closely related to disease prognosis. The substantial reduction in the initial number of features at these critical time points allows feature selection to focus more effectively on a smaller set of high-quality features. This not only improves the efficiency of model training but also reduces the risk of overfitting. Therefore, analyzing all the sequences is unnecessary, increasing the workload and possibly decreasing prediction performance.

Recent studies have found that perfusion parameters visualize the ischemic condition of brain tissues and reflect the degree of blood–brain barrier (BBB) damage to a certain extent, making them valuable for diagnosis and prognosis in AIS (46). This study explored the prognostic predictive performance of four perfusion parameters (CBV, CBF, MTT, and Tmax) in AIS. The final results were as MTT > CBV > CBF > Tmax, in which the AUC value of MTT was higher than that of the other three parameters across 10 ML models. Its optimal AUC reached 0.821 (DA), with a mean AUC of 0.775, surpassing CBF, CBV, and Tmax by 15.3, 17.7, and 20.3%, respectively. In this study, MTT is considered to play a more significant role in predicting the prognosis of AIS among the four perfusion parameters. However, this may be due to MTT's higher sensitivity to the ischemic penumbra (ROI). Further research is needed to validate whether MTT is indeed the optimal predictive parameter. Additionally, it is observed that the predictive performance of the models based on the 3PWI

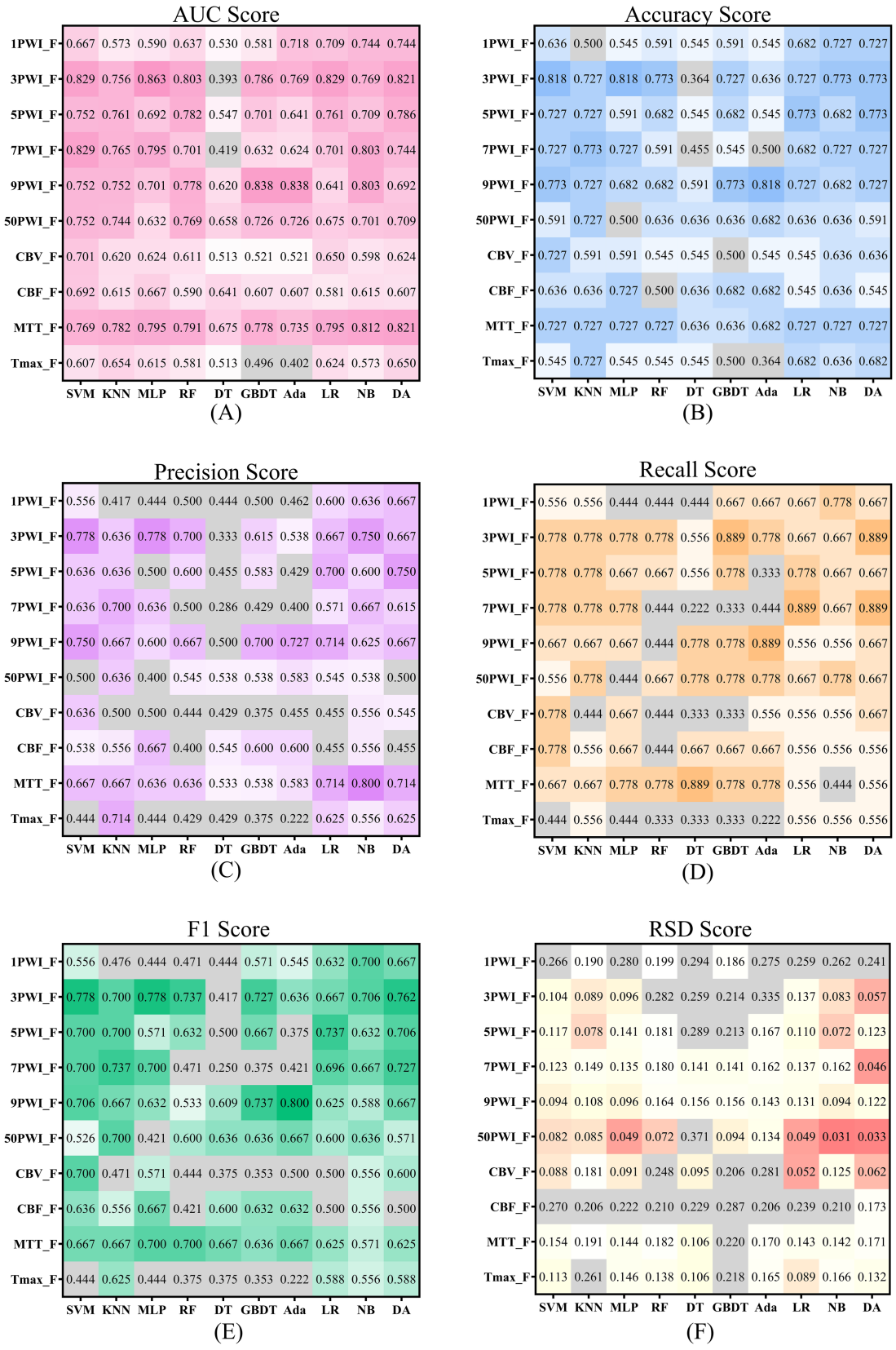

FIGURE 8
Scores for source and parameter features across six evaluation metrics are shown, with darker colors indicating more robust performance. Panels **(A–E)** use color to represent scores above 0.5, where darker shades signify higher scores. Panel **(F)** applies color to scores below 0.2 and red to those below 0.1, with darker hues highlighting better scores.

generally surpassed the four individual perfusion parameters. For example, on MLP, the optimal AUC of the 3PWI group was still 6.8% higher than that of the MTT group which was the best of the four parameters. Except for the DT model, the 3PWI group outperformed the CBV, CBF, and Tmax groups. These findings suggest that we cannot ignore the rich information of the DSC-PWI sequence itself, and even in AIS prognostic prediction, utilizing the source features of the DSC-PWI sequence may be superior to the post-processed perfusion parameter features.

5.2 The feature combination strategy can optimize prognostic prediction performance

Considering that the four perfusion parameters provide different targeted blood flow and tissue information—such as the CBV indicating the ischemic core size, CBF reflecting neuronal activity in ischemic tissue, MTT providing an indirect measure of cerebral perfusion, and Tmax indicating the residual function of the penumbra. This research combined four parametric features to obtain the PerfusionF experimental group. The PerfusionF group achieved an AUC of 0.889 on SVM, significantly better than the four single-parameter features. It indicates that effective integration of relevant information enhances and helps to assess the prognostic results better. Meanwhile, considering the anatomical information in the DSC-PWI sequence, which complements the perfusion parameters, this study continued to combine the perfusion parameter features with the 3PWI features to obtain the CombinedF experimental group. This approach achieved the best AUC of 0.915 using SVM, outperforming all other experimental groups, and is the recommended method in this study. These findings further suggest that the DSC-PWI sequence contains valuable prognosis information related to AIS, emphasizing the need to analyze perfusion parameters and anatomical data. Furthermore, combining multifaceted information can make the information more comprehensive, ultimately improving the accuracy of predicting the prognostic outcome of AIS.

5.3 Predictive performance is influenced by the selected model

Machine learning (ML) employs computer algorithms and mathematical models to learn patterns from large amounts of data and make predictions in unknown data. The ML application has penetrated many aspects of disease diagnosis, image analysis, treatment decision-making, and disease prediction (47–50). However, different ML models exhibit varying levels of sensitivity to features. For example, linear models such as Logistic Regression (LR) are more sensitive to linear relationships among features. In contrast, models such as Random Forest (RF) and Decision Tree (DT) are more capable of capturing nonlinear relationships between features. Our research also supports this observation. For example, the DT model achieved AUC by the 3PWI experimental group is only 0.393, lower than all other source feature groups and single-parameter feature groups. Conversely, across other ML models, the 3PWI_F experimental group performed significantly better than other experimental groups, achieving the highest AUC with the MLP model. It indicates that the ML model strongly influences the prediction results, and it is crucial to choose an appropriate ML model.

5.4 Limitations and future implications

This study has some limitations that require further optimization work. First, the dataset used was limited and from a single medical center, which includes patients with different treatment strategies but does not account for the latest treatments. This could affect the prognosis of patients. Thus, validating our methodology using a broader and more diverse dataset remains essential before applying it to clinical trials for future work. Second, there was a significant imbalance in the proportion of men and women in the dataset. Although it has been demonstrated previously that gender has a minimal effect on the prognosis of stroke patients after intravenous thrombolysis (51), expanding the dataset could minimize this effect in the future. Finally, exploring the optimal number of key time points, we only considered 1, 3, 5, 7, 9, and 50 time points. It concluded that radiomics features at three key time points yielded the best prognostic predictions for AIS. However, further investigation is needed to determine whether increasing the number of time points beyond three would result in superior outcomes.

Exploring the prognostic value of DSC-PWI sequences at different time points, starting from the perfusion curve, offers Implications for future research. First, this approach provides clinicians and translational researchers with a new perspective to uncover potential pathologies. Second, our results show that DSC-PWI sequences at three key time points provide the best prognostic performance. These time points reflect different stages of the pathological process and allow for more accurate assessment of cerebral blood flow changes. In future studies, beyond these three key time points, additional time points or new perfusion parameters could be explored to evaluate their clinical significance in various pathological conditions. Lastly, in clinical practice, future research could focus on optimizing scanning strategies based on the performance of these key time points. Reducing scans at lower-value time points could save patients' time and improve diagnostic efficiency. In conclusion, we hope this study will inspire future researchers to continue innovating and develop more efficient tools for clinical use, further advancing personalized medicine and precision treatment.

6 Conclusion

This study explored the performance of radiomic features derived from DSC-PWI sequences at different time points and various perfusion parameters in predicting the prognosis of AIS. We found that the prediction performance of the three key time points DSC-PWI (3PWI) outperformed traditional perfusion parameters, highlighting the significant value of the 3PWI features in prognostic prediction. In addition, we observed that the combined four perfusion parameters showed a marked improvement over individual perfusion parameters, suggesting that the integration of effective information allows for a more comprehensive assessment, thereby enhancing predictive performance.

Consequently, we combined the 3PWI features with perfusion parameter radiomics features to construct the CombinedF prediction model, which showed even better performance. The AUC reached 0.915, representing a 5.2% improvement over the 3PWI features alone. The proposed method achieves accurate prediction of the prognosis of AIS patients. Furthermore, it could be an objective tool to guide clinical assessment of the prognosis of AIS patients, which has specific application value in helping clinicians develop personalized treatment plans.

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 humans were approved by the Ethics Committee of Shanghai Fourth People's Hospital affiliated with the Tongji University School of Medicine Approval number: 20200066-01; Approval date: 15th May 2020. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. YG: Conceptualization, Data curation, Methodology, Writing – review & editing. JL: Conceptualization, Methodology, Project administration, Writing – review & editing. HH: Writing – review & editing. AC: Conceptualization, Validation, Writing – review & editing. YY: Writing – review & editing, Software. MY: Validation, Writing – review & editing. AZ: Methodology, Writing – review & editing. XZ: Writing – review & editing, Validation. XM: Methodology, Writing – review & editing. ZC: Writing – review & editing, Methodology. GH: Validation, Writing – review & editing. TH: Writing – review & editing. HQ: Resources, Supervision, Writing – review & editing. YL: Data curation, Software, Writing – review & editing. YK: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

YY was employed by Shenzhen Lanmage Medical Technology Co., Ltd.

The remaining 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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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Endovascular thrombectomy versus intravenous tissue plasminogen activator for vertebrobasilar stroke treatment: insights from the national inpatient sample

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Introduction: Approximately 20% of patients, who present with acute ischemic stroke are diagnosed with acute vertebrobasilar artery occlusion (VBAO), which is caused by an embolus or ruptured atherosclerotic plaque leading to the formation of an acute thrombus. The mortality rate of VBAO is extremely high without treatment, ranging from 80 to 95%, underscoring the urgent need for effective and timely treatment strategies. In this study, we examined the trends of hospitalizations for Endovascular Thrombectomy (EVT) or intravenous tissue plasminogen activator (IV-tPA) as interventions for VBAO, their outcomes, associated complications, and predictors of mortality in patients undergoing these procedures.

Methods: We utilized the National Inpatient Sample (NIS) database to extract data from the years 2016 to 2018, using ICD-10 diagnosis and procedure codes specific to occlusion or thrombosis of the vertebral artery or basilar artery, IV-tPA, and EVT.

Results: Between 2016 and 2018, a total of 37,310 patients were admitted with VBAO. Among these, tPA was administered in 2,530 admissions (6.8%), while EVT was performed in 2,330 admissions (6.2%). IV-tPA was more frequently used in the age groups of 65–84 years and, ≥85 years, whereas EVT was more commonly used in the age groups of 18–44 years and 45–64 years. There was no significant difference in usage between men and women. In large hospitals, EVT was more commonly used than IV-tPA (8.1% vs. 7%, $p < 0.0001$), while in small hospitals, IV-tPA usage was significantly higher (3.8% vs. 2%, $p < 0.0001$). The all-cause mortality rate was significantly higher in EVT admissions compared to IV-tPA admissions (16.8% vs. 8.1%, $p < 0.0001$). However, there was no significant difference in the mean length of stay (LOS) between the two modalities.

Conclusion: A trend of higher rates of EVT was observed in the younger age group (18–64 years) compared to the older age group, but no significant difference was noted based on sex. The all-cause mortality rate was found to

be higher in the EVT group compared to the IV-tPA group. However, there was no significant difference in the length of hospital stay between the two groups.

KEYWORDS

endovascular thrombectomy, intravenous tissue plasminogen activator, IV-tPA, vertebrobasilar artery, vertebrobasilar stroke

Introduction

Diagnosing posterior circulation strokes and TIAs can be trickier due to the diverse and subtle symptoms they present (1). The debate between endovascular therapy (EVT) and medical therapy for acute ischemic stroke (AIS) caused by vertebrobasilar artery occlusion (VBAO) is an ongoing challenge. The consequences of VBAO can be severe, and the urgency of early reperfusion is crucial to minimize the associated mortality and morbidity (2, 3). Recognizing and addressing the need for optimal management in posterior circulation strokes is vital for comprehensive stroke care (1).

Prior studies have explored treatment modalities for VBAO, highlighting their potential impact on morbidity and mortality. The BASICS trial demonstrated that EVT could offer a marginal survival advantage in patients with basilar artery occlusion when performed within a specific time window, though it did not show a significant difference in functional outcomes compared to standard medical therapy (4). Similarly, the BEST trial revealed the feasibility of EVT in achieving recanalization; however, complications such as procedural-related hemorrhages and delayed neurological recovery remain concerns (5). These findings emphasize the need for further exploration of EVT and intravenous tissue plasminogen activator (IV-tPA) in real-world hospital settings. This study aims to address these gaps by analyzing trends and outcomes associated with EVT and IV-tPA in a large inpatient population.

Methods

Data source

Our research utilized a retrospective observational design, analyzing data from the National Inpatient Sample (NIS) database files spanning from 2016 to 2018. The NIS files are published annually by the Agency for Healthcare Research and Quality (AHRQ) as part of the Healthcare Cost and Utilization Project (HCUP) (6, 7). The NIS is the largest all-payer inpatient database in the United States, publicly available, and represents approximately 20% stratified sample of discharges from community hospitals nationwide (7, 8). HCUP provides discharge weights for each record, enabling national estimates to be derived (9). Strict measures are in place to ensure patient information confidentiality in this restricted dataset. In accordance with Health Insurance Portability and Accountability Act (HIPAA) guidelines, Institutional Review Board (IRB) approval was not required for our study, as the use of this dataset for research purposes is exempt from IRB review (10).

Study population and description of date elements

We identified cases of occlusion or thrombosis of the vertebral artery or basilar artery, IV-tPA administration, and EVT procedures using specific International Classification of Diseases-Tenth Revision-Clinical Modification (ICD-10-CM) diagnosis and procedure codes. We then calculated rates of complications using specific codes. All pertinent codes are listed in Supplementary file 1. In our analysis, patients who underwent both IV-tPA and subsequent EVT were included in the EVT group for statistical purposes. This classification aligns with current clinical practices, which consider EVT as the definitive treatment in combined therapy scenarios due to its mechanical recanalization capability. The overlap between IV-tPA and EVT was accounted for to ensure accurate representation of treatment outcomes, minimizing potential bias in the comparison between the two modalities. In our analysis, we examined multiple variables including age, gender, race, hospital type, hospital location, and disposition status. We also examined additional variables, such as hospital region, median household income, insurance status, and bed size; their description can be found in Supplementary file 2. Discharge disposition was included as a secondary endpoint to assess patient outcomes post-treatment. Patients' discharge statuses were categorized into the following groups: discharged to home, discharged to a rehabilitation or skilled nursing facility, transferred to another acute care facility, or died during hospitalization. These categorizations were based on data fields available in the NIS database, as outlined in Supplementary file 2. Such categorizations align with standard practices in using administrative datasets for outcome assessment. In the NIS database, diagnoses are listed in a hierarchical manner, with the principal diagnosis being the primary reason for hospitalization, and secondary diagnoses being those that coexist or develop during hospitalization (11). ICD is a standardized coding system that uses alphanumeric codes arranged in a comprehensive and hierarchical manner to define diseases, injuries, and other health-related conditions (12). Our study excluded patients who were under 18 years of age. Figure 1 depicts the rigorous and methodical approach to our statistical analysis.

Statistical analysis

Study variables were compared using univariate and multivariate analyses. Chi-squared ($\chi 2$) test was used to compare categorical variables, while the Wilcoxon rank-sum test was employed for comparing continuous variables (13, 14). Categorical variables were expressed as frequency or percentage, and continuous variables were presented as mean ± error (SE). We used odds ratios (ORs) with 95% confidence intervals (CIs) to report predictors of mortality, which were identified using multivariate regression analysis. For the

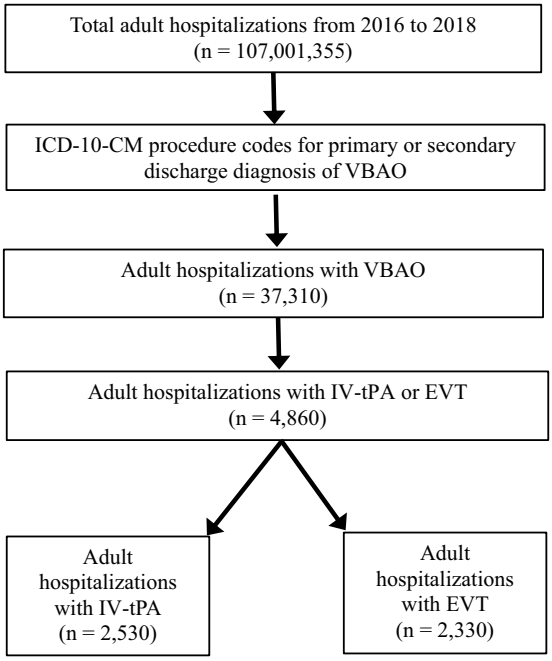

FIGURE 1
Sequential derivation of the study population.

multivariate regression analyses, we adjusted for the following covariates to control for potential confounding factors: age, gender, race, median household income quartile, hospital characteristics (type, location, and teaching status), primary insurance payer, and region (Northeast, Midwest, South, and West). These covariates were selected based on their relevance to stroke outcomes and treatment utilization patterns, as described in prior studies. These statistical methods have been commonly used in previous studies based on the NIS dataset (15–18). All reported differences in estimates were considered statistically significant ($p < 0.05$) unless otherwise indicated. We used SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) software for data analysis.

Endpoints

Primary endpoints of the study were rates of complications like cerebral edema, intracerebral hemorrhage (ICH), angioedema, hemoperitoneum, arterial dissection, aneurysm of upper or lower extremities, postprocedural hemorrhage or hematoma of skin and subcutaneous tissue following EVT, and postprocedural hemorrhage of a nervous system organ or structure following EVT. Secondary endpoints were all-cause mortality rate and LOS.

Results

Number of hospitalizations

From 2016 to 2018, there were 37,310 patients admitted with VBAO. Out of these, IV-tPA was administered in 2,530 (6.8%) admissions, whereas EVT was done in 2,330 (6.2%) admissions (Table 1; Figure 1). Figure 2 shows the trends in admissions for IV-tPA versus EVT.

Baseline characteristics

There was a statistically significant difference in the utilization of IV-tPA and EVT based on age groups (Table 2). IV-tPA was used significantly more frequently in patients older than 65 years, whereas EVT was utilized significantly more often in adult patients under 64 years. These findings reflect established trends in stroke treatment where EVT, requiring specialized expertise, is often preferred in younger patients with fewer comorbidities and greater procedural tolerance. In contrast, IV-tPA is more commonly administered in older patients who may not be eligible for EVT due to medical contraindications or anatomical considerations. There were no statistically significant differences based on gender in the utilization of IV-tPA or EVT. There was no statistically significant difference in the utilization of IV-tPA or EVT for VBAO between White patients and Hispanics patients. However, EVT was used significantly more frequently than IV-tPA in Black patients, with a utilization rate of 6.3% compared to 5.4% ($p = 0.0001$). IV-tPA was utilized more often than EVT irrespective of the hospital bed size. In Midwestern hospitals, EVT was utilized more frequently than IV-tPA, with utilization rates of 6.4 and 5.9%, respectively ($p = 0.002$). On the other hand, in Western hospitals, IV-tPA was used more often than EVT, with utilization rates of 9.5 and 6.9%, respectively ($p < 0.0001$). However, no statistically significant differences were observed in Northeastern and Southern hospitals in terms of IV-tPA and EVT utilization for VBAO. In rural and urban non-teaching hospitals, IV-tPA was utilized more frequently than EVT for VBAO. However, in teaching hospitals, EVT was utilized more often than IV-tPA, with utilization rates of 5.7 and 5.6%, respectively ($p < 0.0001$). The observed variation in treatment modality utilization between teaching and non-teaching hospitals reflects differences in resource availability and expertise. Teaching hospitals, often better equipped with advanced neurointerventional capabilities, perform more EVT procedures, while non-teaching and rural hospitals rely predominantly on IV-tPA due to limitations in infrastructure and specialist availability. There were no significant differences in utilization of these modalities based on primary insurance of the patients. EVT was more commonly utilized in low-income groups (Quartile 1 and Quartile 2), while IV-tPA was more frequently employed in high-income groups (Quartile 3 and Quartile 4); these differences in their utilization were statistically significant (Table 2).

Primary endpoints

Complications related to IV-tPA were cerebral edema (10.7%), ICH (2.4%), angioedema (0.4%), and hemoperitoneum (0.2%) (Table 3). Complications related to EVT were cerebral edema (19%), arterial dissection (8.5%), aneurysm of upper or lower extremities (0.7%), postprocedural hemorrhage or hematoma of skin and subcutaneous tissue following the procedure (0.6%), and postprocedural hemorrhage of a nervous system organ or structure following the procedure (0.4%) (Table 3).

TABLE 1 Number of VBAO hospitalizations: no procedure vs. IV-tPA vs. EVT.

	2016	2017	2018	Total	Percentage
No procedure	10,015	11,215	11,220	32,450	87.0
IV t-PA	720	760	1,050	2,530	6.8
EVT	620	685	1,025	2,330	6.2
Total VBAO hospitalizations (*n*)	11,355	12,660	13,295	37,310	

Secondary endpoints

Compared to EVT, patients who received IV-tPA were more likely to be discharged to home (6.3% vs. 2.9%; $p < 0.0001$) (Table 2). The all-cause mortality rate was significantly higher in the EVT group compared to the IV-tPA group (16.8% vs. 8.1%, $p < 0.0001$). The mean LOS did not show a statistically significant difference between the two treatment modalities (Table 2).

