frontiers | Research Topics

Post-stroke complications: Mechanisms, diagnosis, and therapies

Edited by
Yinong Huang, Cheong-Meng Chong, Haiqing Zheng and Wenqiang Chen

Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-3683-4
DOI 10.3389/978-2-8325-3683-4

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Post-stroke complications: Mechanisms, diagnosis, and therapies

Topic editors

Yinong Huang — Sun Yat-sen University, China
Cheong-Meng Chong — University of Macau, China
Haiqing Zheng — Third Affiliated Hospital of Sun Yat-sen University, China
Wenqiang Chen — Section on Integrative Physiology and Metabolism, Joslin Diabetes Center, Harvard Medical School, United States

Citation

Huang, Y., Chong, C.-M., Zheng, H., Chen, W., eds. (2023). *Post-stroke complications: Mechanisms, diagnosis, and therapies*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3683-4

Table of contents

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 27 September 2023
DOI 10.3389/fneur.2023.1292562

OPEN ACCESS

EDITED AND REVIEWED BY
Jean-Claude Baron,
University of Cambridge, United Kingdom

*CORRESPONDENCE
Wenqiang Chen
✉ wenqiang.chen@joslin.harvard.edu

RECEIVED 11 September 2023
ACCEPTED 13 September 2023
PUBLISHED 27 September 2023

CITATION
Chen W, Huang Y, Chong C-M and Zheng H (2023) Editorial: Post-stroke complications: mechanisms, diagnosis, and therapies. *Front. Neurol.* 14:1292562. doi: 10.3389/fneur.2023.1292562

Editorial: Post-stroke complications: mechanisms, diagnosis, and therapies

Wenqiang Chen[1]*, Yinong Huang[2,3], Cheong-Meng Chong[4] and Haiqing Zheng[5]

[1]Section of Integrative Physiology and Metabolism, Joslin Diabetes Center and Department of Medicine, Harvard Medical School, Boston, MA, United States, [2]Department of Endocrinology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [3]Center for Stem Cell Biology and Tissue Engineering, Key Laboratory for Stem Cells and Tissue Engineering, Ministry of Education, Sun Yat-sen University, Guangzhou, China, [4]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, China, [5]Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

KEYWORDS

stroke, complications, diagnosis, clinical trials, neuropathology

Editorial on the Research Topic
Post-stroke complications: mechanisms, diagnosis, and therapies

Introduction

Stroke is a leading cause of disability and death that primarily affects arteries in the brain (1). When a stroke occurs, blood vessel blockages or narrowing restrict the supply of oxygen and nutrients to the brain, resulting in severe consequences including cell death and subsequent brain damage. Depending on the volume of ischemic lesion and the availability of immediate medical treatment following a stroke, the severity of post-stroke complications varies, spanning from temporary to permanent disabilities. These complications encompass pain, paralysis, language or swallowing difficulties, and sensory deficits, ultimately leading to psychiatric and cognitive impairments that profoundly impact patients' daily existence. While tremendous progress has been made in understanding the mechanisms underlying post-stroke complications in recent decades, the diagnosis and treatment of these complications are still in need of further development.

Within this Research Topic titled "*Post-stroke complications mechanisms, diagnosis, and therapies*," we have presented novel research focused on different aspects of post-stroke complications. These studies advance our understanding of the pathogenesis and prognosis of post-stroke complications. In this editorial, our goal is to present a summary of the key findings in each published article. Besides the text discussion, a summary of the main findings of these articles is depicted in Figure 1.

Post-stroke complications and inflammation

Systemic inflammation has been identified as an important factor that can impact both the early and long-term prognosis in stroke survivors (2). Within this Research Topic, we have three articles that delve into this subject.

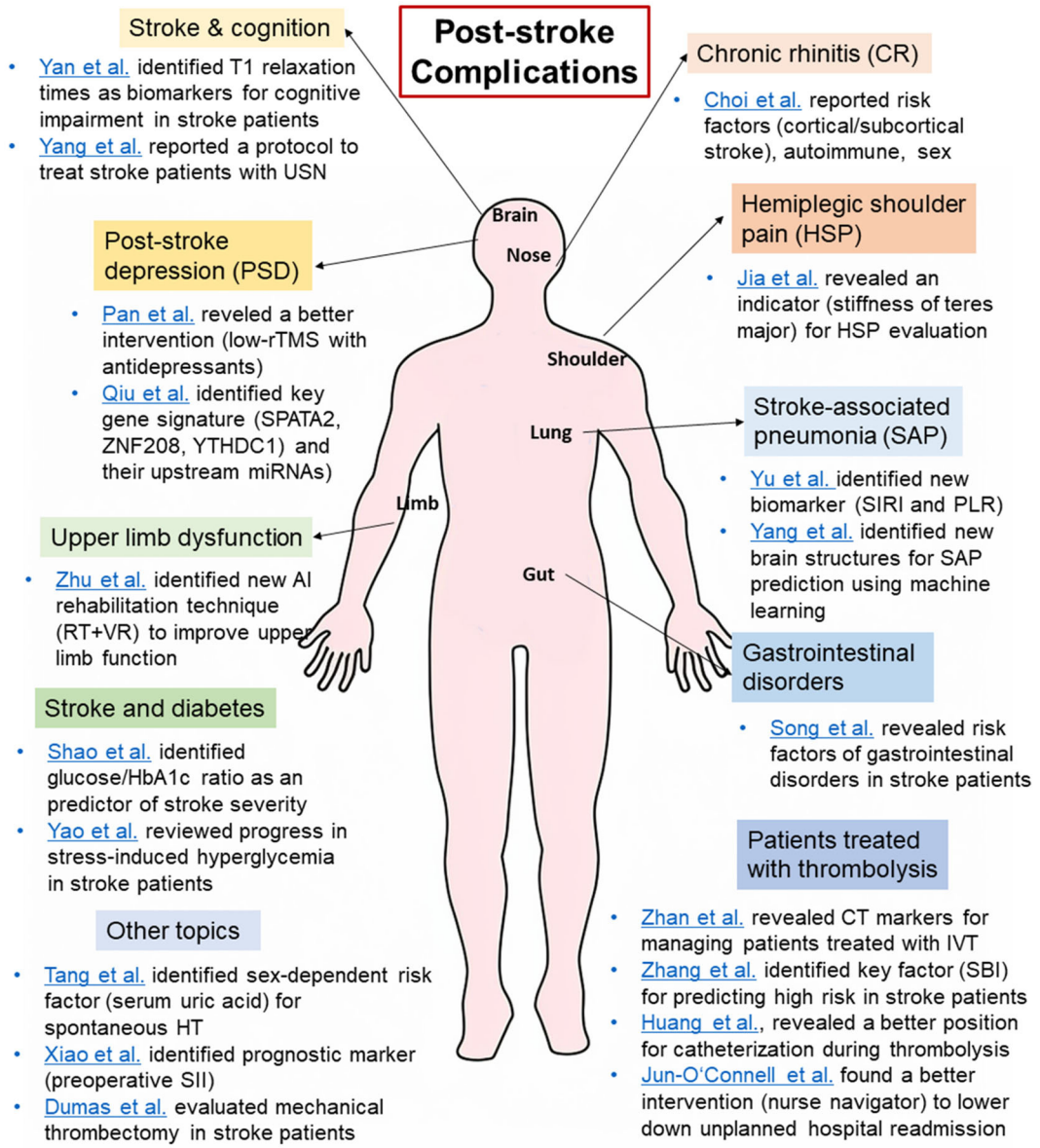


FIGURE 1
A summary of the main findings of the articles in the Research Topic "*Post-stroke complications: mechanisms, diagnosis, and therapies*". CR, chronic rhinitis; HSP, hemiplegic shoulder pain, HT, hemorrhagic transformation; IVT, intravenous thrombolysis; PLR, platelet/lymphocyte ratio; PSD, post-stroke depression; rTMS, repetitive transcranial magnetic; SAP, stroke-associated pneumonia; SBI, silent brain infarction; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; USN, unilateral spatial neglect.

First, Yu et al. perform a retrospective study that enrolls patients with spontaneous intracerebral hemorrhage (SICH). Through the analysis of data from these patients, the authors develop a predictive nomogram that incorporates factors such as systemic inflammation response index (SIRI) and platelet/lymphocyte ratio (PLR). They demonstrate the prognostic significance of these inflammatory biomarkers, outperforming conventional factors, in predicting stroke-associated pneumonia (SAP) following SICH. This study could help identify the risks of SAP, thus potentially improving patients' clinical outcomes and shorten the length of hospital stays.

Second, Xiao et al. conduct a retrospective study in patients with spontaneous basal ganglia intracerebral hemorrhage (ICH) who underwent surgical procedures. The authors discover that lower levels of preoperative systemic immune-inflammation index (SII) are linked to a reduced risk of prolonged mechanical ventilation (PMV) in these patients. Therefore, the study suggests that preoperative SII can serve as a prognostic marker for PMV.

Patients with stroke are reported to suffer from chronic rhinitis (CR), which results in symptoms such as rhinorrhea, nasal obstruction, and sneezing. Choi et al. conduct a retrospective study examining the association between CR and stroke in stroke

patients. They find that, while clinical evaluation does not reveal a significant difference between CR and non-CR patients, patients with cortical and subcortical stroke are at a higher risk of developing CR. Furthermore, they identify autonomic symptoms and gender as risk factors for stroke patients to develop CR.

Intervening and predicting post-stroke depression

Depression is commonly seen among individuals who have survived a stroke. According to the DSM-5, post-stroke depression (PSD) is characterized as a mood disorder with depressive features resulting from stroke (3). Our Research Topic has published three articles that reveal the key connection between PSD and stroke.

First, Pan et al. conduct a meta-analysis comprising 16 randomized controlled trials that enrolled 1,463 PSD patients. They find that combining low-frequency repetitive transcranial magnetic stimulation (low-frequency rTMS) with antidepressants leads to a significant reduction in depression scores, improved cognitive function, and lower levels of inflammatory factor when compared to antidepressant therapy alone. Furthermore, this analysis demonstrates that low-rTMS is generally considered safe with fewer adverse effects. Nonetheless, the authors recommend that future research should investigate the optimal intervention sites and frequencies for the treatment of PSD.

To investigate miRNA and mRNA biomarkers with predictive potential for PSD, Qiu et al. conduct a transcriptional analysis using data from two GEO databases that include patients diagnosed with both stroke and depression. Following the identification of differentially expressed miRNA and mRNA, the authors employ three machine-learning methods to uncover key signatures, including three genes (SPATA2, ZNF208, and YTHDC1) and their upstream miRNAs, forming a miRNA-mRNA network. This network could offer novel insights into the pathogenesis of PSD.

Another frequently occurring post-stroke complication, known as hemiplegic shoulder pain (HSP), has been reported to have a high prevalence of 80% among post-stroke patients even after recovery (4). HSP can evolve into a chronic condition and become associated with higher rates of depression, ultimately leading to poor quality of life (5). In order to examine the relationship between HSP and muscle stiffness, specifically focusing on internal rotation muscle stiffness, Jia et al. perform a prospective observational study. They enroll 20 stroke patients with HSP and 20 healthy controls and discover that increased stiffness of the teres major muscle is correlated with greater pain intensity and reduced shoulder mobility in patients with HSP. Thus, this study proposes that stiffness of internal rotation muscles can be used as an indicator for the evaluation and management pf HSP.

Applying AI and machine learning tools to the treatment of post-stroke complications

Zhu et al. perform a network meta-analysis that includes randomized controlled trials. Through a comparison of the efficacy of six different artificial intelligence (AI)-based rehabilitation techniques aimed at enhancing upper limb function and daily living ability in stroke patients, the authors identify one technique that can effectively enhance both proximal and distal upper limb function. Thus, these findings not only indicate the potential advantages of AI-based interventions for stroke patients but also underscore the importance of taking patient characteristics into account in future research.

To predict SAP using a readily accessible approach like brain CT scans, Yang G. et al. introduce a registration method that aligns brain images from both CT and MRI scans. The authors use three machine learning models (logistic regression, support vector machine, random forest) based on these scans and extract image features pertaining to the distribution and lesion areas of ICH. The results reveal key brain structures that exhibit a strong correlation with SAP, as determined through feature extraction from the scanned images. This provides potential insights into predicting SAP and its relationship with brain lesions.

Managing stroke patients receiving thrombolysis

Zhan et al. perform a retrospective study in which they analyze CT data from patients diagnosed with acute ischemic stroke (AIS) who underwent intravenous thrombolysis (IVT) treatment. The findings indicate that severe leukoaraiosis, severe brain atrophy, and a greater burden of cerebral small vessel disease (CSVD) are linked to an elevated risk of hemorrhagic transformation (HT) occurring within 24–36 h of IVT. Therefore, this study provides potential therapeutic strategies for preventing HT in stroke patients.

Zhang et al. perform a retrospective study on patients diagnosed with ischemic stroke who underwent IVT. Using clinical and neuroimaging data, the authors categorize the patients into groups with silent brain infarction (SBI) and those without (non-SBI group), revealing that patients with SBI have a reduced likelihood of achieving favorable functional outcomes at 3 months compared to non-SBI patients. Thus, the authors conclude that SBI is an independent factor that predicts a higher risk of unfavorable outcomes in AIS patients receiving IVT treatment.

Huang et al., perform a randomized, controlled clinical trial to assess the efficacy of different stereotactic minimally invasive catheter placement positions during urokinase thrombolysis for small- to medium-sized basal ganglia hemorrhages. The results show that catheterization along the long axis of the hematoma led to shorter catheterization times, reduced urokinase dosage, improved hematoma clearance, and fewer complications when compared to catheterization at the hematoma center. However, there are no significant differences in short-term patient outcomes as measured by NIHSS scores.

Unplanned readmission, which is defined as hospital admission for the same diagnosis within 30 days of discharge after the initial admission (6), has long been viewed as a challenge to healthcare performance and a potential risk to patients. It has been reported that unplanned readmission rates following a stroke are 20% within 30 days. To identify methods for reducing unplanned readmission, Jun-O'Connell et al. conduct a retrospective cohort

study that enrolls 447 stroke patients who underwent thrombolysis. By utilizing a stroke nurse navigator team, comprising two professionally trained nurses with expertise in stroke care, the authors find a substantial reduction in unplanned readmission rates within the implementation period (i.e., 3 days following hospital discharge). This indicates that the nurse navigator intervention, which encompasses medication reviews and follow-up planning, contributes to improved outcomes in stroke patients treated with thrombolysis.

Managing stroke patients with diabetes

Shao et al. examine the relationship between stress hyperglycemia and AIS through a retrospective study that enrolls patients with AIS. The study reveals that the primary functional outcome, the glucose-to-HbA1c ratio, is associated with more severe AIS, particularly in patients without diabetes. Thus, the authors conclude that the glucose-to-HbA1c ratio is an independent predictor of stroke severity in non-diabetic patients.

Yao et al. review stress-induced hyperglycemia (SIH) in AIS patients. SIH is characterized by elevated blood glucose levels during and after AIS, and it is linked to larger infarct sizes and poorer outcomes. Despite efforts to control it with insulin therapy, clinical outcomes continue to be unsatisfactory, pressing need for new therapeutic approaches. Furthermore, this review explores the definitions, mechanisms, and challenges in achieving effective glucose control in patients with AIS.

Other topics

Yan et al. recruit patients with acute cerebral infarction (CI) and healthy controls and evaluate cognitive performance and early brain microstructural changes, revealing a significant correlation between T1 relaxation times in various brain regions and cognitive test scores. Specifically, CI patients exhibit a significantly reduced cerebral blood flow, reflecting dysfunction in brain microstructure. Furthermore, the authors identify T1 relaxation times in the right temporal and frontal lobes as potential biomarkers for cognitive impairment following acute cerebral infarction. Thus, this study suggests a link between brain microstructure and cognitive function through cerebral hemodynamics.

Yang Y.-x. et al. describe a study protocol for a prospective randomized controlled clinical trial. Their objective is to examine the efficacy of a combined therapeutic approach, namely, prism adaptation with eye movement training, for patients with unilateral spatial neglect (USN) following a stroke. After evaluations at baseline and post-intervention follow-ups, the authors seek to identify an innovative treatment strategy, thereby providing a new evidence-based treatment option for patients with USN.

Tang et al. perform a retrospective study to investigate the sex-dependent relationship between serum uric acid (UA) levels and the occurrence of spontaneous HT in ischemic stroke patients. They discover that elevated UA levels are independently linked to a higher risk of spontaneous HT in males but not in female patients. These findings indicate a sex-dependent association between UA and the occurrence of spontaneous HT in male patients who have suffered from ischemic stroke.

Song et al. investigate the potential link between stroke and common gastrointestinal disorders such as peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Using Mendelian randomization, the authors do not uncover any evidence suggesting that genetic predisposition to ischemic stroke directly influences the development of gastrointestinal disorders. However, the authors do identify an association between complications arising from intracerebral hemorrhage, specifically deep ICH, and an increased risk of developing PUD and GERD. Therefore, this study suggests a brain-gut axis connection that links stroke and common gastrointestinal disorders.

Dumas et al. perform a retrospective study to evaluate the impact of infarct laterality on functional clinical outcomes in AIS patients who had low ASPECT (0–5), the main quantitative score used by brain imaging studies including CT and MRI scans (7). The study enrolls patients with either intracranial internal carotid artery or middle cerebral artery occlusions with a low ASPECT score (0–5) and finds that clinical outcomes at day 90 post-stroke do not significantly differ based on the laterality of the stroke. This suggests that mechanical thrombectomy treatment is equally valuable regardless of stroke laterality in this patient group.

Conclusion

In conclusion, although post-stroke complications still represent a significant challenge in stroke care and management, the articles published in this Research Topic represent a substantial contribution to enhancing our understanding of the mechanisms and diagnosis of, and therapies for, post-stroke complications. The newly identified diagnostic tools, including neuroimaging and biomarkers such as miRNA and mRNA, hold promise for the early detection of and intervention in post-stroke complications, thus potentially increasing the efficacy of treatment and improving the recovery journey for stroke survivors.

Author contributions

WC: Conceptualization, Validation, Visualization, Writing—original draft, Writing—review and editing. YH: Validation, Writing—review and editing. C-MC: Writing—review and editing. HZ: Writing—review and editing.

Funding

This work was supported in part by NIH Training Grant (No. T32 DK007260, to WC), the National Natural Science Foundation of China (82101367, to YH), the Natural Science Foundation of Guangdong Province (2022A1515012370, to YH), and the Research Fund of University of Macau (File no. MYRG2020-00004-ICMS, to C-MC).

Acknowledgments

The authors thank all the authors and reviewers who contributed to this Research Topic. The authors also thank the co-editors of this Research Topic, for their dedication and involvement in all stages of the editorial process.

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

References

1. GBD 2017 DALYs HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* (2018) 392:1859–922. doi: 10.1016/S0140-6736(18)32335-3

2. Simats A, Liesz A. Systemic inflammation after stroke: implications for post-stroke comorbidities. *EMBO Mol Med.* (2022) 14:e16269. doi: 10.15252/emmm.202216269

3. Robinson RG, Jorge RE. Post-stroke depression: a review. *Am J Psychiatry.* (2016) 173:221–31. doi: 10.1176/appi.ajp.2015.15030363

4. Wilson RD, Chae J. Hemiplegic shoulder pain. *Phys Med Rehabil Clin N Am.* (2015) 26:641–55. doi: 10.1016/j.pmr.2015.06.007

5. Kumar P. Hemiplegic shoulder pain in people with stroke: present and the future. *Pain Manag.* (2019) 9:107–10. doi: 10.2217/pmt-2018-0075

6. Lo YT, Chang CM, Chen MH, Hu FW, Lu FH. Factors associated with early 14-day unplanned hospital readmission: a matched case-control study. *BMC Health Serv Res.* (2021) 21:870. doi: 10.1186/s12913-021-06902-6

7. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group Alberta Stroke Programme Early CT Score. *Lancet.* (2000) 355:1670–4. doi: 10.1016/S0140-6736(00)02237-6

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 06 December 2022
DOI 10.3389/fneur.2022.1056423

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
Ali Golestani,
Tom Baker Cancer Centre, Canada
Giuseppe Lanza,
University of Catania, Italy

*CORRESPONDENCE
Chun Wang
wangchun36@126.com
Yusong Ge
geyusongmed@sina.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 28 September 2022
ACCEPTED 23 November 2022
PUBLISHED 06 December 2022

CITATION
Yan H, Chen H, Liu Y, Zhang Q, Guo Y, Fu Y, Ren H, Wang H, Wang C and Ge Y (2022) Assessment of cognitive impairment after acute cerebral infarction with T1 relaxation time measured by MP2RAGE sequence and cerebral hemodynamic by transcranial Doppler. *Front. Neurol.* 13:1056423. doi: 10.3389/fneur.2022.1056423

Assessment of cognitive impairment after acute cerebral infarction with T1 relaxation time measured by MP2RAGE sequence and cerebral hemodynamic by transcranial Doppler

Hongting Yan[1†], Honghai Chen[2†], Yanzhi Liu[1†], Qiannan Zhang[1], Yunchu Guo[1], Yu Fu[1], Hongling Ren[1], Hairong Wang[1], Chun Wang[1*] and Yusong Ge[1*]

[1]The Department of Neurology, The Second Hospital of Dalian Medical University, Dalian, Liaoning, China, [2]The Department of Radiology, The Second Hospital of Dalian Medical University, Dalian, Liaoning, China

Objective: This study aimed to investigate early brain microstructural changes discovered using magnetization-prepared two rapid acquisition gradient echo (MP2RAGE) sequence and cerebral hemodynamic using TCD for cognitive impairment after acute cerebral infarction.

Methods: We enrolled 43 patients with acute cerebral infarction and 21 healthy people in the study, who were subjected to cognitive assessments, the MP2RAGE sequence, and a cerebral hemodynamic examination. A total of 26 brain regions of interest were investigated. Furthermore, we used cerebral hemodynamics to explain brain microstructural changes, which helped us better understand the pathophysiology of cognitive impairment after acute cerebral infarction and guide treatment.

Results: T1 relaxation times in the left frontal lobe, right frontal lobe, right temporal lobe, left precuneus, left thalamus, right hippocampus, right head of caudate nucleus, and splenium of corpus callosum were substantially different across the three groups, which were significantly correlated with neuropsychological test scores. CI group patients had significantly lower cerebral blood flow velocity than those in the N-CI and Normal groups. The receiver operating curve analysis revealed that most T1 relaxation times had high sensitivity and specificity, especially on the right temporal lobe and right frontal lobe. There was a potential correlation between T1 relaxation times and MMSE scores through TCD parameters.

Conclusion: The MP2RAGE sequence can detect alterations in whole brain microstructure in patients with cognitive impairment after acute cerebral infarction. Brain microstructural changes could influence cognitive function through cerebral hemodynamics. T1 relaxation times on the right temporal lobe and the right frontal lobe are expected to be a prospective biomarker of cognitive impairment after acute cerebral infarction.

KEYWORDS

cognitive impairment, acute cerebral infarction, MP2RAGE sequence, neuroimaging, microstructural change

Introduction

According to epidemiological studies, 12.2 million new stroke incidents occurred worldwide in 2019 (1). Approximately two-thirds of stroke patients have some degree of cognitive impairment (2). Cognitive impairment following a stroke impairs the patient's capacity to execute daily living activities and increases mortality (3). According to previous research, screening patients for cognitive function during the acute phase of stroke is critical. Early diagnosis and timely care can dramatically improve a patient's prognosis and control disease progression (4). The American Heart Association recommends in its *Guidelines for Adult Stroke Rehabilitation and Recovery* that all patients with acute cerebral infarction be assessed for cognitive impairment before being discharged from the hospital (5).

However, today's cognitive impairment diagnosis is primarily based on the patient's clinical presentation and neuropsychological measures. The scales are susceptible to a number of factors, including subject compliance and the test taker's subjective opinion. Patients with impaired hearing, manual dexterity, or who are bedridden are unable to cooperate with the scale. As a result, the neuropsychological scales have some limitations. Clinicians require a more objective biomarker to diagnose cognitive impairment following acute cerebral infarction.

Many studies in recent years have found a clear correlation between cognitive impairment and neuroimaging (white matter hyperintensities, cortical thickness, and so on) (6–8). However, traditional neuroimaging techniques cannot be quantified. Breakthroughs in neuroimaging may improve the ability to detect cognitive impairment and open up new avenues for early diagnosis. The magnetization-prepared two rapid acquisition gradient echo (MP2RAGE) sequence is a novel quantitative MRI approach. It successfully corrects inhomogeneity in the B1 radio-frequency transmit field and lowers proton contamination as well as T2* contrast (9). It produces quantitative T1 images in order to calculate T1 relaxation time. It is utilized to analyse microstructural alterations in the brain as well as detect diffuse white and gray matter damage in the cranial brain (10). A prior study used relaxation time to detect permanent cerebral ischemia and found that it can predict stroke onset time (11).

The incidence and the recurrence rate of ischemic stroke can often be affected by intracranial arterial lesions (12). The intracranial vascular lesion is the most fundamental cause of cerebrovascular disease, so the detection and evaluation of cerebral vessels and cerebral hemodynamics are significant for preventing and treating cerebrovascular disease. Transcranial Doppler (TCD) is commonly used in clinical practice to examine cerebral hemodynamics, and TCD parameters can reflect various pathological conditions, including atherosclerosis and vascular endothelial dysfunction (13). TCD technique has a high research value in the diagnosis of cerebrovascular diseases and can even identify preclinical cerebral blood flow changes (14, 15). Several investigations have found a clear correlation between cerebral hemodynamic alterations and cognitive impairment (16–18). Many researchers have used TCD to investigate cerebral hemodynamic changes in patients with cognitive impairment. Some researchers found that hemodynamic dysfunction measured by TCD might play a pathogenic role in the development of cognitive impairment also in patients with subcortical ischemic vascular disease (19). It has also been found that the severity of cerebral hemodynamic abnormalities observed by TCD may, to some extent, represent the severity of cognitive impairment (20).

This study aimed to look at microstructural changes at the whole-brain level in individuals with cognitive impairment after an acute cerebral infarction utilizing the MP2RAGE sequence, as well as the relationship between microstructural alterations and cerebral hemodynamics. We hypothesized that the altered brain microstructure measured by the MP2RAGE sequence could provide neuroimaging evidence to assist in the diagnosis of patients with cognitive impairment after acute cerebral infarction, and TCD might be able to provide evidence of cerebral hemodynamic for this altered brain microstructure.

Materials and methods

Study participants

This study included 43 patients with acute cerebral infarction, including 23 with cognitive impairment (CI group, mean age 68.91 years, 9 males, and 14 females) and 20 without cognitive impairment (N-CI group, mean age 67.95 years, 12 males, and 8 females) in the Second Hospital of Dalian Medical University. Our institution's Ethics Review Board examined and approved this study procedure. The following were the inclusion criteria for patients with acute cerebral infarction: (1) first acute onset within 7 days of cerebral infarction; (2) symptoms or signs lasting $>$ 24 h; (3) imaging revealing a single ischemic lesion on the relevant side with no intercerebral hemorrhage. The following were the exclusion criteria: (1) recurrent stroke; (2) pre-stroke significant cognitive dysfunction, which was assessed using the informant questionnaire on cognitive decline in the elderly (IQCODE $>$ 3.3) by asking the informant and caregiver; (3) aphasia, dysarthria, hearing impairment, and inability to cooperate with examinations; (4) any other structural brain structure damage detected by MRI; (5) Fazekas classification for white matter hyperintensity $>$ grade 1; (6) a history of alcohol or drug addiction; (7) major folic acid and Vitamin B_{12} abnormalities; (8) pre-existing schizophrenia, severe anxiety, depression, or other mental health disorders; (9) patients with severe disease or severe disease aggravated by vital organ malfunction; (10) patients with metallic materials or other implants in the body that preclude the use of MRI; and (11) patients who lack informed capacity and refuse to sign the informed consent form. Simultaneously, 21 healthy individuals of similar ages were recruited (control group, mean age 65.86 years, 9 males, and 12 females). The following were the inclusion criteria for healthy individuals: (1) matched by gender, age, and education to the CI and N-CI groups; (2) no history of clinical stroke; (3) no neurological dysfunction; (4) cognitive assessment test scores within normal range; (5) MRI studies revealed no brain structural damage; (6) Fazekas classification for white matter hyperintensity $\leq$ grade 1; (7) no history of alcohol or drug dependency; (8) no substantial abnormalities in folic acid and Vitamin B_{12}; (9) no schizophrenia, severe anxiety, depression, or other mental health conditions; (10) no severely advanced disease or severe disease complicated by vital organ dysfunction; (11) no metallic materials or other implants in the body prohibiting the use of MRI; and (12) have the capacity to learn and agree to sign the informed consent form.

Neuropsychological assessment

A properly trained clinician used neuropsychological measures to assess all patients. The Mini-mental state examination (MMSE), the Montreal cognitive assessment scale (MoCA), and the Activity of daily living scale (ADL) were among the neuropsychological assessment used. MMSE values were used to categorize, with a score of $<$27 indicating objective cognitive impairment. To determine if respondents had anxiety or depressive disorders, the Hamilton Anxiety (HAMA) and Hamilton Depression (HAMD) scales were employed.

Magnetic resonance imaging acquisition

All brain MRI scans were performed using a Skyra 3.0 T equipment (Siemens) and a 20-channel head/neck coil. The MP2RAGE sequence took 5 min and 47 s [voxel size=1 mm $\times$ 1 mm $\times$ 1 mm, the field of view = 256*240 mm, repetition time (TR) = 5,000 ms, echo time (TE) = 2.98 ms, TI1 = 700 ms, TI2 = 2,500 ms, flip angle1 = 4°, flip angle2 = 5°, 176 slices]. The MP2RAGE sequence created four sets of images automatically: INV1, INV2, UNI-Images, and T1-Images, and we used the last set of data to do quantitative measurements. No contrast was administered during the MP2RAGE sequence. T1-weighted images, T2-weighted images, T2 fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences were also included in the MRI protocol.

Image processing and analysis

The expert radiologist collected raw MP2RAGE images from patients for post-processing in order to generate quantitative T1 maps. T1 relaxation times were calculated using T1 maps generated by the MP2RAGE sequence. In consideration of the possibility of misidentifying brain regions by using automated whole-brain analysis and our extensive experience in the manual region of interest (ROI) analysis, we selected the latter as a follow-up work. T1 maps were used to manually draw regions of interest (ROI) on the following brain regions: bilateral frontal lobe, bilateral parietal lobe, bilateral temporal lobe, bilateral occipital lobe, bilateral precuneus, bilateral internal capsule, bilateral corona radiata, bilateral centrum semiovale, genu of corpus callosum, splenium of corpus callosum, bilateral hippocampus, bilateral thalamus, bilateral lentiform nucleus, and bilateral head of caudate nucleus. The radiologist chose the central part of the biggest layer, as well as the structures of the upper and lower adjacent layers, and drew ROIs of the same size (10 mm^2) in the bilateral lobes' symmetrical regions. When drawing ROIs, interfering regions such as the infarct zone, vascular space, cerebral sulcus and gray matter were avoided. The measurements were repeated five times, and the average of the five repeated measurements was used in the statistical analysis.

TABLE 1 General characteristics of the study subjects.

		CI group ($N = 23$)	N-CI group ($N = 20$)	NORM group ($N = 21$)	$X^2/T/F$	p
Age (years)		68.91 ± 8.43	67.95 ± 4.17	65.86 ± 4.83	1.37	0.26
Gender	Male	9 (39.1)	12 (60.0)	9 (42.9)	2.07	0.36
	Female	14 (60.9)	8 (40.0)	12 (57.1)		
Hypertension	No	3 (13.0)	8 (40.0)	4 (19.0)	4.67	0.10
	Have	20 (87.0)	12 (60.0)	17 (81.0)		
Diabetes mellitus	No	10 (43.5)	7 (35.0)	5 (23.8)	1.89	0.39
	Have	13 (56.5)	13 (65.0)	16 (76.2)		
History of smoking	No	17 (73.9)	10 (50.0)	16 (76.2)	3.92	0.14
	Have	6 (26.1)	10 (50.0)	5 (23.8)		
History of drinking	No	20 (87.0)	16 (80.0)	19 (90.5)	0.96	0.62
	Have	3 (13.0)	4 (20.0)	2 (9.5)		
Duration of education	<9	6 (26.1)	6 (30.0)	6 (28.6)	0.08	0.96
	≥9	17 (73.9)	14 (70.0)	15 (71.4)		
Fazekas	Grade 0	16 (69.6)	15 (75.0)	15 (71.4)	0.08	0.93
	Grade 1	7 (30.4)	5 (25.0)	6 (28.6)		
Size of the infarction	0–20 mm	17 (73.9)	15 (75.0)	–	0.25	0.88
	20–40 mm	4 (17.4)	4 (20.0)	–		
	>40 mm	2 (8.7)	1 (5.0)	–		
Side of the infarction	Left	11 (47.8)	9 (45.0)	–	0.03	0.86
	Right	12 (52.2)	11 (55.0)	–		
Site of the infarction	Frontal lobe	5 (21.7)	5 (21.7)	–	9.17	0.33
	Parietal lobe	5 (25.0)	5 (25.0)	–		
	Temporal lobe	3 (13.0)	1 (5.0)	–		
	Occipital lobe	2 (8.7)	0	–		
	Thalamus	2 (8.7)	3 (15.0)	–		
	Pons	2 (8.7)	0	–		
	Medulla oblongata	1 (4.3)	2 (10.0)	–		
	Cerebellum	2 (8.7)	0	–		
	Corona radiata	1 (4.3)	4 (20.0)	–		
Duration	(Apopiecticus insultus to examination)	45.39 ± 11.78	45.65 ± 11.92	–	0.01	0.94
TOAST classification	Large-artery atherosclerotic	17 (73.9)	16 (80.0)	–	0.21	0.65
	Cardioembolism	0	0	–		
	Small-vessel disease	6 (26.1)	4 (20.0)	–		
	Other and undetermined etiologies	0	0	–		
Intravenous thrombolysis	No	19 (82.6)	16 (80.0)	–	0.05	0.83
	Have	4 (17.4)	4 (20.0)	–		
Antiplatelet aggregation		23 (100.00)	20 (100.00)	–		–
Intensive lipid lowering		23 (100.00)	20 (100.00)	–		–
NIHSS		1.69 ± 1.18	1.70 ± 1.12	–	−0.01	0.99
mRS		1.13 ± 0.69	1.05 ± 0.51	–	0.43	0.67

(Continued)

TABLE 1 (Continued)

	CI group ($N = 23$)	N-CI group ($N = 20$)	NORM group ($N = 21$)	$X^2/T/F$	p
BMI	24.1 ± 3.05	24.85 ± 2.57	26.14 ± 3.14	2.29	0.08
TG (mmol/L)	1.47 ± 0.34	1.68 ± 0.38	1.44 ± 0.32	2.77	0.07
TC (mmol/L)	4.9 ± 1.17	4.26 ± 1.54	4.52 ± 0.83	1.54	0.22
LDL-C (mmol/L)	3.02 ± 0.84	3.02 ± 1.06	2.7 ± 0.66	0.96	0.39
HCY (umol/L)	12.79 ± 3.95	11.64 ± 3.87	11.21 ± 3.16	1.09	0.34
UA (umol/L)	300.53 ± 126.29	321.64 ± 78.84	318.47 ± 107.28	0.25	0.78

CI, cognitive impairment; N-CI, no-cognitive impairment; NORM, normal; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Ranking Scale; BMI, Body Mass Index; TG, Triglyceride; TC, Total cholesterol; LDL-C, Low-density lipoprotein; HCY, Homocysteine; UA, Uric Acid; Statistical significance was set to $p < 0.05$.

TABLE 2 Neuropsychological tests of the study subjects.

	CI group ($N = 23$)	N-CI group ($N = 20$)	NORM group ($N = 21$)	F	p
MMSE	19.61 ± 4.68*#	27.9 ± 1.12	28.48 ± 1.25	61.95	<0.01
MoCA	15.65 ± 5.49*#	27.4 ± 0.6	27.48 ± 0.81	91.38	<0.01
ADL	44.74 ± 16.03*#	24.55 ± 4.07	20 ± 0.00	39.29	<0.01
HAMA	3.69 ± 1.58	4.00 ± 1.62	3.71 ± 2.02	0.20	0.82
HAMD	4.13 ± 1.89	3.40 ± 1.53	3.52 ± 1.80	1.09	0.34

MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; ADL, Activity of daily living; HAMA, Hamilton Anxiey Scale; HAMD, Hamilton Depression Scale; *$p <$ 0.01 vs. NORM group, #$p < 0.01$ vs. N-CI group.

Transcranial Doppler ultrasound procedure

A professional sonographer who was blind to the clinical diagnosis performed TCD measurements (TCD 2000S, Chioy, equipped with a 2-MHz probe). The individuals were positioned supine, with the TCD probe situated on the temporal window. The middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), basilar artery (BA) and vertebral artery (VA) were probed bilaterally at depths of 45–60 mm, 63–72 mm, and 63–76 mm, respectively, and the systolic velocity (Vs), diastolic velocity (Vd), mean velocity (Vm), pulsatility index (PI) and resistivity index (RI) of each vessel were recorded.

Statistical analysis

SPSS 11.0 was used for statistical analysis. The data is displayed as mean ± standard deviation (SD). The Shapiro-Wilk test was employed to determine the normality of the data. The association between categorical variables was used to analyse its relationship. Chi-square tests were used to compare categorical differences across groups. To compare the two groups of measures, the independent samples t-test was utilized. The quantitative differences between groups were investigated using the one-way analysis of variance (ANOVA). The Bonferront test was used to compare factors among groups that met the homogeneity of variance criteria. P-values < 0.05 were deemed statistically significant (with Bonferroni corrections for multiple testing where necessary). Pearson's correlation analysis was used to examine the relationship between two continuous variables. The area under the curve (AUC), specificity, and sensitivity of significant correlation values were assessed individually using receiver operating characteristic (ROC) curves. The discriminatory capacity of measured factors to predict cognitive impairment following an acute cerebral infarction was evaluated using ROC curves. All P-values presented are two-tailed. In addition, SPSS 11.0 was adopted to perform the mediation analysis.

Results

General characteristics and neuropsychological tests

Table 1 showed that there were no significant differences among the three groups in terms of age, gender, history of hypertension, history of diabetes, history of smoking, history of drinking, duration of education, Body Mass Index (BMI), triglyceride, total cholesterol, low-density lipoprotein, homocysteine or uric acid. Furthermore, there were no

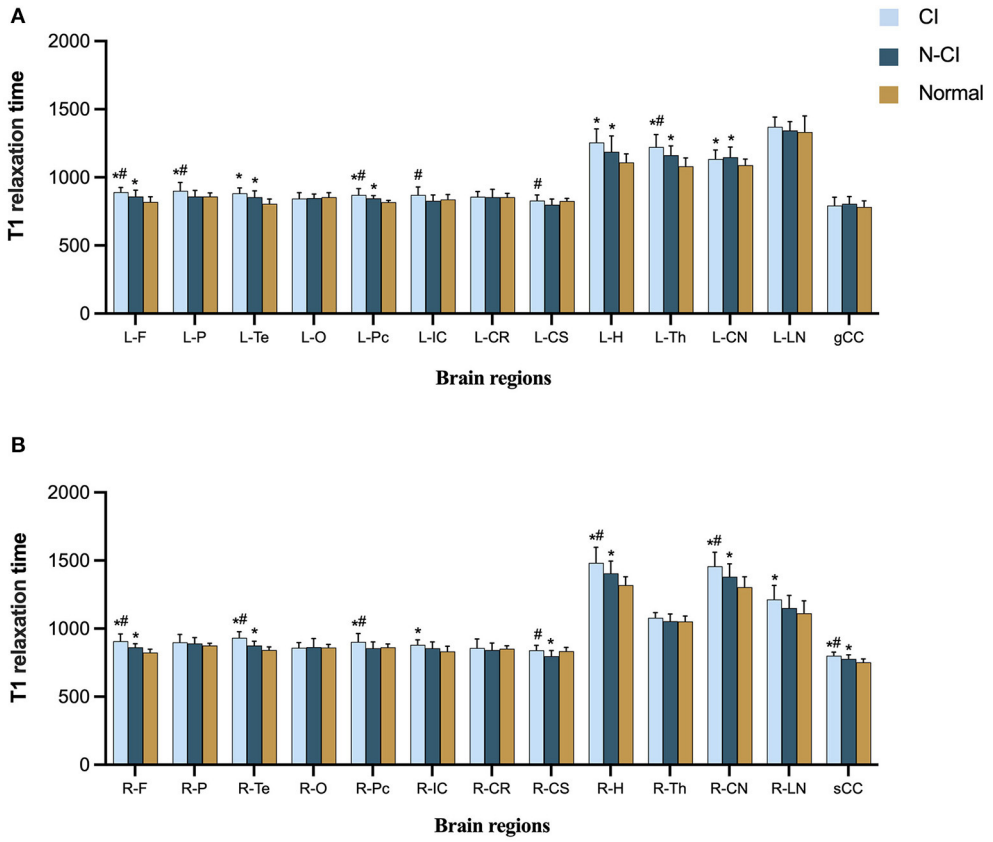


FIGURE 1
Means (±SD) of T1 relaxation times in each ROI, for each study group. **(A)** Left hemisphere and genu of corpus callosum; **(B)** right hemisphere and splenium of corpus callosum. CI patients had significantly higher T1 relaxation times in most ROIs than the N-CI and Normal groups. ROIs: L-F, left frontal lobe; L-P, left parietal lobe; L-Te, left temporal lobe; L-O, left occipital lobe; L-Pc, left precuneu; L-IC, left internal capsule; L-CR, left corona radiata; L-CS, left centrum semiovale; L-H, left hippocampus; L-Th, left thalamus; L-CN, left corona radiata; L-LN, left lentiform nucleus; R-F, right frontal lobe; R-P, right parietal lobe; R-Te, right temporal lobe; R-O, right occipital lobe; R-Pc, right precuneu; R-IC, right internal capsule; R-CR, right corona radiata; R-CS, right centrum semiovale; R-H, right hippocampus; R-Th, right thalamus; R-CN, right corona radiata; R-LN, right lentiform nucleus; gCC, genu of corpus callosum; sCC, splenium of corpus callosum.*$p < 0.05$ vs. Normal group, #$p < 0.05$ vs. N-CI group.

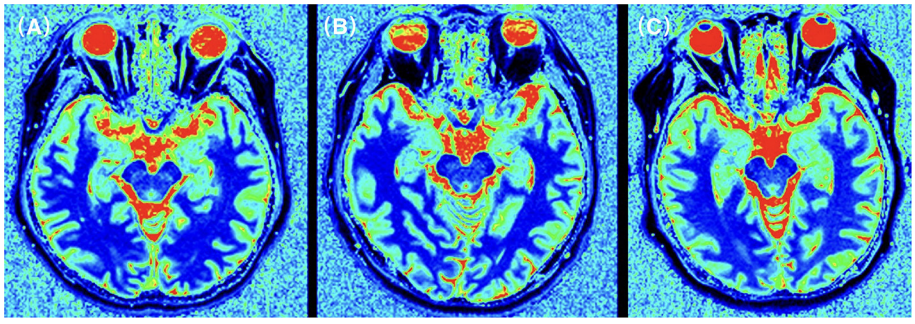


FIGURE 2
T1 relaxation times for the temporal lobe in an CI patient **(A)**, a N-CI patient **(B)**, and a healthy control **(C)**. T1 relaxation maps was generated for each subject. ROIs were manually plotted on these maps and parameter values were recorded. The results showed that the T1 relaxation times in the frontal lobe of the CI group were higher than those in the N-CI and normal groups ($p < 0.05$).

significant changes between the CI and N-CI groups in NIHSS (National Institutes of Health Stroke Scale) scores, mRS (Modified Ranking Scale) scores, or the characteristics (side, site, type) and treatments of cerebral infarction ($P > 0.05$).

There were significant differences in MMSE, MoCA, and ADL scores among the three groups ($p < 0.01$). The MMSE and MoCA scores were lowest in the CI group and highest in the Normal group. The ADL scores of the CI group were greater than those of the Normal and N-CI groups. The HAMA and HAMD scores did not differ significantly across the three groups (Table 2).

Comparisons of T1 relaxation times among the three groups

T1 relaxation times in the left frontal lobe, right frontal lobe, right temporal lobe, left precuneus, left thalamus, right hippocampus, right head of caudate nucleus, and splenium of corpus callosum ($P < 0.05$) were substantially different across the three groups.

The following ROIs had significant differences in T1 relaxation times between the CI and Normal groups ($P < 0.05$): left frontal lobe, right frontal lobe, left parietal lobe, left temporal lobe, right temporal lobe, left praecuneus, right praecuneus, right internal capsule, left hippocampus, right hippocampus, left thalamus, left head of the caudate nucleus, right head of caudate nucleus, right lentiform nucleus, and splenium of the corpus callosum.

T1 relaxation times for each ROI differed significantly between the N-CI and Normal groups ($P < 0.05$): left frontal lobe, right frontal lobe, left temporal lobe, right temporal lobe, left precuneus, right centrum semiovale, left hippocampus, right hippocampus, left thalamus, left head of the caudate nucleus, right head of caudate nucleus, splenium of the corpus callosum.

T1 relaxation times differed significantly between the N-CI and CI groups in the following ROIs ($P < 0.05$): left frontal lobe, right frontal lobe, left parietal lobe, right temporal lobe, left praecuneus, right praecuneus, left internal capsule, left centrum semiovale, right centrum semiovale, right hippocampus, left thalamus, right head of caudate nucleus, splenium of corpus callosum (Figures 1, 2).

Abnormalities in TCD parameters

Table 3 showed significant differences in Left MCA Vd, Left MCA Vm, Left MCA PI, Left MCA RI, Right MCA Vd, Right MCA Vm Left ACA Vd, Left ACA Vm, Left ACA PI, Right ACA Vs, Right ACA RI, Right PCA Vd, BA Vd, BA Vm, BA PI, and BA RI, among the three groups.

There were significant variations in TCD parameters between the CI, and the Normal groups were as follows ($P < 0.05$): Left MCA Vd, Left MCA Vm, Left MCA PI, Left MCA RI, Right MCA Vd, Right MCA Vm, Left ACA Vd, Left ACA Vm, Right ACA RI, Left ACA PI, Right ACA Vs, BA Vd, BA Vm, BA PI, and BA RI.

There was a significant variation in Right PCA Vd between the N-CI and Normal groups ($P < 0.05$).

Correlation analysis between T1 relaxation times and neuropsychological tests

The examination of T1 relaxation times revealed a total of 8 ROIs that differed considerably, as indicated above. T1 relaxation times were thought to be helpful in assessing the pathological alterations in brain tissue associated with cognitive impairment in patients with acute cerebral infarction. As a result, we did a follow-up correlation study for T1 relaxation times and Neuropsychological Tests.

T1 relaxation times in the left frontal lobe, right frontal lobe, right temporal lobe, left praecuneus, right hippocampus, left thalamus, right head of caudate nucleus, and splenium of the corpus callosum were significantly negatively correlated with MMSE scores, significantly negatively correlated with MoCA scores, and significantly positively correlated with ADL scores. The most robust correlation coefficient was found between T1 relaxation times in the right frontal lobe and MMSE scores (full Pearson's coefficient values are included in Table 4).

Correlation analysis between TCD parameters and neuropsychological tests

Neuropsychological scores, except for Left MCA PI, Left MCA RI, Right MCA Vd, Right MCA Vm, Right ACA Vs and BA Vm (Table 5), all cerebral hemodynamic indicators with statistical significance, were substantially linked with cognitive scores.

Correlation analysis between T1 relaxation times and TCD parameters

To determine if cerebral hemodynamic variations can partially explain brain microstructure changes. For the correlation study, we chose T1 relaxation times and TCD parameters that differed statistically across the three groups. T1 relaxation times in most ROIs, save the left praecuneus, were strongly linked with TCD parameters, as shown in Table 6.

TABLE 3 TCD parameters of the study subjects.

	CI group ($N = 23$)	N-CIgroup ($N = 20$)	Normal group ($N = 21$)	F	p
Left MCA Vs	109.09 ± 25.38	126.75 ± 48.77	127.33 ± 27.1	1.96	0.15
Left MCA Vd	33.3 ± 8.28*	41.85 ± 18.1	49.81 ± 12.67	8.35	**<0.01**
Left MCA Vm	58.57 ± 11.17*	70.15 ± 26.31	75.65 ± 16.28	4.84	**0.01**
Left MCA PI	1.29 ± 0.29*	1.21 ± 0.26	1.03 ± 0.19	5.86	**<0.01**
Left MCA RI	0.69 ± 0.79*	0.66 ± 0.08	0.61 ± 0.06	6.04	**<0.01**
Right MCA Vs	109.52 ± 30.74	118.25 ± 38.36	130.24 ± 35.83	1.94	0.15
Right MCA Vd	42.78 ± 14.34*	43.85 ± 16.34	56.67 ± 20.17	4.37	**0.02**
Right MCA Vm	65.03 ± 16.62*	68.65 ± 22.41	81.19 ± 22.92	3.62	**0.03**
Right MCA PI	1.04 ± 0.34	1.09 ± 0.23	0.93 ± 0.25	1.91	0.16
Right MCA RI	0.60 ± 0.12	0.63 ± 0.08	0.56 ± 0.11	1.78	0.18
Left ACA Vs	65.53 ± 21.23	69.53 ± 13.02	72.7 ± 16.51	0.93	0.40
Left ACA Vd	21.07 ± 8.19*	26.95 ± 5.8	28.83 ± 6.14	7.71	**<0.01**
Left ACA Vm	35.89 ± 11.56*	41.14 ± 6.36	43.45 ± 7.92	4.09	**0.02**
Left ACA PI	1.25 ± 0.31*	1.04 ± 0.27	1 ± 0.28	4.60	**0.01**
Left ACA RI	0.60 ± 0.14	0.60 ± 0.11	0.63 ± 0.80	0.79	0.46
Right ACA Vs	64.69 ± 12.89*	66.2 ± 11.44	74.93 ± 10.78	4.71	**0.01**
Right ACA Vd	26.28 ± 7.68	25.29 ± 6.94	27.31 ± 6.51	0.45	0.64
Right ACA Vm	38.42 ± 6.52	39.59 ± 7.15	43.18 ± 6.76	2.87	0.06
Right ACA PI	1.04 ± 0.35	1.03 ± 0.31	1.12 ± 0.24	0.55	0.58
Right ACA RI	0.67 ± 0.10*	0.60 ± 0.10	0.59 ± 0.10	3.73	**0.03**
Left PCA Vs	53.6 ± 21.66	56.42 ± 25.17	68.84 ± 23.5	2.58	0.08
Left PCA Vd	21.47 ± 11.08	21.54 ± 10.4	27.92 ± 12.41	2.27	0.11
Left PCA Vm	32.18 ± 14	33.16 ± 14.7	41.56 ± 15.35	2.64	0.08
Left PCA PI	1.04 ± 0.28	1.06 ± 0.24	1.02 ± 0.28	0.11	0.90
Left PCA RI	0.61 ± 0.13	0.61 ± 0.08	0.60 ± 0.92	0.19	0.83
Right PCA Vs	60.72 ± 20.74	56.45 ± 15.04	65.05 ± 21.04	1.02	0.37
Right PCA Vd	24.83 ± 10.14	18.66 ± 4.73*	26.88 ± 10.74	4.57	**0.01**
Right PCA Vm	36.8 ± 12.71	31.26 ± 6.5	39.6 ± 12.59	2.99	0.06
Right PCA PI	0.99 ± 0.29	1.2 ± 0.33	0.99 ± 0.34	2.89	0.06
Right PCA RI	0.59 ± 0.11	0.65 ± 0.11	0.58 ± 0.13	2.57	0.09
BA Vs	56.66 ± 13.01	63.39 ± 27.14	65.89 ± 20.62	1.17	0.32
BA Vd	15.85 ± 3.62*#	24.63 ± 10.34	24.98 ± 10.38	8.06	**<0.01**
BA Vm	29.45 ± 5.14*#	37.55 ± 15.4	38.62 ± 12.07	4.24	**0.02**
BA PI	1.37 ± 0.31*#	1.03 ± 0.26	1.08 ± 0.35	7.60	**<0.01**
BA RI	0.71 ± 0.09*#	0.6 ± 0.10	0.61 ± 0.13	6.53	**<0.01**
Left VA Vs	35.08 ± 9.57	44.27 ± 16.51	41.52 ± 9.86	3.23	0.05
Left VA Vd	14.11 ± 4.44	17.25 ± 9.23	16.35 ± 5.58	1.30	0.28
Left VA Vm	21.1 ± 5.43	26.25 ± 10.6	24.74 ± 6.48	2.58	0.08
Left VA PI	1.00 ± 0.34	1.09 ± 0.49	1.05 ± 0.28	0.28	0.76
Left VA RI	0.59 ± 0.12	0.61 ± 0.14	0.61 ± 0.10	0.20	0.80
Right VA Vs	32.63 ± 15.85	39.23 ± 26.73	41.41 ± 14.36	1.22	0.30
Right VA Vd	12.4 ± 4.48	15.74 ± 8.62	15.55 ± 6.8	1.70	0.19
Right VA Vm	19.14 ± 7.89	23.57 ± 14.14	24.17 ± 8.83	1.51	0.23
Right VA PI	1.02 ± 0.31	0.97 ± 0.31	1.08 ± 0.28	0.62	0.54
Right VA RI	0.59 ± 0.11	0.58 ± 0.13	0.62 ± 0.09	0.77	0.47

Left MCA, left middle cerebral artery; Right MCA, right middle cerebral artery; Left ACA, left anterior cerebral artery; Right ACA, right anterior cerebral artery; Left PCA, left posterior cerebral artery; Right PCA, right posterior cerebral artery; BA, basilar artery; Left VA, left vertebral artery; Right VA, right vertebral artery; Vs, systolic velocity; Vd, diastolic velocity; Vm, mean velocity; PI, pulsatility index; RI, resistivity index.* $p < 0.05$ vs. Normal group, # $p < 0.05$ vs. N-CI group.
The bold values mean $p < 0.05$.

TABLE 4 Pearson's correlations of T1 relaxation times with neuropsychological tests.

	L-F	R-F	R-Te	L-Pc	sCC	R-H	L-Th	R-CN
MMSE	−0.40**	−0.70**	−0.58**	−0.43**	−0.45**	−0.36**	−0.58**	−0.56**
MoCA	−0.44**	−0.68**	−0.58**	−0.42**	−0.45**	−0.39**	−0.55**	−0.63**
ADL	0.37**	0.49**	0.64**	0.43**	0.42**	0.33**	0.53**	0.37**

MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; ADL, Activity of daily living; L-F, left frontal lobe; R-F, right frontal lobe; R-Te, right temporal lobe; L-Pc, left precuneu; sCC, splenium of corpus callosum; R-H, right hippocampus; L-Th, left thalamus; R-CN, right corona radiata; $^{**}p < 0.01$.

TABLE 5 Pearson's correlations between TCD parameters and neuropsychological tests.

	MMSE	MoCA	ADL
Left MCA Vd	0.31*	0.32*	−0.40**
Left MCA Vm	0.29*	0.27*	−0.32*
Left MCA PI	−0.16	−0.22	0.34*
Left MCA RI	−0.17	−0.22	0.34**
Right MCA Vd	0.11	0.11	−0.22
Right MCA Vm	0.19	0.16	−0.21
Left ACA Vd	0.45**	0.51**	−0.42**
Left ACA Vm	0.40**	0.44**	−0.34**
Left ACA PI	−0.27*	−0.33**	0.33**
Right ACA Vs	0.13	0.17	−0.1
Right ACA RI	−0.26*	−0.30*	0.28
BA Vd	0.34**	0.38**	−0.42**
BA Vm	0.22	0.24	−0.36**
BA PI	−0.41**	−0.45**	0.34**
BA RI	−0.38**	−0.41**	0.33**

MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; L-F, left frontal lobe; R-F, right frontal lobe; R-Te, right temporal lobe; L-Pc, left precuneu; sCC, splenium of corpus callosum; R-H, right hippocampus; L-Th, left thalamus; R-CN, right corona radiata; Left MCA, left middle cerebral artery; Right MCA, right middle cerebral artery; Left ACA, left anterior cerebral artery; Right ACA, right anterior cerebral artery; BA, basilar artery; Vs, systolic velocity; Vd, diastolic velocity; Vm, mean velocity; PI, pulsatility index; RI, resistivity index. $^{**}p < 0.01$; $^{*}p < 0.05$.

Receiver operating characteristic curve analysis

We plotted the ROC curve using the T1 relaxation time in all the ROIs that showed a significant effect. Table 7 showed the AUC for the ability of T1 relaxation time to distinguish between healthy controls and patients with cognitive impairment after acute cerebral infarction. T1 relaxation time in the right temporal lobe was identified as an excellent individual discriminator of cognitive impairment after acute cerebral infarction from healthy controls using ROC analysis; T1 relaxation time of 887.4, sensitivity and specificity were 91.30 and 95.24%, respectively, with an AUC value of 0.98 (Figure 3).

Mediation analysis

The statistically significant T1 relaxation times were used as independent variables. MMSE scores were used as dependent variables. TCD parameters that correlated with both T1 relaxation times and MMSE were used as mediators. The results showed a potential correlation between T1 relaxation times and MMSE through cerebral TCD parameters (Figure 4).

Discussion

Cognitive impairment commonly occurs after acute cerebral infarction. This cognitive impairment is influenced by a variety of factors. In order to avoid these interferences, the CI, N-CI, and Normal groups did not significantly differ from one another in terms of age, gender, years of education, vascular risk factors, or especially white matter lesions (WML). The impact of potential confounding factors on the evaluation of cognitive performance was substantially mitigated or abolished. Subcortical ischemic vascular disease is particularly prevalent in the general population, which includes white matter lesions. T2 sequences and Flair (fluid-attenuated inversion recovery) sequences were used to quantify white matter lesions using the Fazekas scale (21). The mechanism underlying the associations of WML with cognitive impairment after stroke is unclear. Previous literature demonstrated that white matter lesions impaired executive function and slowed processing speed, which increased the risk of cognitive impairment after stroke (21, 22). Another potential explanation was that WML may disrupt neuronal networks relevant to cognitive reserve and rehabilitation thereby affecting stroke prognosis (23).

Previous studies have clearly demonstrated that the site of cerebral infarction was strongly associated with cognitive impairment after stroke (24, 25). In our experiment, there were no significant differences in stroke location, size and severity between the CI group and the N-CI group, which largely eliminated the influence of cerebral infarction location on T1 relaxation times.

Structural imaging-based assessment of cognitive function alone has some limitations (26). We combined the MP2RAGE sequence, TCD technique and neuropsychological assessment to evaluate cognitive function, which was much more supportive

TABLE 6 Pearson's correlations between T1 relaxation times and TCD parameters.

	L-F	R-F	R-Te	L-Pc	R-H	L-Th	R-CN	sCC
Left MCA Vd	−0.16	−0.24	−0.37**	−0.19	−0.29*	−0.36**	−0.22	−0.13
Left MCA Vm	−0.03	−0.16	−0.38*	−0.15	−0.20	−0.31*	−0.19	−0.14
Left MCA PI	0.33**	0.27*	0.29*	0.16	0.28*	0.25*	0.15	0.06
Left MCA RI	0.34**	0.27*	0.30*	0.16	0.27*	0.25*	0.15	0.07
Right MCA Vd	−0.33	−0.19	−0.34	−0.19	−0.20	−0.14	−0.26	−0.30
Right MCA Vm	−0.23	−0.22	−0.36**	−0.21	−0.16	−0.14	−0.24	−0.28
Left ACA Vd	−0.25*	−0.46**	−0.37**	−0.23	−0.18	−0.41**	−0.31*	−0.25*
Left ACA Vm	−0.21	−0.46**	−0.24	−0.19	−0.14	−0.38**	−0.33**	−0.22
Left ACA PI	0.20	0.23	0.34**	0.21	0.17	0.21	0.11	0.16
Right ACA Vs	−0.17	−0.21	−0.26*	−0.24	−0.19	−0.09	−0.20	−0.21
Right ACA RI	0.19	0.21	0.30*	0.17	0.13	0.21	0.07	0.15
BA Vd	−0.27*	−0.37**	−0.33**	−0.16	−0.26*	−0.21	−0.18	−0.15
BA Vm	−0.12	−0.26*	−0.32**	−0.14	−0.28*	−0.17	−0.05	−0.14
BA PI	0.42**	0.39**	0.20	0.10	0.05	0.21	0.31*	0.11
BA RI	0.43**	0.37**	0.21	0.12	0.08	0.18	0.29*	0.12

L-F, left frontal lobe; R-F, right frontal lobe; R-Te, right temporal lobe; L-Pc, left precuneu; sCC, splenium of corpus callosum; R-H, right hippocampus; L-Th, left thalamus; R-CN, right corona radiata; Left MCA, left middle cerebral artery; Right MCA, right middle cerebral artery; Left ACA, left anterior cerebral artery; Right ACA, right anterior cerebral artery; BA, basilar artery; Vs, systolic velocity; Vd, diastolic velocity; Vm, mean velocity; PI, pulsatility index; RI, resistivity index. $^{**}p < 0.01$; $^{*}p < 0.05$.

TABLE 7 Coordinate points of receiver operating characteristic (ROC) curve.

(CI vs. normal)	AUC	Threshold	Sensitivity	Specificity
L-F	0.91	853.2	91.30%	85.71%
R-F	0.94	860.3	82.61%	100.00%
R-Te	0.98	887.4	91.30%	95.24%
L-Pc	0.92	827.1	91.30%	85.71%
R-H	0.89	1,406	78.26%	95.24%
L-Th	0.91	1,117	91.30%	80.95%
R-CN	0.88	1,332	91.30%	76.19%
sCC	0.92	771.8	91.30%	85.71%

AUC, area under the curve; L-F, left frontal lobe; R-F, right frontal lobe; R-Te, right temporal lobe; L-Pc, left precuneu; R-H, right hippocampus; L-Th, left thalamus; R-CN, right corona radiata; sCC, splenium of corpus callosum.

in our diagnosis of the disease. Concerning TCD, a plethora of studies have investigated the connections between changes in cerebral hemodynamics and changes in cognitive function (20, 27, 28). One of the investigations mentioned above indicated that individuals with vascular cognitive impairment but no dementia reached the conclusion that most cerebral blood flow velocity was reduced while PI rose (20). According to our research findings, parts of the TCD parameters were considerably distinct among the three groups. There were statistically significant differences between the CI group and the normal group, which was mainly in line with the previous study's findings. But the N-CI and the Normal groups were compared, and no statistically significant difference was found between them. Previous studies have demonstrated that cerebral hemodynamics impairment is associated with the severity of stroke (29, 30), and not all stroke patients presented with significant cerebral hemodynamic impairment. Our results only showed significant cerebral hemodynamic impairment in patients with cognitive impairment after acute cerebral infarction. We think it may be caused by relatively higher demand for cerebral blood flow oxygen consumption in those patients. As a result, there were statistically significant differences between the CI group and the normal group.

T1 relaxation times primarily provide information about the myelin composition of the tissue and sensitively reflect injury to diffuse white and gray matter in the cranial brain (31). Earlier research conducted on patients suffering from neurological disorders found that their T1 relaxation times were significantly longer. T1 relaxation times tend to lengthen when pathological processes like myelin loss, axonal loss, and gliosis

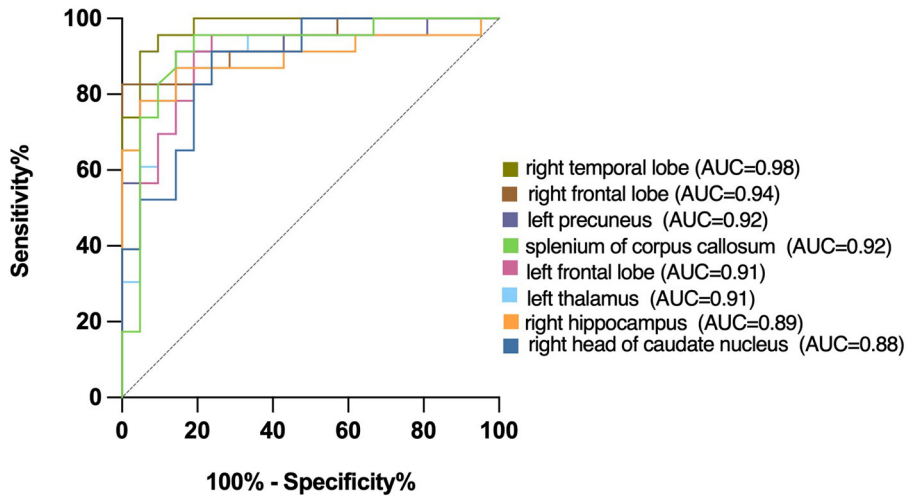


FIGURE 3
Receiver operating characteristic (ROC) curves for T1 relaxation times, distinguishing CI group from Normal group. T1 relaxation time in the right temporal lobe was identified as a good individual discriminator of cognitive impairment after acute cerebral infarction from healthy controls using ROC analysis; at the optimal cut-off T1 relaxation time of 887.4, sensitivity and specificity were 91.30 and 95.24%, respectively, with an AUC value of 0.98.

are present (32–34). T1 relaxation time has been utilized in several studies to evaluate changes in brain structure within neurological disorders, such as ischemic stroke or cognitive impairment (11, 35, 36). According to our research findings, the three different groups all had noticeably distinct T1 relaxation times for the aforementioned 8 brain regions. Therefore, this gave rise to the hypothesis that T1 relaxation times may be employed as a potential biomarker for identifying cognitive impairment after acute cerebral infarction.

It was generally understood that a stroke had an effect on the entirety of the brain as well as the features of its network rather than being a focal disease with restricted damage (37). In individuals who had cognitive impairment following an acute cerebral infarction, we found that varying T1 relaxation times were a phenomenon that occurred throughout the entire brain and were not confined to a particular brain region. The findings of our study confirmed this. Executive function, attention, psychomotor speed, and visual scanning are considered frontal lobe-related functions (38). In the literature, infarcts in the cortical region are more likely to lead to disruption of frontal-subcortical circuits, thereby disrupting local structures and functions within the networks that control cognitive functions. The temporal lobe is the primary region of the brain that is accountable for forming and maintaining long-term memories. The hippocampus plays a vital role in the process of learning. A recent study indicated that the precuneus is connected with numerous high levels of cognitive activities, including the processing of self-related information, situational memory, and visuospatial (39). The thalamus plays a vital role in various cognitive processes, including attention, executive ability, and working memory. The head of the caudate nucleus is an essential component of the cognitive circuit because it links the frontal lobe, the thalamus, the limbic system, and other structures; it also receives signals from frontal and temporoparietal regions bilaterally and sends out efferent fibers to the different areas of the basal ganglia (40). We considered that acute cerebral infarction caused the aforementioned microstructural disruption in 8 brain regions intimately connected to cognitive function. This microstructural disruption led to severe pathological myelin loss and axonal injury. There was a link between T1 relaxation times and cognitive performance, and this association could indicate, to some extent, the severity of cognitive impairment after acute cerebral infarction.

Our findings validated that the potential relationship between brain microstructural alterations and cognitive impairment could be explained by cerebral hemodynamics. Some studies showed that white matter microstructural change altered cerebral hemodynamic (41, 42). A possible mechanism was that pathological changes in the whole brain microstructure occurred after acute cerebral infarction. When the structural integrity of the white matter was disrupted, the compliance of the cerebral vessels was reduced, further causing cerebral hemodynamic disturbances. And hypoperfusion may lead to ischemia in various brain regions, resulting in cognitive impairment (43, 44). In addition, previous research has revealed that the blood-brain barrier is disrupted during the acute phase of cerebral infarction (45–47), followed by the deposition of substantial amounts of reactive oxygen species and circulating proteins in the brain (48, 49). These changes were not only

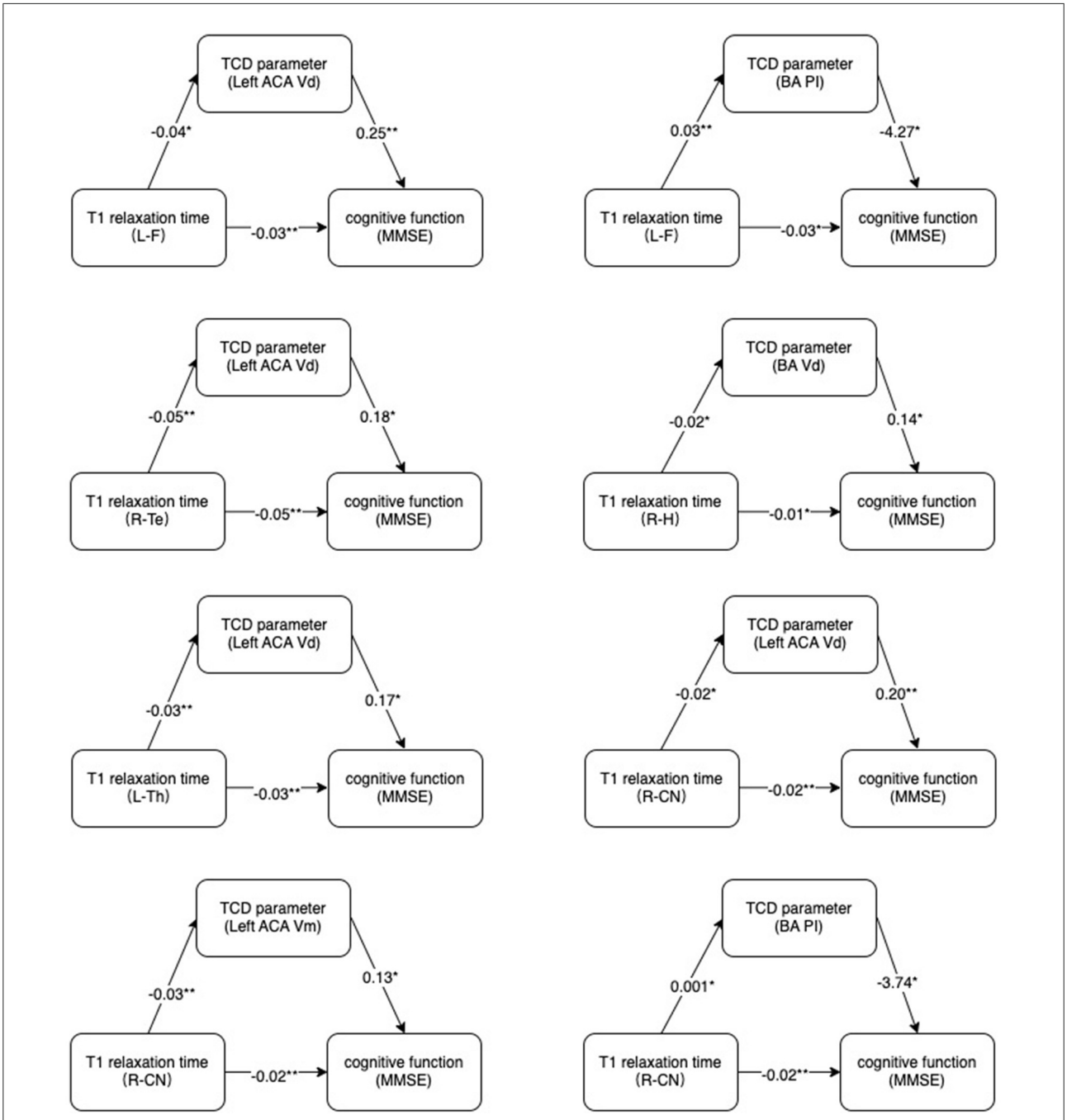


FIGURE 4
Mechanism diagram. Hypothesized direct and indirect pathways linking brain microstructure (T1 relaxation times) to cognitive impairment (MMSE) through a mediator (TCD parameters).MMSE, Mini-Mental State Examination. *$p < 0.05$, **$p < 0.01$.

limited to the brain region innervated by the damaged vessels, but also circulated throughout the brain with cerebral blood flow. Cerebral vasoconstriction, cerebral arteriosclerosis, and increased cerebral microvascular resistance were all produced by reactive oxygen species and circulating proteins, resulting in cerebral blood flow disorders (49). Endothelin and prostacyclin were the inflammatory cytokines generated during microangiopathy (50). These inflammatory cytokines interfered with the autoregulation of whole brain blood flow (51). All of the aforementioned pathophysiological alterations resulted in cerebral hypoperfusion. Cerebral hypoperfusion produced pathological myelin loss and axonal injury, altered nerve cell

metabolism, promoted neurodegeneration, caused white matter bundle ischemia, disrupted subcortical circuits, and eventually resulted in abnormalities in brain tissue microstructure (20, 52, 53).

As well known, it has been confirmed that the right anterior temporal lobe has an important role in magnitude knowledge (54). In addition, there have been research confirming that the right temporal lobe was closely associated with visual memory impairment and verbal memory (55). In our study, ROC analysis demonstrated that AUC from T1 relaxation time on the right temporal lobe was biggest among all data, therefore it could be validated as a good individual discriminator of cognitive dysfunction after acute cerebral infarction in the future.

Limitations

There were several limitations in this study as well. In the current study, patients with severe dementia who lacked informed capacity were excluded. Therefore, changes in T1 relaxation time did not represent a range of values for different levels of cognitive impairment. In the future, we will try to enroll these patients for further analysis in the study. In addition, we will try to carry out the research on the relation of scores on different aspects of cognition with T1 relaxation time. The content of various substances in brain tissue changes with time. Therefore, we inferred that T1 relaxation times would change consequently. In this experiment, we controlled for no statistical difference in the time interval between the stroke onset and imaging time among the three groups. In the future, we will conduct further cross-sectional analyses to compare the changes in T1 relaxation times of all ROIs at different examination times. Based on the definition of stroke, we will consider enrolling patients whose symptoms or signs lasted $\leq$ 24 h but with imaging revealing an ischemic lesion on the relevant side and location. The sample size of this study was modest, and it is expected that the sensitivity of T1 relaxation times in the diagnosis of cognitive impairment after acute cerebral infarction would be raised further.

Conclusion

In conclusion, microstructural alterations in the whole brain occurred after acute cerebral infarction and could be identified by MP2RAGE sequences. Such microstructural alterations may contribute to cognitive impairment through changes in cerebral hemodynamics. T1 relaxation times on the right temporal lobe and the right frontal lobe are expected to be a biomarker of cognitive impairment after acute cerebral infarction.

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 human participants were reviewed and approved by the Ethics Committee of Second Affiliated Hospital of Dalian Medical University. The patients/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

YG and HC conceptualized this study and designed this project. HY and YL performed the major procedures and wrote the manuscript. CW revised the manuscript and approved the final manuscript. HY, QZ, YG, YF, and HR contributed to the data collection. HY, YG, and HW assisted in the analysis of the data. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Natural Science Foundation of Liaoning Province (2022-MS-317), United Fund of the Second Hospital of Dalian Medical University and Dalian Institute of Chemical Physics, Chinese Academy of Sciences (UF-ZD-202012), and the 1+X program for Clinical Competency enhancement–Improvement of Clinical Technology Project, The Second Hospital of Dalian Medical University (2022LCJSGC04).

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

2. Wang F, Hua S, Zhang Y, Yu H, Jiang Z. Association between small vessel disease markers, medial temporal lobe atrophy and cognitive impairment after stroke: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* (2021) 30:105460. doi: 10.1016/j.jstrokecerebrovasdis.2020.105460

3. De Wit L, Putman K, Devos H, Brinkmann N, Dejaeger E, De Weerdt W, et al. Five-year mortality and related prognostic factors after inpatient stroke rehabilitation: a European multi-centre study. *J Rehabil Med.* (2012) 44:547–52. doi: 10.2340/16501977-0991

4. Lim J, Oh M, Lee J, Jung S, Kim C, Jang M, et al. Prediction of post-stroke dementia using NINDS-CSN 5-minute neuropsychology protocol in acute stroke. *Int Psychogeriatr.* (2017) 29:777–84. doi: 10.1017/S1041610216002520

5. Winstein C, Stein J, Arena R, Bates B, Cherney L, Cramer S, et al. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2016) 47:e98–169. doi: 10.1161/STR.0000000000000098

6. Meng D, Li X, Bauer M, Taylor J, Auer D. Altered nucleus basalis connectivity predicts treatment response in mild cognitive impairment. *Radiology.* (2018) 289:775–85. doi: 10.1148/radiol.2018180092

7. Huang W, Li X, Li H, Wang W, Chen K, Xu K, et al. Accelerated brain aging in amnestic mild cognitive impairment: relationships with individual cognitive decline, risk factors for Alzheimer disease, and clinical progression. *Radiol Artif Intelligence.* (2021) 3:e200171. doi: 10.1148/ryai.2021200171

8. Ossenkoppele R, Lyoo C, Jester-Broms J, Sudre C, Cho H, Ryu Y, et al. Assessment of demographic, genetic, and imaging variables associated with brain resilience and cognitive resilience to pathological tau in patients with Alzheimer disease. *JAMA Neurol.* (2020) 77:632–42. doi: 10.1001/jamaneurol.2019.5154

9. Metere R, Kober T, Möller H, Schäfer A. Simultaneous quantitative MRI mapping of T1, T2* and magnetic susceptibility with multi-echo MP2RAGE. *PLoS ONE.* (2017) 12:e0169265. doi: 10.1371/journal.pone.0169265

10. Steenwijk M, Vrenken H, Jonkman L, Daams M, Geurts J, Barkhof F, et al. High-resolution T1-relaxation time mapping displays subtle, clinically relevant, gray matter damage in long-standing multiple sclerosis. *Multiple Sclerosis.* (2016) 22:1279–88. doi: 10.1177/1352458515615953

11. McGarry BL, Jokivarsi KT, Knight MJ, Grohn OHJ, Kauppinen RA. A magnetic resonance imaging protocol for stroke onset time estimation in permanent cerebral ischemia. *J Vis Exp.* (2017) 127:55277. doi: 10.3791/55277

12. Kim HJ, Choi EH, Chung JW, Kim JH, Kim YS, Seo WK, et al. Luminal and wall changes in intracranial arterial lesions for predicting stroke occurrence. *Stroke.* (2020) 51:2495–504. doi: 10.1161/STROKEAHA.120.030012

13. Shim Y, Yoon B, Shim DS, Kim W, An JY, Yang DW. Cognitive correlates of cerebral vasoreactivity on transcranial doppler in older adults. *J Stroke Cerebrovasc Dis.* (2015) 24:1262–9. doi: 10.1016/j.jstrokecerebrovasdis.2015.01.031

14. Vagli C, Fisicaro F, Vinciguerra L, Puglisi V, Rodolico M, Giordano A, et al. Cerebral hemodynamic changes to transcranial doppler in asymptomatic patients with Fabry's disease. *Brain Sci.* (2020) 10:546. doi: 10.3390/brainsci10080546

15. D'Andrea A, Conte M, Cavallaro M, Scarafile R, Riegler L, Cocchia R, et al. Transcranial Doppler ultrasonography: From methodology to major clinical applications. *World J Cardiol.* (2016) 8:383–400. doi: 10.4330/wjc.v8.i7.383

16. Xiao Z, Ren X, Zhao Q, Wu W, Liang X, Tang J, et al. Relation of middle cerebral artery flow velocity and risk of cognitive decline: A prospective community-based study. *J Clin Neurosci.* (2022) 97:56–61. doi: 10.1016/j.jocn.2021.12.028

17. Blair G, Thrippleton M, Shi Y, Hamilton I, Stringer M, Chappell F, et al. Intracranial hemodynamic relationships in patients with cerebral small vessel disease. *Neurology.* (2020) 94:e2258–69. doi: 10.1212/WNL.0000000000009483

18. Marshall R. Effects of altered cerebral hemodynamics on cognitive function. *J Alzheimers Dis.* (2012) 32:633–42. doi: 10.3233/JAD-2012-120949

19. Puglisi V, Bramanti A, Lanza G, Cantone M, Vinciguerra L, Pennisi M, et al. Impaired cerebral haemodynamics in vascular depression: insights from transcranial Doppler ultrasonography. *Front Psychiatry.* (2018) 9:316. doi: 10.3389/fpsyt.2018.00316

20. Vinciguerra L, Lanza G, Puglisi V, Pennisi M, Cantone M, Bramanti A, et al. Transcranial Doppler ultrasound in vascular cognitive impairment-no dementia. *PLoS ONE.* (2019) 14:e0216162. doi: 10.1371/journal.pone.0216162

21. Kandiah N, Chander RJ, Lin X, Ng A, Poh YY, Cheong CY, et al. Cognitive impairment after mild stroke: development and validation of the SIGNAL2 risk score. *J Alzheimers Dis.* (2016) 49:1169–77. doi: 10.3233/JAD-150736

22. Gong L, Wang H, Zhu X, Dong Q, Yu Q, Mao B, et al. Nomogram to predict cognitive dysfunction after a minor ischemic stroke in hospitalized-population. *Front Aging Neurosci.* (2021) 13:637363. doi: 10.3389/fnagi.2021.637363

23. Georgakis MK, Duering M, Wardlaw JM, Dichgans M. WMH and long-term outcomes in ischemic stroke: A systematic review and meta-analysis. *Neurology.* (2019) 92:e1298–308. doi: 10.1212/WNL.0000000000007142

24. Weaver NA, Kuijf HJ, Aben HP, Abrigo J, Bae HJ, Barbay M, et al. Strategic infarct locations for post-stroke cognitive impairment: a pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts. *Lancet Neurol.* (2021) 20:448–59. doi: 10.1016/S1474-4422(21)00060-0

25. Zhao L, Biesbroek JM, Shi L, Liu W, Kuijf HJ, Chu WW, et al. Strategic infarct location for post-stroke cognitive impairment: A multivariate lesion-symptom mapping study. *J Cereb Blood Flow Metab.* (2018) 38:1299–311. doi: 10.1177/0271678X17728162

26. Di Lazzaro V, Bella R, Benussi A, Bologna M, Borroni B, Capone F, et al. Diagnostic contribution and therapeutic perspectives of transcranial magnetic stimulation in dementia. *Clin Neurophysiol.* (2021) 132:2568–607. doi: 10.1016/j.clinph.2021.05.035

27. Kimura K, Kubo Y, Dobashi K, Katakura Y, Chida K, Kobayashi M, et al. Angiographic, cerebral hemodynamic, and cognitive outcomes of indirect revascularization surgery alone for adult patients with misery perfusion due to ischemic moyamoya disease. *Neurosurgery.* (2022) 90:676–83. doi: 10.1227/neu.0000000000001907

28. Xiong Z, Lu W, Zhu L, Zeng L, Shi C, Jing Z, et al. Dl-3-n-butylphthalide treatment enhances hemodynamics and ameliorates memory deficits in rats with chronic cerebral hypoperfusion. *Front Aging Neurosci.* (2017) 9:238. doi: 10.3389/fnagi.2017.00238

29. Sim J, Jo A, Kang B, Lee S, Bang O, Heo C, et al. Cerebral hemodynamics and vascular reactivity in mild and severe ischemic rodent middle cerebral artery occlusion stroke models. *Exp Neurobiol.* (2016) 25:130–8. doi: 10.5607/en.2016.25.3.130

30. Llwyd O, Salinet ASM, Panerai RB, Lam MY, Saeed NP, Brodie F, et al. Cerebral haemodynamics following acute ischaemic stroke: effects of stroke severity and stroke subtype. *Cerebrovasc Dis Extra.* (2018) 8:80–9. doi: 10.1159/000487514

31. Kühne F, Neumann W, Hofmann P, Marques J, Kaindl A, Tietze A. Assessment of myelination in infants and young children by T1 relaxation time measurements using the magnetization-prepared 2 rapid acquisition gradient echoes sequence. *Pediatr Radiol.* (2021) 51:2058–68. doi: 10.1007/s00247-021-05109-5

32. Thaler C, Hartramph I, Stellmann J, Heesen C, Bester M, Fiehler J, et al. T1 relaxation times in the cortex and thalamus are associated with working memory and information processing speed in patients with multiple sclerosis. *Front Neurol.* (2021) 12:789812. doi: 10.3389/fneur.2021.789812

33. Muñoz Maniega S, Chappell F, Valdés Hernández M, Armitage P, Makin S, Heye A, et al. Integrity of normal-appearing white matter: Influence of age, visible lesion burden and hypertension in patients with small-vessel disease. *J Cereb Blood Flow Metab.* (2017) 37:644–56. doi: 10.1177/0271678X16635657

34. Gracien R, Reitz S, Hof S, Fleischer V, Zimmermann H, Droby A, et al. Changes and variability of proton density and T1 relaxation times in early multiple sclerosis: MRI markers of neuronal damage in the cerebral cortex. *Eur Radiol.* (2016) 26:2578–86. doi: 10.1007/s00330-015-4072-x

35. McGarry B, Rogers H, Knight M, Jokivarsi K, Sierra A, Gröhn O, et al. Stroke onset time estimation from multispectral quantitative magnetic resonance imaging in a rat model of focal permanent cerebral ischemia. *Int J Stroke.* (2016) 11:677–82. doi: 10.1177/1747493016641124

36. Bowler R, Yeh C, Adams S, Ward E, Ma R, Dharmadhikari S, et al. Association of MRI T1 relaxation time with neuropsychological test performance in manganese- exposed welders. *Neurotoxicology.* (2018) 64:19–29. doi: 10.1016/j.neuro.2017.05.010

37. Guggisberg AG, Koch PJ, Hummel FC, Buetefisch CM. Brain networks and their relevance for stroke rehabilitation. *Clin Neurophysiol.* (2019) 130:1098–124. doi: 10.1016/j.clinph.2019.04.004

38. Sugimoto T, Yoshida M, Ono R, Murata S, Saji N, Niida S, et al. Frontal lobe function correlates with one-year incidence of urinary incontinence in elderly with Alzheimer disease. *J Alzheimers Dis.* (2017) 56:567–74. doi: 10.3233/JAD-160923

39. Yokosawa K, Kimura K, Takase R, Murakami Y, Boasen J. Functional decline of the precuneus associated with mild cognitive impairment: Magnetoencephalographic observations. *PLoS ONE.* (2020) 15:e0239577. doi: 10.1371/journal.pone.0239577

40. Wang Z, Bai L, Liu Q, Wang S, Sun C, Zhang M, et al. Corpus callosum integrity loss predicts cognitive impairment in Leukoaraiosis. *Ann Clin Trans Neurol.* (2020) 7:2409–20. doi: 10.1002/acn3.51231

41. Camara E, Rodriguez-Fornells A, Münte TF. Microstructural brain differences predict functional hemodynamic responses in a reward processing task. *J Neurosci.* (2010) 30:11398–402. doi: 10.1523/JNEUROSCI.0111-10.2010

42. Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, et al. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. *J Cereb Blood Flow Metab.* (2014) 34:228–34. doi: 10.1038/jcbfm.2013.180

43. Zhou Z, Ma Y, Xu T, Wu S, Yang GY, Ding J, et al. Deeper cerebral hypoperfusion leads to spatial cognitive impairment in mice. *Stroke Vasc Neurol.* (2022) svn-2022–001594. doi: 10.1136/svn-2022-001594. [Epub ahead of print].

44. Malojcic B, Giannakopoulos P, Sorond FA, Azevedo E, Diomedi M, Oblak JP, et al. Ultrasound and dynamic functional imaging in vascular cognitive impairment and Alzheimer's disease. *BMC Med.* (2017) 15:27. doi: 10.1186/s12916-017-0799-3

45. Yin K, Hamblin M, Chen Y. Non-coding RNAs in cerebral endothelial pathophysiology: emerging roles in stroke. *Neurochem Int.* (2014) 77:9–16. doi: 10.1016/j.neuint.2014.03.013

46. Lucke-Wold B, Logsdon A, Turner R, Rosen C, Huber J. Aging, the metabolic syndrome, and ischemic stroke: redefining the approach for studying the blood-brain barrier in a complex neurological disease. *Adv Pharmacol.* (2014) 71:411–49. doi: 10.1016/bs.apha.2014.07.001

47. Okada T, Suzuki H, Travis ZD, Zhang JH. The stroke-induced blood-brain barrier disruption: current progress of inspection technique, mechanism, and therapeutic target. *Curr Neuropharmacol.* (2020) 18:1187–212. doi: 10.2174/1570159X18666200528143301

48. Takeda H, Yamaguchi T, Yano H, Tanaka J. Microglial metabolic disturbances and neuroinflammation in cerebral infarction. *J Pharmacol Sci.* (2021) 145:130–9. doi: 10.1016/j.jphs.2020.11.007

49. Beishon L, Haunton VJ, Panerai RB, Robinson TG. Cerebral hemodynamics in mild cognitive impairment: a systematic review. *J Alzheimers Dis.* (2017) 59:369–85. doi: 10.3233/JAD-170181

50. Harris S, Reyhan T, Ramli Y, Prihartono J, Kurniawan M. Middle cerebral artery pulsatility index as predictor of cognitive impairment in hypertensive patients. *Front Neurol.* (2018) 9:538. doi: 10.3389/fneur.2018.00538

51. Yun J, Washington C, Mccormick J, Stevenson E, Alexander J. Amyloid beta peptides and Th1 cytokines modulate human brain vascular smooth muscle tonic contractile capacity in vitro: relevance to Alzheimer's disease? *Pathophysiology.* (2021) 28:64–75. doi: 10.3390/pathophysiology28010006

52. Choi B, Kim D, Back D, Kang C, Moon W, Han J, et al. Characterization of white matter injury in a rat model of chronic cerebral hypoperfusion. *Stroke.* (2016) 47:542–7. doi: 10.1161/STROKEAHA.115.011679

53. Bouhrara M, Alisch J, Khattar N, Kim R, Rejimon A, Cortina L, et al. Association of cerebral blood flow with myelin content in cognitively unimpaired adults. *BMJ Neurol Open.* (2020) 2:e000053. doi: 10.1136/bmjno-2020-000053

54. Pflugshaupt T, Bauer D, Frey J, Vanbellingen T, Kaufmann BC, Bohlhalter S, et al. The right anterior temporal lobe critically contributes to magnitude knowledge. *Brain Commun.* (2020) 2:fcaa157. doi: 10.1093/braincomms/fcaa157

55. Shinoura N, Midorikawa A, Kurokawa K, Onodera T, Tsukada M, Yamada R, et al. Right temporal lobe plays a role in verbal memory. *Neurol Res.* (2011) 33:734–8. doi: 10.1179/1743132811Y.0000000005

frontiers | Frontiers in Neurology

TYPE Study Protocol
PUBLISHED 05 January 2023
DOI 10.3389/fneur.2022.1081895

OPEN ACCESS

EDITED BY
Haiqing Zheng,
Third Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Sungju Jee,
Chungnam National University, Republic of Korea
Zhi-Ming Tang,
Third Affiliated Hospital of Sun Yat-sen University, China

*CORRESPONDENCE
Bo Zhang
email@uni.edu:79915726@qq.com
Han Zhang
18281717788@163.com

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 27 October 2022
ACCEPTED 06 December 2022
PUBLISHED 05 January 2023

CITATION
Yang Y-x, Wang L-l, Du J, Luo Y-m, Xie Y-l, Zhang B and Zhang H (2023) Prism adaptation combined with eye movement training for unilateral spatial neglect after stroke: Study protocol for a single-blind prospective, randomized controlled trial. *Front. Neurol.* 13:1081895. doi: 10.3389/fneur.2022.1081895

Prism adaptation combined with eye movement training for unilateral spatial neglect after stroke: Study protocol for a single-blind prospective, randomized controlled trial

Yu-xuan Yang[1], Ling-ling Wang[2], Juan Du[1], Yao-min Luo[2], Yu-lei Xie[3], Bo Zhang[1]* and Han Zhang[1]*

[1]Department of Rehabilitation Medicine, The Second Clinical Medical School of North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China, [2]Department of Rehabilitation Medicine, The Affiliated Hospital of North Sichuan Medical College, Nanchong, China, [3]School of Rehabilitation, China Rehabilitation Research Center, Capital Medical University, Beijing, China

Background: Unilateral spatial neglect (USN) is a complex neurological syndrome that often reduces rehabilitation outcomes, prolongs patients' hospital stays, and decreases their quality of life. However, the current therapies for USN have varying efficacy. We will explore a new treatment option that combines prism adaptation (PA) with eye movement training (EMT) for the treatment of USN after stroke.

Methods: We will conduct a single-blind, prospective, randomized controlled trial to assess the efficacy of the combined intervention (PA & EMT) on USN in an inpatient rehabilitation setting. The study aims to recruit 88 patients with USN after an ischemic or hemorrhagic stroke. Participants will be randomly assigned to the following four groups: (1) PA group (n = 22), (2) EMT group (n = 22), (3) PA and EMT group (n = 22), and (4) control group (n = 22). All groups will receive 10 sessions of interventions over 2 weeks, 5 times per week. Blinded assessors will conduct a baseline assessment, a post-intervention assessment, and a follow-up assessment (2 weeks post-intervention). The primary outcome measure will use the Behavioral Inattention Test-Conventional Subset (BIT-C) and Catherine Bergego Scale (CBS) to assess the levels of USN. Secondary outcome measures will assess the patient's ability to perform activities of daily living using the Modified Barthel Index (MBI). Patients who completed all treatment and assessment sessions will be included in the final analysis.

Discussion: This study will explore the effects of 10 sessions of combined interventions (PA & EMT) on USN and functional capacity. This study has the potential to identify a new, evidence-based treatment option and provide new ideas for the treatment of USN.

Ethics and dissemination: The study protocol has been approved by the Nanchong Central Hospital. Written informed consent will be obtained from all the participants. The results of this study will be disseminated to the public through scientific conferences and a peer-reviewed journal.

Trial registration: ChiCTR, ChiCTR2100049482. Registered on 2 August 2021, http://www.chictr.org.cn/showproj.aspx?proj=130823.

KEYWORDS

stroke, unilateral spatial neglect, prism adaptation, eye movement training, combined therapy

1. Introduction

Stroke is the second cause of death and the leading cause of disability worldwide (1). Poststroke patients usually suffer from multiple dysfunctions and complications that affect their health-related quality of life (2). Unilateral spatial neglect (USN) is a frequent and disabling condition after stroke, affecting approximately 30% of acute and subacute stroke survivors (3). USN is mainly related to damage to neural networks associated with spatial information processing and attentional control (4) and is defined as the inability to orient, detect, or respond to relevant stimuli in the visual field opposite to the brain lesion and unrelated to sensory and motor dysfunction (5). In clinical, approximately 40% of patients with USN are consistently affected by neglect symptoms (6). Compared to other stroke survivors, patients with USN are associated with poorer rehabilitation outcomes of other stroke symptoms (7) and longer hospital stays (8, 9). In addition, USN increases the consumption of health resources and adds to the burden on families (10, 11).

Since the early 1970s, various rehabilitation techniques have been proposed to reduce the disability caused by USN after stroke, including visual scanning training, trunk rotation, optokinetic stimulation, feedback or cueing, virtual reality, repetitive transcranial magnetic stimulation, and prism adaptation (PA) (12, 13). Monotherapy is frequently used in clinical research for USN, but overall, the level of evidence remains low. PA has been a hot research topic in recent years for the treatment of USN, with most studies supporting PA as an effective intervention while other studies were contradictory (14, 15). One possible explanation for the inconsistent results is that USN is a complex neurological syndrome with different manifestations for different neglect types and crossover symptoms between various neglect subtypes (16). Some researchers have suggested that combination therapy may produce more intense and long-lasting effects (17), and combination therapy is also the most frequently investigated USN intervention and shows promise for improving USN symptoms (18). The combination of different treatments may produce greater efficacy through similarities and differences in treatment mechanisms. Based on this, we speculate that combining PA with one approach will yield better results. In previous studies, Saevarsson et al. (19) and Choi et al. (20) combined PA with neck vibration and functional electrical stimulation, respectively, and both showed that the combined intervention better improved USN symptoms. However, the combination of these two studies only increased the number of interventions without mentioning the possible theoretical basis. Barrett et al. (21) inferred from animal models that stroke can induce classic visual–perceptual spatial neglect and motor intention deficits. Choosing a treatment option that intervenes in both areas may be a viable approach.

In this trial, we plan to combine PA and eye-tracking-based eye movement training (EMT) to treat poststroke USN. PA is a "bottom-up" approach (22), and it influences the level of sensory-motor through visuomotor adaptation to reduce symptoms of spatial neglect and, in particular, to improve spatial motor-intentional "aiming" deficits (23). PA was first proposed to treat patients with USN in 1998 (24), and a battery of studies has shown that PA improves not only the performance of patients with USN on neglect assessments (25–27) (e.g., BIT-C, CBS, and bell test) but also on neglect-related processes (15, 28–30). In addition, the sensorimotor after-effects of PA extend to the cognitive domain of patients with USN, for example, in complex spatial cognitive tasks required in daily life (navigation and terrain memory) (31), simple sound source localization abilities (32), etc. EMT is another USN treatment based on the attention disorder doctrine and belongs to the "top-down" approach. Similar to visual scanning training, EMT aims to improve the patient's ability to voluntarily orient his spatial attention toward the neglected side (33) and is characterized by repetitive practice of compensatory visual behaviors. Previous studies have shown that repetitive practice of compensatory visual behaviors can improve USN (34), and Leal Rato, M et al. also showed that eye gaze direction in patients with USN modulates spatial attention and that perception of direct gaze reduces visuospatial deficits in neglected patients (35). Although USN had been classically thought of as a "parietal syndrome" associated with lesions in visuospatial integration at the posterior parietal cortex (36), it has become evident that USN involves a disturbance in the widespread attention network (4), as well as the impact of attention deficits on visuospatial neglect, such as poor sustained attention and

Abbreviations: USN, unilateral spatial neglect; PA, prism adaptation; EMT, eye movement training; BIT-C, behavioral inattention test-conventional subset; CBS, catherine bergego scale; MBI, modified barthel index; MMSE, mini-mental state examination.

attentional shifting disorders (37). Therefore, EMT to improve visuospatial attention may be a treatment for USN, and this technique is still widely used in clinical practice (22).

Our study aims to investigate the efficacy of PA combined with EMT in the treatment of USN. We hypothesized that sequential use of these two interventions would produce a positive synergistic effect of 1 + 1 over 2, resulting in better improvement of USN symptoms in patients with poststroke.

2. Methods

This study was confirmed using a checklist in the SPIRIT reporting guidelines (38).

2.1. Study design

The study will be conducted as a single-blind, prospective, randomized controlled trial that will be conducted at the Second Clinical Medical College of North Sichuan Medical University. The protocol has been registered with the China Clinical Trial Registry (Item No.: ChiCTR2100049482). Our study will evaluate the effectiveness of EMT combined with PA in patients with poststroke USN, and the findings might provide a rationale for an approach of EMT combined with PA in patients with USN. A total of 72 patients will be recruited for this study and will be randomly assigned to four groups (1:1:1:1). All patients will receive conventional rehabilitation, as well as one of the three types of training: PA, EMT, PA, and EMT. To assess the efficacy, all participants will be assessed at three visits, including baseline, posttreatment, and 2 weeks after the end of treatment. The diagram and schedule for the study are shown in Figure 1 and Table 1.

2.2. Consent and eligibility

Potential participants will be primarily screened and those who meet inclusion and exclusion criteria will be invited to participate in this study. All subjects will have an informed consent form signed by themselves or a legal representative prior to undergoing any study procedures. The inclusion and exclusion criteria for selecting participants are listed as follows.

2.2.1. Inclusion criteria

a) Adult patients older than 18 and younger than 80 years.
b) First stroke with ischemic or hemorrhagic brain injury on CT and MRI.
c) The subacute phase of stroke: Duration 1 to 12 weeks after stroke onset.
d) Diagnosis and confirmation of USN: a pathological performance on one subtest of the Behavioral Inattention Test-Conventional Subset (BIT-C).
e) The patient can sit in a stable position.
f) Complete vision or normal after correction.
g) The patient is right-handed.

2.2.2. Exclusion criteria

a) Severe cognitive impairment (MMSE $<$ 16) and non-cooperation.
b) Severe USN (star cancellation tests $<$ 8).
c) Severe non-spatial attention deficit (digital checking method).
d) Patients with severe organ diseases.
e) Inability to comply with the time frame of this study.
f) Unsigned informed consent.

All subjects will sign an informed consent document before undergoing any study procedures.

2.3. Sample and recruitment

Patients with USN in the subacute phase of stroke will be recruited from 2 November 2021 to 1 June 2023 at the Second Clinical Medical College of North Sichuan Medical University. Recruited participants will be required to meet the USN diagnostic criteria, including nurse or family member reports of disproportionate orientation toward the impaired side, and $<$ 52 stars were removed from the cancellation test. Patients will be initially screened through a case system or clinician notification and will be carefully evaluated for meeting eligibility criteria once they have signed an informed consent form.

2.4. Sample size estimation

In the preexperiment, the changes in BIT-C scores before and after the intervention were 39.33 $\pm$ 18.717 for the combined intervention group, 26.33 $\pm$ 7.638 for the eye-movement training group, and 20 $\pm$ 2.828 for the PA training group. Using the PASS software, the probability α of occurrence of the Type I error was set to 0.05, the probability β of occurrence of the Type II error was calculated as 0.2, the calculation results showed that the combined intervention and eye-movement training groups required 20 samples each, and 9 samples were required for each of the combined intervention and PA training groups. Therefore, taking into account a 10% sample dropout rate, the total sample size was finally determined to be 88 cases, with 22 cases in each group.

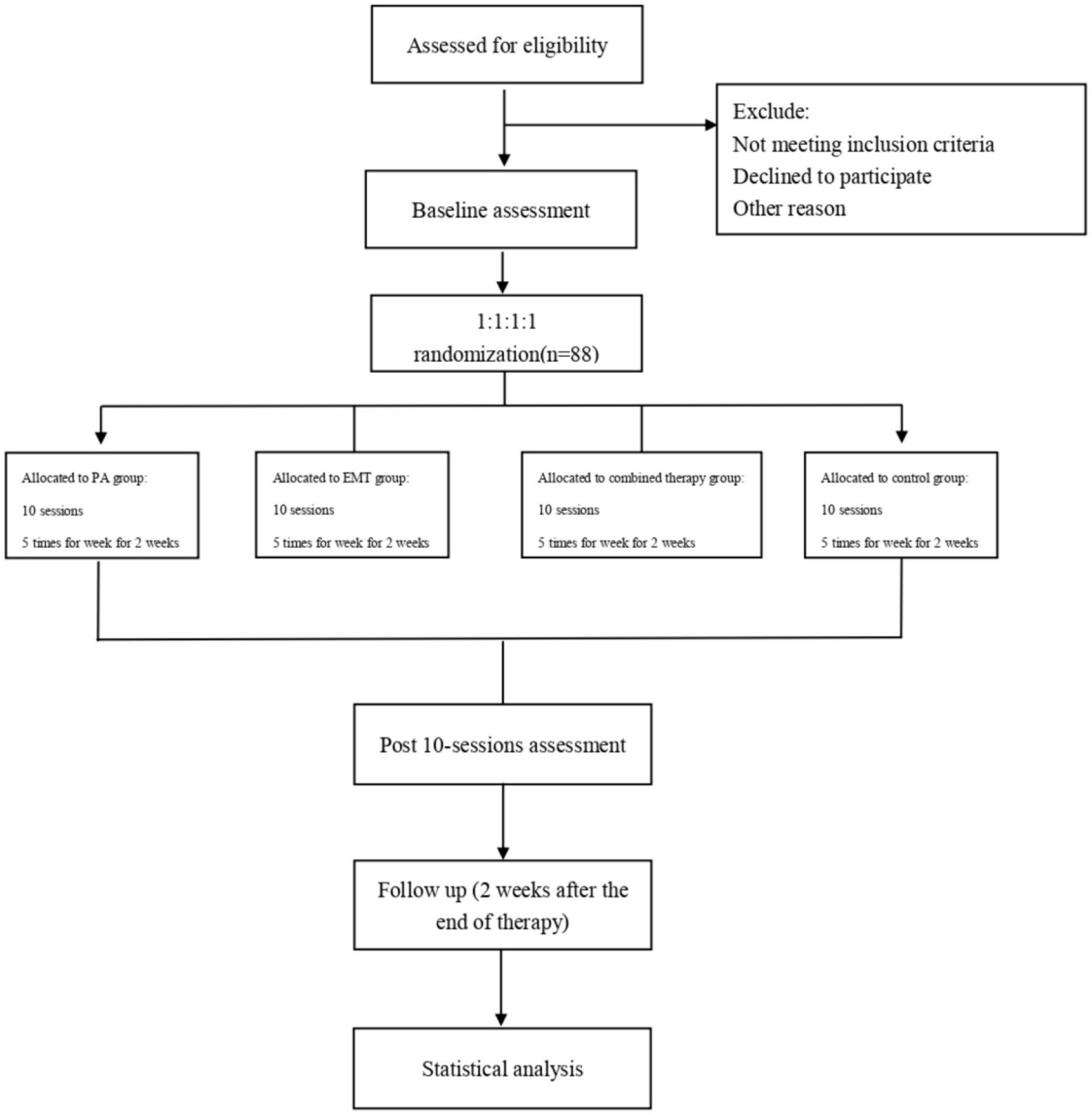


FIGURE 1
Flowchart of the study design. PA, prism adaptation. EMT, eye movement training.

2.5. Randomization and blinding

A random number list is generated by a computer and consists of 88 random numbers. The random numbers were arranged from the smallest to the largest to obtain the serial number R. It is stipulated that group A (PA) with $R = 1–22$, group B (EMT) with $R = 23–44$, group C (PA & EMT) with $R = 45–66$, and group D (control) with $R = 67–88$. The resulting sequence of random assignments was placed in sequentially coded, sealed, impermeable envelopes. The investigator in charge of recruitment opens the envelope according to the order of patient enrollment and assigns the subjects to the appropriate subject group.

This study is a single-blind design, and only the investigator conducting the assessment is blinded to group assignment. The therapist cannot be blinded due to using the supervised intervention. In addition, blinding of subjects is not feasible due to the difference in intervention methods. All outcome assessments for this study will be conducted by a separate professional therapist who is not involved in any other part of the study. Moreover, participants will be unblinded when any clinical situation associated with adverse events or patient withdrawal occurs.

TABLE 1 Schedule of enrollments, interventions, and assessments.

Time point		Screening	Randomization	Intervention	Follow up
		Within one weeks	Day 0	2 weeks (10 sessions)	Post-2 weeks
			T_0	T_1	T_2
Enrollments	Informed consent	√			
	Demographic characteristics	√			
	Medical history	√			
	Eligibility assessment	√			
	Radom allocation		√		
Intervention	Conventional rehabilitation			√	
	PA			√	
	EMT			√	
	PA & EMT			√	
Assessment	Cognitive level (MMSE)	√		√	
	Behavioral inattention test-conventional subset			√	√
	Catherine bergego scale			√	√
	Modified barthel index			√	√

PA, prism adaptation; EMT, eye movement training; MMSE, Mini-mental State Examination.

2.6. Interventions

All subjects will receive conventional rehabilitation during the intervention period, as well as appropriate interventions according to the group.

2.6.1. Conventional intervention

Conventional rehabilitation therapy includes physical therapy, occupational therapy, and acupuncture. Physical therapy includes muscle strength and endurance training, joint range of motion training, balance and coordination training, gait training, etc. Occupational therapy includes training in activities of daily living (ADL) (e.g., dressing, eating, brushing teeth, and washing face, etc.). Acupuncture includes acupuncture points such as Baihui, DiCang, Shoulder, Quchi, Hand SanLi, Neiguan, HeGu, LiangQiu, Blood Sea, FengShi, Foot SanLi, YangLingQuan, SanyinJiao, and Taichong.

2.6.2. Prism adaptation

Prism adaptation is a non-invasive, affordable, convenient technique to assess visuomotor plasticity and ameliorate the symptoms of USN (39). During a PA session, the patient wears goggles with prism lenses that induce a deviation of the visual field toward the ipsilesional side of space and perform a series of pointing movements toward a visual target. PA training was performed using a black box with parameters as described by Spaccavento et al. (height = 30 cm, depth = 34 cm at the center and 18 cm at the periphery, and width = 72 cm) (33). The PA process consists of three steps: (1) aiming in the direction of visual targets without goggles to obtain a reference frame (pretest); (2) 90 aiming movements in the direction of visual targets with prisms that deviate from the environment approximately 10° to the right or left (prismatic exposure). Initially, the movements are deviated toward the right or left, and then, the subject progressively corrects his errors; (3) aiming toward visual targets without the prisms to measure the after-effects. According to the patient's training performance, the PA training schedule was 15–20 min/session, 1 session/day, and 5 days/week, with a treatment period of 2 weeks.

2.6.3. Eye movement training

The eye movement training will be performed based on a high-performance EMT instrument (Figure 2, Hangzhou Jizhi Medical Technology Co., Ltd., Model: JZ-RZ-20US). The insect shoot-down task of the cognitive rehabilitation training and assessment system will be selected as the EMT task (search and gaze). The insect shoot-down task will be set at easy, moderate, and difficult levels (depending on the patient's training performance), left or right field of view (the choice of left or right visual field depends on the patient's side of neglect), during which the insect will randomly present on the left or right side of the screen and move from bottom to top. Under the guidance of the therapist, the patient spontaneously searches for these signs, eliminates them by gazing, and then searches for

FIGURE 2
Eye movement training device (image from ourselves).

the next sign until the end of the training. At the same time, this eye-tracking device has an eye-tracking function, which can visually show the patient's eye movement trajectory and facilitate the therapist to better train the patient. The EMT schedule was 15 min/session, 1 session/day, and 5 days/week, with a treatment period of 2 weeks.

2.7. Baseline data

Baseline data are collected after informed consent and before randomization. The baseline assessment includes demographic characteristics such as sex, age, time of onset, cause of damage, and assessment scales including the Mini-Mental State Examination, Catherine Bergego Scale, Behavioral Inattention Test-Conventional Subset (BIT-C), and Modified Barthel Index (MBI). All baseline data will be collected *via* paper forms.

2.8. Outcome measures

This study will measure outcome indicators at two time points: after the end of the intervention and 2 weeks after the end of the intervention. The measurement of outcome indicators will be conducted by independent therapists. The relevant test nodes can be seen in the study schedule (Table 1).

2.8.1. Mini-mental state examination

The Chinese version of the MMSE was initially developed by Katzman et al. (40) and later widely used in clinical practice and studies. The test includes cognitive assessments in five domains: time and place orientation, memory, attention and calculation, immediate and long-term memory, and language and comprehension. The total score of the test is 30, and the cutoff points for dementia screening are 16/17 for illiterate, 19/20 for those with 1–6 years of education, and 23/24 for those with 7 or more years of education (41).

2.8.2. Primary outcomes

Two main scales are used to assess changes in UNS levels including Catherine Bergego Scale (CBS) and Behavioral Inattention Test-Conventional Subset (BIT-C).

The Catherine Bergego Scale, published by Azouvi et al. in 1996, is an ecologically valid screening tool for spatial neglect with excellent reliability and validity (42). The scale is composed of 10 items and each with a score ranging from 0 (normal) to 3 (severe unilateral neglect). According to the scores, three levels of severe neglect can be distinguished as follows: 1–10 (mild neglect), 11–20 (moderate neglect), and 21–30 (severe neglect).

The behavior inattention test-conventional subset consists of the widely used paper–pencil tests (43): (a) line, letter, and star cancellation tests, (b) figure and shape copying, (c) line bisection, and (d) representative drawing. The sum of scores for each test yields a total BIT-C score, ranging from 0 to 146. The cutoff score for the BIT-C test is 129, and a score below 129 is diagnosed as USN, with lower scores indicating more severe neglect.

(a) In cancellation tests, the signs are presented on an A4 (210 × 297 mm) paper, and the participant was required to respectively cross out all lines, all letters "E" and "R," and all small stars. There is no time restriction. The number of omitted targets is counted. The maximum scores for these subtests are 36, 40, and 54, respectively.
(b) In the figure and shape copying, the participant has to copy three figures (a four-pointed star, a cube, and a flower) on a sheet of A4 paper, as well as three figures composed of lines. The maximum score is 4.
(c) In the line bisection test, there are three 20 cm horizontal lines on an A4 paper. The participant was asked to search for spatially distributed lines and bisect each line in the middle as accurately as possible. The score ranges from 0 to 3, according to the distance between the mark and the midpoint of each line (0–1 cm 3; 1–2 cm 2; 2–3 cm 1; >3 cm 0). The maximum score is 9.
(d) In the representative drawing, the participant should draw a clock, a human, and a butterfly on an A4 paper based on their memory. The score ranges from 0 to 1 for each drawing, according to symmetry, with a maximum score of 3.

2.8.3. Secondary outcomes

A scale to assess changes in the level of ADL (autonomy) is Modified Barthel Index (MBI).

Modified Barthel Index is a five-level rating scale and evaluates the functional independence and autonomy of the subjects in 10 activities, including (1) bathing, (2) personal

grooming, (3) feeding, (4) dressing and undressing, (5) bowel, (6) bladder continence, (7) getting on/off the toilet, (8) stair climbing, (9) moving from wheelchair to bed and return, and (10) walking, with high reliability and stability in people of different sexes and ages (44). The highest score of the MBI is 100, with higher scores indicating increased ADL.

2.9. Adverse events

A safety questionnaire will be administered to all participants prior to the administration of the first PA or EMT to reduce the risk of possible symptoms, including dry eyes, headache, and irritability, and will be recorded at the end of each session. Descriptive statistics will be provided for all adverse events.

The following measures will be taken to prevent these events: (a) prior to the intervention, the investigator will communicate adequately to ensure that the patient is in a good state after rest; (b) during the intervention, the investigator will closely monitor the patient's condition and keep records; (c) if the patient feels any discomfort, the intervention will be suspended immediately, the intervention protocol will be adjusted (by increasing the interval of rest), or the intervention will be stopped. If a serious adverse event occurs, we will seek professional evaluation, cover the cost of treatment for the adverse event caused by the trial, and provide some financial compensation.

2.10. Dropout criteria

The intervention will be discontinued if the subject meets one or more of the following criteria: (a) the subject has poor compliance and fails to perform the treatment as required, e.g., the subject does not cooperate with the investigator or the subject does not come to treatment on time; (b) medical records are incomplete and affect efficacy or safety evaluation; (c) subject voluntarily withdraws; (d) subject experiences an adverse event (including episodes of ocular pain, headache, and irritability); and (e) the subject has a severely progressive disease or some comorbidity, complications, or specific physiological changes.

Patients who drop out will not be included in the efficacy analysis; if they drop out for reasons such as the occurrence of an adverse event, they will be included in the safety analysis.

2.11. Data collection and management

The trial process will be recorded *via* the audio or written form to ensure the authenticity of the intervention. A case report form (CRF) will be used to collect data. Two data managers will enter the data from the CRF into a computer database and cross-check the electronic data for uniformity. All data will be confidential to those outside the study, except for the ethics committee. Experimental data will be used to write clinical research studies. During the course of the study, if subjects discontinue or deviate from the intervention protocol, we will collect as much data as possible for further analysis.

We will use the following methods to facilitate participants' completion of the trial and follow-up: (a) enhance communication between investigators and patients and obtain patients' cooperation whenever possible and (b) provide relevant test results to study patients free of charge.

2.12. Data analysis

IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, United States) will be used for statistical analysis. 2-tailed $P < 0.05$ will be considered a statistically significant difference. Continuous variables will be expressed as mean with standard deviation or median with interquartile range, whereas categorical data will be expressed as counts and percentages. Baseline comparisons will be used to examine potential differences between 4 groups. Age, time of onset, and MMSE will be analyzed by ANOVA or Kruskal-Wallis test. Sex, cause of damage will be measured using Chi-square tests. The Kolmogorov-Smirnov test will be used to evaluate the normality of distributions. If a normal distribution is confirmed, one-way ANOVA will be used to examine the effectiveness of intervention between the 4 groups at T1, T2, with Bonferroni correction for multiple comparisons as a *post hoc* test. Otherwise, Kruskal-Wallis (non-parametric test) will be used.

3. Discussion

Unilateral spatial neglect is a complex neurological syndrome with a high prevalence and adverse effects. In this study, we design a random and comparison clinical trial to observe the effectiveness of PA and EMT and combined therapy for USN of patients with poststroke.

A major consideration of this study is based on the theoretical model of Barrett et al. (21), who mentioned that stroke-induced unilateral spatial neglect can be characterized by visual–perceptual spatial neglect and motor intention deficits. Many studies have investigated the effectiveness of PA for USN, indicating that PA is a promising intervention to alleviate symptoms of neglect and improve functional outcomes. However, some contrary studies have shown that patients improved only motor-intentional deficits after PA intervention (45, 46). EMT is another effective intervention used in the study. Balslev and Odoj (47) supported the coupling of attention and gaze and argued that interventions on target gaze signals can alleviate visual–perceptual spatial neglect. Therefore, we

hypothesized that the combination of the two interventions might both treat the patients' classic visual–perceptual spatial neglect and motor intention deficits, resulting in a more positive and comprehensive effect.

In contrast, although previous studies have explored PA in combination with other treatments, most studies have selected therapies with the same bottom-up approach (19, 20, 48). It is notable that the two interventions chosen for the present study stem from the following two different approaches: the "top-down" approach aims to improve perceptual and behavioral biases by acting on disrupted consciousness and thus on higher-level cognitive processes, and the "bottom-up" approach is a physiological approach that aims to influence sensory-motor levels through passive sensory manipulation or visuomotor adaptation. PA belongs to a bottom-up intervention approach, while EMT belongs to a top-down intervention approach. PA may ameliorate neglect symptoms by improving patients' spatial cognitive processes: recalibration and spatial alignment (49, 50), and imaging studies have shown that PA activates the parietal cortex and cerebellum associated with recalibration and spatial rearrangement (39, 51, 52), as well as altering the balance of activity in bilateral parietal, frontal, and temporal regions (53), and altering frontal-parietal, parietal-temporal, and cerebellar-parietal-hippocampal network connections in the resting state (54, 55). EMT improves spontaneous eye exploration and spatial attention to the space contralateral to the brain injury. An fMRI study showed that EMT induced alterations in brain activation in the striate and extrastriate cortex as well as in oculomotor areas (56). The two showed more differences in neural mechanisms, so the combined intervention of these two approaches may affect the broader brain network associated with USN. Based on this, we chose to combine these two approaches in the present study, which we hypothesized would have positive effects.

Since patients with USN themselves suffer from attention deficits and other cognitive dysfunctions, an unreasonable combination of therapies rather leads to an aggravation of neglect symptoms (48), and therefore, the selection of the combination of different interventions needs to take into account the relevant influencing factors and the patient's tolerance. Saevarsson et al. (19) and Choi et al. (20) combined an active engagement (PA) with a passively received (neck vibration or FES) intervention, both of which showed better efficacy of the combined intervention, but both interventions used in our trial required patients to actively participate, so this may be a limitation of this interventional approach. However, the few patients who completed the intervention described that they were able to accept the intensity of the training and did not experience any particular fatigue or difficulty accomplishing it.

There are other limitations to our study. (a) Our target population was set to patients with subacute stroke, and the efficacy of patients in the chronic phase was not discussed. (b) The efficacy of interventions with active engagement is influenced by cognitive level, and we only mentioned the ability to cooperate with the therapist in the eligibility criteria, discussed the overall efficacy, and did not stratify the analysis of the efficacy of patients with different cognitive levels. (c) Patients with severe USN were excluded from the study, so the efficacy for this group is not yet clear. (d) This is a preliminary exploratory study, and the follow-up time in this trial is only 2 weeks after the end of treatment.

We aimed to conduct a randomized controlled trial to investigate whether the PA combined with EMT has the potential to be a promising treatment option for poststroke USN. If this study provides positive results, it will be possible to recommend that these techniques be implemented in treatment protocols for patients with USN.

Trial status

This publication is based on version 1 of the PA combined eye movement protocol dated 2 August 2021. The official start of recruitment was on 2 November 2021. The estimated end date of the trial is 1 June 2023, and the recruitment of patients is ongoing.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Nanchong Central Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Y-xY conceptualized and wrote the study. L-lW and Y-lX prepared the manuscript and contributed to the study design. JD provided statistical expertise in clinical trial design. Y-mL is responsible for the assessment of the trial. BZ and HZ reviewed and approved the manuscript for final submission. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Acknowledgments

We thank all the study participants for their involvement and patient advisers in this trial.

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

References

1. Collaborators GBDS. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

2. Bejot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *Presse Med.* (2016) 45:e391–e8. doi: 10.1016/j.lpm.2016.10.003

3. Esposito E, Shekhtman G, Chen P. Prevalence of spatial neglect post-stroke: A systematic review. *Ann Phys Rehabil Med.* (2021) 64:101459. doi: 10.1016/j.rehab.2020.10.010

4. Corbetta M, Shulman GL. Spatial neglect and attention networks. *Annu Rev Neurosci.* (2011) 34:569–99. doi: 10.1146/annurev-neuro-061010-113731

5. Heilman KM, Valenstein E, Watson RT. Neglect and related disorders. *Semin Neurol.* (2000) 20:463–70. doi: 10.1055/s-2000-13179

6. Nijboer TC, Kollen BJ, Kwakkel G. Time course of visuospatial neglect early after stroke: a longitudinal cohort study. *Cortex.* (2013) 49:2021–7. doi: 10.1016/j.cortex.2012.11.006

7. Di Monaco M, Schintu S, Dotta M, Barba S, Tappero R, Gindri P. Severity of unilateral spatial neglect is an independent predictor of functional outcome after acute inpatient rehabilitation in individuals with right hemispheric stroke. *Arch Phys Med Rehabil.* (2011) 92:1250–6. doi: 10.1016/j.apmr.2011.03.018

8. Chen P, Hreha K, Kong Y, Barrett AM. Impact of spatial neglect on stroke rehabilitation: evidence from the setting of an inpatient rehabilitation facility. *Arch Phys Med Rehabil.* (2015) 96:1458–66. doi: 10.1016/j.apmr.2015.03.019

9. Tarvonen-Schroder S, Niemi T, Koivisto M. Comparison of functional recovery and outcome at discharge from subacute inpatient rehabilitation in patients with right or left stroke with and without contralateral spatial neglect. *J Rehabil Med.* (2020) 52:jrm00071. doi: 10.2340/16501977-2698

10. Buxbaum LJ, Ferraro MK, Veramonti T, Farne A, Whyte J, Ladavas E, et al. Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology.* (2004) 62:749–56. doi: 10.1212/01.WNL.0000113730.73031.F4

11. Chen P, Fyffe DC, Hreha K. Informal caregivers' burden and stress in caring for stroke survivors with spatial neglect: an exploratory mixed-method study. *Top Stroke Rehabil.* (2017) 24:24–33. doi: 10.1080/10749357.2016.1186373

12. Teasell R, Salbach NM, Foley N, Mountain A, Cameron JI, Jong A, et al. Canadian stroke best practice recommendations: rehabilitation, recovery, and community participation following stroke. Part One: Rehabilitation and Recovery Following Stroke; 6th Edition Update 2019. *Int J Stroke.* (2020) 15:763–88. doi: 10.1177/1747493019897843

13. Luaute J, Halligan P, Rode G, Rossetti Y, Boisson D. Visuo-spatial neglect: a systematic review of current interventions and their effectiveness. *Neurosci Biobehav Rev.* (2006) 30:961–82. doi: 10.1016/j.neubiorev.2006.03.001

14. Ten Brink AF, Visser-Meily JMA, Schut MJ, Kouwenhoven M, Eijsackers ALH, Nijboer TCW. Prism adaptation in rehabilitation? No additional effects of prism adaptation on neglect recovery in the subacute phase poststroke: a randomized controlled trial. *Neurorehabil Neural Repair.* (2017) 31:1017–28. doi: 10.1177/1545968317744277

15. Mizuno K, Tsujimoto K, Tsuji T. Effect of prism adaptation therapy on the activities of daily living and awareness for spatial neglect: a secondary analysis of the randomized, controlled trial. *Brain Sci.* (2021) 11:347. doi: 10.3390/brainsci11030347

16. Zhang R G, He C X, Wang D, Huang Y K, Wang F Y, Yang Y H. Progress of visual-motor stimulation intervention for unilateral neglect after stroke. *China Rehabilitation.* (2021) 36:495–8.

17. Saevarsson S, Halsband U, Kristjansson A. Designing rehabilitation programs for neglect: could 2 be more than 1 + 1? *Appl Neuropsychol.* (2011) 18:95–106. doi: 10.1080/09084282.2010.547774

18. Umeonwuka C, Roos R, Ntsiea V. Current trends in the treatment of patients with post-stroke unilateral spatial neglect: a scoping review. *Disabil Rehabil.* (2020) 44:1–28. doi: 10.1080/09638288.2020.1824026

19. Saevarsson S, Kristjansson A, Halsband U. Strength in numbers: combining neck vibration and prism adaptation produces additive therapeutic effects in unilateral neglect. *Neuropsychol Rehabil.* (2010) 20:704–24. doi: 10.1080/09602011003737087

20. Choi HS, Kim DJ, Yang YA. The Effect of a Complex Intervention Program for Unilateral Neglect in Patients with Acute-Phase Stroke: A Randomized Controlled Trial. *Osong Public Health Res Perspect.* (2019) 10:265–73. doi: 10.24171/j.phrp.2019.10.5.02

21. Barrett AM, Goedert KM, Basso JC. Prism adaptation for spatial neglect after stroke: translational practice gaps. *Nat Rev Neurol.* (2012) 8:567–77. doi: 10.1038/nrneurol.2012.170

22. Azouvi P, Jacquin-Courtois S, Luaute J. Rehabilitation of unilateral neglect: Evidence-based medicine. *Ann Phys Rehabil Med.* (2017) 60:191–7. doi: 10.1016/j.rehab.2016.10.006

23. Gammeri R, Iacono C, Ricci R, Salatino A. Unilateral spatial neglect after stroke: current insights. *Neuropsychiatr Dis Treat.* (2020) 16:131–52. doi: 10.2147/NDT.S171461

24. Rossetti Y, Rode G, Pisella L, Farne A, Li L, Boisson D, et al. Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature.* (1998) 395:166–9. doi: 10.1038/25988

25. Facchin A, Figliano G, Daini R. Prism adaptation and optokinetic stimulation comparison in the rehabilitation of unilateral spatial neglect. *Brain Sci.* (2021) 11:1488. doi: 10.3390/brainsci11111488

26. Mizuno K, Tsuji T, Takebayashi T, Fujiwara T, Hase K, Liu M. Prism adaptation therapy enhances rehabilitation of stroke patients with unilateral spatial neglect: a randomized, controlled trial. *Neurorehabil Neural Repair.* (2011) 25:711–20. doi: 10.1177/1545968311407516

27. Fortis P, Ronchi R, Velardo V, Calzolari E, Banco E, Algeri L, et al. A home-based prism adaptation training for neglect patients. *Cortex.* (2020) 122:61–80. doi: 10.1016/j.cortex.2018.09.001

28. Anelli F, Avanzi S, Damora A, Mancuso M, Frassinetti F. Mental time travel and functional daily life activities in neglect patients: Recovery effects of rehabilitation by prism adaptation. *Cortex.* (2019) 113:141–55. doi: 10.1016/j.cortex.2018.12.003

29. Champod AS, Frank RC, Taylor K, Eskes GA. The effects of prism adaptation on daily life activities in patients with visuospatial neglect: a systematic review. *Neuropsychol Rehabil.* (2018) 28:491–514. doi: 10.1080/09602011.2016.1182032

30. Zhu HF, Zhang J, Wu QF. Study on the improvement effect of prismatic adaptation technique on unilateral spatial neglect after stroke. *Hebei Med.* (2017) 39:2235–7.

31. Glize B, Lunven M, Rossetti Y, Revol P, Jacquin-Courtois S, Klinger E, et al. Improvement of Navigation and Representation in Virtual Reality after Prism Adaptation in Neglect Patients. *Front Psychol.* (2017) 8:2019. doi: 10.3389/fpsyg.2017.02019

32. Matsuo T, Moriuchi T, Iso N, Hasegawa T, Miyata H, Maruta M, et al. Effects of prism adaptation on auditory spatial attention in patients with left unilateral spatial neglect: a non-randomized pilot trial. *Int J Rehabil Res.* (2020) 43:228–34. doi: 10.1097/MRR.0000000000000413

33. Spaccavento S, Cellamare F, Cafforio E, Loverre A, Craca A. Efficacy of visual-scanning training and prism adaptation for neglect rehabilitation. *Appl Neuropsychol Adult.* (2016) 23:313–21. doi: 10.1080/23279095.2015.1038386

34. Metzler MJ, Maiani M, Jamieson B, Dukelow SP. Clinical provision of compensatory visual training after neurological injury: example of a multisite outpatient program. *Disabil Rehabil.* (2021) 43:118–25. doi: 10.1080/09638288.2019.1616835

35. Leal Rato M, Mares I, Aguiar de Sousa D, Senju A, Martins IP. Direct gaze partially overcomes hemispatial neglect and captures spatial attention. *Front Psychol.* (2018) 9:2702. doi: 10.3389/fpsyg.2018.02702

36. Driver J, Mattingley JB. Parietal neglect and visual awareness. *Nat Neurosci.* (1998) 1:17–22. doi: 10.1038/217

37. Rengachary J, He BJ, Shulman GL, Corbetta M. A behavioral analysis of spatial neglect and its recovery after stroke. *Front Hum Neurosci.* (2011) 5:29. doi: 10.3389/fnhum.2011.00029

38. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* (2013) 346:e7586. doi: 10.1136/bmj.e7586

39. Panico F, Rossetti Y, Trojano L. On the mechanisms underlying Prism Adaptation: A review of neuro-imaging and neuro-stimulation studies. *Cortex.* (2020) 123:57–71. doi: 10.1016/j.cortex.2019.10.003

40. Katzman R, Zhang MY, Ouang Ya Q, Wang ZY, Liu WT Yu E, et al. A Chinese version of the Mini-Mental State Examination; impact of illiteracy in a Shanghai dementia survey. *J Clin Epidemiol.* (1988) 41:971–8. doi: 10.1016/0895-4356(88)90034-0

41. Li H, Jia J, Yang Z. Mini-Mental State Examination in Elderly Chinese: A Population-Based Normative Study. *J Alzheimers Dis.* (2016) 53:487–96. doi: 10.3233/JAD-160119

42. Azouvi P, Samuel C, Louis-Dreyfus A, Bernati T, Bartolomeo P, Beis JM, et al. Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *J Neurol Neurosurg Psychiatry.* (2002) 73:160–6. doi: 10.1136/jnnp.73.2.160

43. Wilson B, Cockburn J, Halligan P. Behavioural Inattention Test; Manual, Fareham. (1987).

44. Yang H, Chen Y, Wang J, Wei H, Chen Y, Jin J. Activities of daily living measurement after ischemic stroke: Rasch analysis of the modified Barthel Index. *Medicine (Baltimore).* (2021) 100:e24926. doi: 10.1097/MD.0000000000024926

45. Striemer CL, Danckert J. Dissociating perceptual and motor effects of prism adaptation in neglect. *Neuroreport.* (2010) 21:436–41. doi: 10.1097/WNR.0b013e328338592f

46. Fortis P, Chen P, Goedert KM, Barrett AM. Effects of prism adaptation on motor-intentional spatial bias in neglect. *Neuroreport.* (2011) 22:700–5. doi: 10.1097/WNR.0b013e32834a3e20

47. Balslev D, Odoj B. Distorted gaze direction input to attentional priority map in spatial neglect. *Neuropsychologia.* (2019) 131:119–28. doi: 10.1016/j.neuropsychologia.2019.05.017

48. Keller I, Lefin-Rank G, Losch J, Kerkhoff G. Combination of pursuit eye movement training with prism adaptation and arm movements in neglect therapy: a pilot study. *Neurorehabil Neural Repair.* (2009) 23:58–66. doi: 10.1177/1545968308317438

49. Redding GM, Wallace B. Strategic calibration and spatial alignment: a model from prism adaptation. *J Mot Behav.* (2002) 34:126–38. doi: 10.1080/00222890209601935

50. Redding GM, Rossetti Y, Wallace B. Applications of prism adaptation: a tutorial in theory and method. *Neurosci Biobehav Rev.* (2005) 29:431–44. doi: 10.1016/j.neubiorev.2004.12.004

51. Kuper M, Wunnemann MJ, Thurling M, Stefanescu RM, Maderwald S, Elles HG, et al. Activation of the cerebellar cortex and the dentate nucleus in a prism adaptation fMRI study. *Hum Brain Mapp.* (2014) 35:1574–86. doi: 10.1002/hbm.22274

52. Terruzzi S, Crivelli D, Pisoni A, Mattavelli G, Romero Lauro LJ, Bolognini N, et al. The role of the right posterior parietal cortex in prism adaptation and its aftereffects. *Neuropsychologia.* (2021) 150:107672. doi: 10.1016/j.neuropsychologia.2020.107672

53. Crottaz-Herbette S, Fornari E, Notter MP, Bindschaedler C, Manzoni L, Clarke S. Reshaping the brain after stroke: The effect of prismatic adaptation in patients with right brain dam age. *Neuropsychologia.* (2017) 104:54–63. doi: 10.1016/j.neuropsychologia.2017.08.005

54. Tsujimoto K, Mizuno K, Nishida D, Tahara M, Yamada E, Shindo S, et al. Prism adaptation changes resting-state functional connectivity in the dorsal stream of visual attention networks in healthy adults: A fMRI study. *Cortex.* (2019) 119:594–605. doi: 10.1016/j.cortex.2018.10.018

55. Schintu S, Freedberg M, Gotts SJ, Cunningham CA, Alam ZM, Shomstein S, et al. Prism adaptation modulates connectivity of the intraparietal sulcus with multiple brain networks. *Cereb Cortex.* (2020) 30:4747–58. doi: 10.1093/cercor/bhaa032

56. Nelles G, Pscherer A, de Greiff A, Forsting M, Gerhard H, Esser J, et al. Eye-movement training-induced plasticity in patients with post-stroke hemianopia. *J Neurol.* (2009) 256:726–33. doi: 10.1007/s00415-009-5005-x

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 12 January 2023
DOI 10.3389/fneur.2022.1084616

OPEN ACCESS

EDITED BY
Cheong-Meng Chong,
University of Macau, China

REVIEWED BY
Wei Yue,
Tianjin Huanhu Hospital, China
Yanan Wang,
West China Hospital of Sichuan University, China

*CORRESPONDENCE
Jianxin Jiang
jjx830829@163.com
Ying Liu
13952618801@163.com

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 30 October 2022
ACCEPTED 01 December 2022
PUBLISHED 12 January 2023

CITATION
Yu T, Liu H, Liu Y and Jiang J (2023) Inflammatory response biomarkers nomogram for predicting pneumonia in patients with spontaneous intracerebral hemorrhage. *Front. Neurol.* 13:1084616. doi: 10.3389/fneur.2022.1084616

Inflammatory response biomarkers nomogram for predicting pneumonia in patients with spontaneous intracerebral hemorrhage

Tingting Yu[1,2,3], Haimei Liu[1,2,3], Ying Liu[2,3]* and Jianxin Jiang[4,5]*

[1]Graduate School of Dalian Medical University, Dalian, China, [2]Department of Neurology, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou, China, [3]Department of Neurology, Taizhou People's Hospital, Taizhou, China, [4]Department of Neurosurgery, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou, China, [5]Department of Neurosurgery, Taizhou People's Hospital, Taizhou, China

Objectives: Inflammatory response biomarkers are promising prognostic factors to improve the prognosis of stroke-associated pneumonia (SAP) after ischemic stroke. This study aimed to investigate the prognostic significance of inflammatory response biomarkers on admission in SAP after spontaneous intracerebral hemorrhage (SICH) and establish a corresponding nomogram.

Methods: The data of 378 patients with SICH receiving conservative treatment from January 2019 to December 2021 at Taizhou People's Hospital were selected. All eligible patients were randomized into the training (70%, 265) and validation cohorts (30%, 113). In the training cohort, multivariate logistic regression analysis was used to establish an optimal nomogram, including inflammatory response biomarkers and clinical risk factors. The area under the receiver operating characteristic (ROC) curve (AUC), calibration curve, and decision curve analysis (DCA) were used to evaluate the nomogram's discrimination, calibration, and performance, respectively. Moreover, this model was further validated in a validation cohort.

Results: A logistic regression analysis showed that intraventricular hemorrhage (IVH), hypertension, dysphagia, Glasgow Coma Scale (GCS), National Institute of Health Stroke Scale (NIHSS), systemic inflammation response index (SIRI), and platelet/lymphocyte ratio (PLR) were correlated with SAP after SICH ($P < 0.05$). The nomogram was composed of all these statistically significant factors. The inflammatory marker-based nomogram showed strong prognostic power compared with the conventional factors, with an AUC of 0.886 (95% CI: 0.841–0.921) and 0.848 (95% CI: 0.799–0.899). The calibration curves demonstrated good homogeneity between the predicted risks and the observed outcomes. In addition, the model has a significant net benefit for SAP, according to DCA. Also, internal validation demonstrated the reliability of the prediction nomogram. The length of hospital stay was shorter in the non-SAP group than in the SAP group. At the 3-month follow-up, clinical outcomes were worse in the SAP group ($P < 0.001$).

Conclusion: SIRI and PLR at admission can be utilized as prognostic inflammatory biomarkers in patients with SICH in the upper brain treated with SAP. A nomogram covering SIRI and PLR can more accurately predict SAP in patients' supratentorial SICH. SAP can influence the length of hospital stay and the clinical outcome.

KEYWORDS

spontaneous intracerebral hemorrhage, pneumonia, nomogram, inflammatory response biomarkers, systemic inflammation response index, platelet/lymphocyte ratio

1. Introduction

Spontaneous intracerebral hemorrhage (SICH) has high morbidity, mortality, and medical complications, in addition to primary brain injury, are significant causes of adverse outcomes (1, 2). After the development of stroke-associated pneumonia (SAP), unfavorable conditions may result in prolonged hospitalization, poor functional recovery, high social and economic burden, and even death (3). A study found that the median length of hospital stay was longer in patients with SAP (13 days) than in those without SAP (5 days) (4). Therefore, as a rapidly progressive disease with high mortality, early identification and effective indicators of SAP prevention are essential. Several risk factors for pneumonia in stroke patients, namely age, immunosuppression, dysphagia, previous medical history (i.e., diabetes, atrial fibrillation, alcohol consumption, and COPD), and stroke severity, were highlighted (5–8). However, these risk factors largely depend on clinical symptoms, and clinical monitoring of SAP remains imprecise. To predict SAP occurrence, an objective predictor is essential.

There is growing evidence that the immunodeficiency syndrome caused by stroke promotes the development of SAP, suggesting the significance of immune-inflammatory processes in SAP (9, 10). Routine blood markers (i.e., neutrophils, lymphocytes, and monocytes) are common systemic inflammation and infection markers. In addition, the systemic inflammation response index (SIRI), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and platelet/lymphocyte ratio (PLR) have better predictive power than conventional inflammatory factors (11–14). Most studies on risk factors for SAP are based on ischemic stroke. The pathophysiological mechanisms of SICH and acute ischemic stroke (AIS) are very different. Previous studies have shown that high NLR and SIRI predict SAP in patients with AIS (15, 16). However, the clinical significance of these inflammatory factors for SAP after SICH remains questionable. Furthermore, no predictive models of inflammatory indicators have been developed to predict the occurrence of SAP after SICH. Identifying risk factors is based on targeted primary prevention strategies and may influence clinical management by optimizing patient care.

This study established a predictive nomogram as a simple statistical visualization tool to predict disease onset, progression, prognosis, and survival (17–19). This study aimed to assess whether inflammatory response biomarkers on admission contribute to the early prediction of SAP after SICH.

2. Methods

2.1. Study population

This observational study was approved by the local Ethics Committee of Taizhou People's Hospital and did not require individual patient consent (KY2022-094-01). The subjects of this retrospective study were patients with SICH who were admitted to Taizhou People's Hospital for conservative treatment from January 2019 to December 2021. SICH was determined by admission computed CT scanning. The decision of treatment modality of SICH (conservative treatment) was determined according to the diagnosis and treatment protocol, guidelines, and specific conditions of each patient. Inclusion criteria were: (1) CT diagnosis of SICH following the fourth national diagnostic criteria for cerebrovascular disease in 1995 in China, (2) CT follow-up within 24 h after admission, (3) age $\geq$18 years, (4) all patients were treated conservatively, and (5) diagnosing pneumonia was based on the diagnostic criteria for SAP in 2015 (20). We excluded patients with (1) infectious diseases, fever, or prophylactic antibiotics within 2 weeks before patient admission; (2) patients with infratentorial SICH; (3) cerebral hemorrhage due to trauma, subarachnoid hemorrhage due to aneurysm rupture and trauma; (4) patients after surgical treatment; (5) patients with autoimmune diseases, malignancies, hematological diseases, severe liver and kidney diseases, and history of major surgery; and (6) patients with incomplete information. We excluded patients with infratentorial cerebral hemorrhage. Patients with severe symptoms (GCS score $\leq$3) were excluded. Ultimately, 378 eligible patients were recruited. Patients were randomly classified into the training and validation cohorts in a 7:3 ratio (Figure 1).

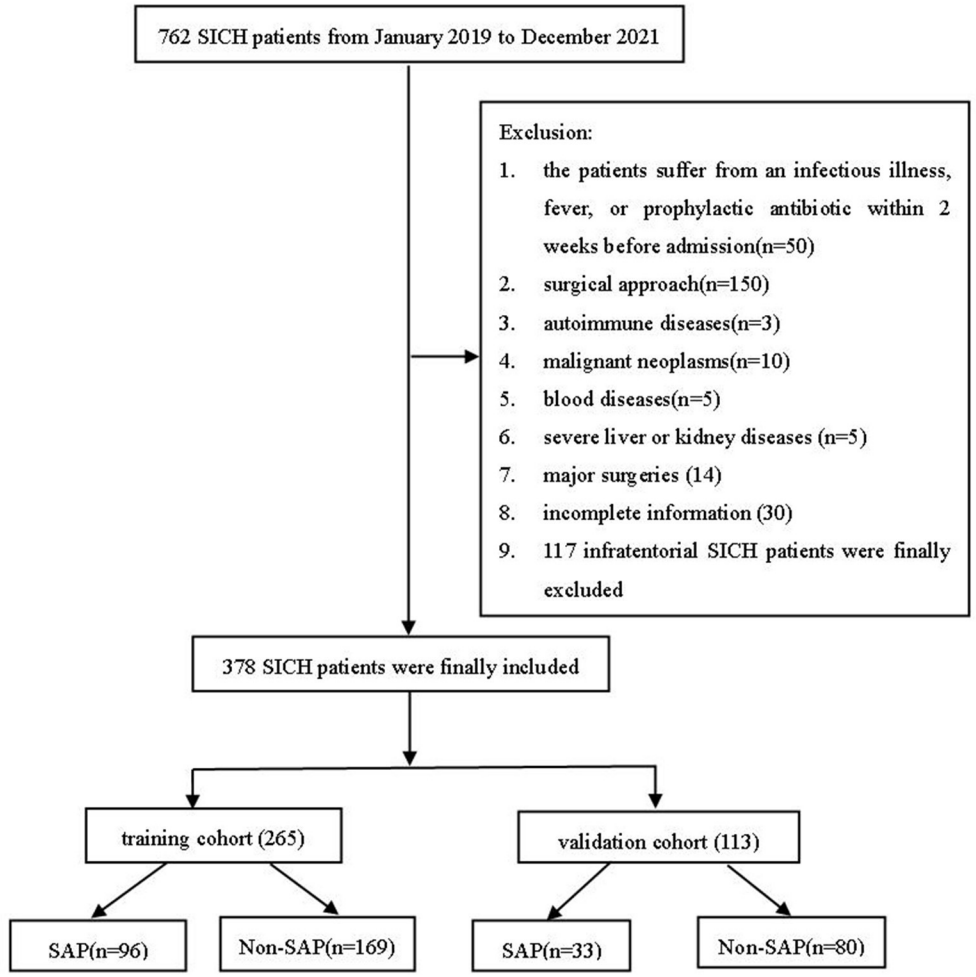


FIGURE 1
A flowchart of the present study. SICH, spontaneous intracerebral hemorrhage; SAP, stroke-associated pneumonia.

2.2. Data collection

All participating patients were reviewed for a range of risk factors associated with SAP, including age, gender, body mass index (BMI), Glasgow Coma Scale (GCS), National Institute of Health Stroke Scale (NIHSS) score, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission, time from onset to hospitalization, dysphagia, hematoma volume, hematoma location, and intraventricular hemorrhage (IVH). Medical history was collected, that is, hypertension, diabetes, atrial fibrillation, smoking, drinking, and antiplatelet or anticoagulation. Laboratory parameters (red blood cells (RBC), white blood cells (WBC), platelets, absolute neutrophil count (ANC), absolute monocyte count (AMC), absolute lymphocyte count (ALC), and albumin) were obtained within 24 h of admission for all subjects. We collected the length of hospital stay and the functional recovery of the patients. To obtain their functional recovery, we followed up the patients or their families 3 months after discharge using a telephone.

2.3. Measurements and study outcomes

A trained neurologist assessed the GCS and NIHSS scores at admission to assess the severity of SICH. The following formulae were used to compute the lymphocyte-based inflammatory index in this study: SIRI (21), NLR (15), MLR (14), and PLR (22) from the first peripheral blood count at admission.

The primary outcome of our study was SAP after SICH. Patients with signs or symptoms of respiratory infection underwent routine blood tests, and chest CT scans to diagnose pneumonia. Physicians from neurology and radiology jointly diagnosed pneumonia (20). Secondary outcomes were the length of stay and functional recovery. The modified Rankin Scale (mRS) score was utilized to evaluate functional recovery

10.3389/fneur.2022.1084616

TABLE 1 Baseline characteristics of all patients in the training cohort and validation cohort.

	Total (n = 378)	Training cohort (n = 265, 70.1%)	Validation cohort (n = 113, 29.9%)	P
Demographics				
Age [year, M (Q1, Q3)]	63.54 ± 13.72	63.48 ± 13.75	63.67 ± 13.69	0.900
Gender, *n* (%)				0.572
Male	253 (66.9)	175 (66.0)	78 (69.0)	
Female	125 (33.1)	90 (34.0)	35 (31.0)	
BMI[kg/m^2, M (Q1, Q3)]	24.49 (21.26, 27.08)	24.49 (21.48, 27.04)	24.22 (20.58, 27.31)	0.845
Medical history				
Hypertension, *n* (%)	283 (74.9)	198 (74.7)	85 (75.2)	0.918
Diabetes mellitus, *n* (%)	29 (7.7)	20 (7.5)	9 (8.0)	0.889
Atrial fibrillation, *n* (%)	26 (6.9)	19 (7.2)	7 (6.2)	0.732
Smoking, *n* (%)	97 (25.7)	71 (26.8)	26 (23.0)	0.441
Drinking (>3 drinks per 24 h), *n* (%)	86 (22.8)	57 (21.5)	29 (25.7)	0.378
Antiplatelet or anticoagulation, *n* (%)	26 (6.9)	18 (6.8)	8 (7.1)	0.920
Clinical characteristics				
NIHSS [score, M (Q1, Q3)]	3 (2, 8)	4 (2, 8)	3 (2, 6)	0.144
GCS [score, M (Q1, Q3)]	13 (10, 15)	13 (9, 15)	14 (12, 15)	0.002#
Admission SBP [mmHg, M (Q1, Q3)]	162 (150, 179.50)	164 (150, 181)	161.23 ± 20.17	0.106
Admission DBP [mmHg, M (Q1, Q3)]	95 (85, 105.5)	95.87 ± 16.12	94 (81, 105)	0.467
Duration from onset to hospitalization [h, M (Q1, Q3)]	5 (3, 12)	5 (3, 11)	5 (3, 12)	0.749
Dysphagia, *n* (%)	169 (44.7)	123 (46.4)	46 (40.7)	0.307
ICH parameters				
Hematoma volume[ml, M (Q1, Q3)]	12.16 (5.35, 23.34)	12.54 (5.38, 23.02)	12.00 (5.21, 24.65)	0.881
Hematoma location, *n* (%)				0.315
Lobar	82 (21.7)	52 (19.6)	30 (26.5)	
Basal ganglia region	225 (59.5)	161 (60.8)	64 (56.6)	
Thalamus	71 (18.8)	52 (19.6)	19 (16.8)	
IVH, *n* (%)	108 (28.6)	79 (29.8)	29 (25.7)	0.414
Laboratory data				
RBC [10^{12}/L, (M ± SD)]	4.41 ± 0.62	4.37 (3.98, 4.82)	4.48 ± 0.62	0.195
Hemoglobin [g/L]	136 (122.5, 148)	135.03 ± 18.09	137 (122.25, 151.75)	0.541
WBC [10^9/L, M (Q1, Q3)]	7.61 (6.08, 10.07)	7.63 (6.27, 9.80)	7.60 (5.92, 10.55)	0.884
ANC [10^9/L, M (Q1, Q3)]	5.52 (4.14, 8.09)	5.53 (4.26, 8.03)	5.34 (4.03, 8.40)	0.606
ALC [10^9/L, M (Q1, Q3)]	1.22 (0.82, 1.87)	1.20 (0.82, 1.84)	1.28 (0.82, 1.97)	0.389
AMC [10^9/L, M (Q1, Q3)]	0.40 (0.31, 0.53)	0.40 (0.30, 0.52)	0.41 (0.32, 0.55)	0.262
Platelet [109/L, M (Q1, Q3)]	170.50 (123, 220)	170 (122.50, 219.50)	175 (124, 223.50)	0.794
Albumin [g/L, M (Q1, Q3)]	39.20 (36.40, 41.73)	39.20 (36.45, 41.70)	39.20 (36.35, 41.70)	0.966
SIRI [M (Q1, Q3)]	1.74 (0.96, 3.43)	1.95 (0.98, 3.39)	1.68 (0.93, 3.49)	0.646
NLR [M (Q1, Q3)]	4.85 (2.60, 7.63)	5.01 (2.67, 7.85)	4.27 (2.45, 7.35)	0.335
MLR [M (Q1, Q3)]	0.32 (0.22, 0.49)	0.32 (0.23, 0.48)	0.31 (0.21, 0.50)	0.750

(Continued)

TABLE 1 (Continued)

	Total ($n = 378$)	Training cohort ($n = 265$, 70.1%)	Validation cohort ($n = 113$, 29.9%)	*P*
PLR [M (Q1, Q3)]	135.02 (93.02, 191.51)	134.25 (96.40, 193.92)	139.13 (87.76, 185.47)	0.794
SAP, *n* (%)	129 (34.1)	96 (36.2)	33 (29.2)	0.187
Clinical outcomes				
Length of hospital stay, [days, M (Q1, Q3)]	15 (11, 20)	15 (11, 21)	15 (11, 19)	0.426
mRS score at 3 months [score, M (Q1, Q3)]	4 (2, 5)	4 (2, 5)	3 (2, 5)	0.575
Poor clinical outcome (mRS3–6) at 3 months, *n* (%)	220 (58.2)	152 (57.4)	68 (60.2)	0.611

SICH, spontaneous intracerebral hemorrhage; SAP, stroke-associated pneumonia; BMI, body mass index; NIHSS, National Institute of Health Stroke; Scale GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; IVH, intraventricular hemorrhage; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; SIRI, systemic inflammation response index; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio; M, mean or median; mRS, modified Rankin Scale.
#Statistically significant.

after 3 months, that is, an mRS score of 3–6 indicates poor clinical outcome.

2.4. Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (M ± SD), and skewed distributions were expressed as median with interquartile range (IQR, Q1–Q3). Categorical variables are expressed as frequencies and percentages (%). Where appropriate, the *t*-test, the Mann–Whitney *U*-test, and the chi-square test were utilized for comparisons.

Multivariate logistic regression models considered variables with $P < 0.05$ in the univariate analysis results to obtain independent predictors. The Hosmer–Leeshawn test was utilized to assess the model's goodness of fit. In addition, a Nomogram with independent predictors was constructed from the training cohort. The area under the receiver operating characteristic (ROC) curve (AUC) and the calibration curves were utilized to assess the predictive power and compliance of the model. We performed a decision curve analysis (DCA) to quantify the net benefit of different threshold probabilities to determine the clinical utility of the nomogram we developed. After that, the visual prediction model was validated internally. Statistical analyses were performed on SPSS 26.0 (IBM Corporation, Chicago, IL) and R statistical software (R, version 4.1.1). Statistically significant differences were considered to be two-tailed at a *P*-value of < 0.05.

3. Results

3.1. Baseline characteristics

A total of 378 patients with SICH, including 265 in the training and 113 in the validation cohort, were included. Except for a statistically significant difference in GCS at admission ($P < 0.05$) regarding baseline characteristics, other variables did not differ between the two cohorts (Table 1). Patients with SAP (36. 2%) tended to be older, had higher rates of hypertension, antiplatelet or anticoagulation, dysphagia, and IVH, and had larger hematoma volumes, lower GCS scores, RBCs, ALC, hemoglobin, and albumin, and higher NIHSS scores, WBCs, ANC, SIRI, NLR, MLR, and PLR in the training cohort ($P < 0.05$, Table 2). Patients in the SAP group had a longer length of hospital stay ($P < 0.05$, Table 2). Three months after discharge, the mRS score of the SAP group differed from that of the non-SAP group (Table 2, $P < 0.001$). Clinical outcomes (mRS3-6) were significantly worse in the SAP group than in the non-SAP group (71.9 vs. 49.1%, $P < 0.001$, Table 2).

3.2. Screening factors for SAP after SICH

The variables with $P < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis. IVH, hypertension, dysphagia, GCS, NIHSS, SIRI, and PLR were independent predictors of SAP after SICH ($P < 0.05$, Table 3). The Hosmer–Lemeshow test showed a good fit for the model ($P = 0.961$).

3.3. A novel nomogram for SAP after SICH

An SAP predictive nomogram was established using the seven significant predictors mentioned earlier (Figure 2). The predictors were scored, and then a straight line was plotted through the total score to investigate the likelihood of assessing post-SICH SAP based on the total score.

TABLE 2 General characteristics of patients with SICH according to the presence of SAP in the training cohort.

	Total ($n = 265$)	SAP ($n = 96$, 36.2%)	Non-SAP ($n = 169$, 63.8%)	*P*
Demographics				
Age [year, M (Q1, Q3)]	63.48 ± 13.75	67.2 ± 13.39	61.37 ± 13.55	0.001#
Gender, *n* (%)				0.871
Male	175 (66.0)	64 (66.7)	111 (65.7)	
Female	90 (34)	32 (33.3)	58 (34.3)	
BMI [kg/m^2 M (Q1, Q3)]	24.49 (21.49, 27.04)	24.45 ± 4.41	24.60 ± 4.12	0.796
Medical history				
Hypertension, *n* (%)	198 (74.7)	79 (82.3)	119 (70.4)	0.032#
Diabetes mellitus, *n* (%)	20 (7.5)	10 (10.5)	10 (5.9)	0.183
Atrial fibrillation, *n* (%)	19 (7.2)	9 (9.4)	10 (5.9)	0.294
Smoking, *n* (%)	71 (26.8)	25 (26.0)	46 (27.2)	0.835
Drinking (>3 drinks per 24 h), *n* (%)	57 (21.5)	26 (27.1)	31 (18.3)	0.096
Antiplatelet or anticoagulation, *n* (%)	18 (6.8)	12 (12.5)	6 (3.6)	0.005#
Clinical characteristics				
NIHSS [score, M (Q1, Q3)]	3 (2, 7.5)	6 (3, 15)	3 (2, 6)	<0.001#
GCS [score, M (Q1, Q3)]	13 (9, 15)	10 (7, 13)	14 (11, 15)	<0.001#
Admission SBP [mmHg, M (Q1, Q3)]	164 (150, 181)	167 (150, 185)	162 (150, 180)	0.343
Admission DBP [mmHg, M (Q1, Q3)]	95.87 ± 16.12	92.50 (83.25, 103.75)	97 (86, 108)	0.099
Duration from onset to hospitalization [h, M (Q1, Q3)]	5 (3, 11)	5 (3, 11)	5 (3, 11.5)	0.389
Dysphagia, *n* (%)	123 (46.4)	71 (74)	52 (30.8)	<0.001#
ICH parameters				
Hematoma volume[ml, M (Q1, Q3)]	12.54 (5.38, 23.02)	33.10 (18.17, 33.10)	8.93 (4.06, 17.17)	<0.001#
Hematoma location, *n* (%)				0.156
Lobar	52 (19.6)	22 (22.9)	30 (17.8)	
Basal ganglia region	161 (60.8)	51 (53.1)	110 (65.1)	
Thalamus	52 (19.6)	23 (24.0)	29 (17.2)	
IVH, *n* (%)	79 (29.8)	43 (44.8)	36 (21.3)	<0.001#
Laboratory data				
RBC [10^{12}/L, (M ± SD)]	4.37 ± 0.62	4.27 ± 0.65	4.44 ± 0.60	0.030#
Hemoglobin [g/L, (M ± SD)]	135.03 ± 18.09	131.41 ± 18.53	137.10 ± 17.56	0.014#
WBC [10^9/L, M (Q1, Q3)]	7.63 (6.27, 9.80)	9.06 (6.99, 11.82)	7.37 (5.98, 8.61)	<0.001#
ANC [10^9/L, M (Q1, Q3)]	5.53 (4.26, 8.03)	7.46 (4.97, 10.47)	5.15 (3.86, 6.57)	<0.001#
ALC [10^9/L, M (Q1, Q3)]	1.20 (0.82, 1.84)	0.90 (0.60, 1.35)	1.42 (0.99, 1.96)	<0.001#
AMC [10^9/L, M (Q1, Q3)]	0.40 (0.30, 0.52)	0.44 (0.28, 0.57)	0.39 (0.31, 0.51)	0.351
Platelet [10^9/L, M (Q1, Q3)]	170 (122.50, 219.5)	159.50 (115, 219.75)	173 (130, 219)	0.254
Albumin [g/L, M (Q1, Q3)]	39.20 (34.45, 41.70)	38.40 (35.35, 41.8)	39.50 (37.1, 41.70)	0.068
SIRI [M (Q1, Q3)]	1.95 (0.98, 3.39)	3.04 (1.60, 5.19)	1.50 (0.87, 2.52)	<0.001#
NLR [M (Q1, Q3)]	5.01 (2.67, 7.85)	7.09 (5.02, 12.39)	3.61 (2.33, 6.13)	<0.001#
MLR [M (Q1, Q3)]	0.32 (0.23, 0.48)	0.44 (0.29, 0.63)	0.28 (0.21, 0.39)	<0.001#

(Continued)

TABLE 2 (Continued)

	Total ($n = 265$)	SAP ($n = 96$, 36.2%)	Non-SAP ($n = 169$, 63.8%)	P
PLR [M (Q1, Q3)]	134.25 (96.40, 193.92)	154.51 (108.18, 267.32)	120.51 (86.67, 164.90)	<0.001#
Clinical outcomes				
Length of hospital stay, [days, M (Q1, Q3)]	15 (11, 21)	19 (14, 16)	14 (11, 17)	<0.001#
mRS score at 3 months [score, M (Q1, Q3)]	4 (2, 5)	5 (2, 5)	2 (2, 4)	<0.001#
Poor clinical outcome (mRS3–6) at 3 months, *n* (%)	152 (57.4)	69 (71.9)	83 (49.1)	<0.001#

SICH, spontaneous intracerebral hemorrhage; SAP, stroke-associated pneumonia; BMI, body mass index; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; IVH, intraventricular hemorrhage; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; SIRI, systemic inflammation response index; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio; M, mean or median; SD, standard deviation; mRS, modified Rankin Scale.
#Statistically significant.

3.4. Predictive accuracy and net benefit of the nomogram

In the training cohort, ROC analysis revealed an AUC of 0.886 (95% CI: 0.841–0.921, $P < 0.001$) for the nomogram for SAP (Figure 3A), higher than that without inflammatory factors (SIRI and PLR) (AUC = 0.848, 95% CI: 0.799–0.899, $P < 0.001$). The calibration curve was close to the ideal diagonal (Figure 4A).

Furthermore, 113 patients were utilized for the internal validation of the nomogram. The AUC of it was also 0.837 (95% CI: 0.756–0.900, $P < 0.001$), higher than the AUC without inflammatory factors (AUC = 0.752, 95% CI: 0.662–0.828, $P < 0.001$) (Figure 3B), confirming the nomogram's reliable accuracy. The calibration curve showed good consistency between the predicted and actual observed results in predicting SAP after SICH (Figure 4B). In addition, the DCA graph showed that the net benefit of the prediction model was better than that of the model without inflammatory factors over the risk range of SAP in both cohorts (Figure 5). These data suggest that our nomogram has important implications for clinical decision-making.

TABLE 3 Multivariate logistic regression analysis of the screening predictors of SAP after SICH.

Variables	OR	95% CI	P
IVH	2.909	1.384–6.113	0.005
Hypertension	2.810	1.174–6.722	0.020
Dysphagia	3.984	1.969–8.060	<0.001
GCS	0.885	0.783–1.000	0.049
NIHSS	1.133	1.053–1.218	0.001
SIRI	1.346	1.104–1.641	0.003
PLR	1.007	1.002–1.012	0.003

OR, odds ratio; CI, confidence interval; SICH, spontaneous intracerebral hemorrhage; SAP, stroke-associated pneumonia; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage; PLR, platelet/lymphocyte ratio.

4. Discussion

Our single-center retrospective study showed that IVH, hypertension, dysphagia, GCS, NIHSS, SIRI, and PLR were independent predictors of SAP after SICH. We further developed a nomogram to predict the incidence of SAP after SICH by these seven essential predictors. This nomogram yielded better accuracy and presented better clinical utility for the individualized prediction of SAP after SICH compared with the conventional factors without inflammatory factors. Our study is the first to include inflammatory markers in a predictive model for predicting SAP after SICH. Furthermore, this study makes predicting the probability of SAP after SICH easier. In addition, the nomogram underwent rigorous internal validation, implying stable prognostic performance.

SAP is the most common stroke-associated infection that can prolong hospitalization and even severely influence the prognosis and mortality of stroke patients (5). Therefore, early determination of disease trends and aggressive and effective treatment and prevention of patients who may develop SAP can reduce adverse outcomes. Despite the clinical significance of SAP after SICH, no substantial progress has been made in preventing SAP, including the prophylactic use of antibiotics and the process of care (23). It is well known that inflammatory factors, namely NLR, PLR, MLR, and SIRI, are new composite inflammatory markers based on traditional inflammatory cell counts that provide a more comprehensive picture of the inflammatory symptom status of the body. Numerous clinical studies (14, 15, 24–27) have confirmed that the above indicators have good predictive value for the occurrence, development, and prognosis of tumors, stroke, and other diseases. However, do these indicators have a similar clinical value for SAP after SICH?

We analyzed the relationship between peripheral blood and SAP in patients with SICH on admission. This study showed that SICH patients with hypertension, IVH, dysphagia, higher NIHSS scores, and lower GCS scores were more likely to

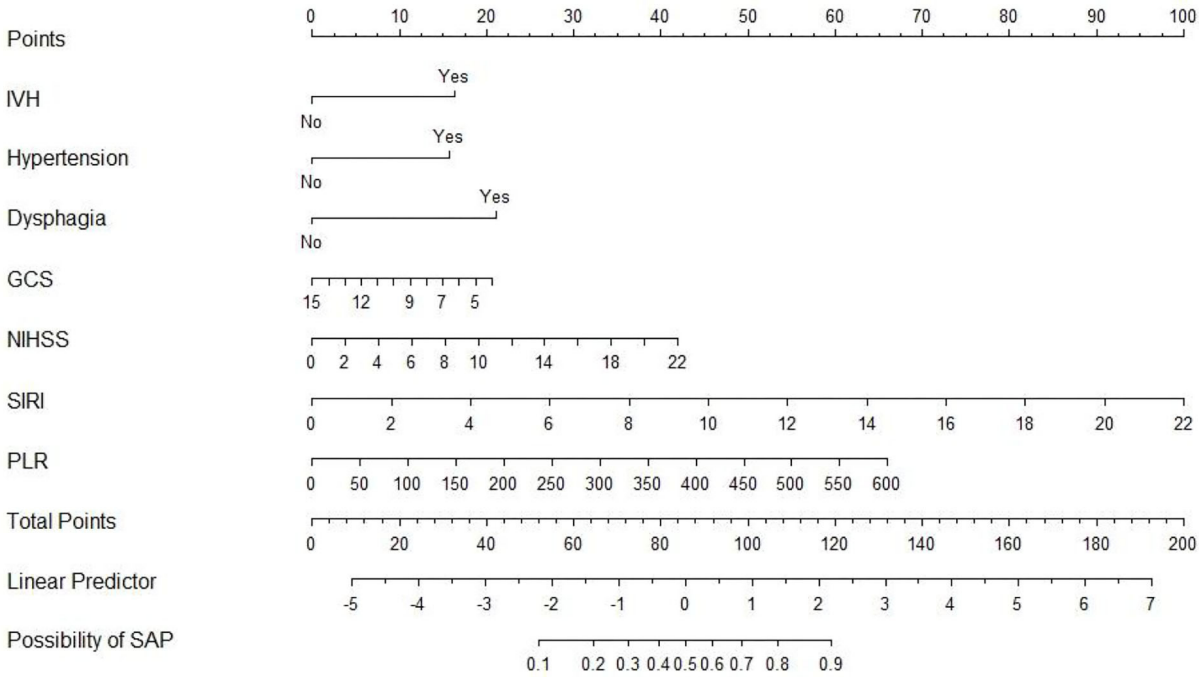


FIGURE 2
Nomogram for predicting SAP after SICH.

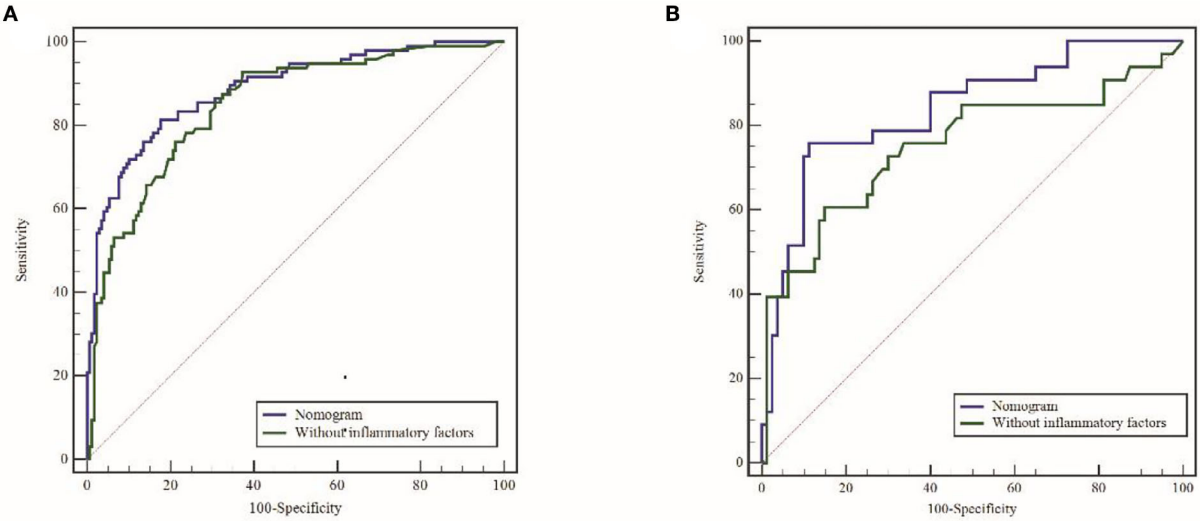


FIGURE 3
ROC curves for the raining cohort **(A)** and validation cohort **(B)**. ROC, receiver operating characteristic; AUC, area under the ROC.

have SAP. These results are similar to previous studies (5–7). In addition, this study added some inflammatory markers according to inflammatory cells in peripheral blood. Patients with SICH with higher SIRI and PLR were more likely to develop SAP. This result may provide a new idea to differentiate SAP and non-SAP individuals after SICH quantitatively and to develop targeted medical interventions for individuals.

It was revealed that elevated SIRI is an independent indicator of poor prognosis in stroke (24–26), aneurysmal subarachnoid hemorrhage (28), and some tumors (29–31). Yan et al. (16) found that higher SIRI was a significant risk factor for pneumonia in patients with acute ischemic stroke. A SIRI threshold of $\geq$2.74 was correlated with an increased incidence of SAP in patients with AIS (OR: 5.82, 95% CI: 4.54, 7.49, $P < 0.001$). In addition,

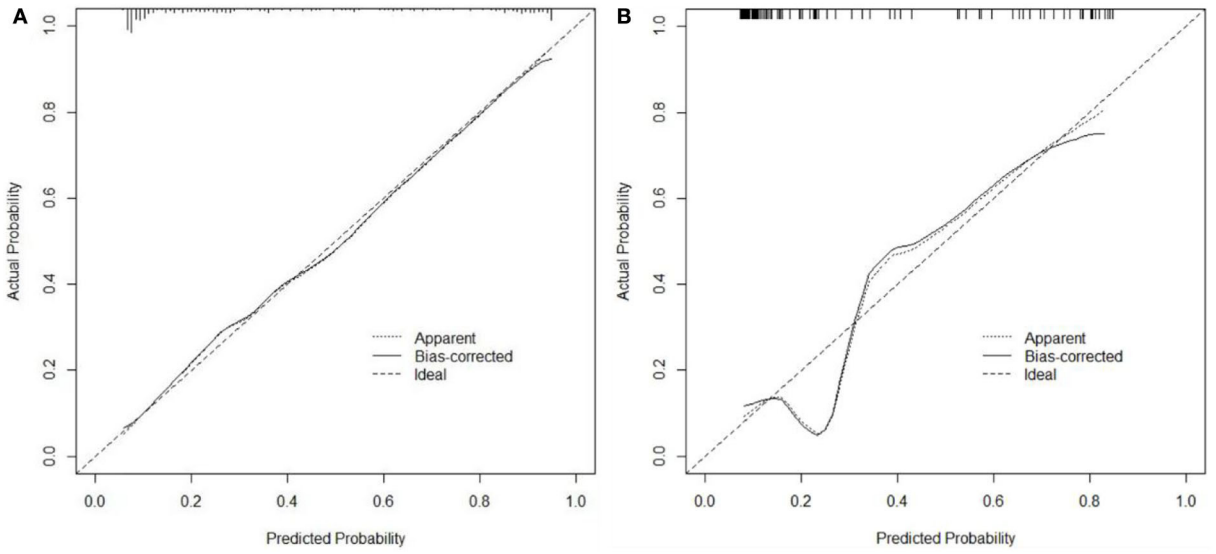


FIGURE 4
Calibration curves for predicting the probability of SAP after SICH. **(A)** Training cohort. **(B)** Validation cohort.

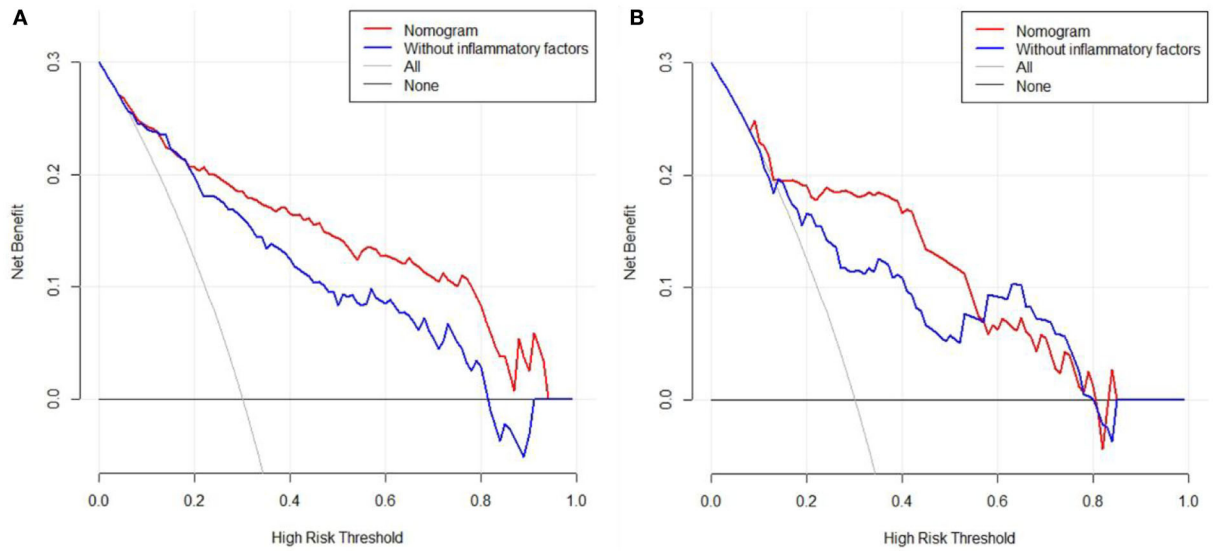


FIGURE 5
Decision curve analysis for the training cohort **(A)** and the validation cohort **(B)**.

the RCS model showed an increasing trend in the risk of SAP with increasing SIRI. Our study included patients with SICH who received conservative treatment. These results were similar to the previous studies mentioned above. SIRI revealed a positive association with SAP after SICH.

It was reported that PLR is a prognostic indicator of inflammatory response in various conditions, such as acute pulmonary embolism (32), myocardial infarction (33), various cancers (34), and stroke (27). Deng et al. (35) revealed that PLR was a predictor of stroke-associated infection in patients with AIS. A recent study reported that changes in peripheral PLR during treatment could reflect disease progression and prognosis in patients with COVID-19. Furthermore, the greater ΔPLR correlated with a more severe cytokine storm, a longer hospital stay, and a worse prognosis (36). The predictive value of PLR in patients with SAP vs. SICH has not been investigated. Furthermore, the combined effect of inflammatory factors on SAP has been well reported. We built a new nomogram to predict SAP risk in patients with SICH during hospitalization. The nomogram we constructed with inflammatory factors showed better and more accurate predictions than the nomogram without inflammatory factors.

Internal validation further validated the predictive ability of the nomogram. Therefore, SIRI and PLR should be considered when predicting SAP in patients with SICH receiving conservative treatment.

Consistent with other reports (16, 37), the hospital stay length was prolonged in the SAP group. Studies have shown that stroke-related infections, especially pneumonia, are independently associated with poor functional prognosis after stroke. Our study also observed that subjects with SAP had worse functional outcomes at 3-month follow-up, consistent with previous studies (38–40). Two phase-II studies on prophylactic antibiotic therapy showed benefits on temperature, the incidence of infection, and even functional outcomes (41, 42). The current management of SAP does not prescribe prophylactic antibiotics (43). The challenge now is to study the effect of preventive treatment on functional outcomes. A phase-III trial was conducted but was stopped early.

There may be several possible mechanisms between the inflammatory response and SAP. First, experimental studies have shown that many inflammatory processes occur after cerebral hemorrhage, including infiltration of leukocytes (44), activation of microglia (45), and release of inflammatory cytokines (46). However, brain injury affects the physiological interaction between the central nervous system and the immune system, resulting in a systemic immunosuppressive syndrome (47) manifested by a decrease in lymphocytes (40) that promotes susceptibility to infection. Finally, inflammatory factors may be the connecting point between cerebral hemorrhage severity and SAP.

Despite the good performance of our nomogram, several limitations should be noted in our study. First, incomplete statistical indicators, such as the time of SAP, pathogenic spectrum analysis, mechanical ventilation use, indwelling gastric tubes, and aspiration events, were not well documented. Therefore, this classification of suspected risk factors and pathogens was not included in the statistical analysis, resulting in the exclusion of confounding confounders in the multivariate logistic regression. Second, the retrospective analysis was limited to a single center, and did not further comparison of the dynamics of inflammatory indicators. Therefore, the results of this study were further validated in prospective multicenter cohort studies and other populations. Finally, the training and validation cohorts were from the same hospital. Therefore, multicenter studies need to seek external validation assessments before clinical application.

5. Conclusion

Admission SIRI and PLR can be utilized as potential prognostic inflammatory biomarkers in patients with SICH who underwent SAP. It helps to select high-risk patients for timely initiation of individualized therapy as these variables can be easily and rapidly obtained from blood cell counts. Combining nomograms for admission SIRI, PLR, and clinical risk factors will more reliably predict SAP in patients with SICH. In the future, large studies are needed to externally validate the nomograms for SAP after SICH in different populations. If proven valid, it will provide clinicians with an accurate and effective tool for early prediction and timely management of SAP after SICH. SAP can influence the length of hospital stay and the clinical outcome.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access the datasets should be directed to JJ, jjx830829@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Taizhou People's Hospital. 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

JJ and YL: study design, result interpretation, writing, reviewing, and editing. HL: data acquisition. TY: writing of the original draft and statistical analysis. All authors contributed to the execution of this work and the preparation of this manuscript. All authors have read and agreed to publish the final version of the manuscript.

Funding

This study was supported by Taizhou, the fifth "311 Project" scientific research support project (RCPY 202129) to JJ, Science and Technology Development Fund of Shanghai Pudong New Area (Grant No. PKJ2021-Y09), and Scientific research start-up fund from the Affiliated Taizhou People's Hospital of Nanjing Medical University (2021).

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

References

1. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol.* (2010) 9:167–76. doi: 10.1016/S1474-4422(09)70340-0

2. Koennecke HC, Belz W, Berfelde D, Endres M, Fitzek S, Hamilton F, et al. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. *Neurology.* (2011) 77:965–72. doi: 10.1212/WNL.0b013e31822dc795

3. Tinker RJ, Smith CJ, Heal C, Bettencourt-Silva JH, Metcalf AK, Potter JF, et al. Predictors of mortality and disability in stroke-associated pneumonia. *Acta Neurol Belg.* (2021) 121:379–85. doi: 10.1007/s13760-019-01148-w

4. Lakshminarayan K, Tsai AW, Tong X, Vazquez G, Peacock JM, George MG, et al. Utility of dysphagia screening results in predicting poststroke pneumonia. *Stroke.* (2010) 41:2849–54. doi: 10.1161/STROKEAHA.110.597039

5. Badve MS, Zhou Z, van de Beek D, Anderson CS, Hackett ML. Frequency of post-stroke pneumonia: systematic review and meta-analysis of observational studies. *Int J Stroke.* (2019) 14:125–36. doi: 10.1177/1747493018806196

6. Liu DD, Chu SF, Chen C, Yang PF, Chen NH, He X. Research progress in stroke-induced immunodepression syndrome (sids) and stroke-associated pneumonia (Sap). *Neurochem Int.* (2018) 114:42–54. doi: 10.1016/j.neuint.2018.01.002

7. Lord AS, Langefeld CD, Sekar P, Moomaw CJ, Badjatia N, Vashkevich A, et al. Infection after intracerebral hemorrhage: risk factors and association with outcomes in the ethnic/racial variations of intracerebral hemorrhage study. *Stroke.* (2014) 45:3535–42. doi: 10.1161/STROKEAHA.114.006435

8. Soares R, Fernandes A, Taveira I, Marreiros A, Nzwalo H. Predictors of pneumonia in patients with acute spontaneous intracerebral hemorrhage in Algarve, Southern Portugal. *Clin Neurol Neurosurg.* (2022) 221:107387. doi: 10.1016/j.clineuro.2022.107387

9. Prass K, Meisel C, Höflich C, Braun J, Halle E, Wolf T, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by Poststroke T Helper Cell Type 1-like immunostimulation. *J Exp Med.* (2003) 198:725–36. doi: 10.1084/jem.20021098

10. Chamorro Á, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. *Nat Rev Neurol.* (2012) 8:401–10. doi: 10.1038/nrneurol.2012.98

11. Curbelo J, Luquero Bueno S, Galván-Román JM, Ortega-Gómez M, Rajas O, Fernández-Jiménez G, et al. Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. *PLoS ONE.* (2017) 12:e0173947. doi: 10.1371/journal.pone.0173947

12. Yun S, Yi HJ, Lee DH, Sung JH. Systemic inflammation response index and systemic immune-inflammation index for predicting the prognosis of patients with aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis.* (2021) 30:105861. doi: 10.1016/j.jstrokecerebrovasdis.2021.105861

13. Urbanowicz T, Michalak M, Olasińska-Wiśniewska A, Rodzki M, Witkowska A, Gasecka A, et al. Neutrophil counts, neutrophil-to-lymphocyte ratio, and systemic inflammatory response index (siri) predict mortality after off-pump coronary artery bypass surgery. Cells (2022) 11. doi: 10.3390/cells11071124

14. Cao F, Wan Y, Lei C, Zhong L, Lei H, Sun H, et al. Monocyte-to-lymphocyte ratio as a predictor of stroke-associated pneumonia: a retrospective study-based investigation. *Brain Behav.* (2021) 11:e02141. doi: 10.1002/brb3.2141

15. Nam KW, Kim TJ, Lee JS, Kwon HM, Lee YS, Ko SB, et al. High neutrophil-to-lymphocyte ratio predicts stroke-associated pneumonia. *Stroke.* (2018) 49:1886–92. doi: 10.1161/STROKEAHA.118.021228

16. Yan D, Dai C, Xu R, Huang Q, Ren W. Predictive ability of systemic inflammation response index for the risk of pneumonia in patients with acute ischemic stroke. *Gerontology.* (2022) 18:1–8. doi: 10.1159/000524759

17. Mu X, Li Y, He L, Guan H, Wang J, Wei Z, et al. Prognostic nomogram for adenoid cystic carcinoma in different anatomic sites. *Head Neck.* (2021) 43:48–59. doi: 10.1002/hed.26443

18. Hu Q, Shi Y, Hua ZY, Bao L, Li F, Wei H, et al. A prediction nomogram for acute kidney injury in very-low-birth-weight infants: a retrospective study. *Front Pediatr.* (2020) 8:575097. doi: 10.3389/fped.2020.575097

19. Zhang W, Fang M, Dong D, Wang X, Ke X, Zhang L, et al. Development and validation of a Ct-based radiomic nomogram for preoperative prediction of early recurrence in advanced gastric cancer. *Radiother Oncol.* (2020) 145:13–20. doi: 10.1016/j.radonc.2019.11.023

20. Smith CJ, Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, et al. Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group. *Stroke.* (2015) 46:2335–40. doi: 10.1161/STROKEAHA.115.009617

21. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H, et al. A novel systemic inflammation response index (siri) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer.* (2016) 122:2158–67. doi: 10.1002/cncr.30057

22. Deng Q, He B, Liu X, Yue J, Ying H, Pan Y, et al. Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. *J Transl Med.* (2015) 13:66. doi: 10.1186/s12967-015-0409-0

23. Ingeman A, Andersen G, Hundborg HH, Svendsen ML, Johnsen SP. Processes of care and medical complications in patients with stroke. *Stroke.* (2011) 42:167–72. doi: 10.1161/STROKEAHA.110.599738

24. Zhang Y, Xing Z, Zhou K, Jiang S. The predictive role of systemic inflammation response index (siri) in the prognosis of stroke patients. *Clin Interv Aging.* (2021) 16:1997–2007. doi: 10.2147/CIA.S339221

25. Li J, Yuan Y, Liao X, Yu Z, Li H, Zheng J. Prognostic significance of admission systemic inflammation response index in patients with spontaneous intracerebral hemorrhage: a propensity score matching analysis. *Front Neurol.* (2021) 12:718032. doi: 10.3389/fneur.2021.718032

26. Yi HJ, Sung JH, Lee DH. Systemic inflammation response index and systemic immune-inflammation index are associated with clinical outcomes in patients treated with mechanical thrombectomy for large artery occlusion. *World Neurosurg.* (2021) 153:e282–e9. doi: 10.1016/j.wneu.2021.06.113

27. Zhang W, Shen Y. Platelet-to-lymphocyte ratio as a new predictive index of neurological outcomes in patients with acute intracranial hemorrhage: a retrospective study. *Med Sci Monit.* (2018) 24:4413–20. doi: 10.12659/MSM.910845

28. Zhang P, Li Y, Zhang H, Wang X, Dong L, Yan Z, et al. Prognostic value of the systemic inflammation response index in patients with aneurismal subarachnoid hemorrhage and a nomogram model construction. *Br J Neurosurg.* (2020) 12:1–7. doi: 10.1080/02688697.2020.1831438

29. Topkan E, Selek U, Kucuk A, Haksoyler V, Ozdemir Y, Sezen D, et al. Prechemoradiotherapy systemic inflammation response index stratifies stage iiib/c non-small-cell lung cancer patients into three prognostic groups: a propensity score-matching analysis. *J Oncol.* (2021) 2021:6688138. doi: 10.1155/2021/6688138

30. Xin Y, Zhang X, Li Y, Yang Y, Chen Y, Wang Y, et al. A systemic inflammation response index (siri)-based nomogram for predicting the recurrence of early stage hepatocellular carcinoma after radiofrequency ablation. *Cardiovasc Intervent Radiol.* (2022) 45:43–53. doi: 10.1007/s00270-021-02965-4

31. Zhang Y, Sun Y, Zhang Q. Prognostic value of the systemic immune-inflammation index in patients with breast cancer: a meta-analysis. *Cancer Cell Int.* (2020) 20:224. doi: 10.1186/s12935-020-01308-6

32. Kundi H, Balun A, Cicekcioglu H, Cetin M, Kiziltunc E, Cetin ZG, et al. The relation between platelet-to-lymphocyte ratio and pulmonary embolism severity index in acute pulmonary embolism. *Heart Lung.* (2015) 44:340–3. doi: 10.1016/j.hrtlng.2015.04.007

33. Ozcan Cetin EH, Cetin MS, Aras D, Topaloglu S, Temizhan A, Kisacik HL, et al. Platelet to lymphocyte ratio as a prognostic marker of in-hospital and long-term major adverse cardiovascular events in st-segment elevation myocardial infarction. *Angiology*. (2016) 67:336–45. doi: 10.1177/0003319715591751

34. Yang W, Liu Y. Platelet-lymphocyte ratio is a predictor of venous thromboembolism in cancer patients. *Thromb Res.* (2015) 136:212–5. doi: 10.1016/j.thromres.2014.11.025

35. Deng QW, Gong PY, Chen XL, Liu YK, Jiang T, Zhou F, et al. Admission blood cell counts are predictive of stroke-associated infection in acute ischemic stroke patients treated with endovascular therapy. *Neurol Sci.* (2021) 42:2397–409. doi: 10.1007/s10072-020-04827-2

36. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. *J Med Virol.* (2020) 92:1533–41. doi: 10.1002/jmv.25767

37. Teh WH, Smith CJ, Barlas RS, Wood AD, Bettencourt-Silva JH, Clark AB, et al. Impact of stroke-associated pneumonia on mortality, length of hospitalization, and functional outcome. *Acta Neurol Scand.* (2018) 138:293–300. doi: 10.1111/ane.12956

38. Lindner A, Kofler M, Rass V, Ianosi B, Gaasch M, Schiefecker AJ, et al. Early predictors for infectious complications in patients with spontaneous intracerebral hemorrhage and their impact on outcome. *Front Neurol.* (2019) 10:817. doi: 10.3389/fneur.2019.00817

39. Huang L, Zhang R, Ji J, Long F, Wang Y, Lu J, et al. Hypersensitive C-reactive protein-albumin ratio is associated with stroke-associated pneumonia and early clinical outcomes in patients with acute ischemic stroke. *Brain Behav.* (2022) 12:e2675. doi: 10.1002/brb3.2675

40. Morotti A, Marini S, Jessel MJ, Schwab K, Kourkoulis C, Ayres AM, et al. Lymphopenia, infectious complications, and outcome in spontaneous intracerebral hemorrhage. *Neurocrit Care.* (2017) 26:160–6. doi: 10.1007/s12028-016-0367-2

41. Harms H, Prass K, Meisel C, Klehmet J, Rogge W, Drenckhahn C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. *PLoS ONE.* (2008) 3:e2158. doi: 10.1371/journal.pone.0002158

42. Schwarz S, Al-Shajlawi F, Sick C, Meairs S, Hennerici MG. Effects of prophylactic antibiotic therapy with mezlocillin plus sulbactam on the incidence and height of fever after severe acute ischemic stroke: the mannheim infection in stroke study (Miss). *Stroke.* (2008) 39:1220–7. doi: 10.1161/STROKEAHA.107.499533

43. Shi K, Wood K, Shi FD, Wang X, Liu Q. Stroke-induced immunosuppression and poststroke infection. *Stroke Vasc Neurol.* (2018) 3:34–41. doi: 10.1136/svn-2017-000123

44. Del Bigio MR, Yan HJ, Buist R, Peeling J. Experimental intracerebral hemorrhage in rats. magnetic resonance imaging and histopathological correlates. *Stroke*. (1996) 27:2312–9. doi: 10.1161/01.STR.27.12.2312

45. Gong C, Hoff JT, Keep RF. Acute inflammatory reaction following experimental intracerebral hemorrhage in rat. *Brain Res.* (2000) 871:57–65. doi: 10.1016/S0006-8993(00)02427-6

46. Castillo J, Dávalos A, Alvarez-Sabín J, Pumar JM, Leira R, Silva Y, et al. Molecular signatures of brain injury after intracerebral hemorrhage. *Neurology*. (2002) 58:624–9. doi: 10.1212/WNL.58.4.624

47. Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci.* (2005) 6:775–86. doi: 10.1038/nrn1765

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 23 January 2023
DOI 10.3389/fneur.2023.1081390

OPEN ACCESS

EDITED BY
Cheong-Meng Chong,
University of Macau, China

REVIEWED BY
Leonardo Franz,
University of Padua, Italy
Nuray Bayar Muluk,
Kirikkale University, Türkiye
Xicheng Song,
Yantai Yuhuangding Hospital, China

*CORRESPONDENCE
Sungju Jee
✉ drjeesungju@cnuh.co.kr
Min Kyun Sohn
✉ mksohn@cnuh.co.kr

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 27 October 2022
ACCEPTED 05 January 2023
PUBLISHED 23 January 2023

CITATION
Choi JE, Kim YW, Jee S and Sohn MK (2023) Clinical characteristics of chronic rhinitis following stroke. *Front. Neurol.* 14:1081390. doi: 10.3389/fneur.2023.1081390

Clinical characteristics of chronic rhinitis following stroke

Jae Eun Choi[1], Yeong Wook Kim[1], Sungju Jee[1,2]* and Min Kyun Sohn[1]*

[1]Department of Rehabilitation Medicine, Chungnam National University, Daejeon, Republic of Korea, [2]Chungnam Regional Cardiocerebrovascular Center, Chungnam National University, Daejeon, Republic of Korea

Background: We previously observed that patients with stroke complained of rhinitis symptoms that developed following the occurrence of stroke.