Factors associated with mortality

Multivariate logistic regression analysis identified significant factors associated with mortality in patients with VBAO. Patients aged 45–64 years (OR: 3.0, 95% CI: 1.4–6.4, $p = 0.01$) and 65–84 years (OR: 2.8, 95% CI: 1.3–5.9, $p = 0.01$) had higher odds of mortality compared to the reference group (aged 18–44 years). Gender did not significantly affect mortality risk, with females showing an OR of 1.2 (95% CI: 0.7–2.1, $p = 0.56$) compared to males. Race also did not show significant differences in mortality risk, with Hispanics (OR: 2.1, 95% CI: 0.4–10.9, $p = 0.36$), "Others" (OR: 1.3, 95% CI: 0.4–4.0, $p = 0.68$), and White patients (OR: 0.9, 95% CI: 0.4–2.0, $p = 0.79$) having no statistically significant differences compared to Black patients.

Hospital characteristics were another key factor, with rural hospitals showing a trend toward lower mortality (OR: 0.4, 95% CI: 0.0–3.0, $p = 0.37$) and urban non-teaching hospitals showing higher odds of mortality (OR: 1.3, 95% CI: 0.7–2.4, $p = 0.34$) compared to teaching hospitals, though these findings were not statistically significant. Notably, the presence of complications significantly reduced mortality risk (OR: 0.3, 95% CI: 0.2–0.6, $p = 0.001$). These findings, summarized in Table 4, highlight the complexity of mortality risk in VBAO patients and suggest that patient demographics, hospital characteristics, and clinical complications play a role in outcomes.

Discussion

The efficacy of EVT for VBAO remains uncertain. Although VBAO is a rare form of stroke, comprising roughly 1% of all ischemic strokes and 5–10% of all proximal intracranial occlusions, its consequences are devastating. Without prompt treatment, around 70% of patients suffer from severe disability or face mortality (5). This study aimed to analyze the trends in hospitalizations for two treatment interventions, EVT and IV-tPA, for VBAO. The study also investigated the outcomes, complications, and factors associated with mortality.

The research involved a total of 37,310 patients who were admitted with VBAO between the years 2016 and 2018. Within this group, IV-tPA was administered in 6.8% of cases, while EVT was performed in 6.2% of cases. Comparatively, a previous study conducted in 2015 on the NIS cohort, which identified 1,120 patients with a diagnosis of basilar artery occlusion, reported an EVT rate of 16.43%. Despite our study encompassing both vertebral artery and basilar artery occlusions and utilizing more recent data from 2016 to 2018, our EVT utilization rate was lower. This disparity is challenging to explain, but it may be attributed to the inclusion of the subgroup with vertebral artery occlusion in our study (19).

The usage of IV-tPA and EVT demonstrated notable variations among different age groups. IV-tPA administration was more prevalent among patients aged 65 and above, whereas EVT was favored for individuals between 18 and 64 years old. The lower utilization of EVT in older age groups can be attributed to several factors. These include the higher occurrence of comorbidities that heighten the risk of complications, the presence of delicate blood vessels and intricate anatomy, as well as considerations regarding the overall health and functional status of elderly patients. It is important to acknowledge that clinical trials focusing on EVT in cases of VBAO, such as the ATTENTION, BEST, BASICS, and BAOCHE trials, have predominantly enrolled participants in their 60s, potentially excluding a significant portion of the elderly population (4, 5, 20, 21). Consequently, IV-tPA is frequently employed in this subgroup of patients.

Irrespective of hospital size, IV-tPA was more frequently employed than EVT for treating VBAO. In non-teaching hospitals, IV-tPA was the preferred treatment option, surpassing EVT in usage. However, in teaching hospitals, EVT was utilized more frequently than IV-tPA. These results highlight the complexity of treating VBAO and the critical influence of resource availability and patient factors on treatment decisions. For example, the preference for EVT in younger patients and at teaching hospitals suggests that procedural expertise and hospital infrastructure are significant determinants of treatment modality. Conversely, the reliance on IV-tPA in older populations and non-teaching hospitals underscores the challenges of accessibility to EVT in resource-limited settings. This emphasizes the need for a more equitable distribution of advanced neurointerventional services to ensure optimal stroke care across all demographics. This observation is consistent with a previous study conducted by Farooqui et al., which analyzed the NIS database and revealed that

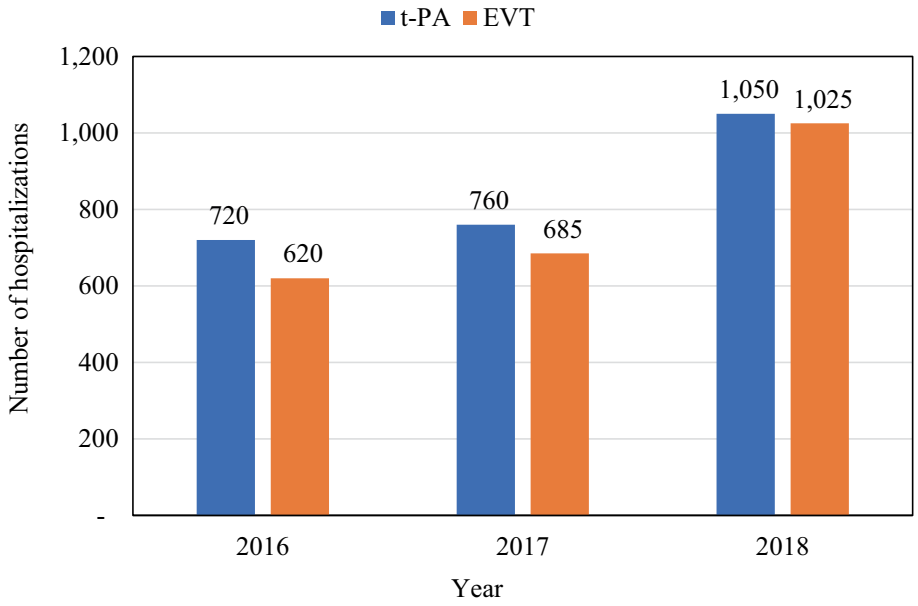

FIGURE 2
Number of hospitalizations for IV t-PA vs. EVT.

rural non-teaching hospitals did not perform any EVT procedures. The majority of EVT procedures were carried out in teaching hospitals (19). These findings support the notion that nonacademic hospitals lack the necessary capabilities for performing EVT and providing multidisciplinary critical care services. Consequently, these hospitals mainly handle mild to moderate stroke cases and refer severe cases to more specialized facilities with better resources.

In terms of outcomes, the study findings indicated that the all-cause mortality rate was notably higher in the EVT group compared to the IV-tPA group, with rates of 16.8 and 8.1%, respectively. It is important to note that the reported mortality rate in our study is lower than those reported in clinical trials (4, 5, 20, 21). Meta-analyses of these trials have demonstrated that EVT has a mortality rate of 35% compared to 45% for the best medical management option (22, 23). Furthermore, they have revealed that EVT is associated with a significantly reduced risk of mortality within 90 days in patients with VBAO when compared to the best medical management option (22, 23).

Our study did not find any notable disparity in the average duration of hospitalization between the two treatment approaches. However, a *post hoc* analysis of DEFUSE 3 revealed that the median length of hospital stay was significantly shorter in the EVT group, with patients in this group staying for an average of 6.5 days compared to 9.1 days in the medical group. Additionally, within the same study, EVT demonstrated an increase in the amount of time spent at home and improved living situations for patients during the 90-day period following a stroke (24). Another study demonstrated that individuals who underwent thrombectomy were discharged, on average, 36 days earlier. Moreover, a greater number of patients were able to return home upon discharge, while fewer individuals required placement in care homes or rehabilitation centers. Furthermore, the thrombectomy group necessitated a reduced number of physiotherapy sessions (25).

The research also investigated the potential complications associated with EVT for the treatment of VBAO. The identified complications included cerebral edema, arterial dissection, aneurysm formation in the upper or lower extremities, as well as postprocedural hemorrhage or hematoma. The complications associated with EVT were discussed broadly in this study; however, it is important to recognize that not all complications contribute equally to morbidity or mortality. While complications such as vessel perforation or arterial dissection can result in catastrophic outcomes, others like pseudoaneurysms or minor vascular access complications are typically of lower clinical significance and rarely lead to mortality. The higher mortality rate observed in EVT compared to IV-tPA is likely multifactorial, involving both procedural complications and baseline differences in patient severity that were not fully accounted for due to the limitations of the dataset. This distinction underscores the importance of separating major complications, which directly impact survival, from minor complications that primarily affect morbidity. While EVT is generally considered a safe technique, there is a potential risk of bleeding. Manipulation of the vessel wall during the procedure, especially using devices, can result in vessel damage and subsequent intimal injury. This damage can range from subintimal dissection to the formation of an intramural hematoma, which may eventually lead to the occlusion of the treated vessel. The extent of the damage may vary based on factors such as the design of the device, the number of device passes, and the diameter of the target vessel.

The differences observed between our study findings and those from previous clinical trials, such as the BASICS, BEST, ATTENTION, and BAOCHE trials, can be attributed to several factors. First, our study utilized a real-world, population-based dataset from the NIS, which includes a broader and more diverse

TABLE 2 Baseline characteristics of VBAO hospitalizations.

Variables	No procedure#	IV-tPA	EVT	*p*-value
Age in years (%)				
18–44	87.8	5.2	7.0	0.0003
45–64	86.6	6.3	7.1	<0.0001
65–84	87.1	7.0	5.9	0.0008
> = 85	86.9	8.5	4.7	<0.0001
Gender (%)				
Male	87.2	6.6	6.2	0.18
Female	86.6	7.1	6.3	
Race (%)				
White	86.5	7.1	6.4	0.21
Black	88.3	5.4	6.3	0.0001
Hispanic	90.0	5.5	4.5	0.16
Others	83.5	9.5	7.0	0.02
Hospital bed size (%)				
Small	94.2	3.8	2.0	<0.0001
Medium	88.3	7.7	4.0	<0.0001
Large	84.9	7.0	8.1	<0.0001
Hospital region (%)				
Northeast	88.0	5.9	6.1	0.05
Midwest	87.7	5.9	6.4	0.002
South	87.8	6.3	5.9	0.3
West	83.6	9.5	6.9	<0.0001
Hospital type (%)				
Rural	96.7	2.7	0.7	<0.0001
Urban non-teaching	90.4	6.3	3.3	<0.0001
Teaching	67.8	5.6	5.7	<0.0001
Primary insurance (%)				
Medicare/Medicaid	87.3	6.6	6.2	0.09
Private including HMO	86.1	7.4	6.5	0.13
Uninsured/Self-pay	87.2	6.8	6.0	0.31
Median household income (%)				
Quartile 1	88.1	5.5	6.4	<0.0001
Quartile 2	88.5	5.5	6.0	0.0008
Quartile 3	86.4	7.5	6.1	0.007
Quartile 4	84.3	9.3	6.5	<0.0001
Disposition status (%)				
Home	90.8	6.3	2.9	<0.0001
Facility	86.8	6.8	6.4	0.23
Died	75.1	8.1	16.8	<0.0001
Mean LOS (days ± SE)	6.5 ± 0.1	7.3 ± 0.6	9 ± 0.5	0.62

#"No procedure" column is for explanatory purposes only. Chi-square test was performed between IV t-PA and EVT groups.

patient population compared to the highly selective cohorts enrolled in clinical trials. For instance, clinical trials often exclude elderly patients or those with significant comorbidities, whereas the NIS database captures a wide range of patient demographics and clinical presentations. This inclusivity may explain the lower overall rates of EVT observed in our study compared to trials like BEST and BASICS, which focused on carefully selected patients with favorable characteristics.

TABLE 3 Complications: IV-tPA vs. EVT.

IV-tPA %		EVT %	
Cerebral edema	10.7	Cerebral edema	19
Intracerebral Hemorrhage	2.4	Arterial dissection	8.5
Angioedema	0.4	Aneurysm of artery of upper/lower extremity	0.7
Hemoperitoneum	0.2	Postprocedural hemorrhage/ hematoma of skin and subcutaneous tissue following a procedure	0.6
		Postprocedural hemorrhage of a nervous system organ or structure following a procedure	0.4

TABLE 4 Predictors of mortality.

Variables	OR	Confidence interval	*P*-value
Age			
18–44	2.3	0.7–7.5	0.18
45–64	3.0	1.4–6.4	0.01
65–84	2.8	1.3–5.9	0.01
> = 85	Control		
Gender			
Female	1.2	0.7–2.1	0.56
Male	Control		
Race			
White	0.9	0.4–2.0	0.79
Hispanic	2.1	0.4–10.9	0.36
Others	1.3	0.4–4.0	0.68
Black	Control		
Hospital type			
Rural	0.4	0.0–3.0	0.37
Urban non-teaching	1.3	0.7–2.4	0.34
Teaching	Control		
Any complication			
Yes	0.3	0.2–0.6	0.001
No	Control		

Second, differences in study design contribute to the observed discrepancies. Clinical trials are conducted in controlled environments with standardized protocols and expert centers, ensuring uniformity in treatment practices. In contrast, the NIS database reflects real-world variability in resource availability, procedural expertise, and adherence to guidelines across different hospital types and regions. For example, our finding that EVT utilization is higher in teaching hospitals highlights the influence of institutional capabilities on treatment practices, a factor not typically accounted for in clinical trials.

Third, the absence of granular clinical data in the NIS database, such as imaging findings, stroke severity scores (e.g., NIHSS), and precise treatment timing, limits direct comparisons with clinical trials, which rely on such detailed metrics to define eligibility and assess outcomes. The absence of this data may lead to residual confounding and limits the ability to fully align our results with those of clinical trials.

Strengths of the study

- The utilization of the NIS database enabled us to conduct a study on a substantial population, thereby mitigating the bias commonly observed in studies limited to a single region or hospital.
- Our analysis provides a framework for future clinical trials to compare outcomes for IV-tPA versus EVT.

Limitations of the study

- Due to the limited scope of NIS, our assessment of 90-day outcomes was not possible as NIS solely focuses on inpatient populations.
- We could not assess rates of complications related to EVT like distal embolization, vessel rupture, vessel re-occlusion post mechanical thrombectomy, post reperfusion injury, seizures. Also, we could not calculate rates of access site related complications like vessel occlusion, arterio-venous fistula, rectus sheath hematoma, femoral neuropathies, and infections, and treatment outcomes like hemorrhagic infarction, intraparenchymal hemorrhage, and subarachnoid hemorrhage.
- The number of patients with VBAO in our analysis may be overestimated. This is because the NIS treats each hospitalization as a distinct entry, without a coding method to differentiate between initial admissions and subsequent readmissions.
- Major limitation of this study is the inability to account for stroke severity directly, as the NIS database does not include measures such as the NIHSS. Stroke severity is a critical mediator in the selection of IV-tPA versus EVT and significantly impacts outcomes. Although we used proxy variables such as age, the presence of complications (e.g., cerebral edema and hemorrhage), and hospital characteristics to partially account for severity, these proxies are not a substitute for direct clinical measures. This limitation may result in residual confounding and should be considered when interpreting the study's findings.
- Another important limitation of our study is the absence of data on the time interval between the diagnosis of VBAO and the initiation of EVT or IV-tPA treatment. The timing of treatment initiation is a critical determinant of outcomes in acute ischemic stroke, as earlier intervention within the therapeutic window is associated with better functional outcomes and reduced mortality. Unfortunately, the NIS database does not capture this information, which limits our ability to evaluate the time-dependent efficacy of these

treatment modalities. Future studies leveraging datasets with detailed timing variables are necessary to provide a more comprehensive understanding of the real-world effectiveness of EVT and IV-tPA.

Future directions

To further explore the treatment of VBAO, future research should focus on the following:

- Understanding clot composition and its effects on treatment efficacy. This entails analyzing clot characteristics like size and density, and their responsiveness to treatments like EVT and IV-tPA.
- Assessing diverse patient demographics to understand how factors like age and comorbidities influence treatment outcomes.
- Integrating advanced imaging techniques to enhance diagnostic precision and guide treatment choices.
- Exploring new therapies alongside EVT and IV-tPA, and investigating the potential of AI and machine learning in personalizing treatment and improving diagnostic accuracy.
- Understanding the underlying factors influencing treatment decisions, such as hospital infrastructure, socioeconomic disparities, and referral pathways, to identify strategies for improving access to EVT for underserved populations.
- Incorporating clinical measures, such as NIHSS scores, stroke risk factors, baseline functional status, and stroke mechanisms, to provide a more comprehensive understanding of the comparative safety and efficacy of IV-tPA and EVT.
- Utilizing longitudinal datasets or prospective designs that include 90-day outcomes, such as functional status and recurrent events, to provide a more complete understanding of the long-term efficacy and safety of IV-tPA and EVT.

Conclusion

This study highlights significant trends and outcomes associated with EVT and IV-tPA in patients with VBAO, shedding light on the variability in treatment utilization and associated mortality rates. However, the findings should be interpreted with caution, considering the inherent limitations of the NIS database, such as the absence of critical time-dependent and clinical severity variables, as well as the lack of long-term outcome data. While these results provide valuable real-world insights, they are restricted in scope and should not be generalized without validation from prospective studies or clinical trials. Further research is warranted to address these gaps, explore the long-term efficacy and safety of these treatment modalities, and assess their impact in diverse patient populations and healthcare settings.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: In order to reproduce the data used in our research, you have get access from HCUP directly. Requests to access these datasets should be directed to https://hcup-us.ahrq.gov/team/NationwideDUA.jsp.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

RS: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. GN: Writing – original draft, Writing – review & editing. DS: Writing – original draft, Writing – review & editing. AS: Writing – original draft, Writing – review & editing. MA-S: Writing – original draft, Writing – review & editing. SD: Writing – original draft, Writing – review & editing. AR: Writing – original draft, Writing – review & editing.

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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.

The reviewer DE declared a shared affiliation with the author AS at the time of review.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1417188/full#supplementary-material

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A systematic review of alterations in sensorimotor networks following stroke: implications for integration and functional outcomes across recovery stages

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Introduction: Stroke can result in a wide range of impairments, with sensorimotor dysfunction being among the most common, particularly when the sensorimotor network (SMN) is affected. As the SMN plays a critical role in movement control and coordination, understanding the changes in this network post-stroke is essential for informing recovery and rehabilitation strategies.

Methods: A systematic review was conducted following PRISMA guidelines. Two electronic databases, PubMed and Scopus, were searched for relevant studies investigating the effects of stroke on the SMN across different phases of recovery. Reference lists of selected articles were also reviewed using Google Scholar. A total of 20 eligible studies involving 618 stroke patients and 606 healthy controls were included.

Results: The review revealed consistent findings of altered functional connectivity within the SMN following stroke. Despite initial impairments, most studies reported improvement in SMN connectivity over time, attributed to compensatory mechanisms, cortical reorganisation, and functional rewiring. Stroke location significantly influenced recovery outcomes. Supratentorial strokes were associated with poorer motor assessments and slower recovery, while infratentorial strokes had comparatively better outcomes. Lesions in the pontine region were found to cause severe disturbances in both sensory and motor functions depending on lesion extent.

Discussion: The findings underscore the brain's capacity for neuroplasticity and reorganisation following stroke. Understanding the temporal and spatial changes in the SMN post-stroke can inform more targeted and effective rehabilitation strategies. These insights are crucial for tailoring interventions that align with individual stroke profiles and promote optimal functional recovery.

KEYWORDS

stroke, functional connectivity, sensorimotor networks, Fugl-Mayer Assessment, functional magnetic resonance imaging

Highlights

- The motor cortex, integral to the sensorimotor network (SMN) is directly affected by stroke, contributing to muscle weakness and challenges in executing specific motor tasks.
- The correlation between motor deficiencies and altered brain activity across multiple neural networks showed potential dysfunctions in complex motor behaviors even in well-recovered patients.
- Disruptions in connections within the SMN contribute to a global alteration in the functioning of this neural network.
- Activation patterns in the contralateral and ipsilateral SMC and premotor cortex may signify variances in cortical reorganization during the chronic phase.

1 Introduction

A stroke is a medical emergency caused by disruption of blood supply due to blood vessel occlusion or bleeding due to burst blood vessels, resulting in the death of brain cells. After a stroke, changes in the brain's neuronal network connectivity have been observed (1). Studies have shown that the brain network may evolve to a more complex and random mode during the process of rehabilitation after a stroke (1–3). This evolution involves the production of new connections to compensate for damaged connections and nerves, as well as the reorganization of functional network connectivity, which is central to the process of rehabilitation. The sensorimotor network (SMN) plays a crucial role in daily functioning, encompassing the integration of sensory and motor formation to execute purposeful movements. These networks include the primary motor cortex (M1), the somatosensory cortex, the premotor cortex (PMC), and the supplementary motor area (SMA).

The SMN is responsible for the planning, execution, and control of voluntary movements, and the somatosensation (4). The SMN is also involved in the processing of proprioceptive information, which is essential for the perception of body position and movement (5). The SMN is connected to wider functional networks that coordinate the activity of separate cortical regions. These pathways link the SMN to other brain regions involved in higher-order cognitive processes, such as attention, memory, and decision-making (6, 7) The SMN is also connected to subcortical structures, including the basal ganglia and the cerebellum, which is pivotal in motor control and learning (8). Therefore, it is important to evaluate the post-stroke changes and the recovery mechanism particularly strokes that involve this SMN.

Research has shown that the impact of stroke depends on the location of the stroke (9, 10). Stroke can lead to sensorimotor deficits, affecting the ability to incorporate sensory inputs for motor output, thereby compromising goal-directed functional movements and motor abilities (11–13). The significance of SMN in daily functioning is evident in the context of stroke, as they are essential for activities of daily living and overall quality of life. Stroke survivors often experience motor and sensory impairments, cognitive deficits, and emotional disorders, which can significantly impact their independence and wellbeing (14). Stroke-induced damage to the M1 can result in weakness or paralysis of the contralateral limbs. However, the brain can undergo reorganization and plasticity to compensate for the damage, leading to the recruitment of alternative motor pathways and the development of new connections between brain regions (15). The recovery process after stroke involves multiple mechanisms, some of which are still not fully understood. This includes the resolution of harmful local factors and neuroplasticity. The neural reorganization is the most critical driver of functional recovery post-stroke (16–19). However, a clearer understanding of the mechanisms underlying cerebral reorganization is required to develop more effective strategies to enhance the human brain's response to injury. The degree to which mechanisms underlying cerebral reorganization are successful is likely to depend on the functional state of the brain, the chronicity of the stroke, and the degree of damage.

The principal aim of this systematic review is to evaluate the existing literature on alterations in SMN in stroke patients, with a specific emphasis on delineating the repercussions of stroke on sensorimotor integration and its consequences on daily functioning throughout the different stages. Functional magnetic resonance imaging (fMRI) plays a crucial role in this evaluation, as it provides detailed insights into the brain's activity and connectivity patterns. fMRI studies have demonstrated that stroke can lead to significant changes in the SMN, affecting both structural and functional connectivity. These alterations can manifest as impaired sensorimotor integration, which can hinder the patient's ability to perform daily tasks effectively. By analyzing fMRI data across different stages of stroke recovery, researchers can better understand the dynamic changes in SMN and their impact on motor and sensory functions, thereby informing rehabilitation strategies to improve patient outcomes.

2 Methodology

2.1 Search strategy and study selection

This systematic review was conducted in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (20) and previous studies (21–24) are used as the reporting guidelines.

The National Center for Biotechnology Information (PubMed) and Scopus electronic databases were searched on April 2024, using the following keywords: "sensorimotor" or "motor cortex" or "supplementary motor area" or "sensorimotor network" and "stroke" or "acute stroke" or "ischemic stroke" or "hemorrhage stroke" and "functional MRI" or "fMRI". Advanced search keyword chains in PubMed and Scopus used are in Supplementary Table S1. The references of the selected studies were cross-checked using Google Scholar. One independent reviewer (N.S.A.S) performed the systematic search and screened the title and abstract of the articles, with duplicates being removed. The full text of eligible papers was carefully read to decide whether the eligibility criteria were met. The second and third reviewers (H.A.M and N.Y) verified the findings and any possible discrepancies were solved if necessary. Associated articles in references and citations were manually checked through the Google Scholar database.

TABLE 1 PICOS strategy for the selection of the study.

PICOS	Criteria
Population	Adult stroke patients (age >18 years old)
Intervention	Functional magnetic resonance imaging of sensorimotor network and Fugl-Mayer Assessment
Comparison	Healthy controls
Outcome	Motor deficits measured by clinical assessment and fMRI
Study	All studies related to stroke patients assessed with fMRI except case report, case series, all types of review, letter to editor

Inclusion criteria to select the studies: (a) adult patients with stroke (age >18 years old), (b) motor assessment using Fugl-Mayer Assessment (FMA) whole extremity. FMA is a widely used tool for assessing motor function in patients with stroke. The average FMA score is calculated based on the total score obtained from the assessment, which ranges from 0 to 226, with higher scores indicating better motor function (89). The FMA consists of five domains: motor function, sensory function, balance, range of motion, and joint pain. The FMA is a crucial tool in stroke studies due to its comprehensive, reliable, and standardized approach to evaluating motor function and other critical domains affected by stroke. Its ability to track changes over time, predict outcomes, and compare the effectiveness of interventions makes it indispensable for both clinical practice and research in stroke rehabilitation. (c) assessment using functional magnetic resonance imaging (fMRI) post-stroke, (d) comparison with healthy controls (HC), (e) original studies in English reported in peer-reviewed journals. Pre-clinical studies, reviews, articles that are not in English, and articles without full text were excluded. Articles that utilized other imaging modalities such as computed tomography (CT), positron emission tomography (PET), ultrasound, and navigated transcranial magnetic stimulation (nTMS) were also excluded. The summary of the inclusion criteria is tabulated in Table 1, PICOS strategy for the selection of the study.

The PRISMA flow diagram (Figure 1) illustrates the screening process. The electronic search identified 1999 records after removing duplicate articles, 2 other results were added through alternative sources. Thousand seven hundered and sixty-two were excluded after title and abstract screening based on the exclusion criteria. From the 237 articles selected, 219 of them were removed for not meeting the eligibility criteria, finally, 20 articles were included in this study. This systematic review was registered under the International Prospective Register of Systematic Review (PROSPERO). The tabulated data in all the tables were assessed to fulfil our primary objective. The information included (1) average FMA score at different time points and one-time points, and (2) fMRI findings after stroke onset.

2.2 Data extraction

After the selected articles were considered suitable for inclusion, one reviewer (N.S.A.S) extracted the following information: (a) study author(s), (b) year of publication, (c) country of origin, (d) number of participants, (e) mean age of participants ± standard deviation, (f) type of strokes, (g) post-stroke onset, (h) lesion location, (i) motor assessments, and (j) analysis of fMRI (Table 2). The second and third reviewers (H.A.M and N.Y) verified the information and any possible discrepancies were discussed and solved if necessary.

2.3 Quality assessment

Assessment tools from the National Heart, Lung and Blood Institute—Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies—have been used to assess the quality of included studies. Details of the study selection assessment can be found in the Supplementary Table S2.

3 Results

A total of 20 studies that match the PICOS criteria were selected in this study. Tables 3, 4 summarize the study's characteristics; investigating the alterations of SMN due to stroke. The selected studies comprise 1,224 participants: 618 patients with different types and locations of stroke, and 606 healthy controls (HC). Generally, all the selected studies have moderate and high quality, as shown in Supplementary Table S2. The sample data collection techniques, and study designs used in the selected studies adhere to the established standards. All studies involved adult patients with stroke in various locations and used reliable and valid data collection methods.

3.1 Study details

Table 2 provides a summary of the study characteristics and demographic data. Most of the studies were conducted in China (n = 16), while other studies were conducted in South Korea (n = 2), Japan (n = 1), and the United States of America (n = 1). Participants included in the studies have an age range between 18 and 80 years old. Most studies matched the age and gender of the HC. Additionally, none of the studies conducted separate analyses based on age and gender.

Most studies reported ischaemic stroke, while only two studies included patients with hemorrhagic stroke (25, 26). Lesion locations were reported in multiple brain areas with basal ganglia being the most common location reported (n = 9), followed by internal capsule (n = 8) and, corona radiata (n = 6). Other locations include the temporal lobe, pontine, thalamus, and parietal lobe.

The research included nine longitudinal studies with follow-up periods ranging from 10-days post-stroke to 6 months (27–34).

Four cross-sectional studies recruited patients with <2-week post-stroke onset (25, 26, 33, 35), two studies with patients within 3 months post-stroke onset (36, 37), and the remainder reported patients up until after 6 months post-stroke onset (38–43).

Seven studies provided reports on multiple scanning and motor assessment at different time points, Four studies featured other motor assessments aside from FMA, which include Wolf motor, box and blocks, grip strength, Trail Making Test, Flanker

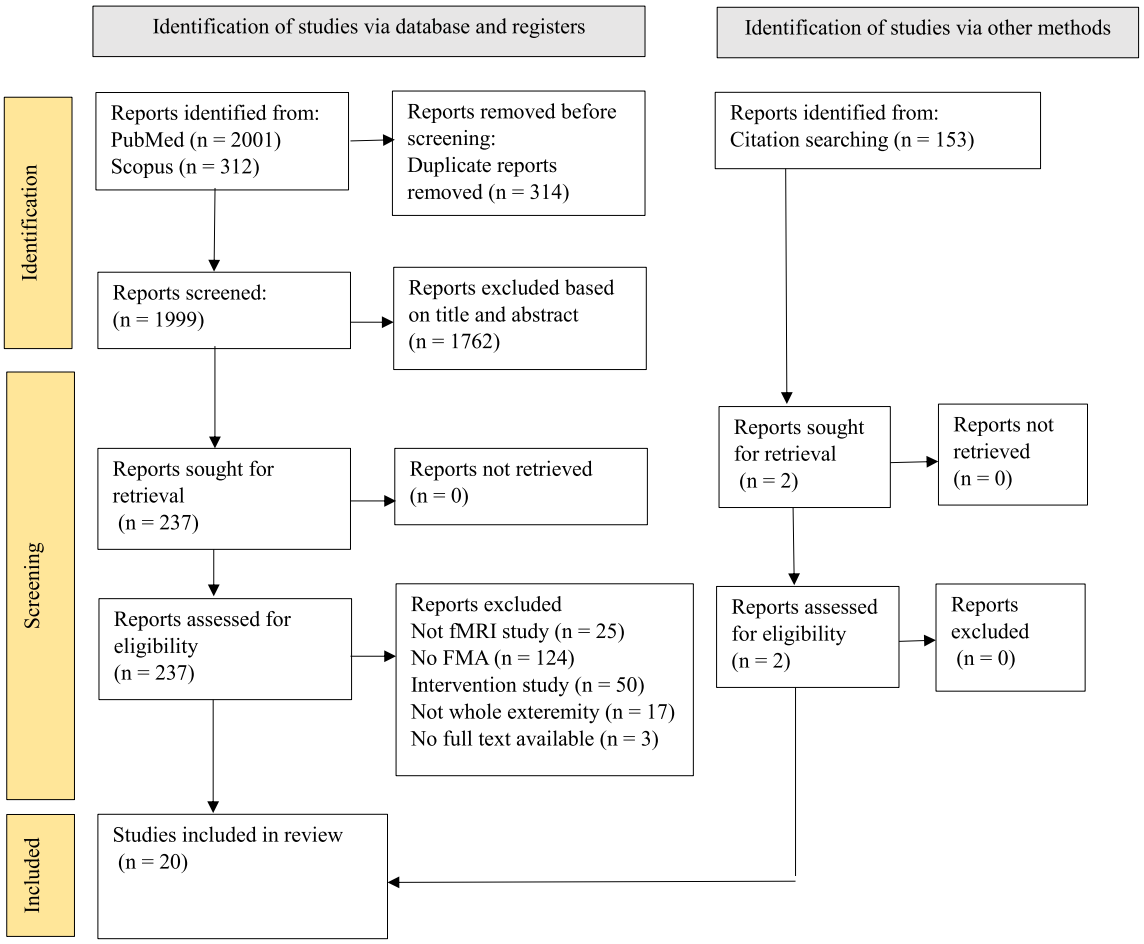

FIGURE 1
Flow diagram of the PRISMA study selection process.

Task, Number back Task, and Spatial back Task (32, 40, 42, 43), Additionally, fMRI analysis used in each study includes Voxel-based Morphometry, General Linear Model, Seed-based Analysis, Independent Component Analysis, Degree Centrality, and Intra- and Inter-networks analysis.

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3.2 Fugl-Mayer Assessment

3.2.1 Within 2 weeks of stroke

Seven studies observed moderate motor impairment within 2 weeks of stroke onset (26, 28, 31–35), while two studies reported severe motor impairment at the same timeframe (27, 30). Noteworthy is Lee et al. (30), found that patients with supratentorial stroke exhibited slightly lower average FMA scores compared to patients with infratentorial stroke. The details tabulation of correlation between FMA and brain activity is in Table 5. On the other hand, Wei et al. (33) demonstrated that patients with left pontine stroke had marginally lower average FMA scores compared to their right pontine stroke counterparts. The number of studies reporting FMA scores at different time points is detailed in Figure 2.

3.2.2 1-month stroke onset

Five studies documented patients' average FMA scores, revealing significant improvement compared to scores within the initial 2 weeks post-stroke onset (27, 28, 31–33).

Furthermore, four studies documented that despite significant improvement, patients' average scores continue to reflect moderate motor impairment (28, 31, 32). Park et al. (27) reported sustained severe motor impairment within the first month after stroke onset.

Two studies showed that left-sided lesion patients have lower average FMA scores compared to right-sided lesion patients (25, 33).

3.2.3 3-months stroke onset

Six studies documented a significant improvement in patients' average scores compared to earlier assessments (27, 28, 30–33). However, only two studies categorized patients as having mild motor impairment (31, 33). Notably, Wei et al. (33) observed that left pontine stroke patients still displayed consistently lower average scores than their counterparts while Chen et al. (36) reported slightly lower scores for patients with pontine stroke compared to those with basal ganglia stroke.

TABLE 2 Demographic of selected studies.

No.	Author (year): country	No of participants	Mean age ± SD (age range)	Female (%)	Type of stroke	Post-stroke onset (days)	Study type	Lesion location	Motor assessments	fMRI analysis
1	Li et al. (2022): China	28 PT, 42 HC	54.6 (30–70)	17.9	Ischemic	<7	Cross-sectional	BG	FMA	SBA
2	Chen et al. (2018a): China	76 PT, 55 HC	NR	43.5	Ischemic, hemorrhage	7–30	Cross-sectional	CR, IC, BG, thalamus, pons, cerebellum	FMA	SBA
3	Park et al. (2011): South Korea	12 PT, 11 HC	58.4 (47–74)	58.3	Ischemic	<14	Longitudinal (2-week, 1-month, 3-month, 6-month)	Middle cerebral artery, CR, anterior cerebral artery, striatocapsular	FMA	NR
4	Liu et al. (2015): China	22 PT, 22 HC	NR (34–75)	36.4	Ischemic	<7	Longitudinal (1-week, 1-month, 3-month)	Left hemisphere	FMA	ALFF, cortical thickness
5	Chen et al. (2019): China	31 PT, 20 HC	NR (40–80)	32.3	Ischemic	>30	Cross-sectional	BG, pontine	FMA	SBA
6	Cheng et al. (2015): China	12 PT, 16 HC	61.5 (47–77)	33.3	Ischemic	<90	Longitudinal (10-day. 2-week, 1-month, and 3-month)	BG, parietal lobe, CR, lateral ventricle	FMA	ROI-based
7	Wang et al. (2022): China	47 PT, 56 HC	57.8 (40–80)	44.7	Ischemic	>180	Cross-sectional	Pontine	FMA, FT, NBT, SBT, TMT	ICA, intra- and inter-network
8	Lee et al. (2018): South Korea	40 PT, 24 HC	NR (33–79)	37.5	Ischemic	>14	Longitudinal (2-weeks, 3-months)	Supratentorial, infratentorial	FMA	ROI-based
9	Lu et al. (2019): China	17 PT, 17 HC	52.0 (18–65)	5.8	Ischemic	7–90	Longitudinal (1-week, 1-month, 3-month)	IC	FMA	ICA, ROI-based, intra-network
10	Diao et al. (2020): China	86 PT, 75	NR (40–75)	25.6	Ischemic	>180	Cross-sectional	IC, BG, thalamus	FMA, TMT	SBA
11	Wang et al. (2014): China	25 PT, 22 HC	56.2 (42–72)	28.0	Ischemic	>180	Cross-sectional	IC, CR, BG, thalamus	FMA	ICA, intra- and inter-network
12	Miyai et al. (2001): Japan	18 PT, 5 HC	NR (38–71)	38.9	Ischemic	<140	Cross-sectional	IC	FMA	ROI-based
13	Liu et al. (2020): China	25 PT, 22 HC	56.2 (42–72)	28.0	Ischemic	>180	Cross-sectional	IC, CR LN, thalamus, Cau	FMA	ROI-based
14	Li et al. (2020): China	25 PT, 26 HC	52.7 (NR)	28.0	Ischemic	<180	Longitudinal (7-day, 2-week, 1-month, 3-month, 6-month)	BG	FMA, grip strength	Voxel-based, LI
15	Chen et al. (2023): China	34 PT, 44 HC	56.5 (30–75)	26.4	Ischemic	<10	Longitudinal (2-week, 3-month, 6-month)	BG, CR	FMA	DC
16	Wei et al. (2020): China	20 PT, 20 HC	NR (40–80)	45.0	Ischemic	<7	Longitudinal (1-week, 1-month, 3-month, 6-month)	Pontine	FMA	SBA
17	Kalinosky et al. (2019): USA	10 PT, 21 HC	66.7 (NR)	40.0	Ischemic	<180	Cross-sectional	Temporal lobe, pons, IC, CST, pre-CG, post-CG	FMA, Wolf motor, box and blocks	ICA
18	Chen et al. (2018b): China	42 PT, 55 HC	57.9 (40–80)	50.0	Ischemic, hemorrhage	<14	Cross-sectional	CR, IC, BG thalamus	FMA	SWB
19	Hong et al. (2022): China	36 PT, 38 HC	56.7 (NR)	8.3	Ischemic	>90	Cross-sectional	Sub-cortical	FMA	ROI-based

PT, patient; HC, healthy controls; SD, standard deviation; NR, not recorded; BG, basal ganglia; CR, corona radiata; IC, internal capsule; CG, central gyrus; FMA, Fugl-Mayer Assessment; FT, Flanker Task; NBT, Number back Task; SBT, Spatial back Task; TMT, Trail Making Test; VBM, voxel-based morphometry; GLM, general linear model; SBA, seed-based analysis; ROI, region of interest; ICA, independent component analysis; DC, degree centrality; SWB, sliding-window based analysis.

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TABLE 3 Motor assessments and fMRI findings in different time points.

Author(s)	Average FMA score (range)				fMRI findings
	1–2 weeks post-stroke	1-month post-stroke	3-months post-stroke	6-months post-stroke	
Park et al. (2011): South Korea	24.2 (8–52)	30.8 (8–59)	50.5 (17–100)	53.8 (21–100)	Increased connectivity of ipsilesional M1 with cerebellum, thalamus and MFG since onset
Cheng et al. (2015): China	72.8 (50–95)	77.1 (53–95)	81.4 (57–99)	NR	Several functional connections strongly correlated with recovery time
Lee et al. (2018): South Korea	STS: 44.5 (11–83) ITS: 44.8 (12–75)	NR	STS: 66.8 (24–100) ITS: 71.7 (26–100)	NR	Network distance and interhemispheric connectivity were significantly disrupted in STS group after stroke onset
Lu et al. (2019): China	72.4 (NR)	81.0 (NR)	95.0 (NR)	NR	Altered intra-network observed in PT compared to HC
Li et al. (2020): China	64.3 (NR)	68.4 (NR)	69.2 (NR)	73.2 (NR)	PT exhibit increased FC in MPFC and MFG
Wei et al. (2020): China	LPI: 73.9 (NR) RPI: 83.2 (NR)	LPI: 85.9 (NR) RPI: 96.3 (NR)	LPI: 89.6 (NR) RPI: 98.4 (NR)	LPI: 91.2 (NR) RPI: 99.0 (NR)	Altered CBF and FC found in PT

FMA, Fugl-Mayer Assessment; fMRI, functional magnetic resonance imaging; NR, not recorded; PT, patients; STS, supratentorial stroke; ITS, infratentorial stroke; LPI, left pontine infarction; RPI, right pontine infarction; HC, healthy controls; MFG, middle frontal gyrus; FC, functional connectivity; MPFC, middle prefrontal cortex; CBF, cerebral blood flow.

TABLE 4 Motor assessments and fMRI findings in one-time point.

Author(s)	Average FMA scores (range)	fMRI findings
Li et al. (2022): China	77.03 (NR)	PT had frequency-specific alterations in FC
Chen et al. (2018): China	Right-sided PT: 76.53 (NR) Left-sided PT: 72.24 (NR)	Patterns of both static FC and dynamic FC changed after stroke
Chen et al. (2019a): China	Pontine: 89.14 (NR) BG: 91.00 (NR)	Different patterns of FC damage observed in PT
Wang et al. (2022): China	94.89 (NR)	Altered inter-network and intra-network observed in PT
Diao et al. (2020): China	Right-sided PT: 87.1 (28–100) Left-sided PT: 92.9 (19–100)	PT with left-sided lesion exhibit stronger global- and long-range FC in SMC
Wang et al. (2014): China	98.8 (94–100)	Altered inter-network and intra-network observed in PT
Liu et al. (2020): China	98.8 (94–100)	SMA subregions and preSMA showed decreased rsFC
Chen et al. (2023): China	74.9 (NR)	Altered dynamic centrality observed in PT in comparison to HC
Chen et al. (2019b): China	76.4 (NR)	Pattern of intrinsic brain activity is altered in PT compared to HC

FMA, Fugl-Mayer Assessment; fMRI, functional magnetic resonance imaging; NR, not recorded; PT, patients; BG, basal ganglia; FC, functional connectivity; SMC, sensorimotor cortex; SMA, supplementary motor area; rsFC, resting-state functional connectivity; HC, healthy controls.

Four studies indicated the persistence of moderate motor impairment in patients (25, 28, 30, 32). Lee et al. (30) found that supratentorial stroke patients had lower average recovery scores than those with infratentorial strokes, with the latter showing significant improvement within the first 2 weeks. In contrast, Park et al. (27) reported lingering severe motor impairment 3 months post-stroke, although acknowledging a substantial improvement compared to the first month.

3.2.4 6-months stroke onset

Among the seven studies longitudinal studies, only three studies followed up patients up to the 6-month mark post-stroke (27, 32, 33). Two studies, although reported improvement in FMA scores during this period remained in the same category, Park et al. (27) in severe group while Li et al. (32) in the moderate group. In studies employing one-time point assessments, four studies identified mild motor impairment in patients (36, 41–43).

Wei et al. (33) found near-normal motor recovery in right pontine stroke patients, while Diao et al. (42) reported slightly better outcomes for left-sided strokes.

3.3 Resting state-FMRI analysis

FMRI analysis used includes General Linear Model ($n = 1$), Seed-based Analysis ($n = 10$), Independent Component Analysis

TABLE 5 Correlation between FMA and brain activity.

Authors	Stroke stages	Correlation fMRI findings with clinical assessment
Chen (2018a)	Sub-acute	**Contralesional** Negative correlation between M1 and FMA
Chen (2018b)		Positive correlation between SMA and FMA
Liu (2015)	Acute to chronic	Positive correlation between SMC and FMA
Wei (2020)	Acute to chronic	Negative correlation between SMA and FMA
Li (2022)	Acute	No correlation between FC and FMA
Chen (2023)	Subacute to chronic	Positive correlation between precentral gyrus and FMA
Cheng (2015)	Acute to chronic	**Ipsilesional** Positive correlation between FC for SMN and FMA
Wu (2017)	Chronic	Negative correlation between aGMV and FMA
Lu (2019)	Acute to chronic	No correlation between SMN FC and FMA
Miyai (2001)	Chronic	
Wang (2014)	Subacute	No correlation mentions between region and FMA
Chen (2019)		
Kalinosky (2019)	Chronic	No correlation between region and FMA
Liu (2019)	Chronic	No correlation mention
Diao (2020)	Chronic	No correlation between SMN FC strength and FMA
Li (2020)	Acute to chronic	No correlation between FC strength and FMA
Wang (2022)	Chronic	
Park (2011)	Chronic	Positive correlation between SMN region and FMA
Lee (2018)	Subacute to chronic	Positive correlation between altered network and FMA

FMA, Fugl-Meyer Assessment; SMA, supplementary motor area; PMC, premotor cortex; FC, functional connectivity; SMC, supplementary motor cortex; _R, right side; _L, left side; TH, thalamus; aGMV, average gray matter volume

($n = 5$), Degree Centrality ($n = 1$), and Intra- and Inter-networks analysis ($n = 3$).

Two studies revealed asymmetrical resting-state connectivity and altered functional connectivity (26, 27). Three studies mentioned diminished functional connectivity (FC) in multiple locations and several networks, including intra-hemispheric networks (32, 40, 43) and one study reported a decreased degree of centrality in multiple supratentorial locations in basal ganglia and corona radiata stroke (34). The decreased functional connectivity locations were found in the inferior occipital gyrus, medial prefrontal cortex, and middle frontal gyrus in the left basal ganglia stroke, and ipsilesional hemisphere in supratentorial stroke (32).

On the other hand, one study showed an increased degree of centrality (34) and six studies reported increased functional connectivity in multiple networks and different locations of strokes (28, 31, 32, 37, 38, 43). Cheng et al. (28) observed an initial in FC at the acute stage followed by a gradual decrease during the subacute phase of motor recovery. This finding was supported by Miyai et al. (38) demonstrating contralateral SMC activation in early subacute patients. Moreover, Liu et al. (29) also observed increased ALFF in bilateral PMC at 12 weeks post-stroke.

Li et al. (32) observed diminished functional connectivity (FC) strength in the calcarine and inferior occipital gyrus (IOG) regions, coupled with heightened FC in the medial prefrontal cortex (MPFC), middle frontal gyrus (MFG), and insula among patients with left basal ganglia stroke. Moreover, the FC strength pronounced lateralization between the bilateral cerebral hemispheres, favoring the contralesional hemisphere in patients. This is supported by Wang et al. (43) that identified diminished intra-network FC in primary perceptual and higher cognitive control networks, including the SMN, visual network (VIS), DMN, and salience network. Reduced inter-network FC was also observed in the primary perceptual (VIS-SMN) and higher cognitive control networks (43). Moreover, there was decreased intra-network FC in three left hemispheric brain regions (left paracentral lobule, left praecuneus, and left middle cingulum (43) and within the frontoparietal network and anterior DMN compared to HC (39). Kalinosky et al. (40) also found decreased inter-network FC between the ipsilesional SMC and the contralesional cerebellum which notably correlated with task performance, specifically hand function scores in the box and blocks scores. Subsequently, Park et al. (27) also showed decreased connectivity with the SMC, occipital cortex, and MFG could persist over 6 months after stroke.