Objectives: To investigate the relationship between chronic rhinitis (CR) and stroke.

Methods: This retrospective study analyzed the medical records and questionnaires of patients with stroke who visited our outpatient clinic from June to December 2020. Stroke lesions were mainly classified as supratentorial, infratentorial, and supra/infratentorial lesions. Supratentorial lesions were further divided into cortex, subcortex, and mixed. Participants were screened for CR and were subsequently divided into the CR and non-CR groups. The Sino-Nasal Outcome Test questionnaire and a questionnaire on autonomic nervous system symptoms were administered to all patients.

Results: Clinically evaluated indicators were not significantly different between the two groups. The number of patients with lesions in both the cortex and subcortex was significantly higher in the CR group than in the non-CR group. The risk of CR was higher in male patients with stroke than their female counterparts; additionally, the risk of CR was higher in patients with stroke who had both cortical and subcortical lesions, as well as autonomic dysfunction.

Conclusions: Individuals with subcortical stroke damage had a greater probability of developing CR. The risk was increased in men, as compared with that in women, when autonomic symptoms were present.

KEYWORDS

rhinitis, stroke, retrospective study, autonomic symptoms, subcortex

1. Introduction

Stroke is the third leading cause of death and disability and the second leading cause of death worldwide (1, 2). It is also the second leading cause of disability-adjusted life years in developing countries and the third leading cause in developed countries (after ischemic heart disease and back/neck pain) (3, 4).

We previously observed that, at outpatient clinic visits after discharge, patients with stroke, who had no history of allergic diseases, complained of rhinitis symptoms that developed following the occurrence of stroke. Most patients complained of discomfort during meals because of rhinorrhea. These symptoms could be defined as non-allergic rhinitis, a type of chronic rhinitis (CR) that causes rhinorrhea, nasal obstruction, sneezing, and/or itchy nose without any clinical evidence of infection or allergic diseases (5). Non-allergic rhinitis is affected by the sympathetic and parasympathetic nervous system of the nasal cavity, and rhinitis symptoms are thought to develop due to autonomic dysfunction that occurs after stroke (6).

It is well known that cerebrovascular diseases, particularly ischemic stroke, can either acutely or chronically alter the function of the autonomic nervous system (7–9). Autonomic dysfunction can also cause sino-nasal symptoms. While no studies on nasal symptoms have been conducted,

among autonomic symptoms that occur after stroke, there have been cases of patients reporting symptoms of rhinorrhea following a stroke. Chen et al. reported a case of a 57-year-old Taiwanese male patient with ischemic stroke who had lesions in the right caudate nucleus and developed contralateral rhinorrhea. The patient complained of rhinorrhea on the left side after mastication or gustation at 2 months after the onset of cerebral infarction (10). Another case was a 74-year-old female patient with ischemic stroke who had lesions in the right lateral medulla and inferior cerebellum. She had episodes of clear secretions from her nose about 1 month after the onset of ischemic stroke. The otolaryngological evaluation did not reveal a clear cause of rhinorrhea (11).

Rhinitis symptoms that newly occur after stroke can be confusing and difficult for patients to manage. Non-allergic rhinitis has clinical symptoms that are similar to those of allergic rhinitis and equally or further worsen the quality of life (QOL). Early diagnosis and appropriate management of rhinitis can help improve the QOL of patients with stroke (12, 13). Therefore, the present study aimed to investigate the characteristics of CR in patients with stroke and determine whether the occurrence of CR is related to a specific lesion site. This study also subjectively evaluated autonomic dysfunction after stroke to confirm its relationship with the occurrence of CR.

2. Materials and methods

2.1. Participants

This survey was conducted by reviewing the medical records and questionnaires of patients who visited the outpatient clinic in the Department of Physical Medicine and Rehabilitation at the Chungnam National University Hospital (Daejeon, Korea) from June 1, 2020, to December 31, 2020. This study was approved by the hospital's Institutional Review Board (approval number: IRB 2020-01-059-006).

2.2. Data collection

The electronic medical records of the participants were reviewed, and necessary clinical data were collected. Demographic data such as age, sex, and smoking history were obtained, and scores for the Korean version of the National Institutes of Health Stroke Scale (K-NIHSS), Korean version of the modified Barthel Index (K-MBI), modified Rankin Scale (MRS), Functional Ambulatory Category (FAC), and Korean Mini-Mental Status Examination (K-MMSE) were examined as clinical data at the time of stroke onset. Patients were considered to have a smoking history if they had smoked at least once (14).

Additionally, stroke lesions were recorded based on patients' brain magnetic resonance imaging or computed tomography results. Lesions were divided according to lesion site into supratentorial, infratentorial, and supra/infratentorial (lesions in both supra- and infratentorial regions) regions. Supratentorial lesions were further divided into Supra_Cortex, Supra_Subcortex, and Supra_mixed, which included both subcortical and cortical locations (15).

2.3. Questionnaire

Participants were judged to have CR if they displayed two out of four symptoms, including nasal obstruction, rhinorrhea, sneezing, and itchy nose/eyes, for at least 12 weeks for 1 h or more daily. The questionnaire was used to evaluate whether the symptoms of CR appeared after the occurrence of stroke. Only those participants who responded "yes" to this question were included in the CR group. Based on this, the participants were further divided into the CR and non-CR groups (16). The characteristics of rhinorrhea, among the symptoms of CR, were recorded for patients assigned to the CR group.

The Sino-Nasal Outcome Test (SNOT-22) questionnaire, consisting of 22 CR-related questions, was administered to all participants and was used to evaluate the severity of nasal symptoms and their effect on the QOL. The questionnaire is divided into two parts: 12 questions on physical symptoms (rhinologic symptoms, cough, ear fullness, and facial symptoms) and 10 questions on QOL (sleep, fatigue, and mood). All questions were scored from 0 to 5, with 0 indicating no problem and 5 indicating a very serious problem. The questionnaire has a total minimum score of 0 and a maximum score of 110 points (17, 18). Notably, a high SNOT-22 score indicates low QOL and severe symptoms (19).

A questionnaire evaluation of autonomic symptoms was also administered to all participants to compare changes in the patients' autonomic function before and after stroke onset. The questionnaire consisted of questions about symptoms arising from autonomic dysfunction reported by Ewing et al. (20, 21). The questions included symptoms that occur while the participant assumed a standing position (palpitation, blurred vision, gastrointestinal discomfort, dizziness, and sticky skin), symptoms related to perspiration (increased or decreased perspiration in certain areas and increased perspiration in meals), and gastrointestinal symptoms (diarrhea, fullness, and bowel control), and the participants selected from 0–2 points based on the degree of subjective changes experienced during the past month compared to their status before stroke onset. In terms of scoring, 0 was selected if there was no change in symptoms, 1 was selected if the change in symptoms caused some problems in the patient's life, and 2 was selected if the change in symptoms always caused problems (20, 21).

The following rhinorrhea symptoms were confirmed in the CR group: the side of nasal discharge according to the side of stroke lesion, color of nasal discharge, viscosity of nasal discharge, time of nasal discharge, possibility of discharge occurring in a specific season or place, and improvement of symptoms (Table 1).

2.4. Statistical analysis

An independent *t*-test or the Mann-Whitney U test was used to compare age and clinical evaluation data, including K-NIHSS, K-MBI, MMSE, FAC, MRS, and SNOT-22 scores, between the two groups. The chi-squared test or Fisher's exact test was used to determine the correlation between categorical data in the CR and non-CR groups. Logistic regression analysis was conducted to identify risk factors for CR. $P < 0.05$ were considered statistically significant, and all statistical analyses were performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, N.Y., USA).

3. Results

3.1. Study population

A total of 131 patients were assessed for eligibility in this study; however, 13 were excluded due to a history of allergic diseases before stroke onset. Among 118 participants who were enrolled, 31 and 87 participants were assigned to the CR and non-CR groups, respectively (Figure 1).

TABLE 1 Clinical characteristics of rhinorrhea in the chronic rhinitis group.

Characteristic		
Color	Clear	31
	Yellow	0
	Green	0
	Others	0
Viscosity	Thin	24
	Moderate	7
	Thick	0
Time	During meal	25
	Anytime	5
	Etc.	1
Correlation with season or place	Yes	9
	No	22
Side	Rt.	5
	Lt.	13
	Both	13
Side compared with Stroke lesion	Ipsilateral	8
	Contralateral	9
	Both	13
	Undecided	1

3.2. Demographic data and clinically evaluated indicators

Of the 31 participants, 27 (87.1%) in the CR group were men, which was significantly higher than that of the non-CR group, in which 54 of the 87 participants (62.1%) were men ($P = 0.01$). There was no significant difference in the mean age between the two groups ($P = 0.52$). The SNOT-22 score in the CR group was significantly higher ($P = 0.04$) than that in the non-CR group. Participants with smoking history were 14 (45.2%) in the CF group and 31 (35.6%) in the non-CR group, showing a similar distribution ($P = 0.348$). The K-NIHSS, K-MBI, and MMSE scores were not significantly different between the two groups ($P = 0.487$, $P = 0.63$, and $P = 0.551$, respectively). For the FAC and MRS scores, the participants were divided into two groups according to their ability to walk independently or not, but walking was shown to be significantly related to CR (P=0.934 and $P = 0.625$, respectively).

3.3. Clinical characteristics related to stroke

Participants with ischemic and hemorrhagic stroke were 22 (71.0%) and 9 (19.0%) participants, respectively, in the CR group, and 67 (77.0%) and 20 (23.0%) participants in the non-CR group, respectively, displaying no significant difference ($P = 0.502$). In terms of whether the stroke was first-time or recurrent, 24 (77.4%) and 7 (22.6%) participants in the CR group had a first-time stroke and recurrent stroke, respectively, whereas 79 (90.8%) and 8 (9.2%) participants in the non-CR group had a first-time stroke and recurrent stroke, respectively. There was no significant difference in the distribution between the two groups ($P = 0.055$).

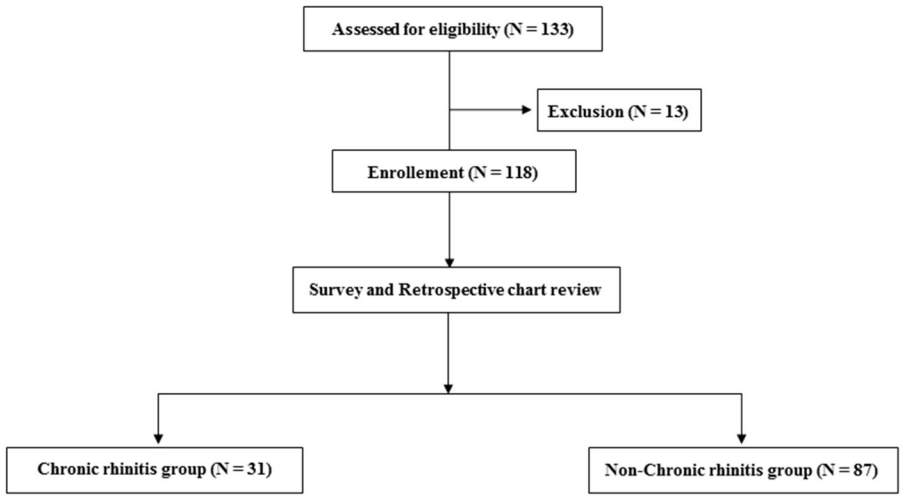


FIGURE 1
Flow chart depicting the number of included and excluded participants and the two groups of the included participants.

10.3389/fneur.2023.1081390

TABLE 2 Participants' demographics, smoking history, SNOT-22 score, and clinical characteristics related to stroke ($N = 118$).

		Chronic rhinitis	Non-chronic rhinitis	P-value
Participants		31 (26.3%)	87 (73.7%)	
Demographics				
Sex, (M:F)		27 (87.1%): 4 (12.9%)	54 (62.1%): 33 (37.9%)	0.01*
Age, years		63.00 ± 9.61	64.57 ± 12.32	0.52
Diabetes mellitus		9 (29.0%)	26 (29.9%)	0.929
Smoking history		14 (45.2%)	31 (35.6%)	0.348
SNOT-22		18.29 ± 14.43	9.59 ± 11.13	0.04*
Stroke type				
Ischemic		22 (71.0%)	67 (77.0%)	
Hemorrhagic		9 (29.0%)	20 (23.0%)	0.502
First/recurrent stroke				
First		24 (77.4%)	79 (90.8%)	
Recurrent		7 (22.6%)	8 (9.2%)	0.055
Stroke lesion				
Supra_Cortex		4 (12.9%)	22 (25.3%)	
Supra_Subcortex		13 (41.9%)	33 (37.9%)	
Supra_mixed		9 (29.0%)	6 (6.9%)	
Infratentorium		4 (12.9%)	20 (23.0%)	
(Supra) Infratentorium		1 (3.2%)	6 (6.9%)	0.025*
Right		16 (51.6%)	46 (52.9%)	
Left		11 (35.5%)	34 (39.1%)	
Both		4 (12.9%)	7 (8.0%)	0.718
Initial clinical evaluation				
K-NIHSS		5.00 ± 4.46	4.36 ± 4.00	0.487
K-MBI		19.93 ± 8.47	20.78 ± 7.96	0.63
K-MMSE		53.97 ± 25.92	57.05 ± 23.41	0.551
FAC				
	0,1,2	17 (65.4%)	55 (66.3%)	
	3,4,5	9 (34.6%)	28 (33.7%)	0.934
MRS				
	0,1,2,3	8 (32.0%)	31 (37.3%)	
	4,5,6	17 (68.0%)	52 (62.7%)	0.625
Autonomic symptoms		27 (87.1%)	54 (62.1%)	0.010*

Data are presented as n (%) or mean ± standard deviation.
SNOT-22, Sino-Nasal Outcome Test; SD, standard deviation; K-NIHSS, Korean version of the National Institutes of Health Stroke Scale; K-MBI, Korean version of the modified Barthel Index; K-MMSE, Korean Mini-Mental State Examination; FAC, Functional Ambulatory Category; MRS, modified Rankin Scale.
*$P < 0.05$ indicates a statistically significant difference.

When the stroke lesions were divided into right, left, and bilateral, there was no significant difference in the distribution between the chronic and non-CR groups ($P = 0.718$). Supra_Subcortex and Supra_mixed accounted for 22 of the 31(70.9%) participants in the CR group, which was significantly higher than 39 of the 87 (44.8%) participants in the non-CR group ($P = 0.025$; Table 2). Furthermore, only 4 (12.9%) patients had cortical lesions in the CR group, which was a significantly lower distribution than that of the 22 (25.3%) patients in the non-CR group.

3.4. Clinical characteristics of rhinorrhea

The characteristics of rhinorrhea in patients in the CR group are summarized in Table 1.

3.5. Risk factors for CR

A logistic regression analysis was performed to determine whether the site of stroke lesion, sex, and autonomic dysfunction

TABLE 3 Risk factors for chronic rhinitis.

Covariate	Stroke lesion	B	S.E.	Exp(B)	95% CI	P-value
Stroke lesion	Supra_Cortex			1.0		
	Supra_Subcortex	0.860	0.673	2.364	0.631–8.848	0.201
	Supra_mixed	2.515	0.860	12.369	2.293–66.717	0.003*
	Infratentorium	- 0.132	0.807	0.876	0.180–4.265	0.870
	Supra_Infratentorium	0.176	1.273	1.1934	0.098–14.473	0.890
Autonomic symptoms	No			1.0		
	Yes	1.904	0.684	6.713	1.757–25.652	0.005*
Sex	Female			1.0		
	Male	1.510	0.631	4.527	1.314–15.596	0.017*
Constant		−4.376	1.009	0.013		0.000*

*P < 0.05 indicates a statistically significant difference.

were potential risk factors for CR. The Nagelkerke R^2 was confirmed to be 0.315, and $P = 0.853$ was obtained in the Hosmer-Lemeshow goodness-of-fit test, suggesting that the model fitted the data. An overall predictive value of 78.0% was obtained. The risk of developing CR was 12.369 times higher in patients with stroke with lesions in both the cortex and subcortex than in patients with lesions in only the cortex ($P = 0.003$). Furthermore, the risk of developing CR was 4.527 times higher in men than in women ($P = 0.017$) and 6.173 times higher in participants with autonomic symptoms than in participants without autonomic symptoms ($P = 0.005$; Table 3).

3.6. Autonomic dysfunction

The number of participants who reported subjective changes in autonomic symptoms in one of the following areas, including cardiovascular, sudomotor, and gastrointestinal, in the autonomic symptom questionnaires was 27 of the 31 participants (87.1%) in the CR group, which was significantly higher number than 54 participants (62.1%) in the non-CR group ($P = 0.01$; Table 2). Among the 31 participants in the CR group, 16 participants reported abnormal symptoms when standing, 19 participants reported abnormal perspiration, and 18 participants complained of gastrointestinal symptoms. Among the 54 participants in the non-CR group, 32 reported abnormal symptoms when standing, 21 participants reported abnormal perspiration, and 34 participants complained of gastrointestinal symptoms. In the CR group, the number of participants who complained of gastrointestinal symptoms was significantly higher when the stroke lesion was on the right side than when it was on the left side ($P = 0.001$). Of the 118 participants in this study, 81 (68.6%) reported subjective changes in autonomic function after stroke, and there was no correlation (three symptoms: $P = 0.351$, $P = 0.3245$, and $P = 0.214$, respectively; Table 4) between the occurrence of each of the three symptoms and the location of the stroke lesion (right, left, or both). Among the patients who complained of subjective changes in autonomic function after stroke, 24 patients (29.6%) were diabetic. In the patient group that said there was no change in autonomic nervous system symptoms, 11 patients (29.7%) were diagnosed with diabetes ($P = 0.991$). It was confirmed that there was no association between the presence of autonomic nervous system symptoms and the presence of diabetes.

4. Discussion

Symptoms of autonomic dysfunction after stroke have been confirmed in several studies; nonetheless, studies reporting nasal symptoms, excluding case reports, have not been reported. The purpose of this study was to determine the occurrence of CR symptoms such as rhinorrhea and nasal obstruction in patients with stroke and to evaluate the risk that stroke lesions and sex pose on the morbidity of CR. Logistic regression analysis showed that the location of the lesion (Supra_Subcortex and Supra_mixed), presence of autonomic symptoms, and sex were risk factors for CR in patients with stroke. Age was not a risk factor for CR in patients with stroke.

Compared with patients with stroke who have lesions in the cortex, the risk of CR was 12.369 times higher in patients with stroke lesions in both the cortex and subcortex. According to Chen et al. (10), a patient with right caudate cerebral infarction developed contralateral rhinorrhea 2 months after stroke onset. They reported that damage to the caudate nucleus in patients with caudate stroke affected the superior salivatory nucleus, which induced reflex nasal secretion. In this study, patients with subcortex damage, including those with stroke lesions in both the cortex and subcortex (Supra_mixed), showed a higher risk of CR. Therefore, it can be inferred that the presence of lesions in the subcortex, including the basal ganglia, is related to the occurrence of CR; however, it is unknown whether rhinitis symptoms occur simply due to the large size of the lesion.

Several studies have suggested a relationship between specific stroke lesions and autonomic symptoms. Purwata et al. reported that the left hemisphere regulates parasympathetic modulation. Further, the left hemisphere stroke lesions were positively correlated with erectile dysfunction (22). In animal experimental studies, it has been reported that the head of the caudate nucleus showed a dual effect on secretory reflex, and it is thought that the inhibitory effect occurs through the action of acetylcholine on the dorsal part of the head of the nucleus and stimulatory effect through the action of adrenaline (23, 24). Among the participants with CR, the side of rhinorrhea was ipsilateral to the stroke lesion in eight participants, contralateral

TABLE 4 Autonomic function evaluation by brain lesion.

	Cardiovascular symptoms	Sudomotor symptoms	Gastrointestinal symptoms	Any changes
Chronic rhinitis				
Right	9 (56.3%)	12 (63.2%)	14 (77.8%)	15 (55.6%)
Left	6 (37.5%)	5 (26.3%)	4 (22.2%)	9 (33.3%)
Both	1 (6.3%)	2 (10.5%)	0 (0.0%)	3 (11.1%)
P-value	0.621	0.277	0.001*	0.427
Non-chronic rhinitis				
Right	20 (62.5%)	13 (61.9%)	15 (44.1%)	29 (53.7%)
Left	10 (31.3%)	7 (33.3%)	17 (50.0%)	21 (38.9%)
Both	2 (6.3%)	1 (4.8%)	2 (5.9%)	4 (7.4%)
P-value	0.368	0.686	0.246	1.000
Brain lesion				
Right	29 (60.4%)	25 (62.5%)	29 (55.8%)	44 (54.3%)
Left	16 (33.3%)	12 (30.0%)	21 (40.4%)	30 (37.0%)
Both	3 (6.3%)	3 (7.5%)	2 (3.8%)	7 (8.6%)
P-value	0.351	0.324	0.214	0.800

*$P < 0.05$ indicates a statistically significant difference.

to the lesion in nine participants, present on both sides in thirteen participants, and not specific in one participant, suggesting that most participants experienced rhinorrhea on both sides. This study did not identify any correlation between the side of CR symptoms and side of the lesion.

The autonomic nervous system maintains physiological homeostasis and is composed of the sympathetic nervous system and parasympathetic nervous system. Both have a central nervous system and peripheral nervous system components. In addition to stroke, the causes of autonomic dysfunction are diverse, including primary causes such as Parkinson's disease, multiple system atrophy, and Lewy body dementia, and secondary causes such as diabetes, amyloidosis, and immune-mediated diseases (25). We found that more than half of patients with stroke complained of autonomic dysfunction after stroke onset, with 68.6% of all patients complaining of subjective autonomic dysfunction. As expected, the prevalence of CR was 6.173 times higher in patients with autonomic dysfunction than in patients without autonomic dysfunction. The symptoms of CR reported in this study can be viewed as complications caused by autonomic dysfunction after stroke (6).

Meyer et al. confirmed that norepinephrine was increased in patients with cerebral infarction compared to the control group and patients with a transient ischemic attack. This was not related to blood pressure and age (26). Studies have also reported that a right-sided ischemic stroke is more potent in increasing sympathetic function than a left-sided ischemic stroke (27, 28). In this study, changes in autonomic symptoms were subjectively evaluated, and its relationship with right and left lesions was analyzed (Table 4), but no significant relationship was found. According to Im et al., even patients who do not display symptoms of autonomic dysfunction may have autonomic nervous system failure in an objective examination. Although no statistical correlation was observed between the subjective autonomic dysfunction in patients with stroke and an objective examination of the nervous system, it is necessary to confirm symptoms through an objective examination in future studies (21).

Rhinorrhea indicates an imbalance between parasympathetic and sympathetic nerve activities, and it occurs under dominant parasympathetic hyperactivity (6). A decrease in sympathetic tone or an increase in parasympathetic tone leads to the dilation of venous sinusoids, thereby causing nasal obstruction. In the case of a stroke lesion, it can be considered that an abnormality has occurred in the pathways related to the superior salivatory nucleus of the parasympathetic nerve. As mentioned above, the sympathetic nerve tone increases after stroke; however, the extent to which the tone increases after stroke onset remains unknown.

In other words, the risk of CR was high in patients with cortex or subcortex lesions or subjectively assessed autonomic dysfunction. Since the symptoms of chronic rhinitis, such as runny nose, tears, and sneezing, are controlled by the autonomic nervous system, it is thought that nasal symptoms may be affected in patients with autonomic dysfunction as a complication after stroke. The importance of subcortical brain areas in autonomic function has been confirmed by several earlier investigations. Previously, the brainstem, amygdala, nucleus accumbens, and pallidum have been linked to the modulation and maintenance of SNS tone (29). Studies in rabbits and rats employing regional cutaneous vascular flow as a substitute for sympathetic activity showed that amygdala neuronal inhibition decreased cutaneous vasoconstriction, emphasizing the role of the amygdala in the sympathetic pathway (30). Subcortical brain regions have also been implicated in regulating PNS function, and the amygdala and palladium have both previously been implicated in key parasympathetic tones (29).

In our study, the results were similar, but the risk of CR increased in lesions that invaded the cortex and subcortex together, not lesions that invaded only the subcortex. This result suggests that autonomic dysfunction, which is the cause of CR, is affected by the interaction between the subcortex and the cortex. The relationship between

stroke lesions and the development of CR has not yet been clearly elucidated. Further studies are needed to confirm clear evidence between CR and stroke lesions. Large-scale studies with increased sample sizes are needed for the results of males having a higher risk of CR.

Non-allergic rhinitis can be subdivided into senile rhinitis, gustatory rhinitis, occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, and idiopathic rhinitis (16). The non-allergic rhinitis we refer to in this article falls under the category of idiopathic rhinitis. Senile rhinitis, gustatory rhinitis, and occupational rhinitis could be excluded, considering the patient's medical history and time of onset, but hormonal rhinitis and drug-induced rhinitis could not be clearly excluded. There is a limitation in clarifying further classification because it was not possible to investigate the use of drugs that can cause specific endocrine disease or rhinitis, such as NSAIDs like aspirin and ibuprofen, and beta-blockers (16).

Similarly, the SNOT-22 score was high among participants in the CR group in this study, and it can be concluded that the participants in the CR group had reduced QOL or discomfort due to CR. Patients with allergic symptoms before the occurrence of stroke were excluded to prevent the inclusion of allergic rhinitis during patient enrollment. However, the lack of objective tests, such as the skin prick test and serum allergen-specific IgE, can be a limitation in this process. CR was diagnosed solely based on the examination of medical history without an objective examination, such as the skin prick test. Although the SNOT-22 shows that there is a difference in QOL due to the development of CR in patients with stroke, further research is necessary because this index is insufficient to evaluate the overall QOL. Subjective evaluation was performed to determine the presence of autonomic dysfunction. In future studies, if objective tests such as sympathetic skin response or R-R interval variation are included, it is considered that they can be used as clear evidence of autonomic dysfunction (8). Additionally, further research on drugs (anticholinergics) that can affect autonomic dysfunction needs to be conducted.

In conclusion, we confirmed that the risk of CR was high in patients with stroke lesions in the subcortex. The risk was also higher in men than in women and when accompanied by autonomic symptoms. We also found that these rhinitis symptoms reduced the patients' QOL. Therefore, it is necessary to identify risk factors related to CR and to improve symptoms for the long-term management of the QOL of patients with stroke. Since the evaluation of patients with CR and autonomic nervous system symptoms is subjective, a prospective cohort study, which includes an objective diagnosis and severity evaluation of symptoms, is planned in the future. Finally, although rare, nasal symptoms can also occur in bell's palsy, which could be a limitation because they were not identified in the questionnaire.

Data availability statement

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

Ethics statement

This study was approved by the Hospital's Institutional Review Board (approval number: IRB 2020-01-059-006) and written informed consent was obtained from all patients included in this study. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MS contributed to the conception of the study. JC, YK, SJ, and MS performed clinical assessments. JC organized the database and performed statistical analysis. All authors contributed to the manuscript revision, read, and approved the submitted version.

Funding

This research was supported by Chungnam National University Hospital Research Fund, 2022.

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

References

1. Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet.* (2018) 392:1859–922. doi: 10.1016/S0140-6736(18)32335-3

2. Krishnamurthi RV, Ikeda T, Feigin VL. Global, regional and country-specific burden of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage: a systematic analysis of the global burden of disease study 2017. *Neuroepidemiology.* (2020) 54:171–9. doi: 10.1159/000506396

3. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: the GBD 2013 Study. *Neuroepidemiology.* (2015) 45:161–76. doi: 10.1159/000441085

4. Katan M, Luft A. Global burden of stroke. *Semin Neurol.* (2018) 38:208–11. doi: 10.1055/s-0038-1649503

5. Avdeeva KS, Fokkens WJ, Segboer CL, Reitsma S. The prevalence of non-allergic rhinitis phenotypes in the general population: a cross-sectional study. *Allergy.* (2022) 77:2163–74. doi: 10.1111/all.15223

6. Yao A, Wilson JA, Ball SL. Autonomic nervous system dysfunction and sinonasal symptoms. *Allergy Rhinol (Providence).* (2018) 9:2152656718764233. doi: 10.1177/2152656718764233

7. Korpelainen JT, Sotaniemi KA, Myllylä VV. Autonomic nervous system disorders in stroke. *Clin Auton Res.* (1999) 9:325–33. doi: 10.1007/BF02318379

8. Muslumanoglu L, Akyuz G, Aki S, Karsidag S, Us O. Evaluation of autonomic nervous system functions in post-stroke patients. *Am J Phys Med Rehabil.* (2002) 81:721–5. doi: 10.1097/00002060-200210000-00001

9. Meyer S, Strittmatter M, Fischer C, Georg T, Schmitz B. Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. *Neuroreport.* (2004) 15:357–61. doi: 10.1097/00001756-200402090-00029

10. Chen WH, Chen JJ, Lan MY. Reflex rhinorrhea after a right caudate infarct. *Acta Neurol Belg.* (1997) 97:255–7.

11. Uchino K, Lu M. Paroxysmal rhinorrhea after medullary infarct. *Case Rep Neurol.* (2012) 4:28–30. doi: 10.1159/000336233

12. Segboer CL, Terreehorst I, Gevorgyan A, Hellings PW, van Drunen CM, Fokkens WJ. Quality of life is significantly impaired in non-allergic rhinitis patients. *Allergy.* (2018) 73:1094–100. doi: 10.1111/all.13356

13. Kalmarzi RN, Khazaei Z, Shahsavar J, Gharibi F, Tavakol M, Khazaei S, et al. The impact of allergic rhinitis on quality of life: a study in western Iran. *Biomed Res Ther.* (2017) 4:1629–37. doi: 10.15419/bmrat.v4i9.370

14. Hisinger-Mölkänen H, Piirilä P, Haahtela T, Sovijärvi A, Pallasaho P. Smoking, environmental tobacco smoke and occupational irritants increase the risk of chronic rhinitis. *World Allergy Organ J.* (2018) 11:6. doi: 10.1186/s40413-018-0184-5

15. Ameli M, Grefkes C, Kemper F, Riegg FP, Rehme AK, Karbe H, et al. Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Ann Neurol.* (2009) 66:298–309. doi: 10.1002/ana.21725

16. Hellings PW, Klimek L, Cingi C, Agache I, Akdis C, Bachert C, et al. Non-allergic rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy.* (2017) 72:1657–65. doi: 10.1111/all.13200

17. Mozzanica F, Preti A, Gera R, Gallo S, Bulgheroni C, Bandi F, et al. Cross-cultural adaptation and validation of the SNOT-22 into Italian. *Eur Arch Otorhinolaryngol.* (2017) 274:887–95. doi: 10.1007/s00405-016-4313-x

18. Lauriello M, Di Rubbo V, Sinatti G, Pasqua M, Tucci C, di Marco GP, et al. Correlation between SNOT-22, nasal cytology, and mood disorders in patients with allergic rhinitis treated with a liposomal nasal spray. *Allergy Rhinol (Providence).* (2019) 10:2152656719866809. doi: 10.1177/2152656719866809

19. Marambaia PP, Lima MG, Santos KP, Gomes Ade M, de Sousa MM, Marques ME. Evaluation of the quality of life of patients with chronic rhinosinusitis by means of the SNOT-22 questionnaire. *Braz J Otorhinolaryngol.* (2013) 79:54–8. doi: 10.5935/1808-8694.20130010

20. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med.* (1980) 49:95–108.

21. Im SH, Park YG, Moon JH, Nam HS, Lee SC, Park JH. The subjective and objective evaluations of autonomic nervous system function in stroke patients. *J Korean Acad Rehabil Med.* (2007) 31:162–8. doi: 10.1016/j.clinph.2007.11.141

22. Purwata TE, Andaka D, Nuartha A, Wiratni C, Sumada K. Positive correlation between left hemisphere lesion and erectile dysfunction in post-stroke patients. *Open Access Maced J Med Sci.* (2019) 7:363–8. doi: 10.3889/oamjms.2019.125

23. Danilova LK. Effect of long-term electric stimulation of the head of the caudate nucleus on alimentary secretory reflexes in dogs. *Zh Vyssh Nerv Deiat Im I P Pavlova.* (1979) 29:237–44.

24. Danilova LK, Shefer SI, Voronin VM. Features of the formation of conditioned secretory reflexes in response to the stimulation of different areas of the caudate nucleus of the dog. *Zh Vyssh Nerv Deiat Im I P Pavlova.* (1986) 36:864–72.

25. Rafanelli M, Walsh K, Hamdan MH, Buyan-Dent L. Autonomic dysfunction: diagnosis and management. *Handb Clin Neurol.* (2019) 167:123–37. doi: 10.1016/B978-0-12-804766-8.00008-X

26. Myers MG, Norris JW, Hachniski VC, Sole MJ. Plasma norepinephrine in stroke. *Stroke.* (1981) 12:200–4. doi: 10.1161/01.STR.12.2.200

27. Sander D, Klingelhöfer J. Changes of circadian blood pressure patterns and cardiovascular parameters indicate lateralization of sympathetic activation following hemispheric brain infarction. *J Neurol.* (1995) 242:313–8. doi: 10.1007/BF00878874

28. Strittmatter M, Meyer S, Fischer C, Georg T, Schmitz B. Location-dependent patterns in cardio-autonomic dysfunction in ischaemic stroke. *Eur Neurol.* (2003) 50:30–8. doi: 10.1159/000070856

29. Ruffle JK, Coen SJ, Giampietro V, Williams SCR, Apkarian AV, Farmer AD, et al. Morphology of subcortical brain nuclei is associated with autonomic function in healthy humans. *Hum Brain Mapp.* (2018) 39:381–92. doi: 10.1002/hbm.23850

30. Blessing WW. Lower brainstem pathways regulating sympathetically mediated changes in cutaneous blood flow. *Cell Mol Neurobiol.* (2003) 23:527–38.

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 21 February 2023
DOI 10.3389/fneur.2023.1131250

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
HaoRan Tao,
Sun Yat-sen Memorial Hospital, Sun Yat-sen University, China
Xiong Chen,
Guangzhou Medical University, China

*CORRESPONDENCE
Wei Ye
✉ yewei7752@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 24 December 2022
ACCEPTED 30 January 2023
PUBLISHED 21 February 2023

CITATION
Song J, Chen W and Ye W (2023) Stroke and the risk of gastrointestinal disorders: A Mendelian randomization study.
Front. Neurol. 14:1131250.
doi: 10.3389/fneur.2023.1131250

Stroke and the risk of gastrointestinal disorders: A Mendelian randomization study

Jingru Song†, Wenjing Chen† and Wei Ye*

Department of Gastroenterology, Hangzhou Traditional Chinese Medicine (TCM) Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

Background: The issue of whether a stroke is causally related to gastrointestinal disorders was still not satisfactorily understood. Therefore, we investigated if there is a connection between stroke and the most prevalent gastrointestinal disorders, including peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD).

Methods: We applied two-sample Mendelian randomization to investigate relationships with gastrointestinal disorders. We obtained genome-wide association study (GWAS) summary data of any stroke, ischemic stroke, and its subtypes from the MEGASTROKE consortium. From the International Stroke Genetics Consortium (ISGC) meta-analysis, we acquired GWAS summary information on intracerebral hemorrhage (ICH), including all ICH, deep ICH, and lobar ICH. Several sensitivity studies were performed to identify heterogeneity and pleiotropy, while inverse-variance weighted (IVW) was utilized as the most dominant estimate.

Results: No evidence for an effect of genetic predisposition to ischemic stroke and its subtypes on gastrointestinal disorders were found in IVW. The complications of deep ICH are a higher risk for PUD and GERD. Meanwhile, lobar ICH has a higher risk of complications for PUD.

Conclusion: This study provides proof of the presence of a brain–gut axis. Among the complications of ICH, PUD and GERD were more common and associated with the site of hemorrhage.

KEYWORDS

stroke, gastrointestinal disorders, Mendelian randomization, causality, risk

1. Introduction

Stroke is one of the leading causes of death and disability worldwide (1, 2). Based on neuropathology, there are two main categories of stroke: ischemic stroke (IS) and hemorrhagic stroke. Of the two major types of stroke, IS is the more frequent type (3). There are various subtypes of IS, such as large artery stroke, cardioembolic stroke, and small vessel stroke (4). Hemorrhagic stroke includes subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). After a stroke, most patients will have varying degrees of motor impairment, cognitive impairment, speech dysphagia, depression, and other sequelae (5). In addition, up to 50% of patients usually experience gastrointestinal sequelae (6). The most common gastrointestinal disorders include PUD, GERD, IBS, and IBD. Among these four diseases, the prevalence of GERD is the highest, up to 18.1–27.8% in North America, followed by IBS and PUD, and the prevalence of IBD is lower. Patients with IBD commonly have abdominal pain, diarrhea, and bloody stools, while IBS has abdominal pain and altered bowel habits. GERD is usually characterized by regurgitation symptoms and

heartburn, while PUD symptoms are not specific and abdominal pain is common (7–10). They sometimes have similar symptoms, such as abdominal pain, and the development of these disorders is all related to the brain–gut axis (11–13). Some observational studies have given attention to the relationship between stroke and peptic ulcer disease (PUD) (14) and also stroke and gastroesophageal reflux disease (GERD) (15). The study found that the GERD risk of patients with stroke is about 1.51 times that of patients without stroke (15). However, so far, it is not clear whether there is a causal relationship between the two diseases.

A growing number of observational studies have demonstrated complex interactions between stroke and gastrointestinal disorders (16–18). Furthermore, studies have shown that stroke promotes the destruction of the intestinal barrier and the imbalance of gut microbiota (19, 20). These proved that there is bidirectional communication between the brain and the gut, usually referred to as the brain–gut or gut–brain axis (21). After a stroke, the bidirectional communications between the brain and the gut may relate to the dysfunction of the autonomic nervous system, resulting in gastrointestinal disorders (22, 23). However, the exact mechanism accounting for the brain–gut axis is still widely considered as unsatisfactorily understood.

In systematic reviews and meta-analyses, their causal relationship is unclear or confusing. Mendelian randomization (MR) is a research method using a genetic variation to evaluate the causal relationship between exposures and outcomes based on Mendel's second law. MR overcomes the limitations of observational research by exposing potential causal links and has proved valuable in exploring the causality by using single-nucleotide polymorphisms (SNPs). SNPs are required to be associated with exposures and should not be independently associated with outcomes, except through exposures. Furthermore, SNPs must not be associated with confounders (24, 25). Moreover, we can further explore the outcomes of insufficient data in RCT through large samples in the genome-wide association study (GWAS). To our knowledge, there are relatively few studies on the causal relationship between stroke and gastrointestinal disorders, and gastrointestinal disorders have received less attention than other stroke complications, yet gastrointestinal disorders after stroke may lead to poor prognosis or even death (26). PUD, GERD, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD) are common diseases of the digestive system (27, 28). Therefore, we are committed to studying the causal effects of stroke and its subtypes and common gastrointestinal disorders by applying two-sample Mendelian randomization.

2. Material and methods

The conceptual MR framework is presented in Figure 1.

2.1. Study design and ethical approval

According to the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) recommendations (29), the MR design was based on three hypotheses: (1) in this investigation, genetic variation was highly linked with the exposure of interest (stroke and its subtypes); (2) genetic variation was not associated with possible confounders; and (3) genetic variation solely had an impact on the outcome through the exposure of interest (gastrointestinal disorders in this study).

TABLE 1 Details of the GWAS included in the MR.

Phenotype	Data source	Sample size	%European
Exposures			
Any stroke	MEGASTROKE (30)	40,585 cases/406,111 controls	100%
Any ischemic stroke	MEGASTROKE (30)	34,217 cases/406,111 control	100%
Cardioembolic stroke	MEGASTROKE (30)	7,193 cases/406,111 control	100%
Small vessel stroke	MEGASTROKE (30)	5,386 cases/406,111 control	100%
Large artery stroke	MEGASTROKE (30)	4,373 cases/406,111 control	100%
All ICH	ISGC (31)	1,545 cases/1,481 controls	100%
Deep ICH	ISGC (31)	664 cases/1,481 controls	100%
Lobar ICH	ISGC (31)	881 cases/1,481 controls	100%
Outcomes			
PUD	Wu et al. (28)	16,666 cases/406,111 controls	100%
GERD	Wu et al. (28)	54,854 cases/401,473 controls	100%
IBS	Wu et al. (28)	29,524 cases/426,803 controls	100%
IBD	Wu et al. (28)	7,045 cases/449,282 controls	100%

ICH, intracerebral hemorrhage; PUD, peptic ulcer disease; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease.

2.2. Data sources for stroke and gastrointestinal disorders

To investigate the potential causative relationship between stroke and gastrointestinal disorders such as PUD, GERD, IBS, and IBD, we used a two-sample MR method. The largest meta-analysis of genome-wide association studies (GWASs) produced by the MEGASTROKE consortium provided pooled statistics for any stroke, any ischemic stroke, and its subtypes (cardioembolic stroke, small vessel stroke, and large artery stroke) confirmed by clinical and imaging criteria (30). The International Stroke Genetics Consortium (ISGC), a group with European roots, provided the exposure dataset for hemorrhagic stroke (Table 1) (31). Regarding the outcome dataset, we selected the results according to Wu et al. (28). PUD, GERD, IBS, and IBD are common gastrointestinal diseases.

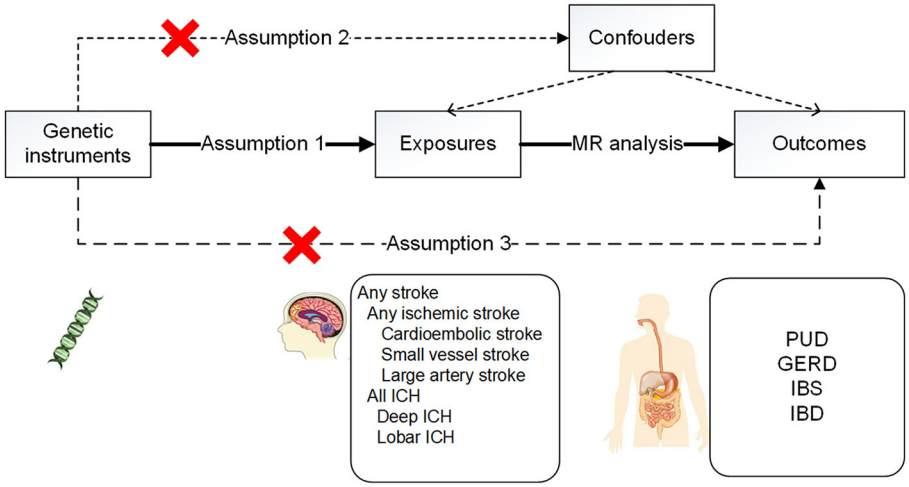


FIGURE 1
Conceptual MR framework.

2.3. Selection of genetic instruments

First, in line with the findings of Kwok et al. (32), we relaxed the correlation threshold with $P < 5 \times 10^{-6}$ and linkage disequilibrium (LD) ($r^2 < 0.001$) to obtain the top independent SNPs. This was done in light of the small number of SNPs ($P < 5 \times 10^{-8}$) that reached genome-wide significance. This strategy has been applied extensively in earlier MR investigations (33, 34). Second, the results of MR analysis are believed to be unaffected by weak instrumental bias if there is an F-statistic larger than 10. We used the following:

$$R^2 = 2 \times (1 - MAF) \times MAF \times (\beta)^2,$$
$$F = \left(\frac{R^2}{1 - R^2}\right)\left(\frac{n - k - 1}{k}\right).$$

Third, we extracted the secondary phenotypes of each SNP from a PhenoScanner V2 (35) and the GWAS library to exclude any putative polymorphism effects. The radial MR and MR pleiotropy residual sum and outlier (MR-PRESSO) tests were used to eliminate outliers before each MR analysis.

2.4. Statistical analysis

Three methods, including MR-Egger, weighted median, and random effect inverse-variance weighting (IVW), were utilized in the MR analysis to evaluate robust effects. The primary analysis method was the IVW method with various models, depending on the heterogeneity. At least half of the data for the Mendelian randomization study must originate from reliable instruments to use the weighted median estimator (36, 37). The effectiveness of potential pleiotropic tools must be independent of their direct relationships with the outcome for MR-Egger regression to be valid. Radial MR-Egger was used to estimate the horizontal pleiotropy and to identify outlier variants (38). Heterogeneity was also assessed using Cochran's *Q*-test. With the Cochran Q test (statistics were deemed to be significant if $P < 0.05$) and the intercept from MR-Egger regression (statistics were deemed to be significant if $P < 0.05$), we evaluated heterogeneity between Mendelian randomization estimates. We also evaluated potential directional polymorphisms using funnel plots. We used fixed-effects IVW and limited our instrument selection for sensitivity analyses to a lower LD correlation threshold. In conclusion, we conducted a thorough investigation of causation using all these techniques. Given the 32 MR estimates, the Bonferroni-corrected *P*-value for the study of gastrointestinal disorders was set at 0.05/32 (1.563×10^{-3}), and $P < 0.05$ was regarded as nominally significant. The statistical study was performed using R (version 4.2.0) and the "TwoSampleMR" and "RadialMR" packages.

3. Results

The SNPs of stroke subtypes on gastrointestinal disorders are listed in Supplementary Tables 1–8. Looking over the Phenoscanner, three SNPs (rs10850001, rs10774624, and rs3184504) were associated with smoking and were removed when analyzing PUD-associated SNPs. A total of 10 SNPs (rs12932445, rs1537375, rs2107595, rs2466455, rs4444878, rs4932370, rs6536024, rs6838973, rs72700114, and rs2634074) were related to the anticoagulant use, which was analyzed for PUD-related SNPs removed during the analysis. A total of 10 SNPs (rs10774624, rs1549758, rs1975161, rs2107595, rs2284665, rs34416434, rs42039, rs616154, rs78893982, and rs8103309) were associated with obesity and were removed in the analysis of GERD-related SNPs.

We performed a comprehensive MR study of stroke and its subtypes on gastrointestinal diseases (Supplementary Table 9). Among them, using IVW as the primary analysis, it could be seen that genetics predicted that any ischemic stroke had a normal significance with GERD ($P < 0.05$). All ICHs had normal significance with PUD and IBD ($P < 0.05$). Meanwhile, deep ICH had signed with the PUD and GERD ($P < 1.563 \times 10^{-3}$). Lobar ICH had signed with the PUD and IBS ($P < 1.563 \times$

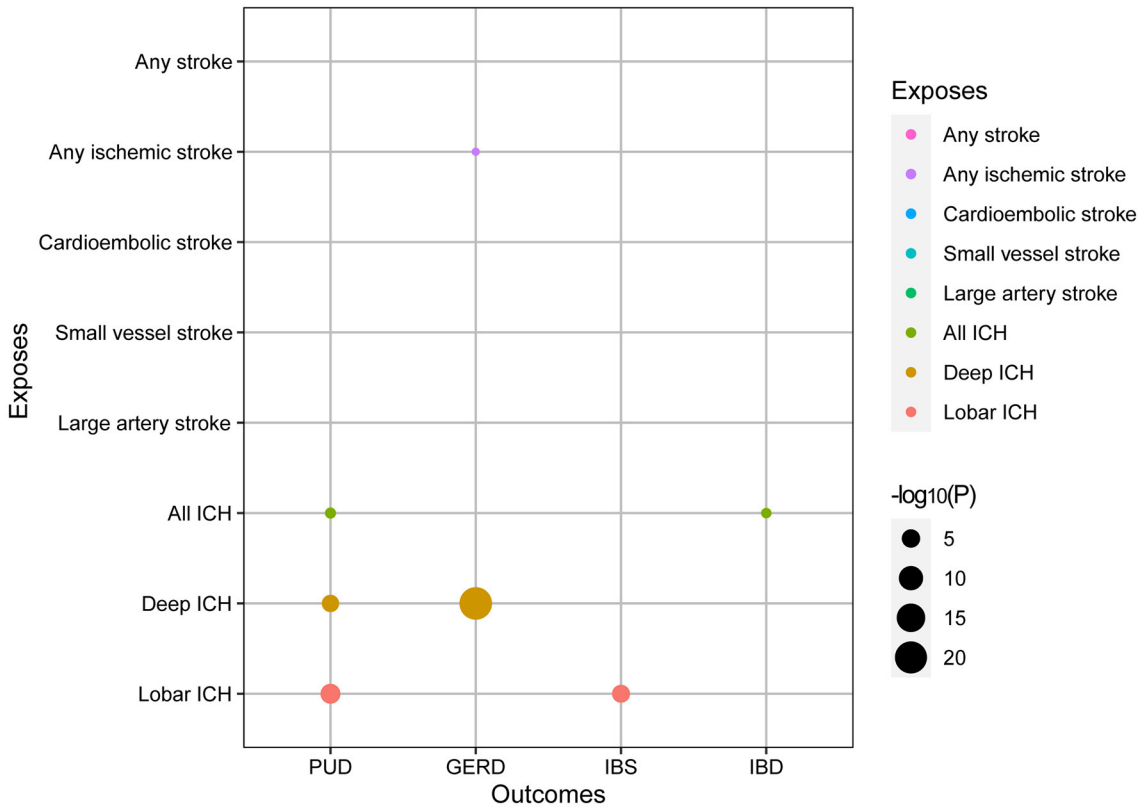


FIGURE 2
Bubble plot of MR study of stroke on gastrointestinal disorders derived from IVW.

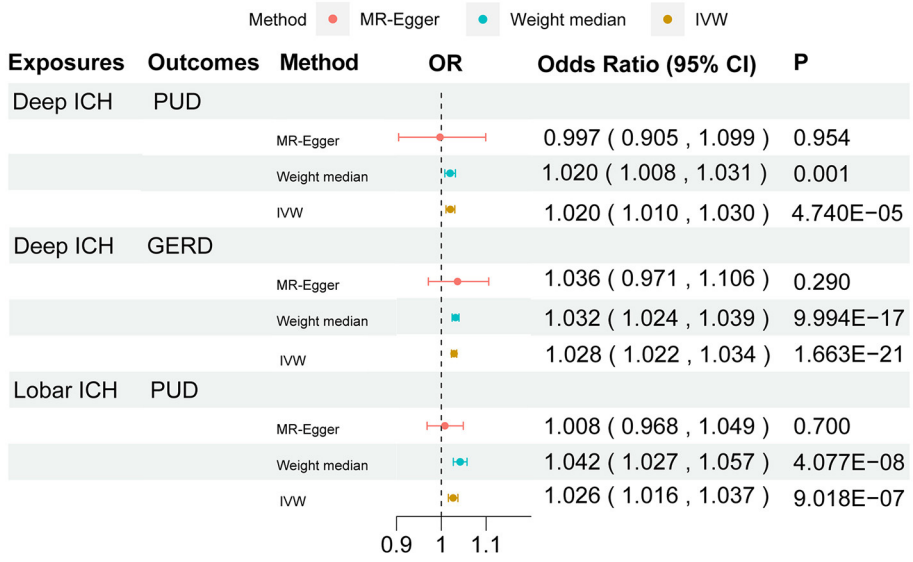


FIGURE 3
Forest plot for the causal effect of stroke on the risk of gastrointestinal disorders. OR, odds ratio; CI, confidence interval.

10^{-3}). A bubble plot was used to show the statistical significance of the analysis (Figure 2). After that, the MR analyses with significant *P*-values were demonstrated in a forest plot (Figure 3). For ischemic stroke, there was no significant causal relationship with gastrointestinal disorders. For hemorrhagic stroke, the result of IVW showed that deep ICH [odds ratio (OR): 1.020; 95% confidence interval (CI): 1.010–1.030; $P = 4.740 \times 10^{-5}$] was associated with an increased risk of PUD and greater disease

severity with the weight median method (OR: 1.020; 95% CI: 1.010–1.030; $P = 4.740 \times 10^{-5}$). The results of the MR-Egger method showed consistent directions but were not statistically significant (OR: 0.997; 95% CI: 0.905–1.099; $P = 0.954$). In addition, similar causal estimates of lobar ICH on PUD were obtained, and IVW (OR: 1.026; 95% CI: 1.016–1.037; $P = 9.018 \times 10^{-7}$) and weight median (OR: 1.042; 95% CI: 1.027–1.057; $P = 4.077 \times 10^{-8}$) were included, while the same result was observed using the MR-Egger method but without any statistical difference (OR: 1.008, 95% CI: 0.968–1.049, $P = 0.700$). Deep ICH was associated with an increased risk of GERD with the IVW (OR: 1.028; CI: 1.022–1.034; $P = 1.663 \times 10^{-21}$) and weight median (OR: 1.032; CI: 1.024–1.030; $P = 9.994 \times 10^{-17}$); however, there was no statistical difference in the MR-Egger method (OR: 1.036; CI: 0.971–1.106; $P = 0.290$), where all $p > 0.05$ for the MR-Egger intercept test, except for the MR analysis of lobar ICH on the IBS of lingual without weight median, indicated no horizontal pleiotropy. For significance and nominal significance estimates, Cochran's *Q*-test, the MR-Egger intercept test, the leave-one-out analysis, and the funnel plot were used to assess horizontal multiplicity (Supplementary Figures 1–4). Finally, we determined that deep ICH and labor ICH were causally related to PUD, and deep ICH was causally related to GERD.

4. Discussion

Previous studies have not found a clear causal relationship between stroke and gastrointestinal diseases. In our study, the relationship between stroke and its subtypes of gastrointestinal disorders was determined by the MR analysis. It is reported that obesity, smoking, anticoagulant, and other risk factors are often related to gastrointestinal diseases (39–41). The GWAS of GERD and PUD found genetic overlapping with the identified aforementioned hazardous factors (42, 43). We cannot rule out that SNP affects the outcome through other related variables. Therefore, we should try our best to reduce the bias caused by pleiotropy. To reduce pleiotropy, we look over the PhenoScanner and eliminate those pleiotropic genetic variants. Thus, we successfully removed SNPs that were highly correlated with possible confounders such as obesity, smoking, and anticoagulation therapy. In addition, we also conducted some sensitivity analyses, such as a leave-one-out analysis and a funnel plot, and other methods such as Cochran's *Q*-test and the MR-Egger intercept test to assess horizontal multiplicity.

Stroke is often associated with PUD. A retrospective review including 808 cases found that the incidence of gastrointestinal bleeding caused by PUD in patients with ICH was 26.7% (18). Moreover, the incidence of gastrointestinal bleeding was significantly higher in patients who often use stress ulcer prophylaxis (SUP) for stress ulcer prevention compared with patients not receiving SUP (18). Another observational study examined 177 patients with acute stroke by gastroscopy, of which 92 (52%) had gastric changes, 10 of which were acute ulcers (44). For patients with severe ICH, an observational study found that 28.0% of 715 patients with severe ICH developed stress-related gastrointestinal bleeding (SGIB) or stress ulcers during hospitalization (45). Regrettably, none of these observational studies had a large sample size. Our MR study suggested that stroke has a causal impact on PUD but only on deep ICH and lobar ICH and not ischemic stroke.

The pathogenesis of ICH complicated by peptic ulcers is still unclear and may be related to the damage to the thalamus and the subthalamus. To summarize various studies, the possible mechanisms are as follows: first, patients with acute ICH often experience intracranial hypertension and cerebral edema, which directly or indirectly causes damage to the brain stem, the hypothalamus, and other parts and finally affects their normal physiologic functions, leading to a dysfunction of the autonomic nervous system and gastric hyperchlorhydria. It lessens the blood flow of gastrointestinal mucosa and damages the gastric mucosal barrier, resulting in stress gastrointestinal ulcer peptic ulcers as well as peptic ulcer bleeding (46). According to previous studies, the development of stress ulcers in patients with ICH can be better predicted by the hematoma volume of ICH (47, 48). Mechanistically, larger hematomas in the case of cerebral hemorrhage are more likely to lead to increased intracranial pressure (45). As mentioned earlier, elevated intracranial pressure may cause strong sympathetic excitation and gastrointestinal vasoconstriction, causing a decrease in gastrointestinal blood flow, which subsequently leads to mucosal ischemia and increased gastric acid secretion. Second, post-stroke sepsis plays a very important role in the development of stress ulcers induced by severe ICH (45). Inflammatory cytokines are released in large amounts in the development of sepsis, thus exacerbating the ischemia of the gastrointestinal mucosa caused by intracerebral hemorrhage and driving the development of stress ulcers (49, 50). In an observational study, the incidence of gastrointestinal bleeding in patients with ischemic stroke was 7.8%, 74% of which were caused by peptic ulcers (51). Combined with our findings, it is clear that hemorrhagic strokes are more likely to develop peptic ulcers than ischemic strokes. The development of peptic ulcers in ischemic stroke may be associated with vagal hyperactivity, stress, and neuroendocrine dysregulation (51, 52). However, the trigger for gastrointestinal bleeding in most patients with ischemic stroke is not stress, and stress ulcers due to acute ischemic brain injury may be very rare (52, 53). One possible explanation for the aforementioned results is that compared to ischemic strokes, hemorrhagic strokes are a more devastating subtype of stroke (54). Hemorrhagic stroke may have a stronger effect on the brain–gut axis than ischemic stroke. The study finding that hemorrhagic stroke disrupts the gut microbiota more than ischemic stroke may prove this (55). The incidence of stress ulcer bleeding in patients with brain injury is closely related to the severity of the injury (56). In our MR study, the risk of lobar ICH is more associated with an increased risk of PUD compared to the risk of deep ICH. The size of the hematoma, sepsis, and prognosis have been reported to be the strongest predictors of gastrointestinal bleeding in patients with ICH in previous research (48). A Japanese observational study found a higher rate of poor prognosis in patients with lobar ICH than in those with non-lobar ICH (57). Even lobar ICH is associated with more severe cognitive impairment (58). It suggests clinical vigilance for PUD for hemorrhagic stroke.

Several studies have proposed an association between stroke and GERD. A population-based Taiwanese cohort study including 18,412 patients with stroke and 18,412 without stroke found that the risk of GERD in patients with stroke was 1.51 times higher than that in patients without stroke (95% CI, 1.40–1.67) (15). Moreover, they separated the stroke cohort into two subgroups: hemorrhagic stroke and ischemic stroke. Compared with the subjects without stroke, the HRs for GERD in the intracerebral hemorrhage and ischemic stroke cohorts were 1.45 and 1.52 (95% CI, 1.22–1.71 and 95% CI, 1.39–1.67) (15). Our MR study found that the higher risk of GERD is complicated by the risk of deep ICH, and there is a positive causal relationship between them. We reviewed the relevant literature to explain the mechanisms by which stroke leads to the development of GERD. For ischemic stroke, GERD may be induced by drugs used to treat IS, such as aspirin. One of the independent risk factors associated with the clinical symptoms of GERD is NSAIDs. The study also found an increased incidence of GERD in patients with stroke treated with antiplatelet therapy (15, 59). In addition, ischemic stroke may disrupt the neural regulation of oropharyngeal, esophageal, and gastrointestinal motility, resulting in an extensive impairment of oropharyngeal and gastrointestinal motility and a reduced tone of the lower esophageal sphincter (52). ICH has a similar effect on the vagus nerve, resulting in the malfunction of esophageal peristalsis, gastrointestinal motility, and the lower esophageal sphincter (48, 60). Parasympathetic dysfunction in patients with stroke may lead to impaired esophageal motility, the abnormal transmission of food, and the abnormal relaxation of the lower esophageal sphincter (15, 61). Hypertension is one of the most important risk factors for stroke, and treatment to lower blood pressure to prevent stroke, including the use of calcium channel blockers, often leads to lower esophageal sphincter (LES) pressure and eventually GERD (62, 63). A community study found that calcium channel blockers were independently associated with GERD symptoms as a risk factor (63). To explain why deep ICH is more prone to GERD than other subtypes of stroke, we looked through many studies. Deep ICH is often thought to be closely associated with hypertension, while lobar ICH is often thought to be caused by cerebral amyloid angiopathy (CAA) (64). Among the drugs used to treat hypertension, calcium channel blockers have the effect of lowering the pressure of the LES and impeding gastric emptying, thus inducing GERD (65). Therefore, compared to lobar ICH, deep ICH is more prone to GERD.

According to our MR results, intracerebral hemorrhage is more likely to cause gastrointestinal disease than ischemic stroke, and we are thinking about the reasons for this result. It is well-known that ischemic stroke and intracerebral hemorrhage do not occur by similar mechanisms, and their degree of criticality is different. ICH is the most severe subtype of stroke. Furthermore, the most devastating type of pathology among the subtypes of stroke is ICH (54). In general, ICH produces more severe strokes than cerebral infarct (66, 67). ICH typically manifests as elevated intracranial pressure, hematoma compression, and serious cerebral edema, which can cause many negative effects, such as neuroinflammation, mitochondrial dysfunction, and apoptosis, resulting in a sudden disruption of the blood–brain barrier (68). Contrary to ICH, the structural stability of brain cells and the blood–brain barrier is retained for a longer length of time following the beginning of symptoms in ischemic stroke (69). One possible explanation for our findings is that compared to ischemic stroke, ICH is more damaging to the brain–gut axis, causing a more severe dysbiosis in the gut microbiota, abnormal gastrointestinal motor function, and impaired gastrointestinal motility, which leads to gastrointestinal disorders. Compared to patients with ischemic stroke, patients with ICH have more severe gut microbiota destruction (70). ICH causes rapid damage to astrocytes and the blood–brain barrier in patients (69). Contemporary genetics considers stroke not as a disease but as a syndrome. Stroke is an acute manifestation of a range of chronic cerebrovascular diseases (71). Another possible explanation for our findings is that some subtypes of ischemic stroke present additional phenotypic dilemmas, such as the cardiogenic stroke subtype, whereas the phenotype of ICH is more uniform (71). Moreover, genetic factors are important in the pathogenesis of ICH (72). It is estimated that up to 44% of cases of ICH are heritable, and possessing an ICH first-degree relative increases the risk of developing the condition by a factor of six (73).

To explain the causal relationship between hemorrhagic stroke and several gastrointestinal diseases, we have found several possible mechanisms. Intracerebral smoke can affect the function of the autonomic nervous system. Through the enteric nervous system, the extrinsic and autonomic nervous systems can regulate the motor, sensory, and secretory functions of the gastrointestinal tract. ICH affects gastrointestinal function in this way, mainly with motor dysfunction (74). For example, strokes are often complicated by dysphagia, which may be due to cranial nerve involvement in the region of the vertebrobasilar artery (75). This is one of the possible causes of stroke complicating gastrointestinal motility disorder-related disease. Moreover, the change in gut microbes caused by intracerebral hemorrhage may be one of the causes of some gastrointestinal diseases (68). A prospective case–control study found that compared with the control group, the intestinal microbiota composition of both patients with ischemic stroke and patients with intracerebral hemorrhage changed (55). More specifically, compared with the control group, the abundance of invasive aerobic bacterial genera (*Enterococcus* species and *Escherichia/Shigella* species) in all patients with stroke increased, while obligate anaerobic genera decreased (55). The authors observed that the extent of gut microbiota destruction was positively associated with the severity of stroke. An intracerebral hemorrhage causes more severe disruption of the gut microbiota than an ischemic stroke (55). The autonomic nervous system abnormally releases norepinephrine to the intestine, which may change the intestinal microbiota (23). Another study found that the immune system of model mice is disturbed after intracerebral hemorrhage. Furthermore, the gut barrier function of model mice was impaired, and intestinal permeability increased (70). In addition, experimental studies also found that inflammatory cytokines were upregulated in the intestine, malondialdehyde (MDA) levels were elevated, the superoxide (SOD) dismutase activity was reduced, severe intestinal mucosal damage and plasma endotoxin levels were elevated 2 h after intracerebral hemorrhage in model mice, and intestinal propulsion was reduced 12 h later, and these symptoms persisted for 7 days after the appearance of the above symptoms (76). These suggest that

intracerebral hemorrhage significantly increases inflammatory cytokine levels and myeloperoxidase activity, which, in turn, promotes an inflammatory response in the intestine, leading to gastrointestinal disorders associated with intestinal motility and barrier dysfunction. In contrast, elevated malondialdehyde levels and reduced superoxide dismutase also suggest that intracerebral hemorrhage induced excessive oxygen radical production in the intestine during ischemia-reperfusion. The pathological imbalance of the intestinal oxidative–antioxidant system may also be involved in the pathogenesis of gastrointestinal disorders after intracerebral hemorrhage (76). In a word, intracerebral hemorrhage may lead to impaired communication between the brain and intestinal axis, which may directly result in gastrointestinal motility dysfunction or intestinal flora disorders. Although there are many studies on how the brain–gut axis interacts, the exact mechanism has not been clarified.

Our MR study has some strengths. First, compared with one-sample MR, our research has a larger sample size and higher statistical efficiency. Second, our research overcame the shortcomings of traditional causal inference. Since the alleles followed the principle of random assignment, we obtained results independent of the confounding factors and reversed causal associations found in traditional epidemiological studies. Furthermore, there is Cochran's *Q*-test, the MR-Egger intercept test, and sensitivity analysis to test the pleiotropy of instrumental variables, which enhances the reliability of the results. At the same time, our analysis has some limitations. First of all, the estimates mentioned in our MR study cannot be directly compared with those of other observational studies. Second, we have selected only four common gastrointestinal disorders, and it is unknown whether a stroke has a causal effect on other gastrointestinal disorders. Third, the dataset on which our study is primarily based includes only individuals of European ancestry and thus may not be applicable to other humans, which would make our findings not generalizable. Finally, because of the limitation of the number of SNPs, the *p*-value limits were adjusted in our article.

Our MR study provides evidence for a causal relationship between deep ICH on PUD and GERD and a causal relationship between lobar ICH on PUD, and our results add to the gap in observational studies in this regard and warrant further research for the prevention of gastrointestinal disorders after deep ICH and lobar ICH.

5. Conclusion

Our research supports a possible causal link between stroke and its subtypes and gastrointestinal disorders. Early gastrointestinal disease risk assessment and prevention in hemorrhagic stroke is crucial and could aid in the introduction of tailored treatment as soon as possible.

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

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 for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JS contributed to the methodology and wrote the manuscript. WC contributed to conceptualization and investigation. WY contributed to the funding, writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by Hangzhou Medical Key Cultivation Discipline (Spleen and Gastroenterology, Grant No. 2020SJZDXK13) and Zhejiang Provincial TCM Science and Technology Program Project (Grant No. 2021ZA107).

Acknowledgments

The authors gratefully thank the MEGASTROKE Consortium for providing summary statistics data. All MEGASTROKE Consortium authors are listed online (https://www.megastroke.org/authors.html). The MEGASTROKE project received funding from sources specified at https://www.megastroke.org/acknowledgements.html. For the source of data on hemorrhagic stroke, the authors thank the ISGC genome-wide association study.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1131250/full#supplementary-material

References

1. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet.* (2018) 392:2052–90. doi: 10.1016/S0140-6736(18)31694-5

2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet.* (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9

3. Petro M, Jaffer H, Yang J, Kabu S, Morris VB, Labhasetwar V. Tissue plasminogen activator followed by antioxidant-loaded nanoparticle delivery promotes activation/mobilization of progenitor cells in infarcted rat brain. *Biomaterials.* (2016) 81:169–80. doi: 10.1016/j.biomaterials.2015.12.009

4. Regenhardt RW, Das AS, Lo EH, Caplan LR. Advances in understanding the pathophysiology of lacunar stroke: a review. *JAMA Neurol.* (2018) 75:1273–81. doi: 10.1001/jamaneurol.2018.1073

5. Rost NS, Brodtmann A, Pase MP, van Veluw SJ, Biffi A, Duering M, et al. Post-Stroke cognitive impairment and dementia. *Circ Res.* (2022) 130:1252–71. doi: 10.1161/CIRCRESAHA.122.319951

6. Pluta R, Januszewski S, Czuczwar SJ. The role of gut microbiota in an ischemic stroke. *Int J Mol Sci.* (2021) 22:915. doi: 10.3390/ijms22020915

7. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet.* (2017) 390:2769–78. doi: 10.1016/S0140-6736(17)32448-0

8. Sandhu DS, Fass R. Current trends in the management of gastroesophageal reflux disease. *Gut Liver.* (2018) 12:7–16. doi: 10.5009/gnl16615

9. Lanas A, Chan FKL. Peptic ulcer disease. *Lancet.* (2017) 390:613–24. doi: 10.1016/S0140-6736(16)32404-7

10. Defrees DN, Bailey J. Irritable bowel syndrome: epidemiology, pathophysiology, diagnosis, and treatment. *Prim Care.* (2017) 44:655–71. doi: 10.1016/j.pop.2017.07.009

11. Tache Y. The peptidergic brain-gut axis: influence on gastric ulcer formation. *Chronobiol Int.* (1987) 4:11–7. doi: 10.1080/07420528709078504

12. Ancona A, Petito C, Iavarone I, Petito V, Galasso L, Leonetti A, et al. The gut-brain axis in irritable bowel syndrome and inflammatory bowel disease. *Dig Liver Dis.* (2021) 53:298–305. doi: 10.1016/j.dld.2020.11.026

13. Yadlapati R, Gyawali CP, Pandolfino JE. Aga clinical practice update on the personalized approach to the evaluation and management of gerd: expert review. *Clin Gastroenterol Hepatol.* (2022) 20:984–94.e1. doi: 10.1016/j.cgh.2022.01.025

14. Xu Z, Wang H, Lin Y, Zhai Q, Sun W, Wang Z, et al. The impacts of peptic ulcer on functional outcomes of ischemic stroke. *J Stroke Cerebrovasc Dis.* (2019) 28:311–6. doi: 10.1016/j.jstrokecerebrovasdis.2018.09.056

15. Chang CS, Chen HJ, Liao CH. Patients with cerebral stroke have an increased risk of gastroesophageal reflux disease: a population-based cohort study. *J Stroke Cerebrovasc Dis.* (2018) 27:1267–74. doi: 10.1016/j.jstrokecerebrovasdis.2017.12.001

16. Satou Y, Oguro H, Murakami Y, Onoda K, Mitaki S, Hamada C, et al. Gastroesophageal reflux during enteral feeding in stroke patients: a 24-hour esophageal ph-monitoring study. *J Stroke Cerebrovasc Dis.* (2013) 22:185–9. doi: 10.1016/j.jstrokecerebrovasdis.2011.07.008

17. Kristensen SL, Lindhardsen J, Ahlehoff O, Erichsen R, Lamberts M, Khalid U, et al. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace.* (2014) 16:477–84. doi: 10.1093/europace/eut312

18. Yang TC, Li JG, Shi HM, Yu DM, Shan K, Li LX, et al. Gastrointestinal bleeding after intracerebral hemorrhage: a retrospective review of 808 cases. *Am J Med Sci.* (2013) 346:279–82. doi: 10.1097/MAJ.0b013e318271a621

19. Wen SW, Wong CHY. An unexplored brain-gut microbiota axis in stroke. *Gut Microbes.* (2017) 8:601–6. doi: 10.1080/19490976.2017.1344809

20. Stanley D, Moore RJ, Wong CHY. An insight into intestinal mucosal microbiota disruption after stroke. *Sci Rep.* (2018) 8:568. doi: 10.1038/s41598-017-18904-8

21. Arya AK, Hu B. Brain-Gut axis after stroke. *Brain Circ.* (2018) 4:165–73. doi: 10.4103/bc.bc_32_18

22. Yang Z, Wei F, Zhang B, Luo Y, Xing X, Wang M, et al. Cellular immune signal exchange from ischemic stroke to intestinal lesions through brain-gut axis. *Front Immunol.* (2022) 13:688619. doi: 10.3389/fimmu.2022.688619

23. Houlden A, Goldrick M, Brough D, Vizi ES, Lénárt N, Martinecz B, et al. Brain injury induces specific changes in the caecal microbiota of mice via altered autonomic activity and mucoprotein production. *Brain Behav Immun.* (2016) 57:10–20. doi: 10.1016/j.bbi.2016.04.003

24. Holmes MV, Ala-Korpela M, Smith GD. Mendelian randomization in cardiometabolic disease: challenges in evaluating causality. *Nat Rev Cardiol.* (2017) 14:577–90. doi: 10.1038/nrcardio.2017.78

25. Cui G, Li S, Ye H, Yang Y, Huang Q, Chu Y, et al. Are neurodegenerative diseases associated with an increased risk of inflammatory bowel disease? A two-sample mendelian randomization study. *Front Immunol.* (2022) 13:956005. doi: 10.3389/fimmu.2022.956005

26. Wang WJ, Lu JJ, Wang YJ, Wang CX, Wang YL, Hoff K, et al. Clinical characteristics, management, and functional outcomes in chinese patients within the first year after intracerebral hemorrhage: analysis from china national stroke registry. *CNS Neurosci Ther.* (2012) 18:773–80. doi: 10.1111/j.1755-5949.2012.00367.x

27. Freuer D, Linseisen J, Meisinger C. Asthma and the risk of gastrointestinal disorders: a mendelian randomization study. *BMC Med.* (2022) 20:82. doi: 10.1186/s12916-022-02283-7

28. Wu Y, Murray GK, Byrne EM, Sidorenko J, Visscher PM, Wray NR. Gwas of peptic ulcer disease implicates helicobacter pylori infection, other gastrointestinal disorders and depression. *Nat Commun.* (2021) 12:1146. doi: 10.1038/s41467-021-21280-7

29. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the strobe-Mr statement. *Jama.* (2021) 326:1614–21. doi: 10.1001/jama.2021.18236

30. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, et al. Publisher correction: multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet.* (2019) 51:1192–3. doi: 10.1038/s41588-019-0449-0

31. Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, et al. Meta-Analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet.* (2014) 94:511–21. doi: 10.1016/j.ajhg.2014.02.012

32. Kwok MK, Kawachi I, Rehkopf D, Schooling CM. The role of cortisol in ischemic heart disease, ischemic stroke, type 2 diabetes, and cardiovascular disease risk factors: a bi-directional mendelian randomization study. *BMC Med.* (2020) 18:363. doi: 10.1186/s12916-020-01831-3

33. Du W, Wang T, Zhang W, Xiao Y, Wang X. Genetically supported causality between benign prostate hyperplasia and urinary bladder neoplasms: a mendelian randomization study. *Front Genet.* (2022) 13:1016696. doi: 10.3389/fgene.2022.1016696

34. Müller R, Freitag-Wolf S, Weiner J, 3rd Chopra A, Top T, Dommisch H, et al. Case-only design identifies interactions of genetic risk variants at siglec5 and plg with the lncrna Ctd-2353f22.1 implying the importance of periodontal wound healing for disease aetiology. *J Clin Periodontol.* (2023) 50:90–101. doi: 10.1111/jcpe.13712

35. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, et al. Phenoscanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics.* (2019) 35:4851–3. doi: 10.1093/bioinformatics/btz469

36. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through egger regression. *Int J Epidemiol.* (2015) 44:512–25. doi: 10.1093/ije/dyv080

37. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. *Epidemiology.* (2017) 28:30–42. doi: 10.1097/EDE.0000000000000559

38. Bowden J, Spiller W, Del Greco MF, Sheehan N, Thompson J, Minelli C, et al. Improving the visualization, interpretation and analysis of two-sample summary data mendelian randomization via the radial plot and radial regression. *Int J Epidemiol.* (2018) 47:1264–78. doi: 10.1093/ije/dyy101

39. Bilski J, Mazur-Bialy A, Wojcik D, Surmiak M, Magierowski M, Sliwowski Z, et al. Role of obesity, mesenteric adipose tissue, and adipokines in inflammatory bowel diseases. *Biomolecules.* (2019) 9:780. doi: 10.3390/biom9120780

40. Korman MG, Hansky J, Eaves ER, Schmidt GT. Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. *Gastroenterology.* (1983) 85:871–4. doi: 10.1016/0016-5085(83)90438-9

41. Kawamura N, Ito Y, Sasaki M, Iida A, Mizuno M, Ogasawara N, et al. Low-Dose aspirin-associated upper gastric and duodenal ulcers in japanese patients with no previous history of peptic ulcers. *BMC Res Notes.* (2013) 6:455. doi: 10.1186/1756-0500-6-455

42. Ong JS, An J, Han X, Law MH, Nandakumar P, Schumacher J, et al. Multitrait genetic association analysis identifies 50 new risk loci for gastro-oesophageal reflux, seven new loci for barrett's oesophagus and provides insights into clinical heterogeneity in reflux diagnosis. *Gut.* (2022) 71:1053–61. doi: 10.1136/gutjnl-2020-323906

43. Li Z, Chen H, Chen T. Genetic liability to obesity and peptic ulcer disease: a mendelian randomization study. *BMC Med Genomics.* (2022) 15:209. doi: 10.1186/s12920-022-01366-x

44. Kitamura T, Ito K. Acute gastric changes in patients with acute stroke. Part 1: with reference to gastroendoscopic findings. *Stroke.* (1976) 7:460–3. doi: 10.1161/01.STR.7.5.460

45. Liu S, Wang Y, Gao B, Peng J. A nomogram for individualized prediction of stress-related gastrointestinal bleeding in critically ill patients with primary intracerebral hemorrhage. *Neuropsychiatr Dis Treat.* (2022) 18:221–9. doi: 10.2147/NDT.S342861

46. Alhazzani W, Jaeschke R. Stress ulcer prophylaxis in critical care: a 2016 perspective Dr. Waleed Alhazzani in an interview with Dr. Roman Jaeschke: part 2. *Pol Arch Med Wewn.* (2016) 126:796–7. doi: 10.20452/pamw.3606

47. Liu BL, Li B, Zhang X, Fei Z, Hu SJ, Lin W, et al. A randomized controlled study comparing omeprazole and cimetidine for the prophylaxis of stress-related upper gastrointestinal bleeding in patients with intracerebral hemorrhage. *J Neurosurg.* (2013) 118:115–20. doi: 10.3171/2012.9.JNS12170

48. Misra UK, Kalita J, Pandey S, Mandal SK. Predictors of gastrointestinal bleeding in acute intracerebral haemorrhage. *J Neurol Sci.* (2003) 208:25–9. doi: 10.1016/S0022-510X(02)00415-X

49. Pastores SM, Katz DP, Kvetan V. Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. *Am J Gastroenterol.* (1996) 91:1697–710.

50. Overhaus M, Tögel S, Pezzone MA, Bauer AJ. Mechanisms of polymicrobial sepsis-induced ileus. *Am J Physiol Gastrointest Liver Physiol.* (2004) 287:G685–94. doi: 10.1152/ajpgi.00359.2003

51. Hsu HL, Lin YH, Huang YC, Weng HH, Lee M, Huang WY, et al. Gastrointestinal hemorrhage after acute ischemic stroke and its risk factors in Asians. *Eur Neurol.* (2009) 62:212–8. doi: 10.1159/000229018

52. Schaller BJ, Graf R, Jacobs AH. Pathophysiological changes of the gastrointestinal tract in ischemic stroke. *Am J Gastroenterol.* (2006) 101:1655–65. doi: 10.1111/j.1572-0241.2006.00540.x

53. Wijdicks EF, Fulgham JR, Batts KP. Gastrointestinal bleeding in stroke. *Stroke.* (1994) 25:2146–8. doi: 10.1161/01.STR.25.11.2146

54. Tsai CF, Jeng JS, Anderson N, Sudlow CLM. Comparisons of risk factors for intracerebral hemorrhage versus ischemic stroke in chinese patients. *Neuroepidemiology.* (2017) 48:72–8. doi: 10.1159/000475667

55. Haak BW, Westendorp WF, van Engelen TSR, Brands X, Brouwer MC, Vermeij JD, et al. Disruptions of anaerobic gut bacteria are associated with stroke and post-stroke infection: a prospective case-control study. *Transl Stroke Res.* (2021) 12:581–92. doi: 10.1007/s12975-020-00863-4

56. Kamada T, Fusamoto H, Kawano S, Noguchi M, Hiramatsu K. Gastrointestinal bleeding following head injury: a clinical study of 433 cases. *J Trauma.* (1977) 17:44–7. doi: 10.1097/00005373-197701000-00006

57. Matsukawa H, Shinoda M, Fujii M, Takahashi O, Yamamoto D, Murakata A, et al. Factors associated with lobar vs. non-lobar intracerebral hemorrhage. *Acta Neurol Scand.* (2012) 126:116–21. doi: 10.1111/j.1600-0404.2011.01615.x

58. Tveiten A, Ljøstad U, Mygland Å, Naess H. Functioning of long-term survivors of first-ever intracerebral hemorrhage. *Acta Neurol Scand.* (2014) 129:269–75. doi: 10.1111/ane.12185

59. Ercelep OB, Caglar E, Dobrucali A. The prevalence of gastroesophageal reflux disease among hospital employees. *Dis Esophagus.* (2014) 27:403–8. doi: 10.1111/j.1442-2050.2012.01402.x

60. Cunningham KM, Horowitz M, Riddell PS, Maddern GJ, Myers JC, Holloway RH, et al. Relations among autonomic nerve dysfunction, oesophageal motility, and gastric emptying in gastro-oesophageal reflux disease. *Gut.* (1991) 32:1436–40. doi: 10.1136/gut.32.12.1436

61. Orlando RC. Pathophysiology of gastroesophageal reflux disease. *J Clin Gastroenterol.* (2008) 42:584–8. doi: 10.1097/MCG.0b013e31815d0628

62. Schrader J, Lüders S, Kulschewski A, Hammersen F, Plate K, Berger J, et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (moses). *Stroke.* (2005) 36:1218–26. doi: 10.1161/01.STR.0000166048.35740.a9

63. Mohammed I, Nightingale P, Trudgill NJ. Risk factors for gastro-oesophageal reflux disease symptoms: a community study. *Aliment Pharmacol Ther.* (2005) 21:821–7. doi: 10.1111/j.1365-2036.2005.02426.x

64. Labovitz DL, Sacco RL. Intracerebral hemorrhage: update. *Curr Opin Neurol.* (2001) 14:103–8. doi: 10.1097/00019052-200102000-00016

65. Osadchuk AM, Davydkin IL, Gricenko TA, Osadchuk MA. [Gastroesophageal reflux disease and esophagitis associated with the use of drugs: the modern state of the problem]. *Ter Arkh.* (2019) 91:135–40. doi: 10.26442/00403660.2019.08.000228

66. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Intracerebral hemorrhage versus infarction: stroke severity, risk factors, and prognosis. *Ann Neurol.* (1995) 38:45–50. doi: 10.1002/ana.410380110

67. Ratha Krishnan R, Yeo EQY, Lim CJ, Chua KSG. The impact of stroke subtype on recovery and functional outcome after inpatient rehabilitation: a retrospective analysis of factors. *Life.* (2022) 12:1295. doi: 10.3390/life12091295

68. Zou X, Wang L, Xiao L, Wang S, Zhang L. Gut microbes in cerebrovascular diseases: gut flora imbalance, potential impact mechanisms and promising treatment strategies. *Front Immunol.* (2022) 13:975921. doi: 10.3389/fimmu.2022.975921

69. Zhang J, Zhang CH, Lin XL, Zhang Q, Wang J, Shi SL. Serum glial fibrillary acidic protein as a biomarker for differentiating intracerebral hemorrhage and ischemic stroke in patients with symptoms of acute stroke: a systematic review and meta-analysis. *Neurol Sci.* (2013) 34:1887–92. doi: 10.1007/s10072-013-1541-3

70. Zhang H, Huang Y, Li X, Han X, Hu J, Wang B, et al. Dynamic process of secondary pulmonary infection in mice with intracerebral hemorrhage. *Front Immunol.* (2021) 12:767155. doi: 10.3389/fimmu.2021.767155

71. Rost NS. Clinical neurogenetics: stroke. *Neurol Clin.* (2013) 31:915–28. doi: 10.1016/j.ncl.2013.05.001

72. Ekkert A, Šliachtenko A, Utkus A, JatuŽis D. Intracerebral hemorrhage genetics. *Genes.* (2022) 13:1250. doi: 10.3390/genes13071250

73. Hostettler IC, Seiffge DJ, Werring DJ. Intracerebral hemorrhage: an update on diagnosis and treatment. *Expert Rev Neurother.* (2019) 19:679–94. doi: 10.1080/14737175.2019.1623671

74. Camilleri M. Gastrointestinal motility disorders in neurologic disease. *J Clin Invest.* (2021) 131:e143771. doi: 10.1172/JCI143771

75. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke.* (2005) 36:2756–63. doi: 10.1161/01.STR.0000190056.76543.eb

76. Cheng Y, Zan J, Song Y, Yang G, Shang H, Zhao W. Evaluation of intestinal injury, inflammatory response and oxidative stress following intracerebral hemorrhage in mice. *Int J Mol Med.* (2018) 42:2120–8. doi: 10.3892/ijmm.2018.3755

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 03 March 2023
DOI 10.3389/fneur.2023.1103270

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
Raffaele Ornello,
University of L'Aquila, Italy
Hipólito Nzwalo,
University of Algarve, Portugal

*CORRESPONDENCE
Guang-Qin Li
✉ liguangqin@tom.com

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 20 November 2022
ACCEPTED 07 February 2023
PUBLISHED 03 March 2023

CITATION
Tang Y, Liu M-S, Fu C and Li G-Q (2023) Sex-dependent association analysis between serum uric acid and spontaneous hemorrhagic transformation in patients with ischemic stroke. *Front. Neurol.* 14:1103270. doi: 10.3389/fneur.2023.1103270

Sex-dependent association analysis between serum uric acid and spontaneous hemorrhagic transformation in patients with ischemic stroke

Ye Tang, Ming-Su Liu, Chong Fu and Guang-Qin Li*

Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Objective: The association between serum uric acid (UA) and spontaneous hemorrhagic transformation (HT) has been seldom studied, and the role of UA in spontaneous HT remains unclear. This study aims to investigate the sex-dependent association between UA and spontaneous HT in patients with ischemic stroke.

Method: We retrospectively included patients with ischemic stroke in a tertiary academic hospital between December 2016 and May 2020. Patients were included if they presented within 24 h after the onset of symptoms and did not receive reperfusion therapy. Spontaneous HT was determined by an independent evaluation of neuroimaging by three trained neurologists who were blinded to clinical data. A univariate analysis was performed to identify factors related to spontaneous HT. Four logistic regression models were established to adjust each factor and assess the association between UA and spontaneous HT.

Results: A total of 769 patients were enrolled (64.6% were male patients and 3.9% had HT). After adjusting the confounders with a $P < 0.05$ (model A) in the univariate analysis, the ratio of UA and its interquartile range (RUI) was independently associated with spontaneous HT in male patients (OR: 1.85; 95% CI: 1.07–3.19; $P = 0.028$), but not in female patients (OR: 1.39; 95% CI: 0.28–6.82; $P = 0.685$). In models B–D, the results remain consistent with model A after the adjustment for other potential confounders.

Conclusions: Higher serum UA was independently associated with a higher occurrence of spontaneous HT in male patients who were admitted within 24 h after the stroke onset without receiving reperfusion therapy.

KEYWORDS

uric acid, hemorrhagic transformation, reperfusion therapy, admission time, male

Introduction

Spontaneous hemorrhagic transformation (HT) is defined as the blood stain of an infarcted cerebral area formed by the overflow of red blood cells and other blood components from blood vessels to the infarcted brain tissue, which is a part of the natural course of ischemic stroke and a crucial complication of treatment (1). Spontaneous HT occurs in ~13–43% of patients with ischemic stroke, and parenchymal hematoma is a critical factor in poor outcomes (2). Thus, it is important to identify the factors that determine the occurrence of HT. However, the pathophysiological mechanism of spontaneous HT remains uncertain.

Uric acid (UA) is an endogenous antioxidant produced by purine metabolism (3, 4). If the antioxidant substances are abundant, UA will show antioxidant properties. If there are more pro-oxidant substances, it will show pro-oxidant properties (5). In patients with acute ischemic stroke, oxygen free radicals will be produced after tissue ischemia–reperfusion, and UA presents antioxidant or pro-oxidant properties depending on the surrounding substances. It has been demonstrated that the dose–response relationship between UA and HT and higher UA was independently associated with a lower incidence of HT. On the contrary, higher UA levels are reported to be associated with a lower incidence of HT in different settings (6). An examination of UA is widely available in almost all clinical settings. For these reasons, UA may be a protective factor for spontaneous HT. Therefore, the critical clinical significance of the relationship between UA and spontaneous HT is a topic of research interest.

Nevertheless, reperfusion injury and blood–brain barrier damage after infarction are considered the two major causes of spontaneous HT, and the reactive oxygen species (ROS)-mediated oxidative stress response has an important role in these two mechanisms (7). Many studies have explored the role of thrombolysis in HT occurrence (1, 7, 8). Although thrombectomy is not independently associated with spontaneous HT (9), given its mechanism of reperfusion therapy (e.g., thrombolysis or thrombectomy), the restoration of blood flow to the salvageable ischemic brain tissue is consistent with the aforementioned mechanism of spontaneous HT and the high incidence of spontaneous HT found by previous studies (10–12). None of these prior studies assessed spontaneous HT with respect to non-reperfusion strategies.