On the other hand, Lu et al. (31) reported heightened intra-network FC in two right hemispheric regions (right PreCG and right paracentral lobule) among patients compared to HC. Wang et al. (39) also found that stroke patients had increased intra-network FC in the SMN, VIS, auditory network, dorsal attention network, and DMN. This finding is supported by Cheng et al. (28) who observed an initial increase in FC at the acute stage, followed by a gradual decrease during the sub-acute phase of motor recovery, and Miyai et al. (38) who demonstrated contralateral SMC activation in early subacute patients, accompanied by frequent ipsilateral SMC activation. Two other studies also supported the findings: Hong et al. (37) identified specific FC increases between the cerebellar anterior lobe and cerebellar posterior lobe with cerebral regions in chronic stroke patients compared to HC, and Liu et al. (29) showed an increased amplitude of low-frequency fluctuations (ALFF) was observed only in bilateral M1 and only at 12 weeks post-stroke, as also reported by Chen et al. (26) about significant altered dynamic ALFF in various brain regions in patients compared to HC. Then, Park et al. (27) also showed a persisting findings for increased connectivity in the cerebellum, thalamus, and posterior parietal cortex over 6 months after stroke.

Liu et al. (41) reported distinct functional reorganization patterns within the SMA, with the SMA proper exhibiting increased resting-state FC (rs-FC) with the primary sensorimotor area and caudal cingulate motor area, while the preSMA showed increased

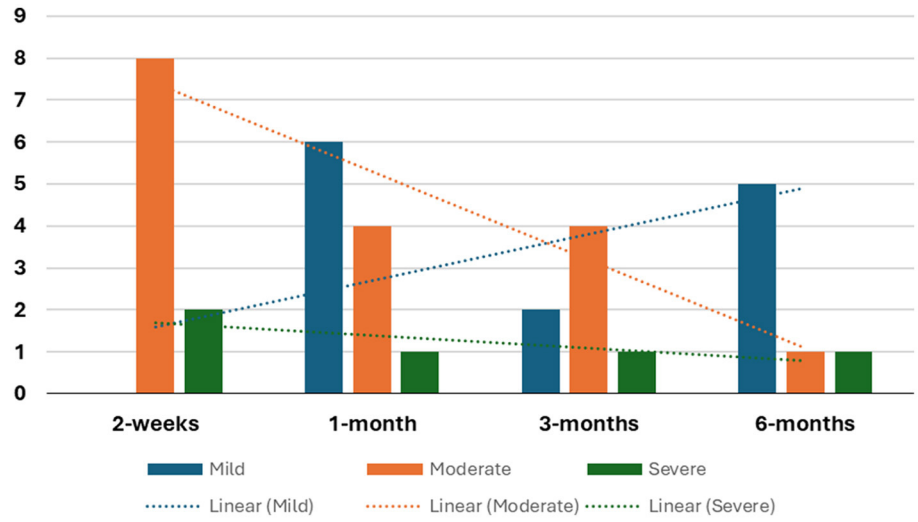

FIGURE 2
The number of studies revealing FMA scores at different time points.

rs-FC with the rostral cingulate motor area of the motor control network. Moreover, both SMA subregions displayed decreased rs-FC with the fronto-insular cortex (41). Then, Chen et al. (34) noted an increased degree of centrality in the right superior temporal gyrus and the left praecuneus, while decreases were observed in the right inferior temporal gyrus, right IOG, right PreCG, and right SMA.

3.4 Correlation analysis

Several studies performed correlation analysis between neurophysiological assessment and fMRI findings, particularly emphasizing the precentral gyrus (PreCG) and supplementary motor area (SMA) as key components of the SMN. Notably, conflicting reports exist regarding its relationship with the FMA scores: one study found a negative correlation with the contralesional PreCG (25), while another study reported a positive correlation (34). Additionally, two studies reported positive correlations between SMC-M1 connectivity with the FMA scores (27, 29). The SMA also demonstrated mixed results: one study reported a positive correlation (26), while another found a negative correlation (33). These discrepancies suggest a complex and context-dependent role for the PreCG and SMA in sensorimotor functions and recovery.

Furthermore, seven studies reported no correlation between the SMN and the FMA scores (31, 32, 35, 39, 40, 42) indicating variability across different populations or methodologies.

Moreover, additional studies have linked fMRI findings with other neurophysiological measures. For instance, Wang et al. (43) found a negative correlation between FC and attention, working memory, and overall memory scores. Lee et al. (30) identified a positive correlation between motor function and altered network measures in both supratentorial and infratentorial strokes, underscoring the importance of network dynamics in understanding motor recovery.

3.5 Lesion location analysis

3.5.1 Basal ganglia lesion

The studies by Li et al. (32), Li et al. (35), and Chen et al. (36) all investigate functional connectivity (FC) changes in patients with basal ganglia strokes, finding that the frontal cortex is particularly affected. Chen et al. (36) reported decreased FC in specific brain regions, including the left precuneus, right SMA, and right SFG. Li et al. (35) focused on frequency-specific FC changes, finding that different frequency bands (conventional, Slow-4, Slow-5) exhibited distinct patterns in FC between motor and visual regions. They consistently observed higher FC between bilateral M1 and bilateral medial SFG and lower FC with bilateral lingual gyrus across multiple frequency bands, compared to healthy controls. They also employed SVM analysis, achieving high accuracy in predicting stroke patients using combined features from the Slow-4 and Slow-5 bands. In contrast, Li et al. (32) explored longitudinal changes in FC, showing that stroke patients exhibited stronger FC in the contralesional middle prefrontal cortex (MPFC) over 6 months post-stroke, with initially stronger FC in the middle frontal gyrus (MFG) shifting to the insula at 6 months.

3.5.2 Pontine lesion

Wei et al. (33), Chen et al. (36), and Wang et al. (43) all examine FC alterations in pontine stroke patients, consistently reporting decreased FC in key brain networks, particularly in language and visual networks. Both Chen et al. (36) and Wang et al. (43) showed reduced FC in the DMN. Wang et al. (43) further identified decreased intra-network FC in the DMN, VIS, and SAN networks. as well as decreased FC between perceptual and motor networks

(VIS-SMN) and increased FC between perceptual and cognitive control networks (VIS-DMN, VIS-frontoparietal) were found.

A study by Wei et al. (33) uniquely explored differences in cerebral blood flow (CBF) and FC changes between left and right pontine stroke patients. In left pontine stroke patients, changes during the follow-up period were observed in regions associated with language and visual networks, specifically the contralesional supramarginal gyrus (SpMG) showed decreased CBF with time. These patients also demonstrated a recovery pattern where FC between the contralesional SpMG and the contralesional middle temporal gyrus (MTG), middle occipital gyrus (MOG), and inferior frontal gyrus (IFG) decreased until 3 months post-stroke before increasing. In contrast, right pontine stroke patients exhibited CBF changes in integrative brain regions, including increased CBF in the contralesional cingulate gyrus and middle occipital gyrus over time, while CBF in the ipsilesional SMA was initially high, decreased at 1 month, and then increased again.

3.5.3 Supratentorial vs. infratentorial lesion

Lee et al. (30) found that patients with supratentorial strokes showed disrupted interhemispheric balance, with increased network distance and reduced interhemispheric connectivity strength compared to healthy controls. Infratentorial stroke patients, by contrast, exhibited minimal disruption in these measures. During recovery, only the infratentorial stroke group showed improvements, with decreased network distance and increased interhemispheric connectivity.

3.5.4 Left vs. right lesion

Three studies, along with the results from Wei et al. (33) described in the pontine section, examined the effects of left- vs. right-sided lesions. Diao et al. (42) found that patients with left-sided strokes exhibited a significant increase in FC strength and long-range FC strength within the ipsilesional SMC. Additionally, left-sided stroke patients showed increased global-range FC between the ipsilesional SMC and contralesional MFG, whereas right-sided patients did not exhibit significant differences compared to healthy controls in any analysis.

A study by Chen et al. (25) found no difference between left- and right-sided stroke patients in terms of static FC increases in sensorimotor network (SMN) regions. However, when dynamic FC was analyzed, right-sided stroke patients exhibited significant increases in FC between SMN and task-positive regions, particularly the ipsilesional MOG and contralesional PreCG or MFG. Left-sided lesions, in contrast, showed increased FC between SMN and DMN regions, specifically the ipsilesional precuneus and calcarine gyrus. The increased dynamic FC was suggested to be due to rewiring in the perilesional zone.

4 Discussion

The studies reviewed report significant alterations in functional connectivity (FC) in various brain regions following a stroke, with notable lateralization differences between hemispheres (32). Post-stroke, dynamic FC changes are linked to task performance during recovery, highlighting the importance of connections both within and between the SMN and other networks. Distinct patterns emerge based on lesion location, where basal ganglia lesions affect SMN connections with frontal areas, and pontine lesions impact connections with the visual and language networks. Additionally, supratentorial strokes lead to more significant SMN disruptions than infratentorial strokes, and left-hemisphere lesions disrupt SMN connectivity more than right-hemisphere lesions.

4.1 Motor deficits related to FC changes in sensorimotor networks

Both the initial stroke lesion and subsequent changes in FC contribute significantly to motor impairments. Stroke disrupts local neural circuits and broader connectivity across brain networks, diminishing the brain's capacity to coordinate motor functions. Alterations in FC within the SMN are common post-stroke and lead to symptoms like muscle weakness, poor coordination, and abnormal muscle tone (32, 44). These changes in FC fluctuate over time and are linked to motor performance improvements, reflecting the brain's dynamic recovery processes (28, 40).

Core regions within the SMN, such as the M1, are heavily impacted by stroke, leading to motor impairments (45, 46). Additionally, reduced FC between the DLPFC and SMN has been linked to improved processing speed and decreased reliance on cognitive-motor functions in chronic stroke survivors (47). Rehabilitation targeting both motor and cognitive domains is essential for addressing the complex effects of these SMN adaptations on motor recovery (90).

4.2 Regions important for motor function recovery

The SMA and M1 (also referred to as PreCG) have been consistently reported to correlate significantly with FMA scores, emphasizing their role in motor recovery. Several studies also found that improvement in functional outcomes is often linked to increased activation and connection with M1 and SMA, providing a valuable marker for evaluating therapeutic interventions (48–50). These highlights the need of therapeutic strategies that engage these regions to promote neuroplasticity (51). For instance, physical therapy exercises targeting M1 can enhance strength and coordination (52, 53), while interventions focused on SMA aid in retraining movement sequencing and planning (54).

However, challenges persist, particularly in cases of unilateral damage where contralesional M1 activation may increase, potentially complicating recovery (25, 28). Notably, early changes in FC within contralesional motor networks can significantly influence recovery in severe cases, with interhemispheric network adjustments playing a key role in motor function restoration (55, 56).

The interplay between the SMN and other resting-state networks in the brain is complex, with alterations in one network exerting influence on other networks due to their interconnected nature (7, 57, 58). Beyond the SMN, stroke also affects connections

between the SMN and other networks, with recovery potentially linked to restoring these inter-network connections. Wang et al. (43) and Javaheripour et al. (59) reported disrupted FC both within the SMN and between other networks post-stroke, which is associated with motor deficits and broader cognitive effects. In cases where the motor network is significantly damaged, cognitive-related networks play a vital role in supporting motor recovery (58). Additionally, research found that motor rehabilitation enhances synergy among motor, default mode, and executive control networks, further promoting recovery and emphasizing the importance of network collaboration (60). Furthermore, stronger baseline FC and more efficient network reconfigurations have been correlated with improved long-term motor recovery in stroke patients (61).

4.3 Comparison of stroke location

The impact of stroke on sensorimotor integration, the process of incorporating sensory inputs to shape motor output (62–64), is contingent on the lesion's location. Evident in this review when fMRI findings are separated according to the lesion location.

This review found that basal ganglia lesions prominently affect frontal regions, aligning with reports that symptoms in patients with basal ganglia lesions are associated with disruptions in non-motor frontal subcortical circuits (65). Several studies found that basal ganglia dysfunction can interfere with motor planning and execution by disrupting normal frontal lobe functions (66), as well as contribute to imbalances between facilitatory and inhibitory processes in the frontal cortex (67). This disruption can lead to deficiencies in higher-order motor control and affect the emotional and motivational components of movement (68, 69).

Pontine stroke patients on the other hand seemed to affect the visual and language network connecitivity with DMN to some extrent. Potentially due to pontine is in pathways that connect cortical areas to the cerebellum (the pontocerebellar fibers), which is essential for integrating sensory input between the cerebellum and contralateral cortical areas; lesions here lead to reduced coordination in motor and sensory processing, impacting language functions and eye movement control (70). Alteration in the DMN indicated that pontine damage is also associated with higher cognitive processes, potentially affecting attention, language processing, and sensory integration (36). Additionally, the severity of cognitive decline due to pontine infarcts has been linked to changes in SMA activation, highlighting the phenomenon of diaschisis, where remote brain areas—particularly cortical and cerebellar regions—are affected by the injury (71).

Furthermore, alterations in intra- and inter-hemispheric sensorimotor coupling post-stroke significantly influence the planning and execution of voluntary movements (72). Notably, a study by Lee et al. (30) highlighted lower interhemispheric connectivity strength in patients with supratentorial stroke compared to those with infratentorial stroke. Recovery dynamics differed, with infratentorial stroke patients demonstrating improved interhemispheric connectivity over time, contrasting the static nature observed in supratentorial stroke cases (30). Lesions in supratentorial structure have been associated with poorer functional outcomes and persistent cognitive dysfunction (10, 73).

4.4 Recovery mechanisms after stroke

Following a stroke, there is a dynamic evolution in FC within the brain, characterized by distinct phases. In the acute stage, immediate neural impacts disrupt FC, leading to motor impairments (1). The insult triggers excitotoxicity, causing neuronal death in affected regions (74). An ensuing inflammatory reaction exacerbates damage, disrupting normal neural network functioning and causing loss of FC in other brain regions (75, 76).

During the sub-acute phase, characterized by recovery and repair, the inflammatory response diminishes, providing a more stable environment for neural tissue repair (77). Neuroplasticity becomes more noticeable as neurons in nearby regions undergo both structural and functional modifications to make up for the functions that have been lost (78). This results in the creation or fortification of connections, which is evident in the changes in FC patterns and enhancements in motor abilities, language, or cognitive functions (78).

In the initial 1–2 weeks post-stroke, patients exhibit severe to moderate motor impairment based on the FMA score (27, 28, 30–33, 35). Subsequently, during the sub-acute phase, significant improvement occurs, influenced by factors such as lesion size, location, individual variability, and the efficacy of rehabilitation interventions. A study reported restored connectivity between contralateral regions in the language network during the sub-acute stage (79). Changes in FC, particularly in the contralesional hemisphere, are proposed compensatory mechanisms for motor impairment (55, 56). Temporal variability analysis revealed increased dynamic FC, notably in the perilesional zone, indicating compensatory reorganization and integration of rs-FC (25, 80). These findings underscore the temporal dynamics of FC alterations post-stroke, emphasizing the potential for enhance neural plasticity during early rehabilitation (30, 81–83).

In stroke recovery, the early sub-acute phase occurs from 7 days to 3 months post-stroke, characterized by significant spontaneous neurological recovery and high neuroplasticity. Whereas, the late sub-acute phase spans from 3 to 6 months post-stroke, where neurological recovery stabilizes, and the rate of improvement slows. In the late sub-acute phase post-stroke, the cerebral adaptive processes persist, albeit at a potentially decelerated rate compared to the earlier sub-acute period (19). Behavioral assessment using FMA indicates continued patient improvement, though there were no significant changes in average scores between the late and early sub-acute phases (27, 28, 30–33). This stabilization in FMA scores during the late sub-acute phase may be attributed to the gradual attenuation of the initial rapid improvements observed in the preceding sub-acute period. Compensatory changes in FC, instigated during the sub-acute phase, may persists, or undergo further refinement during the late sub-acute phase. The brain relies on these modified connectivity patterns, particularly in regions proximal to the stroke-affected area (84).

In the chronic phase of stroke, the cerebral landscape undergoes substantial adaptive transformations, culminating in a more

stabilized state of recovery (85). During this period, FC achieves a state of stability, indicative of a settled pattern within the neural network organization (85). Although the tempo of neuroplasticity tends to decelerate compared to earlier phases, the brain retains a discernible degree of plasticity during the chronic phase (86). Late recovery may manifest in some individuals during the chronic phase, attributed to multifaceted factors such as sustained rehabilitation endeavors, lifestyle adjustments, or spontaneous improvements in neural functionality. A study by Park et al. (27) observed that patients in this phase exhibited moderate motor impairment, yet alterations in connectivity endured for up to 6 months post-stroke onset. Additionally, asymmetry in FC demonstrated a dynamic shift, increasing until 1 month after the stroke, followed by a subsequent decrease, implying an evolving connectivity pattern during the initial stages of recovery (27). Miyai et al. (38) contributed insights by noting that activation patterns in contralateral and ipsilateral SMC and PMC may signify variances in cortical reorganization during this chronic phase. Notably, patients with Wallerian degeneration despite achieving similar functional outcomes might necessitate more substantial cortical reorganization for motor recovery (38).

Moreover, within this phase, a considerable number of patients attain noteworthy recovery; nevertheless, some may endure enduring deficits attributed to the initial damage extent or individual variabilities in recovery capacity (64). It is also worth noting that compensatory movement patterns have the potential to impede or obstruct genuine recovery, fostering the formation of maladaptive motor programs (87, 88). Such maladaptive programs may contribute to a deficiency in limb-girdle mobility, consequently exerting a detrimental influence on the comprehensive recovery trajectory (87, 88).

4.5 Limitations and challenges

While this study provides valuable insights into the relationship between SMN alterations and motor recovery in stroke patients, several limitations must be acknowledged to provide a balanced interpretation of the findings.

A significant limitation is the geographical and ethnic bias in the literature reviewed. The majority of studies were conducted in Asian populations, raising concerns about the generalizability of the findings to other ethnic groups. Differences in genetic predisposition, stroke risk factors, rehabilitation accessibility, and cultural influences on recovery behavior may lead to variations in FC patterns and recovery trajectories. Future research should incorporate multi-center, cross-cultural studies to enhance external validity.

Secondly, stroke is inherently heterogeneous, with considerable variability in lesion size, location, and severity, which complicates direct comparisons across studies. Lesions affecting different regions—such as the motor cortex, basal ganglia, or pontine areas—may lead to distinct recovery patterns due to differences in neuroplastic potential. While our review attempts to account for these variations, a more systematic classification of lesion-specific FC alterations is necessary to refine predictive models for motor recovery. Additionally, although our review focuses on ischemic stroke, differences between ischemic and hemorrhagic stroke could still introduce inconsistencies, as underlying pathophysiological mechanisms and recovery trajectories differ. Future research should explore whether shared or distinct neuroplasticity mechanisms govern motor recovery in different stroke subtypes.

Thirdly, a major challenge in synthesizing findings across studies is methodological heterogeneity, including variations in imaging protocols, FC analysis techniques, sample sizes, and statistical approaches. Differences in MRI acquisition parameters, preprocessing pipelines, and functional connectivity metrics (e.g., seed-based vs. independent component analysis) can lead to variability in reported outcomes, making direct comparisons difficult. Furthermore, small sample sizes in some studies may limit statistical power and increase the risk of false-positive findings. There is a pressing need for larger, well-controlled longitudinal studies to track FC changes over time and differentiate between transient and long-term neuroplasticity effects. Establishing standardized reporting guidelines and harmonized imaging protocols across studies could help improve reproducibility and robustness in future research.

Fourthly, despite significant progress, several fundamental questions remain unanswered. The precise temporal dynamics of FC changes during different phases of stroke recovery are not fully understood. While some studies suggest early disruptions in SMN connectivity followed by later-stage compensation, the critical time windows for targeted interventions remain unclear. Additionally, the interaction between motor and cognitive networks in stroke recovery is an area that warrants deeper exploration, particularly in patients with co-occurring cognitive impairment or aphasia. Moreover, the potential clinical translation of FC findings remains a major challenge. While FC alterations provide valuable insights into brain plasticity, their direct applicability in guiding personalized rehabilitation protocols is still evolving. AI-driven predictive models, multimodal neuroimaging integration (e.g., DTI + rs-fMRI), and neuromodulation techniques (e.g., TMS, tDCS) should be further investigated to bridge the gap between theoretical findings and practical therapeutic applications.

Finally, our database search was restricted to PubMed and Scopus, which, while comprehensive, may have excluded relevant studies indexed in other databases such as Web of Science or Embase. However, to mitigate this limitation, we cross-referenced Google Scholar to identify any additional relevant studies that were not captured in our primary search.

5 Conclusion

The findings from the selected literature underscore the complex interplay between sensorimotor network (SMN) alterations and motor deficits in stroke patients, highlighting the critical role of the stroke location in shaping sensorimotor integration and recovery trajectories. The evidence suggests that functional connectivity (FC) undergoes dynamic reorganization post-stroke, with compensatory mechanisms facilitating adaptive neuroplasticity. However, the extent and effectiveness of these compensatory changes appear to be influenced by multiple factors, including lesion site, stroke severity, and pre-existing

neural reserve. These findings have significant implications for rehabilitation strategies, as a deeper understanding of SMN reorganization could enable the development of personalized, targeted interventions that optimize motor recovery. Despite these insights, challenges remain in translating these findings into clinically viable therapeutic approaches. Current limitations include the heterogeneity of patient responses, the variability in neuroimaging methodologies, and the need for longitudinal studies to track the evolution of FC changes over time.

Future research should focus on integrating multimodal imaging techniques, such as diffusion tensor imaging (DTI), task-based fMRI, and electrophysiological assessments, to provide a more comprehensive understanding of SMN plasticity and its interaction with cognitive recovery mechanisms. Additionally, the potential of AI-driven predictive models and brain-computer interface (BCI)-based rehabilitation strategies should be explored to enhance recovery outcomes. Further studies should also investigate the role of non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), in modulating SMN connectivity and promoting neuroplasticity. By advancing our knowledge of the neurobiological underpinnings of post-stroke recovery, future research can bridge the gap between neuroscientific discoveries and clinical application, ultimately improving functional outcomes and quality of life for stroke survivors.

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

NS: Conceptualization, Data curation, Writing – original draft. NY: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization. ZL: Supervision, Writing – review & editing, Validation. WW: Writing – review & editing, Conceptualization, Resources, Supervision. UN: Visualization, Writing – review & editing. NA: Resources, Visualization, Writing – review & editing. AA: Resources, Visualization, Writing – review & editing. HA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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.2025.1456146/full#supplementary-material

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Anticoagulant versus antiplatelet treatment for secondary stroke prevention in patients with active cancer

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Background: Approximately 5–10% of patients with acute ischemic stroke (AIS) have known active cancer. These patients are at high risk for both recurrent AIS and major bleeding. The optimal antithrombotic strategy for cancer-related stroke is uncertain. This study compared clinical outcomes among patients with cancer-related stroke treated with anticoagulant versus antiplatelet therapy for secondary prevention.

Methods: We identified consecutive patients with AIS and active cancer hospitalized at our comprehensive stroke center from 2015 through 2020. Patients with cardioembolic mechanisms were excluded. We used Cox regression and inverse probability of treatment weighting (IPTW) analyses to evaluate the associations between type of antithrombotic therapy at discharge (anticoagulant versus antiplatelet therapy) and the main outcomes of 1-year mortality and long-term recurrent AIS.

Results: Among 5,012 AIS patients, 306 had active cancer. After applying study eligibility criteria, we analyzed 135 patients (median age 72 years; 44% women), of whom 58 (43%) were treated with anticoagulant and 77 (57%) with antiplatelet therapy. The median follow-up time was 495 days (IQR, 57–1,029). Patients treated with anticoagulants, compared to patients treated with antiplatelet therapy, were younger (median 69 versus 75 years), had more metastatic disease (72% versus 41%), and higher median baseline D-dimer levels (median 8,536 μg/L versus 1,010 μg/L). Anticoagulant versus antiplatelet therapy was associated with similar risks of 1-year mortality (adjusted hazard ratio [aHR], 0.76; 95% confidence interval [CI], 0.36–1.63) and long-term recurrent AIS (aHR 0.49; 95% CI 0.08–2.83). The IPTW analyses for 1-year mortality confirmed the results of the main analyses (HR 0.82; 95%CI: 0.39–1.72, $p = 0.61$).

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Conclusion: Factors associated with anticoagulant use in patients with cancer-related stroke include younger age, more advanced cancer, and elevated D-dimer. Similar outcomes were seen with anticoagulant versus antiplatelet therapy in these patients highlighting the need for future randomized trials to determine the preferred antithrombotic strategy.

KEYWORDS

acute ischemic stroke, secondary prevention, antithrombotic drugs, cancer, embolic stroke of unknown source (ESUS)

Introduction

Acute ischemic stroke (AIS) and cancer are major causes of morbidity and mortality. Worldwide, approximately 40% of people are expected to develop cancer in their lifetime, while approximately 25% will suffer an AIS (1). Active cancer is a comorbid condition in 5–10% of patients with AIS, and this stroke subgroup is often referred to as "cancer-related stroke" (2).

Paraneoplastic coagulopathy is often implicated in cancer-related stroke (3). This prothrombotic process is multifactorial and involves platelet, coagulation, and endothelium activation; circulating cancer- and platelet-derived extracellular vesicles; and increased neutrophil extracellular trap formation (4). Patients with cancer-related stroke face an increased risk of more severe strokes, AIS recurrence, and mortality compared to other AIS patients (5).

There are no clear guideline-based recommendations for the preferred antithrombotic strategy in cancer-related stroke. According to the American Heart Association guidelines, further research should be conducted to evaluate the benefit of anticoagulation in persons with stroke attributed to cancer-related hypercoagulability as robust data is lacking (6). In clinical practice, anticoagulants are sometimes empirically administered to patients with cancer-related stroke to treat presumed paraneoplastic coagulopathy (7). However, there are few data to support these practices apart from small biomarker-focused studies without comparator antiplatelet arms (8). Secondary analyses of the NAVIGATE ESUS and ARCADIA randomized controlled trials have demonstrated neutral results in recurrent stroke risk between the anticoagulant and antiplatelet treatment groups (9, 10). However, because both studies included patients with both active and inactive cancer, with the exact proportions of each uncertain, these data should be interpreted with caution.

Given the lack of dedicated, adequately powered clinical trials assessing the most appropriate secondary prevention strategy for cancer-related stroke, more retrospective data are needed. Therefore, we investigated the short- and long-term outcomes of patients with active cancer and AIS stratified by the employed antithrombotic treatment strategy (anticoagulant versus antiplatelet therapy) at discharge in a large institutional registry.

Methods

Design

We conducted a retrospective cohort study of consecutive patients treated for AIS at a comprehensive stroke center in Bern, Switzerland between January 1, 2015 and December 31, 2020. These patients were prospectively enrolled in the Swiss Stroke Registry, which was accessed for data analysis.

The study was approved by the local ethics committee in accordance with Swiss regulations (project ID: 2022-01560; Kantonale Ethikkommission Bern), and the requirements for written consent was waived. Access to the study data can be requested from the corresponding author and is subject to clearance by the local ethics committee. This analysis adhered to the STROBE checklist guidelines for cohort studies.

Population

The study population consisted of patients with AIS and known active cancer at the time of AIS or new cancer diagnosed during the hospitalization for the index AIS. Active cancer was defined according to the criteria recommended by the International Society on Thrombosis and Haemostasis (11). This comprised a new or recurrent cancer that was diagnosed or treated within six months prior to the index AIS, or known metastatic cancer. Hematological malignancies that were not in complete remission for more than 5 years were also considered active. Patients diagnosed with a new cancer during the index hospitalization were considered to have occult cancer at the time of AIS, and were included in the known active cancer group for analyses (12, 13). We excluded patients who were diagnosed with cancer after hospital discharge for the index AIS, as this sequence of events may have influenced antithrombotic management decisions and clinical outcomes.

We excluded patients with focal non-melanoma skin cancer because of their low risk of dissemination as well as patients with breast cancer in complete remission who were receiving maintenance hormonal therapy (11, 14, 15). Other exclusion criteria were (i) death during the index hospitalization or missing follow-up data regarding vital status, (ii) no antithrombotic therapy prescription at discharge, and (iii) a cardioembolic stroke mechanism at discharge necessitating anticoagulation (e.g., atrial fibrillation, mechanical valve). Patients with a determined stroke mechanism typically treated with antiplatelet therapy, such as large artery atherosclerosis, were not excluded because these patients may still have cancer-mediated hypercoagulability and could preferentially benefit from anticoagulant therapy.

Measurements

Demographic and clinical characteristic data were collected from the Swiss Stroke Registry and electronic health records. These included

age at admission, sex, pre-stroke functional status (independency defined as a pre-stroke modified Rankin Scale [mRS] score ≤2), baseline imaging modality, and history of cardiovascular risk factors (prior stroke, hypertension, diabetes mellitus, hyperlipidemia, smoking history, and atrial fibrillation). The presence of multi-territory brain infarcts (involving at least two different cerebrovascular territories) was determined using data from baseline neuroradiological imaging. Data on the primary cancer type, stage (16), and presence of metastasis at the time of AIS was collected from electronic health records. Laboratory measurements included D-dimer, C-reactive protein (CRP), hemoglobin, platelet count, fibrinogen, and lactate dehydrogenase (LDH). For patients with multiple measurements during the index AIS hospitalization, the baseline value was recorded. Two neurologists determined the AIS mechanism at discharge, classified according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria and the embolic stroke of undetermined source (ESUS) classification (17, 18). Recent data have indicated that among patients with AIS, there is an inverse association between the presence of a right-to-left shunt (patent foramen ovale [PFO] or atrial septal defect [ASD]) and the presence of cancer, suggesting that paradoxical embolism is not a major cause of AIS in patients with cancer (19). Therefore, we classified patients with PFO/ASD and no other apparent cause of AIS as "undetermined stroke etiology" and, if meeting criteria, as ESUS. The diagnosis of venous thromboembolism (VTE), including deep vein thrombosis and/or pulmonary embolism, in the year before and after the index AIS was recorded.

The study exposure was the type of antithrombotic therapy (anticoagulant or antiplatelet therapy) prescribed at hospital discharge from the index AIS. The anticoagulant group consisted of patients treated with therapeutic doses of any oral or parenteral anticoagulant. These included vitamin K antagonists, low-molecular-weight heparins (LMWH) such as enoxaparin or tinzaparin, and direct oral anticoagulants (DOACs) such as edoxaban, rivaroxaban, dabigatran, or apixaban. Patients treated with recommended dosing regimens adjusted for age, weight, or renal function were classified as receiving therapeutic anticoagulation. The antiplatelet group included standard-dose aspirin, clopidogrel, or both. Patients treated with both therapeutic-dose anticoagulant and antiplatelet therapy were included in the anticoagulant group. The treatment decision was left to the treating physician. According to our internal stroke guidelines, if D-dimer levels at baseline exceed 3,000 µg/L and cancer is present, paraneoplastic coagulopathy should be considered as AIS etiology. When a paraneoplastic coagulopathy is suspected, anticoagulation with LMWH at therapeutic dosage (twice daily) or oral anticoagulants should be considered. As tolerance to LMWH is known to be low in cancer-related strokes (in opposition to patients with VTE), we reported continuation of LMWH prescribed at discharge versus regimen change for secondary prevention at the 3-month clinical follow-up (20, 21).

The primary study outcome was mortality at 1 year after the index AIS. To determine patients' vital status, we analyzed data from the Swiss Population Registry, which records the vital status of Swiss residents on a monthly basis. Secondary outcomes were (i) a good functional outcome at 90 days, defined as a mRS score of ≤2, (ii) all-cause long-term mortality, (iii) recurrent AIS at 90 days and during the entire follow-up period (iv) symptomatic intracranial hemorrhage (sICH) at 90 days and during the entire follow-up period, and (v) major bleeding besides intracranial hemorrhage or clinically relevant non-major bleeding during the entire follow-up period. The criteria used to define the composite bleeding outcome is provided in the Supplemental methods. For long-term mortality, follow-up time was defined as the time from the index AIS to the date of death for deceased patients or to the last update of the Swiss Population Registry for surviving patients. For incident cerebrovascular events (recurrent AIS or sICH), follow-up time was defined as the time from index AIS to the date of event or to the last documented follow-up in the electronic health record if no event was reported. For 90 days follow-up, only patients with available clinical or telephone follow-up were assessed. The mRS score and incident cerebrovascular events at 90 days were determined through telephone survey or clinical visit by investigators certified in mRS assessment. Symptomatic ICH was determined based on the ECASS III definition (22).

Analysis

Baseline characteristics were reported as median and interquartile range (IQR) for continuous variables and frequency (percentage) for categorical variables. Differences between groups were assessed using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Kaplan–Meier curves were used to estimate the cumulative rates of time-to-event endpoints. The log-rank test and multivariable Cox regression were used to compare the outcomes between antithrombotic treatment groups. All multivariable models were adjusted for patient age, sex, initial D-dimer level, documented metastases at the time of the index AIS, and the presence of multi-territory brain infarcts. These covariates were selected because they either significantly differed between study groups or they were previously associated with adverse clinical outcomes in patients with cancer-related stroke (5). Adjusted hazard ratios (aHRs) were reported with their associated 95% confidence interval (CI). To investigate the association between treatment groups and recurrent cerebrovascular events (AIS or sICH), additional analyses using mortality as a competing risk were performed (see Supplementary methods). Patients who received intravenous thrombolysis before D-dimer assessment were excluded from the multivariable analyses because intravenous thrombolysis can influence levels of coagulation parameters such as D-dimer and fibrinogen (23).

Subgroup analyses were performed in (1) patients whose index AIS mechanism was cryptogenic and who met ESUS criteria. (2) patients with ESUS and an elevated D-dimer level (defined as a value above the median for the cohort), and (3) patients with ESUS and multiterritory infarcts.

In sensitivity analyses, we excluded (1) patients with combined antiplatelet and anticoagulant therapy and (2) patients with a history of VTE treated with anticoagulant therapy at discharge for the index AIS. Because antithrombotic prescription patterns likely varied according to physicians' perceptions of how prothrombotic and high-risk individual patients were, we performed a second set of analyses calculating propensity scores and using the Inverse Probability of Treatment Weighting (IPTW) method with stabilized weights to minimize potential confounding (24). For IPTW, we reported hazard ratios (HRs) with their associated 95% CI.

Continuous variables with skewed distributions were logarithmically transformed. Missing data were not imputed. Statistical significance was defined as a p-value of <0.05. All analyses

were performed using Stata 16 (StataCorp LLC) and R (version 3.6.0, R Core Team).

Results

Patient characteristics

Of 5,012 patients with AIS assessed for eligibility, 306 had active cancer at the time of the index hospitalization (Figure 1 – study flowchart). Among these patients, we excluded 35 who died during the hospitalization, 30 whose cancer was diagnosed after hospital discharge, 33 without available follow-up, 63 with a cardioembolic indication for anticoagulation, and 10 who were not prescribed an antithrombotic medication at discharge. The baseline characteristics of included and excluded AIS patients with active cancer are shown in Supplementary Table 1. The final study population comprised 135 patients, including 58 (43%) in the anticoagulant group and 77 (57%) in the antiplatelet group.

Per TOAST criteria, an undetermined cause (i.e., cryptogenic) was the leading mechanism in both treatment groups: 82% of patients in the anticoagulant group ($n = 48/58$) and 69% in the antiplatelet group ($n = 53/77$). In these cryptogenic cases, ESUS criteria were met in 100% of the anticoagulant group ($n = 48/48$) and 72% of the antiplatelet group ($n = 38/53$). Large-artery atherosclerosis was identified in 9% of patients treated with anticoagulation ($n = 5/58$) and 25% of those treated with antiplatelet therapy ($n = 19/77$). Other determined causes were present in 9% of the anticoagulant group ($n = 5/58$) and 2% of the antiplatelet group ($n = 2/77$). Small-vessel disease was only observed in the antiplatelet group (4%, $n = 3/77$).

Of the 58 patients treated with anticoagulation, 41 (71%) received LMWH, 4 (7%) received vitamin K antagonists, 8 (14%) received DOACs (edoxaban, rivaroxaban, or apixaban), and 5 received (9%) a combination of antiplatelet plus anticoagulant therapy. Among the 41 patients discharged with LMWH, 21 (51%) had died at 3-months, 14 (34%) were lost to follow-up, 4 (10%) were switched to DOAC, and 2 were still receiving LMWH (5%). Median follow-up time for long-term mortality was 495 days (IQR 57–1,029) for the overall cohort, 133 days (IQR 43–506) for the anticoagulant group, and 797 days (IQR 218–1,483) for the antiplatelet group.

Patients treated with anticoagulant therapy, compared to patients treated with antiplatelet therapy, were younger (69 years [IQR 62–75] versus 75 years [IQR 65–82], $p = 0.01$), had more multi-territory brain infarcts (47% versus 17%, $p < 0.001$), and more often had an ESUS mechanism (82% versus 50%, $p < 0.001$; Table 1). Data on the primary cancer site in the overall study population and stratified by the individual treatment groups are provided in Figure 2. The distribution of primary cancer sites differed between groups with higher rates of lung and pancreatic cancers in the anticoagulant group ($p < 0.001$). Additionally, patients in the anticoagulant group had a higher median cancer stage (4 [IQR 3–4] versus 3 [IQR 2–4], $p < 0.001$) and more frequent metastases at the time of AIS (72% versus 41%, $p < 0.001$). There were 23 patients with documented VTEs, of whom 22 were prescribed anticoagulant therapy at hospital discharge.

Four patients in the antiplatelet group received intravenous thrombolysis before D-dimer sampling and were excluded from analyses including laboratory parameters. Compared to patients in the antiplatelet group, patients in the anticoagulant group had higher D-dimer levels in µg/L (median [IQR]: 8536 [2080–13,726] versus 1,010 [495–2,090], $p < 0.001$), higher CRP levels in mg/L (median [IQR]:18 [5–50] versus 4 [2–24], $p = 0.01$) and lower hemoglobin levels in g/dL (median [IQR]:11.8 [10.8–13.4] versus 13.0 [10.5–14.2], $p = 0.03$).

Primary outcome

As depicted in Figure 3, the estimated cumulative 1-year mortality rate was higher in the anticoagulant group (66, 95% CI 53–77%) than

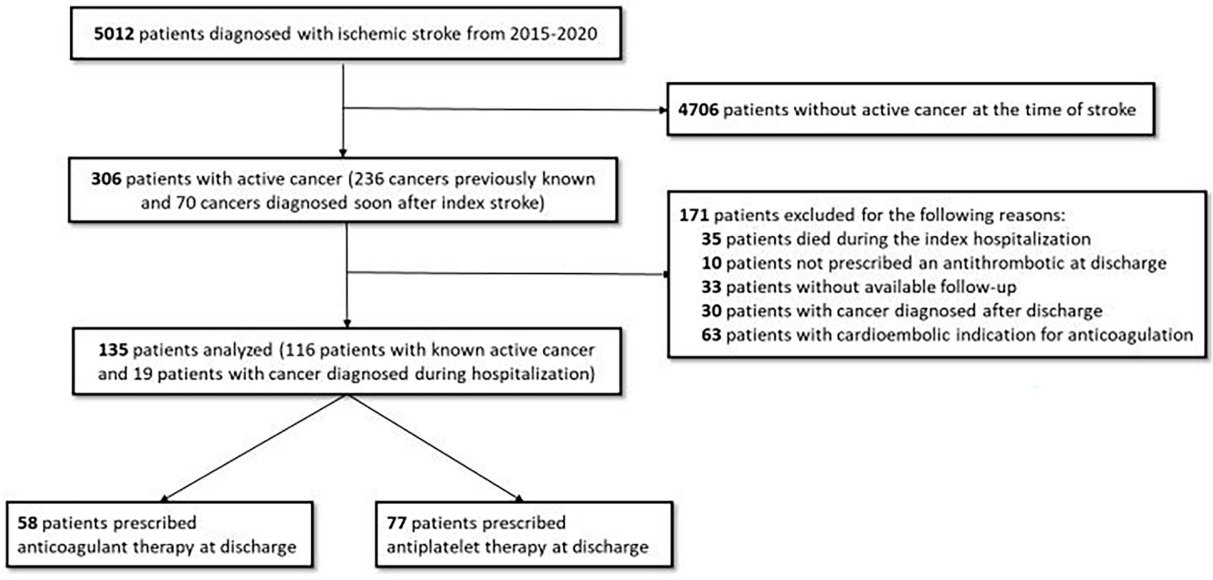

FIGURE 1
Study flowchart with inclusion and exclusion of patients.

TABLE 1 Baseline characteristic data in included patients with active cancer and ischemic stroke stratified by antiplatelet versus anticoagulant therapy.

	All patients (*N* = 135)	Antiplatelet therapy (*N* = 77)	Anticoagulant therapy (*N* = 58)	*p*-value
Demographics				
Sex, female	60/135 (44)	31/77 (40)	29/58 (50)	0.30
Age at admission, median	72 (64–80)	75 (65–82)	69 (62–75)	0.01
Medical history				
Previous ischemic stroke	20/96 (21)	8/53 (15)	12/43 (28)	0.14
Hypertension	65/96 (68)	38/53 (72)	27/43 (63)	0.39
Diabetes Mellitus	21/95 (22)	10/52 (19)	11/43 (26)	0.47
Hyperlipidemia	66/95 (70)	38/52 (73)	28/43 (65)	0.50
Smoking history	28/90 (31)	15/49 (31)	13/41 (32)	1.00
Venous thromboembolic events				
Any venous thromboembolism	23/135 (17)	1/77 (1)	22/58 (38)	<0.001
Deep venous thrombosis	14/135 (10)	1/77 (1)	13/58 (22)	<0.001
Pulmonary embolism	16/135 (12)	0/77 (0.0)	16/58 (28)	<0.001
Stroke characteristics				
Independence before stroke (mRS ≤ 2)	54/135 (44)	30/33 (91)	24/27 (89)	1.00
Initial NIHSS, median	5 (2–9)	4 (2–8)	6 (3–10)	0.31
MRI during admission	59/80 (73)	36/48 (75)	23/32 (72)	0.80
Multi-territory infarct	40/135 (30)	13/77 (17)	27/58 (47)	<0.001
Stroke etiology according to TOAST				
Large-artery atherosclerosis	24/135 (18)	19/77 (25)	5/58 (9)	0.011
Cardioembolic	0/135 (0)	0/77 (0)	0/58 (0)	
Small-vessel disease	3/135 (2)	3/77 (4)	0/58 (0)	
Other determined cause	7/135 (5)	2/77 (2)	5/58 (9)	
Undetermined cause	101/135 (75)	53/77 (69)	48/58 (82)	
ESUS	86/135 (64)	38/77 (50)	48/58 (82)	<0.001
Cancer characteristics at time of AIS				
Cancer stage, median	4 (2–4)	3 (2–4)	4 (3–4)	<0.001
Distant metastases	65/135 (48)	27/77 (41)	38/58 (72)	<0.001
Baseline laboratory findings, median				
D-dimer in µg/L	2037 (684–9,118)	1,010 (495–2090)	8,536 (2080–13,726)	<0.001
Elevated D-Dimer (≥2037 µg/L)	48/74 (65)	12/32 (38)	36/42 (86)	<0.001
CRP in mg/L	3 (1–8)	4 (2–24)	18 (5–50)	0.005
Fibrinogen in g/L	3.1 (2.6–3.7)	3.3 (2.6–3.9)	2.7 (2.0–3.5)	0.003
LDH in U/l	396 (339–480)	387 (344–499)	650 (446–833)	<0.001
Platelet count in G/L	225 (186–271)	229 (191–267)	181 (144–250)	0.01
Hemoglobin in g/dL	13.8 (12.6–14.9)	13 (10.5–14.2)	11.8 (10.8–13.4)	0.25

Categorical variables are listed as number/total number (percentage) and continuous or ordinal variables are listed as median (interquartile range). CRP, C-reactive protein; ESUS indicates embolic stroke of undetermined source; LDH, Lactate dehydrogenase; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; VTE, venous thromboembolism.

in the antiplatelet group (33, 95% CI 23–44%) (log-rank test $p < 0.001$). In multivariable Cox regression analysis, anticoagulant use was associated with a similar 1-year mortality rate as antiplatelet use (aHR 0.76; 95% CI 0.36–1.63; $p = 0.47$) (Figure 4). Factors independently associated with 1-year mortality after AIS were initial D-dimer levels (aHR 4.59; 95% CI 2.24–9.38; $p < 0.001$) and multi-territory brain infarction (aHR 2.13; 95% CI 1.19–3.82; $p = 0.01$). After excluding five patients who received combined antiplatelet and anticoagulant therapy, no difference remained between groups for 1-year mortality (aHR 0.81; 95% CI 0.38–1.74; $p = 0.59$) (Supplementary Figure 1).

Secondary outcomes

As shown in Table 2, patients in the anticoagulant group had a lower rate of good functional outcomes (mRS ≤ 2) at 90 days

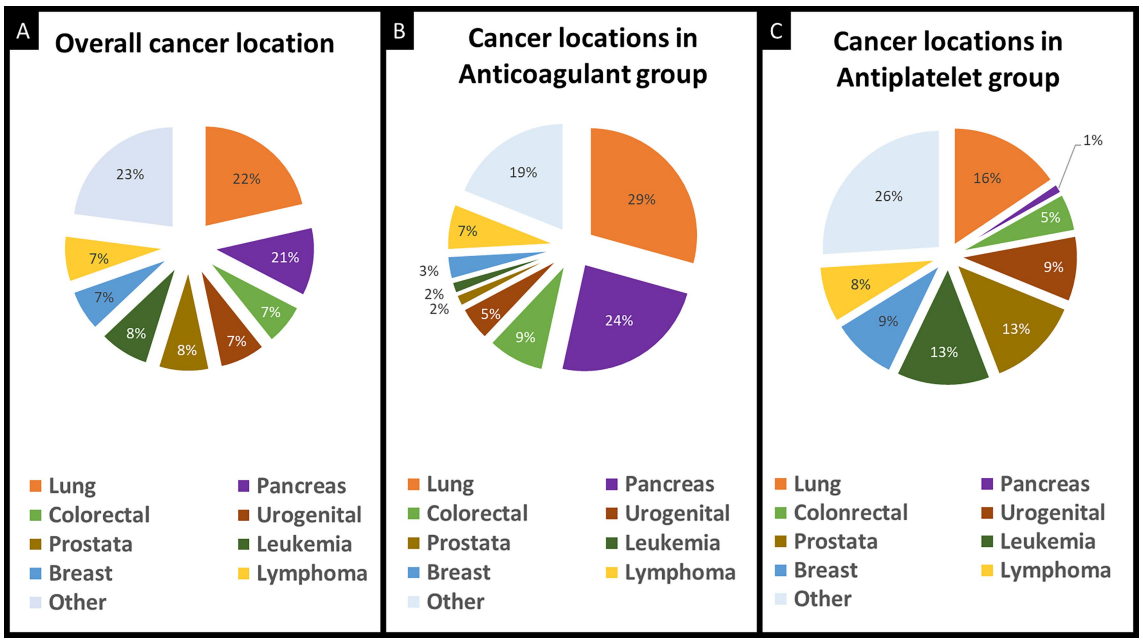

FIGURE 2
Distribution of primary cancer location in included patients. Primary cancer location in the overall study population **(A)**, in the anticoagulant group **(B)**, and in the antiplatelet group **(C)**.