There is no consensus on the association between UA and spontaneous HT in patients with acute ischemic stroke. Studies of the relationship between UA levels and spontaneous HT are contradictory. Positive and negative in the male population or both positive in men and women have been described (8, 10, 13, 14). Furthermore, Brouns et al. found that UA changed with time in patients with stroke and exhibited a U-shaped curve in general, which decreased within 7 days after the stroke onset and then gradually increased to the baseline value (15). Few studies have explored the impact of UA levels in specific stroke subtypes and treatment strategies in the acute stage. UA levels are sex-dependent and are higher in males. Therefore, a sex-dependent explorative analysis was made using patients with acute ischemic stroke within 24 h after the stroke onset and who did not receive reperfusion therapy (thrombolysis or thrombectomy) after the onset to investigate whether UA was associated with spontaneous HT.

Abbreviations: UA, uric acid; IQR, inter-quartile range; RUI, the ratio of UA and its IQR (RUI = UA/IQR); HT, hemorrhagic transformation; R2, R-square of Hosmer–Lemeshow Test; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke; HbA1c, hemoglobin A1c, eGFR, estimated glomerular filtration rate.

Methods

Population

We retrospectively reviewed the medical records of patients with ischemic stroke admitted to the Department of Neurology, the First Affiliated Hospital of Chongqing Medical University, from December 2016 to May 2020. For this analysis, the patients were included if they: (1) met the diagnostic criteria of acute ischemic stroke (AIS) in the Guidelines for Early Management of Patients With Acute Ischemic Stroke (2019) of the American Heart Association (AHA) (14), (2) were admitted within 24 h from the onset, (3) completed a serum UA test within 24 h after admission, and (4) had an initial neuroimaging scan [computed tomography (CT) scanning or magnetic resonance imaging (MRI)] within 24 h after admission and at least one follow-up neuroimaging scan within 7 days after admission. The exclusion criteria were as follows: (1) patients who received reperfusion therapy (thrombolysis or thrombectomy) after the onset, (2) patients with platelet abnormalities or coagulation dysfunction, (3) patients who received UA-lowering treatment within 1 month before admission, and (4) patients with intracranial arteriovenous malformation or tumor or head trauma. The First Affiliated Hospital of Chongqing Medical University Institutional Review Board approved this study. Written informed consent was obtained from participants or their legal representatives.

Data collection

The clinical data were collected from each patient by two researchers: (1) demographic characteristics, such as age and sex; (2) medical histories, such as the history of smoking, alcohol consumption, hypertension, diabetes, dyslipidemia, and atrial fibrillation (AF); (3) clinical variables, such as National Institute of Health Stroke Scale (NIHSS), the Trial of ORG 10172 in Acute Stroke classification (TOAST), systolic blood pressure (SBP), diastolic blood pressure (DBP), and time from the stroke onset to admission; (4) laboratory tests, such as platelet count, activated partial thromboplastin time, serum UA, estimated glomerular filtration rate (eGFR), serum creatinine, low-density lipoprotein cholesterol (LDL-C), and hemoglobin A1c (HbA1c); (5) radiological characteristics, such as large hemispheric infarction (LHI) and spontaneous HT; and (6) treatment, such as anticoagulants, antiplatelet drugs, antihypertensive drugs, and antidiabetic drugs. Among them, eGFR was calculated by the serum creatinine level according to the formula of the Chronic Kidney Disease Epidemiology Collaboration (16). The cerebral infarct, of size >2/3 of MCA territory, was defined as LHI (17).

Serum UA concentration was tested by the enzymatic method (Roche Cobas C701) or the dry chemistry method (Ortho-Clinical Diagnostics). The diagnosis of spontaneous HT is based on the following criteria: abnormal hyperdensity within the area of low attenuation (CT) or abnormal hypointensity within the identified ischemic area (MRI) (13). The images were evaluated by two neurologists who were blinded to the patient's information. For inconsistent interpretations, the imaging was independently

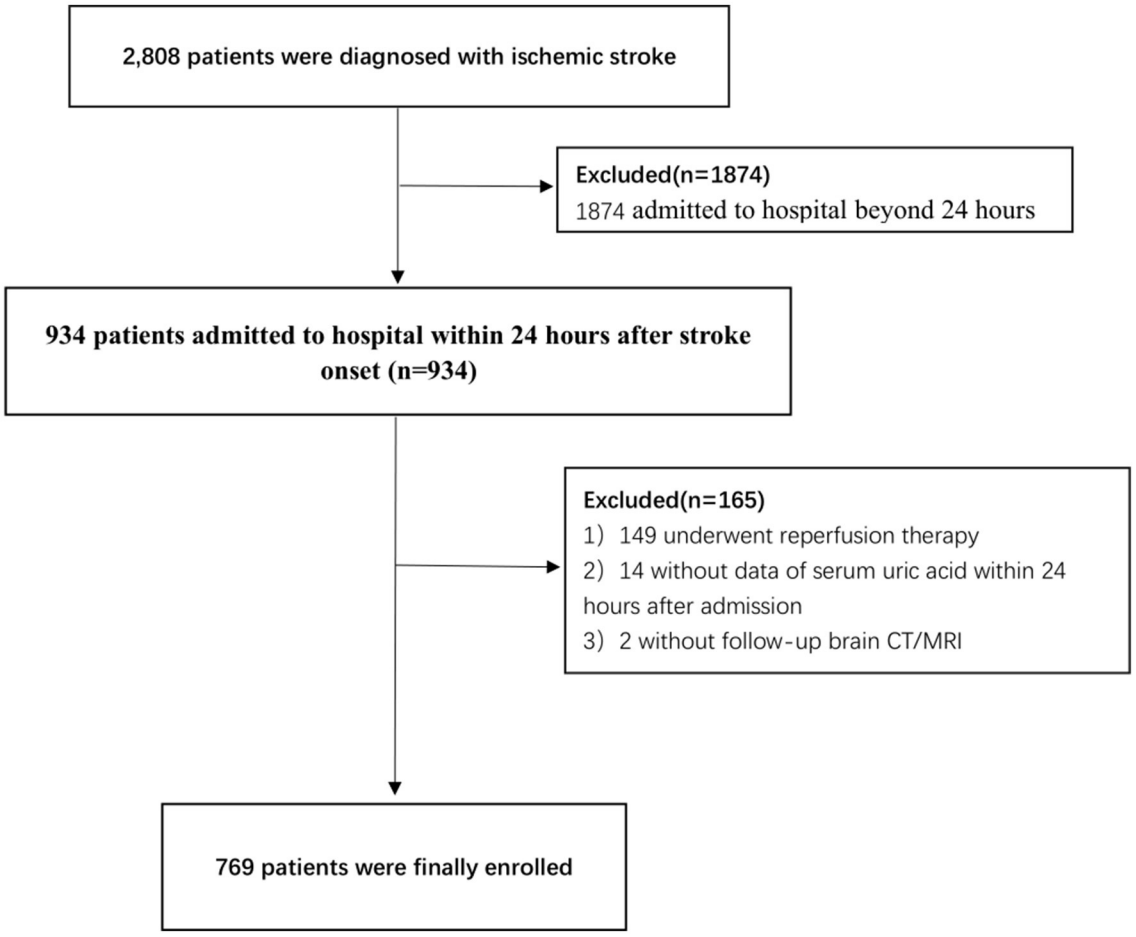


FIGURE 1
Flowchart of patients' selection.

assessed by another senior neurologist, and the final diagnosis was determined on the principle of subordination of the minority to the majority. Furthermore, we classified spontaneous HT into four subtypes [type 1 and 2 hemorrhagic infarction (HI1 and 2) and type 1 and 2 parenchymal hemorrhage (PH1 and 2)] according to the European Cooperative Acute Stroke Study III (ECASS III) (18).

Statistical analysis

Since there is no clinical significance of a 1-unit (1 μmol/L) change in UA in clinical practice, in this study, the ratio of UA and its interquartile range [RUI, male: RUI = (UA of individual male patient)/(IQR of UA in the male group), female: RUI = (UA of individual female patient)/(IQR of UA in the female group)] was used to replace UA in the statistical analysis, for increasing the practicability of the conclusions in clinical diagnosis and treatment. Continuous variables were expressed as the mean and standard deviation, and categorical variables were expressed as frequency and percentage. The comparison of continuous variables between groups was made by performing the *t*-test or Mann–Whitney U-test, whereas the comparison of categorical variables was made by performing the chi-square test or Fisher's exact test. In addition, the factors with a $P < 0.05$ in the univariate analysis and other factors that potentially could affect the study results were included in the subsequent logistic regression analysis. UA levels are lower in female patients, and a sex-dependent association between UA and cardiovascular disease was reported. Therefore, sex-dependent analysis was performed to investigate the impact of UA levels on HT occurrence. In total, four logistic regression models were built, and the association between UA and spontaneous HT was determined by dividing patients into two subgroups of male and female. These variables were chosen based on their known associations with the occurrence of HT, and their demonstrated link to HT in the logistical regression: Model A is adjusted for variables with a $P < 0.05$ in male (or female) patient subgroup univariate analysis; model B is adjusted for variables with a $P < 0.05$ in both subgroup univariate analysis; model C is adjusted for variables in model B, antiplatelet treatment, and anticoagulant treatment; model D is adjusted for variables in model C, smoking, alcohol consumption, systolic blood pressure, and eGFR. A $P < 0.05$ was considered statistically significant. Data analysis of the present study was performed by using SPSS Statistics Software (version 26.0; IBM Corporation) and GraphPad Prism (version 7.0; GraphPad Software Corporation).

10.3389/fneur.2023.1103270

TABLE 1 Baseline characteristics of participants.

Variables	Male ($n = 497$)	Female ($n = 272$)	*P* value
Demographic			
Mean age, y (SD)	65.0 (12.4)	70.3 (12.0)	<0.001
Medical history			
Alcohol consumption, *n* (%)	251 (50.5%)	9 (3.3%)	<0.001
Smoking, *n* (%)	353 (71%)	13 (4.8%)	<0.001
Hypertension, *n* (%)	361 (72.6%)	199 (73.2%)	0.875
Diabetes mellitus, *n* (%)	152 (30.6%)	83 (30.5%)	0.984
Dyslipidemia, *n* (%)	97 (19.5%)	46 (16.9%)	0.375
Atrial fibrillation, *n* (%)	57 (11.5%)	47 (17.3%)	0.024
Clinical features			
Time from onset to Admission, h (SD)	14.1 (8.5)	14.0 (8.5)	0.584
Systolic blood pressure, mmHg (SD)	151.8 (23.7)	154.0 (24.4)	0.233
Diastolic blood pressure, mmHg (SD)	88.3 (16.1)	86.4 (14.5)	0.103
Admission NIHSS score, mean (SD)	4.6 (5.0)	5.0 (4.9)	0.404
TOAST classification, n (%)			0.038
Large-artery atherosclerosis	234 (47.1%)	110 (40.4%)	0.077
Small-artery occlusion	191 (38.4%)	100 (36.8%)	0.649
Cardio-embolism	53 (10.7%)	46 (16.9%)	0.013
Undetermined etiology	15 (3.0%)	10 (3.7%)	0.623
Other etiology	4 (0.8%)	6 (2.2%)	0.179
Laboratorial index			
Platelet count, $*10^9$/L (SD)	193.6 (75.8)	198.9 (65.7)	0.354
APTT, s (SD)	26.1 (4.9)	25.9 (7.9)	0.808
Serum UA, μmol/L (SD)	362.8 (96.0)	304.8 (87.5)	<0.001
RUI, mean (SD)	3.2 (0.8)	2.7 (0.8)	<0.001
Serum creatinine, μmol/L (SD)	82.6 (32.8)	65.2 (20.1)	<0.001
eGFR, mL/min/1.73 m^2, (SD)	86.1 (21.0)	82.2 (19.4)	0.012
HbA1c, %, (SD)	6.8 (1.6)	6.8 (1.9)	0.556
LDL-C, μmol/L (SD)	2.9 (1.1)	3.0 (1.8)	0.148
Radiological characteristics			
Spontaneous HT, *n* (%)	18 (3.6%)	12 (4.4%)	0.589
Large hemispheric infarction, *n* (%)	60 (12.1%)	25 (9.2%)	0.223
Treatment			
Antiplatelet, *n* (%)	486 (97.8%)	253 (93.0%)	0.001
Anticoagulant, *n* (%)	45 (9.1%)	49 (18.0%)	<0.001
Antihypertensive, *n* (%)	272 (54.7%)	135 (49.6%)	0.176
Antidiabetic, *n* (%)	140 (28.2%)	72 (26.5%)	0.614

HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke; APTT, activated partial thromboplastin time; UA, uric acid; IQR, inter-quartile range; RUI, the ratio of UA and its IQR (RUI=UA/IQR); eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Results

A total of 769 patients were finally included in this study (Figure 1), of whom 64.6% were male patients, with a mean age of (66.9 ± 12.5) years and 30 (3.9%) had spontaneous HT. In this study, 70% of spontaneous HT was diagnosed by CT, 30% of spontaneous HT was diagnosed by MRI (T2WI and T1WI), 13.3% of patients with spontaneous HT performed SWI, and the result of SWI supports the diagnosis of CT/MRI. No patient with spontaneous HT was diagnosed by SWI alone. Among patients with spontaneous HT, one (3.3%) patient with PH2, seven (23.3%) patients with PH1, 13 (43.3%) patients with HI2, and nine (30.0%) patients with HI1 were identified. Compared with female patients, the male patients had a higher UA level (362.8 ± 96.0 vs. 304.8 ± 87.5, respectively; $P < 0.001$), RUI (3.2 ± 0.8 vs. 2.7 ± 0.8, respectively; $P < 0.001$), drinking, smoking, creatinine level, and eGFR and antiplatelet drug use rate. Female patients were older (70.3 ± 12.0 vs. 65.0 ± 12.4, respectively, $P < 0.001$) and have higher occurrences of AF (17.3 vs. 11.5%, respectively, $P = 0.024$) and anticoagulant use than those of men (Table 1).

The male patients with spontaneous HT tended to have higher UA levels (428.3 ± 124.5 vs. 360.3 ± 94.0, respectively, P =0.003), RUI (3.7 ± 1.1 vs. 3.1± 0.8, respectively, $P = 0.003$), age, admission NIHSS score, higher occurrence of AF and LHI, and shorter time from the onset to admission compared to patients without. However, there was no significant association between UA/RUI and spontaneous HT in the female patients ($P = 0.336$) (Table 2).

After adjustment for factors with a $P < 0.05$ (model A) in the univariate analysis of each group by logistic regression, the ratio of UA/IQR was found to be independently associated with spontaneous HT in male patients (OR: 1.85; 95% CI: 1.07–3.19; $P = 0.028$), but not in female patients (OR: 1.39; 95% CI: 0.28–6.82; $P = 0.685$). Furthermore, in the other three multivariate logistic regression models, the statistical results were consistent with model A after being adjusted for the factors with a $P < 0.05$ in the univariate analyses of both subgroups (model B), anticoagulant use and antiplatelet drug (model C), and smoking, alcohol consumption, SBP, and eGFR (model D) (Figure 2).

Discussion

In this study, the RUI was independently associated with spontaneous HT in male patients admitted within 24 h after the onset, and the incidence of spontaneous HT increased by 85.0% for each IQR increase in the UA level. Interestingly, no similar association between the UA level and spontaneous HT was found in female patients.

Furthermore, we reported that UA levels were associated with spontaneous HT in male patients with acute ischemic stroke. However, this association was not found in female patients. UA levels are commonly available in medical settings, and the results of our study suggested that UA may be a potential target for interventions. Several previous studies have investigated the sex differences of UA in patients with cerebrovascular diseases (19, 20). Recently, a similar study reported that the incidence of spontaneous

10.3389/fneur.2023.1103270

TABLE 2 Univariate analysis to identify risk factors of spontaneous HT.

Variables	Male ($n = 497$)			Female ($n = 272$)		
	With HT	Without HT	*P* value	With HT	Without HT	*P* value
Demographic						
Mean age, y (SD)	71.3 (13.8)	64.8 (12.3)	0.028	73.5 (14.5)	70.2 (11.9)	0.451
Medical history						
Alcohol consumption, *n* (%)	10 (55.6%)	241 (50.3%)	0.662	0 (0.0%)	9 (3.5%)	1.000
Smoking, *n* (%)	13 (72.2%)	340 (71.0%)	0.909	0 (0.0%)	13 (5.0%)	1.000
Hypertension, *n* (%)	14 (77.8%)	347 (72.4%)	0.790	9 (75.0%)	190 (73.1%)	1.000
Diabetes mellitus, *n* (%)	9 (50.0%)	143 (29.9%)	0.690	4 (33.3%)	79 (30.4%)	0.760
Dyslipidemia, *n* (%)	6 (33.3%)	91 (19.0%)	0.136	2 (16.7%)	44 (16.9%)	1.000
Atrial fibrillation, *n* (%)	6 (33.3%)	51 (10.6%)	0.011	8 (66.7%)	39 (15.0%)	<0.001
Clinical features						
Time from onset to admission, h (SD)	8.5 (8.0)	14.3 (8.5)	0.007	9.8 (9.2)	14.1 (8.4)	0.082
Systolic blood pressure, mmHg (SD)	148.8 (22.5)	151.9 (23.8)	0.586	161.7 (29.9)	153.6 (24.1)	0.265
Diastolic blood pressure, mmHg (SD)	83.9 (13.3)	88.5 (16.1)	0.236	85.9 (11.1)	86.4 (14.7)	0.901
Admission NIHSS score, mean (SD)	11.8 (8.1)	4.4 (4.6)	0.001	10.3 (6.8)	4.7 (4.7)	0.015
TOAST classification, *n* (%)			<0.001			0.023
Large-artery atherosclerosis	9 (50.0%)	225 (47.0%)	0.801	8 (66.7%)	102 (39.2%)	0.073
Small-artery occlusion	0 (0.0%)	191 (39.9%)	0.001	0 (0.0%)	100 (38.5%)	0.005
Cardio-embolism	7 (38.9%)	46 (9.6%)	0.001	4 (33.3%)	42 (16.2%)	0.126
Undetermined etiology	2 (11.1%)	13 (2.7%)	0.098	0 (0.0%)	10 (3.8%)	1.000
Other etiology	0 (0.0%)	4 (0.8%)	1.000	0 (0.0%)	6 (2.3%)	1.000
Laboratorial index						
Platelet count, $*10^9$/L (SD)	179.7 (70.6)	194.2 (76.0)	0.438	178.5 (72.4)	199.8 (65.4)	0.294
APTT, s (SD)	25.7 (3.5)	26.02 (4.9)	0.795	27.0 (5.2)	25.9 (8.0)	0.662
Serum UA, μmol/L (SD)	428.3 (124.5)	360.3 (94.0)	0.003	328.6 (57.5)	303.7 (88.6)	0.336
RUI, mean (SD)	3.7 (1.1)	3.1 (0.8)	0.003	2.9 (0.5)	2.7 (0.8)	0.336
Serum creatinine, μmol/L(SD)	88.9 (36.6)	82.3 (32.7)	0.401	68.6 (16.6)	65.0 (20.9)	0.550
eGFR, mL/min/1.73 m^2, (SD)	77.7 (25.7)	86.4 (20.8)	0.086	76.7 (18.6)	82.4 (19.4)	0.320
HbA1c, %,(SD)	7.2 (2.3)	6.7 (1.6)	0.158	5.6 (2.1)	6,8 (1.9)	0.050
LDL-C, μmol/L (SD)	2.7 (0.8)	2.9 (1.1)	0.597	3.1 (1.1)	3.0 (1.8)	0.860
Radiological characteristics						
Large hemispheric infarction, *n* (%)	10 (55.6%)	50 (10.4%)	<0.001	9 (75%)	16 (6.2%)	<0.001
Treatment						
Antiplatelet, *n* (%)	18 (100%)	468 (97.7%)	1.000	10 (83.3%)	243 (93.5%)	0.201
Anticoagulant, *n* (%)	4 (22.2%)	41 (8.6%)	0.700	1 (8.3%)	48 (18.5%)	0.700
Antihypertensive, *n* (%)	8 (44.4%)	264 (55.1%)	0.372	4 (33.3%)	131 (50.4%)	0.248
Antidiabetic, *n* (%)	8 (44.4%)	132 (27.6%)	0.118	4 (33.3%)	68 (26.2%)	0.524

NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke; APTT, activated partial thromboplastin time; UA, uric acid; IQR, inter-quartile range; RUI, the ratio of UA and its IQR (RUI=UA/IQR); eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein cholesterol; SD, standard deviation.

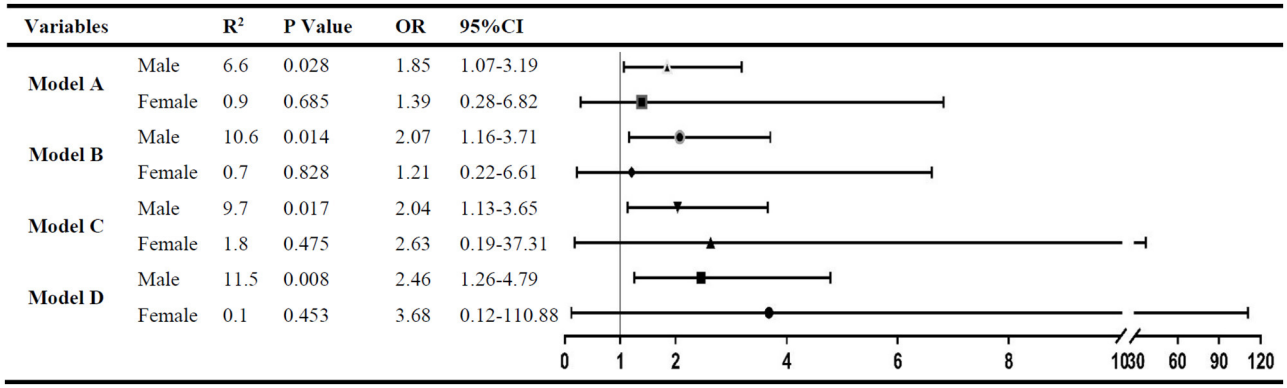


FIGURE 2
The multivariate analysis to identify the association between RUI and spontaneous HT. Variables adjusted in logistic regression models: Model A. Factors with a $P < 0.05$ in male (or female) subgroup univariate analysis were included; model B: factors with a $P < 0.05$ in both subgroup univariate analysis were included; model C: variables in model B plus antiplatelet treatment and anticoagulant treatment; and model D: variables in model C plus smoking, alcohol consumption, systolic blood pressure, and eGFR.

HT was higher in patients with low UA levels than in patients with high UA levels (13). They included 1,230 patients who received reperfusion therapy within 7 days from the onset of the symptoms. However, in the context of our study, this finding was not confirmed. The reason for these contradictory results may partly be due to inclusion criteria. Moreover, it has been proven that the UA level of patients with stroke decreased gradually within 7 days after the onset, but there was no significant difference between the UA level measured 24 h after admission (15). This also may reflex the dual effect of UA. In a cross-sectional study of 2,686 patients, Jeong et al. reported that a high UA level was a risk factor for cerebral microbleeds only in male patients (19), and we confirmed and extended this finding in our study. Further studies are needed to explore whether these patients are potential candidates for interventions.

In previous studies, reperfusion treatment is one of the mechanisms of spontaneous HT, subsequently affecting the outcome. Previous studies regarding the relationship between UA and spontaneous HT have shown conflicting results in the thrombolysis population and non-thrombolysis group. Thrombectomy, the restoration of blood flow to the salvageable ischemic brain tissue, is consistent with the aforementioned mechanism of spontaneous HT, and a higher incidence of spontaneous HT was reported in previous studies. The reason for these contradictory results may partly be due to the modifying effect of reperfusion strategies on spontaneous HT in these studies. Thus, we excluded those patients from this study.

The exact underlying mechanism of UA levels on spontaneous HT remains unknown. Generally, UA is an abundant antioxidant in humans and is supposed to play a protective role in cardio-cerebral vascular diseases. The possible explanation of sex-dependent differences in UA levels on spontaneous HT was the uricosuric effect of estrogen (21), the inhibition of oxidative stress of blood vessels by estrogen (22), and the redox shuttle mechanism of UA (23). These three factors result in higher UA and lower antioxidant capacity in male patients than in female patients. In addition, UA is more effective in promoting oxidation in an environment with relatively lower-antioxidative substances. Therefore, the stronger oxidation-promoting property of UA in male patients may be responsible for the sex difference in the occurrence of spontaneous HT. However, the opposite result has been found in many large-scale clinical studies (24–26). A literature review revealed that UA, which carries over half of the antioxidant capacity in plasma, may be involved in spontaneous HT through oxidative stress (4). This involvement can be partly explained by the following reasons: first, the production of UA by xanthine oxidase itself produces oxygen free radicals (27) and second, more oxygen free radicals will be produced after ischemia–reperfusion (5). UA has a redox shuttle effect in which the presentation of the antioxidant or pro-oxidant properties of UA depends on the surrounding environment. Specifically, antioxidant activity occurs when antioxidant substances are abundant, and pro-oxidant activity occurs if there are more pro-oxidants (23). In the environment of more oxygen free radicals in the ischemia–reperfusion tissue, UA tends to be pro-oxidative. Therefore, UA may further aggravate oxidative stress and increase blood–brain barrier damage through the aforementioned mechanisms, which leads to spontaneous HT.

It should be noted that our study had some limitations. First, it was a single-center retrospective study with a relatively small sample size. The impact of UA on spontaneous HT seems to be limited in the sex-specific subgroups, and this clinical relevance may not be generalizable to patients with reperfusion treatment. In addition, a multicenter prospective study with a large sample size is required to further confirm and explore the association between UA and the subtypes of HT. Second, UA levels have been found to change over time in patients with stroke (15), whereas our study enrolled patients admitted to the hospital within 24 h after the stroke onset only. Hence, there will be a limited scope of application in terms of the findings in our study. In addition, our study retrospectively explained the association between the single UA level and spontaneous HT at admission, so it is still necessary to further clarify such a relationship by dynamical examination of the UA level in a prospective study.

Conclusion

In conclusion, among the non-reperfusion patients with acute ischemic stroke within 24 h after admission, the level of UA was independently and positively associated with the occurrence of spontaneous HT in male patients. More prospective research is needed to confirm these results.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Board of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YT and M-SL: study concept and design. YT, M-SL, and CF: acquisition of data. YT: statistical analysis and drafting of the manuscript. G-QL: critical revision of the manuscript for important intellectual content and study supervision. Analysis and interpretation of data were done by all authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Álvarez-Sabín J, Maisterra O, Santamarina E, Kase CS. Factors influencing haemorrhagic transformation in ischaemic stroke. *Lancet Neurol.* (2013) 12:689–705. doi: 10.1016/S1474-4422(13)70055-3

2. Zhang J, Yang Y, Sun H, Xing Y. Hemorrhagic transformation after cerebral infarction: current concepts and challenges. *Ann Transl Med.* (2014) 2:81. doi: 10.3978/j.issn.2305-5839.2014.08.08

3. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. *Arch Biochem Biophys.* (2000) 376:333–7. doi: 10.1006/abbi.2000.1721

4. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci U S A.* (1981) 78:6858–62. doi: 10.1073/pnas.78.11.6858

5. Vassalle C, Mazzone A, Sabatino L, Carpeggiani C. Uric acid for cardiovascular risk: Dr. Jekyll or Mr. Hide? *Diseases.* (2016) 4:12. doi: 10.3390/diseases4010012

6. Chen Z, Chen H, Zhang Y, He Y, Su Y. Lower uric acid level may be associated with hemorrhagic transformation, but not functional outcomes in patients with anterior circulation acute ischemic stroke undergoing endovascular thrombectomy. *Metab Brain Dis.* (2020) 35:1157–64. doi: 10.1007/s11011-020-00601-7

7. Jickling GC, Liu D, Stamova B, Ander BP, Zhan X, Lu A, et al. Hemorrhagic transformation after ischemic stroke in animals and humans. *J Cereb Blood Flow Metab.* (2014) 34:185–99. doi: 10.1038/jcbfm.2013.203

8. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet.* (2004) 363:768–74. doi: 10.1016/S0140-6736(04)15692-4

9. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X

10. Hao Y, Yang D, Wang H, Zi W, Zhang M, Geng Y, et al. Predictors for symptomatic intracranial hemorrhage after endovascular treatment of acute ischemic stroke. *Stroke.* (2017) 48:1203–9. doi: 10.1161/STROKEAHA.116.016368

11. Jovin TG, Li C, Wu L, Wu C, Chen J, Jiang C, et al. BAOCHE investigators. Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. *N Engl J Med.* (2022) 387:1373–84. doi: 10.1056/NEJMoa2207576

12. Tao C, Nogueira RG, Zhu Y, Sun J, Han H, Yuan G, et al. ATTENTION investigators. Trial of endovascular treatment of acute basilar-artery occlusion. *N Engl J Med.* (2022) 387:1361–72. doi: 10.1056/NEJMoa2206317

13. Chen G, Wang A, Zhao X, Wang C, Liu L, Zheng H, et al. Frequency and risk factors of spontaneous hemorrhagic transformation following ischemic stroke on the initial brain CT or MRI: data from the China National Stroke Registry (CNSR). *Neurol Res.* (2016) 38:538–44. doi: 10.1080/01616412.2016.1187864

14. Song Q, Wang Y, Cheng Y, Liu J, Wei C, Liu M. Serum uric acid and risk of hemorrhagic transformation in patients with acute ischemic stroke. *J Mol Neurosci.* (2020) 70:94–101. doi: 10.1007/s12031-019-01404-x

15. Brouns R, Wauters A, Van De Vijver G, De Surgeloose D, Sheorajpanday R, De Deyn PP. Decrease in uric acid in acute ischemic stroke correlates with stroke severity, evolution and outcome. *Clin Chem Lab Med.* (2010) 48:383–90. doi: 10.1515/CCLM.2010.065

16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF. 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* (2009) 150:604–12. doi: 10.7326/0003-4819-150-9-200905050-00006

17. Torbey MT, Bösel J, Rhoney DH, Rincon F, Staykov D, Amar AP, et al. Evidence-based guidelines for the management of large hemispheric infarction: a statement for health care professionals from the Neurocritical Care Society and the German Society for Neuro-intensive Care and Emergency Medicine. *Neurocrit Care.* (2015) 22:146–64. doi: 10.1007/s12028-014-0085-6

18. Kissela BM, Flaherty ML. Alwell K, Moomaw CJ, et al. Eligibility for intravenous recombinant tissue-type plasminogen activator within a population: the effect of the European Cooperative Acute Stroke Study (ECASS) III. *Trial Stroke.* (2012) 43:1591–5. doi: 10.1161/STROKEAHA.111.645986

19. Jeong SM, Yoo TG, Nam YS, Kim SH, Lee JE, Kim S, et al. Sex-dependent effects of uric acid on cerebral microbleed: a cross-sectional study in the general population. *Eur J Neurol.* (2017) 24:1300–6. doi: 10.1111/ene.13378

20. Chen LH, Zhong C, Xu T, Xu T, Peng Y, Wang A, et al. Sex-specific association between uric acid and outcomes after acute ischemic stroke: a prospective study from CATIS. *Trial Sci Rep.* (2016) 6:38351. doi: 10.1038/srep38351

21. Quiñones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, et al. Effect of insulin on uric acid excretion in humans. *Am J Physiol.* (1995) 268:E1–5. doi: 10.1152/ajpendo.1995.268.1.E1

22. Miller AA, De Silva TM, Jackman KA, Sobey CG. Effect of gender and sex hormones on vascular oxidative stress. *Clin Exp Pharmacol Physiol.* (2007) 34:1037–43. doi: 10.1111/j.1440-1681.2007.04732.x

23. Hayden MR, Tyagi SC. Uric acid: a new look at an old risk marker for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus: the urate redox shuttle. *Nutr Metab (Lond).* (2004) 1:10. doi: 10.1186/1743-7075-1-10

24. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National health and nutrition examination Survey. *JAMA.* (2000) 283:2404–10. doi: 10.1001/jama.283.18.2404

25. Gerber Y, Tanne D, Medalie JH, Goldbourt U. Serum uric acid and long-term mortality from stroke, coronary heart disease and all causes. *Eur J Cardiovasc Prev Rehabil.* (2006) 13:193–8. doi: 10.1097/01.hjr.0000192745.26973.00

26. Storhaug HM, Norvik JV, Toft I, Eriksen BO, Løchen ML, Zykova S, et al. Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromsø Study. *BMC Cardiovasc Disord.* (2013) 13:115. doi: 10.1186/1471-2261-13-115

27. Zweier JL, Kuppusamy P, Lutty GA. Measurement of endothelial cell free radical generation: evidence for a central mechanism of free radical injury in postischemic tissues. *Proc Natl Acad Sci U S A.* (1988) 85:4046–50. doi: 10.1073/pnas.85.11.4046

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 20 March 2023
DOI 10.3389/fneur.2023.1142084

OPEN ACCESS

EDITED BY
Cheong-Meng Chong,
University of Macau, China

REVIEWED BY
Giovanni Merlino,
Udine University Hospital, Italy
Klára Fekete,
University of Debrecen, Hungary

*CORRESPONDENCE
Jinping Zhang
✉ zjp16500@163.com
Yun Xu
✉ xuyun20042001@aliyun.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 11 January 2023
ACCEPTED 27 February 2023
PUBLISHED 20 March 2023

CITATION
Shao T, Liu H, Yang G, Wang H, Li D, Ni H, Xu Y and Zhang J (2023) Fasting blood glucose-to-glycated hemoglobin ratio for evaluating clinical outcomes in patients with ischemic stroke. *Front. Neurol.* 14:1142084. doi: 10.3389/fneur.2023.1142084

Fasting blood glucose-to-glycated hemoglobin ratio for evaluating clinical outcomes in patients with ischemic stroke

Tengfei Shao[1†], Hui Liu[1,2†], Guochao Yang[3], Huan Wang[4], Di Li[5], Huanyu Ni[1], Yun Xu[6*] and Jinping Zhang[1,2*]

[1]Department of Pharmacy, Affiliated Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China, [2]China Pharmaceutical University Nanjing Drum Tower Hospital, Nanjing, Jiangsu, China, [3]Ministry of Education (MOE) Key Laboratory of Model Animal for Disease Study, Model Animal Research Center, Jiangsu Key Laboratory of Molecular Medicine, Medical School, Nanjing University, Nanjing, Jiangsu, China, [4]Department of Pharmacy, Wuhan Fourth Hospital, Wuhan, Hubei, China, [5]Department of Pharmacy, Wuhan No. 1 Hospital, Wuhan, Hubei, China, [6]Department of Neurology, Affiliated Drum Tower Hospital, Nanjing University Medical School, Nanjing, Jiangsu, China

Background: Stress hyperglycemia frequently occurs in patients with acute ischemic stroke (AIS). The influence of stress hyperglycemia on the outcomes of patients with AIS remains ambiguous.

Methods: Data from our institution on patients with AIS between June 2020 and June 2021 were retrospectively analyzed. The severity of the stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS) at admission, and the primary endpoint was functional outcomes. Stress hyperglycemia was measured by the glucose-to-HbA1c ratio. In the multivariable analysis, two models that retained or excluded the NIHSS were adopted to explore the relationship between stress hyperglycemia and outcomes. The receiver operating characteristic curve (ROC) was calculated to determine an optimized cutoff value.

Results: The optimal cutoff value was 1.135. When all patients were included, model 1 did not find an association between the glucose-to-HbA1c ratio and functional outcomes. In model 2, the glucose-to-HbA1c ratio$^{\times 10}$ (Glucose-to-HbA1c ratio $\times 10$) was the independent predictor of functional outcomes (OR 1.19, 95% CI 1.07–1.33, $p < 0.01$). Separately, in patients without diabetes, the glucose-to-HbA1c ratio$^{\times 10}$ was the independent predictor of functional outcomes in both model 1 (OR 1.37, 95% CI 1.08–1.73, $p = 0.01$) and model 2 (OR 1.48, 95% CI 1.22–1.79, $p < 0.01$), but not in patients with diabetes. In addition, the glucose-to-HbA1c ratio$^{\times 10}$ was the independent predictor of stroke severity (OR 1.16, 95% CI 1.05–1.28, $p < 0.01$).

Conclusion: The glucose-to-HbA1c ratio was associated with more severe AIS. Specifically, the glucose-to-HbA1c ratio was associated with the functional outcomes in patients without diabetes but not in patients with diabetes.

KEYWORDS

stress hyperglycemia, acute ischemic stroke, clinical outcomes, fasting blood glucose, glycated hemoglobin

Introduction

Stress hyperglycemia is regarded as transient hyperglycemia secondary to inflammatory and neurohormonal disturbances in the context of acute illnesses (1–3). To our knowledge, the relationship between stress hyperglycemia and clinical outcomes has been studied in patients with AIS (4) and those with cardiovascular disease (5). In addition, studies have shown that stress hyperglycemia in patients with myocardial infarction is associated with an increased risk of in-hospital mortality, whether or not patients have diabetes (5). Stress hyperglycemia is frequently observed in patients with AIS (6), whether or not they have diabetes. Previous studies focused on patients without diabetes (7) or only considered fasting blood glucose (FBG) (8). Therefore, the relationship between stress hyperglycemia and clinical outcomes after AIS in patients with or without diabetes has not been well characterized.

Recently, an increasing number of studies have focused on the role of background blood glucose in assessing stress hyperglycemia. According to Roberts et al. (1), the stress hyperglycemia ratio (SHR), a novel index, can be used for accessing stress hyperglycemia. It was defined as admission blood glucose divided by the estimated mean blood glucose derived from glycated hemoglobin (HbA1c). Furthermore, considering HbA1c is a well-validated index that reflects the background blood glucose levels over the past 8–12 weeks (9) and that FBG is a more recognized index of the current blood glucose level, several studies have begun to use the FBG/HbA1c ratio to assess relative hyperglycemia, which is calculated by dividing FBG by HbA1c (7, 10, 11). Therefore, this calculation formula is convenient, practical, and reasonable.

Using this easy-to-perform method to identify and quantify stress hyperglycemia, our study explored the relationship between stress hyperglycemia and clinical outcomes in patients with AIS.

Methods

Study participants

A total of 283 patients with a clinical diagnosis of AIS derived from our institution between June 2020 and June 2021 were finally enrolled. AIS was diagnosed according to the World Health Organization criteria (12) and confirmed by brain computerized tomography (CT) or magnetic resonance imaging (MRI). The severity of the stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS) (13) by trained neurologists at admission. The severity of the stroke was classified as mild stroke (NIHSS score $\leq$4 at admission) and moderate-to-severe stroke (NIHSS score>4 at admission). Stroke types were classified as large-artery atherosclerosis, cardioembolic, small vessel disease, and others or undetermined.

Patients were eligible for the study if they were >18 years old, were admitted within 7 days after the occurrence of the stroke, underwent routine laboratory investigations after an overnight fast on the first day after admission, underwent MRI or CT, and had the diagnosis of AIS confirmed after admission. Patients were excluded from the study if they had incomplete clinical data or a premorbid mRS score of >1.

Data collection

The clinical data and baseline demographics of patients were consecutively collected through an electronic medical record system. All enrolled patients received routine therapy and nursing care according to their conditions.

Assessment of stress hyperglycemia

Stress hyperglycemia was evaluated by the glucose-to-HbA1c ratio. We used the following formula to calculate the glucose-to-HbA1c ratio: FPG (mmol/L)/HbA1c (%). This index reflected the extent of increase in acute blood glucose level based on the background blood glucose level.

Follow-up and outcomes

All patients completed a 12-month follow-up. During the follow-up period, outcomes were recorded using our hospital's electronic medical record system or through a telephone interview. Functional outcomes were measured using the mRS score at 1 year. A score of 3–6 was defined as a poor functional outcome. Patients' stroke recurrence and all-cause death were also recorded as clinical outcomes.

Statistical analysis

Independent sample *t*-tests or the Mann-Whitney U-test were used for continuous variables, and the chi-squared test or Fisher's exact test was used for binary variables to perform univariable analyses as appropriate. The receiver operating characteristic curve (ROC) was used to determine an optimized cutoff value for the glucose-to-HbA1c ratio in predicting poor functional outcomes. According to the optimized cutoff, the characteristics of patients with high and low glucose-to-HbA1c ratios were compared.

Univariable analysis variables with significant effects were included in the multivariable regression analysis for further analysis to identify independent predictors of poor functional outcome, stroke recurrence, and stroke severity. To explore whether stress hyperglycemia was related to stroke severity, the two models that retained or excluded the NIHSS score in the multivariable analysis were adopted. The patients were also divided into three groups: those with diabetes, those without diabetes, and all patients. All results were reported using 95% CIs. A p-value of < 0.05 (two-sided) was considered statistically significant. All data were analyzed using the statistical package SPSS (version 23.0; SPSS, Chicago, IL, USA). The study protocol was compliant with the Declaration of Helsinki and was approved by the ethical committee of our institution; individual informed consent was not required. The study was registered in the Chinese Clinical Trial Register (ChiCTR-ROC-17012225).

Results

Participant characteristics

A total of 283 patients with AIS were finally included in our study, with a median age of 65 years, and 196 (69.2%) of them were men. The baseline demographic and disease characteristics of participants are shown in Table 1. The flowchart of the study is displayed in Figure 1.

Characteristics of the patients according to the glucose-to-HbA1c ratio

The ROC curve analysis was employed to determine the predicted value of the glucose-to-HbA1c ratio. The optimal cutoff derived from the glucose-to-HbA1c ratio was 1.135, which helped to predict poor functional outcomes in patients with AIS (area under the curve 0.601, 95% CI 0.53–0.67, $p < 0.01$), with 50% sensitivity and 70.2% specificity (Figure 2).

Patients with a higher glucose-to-HbA1c ratio tended to have higher NIHSS scores at admission [3 (1–10) vs. 2 (1–4), $p = 0.02$]. Furthermore, patients with a higher glucose-to-HbA1c ratio were related to an increased risk of poor functional outcomes and mortality at the end of 12 months of follow-up [44.7 vs. 24.4%, $p < 0.01$, 6.8 vs. 1.7%, $p = 0.03$, respectively). However, there was no significant difference in stroke recurrence between the high and low glucose-to-HbA1c ratio groups [8.7 vs. 11.7%, $p = 0.44$] (Table 1).

We did not observe any significant difference regarding stroke etiology between the two groups ($p = 0.55$). In terms of previous drugs, patients in the low glucose-to-HbA1c ratio group had a history of a higher statin usage rate [24.4 vs. 10.7%, $p < 0.01$] (Table 1).

The associations between glucose-to-HbA1c ratio and poor functional outcomes in patients with or without diabetes

A total of 90 patients had poor functional outcomes at 12 months, including 34 in the diabetes group and 56 in the patients without diabetes (Supplementary Table 1). When all patients were included, the multivariable logistic regression analysis (model 1) found that independent predictors of poor functional outcomes were age (OR 1.05, 95% CI 1.01–1.08, $p = 0.02$), NIHSS score at admission (OR 1.30, 95% CI 1.19–1.42, $p < 0.01$), atrial fibrillation (OR 4.10, 95% CI 1.18–14.28, $p = 0.03$), SBP (OR 1.03, 95% CI 1.01–1.05, $p < 0.01$), and DBP (OR 0.96, 95% CI 0.93–0.99, $p = 0.02$). When the NIHSS score at admission was removed from the multivariable model (model 2), independent predictors of poor functional outcomes were atrial fibrillation (OR 4.49, 95% CI 1.43–14.14, $p = 0.01$), SBP (OR 1.03, 95% CI 1.01–1.05, $p < 0.01$), DBP (OR 0.95, 95% CI 0.92–0.98, $p < 0.01$), and glucose-to-HbA1c ratio$^{\times 10}$ (OR 1.19, 95% CI 1.07–1.33, $p < 0.01$) (Table 2).

In patients with diabetes, we did not observe a relationship between the glucose-to-HbA1c ratio and poor functional outcomes. However, in patients without diabetes, the glucose-to-HbA1c ratio$^{\times 10}$ was the independent predictor in both model 1 (OR 1.37, 95% CI 1.08–1.73, $p = 0.01$) and model 2 (OR 1.48, 95% CI 1.22–1.79, $p < 0.01$) (Table 2).

The associations between glucose-to-HbA1c ratio and stroke recurrence

In total, 30 patients underwent stroke recurrence during the 12 months of follow-up. There was no difference in the glucose-to-HbA1c ratio between the stroke recurrence and nonrecurrence groups (Supplementary Table 2). In multivariable logistic regression analysis, the glucose-to-HbA1c ratio had no relationship with stroke recurrence (Supplementary Tables 2, 3).

The associations between glucose-to-HbA1c ratio and stroke severity at admission

The patients were divided into two groups according to the NIHSS score at admission as follows: mild stroke was defined as an NIHSS score ≤4 and moderate-to-severe stroke was defined as an NIHSS score >4. A total of 83 patients had a moderate-to-severe stroke at admission (Supplementary Table 4). The glucose-to-HbA1c ratio$^{\times 10}$ was related to an increased risk of more severe stroke (OR 1.16, 95% CI 1.05–1.28, $p < 0.01$). In addition, cardioembolic was also associated with a more severe stroke (OR 4.02, 95% CI 1.23–13.21, $p = 0.02$) (Table 3).

Discussion

In this study, we explored the relationship between the glucose-to-HbA1c ratio and the clinical outcomes in patients with AIS. The major findings of the present study were as follows: Stress hyperglycemia, *via* the glucose-to-HbA1c ratio, was related to poor functional outcomes in patients without diabetes but not in patients with diabetes. In addition, regardless of whether patients had diabetes or not, the glucose-to-HbA1c ratio was significantly associated with poor functional outcomes only in model 2, that is, a multivariable analysis excluding NIHSS score at admission. Through analyzing the severity of stroke at admission, we found that the glucose-to-HbA1c ratio was an independent predictor for moderate-to-severe stroke at admission. The association between stress hyperglycemia and poor outcomes tended to be attributed to higher stroke severity in patients with stress hyperglycemia.

Although a range of evidence suggests that stress hyperglycemia is a marker of poor outcomes in patients with AIS (14–21), this relationship is controversial when stroke severity is considered in further analysis (8). However, a recent meta-analysis found that stress hyperglycemia could reflect the extent of ischemic damage and lead to poor clinical outcomes in patients with stroke (22). This finding was consistent with part of our results that stress hyperglycemia is more common in patients with severe

TABLE 1 Comparison of low-stress hyperglycemia ratio (glucose-to-HbA1c ratio <1.135) vs. high-stress hyperglycemia ratio (glucose-to-HbA1c ≥ 1.135) in patients with acute ischemic stroke.

	ALL ($N = 283$)	Low Glucose-to-HbA1c ratio ($N = 180$)	High Glucose-to-HbA1c ratio ($N = 103$)	$P^{\#}$
Baseline characteristics				
Age, years	65 (57, 73)	64.9 ± 12.1	63.7 ± 13.3	0.44
Gender (men, *n*%)	196 (69.2)	131 (72.8)	65 (63.1)	0.09
BMI, kg/m^2, median (IQR)	24.5 (23.0, 26.4)	24.5 (23.0, 26.4)	24.7 (22.6, 26.0)	0.75
NIHSS score at admission, median (IQR)	2 (1, 5)	2 (1, 4)	3 (1, 10)	0.02*
Mild stroke (NIHSS score ≤4, *n*%)	200 (70.6)	136 (75.6)	64 (62.1)	0.02*
Previous history, *n* (%)				
History of stroke	63 (22.2)	43 (23.9)	20 (19.4)	0.38
Coronary heart disease	34 (12.0)	22 (12.2)	12 (11.7)	0.89
Atrial Fibrillation	21 (7.4)	15 (8.3)	6 (5.8)	0.44
Hypertension	197 (69.6)	125 (69.4)	72 (69.9)	0.94
Diabetes	104 (36.7)	64 (35.8)	40 (38.8)	0.61
Smoking	108 (38.1)	73 (40.6)	35 (34.0)	0.27
Previous drugs, *n* (%)				
Antihypertensive agents	158 (55.8)	102 (56.7)	56 (54.4)	0.71
Antidiabetic agents	91 (32.1)	52 (28.9)	39 (37.9)	0.12
Statins	55 (19.4)	44 (24.4)	11 (10.7)	<0.01*
Antiplatelets	68 (24.0)	49 (27.2)	19 (18.4)	0.10
Stroke etiology, *n* (%)				0.60[a]
Large-artery atherosclerosis	251 (88.6)	161 (89.4)	90 (87.4)	
Cardioembolic	13 (4.5)	9 (5.0)	4 (3.9)	
Small vessel disease	18 (6.4)	9 (5.0)	9 (8.7)	
Other or undetermined	1 (0.004)	1 (0.005)	0 (0)	
Recanalization therapy	34 (12.0)	20 (11.1)	14 (13.6)	0.54
Hemorrhagic transformation	9 (3.2)	5 (2.8)	4 (3.9)	0.73[a]
Biochemical indexes				
SBP (mmHg), median (IQR)	148 (133, 161)	145.5 (133, 157)	151 (136, 165)	0.07
DBP (mmHg), median (IQR)	81 (75, 92)	81.5 (76, 92)	81 (73, 91)	0.56
FBG (mmol/L), median (IQR)	6.6 (5.6, 8.6)	5.9 (5.3, 6.6)	8.6 (7.3, 10.8)	<0.01*
HbA1c (%), median (IQR)	6.0 (5.6, 7.7)	6 (5.6, 7.5)	6.1 (5.6, 7.8)	0.66
Glucose-to-HbA1c ratio, median (IQR)	1.1 (0.9, 1.2)	-	-	-
LDL-C, mg/dl, median (IQR)	2.2 (1.72.9)	2.3 (1.7, 2.9)	2.2 (1.7, 2.8)	0.42
HDL-C, mg/dl, median (IQR)	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.78
TC, mg/dl, median (IQR)	3.8 (3.2, 4.6)	3.9 (3.2, 4.6)	3.8 (3.2, 4.6)	0.61
TG, mg/dl, median (IQR)	1.3 (1.0, 1.8)	1.3 (1.0, 1.8)	1.2 (0.9, 1.8)	0.43
Outcomes, *n* (%)				
mRS score at 1 year	1 (0, 3)	1 (0, 2)	2 (0, 4)	0.03*
Poor functional outcome (mRS score>2 at 1 year)	90 (31.8)	44 (24.4)	46 (44.7)	<0.01*
Stroke recurrence	30 (10.6)	21 (11.7)	9 (8.7)	0.44
All-cause death at 1 year	10 (23.5)	3 (1.7)	7 (6.8)	0.03[a]

IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; NIHSS, National Institutes of Health Stroke Scale.

[#]Comparison of the low glucose/HbA1c ratio with high glucose/HbA1c ratio.

[a]The comparisons were accomplished by Fisher's exact test.

*$p < 0.05$.

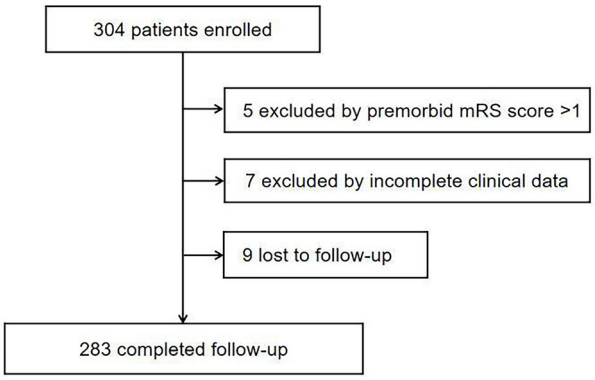


FIGURE 1
The flowchart of the study.

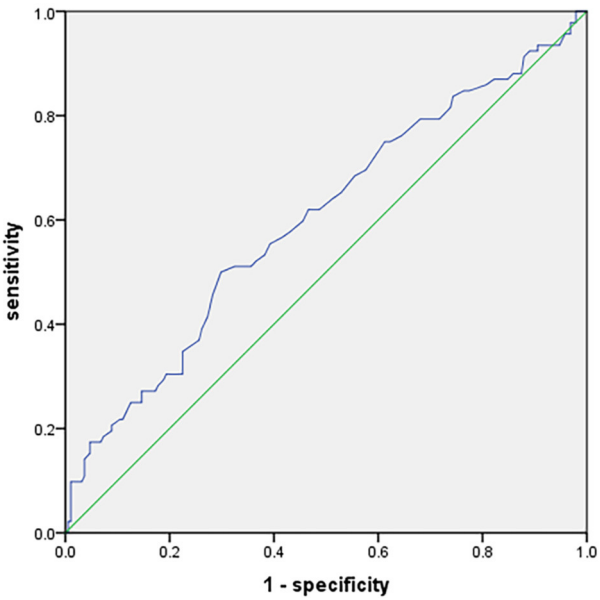


FIGURE 2
Receiver operating characteristic curve showing optimized cutoff for the glucose-to-HbA1c ratio in predicting poor functional outcomes (mRS score 3–6).

TABLE 2 Independent predictors of poor functional outcomes after 1 year in binary logistic regression analysis.

	Variables	OR	95%CI	*P*
All	**Model 1$^{\alpha}$**			
	Age	1.05	1.01∼1.08	0.02*
	NIHSS score at admission	1.30	1.19∼1.42	<0.01*
	Atrial fibrillation	4.10	1.18∼14.28	0.03*
	SBP	1.03	1.01∼1.05	<0.01*
	DBP	0.96	0.93∼0.99	0.02*
	Model 2$^{\alpha}$			
	Atrial fibrillation	4.49	1.43∼14.14	0.01*
	SBP	1.03	1.01∼1.05	<0.01*
	DBP	0.95	0.92∼0.98	<0.01*
	Glucose-to-HbA1c ratio$^{\times 10}$	1.19	1.07∼1.33	<0.01*
With diabetes	**Model 1$^{\beta}$**			
	Age	1.06	1.01∼1.12	0.03*
	NIHSS score at admission	1.23	1.07∼1.43	<0.01*
	Model 2$^{\beta}$			
	Age	1.06	1.01∼1.11	0.04*
	Hypertension	3.41	1.01∼11.50	<0.05*
Without diabetes	**Model 1$^{\gamma}$**			
	Age	1.08	1.03–1.13	<0.01*
	Atrial fibrillation	5.17	1.05∼25.51	0.04*
	NIHSS score at admission	1.28	1.15∼1.42	<0.01*
	Glucose-to-HbA1c ratio$^{\times 10}$	1.37	1.08∼1.73	0.01*
	Model 2$^{\gamma}$			
	Age	1.06	1.03∼1.10	<0.01*
	BMI	0.85	0.74∼0.98	0.02*
	Atrial fibrillation	4.97	1.10∼22.39	0.04*
	Glucose-to-HbA1c ratio$^{\times 10}$	1.48	1.22∼1.79	<0.01*

Glucose-to-HbA1c ratio$^{\times 10}$ = Glucose-to-HbA1c ratio ×10.
Model 1$^{\alpha}$: adjusted for gender, age, BMI, NIHSS score at admission, medical histories of stroke, atrial fibrillation, hypertension, smoking, previous use of statins, antihypertensive agents, SBP, DBP, HDL-C, TG, and glucose-to-HbA1c ratio$^{\times 10}$.
Model 2$^{\alpha}$: adjusted for gender, age, BMI, medical histories of stroke, atrial fibrillation, hypertension, smoking, previous use of statins and antihypertensive agents, SBP, DBP, HDL-C, TG, and glucose-to-HbA1c ratio$^{\times 10}$.
Model 1$^{\beta}$: adjusted for age, NIHSS score at admission, hypertension, DBP, and HbA1c.
Model 2$^{\beta}$: adjusted for age, hypertension, DBP, and HbA1c.
Model 1$^{\gamma}$: adjusted for gender, age, BMI, medical history of atrial fibrillation, smoking, NIHSS score at admission, FBG, HDL-C, TG, and glucose-to-HbA1c ratio$^{\times 10}$.
Model 2$^{\gamma}$: adjusted for gender, age, BMI, medical history of atrial fibrillation, smoking, FBG, HDL-C, TG, and glucose-to-HbA1c ratio$^{\times 10}$.
OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; NIHSS, National Institutes of Health Stroke Scale.
*$p < 0.05$.

stroke, similar to that observed in a previous study (23). However, the underlying mechanism of the relationship between stress hyperglycemia and poor outcomes in patients with AIS is still unclear. In particular, it is necessary to differentiate between patients with and without diabetes.

Our study showed that stress hyperglycemia was a predictor of poor outcomes in patients without diabetes but not in patients with diabetes. Merlino et al. (24) reported that premorbid diabetic status tended to influence outcomes in patients with AIS who were treated with intravenous thrombolysis. Mortality and hemorrhagic complications were significantly increased in patients with more severe stress hyperglycemia only when they were not affected by diabetes. Similar results were also found in several other previous studies (4, 21, 25–27). The underlying mechanism of this phenomenon may be explained by cellular adaptation to hyperglycemia due to physiological readjustments to higher glucose concentrations in patients with diabetes (28, 29). In addition, diabetes may improve antioxidant defenses, which can protect cells from oxidative stress caused by acute hyperglycemia and thus attenuate inflammation caused by oxidative stress (30, 31).

TABLE 3 Independent predictors of a moderate-to-severe stroke at admission in binary logistic regression analysis.

Variables	OR	95%CI	*P*
Glucose-to-HbA1c ratio$^{\times 10}$	1.16	1.05∼1.28	<0.01*
Stroke etiology			
Cardioembolic	4.02	1.23∼13.21	0.02*
Large-artery atherosclerosis	-	-	-

Glucose-to-HbA1c ratio$^{\times 10}$ = Glucose-to-HbA1c ratio ×10.
OR, odds ratio; CI, confidence interval.
Adjusted for stroke etiology, glucose-to-HbA1c ratio*10, high-density lipoprotein cholesterol, and HbA1c.
Moderate-to-severe stroke means an NIHSS score of >4 at admission.
*$p < 0.05$.

Treatment and risk factor management in patients with AIS greatly influence overall prognosis. Finding indicators that can help us choose different treatments for different patients is therefore crucial, especially in glucose control and intensive glucose-lowering therapy. However, while random blood glucose and FBG are more available and intuitive, both have limitations in ignoring background blood glucose levels and physiological stress responses to AIS. In contrast, using the glucose-to-HbA1c ratio overcomes these shortcomings.

In our study, patients with a higher glucose-to-HbA1c ratio had higher NIHSS scores at admission, which might indicate that stress hyperglycemia was associated with stroke severity, and the glucose-to-HbA1c ratio was an independent predictor of stroke severity. Several previous studies have found that the glucose-to-HbA1c ratio influences clinical outcomes in both patients with and without diabetes (8, 20, 32–34). In these studies, a higher glucose-to-HbA1c ratio was related to poorer outcomes. These results might be explained by poorer outcomes that more severe patients always experience. However, in our study, when the patients were divided into groups with and without diabetes for separate analysis, it was found that the glucose-to-HbA1c ratio did not show a relationship with poor functional outcomes in patients with diabetes, while it was significantly associated with the poor functional outcomes in patients without diabetes.

Regardless, we found that the optimal glucose-to-HbA1c ratio was highly correlated with 1-year functional outcomes and all-cause mortality with the cutoff value of 1.135 but had no relationship with stroke recurrence. Patients with a higher glucose-to-HbA1c ratio had poorer functional outcomes. These results suggested that stress hyperglycemia might influence patients' clinical outcomes. Although the POINT trial found that hyperglycemia was associated with an increased risk of subsequent ischemic stroke (14), there are two possible explanations for the difference. First, the enrolled patients were those who presented with a high-risk TIA or acute minor ischemic stroke, while our study did not limit the stroke characteristics. Second, they defined hyperglycemia as random serum glucose on presentation ≥180 mg/dl, which differs from our study, which used the glucose-to-HbA1c ratio to define hyperglycemia. To our knowledge, diabetes is an independent risk factor for stroke recurrence (35). However, research on the impact of stress hyperglycemia on stroke recurrence is insufficient, and further studies are needed.

Our study had several limitations. First, this was a single-center, retrospective study with a limited sample size, which might reduce the generalizability of the results. Second, since the time of stroke recurrence was not recorded, survival analysis could not be performed, which was a shortcoming of our study. In addition, early control of hyperglycemia might impact the outcomes, as hyperglycemia can exacerbate brain damage in ischemic stroke, which we had not considered. In addition, the time from onset to laboratory investigations might influence our results, which had been ignored. Finally, the absence of 3-month follow-up data was also a shortcoming of this article. Therefore, the impact of stress hyperglycemia on patients with AIS remains a concern, and a multicenter prospective trial with a large sample size is needed in the future. In addition, patients with or without diabetes will also need to be studied separately.

In conclusion, our study showed that the glucose-to-HbA1c ratio was associated with more severe AIS and might be a marker of the severity of the stroke. More specifically, a high glucose-to-HbA1c ratio was associated with poor functional outcomes in patients without diabetes but not in patients with diabetes.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Affiliated Drum Tower Hospital, Nanjing University Medical School. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JZ and YX designed the experiments and revised the manuscript. TS enrolled patients and drafted the manuscript. HL did the analysis work and drafted the manuscript with TS. GY, HW, DL, and HN contributed to patient enrollment and data collection. GY helped revise the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the Hengrui Hospital Pharmacy Foundation of the Jiangsu Pharmaceutical Association (No. H202006) and the Jiangsu Research Hospital Association for Precision Medication (JY202122).

Acknowledgments

We thank all the doctors and nurses in the Neurology Department for their assistance.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1142084/full#supplementary-material

References

1. Roberts GW, Quinn SJ, Valentine N, Alhawassi T, O'Dea H, Stranks SN, et al. Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. *J Clin Endocrinol Metab.* (2015) 100:4490–7. doi: 10.1210/jc.2015-2660

2. Dungan KM, Braithwaite SS, Preiser J-C. Stress hyperglycaemia. *Lancet.* (2009) 373:1798–807. doi: 10.1016/S0140-6736(09)60553-5

3. Chen G, Ren J, Huang H, Shen J, Yang C, Hu J, et al. Admission random blood glucose, fasting blood glucose, stress hyperglycemia ratio, and functional outcomes in patients with acute ischemic stroke treated with intravenous thrombolysis. *Front Aging Neurosci.* (2022) 14:782282. doi: 10.3389/fnagi.2022.782282

4. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke.* (2001) 32:2426–32. doi: 10.1161/hs1001.096194

5. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet.* (2000) 355:773–8. doi: 10.1016/S0140-6736(99)08415-9

6. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, et al. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the shine randomized clinical trial. *JAMA.* (2019) 322:326–35. doi: 10.1001/jama.2019.9346

7. Zhu B, Pan Y, Jing J, Meng X, Zhao X, Liu L, et al. Stress hyperglycemia and outcome of non-diabetic patients after acute ischemic stroke. *Front Neurol.* (2019) 10:1003. doi: 10.3389/fneur.2019.01003

8. Tziomalos K, Dimitriou P, Bouziana SD, Spanou M, Kostaki S, Angelopoulou SM, et al. Stress hyperglycemia and acute ischemic stroke in-hospital outcome. *Metabolism.* (2017) 67:99–105. doi: 10.1016/j.metabol.2016.11.011

9. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, Khan H, Butterworth AS, Wormser D, et al. Glycated hemoglobin measurement and prediction of cardiovascular disease. *JAMA.* (2014) 311:1225–33. doi: 10.1001/jama.2014.1873

10. Li J, Quan K, Wang Y, Zhao X, Li Z, Pan Y, et al. Effect of stress hyperglycemia on neurological deficit and mortality in the acute ischemic stroke people with and without diabetes. *Front Neurol.* (2020) 11:576895. doi: 10.3389/fneur.2020.576895

11. Yuan C, Chen S, Ruan Y, Liu Y, Cheng H, Zeng Y, et al. The stress hyperglycemia ratio is associated with hemorrhagic transformation in patients with acute ischemic stroke. *Clin Interv Aging.* (2021) 16:431–42. doi: 10.2147/CIA.S280808

12. Stroke—1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the who task force on stroke and other cerebrovascular disorders. *Stroke.* (1989) 20:1407–31. doi: 10.1161/01.STR.20.10.1407

13. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the nih stroke scale using video training. *Stroke.* (1994) 25:2220–6. doi: 10.1161/01.STR.25.11.2220

14. Mac Grory B, Piccini JP, Yaghi S, Poli S, De Havenon A, Rostanski SK, et al. Hyperglycemia, risk of subsequent stroke, and efficacy of dual antiplatelet therapy: a post hoc analysis of the point trial. *J Am Heart Assoc.* (2022) 11:e023223. doi: 10.1161/JAHA.121.023223

15. Merlino G, Pez S, Gigli GL, Sponza M, Lorenzut S, Surcinelli A, et al. Stress hyperglycemia in patients with acute ischemic stroke due to large vessel occlusion undergoing mechanical thrombectomy. *Front Neurol.* (2021) 12:725002. doi: 10.3389/fneur.2021.725002

16. Merlino G, Smeralda C, Gigli GL, Lorenzut S, Pez S, Surcinelli A, et al. Stress hyperglycemia is predictive of worse outcome in patients with acute ischemic stroke undergoing intravenous thrombolysis. *J Thromb Thrombolysis.* (2021) 51:789–97. doi: 10.1007/s11239-020-02252-y

17. Tao J, Hu Z, Lou F, Wu J, Wu Z, Yang S, et al. Higher stress hyperglycemia ratio is associated with a higher risk of stroke-associated pneumonia. *Front Nutr.* (2022) 9:784114. doi: 10.3389/fnut.2022.784114

18. Mi D, Li Z, Gu H, Jiang Y, Zhao X, Wang Y, et al. Stress hyperglycemia is associated with in-hospital mortality in patients with diabetes and acute ischemic stroke. *CNS Neurosci Ther.* (2022) 28:372–81. doi: 10.1111/cns.13764

19. Roberts G, Sires J, Chen A, Thynne T, Sullivan C, Quinn S, et al. A comparison of the stress hyperglycemia ratio, glycemic gap, and glucose to assess the impact of stress-induced hyperglycemia on ischemic stroke outcome. *J Diabetes.* (2021) 13:1034–42. doi: 10.1111/1753-0407.13223

20. Roquer J, Giralt-Steinhauer E, Cerda G, Rodriguez-Campello A, Cuadrado-Godia E, Jimenez-Conde J, et al. Glycated hemoglobin value combined with initial glucose levels for evaluating mortality risk in patients with ischemic stroke. *Cerebrovasc Dis.* (2015) 40:244–50. doi: 10.1159/000440735

21. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med.* (2008) 36:2249–55. doi: 10.1097/CCM.0b013e318181039a

22. Huang YW, Yin XS, Li ZP. Association of the stress hyperglycemia ratio and clinical outcomes in patients with stroke: a systematic review and meta-analysis. *Front Neurol.* (2022) 13:999536. doi: 10.3389/fneur.2022.999536

23. Murros K, Fogelholm R, Kettunen, S, Vuorela, A-L, Valve J. Blood glucose, glycosylated haemoglobin, and outcome of ischemic brain infarction. *J Neurol Sci.* (1992) 111:59–64. doi: 10.1016/0022-510X(92)90112-X

24. Merlino G, Pez S, Tereshko Y, Gigli GL, Lorenzut S, Surcinelli A, et al. Stress hyperglycemia does not affect clinical outcome of diabetic patients receiving intravenous thrombolysis for acute ischemic stroke. *Front Neurol.* (2022) 13:903987. doi: 10.3389/fneur.2022.903987

25. Chen X, Liu Z, Miao J, Zheng W, Yang Q, Ye X, et al. High stress hyperglycemia ratio predicts poor outcome after mechanical thrombectomy for ischemic stroke. *J Stroke Cerebrovasc Dis.* (2019) 28:1668–73. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.022

26. Stollberger C, Exner I, Finsterer J, Slany J, Steger C. Stroke in diabetic and non-diabetic patients: course and prognostic value of admission serum glucose. *Ann Med.* (2005) 37:357–64. doi: 10.1080/07853890510037356

27. Hu GC, Hsieh SF, Chen YM, Hsu HH, Hu YN, Chien KL. Relationship of initial glucose level and all-cause death in patients with ischaemic stroke: the roles of diabetes mellitus and glycated hemoglobin level. *Eur J Neurol.* (2012) 19:884–91. doi: 10.1111/j.1468-1331.2011.03647.x

28. Bosarge PL, Shoultz TH, Griffin RL, Kerby JD. Stress-induced hyperglycemia is associated with higher mortality in severe traumatic brain injury. *J Trauma Acute Care Surg.* (2015) 79:289–94. doi: 10.1097/TA.0000000000000716

29. Krinsley JS, Meyfroidt G, van den Berghe G, Egi M, Bellomo R. The impact of premorbid diabetic status on the relationship between the three domains of glycemic control and mortality in critically ill patients. *Curr Opin Clin Nutr Metab Care.* (2012) 15:151–60. doi: 10.1097/MCO.0b013e32834f0009

30. Sechi LA, Ceriello A, Griffin CA, Catena C, Amstad P, Schambelan M, et al. Renal antioxidant enzyme mrna levels are increased in rats with experimental diabetes mellitus. *Diabetologia.* (1997) 40:23–9. doi: 10.1007/s001250050638

31. Ceriello A. dRP, Amstad P, Cerutti P. High glucose induces antioxidant enzymes in human endothelial cells in culture: evidence linking hyperglycemia and oxidative stress. *Diabetes.* (1996) 45:471–7. doi: 10.2337/diab.45.4.471

32. Stead LG, Gilmore RM, Bellolio MF, Mishra S, Bhagra A, Vaidyanathan L, et al. Hyperglycemia as an independent predictor of worse outcome in non-diabetic

patients presenting with acute ischemic stroke. *Neurocrit Care.* (2009) 10:181–6. doi: 10.1007/s12028-008-9080-0

33. Wong AA, Schluter PJ, Henderson RD, O'Sullivan JD, Read SJ. Natural history of blood glucose within the first 48 hours after ischemic stroke. *Neurology.* (2008) 70:1036–41. doi: 10.1212/01.wnl.0000306635.08410.68

34. Szczudlik A, Slowik A, Turaj W, Wyrwicz-Petkow U, Pera J, Dziedzic T, et al. Transient hyperglycemia in ischemic stroke patients. *J Neurol Sci.* (2001) 189:105–11. doi: 10.1016/S0022-510X(01)00566-4

35. Zhang L, Li X, Wolfe CDA, O'Connell MDL, Wang Y. Diabetes as an independent risk factor for stroke recurrence in ischemic stroke patients: an updated meta-analysis. *Neuroepidemiology.* (2021) 55:427–35. doi: 10.1159/000519327

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 21 March 2023
DOI 10.3389/fneur.2023.1149671

OPEN ACCESS

EDITED BY
Cheong-Meng Chong,
University of Macau, China

REVIEWED BY
Chen-Chih Chung,
Taipei Medical University, Taiwan
Giovanni Merlino,
Udine University Hospital, Italy

*CORRESPONDENCE
Di Ma
✉ madi2017@jlu.edu.cn
Liangshu Feng
✉ fengliangshu@jlu.edu.cn

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 22 January 2023
ACCEPTED 21 February 2023
PUBLISHED 21 March 2023

CITATION
Yao M, Hao Y, Wang T, Xie M, Li H, Feng J, Feng L and Ma D (2023) A review of stress-induced hyperglycaemia in the context of acute ischaemic stroke: Definition, underlying mechanisms, and the status of insulin therapy. *Front. Neurol.* 14:1149671. doi: 10.3389/fneur.2023.1149671

A review of stress-induced hyperglycaemia in the context of acute ischaemic stroke: Definition, underlying mechanisms, and the status of insulin therapy

Mengyue Yao[1†], Yulei Hao[1†], Tian Wang[1], Meizhen Xie[1], Hui Li[1], Jiachun Feng[1], Liangshu Feng[2*] and Di Ma[1*]

[1]Department of Neurology and Neuroscience Centre, The First Hospital of Jilin University, Changchun, Jilin, China, [2]Stroke Centre, Department of Neurology, The First Hospital of Jilin University, Changchun, Jilin, China

The transient elevation of blood glucose produced following acute ischaemic stroke (AIS) has been described as stress-induced hyperglycaemia (SIH). SIH is common even in patients with AIS who have no previous diagnosis of diabetes mellitus. Elevated blood glucose levels during admission and hospitalization are strongly associated with enlarged infarct size and adverse prognosis in AIS patients. However, insulin-intensive glucose control therapy defined by admission blood glucose for SIH has not achieved the desired results, and new treatment ideas are urgently required. First, we explore the various definitions of SIH in the context of AIS and their predictive value in adverse outcomes. Then, we briefly discuss the mechanisms by which SIH arises, describing the dual effects of elevated glucose levels on the central nervous system. Finally, although preclinical studies support lowering blood glucose levels using insulin, the clinical outcomes of intensive glucose control are not promising. We discuss the reasons for this phenomenon.

KEYWORDS

stress-induced hyperglycaemia, acute ischaemic stroke, admission blood glucose, intensive glucose control, insulin

1. Introduction

Acute ischaemic stroke (AIS) is an acute brain injury that often occurs when an artery is suddenly blocked. It is one of the most common causes of severe disability and mortality worldwide (1). One description of stress-induced hyperglycaemia (SIH) is increased blood glucose due to a sudden clinical event that returns to baseline following the acute phase (2). SIH is commonly seen in AIS patients, even those with no history of diabetes mellitus (DM) diagnosis (3). Hyperglycaemia has been demonstrated to be independently linked to an adverse prognosis in AIS patients (4). Patients with previously undiagnosed DM are more likely to have increased short- and long-term mortality due to elevated blood glucose on admission to the hospital than patients with previously identified DM (3, 5). Hyperglycaemia has a dual effect on the central nervous system, with blood glucose above a specific range accelerating thrombosis, increasing stress and inflammatory responses, exacerbating reperfusion injury, and leading to lactate accumulation and mitochondrial

dysfunction. This ultimately contributes to the transformation of the ischaemic penumbra into an infarcted region (6, 7). Therefore, it appears to be essential to maintain blood glucose levels in AIS. Although there are many published studies on SIH, there is no agreed-upon definition of SIH with AIS, such as admission blood glucose (ABG), stress hyperglycaemia ratio (SHR), or glucose variability (GV). The current large prospective controlled studies of SIH in patients with AIS treated with intravenous insulin have been designed using ABG as a definition and have not yielded desirable results (8–13).

Thus, in this review, we will discuss which optimal glycaemic definition of SIH is most associated with poor prognosis following AIS and whether the best definition cut-off value makes a difference in the presence and absence of recognized DM. Finally, we discuss whether insulin-intensive glucose control therapy can aid AIS patients with an improved prognosis.

2. Definition of stress-induced hyperglycaemia in acute ischaemic stroke

In the context of AIS, SIH is measured in different ways. However, it is still being determined which are the optimal glucose metrics for measuring SIH, as well as the definition and cut-off value of SIH that lead to adverse outcomes in AIS patients in the presence and absence of recognized DM (Table 1).

Abbreviations: ABG, admission blood glucose; ACTH, adrenocorticotrophic hormone; AIS, acute ischaemic stroke; AP-1, activated protein-1; ASICs, acid-sensitive ion channels; BBB, blood-brain barrier; BG, blood glucose; CRH, corticotrophin-releasing hormone; CV, coefficient of variance; Cyt c, cytochrome c; DM, diabetes mellitus; DPP-4, dipeptidyl-peptidase-4; END, early neurological deterioration; eNOS, endothelial nitric oxide synthase; FBG, fasting blood glucose; FFA, free fatty acids; GABA, gamma-aminobutyric acid; GAP, glycaemic gap = ABG (mg/dl) - [28.7 × HbA1c (%) - 46.7]; GKI, glucose-potassium-insulin; GLP-1, Glucose-like peptide-1; GLUT, glucose transporter; GV, glucose variability; HPA axis, hypothalamic–pituitary–adrenal axis; IAT, intra-arterial treatment; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor-1; IL-1, interleukin-1; IL-6, interleukin-6; IML, intermediolateral nucleus; IVT, intravenous thrombolysis; JNK, c-Jun N-terminal kinase; MAG, mean absolute glucose; MAGE, the mean amplitude of glycaemic excursions; MCAO, middle cerebral artery occlusion; MCP-1, monocyte chemotactic protein-1; MMP-9, matrix metalloproteinase-9; MPTP, mitochondrial permeability transition pore; MT, mechanical thrombectomy; NMDA, N-methyl-D-aspartate; ROS, reactive oxygen species; SHR, stress hyperglycaemia ratio; SHR1, ABG (mg/dl) / HbA1c (%); SHR2, FBG (mg/dl) / HbA1c (%); SHR3, FBG (mg/dl) / HbA1c (%) (derived from the glycosylated hemoglobin level); SIH, stress-induced hyperglycaemia; PAI-1, plasminogen activator inhibitor type 1; PSCI, post-stroke cognitive impairment; PVN, paraventricular nucleus; SD, standard deviation; SICH, symptomatic intracranial hemorrhage; TAT, thrombin-antithrombin; TF, tissue factor; TNF-α, tumor necrosis factor-α; t-PA, tissue-type plasminogen activator; TR, time rate; VCAM-1, vascular cell adhesion molecule-1; VLM, ventrolateral medulla.

2.1. ABG/FBG

Several earlier clinical studies defined hyperglycaemia in terms of the blood glucose value, or ABG, within 24 h of admission to the hospital for AIS patients. The cut-off values for ABG to define hyperglycaemia in AIS patients vary between studies.

Whether elevated ABG has different effects on the prognosis of AIS patients with and without a DM diagnosis has been widely discussed. In a meta-analysis of 32 cohort studies, Capes and colleagues (3) observed that non-DM patients with ABG above 126 mg/dl had a threefold increased admission and 30-day mortality compared to patients with normal ABG. In addition, the researchers found that ABG was unrelated to an increase in short-term mortality in DM patients. A prospective study (5) including 447 AIS patients suggests that, in non-DM patients, 90-day mortality was 3.4 times greater in patients with ABG above 130 mg/ dl than in those with normoglycaemia. In comparison, for DM patients, the hazard ratio was 1.6. Another observational study (15) of 2,550 AIS patients found that ABG ≥140 mg/dl was independently correlated with post-stroke infection in non-DM patients. In contrast, the same result was not found in DM patients. However, a series of studies suggested that ABG ≥140 mg/dl is strongly correlated with the risk of symptomatic intracranial hemorrhage (SICH) after intravenous thrombolysis (IVT), mechanical thrombectomy (MT) or intra-arterial treatment (IAT) and a poor 3-month clinical prognosis in AIS patients. These studies did not specifically distinguish between non-DM and DM patient populations (16, 18–20). A later study (17) carefully differentiated between these two groups and showed that ABG ≥140 mg/dl was related to an adverse prognosis after IVT in non-DM AIS patients. In conclusion, absolute increases in hyperglycaemia were more strongly related to short- or long-term mortality, post-stroke infection, and adverse prognosis in AIS patients with non-DM than in patients with previously diagnosed DM.

Furthermore, Snarska et al. (22) discovered that the cut-off values for ABG, which predicted the risk of in-hospital death, were distinct in AIS patients without and with DM (113.5 mg/dl and 210.5 mg/dl). This difference is consistent with that reported by Farrokhnia et al. (21) and has been found similarly in patients with myocardial infarction (43). The reason for this discrepancy may be that the baseline glucose metabolism levels are usually significantly higher in DM patients than in non-DM patients. The ABG values reflect both acute stress and chronic glucose metabolism levels.

In addition, several studies (44) have focused on fasting blood glucose (FBG), an alternative metric for ABG. Elevated FBG on admission following AIS was reported to be appreciably correlated with poor function only in pre-DM patients, with no correlation in DM patients. It is inconclusive to define SIH in terms of ABG or FBG without considering the prior glucose metabolic status. As a result, new indexes such as glycaemic gap (GAP) and SHR were introduced, eliminating the interference of chronic glycaemic levels.

TABLE 1 The definition and a cut-off value of SIH related to adverse prognosis in ischaemic stroke patients with or without a previous DM diagnosis.

Definition	Cut-off value (patients)	Primary relevant endpoint (in non-DM)	Primary relevant endpoint (in DM)	References
ABG	110–126 mg/dl	In-hospital mortality; 30-day mortality	Not relevant	(3)
	130 mg/dl	Greater stroke severity; functional impairment; 90-day mortality	Not as strong as non-DM	(5)
	131.4 mg/dl	12-month poor functional outcomes	Same as non-DM	(14)
	140 mg/dl	Post-stroke infection; 3-month mortality; 3-month poor functional outcomes	-	(15)
	140 mg/dl (IVT)	Low complete recanalization rate; SICH; 3-month poor functional outcomes	Same as non-DM	(16)
	140.4 mg/dl (IVT)	3-month poor functional outcomes	Not relevant	(17)
	200 mg/dl (IVT)	7-day mortality; 3-month mortality; END		
	140 mg/dl (MT)	3-month poor functional outcomes; 3-month mortality; SICH	Same as non-DM	(18)
	140.4 mg/dl (IAT)	Poor functional outcomes at discharge	Same as non-DM	(19)
	140.4 mg/dl (IVT)	Not relevant with 3-month poor functional outcomes and SICH	Same as non-DM	(20)
	113.4 mg/dl	30-day case-fatality	-	(21)
	185.4 mg/dl	-	30-day case-fatality	
	113.5 mg/dl	In-hospital mortality	-	(22)
	210.5 mg/dl	-	In-hospital mortality	
Random blood glucose <48 h	155 mg/dl	Admission stroke severity; 3-month poor functional outcomes; 3-month mortality	Same as non-DM	(23)
GAP	45 mg/dl	-	Stroke severity; poor neurological status	(24)
SHR	SHR1 ≥ 27.59			
	SHR2	1-year stroke recurrence; 1-year all-cause death	-	(25)
	SHR2	1-year poor functional outcomes; 1-year all-cause death	Same as non-DM	(26)
	SHR2	Haemorrhagic transformation	Same as non-DM	(27)
	SHR2	-	In-hospital mortality	(28)
	SHR2 (IVT)	3-month poor outcomes; 3-month mortality; SICH	Same as non-DM	(29)
	SHR2, SHR3 (IVT)	3-month poor functional outcomes	Same as non-DM	(30)
	SHR2 (IVT)	END and poor functional outcomes at discharge	Only END	(31)
	SHR2 (IVT)	3-month poor outcomes; 3-month mortality; SICH	Not relevant	(32)
	SHR2 ≥ 0.97 (IVT)	3-month poor functional outcomes	Same as non-DM	(33)
	SHR2 (MT)	3-month poor outcomes; 3-month mortality; SICH	Same as non-DM	(34)
	SHR3 ≥ 0.96 (MT)	3-month poor functional outcomes	Same as non-DM	(35)
GV	MAGE	-	END	(36)
	SD, CV	28-day, 90-day mortality	Same as non-DM	(37)
	SD (IVT and MT)	3-month poor functional outcomes	Same as non-DM	(38)
	MAG	Not relevant	3-month PSCI	(39)
	TR (MT)	3-month poor functional outcomes; SICH	Same as non-DM	(40)
	Max BG– min BG during hospitalization	-	3-month poor functional outcomes	(41)
	J-index	-	3-month increased cardiovascular events	(42)

–, Not mentioned.

2.2. GAP/SHR

GAP is calculated as the difference between ABG and long-term mean glucose values determined from HbA1c. In a study aimed at comparing the ability of SHR, GAP, and ABG to assess poor prognosis in AIS patients, Yang et al. (24) demonstrated that a GAP of 45 mg/dl showed a superior ability to differentiate between AIS patients' severity and prognosis compared to ABG, as did SHR.

SHR is measured as ABG or FBG divisible by long-term mean glucose values determined from HbA1c and is also measured as FBG divisible directly by HbA1c in some articles. An analysis (26) of 8,622 AIS patients reported an association between high SHR and severe neurological deficits and all-cause mortality at 1 year in patients with and without DM. Interestingly, the mortality outcome was more significant in patients without DM, as found in a nationwide prospective registry study among AIS patients with non-DM in China (25). A recent retrospective study (28) assessed the impact of SHR, FBG, and HbA1c on in-hospital mortality in AIS patients with DM. SHR appeared to have a better predictive value than other absolute measures. Ngiam and colleagues (33) discovered that high SHR, particularly at SHR $\geq$ 0.97, was strongly related to 3-mouth adverse outcomes in AIS patients after IVT with or without DM. Other studies have also found this correlation (29, 31). The same has been confirmed in AIS patients after MT (34, 35). In addition, some studies have shown that in the above calculation, SIH obtained by direct division of FBG by HbA1c correlates more with poor functional outcomes after IVT (30, 45).

2.3. GV

ABG and SHR cannot truly reflect the fluctuations in blood glucose under the influence of certain diseases due to the limitations of their numerical sources (obtained from HbA1c). Hyperglycaemic fluctuations caused by acute disease tend to exacerbate oxidative stress and damage endothelial cells, which results in a poor prognosis (46, 47). GV is the extent to which blood glucose levels fluctuate through time (48). An elevated GV is regarded as a sign of hypoglycaemia (49). There are two common types of GV, long-term with continuous blood glucose monitoring in years and short-term with days and months, and the most studied concerning stroke prognosis is short-term GV (50). Short-term GV is calculated in several ways, such as the mean amplitude of glycaemic excursions (MAGE), standard deviation, and coefficient of variation (50). In a 7.5-year follow-up of 28,354 patients with type 2 DM, the study observed that long-term high GV significantly enhanced stroke risk in DM patients (51). In a series of explorations of short-term GV, Hui et al. (36) found that altered GV in the first 3 days of hospitalization in AIS with DM patients was strongly related to early neurological deterioration (END) and that GV may be a more appropriate indicator than HbA1c. Yoon and colleagues (42) demonstrated that initial GV significantly enhanced the cardiovascular mortality risk at 3 months. In addition, elevated acute GV was related to poor functional outcomes (38, 41), impaired cognitive function (39), and a higher risk of haemorrhagic transformation (40), although GV was defined differently in these studies. GV has not been specifically studied in AIS populations with non-DM, possibly because diabetic populations are more likely to have measurable blood glucose changes.

In summary, we explored glycaemic indicators that could describe the full range of SIH following AIS. SHR has a similar predictor value for short- and long-term adverse outcomes in patients with and without DM and is independent of background glucose. Thus, SHR is expected to be a biomarker for SIH. Nevertheless, the current relevant studies do not provide a good head-to-head comparison of the different glucose markers. In the future, more prospective trials are needed to compare the clinical applicability of glycaemic indicators such as ABG, SHR, and GV or to attempt to apply them in combination.

3. Underlying mechanisms of SIH after AIS

The combined synergistic effects of SIH in patients with AIS can be induced by the glucose regulatory center, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic adrenomedullary system, and humoral factors (Figure 1).

3.1. Glucose regulatory center

The insular cortex controls the output of the sympathetic and parasympathetic nervous systems, and several studies have shown it to be associated with elevated blood glucose following acute ischaemia (52–54). Many brain regions, including the hypothalamus and brainstem, have also been demonstrated to alter blood sugar levels and stress responses. The catecholamine neuronal system in the brainstem, including the locus coeruleus, nucleus tracts solitaries, and ventrolateral medulla (VLM), significantly contribute to stress responses. Catecholamine neurons in the VLM are the control centers of SIH and receive inputs directly from multiple stress-responsive brain regions, including the hyperglycaemic excitability of the hypothalamic paraventricular nucleus (PVN)-VLM pathway (55). In addition, the preganglionic neurons of the sympathetic medullary system are located in the intermediolateral nucleus (IML) (56, 57).

3.2. HPA axis and the sympathetic adrenomedullary system

Gluconeogenesis, glycogenolysis, and excessive insulin resistance contribute significantly to the production and maintenance of hyperglycaemia during AIS (2, 58). Stressor stimulation causes excitation of the HPA axis and increases circulating cortisol. Cortisol has several metabolic effects to achieve elevated blood glucose levels, including activating vital hepatic gluconeogenesis enzymes and reducing glucose uptake in peripheral tissues (2). Stressor stimuli also converge on the brainstem catecholaminergic neurons and spinal cord efferent neurons in the medial column of preganglionic sympathetic neurons, activating the sympathetic adrenomedullary system

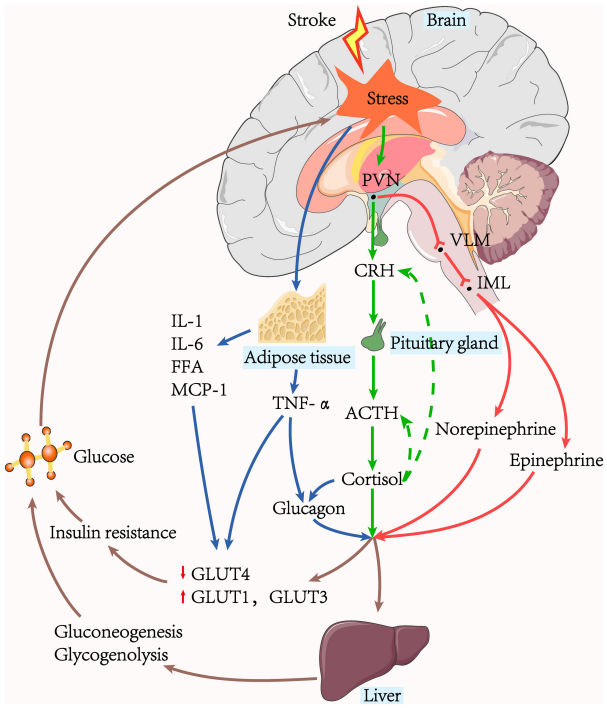


FIGURE 1
The pathway of stress-induced hyperglycaemia generation. Hepatic gluconeogenesis, glycogenolysis, and insulin resistance are the leading causes of hyperglycaemia. The sympathoadrenal system and the HPA axis are active in acute ischaemic stroke. The stressors stimulate the adrenal medulla to release catecholamine *via* the PVN-VLM-IML pathway, while the HPA axis stimulates the adrenal cortex to produce cortisol. Glucagon can be stimulated by cortisol, and TNF-α secreted from surrounding tissues. Glycaemic hormones such as catecholamine, cortisol, and glucagon, act on the liver to promote hepatic gluconeogenesis and glycogenolysis. Hyperglycaemia further exacerbates the stress response and contributes to the increased release of pro-inflammatory factors, creating a vicious cycle.

and increasing blood levels of norepinephrine and epinephrine. Both epinephrine and norepinephrine stimulate the expression of essential genes that regulate glycogenolysis and gluconeogenesis (55). Norepinephrine additionally has the impact of increasing glycerol supply to the liver *via* lipolysis.

3.3. Humoral factors

3.3.1. Hormones

Excess glucagon is the main mediator of glucose metabolism and can be stimulated by cortisol (59). Studies have shown that glucagon, catecholamine, and cortisol act synergistically in changes in glucose metabolism to rapidly raise fasting plasma glucose. Insulin is a naturally significant hormone that lowers blood glucose levels. Its action mechanism is mainly through the mobilization of cells in the liver, skeletal muscle, and other peripheral tissues to synthesize and store glycogen, fats, and proteins and reduce their catabolism (60). Under physiological conditions, the increase of the plasma insulin level stimulates the onset of glucose storage activity mediated by the insulin-sensitive glucose transporter (GLUT)-4, occurring primarily in muscle and adipose tissue, where GLUT-4 translocates from intracellular storage to the membrane, thus enhancing glucose uptake (61). However, following AIS, decreased insulin-mediated glucose uptake was paralleled with over-expression of the insulin-insensitive GLUT-1 and GLUT-3 in other tissues throughout the body, blocking GLUT-4-mediated glucose storage, further exacerbating the increase in peripheral blood glucose (2).

3.3.2. Cytokines

Acute insulin resistance manifests as insulin-mediated glucose uptake reduction, mainly due to defective post-receptor insulin signaling and down-regulation of GLUT-4. Tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6 can inhibit post-receptor insulin signaling, and TNF-α can also directly down-regulate the expression of the messenger RNA of GLUT-4 (62). An activated sympathetic nervous system induces adipocyte decomposition and increases free fatty acids (63). Excess circulating free fatty acids inhibit post-receptor insulin signaling and glycogen synthase to reduce glucose uptake (64, 65). In addition, fatty tissue secretes large amounts of pro-inflammatory cytokines, such as monocyte chemotactic protein-1 (MCP-1), an essential participant in insulin resistance (66, 67). TNF-α may also contribute to elevated blood glucose levels *via* the promotion of glucagon production (68).

4. SIH-induced protective effects after AIS

4.1. Phenomenon of protection

Glucose is a major energy supplier to brain tissue and provides a valuable metabolic substrate during the acute disruption of cerebral blood flow. In animal models of recirculation after ischaemia, ATP (indicating the recovery of energy metabolism) tended to increase in hyperglycaemia groups more than in hypo- and normoglycaemia groups (69). A study of rabbit models of focal cerebral ischaemia observed a smaller area of cortical brain infarction in the glucose-perfused group compared to the saline group (70). Moreover, an animal model of haemorrhagic shock demonstrated that rapidly induced hyperglycaemia resulted in a significant elevation in blood pressure, cardiac output, and viability (71). However, saline or mannitol at similar osmolar doses did not achieve the above effects. These studies suggest that elevated glucose rescues damaged brain tissue to some extent and improves survival.