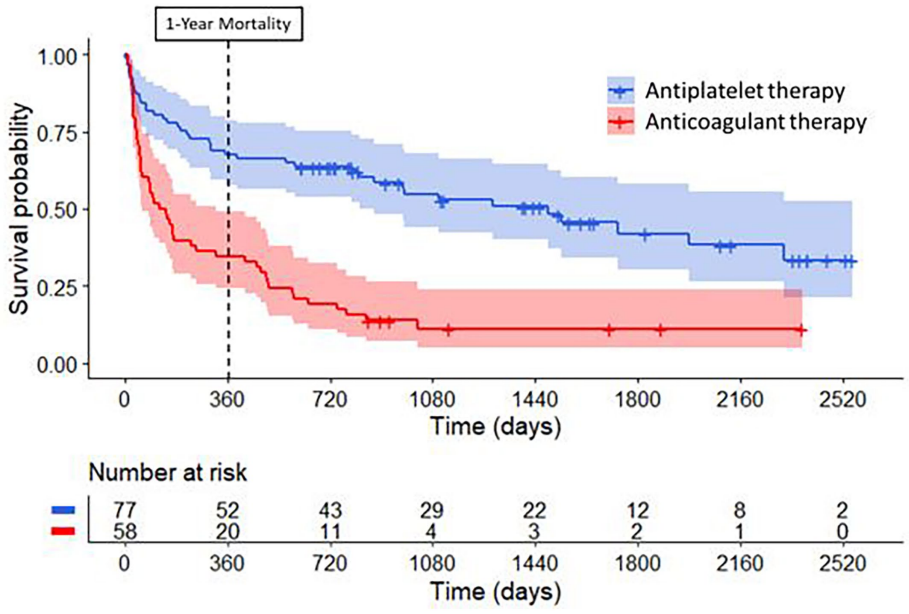

FIGURE 3
Long-term survival curves for patients with cancer treated with antiplatelet therapy or anticoagulant therapy for secondary stroke prevention. Compared to patients treated with antiplatelet therapy (in blue), patients treated with anticoagulant therapy (in red) had higher mortality rates at one year (log-rank test, $p < 0.001$) and during long-term follow-up (log-rank test, $p < 0.001$) after their index ischemic stroke.

compared to those in the antiplatelet group (29% versus 66%, $p = 0.003$). After adjustment for potential confounders, there was no difference in 90-day good functional outcomes between study groups (aHR 1.36; 95% CI 0.58–3.19, $p = 0.49$, Supplementary Figure 2).

At 90-days, 0% of patients in the anticoagulant group ($n = 0/23$) were diagnosed with recurrent AIS compared to 7% in the antiplatelet group ($n = 3/43$, $p = 0.55$). There were no sICHs in either group during the first 90 days of follow-up.

Patients treated with anticoagulant therapy had higher long-term mortality compared to patients treated with antiplatelet therapy (88, 95% CI 77–94% versus 52, 95% CI 41–63%, log-rank test $p < 0.001$). However, after adjustment for potential confounders, there was no

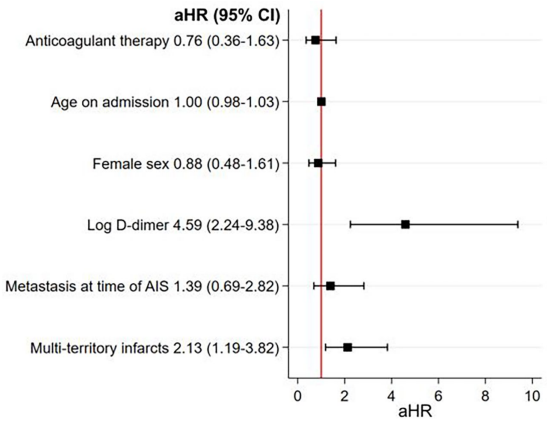

FIGURE 4
Multivariable model studying the association between antithrombotic treatment strategies at hospital discharge for AIS and 1-year mortality. There was no association between anticoagulant therapy, as compared to antiplatelet therapy, and 1-year mortality in the main analysis. Higher D-dimer levels and multi-territory brain infarcts were both strongly associated with 1-year mortality in these patients. D-dimer was abnormally distributed so it was log transformed. aHR, adjusted hazard ratio; AIS, acute ischemic stroke.

difference in long-term mortality between the groups (aHR 1.29; 95% CI 0.67–2.47; $p = 0.44$) (Supplementary Figure 3).

The median total follow-up time for cerebrovascular events was 165 days (IQR 80–707) for the overall cohort, 107 days (IQR 40–232) for the anticoagulant group, and 178 days (IQR 99–940) for the antiplatelet group. After one year and also during the entire follow-up period, 9% ($n = 5/58$) of patients treated with anticoagulant therapy had a recurrent AIS compared to 8% ($n = 6/77$) of patients treated with antiplatelet therapy (aHR 0.49; 95% CI 0.08–2.83; $p = 0.83$, Supplementary Figure 4). There were no cases of sICH in either group during long-term follow-up. Major bleeding besides intracranial hemorrhage or clinically relevant non-major bleeding were reported in three patients (2% of the entire cohort), all occuring within one year after AIS, with no differences between treatment groups. When accounting for mortality as a competing risk, the recurrence of AIS did not differ between patients receiving anticoagulants and those receiving antiplatelet therapy (Supplementary results I).

Subgroup analyses

Of the 135 index AIS, 86 (64%) were classified as ESUS. In the ESUS subgroup (Supplementary Table 2), patients treated with anticoagulant therapy were on average younger and more often had metastatic disease compared to those treated with antiplatelet therapy. After multivariable adjustment, anticoagulant therapy, compared to antiplatelet therapy, was associated with similar mortality at one year after AIS (aHR 0.51; 95% CI 0.21–1.22; $p = 0.11$, Supplementary Figure 5). In patients with ESUS and D-dimer levels above the median (2,037 µg/L) for the cohort ($n = 35$), there was no difference in 1-year mortality rates between antithrombotic treatment groups after multivariable adjustment (aHR 0.26; 95% CI 0.05–1.27; $p = 0.10$, Supplementary Figure 10). Results were similar in patients with ESUS and multiterritory infarcts ($n = 29$) (aHR 1.17; 95% CI 0.32–4.19; $p = 0.81$, Supplementary Figure 11).

Sensitivity analyses

After exclusion from the initial study population of 22 patients with documented VTE treated with anticoagulant therapy at the time of index AIS hospital discharge, the risk of 1-year mortality remained similar between patients treated with anticoagulant therapy and those treated with antiplatelet therapy (aHR 0.65; 95% CI 0.28–1.47; $p = 0.30$, Supplementary Figure 6). Of the remaining 36 patients discharged on anticoagulant therapy, 24 (67%) were treated with LMWH, 3 (8%) with vitamin K antagonists, 7 (19%) with DOACs, and 2 (6%) with combination therapy. After excluding the same 22 patients with documented VTE treated with anticoagulant therapy at index AIS hospital discharge from the ESUS cohort, 1-year mortality remained similar between antithrombotic treatment groups (aHR 0.38; 95% CI 0.14–1.05; $p = 0.06$, Supplementary Figure 7).

Inverse probabilty of treatment weighting analyses

In the second round of analyses employing IPTW, the stabilized weights exhibited a near-normal distribution centered around one, albeit with a few weights surpassing two, which could have a significant impact on study outcomes (Supplementary Figure 8).

The IPTW analysis for 1-year mortality (Figure 5) corroborated the main analyses for the primary AIS cohort (HR 0.82; 95% CI 0.39–1.72, $p = 0.61$) and the ESUS subgroup (HR 0.51; 95% CI 0.20–1.29; $p = 0.15$). These results were unchanged after excluding patients with documented VTE from the primary cohort (HR 0.73; 95% CI 0.32–1.66; $p = 0.46$) and the ESUS subgroup (HR 0.46; 95% CI 0.16–1.34; $p = 0.30$).

Discussion

Among 135 patients with active cancer and non-cardioembolic AIS at a comprehensive stroke center in Switzerland, short- and long-term clinical outcomes did not differ between patients treated with anticoagulant therapy at discharge and those treated with antiplatelet therapy. Study groups differed substantially, as treatment with anticoagulation was associated with more advanced and historically aggressive cancer types with predilections for hypercoagulability. These neutral findings persisted when analyses were limited to patients with ESUS and when excluding patients with VTE.

In the absence of specific guidelines and robust prospective data on secondary prevention in patients with AIS and active cancer, neurologists often rely on theoretical considerations and institutional practice patterns to guide treatment decisions (6). As prothrombotic processes play a central role in many cancer-related strokes, some neurologists favor empiric anticoagulant therapy in these patients (25). Some experts have argued that anticoagulant therapy may preferentially benefit cancer patients whose AIS is due to cerebral intravascular coagulation, non-bacterial thrombotic endocarditis, or paradoxical embolism (26). In patients with cancer-mediated hypercoagulability, it is purported that

TABLE 2 Clinical outcomes in included patients with active cancer and AIS stratified by antiplatelet versus anticoagulant therapy.

	All patients (*N* = 135)	Antiplatelet therapy (*N* = 77)	Anticoagulant therapy (*N* = 58)	*p*-value
90-day follow-up				
Good functional outcomes (mRS ≤ 2)	39/78 (50)	29/44 (66)	10/34 (29)	0.003
Mortality rate	19/78 (24)	5/44 (11)	14/34 (41)	0.003
Recurrent AIS	3/66 (5)	3/43 (7)	0/23 (0)	0.55
Occurrence of sICH	0/66 (0)	0/43 (0)	0/23 (0)	NA
Major clinical bleeding besides ICH	0/135 (0)	0/43 (0)	0/23 (0)	NA
Clinically relevant non-major bleeding	1/135 (0.7)	1/43 (2.33)	0/23 (0)	1.00
Long-term follow-up				
Follow-up time for long-term mortality in days, median	495 (57–1,029)	797 (218–1,483)	133 (43–506)	<0.001
Mortality rate at one year	63/135 (47)	25/77 (33)	38/58 (66)	<0.001
Mortality rate in the long-term	121/135 (90)	40/77 (52)	51/58 (88)	<0.001
Follow-up time for cerebrovascular events in days, median	165 (80–707)	178 (99–940)	107 (40–232)	0.002
Recurrent AIS	11/135 (8)	6/77 (8)	5/58 (9)	1.00
Occurrence of sICH	0/135 (0)	0/77 (0)	0/58 (0)	NA
Major clinical bleeding besides ICH	1/135 (0.7)	0/77 (0)	1/58 (1.7)	0.43
Clinically relevant non-major bleeding	2/135 (1.5)	1/77 (1.3)	1/58 (1.7)	1.00

Categorical variables are listed as number/total number (percentage) and continuous or ordinal variables are listed as median (interquartile range). AIS, acute ischemic stroke; mRS modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage.

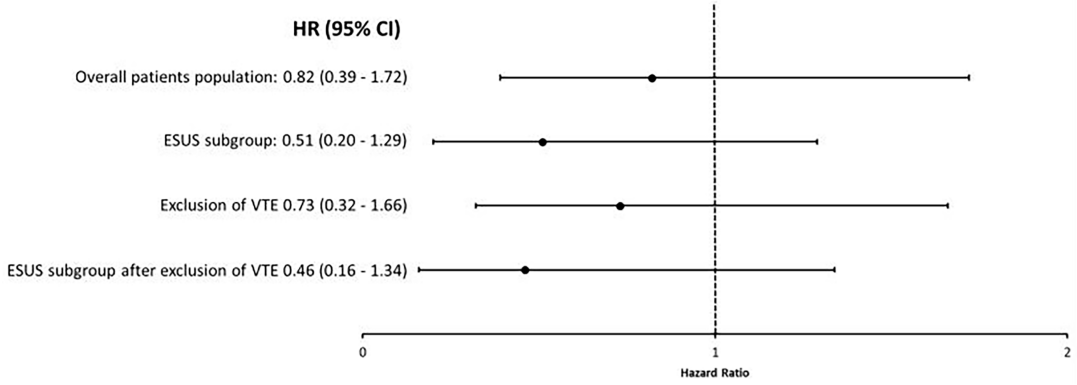

FIGURE 5
Univariable analyses studying the association between anticoagulant versus antiplatelet therapy at hospital discharge for AIS and 1-year mortality using IPTW with stabilized weights in the different study groups. There was no association between anticoagulant therapy, as compared to antiplatelet therapy, and 1-year mortality in weighted analysis using IPTW. This was the case in the overall study population as well as in patient subgroups. CI, confidence interval; ESUS, embolic stroke of undetermined source; HR, Hazard ratio; IPTW, inverse probability of treatment weighting and VTE, venous thromboembolism.

high thrombin levels promote the conversion of fibrinogen to fibrin and platelet activation, and this may be more effectively targeted by anticoagulant therapy than by antiplatelet therapy (26). D-dimer, a degradation product of cross-linked fibrin, is widely used as a surrogate marker of hypercoagulability in patients with cancer-related stroke (27). The OASIS-Cancer study demonstrated a reduction in 1-year mortality among patients whose D-dimer levels were effectively lowered with anticoagulant therapy (8). However, this study lacked an antiplatelet arm, and provided little information on cancer treatments administered, which, by targeting the underlying cancer driving hypercoagulability, may influence clinical outcomes more than the type of antithrombotic therapy selected (8). D-dimer levels have also been shown to correlate with microemboli on transcranial Doppler ultrasound, another marker of hypercoagulability (28, 29). In contrast, patients with active cancer and AIS also face an increased risk of major bleeding, approaching 20% at 1-year in prospective studies (30), and anticoagulant therapy is known to increase the risk of bleeding compared with antiplatelet therapy (31). These countervailing considerations may offset any potential reduction in thromboembolic risk with anticoagulation.

Given our neutral findings and the existing data (26), the potential efficacy of antiplatelet therapy in cancer-related stroke warrants further investigation. Large vessel occlusive thrombi endovascularly retrieved

from patients with active cancer and AIS have been shown to be platelet-rich and erythrocyte-poor, particularly in subgroups with confirmed nonbacterial thrombotic endocarditis or ESUS (32). The MOST-Cancer study showed that P-selectin, a marker of platelet activation, is significantly elevated in patients with active cancer and AIS compared with cancer-only and stroke-only controls (29). This prospective study also found that P-selectin was predictive of major thromboembolic events or death in the cancer-related stroke group (30).

Few studies have compared clinical outcomes in cancer-related stroke by antithrombotic treatment strategy. In a retrospective analysis of 172 patients with active cancer and AIS at a comprehensive cancer center in New York, the rates of recurrent thromboembolism or death did not differ between patients treated with antiplatelet versus anticoagulant therapy (33). A subgroup analysis of the NAVIGATE ESUS trial evaluating 543 ESUS patients with any history of cancer reported no difference in the risk of recurrent AIS or mortality between patients treated with rivaroxaban versus aspirin (10). However, only 9% of patients in this post-hoc analysis had their cancer diagnosed in the year prior to the index AIS, so many of the included cancers were likely inactive during follow-up. A *post hoc* analysis investigated 137 patients with history of cancer in the ARCADIA trial, which compared apixaban to aspirin in patients with cryptogenic stroke and biomarker evidence for atrial cardiopathy (9). This study showed no significant difference in the risk of major ischemic and hemorrhagic events between antithrombotic treatment groups. However, once again, cancer status at the time of stroke was unknown, making it difficult to draw conclusions about optimal secondary stroke prevention for patients with active cancer based on these data. The TEACH trial randomized 20 patients with cancer-related stroke to subcutaneous enoxaparin (1 mg/kg twice daily) or oral aspirin (81-325 mg daily), and found similar rates of adverse clinical outcomes between groups (21). However, TEACH focused on demonstrating the feasibility of randomizing patients with cancer and AIS to these competing antithrombotic strategies, which it did, but was not powered for safety or efficacy.

In the current study, because of our institution's guidelines, LMWH was the preferred anticoagulant for patients with ischemic stroke attributed to paraneoplastic coagulopathy. The continued use of LMWH beyond the acute phase appears to be inappropriate, as only 7% of patients with available follow-up ($n = 2/27$) remained on LMWH at 3 months in our study. This lack of compliance for LMWH is further supported by the TEACH trial, in which 40% of patients initially assigned to LMWH switched to aspirin due to discomfort with injections (21). The results of the current analysis support the existence of clinical equipoise between anticoagulant and antiplatelet therapy for the treatment of cancer-related stroke, and further support calls for randomized trials to determine the optimal strategy. An important consideration when deciding on the antithrombotic management of this patient group is the presumed stroke mechanism. As many ESUS in cancer patients are attributed to paraneoplastic coagulopathy, this subgroup may be the most likely to preferentially benefit from anticoagulant therapy. In this vein, when we analyzed ESUS patients only, there was a trend towards lower 1-year mortality with anticoagulation (aHR 0.51; 95% CI 0.2–1.2). Furthermore, this nonsignificant trend was even stronger in ESUS patients with elevated D-dimer levels (aHR 0.26; 95% CI 0.05–1.27).

Our study has several limitations. Firstly, confounding by indication bias is possible because patients treated with anticoagulant therapy were more likely to have elevated D-dimer levels, multi-territory brain infarcts, and metastatic disease at the time of AIS, all of which are associated with cancer-associated hypercoagulability and worse outcomes after cancer-related stroke (30). The presence of these markers of high tumor burden and paraneoplastic coagulopathy may have driven clinicians to preferentially prescribe anticoagulant therapy, thus potentially biasing our results. In fact, patients treated with anticoagulant therapy had a higher average cancer stage and frequency of metastases than patients treated with antiplatelet therapy, and these factors likely led to higher mortality and shorter follow-up time in the anticoagulant group through confounding, even despite multivariable adjustments. In such scenarios, IPTW is the recommend method for addressing casual inference, but residual confounding remains a concern (24, 34). Secondly, our study was conducted before widespread DOAC use in patients with cancer at a single comprehensive stroke center in Switzerland with predominantly Caucasian patients, which limits generalizability. Future studies should investigate more contemporary and heterogeneous patient cohorts. Thirdly, because of the retrospective study design, we relied on electronic health records to determine clinical data, which may have led to measurement error in patients' clinical characteristics as well as missed clinical outcomes during follow-up. In particular, rates of recurrent AIS and bleeding outcomes may have been underestimated because incident diagnoses made in the outpatient setting or at other medical centers may have been missed. Fourthly, our study exposure was the type of antithrombotic therapy administered at hospital discharge, a single timepoint, and antithrombotic prescription patterns may have changed during follow-up due to clinical events and patient and physician preferences. For instance, some patients initially treated with antiplatelet therapy at hospital discharge may have been subsequently treated with anticoagulant therapy during follow-up and vice versa. Fifthly, our cohort was a convenience sample and the CIs for some analyses were wide and possibly underpowered to detect clinically meaningful differences between treatment groups. This includes recurrent AIS and long-term mortality. Sixthly, our database lacked data on the specific cause of death. Seventhly, we did not perform a formal power calculation or adjust for multiple comparisons meaning that all results should be considered hypothesis-generating.

Conclusion

In our study, there were no differences in functional outcomes, mortality, or recurrent AIS in patients with active cancer and AIS treated with anticoagulant therapy versus those treated with antiplatelet therapy. These data combined with those from existing studies as well as the lack of clear recommendations by major guidelines highlight the need for dedicated fully-powered clinical trials to determine the optimal antithrombotic strategy for the secondary prevention of cancer-related stroke.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the dataset used in this study is derived from the Swiss Stroke Register (SSR). Access to the data requires a formal application and approval from the relevant authorities. The SSR dataset is of high quality, ensuring robust and reliable statistical analyses. Furthermore, the dataset is well-documented, allowing for full reproducibility of the statistical

analyses performed in this study. Information about the dataset can be found on https://www.neurovasc.ch/fileadmin/files/arbeitsgruppen/SSR_Data_management_04.07.2024.pdf. Requests to access these datasets should be directed to https://kontaktformular.dkfbasel.ch/.

Ethics statement

The studies involving humans were approved by project ID: 2022-01560; Kantonale Ethikkommission Bern. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MK: Data curation, Writing – original draft, Writing – review & editing. JG: Data curation, Writing – review & editing. SV: Data curation, Writing – review & editing. FS: Data curation, Writing – review & editing. MatB: Formal analysis, Methodology, Writing – review & editing. AB: Data curation, Writing – review & editing. MG: Writing – review & editing. JK: Writing – review & editing. AM: Writing – review & editing. GC: Writing – review & editing. TM: Writing – review & editing. DS: Writing – review & editing. PB: Writing – review & editing. MH: Writing – review & editing. AL: Writing – review & editing. HK: Writing – review & editing. UF: Writing – review & editing. MA: Writing – review & editing. TP: Writing – review & editing. MaB: Writing – review & editing. SJ: Writing – review & editing. AS: Conceptualization, Data curation, Methodology, Writing – review & editing. BN: Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. MoB: Conceptualization, Data curation, Formal analysis, Supervision, Writing – review & editing, Writing – original draft.

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Conflict of interest

MoB reports research support from the Department of Neurology, Inselspital, Bern University Hospital and the University of Bern, Switzerland within the framework of this research project.

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Prediction of hemorrhagic transformation after thrombolysis based on machine learning models combined with platelet distribution width-to-count ratio

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Background: Hemorrhagic transformation (HT) is a common and potentially serious complication following intravenous thrombolysis (IVT) in patients with acute ischemic stroke (AIS). Despite its high incidence, there remains a lack of simple and effective tools for predicting HT risk.
Objective: This study aimed to develop an interpretable machine learning (ML) model incorporating the platelet distribution width to platelet count ratio (PPR) to predict HT occurrence in AIS patients after IVT.
Methods: We included AIS patients who underwent IVT at the First Affiliated Hospital of Kunming Medical University between July 2019 and April 2024. Four ML models—logistic regression (LR), random forest (RF), support vector machine (SVM), and extreme gradient boosting (Xgboost)—were constructed using 5-fold cross-validation, with HT after IVT as the outcome. Feature selection was performed using least absolute shrinkage and selection operator (LASSO) regression. Model performance was evaluated based on the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, and balanced F-score. The best-performing model was selected for interpretability analysis, and feature importance was assessed.
Results: LASSO regression identified six predictive features with non-zero coefficients: age, diabetes, malignancy, onset-to-treatment time (OTT), baseline National Institutes of Health Stroke Scale (NIHSS) score, and PPR. Among the models, LR demonstrated the highest predictive performance, achieving an optimal AUC of 0.919, along with average accuracy, sensitivity, and specificity of 0.825, 0.830, and 0.832, respectively. Feature importance in the LR model ranked as follows: baseline NIHSS score, diabetes, PPR, malignancy, age, and OTT.
Conclusion: The LR-based model incorporating PPR effectively predicts HT risk in AIS patients after IVT, providing clinicians with a rapid and accurate tool to assess thrombolytic hemorrhage risk and support treatment decision-making.