4.2. Physical mechanisms of protection

Glucose diffuses along a concentration gradient from the bloodstream into the cells in the ischaemic area. Appropriate hyperglycaemia maximizes the guarantee of cellular metabolism. Uytenboogaart et al. (72) reported the concentration-effect phenomenon in lacunar stroke, where glucose values above 144 mg/dl were linked to a good functional prognosis. It is worth

noting that hyperglycaemia worsens the clinical prognosis in non-lacunar stroke compared with lacunar stroke (73). This is possibly due to non-lacunar infarction of an area known as the ischaemic penumbra, the site of reduced blood flow around the ischaemic core. Hyperglycaemia causes cellular acidosis by increasing its intracellular lactate content, leading to a poor prognosis (74). In lacunar infarcts, this is absent, and elevated blood glucose can supply energy to the surrounding tissues, leading to a better prognosis. However, its beneficial effects are diminished when severe hyperglycaemia exceeds 216 mg/dl (72).

4.3. Biological mechanisms of protection

The physiological protective mechanisms of short-term increases in hyperglycaemia have been extensively explored in cardiac ischaemia (75, 76). Acute hyperglycaemia reduces post-ischaemic cell death by producing cell survival proteins, releasing cellular survival factors, and favoring angiogenesis. In a porcine coronary ischaemia-reperfusion model, Chu et al. (77) demonstrated that hyperglycaemia during acute ischaemia increased the production of cell survival proteins, such as phosphorylated endothelial nitric oxide synthase (eNOS) and heat shock protein 27 and thus reduced infarct size. Malfitano et al. (78) showed that hyperglycaemia decreased pro-inflammatory cytokines, increased cell survival factors (hypoxia-inducible factor-1α, vascular endothelial growth factor), and reduced apoptosis in the rat myocardial infarction model, thereby improving systolic myocardial function and reducing the size of the myocardial infarction. In addition, hyperglycaemia contributes to an increase in capillaries and a reduction in fibrosis. Subsequently, the protective effect of hyperglycaemia on ischaemic injury in myocardial infarction was also shown to increase antioxidant enzyme activity, improve glutathione redox balance, and reduce sympathetic activity after infarction (79).

5. SIH-induced damage after AIS

The presence of acute hyperglycaemia leading to adverse prognosis has been repeatedly validated in patients with AIS, irrespective of a prior diagnosis of DM, suggesting a possible causal relationship. Various studies have extensively explored these potential mechanisms (7), which are discussed below (Figure 2).

5.1. Impaired recanalization

Impaired recanalization is associated with enhanced coagulation and reduced fibrinolytic activity (80). In human studies, hyperglycaemia elevates thrombin-antithrombin (TAT) complexes and tissue factor (TF) to produce procoagulant effects (81). Animal and cytological studies revealed that acute hyperglycaemia resulted in elevated plasminogen activator inhibitor type 1 (PAI-1) and decreased plasminogen activator (t-PA) activity levels, leading to a hypercoagulable state by affecting fibrinolytic homeostasis, which was confirmed in human studies (82, 83). Ribo et al. (84) found that during tissue-type t-PA-induced recanalization, acute hyperglycaemia was related to lower recanalization rates compared to chronic hyperglycaemia, suggesting that hyperglycaemia affects reperfusion in the ischaemic penumbra by impairing the fibrinolytic system.

5.2. Reperfusion reduction

A considerable number of studies have reported the phenomenon of cerebral blood flow reduction in hyperglycaemic animals (85–87). In an animal model experiment, acute hyperglycaemia-induced by intraperitoneal injection of glucose was linked to a 24% decrease in cerebral blood flow in rats. Following the intraperitoneal injection of mannitol, the plasma osmolarity increased as much as that observed following glucose injection. In contrast, cerebral blood flow decreased by only 10% (88). This suggests hyperglycaemia may deteriorate brain function by inhibiting compensatory blood circulation after ischaemic injury. The possible mechanism is acute hyperglycaemia promoting the formation of eNOS uncoupling phenomenon in the microvascular system surrounding the ischaemic region, leading to increased reactive oxygen species (ROS) production and decreased NO production (89). The reaction between ROS and NO can rapidly form ONOO–, which exacerbates eNOS uncoupling and produces a vicious cycle of oxidative stress. Reduced NO production and bioavailability leads to local vasodilation and impaired reperfusion (90).

5.3. Oxidative stress and inflammatory response

5.3.1. Oxidative stress

Oxidative stress is a condition where the body is out of balance concerning oxidation and antioxidation, with a tendency to oxidize and produce large amounts of free radicals. ROS are mainly generated by the mitochondria and nicotinamide adenine dinucleotide phosphate oxidase (NOX) in biological systems (91). Notably, NOX is a major origin of ROS in neuronal cells after transient cerebral ischaemia-reperfusion (92). In a model in which endothelial cells were co-cultured with astrocytes to mimic the blood-brain barrier (BBB) environment, high glucose caused a marked increase in BBB permeability through enhanced oxidative stress. The mechanism was shown to be that high glucose enhanced NOX activity and expression levels (93). In addition, a neuronal cell culture experiment revealed that glucose provided the essential electron donor for ROS production in neurons after reperfusion (92). Excess reactive oxygen species lead to increased BBB permeability, brain oedema, and ultimately increased infarct size by peroxidising lipids, proteins, and nucleic acids (94–96). Furthermore, reactive oxygen species consume NO and generate a range of oxygen-free radicals and nitro compounds. The

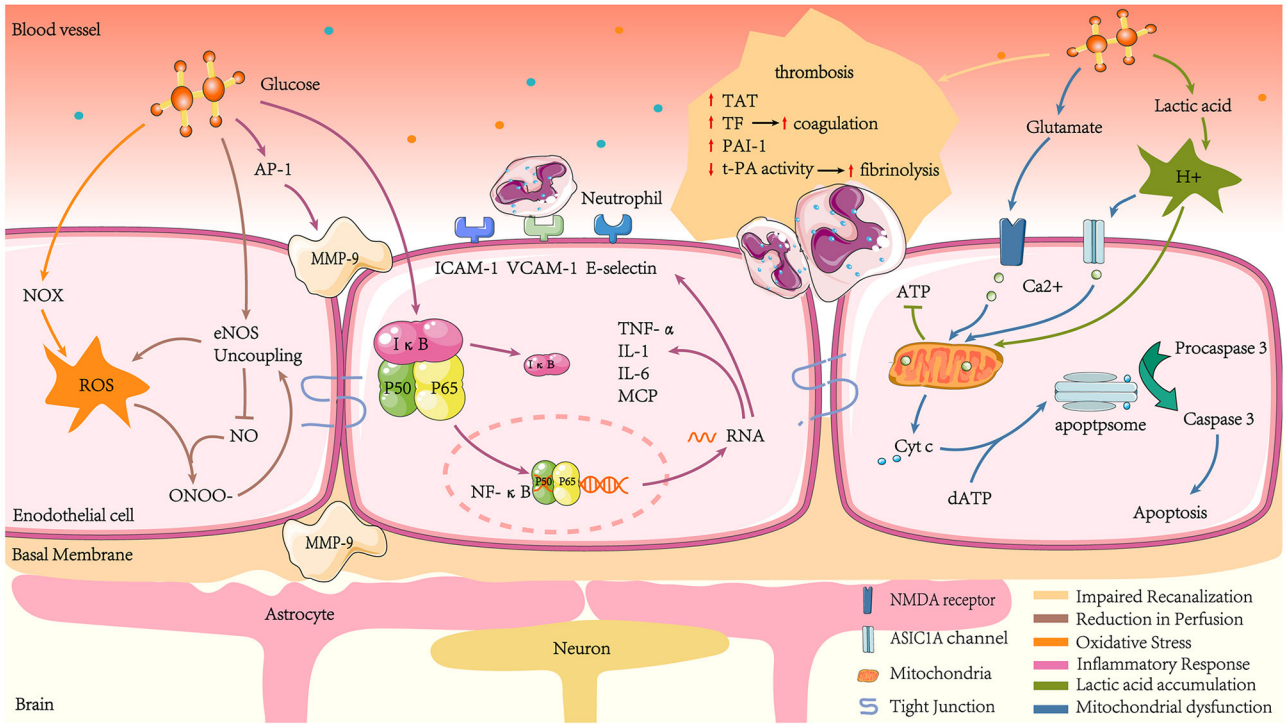


FIGURE 2
Mechanisms of hyperglycaemia-mediated damage in ischaemic stroke. Acute hyperglycaemia increases thrombosis by promoting coagulation and inhibiting hyperfibrinolysis, such as increased TAT, TF, and elevated PAI-1 activity, while t-PA activity decreases. Hyperglycaemia amplifies ROS production, which, together with NO, produces ONOO- and reduces NO bioavailability. At the same time, hyperglycaemia reduces NO production by promoting eNOS uncoupling, leading to endothelial cell diastolic dysfunction and reduced cerebral blood flow. Hyperglycaemia also increases NF-κB translocation to the nucleus by regulating IκB proteasomal degradation. NF-κB combines with specific κB sites on DNA sequence promoters to transcribe inflammatory factors such as TNF-α, IL-1, and IL-6. The NF-κB pathway also transcribes the chemokine MCP and adhesion factors such as ICAM-1, VCAM-1, and E-selectin, which induce leukocyte adhesion. Hyperglycaemia stimulates MMP-9 production, which can damage tight junctions, basement membrane proteins, and astrocyte peduncles, leading to BBB leakage. Hyperglycaemia exacerbates lactate accumulation in the ischaemic zone, leading to mitochondrial dysfunction and reduced ATP production, which fails to maintain intra- and extracellular osmotic and ionic gradients and mediates cytotoxic cell death. In addition, the overproduction of excitatory glutamate in response to hyperglycaemic stimulation activates NMDA receptors. At the same time, the lactate aggregation environment leads to increased H^+ and promotes the opening of ASIC1 channels. Together, this results in increased intra-mitochondrial Ca^{2+}. The imbalance of intra-mitochondrial Ca^{2+} exacerbates the leakage of Cyt c into the cytosol. Cyt c then interacts with dATP to activate downstream apoptogenic proteins, eventually triggering apoptosis.

decrease in circulating NO levels leads to vascular endothelial relaxation dysfunction.

5.3.2. Inflammatory response

Another effect following ischaemia-reperfusion that is significantly enhanced by hyperglycaemia is inflammation. A study in rat stroke models demonstrated that hyperglycaemia triggers a thrombo-inflammatory cascade response and amplifies and exacerbates middle cerebral artery occlusion (MCAO)-induced downstream microvascular thrombosis. The thrombo-inflammatory cascade begins immediately after MCAO in hyperglycaemic rats and continues throughout the reperfusion phase, accompanied by increased matrix metalloproteinase-9 (MMP-9), serotonin, and TAT complex (97). The increase in MMP-9 may be explained by hyperglycaemia promoting the expression of the pro-inflammatory transcription factor nuclear factor-activated protein-1 (AP-1) (98, 99). The increased MMP-9 is implicated in BBB destruction, resulting in plasma protein and inflammatory cell leakage, brain oedema formation, and a worse neurological prognosis (100, 101). Further investigations of hyperglycaemia-induced BBB leakage during ischaemia/reperfusion may be due to tight junction injury, basement membrane proteins, and astrocytic peduncles (97).

In addition, glucose causes an increase in transcription factors in the nucleus: nuclear factor-kappaB (NF-κB) (102). NF-κB is stably coupled to the inhibitory protein IκB in the cytoplasm. After phosphorylation and hydrolysis of IκB due to inflammatory stimuli, the heterodimers of p50 and p65 (the active form of NF-κB) undergo nuclear translocation. They are transcribed and translated into inflammatory proteins, such as TNF- α, IL-1, IL-6, and MCP-1, amplifying and maintaining the inflammatory response (103). Hyperglycaemia induces the promoter of the NF-κB subunit p65, causing an increase in p65 gene expression, which accelerates inflammatory factor production (104). Intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin are also induced by NF-κB (105, 106). These cytokines, chemokines, and adhesion molecules attract

leukocytes to areas of ischaemia (107–109). Excessive leukocyte infiltration destroys the BBB, which causes irreversible infarction in the ischaemic penumbra.

5.4. Lactic acid accumulation

Lactic acid is a source of energy that is metabolized in the brain in the absence of energy (110, 111). Lactic acid accumulation is another risk factor caused by hyperglycaemia following a stroke. Compared with normoglycaemic animals, hyperglycaemia significantly increases lactate concentrations in ischaemic regions of a cat's brain, decreases high-energy phosphate and pH, and converts the ischaemic penumbra into infarct regions (112, 113). A human study found a similar phenomenon that hyperglycaemia in perfusion-diffusion mismatched patients led to enhanced brain lactate production, reducing rescue rates post-infarct penumbra (74). The cause of this phenomenon may be that the accumulation of lactic acidosis causes acidosis, damaging mitochondria and affecting ATP production, leading to depolarisation of cell membranes and the inability to maintain osmotic and ionic gradients inside and outside cells, ultimately leading to cytotoxic cell death (114).

5.5. Mitochondrial dysfunction

The brain's energy supply is disrupted during AIS, and hypoxia depolarisation at presynaptic terminals results in the liberation of excitatory neurotransmitters such as glutamate (115). A study suggested that hyperglycaemia enhances extracellular glutamate build-up during cortical ischaemia (116). N-methyl-D-aspartate (NMDA) receptors are typically ionotropic glutamate receptors and are essential mediators of neuronal death during cerebral ischaemia (117). Excitatory glutamate activates NMDA receptors, allowing Ca^{2+} to effectively enter the cell and mitochondria. Hyperglycaemia induces cell apoptosis following a stroke by increasing Ca^{2+} in the mitochondria, a vital link being the entry of cytochrome c (Cyt c) across the mitochondrial membrane into the cytosol (118). Upon entry into the cytosol, Cyt c interacts with procaspase-9, apoptotic protease-activating factor-1, and dATP to form an activation complex (119). This complex then drives caspase-3 activation, which ultimately induces apoptosis (120).

The glutamate non-dependent Ca^{2+} loading pathway also contributes to Ca^{2+} toxicity in ischaemia. Acid-sensitive ion channels (ASICs) are proton-gated ion channels activated by protons and widely exist in the central and surrounding system (121, 122). In the center, ASICs are primarily expressed in neurons and act as pH sensors to cause neuronal excitation. In physiological conditions, pH is relatively stable in brain tissue. However, massive anaerobic glycolysis of glucose during hypoxic-ischaemia leads to higher lactate accumulation in ischaemic tissue, and the pH drops rapidly (112). ASIC1A, a subtype of ASIC, can be activated by acidosis and conduct Ca^{2+}. An animal experiment has confirmed that ASIC1A knock-out mice resist ischaemia and acid damage (123). Acidosis induces Ca^{2+} into cells via ASIC1, independent of the glutamate pattern, leading to increased intracellular Ca^{2+} concentration, which activation can trigger/regulate multiple cellular processes (124). In addition, during the early stage of ischaemia-reperfusion, hyperglycaemia hinders Ca^{2+} recovery during reperfusion, prolonging the existence of intracellular Ca^{2+} (125).

6. Laboratory recommendations for glucose control therapy

Several laboratory studies have extensively explored the effects on infarct volume of pre- and post-infarction insulin administration in global or focal ischaemic stroke. All the results have shown that insulin has a potent neuroprotective effect, reducing infarct size in crucial brain areas such as the hippocampus, striatum, and cerebral cortex (12, 126). In a transient forebrain ischaemia model, direct injection of insulin or insulin-like growth factor-1 (IGF-1) into the ventricles reduced ischaemic neuronal damage, suggesting that insulin can achieve neuroprotective results through direct interaction action with brain tissue, possibly in part through the IGF-1 receptor (127). In a transient focal ischaemic stroke model, the combination of insulin and glucose nullified most of the apparent protective effects (128), suggesting that insulin's significant neuroprotective effect could be achieved by lowering blood glucose, in agreement with the results of another experiment (129). Additional animal experiments have confirmed that possible mechanisms for the protective effects of insulin also include the regulation of neurotransmitters, the promotion of glycogen synthesis, and the prevention of neuronal necrosis and apoptosis (Table 2).

7. Clinical evidence of intravenous insulin therapy

7.1. Clinical practice of intravenous insulin therapy

Intensive glucose control with intravenous insulin effectively reduces in-hospital mortality in critically ill non-stroke patients (141, 142). Thus, in recent years, some clinical trials have explored the optimal glycaemic targets for intensive insulin treatment in AIS patients with elevated ABG (Table 3).

A total of 933 patients with acute stroke (ischaemic or haemorrhagic) were enrolled in the GIST-UK trial within 24 h (8), 80% of whom did not have a diagnosis of DM and had a median ABG of only 140.4 mg/dl. The experimental group maintained capillary glucose at 72–126 mg/dl by 24-h continuous intravenous infusion of glucose-potassium-insulin (GKI). Surprisingly, compared to the control group, the 90-day functional outcomes of the experimental group did not improve, and hypoglycaemic events occurred. By analyzing changes in blood glucose and blood pressure over 24 h, the benefits of lowering blood glucose may have been masked by lower blood pressure. The study was criticized for including a heterogeneous stroke type, with slow recruitment, late treatment initiation, and variability in glycaemic control of only 10 mg/dl (12, 13). Subsequent studies assessing the feasibility and safety of intensive glucose control with insulin

TABLE 2 Mechanism of the neuroprotective effect of insulin in acute ischaemic stroke animals during hyperglycaemia.

References	Ischaemia model	Species	Results
Zhu and Auer (127)	Transient forebrain 15 s	Rat	Insulin may be reducing the size of brain infarcts through the direct interaction of IGF-1 with brain tissue.
Shuaib et al. (130)	Transient forebrain 10 min	Gerbil	Insulin increases brain extracellular GABA levels.
Hamilton et al. (128)	Transient MCAO 2 h + hypotension	Rat	Insulin lowers blood sugar from 8–9mM to 3–4mM, reducing the area of infarction in the cerebral cortex and striatum.
Lanier et al. (131)	Transient forebrain 10 min + hypotension	Rat	Insulin may exert neuroprotective effects through the regulation of glycogen metabolism.
Sullivan et al. (132)	Cardiac arrest 10 min + reperfusion	Rat	Insulin resumes neuronal protein synthesis after cerebral ischaemia by inducing dephosphorylation of eukaryotic initiation factor 2α.
Guyot et al. (133)	Transient global 10 min	Rat	Insulin increases brain extracellular GABA levels resulting in neuron inhibition.
Hui et al. (134)	Transient global 15 min	Rat	Insulin exerts neuroprotective effects by activating PI3K/Akt negative regulation of the JNK signaling pathway.
Sanderson et al. (135)	Transient forebrain 10 min + hypotension	Rat	Insulin activates the PI3K-Akt survival pathway.
Fanne et al. (136)	Transient MCAO 2 h	Rat	Insulin exerts a neuroprotective effect by lowering glutamate levels.
fan et al. (137)	Embolic focal strokes (blood clot)	Rat	Insulin glucose control during t-PA treatment reduces plasma PAI-1 levels and activities.
Sanderson et al. (138)	Transient forebrain 8 min + hypotension	Rat	Insulin prevents apoptosis upon entry of Cyt c into the cytosol by promoting Cyt c Tyr97-phosphorylation.
Hung et al. (139)	Transient forebrain 1 h + MCAO permanently	Rat	Insulin arrests NO reaction with superoxide to form peroxynitrite.
Huang et al. (140)	Transient forebrain 1 h + MCAO permanently	Rat	Insulin increases cerebral Akt/eNOS phosphorylation and improves neurologic function.
Ahmadi-Eslamloo et al. (129)	Transient MCAO 1 h+ reperfusion	Rat	Insulin attenuates focal brain tissue damage after ischemia-reperfusion in diabetic rats through hypoglycemic effects.

Transient forebrain, bilateral carotid occlusion plus reperfusion; Transient global, four-vessel occlusion plus reperfusion.

after AIS have shown that such trials are feasible and necessary (9, 144–146).

In the SELESTIAL trial (10), 30% of AIS patients with a previous DM diagnosis were maintained on serum glucose between 72–126 mg/dl by GKI infusion. Brain lactate production level decreased at 6–12 h following insulin administration. However, insulin treatment was linked to a marked increase in cerebral infarct size in patients with complete intracranial vascular occlusion. In addition, 76% of patients in the experimental group developed asymptomatic hypoglycaemia. Similarly, a large study explored the effects of an intensive glycaemic regimen compared with usual care on glycaemic control and infarct size expansion. In the INSULINFARCT trial (12), 180 AIS patients were randomized within 6 h to receive 24 h of intravenous insulin therapy, with the vast majority of subjects having no history of DM. The study found that keeping blood glucose below 126 mg/dl did not prevent the transition from an ischaemic penumbra to an infarcted area.

Since all of the above studies failed to demonstrate a positive effect of intensive glucose therapy on stroke prognosis, Johnston and colleagues began to consider that variability in glycaemic control and duration of treatment may be the problem. In the SHINE trial (13), a large multicenter randomized controlled trial, 1,151 AIS patients underwent conventional (80–180 mg/dl) or strict glycaemic control (80–130 mg/dl) within 12 h. Of the enrolled patients, 68% had received reperfusion therapy, and 80% were diagnosed with DM. The change in glycaemic control compared to GIST-UK was significant (61 mg/dl). Intensive glucose control at up to 72 h did not significantly improve 90-day functional outcomes.

7.2. Discussion on the ineffectiveness of insulin therapy

In reviewing the above clinical trials of intensive insulin glucose-lowering, only two studies distinguished between the two populations of AIS patients, with or without previously recognized DM, and discussed treatment prognosis. One study in AIS patients with DM revealed that maintaining blood glucose below 130 mg/dl with intensive insulin treatment was feasible but did not improve the prognosis at three months (9). In another clinical study of mild hyperglycaemia in non-DM patients after AIS, it was found that maintaining blood glucose levels at 81–126 mg/dl was relatively safe in the experimental group and improved neurological status after 30 days. However, there was no difference in functional outcomes compared to controls (11). The SHINE trial (13) did not yield the desired results. Torbey et al. (149) considered whether the different definitions of SIH determined the outcome. They performed a further subgroup analysis of SHINE, carefully selecting six glycaemic parameters: ABG, absence versus presence of diagnosed and undiagnosed DM, HbA1c, GAP, SHR (ABG/ average HbA1c-based daily blood glucose), and GV (SD). The results identified that patients with undiagnosed DM had the

TABLE 3 Randomized trials aimed at comparing the effectiveness of intensive glycaemic treatment with standard treatment in acute ischaemic stroke patients with enhanced admission blood glucose.

Patients (*n*)	Admission blood glucose (mg/dL)*	Intervention (time of treatment)	Mean blood glucose (mg/dl)	The difference in mean blood glucose after treatment (mg/dl)	Primary and relevant endpoint	References
AIS <12 h (24)	264 ± 88	Intravenous insulin + meal-related subcutaneous insulin (72 h)	131 ± 20	Not reported	Feasibility of insulin infusion	(143)
AIS <24 h (13)	190.8 ± 34.2	Intravenous insulin (48 h)	124.5 ± 34.2	Not reported	Support insulin treatment within 48 h, not outside 48 h	(144)
All strokes <24 h (460)	140.4 [112.4–165.6]	Intravenous GKI (24 h)	Not reported	10	3-month mortality, avoidance of severe disability or severe functional impairment (*N*)	(8)
AIS <12 h (31)	259.2 ± 79.2	Intravenous insulin + meal-related subcutaneous insulin (72 h)	133	57	Feasibility and tolerability of insulin infusion; 90-day Functional outcomes (*N*)	(9)
AIS <24 h (25 moderate glycaemic control; 24 tight glycaemic control)	167.4 [127.8–221.4]	Intravenous insulin (5 days)	111	Not reported	Feasibility and safety of insulin infusion	(145)
	167.4 [126–228.6]	Intravenous insulin (5 days)	151			
AIS <24 h (20)	136.8 ± 84.6	Intravenous insulin (5 days)	116.8 ± 39.42	27.36	Feasibility and safety of insulin infusion	(146)
AIS <24 h (10 insulin and tube feeding; 13 insulin only)	163.8 ± 43.2	Intravenous insulin + continual tube feeding (5 days)	104.4 ± 5.4	Not reported	Safety of intravenous insulin + continuous tube feeding	(147)
	189 ± 59.4	Intravenous insulin (5 days)	136.8 ± 27	Not reported		
AIS <24 h (13 and 10 strict glycaemic control)	9.6 (7.3–18.6)	Intravenous insulin (5 days)	The target range of glucose control is 79.2–109.8	Not reported	Safety of intravenous and subcutaneous insulin in intermittently fed AIS patients	(148)
	8.6 (7.3–13.2)	Subcutaneous insulin (5 days)				
AIS <24 h (25)	149.6 ± 50.22	Intravenous GKI (24 h/48 h/72 h)	6 h: 97.2	Not reported	Infarct growth at 7 days (*N*); ↓Brain lactate levels	(10)
			12 h: 104.4			
AIS <12 h (26)	149 ± 16	Intravenous insulin (24 h)	88 ± 9	Not reported	Improved 30-day neurologic status; 24-hour and 30-day functional outcomes, 30-day mortality (*N*)	(11)
AIS <6 h (87)	120.6 [109.8–140.4]	Intravenous insulin (24 h)	126	Not reported	Improved glucose control; ↑Infarct growth at 7 days; 90-day functional outcomes, mortality, serious adverse events (*N*)	(12)
AIS <12 h (581)	188 [153–250]	Intravenous insulin (72 h)	118	61	90-day functional outcomes (*N*)	(13)

*Figures denote mean ± SE, median [inter quartile range]; n, number of non-diabetic patients receiving glucose-lowering treatment as a percentage of total; N, no difference compared to conventional treatment group.

10.3389/fneur.2023.1149671

lowest likelihood of a good prognosis compared to those with true non-DM. However, no apparent benefit of SHINE treatment was observed in the small group of undiagnosed DM patients. After adjusting for baseline stroke severity and thrombolytic therapy, the researchers still found no benefit of intensive insulin therapy in any of the above subgroups. This study was a secondary analysis of the SHINE trial, and the results had unavoidable limitations. Because ABG cut-off values associated with poor prognosis are not the same in AIS patients with and without previously recognized DM, we suggest that future clinical studies should consider the different glycaemic backgrounds of the two populations, whose criteria for initiating glucose lowering, time of initiation and duration of glucose-lowering, and even glucose lowering goals may not be the same. Each characteristic needs to be determined by relevant basic and clinical trials. Next, we discuss the results based on the available experiments.

7.2.1. Glucose reduction criteria

There is considerable heterogeneity in ABG treatment criteria in each study reporting functional outcomes, for example, 140.4 mg/dl (8), 259.2 mg/dl (9), 149 mg/dl (11), 120.6 mg/dl (12), and 188 mg/dl (13). Subsequent studies should include patients with glucose values above the cut-off value related to a worse prognosis, which is considered to be approximately 155 mg/dl (23). For patients treated with IVT or MT, or IAT, it is recommended to use ∼140 mg/dl (16, 18, 19). Also, for non-DM patients with post-AIS hyperglycaemia, we recommend a glucose reduction criteria of ∼126 mg/dl (3).

7.2.2. Start time and duration of glucose lowering

In studies exploring the effects of intensive glucose control, glucose lowering was initiated at 6 h (12), 12 h (9, 11, 13), and 24 h (8) after stroke. The duration of glucose lowering ranged from 24 to 72 h. Rosso and colleagues (12) found that in AIS patients who underwent intensive insulin treatment immediately within 6 h, baseline and day 7 MRI comparison revealed a more significant infarct growth in the experimental group. Therefore, intensive insulin treatment is not recommended in the hyperacute phase of cerebral infarction. The proper duration of glucose lowering after AIS is still being determined. Data obtained from continuous glucose monitoring indicate that continuous glycaemic control for 72 h after AIS is necessary (150–152).

7.2.3. Glucose-lowering targets

Glucose-lowering targets are controversial. In a rodent model of focal ischaemia, insulin treatment after ischaemia resulted in minimal infarct size between 108–126 mg/dl glucose and increased infarct size between 36–54 mg/dl glucose (153). However, in two subsequent clinical trials measuring the controversial infarct size increase, serum glucose was kept below 126 mg/dl using insulin infusion. One of these trials did not find any marked variation in infarct size increase over 1 week between the intervention group and the control group (10). In the other trial, the intervention group's infarct size was more remarkable (12). Furthermore, in a study of patients with AIS, ABG values between 66.6–131.4 mg/dl were associated with 12-month positive functional outcomes (14). Gentile et al. (154) found a 4.6-fold lower in-hospital mortality rate in AIS patients who controlled their blood glucose below 130 mg/dl within 48 h of admission compared with those experiencing persistent hyperglycaemia. However, several clinical studies have shown similar mortality and neurological prognosis in intensive insulin therapy (118–133 mg/dl) and conventional insulin therapy groups (8, 9, 12, 13). There are no consistent recommendations for optimal glycaemic targets for SIH in treating AIS due to limited clinical trial results. Current American Heart Association/American Stroke Association (AHA/ASA) guidelines for AIS recommend treating hyperglycaemia to stabilize blood glucose levels at 140 to 180 mg/dl (155). However, most guidelines endorse that tight glycaemic control (blood glucose <126 mg/dl) or hypoglycaemia is harmful and should be avoided (12, 156).

7.2.4. Hypoglycaemia

A recent meta-analysis on selecting an optimal glucose-lowering target for critical patients showed that glucose control levels <110 and 110–144 mg/ dl had a greater hypoglycaemia incidence vs. 144–180 and >180 mg/dl (157). Hypoglycaemia exacerbates brain damage after AIS by increasing oxidative stress and inflammatory response. Studies on rodent models have shown that repeated hypoglycaemia increases post-ischaemic brain injury in diabetic rats by increasing mitochondrial ROS production and decreasing mitochondrial complex I activity after ischaemia (158, 159). In addition, hypoglycaemia induces increased IL-6 production, platelet aggregation, vascular adhesion molecule production, and inhibition of fibrinolytic mechanisms (160–162). These changes eventually lead to vascular injury and new thrombosis, increasing the risk of local cerebral ischaemia. Therefore, repeated hypoglycaemia has been indicated as an essential reason for the unsuccessful intensive glucose-lowering therapy. Future trials should be aimed at controlling blood glucose to "broad" levels rather than intensively lowering glucose to avoid harm from irreversible hypoglycaemic events.

7.3. Other hypoglycaemic drugs

7.3.1. GLP-1 receptor agonists

Glucose-like peptide-1 (GLP-1) receptor agonists include exenatide, liraglutide, albiglutide, semaglutide, and dulaglutide considered to be the first alternative to insulin. GLP-1 is a peptide hormone secreted by the intestine following food stimulation and is implicated in regulating blood glucose homeostasis in the body. Natural GLP-1 is degraded by the endoprotease dipeptidyl-peptidase-4 (DPP-4) *in vivo* with an ∼2-min half-life. GLP-1 receptor agonists can perform the same biological actions as natural GLP-1 but also avoid degradation and loss of activity, thus prolonging the duration of action. GLP-1 maintains glucose endocrine homeostasis through several mechanisms, including but not limited to promoting insulin secretion from pancreatic β-cells, inhibiting glucagon production, improving β cell quality and function, and decreasing appetite and gastric emptying. GLP-1 receptor agonists rarely cause hypoglycaemia, and their main

drawback is mild to moderate gastrointestinal adverse effects. Findings from cardiovascular prognostic studies and meta-analyses suggest that GLP-1 receptor agonists reduce stroke incidence and have neuroprotective effects in DM patients (163). Some studies highlight that the neuroprotective effects of these drugs in AIS patients may be through the improvement of ischaemia-induced inflammation, support of BBB integrity by triggering the PI3K/AKT and mitogen-activated protein kinase (MAPK) pathway, as well as reducing ROS levels in ischaemic neurons (164, 165). The effectiveness and safeness of GLP-1 receptor agonists for treating hyperglycaemia after AIS has been demonstrated with exenatide at 9 h after AIS and continuing for 6 days to lower blood glucose (166). A recent multicenter randomized trial was designed to compare the difference in risk of hypoglycaemia and improvement in neurological prognosis with exenatide vs. standard of care. Exenatide 5 μg was administered subcutaneously twice daily in the treatment group, but the trial results have not yet been published (167).

7.3.2. DPP-4 inhibitors

Another recommended alternative therapy is DPP-4 inhibitors, which exert hypoglycaemic effects mainly by inhibiting the physiological degradation of GLP-1 in the blood, including alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin. Interestingly, DPP-4 inhibitors improve neurological prognosis after stroke in rodents, independent of GLP-1, possibly by increasing the bioavailability of other bioactive DPP-4 substrates, such as stromal cell-derived factor-1α (167). In addition, preclinical studies have found that these drugs can activate the Akt/mTOR pathway and anti-apoptotic and anti-inflammatory mechanisms to exert neuroprotective effects (168). However, two recent extensive randomized clinical studies have shown that DPP-4 inhibitors are ineffective in reducing ischaemic stroke risk following cardiovascular disease (169, 170). This is inconsistent with the neuroprotective conclusions drawn from preclinical studies and requires further experimental validation.

7.3.3. SGLT2 inhibitors

In addition to the two drugs mentioned above, the new glucose-lowering drug type, sodium glucose-linked cotransporter 2 (SGLT2) inhibitors, are recommended. Besides reducing blood glucose, SGLT2 inhibitors have antioxidant, anti-inflammatory, insulin resistance, and atherosclerotic plaque formation-reducing properties (171). In addition, SGLT2 inhibitors reversed hyperglycaemia-induced neuronal damage after acute cerebral ischaemia by inhibiting SGLT in a mouse model of temporary bilateral carotid stenosis (172). However, the current debate on whether SGLT2 inhibitors prevent strokes after cardiovascular disease is divided. In the EMPA-REG OUTCOM trial (173), there was a slight increase in stroke risk with empagliflozin. Some have attributed this trend to an elevated haematocrit in the empagliflozin group, which corresponds to an increased stroke risk due to increased blood viscosity. Fortunately, no such trend was found in the CANVAS trial (174). However, a meta-analysis concluded that SGLT2 inhibitors increased non-fatal stroke risk by 30% (175).

7.3.4. Metformin

Metformin, a biguanide derivative, is the principal drug indicated for type 2 DM (176). The hypoglycaemic pharmacological effects of metformin are mainly through reducing hepatic glycogenolysis and enhancing peripheral tissue glucose uptake and utilization (177). Studies have shown that metformin can exert post-stroke neuroprotective effects, possibly inhibiting ischaemia-induced neuronal death, oxidative stress, and inflammatory responses (178, 179). The opening of the mitochondrial permeability transition pore (MPTP) is a significant cause of neuronal mortality due to ischaemia (180). Metformin may prevent neuronal death by inhibiting mitochondrial respiratory chain complex I, preventing MPTP opening, and activating AMPK (181, 182). Furthermore, metformin was demonstrated to regulate AIS-induced oxidative stress damage and reduce markers of brain inflammation *via* the lncRNA-H19/miR-148a-3p/Rock2 axis (183, 184).

The drawbacks of metformin compared to intravenous insulin application in critical care patients are apparent. First, compared with the immediate hypoglycaemic effect of insulin, the blood dose concentration peaked approximately 3 h following oral metformin (185). It fails to adjust rapidly to the dramatic changes in blood glucose concentration in patients. An exploratory safety study of metformin in patients with the transient ischemic attack or minor ischaemic attack found that 20% of patients in the experimental group permanently discontinued the drug due to gastrointestinal side effects (186) and its metabolic characteristics of being excreted mainly through the kidneys (185), which both limit its application. Finally, intravenous insulin can be quickly adjusted to each patient's diet, facilitating the maintenance of blood glucose stability during hospitalization. Other oral hypoglycaemic agents are available for similar reasons, such as sulfonylureas, glinides, α-glucosidase inhibitors, thiazolidinediones, and DPP-4 inhibitors. Therefore, intravenous insulin application seems to be a more appropriate treatment option than oral agents, such as metformin, in the case of elevated blood glucose after AIS.

8. Conclusion and perspectives

In this review, we discuss the definition of SIH in the background of AIS, its formative mechanisms, and its dual impact on the central nervous system. Insulin is currently a widely accepted clinical treatment for post-AIS hyperglycaemia, but it does not achieve the desired effect in practice. In our analysis of intensive insulin treatment failure, the best definition of SIH should be independent of the existence of DM and strongly linked to short- and long-term efficacy. SHR, or the application of these definitions in combination, is a good option for future studies and needs further exploration. In addition, the treatment of SIH should consider the criteria for initiating glucose lowering after AIS, the timing of dosing and duration of treatment, the target range of glycaemic control, and treatment options other than insulin. GLP-1 receptor agonists are a potential new research target for treating SIH.

Author contributions

MY and YH reviewed the literature and wrote the draft manuscript. TW helped assess the literature. MX, HL, and JF drew the pictures. LF designed and revised the work. DM supervised the work. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Natural Science Foundation of Jilin Province (212558JC010685134 and 202512JC010376367).

Acknowledgments

We would like to thank Editage (www.editage.cn) for English language editing. Figures 1, 2 were modified from Servier Medical Art (http://smart.servier.com/), licensed under a Creative Common Attribution 3.0 Generic License (https://creativecommons.org/licenses/by/3.0/).

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Donkor ES. Stroke in the 21(st) century: A snapshot of the burden, epidemiology, and quality of life. *Stroke Res Treat.* (2018) 2018:3238165. doi: 10.1155/2018/3238165

2. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet.* (2009) 373:1798–807. doi: 10.1016/S0140-6736(09)60553-5

3. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke.* (2001) 32:2426–32. doi: 10.1161/hs1001.096194

4. Kim JT, Jahan R, Saver JL, Investigators S. Impact of glucose on outcomes in patients treated with mechanical thrombectomy: a post hoc analysis of the solitaire flow restoration with the intention for thrombectomy study. *Stroke.* (2016) 47:120–7. doi: 10.1161/STROKEAHA.115.010753

5. Stead LG, Gilmore RM, Bellolio MF, Mishra S, Bhagra A, Vaidyanathan L, et al. Hyperglycemia as an independent predictor of worse outcome in non-diabetic patients presenting with acute ischemic stroke. *Neurocrit Care.* (2009) 10:181–6. doi: 10.1007/s12028-008-9080-0

6. Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! *Crit Care.* (2013) 17:305. doi: 10.1186/cc12514

7. Kruyt ND, Biessels GJ, Devries JH, Roos YB. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. *Nat Rev Neurol.* (2010) 6:145–55. doi: 10.1038/nrneurol.2009.231

8. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the uk glucose insulin in stroke trial (gist-uk). *Lancet Neurol.* (2007) 6:397–406. doi: 10.1016/S1474-4422(07)70080-7

9. Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, et al. Treatment of hyperglycemia in ischemic stroke (this): a randomized pilot trial. *Stroke.* (2008) 39:384–9. doi: 10.1161/STROKEAHA.107.493544

10. McCormick M, Hadley D, McLean JR, Macfarlane JA, Condon B, Muir KW. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol.* (2010) 67:570–8. doi: 10.1002/ana.21983

11. Staszewski J, Brodacki B, Kotowicz J, Stepien A. Intravenous insulin therapy in the maintenance of strict glycemic control in nondiabetic acute stroke patients with mild hyperglycemia. *J Stroke Cerebrovasc Dis.* (2011) 20:150–4. doi: 10.1016/j.jstrokecerebrovasdis.2009.11.013

12. Rosso C, Corvol JC, Pires C, Crozier S, Attal Y, Jacqueminet S, et al. Intensive versus subcutaneous insulin in patients with hyperacute stroke: results from the randomized insulinfarct trial. *Stroke.* (2012) 43:2343–9. doi: 10.1161/STROKEAHA.112.657122

13. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, et al. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: The shine randomized clinical trial. *JAMA.* (2019) 322:326–35. doi: 10.1001/jama.2019.9346

14. Ntaios G, Egli M, Faouzi M, Michel P. J-shaped association between serum glucose and functional outcome in acute ischemic stroke. *Stroke.* (2010) 41:2366–70. doi: 10.1161/STROKEAHA.110.592170

15. Zonneveld TP, Nederkoorn PJ, Westendorp WF, Brouwer MC, van de Beek D, Kruyt ND. Hyperglycemia predicts poststroke infections in acute ischemic stroke. *Neurology.* (2017) 88:1415–21. doi: 10.1212/WNL.0000000000003811

16. Saqqur M, Shuaib A, Alexandrov AV, Sebastian J, Khan K, Uchino K. The correlation between admission blood glucose and intravenous rt-PA-induced arterial recanalization in acute ischemic stroke: a multi-centre TCD study. *Int J Stroke.* (2015) 10:1087–92. doi: 10.1111/ijs.12517

17. Fang HJ, Pan YS, Wang YJ, Wang CX, Wang YL, Zhong LY. Prognostic value of admission hyperglycemia on outcomes of thrombolysis in ischemic stroke patients with or without diabetes. *Chin Med J.* (2020) 133:2244–6. doi: 10.1097/CM9.0000000000001005

18. Goyal N, Tsivgoulis G, Pandhi A, Dillard K, Katsanos AH, Magoufis G, et al. Admission hyperglycemia and outcomes in large vessel occlusion strokes treated with mechanical thrombectomy. *J Neurointerv Surg.* (2018) 10:112–7. doi: 10.1136/neurintsurg-2017-012993

19. Osei E, Den Hertog HM, Berkhemer OA, Fransen PS, Roos YB, Beumer D, et al. Increased admission and fasting glucose are associated with unfavorable short-term outcome after intra-arterial treatment of ischemic stroke in the mr clean pretrial cohort. *J Neurol Sci.* (2016) 371:1–5. doi: 10.1016/j.jns.2016.10.003

20. Osei E, Den Hertog HM, Berkhemer OA, Fransen PSS, Roos Y, Beumer D, et al. Admission glucose and effect of intra-arterial treatment in patients with acute ischemic stroke. *Stroke.* (2017) 48:1299–305. doi: 10.1161/STROKEAHA.116.016071

21. Farrokhnia N, Björk E, Lindbäck J, Terent A. Blood glucose in acute stroke, different therapeutic targets for diabetic and non-diabetic patients? *Acta Neurol Scand.* (2005) 112:81–7. doi: 10.1111/j.1600-0404.2005.00440.x

22. Snarska KK, Bachórzewska-Gajewska H, Kapica-Topczewska K, Drozdowski W, Chorazy M, Kułakowska A, et al. Hyperglycemia and diabetes have different impacts on outcome of ischemic and hemorrhagic stroke. *Arch Med Sci.* (2017) 13:100–8. doi: 10.5114/aoms.2016.61009

23. Fuentes B, Castillo J, San José B, Leira R, Serena J, Vivancos J, et al. The prognostic value of capillary glucose levels in acute stroke: The glycemia in acute stroke (glias) study. *Stroke.* (2009) 40:562–8. doi: 10.1161/STROKEAHA.108.519926

24. Yang CJ, Liao WI, Wang JC, Tsai CL, Lee JT, Peng GS, et al. Usefulness of glycated hemoglobin a1c-based adjusted glycemic variables in diabetic patients presenting with acute ischemic stroke. *Am J Emerg Med.* (2017) 35:1240–6. doi: 10.1016/j.ajem.2017.03.049

25. Zhu B, Pan Y, Jing J, Meng X, Zhao X, Liu L, et al. Stress hyperglycemia and outcome of non-diabetic patients after acute ischemic stroke. *Front Neurol.* (2019) 10:1003. doi: 10.3389/fneur.2019.01003

26. Li J, Quan K, Wang Y, Zhao X, Li Z, Pan Y, et al. Effect of stress hyperglycemia on neurological deficit and mortality in the acute ischemic stroke people with and without diabetes. *Front Neurol.* (2020) 11:576895. doi: 10.3389/fneur.2020.576895

27. Yuan C, Chen S, Ruan Y, Liu Y, Cheng H, Zeng Y, et al. The stress hyperglycemia ratio is associated with hemorrhagic transformation in patients with acute ischemic stroke. *Clin Interv Aging.* (2021) 16:431–42. doi: 10.2147/CIA.S280808

28. Mi D, Li Z, Gu H, Jiang Y, Zhao X, Wang Y, et al. Stress hyperglycemia is associated with in-hospital mortality in patients with diabetes and acute ischemic stroke. *CNS Neurosci Ther.* (2022) 28:372–81. doi: 10.1111/cns.13764

29. Merlino G, Smeralda C, Gigli GL, Lorenzut S, Pez S, Surcinelli A, et al. Stress hyperglycemia is predictive of worse outcome in patients with acute ischemic stroke undergoing intravenous thrombolysis. *J Thromb Thrombolysis.* (2021) 51:789–97. doi: 10.1007/s11239-020-02252-y

30. Shen CL, Xia NG, Wang H, Zhang WL. Association of stress hyperglycemia ratio with acute ischemic stroke outcomes post-thrombolysis. *Front Neurol.* (2021) 12:785428. doi: 10.3389/fneur.2021.785428

31. Wang L, Cheng Q, Hu T, Wang N, Wei X, Wu T, et al. Impact of stress hyperglycemia on early neurological deterioration in acute ischemic stroke patients treated with intravenous thrombolysis. *Front Neurol.* (2022) 13:870872. doi: 10.3389/fneur.2022.870872

32. Merlino G, Pez S, Tereshko Y, Gigli GL, Lorenzut S, Surcinelli A, et al. Stress hyperglycemia does not affect clinical outcome of diabetic patients receiving intravenous thrombolysis for acute ischemic stroke. *Front Neurol.* (2022) 13:903987. doi: 10.3389/fneur.2022.903987

33. Ngiam JN, Cheong CWS, Leow AST, Wei YT, Thet JKX, Lee IYS, et al. Stress hyperglycaemia is associated with poor functional outcomes in patients with acute ischaemic stroke after intravenous thrombolysis. *QJM.* (2022) 115:7–11. doi: 10.1093/qjmed/hcaa253

34. Merlino G, Pez S, Gigli GL, Sponza M, Lorenzut S, Surcinelli A, et al. Stress hyperglycemia in patients with acute ischemic stroke due to large vessel occlusion undergoing mechanical thrombectomy. *Front Neurol.* (2021) 12:725002. doi: 10.3389/fneur.2021.725002

35. Chen X, Liu Z, Miao J, Zheng W, Yang Q, Ye X, et al. High stress hyperglycemia ratio predicts poor outcome after mechanical thrombectomy for ischemic stroke. *J Stroke Cerebrovasc Dis.* (2019) 28:1668–73. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.022

36. Hui J, Zhang J, Mao X, Li Z, Li X, Wang F, et al. The initial glycemic variability is associated with early neurological deterioration in diabetic patients with acute ischemic stroke. *Neurol Sci.* (2018) 39:1571–7. doi: 10.1007/s10072-018-3463-6

37. Lin J, Cai C, Xie Y, Yi L. Acute glycemic variability and mortality of patients with acute stroke: a meta-analysis. *Diabetol Metab Syndr.* (2022) 14:69. doi: 10.1186/s13098-022-00826-9

38. Baudu J, Gerbaud E, Catargi B, Montaudon M, Beauvieux MC, Sagnier S, et al. High glycemic variability: an underestimated determinant of stroke functional outcome following large vessel occlusion. *Rev Neurol.* (2022) 178:732–40. doi: 10.1016/j.neurol.2021.12.010

39. Lim JS, Kim C, Oh MS, Lee JH, Jung S, Jang MU, et al. Effects of glycemic variability and hyperglycemia in acute ischemic stroke on post-stroke cognitive impairments. *J Diabetes Complications.* (2018) 32:682–7. doi: 10.1016/j.jdiacomp.2018.02.006

40. Kim TJ, Lee JS, Park SH, Ko SB. Short-term glycemic variability and hemorrhagic transformation after successful endovascular thrombectomy. *Transl Stroke Res.* (2021) 12:968–75. doi: 10.1007/s12975-021-00895-4

41. Kim YS, Kim C, Jung KH, Kwon HM, Heo SH, Kim BJ, et al. Range of glucose as a glycemic variability and 3-month outcome in diabetic patients with acute ischemic stroke. *PLoS ONE.* (2017) 12:e0183894. doi: 10.1371/journal.pone.0183894

42. Yoon JE, Sunwoo JS, Kim JS, Roh H, Ahn MY, Woo HY, et al. Poststroke glycemic variability increased recurrent cardiovascular events in diabetic patients. *J Diabetes Complications.* (2017) 31:390–4. doi: 10.1016/j.jdiacomp.2016.11.014

43. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet.* (2000) 355:773–8. doi: 10.1016/S0140-6736(99)08415-9

44. Yao M, Ni J, Zhou LX, Peng B, Zhu YC, Cui LY, et al. Elevated fasting blood glucose is predictive of poor outcome in non-diabetic stroke patients: a sub-group analysis of smart. *PLoS ONE.* (2016) 11:e0160674. doi: 10.1371/journal.pone.0160674

45. Chen G, Ren J, Huang H, Shen J, Yang C, Hu J, et al. Admission random blood glucose, fasting blood glucose, stress hyperglycemia ratio, and functional outcomes in patients with acute ischemic stroke treated with intravenous thrombolysis. *Front Aging Neurosci.* (2022) 14:782282. doi: 10.3389/fnagi.2022.782282

46. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes.* (2008) 57:1349–54. doi: 10.2337/db08-0063

47. Allen CL, Bayraktutan U. Oxidative stress and its role in the pathogenesis of ischaemic stroke. *Int J Stroke.* (2009) 4:461–70. doi: 10.1111/j.1747-4949.2009.00387.x

48. Monnier L, Colette C, Owens DR. Glycemic variability: The third component of the dysglycemia in diabetes. Is it important? How to measure it? *J Diabetes Sci Technol.* (2008) 2:1094–100. doi: 10.1177/193229680800200618

49. Rama Chandran S, Tay WL, Lye WK, Lim LL, Ratnasingam J, Tan ATB, et al. Beyond hba1c: comparing glycemic variability and glycemic indices in predicting hypoglycemia in type 1 and type 2 diabetes. *Diabetes Technol Ther.* (2018) 20:353–62. doi: 10.1089/dia.2017.0388

50. Zhou Z, Sun B, Huang S, Zhu C, Bian M. Glycemic variability: adverse clinical outcomes and how to improve it? *Cardiovasc Diabetol.* (2020) 19:102. doi: 10.1186/s12933-020-01085-6

51. Lin CC, Yang CP Li CI, Liu CS, Chen CC, Lin WY, et al. Visit-to-visit variability of fasting plasma glucose as predictor of ischemic stroke: Competing risk analysis in a national cohort of taiwan diabetes study. *BMC Med.* (2014) 12:165. doi: 10.1186/s12916-014-0165-7

52. Allport LE, Butcher KS, Baird TA, MacGregor L, Desmond PM, Tress BM, et al. Insular cortical ischemia is independently associated with acute stress hyperglycemia. *Stroke.* (2004) 35:1886–91. doi: 10.1161/01.STR.0000133687.33868.71

53. Moreton FC, McCormick M, Muir KW. Insular cortex hypoperfusion and acute phase blood glucose after stroke: a ct perfusion study. *Stroke.* (2007) 38:407–10. doi: 10.1161/01.STR.0000254487.73282.4d

54. Pettersen JA, Pexman JH, Barber PA, Demchuk AM, Buchan AM, Hill MD. Insular cortical ischaemia does not independently predict acute hypertension or hyperglycaemia within 3 h of onset. *J Neurol Neurosurg Psychiatry.* (2006) 77:885–7. doi: 10.1136/jnnp.2005.087494

55. Zhao Z, Wang L, Gao W, Hu F, Zhang J, Ren Y, et al. A central catecholaminergic circuit controls blood glucose levels during stress. *Neuron*. (2017) 95:138–52e5. doi: 10.1016/j.neuron.2017.05.031

56. Sawchenko PE, Swanson LW. The organization of noradrenergic pathways from the brainstem to the paraventricular and supraoptic nuclei in the rat. *Brain Res.* (1982) 257:275–325. doi: 10.1016/0165-0173(82)90010-8

57. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci.* (2009) 10:397–409. doi: 10.1038/nrn2647

58. Vanhorebeek I, Van den Berghe G. Diabetes of injury: novel insights. *Endocrinol Metab Clin North Am*. (2006) 35:859–72. doi: 10.1016/j.ecl.2006.09.002

59. Wise JK, Hendler R, Felig P. Influence of glucocorticoids on glucagon secretion and plasma amino acid concentrations in man. *J Clin Invest.* (1973) 52:2774–82. doi: 10.1172/JCI107473

60. Kahn CR, White MF. The insulin receptor and the molecular mechanism of insulin action. *J Clin Invest.* (1988) 82:1151–6. doi: 10.1172/JCI113711

61. Saltiel AR, Pessin JE. Insulin signaling pathways in time and space. *Trends Cell Biol.* (2002) 12:65–71. doi: 10.1016/S0962-8924(01)02207-3

62. Stephens JM, Pekala PH. Transcriptional repression of the glut4 and c/ebp genes in 3t3-l1 adipocytes by tumor necrosis factor-alpha. *J Biol Chem.* (1991) 266:21839–45. doi: 10.1016/S0021-9258(18)54714-1

63. Raje V, Ahern KW, Martinez BA, Howell NL, Oenarto V, Granade ME, et al. Adipocyte lipolysis drives acute stress-induced insulin resistance. *Sci Rep.* (2020) 10:18166. doi: 10.1038/s41598-020-75321-0

64. Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, et al. Effects of free fatty acids on glucose transport and irs-1-associated phosphatidylinositol 3-kinase activity. *J Clin Invest.* (1999) 103:253–9. doi: 10.1172/JCI5001

65. Kelley DE, Mokan M, Simoneau JA, Mandarino LJ. Interaction between glucose and free fatty acid metabolism in human skeletal muscle. *J Clin Invest.* (1993) 92:91–8. doi: 10.1172/JCI116603

66. Wang YY, Lin SY, Chuang YH, Chen CJ, Tung KC, Sheu WH. Adipose proinflammatory cytokine expression through sympathetic system is associated with hyperglycemia and insulin resistance in a rat ischemic stroke model. *Am J Physiol Endocrinol Metab.* (2011) 300:E155–63. doi: 10.1152/ajpendo.00301.2010

67. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol.* (2005) 115:911–9; 20. doi: 10.1016/j.jaci.2005.02.023

68. Blumberg D, Hochwald S, Burt M, Donner D, Brennan MF. Tumor necrosis factor alpha stimulates gluconeogenesis from alanine in vivo. *J Surg Oncol.* (1995) 59:220–4; 4–5. doi: 10.1002/jso.2930590404

69. Ibayashi S, Fujishima M, Sadoshima S, Yoshida F, Shiokawa O, Ogata J, et al. Cerebral blood flow and tissue metabolism in experimental cerebral ischemia of spontaneously hypertensive rats with hyper-, normo-, and hypoglycemia. *Stroke.* (1986) 17:261–6. doi: 10.1161/01.STR.17.2.261

70. Kraft SA, Larson CP Jr, Shuer LM, Steinberg GK, Benson GV, Pearl RG. Effect of hyperglycemia on neuronal changes in a rabbit model of focal cerebral ischemia. *Stroke.* (1990) 21:447–50. doi: 10.1161/01.STR.21.3.447

71. McNamara JJ, Mills D, Aaby GV. Effect of hypertonic glucose on hemorrhagic shock in rabbits. *Ann Thorac Surg.* (1970) 9:116–21. doi: 10.1016/S0003-4975(10)65784-0

72. Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. *Brain*. (2007) 130:1626–30. doi: 10.1093/brain/awm087

73. Bruno A, Biller J, Adams HP Jr, Clarke WR, Woolson RF, Williams LS, et al. Acute blood glucose level and outcome from ischemic stroke. Trial of org 10172 in acute stroke treatment (toast) investigators. *Neurology*. (1999) 52:280–4. doi: 10.1212/WNL.52.2.280

74. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol.* (2002) 52:20–8. doi: 10.1002/ana.10241

75. Xu G, Takashi E, Kudo M, Ishiwata T, Naito Z. Contradictory effects of short- and long-term hyperglycemias on ischemic injury of myocardium via intracellular signaling pathway. *Exp Mol Pathol.* (2004) 76:57–65. doi: 10.1016/j.yexmp.2003.08.003

76. Ma G, Al-Shabrawey M, Johnson JA, Datar R, Tawfik HE, Guo D, et al. Protection against myocardial ischemia/reperfusion injury by short-term diabetes: Enhancement of vegf formation, capillary density, and activation of cell survival signaling. *Naunyn Schmiedebergs Arch Pharmacol.* (2006) 373:415–27. doi: 10.1007/s00210-006-0102-1

77. Chu LM, Osipov RM, Robich MP, Feng J, Oyamada S, Bianchi C, et al. Is hyperglycemia bad for the heart during acute ischemia? *J Thorac Cardiovasc Surg.* (2010) 140:1345–52. doi: 10.1016/j.jtcvs.2010.05.009

78. Malfitano C, Alba Loureiro TC, Rodrigues B, Sirvente R, Salemi VM, Rabechi NB, et al. Hyperglycaemia protects the heart after myocardial infarction: Aspects of programmed cell survival and cell death. *Eur J Heart Fail.* (2010) 12:659–67. doi: 10.1093/eurjhf/hfq053

79. Malfitano C, Barboza CA, Mostarda C, da Palma RK, dos Santos CP, Rodrigues B, et al. Diabetic hyperglycemia attenuates sympathetic dysfunction and oxidative stress after myocardial infarction in rats. *Cardiovasc Diabetol.* (2014) 13:131. doi: 10.1186/s12933-014-0131-x

80. Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost.* (2010) 8:1663–9. doi: 10.1111/j.1538-7836.2010.03910.x

81. Stegenga ME, Van der Crabben SN, Levi M, de Vos AF, Tanck MW, Sauerwein HP, et al. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. *Diabetes.* (2006) 55:1807–12. doi: 10.2337/db05-1543

82. Pandolfi A, Giaccari A, Cilli C, Alberta MM, Morviducci L, De Filippis EA, et al. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. *Acta Diabetol.* (2001) 38:71–6. doi: 10.1007/s005920170016

83. Pandolfi A, Iacoviello L, Capani F, Vitacolonna E, Donati MB, Consoli A. Glucose and insulin independently reduce the fibrinolytic potential of human vascular smooth muscle cells in culture. *Diabetologia.* (1996) 39:1425–31. doi: 10.1007/s001250050594

84. Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, et al. Acute hyperglycemia state is associated with lower tpa-induced recanalization rates in stroke patients. *Stroke.* (2005) 36:1705–9. doi: 10.1161/01.STR.0000173161.05453.90.9f

85. Nakai H, Yamamoto YL, Diksic M, Worsley KJ, Takara E. Triple-tracer autoradiography demonstrates effects of hyperglycemia on cerebral blood flow, ph, and glucose utilization in cerebral ischemia of rats. *Stroke.* (1988) 19:764–72. doi: 10.1161/01.STR.19.6.764

86. Duckrow RB, Beard DC, Brennan RW. Regional cerebral blood flow decreases during chronic and acute hyperglycemia. *Stroke.* (1987) 18:52–8. doi: 10.1161/01.STR.18.1.52

87. Ginsberg MD, Welsh FA, Budd WW. Deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat. I. Local cerebral blood flow and glucose utilization. *Stroke.* (1980) 11:347–54. doi: 10.1161/01.STR.11.4.347

88. Duckrow RB, Beard DC, Brennan RW. Regional cerebral blood flow decreases during hyperglycemia. *Ann Neurol.* (1985) 17:267–72. doi: 10.1002/ana.410170308

89. Fabian RH, Kent TA. Hyperglycemia accentuates persistent "functional uncoupling" of cerebral microvascular nitric oxide and superoxide following focal ischemia/reperfusion in rats. *Transl Stroke Res.* (2012) 3:482–90. doi: 10.1007/s12975-012-0210-9

90. Meza CA, La Favor JD, Kim DH, Hickner RC. Endothelial dysfunction: Is there a hyperglycemia-induced imbalance of nox and nos? *Int J Mol Sci.* (2019) 20:3775. doi: 10.3390/ijms20153775

91. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol.* (2007) 39:44–84. doi: 10.1016/j.biocel.2006.07.001

92. Suh SW, Shin BS, Ma H, Van Hoecke M, Brennan AM, Yenari MA, et al. Glucose and nadph oxidase drive neuronal superoxide formation in stroke. *Ann Neurol.* (2008) 64:654–63. doi: 10.1002/ana.21511

93. Allen CL, Bayraktutan U. Antioxidants attenuate hyperglycaemia-mediated brain endothelial cell dysfunction and blood-brain barrier hyperpermeability. *Diabetes Obes Metab.* (2009) 11:480–90. doi: 10.1111/j.1463-1326.2008.00987.x

94. Zhang Z, Yan J, Shi H. Role of hypoxia inducible factor 1 in hyperglycemia-exacerbated blood-brain barrier disruption in ischemic stroke. *Neurobiol Dis.* (2016) 95:82–92. doi: 10.1016/j.nbd.2016.07.012

95. Venkat P, Chopp M, Chen J. Blood-brain barrier disruption, vascular impairment, and ischemia/reperfusion damage in diabetic stroke. *J Am Heart Assoc.* (2017) 6:e005819. doi: 10.1161/JAHA.117.005819

96. Bémeur C, Ste-Marie L, Montgomery J. Increased oxidative stress during hyperglycemic cerebral ischemia. *Neurochem Int.* (2007) 50:890–904. doi: 10.1016/j.neuint.2007.03.002

97. Guo Y, Dong L, Gong A, Zhang J, Jing L, Ding T, et al. Damage to the blood-brain barrier and activation of neuroinflammation by focal cerebral ischemia under hyperglycemic condition. *Int J Mol Med.* (2021) 48:142. doi: 10.3892/ijmm.2021.4975

98. Aljada A, Ghanim H, Mohanty P, Syed T, Bandyopadhyay A, Dandona P. Glucose intake induces an increase in activator protein 1 and early growth response 1 binding activities, in the expression of tissue factor and matrix metalloproteinase in mononuclear cells, and in plasma tissue factor and matrix metalloproteinase concentrations. *Am J Clin Nutr.* (2004) 80:51–7. doi: 10.1093/ajcn/80.1.51

99. Ahn JD, Morishita R, Kaneda Y, Lee KU, Park JY, Jeon YJ, et al. Transcription factor decoy for activator protein-1 (ap-1) inhibits high glucose- and angiotensin ii-induced type 1 plasminogen activator inhibitor (pai-1) gene expression in cultured human vascular smooth muscle cells. *Diabetologia.* (2001) 44:713–20. doi: 10.1007/s001250051680

100. Hawkins BT, Lundeen TF, Norwood KM, Brooks HL, Egleton RD. Increased blood-brain barrier permeability and altered tight junctions in experimental diabetes in the rat: contribution of hyperglycaemia and matrix metalloproteinases. *Diabetologia.* (2007) 50:202–11. doi: 10.1007/s00125-006-0485-z

101. Kamada H, Yu F, Nito C, Chan PH. Influence of hyperglycemia on oxidative stress and matrix metalloproteinase-9 activation after focal cerebral ischemia/reperfusion in rats: relation to blood-brain barrier dysfunction. *Stroke.* (2007) 38:1044–9. doi: 10.1161/01.STR.0000258041.75739.cb

102. Dhindsa S, Tripathy D, Mohanty P, Ghanim H, Syed T, Aljada A, et al. Differential effects of glucose and alcohol on reactive oxygen species generation and intranuclear nuclear factor-kappab in mononuclear cells. *Metabolism.* (2004) 53:330–4. doi: 10.1016/j.metabol.2003.10.013

103. Barnes PJ, Karin M. Nuclear factor-kappab: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med.* (1997) 336:1066–71. doi: 10.1056/NEJM199704103361506

104. El-Osta A, Brasacchio D, Yao D, Pocai A, Jones PL, Roeder RG, et al. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. *J Exp Med.* (2008) 205:2409–17. doi: 10.1084/jem.20081188

105. Jing L, Wang JG, Zhang JZ, Cao CX, Chang Y, Dong JD, et al. Upregulation of icam-1 in diabetic rats after transient forebrain ischemia and reperfusion injury. *J Inflamm.* (2014) 11:35. doi: 10.1186/s12950-014-0035-2

106. Morigi M, Angioletti S, Imberti B, Donadelli R, Micheletti G, Figliuzzi M, et al. Leukocyte-endothelial interaction is augmented by high glucose concentrations and hyperglycemia in a nf-kb-dependent fashion. *J Clin Invest.* (1998) 101:1905–15. doi: 10.1172/JCI656

107. Okada Y, Copeland BR, Mori E, Tung MM, Thomas WS, del Zoppo GJ. P-selectin and intercellular adhesion molecule-1 expression after focal brain ischemia and reperfusion. *Stroke.* (1994) 25:202–11. doi: 10.1161/01.STR.25.1.202

108. Clark WM, Lauten JD, Lessov N, Woodward W, Coull BM. Time course of icam-1 expression and leukocyte subset infiltration in rat forebrain ischemia. *Mol Chem Neuropathol.* (1995) 26:213–30. doi: 10.1007/BF02815139

109. Del Zoppo GJ, Mabuchi T. Cerebral microvessel responses to focal ischemia. *J Cereb Blood Flow Metab.* (2003) 23:879–94. doi: 10.1097/01.WCB.0000078322.96027.78

110. Gallagher CN, Carpenter KL, Grice P, Howe DJ, Mason A, Timofeev I, et al. The human brain utilizes lactate via the tricarboxylic acid cycle: A 13c-labelled microdialysis and high-resolution nuclear magnetic resonance study. *Brain*. (2009) 132:2839–49. doi: 10.1093/brain/awp202

111. Sotelo-Hitschfeld T, Fernández-Moncada I, Barros LF. Acute feedback control of astrocytic glycolysis by lactate. *Glia.* (2012) 60:674–80. doi: 10.1002/glia.22304

112. Wagner KR, Kleinholz M, de Courten-Myers GM, Myers RE. Hyperglycemic versus normoglycemic stroke: Topography of brain metabolites, intracellular ph, and infarct size. *J Cereb Blood Flow Metab.* (1992) 12:213–22. doi: 10.1038/jcbfm.1992.31

113. Chew W, Kucharczyk J, Moseley M, Derugin N, Norman D. Hyperglycemia augments ischemic brain injury: in vivo mr imaging/spectroscopic study with nicardipine in cats with occluded middle cerebral arteries. *AJNR Am J Neuroradiol.* (1991) 12:603–9.

114. Lipton P. Ischemic cell death in brain neurons. *Physiol Rev.* (1999) 79:1431–568. doi: 10.1152/physrev.1999.79.4.1431

115. Obrenovitch TP, Urenjak J, Richards DA, Ueda Y, Curzon G, Symon L. Extracellular neuroactive amino acids in the rat striatum during ischaemia: Comparison between penumbral conditions and

ischaemia with sustained anoxic depolarisation. *J Neurochem.* (1993) 61:178–86. doi: 10.1111/j.1471-4159.1993.tb03553.x

116. Li PA, Shuaib A, Miyashita H, He QP, Siesjö BK, Warner DS. Hyperglycemia enhances extracellular glutamate accumulation in rats subjected to forebrain ischemia. *Stroke.* (2000) 31:183–92. doi: 10.1161/01.STR.31.1.183

117. Martel MA, Ryan TJ, Bell KF, Fowler JH, McMahon A, Al-Mubarak B, et al. The subtype of glun2 c-terminal domain determines the response to excitotoxic insults. *Neuron.* (2012) 74:543–56. doi: 10.1016/j.neuron.2012.03.021

118. Luetjens CM, Bui NT, Sengpiel B, Münstermann G, Poppe M, Krohn AJ, et al. Delayed mitochondrial dysfunction in excitotoxic neuron death: cytochrome c release and a secondary increase in superoxide production. *J Neurosci.* (2000) 20:5715–23. doi: 10.1523/JNEUROSCI.20-15-05715.2000

119. Jiang X, Wang X. Cytochrome c promotes caspase-9 activation by inducing nucleotide binding to apaf-1. *J Biol Chem.* (2000) 275:31199–203. doi: 10.1074/jbc.C000405200

120. Porter AG, Jänicke RU. Emerging roles of caspase-3 in apoptosis. *Cell Death Differ.* (1999) 6:99–104. doi: 10.1038/sj.cdd.4400476

121. Cheng YR, Jiang BY, Chen CC. Acid-sensing ion channels: dual function proteins for chemo-sensing and mechano-sensing. *J Biomed Sci.* (2018) 25:46. doi: 10.1186/s12929-018-0448-y

122. Storozhuk M, Cherninskyi A, Maximyuk O, Isaev D, Krishtal O. Acid-sensing ion channels: focus on physiological and some pathological roles in the brain. *Curr Neuropharmacol.* (2021) 19:1570–89. doi: 10.2174/1570159X19666210125151824

123. Xiong ZG, Zhu XM, Chu XP, Minami M, Hey J, Wei WL, et al. Neuroprotection in ischemia: blocking calcium-permeable acid-sensing ion channels. *Cell.* (2004) 118:687–98. doi: 10.1016/j.cell.2004.08.026

124. Li M, Inoue K, Branigan D, Kratzer E, Hansen JC, Chen JW, et al. Acid-sensing ion channels in acidosis-induced injury of human brain neurons. *J Cereb Blood Flow Metab.* (2010) 30:1247–60. doi: 10.1038/jcbfm.2010.30

125. Araki N, Greenberg JH, Sladky JT, Uematsu D, Karp A, Reivich M. The effect of hyperglycemia on intracellular calcium in stroke. *J Cereb Blood Flow Metab.* (1992) 12:469–76. doi: 10.1038/jcbfm.1992.64

126. Voll CL, Auer RN. The effect of postischemic blood glucose levels on ischemic brain damage in the rat. *Ann Neurol.* (1988) 24:638–46. doi: 10.1002/ana.410240508

127. Zhu CZ, Auer RN. Intraventricular administration of insulin and igf-1 in transient forebrain ischemia. *J Cereb Blood Flow Metab.* (1994) 14:237–42. doi: 10.1038/jcbfm.1994.30

128. Hamilton MG, Tranmer BI, Auer RN. Insulin reduction of cerebral infarction due to transient focal ischemia. *J Neurosurg.* (1995) 82:262–8. doi: 10.3171/jns.1995.82.2.0262

129. Ahmadi-Eslamloo H, Dehghani GA, Moosavi SMS. Long-term treatment of diabetic rats with vanadyl sulfate or insulin attenuate acute focal cerebral ischemia/reperfusion injury via their antiglycemic effect. *Metab Brain Dis.* (2018) 33:225–35. doi: 10.1007/s11011-017-0153-7

130. Shuaib A, Ijaz MS, Waqar T, Voll C, Kanthan R, Miyashita H, et al. Insulin elevates hippocampal gaba levels during ischemia. This is independent of its hypoglycemic effect. *Neuroscience.* (1995) 67:809–14. doi: 10.1016/0306-4522(95)00093-X

131. Lanier WL, Hofer RE, Gallagher WJ. Metabolism of glucose, glycogen, and high-energy phosphates during transient forebrain ischemia in diabetic rats: effect of insulin treatment. *Anesthesiology.* (1996) 84:917–25. doi: 10.1097/00000542-199604000-00020

132. Sullivan JM, Alousi SS, Hikade KR, Bahu NJ, Rafols JA, Krause GS, et al. Insulin induces dephosphorylation of eukaryotic initiation factor 2alpha and restores protein synthesis in vulnerable hippocampal neurons after transient brain ischemia. *J Cereb Blood Flow Metab.* (1999) 19:1010–9. doi: 10.1097/00004647-199909000-00009

133. Guyot LL, Diaz FG, O'Regan MH, Song D, Phillis JW. The effect of topical insulin on the release of excitotoxic and other amino acids from the rat cerebral cortex during streptozotocin-induced hyperglycemic ischemia. *Brain Res.* (2000) 872:29–36. doi: 10.1016/S0006-8993(00)02426-4

134. Hui L, Pei DS, Zhang QG, Guan QH, Zhang GY. The neuroprotection of insulin on ischemic brain injury in rat hippocampus through negative regulation of jnk signaling pathway by pi3k/akt activation. *Brain Res.* (2005) 1052:1–9. doi: 10.1016/j.brainres.2005.05.043

135. Sanderson TH, Kumar R, Murariu-Dobrin AC, Page AB, Krause GS, Sullivan JM. Insulin activates the pi3k-akt survival pathway in vulnerable neurons following global brain ischemia. *Neurol Res.* (2009) 31:947–58. doi: 10.1179/174313209X382449

136. Fanne RA, Nassar T, Heyman SN, Hijazi N, Higazi AA. Insulin and glucagon share the same mechanism of neuroprotection in diabetic rats: role of glutamate. *Am J Physiol Regul Integr Comp Physiol.* (2011) 301:R668–73. doi: 10.1152/ajpregu.00058.2011

137. Fan X, Ning M, Lo EH, Wang X. Early insulin glycemic control combined with tpa thrombolysis reduces acute brain tissue damages in a focal embolic stroke model of diabetic rats. *Stroke.* (2013) 44:255–9. doi: 10.1161/STROKEAHA.112.663476

138. Sanderson TH, Mahapatra G, Pecina P, Ji Q, Yu K, Sinkler C, et al. Cytochrome c is tyrosine 97 phosphorylated by neuroprotective insulin treatment. *PLoS ONE.* (2013) 8:e78627. doi: 10.1371/journal.pone.0078627

139. Hung LM, Huang JP, Liao JM, Yang MH Li DE, Day YJ, et al. Insulin renders diabetic rats resistant to acute ischemic stroke by arresting nitric oxide reaction with superoxide to form peroxynitrite. *J Biomed Sci.* (2014) 21:92. doi: 10.1186/s12929-014-0092-0

140. Huang SS, Lu YJ, Huang JP, Wu YT, Day YJ, Hung LM. The essential role of endothelial nitric oxide synthase activation in insulin-mediated neuroprotection against ischemic stroke in diabetes. *J Vasc Surg.* (2014) 59:483–91. doi: 10.1016/j.jvs.2013.03.023

141. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (digami study): Effects on mortality at 1 year. *J Am Coll Cardiol.* (1995) 26:57–65. doi: 10.1016/0735-1097(95)00126-K

142. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* (2001) 345:1359–67. doi: 10.1056/NEJMoa011300

143. Bruno A, Saha C, Williams LS, Shankar R. Iv insulin during acute cerebral infarction in diabetic patients. *Neurology.* (2004) 62:1441–2. doi: 10.1212/01.WNL.0000120754.73348.02

144. Walters MR, Weir CJ, Lees KR. A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycaemic acute ischaemic stroke patients. *Cerebrovasc Dis.* (2006) 22:116–22. doi: 10.1159/000093239

145. Johnston KC, Hall CE, Kissela BM, Bleck TP, Conaway MR. Glucose regulation in acute stroke patients (grasp) trial: a randomized pilot trial. *Stroke.* (2009) 40:3804–9. doi: 10.1161/STROKEAHA.109.561498

146. Kreisel SH, Berschin UM, Hammes HP, Leweling H, Bertsch T, Hennerici MG, et al. Pragmatic management of hyperglycaemia in acute ischaemic stroke: Safety and feasibility of intensive intravenous insulin treatment. *Cerebrovasc Dis.* (2009) 27:167–75. doi: 10.1159/000185608

147. Kruyt ND, Biessels GJ, Vriesendorp TM, Devries JH, Hoekstra JB, Elbers PW, et al. Subjecting acute ischemic stroke patients to continuous tube feeding and an intensive computerized protocol establishes tight glycemic control. *Neurocrit Care.* (2010) 12:62–8. doi: 10.1007/s12028-009-9230-z

148. Vriesendorp TM, Roos YB, Kruyt ND, Biessels GJ, Kappelle LJ, Vermeulen M, et al. Efficacy and safety of two 5 day insulin dosing regimens to achieve strict glycaemic control in patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatry.* (2009) 80:1040–3. doi: 10.1136/jnnp.2008.144873

149. Torbey MT, Pauls Q, Gentile N, Falciglia M, Meurer W, Pettigrew CL, et al. Intensive versus standard treatment of hyperglycemia in acute ischemic stroke patient: a randomized clinical trial subgroups analysis. *Stroke.* (2022) 53:1510–5. doi: 10.1161/STROKEAHA.120.033048

150. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke.* (2003) 34:2208–14. doi: 10.1161/01.STR.0000085087.41330.FF

151. Allport L, Baird T, Butcher K, Macgregor L, Prosser J, Colman P, et al. Frequency and temporal profile of poststroke hyperglycemia using continuous glucose monitoring. *Diabetes Care.* (2006) 29:1839–44. doi: 10.2337/dc06-0204

152. Wada S, Yoshimura S, Inoue M, Matsuki T, Arihiro S, Koga M, et al. Outcome prediction in acute stroke patients by continuous glucose monitoring. *J Am Heart Assoc.* (2018) 7:e008744. doi: 10.1161/JAHA.118.008744

153. Zhu CZ, Auer RN. Optimal blood glucose levels while using insulin to minimize the size of infarction in focal cerebral ischemia. *J Neurosurg.* (2004) 101:664–8. doi: 10.3171/jns.2004.101.4.0664

154. Gentile NT, Seftchick MW, Huynh T, Kruus LK, Gaughan J. Decreased mortality by normalizing blood glucose after acute ischemic stroke. *Acad Emerg Med.* (2006) 13:174–80. doi: 10.1197/j.aem.2005.08.009

155. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2019) 50:e344–418. doi: 10.1161/STR.0000000000000211

156. Wijdicks EF, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, et al. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2014) 45:1222–38. doi: 10.1161/01.str.0000441965.15164.d6

157. Yatabe T, Inoue S, Sakaguchi M, Egi M. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. *Intensive Care Med.* (2017) 43:16–28. doi: 10.1007/s00134-016-4558-2

158. Dave KR, Tamariz J, Desai KM, Brand FJ, Liu A, Saul I, et al. Recurrent hypoglycemia exacerbates cerebral ischemic damage in streptozotocin-induced

diabetic rats. *Stroke.* (2011) 42:1404–11. doi: 10.1161/STROKEAHA.110.594937

159. Shukla V, Fuchs P, Liu A, Cohan CH, Dong C, Wright CB, et al. Recurrent hypoglycemia exacerbates cerebral ischemic damage in diabetic rats via enhanced post-ischemic mitochondrial dysfunction. *Transl Stroke Res.* (2019) 10:78–90. doi: 10.1007/s12975-018-0622-2

160. Gogitidze Joy N, Hedrington MS, Briscoe VJ, Tate DB, Ertl AC, Davis SN. Effects of acute hypoglycemia on inflammatory and pro-atherothrombotic biomarkers in individuals with type 1 diabetes and healthy individuals. *Diabetes Care.* (2010) 33:1529–35. doi: 10.2337/dc09-0354

161. Wright RJ, Newby DE, Stirling D, Ludlam CA, Macdonald IA, Frier BM. Effects of acute insulin-induced hypoglycemia on indices of inflammation: putative mechanism for aggravating vascular disease in diabetes. *Diabetes Care.* (2010) 33:1591–7. doi: 10.2337/dc10-0013

162. Dantz D, Bewersdorf J, Fruehwald-Schultes B, Kern W, Jelkmann W, Born J, et al. Vascular endothelial growth factor: a novel endocrine defensive response to hypoglycemia. *J Clin Endocrinol Metab.* (2002) 87:835–40. doi: 10.1210/jcem.87.2.8215

163. Goldenberg RM, Cheng AYY, Fitzpatrick T, Gilbert JD, Verma S, Hopyan JJ. Benefits of glp-1 (glucagon-like peptide 1) receptor agonists for stroke reduction in type 2 diabetes: a call to action for neurologists. *Stroke.* (2022) 53:1813–22. doi: 10.1161/STROKEAHA.121.038151

164. Zhu H, Zhang Y, Shi Z, Lu D, Li T, Ding Y, et al. The neuroprotection of liraglutide against ischaemia-induced apoptosis through the activation of the pi3k/akt and mapk pathways. *Sci Rep.* (2016) 6:26859. doi: 10.1038/srep26859

165. Shan Y, Tan S, Lin Y, Liao S, Zhang B, Chen X, et al. The glucagon-like peptide-1 receptor agonist reduces inflammation and blood-brain barrier breakdown in an astrocyte-dependent manner in experimental stroke. *J Neuroinflammation.* (2019) 16:242. doi: 10.1186/s12974-019-1638-6

166. Daly SC, Chemmanam T, Loh PS, Gilligan A, Dear AE, Simpson RW, et al. Exenatide in acute ischemic stroke. *Int J Stroke.* (2013) 8:E44. doi: 10.1111/ijs.12073

167. Muller C, Cheung NW, Dewey H, Churilov L, Middleton S, Thijs V, et al. Treatment with exenatide in acute ischemic stroke trial protocol: A prospective, randomized, open label, blinded end-point study of exenatide vs. standard care in post stroke hyperglycemia. *Int J Stroke.* (2018) 13:857–62. doi: 10.1177/1747493018784436

168. Zhang G, Kim S, Gu X, Yu SP, Wei L. Dpp-4 inhibitor linagliptin is neuroprotective in hyperglycemic mice with stroke via the akt/mtor pathway and anti-apoptotic effects. *Neurosci Bull.* (2020) 36:407–18. doi: 10.1007/s12264-019-00446-w

169. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* (2013) 369:1317–26. doi: 10.1056/NEJMoa1307684

170. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* (2013) 369:1327–35. doi: 10.1056/NEJMoa1305889

171. Han JH, Oh TJ, Lee G, Maeng HJ, Lee DH, Kim KM, et al. The beneficial effects of empagliflozin, an sglt2 inhibitor, on atherosclerosis in apoe (-/-) mice fed a western diet. *Diabetologia.* (2017) 60:364–76. doi: 10.1007/s00125-016-4158-2

172. Harada S, Yamazaki Y, Nishioka H, Tokuyama S. Neuroprotective effect through the cerebral sodium-glucose transporter on the development of ischemic damage in global ischemia. *Brain Res.* (2013) 1541:61–8. doi: 10.1016/j.brainres.2013.09.041

173. Fitchett D, Inzucchi SE, Cannon CP, McGuire DK, Scirica BM, Johansen OE, et al. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the empa-reg outcome trial. *Circulation.* (2019) 139:1384–95. doi: 10.1161/CIRCULATIONAHA.118.037778

174. Zhou Z, Lindley RI, Rådholm K, Jenkins B, Watson J, Perkovic V, et al. Canagliflozin and stroke in type 2 diabetes mellitus. *Stroke.* (2019) 50:396–404. doi: 10.1161/STROKEAHA.118.023009

175. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* (2016) 4:411–9. doi: 10.1016/S2213-8587(16)00052-8

176. Bailey CJ. Metformin: historical overview. *Diabetologia.* (2017) 60:1566–76. doi: 10.1007/s00125-017-4318-z

177. Hostalek U, Gwilt M, Hildemann S. Therapeutic use of metformin in prediabetes and diabetes prevention. *Drugs.* (2015) 75:1071–94. doi: 10.1007/s40265-015-0416-8

178. Cheng YY, Leu HB, Chen TJ, Chen CL, Kuo CH, Lee SD, et al. Metformin-inclusive therapy reduces the risk of stroke in patients with diabetes: a 4-year follow-up study. *J Stroke Cerebrovasc Dis.* (2014) 23:e99–105. doi: 10.1016/j.jstrokecerebrovasdis.2013.09.001

179. Mima Y, Kuwashiro T, Yasaka M, Tsurusaki Y, Nakamura A, Wakugawa Y, et al. Impact of metformin on the severity and outcomes of acute ischemic stroke in patients with type 2 diabetes mellitus. *J Stroke Cerebrovasc Dis.* (2016) 25:436–46. doi: 10.1016/j.jstrokecerebrovasdis.2015.10.016

180. Baines CP. The mitochondrial permeability transition pore and ischemia-reperfusion injury. *Basic Res Cardiol.* (2009) 104:181–8. doi: 10.1007/s00395-009-0004-8

181. Skemiene K, Rekuviene E, Jekabsone A, Cizas P, Morkuniene R, Borutaite V. Comparison of effects of metformin, phenformin, and inhibitors of mitochondrial complex i on mitochondrial permeability transition and ischemic brain injury. *Biomolecules.* (2020) 10:1400. doi: 10.3390/biom10101400

182. Li J, Benashski SE, Venna VR, McCullough LD. Effects of metformin in experimental stroke. *Stroke.* (2010) 41:2645–52. doi: 10.1161/STROKEAHA.110.589697

183. Zeng J, Zhu L, Liu J, Zhu T, Xie Z, Sun X, et al. Metformin protects against oxidative stress injury induced by ischemia/reperfusion via regulation of the incrna-h19/mir-148a-3p/rock2 axis. *Oxid Med Cell Longev.* (2019) 2019:8768327. doi: 10.1155/2019/8768327

184. Zemgulyte G, Tanaka S, Hide I, Sakai N, Pampuscenko K, Borutaite V, et al. Evaluation of the effectiveness of post-stroke metformin treatment using permanent middle cerebral artery occlusion in rats. *Pharmaceuticals.* (2021) 14:312. doi: 10.3390/ph14040312

185. Tucker GT, Casey C, Phillips PJ, Connor H, Ward JD, Woods HF. Metformin kinetics in healthy subjects and in patients with diabetes mellitus. *Br J Clin Pharmacol.* (1981) 12:235–46. doi: 10.1111/j.1365-2125.1981.tb01206.x

186. Den Hertog HM, Vermeer SE, Zandbergen AA, Achterberg S, Dippel DW, Algra A, et al. Safety and feasibility of metformin in patients with impaired glucose tolerance and a recent tia or minor ischemic stroke (limit) trial - a multicenter, randomized, open-label phase ii trial. *Int J Stroke.* (2015) 10:105–9. doi: 10.1111/ijs.12023

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 03 April 2023
DOI 10.3389/fneur.2023.1144564

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
Haruhiko Hoshino,
Saiseikai Central Hospital, Japan
Yajun Cheng,
West China Hospital of Sichuan University, China
Jie Li,
People's Hospital of Deyang City, China

*CORRESPONDENCE
Zhao Han
✉ wzhanzhao@aliyun.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 14 January 2023
ACCEPTED 20 March 2023
PUBLISHED 03 April 2023

CITATION
Zhan Z, Xu T, Xu Y, Fu F, Cheng Z, Xia L, Wu Y, Xu X, Cao Y and Han Z (2023) Associations between computed tomography markers of cerebral small vessel disease and hemorrhagic transformation after intravenous thrombolysis in acute ischemic stroke patients. *Front. Neurol.* 14:1144564. doi: 10.3389/fneur.2023.1144564

Associations between computed tomography markers of cerebral small vessel disease and hemorrhagic transformation after intravenous thrombolysis in acute ischemic stroke patients

Zhenxiang Zhan[1,2†], Tong Xu[1†], Ye Xu[1], Fangwang Fu[1], Zicheng Cheng[2], Lingfan Xia[1], Yucong Wu[1], Xuan Xu[1], Yungang Cao[1] and Zhao Han[1*]

[1]Department of Neurology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China, [2]Department of Neurology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China

Background: Hemorrhagic transformation (HT) is common among acute ischemic stroke patients after treatment with intravenous thrombolysis (IVT). We analyzed potential relationships between markers of cerebral small vessel disease (CSVD) and HT in patients after IVT.

Methods: This study retrospectively analyzed computed tomography (CT) data for acute ischemic stroke patients before and after treatment with recombinant tissue plasminogen activator at a large Chinese hospital between July 2014 and June 2021. Total CSVD score were summed by individual CSVD markers including leukoaraiosis, brain atrophy and lacune. Binary regression analysis was used to explore whether CSVD markers were related to HT as the primary outcome or to symptomatic intracranial hemorrhage (sICH) as a secondary outcome.

Results: A total of 397 AIS patients treated with IVT were screened for inclusion in this study. Patients with missing laboratory data ($n = 37$) and patients treated with endovascular therapy ($n = 42$) were excluded. Of the 318 patients included, 54 (17.0%) developed HT within 24–36 h of IVT, and 14 (4.3%) developed sICH. HT risk was independently associated with severe brain atrophy (OR 3.14, 95%CI 1.43–6.92, $P = 0.004$) and severe leukoaraiosis (OR 2.41, 95%CI 1.05–5.50, $P = 0.036$), but not to severe lacune level (OR 0.58, 95%CI 0.23–1.45, $P = 0.250$). Patients with a total CSVD burden ≥1 were at higher risk of HT (OR 2.87, 95%CI 1.38–5.94, $P = 0.005$). However, occurrence of sICH was not predicted by CSVD markers or total CSVD burden.

Conclusion: In patients with acute ischemic stroke, severe leukoaraiosis, brain atrophy and total CSVD burden may be risk factors for HT after IVT. These findings may help improve efforts to mitigate or even prevent HT in vulnerable patients.

KEYWORDS

acute ischemic stroke, intravenous thrombolysis, hemorrhagic transformation, brain atrophy, cerebral small vessel disease, leukoaraiosis

Introduction

Ischemic strokes account for 71% of strokes worldwide (1). The preferred treatment for patients with acute ischemic stroke (AIS) is intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator within 4.5 h of onset (2, 3). However, such IVT may cause hemorrhagic transformation (HT), which impedes functional recovery and can even lead to death (4). About 90% of HT cases occur within 24–36 h of stroke onset (5). Some factors have been associated with the development of HT, such as old age (6, 7), hypertension (7), atrial fibrillation (8), cerebral amyloid angiopathy (9–11) and high National Institutes of Health Stroke Scale (NIHSS) score (12, 13).

Cerebral small vessel disease (CSVD) is a disorder involving the brain's small perforating arterioles, capillaries and venules, and is attracting much interest (14). It leads to serious deterioration of cognitive function, gait and balance (15), and may worsen prognosis of AIS patients after IVT (15). A meta-analysis also linked HT risk to the presence of CSVD (16). Magnetic resonance imaging is the gold standard for diagnosing and assessing CSVD (17), but computed tomography (CT) is routinely used in many acute stroke units to identify patients suitable for acute treatments such as IVT. Computed tomography can assess several CSVD markers, including leukoaraiosis, lacune and brain atrophy (17). These markers may be useful for identifying patients at higher risk of intracerebral hemorrhage (18). Although magnetic resonance imaging is typically used to evaluate CSVD markers, CT offers faster assessment, which can be critical in time-sensitive situations such as IVT for AIS (19).

Studies about the association between CSVD markers based on CT and HT are rare. Thus we investigated the relationship between CSVD markers as detected by CT at stroke onset and risk of HT after IVT treatment.

Methods

Patients

This retrospective, observational, single-center study continuously collected clinical data of AIS patients treated with recombinant tissue plasminogen activator in the emergency department of the Second Affiliated Hospital of Wenzhou Medical University from July 2014 to June 2021. This study was approved by the ethics committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, which waived the requirement for written informed consent because the patients or their legal guardians, at the time of treatment, consented for their anonymized medical data to be analyzed and published for research purposes.

Patients were included in the study if they had been diagnosed with ischemic stroke according to the Chinese guidelines for the diagnosis and treatment of acute ischemic stroke, received 0.9 mg/kg of recombinant tissue plasminogen activator within 4.5 h of stroke onset, and underwent head CT before IVT at admission and within 24–36 h after IVT. The timeframe of 24–36 h after IVT was selected based on the European Cooperative Acute Stroke Study (20).

Patients were excluded if they were diagnosed with other central nervous system diseases, such as epilepsy, dementia, or Parkinson's disease; diagnosed with serious systemic diseases; or treated with endovascular therapy after IVT.

Data collection

In addition to sex and age, the following data were extracted from electronic medical records: past medical history, including hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary heart disease, previous stroke history, smoking and drinking history, and previous antithrombotic drug treatment history; clinical parameters, such as systolic and diastolic blood pressure, NIHSS score, and time from onset to thrombolytic therapy; as well as laboratory data, such as venous blood glucose level at admission, international normalized ratio (INR), activated partial thrombin time (APTT), platelet count, total cholesterol and low-density lipoprotein cholesterol.

CSVD assessment

Two experienced neurologists (ZZ, TX), who were blinded to other clinical information and who worked independently from each other, retrospectively assessed CSVD markers from CT scans. Discrepancies between investigators were addressed with a third investigator (ZH) joining the discussion. Disputes were resolved through discussion. Leukoaraiosis was scored according to the 3-point van Swieten scale (21), in which 0 points were given if no imaging evidence was observed, 1 point if the lesions were limited to the lateral ventricle, or 2 points if the lesions had spread from the lateral ventricle to the cerebral cortex.

Brain atrophy was classified as central or cortical, and its severity was assessed as none (0 point), mild to moderate (1 point) or severe (2 points) (22). We defined a "lacuna of presumed vascular origin" to be a round or ovoid, subcortical cavity of diameter 3–15 mm that was filled with a fluid similar in appearance to cerebrospinal fluid (19).

The scores for these individual CSVD markers were summed to a total CSVD score (23), meaning that 1 point for each of the following situations exist: a van Swieten score of 2; presence of at least 2 lacune; a central or cortical brain atrophy score of 2. Thus, the total CSVD burden could range from 0 (no imaging features of severe CSVD) to 3 (each imaging feature of CSVD was serious) (Figure 1).

Primary and secondary outcomes

The same two neurologists also independently evaluated the CT images for the presence of HT as a primary outcome, which encompasses all types of post-ischemic hemorrhages. HT was further classified as hemorrhagic infarction (HI) types I and II and parenchymal hemorrhage (PH) types I and II. HI I is defined as small petechiae along the margins of

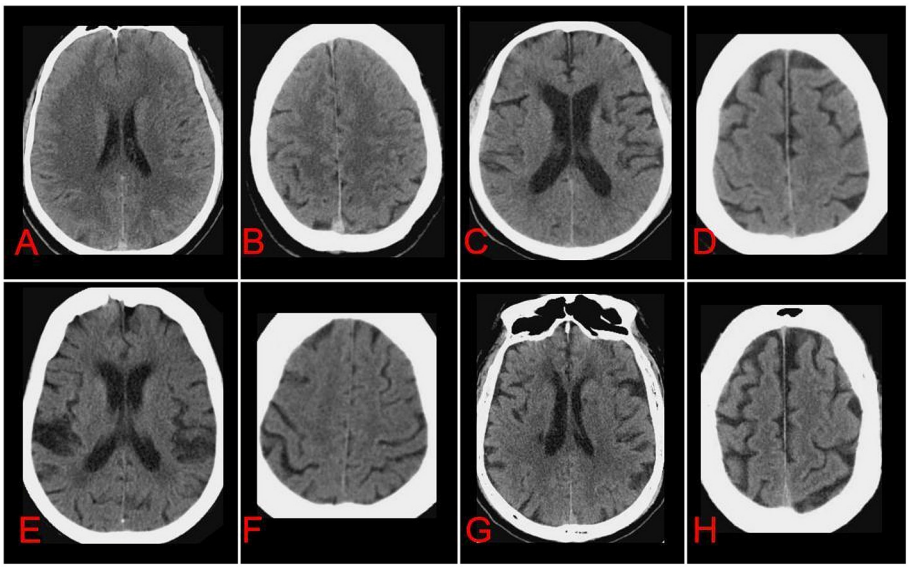


FIGURE 1
Axial non-contrast-enhanced CT images of brains from patients after acute ischemic stroke at the level of choroid plexus **(A, C, E, G)** or semioval center **(B, D, F, H)** of the lateral ventricle. Cerebral small-vessel disease (CSVD) markers were individually assessed and graded according to the appropriate scales, and total CSVD burden was calculated. Images in **(A, B)** are representative of patients with total CSVD burden of 0: anterior leukoaraiosis = 0, posterior leukoaraiosis = 0, no lacune, central atrophy = 0, cortical atrophy = 0. Images in **(C, D)** are representative of patients with total CSVD burden of 1: anterior leukoaraiosis = 1, posterior leukoaraiosis = 1, no lacune, central atrophy = 2, cortical atrophy = 1. Images in **(E, F)** are representative of patients with total CSVD burden of 2: anterior leukoaraiosis = 2, posterior leukoaraiosis = 2, no lacune, central atrophy = 2, cortical atrophy = 1. Images in **(G, H)** are representative of patients with total CSVD burden of 3: anterior leukoaraiosis = 2, posterior leukoaraiosis = 1, lacune in left and right basal ganglia = 2, central atrophy = 2, cortical atrophy = 2.

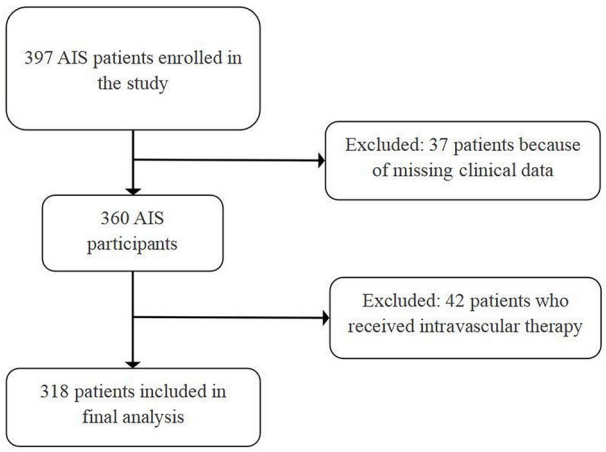


FIGURE 2
Flow diagram of patient enrollment. AIS, acute ischemic stroke.

the infarct, while HI II represents more confluent petechiae within the infarcted area, but without space-occupying effect. PH I is defined as blood clot not exceeding 30% of the infarcted area with some mild space-occupying effect, and PH II represents dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect (20).

The secondary outcome was symptomatic intracerebral hemorrhage (sICH), which was defined as bleeding visible anywhere on the cranial scan, accompanied by clinical deterioration or adverse events, such as drowsiness or aggravation of hemiplegia, leading to an increase in NIHSS score ≥4 points (24).

Statistical analysis

Categorical variables were reported as frequencies and percentages, while continuous variables were reported as mean and standard deviation if the data were normally distributed, or as median and interquartile range if the data were skewed. Pearson's chi-squared test or Fisher's precision probability test was used for unordered categorical variables, while the Mann-Whitney U test was used if the data were continuous.

Binary regression analysis was used for two multivariable models in which variables with $P < 0.1$ after univariate analysis were analyzed further to determine risk factors independently related to HT or sICH. In the first model, the three components of total CSVD score (severe anterior or posterior leukoaraiosis, severe central or cortical atrophy, and severe lacune level) were treated as separate covariates. In the second model, the total burden of CSVD was dichotomized into 0 or ≥1 to evaluate its potential association with risk of HT. Risk of HT was expressed in terms of adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Differences associated with two-sided $P < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS 24.0 (IBM, Armonk, NY, USA).

Results

Clinicodemographic characteristics

A total of 397 AIS patients treated with IVT were screened for inclusion in this study. After excluding patients with missing laboratory data ($n = 37$) and patients treated with endovascular therapy ($n = 42$), 318 patients (66.4% men) were included in the final analysis (Figure 2).

Excellent inter-rater agreement for CSVD rating ($\kappa = 0.83$) was observed. The included sample had a median age of 70 years (interquartile range 61–80, Table 1). Fifty-four (17.0%) patients developed HT within 24–36 h after IVT. HT was significantly more frequent among patients with atrial fibrillation (66.7% vs. 25.4%, $P < 0.001$), higher median NIHSS score (11 vs. 6, $P < 0.001$), higher median baseline diastolic blood pressure (92 vs. 87, $P = 0.045$) and higher median INR (1.04 vs. 1.02, $P = 0.007$). And TOAST classification also had statistical significance ($P < 0.001$).

Associations of CSVD markers with HT

Compared to patients who did not suffer from HT, patients with HT showed higher incidence of severe anterior and posterior leukoaraiosis, severe central and cortical atrophy, and greater total CSVD burden (Tables 2, 3). There was no significant difference in lacune level between HT and non-HT patients ($P = 0.984$).

Risk of HT was independently related to severe brain atrophy (OR 3.14, 95%CI 1.43–6.92, $P = 0.004$) and severe leukoaraiosis scores (OR 2.41, 95%CI 1.05–5.50, $P = 0.036$), but not to severe lacune level (OR 0.58, 95%CI 0.23–1.45, $P = 0.250$). A total CSVD burden of ≥1 greatly increased risk of HT (OR 2.87, 95%CI 1.38–5.94, $P = 0.005$). According to either regression model, risk of HT was also higher in the presence of atrial fibrillation or high baseline NIHSS score.

Associations of CSVD markers with secondary outcomes

Fourteen (4.3%) patients experienced sICH after IVT, and those who did or did not experience sICH did not differ significantly in severe leukoaraiosis, brain atrophy or lacune level (Supplementary Table S1). Total CSVD burden ≥1 was not associated with greater risk of sICH after IVT. Atrial fibrillation, in contrast, was more frequent among patients with sICH (71.4% vs. 30.6%, $P = 0.001$, Supplementary Table S1) and it predicted sICH risk even after adjusting for individual CSVD markers (OR 4.65, 95%CI 1.27–16.95, $P = 0.020$) or adjusting for total CSVD burden (OR 4.23, 95%CI 1.20–14.88, $P = 0.024$; Supplementary Tables S2, S3).

Discussion

To our knowledge, this is the first retrospective study to investigate the relationship between CSVD markers, as visualized

TABLE 1 Clinicodemographic characteristics of acute ischemic stroke patients[a].

Characteristic	HT ($n = 54$)	No HT ($n = 264$)	*P*
Age (years)	76 (63–83)	70 (60–79)	**0.016**
Sex (female)	23 (42.5)	84 (31.8)	0.127
Hypertension	43 (79.6)	201 (76.1)	0.581
Diabetes mellitus	14 (25.9)	85 (32.2)	0.365
Hyperlipidemia	15 (27.7)	110 (41.7)	0.057
Atrial fibrillation	36 (66.7)	67 (25.4)	**<0.001**
Coronary heart disease	5 (9.2)	24 (9.1)	0.969
Previous stroke history	6 (11.1)	35 (13.3)	0.669
Smoking history	8 (14.8)	66 (25.0)	0.107
Drinking history	13 (24.0)	55 (20.8)	0.597
Previous antithrombotic therapy	6 (11.1)	33 (12.5)	0.777
Time from onset to thrombolysis (min)	160 (120–193)	170 (120–210)	0.411
NIHSS score (points)	11 (7–17)	6 (4–10)	**<0.001**
Systolic blood pressure level (mmHg)	162 (141–180)	159 (142–173)	0.360
Diastolic blood pressure (mmHg)	92 (81–104)	87 (78–97)	**0.045**
Blood glucose level (mmol/L)	7.3 (6.1–9.4)	7.0 (6.0–8.8)	0.345
Platelet count (10^9/L)	181 (155–216)	190 (165–227)	0.066
INR	1.04 (1.01–1.10)	1.02 (0.97–1.09)	**0.007**
APTT (sec)	33.8 (31.2–36.7)	33.9 (31.0–36.8)	0.802
Total cholesterol (mmol/L)	4.3 (3.7–4.8)	4.4 (3.7–5.1)	0.419
Low-density lipoprotein cholesterol (mmol/L)	2.5 (1.9–3.1)	2.6 (2.0–3.3)	0.409
TOAST classification			**<0.001**
Large artery atherosclerosis	14 (25.9)	76 (28.8)	
Cardioembolism	31 (57.4)	70 (26.5)	
Small-artery occlusion	4 (7.4)	75 (28.4)	
Stroke of other determined cause	2 (3.7)	5 (1.9)	
Stroke of undetermined cause	3 (5.6)	38 (14.4)	
Anterior leukoaraiosis			
0	20 (37.0)	139 (52.7)	**0.010**
1	25 (46.3)	103 (39.0)	
2	9 (16.7)	22 (8.3)	

(Continued)

TABLE 1 (Continued)

Characteristic	HT ($n = 54$)	No HT ($n = 264$)	*P*
Posterior leukoaraiosis			
0	23 (42.6)	172 (65.2)	**0.001**
1	21 (38.9)	61 (23.1)	
2	10 (18.5)	31 (11.7)	
Severe anterior or posterior leukoaraiosis	14 (25.9)	40 (15.2)	**0.002**
Cortical atrophy			
0	6 (11.1)	65 (24.6)	**<0.001**
1	29 (53.7)	166 (62.9)	
2	19 (35.2)	33 (12.5)	
Central atrophy			
0	10 (18.5)	106 (40.2)	**<0.001**
1	27 (50.0)	129 (48.9)	
2	17 (31.5)	29 (11.0)	
Severe cortical or central atrophy	26 (48.1)	45 (17.0)	**<0.001**
Lacune			
0	28 (51.9)	142 (53.8)	0.984
1	17 (25.9)	70 (26.5)	
≥2	9 (22.2)	52 (19.7)	
Total CSVD score			
0	19 (35.2)	166 (62.9)	**<0.001**
1	19 (35.2)	62 (23.5)	
2	14 (25.9)	33 (12.5)	
3	2 (3.7)	3 (1.1)	
Total CSVD score ≥ 1	35 (64.8)	98 (37.1)	**<0.001**

Values are n (%) or median (interquartile range), unless otherwise noted. Boldfaced values differ significantly between the two groups.

[a]Mann-Whitney U test.

HT, hemorrhagic transformation; APTT, activated partial thromboplastin time; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; CSVD, cerebral small vessel disease.

TABLE 2 Regression analysis to identify associations of clinicodemographic characteristics with risk of hemorrhagic transformation after intravenous thrombolysis[a].

Characteristic	OR (95%CI)	*p*
Age	0.97 (0.94–1.00)	0.067
Atrial fibrillation	5.11 (2.32–11.24)	**<0.001**
Baseline NIHSS score	1.05 (1.00–1.10)	**0.035**
Baseline diastolic blood pressure	1.00 (0.98–1.02)	0.772
Platelet count	0.99 (0.99–1.00)	0.518
Hyperlipidemia	0.62 (0.30–1.29)	0.205
INR	0.16 (0.01–4.58)	0.286
Severe leukoaraiosis (≥2)	2.41 (1.05–5.50)	**0.036**
Severe brain atrophy (≥2)	3.14 (1.43–6.92)	**0.004**
Severe lacune level (≥2)	0.58 (0.23–1.45)	0.250

[a]Adjusted for individual scores for leukoaraiosis, brain atrophy, or lacune.

Boldfaced values indicate statistically significant independent risk factors.

OR, odds ratio; CI, confidence interval; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale.

TABLE 3 Regression analysis to identify associations of clinicodemographic characteristics with risk of hemorrhagic transformation after intravenous thrombolysis[a].

Characteristic	OR (95%CI)	*p*
Age	0.97 (0.94–1.00)	0.144
Atrial fibrillation	5.52 (2.51–12.15)	**<0.001**
Baseline NIHSS score	1.05 (1.00–1.10)	**0.044**
Baseline diastolic blood pressure	1.00 (0.98–1.02)	0.507
Platelet count	0.99 (0.99–1.00)	0.534
Hyperlipidemia	0.60 (0.29–1.24)	0.173
INR	0.41 (0.01–10.78)	0.594
Total CSVD score ≥ 1	2.87 (1.38–5.94)	**0.005**

[a]Adjusted for total cerebral small vessel disease burden.

Boldfaced values indicate statistically significant independent risk factors.

OR, odds ratio; CI, confidence interval; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; CSVD, cerebral small vessel disease.

by CT, and risk of HT in AIS patients after IVT. Our results suggest that severe leukoaraiosis, severe brain atrophy and total CSVD burden in AIS patients prior to IVT are independently associated with increased risk of HT after IVT.

Several studies have already shown strong links between presence of leukoaraiosis and hemorrhage after IVT, but the reasons for this correlation are unclear (16, 25–28). Leukoaraiosis is thought to reflect ischemic white matter injury penetrating small vessels in the distal deep artery or arteriole area, which may reflect chronic endothelial dysfunction (29). At the same time, leukoaraiosis may increase small vessel brittleness and vascular rupture, leading to bleeding complications and breakdown of the blood-brain barrier (29, 30). Inflammation in the central nervous system or its periphery as well as variations in blood pressure may also contribute to leukoaraiosis pathogenesis (31–36).

Similar to leukoaraiosis, brain atrophy has also been associated with HT, though the mechanisms are unclear. One possibility is that brain atrophy in AIS patients at least partly reflects pre-existing brain injury due, for example, to degenerative processes in dementia or subcortical vascular encephalopathy (37). Our study is consistent with earlier work showing that brain atrophy and other markers may reflect risk of intracerebral hemorrhage (38). In contrast, we did not find a significant relationship between lacune level and risk of HT, similar to the few other studies that have examined this question (39, 40).

It is clear that there is no single pathological mechanism explaining how leukoaraiosis or brain atrophy leads to HT after IVT. We found that the aggregate parameter of total CSVD burden, when it was 1 or higher, predicted higher risk of HT

after IVT. Total CSVD burden provides a more complete view of the impact of CSVD on the brain, more so than individual CSVD features, and it may be easier to use in the clinic. It may also facilitate comparisons between medical centers, so long as the definitions of single CSVD features are standardized (19). Arguments could be made that the potential differences in the pathogenic mechanisms leading to these different CSVD features may render an aggregate index unreliable. However, we would reason that leukoaraiosis, brain atrophy, and lacune are all consequences of small vessel diseases and often occur simultaneously, allowing their aggregation into a single, more practical index that does not make detailed assumptions about specific pathogenic mechanisms. The reliability and accuracy of total CSVD burden for predicting HT risk should be examined further in larger studies and benchmarked against magnetic resonance imaging.

We did not find that CSVD markers alone or total CSVD burden predicted increased risk of sICH. A meta-analysis of 13 studies found that presence of leukoaraiosis or total CSVD burden increased risk of sICH after IVT (16). However, only two of those individual studies evaluated CSVD markers through CT. The remaining studies used magnetic resonance imaging because it is better at detecting cerebral microbleeds, which are closely related to sICH (18). This may help explain why we failed to detect correlations between CSVD markers and sICH. Another obstacle to comparing our findings to the literature is that different studies can define sICH differently (28, 41).

This study has some limitations. First, our study was retrospective and included a small sample from a single center. Second, we did not collect additional data relevant to prognosis, such as the modified Rankin scale score after 3 months, which may help clarify relationships between CSVD markers and HT.

Despite these limitations, our results suggest that AIS patients with severe leukoaraiosis, severe brain atrophy and total CSVD burden >1 based on CT before IVT are at increased risk of HT after IVT. These parameters might be useful markers to identity patients with high risk of HT and assist the treatment decision-making, thus it should be verified and further explored in larger, prospective studies.

Data availability statement

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

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 for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZZ, TX, and ZH conceived and designed the study. TX, FF, ZC, LX, YW, and YC performed experiments. ZZ analyzed data. ZZ and ZH wrote the manuscript. All authors revised the manuscript and approved the final version.

Funding

This work was supported by Clinical Scientific Research Foundation of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (SAHoWMU-CR2017-01-212 to ZH).

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1144564/full#supplementary-material

References

1. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, et al. Ischaemic stroke. *Nat Rev Dis Primers.* (2019) 5:70. doi: 10.1038/s41572-019-0118-8

2. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* (2014) 384:1929–35. doi: 10.1016/S0140-6736(14)60584-5

3. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3–45 h after acute ischemic stroke. *N Engl J Med.* (2008) 359:1317–29. doi: 10.1056/NEJMoa0804656

4. He J, Fu F, Zhang W, Zhan Z, Cheng Z. Prognostic significance of the clinical and radiological haemorrhage transformation subtypes in acute ischaemic stroke: a systematic review and meta-analysis. *Eur J Neurol.* (2022) 29:3449–59. doi: 10.1111/ene.15482

5. Strbian D, Sairanen T, Meretoja A, Pitkaniemi J, Putaala J, Salonen O, et al. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. *Neurology*. (2011) 77:341–8. doi: 10.1212/WNL.0b013e3182267b8c

6. Okada Y, Yamaguchi T, Minematsu K, Miyashita T, Sawada T, Sadoshima S, et al. Hemorrhagic transformation in cerebral embolism. *Stroke*. (1989) 20:598–603.

7. Whiteley W, Slot K, Fernandes P, Sandercock P, Wardlaw J. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. *Stroke*. (2012) 43:2904–9. doi: 10.1161/STROKEAHA.112.665331

8. Fisher M, Adams R. Observations on brain embolism with special reference to the mechanism of hemorrhagic infarction. *J Neuropathol Exp Neurol*. (1951) 10:92–4.

9. Charidimou A, Nicoll J, McCarron M. Thrombolysis-related intracerebral hemorrhage and cerebral amyloid angiopathy: accumulating evidence. *Front Neurol*. (2015) 6:99. doi: 10.3389/fneur.2015.00099

10. Eriguchi M, Yakushiji Y, Tanaka J, Nishihara M, Hara H. Thrombolysis-related multiple lobar hemorrhaging in cerebral amyloid angiopathy with extensive strictly lobar cerebral microbleeding. *Intern Med*. (2017) 56:1907–10. doi: 10.2169/internalmedicine.56.8007

11. Vales-Montero M, García-Pastor A, Iglesias-Mohedano A, Esteban-de Antonio E, Salgado-Cámara P, García-Domínguez J, et al. Cerebral amyloid angiopathy-related transient focal neurological episodes: a transient ischemic attack mimic with an increased risk of intracranial hemorrhage. *J Neurol Sci*. (2019) 406:116452. doi: 10.1016/j.jns.2019.116452

12. Ge WQ, Chen J, Pan H, Chen F, Zhou CY. Analysis of risk factors increased hemorrhagic transformation after acute ischemic stroke. *J Stroke Cerebrovasc Dis*. (2018) 27:3587–90. doi: 10.1016/j.jstrokecerebrovasdis.2018.08.028

13. Tan S, Wang D, Liu M, Zhang S, Wu B, Liu B. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. *J Neurol*. (2014) 261:905–12. doi: 10.1007/s00415-014-7297-8

14. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. (2019) 18:684–96. doi: 10.1016/S1474-4422(19)30079-1

15. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. (2010) 9:689–701. doi: 10.1016/S1474-4422(10)70104-6

16. Wang Y, Yan X, Zhan J, Zhang P, Zhang G, Ge S, et al. Neuroimaging markers of cerebral small vessel disease on hemorrhagic transformation and functional outcome after intravenous thrombolysis in patients with acute ischemic stroke: a systematic review and meta-analysis. *Front Aging Neurosci*. (2021) 13:692942. doi: 10.3389/fnagi.2021.692942

17. Chen X, Wang J, Shan Y, Cai W, Liu S, Hu M, et al. Cerebral small vessel disease: neuroimaging markers and clinical implication. *J Neurol*. (2019) 266:2347–62. doi: 10.1007/s00415-018-9077-3

18. Cheng Z, Zhang W, Zhan Z, Xia L, Han Z. Cerebral small vessel disease and prognosis in intracerebral haemorrhage: a systematic review and meta-analysis of cohort studies. *Eur J Neurol*. (2022) 29:2511–25. doi: 10.1111/ene.15363

19. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. (2013) 12:822–38. doi: 10.1016/S1474-4422(13)70124-8

20. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. (1995) 274:1017–25.

21. van Swieten J, Hijdra A, Koudstaal P, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. *J Neurol Neurosurg Psychiatry*. (1990) 53:1080–3.

22. IST-3 Collaborative Group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. *Lancet Neurol*. (2015) 14:485–96. doi: 10.1016/S1474-4422(15)00012-5

23. Arba F, Mair G, Carpenter T, Sakka E, Sandercock PAG, Lindley RI, et al. Cerebral white matter hypoperfusion increases with small-vessel disease burden data from the third international stroke trial. *J Stroke Cerebrovasc Dis*. (2017) 26:1506–13. doi: 10.1016/j.jstrokecerebrovasdis.2017.03.002

24. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet*. (1998) 352:1245–51.

25. Bivard A, Cheng X, Lin LT, Levi C, Spratt N, Kleinig T, et al. Global white matter hypoperfusion on CT predicts larger infarcts and hemorrhagic transformation after acute ischemia. *CNS Neurosci Ther*. (2016) 22:238–43. doi: 10.1111/cns.12491

26. Curtze S, Haapaniemi E, Melkas S, Mustanoja S, Putaala J, Sairanen T, et al. White matter lesions double the risk of post-thrombolytic intracerebral hemorrhage. *Stroke*. (2015) 46:2149–55. doi: 10.1161/STROKEAHA.115.009318

27. Liu Y, Zhang M, Gao P, Zhang Z, Zhou X, Yun W. Influence of intravenous thrombolysis on prognosis of acute ischemic stroke in patients with moderate to severe leukoaraiosis. *Zhonghua yi xue za zhi*. (2018) 98:998–1002. doi: 10.3760/cma.j.issn.0376-2491.2018.13.009

28. Charidimou A, Pasi M, Fiorelli M, Shams S, von Kummer R, Pantoni L, et al. Leukoaraiosis, cerebral hemorrhage, and outcome after intravenous thrombolysis for acute ischemic stroke: a meta-analysis (v1). *Stroke*. (2016) 47:2364–72. doi: 10.1161/STROKEAHA.116.014096

29. del Zoppo G, von Kummer R, Hamann G. Ischaemic damage of brain microvessels: inherent risks for thrombolytic treatment in stroke. *J Neurol Neurosurg Psychiatry*. (1998) 65:1–9.

30. Aries MJ, Uyttenboogaart M, Vroomen PC, De Keyser J, Luijckx GJ. tPA treatment for acute ischaemic stroke in patients with leukoaraiosis. *Eur J Neurol*. (2010) 17:866–70. doi: 10.1111/j.1468-1331.2010.02963.x

31. Jurcau A, Simion A. Neuroinflammation in cerebral ischemia and ischemia/reperfusion injuries: from pathophysiology to therapeutic strategies. *Int J Molecul Sci*. (2021) 23:14. doi: 10.3390/ijms23010014

32. Evans L, Taylor J, Smith C, Pritchard H, Greenstein A, Allan S. Cardiovascular comorbidities, inflammation, and cerebral small vessel disease. *Cardiovasc Res*. (2021) 117:2575–88. doi: 10.1093/cvr/cvab284

33. Riba-Llena I, Jarca C, Mundet X, Tovar J, Orfila F, López-Rueda A, et al. Investigating silent strokes in hypertensives: a magnetic resonance imaging study (ISSYS): rationale and protocol design. *BMC Neurol*. (2013) 13:130. doi: 10.1186/1471-2377-13-130

34. Jickling G, Liu D, Stamova B, Ander B, Zhan X, Lu A, et al. Hemorrhagic transformation after ischemic stroke in animals and humans. *J Cerebral Blood Flow Metabol Off J Int Soc Cerebral Blood Flow Metabol*. (2014) 34:185–99. doi: 10.1038/jcbfm.2013.203

35. Charidimou A, Kakar P, Fox Z, Werring D. Cerebral microbleeds and the risk of intracerebral haemorrhage after thrombolysis for acute ischaemic stroke: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. (2013) 84:277–80. doi: 10.1136/jnnp-2012-303379

36. de Heus R, Reumers S, van der Have A, Tumelaire M, Tully P, Claassen J. Day-to-day home blood pressure variability is associated with cerebral small vessel disease burden in a memory clinic population. *J Alzheimer's Dis JAD*. (2020) 74:463–72. doi: 10.3233/JAD-191134

37. Herweh C, Prager E, Sykora M, Bendszus M. Cerebral atrophy is an independent risk factor for unfavorable outcome after spontaneous supratentorial intracerebral hemorrhage. *Stroke*. (2013) 44:968–71. doi: 10.1161/STROKEAHA.111.670901

38. Rodrigues MA, E-Samarasekera N, Lerpiniere C, Perry LA, Moullaali TJ, Loan J, et al. Association between computed tomographic biomarkers of cerebral small vessel diseases and long-term outcome after spontaneous intracerebral hemorrhage. *Ann Neurol*. (2021) 89:266–79. doi: 10.1002/ana.25949

39. Sato S, Delcourt C, Heeley E, Arima H, Zhang S, Al-Shahi Salman R, et al. Significance of cerebral small-vessel disease in acute intracerebral hemorrhage. *Stroke*. (2016) 47:701–7. doi: 10.1161/STROKEAHA.115.012147

40. Arba F, Inzitari D, Ali M, Warach SJ, Luby M, Lees KR, et al. Small vessel disease and clinical outcomes after IV rt-PA treatment. *Acta Neurol Scand*. (2017) 136:72–7. doi: 10.1111/ane.12745

41. Wang S, Lv Y, Zheng X, Qiu J, Chen H. The impact of cerebral microbleeds on intracerebral hemorrhage and poor functional outcome of acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. *J Neurol*. (2017) 264:1309–19. doi: 10.1007/s00415-016-8339-1

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 17 April 2023
DOI 10.3389/fneur.2023.1125172

OPEN ACCESS

EDITED BY
Cheong-Meng Chong,
University of Macau, China

REVIEWED BY
Jing Wang,
Xi'an Jiaotong University, China
Gauthier Everard,
Laval University, Canada

*CORRESPONDENCE
Peizhen Zhang
✉ zhpzh@bsu.edu.cn

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

RECEIVED 16 December 2022
ACCEPTED 21 March 2023
PUBLISHED 17 April 2023

CITATION
Zhu Y, Wang C, Li J, Zeng L and Zhang P (2023) Effect of different modalities of artificial intelligence rehabilitation techniques on patients with upper limb dysfunction after stroke—A network meta-analysis of randomized controlled trials.
Front. Neurol. 14:1125172.
doi: 10.3389/fneur.2023.1125172

Effect of different modalities of artificial intelligence rehabilitation techniques on patients with upper limb dysfunction after stroke—A network meta-analysis of randomized controlled trials

Yu Zhu[1,2†], Chen Wang[1†], Jin Li[1†], Liqing Zeng[1] and Peizhen Zhang[1*]

[1]School of Sports Medicine and Rehabilitation, Beijing Sport University, Beijing, China, [2]Linfen Central Hospital, Linfen, Shanxi, China

Background: This study aimed to observe the effects of six different types of AI rehabilitation techniques (RR, IR, RT, RT + VR, VR and BCI) on upper limb shoulder-elbow and wrist motor function, overall upper limb function (grip, grasp, pinch and gross motor) and daily living ability in subjects with stroke. Direct and indirect comparisons were drawn to conclude which AI rehabilitation techniques were most effective in improving the above functions.

Methods: From establishment to 5 September 2022, we systematically searched PubMed, EMBASE, the Cochrane Library, Web of Science, CNKI, VIP and Wanfang. Only randomized controlled trials (RCTs) that met the inclusion criteria were included. The risk of bias in studies was evaluated using the Cochrane Collaborative Risk of Bias Assessment Tool. A cumulative ranking analysis by SUCRA was performed to compare the effectiveness of different AI rehabilitation techniques for patients with stroke and upper limb dysfunction.

Results: We included 101 publications involving 4,702 subjects. According to the results of the SUCRA curves, RT + VR (SUCRA = 84.8%, 74.1%, 99.6%) was most effective in improving FMA-UE-Distal, FMA-UE-Proximal and ARAT function for subjects with upper limb dysfunction and stroke, respectively. IR (SUCRA = 70.5%) ranked highest in improving FMA-UE-Total with upper limb motor function amongst subjects with stroke. The BCI (SUCRA = 73.6%) also had the most significant advantage in improving their MBI daily living ability.

Conclusions: The network meta-analysis (NMA) results and SUCRA rankings suggest RT + VR appears to have a greater advantage compared with other interventions in improving upper limb motor function amongst subjects with stroke in FMA-UE-Proximal and FMA-UE-Distal and ARAT. Similarly, IR had shown the most significant advantage over other interventions in improving the FMA-UE-Total upper limb motor function score of subjects with stroke. The BCI also had the most significant advantage in improving their MBI daily living ability. Future studies should consider and report on key patient characteristics, such as stroke severity, degree of upper limb impairment, and treatment intensity/frequency and duration.

Systematic review registration: www.crd.york.ac.uk/prospero/#recordDetail, identifier: CRD42022337776.

KEYWORDS

artificial intelligence rehabilitation, stroke, upper limb function, randomized controlled trials, network meta-analysis

Introduction

Globally, stroke is the leading cause of disability in adults, often resulting in symptoms such as muscle weakness, sensory deficits, spasticity, balance problems, reduced dexterity, communication difficulties and cognitive impairment (1). Evidence shows that 40% of people with a stroke still have upper limb impairment, which can lead to limited movement (2–4). Meanwhile, only 5 to 20% of stroke survivors recover full upper limb function, 25% recover partial upper limb function, and 60% have a complete loss of upper limb function (5). Consequently, reduced motor function of the upper limb (e.g., reaching and grasping) can have a significant negative impact on the ability to perform activities of daily living (ADLs) (e.g., eating, dressing and washing) (6).

One study found changes in the affected upper limbs were usually more apparent than in the affected lower limbs (7), including functional limitations in the affected arms and slow, uncoordinated movements of the hands (8, 9). Another study found that subjects with strokes had difficulty performing reaching tasks and movement when manipulating objects due to changes in timing and coordination as well as abnormal postural adjustments (10, 11) or were unable to control grip and fingertip strength (12, 13). Due to a combination of physical, cognitive and perceptual problems, those who have suffered strokes often have difficulty participating in family, work and community life and performing ADLs such as feeding, dressing and grooming (14).

Functional performance of the affected upper limbs can be improved if the subject with stroke has adequate opportunities for exercise. Different techniques and methods can be used in rehabilitation management (e.g., physiotherapy, occupational therapy, conductive education, splinting, pharmacotherapy and surgery) and specific techniques (e.g., neurodevelopmental therapy (NDT) or constraint-induced movement therapy (CIMT) (15–19). However, no strong evidence exists about successful treatment using any of these techniques or methods.

With the rapid development of rehabilitation management technology, artificial intelligence (AI) technology, represented by rehabilitation robots (RT), has received widespread attention from medical researchers (20). AI is defined as the study of disciplines that enable computers to simulate human thought processes and intelligent behaviors (such as learning, reasoning, thinking, planning, etc.). This study mainly includes assessing the principles by which computers are manufactured to replicate and realize human brain intelligence and can achieve higher-level applications (21). Meanwhile, the upper limb RT is a medical robot that facilitates the recovery of upper limb function by driving the patient through repetitive upper limb movement training with mechanical assistance (22). Additionally, brain-computer interface (BCI) electrical stimulation training is a new method of central neurological intervention that collects signals from the patient's brain during motor imagery tasks, converts them into computer commands, and applies electrical stimulation to the paralyzed limb. This enables the establishment of a "central-peripheral-central" closed-loop rehabilitation training model that promotes central re-modeling and peripheral control, thereby facilitating the recovery of motor function (23, 24).

Remote rehabilitation (RR) is a rehabilitation model that uses Internet communication technology to achieve inter-temporal treatment between medical workers and patients, which is convenient, fast and without time and space boundaries, and supports the continued rehabilitation training of patients after discharge from hospital (25). Intelligent rehabilitation (IR) is a new type of intelligent biofeedback therapy device which uses two-dimensional virtual games as biofeedback to conduct interactive training with patients through visual, auditory and tactile forms. IR can be used to assess and train patients' manual motor and sensory functions and to rehabilitate people with cognitive impairment (26). Similarly, virtual reality (VR) technology is an effective tool for stroke rehabilitation, using computers to generate a virtual environment that simulates reality and uses a variety of sensing devices to "immerse" the user in that environment, enabling the user to interact naturally with the virtual environment (27). Combining the characteristics of the AI technologies mentioned above reveals that BCI, RR and VR share common ground regarding training characteristics. Moreover, IR contains the virtual interactive scenarios found in VR technology. However, the training principles of RR, RT and BCI are different. RT emphasizes mechanical assistance for hemiplegic upper limbs, BCI emphasizes central neural integration, based on central integration and peripheral control to assist rehabilitation training, and RR emphasizes online 5G technology to provide online rehabilitation guidance for home rehabilitation patients. Non-invasive VR, on the other hand, detects the thought activity of the brain through a non-implantable device, and the signal is substantially attenuated as it passes through the skull, resulting in low signal intensity and accuracy. Invasive BCIs require the implantation of electrodes into the cerebral cortex to enable interaction and thus have sufficiently precise and risky properties.

Researchers Erosy and Iyigun demonstrated that virtual and real boxing training significantly restored motor function in the hemiplegic upper limbs of subjects with stroke, which supports the effectiveness of virtual boxing training (28). Rodríguez-Hernández et al. showed that VR was more effective than traditional rehabilitation methods in improving stroke patients' quality of life (29). Also, another study found that combining traditional physical fitness with VR technology increased patients' interest in rehabilitation and made them more engaged, leading to better clinical outcomes (30). Previous research confirms that BCI combined with other treatments such as robotic orthoses, mobile robots, VR devices and functional electrical stimulation (FES) effectively improve limb function in subjects with stroke (31). Another study confirmed that RR technology, based on large data platforms, can enable patients to access quality rehabilitation medical services at home, provide long-term rehabilitation support

Abbreviations: AI, artificial intelligence; CT, control treatment; RT, rehabilitation robots; BCI, brain - computer interface; VR, virtual reality; RR, remote rehabilitation; RT + VR, rehabilitation robots + virtual reality; RCTs, randomized controlled trials; ARAT, action research arm test; NMA, network meta-analysis; ADL, activity of daily life; NDT, neurodevelopmental therapy; CIMT, constraint induced movement therapy; FES, functional electronic stimulation; EG, experimental group; CG, control group; FMA - UE, Fugl-Meyer assessment upper extremity; MBI, modified barthel Index; OT, occupational therapy; MTC, multiple treatment comparison; ITC, indirect treatment comparison.

for patients and their families, reduce the gap between in- and outpatients and facilitate function recovery as well as the continuity of rehabilitation treatment (32).

However, the aforementioned studies all investigated the effect of a single AI technique on upper limb function amongst subjects with strokes. Network meta analysis (NMA) may provide a way to address this issue. In randomized controlled trials (RCTs), a quantitative summary of the "network of evidence" is achieved by combining the direct and indirect effects of three or more interventions compared with the same comparative intervention (usually a control or no-treatment intervention) (33). This is also referred to as a multiple treatment comparison (34). In this way, NMA can quantitatively combine evidence on the effectiveness of interventions directly compared in the same RCTs (direct comparison) and interventions from different RCTs with a common comparator (indirect comparison) (33).

At present, most of the meta-analyses at home and abroad investigating AI rehabilitation focus on the single RR and the effects of BCI, VR and RT on the upper limb function and motor function of subjects with stroke. There are few reports on NMA analysis of various AI techniques used in rehabilitating the upper limb function of subjects with stroke (35–38). There is only one NMA analysis on the use of upper limb RT in upper limb motor function in subjects with stroke. The study observed its effect on upper limb function in subjects with stroke by drawing multiple comparisons among different models of upper limb RT. Its indirect comparison showed that none of the types of upper limb RT were better or worse than any other RT, nor did it provide clear evidence to support the choice of a specific type of robotic device to facilitate arm recovery (39).

The present NMA analysis integrates all new AI technologies based on previous studies. Therefore, this study aimed to provide a systematic overview of current RCTs of different modalities of AI techniques and assess their relative effectiveness using an NMA. We aimed to assess the relative influence of different modalities of AI techniques on ADLs, hand/arm function and overall upper limb motor function amongst subjects with strokes and explore the safety of these techniques.

Methods

Study enrollment and reporting

The protocol was based on the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA guidelines 2020) (40). PRISMA extension statements were used to ensure that all aspects of methods and results were reported (41). The protocol is registered in PROSPERO [registration number CRD42022337776 (https://www.Crd.york.ac.uk/prospero/#recordDetails)].

Search strategy

The study was conducted using PubMed, Embase, Web of Science, the Cochrane Library and CNKI, Wanfang and VIP databases in English and Chinese. A comprehensive and reproducible literature search was undertaken up to September 2022. We developed a search strategy for a combination of thematic terms and free terminology based on the Population, Intervention, Comparison, Outcome, Study Design (PICOS) principles. The specific search protocol included various medical topics and free-text terms related to stroke, cerebrovascular disease, upper limb and hand dysfunction and AI to obtain a broad range of literature for further analysis. PubMed is used as an example, and the specific search strategy is provided in Supplementary Table S1.

Inclusion criteria

The inclusion criteria were as follows: (1) Population: the diagnostic criteria for stroke were met by the Classification of Cerebrovascular Diseases, and a diagnosis of cerebral infarction or cerebral hemorrhage was made by cranial CT or MRI (2, 42, 43). Intervention: six AI technologies (RT, BCI, RR, IR, VR, RT + VR) were used as intervention methods, alone or in combination with artificial intelligence rehabilitation; (3) Comparison: the control group received only conventional rehabilitation or any of the above intervention groups; (4) Outcome: primary outcome: FMA-UE-Total, secondary outcome: FMA-UE-Distal, FMA-UE-Proximal, ARAT and MBI; (5) Study design: only RCTs were included in this study.

Exclusion criteria

The exclusion criteria were as follows: (1) other neurological disorders; (2) no accurate diagnosis or inconsistent with the included diagnosis; (3) no outcome indicators or inconsistent with the study indicators; 4) interventions inconsistent with the inclusion criteria; (5) duplicate published studies or incomplete study data even after contacting the authors; and (6) systematic reviews, meta-analyses, theoretical studies, expert reviews, animal experiments, conference reports, economic analyses or case reports.

Study selection

EndNote (version X20, Clarivate, Philadelphia, Pennsylvania, USA) was used to process the search records. Two reviewers (JL and CW) independently screened the titles and abstracts against the developed inclusion and exclusion criteria. This was followed by reading the full text to exclude documents that did not meet the inclusion criteria. Finally, the two authors identified the remaining literature for inclusion. During this process, any discrepancies were discussed and resolved by the third author (YZ).

Data extraction and quality assessment

We completed the data extraction using Microsoft Excel. The data extraction was strictly based on author(s), year of publication, specific information about treatment and control groups and primary and secondary outcome indicators. Any disagreements

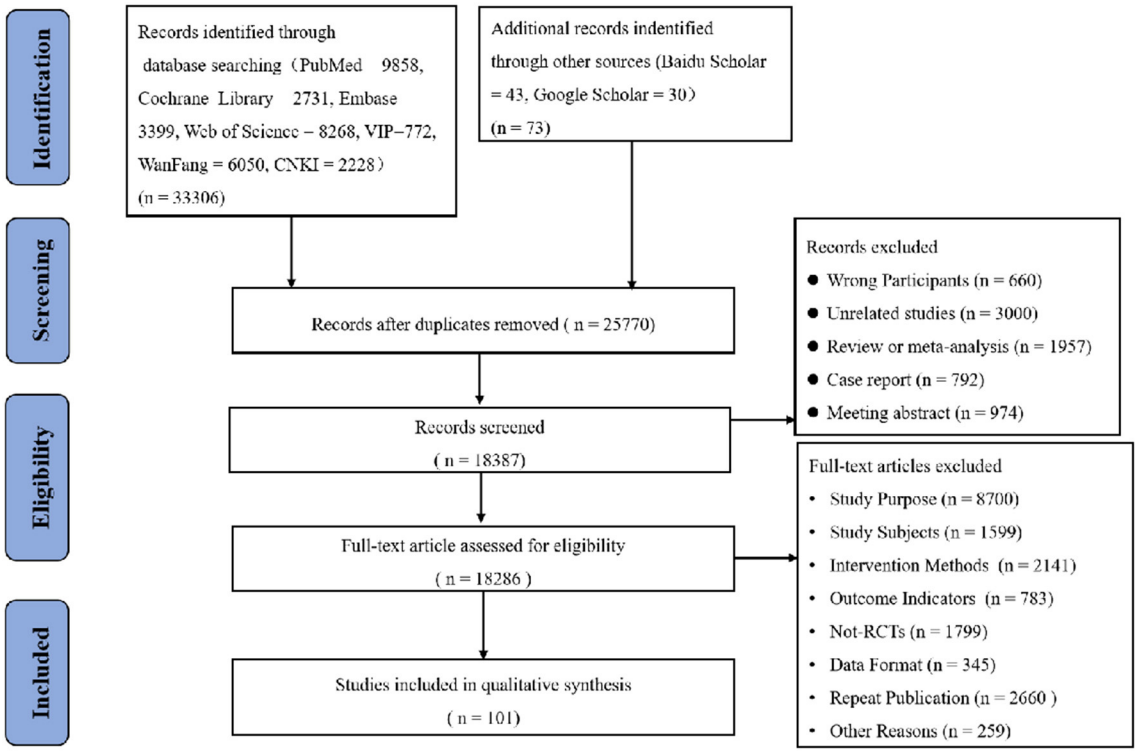


FIGURE 1
Flow diagram of eligible studies selection process. CNKI, China national knowledge infrastructure; WanFang knowledge servise platform; VIP, Chinese sceintific journals database; n, number of publications.

between the two reviewers (LZ and YZ) were judged by a third reviewer (P.Z. Zhang). Two reviewers (YZ and CW) assessed the potential risk of bias in each study by independently using the Cochrane Risk of Bias Tool (44). We assessed seven areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other possible biases. Each item was rated as unknown, low, or high risk of bias. The assessment was performed in Review Manager (version 5.3). The reviewer discrepancies were also addressed through discussions with a third reviewer (PZ) (45).

Statistical analysis

When trials used the same testing procedure (e.g., Barthel Index), we calculated the mean difference (MD) and the corresponding 95% confidence interval (CI). We calculated the standardized mean difference (SMD) using the 95% CI if various outcome measures were used for a given endpoint. For dichotomous endpoints, we determined the index of risk difference (RD) using the 95% CI.

We generated visual forest plots for all direct and indirect comparisons and compiled a relative ranking of each intervention based on the surface under the cumulative ranking line (SUCRA) (46). The SUCRA value calculates the percentage efficacy of each individual intervention compared with the "ideal" treatment. We performed all statistical analyses using the software STATA MP version 16.0 (47).

The network meta-analysis was based on a frequency approach, with weighted least squares for multiple regression with random effects. The method allows full consideration of multi-arm studies and includes restricted maximum likelihood estimates (48).

To test the possible assumptions of the transitivity hypothesis, we assessed global inconsistency utilizing consistency and inconsistency models (48, 49). Transitivity implies no systematic differences between the individual arms of the studies. At the local level, we used a node-splitting approach (48, 50). In addition to quantitative testing, we also qualitatively validated test descriptions that contained significant effect modifiers.

In the network diagram, we assessed the risk of bias between trials for each dimension as a study-level covariate along three dimensions (randomized sequences, hidden and blinded for randomized sequences).

Results

Results of study identification and selection

We included a total of 33,306 studies using the original search terms and 73 original studies in combination with the manual search. After screening for duplicates by de-duplication, we obtained 25,770 original papers. Following this, we obtained 18,387 original papers by applying the inclusion and exclusion

criteria combined with abstract reading. After reading the full texts, we obtained 91 original papers (including 8,700 deleted for study purposes, 1,599 deleted for study subjects, 2,141 deleted for intervention methods, 783 deleted for outcome indicators, 1,799 deleted for non-RCTs, 345 deleted for data format discrepancies, 2,660 deleted for duplicate publications and 259 deleted for other reasons). Finally, we included 101 studies (Among them, 91 were filtered and 10 were manually searched according to the purpose of the study) in the risk assessment and NMA. The process of selection of the eligible studies was shown in Figure 1.

Characteristics of the included studies

We eventually included 101 RCTs, with 2,390 participants in the experimental group (EG) and 2,312 in the control group (CG). Of the 101 studies included, 44 were published in Chinese and 57 in English. The publication period was from 2008 to 2022. The primary outcome indicator was FMA-UE-Total, and the secondary indicators were FMA-UE-Distal, FMA-UE-Proximal, Modified Barthel Index (MBI) and ARAT. Table 1 details the essential characteristics of the included studies.

Quality assessment of the included studies

We assessed the risk of bias for each study using the Cochrane Risk of Bias Tool. All studies included RCTs that reported the random sequence generation and allocation concealment with a low risk of bias. Almost two-thirds of the studies were shown to be at low risk in both the blinding of participants and personnel and the blinding of outcome assessment. Of these, only 10% of the studies in the blinding of participants and personnel showed high risk, and 10% showed unclear risk. In the blinding of outcome assessment, ∼ 20% of the studies showed high risk, and 20% showed unclear risk. Of the incomplete outcome data, ∼ 70% showed unclear risk, 5% showed low risk and 25% showed high risk. In the selective reporting, ∼ 15% showed low risk, 60% showed unclear risk and 25% showed high risk. Of the other biases, ∼ 35% showed low risk, 30% showed unclear risk and 30% showed high risk. Figure 2 contains detailed information on the risk of bias.

Results of the network meta-analysis

Evidence network diagram

A total of 101 studies, 4,702 subjects were included in this study involving six interventions (RT, BCI, RR, IR, VR, RT + VR). A total of 71 studies were included in the network evidence map of the FMA-UE-Total involving the following interventions: CT, RT, BCI, RR, IR, VR, and RT + VR. We included a total of 49 studies in the MBI network evidence map involving interventions such as CT, RT, BCI, RR, IR, VR, and RT + VR. We included 22 studies in the ARAT network evidence map involving CT, RT, BCI, RR, IR, VR, and RT + VR interventions. Moreover, we included a total of 26 studies in the FMA-UE-Proximal network evidence map involving interventions such as CT, RT, BCI, RR, IR, VR, and RT + VR, and we included 28 studies in the network evidence map for the FMA-UE-Distal, involving interventions such as CT, RT, BCI, RR, IR, VR, and RT + VR. Figures 3A–E shows the details of the NMA map.

Primary outcome

FMA-UE-total

We included 71 studies in the FMA-UE-Total in the comparison (51–66, 69–80, 87, 88, 91, 92, 147). As the network evidence map in this study did not form a closed loop, indirect comparisons and inconsistency tests could not be performed (148). However, $P > 0.05$ in the consistency test indicated excellent consistency and stability of the studies.

The NMA results showed that all interventions were not statistically significant, indicating that AI rehabilitation techniques did not significantly improve upper limb motor function amongst subjects with strokes (see Table 2). Figure 4A shows the SUCRA rankings for all treatments. Based on the results of the SUCRA analysis, IR [(SMD = 0.02, 95%CI = (−0.40, 0.43)] (SUCRA, 70.5%) was the most effective intervention for improving upper limb motor function amongst subjects with strokes, followed by BCI [(SMD = 0.001, 95%CI = (−0.46, 0.46)] (SUCRA, 69.5%); RT + VR [(SMD = 0.06, 95%CI = (−0.39, 0.51)] (SUCRA, 65.9%); VR [(SMD = 0.06, 95%CI = (−0.36, 0.48)] (SUCRA, 58.1%); RR [(SMD = 0.07, 95%CI = (−0.30, 0.45)] (SUCRA, 45.6%); RT [(SMD = 0.05, 95%CI = (−0.09, 0.20)] (SUCRA, 28.0%) and CT (SUCRA, 12.3%).

Secondary outcome

Modified barthel index

A total of 49 studies were included in the comparison of the MBI. As the network evidence map in this study did not form a closed loop, inconsistency tests could not be performed (148). However, $P > 0.05$ in the consistency test indicated excellent consistency and stability of the studies.

The NMA results showed no significant differences between the interventions for both direct and indirect comparisons, indicating that different modalities of AI technology had no significant effect on improving MBI function in subjects with stroke (see Table 3). Figure 4B shows the SUCRA rankings for all treatments. According to the results of the SUCRA analysis, BCI [(SMD = 0.03, 95%CI = (−0.24, 0.29)] (SUCRA, 73.6%) was the most effective intervention for improving quality of daily life amongst subjects with strokes, followed by RR [(SMD = 0.001, 95%CI = (−0.22, 0.23)] (SUCRA, 68.1%); RT [(SMD = 0.04, 95%CI = (−0.23, 0.31)] (SUCRA, 67.8%); IR [(SMD = 0.05, 95%CI = (−0.25, 0.36)] (SUCRA, 54.6%); VR [(SMD = 0.09, 95%CI = (−0.34, 0.51)] (SUCRA, 41.1%); RT + VR [(SMD = −0.03, 95%CI = (−0.39, 0.34)] (SUCRA, 26.5%) and CT (SUCRA, 18.4%).

FMA-UE-proximal

We included 26 studies in the FMA-UE-Proximal comparison. As the network evidence map in this study did not form a closed

TABLE 1 Description of the basic characteristics of the included studies.

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Su et al. (51)	China	4 weeks	Sub-acute stroke	EG:RT+CT	60	14/16	65.53 ± 5.46	FMA-UE, FMA-D, FMA-P, MBI
				CG:CT		15/15	64.97 ± 4.88	
Taravati et al. (52)	Turkey	12 weeks	Chronic stroke	EG:RT+CT	37	14/3	50.94 ± 17.20	FMA-UE
				CG:CT		14/6	55.75 ± 11.61	
Sale et al. (53)	Italy	6 weeks	Sub-acute stroke	EG:RT	53	11/15	67.7(65.8–77.0)	FMA-UE
				CG:CT		11/16	67.7(69.0-78.0)	
He et al. (54)	China	4 weeks	Stroke	EG1:RT+CT	60	26/4	57.67 ± 12.98	FMA-UE, MBI
				CG:CT		26/4	57.53 ± 14.61	
Burgar et al. (55)	USA	6 months	Stroke	EG1:RT-Lo	54	9/10	62.5 ± 2.0	FMA -UE,
				EG2:RT-Hi		9/8	58.6 ± 2.3	
				CG:CT		5/13	68.1 ± 3.3	
de Araújo et al. (56)	Brazil	8 weeks	Chronic stroke	EG:RT	12	5/1	42.83 ± 14.04	FMA-UE, FMA-D, FMA-P
				CG:CT		5/1	52.67 ± 17.84	
Housman et al. (57)	USA	6 months	Chronic stroke	EG:RT	28	7/7	54.2 ± 11.9	FMA-UE, MBI
				CG:CT		11/3	56.4 ± 12.8	
Hsieh et al. (58)	Taiwan	4 weeks	Chronic stroke	EG1:HI-RT	18	4/2	56.04 ± 13.07	FMA -UE,
				EG2:LI-RT		4/2	52.45 ± 1.98	
				CG:CT		5/1	54.00 ± 8.05	
Page et al. (59)	USA	8 weeks	Stroke	EG:RT	16	3/5	59.0 ± 12.9	FMA-UE, MBI
				CG:CT		8/0	58.5 ± 9.5	
Timmermans et al. (60)	Netherlands	6 months	Chronic stroke	EG:RT	22	8/3	61.8 ± 6.8	FMA-UE, ARAT
				CG:CT		8/3	56.8 ± 6.4	
Budhota et al. (61)	Singapore	6 weeks	Sub-acute stroke	EG:RT	44	11/11	56.32 ± 10.37	FMA-UE, ARAT
				CG:CT		14/8	54.59 ± 10.92	
Zhang et al. (62)	China	4 weeks	Stroke	EG:RT+CT	40	14/6	67.3 ± 6.0	FMA-UE, MBI,
				CG:CT+OT		12/8	66.4 ± 4.4	
Sun et al. (63)	China	4 weeks	Stroke	EG:RT+CT	70	21/17	59.11 ± 9.99	FMA-UE, MBI
				CG:CT		17/15	58.06 ± 10.70	

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Tomić et al. (64)	Serbia	3 weeks	Stroke	EG:RT	26	12/1	56.5 ± 7.4	FMA-UE, MBI
				CG:CT		9/4	58.3 ± 5.2	
Conroy et al. (65)	USA	12 weeks	Chronic stroke	EG:RT+CT	45	15/8	56.4 ± 12.7	FMA-UE, FMA-D, FMA-P
				CG:CT+TTT		14/8	55.7 ± 10.2	
Fan et al. (66)	China	12 weeks	Acute-stroke	EG:RT+CT	100	29/21	64.46 ± 8.81	FMA-UE, FMA-D, FMA-P, MBI
				CG:CT		30/20	68.00 ± 8.81	
Lee et al. (67)	Korea	2 weeks	Stroke	EG:RT	44	15/7	50.27 ± 11.11	MBI
				CG:CT		14/8	52.32 ± 8.66	
Villafañe et al. (68)	Italy	3 weeks	Stroke	EG:RT+CT	32	11/5	NA	MBI
				CG:CT		10/6	NA	
Zhang et al. (69)	China	4 weeks	Stroke	EG:RT+CT	12	4/2	35.5 ± 9.0	FMA-UE
				CG:CT		5/1	47.0 ± 10.0	
Zhang et al. (70)	China	1 month	Stroke	EG:RT+CT	40	12/8	53.2 ± 9.1	FMA-UE, MBI
				CG:CT		11/9	52.9 ± 8.6	
He et al. (71)	China	12 weeks	Acute-stroke	EG:RT+CT	46	16/7	55.82 ± 11.25	FMA-UE, MBI
				CG:CT+TTT		15/8	54.37 ± 11.02	
Singh et al. (72)	India	4 weeks	Chronic stroke	EG:RT	23	NA	41.1 ± 12.8	FMA-UE, FMA-D, FMA-P, MBI
				CG:CT		NA	42.7 ± 9.3	
Jiang et al. (73)	China	2 weeks	Sub-acute stroke	EG:RT	45	9/14	62.43 ± 11.29	FMA-UE, MBI
				CG:CT		7/15	66 ± 11.51	
Gandolfi et al. (74)	Italy	12 weeks	Chronic stroke	EG:RT	32	12/4	59.31 ± 14.40	FMA -UE
				CG:CT		10/6	59.13 ± 14.97	
Dehem et al. (75)	Belgium	6 months	Stroke	EG:RT	45	11/12	67.1 ± 11.1	FMA-UE,
				CG:CT		10/12	68.6 ± 19.1	
Carpinella et al. (76)	Italy	3 months	Sub-acute stroke	EG:RT	224	63/48	69.5 ± 10.9	FMA-UE, MBI
				CG:CT		64/49	68.5 ± 11.5	
Xu et al. (77)	China	6 weeks	Sub-acute stroke	EG:RT	40	15/5	62.2 ± 10.1	FMA-UE, MBI
				CG:OT		14/6	60.7 ± 10.6	

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Huang et al. (78)	Hong Kong	5 weeks	Chronic stroke	EG:Clinic-RT	32	8/8	53.50 ± 13.08	FMA-UE, ARAT, FMA-D, FMA-P
				CG:Lab-RT		12/4	53.06 ± 10.27	
Susanto et al. (79)	Hong Kong	6 months	Chronic stroke	EG:RT	19	7/2	50.7 ± 9.0	ARAT, FMA-UE, FMA-D, FMA-P
				CG:CT		7/3	55.1 ± 10.6	
Carpinella et al. (76)	Italy	3 months	Chronic stroke	EG:RT	38	9/10	67.0 (58.0–70.0)	FMA-UE, FMA-D, FMA-P
				CG:CT		9/10	59.0 (46.0–69.0)	
Dehem et al. (75)	Korea	4 weeks	Chronic stroke	EG1:EXO-RT	38	15/4	49.47 ± 10.88	FMA-UE, MBI
				CG:EE-RT		11/8	54.00 ± 10.01	
Wu et al. (80)	Taiwan	4 weeks	Chronic stroke	EG1:RBAT	42	10/4	55.13 ± 12.72	FMA-UE, FMA-D, FMA-P, MBI
				EG2:TBAT		12/2	57.04 ± 8.78	
				CG:CT		10/4	51.30 ± 6.23	
Abd El-Kafy et al. (81)	Saudi Arabia	12 weeks	stroke	EG:VRT+RT+CT	36	NA	NA	ARAT
				CG:CT				
Hu et al. (82)	China	4 weeks	stroke	EG1:VRT+CT	65	14/8	56.64 ± 11.37	FMA-UE, MBI, ARAT
				EG2:RT+CT		11/11	59.78 ± 11.13	
				EG3:VRT+RT+CT		14/7	57.89 ± 11.88	
Chen et al. (83)	China	2 weeks	stroke	EG:VRT+RT+CT	30	12/3	59.40 ± 11.06	FMA-UE, MBI
				CG:CT		7/8	63.60 ± 10.04	
Wang et al. (84)	China	8 weeks	Chronic stroke	EG1 :RT+CT	48	13/11	56.16 ± 4.52	FMA-UE, MBI
				EG2:VRT+CT		14/10	55.72 ± 4.66	
Gueye et al. (85)	Czech Republic	3 weeks	Sub-acute stroke	EG :VRT	50	14/11	66.56 ± 12.26	FMA-UE
				CG:CT		15/10	68.12 ± 11.97	
Zhao et al. (86)	China	4 weeks	Sub-acute stroke	EG :BCIT	28	13/1	50.1 ± 11.1	FMA-UE, MBI
				CG:CT		12/2	56.16 ± 11.5	

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Wang et al. (87)	China	4 weeks	stroke	EG:BCIT+CT	40	9/11	69.05 ± 5.79	FMA-UE, MBI, ARAT
				CG:CT		12/8	67.25 ± 4.78	
Lee et al. (88)	Korea	4 weeks	stroke	EG:BCIT+CT	26	4/9	55.15 ± 11.57	FMA-UE, MBI, WMFT
				CG:CT		6/7	58.30 ± 9.19	
Ang et al. (89)	Singapore	6 weeks	stroke	EG1:BCI-Manus	26	9/2	48.5 ± 13.5	FMA-UE
				EG2:Manus		8/7	53.6 ± 9.5	
Xu et al. (90)	China	8 weeks	stroke	EG:BCI+CT	32	15/1	72.42 ± 8.56	FMA-UE, MBI
				CG:CT		15/1	76.81 ± 9.57	
Liang et al. (91)	China	4 weeks	stroke	EG:BCI+CT	30	12/3	57.94 ± 8.84	FMA-UE, MBI
				CG:CT		9/6	50.06 ± 13.46	
Li et al. (92)	China	8 weeks	stroke	EG:BCI+CT	14	5/2	66.29 ± 4.89	FMA-UE, ARAT
				CG:CT		5/2	60.00 ± 6.30	
Xiang et al. (93)	China	6 weeks	stroke	EG:BCI+CT	94	22/25	58.6 ± 2.7	FMA-UE, MBI
				CG:CT		26/21	60.2 ± 1.9	
Ren and Xie (94)	China	4 weeks	stroke	EG:BCI+CT	60	18/12	41.77 ± 8.65	FMA-UE, MBI
				CG:CT		20/10	40.7 ± 8.15	
Chen et al. (95)	China	4 weeks	stroke	EG:BCI	14	7/0	41.6 ± 12.0	FMA-UE
				CG:CT		5/2	52.0 ± 11.1	
Frolov et al. (2019)	American	2 weeks	stroke	EG:BCI+CT	74	34/21	58.0 ± 12.59	FMA-UE, ARAT
				CG:CT		14/5	58.0 ± 11.11	
Kim et al. (96)	American	4 weeks	stroke	EG:BCI+CT	30	6/9	59.07 ± 8.97	FMA-UE, MBI
				CG:CT		6/9	59.93 ± 9.79	
Mihara et al. (97)	American	2 weeks	stroke	EG:BCI+CT	20	8/2	NA	FMA-UE, ARAT
				CG:CT		4/6	NA	

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Zhang et al. (62)	China	8 weeks	stroke	EG:BCIT+CT	30	11/4	60.93 ± 6.76	FMA-UE, MBI
				CG:CT		11/4	57.87 ± 8.61	
Wu et al. (98)	China	8 weeks	Chronic stroke	EG:RR+CT	80	19/21	57.45 ± 9.98	FMA-UE, MBI
				CG:CT		27/13	61.45 ± 9.83	
Xue et al. (99)	China	8 weeks	Chronic stroke	EG:RR+CT	60	NA	NA	FMA-UE, MBI
				CG:CT		NA	NA	
Wang et al. (100)	China	4 weeks	Chronic stroke	EG:RR+CT	38	15/4	53.22 ± 10.65	FMA-UE, MBI
				CG:CT		14/5	53.05 ± 14.83	
Wang et al. (101)	China	48 weeks	stroke	EG:RR+CT	60	24/6	58.0 ± 12	FMA-UE, MBI
Gao et al. (102)	China	12 weeks	stroke	CG:CT EG:RR+CT	40	22/8 12/6	60.00 ± 9 53.2 ± 17.1	FMA-UE, MBI
				CG:CT		14/8	52.2 ± 14.1	
Chen et al. (103)	China	24 weeks	stroke	EG:RR+CT	54	18/9	66.52 ± 12.08	FMA-UE, MBI
				CG:CT		15/12	66.15 ± 12.33	
Chen (104)	China	8 weeks	stroke	EG:RR	44	26/6	65.3 ± 13.2	FMA-UE
				CG:CT		14/8	67.1 ± 10.7	
Maeno et al. (105)	China	24 weeks	stroke	EG:RR	100	31/19	66.50 ± 11.45	MBI
				CG:CT		36/14	66.7 ± 11.76	
Lin et al. (106)	China	4 weeks	stroke	EG:RR	24	2/10	74.6 ± 2.3	MBI
				CG:CT		5/7	75.6 ± 3.4	
Chaiyawat et al. (107)	Thailand	24 weeks	stroke	EG:RR	60	14/16	67 ± 7	MBI
				CG:CT		13/17	66 ± 11	

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Redzuan et al. (108)	Malaya	12 weeks	stroke	EG:RR	90	21/23	63.7 ± 12	MBI
				CG:CT		31/15	59.40 ± 11	
Piron et al. (109)	Venezia	4 weeks	stroke	EG:RR	36	11/7	66 ± 7.9	FMA-UE
				CG:CT		10/8	64.4 ± 7.9	
Li et al. (110)	China	12 weeks	stroke	EG:RR	101	28/23	65.69 ± 11.32	FMA-UE, MBI
				CG:CT		27/23	65.51 ± 13.02	
Kwon et al. (111)	Korea	4 weeks	stroke	EG:VR	26	9/4	57.14 ± 15.42	FMA - UE, FMA - P, FMA - D, MBI
				CG:CT		5/8	57.92 ± 12.32	
Chen et al. (112)	China	48 weeks	stroke	EG:VR+RT	49	19/4	64.31 ± 6.11	FMA - UE, FMA - P, FMA - D, MBI
				CG:CT		14/12	66.42 ± 5.6	
Jiang (113)	China	2 weeks	stroke	EG:VRT+RT+CT	40	9/11	63.15 ± 11.79	FMA - UE, FMA- P, FMA - D, MBI
				CG:CT		15/5	65.10 ± 9.14	
Wei (114)	China	3 weeks	Stroke	EG:IR	120	37/23	66.3 ± 5.2	FMA - UE
				CG:CT		35/25	65.7 ± 5.4	
Wang (115)	China	12 weeks	Stroke	EG:IR+CT	110	27/28	64.23 ± 5.95	FMA - UE
				CG:CT		31/24	63.08 ± 6.14	
Prange et al. (116)	Netherlands	6 weeks	Sub-acute stroke	EG:IR	68	17/18	60.3 ± 9.7	FMA - UE
				CG:CT		14/19	58 ± 11.4	
Lee et al. (117)	Korea	2 weeks	Stroke	EG:IR+CT	50	14/11	55.76 ± 13.6	MBI
				CG:CT		12/13	57.88 ± 11.12	
McNulty et al. (118)	Australia	2 weeks	Stroke	EG:IR	41	13/8	59.9 ± 13.8	FMA - UE
				CG:CT		18/2	56.1 ± 17	

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Norouzi-Gheidari et al. (119)	Canada	4 weeks	Stroke	EG:VR+CT	18	5/4	42.2 ± 9.5	FMA-UE
Lin et al. (120)	China	4 weeks	Chronic stroke	EG:TG	33	12/4	52.63 ± 10.49	FMA - UE, FMA - P, FMA - D
				CG:CT		16/1	57.47 ± 10.29	
Keskin et al. (121)	Turkey	6 weeks	Stroke	EG:VR+CT	24	4/8	63.6 ± 9.2	FMA - UE
				CG:CT		5/7	63.6 ± 7.1	
El-Kafy et al. (122)	Norway	12 weeks	Chronic stroke	EG:VR+CT	40	16/4	54.46 ± 4.27	ARAT
				CG:CT		15/5	53.32 ± 5.13	
				CG:CT		5/4	57.6 ± 10.5	
Choi et al. (123)	Korea	2 weeks	Ischemic stroke	EG:VR+CT	24	7/5	61 ± 15.2	FMA-UE
				CG:CT		6/6	72.1 ± 9.9	
Anwar et al. (124)	Pakistan	6weeks	Stroke	EG:VR	68	20/14	51.56 ± 7.19	FMA-UE
				CG:CT		14/20	51.35 ± 5.78	
Kim et al. (125)	China	4 weeks	Stroke	EG:VR+CT	60	16/14	70.31 ± 3.81	FMA-UE
				CG:CT		17/13	69.83 ± 3.27	
Xiao et al. (126)	China	4 weeks	Sub-acute stroke	EG:VR	35	10/6	56.12 ± 9.01	FMA-UE, MBI
				CG:CT		12/7	53.67 ± 8.03	
Bo et al. (127)	China	4 weeks	Stroke	EG:VR+CT	60	23/7	64.0 ± 7.74	FMA-UE, MBI
				CG:CT		25/5	62.4 ± 9.77	
Kim (128)	China	2 weeks	Stroke	EG:VR	30	10/5	61.4 ± 8.1	FMA-UE
				CG:CT		9/6	58.8 ± 9.5	
Tian et al. (129)	China	4 weeks	Stroke	EG:VR+CT	60	21/9	57.4 ± 11.34	FMA-UE, MBI

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
				CG:CT		19/11	58.13 ± 12.57	
Lee et al. (130)	Korea	4 weeks	Stroke	EG:VR+CT	10	3/2	65.2 ± 5.0	FMA-UE
				CG:CT		2/3	66.2 ± 3.4	
Kong et al. (131)	Singapore	3 weeks	Stroke	EG1:VR	102	27/5	58.1 ± 9.1	FMA-UE, ARAT
				EG2:CT		25/8	59.0 ± 13.6	
				CG:CC		25/12	55.8 ± 11.5	
Park et al. (132)	Korea	4 weeks	Stroke	EG:VR+CT	25	7/5	53.5 ± 13.0	FMA-UE, FMA-P, FMA-D, MBI
				CG:CT		8/5	51.5 ± 16.7	
Brunner et al. (133)	Norway	4 weeks	Stroke	EG:VR	130	42/20	62 ± 16.5	ARAT
				CG:CT		35/23	62 ± 11.5	
Choi et al. (134)	Korea	4 weeks	Sub-acute stroke	EG:VR	20	5/5	64.30 ± 10.3	FMA-UE
				CG:CT		5/5	64.70 ± 11.3	
Thielbar et al. (135)	USA	6 weeks	Stroke	EG:VR	14	4/3	54 ± 7	ARAT
				CG:CT		5/2	59 ± 6	
Kiper et al. (136)	Italy	4 weeks	Stroke	EG:VR	44	14/9	63.1 ± 9.5	FMA-UE
				CG:CT		15/6	65.5 ± 14.2	
Lee et al. (137)	Korea	4 weeks	Stroke	EG:VR+CT	24	5/7	58.33 ± 10.17	FMA-UE
				CG:CT		6/6	65.42 ± 9.77	
Kwon et al. (111)	Korea	4 weeks	Stroke	EG:VR+CT	26	9/4	57.15 ± 15.42	FMA-UE, MBI
				CG:CT		5/8	57.92 ± 12.32	
Crosbie et al. (138)	UK	3 weeks	Stroke	EG:VR	18	5/4	56.1 ± 14.5	ARAT
				CG:CT		5/4	64.6 ± 7.4	

(Continued)

10.3389/fneur.2023.1125172

TABLE 1 (Continued)

Study	Location	Duration of intervention	Type	Group	*n*	Sex (M/F)	Age (years)	Ending indicators
Yin et al. (139)	Singapore	2 weeks	Stroke	EG:VR+CT	23	6/5	62 ± 16.3	FMA-UE, ARAT
				CG:CT		10/2	56 ± 11.1	
Zhou et al. (140)	China	12 weeks	Stroke	EG:RR+CT	75	21/16	55.00 ± 5.15	ARAT, FMA-UE, MBI
				CG:CT		20/18	55.97 ± 6.17	
Ögün et al. (141)	Türkiye	6 weeks	Ischemic stroke	EG:VR	65	28/5	61.48 ± 10.92	ARAT, FMA-UE, MBI
				CG:CT		23/9	59.75 ± 8.07	
Nijenhuis et al. (142)	Netherlands	6 weeks	Chronic stroke	EG:IR	20	7/3	58 ± 12.59	ARAT
				CG:CT		3/7	62 ± 11.85	
Wolf et al. (143)	USA	8 weeks	Stroke	EG:RR+CT	99	31/17	54.7 ± 12.2	ARAT, FMA-UE, FMA-P, FMA-D
				CG:CT		25/26	59.1 ± 14.1	
Chen et al. (144)	China	2 weeks	Stroke	EG:VR	36	10/8	57.8 ± 8.4	ARAT, FMA-UE
				CG:CT		10/8	58.4 ± 9.3	
Rand et al. (86)	Israel	5 weeks	Chronic stroke	EG:IR	24	9/4	59.1 ± 10.5	ARAT
				CG:CT		6/5	64.9 ± 6.9	
Qian et al. (145)	China	12 weeks	Sub-acute stroke	EG:RR	24	9/5	54.6 ± 11.3	ARAT, FMA-UE, FMA-P, FMA-D
				CG:CT		6/4	64.6 ± 3.43	
Huijgen et al. (146)	Netherlands	4 weeks	Stroke	EG:RR+CT	17	2/9	69 ± 8	ARAT
				CG:CT		4/1	71 ± 7	

ARAT, action research arm test; AST, arm supporting training; BCI, brain-computer interface; CG, control group; CT, conventional rehabilitation; D, distal; RR, remote rehabilitation training; EG, experimental group; EE, end - efector; EXO, exoskeleton; FMA - UE, fugl-meyer assessment upper extremity; HI, higher intensity; IR, intelligent rehabilitation; LI, lower intensity; Lo, low dose; MBI, modified barthel index; mCIMT, modified constraint induced movement therapy; OT, occupational therapy; P, proximal; RBAT, robot-assised bilateral arm training; RT, robot treatment; RR, remote rehabilitation; TBAT, therapist-based arm training; TTT, transition-to-task therapy; VRT, virtual reality training; WMT, wii-based movement therapy.

10.3389/fneur.2023.1125172

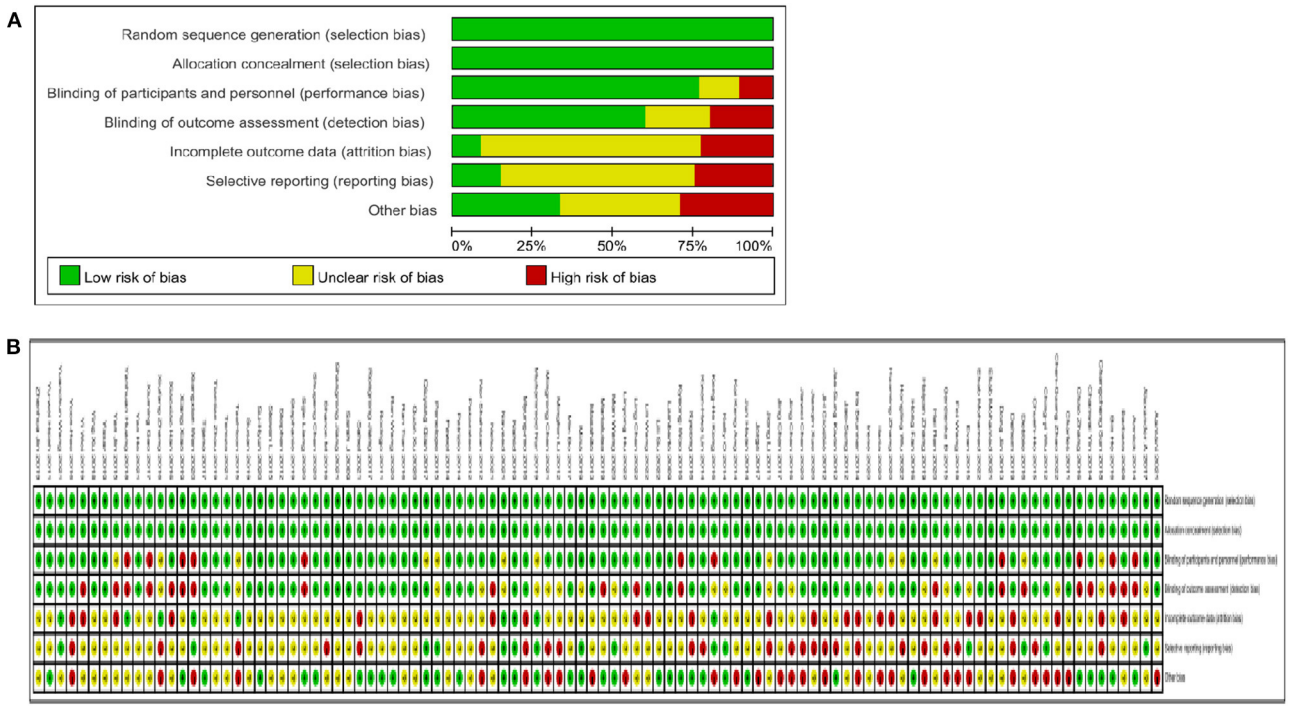


FIGURE 2
Quality assessment of selected studies by the cochrane risk of bias tool. **(A)** Risl of bias graph: review authors judgments about each risk of bias item presents as percentages across all included studies. **(B)** Risk of bias summary: review authors judgements about each risk of bias item for each included study.

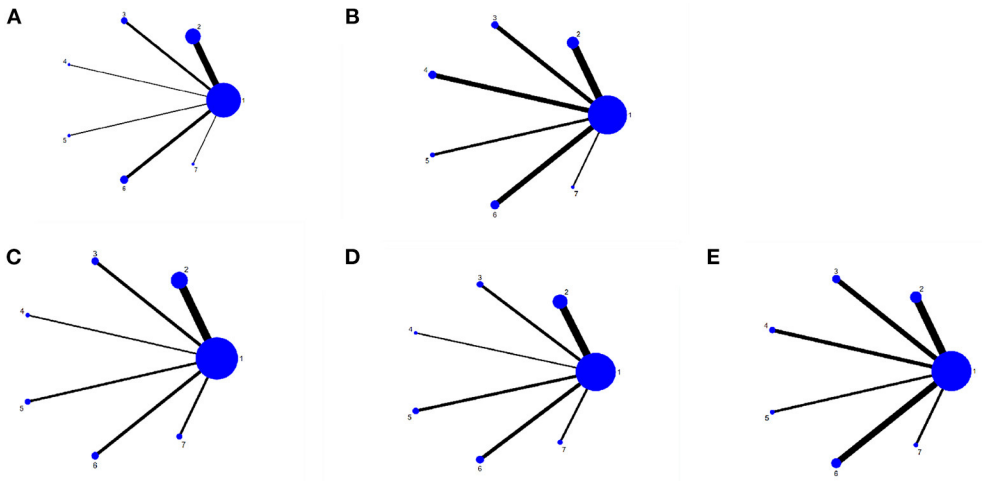


FIGURE 3
Network meta-analysis diagrams of eligible comparisons. **(A)** FMA-UE-Total, **(B)** MBI, **(C)** FMA-UE-Proximol, **(D)** FMA-UE-Distal, **(E)** FMA-UE-ARAT. Width of the lines is proportional to the number of trial. Size of every circle is proportional to the number of randomly assignes participants (sample size). 1, conventional training (CT); 2, Robot training (RT); 3, Brain-computer interface (BCI); 4, Remote rehabilitation (RR); 5, Intelligent rehabilitation (IR); 6, Virtual reality (VR); 7, Robot training + virtual reality (RT+VR).

loop, inconsistency tests could not be performed (148). However, $P > 0.05$ in the consistency test indicates excellent consistency and stability of the studies.

The NMA study showed there were significant differences in direct comparisons between VR + RT [(SMD = 0.43, 95%CI = (0.01, 0.85)], RT [(SMD = 0.32, 95%CI = (0.07, 0.59)] and CT. There were no significant differences in direct and indirect comparisons between the other interventions. This suggests VR + RT and RT effectively improve motor function of the upper limb shoulder and elbow joints amongst subjects with strokes (see Table 4). Figure 4C shows the SUCRA rankings for all treatments. Based on the results of the SUCRA analysis, RT + VR

TABLE 2 Network analysis results of the FMA – UE -total.

IR						
0.02 (−0.40, 0.43)	BCI					
0.02 (−0.50, 0.54)	0.00 (−0.46, 0.46)	RT+VR				
0.08 (−0.33, 0.49)	0.06 (−0.27, 0.39)	0.06 (−0.39, 0.51)	VR			
0.14 (−0.34, 0.62)	0.12 (−0.30, 0.54)	0.12 (−0.40, 0.64)	0.06 (−0.36, 0.48)	RR		
0.21 (−0.16, 0.58)	0.19 (−0.09, 0.47)	0.19 (−0.23, 0.61)	0.13 (−0.14, 0.41)	0.07 (−0.30, 0.45)	RT	
0.26 (−0.07, 0.60)	0.25 (0.01, 0.48)	0.24 (−0.15, 0.63)	0.18 (−0.05, 0.41)	0.13 (−0.22, 0.47)	0.05 (−0.09, 0.20)	CT

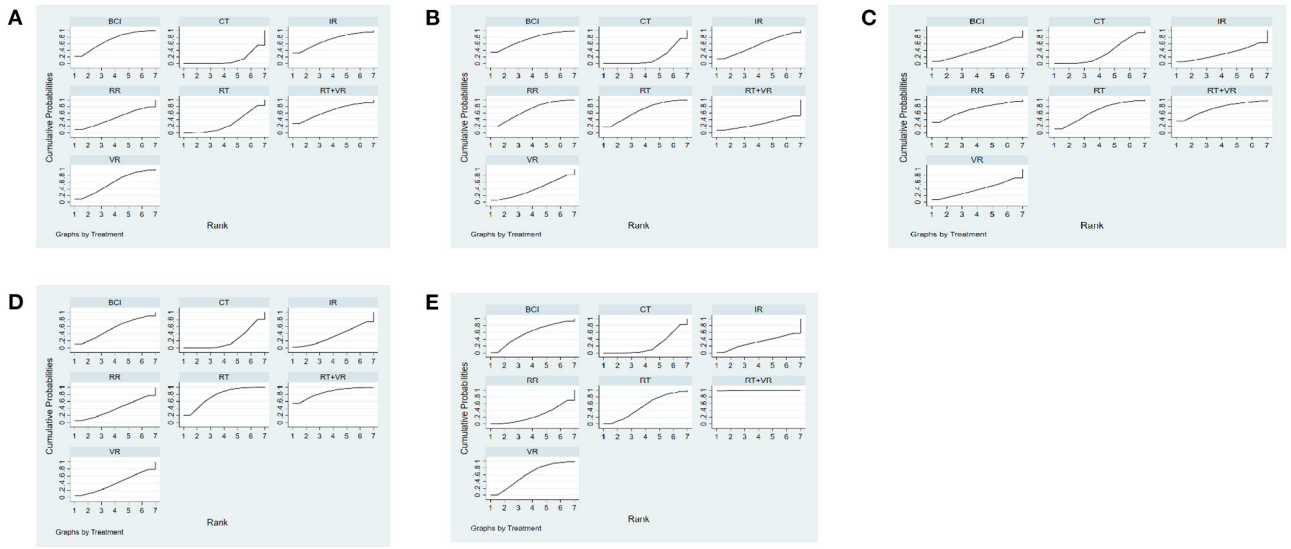


FIGURE 4
Cumulative probability ranking curve of different interventions. **(A)** FMA-UE-Total, **(B)** MBI, **(C)** FMA-UE-Proximal, **(D)** FMA-UE-Distal, **(E)** FMA-UE-ARAT. The fuller the area under the curve, the more effective it is. 1, conventional training (CT); 2, Robot training (RT); 3, Brain-computer interface (BCI); 4, Remote rehabilitation (RR); 5, Intelligent rehabilitation (IR); 6, Virtual reality (VR); 7, Robot training + virtual reality (RT+VR).

(SUCRA, 84.8%) was the most effective intervention for improving shoulder and elbow joint motor function amongst subjects with strokes, followed by RT (SUCRA, 75.5%), BCI [(SMD = 0.10, 95%CI = (−0.49, 0.69)] (SUCRA, 54.7%); VR [(SMD = 0.01, 95%CI = (−0.62, 0.63)] (SUCRA, 39.6%); RR [(SMD = 0.04, 95%CI = (−0.57, 0.65)] (SUCRA, 38.9%), IR [(SMD = 0.05, 95%CI = (−0.36, 0.45)] (SUCRA, 34.2%) and CT (SUCRA, 22.3%).

FMA-UE-Distal

We included 28 studies in the FMA-UE-Distal comparison. As the network evidence map in this study did not form a closed loop, inconsistency tests could not be performed. However, $P > 0.05$ in the consistency test indicates excellent consistency and stability of the studies.

The NMA results showed no significant differences between the interventions, compared directly and indirectly, suggesting different modalities of AI techniques did not significantly influence the improvement of wrist joint motor function in the upper limbs of subjects with stroke (see Table 5). Figure 4D shows the SUCRA rankings for all treatments. Based on the results of the SUCRA analysis, RT + VR [(SMD = 0.03, 95%CI = (−0.47, 0.52)] (SUCRA, 74.1%) was probably the most effective intervention for improving wrist joint motor function amongst subjects with strokes, followed by RR [(SMD = 0.06, 95%CI = (−0.35, 0.46)] (SUCRA, 70.1%); RT [(SMD = 0.11, 95%CI = (−0.29, 0.51)] (SUCRA, 63.8%); BCI [(SMD = 0.02, 95%CI = (−0.52, 0.55)] (SUCRA, 40.8%); VR [(SMD = −0.001, 95%CI = (−0.41, 0.41)] (SUCRA, 38.5%); CT [(SMD = 0.05, 95%CI = (−0.33, 0.44)] (SUCRA, 32.5%) and IR (SUCRA, 30.4%).

Action research arm test

A total of 22 studies were included in the ARAT comparison (60, 81, 82, 131, 133, 139, 142, 144, 149). As the network evidence map in this study did not form a closed loop, inconsistency tests could not be performed (148). However, $P > 0.05$ in the consistency test indicated excellent consistency and stability of the studies.

The NMA results showed significant differences in all interventions compared to CT, suggesting RT + VR [(SMD = 0.73, 95%CI = (0.20, 1.26)], VR [(SMD = 0.73, 95%CI = (0.14, 1.32)], BCI [(SMD = 0.78, 95%CI = (0.25, 1.31)], RT [(SMD = 0.93, 95%CI = (0.17, 1.70)], IR [(SMD = 0.92, 95%CI = (0.36, 1.48)] and RR [(SMD = 0.91, 95%CI = (0.44, 1.39)] were effective

TABLE 3 Network analysis results of the MBI.

BCI						
0.03 (−0.24, 0.29)	RR					
0.03 (−0.24, 0.29)	0.00 (−0.22, 0.23)	RT				
0.07 (−0.23, 0.37)	0.04 (−0.22, 0.31)	0.04 (−0.23, 0.31)	IR			
0.12 (−0.18, 0.42)	0.10 (−0.17, 0.37)	0.09 (−0.17, 0.36)	0.05 (−0.25, 0.36)	VR		
0.21 (−0.22, 0.63)	0.18 (−0.22, 0.58)	0.18 (−0.22, 0.58)	0.14 (−0.29, 0.56)	0.09 (−0.34, 0.51)	RT+VR	
0.18 (−0.03, 0.39)	0.16 (−0.01, 0.32)	0.15 (−0.01, 0.31)	0.11 (−0.10, 0.32)	0.06 (−0.16, 0.27)	−0.03 (−0.39, 0.34)	CT

TABLE 4 Network analysis results of the FMA - UE - Proximal.

RT+VR						
0.11 (−0.38, 0.60)	RT					
0.24 (−0.34, 0.82)	0.13 (−0.34, 0.60)	BCI				
0.34 (−0.26, 0.94)	0.23 (−0.27, 0.72)	0.10 (−0.49, 0.69)	VR			
0.34 (−0.28, 0.96)	0.23 (−0.29, 0.76)	0.10 (−0.51, 0.71)	0.01 (−0.62, 0.63)	RR		
0.38 (−0.20, 0.97)	0.27 (−0.20, 0.75)	0.14 (−0.43, 0.71)	0.05 (−0.54, 0.64)	0.04 (−0.57, 0.65)	IR	
0.43 (0.01, 0.85)	**0.32 (0.07, 0.57)**	0.19 (−0.21, 0.59)	0.09 (−0.34, 0.52)	0.09 (−0.37, 0.55)	0.05 (−0.36, 0.45)	CT

RT+VR, RT and CT for direct comparison, showing that the differences are statistically significant.

in improving ARAT function in subject with stroke (see Table 6). Figure 4E shows the SUCRA rankings for all treatments. Based on the results of the SUCRA analysis, RT + VR (SUCRA, 99.6%) was the most effective intervention for improving hand function amongst subjects with strokes, followed by VR (SUCRA, 60.9%), BCI (SUCRA, 57.7%), RT (SUCRA, 51.9%), IR (SUCRA, 30.1%), RR (SUCRA, 27.0%) and CT (SUCRA, 22.8%).

Presence of adverse effects

A network meta-analysis of adverse reactions could not be completed further as all included studies did not report adverse reactions.

Publication bias and consistency assessment

We constructed a comparative corrected funnel plot of the main results of FMA-UE-Total for evaluation *via* Stata/MP 16.0. Figure 5 shows the funnel plots show a symmetrical distribution, indicating limited publication bias in this study.

Discussion

We conducted a systematic evaluation by NMA analysis, including 101 studies involving 4,702 subjects. The results of the NMA analysis showed that, in ARAT, there were significant differences in direct and indirect comparisons of RT + VR with each of the other interventions. In the FMA-UE-Proximal, there were significant differences in direct comparisons between RT + VR and RT vs. CT. Meanwhile, there were no significant differences between direct and indirect comparisons for each of the other interventions. However, in FMA-UE-Total, FMA-UE-Distal and MBI, there were no significant differences in direct and indirect comparisons between the interventions. Overall, there were no significant adverse effects in any of the studies, indicating the strong reliability and safety of the results.

Our NMA analyses may provide new and valuable insights into using different modalities of AI technology in the functional rehabilitation of the upper limb among subjects with strokes. We believe these analyses may be seen as complementary to previous systematic reviews on this topic.

In this study, we compared the effects of different AI techniques on FMA-UE-Proximal amongst subjects with strokes. The analysis showed that RT + VR [SMD = 0.26; 95% CI (−0.26, 0.78)] was the best treatment for improving overall outcomes in improving wrist and shoulder joint motor function in the upper limbs of subjects with strokes. RT + VR (SUCRA = 84.8%) was also the most effective treatment, according to the SUCRA results. Our NMA results also found a significant difference between RT + VR and RT in improving wrist joint motion amongst subjects with strokes compared with CT. In contrast, a single RCT by Chen and Jiang showed no significant difference between RT + VR in improving wrist motion amongst subjects with strokes (113, 150). Chen and Jiang further mentioned that, due to the absence of other forms of hand function training with RT + VR, the upper limb RT device often left the wrist and hand in a relatively fixed position compared with conventional exercise therapy. The improvement in hand function was not significant when compared with conventional rehabilitation. To some degree, this is inconsistent with the findings of this study. Some studies using RT technology to observe its effect on the function of the upper limb wrist and shoulder elbow joint in subjects with stroke

TABLE 5 Network analysis results of the FMA - UE - distal.

RT+VR						
0.03 (−0.47, 0.52)	RR					
0.08 (−0.32, 0.48)	0.06 (−0.35, 0.46)	RT				
0.19 (−0.29, 0.68)	0.17 (−0.32, 0.66)	0.11 (−0.29, 0.51)	BCI			
0.21 (−0.33, 0.74)	0.18 (−0.35, 0.72)	0.13 (−0.33, 0.58)	0.02 (−0.52, 0.55)	VR		
0.21 (−0.14, 0.55)	0.18 (−0.17, 0.53)	0.13 (−0.08, 0.33)	0.01 (−0.33, 0.36)	−0.00 (−0.41, 0.41)	CT	
0.26 (−0.26, 0.78)	0.24 (−0.29, 0.76)	0.18 (−0.26, 0.62)	0.07 (−0.45, 0.59)	0.05 (−0.51, 0.61)	0.05 (−0.33, 0.44)	IR

TABLE 6 Network analysis results of the ARAT.

RT+VR						
0.73 (0.20, 1.26)	VR					
0.73 (0.14, 1.32)	0.00 (−0.41, 0.42)	BCI				
0.78 (0.25, 1.31)	0.05 (−0.27, 0.37)	0.05 (−0.36, 0.46)	RT			
0.93 (0.17, 1.70)	0.20 (−0.44, 0.85)	0.20 (−0.49, 0.89)	0.15 (−0.49, 0.79)	IR		
0.92 (0.36, 1.48)	0.19 (−0.18, 0.56)	0.19 (−0.27, 0.64)	0.14 (−0.23, 0.51)	−0.01 (−0.68, 0.66)	RR	
0.91 (0.44, 1.39)	0.18 (−0.04, 0.41)	0.18 (−0.16, 0.53)	0.13 (−0.09, 0.36)	−0.02 (−0.62, 0.58)	−0.01 (−0.30, 0.29)	CT

have shown that upper limb RT can effectively improve the wrist and shoulder elbow joint function of the upper limb of subjects with stroke (64). Another large study showed that VR technology can also effectively improve the wrist motor function of the upper limbs of subjects with stroke (151). This also indirectly confirms that the use of RT combined with VR may be more advantageous, such as the NMA results indicated in this study, which showed that RT + VR is the best treatment to improve the function of upper limbs, shoulders, elbows and wrists in subjects with strokes. At the same time, the search at home and abroad found that most scholars did not separately evaluate the three sub-terms of shoulder joint, wrist joint and elbow joint in FMA-UE to observe the effect of RT, VR and RT + VR technology on the motor function of the above three joints in subjects with stroke. The meta-analysis did not classify the three sub-terms of FMA-UE, so it was not possible to observe the effects of RT and VR technology on the motor function of the above three joints in subjects with stroke by meta-synthesis (37, 152).