KEYWORDS

hemorrhagic transformation, intravenous thrombolytic therapy, stroke, platelet distribution width-to-count ratio, machine learning

1 Introduction

Alteplase intravenous thrombolytic therapy (IVT) is effective in treating acute ischemic stroke (AIS) (1). Hemorrhagic transformation (HT) is a frequently occurring potentially adverse complication of intravenous thrombolysis in AIS patients, and the occurrence of HT in AIS patients following thrombolysis is significantly higher than that in AIS patients without thrombolysis (2). HT is further grouped into hemorrhagic infarction (HI) and parenchymal hemorrhage (PH), where PH, as a progressive manifestation of HI, usually indicates poor prognosis (3–5). Therefore, early identification of potential HT during thrombolysis and asymptomatic HI patients after thrombolysis is crucial.

Currently, most of the studies use multiple linear regression (MLR) to identify risk factors (6, 7) for HT following thrombolysis, including white blood cells (8), coagulation function (9), bilirubin (10), and uric acid (11). However, MLR is restrained by linear hypotheses between predicted variables and results, and the sensitivity to outliers may have adverse effects on predictive performance (12). Machine learning (ML), as an emerging discipline in the medical field, leverages computer science and statistical techniques to address healthcare challenges (13), making up for the shortcomings mentioned above and thus being widely applied. Due to the varying performance of different ML algorithms in different application scenarios, it is necessary to select appropriate algorithms to optimize model performance and accuracy before constructing a risk model for predicting HT after thrombolysis.

Platelet is the main component of blood and plays a crucial role in the onset and progression of AIS by maintaining the integrity of vascular endothelial cells, coagulation, and other pathophysiological functions (14, 15). Platelet count changes in hemorrhagic diseases are typically more rapid and pronounced than fibrinolytic markers. Thrombocytopenia or dysfunction is often an early sign of bleeding, while fibrinolytic indicators require some time to accumulate before showing any changes, which may not reflect risks in the early stages of HT. Additionally, fibrinolytic markers can be influenced by more complex factors, such as liver dysfunction and inflammatory responses (16), which can limit their clinical utility. These markers primarily reflect the degree of fibrinolytic activity, and although fibrin degradation products and D-dimer have some predictive value for HT after IVT (17, 18), their accuracy and timeliness are inferior to platelet count. Studies has demonstrated a positive correlation of elevated platelet distribution width (PDW) with a heightened likelihood of severe HT (19). As a new hematological indicator, PDW to platelet count ratio (PPR) can more comprehensively reflect platelet function, and its prognostic value has been confirmed in the prediction of other diseases (20, 21).

The objective of this study is to assess the predictive capabilities of various models utilizing different algorithms, develop a ML model that incorporates the PPR index for predicting the risk of HT after thrombolysis, and compare the performance of models to establish an effective assessment tool.

2 Methods

2.1 Study design and object

A single-center, observational, and retrospective study was conducted, and all subjects were collected from the First Affiliated Hospital of Kunming Medical University. The Ethics Committee of the hospital [No. 2022-L-157] provided approval for this study. Due to the retrospective nature of this study, which entailed anonymous and non-invasive data collection, the requirement for obtaining informed consent was waived. All procedures were performed in compliance with the principles outlined in the Declaration of Helsinki.

This study enrolled AIS patients who received IVT from July 2019 to April 2024. Subsequently, the patients were grouped into two groups, namely HT and non-HT, based on CT or MRI (magnetic resonance imaging) findings. A predictive model was constructed to assess the risk of HT following AIS.

The inclusion criteria were as follows: (1) Patients who met the World Health Organization (WHO) diagnostic criteria for AIS; (2) Hospitalized patients who received rt-PA IVT after excluding cerebral hemorrhage through transcranial CT examination or magnetic resonance imaging; (3) Patients aged $\geq$ 18 years; (4) Participants without a recent history of surgical treatment or brain injury. The exclusion criteria were as follows: (1) Patients with concurrent vital organ diseases, such as liver and kidney impairment; (2) Patients complicated with blood system diseases, coagulation dysfunction, connective tissue diseases, cerebral aneurysms, and cerebrovascular malformations; (3) Patients lacked of PDW and PLT at admission (Figure 1).

2.2 Data collection and processing

The demographic data and clinical characteristics of the study participants (age, gender, diabetes, hypertension, atrial fibrillation, body mass index (BMI), smoking history, drinking history, malignant tumor, previous use of lipid-lowering drugs, previous use of antiplatelet drugs, previous use of anticoagulants, intravascular treatment after onset of disease, blood pressure, baseline National Institutes of Health Stroke Scale (NIHSS) score, time from onset to thrombolysis), along with their initial laboratory test results, which were first obtained before IVT initiation in AIS patients upon admission [blood routine, coagulation function, fibrinolysis, liver function, kidney function, electrolytes, blood lipids, glucose, myoglobin, brain natriuretic peptide (BNP)], were retrieved from the laboratory information system of the First Affiliated Hospital of Kunming Medical University. The PPR was calculated as (PDW/PLT). To predict missing values in continuous variables, a multiple imputation technique was utilized when the proportion of missing values was less than 20%. Categorical variables with more than 20% missing values were excluded. To mitigate multicollinearity, variables exhibiting a variance inflation factor (VIF) exceeding 5 were eliminated from the model.

2.3 LASSO regression for feature selection

LASSO regression was utilized to identify and select features significantly associated with HT, leveraging its ability to perform both variable selection and regularization. The primary strength of LASSO lies in its L1 regularization, which shrinks some regression coefficients to zero, thus effectively excluding irrelevant predictors. This automatic feature selection is conducive to focus the model with the most relevant variables related to HT, thus enhancing its interpretability. The optimal regularization parameter (λ) for LASSO was determined through

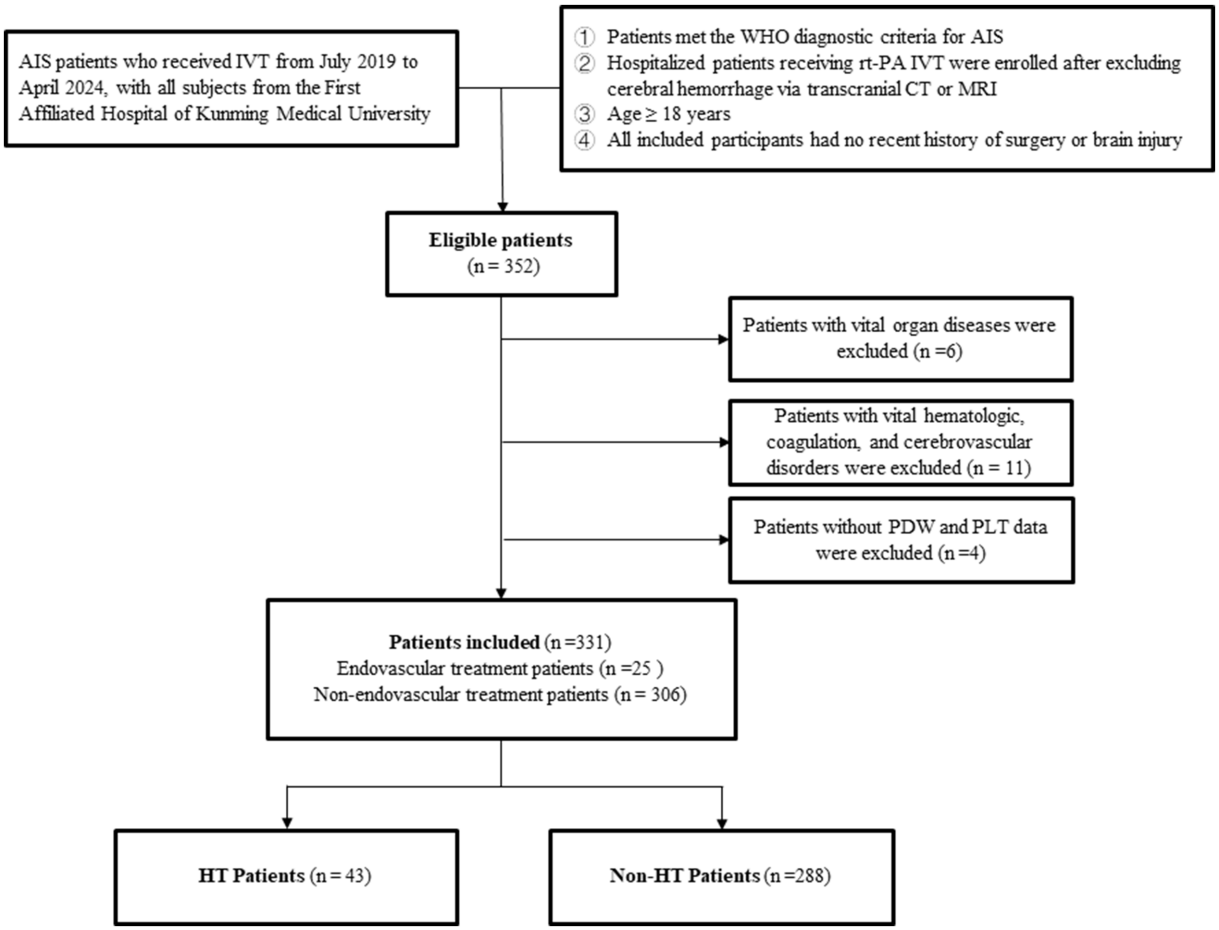

FIGURE 1
Patient selection process. AIS, Acute Ischemic Stroke; IVT, Intravenous Thrombolytic Therapy; PDW, Platelet Distribution Width; PLT, Platelet Count; HT, Hemorrhagic Transformation.

cross-validation, a technique that helped to select the λ value and minimized model error by testing the model on different subsets of the data. By doing so, overfitting was mitigated, ensuring that the model generalized well to new data while still retaining the most meaningful predictors. Through this process of variable selection and regularization, LASSO improved both the accuracy and interpretability of the model, making it more effective for identifying significant predictors of HT.

2.4 Model construction

This retrospective study employed four widely used ML algorithms—Logistic Regression (LR), Random Forest (RF), Support Vector Machine (SVM), and xgboost—to predict the onset of HT following thrombolysis, as illustrated in Figure 2. The process began by selecting a set of significant features that were most strongly associated with the occurrence of HT. These features were then used as the input variables for training each of the four ML models. To ensure optimal model performance, hyperparameter tuning was conducted for each algorithm using a grid search approach. This method systematically explored different combinations of hyperparameters within a predefined parameter space specific to each algorithm. The models were then fine-tuned based on performance metrics obtained from an extensive search, ensuring that they were optimized to achieve their highest performance potential. For the four machine learning models (LR, RF, SVM, and xgboos), the following hyperparameters were fine-tuned: LR: The regularization strength (L1 or L2 regularization) was adjusted. RF: Hyperparameters such as the number of trees, maximum depth, and minimum samples required to split a node were optimized. SVM: The penalty parameter C and the type of kernel function were tuned.xgboos: Key hyperparameters like learning rate, number of trees, and maximum depth were adjusted. These hyperparameters were optimized through techniques like cross-validation, grid search, and random search, to find the optimal combination that maximized the model's generalization ability on the validation set.

2.5 Training model

To train our models and mitigate the risk of overfitting, we implemented 5-fold cross-validation. This method involved dividing the dataset into 5 separate folds. This method involved dividing the dataset into 5 separate folds, maximizing the number of folds while ensuring that each fold contained a sufficient number of HT patient samples (8–9 positive samples per fold). In each round, the model was trained on 4 of the folds and validated on the remaining

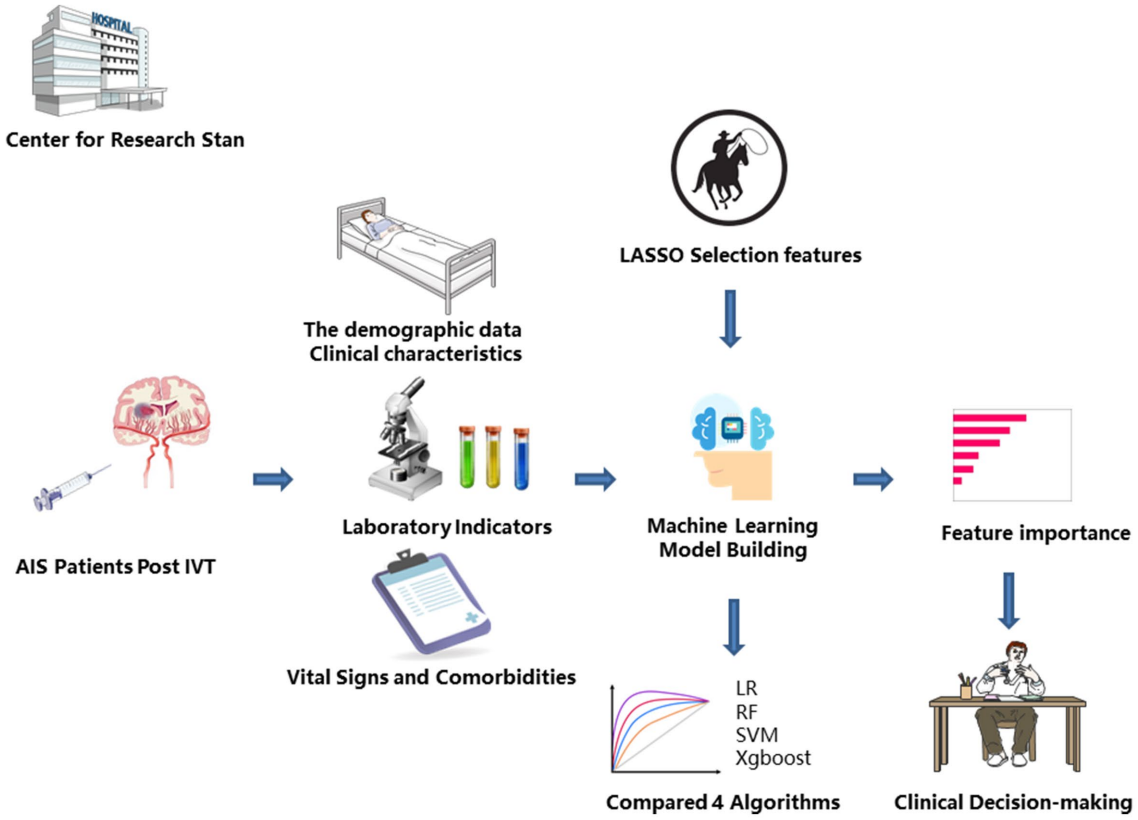

FIGURE 2
Machine learning flowchart for constructing predictive models. AIS, Acute Ischemic Stroke; IVT, Intravenous Thrombolytic Therapy; LR, Logistic Regression; RF, Random Forest; SVM, Support Vector Machine; xgboost, Extreme Gradient Boosting.

fold. The process was repeated 5 times, with each fold acting as the validation set once. The final model performance was calculated by taking the average of the metrics obtained from each iteration. By using this technique, the dataset was effectively split into 5 parts, and the model was trained and validated on different combinations of these parts. This helped to minimize potential bias in the performance assessment. As a result, this strategy provided a more robust and generalizable evaluation, producing performance metrics that were less reliant on any single partition of the data.

2.6 Model evaluation

To evaluate and ensure the generalizability of each model, the performance was assessed by calculating the mean [standard deviation (SD)] of key metrics across the 5-fold cross-validation, including the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC), accuracy, sensitivity, specificity, and balanced F-score. These metrics provided a comprehensive evaluation of each model's predictive capabilities. To explain the impact of predictors in a model, feature importance analysis was used.

2.7 Nomogram for HT prediction after IVT

The best-performing model, selected based on the highest AUC and overall metric scores, was used to identify the key features most strongly associated with HT. These selected features, along with the model's predictions, were then incorporated into the development of a nomogram. The nomogram allows for the calculation of the probability of HT occurrence using multiple clinical variables. For each predictive variable, a horizontal line was drawn, with a scale beneath it indicating the possible values of that variable. Based on the actual observed value of each variable, the corresponding score was located on the scale. The scores for all variables were then summed to obtain a total score. This total score was finally mapped to a probability curve on the nomogram, allowing for the conversion of the total score into the predicted probability of HT occurrence in AIS patients who received IVT. The nomogram provided a visual, intuitive tool that allowed clinicians to estimate the probability of HT in individual patients following thrombolysis, facilitating decision-making and personalized care.

2.8 Statistical analysis

Continuous variables were represented as mean (SD) or median (upper and lower quartiles), and compared through student *t*-tests or non-parametric tests according to specific circumstances. Categorical variables were represented as frequency and percentage (%), and Pearson chi square test or Fisher's exact test was adopted for comparison between groups. $p < 0.05$ was set to indicate a statistically significant difference. The statistical analysis of this study was performed using R software (version 4.3.2).

3 Results

3.1 Characteristics of patients

In this study, 331 AIS patients after IVT were included, of whom 43 (13.0%) developed HT. The patients had a median age of 68 [58, 77] years, and there were 205 (61.9%) males and 126 (38.1%) females. Differences were observed regarding the following variables between the HT group and the non-HT group: age, baseline NIHSS score, hemoglobin (Hb), BNP, D-dimer (D-D) ($p < 0.05$). The details are presented in Table 1.

3.2 Selection of predictive variables

The function selection was carried out using the Least Absolute Shrinkage and Selection Operator (LASSO) method, where the penalty for β coefficient was determined by the tuning parameter λ ($\lambda = 0.02651381$). In this study, 37 variables were included, and 37 lines of different colors were obtained, each representing the change trajectory of a specific independent variable's coefficient. As the value of λ increased, the coefficients gradually decreased, reflecting the regularization effect of the LASSO method (Figure 3A). The dashed line on the left represented λ value, and the value minimized the bias and corresponded to the optimal model fit. Regarding this value, the model selected 6 variables, indicating that these variables provided the most reliable and predictive relationship with the outcome. Consequently, six feature variables with non-zero coefficients were chosen, including age, diabetes, malignancy, onset to treatment time (OTT), baseline NIHSS score, and PPR (Figure 3B).

3.3 Model performance

Four ML algorithms, namely Logistic, Random Forest, SVM, and Xgboost, were selected to construct models. The optimized ML model underwent 5-fold cross-validation, and the mean value obtained from each algorithm was utilized as the prediction result for that algorithm. The mean accuracy values of LR, RF, SVM, and XGBoost models were 0.825, 0.743, 0.773, and 0.813, respectively; the mean AUC values were 0.851, 0.763, 0.711, and 0.718, respectively; the mean sensitivity values were 0.830, 0.821, 0.731, and 0.636, respectively; the mean specificity values were 0.832, 0.725, 0.776, and 0.841, respectively. The details are represented in Table 2. The optimal ROC curves for different models are shown in Figure 4. It could be found that the optimal AUC values for all four models were above 0.8 (LR > Xgboost>SVM > RF), indicating good fitting effect.

The results in Table 2 and Figure 5 indicated that after comprehensive evaluation of the four models, the LR model exhibited the best performance in terms of mean value of AUC, accuracy, sensitivity, precision, and F1. Therefore, it could be considered that the LR model had the best performance among these four models. According to the Nomogram constructed from the LR model and the statistical analysis of the LR mode, for AIS patients undergoing IVT, a total score of 226 corresponded to an estimated probability of 0.64 for HT (Figure 6).

3.4 Feature importance

The LR model demonstrated the best overall performance. We further ranked these features based on their contribution to the model's predictive capability. The feature importance of the LR model are summarized in Figure 5. In addition, based on their contribution to the model, feature variables were ranked in descending order as baseline NIHSS score, diabetes, PPR, malignancy, age, and OTT.

4 Discussion

In this study, the occurrence of HT in AIS patients following IVT was found to be 13.0%, which was similar to the results in previous studies (22). The ML model based on patient PPR exhibited favorable performance in predicting HT, with optimal AUC values exceeding 0.8. Particularly, the LR model performed well in this study, with an optimal AUC value exceeding 0.9. In addition, the mean values of the model in accuracy, sensitivity, specificity, were all over 0.8. Overall, the LR model exhibited well in performance evaluation and model calibration, providing strong support in clinical decision-making. The reason LR may perform optimally compared to other models is that LR is a relatively simple linear model, particularly suitable for situations with small datasets and clear linear relationships between features. While other complex models like XGBoost have advantages in handling non-linear relationships, LR may demonstrate better predictive performance when dealing with linear data, less noise, or a lower risk of overfitting (23). Moreover, the ML-based predictive model developed in this study demonstrated superior risk prediction capabilities compared to previous MLR models (6). Compared with ML models developed by other researchers, the model developed by Wang et al. (24) was slightly inferior in terms of optimal performance (AUC = 0.82), and its inclusion of missing values in variables exceeded 30%, which might cause bias in HT prediction. The study by Li et al. (25) showed that the Xgboost model exhibited the highest performance in terms of AUC (AUC > 0.95). However, the CO2-CP included in this model was not a conventional testing index for AIS admission, which might also affect the promotion and application of the model in primary hospitals (25). The modeling variables in this study included age, diabetes, malignant tumor, OTT, baseline NIHSS score, and PPR. These were convenient for popularization. In summary, the HT risk predictive model developed in this study performed well in multiple performance indicators and had high clinical application potential compared to other ML models.

The role of platelets in ischemia–reperfusion injury has gained increasing attention in the pathophysiological process of AIS. The activation of platelets and activated platelets can exacerbate post-stroke ischemia–reperfusion injury, and the disruption of the blood–brain barrier by reperfusion injury is one of the important causes for HT (26–28). Platelet aggregation and clot retraction play important roles in the bleeding process. Among them, platelet aggregation is a key step in the hemostasis process, while clot retraction helps stabilize thrombosis and reduce the risk of hemorrhage (29). Alteplase can inhibit platelet aggregation and clot retraction by inhibiting ADP, collagen, and adrenaline, thereby affecting platelet function (30). Platelets can also enhance fibrinolysis by participating in the plasminogen activation system, thereby increasing the risk of HT after IVT (31). In addition,

TABLE 1 Clinical baseline characteristics.