The present study, in contrast, is based on a multiple comparison NMA analysis and provides a summary of previous studies. Therefore, the results of this study may be somewhat more convincing than the above studies. Similarly, RT significantly improved wrist motor function in the upper limbs of subjects with strokes, consistent with the findings from Kwon et al. (111). Moreover, the results combined with the NMA analysis further suggest that RT + VR [SMD = 0.43; 95% CI (0.01, 0.85)] may be the optimal treatment in terms of improving wrist motor function amongst subject with strokes. On the one hand, our NMA also found that direct and indirect comparisons between studies showed no significant differences in the FMA-UE-Total and FMA-UE-Distal comparisons. In FMA-UE-Distal, IR ranked first out of seven different AI techniques (SUCRA = 70.5%), reflecting that it was the optimal treatment. In the FMA-UE-Total, RT + VR [SMD = 0.26; 95% CI (−0.07, 0.60)] ranked first out of seven

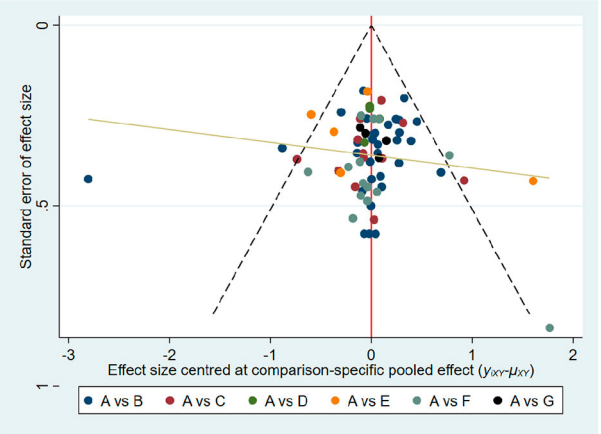


FIGURE 5
Comparison-adjusted funnel plots. FMA-UE total. The fuller the area under the curve, the more effective it is. A, conventional training (CT); B, Robot training (RT); C, Brain-computer interface (BCI); D, Remote rehabilitation (RR); E, Intelligent rehabilitation (IR); F, Virtual reality (VR); G, Robot training + virtual reality (RT+VR).

different AI techniques (SUCRA = 74.1%), reflecting that it was the optimal treatment. We speculate that the reason for this lack of significant difference may be related to the inconsistent duration of disease (acute, sub-acute and chronic), varying age ranges, and inconsistent Brunnstrom motor function staging and balance in the subjects included in the original study (60, 72, 86, 88, 109).

The ARAT assesses changes in limb function, including the ability to manage objects with different physical characteristics. It is a valid and applicable assessment of changes in upper limb motor function following the onset of a stroke. It involves 19 items divided into four sub-scales: grip, grip strength, pinch and gross

motor (153, 154). In this study, our NMA results suggest that RT + VR [SMD = 0.91; 95% CI (0.44, 1.39)] was most effective in improving ARAT in subjects with upper limb dysfunction after a stroke. According to the SUCRA results, RT + VR (SUCRA = 99.6%) was the most effective treatment. Simultaneously, there was a significant difference between RT + VR in improving the motor function of the upper limbs of ARAT amongst subjects with strokes compared with other interventions. However, some high-quality meta-analyses and multi-center RCTs have provided mixed conclusions.

One of the Cochrane meta-analyses showed a significant improvement in upper extremity ARAT function in subjects with stroke who received an upper extremity RT intervention, with significant changes in arm function and no significant difference in arm strength (155). A multi-center large RCT from Lancet also showed that upper extremity RT training was ineffective in improving upper limb ARAT function in subjects with stroke (156). Although there was no statistically significant difference in the results, there was a clear trend toward improvement at 3 and 6 months, with the authors suggesting that the reason for the absence of a difference may be related to wear and tear on the upper extremity RT training apparatus, participant adherence, and attrition rates (156). A multi-center study of VR came to the same conclusion as Lancet, showing that VR did not show significant between-group differences in improving ARAT in subjects with strokes compared with CT (157). Meanwhile, the combined use of VR technology and the upper limb rehabilitation robot allows the two to complement each other, thus effectively improving the ARAT motor function of the upper limbs amongst subjects with strokes (82). In contrast, this study is based on multiple comparative NMA studies, summarizing previous studies' shortcomings through direct and indirect comparisons. Therefore, the reliability of the results of this study is somewhat convincing.

The MBI consists of 10 items, including eating, bathing, grooming, dressing, stooling, urinating, toileting, transferring, walking and ascending and descending stairs and is often used to assess basic ADLs amongst subjects with strokes (96, 158). The results of the NMA by Li et al. (36) found that different modalities of BCI improved upper limb motor function and ADLs amongst subjects with strokes, with BCI and an FES as the driving device having the best effect (36). Our NMA analysis found that direct and indirect comparisons between studies showed no significant differences in improving the quality of daily life amongst subjects with strokes. At the same time, BCI [SMD = 0.18; 95% CI (−0.03, 0.39)] ranked best among seven different AI techniques (SUCRA = 73.6), reflecting that it was the most effective treatment. In conjunction with the study by Li et al., the BCI technique effectively improved the ability of subjects with strokes to perform daily living activities (36). Their findings are not consistent with those of our NMA study. We speculate that this may be related to the age, duration of disease, location of symptoms and functional recovery of the subjects included in the study (95, 159, 160).

This study provides an innovative, systematic integration of various AI rehabilitation techniques for direct and indirect comparison to establish which AI rehabilitation techniques were most effective in improving upper limb function in subjects with stroke. Based on clinical considerations, this study concluded that RT + VR had a significant advantage in improving shoulder and wrist joint motor function and ARAT in subjects with stroke, and IR and BCI had a significant advantage in improving upper limb motor function and MBI in FMA. Therefore, based on the evidence from this study, RT + VR, IR and BCI techniques can be recommended as the preferred treatment method for upper limb functional rehabilitation in subjects with stroke, which also provides evidence-based information for using and promoting AI rehabilitation techniques in clinical practice. Follow-up studies should provide more precise and personalized treatment protocols based on key characteristics of subjects with stroke, such as the severity of a stroke and the degree of upper limb impairment, as well as the intensity, frequency and duration of treatment, depending on their different clinical characteristics and degree of impairment. In terms of methodology, researchers also need to better describe interventions (both tailored and individualized) and ensure that the implementation and delivery of interventions are accurately documented, with attention to symptom reduction, independence and function. There should also be reporting on barriers to implementation and measuring the potential impact and harm of AI technologies.

Strengths and limitations

First, our study included 101 studies and 4,702 patients, indicating a large sample size. Moreover, we involved seven treatment interventions and assessed the impact of the interventions in six ways to provide more comprehensive evidence-based recommendations. Second, most of the systematic reviews and meta-analyses of AI rehabilitation have assessed the effects of single RT, VR and BCI on upper limb function amongst subjects with strokes, with only one network meta-analysis reporting a study of different types of upper limb RT on upper limb function amongst subjects with strokes. We conducted the first NMA of different modalities of AI on upper limb function amongst subjects with strokes, providing the initial basis for further detailed studies in this area (39). This study also had limitations, including the following: (1) Many studies did not specifically report on randomization methods, allocation concealment and reliability of outcomes. The different treatment durations, frequencies and protocols included in the studies may have increased clinical heterogeneity. (2) Most original studies used semi-quantitative scales to assess shoulder-elbow and wrist joint motor function and total upper limb motor function scores and ADLs amongst subjects with strokes and did not use more objective and quantitative indicators. In subsequent studies, we must further use a combination of subjective and objective indicators to assess the improvement in their overall function. (3) We have created network diagrams that clearly illustrate the direct comparisons made in this domain; however, there were no closed loops in the network geometry. This led to our analysis not being an NMA or multiple treatment comparison (MTC) in the strictest sense but rather an adjusted indirect treatment comparison (ITC) belonging to the genus NMA.

Conclusion

The results of our NMA and SUCRA rankings suggest RT + VR appears to have an advantage over other interventions in improving upper limb motor function amongst subjects with stroke with FMA-UE-Proximal, FMA-UE-Distal and ARAT. Similarly, IR had shown the most significant advantage over other interventions in improving the FMA-UE-Total upper limb motor function score of subjects with stroke. The BCI also had the most significant advantage in improving their MBI daily living ability. In addition, it is worth noting that future studies should consider and report key patient characteristics such as stroke severity and degree of upper limb impairment, as well as treatment intensity, frequency and duration. Future meta-analyses should consider sub-group analyses based on the duration of the subject's illness and intervention and their gender to comprehensively explore the impact of different AI modalities and techniques on subjects with stroke from different populations.

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

Conceptualization: YZ and CW. Methodology and software: CW and JL. Validation, investigation, and data management: YZ and LZ. Formal analysis and visualization: LZ. Resources: YZ. Writing—original draft preparation: YZ, CW, and PZ. Writing—review and editing: YZ, CW, JL, LZ, and PZ. Supervision and funding acquisition: PZ. Project management: YZ and PZ. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the National Key Research and Development Program of China (2022YFC2010201) and Fundamental Research Funds for the Central Universities (2020045).

Acknowledgments

We are sincerely grateful to all members of our team and reviewers for their valuable comments.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1125172/full#supplementary-material

References

1. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet.* (2011) 377:1693–702. doi: 10.1016/S0140-6736(11)60325-5

2. Persson HC, Parziali M, Danielsson A, Sunnerhagen KS. Outcome and upper extremity function within 72 hours after first occasion of stroke in an unselected population at a stroke unit. A part of the SALGOT study. *BMC Neurol.* (2012) 12:162. doi: 10.1186/1471-2377-12-162

3. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: Results of a follow-up study. *Disabil Rehabil.* (1999) 21:357–64. doi: 10.1080/096382899297459

4. Nakayama H, Jørgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the copenhagen stroke study. *Arch Phys Med Rehabil.* (1994) 75:394–8. doi: 10.1016/0003-9993(94)90161-9

5. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: A review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol.* (2003) 2:43–53. doi: 10.1016/S1474-4422(03)00266-7

6. Corbetta D, Sirtori V, Castellini G, Moja L, Gatti R. Constraint-induced movement therapy for upper extremities in people with stroke. *Cochrane Database Syst Rev.* (2015) 2015:D4433. doi: 10.1002/14651858.CD004433.pub3

7. Wiklund LM, Uvebrant P. Hemiplegic cerebral palsy: Correlation between CT morphology and clinical findings. *Dev Med Child Neurol.* (1991) 33:512–23. doi: 10.1111/j.1469-8749.1991.tb14916.x

8. Pagliano E, Andreucci E, Bono R, Semorile C, Brollo L, Fedrizzi E. Evolution of upper limb function in children with congenital hemiplegia. *Neurol Sci.* (2001) 22:371–5. doi: 10.1007/s100720100067

9. Chin LF, Hayward KS, Brauer S. Upper limb use differs among people with varied upper limb impairment levels early post-stroke: a single-site, cross-sectional, observational study. *Top Stroke Rehabil.* (2020) 27:224–35. doi: 10.1080/10749357.2019.1690796

10. Hung YC, Charles J, Gordon AM. Bimanual coordination during a goal-directed task in children with hemiplegic cerebral palsy. *Dev Med Child Neurol.* (2004) 46:746–53. doi: 10.1111/j.1469-8749.2004.tb00994.x

11. Steenbergen B, Van J. Control of prehension in hemiparetic cerebral palsy: Similarities and differences between the IPSI- and contra-lesional sides of the body. *Dev Med Child Neurol.* (2004) 46:325–32. doi: 10.1111/j.1469-8749.2004.tb00493.x

12. Duff SV, Gordon AM. Learning of grasp control in children with hemiplegic cerebral palsy. *Dev Med Child Neurol.* (2003) 45:746–57. doi: 10.1111/j.1469-8749.2003.tb00884.x

13. Gordon AM, Lewis SR, Eliasson AC, Duff SV. Object release under varying task constraints in children with hemiplegic cerebral palsy. *Dev Med Child Neurol.* (2003) 45:240–8. doi: 10.1111/j.1469-8749.2003.tb00338.x

14. Sköld A, Josephsson S, Eliasson AC. Performing bimanual activities: the experiences of young persons with hemiplegic cerebral palsy. *Am J Occup Ther.* (2004) 58:416–25. doi: 10.5014/ajot.58.4.416

15. Sakzewski L, Ziviani J, Boyd R. Systematic review and meta-analysis of therapeutic management of upper-limb dysfunction in children with congenital hemiplegia. *Pediatrics.* (2009) 123:e1111–22. doi: 10.1542/peds.2008-3335

16. Helgøy KV, Bonsaksen T, Røykenes K. Research-based education in undergraduate occupational therapy and physiotherapy education programmes: a scoping review. *Bmc Med Educ.* (2022) 22:358. doi: 10.1186/s12909-022-03354-2

17. Lewis KJ, Ross L, Coppieters MW, Vicenzino B, Schmid AB. Education, night splinting and exercise versus usual care on recovery and conversion to surgery for people awaiting carpal tunnel surgery: a protocol for a randomised controlled trial. *BMJ Open.* (2016) 6:e12053. doi: 10.1136/bmjopen-2016-012053

18. Zhu MH, Shi MF, Shen YP, Jin M, Gu XD, Fu JM. Effect of occupational therapy on the quality of life of stroke patients. *Chin J Phys Med Rehabil.* (2009) 31:124–6. doi: 10.3760/cma.j.issn.0254-1424.2009.02.019

19. Li T, Zhang F, Zhang HC Si XY, Liu YR. Effectiveness of the conductive educational approach added to rehabilitation training for stroke patients. *Journal of Nursing Science.* (2022) 37:1–4. doi: 10.3870/j.issn.1001-4152.2022.17.001

20. Chen KY, Liu XY Ji X, Zhang H, Li T. Research Progress on the Application of Artificial Intelligence inRehabilitation Medicine in China. *JACTA ACADEMIAE MEDICINAE SINICAE.* (2021) 43:773–84. doi: 10.3881/j.issn.1000-503X.13926

21. Liu R. Application progress of artificial intelligence technology inrehabilitation and chronic disease management and auxiliary diagnosis. *China Medical Engineering.* (2021) 29:53–5. doi: 10.19338/j.issn.1672-2019.2021.07.013

22. Mazzoleni S, Duret C, Grosmaire AG, Battini E. Combining upper limb robotic rehabilitation with other therapeutic approaches after stroke: current status, rationale, and challenges. *Biomed Res Int.* (2017) 2017:8905637. doi: 10.1155/2017/8905637

23. Biasiucci A, Leeb R, Iturrate I, Perdikis S, Al-Khodairy A, Corbet T, et al. Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke. *Nat Commun.* (2018) 9:2421. doi: 10.1038/s41467-018-04673-z

24. Jia J. Central-peripheral-central closed-loop rehabilitation: a new concept of functional rehabilitation of the hand after stroke. *Chin J Rehab Med.* (2016) 31:1180–2. doi: 10.3969/j.issn.1001-1242.2016.11.001

25. Brennan DM, Mawson S, Brownsell S. Telerehabilitation: enabling the remote delivery of healthcare, rehabilitation, and self management. *Stud Health Technol Inform.* (2009) 145:231–48. doi: 10.3233/978-1-60750-018-6-231

26. Wu QY, Nie JY. Application of an intelligent motor feedback training system in the training of hand function and activities of daily living in stroke patients with hemiplegia. *Chin J Rehab Med.* (2012) 27:167–9. doi: 10.3969/j.issn.1001-1242.2012.02.018

27. Zheng CJ, Yang YW, Xia WG, Hua Q, Zhang YP, Chen YJ. Effect of virtual scenario-based interactive training combined with occupational therapy on the functional recovery of upper limbs in stroke patients. *Chin J Phys Med Rehabil.* (2014) 36:360–2. doi: 10.3760/cma.j.issn.0254-1424.2014.05.011

28. Ersoy C, Iyigun G. Boxing training in patients with stroke causes improvement of upper extremity, balance, and cognitive functions but should it be applied as virtual or real? *Top Stroke Rehabil.* (2021) 28:112–26. doi: 10.1080/10749357.2020.1783918

29. Rodríguez-Hernández M, Criado-Álvarez JJ, Corregidor-Sánchez AI, Martín-Conty JL, Mohedano-Moriano A, Polonio-López B. Effects of virtual reality-based therapy on quality of life of patients with subacute stroke: a three-month follow-up randomized controlled trial. *Int J Environ Res Public Health.* (2021) 18:2810. doi: 10.3390/ijerph18062810

30. Choi YH, Paik NJ. Mobile game-based virtual reality program for upper extremity stroke rehabilitation. *J Vis Exp.* (2018) 133:e56241. doi: 10.3791/56241

31. Camargo-Vargas D, Callejas-Cuervo M, Mazzoleni S. Brain-Computer interfaces systems for upper and lower limb rehabilitation: a systematic review. *Sensors.* (2021) 21:4312. doi: 10.3390/s21134312

32. Giansanti D. The social robot in rehabilitation and assistance: what is the future? *Healthcare.* (2021) 9:244. doi: 10.3390/healthcare9030244

33. Mills EJ, Bansback N, Ghement I, Thorlund K, Kelly S, Puhan MA, et al. Multiple treatment comparison meta-analyses: a step forward into complexity. *Clin Epidemiol.* (2011) 3:193–202. doi: 10.2147/CLEP.S16526

34. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ.* (2013) 346:f2914. doi: 10.1136/bmj.f2914

35. He XY, Ma QQ, Zhai YK. Cui FFg, Lu YY, Chen HT. A meta-analysis of the impact of tele-rehabilitation on the rehabilitation function of stroke patients. *Chin J Rehab Med.* (2020) 35:1466–71. doi: 10.3969/j.issn.1001-1242.2020.12.011

36. Li LL Yu Y, Jia YQ, Huang HQ. Effect of brain-computer interface on upper-limb motor function after stroke: a meta-analysis. *Chin Rehab Theor Prac.* (2021) 27:765–73. doi: 10.3969/j.issn.1006?9771.2021.07.005

37. Zhong C, He HC, Huang SS. Ma Rui, Wang JJ, He CQ. The effectiveness of virtual reality therapy in relieving upper limb hemiparesis after stroke: a meta-analysis of randomized and controlled trials. *Chin J Phys Med Rehabil.* (2019) 41:463–8. doi: 10.3760/cma.j.issn.0254-1424.2019.06.017

38. Zhu C E, Yu B, Chen W H, Zhang W. Systematic evaluation of robot-assisted training to improve upper extremity functional impairment in stroke patients. *Chin J Rehab Med.* (2016) 31:786–9. doi: 10.3969/j.issn.1001-1242.2016.07.015

39. Mehrholz J, Pollock A, Pohl M, Kugler J, Elsner B. Systematic review with network meta-analysis of randomized controlled trials of robotic-assisted arm training for improving activities of daily living and upper limb function after stroke. *J Neuroeng Rehabil.* (2020) 17:83. doi: 10.1186/s12984-020-00715-0

40. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

41. Welch V, Petticrew M, Petkovic J, Moher D, Waters E, White H, et al. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): explanation and elaboration. *Int J Equity Health.* (2015) 14:92. doi: 10.1186/s12939-015-0219-2

42. Feng S, Tang M, Huang G, Wang J, He S, Liu D, et al. EMG biofeedback combined with rehabilitation training may be the best physical therapy for improving upper limb motor function and relieving pain in patients with the post-stroke shoulder-hand syndrome: a Bayesian network meta-analysis. *Front Neurol.* (2022) 13:1056156. doi: 10.3389/fneur.2022.1056156

43. Cho KH, Song WK. Effects of two different robot-assisted arm training on upper limb motor function and kinematics in chronic stroke survivors: a randomized controlled trial. *Top Stroke Rehabil.* (2021) 28:241–50. doi: 10.1080/10749357.2020.1804699

44. Savović J, Weeks L, Sterne JA, Turner L, Altman DG, Moher D, et al. Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst Rev.* (2014) 3:37. doi: 10.1186/2046-4053-3-37

45. Sterne J, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* (2019) 366:l4898. doi: 10.1136/bmj.l4898

46. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: AN overview and tutorial. *J Clin Epidemiol.* (2011) 64:163–71. doi: 10.1016/j.jclinepi.2010.03.016

47. Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: the network graphs package. *Stata J.* (2015) 15:905–50. doi: 10.1177/1536867X1501500402

48. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods.* (2012) 3:111–25. doi: 10.1002/jrsm.1045

49. Kiefer C, Sturtz S, Bender R. Indirect comparisons and network meta-analyses. *Dtsch Arztebl Int.* (2015) 112:803–8. doi: 10.3238/arztebl.2015.0803

50. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med.* (2010) 29:932–44. doi: 10.1002/sim.3767

51. Su LL, Fang XY, Lin L, Li HY. Effects of upper limb robot-assisted training on cognition and upper limb motor function for subacute stroke patients. *Chin J Rehab Theor Prac.* (2022) 28:508–14. doi: 10.3969/j.issn.1006-9771.2022.05.003

52. Taravati S, Capaci K, Uzumcugil H, Tanigor G. Evaluation of an upper limb robotic rehabilitation program on motor functions, quality of life, cognition, and emotional status in patients with stroke: a randomized controlled study. *Neurol Sci.* (2022) 43:1177–88. doi: 10.1007/s10072-021-05431-8

53. Sale P, Franceschini M, Mazzoleni S, Palma E, Agosti M, Posteraro F. Effects of upper limb robot-assisted therapy on motor recovery in subacute stroke patients. *J Neuroeng Rehabil.* (2014) 11:104. doi: 10.1186/1743-0003-11-104

54. He Y, Zhang T. Effect of robot-assisted training on upper-limb function for stroke patients. *Chin J Rehab Theor Prac.* (2021) 27:797–801. doi: 10.3969/j.issn.1006-9771.2021.07.010

55. Burgar CG, Lum PS, Scremin AM, Garber SL, Van der Loos HF, Kenney D, et al. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: department of veterans affairs multisite clinical trial. *J Rehabil Res Dev.* (2011) 48:445–58. doi: 10.1682/JRRD.2010.04.0062

56. de Araújo RC, Junior FL, Rocha DN, Sono TS, Pinotti M. Effects of intensive arm training with an electromechanical orthosis in chronic stroke patients: A preliminary study. *Arch Phys Med Rehabil.* (2011) 92:1746–53. doi: 10.1016/j.apmr.2011.05.021

57. Housman SJ, Scott KM, Reinkensmeyer DJ, A. randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. *Neurorehabil Neural Repair.* (2009) 23:505–14. doi: 10.1177/1545968308331148

58. Hsieh YW, Wu CY, Liao WW, Lin KC, Wu KY, Lee CY. Effects of treatment intensity in upper limb robot-assisted therapy for chronic stroke: a pilot randomized controlled trial. *Neurorehabil Neural Repair.* (2011) 25:503–11. doi: 10.1177/1545968310394871

59. Page SJ, Hill V, White S. Portable upper extremity robotics is as efficacious as upper extremity rehabilitative therapy: a randomized controlled pilot trial. *Clin Rehabil.* (2013) 27:494–503. doi: 10.1177/0269215512464795

60. Timmermans AA, Lemmens RJ, Monfrance M, Geers RP, Bakx W, Smeets RJ, et al. Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: a randomized controlled trial. *J Neuroeng Rehabil.* (2014) 11:1–12. doi: 10.1186/1743-0003-11-45

61. Budhota A, Chua K, Hussain A, Kager S, Cherpin A, Contu S, et al. Robotic assisted upper limb training post stroke: a randomized control trial using combinatory approach toward reducing workforce demands. *Front Neurol.* (2021) 12:622014. doi: 10.3389/fneur.2021.622014

62. Zhang HY, Wu FC Li JH, Liao ZP. Effect of upper limb rehabilitation robot assisted training on upper limb function of stroke survivors. *Chin J Sports Med.* (2019) 38:859–63. doi: 10.16038/j.1000-6710.2019.10.006

63. Sun CC, Wang CF, Ding XJ, Guo D, Han XM, Du JY. Effects of assistant training of upper-limb rehabilitation robot on upper-limb motor of hemiple functiongic stroke patients. *Chin J Rehab Med.* (2018) 33:1162–7. doi: 10.3969/j.issn.1001-1242.2018.10.006

64. Tomić TJ, Savić AM, Vidaković AS, Rodić SZ, Isaković MS. Rodríguez-de-Pablo C, et al. Arm Assist robotic system versus matched conventional therapy for poststroke upper limb rehabilitation: a randomized clinical trial. *Biomed Res Int.* (2017) 2017:7659893. doi: 10.1155/2017/7659893

65. Conroy SS, Wittenberg GF, Krebs HI, Zhan M, Bever CT, Whitall J. Robot-assisted arm training in chronic stroke: addition of transition-to-task practice. *Neurorehabil Neural Repair.* (2019) 33:751–61. doi: 10.1177/1545968319862558

66. Fan H, Wu YF, Dong XQ. Feng L.Robots for the rehabilitation of upper limb motor function after stroke. *Chin J Phys Med Rehabil.* (2016) 38:104–7. doi: 10.3760/cma.j.issn.0254-1424.2016.02.006

67. Lee KW, Kim SB, Lee JH, Lee SJ, Wan Yoo S. Effect of upper extremity robot-assisted exercise on spasticity in stroke patients. *Ann Rehabil Med.* (2016) 40:961–71. doi: 10.5535/arm.2016.40.6.961

68. Villafañe JH, Taveggia G, Galeri S, Bissolotti L, Mullè C, Imperio G, et al. Efficacy of short-term robot-assisted rehabilitation in patients with hand paralysis after stroke: a randomized clinical trial. *Hand.* (2018) 13:95–102. doi: 10.1177/1558944717692096

69. Zhang C, Liu Xn, Hou ZG, Peng L, Yang H, Peng L, et al. Effects of upper limb robot-assisted therapy on motor function and activities of daily living in patients with convalescent stroke. *Chin J Rehab Theor Prac.* (2016) 22:1365–70. doi: 10.3969/j.issn.1006-9771.2016.12.001

70. Zhang XF, Gao XM, Zhao N, Zhang L, Ge SP, Zhang YM, et al. Effect of upper limb rehabilitation robot training on the recovery of upper limb function in stroke patients with hemiplegia. *Chin J Phys Med Rehabil.* (2016) 38:180–2. doi: 10.3760/cma.j.issn.0254-1424.2016.03.005

71. He B, Zhang C, Liu X. Effects of upper limb robot-assisted therapy on motor recovery in patients with acute stroke. *Chin J Rehab Theor Prac.* (2016) 22:688–92. doi: 10.3969/j.issn.1006-9771.2016.06.014

72. Singh N, Saini M, Kumar N, Srivastava M, Mehndiratta A. Evidence of neuroplasticity with robotic hand exoskeleton for post-stroke rehabilitation: a randomized controlled trial. *J Neuroeng Rehabil.* (2021) 18:1–15. doi: 10.1186/s12984-021-00867-7

73. Jiang S, You H, Zhao W, Zhang M. Effects of short-term upper limb robot-assisted therapy on the rehabilitation of sub-acute stroke patients. *Technol Health Care.* (2021) 29:295–303. doi: 10.3233/THC-202127

74. Gandolfi M, Valè N, Dimitrova EK, Mazzoleni S, Battini E, Filippetti M, et al. Effectiveness of robot-assisted upper limb training on spasticity, function and muscle activity in chronic stroke patients treated with botulinum toxin: A randomized Single-Blinded controlled trial. *Front Neurol.* (2019) 10:41. doi: 10.3389/fneur.2019.00041

75. Dehem S, Gilliaux M, Stoquart G, Detrembleur C, Jacquemin G, Palumbo S, et al. Effectiveness of upper-limb robotic-assisted therapy in the early rehabilitation phase after stroke: a single-blind, randomised, controlled trial. *Ann Phys Rehabil Med.* (2019) 62:313–20. doi: 10.1016/j.rehab.2019.04.002

76. Carpinella I, Lencioni T, Bowman T, Bertoni R, Turolla A, Ferrarin M, et al. Effects of robot therapy on upper body kinematics and arm function in persons post stroke: a pilot randomized controlled trial. *J Neuroeng Rehabil.* (2020) 17:1–19. doi: 10.1186/s12984-020-0646-1

77. Xu Q, Li C, Pan Y, Li W, Jia T, Li Z, et al. Impact of smart force feedback rehabilitation robot training on upper limb motor function in the subacute stage of stroke. *NeuroRehabilitation.* (2020) 47:209–15. doi: 10.3233/NRE-203130

78. Huang Y, Lai WP, Qian Q, Hu X, Tam EW, Zheng Y. Translation of robot-assisted rehabilitation to clinical service: a comparison of the rehabilitation effectiveness of EMG-driven robot hand assisted upper limb training in practical clinical service and in clinical trial with laboratory configuration for chronic stroke. *Biomed Eng Online.* (2018) 17:1–17. doi: 10.1186/s12938-018-0516-2

79. Susanto EA, Tong RK, Ockenfeld C, Ho NS. Efficacy of robot-assisted fingers training in chronic stroke survivors: a pilot randomized-controlled trial. *J Neuroeng Rehabil.* (2015) 12:1–9. doi: 10.1186/s12984-015-0033-5

80. Wu CY, Yang CL, Chuang LL, Lin KC, Chen HC, Chen MD, et al. Effect of therapist-based versus robot-assisted bilateral arm training on motor control, functional performance, and quality of life after chronic stroke: a clinical trial. *Phys Ther.* (2012) 92:1006–16. doi: 10.2522/ptj.20110282

81. Abd El-Kafy EM, Alshehri MA, El-Fiky AA-R, Guermazi MA, Mahmoud HM. The effect of robot-mediated virtual reality gaming on upper limb spasticity poststroke: a randomized-controlled trial. *Games Health J.* (2022) 11:93–103. doi: 10.1089/g4h.2021.0197

82. Hu YL, Xiao YH, Hua YP, Lu AM, Lu HD, Huang Y, et al. Effect of virtual reality technology combined with upper limb rehabilitation robot on functional recovery of upper limb in stroke patients. *J Integ Trad Chin Western Med.* (2022) 32:537–9. doi: 10.3969/j.issn.1005-4561.2022.06.012

83. Chen M, Pangdong R, et al. Effect of robot combined with virtual reality technology on upper limb function of hemiplegia after stroke. *Continu Med Educ China.* (2021).

84. Wang Y, Zhu M. Effect of virtual reality combined with upper limb robot training system on upper limb function recovery in stroke. *Modern Chinese Doctor.* (2021).

85. Gueye T, Dedkova M, Rogalewicz V, Grunerova-Lippertova M, Angerova Y. Early post-stroke rehabilitation for upper limb motor function using virtual reality and exoskeleton: equally efficient in older patients. Neurol Neurochir Pol. (2021) 55:91–6. doi: 10.5603/PJNNS.a2020.0096

86. Rand D, Weingarden H, Weiss R, Yacoby A, Reif S, Malka R, et al. Self-training to improve UE function at the chronic stage post-stroke: a pilot randomized controlled trial. *Disabil Rehabil.* (2017) 39:1541–8. doi: 10.1080/09638288.2016.1239766

87. Wang LL, Zhang Y, Wang CF, Sun CC Li M, Liu XY. Clinical study of brain computer interface based electrical stimulation training in improving upper limb dysfunction of patients with stroke. *Biomed Eng Clin Med.* (2022) 26:163–8. doi: 10.13339/j.cnki.sglc.20220218.014

88. Lee S-H, Kim SS, Lee B-H. Action observation training and brain-computer interface controlled functional electrical stimulation enhance upper extremity performance and cortical activation in patients with stroke: a randomized controlled trial. *Physiother Theory Pract.* (2022) 38:1126–34. doi: 10.1080/09593985.2020.1831114

89. Ang KK, Guan C, Phua KS, Wang C, Zhou L, Tang KY, et al. Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke. *Front Neuroeng.* (2014) 7:30. doi: 10.3389/fneng.2014.00030

90. Xu Y, Yun J, Jia J, et al. Efficacy of a brain-computer interface combined with functional electrical stimulation training on upper limb function and cognition in elderly stroke patients. *Chinese J Elderly Cardiovasc Cerebrovasc Dis.* (2018) 20:988–90.

91. Liang SJ, Zhu Y L, Wang W N, Zhuang M, Xu D Y, Liu G P, et al. Application of brain-computer interface technology in the rehabilitation of upper limb dysfunction in stroke patients. *Chin J Rehab Med.* (2020) 35:185–8. doi: 10.3969/j.issn.1001-1242.2020.02.012

92. Li MF, Jia J, Liu Y. Research on cognitive mechanism of motor lmagerytased brain compvter interface rehabilitation training for stroke patients with severe upper limb paralysis. *J Chengdu Med College.* (2012) 7:519–23. doi: 10.3969/j.issn.1674-2257.2012.04.004

93. Xiang X, Zhu J, Sun Y, Sun F, Liu X. Clinical study on the treatment of upper extremity dysfunction in the recovery period of ischemic stroke with brain computer interface rehabilitation training system. *Med Innov China.* (2020) 17:154–8.

94. Ren H, Xie Z. Efficacy of BCI in the rehabilitation of upper limb motor function in patients with stroke. *Pract Med China.* (2020).

95. Chen S, Cao L, Shu X, Wang H, Ding L, Wang SH, et al. Longitudinal electroencephalography analysis in subacute stroke patients during intervention of Brain-Computer interface with exoskeleton feedback. *Front Neurosci.* (2020) 14:809. doi: 10.3389/fnins.2020.00809

96. Kim T, Kim S, Lee B. Effects of action observational training plus Brain-Computer Interface-Based functional electrical stimulation on paretic arm motor recovery in patient with stroke: a randomized controlled trial. *Occup Ther Int.* (2016) 23:39–47. doi: 10.1002/oti.1403

97. Mihara M, Hattori N, Hatakenaka M, Yagura H, Kawano T, Hino T, et al. Near-infrared spectroscopy-mediated neurofeedback enhances efficacy of motor imagery-based training in poststroke victims: a pilot study. *Stroke.* (2013) 44:1091–8. doi: 10.1161/STROKEAHA.111.674507

98. Wu H, Zhang Y, et al. Effect of task-oriented training based on telerehabilitation platform on motor function and activities of daily living in patients discharged after stroke. *Chinese J Phys Med Rehabil.* (2022) 44:40–3.

99. Xue J, Zhu Z, et al. Application of stroke remote continuous home upper limb rehabilitation mode based on cloud platform in upper limb function exercise in stroke patients with hemiplegia. *Famous Doctors.* (2020).

100. Wang R, Zhang Y, et al. Effect of telerehabilitation system on upper limb function in patients discharged with stroke. *Chinas Rehabil.* (2020) 35:522–5.

101. Wang F. Comparative study on the effect of remote video home rehabilitation guidance and routine home rehabilitation guidance for stroke patients. *Shanxi Med Magaz.* (2018) 47:1553–4.

102. Gao X, Xia Y, et al. Efficacy of telerehabilitation model based on video interaction in hemiplegia patients with stroke. *Continu Med Educ China*. (2017) 9:211–3.

103. Chen J, Jin W, Dong WS, Jin Y, Qiao FL, Zhou YF, et al. Effects of home-based telesupervising rehabilitation on physical function for stroke survivors with hemiplegia: a randomized controlled trial. *Am J Phys Med Rehabil*. (2017) 96:152–60. doi: 10.1097/PHM.0000000000000559

104. Chen J. Effect of remote home rehabilitation on motor and cognitive and balance abilities in stroke hemiplegia. *Chinese J Phys Med Rehabil.* (2016) 38:909–11.

105. Maeno R, Fujita C, Iwatsuki H. Effect of remote home rehabilitation care on the rehabilitation of hemiplegia patients with stroke. *Tianjin Nurs.* (2015) 23:393–4.

106. Lin K-H, Chen C-H, Chen Y-Y, Huang W-T, Lai J-S, Yu S-M, et al. Bidirectional and multi-user telerehabilitation system: clinical effect on balance, functional activity, and satisfaction in patients with chronic stroke living in long-term care facilities. *Sensors*. (2014) 14:12451–66. doi: 10.3390/s140712451

107. Chaiyawat P, Kulkantrakorn K. Randomized controlled trial of home rehabilitation for patients with ischemic stroke: impact upon disability and elderly depression. *Psychogeriatrics*. (2012) 12:193–9. doi: 10.1111/j.1479-8301.2012.00412.x

108. Redzuan NS, Engkasan JP, Mazlan M, Abdullah SJF. Effectiveness of a video-based therapy program at home after acute stroke: a randomized controlled trial. *Arch Phys Med Rehabil*. (2012) 93:2177–83. doi: 10.1016/j.apmr.2012.06.025

109. Piron L, Turolla A, Agostini M, Zucconi C, Cortese F, Zampolini M, et al. Exercises for paretic upper limb after stroke: a combined virtual-reality and telemedicine approach. *J Rehabil Med.* (2009) 41:1016–102. doi: 10.2340/16501977-0459

110. Li J, Wu L, Shang S, et al. Effect of remote home rehabilitation guidance on daily living activities ability and motor function in patients with cerebral infarction. *Rehabil Theor Pract China*. (2011) 17:887–8.

111. Kwon JS, Park MJ, Yoon IJ, Park SH. Effects of virtual reality on upper extremity function and activities of daily living performance in acute stroke: a double-blind randomized clinical trial. *Neuro Rehabilitation.* (2012) 31:379–85. doi: 10.3233/NRE-2012-00807

112. Chen J. *Effect of VR-Assisted Upper Limb Robot Training on Upper Limb Function and Cognitive Function in Stroke Patients*. Wuhan Institute of Sport (2020).

113. Jiang RR. *Clinic Research on Robot-Assisted With Virtual Reality Technology for Upper Limb Motor Function and Activity Ability After Stroke*. Guangzhou: Guangzhou Medical University (2017). doi: 10.7666/d.D01289658

114. Wei Y. Comparison of the efficacy between traditional rehabilitation and intelligent rehabilitation in upper limb stage Brunnstrom III patients. *Disabil. Med China.* (2020) 28:21–2.

115. Wang M. Evaluation of the application effect of the upper limb intelligent rehabilitation training system in the rehabilitation treatment of stroke hemiplegia patients. *J Shanxi Health Vocat Coll*. (2020).

116. Prange GB, Kottink AIR, Buurke JH, Eckhardt MMEM, van Keulen-Rouweler BJ, Ribbers GM, et al. The effect of arm support combined with rehabilitation games on upper-extremity function in subacute stroke: a randomized controlled trial. *Neurorehabil Neural Repair*. (2015) 29:174–82. doi: 10.1177/1545968314535985

117. Lee KW, Kim SB, Lee JH, Lee SJ, Wan Kim J. Effect of robot-assisted game training on upper extremity function in stroke patients. *Ann Rehabil Med*. (2017) 41:539–46. doi: 10.5535/arm.2017.41.4.539

118. McNulty PA, Thompson-Butel AG, Faux SG, Lin G, Katrak PH, Harris LR, et al. The efficacy of Wii-based movement therapy for upper limb rehabilitation in the chronic poststroke period: a randomized controlled trial. *Int J Stroke*. (2015) 10:1253–60. doi: 10.1111/ijs.12594

119. Norouzi-Gheidari N, Hernandez A, Archambault PS, Higgins J, Poissant L, Kairy D. Feasibility, safety and efficacy of a virtual reality exergame system to supplement upper extremity rehabilitation post-stroke: a pilot randomized clinical trial and proof of principle. *Int J Environ Res Public Health.* (2020) 17:113. doi: 10.3390/ijerph17010113

120. Lin C-H, Chou L-W, Luo H-J, Tsai P-Y, Lieu F-K, Chiang S-L, et al. Effects of computer-aided interlimb force coupling training on paretic hand and arm motor control following chronic stroke: a randomized controlled trial. *PLoS ONE.* (2015) 10:e0131048. doi: 10.1371/journal.pone.0131048

121. Keskin Y, Atci A, Urkmez B, et al. Efficacy of a video-based physical therapy and rehabilitation system in patients with post-stroke hemiplegia: A randomized, controlled, pilot study. *Turk J Geriatr.* (2020) 23. doi: 10.31086/tjgeri.2020.145

122. El-Kafy EMA, Alshehri MA, El-Fiky AA-R, Guermazi MA. The effect of virtual reality-based therapy on improving upper limb functions in individuals with stroke: a randomized control trial. *Front Aging Neurosci.* (2021) 13:731343. doi: 10.3389/fnagi.2021.731343

123. Choi Y-H, Ku J, Lim H, Kim YH, Paik N-J. Mobile game-based virtual reality rehabilitation program for upper limb dysfunction after ischemic stroke. *Restor Neurol Neurosci*. (2016) 34:455–63. doi: 10.3233/RNN-150626

124. Anwar N, Karimi H, Ahmad A, Mumtaz N, Saqulain G, Gilani SA, et al. novel virtual reality training strategy for poststroke patients: a randomized clinical trial. *J Healthc Eng.* (2021) 2021:1–6. doi: 10.1155/2021/6598726

125. Kim KH, Kim DH. Effect of virtual reality rehabilitation training on limb function and balance function in elderly patients with hemiplegia after stroke. *Chinese J Gerontol*. (2019) 39:5191–4.

126. Xiao X, Huang D, et al. Effect of VR training on upper limb motor function in subacute stroke patients. *Chinese J Rehabil Med*. (2019) 34:1049–53.

127. Bo M, Tian R, et al. Effect of short-term virtual reality rehabilitation training on upper limb function and activities of daily living in stroke hemiplegia patients. *Chinese J Rehabil Med*. (2017) 32:1288–91.

128. Kim J-H. Effect of virtual reality game training on functional recovery of hemiplegia upper limb in stroke patients. *Chinese J Phys Med Rehabil.* (2016) 38:401–5.

129. Tian R, Bai M, et al. Effect of virtual reality technology on the upper limb function and the ability of daily living activities in stroke patients. *Rehabil Theor Pract China*. (2017) 22:1370–1.

130. Lee M-M, Shin D-C, Song C-H. Canoe game-based virtual reality training to improve trunk postural stability, balance, and upper limb motor function in subacute stroke patients: a randomized controlled pilot study. *J Phys Ther Sci*. (2016) 28:2019–24. doi: 10.1589/jpts.28.2019

131. Kong KH, Loh YJ, Thia E, Chai A, Ng CY, Soh YM, et al. Efficacy of a virtual reality commercial gaming device in upper limb recovery after stroke: a randomized, controlled study. *Top Stroke Rehabil.* (2016) 23:333–40. doi: 10.1080/10749357.2016.1139796

132. Park M, Ko M-H, Oh S-W, Lee J-Y, Ham Y, Yi H, et al. Effects of virtual reality-based planar motion exercises on upper extremity function, range of motion, and health-related quality of life: a multicenter, single-blinded, randomized, controlled pilot study. J *Neuroeng Rehabil.* (2019) 16:1–13. doi: 10.1186/s12984-019-0595-8

133. Brunner I, Skouen JS, Hofstad H, Strand LI, Becker F, Sanders AM, et al. Virtual reality training for upper extremity in subacute stroke (VIRTUES): study protocol for a randomized controlled multicenter trial. *BMC Neurol.* (2014) 14:186. doi: 10.1186/s12883-014-0186-z

134. Choi JH, Han EY, Kim BR, Kim SM, Im SH, Lee SY, et al. Effectiveness of commercial gaming-based virtual reality movement therapy on functional recovery of upper extremity in subacute stroke patients. *Ann Rehabil Med*. (2014) 38:485–93. doi: 10.5535/arm.2014.38.4.485

135. Thielbar KO, Lord TJ, Fischer HC, Lazzaro EC, Barth KC, Stoykov ME, et al. Training finger individuation with a mechatronic-virtual reality system leads to improved fine motor control post-stroke. *J Neuroeng Rehabil.* (2014) 11:1–11. doi: 10.1186/1743-0003-11-171

136. Kiper P, Agostini M, Luque-Moreno C, Tonin P, Turolla A. Reinforced feedback in virtual environment for rehabilitation of upper extremity dysfunction after stroke: preliminary data from a randomized controlled trial. *BioMed Res Int*. (2014) 2014:752128. doi: 10.1155/2014/752128

137. Lee D, Lee M, Lee K, Song C. Asymmetric training using virtual reality reflection equipment and the enhancement of upper limb function in stroke patients: a randomized controlled trial. *J Stroke Cerebrovasc Dis*. (2014) 23:1319–26. doi: 10.1016/j.jstrokecerebrovasdis.2013.11.006

138. Crosbie JH, Lennon S, McGoldrick MC, McNeill MDJ, McDonough SM. Virtual reality in the rehabilitation of the arm after hemiplegic stroke: a randomized controlled pilot study. *Clin Rehabil.* (2012) 26:798–806. doi: 10.1177/0269215511434575

139. Yin CW, Sien NY, Ying LA, Chung SF, Tan MLD. Virtual reality for upper extremity rehabilitation in early stroke: a pilot randomized controlled trial. *Clin Rehabil.* (2014) 28:1107–14. doi: 10.1177/0269215514532851

140. Zhou T, Zhang C, et al. Application of mirror therapy combined with telerehabilitation in upper limb functional exercise in stroke hemiplegia patients. *Qilu Nurs J.* (2019) 25:129–31.

141. Ögün MN, Kurul R, Yasar MF, Turkoglu SA, Avci S, Yildiz N. Effect of Leap Motion-based 3D immersive virtual reality usage on upper extremity function in ischemic stroke patients. *Arq Neuropsiquiatr*. (2019) 77:681–8. doi: 10.1590/0004-282X20190129

142. Nijenhuis SM, Prange-Lasonder GB, Stienen AH, Rietman JS, Buurke JH. Effects of training with a passive hand orthosis and games at home in chronic stroke: a pilot randomised controlled trial. *Clin Rehabil.* (2017) 31:207–16. doi: 10.1177/0269215516629722

143. Wolf SL, Sahu K, Bay RC, Buchanan S, Reiss A, Linder S, et al. The HAAPI (Home Arm Assistance Progression Initiative) trial: a novel robotics delivery approach in stroke rehabilitation. *Neurorehabil Neural Repair*. (2015) 29:958–68. doi: 10.1177/1545968315575612

144. Chen L, Chen Y, Fu WB, Huang DF, Lo W. The effect of virtual reality on motor anticipation and hand function in patients with subacute stroke: a randomized trial on movement-related potential. *Neural Plast.* (2022) 2022:7399995. doi: 10.1155/2022/7399995

145. Qian Q, Hu X, Lai Q, Ng SC, Zheng Y, Poon W. Early stroke rehabilitation of the upper limb assisted with an electromyography-driven neuromuscular electrical stimulation-robotic arm. *Front Neurol*. (2017) 8:447. doi: 10.3389/fneur.2017.00447

146. Huijgen BCH, Vollenbroek-Hutten MMR, Zampolini M, Opisso E, Bernabeu M, Van Nieuwenhoven J, et al. Feasibility of a home-based telerehabilitation system compared to usual care: arm/hand function in patients with stroke, traumatic brain injury and multiple sclerosis. *J Telemed Telecare.* (2008) 14:249–56. doi: 10.1258/jtt.2008.080104

147. ZJ, He C, Guo F, Xiong CH, Huang XL. Exoskeleton-Assisted anthropomorphic movement training (EAMT) for post stroke upper limb rehabilitation: a pilot randomized controlled trial. *Arch Phys Med Rehabil.* (2021) 102:2074–82. doi: 10.1016/j.apmr.2021.06.001

148. Li RQ, Wan T, Zi MJ, Duan WH, He LY, Gao RR. Stable angina pectoris of coronary heart disease treated with different acupuncture and moxibustion therapies: a network Meta-analysis. *Chin Acupunct Moxib.* (2022) 42:1431–8. doi: 10.13703/j.0255-2930.20220513-0002

149. Ögün MN, Kurul R, Yaşar MF, Turkoglu SA, Avci S, Yildiz N. Effect of leap motion-based 3D immersive virtual reality usage on upper extremity function in ischemic stroke patients. *Arq Neuropsiquiatr.* (2019) 77:681–8. doi: 10.1590/0004-282x20190129

150. Chen WJ. *Effect of Upper-Limb Robot Training Assisted by Virtual Reality on Upper Limb Function and Cognitive Function of Stroke Patients*. Wuhan: Wuhan Sports Univeristy (2020). doi: 10.27384/d.cnki.gwhtc.2020.000226

151. Kiper P, Szczudlik A, Agostini M, Opara J, Nowobilski R, Ventura L, et al. Virtual reality for upper limb rehabilitation in subacute and chronic stroke: a randomized controlled trial. *Arch Phys Med Rehabil.* (2018) 99:834–42. doi: 10.1016/j.apmr.2018.01.023

152. Chien WT, Chong YY, Tse MK, Chien CW, Cheng HY. Robot-assisted therapy for upper-limb rehabilitation in subacute stroke patients: a systematic review and meta-analysis. *Brain Behav.* (2020) 10:e1742. doi: 10.1002/brb3.1742

153. Nomikos PA, Spence N, Alshehri MA. Test-retest reliability of physiotherapists using the action research arm test in chronic stroke. *J Phys Ther Sci.* (2018) 30:1271–7. doi: 10.1589/jpts.30.1271

154. Spence N, Rodrigues N, Nomikos PA, Yaseen KM, Alshehri MA. Inter-rater reliability of physiotherapists using the action research arm test in chronic stroke. *J Musculoskelet Neuronal Interact.* (2020) 20:480–7.

155. Mehrholz J, Hädrich A, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength after stroke. *Cochrane Database Syst Rev.* (2012) 6: D6876. doi: 10.1002/14651858.CD006876.pub3

156. Rodgers H, Bosomworth H, Krebs HI, van Wijck F, Howel D, Wilson N, et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. *Lancet.* (2019) 394:51–62. doi: 10.1016/S0140-6736(19)31055-4

157. Brunner I, Skouen JS, Hofstad H, Aßmus J, Becker F, Sanders AM, et al. Virtual reality training for upper extremity in subacute stroke (VIRTUES): a multicenter RCT. *Neurology.* (2017) 89:2413–21. doi: 10.1212/WNL.0000000000004744

158. Li X, Wang L, Miao S, Yue Z, Tang Z, Su L, et al. Sensorimotor Rhythm-Brain computer interface with Audio-Cue, motor observation and multisensory feedback for Upper-Limb stroke rehabilitation: a controlled study. *Front Neurosci.* (2022) 16:808830. doi: 10.3389/fnins.2022.808830

159. Frolov AA, Mokienko O, Lyukmanov R, Biryukova E, Kotov S, Turbina L, et al. Post-stroke rehabilitation training with a Motor-Imagery-Based Brain-Computer interface (BCI)-Controlled hand exoskeleton: a randomized controlled multicenter trial. *Front Neurosci.* (2017) 11:400. doi: 10.3389/fnins.2017.00400

160. Zhao CG, Ju F, Sun W, Jiang S, Xi X, Wang H, et al. Effects of training with a brain-computer interface-controlled robot on rehabilitation outcome in patients with subacute stroke: a randomized controlled trial. *Neurol Ther.* (2022) 11:679–95. doi: 10.1007/s40120-022-00333-z

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 11 May 2023
DOI 10.3389/fneur.2023.1147290

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
Lung Chan,
Taipei Medical University, Taiwan
Calin Prodan,
University of Oklahoma Health Sciences Center, United States

*CORRESPONDENCE
Yun Zhou
✉ zhouyun86588069@126.com
Dongxue Ding
✉ wintersnow1988@126.com
Qi Fang
✉ fangqi_008@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 25 January 2023
ACCEPTED 25 April 2023
PUBLISHED 11 May 2023

CITATION
Zhang L, Wang S, Qiu L, Jiang J, Jiang J, Zhou Y, Ding D and Fang Q (2023) Effects of silent brain infarction on the hemorrhagic transformation and prognosis in patients with acute ischemic stroke after intravenous thrombolysis.
Front. Neurol. 14:1147290.
doi: 10.3389/fneur.2023.1147290

Effects of silent brain infarction on the hemorrhagic transformation and prognosis in patients with acute ischemic stroke after intravenous thrombolysis

Lulu Zhang[1†], Shan Wang[1†], Lanfeng Qiu[2†], Juean Jiang[3], Jianhua Jiang[1], Yun Zhou[1*], Dongxue Ding[1*] and Qi Fang[1*]

[1]Department of Neurology, The First Affiliated Hospital of Soochow University, Suzhou, China, [2]Department of Emergency, The First Affiliated Hospital of Soochow University, Suzhou, China, [3]Department of General Medicine, The First Affiliated Hospital of Soochow University, Suzhou, China

Background: Silent brain infarction (SBI) is a special type of stroke with no definitive time of onset, which can be found on pre-thrombolysis imaging examination in some patients with acute ischemic stroke (AIS). However, the significance of SBI on intracranial hemorrhage transformation (HT) and clinical outcomes after intravenous thrombolysis therapy (IVT) is uncertain. We aimed to explore the effects of SBI on intracranial HT and the 3-month clinical outcome in patients with AIS after IVT.

Methods: We consecutive collected patients who were diagnosed with ischemic stroke and received IVT from August 2016 to August 2022, and conducted a retrospective analysis in this study. The clinical and laboratory data were obtained from hospitalization data. Patients were divided into SBI and Non-SBI groups based on clinical and neuroimaging data. We use Cohen's Kappa to assess the interrater reliability between the two evaluators, and multivariate logistic regression analysis was used to further assess the association between SBI, HT and clinical outcomes at 3months after IVT.

Results: Of the 541 patients, 231 (46.1%) had SBI, 49 (9.1%) had HT, 438 (81%) had favorable outcome, 361 (66.7%) had excellent outcome. There was no significant difference in the incidence of HT (8.2 vs. 9.7%, p=0.560) and favorable outcome (78.4% vs. 82.9%, p=0.183) between patients with SBI and Non-SBI. However, patients with SBI had a lower incidence of excellent outcome than the patients with Non-SBI (60.2% vs. 71.6%%, p=0.005). After adjustment for major covariates, multivariate logistic regression analysis disclosed that SBI was independently associated with the increased risk of worse outcome (OR=1.922, 95%CI: 1.229–3.006, p=0.004).

Conclusion: We found that SBI was no effect for HT after thrombolysis in ischemic stroke patients, and no effect on favorable functional outcome at 3months. Nevertheless, SBI remained an independent risk factor for non-excellent functional outcomes at 3months.

KEYWORDS

silent brain infarction, intravenous thrombolysis, acute ischemic stroke, hemorrhage transformation, functional outcomes

Introduction

Silent brain infarction (SBI) refers to a patient who has no history of stroke or transient ischemic attacks (TIA), but cerebral infarction or encephalomalacia lesions are found on computed tomography (CT) or magnetic resonance imaging (MRI), with no corresponding symptoms and signs of neurological impairment (1). Compared with symptomatic cerebral infarction, the lesions of SBI are usually relatively smaller in size and may have undergone a chronic ischemic preconditioning process, contributing to the absence of clinical symptoms of SBI (2). Previous reports have established that SBI is prevalent in both healthy older adults as well as in specific populations, such as those with hypertension, diabetes, atrial fibrillation, and other conditions (3). Imaging examination, especially MRI is indispensable for the diagnosis of SBI. Recent studies have suggested that MRI examination for the diagnosis of SBI should include at least T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) sequences. In this regard, SBI with an infarct diameter of ≥3 mm, were defined as hypointense lesions on T1WI, while on T2WI they were characterized as hyperintense (4).

In acute ischemic stroke (AIS) patients without intravenous thrombolysis therapy (IVT), studies have shown that SBI was independently associated with lower stroke severity at admission and good function outcome at discharge (5). Another retrospective study of 115 patients with first-ever ischemic stroke without advanced leukoaraiosis found that patients with multiple SBI had severer neurological and had larger infarcts in ischemic stroke than those without SBI, these patients also did not receive intravenous thrombolysis (6). Currently, to our knowledge, no retrospective study has probed the effect of SBI on HT and clinical outcome in patients with acute ischemic stroke after IVT. Therefore, the effect of SBI on HT and the clinical outcome after IVT in patients with AIS needs to be further clarified.

In this study, we retrospectively analyzed 541 patients with first-ever ischemic stroke who underwent intravenous thrombolysis therapy. In particular, we examined the HT and clinical outcome after intravenous thrombolysis therapy in the SBI and Non-SBI groups. We further determined the influence of SBI on the risk of worse outcome for patients with AIS following intravenous thrombolysis therapy.

Subjects and methods

Patients

Totally 909 patients who suffered from an ischemic stroke within 4.5 h of onset and received recombinant tissue plasminogen activator (rt-PA) thrombolytic therapy in the emergency green channel of the First Affiliated Hospital of Soochow University between August 2016 and August 2022 were enrolled in this study. Eligible patients were further included if they had: (1) no history of stroke or TIA, (2) completed intravenous thrombolysis therapy, (3) completed a cranial CT scan within 24 h after intravenous thrombolysis therapy, or (4) completed head MRI examination within 1 week. On the other hand, patients were excluded if they had: (1) history of stroke or TIA, (2) not completed intravenous thrombolysis therapy, (3) intravenous thrombolysis combined with thrombectomy, (4) lacking imaging data, or (5) lacking laboratory data. The flow chart of the study is shown in Figure 1. Finally, 541 patients were assigned to the SBI and Non-SBI groups. This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (2020 No.267). In accordance with national legislation and institutional requirements, written informed consent is not required for this study.

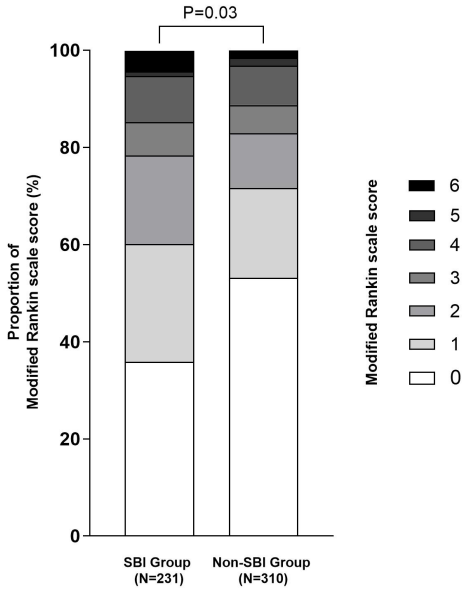


FIGURE 1
The flow chart of the study.

Intravenous rt-PA thrombolysis therapy

The standard dosage was 0.9 mg per kilogram of body weight (10% as a bolus for 1 min and remaining 90% as an infusion for 60 min; maximum dose, 90 mg). The low dosage was 0.6 mg per kilogram of body weight (15% as a bolus for 1 min and remaining 85% as an infusion for 60 min; maximum dose, 60 mg). All patients received only one dose.

Clinical and laboratory data

We recorded the following baseline information of patients: gender, age, NIHSS score on admission, systolic and diastolic blood pressure on admission, head CT and MRI imaging examinations, and TOAST classification. We also collected previous medical history of patients including hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking and drinking history, and antithrombotic medication history (antiplatelet agents or any type of oral anticoagulants). Consequently, we estimated the 3-month outcome using the modified Rankin Scale (mRS). We defined mRS scores ≥3 as poor outcome and mRS scores ≤2 as favorable outcome, mRS scores ≥2 as worse outcome and mRS scores 0 or 1 as excellent outcome. The 3-month follow-up data was obtained by trained nurse through outpatient visits or telephone contact with patients or relatives.

Imaging analysis

MRI data were acquired using a clinical 3.0 Tesla MR scanner, whereas follow-up CT imaging was performed using a clinical 64 slice CT scanner. Specifically, structural MRI comprised of transversal diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery sequence (FLAIR), T1WI, and T2WI. Silent brain infarction on MRI lesions ≥3 mm, were characterized as hypointense on T1WI and hyperintense on T2WI (4). All MRIs were reviewed separately by two experienced neuroradiologists who were blinded to the identity of patients and their clinical information.

Hemorrhage transformation and symptomatic intracranial hemorrhage

Following 24 h thrombolysis, all enrolled patients underwent head CT examination to evaluate whether there was HT. HT was defined as no manifestation of bleeding on head CT at admission, but found on CT or MRI at follow-up within 7 days after intravenous thrombolysis (7). According to ECASSIII (8), symptomatic intracranial hemorrhage (sICH) was defined as any apparent HT that was associated with clinical deterioration (≥4 points in the NIHSS score), or that led to death and that was identified as the predominant cause of the neurologic deterioration. Notably, HT was examined during follow-up imaging by a neurologist and radiologist.

Statistical analysis

Kolmogorov–Smirnov test was used to test normal distribution of the continuous variables. Normally distributed data were presented as mean and standard deviation (SD) and Non-normally distributed data as median with interquartile range (IQR) or counts and percentages. And categorical variables are presented as frequencies and percentages. Moreover, we used student's *t*-test or Mann–Whitney U test for continuous variables according to the normality and χ^2 test or Fisher exact test for categorical variables. The two-tailed *p*-values of <0.05 were considered statistically significant. We used univariate analysis to compare the differences in baseline data between the SBI and non-SBI group. The results showed a statistically significant difference on clinical outcome. To further explore the effect of SBI on clinical outcome after intravenous thrombolysis, we first used univariate analysis to compare baseline data between the excellent outcome group and the worse outcome group. Then, we adjusted for age, sex, and variables with $p < 0.1$ [old age, hypertension, atrial fibrillation history, anti-thrombotic history, admission NIHSS score, TOAST subtypes, glucose level, admission lymphocyte count, admission neutrophil count, admission platelet count, international normalized ratio, homocysteine level and SBI] in univariate analysis as major covariates into the multivariate logistic regression model. The relationship between SBI and clinical outcomes was assessed by multivariate logistic regression analysis. The interrater reliability between the two observers was assessed based on Cohen's Kappa for SBI and HT presence. A Cohen's Kappa (k) of ≤0.1 corresponds to no agreement, $0.1 < k \leq 0.4$ weak agreement, $0.4 < k \leq 0.6$ good agreement, $0.6 < k \leq 0.8$ strong agreement and $0.8 < k \leq 1$ complete agreement. Statistical analyses were performed using the statistical package for social sciences, version 22.0 (IBM SPSS Statistics, Armonk, NY, United States).

Results

Baseline characteristics of patients

A total of 909 patients with AIS who received IVT treatment were screened for eligibility. Of these patients, 172 patients were first excluded because of a previous history of stroke or TIA. 100 patients did not receive cranial MR examination after thrombolysis, and 91 patients received incomplete laboratory data, 5 patients were lost for follow-up. Finally, 541 patients were included in our analysis (Figure 1), and the overall characteristics of participants are shown in Table 1. The median age was 66 (57–75) years and 323 (59.7%) were males. The median NIHSS score on admission was 5 (3–10). The median time to treat was 177.0 min (136.5–215.0). Of these patients, 231 (42.7%) patients had SBI lesions ($k = 0.893$, 95%CI: 0.855–0.929, $p = 0.000$), 49 (9.1%) patients experienced HT ($k = 1.000$, 95%CI: 1.000–1.000, $p = 0.000$), which 18 (3.3%) had sICH ($k = 1.000$, 95%CI: 1.000–1.000, $p = 0.000$). Results for the interrater reliability correspond to a complete agreement. There were 438 (81%) patients with MRS 0–2 and 361 (66.7%) MRS 0–1 at 90 days.

Characteristics between patients with and without SBI

Table 1 shows the baseline characteristics of SBI group and Non-SBI group. 231 (42.7%) patients were classified as SBI group, whereas 310 (57.3%) patients were assigned to the Non-SBI group. Patients with SBI were usually older and consisted more of hypertension, diabetes and smoking history than patients without SBI [69 (69–76) vs. 65 (54–74), $p = 0.000$; 178 (77.1%) vs. 200 (64.5%), $p = 0.020$; 70 (30.3%) vs. 70 (22.6%), $p = 0.040$; 77 (33.3%) vs. 77 (24.8%), $p = 0.030$]. The TOAST subtype distribution also showed statistically significant differences between the two groups ($p = 0.008$). Furthermore, patients with SBI had higher serum homocysteine levels and shorter activated partial thromboplastin time than those without SBI [11.4 (9.4–14.8) vs. 10.35 (8.4–13.1), $p = 0.001$; 31.5 (26.6–35.0) vs. 32.3 (28.6–35.4), $p = 0.034$. Table 1]. For clinical outcome, there was no significant difference in the incidence of HT [19 (8.2%) vs. 30 (9.7%), $p = 0.560$] and sICH [11 (4.8%) vs. 7 (2.3%), $p = 0.108$] between the two groups. Although there was no significant difference in the incidence of favorable outcome between the two groups [181 (78.4%) vs. 257 (82.9%), $p = 0.183$], the incidence of excellent outcome was lower in the SBI group than the Non-SBI group [139 (60.2%) vs. 222 (71.6%), $p = 0.005$, Figure 2].

Relationship between SBI and 3-month excellent outcomes

Table 2 shows the baseline characteristics of the excellent function outcome group versus the worse function outcome group. Univariate analysis showed that age, hypertension, atrial fibrillation, antiplatelet medication history, TOAST classification, and admission NIHSS score were significant differences between two groups ($p < 0.05$). In the laboratory test results, glucose level, admission neutrophil and

10.3389/fneur.2023.1147290

TABLE 1 Characteristics of the patients at baseline between SBI group and Non-SBI group.

	Total patients (*n*=541)	SBI group (*n*=231)	Non-SBI group (*n*=310)	*p* value
Demographics				
Age, (years)	66 (57–75)	69 (69–76)	65 (54–74)	0.000
Male, *n* (%)	323 (59.7%)	107 (67.9%)	216 (69.7%)	0.951
Cardiovascular risk factors, *n* (%)				
Hypertension	378 (69.9%)	178 (77.1%)	200 (64.5%)	0.020
Diabetes	140 (25.9%)	70 (30.3%)	70 (22.6%)	0.040
Atrial fibrillation	107 (19.8%)	50 (21.6%)	57 (18.4%)	0.347
Smoke	154 (28.5%)	77 (33.3%)	77 (24.8%)	0.030
Drink	109 (20.1%)	55 (23.8)	54 (17.4)	0.067
Hyperlipemia	33 (6.1%)	12 (5.2%)	21 (6.8%)	0.448
Medication history, *n* (%)				
Anti-thrombotic	25 (4.6%)	9 (3.9%)	16 (5.2%)	0.488
Physiological data on admission				
SBP (mmHg)	157.4 ± 24.31	159.3 ± 24.88	155.96 ± 23.675	0.113
DBP (mmHg)	88.0 (79.0–98.0)	88.0 (78.0–98.0)	88.0 (79.0–98.3)	0.698
Baseline NIHSS scores	5 (3–10)	5 (3–10)	5 (3–10)	0.893
OTT time	177.0 (136.5–215.0)	175 (135.0–211.0)	177.5 (138.5–215.0)	0.838
Standard-dose rt-PA	511 (94.5%)	218 (94.4%)	293 (94.5%)	0.942
TOAST classification, *n* (%)				0.008
LAA	232 (42.9%)	100 (43.3%)	132 (42.6%)	
CE	96 (17.7%)	44 (19.0%)	52 (16.8%)	
SAA	142 (26.2%)	70 (30.3%)	72 (23.2%)	
SOE	19 (3.5%)	6 (2.6%)	13 (4.2%)	
SUE	52 (9.6%)	11 (4.8%)	41 (13.2%)	
Laboratory test data				
GLU (mmol/L)	6.92 (5.77–8.73)	6.88 (5.66–9.19)	6.925 (5.86–8.45)	0.962
WBC ($\times 10^9$/L)	7.50 (6.38–9.28)	7.52 (6.48–9.26)	7.49 (6.29–9.37)	0.352
LY ($\times 10^9$/L)	1.65 (1.19,2.2445)	1.61 (1.17,2.19)	1.72 (1.22,2.27)	0.390
NE ($\times 10^9$/L)	4.98 (3.86,6.85)	4.98 (4.05,6.87)	4.97 (3.79,6.7375)	0.436
PLT ($\times 10^9$/L)	197.0 (162.5–240.0)	191.0 (159.0–234.0)	201.0 (168.0–242.3)	0.670
LDL-C (mmol/L)	2.81 ± 0.93	2.75 ± 0.85	2.84 ± 0.98	0.261
CHO (mmol/L)	4.45 (3.85–5.16)	4.40 (3.79–5.21)	4.50 (3.88–5.11)	0.431
UA (μmol/L)	303.6(242.8–363.8)	307.9 (247.0–371.1)	301.4 (239.6–361.6)	0.235
Cr (μmol/L)	68 (58–79)	69 (59–81)	67 (58–78)	0.085
INR	1.02 (0.97–1.08)	1.02 (0.97–1.08)	1.02 (0.97–1.08)	0.791
APTT (s)	32.0 (27.9–35.2)	31.5 (26.6–35.0)	32.3 (28.6–35.4)	0.034
FIG (g/L)	3.06 (2.62–3.58)	3.06 (2.61–3.61)	3.05 (2.62–3.55)	0.657
PT (s)	13.0 (12.3–13.6)	12.9 (12.2–13.7)	13.0 (12.4–13.53)	0.268
Hcy	10.7 (8.8–13.6)	11.4 (9.4–14.8)	10.4 (8.4–13.1)	0.001
Outcome, *n* (%)				
HT	49 (9.1%)	19 (8.2%)	30 (9.7%)	0.560
SICH	18 (3.3%)	11 (4.8%)	7 (2.3%)	0.108
mRS (0–2)	438 (81%)	181 (78.4%)	257 (82.9%)	0.183
mRS (0–1)	361 (66.7%)	139 (60.2%)	222 (71.6%)	0.005

Data are expressed as mean ± standard deviation (SD), median with interquartile range (IQR) or percentage. SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, the national institutes of health stroke scale; TOAST, the trial of org 10,172 in acute stroke treatment; LAA, large-artery atherosclerosis; SAA, small-artery occlusion; CE, cardioembolism; SOE, stroke of other determined cause; SUE: stroke of undetermined cause; GLU, glucose; WBC: white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet; LDL-C, low-density lipoprotein cholesterin; CHO, total cholesterol; UA, uric acid; Cr, creatinine; INR, international normalized ratio; APTT, activated partial thromboplastin time; FIG, fibrinogen; PT, prothrombin time; HCY, homocysteine; HT, hemorrhagic transformation; sICH, symptomatic intracranial hemorrhage; SBI, silent brain infarction.

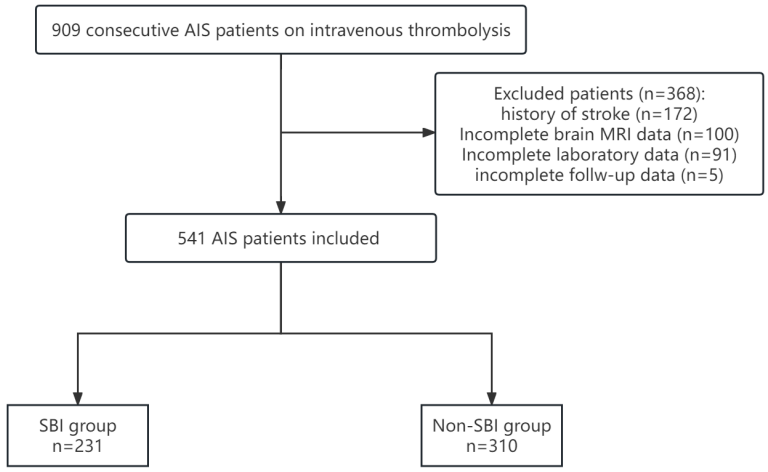


FIGURE 2
Distribution of the total mRS scores as stratified by SBI groups.

lymphocyte count, serum HDL-C level, serum TG level, serum HCY level, and International Normalized Ratio also significant differences ($p < 0.05$). The rate of SBI in patients with worse function outcome was higher than that in patients with excellent function outcome ($p = 0.005$).

Univariable and multivariable analyses of 3-month worse outcomes

In univariable analyses, old age, hypertension and atrial fibrillation history, anti-thrombotic history, admission NIHSS score, TOAST subtypes, glucose level, admission lymphocyte count, admission neutrophil count, admission platelet count, international normalized ratio, homocysteine level and SBI were associated with worse outcome in AIS after rt-PA treatment. After age and sex adjustment, initial NIHSS, TOAST subtypes, glucose level, admission lymphocyte count, admission neutrophil count and SBI were significantly associated with worse outcome at 3 months after discharge. To figure out whether SBI were an independent prognostic indicator for worse outcome in 3 months. Variables with $p < 0.1$ in the univariate analysis and the Age- and sex-adjusted analysis were included in the multivariate logistic regression model. After age, sex, and multivariate adjustment, only initial NIHSS (OR = 1.239, 95% CI: 1.180–1.302, $p = 0.000$), GLU (OR = 1.079, 95%CI: 1.019–1.144, $p = 0.010$), and admission lymphocyte count (OR = 0.658, 95%CI: 0.498–0.869, $p = 0.003$), SBI (OR = 1.922, 95%CI: 1.229–3.006, $p = 0.004$) were significantly related to worse outcomes at 3 months after discharge (Table 3).

Discussion

To our knowledge, this is the first research on the effect of SBI on hemorrhagic transformation and clinical outcomes after thrombolysis in patients with acute ischemic stroke. We found that SBI was relatively common in patients with a first-ever ischemic stroke, and SBI was an independent risk factor for worse outcome (OR = 1.922, 95%CI: 1.229–3.006, $p = 0.004$), but not an independent risk factor for HT and favorable outcome after IVT.

Silent brain infarction (SBI) refers to lesions discovered via neuroimaging that lack associated clinical symptomology (9). The prevalence of SBI is about 10–20% in the general population, with an annual incidence rate of 2 to 4% (10). Previous studies have found that SBI is present in about 33.4% of patients with a first-ever ischemic stroke (11). Risk factors for SBI are consistent with ischemic stroke, such as advanced age, hypertension, and diabetes (3). Kim et al. found that hyperhomocysteinemia is an independent risk factor (OR = 4.78; 95%CI: 2.45–9.33) for SBI (12). Wang and colleagues found that the higher prevalence of SBI was associated with incompleteness of circle of Willis in patients with internal carotid artery stenosis (13). Ito et al. indicated that aortic stenosis was associated with a high prevalence of SBI, and the CHA_2DS_2-VASc score (≥4) and eGFR (<60 mL/min/1.73m^2) are useful for risk stratification (14). Nacafaliyev reported that patients with moderate and severe sleep apnea syndrome were at higher risk of developing SBI and noted that desaturations during sleep may affect infarct formation (15). In the baseline data of this study, we found that not only were TOAST subtype distributions different between the two groups, but also that patients with SBI had shorter activated partial thromboplastin times than those without SBI.

Studies have shown that SBI is not completely asymptomatic, and oldish people with SBI have an increased risk of dementia and a faster decline in cognitive function than those without such lesions (16, 17). In addition, a prospective study concluded that overt and silent brain infarction had similar effects on cognitive decline (18). A meta-analysis of 14,764 subjects with a mean follow-up time of 25.7 to 174 months uncovered that about 20% of the stroke-free older adults had SBI, and indicated that the probability of SBI patients developing symptomatic cerebral infarction was twice as high as that of healthy people (1). Carotid endarterectomy is one of the treatments to reduce the risk of stroke in patients with asymptomatic carotid stenosis, the study found that the presence of SBI was independently associated with a higher risk of postoperative stroke for carotid endarterectomy (19). Multiple SBIs have more severe neurological deficits and larger infarcts for ischemic stroke those without no SBI in patients with first-ever ischemic stroke without advanced leukoaraiosis (6). Another community-based study showed that silent infarcts did not appear to affect the prognosis of stroke (20).

10.3389/fneur.2023.1147290

TABLE 2 Univariate analysis of baseline factors associated with clinical outcome.

	mRS 0–1 (*n*=361)	mRS 2–6 (*n*=180)	*p* value
Demographics			
Age, (years)	65 (55–73)	71.5 (62–79)	0.000
Male, *n* (%)	256 (70.9)	120 (66.7)	0.312
Cardiovascular risk factors, *n* (%)			
Hypertension	240 (66.5)	138 (76.7)	0.015
Diabetes	86 (23.8)	54 (30)	0.122
Atrial fibrillation	58 (16.1)	49 (27.2)	0.020
Smoke	103 (28.5)	51 (28.3)	0.962
Drink	78 (21.6)	31 (17.2)	0.231
Hyperlipemia	23 (6.4)	10 (5.6)	0.709
Medication history, *n* (%)			
Anti-thrombotic	12 (3.3)	13 (7.2)	0.042
Physiological data on admission			
SBP (mmHg)	156.7 ± 24.067	158.77 ± 24.564	0.855
DBP (mmHg)	88 (79–99)	88 (78–98)	0.633
Baseline NIHSS scores	4 (1–7)	10 (6–15)	0.000
OTT time	176 (140–215)	179.5 (135–210.75)	0.835
Standard-dose rt-PA (%)	343 (95)	168 (93.3)	0.421
TOAST classification, *n* (%)			0.000
LAA	142 (39.3)	90 (50.0)	
CE	52 (14.4)	44 (24.4)	
SAA	111 (30.7)	31 (17.2)	
SOE	15 (4.2)	4 (2.2)	
SUE	41 (11.4)	11 (6.1)	
Laboratory test data			
GLU (mmol/L)	6.73 (5.66–8.36)	7.35 (6.00–10.10)	0.001
WBC (×109/L)	7.48 (6.245–9.175)	7.59 (6.515–9.625)	0.381
LY (×109/L)	1.7 (1.250–2.335)	1.455 (1.0225–1.9275)	0.000
NE (×109/L)	4.74 (3.705–6.660)	5.355 (4.1625–7.2250)	0.006
PLT (×109/L)	201.00 (167.00–241.50)	187.5 (154.75–233.75)	0.038
LDL-C (mmol/L)	2.8136 ± 0.948	2.7884 ± 0.893	0.497
CHO (mmol/L)	4.43 (3.830–5.175)	4.455 (3.91–5.085)	0.577
UA	301.3 (244.8–361.85)	307.45 (238.325–375.875)	0.454
CR (μmol/L)	67.50 (58.00–77.75)	68.00 (58.00–83.725)	0.268
INR	1.01 (0.97–1.08)	1.04 (0.98–1.09)	0.026
APTT (S)	32.0 (28.35–35.3)	32.05 (27.00–35.00)	0.410
FIG (g/L)	3.03 (2.60–3.55)	3.085 (2.6425–3.71)	0.294
PT (S)	12.9 (12.3–13.5)	13.1 (12.3–13.7)	0.159
HCY	10.5 (8.6–13.15)	11.25 (9.3–14.9)	0.025
SBI	139 (38.5)	92 (51.1)	0.005

Data are expressed as mean ± standard deviation (SD), median with interquartile range (IQR) or percentage. SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, the national institutes of health stroke scale; TOAST, the trial of org 10,172 in acute stroke treatment; LAA, large-artery atherosclerosis; SAA, Small-artery occlusion; CE, cardioembolism; SOE, stroke of other determined cause; SUE, stroke of undetermined cause; GLU, glucose; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet; LDL-C, low-density lipoprotein cholesterin; CHO, total cholesterol; UA, uric acid; Cr, creatinine; INR, international normalized ratio; APTT, activated partial thromboplastin time; FIG, fibrinogen; PT, prothrombin time; HCY, homocysteine; SBI, silent brain infarction.

TABLE 3 Multivariate logistic regression analysis for worse outcomes predictors at 3months (mRS score 2–6).

Variables	Age-and sex-adjusted		Multivariate adjusted	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Hypertension	1.417 (0.925–2.170)	0.109	1.143 (0.690–1.892)	0.604
Atrial fibrillation	1.296 (0.815–2.060)	0.273	1.062 (0.400–2.820)	0.904
Anti-thrombotic	1.763 (0.774–4.014)	0.177	2.099 (0.759–5.810)	0.153
NIHSS	1.215 (1.164–1.269)	0.000	1.239 (1.180–1.302)	0.000
TOAST classification				
LAA	–	–	–	–
CE	1.101 (0.669–1.813)	0.704	0.493 (0.175–1.392)	0.182
SAA	0.535 (0.329–0.870)	0.012	0.622 (0.356–1.086)	0.095
SOE	0.556 (0.174–1.782)	0.323	0.736 (0.189–2.865)	0.659
SUE	0.490 (0.234–1.023)	0.058	0.741 (0.327–1.679)	0.473
GLU	1.058 (1.006–1.111)	0.027	1.079 (1.019–1.144)	0.010
LY	0.683 (0.540–0.864)	0.001	0.658 (0.498–0.869)	0.003
NE	1.098 (1.025–1.176)	0.008	0.976 (0.895–1.065)	0.590
PLT	1.000 (0.997–1.002)	0.747	1.000 (0.999–1.002)	0.919
INR	0.806 (0.466–1.395)	0.441	0.496 (0.047–5.248)	0.560
HCY	1.006 (0.993–1.019)	0.366	1.009 (0.989–1.030)	0.371
SBI	1.479 (1.020–2.146)	0.039	1.922 (1.229–3.006)	0.004

NIHSS, the national institutes of health stroke scale; TOAST, the trial of org 10,172 in acute stroke treatment; LAA, large-artery atherosclerosis; SAA, small-artery occlusion; CE, cardioembolism; SOE, stroke of other determined cause; SUE, stroke of undetermined cause; GLU, glucose; LY, lymphocyte; NE, neutrophil; PLT, platelet; INR, international normalized ratio; HCY, homocysteine; SBI, silent brain infarction.

Admission glucose level and neutrophil-to-lymphocyte ratio can predict 3-month functional outcome in AIS patients (21, 22). Our data also indicated that patients with high admission glucose levels and lymphocyte were more likely to have worse outcome at 3 months. Another retrospective study included 981 ischemic stroke patients and found that recent clinically silent infarcts (RSIs) was not associated with a worse clinical outcome in AIS patients with IVT. Although clinical outcome were measured by the mRS at discharge, their conclusions argue against RSIs as a contraindication for IVT (23). A small sample study without thrombolysis found lower 3-month mRS Scores and better clinical outcomes in the SBI present group compared to the SBI absent group (24). In this study, we evaluated mRS Scores at 3 months to explore the effect of SBI on clinical outcomes after IVT. The results showed that a similar number of patients achieved favorable outcomes in the Non-SBI group compared to the SBI group, Non-SBI group was slightly superior over SBI group in terms of likelihood of achieving an excellent outcome.

When symptomatic cerebral infarction occurs, intravenous thrombolytic therapy with rt-PA within 4.5 h can effectively improve the clinical prognosis of patients after the removal of thrombolytic contraindications (25). Hemorrhagic transformation remains a primary adverse reaction of intravenous thrombolytic therapy after acute cerebral infarction, which is closely associated with the clinical outcome of patients. Previous studies have found that older age, higher diastolic blood pressure, NIHSS score ≥ 13, OTT ≥ 180 min, etc., are potential risk factors for HT after intravenous thrombolysis (26, 27). Pretreatment MRI can identify recent silent cerebral infarction (RSCI) and two small sample studies suggest that RSCI does not increase the risk of hemorrhagic transformation after intravenous thrombolysis in patients with acute cerebral infarction (28, 29). Although RSCI can be identified by the use of MRI, the onset to treatment time of AIS patients was often prolonged by MRI examination before thrombolytic. Therefore, we systematically reviewed the whole group of AIS patients who completed MRI examination after intravenous thrombolytic, and disclosed the incidence of SBI confirmed by MRI in the entire cohort and its influence on hemorrhagic transformation after intravenous thrombolysis. Our results were similar to the findings of the two retrospective studies described above, and SBI, like RSCI, did not increase the risk of hemorrhagic transformation after intravenous thrombolysis.

However, there are some limitations in this study. Firstly, the present study was a retrospective analysis with limited sample size. Second, the findings of this study are limited by selection bias, as patients who did not complete a cranial MRI examination were not included in the MRI-based study, and these excluded patients may be associated with more severe intracranial hemorrhage and poorer clinical outcomes. Third, acute large cerebral infarction occurred in lobes with previous small SBI lesions in the cortex or medulla of these lobes. SBI lesions may be compressed by edema in acute cerebral infarction and cannot be detected by MRI. This hypothesis has not been proven, but it could lead to information bias. Last, we did not further explore the relationship between SBI and post-stroke cognitive impairment and post-stroke depression. Further multi-faceted exploration should be carried out in multi-center study with a large sample size.

Conclusion

We found that SBI was no effect for HT after thrombolysis in ischemic stroke patients, and no effect on favorable functional outcome at 3 months. Nevertheless, SBI remained an independent risk factor for non-excellent functional outcomes at 3 months.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. The ethics committee waived the requirement of written informed consent for participation. No potentially identifiable human images or data is presented in this study.

Author contributions

YZ, DD, and QF contributed to conception and design of the study. LZ wrote the first draft of the manuscript. SW organized the database. QF contributed the patient follow-up. JiJ and JuJ performed the statistical analysis. YZ and DD revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This work was supported by the National Key Research and Development Program of China (2017YFE0103700), the National Natural Science Foundation of China (No. 82001219 to DD), the Natural Science Foundation of Jiangsu Province (BK20190183), and the Advanced Research Project of Suzhou University of Natural Science Foundation (SDY2012B25).

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Gupta A, Giambrone AE, Gialdini G, Finn C, Delgado D, Gutierrez J, et al. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke*. (2016) 47:719–25. doi: 10.1161/STROKEAHA.115.011889

2. Fanning JP, Wesley AJ, Wong AA, Fraser JF. Emerging spectra of silent brain infarction. *Stroke*. (2014) 45:3461–71. doi: 10.1161/STROKEAHA.114.005919

3. Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, et al. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2017) 48:e44–71. doi: 10.1161/STR.0000000000000116

4. Zhu YC, Dufouil C, Tzourio C, Chabriat H. Silent brain infarcts: a review of MRI diagnostic criteria. *Stroke*. (2011) 42:1140–5. doi: 10.1161/STROKEAHA.110.600114

5. Kim YS, Park SS, Lee SH, Yoon BW. Reduced severity of strokes in patients with silent brain infarctions. *Eur J Neurol*. (2011) 18:962–71. doi: 10.1111/j.1468-1331.2010.03282.x

6. Chen DW, Wang YX, Shi J, Zhang WQ, Yang F, Yin YW, et al. Multiple silent brain infarcts are associated with severer stroke in patients with first-ever ischemic stroke without advanced leukoaraiosis. *J Stroke Cerebrovasc Dis*. (2017) 26:1988–95. doi: 10.1016/j.jstrokecerebrovasdis.2017.06.011

7. Alvarez-Sabin J, Maisterra O, Santamarina E, Kase CS. Factors influencing haemorrhagic transformation in ischaemic stroke. *Lancet Neurol*. (2013) 12:689–705. doi: 10.1016/S1474-4422(13)70055-3

8. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. (2008) 359:1317–29. doi: 10.1056/NEJMoa0804656

9. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. (2007) 6:611–9. doi: 10.1016/S1474-4422(07)70170-9

10. Fanning JP, Wong AA, Fraser JF. The epidemiology of silent brain infarction: a systematic review of population-based cohorts. *BMC Med*. (2014) 12:119. doi: 10.1186/s12916-014-0119-0

11. Oh SH, Kim NK, Kim SH, Kim JK, Kim HS, Kim WC, et al. The prevalence and risk factor analysis of silent brain infarction in patients with first-ever ischemic stroke. *J Neurol Sci*. (2010) 293:97–101. doi: 10.1016/j.jns.2010.02.025

12. Kim NK, Choi BO, Jung WS, Choi YJ, Choi KG. Hyperhomocysteinemia as an independent risk factor for silent brain infarction. *Neurology*. (2003) 61:1595–9. doi: 10.1212/01.wnl.0000096010.98989.49

13. Wang J, Ji J, Qiu J, Wang Y. Incompleteness of circle of Willis and silent brain infarction in patients with internal carotid artery stenosis. *J Clin Neurosci*. (2022) 98:73–7. doi: 10.1016/j.jocn.2022.02.001

14. Ito A, Iwata S, Tamura S, Kim AT, Nonin S, Ishikawa S, et al. Prevalence and risk factors of silent brain infarction in patients with aortic stenosis. *Cerebrovasc Dis Extra*. (2020) 10:116–23. doi: 10.1159/000510438

15. Nacafaliyev V, Ortan P, Sayin SS. Relationship between obstructive sleep apnoea syndrome and silent brain infarction. *Postgrad Med J*. (2022):141911. doi: 10.1136/pmj-2022-141911

16. Lei C, Deng Q, Li H, Zhong L. Association between silent brain infarcts and cognitive function: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. (2019) 28:2376–87. doi: 10.1016/j.jstrokecerebrovasdis.2019.03.036

17. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. (2003) 348:1215–22. doi: 10.1056/NEJMoa022066

18. Kuhne M, Krisai P, Coslovsky M, Rodondi N, Muller A, Beer JH, et al. Silent brain infarcts impact on cognitive function in atrial fibrillation. *Eur Heart J*. (2022) 43:2127–35. doi: 10.1093/eurheartj/ehac020

19. Pini R, Faggioli G, Indelicato G, Palermo S, Vacirca A, Gallitto E, et al. Predictors and consequences of silent brain infarction in patients with asymptomatic carotid stenosis. *J Stroke Cerebrovasc Dis*. (2020) 29:105108. doi: 10.1016/j.jstrokecerebrovasdis.2020.105108

20. Jorgensen HS, Nakayama H, Raaschou HO, Gam J, Olsen TS. Silent infarction in acute stroke patients. prevalence, localization, risk factors, and clinical significance: the Copenhagen stroke study. *Stroke*. (1994) 25:97–104. doi: 10.1161/01.str.25.1.97

21. Desilles JP, Meseguer E, Labreuche J, Lapergue B, Sirimarco G, Gonzalez-Valcarcel J, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: a registry and systematic review. *Stroke*. (2013) 44:1915–23. doi: 10.1161/STROKEAHA.111.000813

22. Qun S, Tang Y, Sun J, Liu Z, Wu J, Zhang J, et al. Neutrophil-to-lymphocyte ratio predicts 3-month outcome of acute ischemic stroke. *Neurotox Res*. (2017) 31:444–52. doi: 10.1007/s12640-017-9707-z

23. Stosser S, Ullrich L, Kassubek J, Ludolph AC, Schocke M, Neugebauer H. Recent silent infarcts do not increase the risk of haemorrhage after intravenous thrombolysis. *Eur J Neurol*. (2020) 27:2483–90. doi: 10.1111/ene.14453

24. Kwon HS, Kim YS, Park HH, Choi H, Lee KY, Lee YJ, et al. Increased VEGF and decreased SDF-1alpha in patients with silent brain infarction are associated with better prognosis after first-ever acute lacunar stroke. *J Stroke Cerebrovasc Dis*. (2015) 24:704–10. doi: 10.1016/j.jstrokecerebrovasdis.2014.11.021

25. National Institute of Neurological, D., and Stroke rt, P.A.S.S.G. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. (1995) 333:1581–8. doi: 10.1056/NEJM199512143332401

26. Qiu L, Fu F, Zhang W, He J, Zhan Z, Cheng Z. Prevalence, risk factors, and clinical outcomes of remote intracerebral hemorrhage after intravenous thrombolysis in acute ischemic stroke: a systematic review and meta-analysis. *J Neurol*. (2023) 270:651–61. doi: 10.1007/s00415-022-11414-2

27. Wu Y, Chen H, Liu X, Cai X, Kong Y, Wang H, et al. A new nomogram for individualized prediction of the probability of hemorrhagic transformation after intravenous thrombolysis for ischemic stroke patients. *BMC Neurol*. (2020) 20:426. doi: 10.1186/s12883-020-02002-w

28. das RR, Tisserand M, Touze E, Meder JF, Oppenheim C. Prevalence of MRI-defined recent silent ischemia and associated bleeding risk with thrombolysis. *Neurology*. (2011) 77:e152. doi: 10.1212/WNL.0b013e318239bd70

29. Gaillard N, Schmidt C, Costalat V, Bousquet JP, Heroum C, Milhaud D, et al. Hemorrhagic risk of recent silent cerebral infarct on prethrombolysis MR imaging in acute stroke. *AJNR Am J Neuroradiol*. (2012) 33:227–31. doi: 10.3174/ajnr.A2768

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 12 May 2023
DOI 10.3389/fneur.2023.1131283

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
Jefferson W. Chen,
University of California, Irvine, United States
Eberval Figueiredo,
University of São Paulo, Brazil
Huaizhang Shi,
First Affiliated Hospital of Harbin Medical University, China

*CORRESPONDENCE
Yifei Liu
✉ lyfgf1022@126.com

RECEIVED 24 December 2022
ACCEPTED 12 April 2023
PUBLISHED 12 May 2023

CITATION
Huang X, Yan Z, Jiang L, Chen S and Liu Y (2023) The efficacy of stereotactic minimally invasive thrombolysis at different catheter positions in the treatment of small- and medium-volume basal ganglia hemorrhage (SMITDCP I): a randomized, controlled, and blinded endpoint phase 1 trial. *Front. Neurol.* 14:1131283. doi: 10.3389/fneur.2023.1131283

The efficacy of stereotactic minimally invasive thrombolysis at different catheter positions in the treatment of small- and medium-volume basal ganglia hemorrhage (SMITDCP I): a randomized, controlled, and blinded endpoint phase 1 trial

Xin Huang[1], Ziwei Yan[2], Lai Jiang[1], Shaojun Chen[1] and Yifei Liu[3]*

[1]Department of Neurosurgery, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, Yichang, Hubei, China, [2]Department of Ultrasound Diagnostics, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, Yichang, Hubei, China, [3]Department of Anesthesiology, The People's Hospital of China Three Gorges University, The First People's Hospital of Yichang, Yichang, Hubei, China

Objective: The aim of this study was to evaluate the effects of stereotactic minimally invasive puncture with different catheter placement positions when combined with urokinase thrombolysis for the treatment of small- and medium-volume basal ganglia hemorrhage. Our goal was to identify the best minimally invasive catheter placement position to enhance therapeutic efficacy for patients with cerebral hemorrhage.