Characteristic	Level	Overall	Non-HT	HT	*p*
Characteristics		331	288	43	
Age [median (IQR)]		68.00 [58.00, 77.00]	68.00 [57.00, 77.00]	72.00 [65.50, 82.00]	0.005
Gender (%)	Female	126 (38.1)	110 (38.2)	16 (37.2)	1
	male	205 (61.9)	178 (61.8)	27 (62.8)	
BMI [median (IQR)]		23.66 [22.04, 26.08]	23.66 [22.04, 26.03]	23.88 [20.39, 26.22]	0.736
Smoking (%)	None	228 (68.9)	195 (67.7)	33 (76.7)	0.309
	Yes	103 (31.1)	93 (32.3)	10 (23.3)	
Drinking (%)	None	275 (83.1)	238 (82.6)	37 (86.0)	0.735
	Yes	56 (16.9)	50 (17.4)	6 (14.0)	
Hypertension (%)	None	138 (41.7)	123 (42.7)	15 (34.9)	0.421
	Yes	193 (58.3)	165 (57.3)	28 (65.1)	
Diabetes (%)	None	251 (75.8)	224 (77.8)	27 (62.8)	0.051
	Yes	80 (24.2)	64 (22.2)	16 (37.2)	
CAD (%)	None	297 (89.7)	261 (90.6)	36 (83.7)	0.262
	Yes	34 (10.3)	27 (9.4)	7 (16.3)	
Stroke (%)	None	277 (83.7)	244 (84.7)	33 (76.7)	0.272
	Yes	54 (16.3)	44 (15.3)	10 (23.3)	
Arrhythmia (%)	None	309 (93.4)	269 (93.4)	40 (93.0)	1
	Yes	22 (6.6)	19 (6.6)	3 (7.0)	
Malignancy (%)	None	321 (97.0)	281 (97.6)	40 (93.0)	0.251
	Yes	10 (3.0)	7 (2.4)	3 (7.0)	
Antiplatelets (%)	None	280 (84.6)	246 (85.4)	34 (79.1)	0.396
	Yes	51 (15.4)	42 (14.6)	9 (20.9)	
Anticoagulants (%)	None	315 (95.2)	275 (95.5)	40 (93.0)	0.748
	Yes	16 (4.8)	13 (4.5)	3 (7.0)	
LLAs (%)	None	288 (87.0)	252 (87.5)	36 (83.7)	0.657
	Yes	43 (13.0)	36 (12.5)	7 (16.3)	
EVT (%)	None	306 (92.4)	268 (93.1)	38 (88.4)	0.438
	Yes	25 (7.6)	20 (6.9)	5 (11.6)	
OTT [median (IQR)] (h)		3.00 [2.10, 3.50]	3.00 [2.10, 3.60]	2.80 [1.85, 3.25]	0.124
NIHSS [median (IQR)]		5.00 [3.00, 10.00]	5.00 [3.00, 9.00]	14.00 [8.50, 18.00]	<0.001
SBP [mean (SD)] (mmHg)		143.51 (22.02)	143.07 (21.73)	146.42 (23.89)	0.353
DBP [median (IQR)] (mmHg)		84.00 [75.00, 93.00]	82.50 [75.00, 92.00]	88.00 [74.50, 95.50]	0.186
WBC [median (IQR)] (109/L)		7.52 [6.08, 9.22]	7.52 [6.04, 9.26]	7.62 [6.16, 9.16]	0.921
ANC [median (IQR)] (109/L)		4.97 [3.76, 6.84]	4.99 [3.76, 6.83]	4.77 [3.78, 6.84]	0.84
LYM [median (IQR)] (109/L)		1.59 [1.13, 2.13]	1.58 [1.13, 2.14]	1.67 [1.19, 2.09]	0.786
RBC [median (IQR)] (1,012/L)		4.85 [4.51, 5.24]	4.86 [4.55, 5.25]	4.69 [4.38, 5.15]	0.152
Hb [median (IQR)] (g/L)		149.00 [137.50, 161.00]	150.00 [139.00, 161.00]	141.00 [130.50, 156.50]	0.027
RDW-CV [median (IQR)] (%)		13.00 [12.80, 14.00]	13.00 [12.78, 14.00]	13.10 [12.90, 14.00]	0.267
CK-MB [median (IQR)] (ng/mL)		35.26 [22.18, 56.89]	34.98 [20.94, 56.72]	38.30 [28.24, 72.89]	0.16
Glucose [median (IQR)] (mmol/L)		7.13 [6.10, 8.95]	7.10 [6.10, 8.89]	7.30 [6.00, 10.07]	0.618
UA [mean (SD)] (μmol/L)		353.50 [275.10, 431.30]	354.05 [282.62, 433.55]	323.60 [238.90, 417.75]	0.188
Creatinine [median (IQR)] (μmol/L)		90.54 (54.95)	90.92 (57.99)	87.98 (27.05)	0.744
K + [median (IQR)] (mmol/L)		3.71 [3.46, 4.01]	3.70 [3.44, 4.01]	3.74 [3.50, 4.03]	0.649

(Continued)

TABLE 1 (Continued)

Characteristic	Level	Overall	Non-HT	HT	*p*
Na + [median (IQR)] (mmol/L)		139.50 [137.47, 141.50]	139.52 [137.64, 141.49]	139.16 [137.00, 141.38]	0.482
Cl + [median (IQR)] (mmol/L)		103.92 [101.47, 106.55]	103.94 [101.70, 106.64]	103.72 [100.28, 106.16]	0.228
Ca2 + [median (IQR)] (mmol/L)		2.23 [2.17, 2.32]	2.24 [2.18, 2.33]	2.21 [2.16, 2.28]	0.056
Dbil [median (IQR)] (μmol/L)		4.00 [2.90, 5.80]	3.95 [2.80, 5.70]	4.60 [3.35, 6.85]	0.174
Ibil [median (IQR)] (μmol/L)		7.60 [5.20, 10.15]	7.50 [5.27, 10.12]	7.80 [5.05, 10.05]	0.686
ALB [median (IQR)] (g/L)		40.09 [37.45, 43.05]	40.10 [37.50, 43.02]	39.90 [36.35, 43.10]	0.731
BNP [median (IQR)] (pg/mL)		37.41 [10.84, 162.75]	31.24 [10.00, 155.10]	125.90 [51.66, 311.12]	<0.001
PTR [median (IQR)]		1.00 [0.97, 1.06]	1.00 [0.96, 1.06]	1.01 [0.97, 1.08]	0.653
PT [median (IQR)] (s)		13.10 [12.50, 13.80]	13.10 [12.50, 13.80]	13.20 [12.65, 13.70]	0.727
TT [median (IQR)] (s)		18.50 [17.60, 19.65]	18.60 [17.60, 19.70]	18.30 [17.60, 19.20]	0.462
INR [median (IQR)]		1.01 [0.96, 1.08]	1.00 [0.95, 1.08]	1.01 [0.96, 1.09]	0.687
FIB [median (IQR)] (g/L)		2.95 [2.58, 3.52]	2.95 [2.56, 3.50]	2.92 [2.68, 3.60]	0.626
D-D [median (IQR)] (mg/mL)		0.40 [0.25, 0.91]	0.36 [0.23, 0.85]	0.65 [0.32, 1.57]	0.003
PPR [median (IQR)]		0.07 [0.05, 0.09]	0.07 [0.05, 0.09]	0.07 [0.05, 0.09]	0.344

p, *p*-value from the statistical test comparing the HT and non-HT groups. BMI, Body Mass Index; CAD, Coronary Artery Disease; LLAs, Lower Limb Arterial Stenosis; EVT, Endovascular Therapy; OTT, Onset to Treatment Time; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell; ANC, Absolute Neutrophil Count; LYM, Lymphocytes; RBC, Red Blood Cell; Hb, Hemoglobin; RDW-CV, Red Cell Distribution Width-Coefficient of Variation; CK-MB, Creatine Kinase-MB; UA, Uric Acid; Dbil, Direct Bilirubin; Ibil, Indirect Bilirubin; ALB, Albumin; BNP, Brain Natriuretic Peptide; PTR, Prothrombin Ratio; PT, Prothrombin Time; TT, Thrombin Time; INR, International Normalized Ratio; FIB, Fibrinogen; D-D, D-dimer; PPR, Platelet Distribution Width to Platelet Count Ratio.

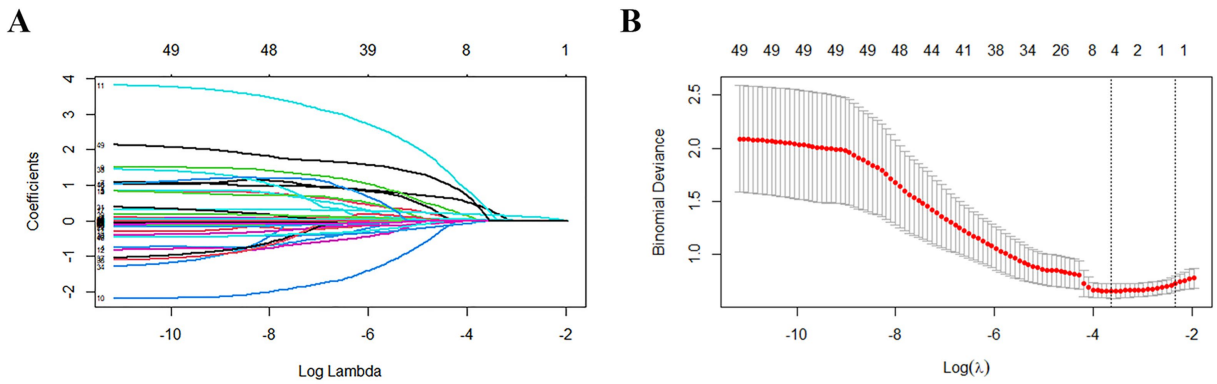

FIGURE 3
Results of variable screening using the LASSO regression. **(A)** The 5-fold cross-validation was performed, and the coefficients of all predictors gradually returned to zero. λ = 0.02651381. **(B)** There were 6 predictors of non-zero coefficients at the far right dotted line.

TABLE 2 Mean and standard deviation of 5-fold cross-validation for four ML Models.

Machine learning	AUC (mean ± SD)	Precision (mean ± SD)	Sensitivity (mean ± SD)	Specificity (mean ± SD)	Accuracy (mean ± SD)	F1 value (mean ± SD)
LR	0.851 ± 0.066	0.825 ± 0.081	0.830 ± 0.195	0.832 ± 0.122	0.477 ± 0.240	0.550 ± 0.136
RF	0.763 ± 0.084	0.743 ± 0.138	0.821 ± 0.142	0.725 ± 0.174	0.356 ± 0.127	0.481 ± 0.119
SVM	0.711 ± 0.115	0.773 ± 0.140	0.731 ± 0.143	0.776 ± 0.168	0.373 ± 0.11	0.479 ± 0.112
XGBoost	0.718 ± 0.104	0.813 ± 0.096	0.636 ± 0.234	0.841 ± 0.138	0.461 ± 0.175	0.478 ± 0.075

LR, Logistic Regression; RF, Random Forest; SVM, Support Vector Machine; XGBoost, Extreme Gradient Boosting.

platelets form platelet-fibrin aggregates around the thrombus, leading to living contracting of cerebral thrombosis, thereby affecting the severity and prognosis of AIS (32). Mean platelet volume (MPV) and PDW together provide comprehensive information on platelet production, activation, and functional status. Compared to MPV, PDW is a more sensitive marker of variation in platelet volume, providing more comprehensive platelet activation information and effectively indicating the

severity of the disease (19, 33, 34). In addition, Chen et al. (35) discovered an obvious association between PDW and the severity of stroke. Unfortunately, PDW may be affected by platelet count (36). Some scholars believe that PDW should not be used alone as a direct indicator of thromboembolic diseases (37). Lin et al.'s (21) study shows that the AUCs for predicting 120-day mortality in severe burn patients using PDW, PLT, and PPR on the third day post-burn are 0.792, 0.782, and 0.816, respectively. Therefore, as a novel biological indicator, PPR, by reflecting both the distribution width and platelet count, can more comprehensively reflect platelet function and predict the risk of HT occurrence. In this study, the baseline PPR lacked statistical significance, but *p*-values can be influenced by sample size and may not accurately reflect the true relationship between variables and outcomes, potentially leading to bias in variable selection. This is especially true when p-values are used as the sole criterion for feature selection, which may result in the inclusion of variables with no practical significance. In contrast, regularization methods like LASSO regression help address this issue by penalizing coefficients and automatically selecting variables, effectively removing less important ones and improving the model's generalizability (38). Given that PPR was included in the LASSO model and ranked third in feature importance, its role as an independent impact factor is justifiable, as it demonstrated a certain effect in predicting HT. Future studies should further explore the predictive ability of PPR in different patient populations and evaluate its application value in clinical practice.

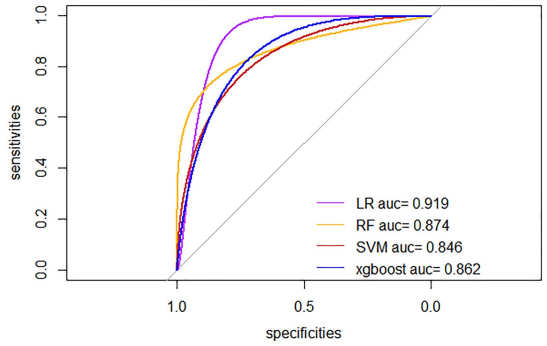

FIGURE 4
Optimal ROC curves for four ML models. LR, Logistic Regression; RF, Random Forest; SVM, Support Vector Machine; xgboost, Extreme Gradient Boosting.

In our study, the key factors influencing the prediction results include malignant tumors and diabetes. Malignant tumor patients have a certain impact on the prediction results, which may be due to the higher coagulation, platelet, and endothelial dysfunction markers, as well as more circulating tumor microemboli in stroke patients complicated with malignant tumors (39). However, patients with malignant tumors may not necessarily develop HT (40–42). Other variables still need to be explored for comprehensive evaluation. In addition, in our model, diabetes may have an important influence on the prediction results (Ranked 2rd in feature importance), which may be due to the combined effect of multiple mechanisms such as endothelial dysfunction, changes in coagulation and fibrinolytic systems, abnormal platelet function, and direct tissue damage caused by hyperglycemia in diabetes patients (43). Previous studies have shown that the admission

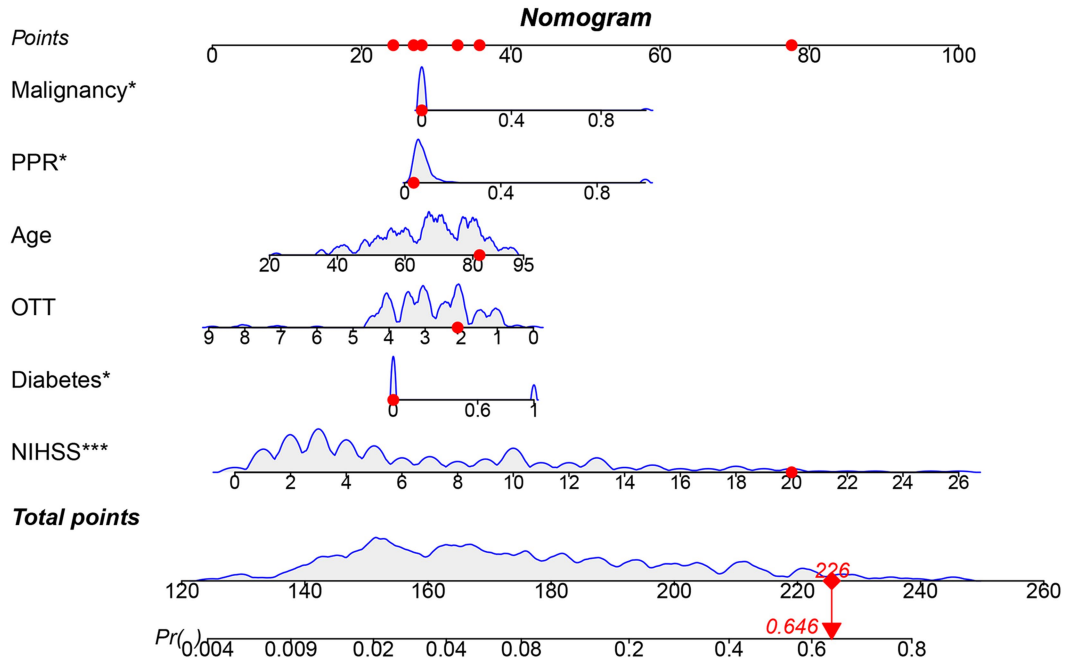

FIGURE 5
Nomogram model constructed based on LR. OTT, Onset to Treatment Time; PPR, Platelet Distribution Width to Platelet Count Ratio; Blue curve: Represents the relationship between one modeling variable and the occurrence of HT in AIS patients who received IVT; Gray shaded area: Represents the range of fluctuations in the occurrence of HT in AIS patients who received IVT as the input variables change.

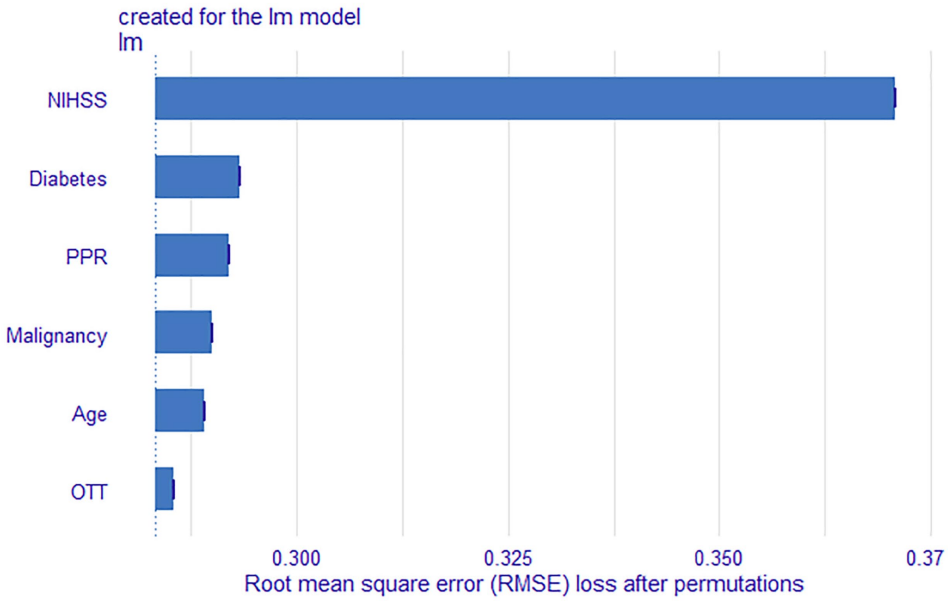

FIGURE 6
Feature importance results of the LR model. OTT, Onset to Treatment Time; PPR, Platelet Distribution Width to Platelet Count Ratio.

glucose performs better in predicting the adverse outcome of AIS patients than diabetes (44, 45). It should be noted that there are differences in physiological mechanism between chronic hyperglycemia and stress hyperglycemia (46). Therefore, it may not fully reflect the actual condition of patients to consider diabetes and admission glucose alone. Future studies should further explore biomarkers and clinical parameters that reflect comprehensive blood glucose levels, and construct more accurate predictive models. By incorporating age, OTT, and baseline NIHSS score into the model, the findings of previous studies have been effectively corroborated and validated (5, 47–49).

Imaging variables may encounter certain challenges in predicting HT risk after IVT. Although IVT can effectively dissolve thrombus and restore cerebral blood flow, it also increases the risk of intracranial hemorrhage (50). Therefore, when deciding to perform IVT on AIS patients, the risk of HT is one of the primary factors that should be considered by clinicians. IVT is suitable for AIS patients within 3 to 4.5 h after onset (51), which requires rapid and accurate evaluation by clinicians. Imaging plays a pivotal role in the rapid diagnosis and treatment of ischemic stroke. Head computed tomography (CT) scan can quickly and accurately determine cerebral hemorrhage; CT angiography (CTA) can locate ischemic blood vessels; CT perfusion (CTP) imaging can detect ischemic penumbra through multiple automated post-processing; MRI and diffusion-weighted imaging (DWI) can clarify the diagnosis of AIS and the extent of cerebral infarction (52). Due to the high risk of radiation exposure and contrast agent application of CT and CTA, as well as the longer duration, higher cost, and limited equipment accessibility of CTP and MRI, it may lead to different imaging protocols chosen by clinicians, resulting in different imaging variables. MRI and CTP may have moderate diagnostic performance in predicting HT in patients with AIS (53, 54), but current clinical evidence is insufficient to support these imaging parameters in predicting HT (55). Therefore, challenges still exist in incorporating imaging variables into predictive models to assess the risk of HT after thrombolysis. Moreover, multi-center studies have shown that early active treatment and dehydration therapy for asymptomatic HT patients can reduce the risk of hematoma enlargement and death (4). This study aims to develop a model based on ML combined with laboratory indicators that enables rapid and accurate prediction of HT following IVT. This will assist clinicians in making informed decisions regarding the administration of thrombolytic therapy and facilitate the early identification of asymptomatic HT patients after IVT, so as to prevent them from developing PH. By comprehensively analyzing various clinical and laboratory data, and combining with ML algorithms, the predictive model developed in this study has been able to efficiently and accurately evaluate the risk of HT (optimal AUC > 0.9). Future studies will focus on standardizing multiple imaging variables to further optimize the predictive ability of HT.

4.1 Limitations

This study used single-center data, lacked external validation, and adopted a retrospective study design, which could potentially limit the generalizability and accuracy of the research findings. Additionally, while HT was assessed as a whole, it was not further divided into its subtypes—HI and PH. PH was generally associated with more severe outcomes and poorer prognosis compared to HI, making it a critical factor for risk stratification and prediction in ischemic stroke patients. Future studies should aim to distinguish between HI and PH to better predict and manage the more severe forms of hemorrhagic transformation. Incorporating multi-center data and adopting prospective designs would also improve the generalizability and accuracy of predictive models.

5 Conclusion

It can be concluded in our research that the independent predictors of HT are age, diabetes, malignancy, OTT, baseline NIHSS score, and PPR. Among the models constructed by four ML algorithms, we have chosen the HT model with the best performance constructed by the LR algorithm. This model offers precise predictions of HT after IVT, providing valuable support to clinicians in promptly and accurately assessing the risk of thrombolytic hemorrhage and identifying asymptomatic HT patients after IVT.

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 humans were approved by the First Affiliated Hospital of Kunming Medical University (Approval number: 2022-L-157). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

XL: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. CL: Formal analysis, Investigation, Resources, Supervision, Writing – review & editing. HX: Conceptualization, Writing – original draft, Writing – review & editing. CY: Methodology, Writing – original draft. YZ: Methodology, Writing – original draft. WJ: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

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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

HT - Hemorrhagic transformation

AIS - acute ischemic stroke

IVT - intravenous thrombolytic therapy

ML - machine learning

PPR - platelet count ratio

AUC - area under curve

ROC - receiver operating characteristic

OTT - onset to treatment time

HI - hemorrhagic infarction

PH - parenchymal hemorrhage

PDW - platelet distribution width

WHO - World Health Organization

BMI - body mass index

NIHSS - National Institutes of Health Stroke Scale

BNP - brain natriuretic peptide

VIF - variance inflation factor

SD - standard deviation

MPV - Mean platelet volume

CT - computed tomography

CTA - CT angiography

CTP - CT perfusion

DWI - diffusion-weighted imaging

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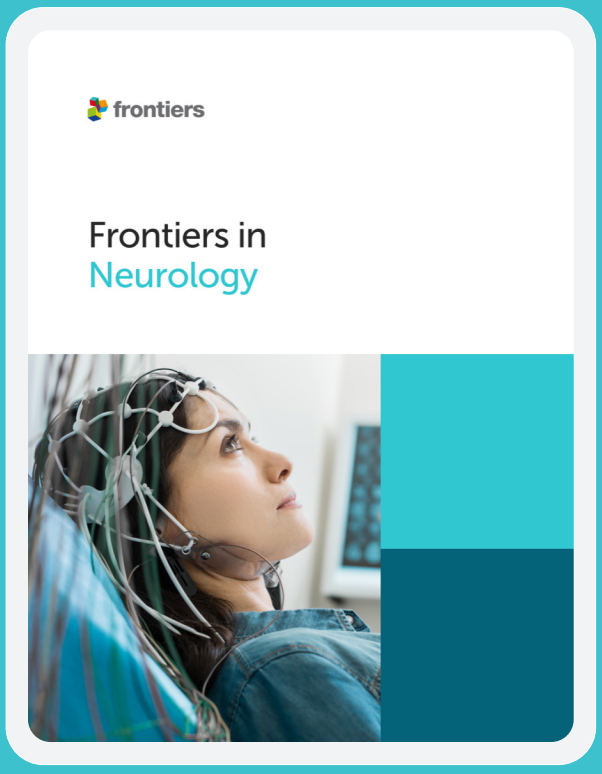

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