Methods: The stereotactic minimally invasive thrombolysis at different catheter positions in the treatment of small- and medium-volume basal ganglia hemorrhage (SMITDCPI) was a randomized, controlled, and endpoint phase 1 trial. We recruited patients with spontaneous ganglia hemorrhage (medium-to-small and medium volume) who were treated in our hospital. All patients received stereotactic, minimally invasive punctures combined with an intracavitary thrombolytic injection of urokinase hematoma. A randomized number table method was used to divide the patients into two groups concerning the location of catheterization: a penetrating hematoma long-axis group and a hematoma center group. The general conditions of the two groups of patients were compared, and the data were analyzed, including the time of catheterization, the dosage of urokinase, the amount of residual hematoma, the hematoma clearance rate, complications, and the National Institute of Health stroke scale (NIHSS) score data at 1 month after surgery.

Results: Between June 2019 and March 2022, 83 patients were randomly recruited and assigned to the two groups as follows: 42 cases (50.60%) to the penetrating hematoma long-axis group and 41 cases (49.40%) to the hematoma center group. Compared with the hematoma center group, the long-axis group was associated with a significantly shorter catheterization time, a lower urokinase dose, a lower residual hematoma volume, a higher hematoma clearance rate, and fewer complications ($P < 0.05$). However, there were no significant differences between the two groups in terms of the NIHSS scores when tested 1 month after surgery ($P > 0.05$).

Conclusion: Stereotactic minimally invasive puncture combined with urokinase for the treatment of small- and medium-volume hemorrhage in the basal ganglia, including catheterization through the long axis of the hematoma, led to significantly better drainage effects and fewer complications. However, there was no significant difference in short-term NIHSS scores between the two types of catheterization.

KEYWORDS

stereotactic, minimally invasive, catheter location, hypertensive cerebral hemorrhage, small to medium volume basal ganglia hemorrhage

1. Introduction

Stroke is currently regarded as the second largest contributor to global disability-adjusted life years (DALYs) in developing countries (1). Although spontaneous intracerebral parenchymal hemorrhage (IPH) accounts for <20% of strokes, this condition is associated with high rates of morbidity and mortality. The bleeding site is usually located in the deep gray matter, including the basal ganglia and the thalamus (2). The recent results arising from the minimally invasive surgery plus alteplase for cerebral hemorrhage (MISTIE) III trial showed that minimally invasive surgery is safer than drug therapy and that thrombolysis after minimally invasive catheter evacuation reduces the size of hematomas by up to 15 ml, thus reducing mortality and improving prognosis (3). The MISTIE II trial demonstrated that the effects of surgery were directly associated with the position of the catheter. In this trial, the catheter was positioned along the entire longitudinal axis of the hematoma (defined as at least two-thirds of the longitudinal length). Stereotactic techniques for the placement of the drainage tube are known to be more accurate and controlled in the treatment of small-volume hemorrhage in the basal ganglia and have achieved effective outcomes (4, 5). Therefore, the purpose of this manuscript is to explore the effect of different catheter placement positions on the treatment of moderate to small amounts of hypertensive intracerebral hemorrhage.

2. Objects and methods

2.1. Research objects

In this trial, we recruited 95 neurosurgery patients from Yichang Three Gorges Central People's Hospital between June 2019 and March 2022 to receive stereotactic minimally invasive puncture and catheter placement combined with urokinase for the treatment of medium-to-small hemorrhages in the basal ganglia. Of these, 12 patients were surgical patients in the early stage of hemorrhages, and 83 patients were in the later stage of hemorrhages. The patients were divided into two groups by using a randomized number table method. According to the location of the catheter, the patients were divided into two groups as follows: those who were catheterized through the long axis of the hematoma (42 cases through the frontal approach) and those who received catheterization through the center of the hematoma (41 cases through the frontal–parietal approach). This trial complied with the relevant ethical standards and was approved by our hospital's ethics committee (KY-2022-0040). Signed and informed consent was obtained from all the patients or their legal representatives. The inclusion criteria were as follows: (1) all patients who were diagnosed with basal ganglia hemorrhage by head Computed Tomography (CT) and Computed Tomography Artery (CTA) examination on admission, according to the Guidelines for the Diagnosis and Treatment of Cerebral Hemorrhage in China (2019); (2) patients with a history of hypertension; (3) patients affected by basal ganglia hemorrhage for the first time and having no previous neurological dysfunction; and (4) patients with a bleeding volume in the basal ganglia of 20–40 ml. The exclusion criteria were as follows: (1) patients with severe coagulation dysfunction or severe basic diseases; (2) patients with surgical contraindications; (3) patients whose hemorrhage had broken into ventricles; and (4) patients whose hemorrhage was caused by brain tumors, cerebral aneurysms, cerebral vascular malformations, and other reasons (6).

2.2. Methods

We collated a range of general clinical data for each patient (Table 1), including gender, age, hematoma volume at admission, time from onset to visit, blood pressure at admission, Glasgow Coma Scale (GCS) at admission, smoking history, compliance with hyperlipidemia drugs, antiplatelet therapy, diabetes, hypertension, random blood pressure, other cardiovascular diseases, NIHSS score, and the time from stroke to first CT at admission.

2.2.1. Calculation of cerebral hemorrhage

According to the maximum level of hematoma selected by the CT cross-section, the longest diameter of the hematoma (cm) and the widest diameter of the hematoma (cm) were measured on the imaging system. The layer thickness was determined from the CT film, and the number of layers was defined as the total number of layers showing all hematomas. The volume of cerebral hematoma was calculated by the Toda formula (7), where hematoma volume (ml) = 1/2 × the longest diameter of the hematoma (cm) × the widest diameter of the hematoma (cm) × slice thickness (cm) × layers.

TABLE 1 Clinical data of 83 patients with a medium-to-small basal ganglia hemorrhage.

Items	Penetrating hematoma long-axis group ($n = 42$)	Hematoma center group ($n = 41$)	*P* (group penetrating the long axis of hematoma vs. group at the center of hematoma)
Gender (Men, %)	57.14%	48.78%	0.445[a]
Age (x ± s, age)	61.50 ± 8.18	64.04 ± 6.62	0.123[b]
Smoking (case, %)	26.19%	17.07%	0.314[a]
Diabetes (case, %)	9.52%	12.12%	0.696[a]
Hyperlipidemia (case, %)	66.67%	53.66%	0.226[a]
Use of Bayaspirin (case, %)	7.14%	9.76%	0.668[a]
History of cardiovascular disease (case, %)	11.90%	12.20%	0.968[a]
NIHSS score on admission (x ± s, score)	12.69 ± 3.69	12.14 ± 2.82	0.754[b]
GCS score on admission (x ± s, score)	10.98 ± 1.55	11.41 ± 1.96	0.262[b]
3-8 score (case)	4	2	
9-12 score (case)	26	27	
13-15 score (case)	12	12	
First CT bleeding volume (x ± s, ml)	26.40 ± 3.34	25.17 ± 3.68	0.114[b]
Preoperative CT bleeding volume (x ± s, ml)	26.64 ± 3.48	25.41 ± 3.78	0.128[b]
Time of admission after stroke (x ± s, hour)	2.91 ± 1.98	2.64 ± 1.79	0.520[b]
Time from stroke to operation (x ± s, hour)	21.98 ± 4.80	20.37 ± 4.71	0.127[b]
Systolic blood pressure at visit (x ± s, mmHg)	182.64 ± 8.61	181.12 ± 9.34	0.772[b]
Diastolic blood pressure at visit (x ± s, mmHg)	102.19 ± 4.67	101.31 ± 4.83	0.838[b]
Operative duration (x ± s, minute)	36.26 ± 5.21	35.82 ± 5.21	0.706[b]
Catheter accuracy (%)	97.62%	97.56%	0.986[a]

[a]chi-squared value, [b]t value.

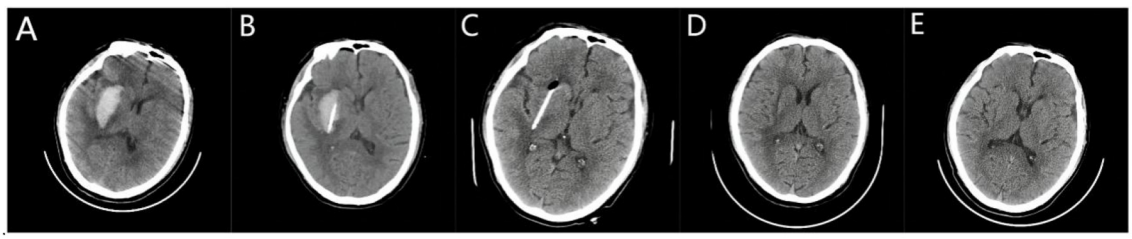


FIGURE 1
Stereotactic catheterization through the long axis of hematoma for basal ganglia hemorrhage. **(A)** A preoperative head Computed Tomography (CT) showed that the bleeding volume was ~29 ml. **(B)** A three-dimensional CT performed 6 h after surgery confirmed the position of the drainage tube along the long axis of the hematoma, with a hematoma volume of ~20 ml. **(C)** Following the injection of urokinase, the hematoma was completely drained by the third day after surgery. The high-density area indicates the drainage tube with a hematoma volume of 0 ml. **(D)** The bleeding site 7 days after surgery was slightly softer. **(E)** On the 20th day post-surgery, the softening lesion at the bleeding site was reduced.

2.2.2. The stereotactic minimally invasive catheter drainage surgery method

Surgery can be completed using a frameless navigation system or a frame-based stereotactic system; in this trial, we used the Leskell G-frame system (Elekta Instrument AB, Box 7593,Kungstensgatan 18, SE-103 93 Stockholm, Sweden). Patients underwent surgery if CT reexamination indicated that the hematoma was stable after 6 h or more. All patients received stereotactic minimally invasive catheter drainage surgery. For patients in the long-axis group, the incision was 2–3 cm above the eyebrow arch on the same side of the hematoma and 2–2.5 cm beside the midline. The planned puncture approach and target point before surgery were through the hematoma (Figures 1A–E). The incision was made 9–11 cm above the eyebrow arch on the same side of the hematoma and 3–3.5 cm beside the midline for patients in the central group. The planned puncture approach and target were in the center of the hematoma before surgery (Figures 2A–E). The first step was to install a square Leksell

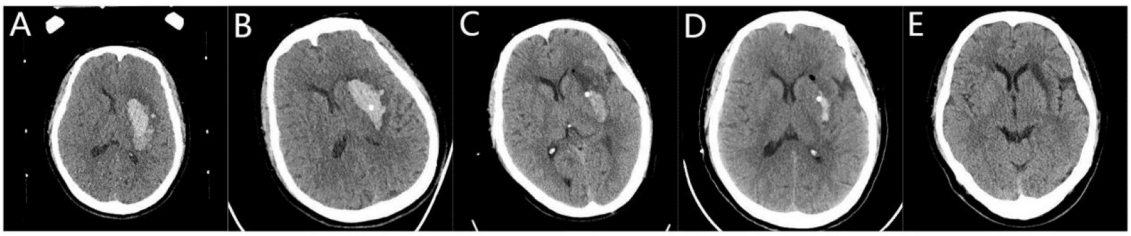


FIGURE 2
Stereotactic central catheterization for basal ganglia hemorrhage. **(A)** A preoperative head Computed Tomography (CT) showed that the volume of bleeding was ~26 ml. **(B)** A three-dimensional CT performed 6 h after surgery showed the drainage tube located in the center of the hematoma with a hematoma volume of ~17 ml. **(C)** Following the injection of urokinase, there was a small amount of residual hematoma on the third day after the operation, with a hematoma volume of 5 ml. **(D)** On the 7th day after surgery, the hematoma volume was 1.2 ml. **(E)** On the 20th day after surgery, the bleeding site softened.

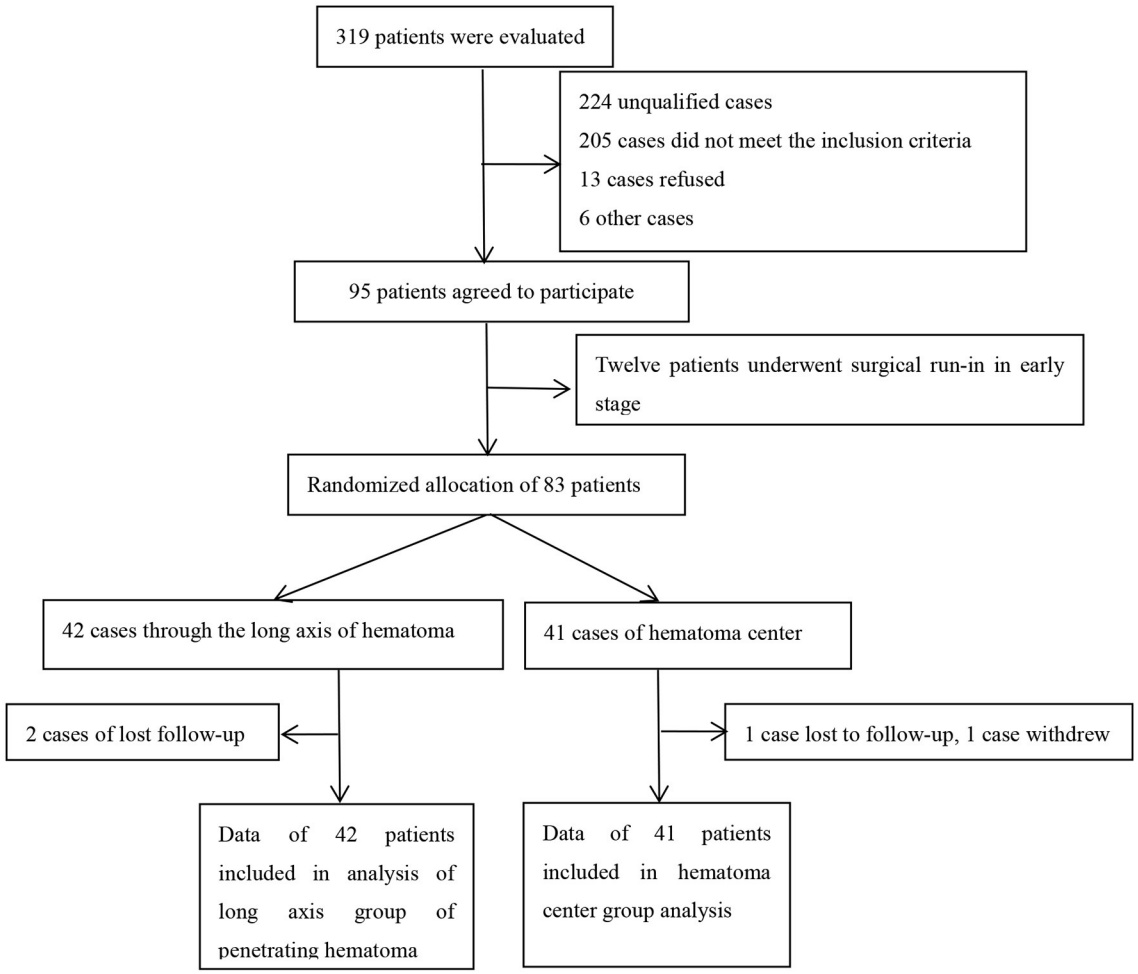


FIGURE 3
Overview of patient recruitment.

headrest on the patient's head under local anesthesia. The second step was to perform 64 rows of Siemens head 3D CT scanning. Third, according to the preoperative surgical plan, we needed to directly measure and calculate the target coordinates (X, Y, and Z space coordinates) using a CT three-dimensional film reading system. Fourth, for patients in the long-axis group, we removed a fixed strut at the surgical side of the forehead; this action was not required for patients in the center group. The Leskell headstand was connected and fixed to a special neurosurgery operating table by an adapter. Next, surgery was performed under local anesthesia and ECG monitoring. The size of the incision was generally 2 cm. After drilling the skull, a 5-mm incision was made in the dura

TABLE 2 Comparison of the hematoma drainage effect between the two groups ($\bar{x} \pm s$).

	Penetrating hematoma long-axis group	Hematoma center group	*T*-value	*p*
Tube setting time (d)	4.29 ± 0.60	4.65 ± 0.53	−3.009	0.003
Total urokinase (ten thousand U)	22.97 ± 4.82	27.92 ± 5.12	−4.536	0.000
Residual amount of extubation hematoma (ml)	1.31 ± 1.22	2.34 ± 1.49	−3.452	0.001
NIHSS score a month after operation	7.81 ± 2.21	8.66 ± 2.02	−1.825	0.072
Hematoma clearance rate (%)	93.71 ± 4.33	90.83 ± 5.80	2.564	0.012

TABLE 3 Comparison of complications between the two groups during treatment (%).

	Penetrating hematoma long-axis group $n = 42$	Hematoma center group $n = 41$	x^2 value	*p*
Intracranial infection (case, %)	0%	9.76%	4.305	0.038
Pulmonary infection (case, %)	19.05%	17.07%	0.055	0.815
Secondary intracranial hemorrhage (case, %)	4.76%	2.44%	0.321	0.571
Urinary system infection (case, %)	11.90%	21.95%	1.493	0.222
Stress ulcer (case, %)	7.14%	12.20%	0.608	0.436
Deep vein thrombosis (case, %)	9.52%	26.83%	4.196	0.041
Anemia (case, %)	19.05%	29.27%	1.185	0.276
Hypoalbuminemia (case, %)	14.29%	34.15%	4.474	0.034
Mortality rate within a month (case, %)	0%	2.44%	1.037	0.309

mater to avoid the excessive outflow of cerebrospinal fluid. The Leskell guide arc was then installed, and the drainage tube was inserted under the guidance of the stereotactic instrument to reach the target point. During surgery, 1 ml of negative pressure was used to draw ∼5 ml of blood; the same volume of normal saline was injected for replacement. When the drainage was smooth, the surgical procedure was completed, and the drainage tube was led out through another subcutaneous tunnel.

2.2.3. The urokinase injection method and extubation index

We performed another three-dimensional CT scan of the head 6 h after surgery to determine the position of the drainage tube, the size of the hematoma, and the extent of bleeding in the puncture tunnel. If the drainage tube position was satisfactory, we fully dissolved 50,000 units of urokinase in 5 ml of normal saline. After surgery, the dissolved urokinase was injected into the drainage tube 1–2 times a day, and the drainage tube was closed for 3 h before natural drainage. According to the residual situation of the hematoma, urokinase was injected multiple times into the hematoma cavity, as required. The CT reexamination showed that the drainage tube cannot effectively drain the hematoma, which was the extubation index. The catheterization time did not exceed 7 days.

2.2.4. Observation index

We compared the general clinical data from the two groups of patients. A range of statistical data was collated, including the time of catheter insertion, the total dose of urokinase, the clearance rate of hematoma before extubation, the amount of residual hematoma, and the NIHSS score 1 month after surgery. We also recorded complications experienced by the two groups of patients during treatment, including intracranial infection, pulmonary infection, urinary system infection, secondary intracranial hemorrhage, lower limb vein thrombosis, stress ulcer, anemia, hypoproteinemia, and mortality within 1 month.

2.2.5. Statistical analysis

The SPSS version 25.0 statistical software (IBM, International Business Machines Corporation, New York, USA) was used for data analysis. Measurement data were expressed as mean ± standard deviation (x ± s). Comparisons between groups of normally distributed data were performed using the independent sample *t*-test and analysis of variance (ANOVA). The Mann–Whitney U-rank sum test was used for the data that were not normally distributed. Numerical data were expressed as the number of cases and as percentages (%), and the data were compared using the chi-square test. A *P*-value of < 0.05 (bilateral) was considered to be statistically significant.

3. Results

3.1. Clinical materials

From June 2019 to March 2022, we recruited 95 patients, including 12 who underwent surgery in the early stage. In this trial, 83 patients with medium-to-small volumes of hemorrhage

in the basal ganglia were included for final analysis (Figure 3). Of these patients, 42 of them were catheterized through the long axis of the hematoma, and 41 were catheterized through the center of the hematoma. Both patient groups were injected with urokinase through the drainage tube after surgery, as shown in Table 1.

3.2. A comparison of the hematoma drainage effect between the two groups

Compared with the central group, patients in the long-axis group had a significantly shorter catheterization time, a lower dose of urokinase, less residual hematoma, and a higher hematoma clearance rate ($P < 0.05$). There was no significant difference between the two groups in terms of NIHSS scores 1 month after surgery ($P > 0.05$) as shown in Table 2.

3.3. A comparison of complications between the two groups during treatment

There was no significant difference between the two groups in terms of pulmonary infection, intracranial hemorrhage, urinary system infection, stress ulcer, anemia, and mortality within 1 month of surgery ($P > 0.05$). Compared with the central hematoma group, the incidence of intracranial infection, deep vein thrombosis, and hypoproteinemia in the long-axis group was significantly lower ($P < 0.05$), as shown in Table 3.

4. Discussion

Hypertensive intracerebral hemorrhage (HICH) accounts for 21–48% of all patients with stroke. The most common type of HICH is basal ganglia hemorrhage (8), which accounts for 50% of patients with cerebral hemorrhage. In addition, patients often experience symptoms such as hemianopsia, hemiplegia, and hemiparesia due to damage to the cystic conduction tract in the basal ganglia region. It is very important to evaluate the neurological function of patients with cerebral hemorrhage in a timely fashion and determine whether surgical treatment is needed. There is no definite conclusion on the effects of surgical treatment for supratentorial intracerebral hemorrhage, although surgery is an option for patients with a large hematoma, with severe neurological dysfunction, or in coma. The surgical methods involve craniotomy and minimally invasive surgery. The mortality rate associated with craniotomy is very high. The surgical trials in intracerebral hemorrhage (STICH) and STICH II trials showed that patients with spontaneous supratentorial intracerebral hemorrhage did not have any overall benefit from early surgery when compared with conservative treatment (9, 10). However, 98% of patients in the STICH study underwent craniotomy; the researchers thus proposed that minimally invasive technology is more conducive for deep brain hematoma. Studies have reported that minimally invasive surgery is better than craniotomy (11–13). Minimally invasive surgical methods involve keyhole craniotomy, neuroendoscopy hematoma removal, and minimally invasive catheter drainage. In the MISTIE II trial, a stereotactic catheter was used for catheter placement and continuous thrombolysis; this method achieved accurate catheter placement. This procedure is highly reproducible and can safely and accurately drain a cerebral hemorrhage; the effects of hematoma drainage are closely associated with the accuracy of catheter placement. Currently, most minimally invasive catheters for intracerebral hemorrhage are placed at the midpoint of the largest hematoma layer in the brain as the puncture sites (14–16). However, few studies have investigated the effects of different catheter positions on hematoma drainage. In this study, we describe the results of our recent trial that examined the effects of different catheter positions for intracerebral hemorrhage.

4.1. The application of stereotactic minimally invasive catheterization technology for medium- and small-volume cerebral hemorrhage

The target error for stereotactic technology was previously determined to be 2.02 mm (17). This type of technology is widely adopted in minimally invasive neurosurgery, such as deep brain electrical stimulation in Parkinson's disease, epileptic electrode implantation, brain tumor biopsy, stereotactic puncture, and the aspiration of cerebral hemorrhage (18, 19). Compared with conservative treatment, the rebleeding rate of minimally invasive stereotactic catheterization in 20–40 ml HICH was significantly lower than that for conservative medical treatment. Furthermore, a hematoma can be cleared quickly, thus reducing compression caused by the hematoma on the brain tissue and the risk of secondary damage; this is conducive to the recovery of a patient's neural function, thus reducing hospital stay (20). In previous studies, when the amount of cerebral hemorrhage was >30 ml, craniotomy or endoscopic surgery was mostly used. Compared with craniotomy, stereotactic catheterization for an intracerebral hemorrhage of more than 30 ml is safe and effective and has fewer complications (21). The clinical effect of this treatment is better than that of traditional craniotomy and can thus avoid secondary cranioplasty. In our research, we found that the hematoma volume was more than 30 ml in some patients and 20–30 ml in others. The preoperative hematoma volume was 26.64 ± 3.48 ml in the long-axis group and 25.41 ± 3.78 ml in the central group. We found a relationship between hematoma volume and the enrollment data. Currently, minimally invasive surgery for intracerebral hemorrhage is regarded as a trend, but there is no specific standard for endoscopic surgery and stereotactic minimally invasive puncture (19). For 40–60 ml of bleeding, we prioritize craniotomy or endoscopic hematoma evacuation. Endoscopic intracerebral hemorrhage clearance has also advanced significantly. Endoscopic surgery can enhance the neurological function of patients with more than 40 ml of intracerebral hemorrhage at 6 months after surgery and can reduce the mortality of patients with a GCS score of 3–8 (22). Endoscopic surgery can quickly remove a hematoma, although the trauma incurred is relatively significant, thus requiring high levels of surgical skill. Moreover, the operation

takes a long period and requires general anesthesia. Stereotactic minimally invasive catheterization is minimally invasive and can be performed under local anesthesia. Furthermore, the surgical time is reduced, and the operation is reproducible; however, the disadvantage of this technique is that a hematoma cannot be quickly removed, and the rate of rebleeding can be high (23). Stereotactic guidance can clear a hematoma along the long axis of the hematoma, combined with endoscopic removal of the intracerebral hemorrhage. Most blood clots can be cleared only once through the endoscopic sheath; this can minimize damage to normal brain tissue (8). Some studies have shown that the disability rate associated with stereotactic catheterization for 20–50 ml superficial and deep hemorrhage is lower than that of small bone window craniotomy and endoscopic surgery (19). Some elderly patients have a strong tolerance to increased intracranial pressure due to the presence of brain atrophy. We have attempted to use stereotactic minimally invasive catheterization in elderly patients with cerebral hemorrhage volumes exceeding 40 ml. Currently, only 10 cases of surgery have been attempted, although the final treatment effect is very good.

4.2. Selection of the best puncture path and target for stereotactic minimally invasive catheterization

In the MISTIE III trial, three methods of catheterization were adopted. The first method was to cut the forehead and insert a catheter along the longitudinal axis of the hematoma. The second method was to cut the parietal–occipital part and place a tube along the longitudinal axis of the hematoma. The third method was to cut the temporal part and place a tube along the transverse axis of the hematoma (3). The highest proportion of patients with hematomas smaller than 15 ml was the highest (79.3%) at the end of tube insertion when using the first method. When the drainage tube is located in the center of the hematoma, theoretically, it can make urokinase contact the hematoma more evenly, thus improving the dissolution effect of the hematoma; this can improve the hematoma clearance rate when the tube is withdrawn (24). In fact, in most cases, we found that when the catheter was placed in the center of the hematoma, although the effect of early hematoma dissolution was very good, there was a residual hematoma at the back when the catheter was removed. In our 41 patients, we found that the hematoma clearance rate was 90.83 ± 5.80%. We analyzed the causes of residual hematoma in the posterior regions. Most patients with intracerebral hemorrhage had their heads raised by 30° during surgery. Due to positional factors and the gravity of the brain tissue itself, the hematoma around and in front of the drainage tube hole can often provide easy contact with urokinase. Most of the hematomas were successfully drained, thus resulting in the drainage tube hole being located at the edge of the posterior residual hematoma. Without further surgery, the drainage tube hole cannot be adjusted to contact the hematoma again; therefore, the urokinase injected through the catheter cannot fully contact the posterior hematoma because of the residue. When inserting the tube through the long axis of the hematoma, the catheter hole is located at the rear of the hematoma, and the urokinase can dissolve the hematoma around the drainage tube hole (25). The direction of hematoma dissolution occurs from back to front. When the current hematoma dissolution and drainage were poor, we rechecked the CT to investigate the relationship between the drainage tube and the hematoma. Because the tube is placed through the long axis of the hematoma, this was performed by withdrawing part of the drainage tube to make the tube hole make full contact with the hematoma again, thus reducing residuals. The clearance rate of hematoma for the 42 patients was 93.71 ± 4.33%. In four cases, the drainage tube was partially withdrawn to achieve a satisfactory drainage effect. According to the MISTIE III trial and other research results, we recommend transfrontal long-axis catheterization for hematomas. This method has a good drainage effect, can reduce the number of urokinase injections, and can reduce the risk of intracranial infection.

4.3. Analysis of residual hematoma volume, patient prognosis, and complications

The survival rate of patients with intracerebral hemorrhage and the recovery of neurological function are related to the location of the hematoma, space-occupying effects, and intracranial pressure; these factors are also related to the long-term neurological dysfunction caused by neurotoxicity or inflammatory brain edema around the hematoma (26, 27). Numerous preclinical and clinical studies have shown that perihematoma edema (PHE) is a quantifiable marker for secondary brain injury after intracerebral hemorrhage (ICH) and is associated with poor prognosis (28). In ∼30% of patients, the volume of PHE 2–3 weeks after ICH was 3 ml larger than that 1 week after ICH; this increase in volume was reported to represent an independent risk factor for poor prognosis (29). Minimally invasive surgery may change the course of PHE. The extent of edema in PHE was associated with hematoma clearance, and a higher percentage of hematoma clearance has been shown to result in a slower increase in PHE (30). In a previous study, 28% of patients with a residual hematoma volume of >15 ml had an Modified Rankin Scale (mRS) of ≤ 3 at 180 days, and 49% of patients with a residual hematoma volume of ≤ 15 ml had an mRS of ≤ 3 at 180 days (31). The increase in PHE at 72 h may have had adverse effects on the neurological recovery of ICH, especially in patients with small-to-medium volume hematomas (32). Increasing the clearance rate of residual hematomas after surgery is conducive to reducing brain injury after ICH (33). Our study showed that there was no significant difference in short-term neurological recovery between the two groups; this may be related to the reduction in a residual hematoma or the short follow-up time of the two groups of patients during extubation. There was a certain difference in the residual amount of hematoma between the two different methods of catheter insertion, although the hematoma was <15 ml in volume when the catheter was removed. Common medical complications after intracerebral hemorrhage include pneumonia (24%), acute renal injury (9%), ventricular inflammation (5%), asymptomatic rebleeding (4%), ischemic stroke (3%), surgical infection (1%), and others (31, 34). In the acute phase of intracerebral hemorrhage, the reduction in hematoma volume is conducive to reducing potential medical complications (35).

Our study also confirmed that patients with a higher hematoma clearance rate had fewer complications in the short term.

4.4. Advancing the accuracy of stereotactic catheterization and reducing surgical-related complications

Because the stereotactic technique was not adopted in the MISTIE III trial, the rate of good catheter placement was 62%, although 6.8% of patients with poor catheter placement needed replacement of the drainage tube. We adopted the stereotactic technique to insert the catheter in 83 cases; proper placement of the drainage tube was achieved in 97.59% of cases. No cases required replacement of the drainage tube; this instance depends on the improvement of the method used to replace the catheter during surgery. To improve the accuracy of stereotactic catheterization, the following points should be considered: (1) avoiding the implantation of soft drainage tubes through the broken suction needle path in the hematoma; (2) selecting a drainage tube that matches the aperture of the guide sub; (3) directly using a soft drainage tube with a hard tube core for puncture; (4), when the drainage tube is located at the target position, the first suction of blood does not exceed 5 ml; and (5) adjusting the position of the Leksell head frame bone nail according to the hematoma location to avoid the influence of artifacts of skull bone nails during CT scanning. The following points should also be considered to reduce surgical-related complications: (1) reducing the number of urokinase injections can reduce the risk of infection; (2) as some patients may experience complete drainage of a hematoma on the second day, it is important to avoid removal of the drainage tube at this time. Removal of the drainage tube too early may increase the risk of bleeding; (3) the retention time of the drainage tube shall not exceed 7 days. Even if there is residual hematoma at this time, the drainage tube should be removed. If the drainage tube is left for too long, it will increase the risk of intracranial infection; and (4) if the costs are not considered, we would recommend the use of alteplase as this drug has a lower risk of bleeding. However, the clinical application of alteplase has proven that it is safe, effective, and controls the amount of urokinase used for each hematoma dissolution (36).

For the surgical treatment of small and medium volumes of ICH in the basal ganglia, patients can undergo stereotactic catheter drainage (37). We found that the placement of the catheter was accurate, and the residual amount of hematoma after drainage was <15 ml. There was no significant difference in short-term neurological function scores between hematoma long-axis catheterization and hematoma central catheterization. However, we recommend inserting a tube through the long axis of the hematoma through the forehead approach, because the hematoma clearance rate is high and the dose of urokinase required is small, thus reducing medical complications. One limitation of this study is that it was a single-center study with a small number of cases and a short follow-up time. Currently, multicenter case data are being collected for further analysis.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Human Ethics Committee of People's Hospital of China Three Gorges University (KY-2022-0040). The patients/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

LJ and ZY prepared Tables 1, 2. All authors made substantial contributions to the conception and design, the acquisition of data, analysis and interpretation of data, drafting, critical revision, and approval of the final version of this manuscript.

Funding

This study was funded by the Hubei Natural Science Foundation Project (Reference: 2022CFC044) and the Science and Technology Research Project of the Hubei Provincial Department of Education (Reference: B2021029).

Acknowledgments

We thank SC for revising the manuscript.

Conflict of interest

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

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990–2013: the GBD 2013 study. *Neuroepidemiology.* (2015) 3:161–76. doi: 10.1159/000441085

2. Guo W, Liu H, Tan Z, Zhang X, Gao J, Zhang L, et al. Comparison of endoscopic evacuation, stereotactic aspiration, and craniotomy for treatment of basal ganglia hemorrhage. *J Neurointerv Surg.* (2020)12:55–61. doi: 10.1136/neurintsurg-2019-014962

3. Hanley DF, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, et al. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. *Lancet.* (2019) 393:1021–32. doi: 10.1016/S0140-6736(19)30195-3

4. Huang X, Jiang L, Chen S, Li G, Pan W, Peng L, et al. Comparison of the curative effect and prognosis of stereotactic drainage and conservative treatment for moderate and small basal ganglia haemorrhage. *BMC Neurol.* (2021) 21:268. doi: 10.1186/s12883-021-02293-7

5. Brouwers HB, Goldstein JN. Therapeutic strategies in acute intracerebral hemorrhage. *Neurotherapeutics.* (2012) 9:87–98. doi: 10.1007/s13311-011-0091-8

6. Hanley DF, Lane K, McBee N, Ziai W, Tuhrim S, Lees KR, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet.* (2017) 389:603–11. doi: 10.1016/S0140-6736(16)32410-2

7. Khan M, Baird GL, Elias R, Rodriguez-Srednicki J, Yaghi S, Yan S, et al. Comparison of intracerebral hemorrhage volume calculation methods and their impact on scoring tools. *J Neuroimaging.* (2017) 27:144–8. doi: 10.1111/jon.12370

8. Dye JA, Dusick JR, Lee DJ, Gonzalez NR, Martin NA. Frontal bur hole through an eyebrow incision for image-guided endoscopic evacuation of spontaneous intracerebral hemorrhage. *J Neurosurg.* (2012) 117:767–73. doi: 10.3171/2012.7.JNS111567

9. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet.* (2005) 365:387–97. doi: 10.1016/S0140-6736(05)70233-6

10. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet.* (2013) 382:397–408. doi: 10.1016/S0140-6736(13)60986-1

11. Xu X, Chen X, Li F, Zheng X, Wang Q, Sun G, et al. Effectiveness of endoscopic surgery for supratentorial hypertensive intracerebral hemorrhage: a comparison with craniotomy. *J Neurosurg J Neurosurg.* (2018) 128:553–9. doi: 10.3171/2016.10.JNS161589

12. Eroglu U, Kahilogullari G, Dogan I, Yakar F, Al-Beyati ESM, Ozgural O, et al. Surgical management of supratentorial intracerebral hemorrhages: endoscopic versus open surgery. *World Neurosurg.* (2018) 114:e60–5. doi: 10.1016/j.wneu.2018.02.056

13. Zhou X, Chen J, Li Q, Ren G, Yao G, Liu M, et al. Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. *Stroke.* (2012) 43:2923–30. doi: 10.1161/STROKEAHA.112.667535

14. Hanley DF, Thompson RE, Muschelli J, Rosenblum M, McBee N, Lane K, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *Lancet Neurol.* (2016) 15:1228–37. doi: 10.1016/S1474-4422(16)30234-4

15. Wu J, Zhang S. Analysis of the therapeutic effect and prognostic factors of 126 patients with hypertensive cerebral hemorrhage treated by soft-channel minimally invasive puncture and drainage. *Front Surg.* (2022) 9:885580. doi: 10.3389/fsurg.2022.885580

16. Zhou H, Zhang Y, Liu L, Huang Y, Tang Y, Su J, et al. Minimally invasive stereotactic puncture and thrombolysis therapy improves long-term outcome after acute intracerebral hemorrhage. *J Neurol.* (2011) 258:661–9. doi: 10.1007/s00415-011-5902-7

17. Zhang D, Cui X, Zheng J, Zhang S, Wang M, Lu W, et al. Neurosurgical robot-assistant stereoelectroencephalography system: operability and accuracy. *Brain Behav.* (2021) 11:e2347. doi: 10.1002/brb3.2347

18. Habets JGV, Heijmans M, Kuijf ML, Janssen MLF, Temel Y, Kubben PL. An update on adaptive deep brain stimulation in Parkinson's disease. *Mov Disord.* (2018) 33:1834–43. doi: 10.1002/mds.115

19. Chi F-L, Lang T-C, Sun S-J, Tang X-J, Xu S-Y, Zheng H-B, et al. Relationship between different surgical methods, hemorrhage position, hemorrhage volume, surgical timing, and treatment outcome of hypertensive intracerebral hemorrhage. *World J Emerg Med.* (2014) 5:203–8. doi: 10.5847/wjem.j.issn.1920-8642.2014.03.008

20. Zhang X, Zhou S, Zhang Q, Fu X, Wu Y, Liu J, et al. Stereotactic aspiration for hypertensive intracerebral haemorrhage in a Chinese population: a retrospective cohort study. *Stroke Vasc Neurol.* (2019) 4:14–21. doi: 10.1136/svn-2018-000200

21. Shi J, Cai Z, Han W, Dong B, Mao Y, Cao J, et al. Stereotactic catheter drainage versus conventional craniotomy for severe spontaneous intracerebral hemorrhage in the basal ganglia. *Cell Transplant.* (2019) 28:1025–32. doi: 10.1177/0963689719852302

22. Du Y, Gao Y, Liu HX, Zheng LL, Tan ZJ, Guo H, et al. Long-term outcome of stereotactic aspiration, endoscopic evacuation, and open craniotomy for the treatment of spontaneous basal ganglia hemorrhage: a propensity score study of 703 cases. *Ann Transl Med.* (2021) 9:1289. doi: 10.21037/atm-21-1612

23. Fu C, Wang N, Chen B, Wang P, Chen H, Liu W, et al. Surgical management of moderate basal ganglia intracerebral hemorrhage: comparison of safety and efficacy of endoscopic surgery, minimally invasive puncture and drainage, and craniotomy. *World Neurosurg.* (2019) 122:e995–e1001. doi: 10.1016/j.wneu.2018.10.192

24. Malinova V, Stockhammer F, Atangana EN, Mielke D, Rohde V. Catheter placement for lysis of spontaneous intracerebral hematomas: is a navigated stylet better than pointer-guided frameless stereotaxy for intrahematomal catheter positioning? *Transl Stroke Res.* (2014) 5:407–14. doi: 10.1007/s12975-014-0326-1

25. Malinova V, Schlegel A, Rohde V, Mielke D. Catheter placement for lysis of spontaneous intracerebral hematomas: does a catheter position in the core of the hematoma allow more effective and faster hematoma lysis? *Neurosurg Rev.* (2017) 40:397–402. doi: 10.1007/s10143-016-0792-x

26. Zheng F, Zhou J, Wang C, Hu W, Krischek B. Reader response: location-specific risk factors for intracerebral hemorrhage: systematic review and meta-analysis. *Neurology.* (2021) 96:1010–1. doi: 10.1212/WNL.0000000000012001

27. Gross BA, Jankowitz BT, Friedlander RM. Cerebral intraparenchymal hemorrhage: a review. *JAMA.* (2019) 321:1295–303. doi: 10.1001/jama.2019.2413

28. Chen Y, Chen S, Chang J, Wei J, Feng M, Wang R. Perihematomal edema after intracerebral hemorrhage: an update on pathogenesis, risk factors, and therapeutic advances. *Front Immunol.* (2021) 12:740632. doi: 10.3389/fimmu.2021.740632

29. Peng W-J, Li Q, Tang J-H, Reis C, Araujo C, Feng R, et al. The risk factors and prognosis of delayed perihematomal edema in patients with spontaneous intracerebral hemorrhage. *CNS Neurosci Ther.* (2019) 2510:1189–94. doi: 10.1111/cns.13219

30. Horowitz ME, Ali M, Chartrain AG, Allen OS, Scaggiante J, Glassberg B, et al. Definition and time course of pericavity edema after minimally invasive endoscopic intracerebral hemorrhage evacuation. *J Neurointerv Surg.* (2022) 14:149–54. doi: 10.1136/neurintsurg-2020-017077

31. Kellner CP, Song R, Pan J, et al. Long-term functional outcome following minimally invasive endoscopic intracerebral hemorrhage evacuation. *J Neurointerv Surg.* (2020) 12:489–94. doi: 10.1136/neurintsurg-2019-015528

32. Murthy SB, Moradiya Y, Dawson J, Lees KR, Hanley DF, Ziai WC, et al. Perihematomal edema and functional outcomes in intracerebral hemorrhage: influence of hematoma volume and location. *Stroke.* (2015) 46:3088–92. doi: 10.1161/STROKEAHA.115.010054

33. Jing C, Bian L, Wang M, Keep RF Xi G, Hua Y. Enhancement of hematoma clearance with CD47 blocking antibody in experimental intracerebral hemorrhage. *Stroke.* (2019) 50:1539–47. doi: 10.1161/STROKEAHA.118.024578

34. Gong S, Lin C, Zhang D, Kong X, Chen J, Wang C, et al. Effects of intensive blood pressure reduction on acute intracerebral hemorrhage: a systematic review and meta-analysis. *Sci Rep.* (2017) 7:10694. doi: 10.1038/s41598-017-10892-z

35. LoPresti MA, Bruce SS, Camacho E, Kunchala S, Dubois BG, Bruce E, et al. Hematoma volume as the major determinant of outcomes after intracerebral hemorrhage. *J Neurol Sci.* (2014) 345:3–7. doi: 10.1016/j.jns.2014.06.057

36. rd JCH, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2015) 46:2032–60. doi: 10.1161/STR.0000000000000069

37. Lu TS, An CL, Guan JY. Clinical experience of individual surgical therapy in hypertensive basal ganglia hemorrhage. *J Neurosurg Sci.* (2018) 62:140–5. doi: 10.23736/S0390-5616.16.03383-X

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 19 May 2023
DOI 10.3389/fneur.2023.1168333

OPEN ACCESS

EDITED BY
Haiqing Zheng,
Third Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Gerasimos N. Konstantinou,
University of Toronto, Canada
Wen-Jun Tu,
Peking Union Medical College, China

*CORRESPONDENCE
Song Jin
✉ 1049147000@qq.com
Di Zhang
✉ erinzd53@126.com
Tianyu Zhao
✉ 549271356@qq.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 17 February 2023
ACCEPTED 20 April 2023
PUBLISHED 19 May 2023

CITATION
Pan J, Li H, Wang Y, Lu L, Wang Y, Zhao T, Zhang D and Jin S (2023) Effects of low-frequency rTMS combined with antidepressants on depression in patients with post-stroke depression: a systematic review and meta-analysis. *Front. Neurol.* 14:1168333. doi: 10.3389/fneur.2023.1168333

Effects of low-frequency rTMS combined with antidepressants on depression in patients with post-stroke depression: a systematic review and meta-analysis

Juanhong Pan [1†], Hongpeng Li[2†], Yongshen Wang[1], Li Lu[2], Ying Wang[2], Tianyu Zhao[3*], Di Zhang [3*] and Song Jin [3*]

[1]School of Health Preservation and Rehabilitation, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China, [2]School of Medical and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China, [3]Rehabilitation Department, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China

Objective: To evaluate the effect of low-frequency (≤1 Hz) repetitive transcranial magnetic stimulation (low-frequency rTMS) combined with antidepressants on depression and the levels of inflammatory factors IL-6 and TNF-α in patients with post-stroke depression (PSD).

Design: PubMed, Embase, Web of Science, Cochrane Library (CBM), China National Knowledge Infrastructure, Technology Periodical Database, and Wanfang Database were searched until October 2022 for randomized controlled trials.

Participants: Patients with post-stroke depression (PSD) participated in the study.

Results: A total of 16 randomized controlled trials (RCTs) involving 1,463 patients with PSD were included. According to the Physiotherapy Evidence Database (PEDro) quality assessment, three studies received high quality (eight scores) and 13 RCTs received moderate quality (six scores) results. The meta-analysis showed that low-rTMS combined with an antidepressant significantly reduced the Hamilton Depression Scale (HAMD) score and the National Institutes of Health Stroke Scale (NIHSS) score, reduced IL-6 and TNF-α levels, and improved the MMSE score in PSD compared to an antidepressant alone.

Conclusion: The results of this meta-analysis evidenced the efficacy and safety of low-rTMS combined with antidepressants in the treatment of depression in PSD patients. The combined therapy could reduce The depression state and the levels of IL-6 and TNF-α, and enhance the cognitive function of patients. In addition, low-rTMS had fewer adverse effects, proving safety. However, there are shortcomings, such as a lack of long-term follow-up, different intervention sites of low-rTMS, and different intervention frequencies (0.5 or 1 Hz). Thus, in the future, RCTs with a larger sample size and longer-term observation are required to verify the efectiveness of low-rTMS combined therapy on PSD. Meantime, a new meta-analysis could be analysized, which intervention sites and frequency are more effective in treating PSD.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42022376845.

KEYWORDS

low-rTMS, antidepressants, PSD, depressive state, IL-6 and TNF-α levels, systematic review, meta-analysis

Introduction

According to current reports, stroke is the second leading cause of death and the third leading cause of disability globally (1). The estimated prevalence, incidence, and mortality rate of stroke in China in 2020 were 2.6%, 505.2 per 100,000 persons per year, and 343.4 per 100,000 persons per year, respectively (2). Post-stroke depression (PSD) is one of the common complications after stroke. The incidence of PSD in China is at a high level, ranging from 20 to 70% (3–5), including 33% mild depression, 20% moderate depression, and 4% severe depression (6), and all-cause mortality in PSD patients increased by 59% (7). The main clinical manifestations of PSD are the experience of loss of interest, depression, sleep disorders, and anhedonia after stroke, which could accompany physical discomforts, such as pain and fatigue (8, 9). These not only lead to the aggravation of physical symptoms of stroke patients but also increase the burden on patients and their families, negatively impact their rehabilitation, and seriously reduce their quality of life.

The pathogenesis of PSD needs to be clarified, mainly including neurobiological mechanisms and social-psychological mechanisms. In studies of neurobiological mechanisms, some scholars have shown that the level of BDNF correlated with the incidence of PSD (10). At the same time, it is moderately positively correlated with the inflammatory factor tumor necrosis factor-α (TNF-α) in serum and highly positively correlated with the level of interleukin IL-6 (11).

There are two types of clinical treatment methods for PSD: drug and non-drug. Drug therapy is the primary treatment method, including selective serotonin reuptake inhibitors (SSRIs), SNRIs (serotonin-norepinephrine reuptake inhibitors), Na SSAs (non-noradrenergic and specific serotonergic antidepressants), and TCA (tricyclic antidepressant). However, the drug treatment has many adverse reactions, such as nausea, constipation, dizziness, insomnia, arrhythmia (12, 13), and even non-response to drugs (14). Therefore, we must find a better therapy to achieve a better therapeutic effect while reducing adverse reactions.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain neuro-modulation treatment method, can stimulate specific brain parts with specific frequencies to regulate the degree of nerve excitation and cortical function. It is the only brain stimulation treatment approved by the US Food and Drug Administration (FDA) as a non-invasive treatment for depression (15). In 2022, "Shanghai Expert Consensus on the Clinical Application and Operation Specification of Repetitive Transcranial Magnetic Stimulation" (16) also pointed out that rTMS were effective and safe in treating stroke. Many clinical studies have shown that rTMS combined with other therapies may be more effective than simple drug treatment (17, 18) or non-drug treatment (19, 20) in treating PSD.

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; PSD, post-stroke depression; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; Na SSAs, noradrenergic and specific serotonergic antidepressants; TCA, tricyclic antidepressant; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; TES, transcranial electrical stimulation.

Currently, many clinical studies were conducted on low-frequency rTMS combined with antidepressant therapy in treating PSD, but only a few systematic reviews exist (21, 22). Among them, Liang et al. (21) analyzed rTMS and transcranial electrical stimulation (TES) as non-invasive stimulation. However, only six studies analyzed low-rTMS combined antidepressants; the latest was only in 2018. Liang et al. (22) conducted a previous meta-analysis in 2018. Many of new literature has been published since 2018 (23–27). Some studies by some scholars have also shown that the appearance of PSD is related to the increase in IL-6 and TNF-α levels of the inflammatory factors IL-6 and TNF-α levels (28). However, these two relevant meta-analyses did not analyze the outcome indicators.

This meta-analysis aimed to update the efficacy and safety of low-rTMS (≤1 HZ) combined with antidepressant therapy in the treatment of PSD and to analyze the results of IL-6 and TNF-αlevels to provide a more reliable basis for the development of subsequent clinical research.

Materials and methods

Search strategy

Two investigators (LL and JHP) conducted the study according to the search strategy for randomized controlled trials (RCTs) developed by the Cochrane Collaboration. We searched for seven major databases, PubMed, Embase, Web of Science, Cochrane Library (CBM), China's National Knowledge Infrastructure (CNKI), Technology Periodical Database (VIP), and Wanfang Database. The search time was from establishing the database to 10 October 2022. Chinese search keywords included "#1 stroke/ cerebrovascular accident/ cerebral hemorrhage/ cerebral ischemia/ cerebral thrombosis/ cerebral hemorrhage/ hemiplegia"; #2 "transcranial magnetic stimulation/ magnetic stimulation/ repetitive transcranial magnetic stimulation/ TMS/ rTMS"; #3 "depression/ depressive state." English search was conducted using subject terms and free words (Figure 1), including "stroke," "transcranial Magnetic Stimulation," and "depression." The language was limited to Chinese and English, and the study type was only required to be a randomized controlled trial (RCT).

Inclusion criteria

After a review of the literature, we determined the eligibility criteria. This review uses the PICOS framework (population, intervention and research, comparison, and conclusion).

(1) People: The patients conforming to the Fourth National Cerebrovascular Disease Conference set criteria for diagnosing cerebral apoplexy and the International Classification of Diseases, 10th edition (ICD-10). These criteria regardless of gender differences, age, country, time, and race. (2) Intervention: Low-frequency repetitive transcranial magnetic stimulation (≤1 Hz) combined with antidepressants (such as duloxetine, mirtazapine,

#1 "Stroke"[MeSH Terms]
#2 ((((((((((((((((((((((((Strokes)OR(Cerebrovascular Accident))OR(Cerebrovascular Accidents))OR(CVA(Cerebrovascular Accident)))
OR(CVAs (CerebrovascularAccident)))OR(CerebrovascularApoplexy)) OR (Apoplexy, Cerebrovascular)) OR (Vascular Accident, Brain))
OR(Brain Vascular Accident))OR(Brain Vascular Accidents))OR(Vascular Accidents, Brain))OR (Cerebrovascular Stroke))
OR(CerebrovascularStrokes))OR(Stroke,Cerebrovascular))OR(Strokes, Cerebrovascular))OR(Apoplexy))OR(Cerebral Stroke))
OR(Cerebral Strokes))OR(Stroke,Cerebral))OR(Strokes,Cerebral))OR(Stroke, Acute))OR(Acute Stroke))OR(Acute Strokes))
OR (Strokes, Acute)) OR (Cerebrovascular Accident, Acute)) OR (Acute Cerebrovascular Accident))OR(AcuteCerebrovascularAccidents))
OR(Cerebrovascular Accidents, Acute)
#3 #1 OR #2
#4 "Transcranial Magnetic Stimulation"[MeSH Terms]
#5(((((((MagneticStimulation,Transcranial)OR(MagneticStimulation, Transcranial))OR(Stimulation, Transcranial Magnetic))
OR (Stimulations, Transcranial Magnetic))OR(Transcranial Magnetic Stimulations))OR(TranscranialMagneticStimulation,SinglePulse)
OR(Transcranial Magnetic Stimulation, Paired Pulse))OR(Transcranial Magnetic Stimulation, Repetitive)
#6 #4 OR #5
#7 "Depression"[MeSH Terms]
#8 (((((Depressive Symptoms)OR(Depressive Symptom))OR(Symptom, Depressive))OR(Symptoms, Depressive))
OR(EmotionalDepression))OR (Depression, Emotional)
#9 #7 OR #8
#10 #3 AND #6 AND #9

FIGURE 1
PubMed search history.

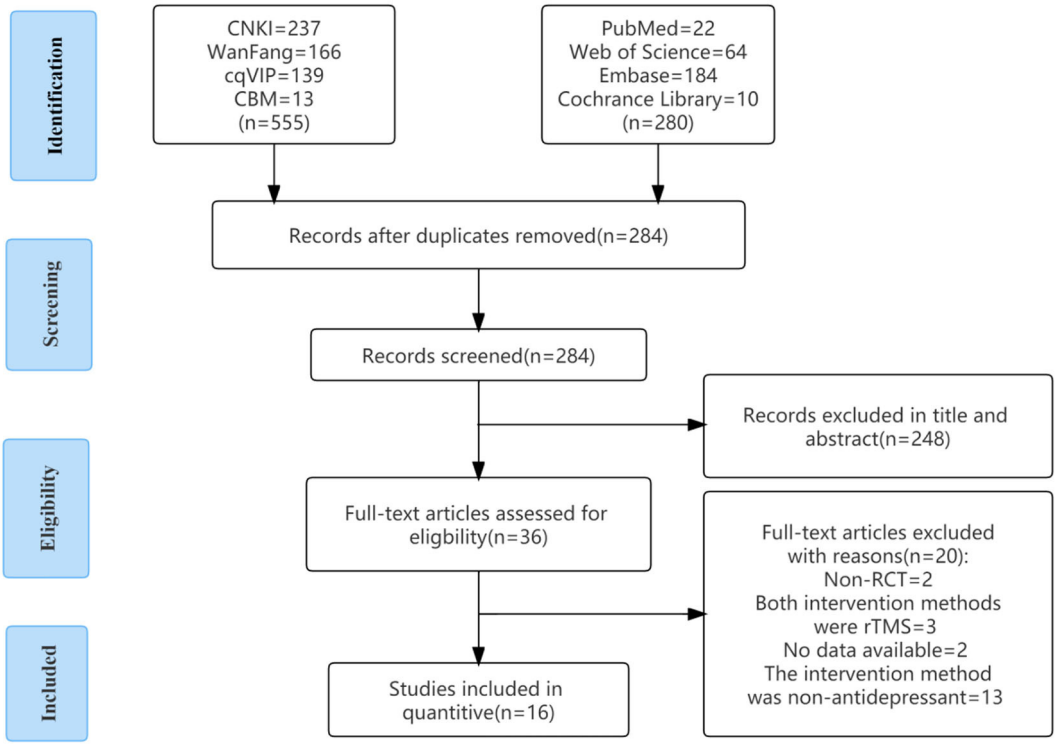


FIGURE 2
Flow chart of article selection. CBM, China Biology Medicine; CNKI, China National Knowledge Infrastructure; RCT, randomized controlled trial; VIP, Technology Periodical Database.

and fluoxetine) administered to patients, and both groups given essential treatment (such as nerve nutrition and vasodilatation) and rehabilitation training (passive movement, muscle strength training, and activities of daily living training). (3) Comparison:

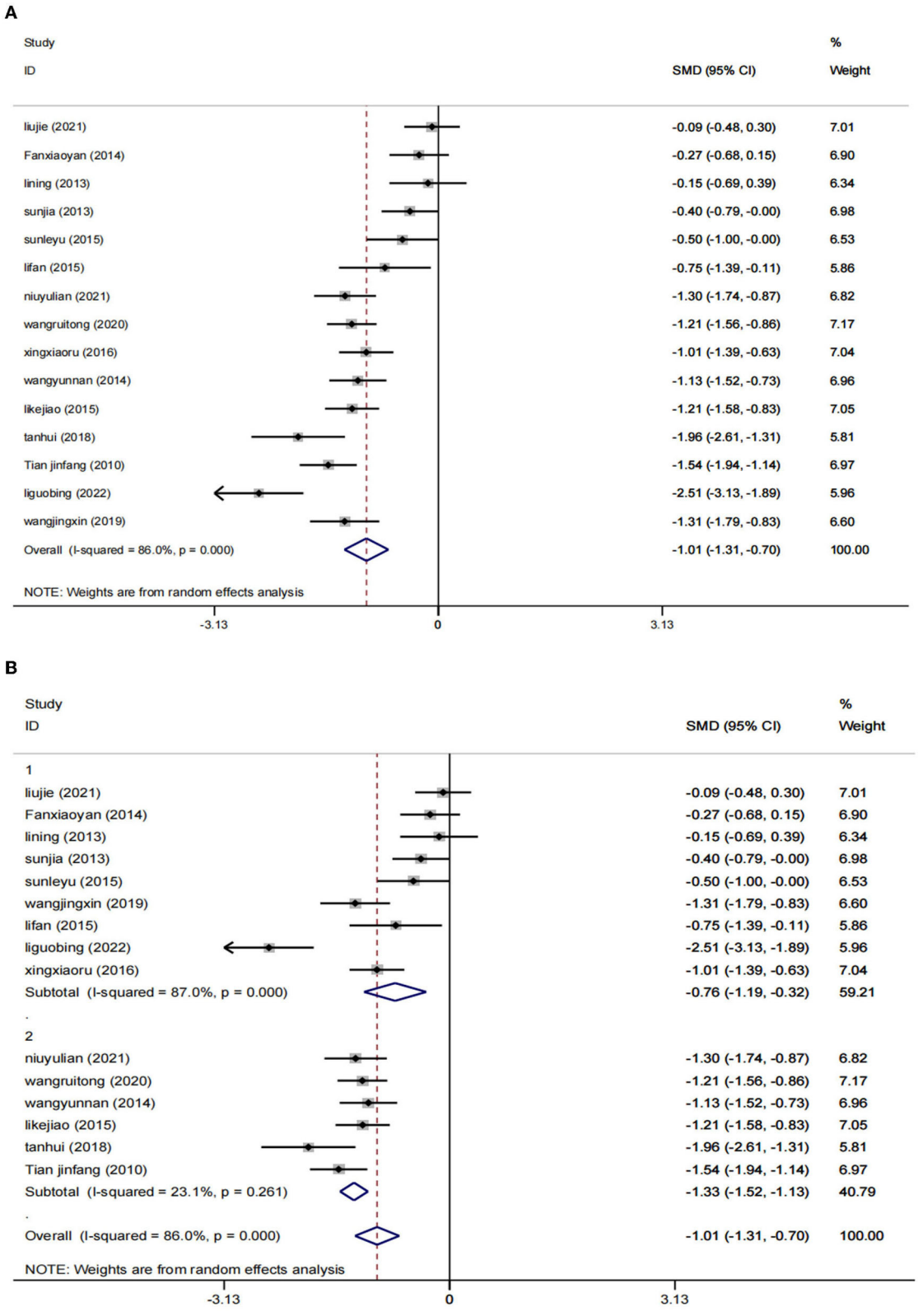


FIGURE 3
Results of HAMD score. **(A)** All studies. **(B)** After subgroup analysis (1: ≤4 weeks; 2: ≥8 weeks).

Antidepressants as a control intervention. (4) Outcome: At least one outcome index, namely, Hamilton Depression Scale (HAMD), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), National Institutes of Health Stroke Scale (NIHSS), and overall efficacy. (5) Study: Randomized controlled trial (RCT) published in English or Chinese.

TABLE 1 Characteristics of included studies.

Study	Patients	Treatment group						Control group					Times	Outcomes	Positive/ negative
		Age (year)	Sample size	Intervention	Dose	Parts	Frequency	Age (year)	Sample size	Intervention	Dose	Frequency			
Leyu and Lijun (29)	PSD	57.7 ± 4.3	32	rTMS + SSRI (fluoxetine)	0.5 Hz, 60% MT, 30 pulses/sequence, 1 sequence/day	Bilateral frontal lobe	1/day	58.3 ± 4.3	32	SSRI (fluoxetine)	20 mg/day	1/day	10 days	A + F	+
Guobing (26)	PSD	60.57 ± 5.38	36	rTMS + fluoxetine	0.5 Hz, 60% MT, 2.0 T	Bilateral frontal lobe	1/day	60.49 ± 5.31	36	fluoxetine	20 mg/day	1/day	4 weeks	A	+
Tian and Jia (30)	PSD	56.3 ± 7.1	63	rTMS + fluoxetine	0.5 Hz, 60% MT, 30 pulses/sequence, 1 sequence/day	Bilateral frontal lobe	1/day	56.0 ± 7.1	63	fluoxetine	20 mg/day	1/day	12 weeks	A + E	+
Xiaoyan (31)	PSD	61.43 ± 8.74	45	rTMS + duloxetine	1 Hz, 100% MT, 30 pulses/sequence, 10 sequence/day	Bilateral frontal lobe	1/day	64.78 ± 7.23	45	Duloxetine	60 mg/day	1/day	4 weeks	A + F	+
Jia et al. (32)	PSD	64.62 ± 11.45	50	rTMS + Flupentixol, melitracen tablets	1 Hz, 90% MT, 30 pulses/sequence, 1 sequence/day	Bilateral frontal lobe	1/day	66.50 ± 11.09	50	Flupentixol, melitracen tablets	10.5 mg/day	1/day	2 weeks	A	+
Jie (23)	PSD	57.66 ± 3.41	51	rTMS + fluoxetine	0.5 Hz, 80% MT, 30 pulses/sequence, 1 sequence/day	Right frontal lobe	1/day	58.27 ± 3.53	51	Fluoxetine	20 mg/day	1/day	4 weeks	A	+
Li et al. (33)	PSD	64.8 ± 5.4	26	rTMS + mirtazapine	1 Hz, 90% MT	Right frontal lobe	1/day	65.2 ± 4.8	27	Mirtazapine	15 mg/day−30 mg/day	1/day	4 weeks	A + D + F	+
Fan (34)	PSD	58.65 ± 6.01	20	rTMS + fluoxetine	1 Hz, 80% MT 800 pulses/day	Right frontal lobe	1/day	56.70 ± 5.95	20	Fluoxetine	20 mg/day	1/day	4 weeks	A + D	+
Niu et al. (24)	PSD	62.4 ± 4.3	50	rTMS + Paroxetine hydrochloride tablets	1 Hz, 90% MT, 1,500 pulses/day	Right frontal lobe	1/day	61.5 ± 4.1	50	Paroxetine hydrochloride tablets	20 mg−40 mg/day	1/day	8 weeks	A + B + C + D	+
Wang et al. (25)	PSD	68.52 ± 5.71	76	rTMS + paroxetine hydrochloride tablets	1 Hz, 800 pluses/day	Right frontal lobe	1/day, 5 days/week	68.39 ± 5.02	76	Paroxetine hydrochloride tablets	20 mg−40 mg/day	1/day	8 weeks	A + B + C + F	+
Tan et al. (35)	PSD	59.2 ± 4.2	26	rTMS + Escitalopram	1 Hz, 80% MT	Right frontal lobe	1/day, 5 days/week	57.4 ± 3.9	26	Escitalopram	10 mg/day−20 mg/day	1/day	6 weeks	A	+
Yunnan et at. (36)	PSD	55.4 ± 9.5	56	rTMS + fluoxetine	0.5 Hz, 30/sequence, 1 sequence/day	Left frontal lobe	1/day, 5 days/week	55.4 ± 9.5	56	fluoxetine	20 mg/day	1/day	8 weeks	A + E	+
Wang et al. (27)	PSD	64.98 ± 4.86	40	rTMS + Escitalopram	1 Hz, 90% MT, 50 pulses/sequence	Left frontal lobe	1/day, 5 days/week	65.27 ± 4.71	40	Escitalopram	5 mg/day−20 mg/day	1/day	4 weeks	A + B + C + F	+
Xiaoru et al. (37)	PSD	55.6 ± 5.8	60	rTMS + fluoxetine	1 Hz, 80% MT, 50 pulses/sequence, 30 sequences/day	Left frontal lobe	1/day, 5 days/week	55.8 ± 5.5	60	fluoxetine	20 mg/day	1/day	8 weeks	A + E + F	+
Kejiao (38)	PSD	54.77 ± 9.80	64	rTMS + fluoxetine	1 Hz, 80% MT, 50 pulses/sequence, 30 sequences/day	Left frontal lobe	1/day, 5 days/week	55.36 ± 10.90	64	fluoxetine	20 mg/day	1/day	8 weeks	A + E	+
Liu et al. (2)	PSD	55.61 ± 6.84	35	rTMS + paroxetine hydrochloride tablets	1 Hz, 70% MT, 30 s/sequence, 1 sequences/day	bilateral dorolateral	1/day, 5 days/week	50.20 ± 6.28	35	Paxil hydrochloride tablet	20 mg/day	1/day	8 weeks	B + C	+

rTMS, repeated transcranial magnetic stimulation; A, HAMD score; B, IL-6 level; C, TNF-α level; D, NIHSS score; E, MMSE score; F, effective rate.

10.3389/fneur.2023.1168333

TABLE 2 Evaluation of the quality of the included documents through PEDro.

Study	1	2	3	4	5	6	7	8	9	10	11	Total score	Level
Li et al. (33)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Jia et al. (32)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Fan (31)	√	√	×	√	√	√	×	√	√	√	√	8	High
Yunnan et al. (36)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Li (34)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Kejiao (38)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Leyu and Liju (29)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Xiaoru et al. (37)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Tan et al. (35)	√	√	√	√	√	×	×	√	√	√	√	8	High
Wang et al. (27)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Wang et al. (25)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Jie (23)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Niu and Wu (24)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Guobing (26)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Tian and Jia (30)	√	√	×	√	×	×	×	√	√	√	√	6	Medium
Liu et al. (2)	√	√	√	√	√	×	×	√	√	√	√	8	High

1 = inclusion exclusion criteria; 2 = randomized group; 3 = allocation concealment; 4 = similar baseline; 5 = subject blinding; 6 = therapist blinding; 7 = assessor blinding; 8 = more than 85% of patient measures; 9 = intention to treat; 10 = between-group analysis; 11 = at least one point measure (√: yes, no risk; ×: no, risky).

Data extraction and management

Two researchers (JHP and HPL) independently searched and browsed seven databases according to the search strategy, imported the obtained literature into the Endnote X9 literature manager, selected the studies, and collected the data independently according to the inclusion and exclusion criteria. The extracted content included general information (name of the author, year of publication, and age of the participants) and study characteristics (experimental group and control intervention method, sample size, stimulation site, stimulation frequency, and duration). Any disagreements were negotiated and discussed with a third investigator (YSW) and finally reached a consensus.

Quality assessment

The Physiotherapy Evidence Database (PEDro) was used to assess the quality of the literature. The PEDro scale uses 11 criteria, each rated as "yes" or "no," and one point is awarded for each response. The first item is not included in the PEDro scoring, and the total score is 10 points. The total PEDro score of ≥7 points is of high quality, 5–6 points are of moderate quality, and ≤4 points are of low quality (39). The scores were given independently by two researchers (JHP and YW); if the results were inconsistent, they discussed them with a third researcher (YSW).

The two reviewers (LL and YW) also completed the risk of bias. The evaluation was carried out according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.3. Items included the following: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other bias. The quality of the included studies was classified as low/unclear/high risk of bias (low risk of bias was "yes," high risk of bias was "no," otherwise was "unclear").

Statistical analysis

We used StataMP 17. for meta-analysis. Weighted mean difference (WMD) was used for continuous variables, while odd ratio (OR) was used as the effective statistics for dichotomous variables, and 95% confidence intervals (95% CI) were calculated for all data. The heterogeneity of the treatment effect was tested by calculating the I^2 index. When $p > 0.05$ or $I^2 < 50\%$, it was considered low heterogeneity, and the fixed effect model was used for meta-analysis. When $p < 0.05$ or $I^2 > 50\%$ was considered as high heterogeneity, meta-analysis was performed using a random-effects model, and sensitivity analysis was performed to identify the source of heterogeneity. Egger's test analyzed publication bias.

Results

Selection of the results

As of October 2022, we retrieved 835 pieces of literature according to the search strategy and excluded 551 duplicate literature. After reading the title and abstract, 248 articles were

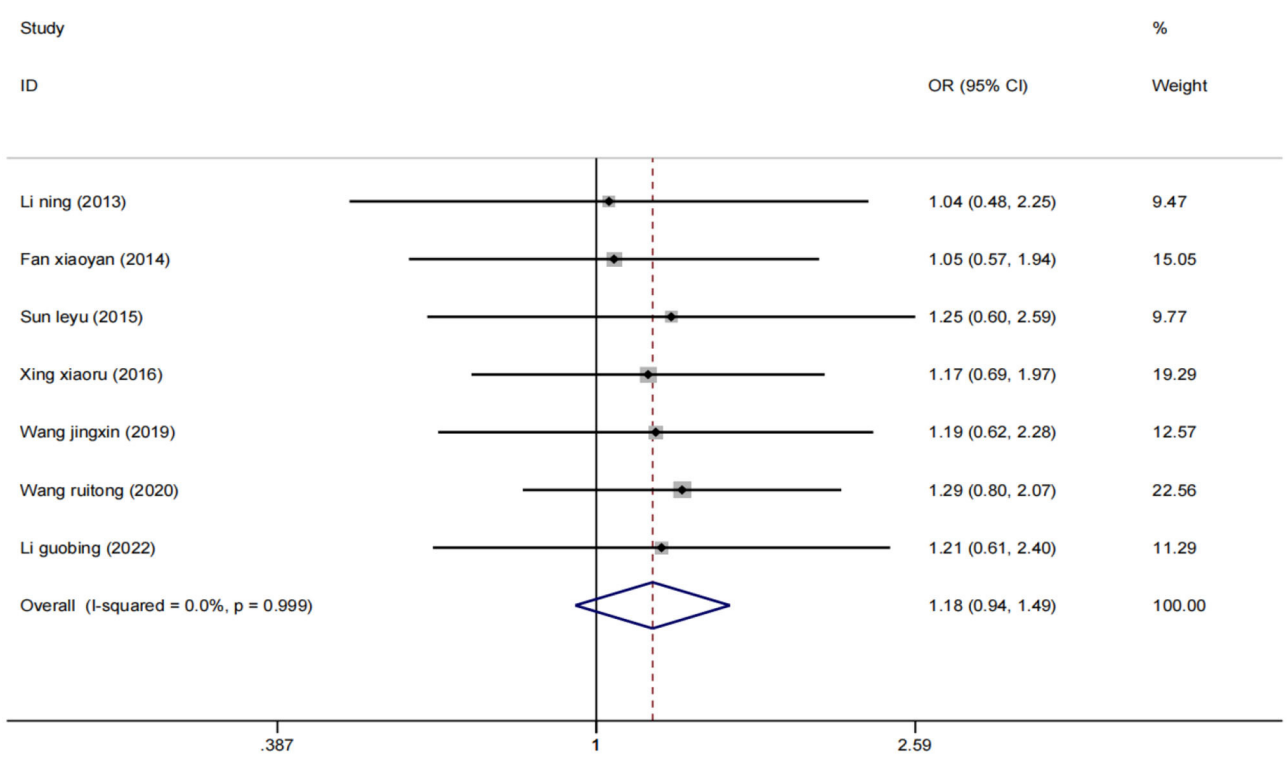


FIGURE 4
Forest plot of total effective rate.

excluded. After reading the complete text, there were two randomized controlled trials, three studies with rTMS, two with no data extraction, and 13 with non-antidepressants. A total of 16 articles were included. The detailed screening procedure is shown in Figure 2.

Study characteristics

The 16 (2, 23–27, 29–38) included articles were all randomized controlled trials on the effect of low-rTMS combined with antidepressants on PSD patients. A total of 1463 patients with PSD. Age was 18 years and older, a frequency of 5–7 days/week, and a course of treatment of 10 days to 12 weeks. The intervention group used rTMS combined with an antidepressant, and the control group's method was an antidepressant. The primary outcomes included the HAMD score and the overall response rate. The secondary outcomes included IL-6, TNF-α, NIHSS score, and MMSE score. Table 1 shows the detailed characteristics. There were no significant differences in the baseline data between the two groups.

Quality assessment

We evaluated the quality of the included studies according to the PEDro quality assessment scale (Table 2), and most of the included studies had methodological deficiencies in the blinding of subjects, therapists, and assessors. Three studies scored as high quality (eight scores), and 13 were scored as high quality (six scores).

Meta-analysis results

Primary outcomes

Result of the HAMD score

A total of 15 RCTs (23–27, 29–38), including 1,393 patients, reported HAMD scores. The HAMD scores of 15 studies were analyzed, showing statistical heterogeneity among the studies (I^2 = 86.0%, p = 0.000). The random effect model was used for meta-analysis. The results showed that the treatment effect of the intervention group was better than that of the control group [SMD = −1.01, 95% CI (−1.31, −0.70); Figure 3A], which could prove that low-frequency rTMS combined with antidepressants had a positive effect on the improvement of depression in PSD patients.

The studies were stratified according to the intervention period of ≥8 weeks (six RCTs) or ≤4 weeks (nine RCTs). The results showed that a total of 9 RCTs (23, 26, 27, 29, 31–34, 37) were included in the subgroup of the intervention period ≤4 weeks, including 721 patients. Compared to the control group [SMD = −0.76, 95% CI (−1.19, −0.32), I^2 = 87%, p = 0.001 < 0.05], the combination of low-frequency rTMS and antidepressants was more effective in improving the symptoms of patients with PSD. In the subgroup of the intervention period of ≥8 weeks, six RCTs (24, 25, 30, 35, 36, 38) were included, totaling 672 patients. The

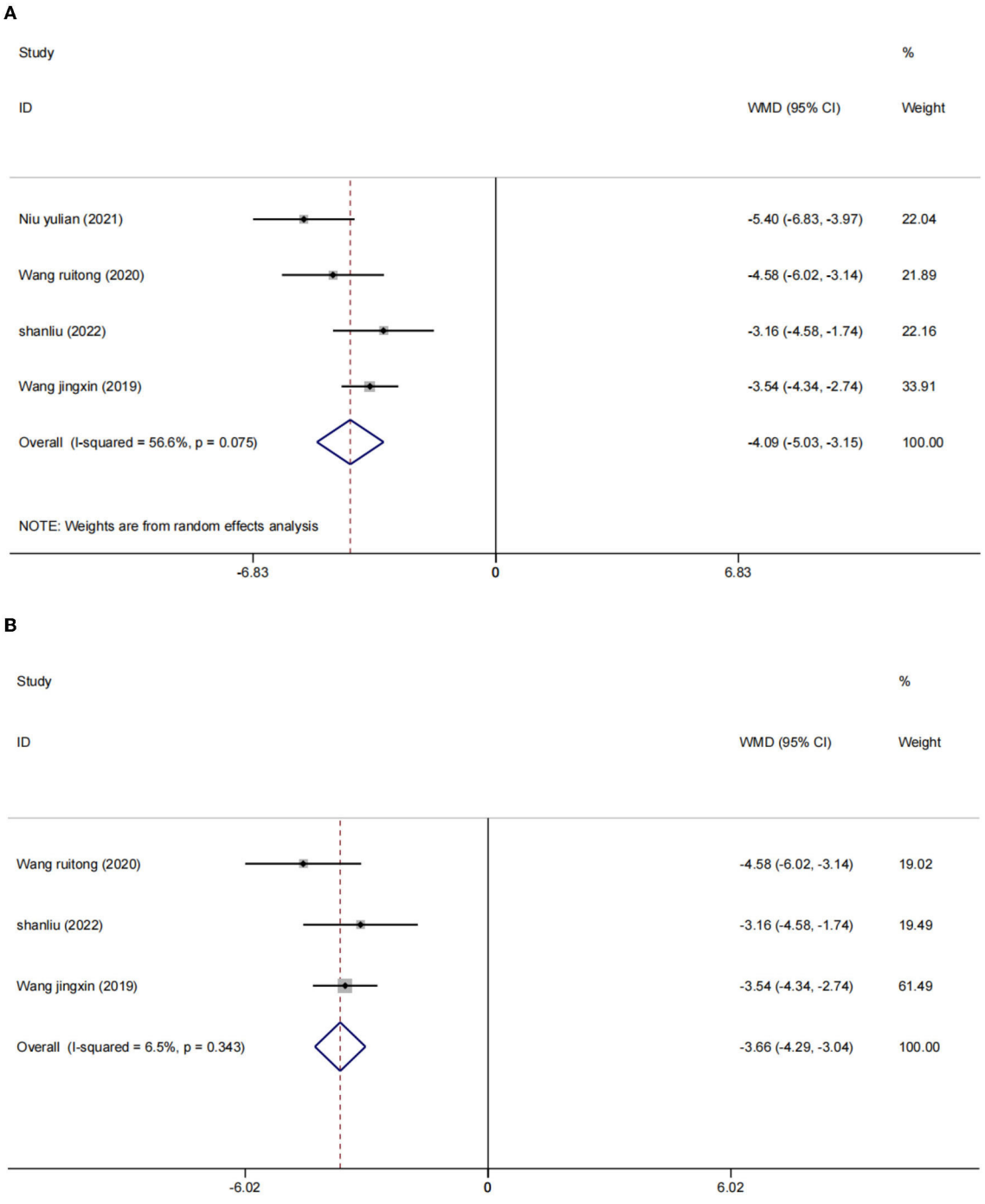


FIGURE 5
Forest plot of IL-6 level in serum. **(A)** All studies. **(B)** After sensitivity analysis.

results were statistically significant compared to the control group [SMD = −1.33, 95% CI (−1.31, −0.70), $p = 0.000 < 0.05$] by the random effects model ($I^2 = 23.1\%$). This proves that low-frequency rTMS combined with antidepressants has positive significance in improving patients' symptoms. Furthermore, we can speculate from the results that the duration of the intervention ≥8 weeks may be more effective (Figure 3B).

Effective rate

Seven studies (25–27, 29, 31, 33, 37) evaluated 631 participants and reported overall response rates. Data were pooled using a fixed effect model ($I^2 = 0\%$) (Figure 4), and the results showed that low-frequency rTMS combined with antidepressants was adequate for the treatment of PSD compared with the control group [OR = 1.18, 95% CI (0.94, 1.49), $p = 0.999$].

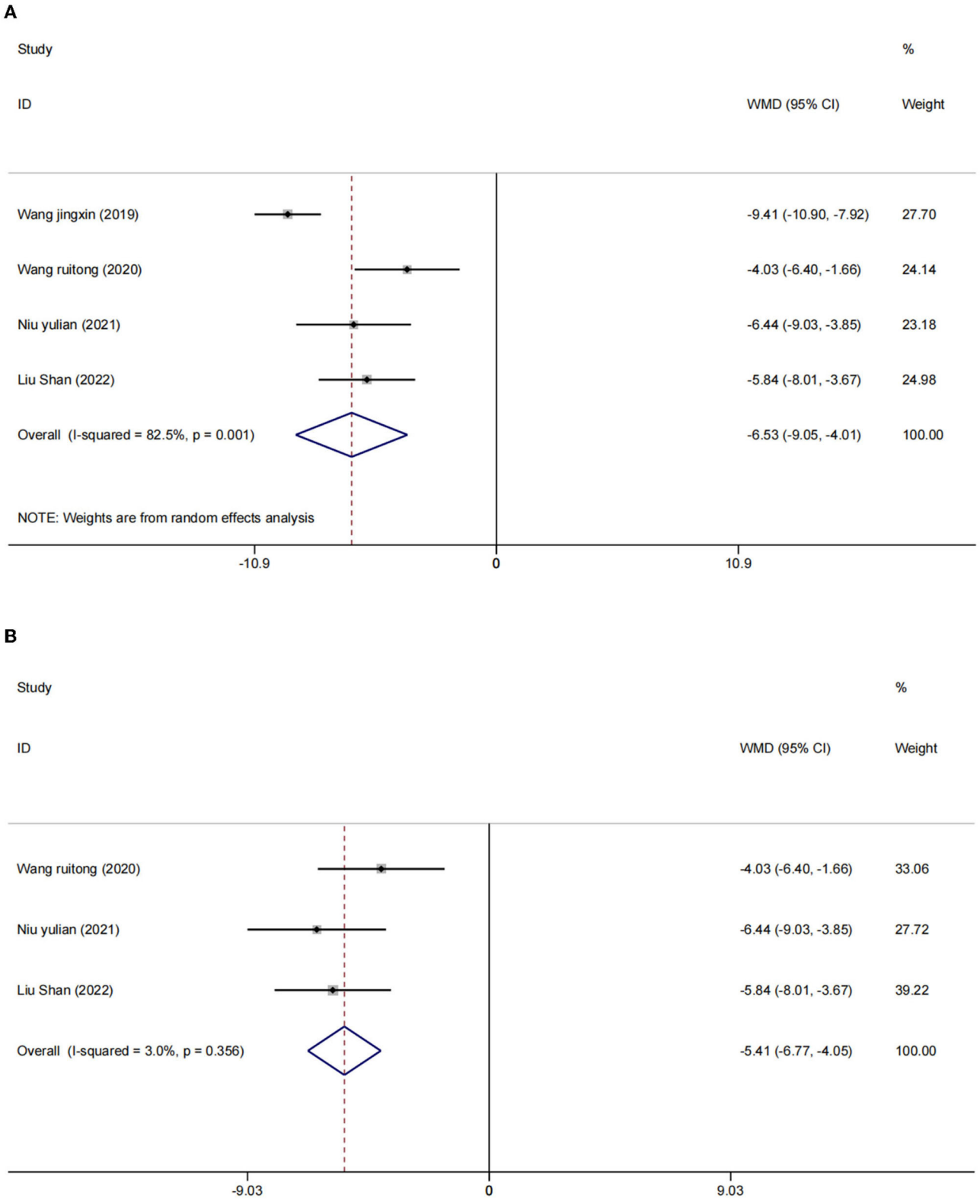


FIGURE 6
Forest plot of TNF-α level in serum. **(A)** All studies. **(B)** After sensitivity analysis.

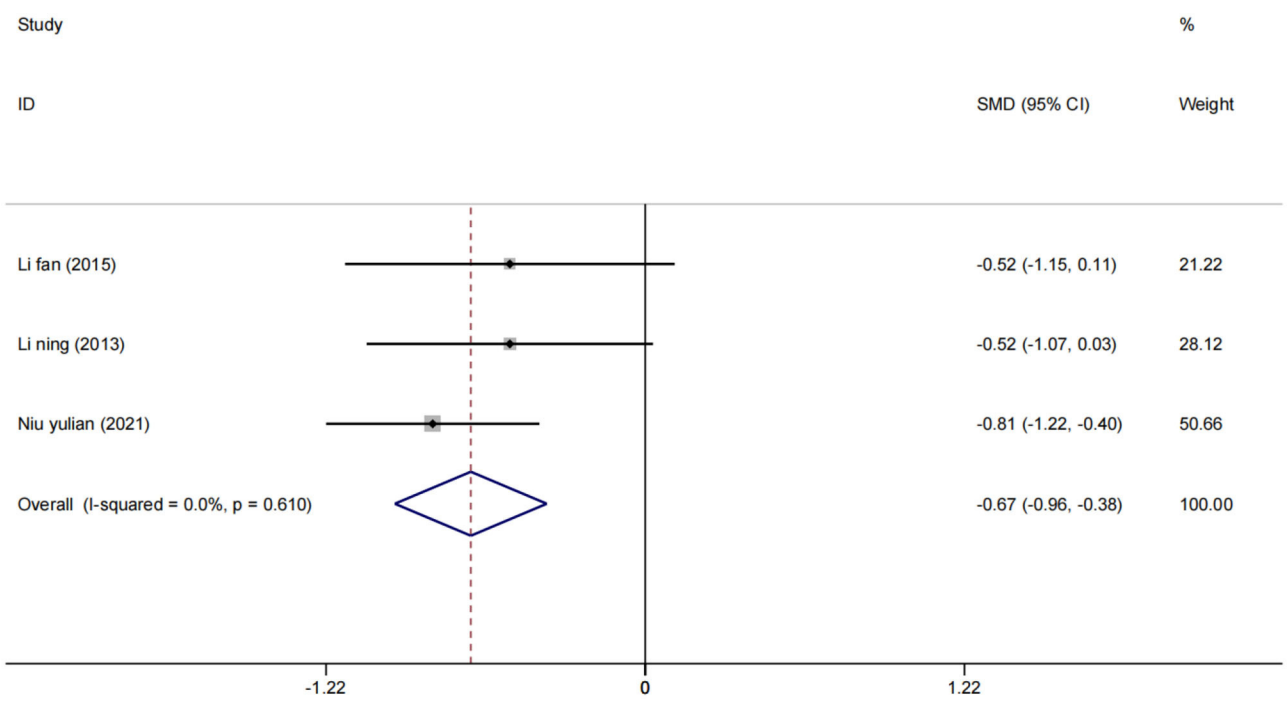


FIGURE 7
Forest plot of the NIHSS score.

The secondary outcomes

Serum IL-6 and TNF-α levels

There were four studies (2, 24, 25, 27) in which the blood inflammatory factors interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured in 402 participants. We used a random effects model to combine the data. The results showed that compared to the control group, the intervention group had a significant reduction in IL-6 [WMD = −4.09, 95% CI (−5.03, −3.15), $I^2 = 56.6\%$, $p = 0.075$] (Figure 5A) and TNF-α [$I^2 = 82.5\%$, $p = 0.001$], WMD = −6.53, 95% CI (−9.05, −4.01; Figure 6A) were more effective.

After sensitivity analysis, we found that the heterogeneity decreases after the exclusion of two studies (24, 27). We used the fixed effect model [IL-6 (WMD = −3.66, 95% CI (−4.29, −3.04), $I^2 = 6.5\%$, $p = 0.075$); Figure 5B] and [TNF-α (WMD = −5.41, 95% CI (−6.77, −4.05), $I^2 = 3.0\%$, $p = 356$); Figure 6B]. We considered that the heterogeneity might be due to the different stimulation sites and the intervention period (left frontal lobe, 4 weeks) in this study compared with the other two studies (right frontal lobe, 8 weeks).

NIHSS score

A total of three studies (24, 33, 34) assessed NIHSS scores in 193 patients. Using a fixed effect model, the statistical significance was found compared to the control group [SMD = −0.67, 95% CI (−0.96, −0.38), ($I^2 = 0\%$), $p = 0.610$; Figure 7], which showed that low-frequency rTMS combined with antidepressants also helped to improve neurological function in stroke patients.

MMSE score

A random effect model was used to perform a meta-analysis of the MMSE scores of 486 participants included in four studies (30, 36–38). The increase of MMSE score in the low-rTMS combined with the antidepressant group was significantly higher than that in the control group [WMD = 4.19, 95% CI (2.11, 6.26), $I^2 = 79.4\%$, $p = 0.002$] (Figure 8A).

Due to the significant heterogeneity ($I^2 = 79.4\%$), the intervention frequency (NOTE. 1: 0.5 Hz; 2: 1 Hz) performed a subgroup stratified analysis, reducing the heterogeneity to a reasonable range. Using the fixed effects model, the results show that WMD = 5.61, 95% CI (4.51, 6.71), $I^2 = 44.5\%$, $p = 0.180$ and WMD = 2.27, 95% CI (0.79, 3.74), $I^2 = 0\%$, $p = 0.746$. Low rTMS combined with antidepressants can significantly improve the MMSE score of PSD patients, which can improve the cognitive function of PSD patients (Figure 8B).

Sensitivity analysis

We used StataMP 17 for sensitivity analysis on the result of the HAMD score; the results are shown in Figure 9. There were 15 studies included in the meta-analysis, and the pooled results of the remaining studies were not statistically significant regardless of which one was excluded. The results were consistent with the original combined results [SMD = −1.01, 95% CI (−1.31, −0.70)], which proved that the meta-results were stable.

Meta-regression results

Since the combined results of HAMD score data showed significant heterogeneity ($I^2 = 86.0\% > 50\%$), we conducted meta-regression according to the intervention frequency, site, and intervention period of the included literature to find the source

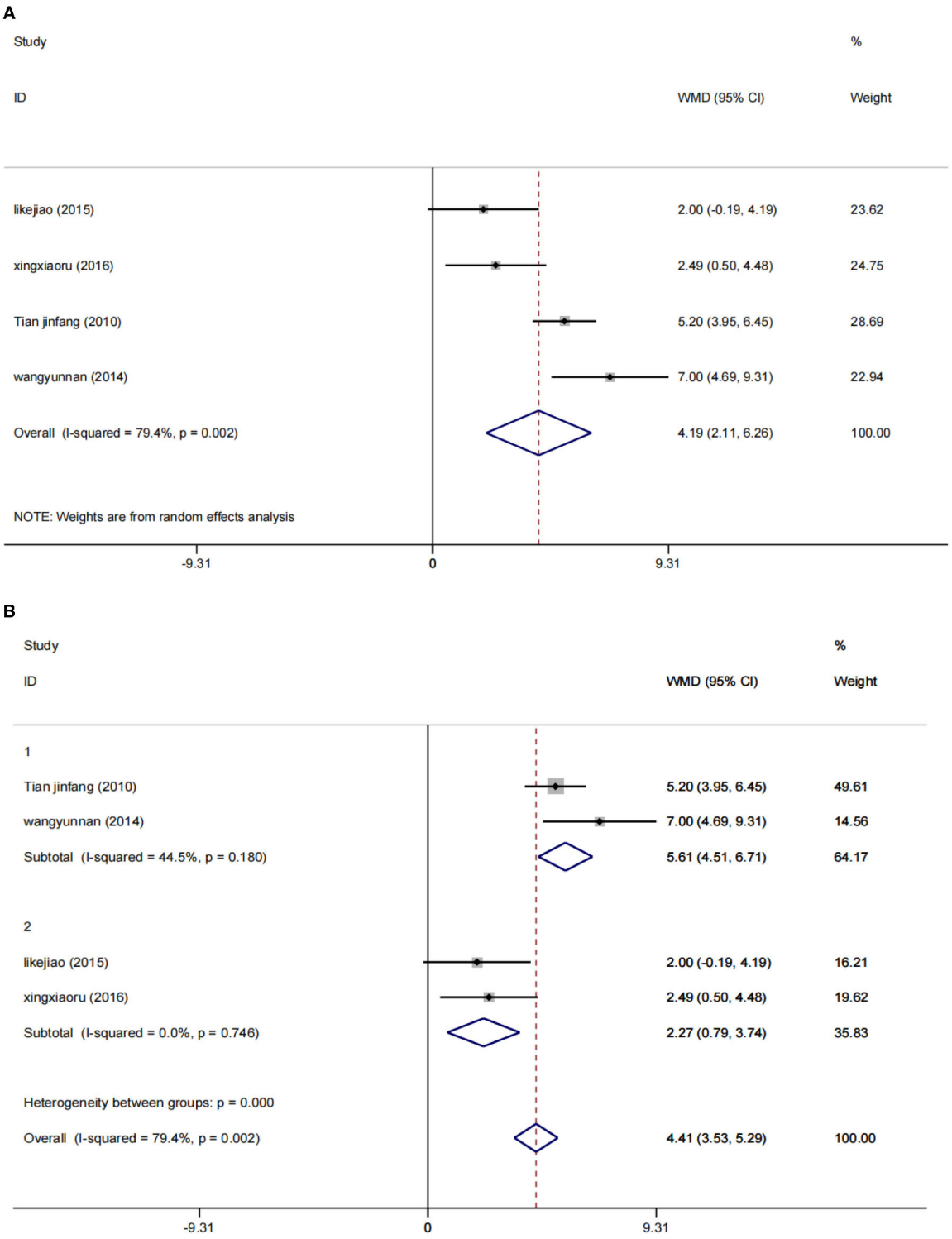


FIGURE 8
Result of MMSE score. **(A)** All studies. **(B)** After subgroup analysis (1: 0.5 HZ; 2: 1 HZ).

of heterogeneity. The results showed that the intervention period ($p = 0.044 < 0.05$) was the source of heterogeneity (Figure 10). Neither the frequency of intervention ($p = 0.636 > 0.05$) nor the site of intervention ($p = 0.542 > 0.05$) was the source of heterogeneity.

Risk of bias

We followed the Cochrane Handbook for Systematic Reviews of Interventions 5.3 to evaluate the risk of bias, and two researchers (JHP and YW) independently evaluated the risk of bias in the included studies. After integrating

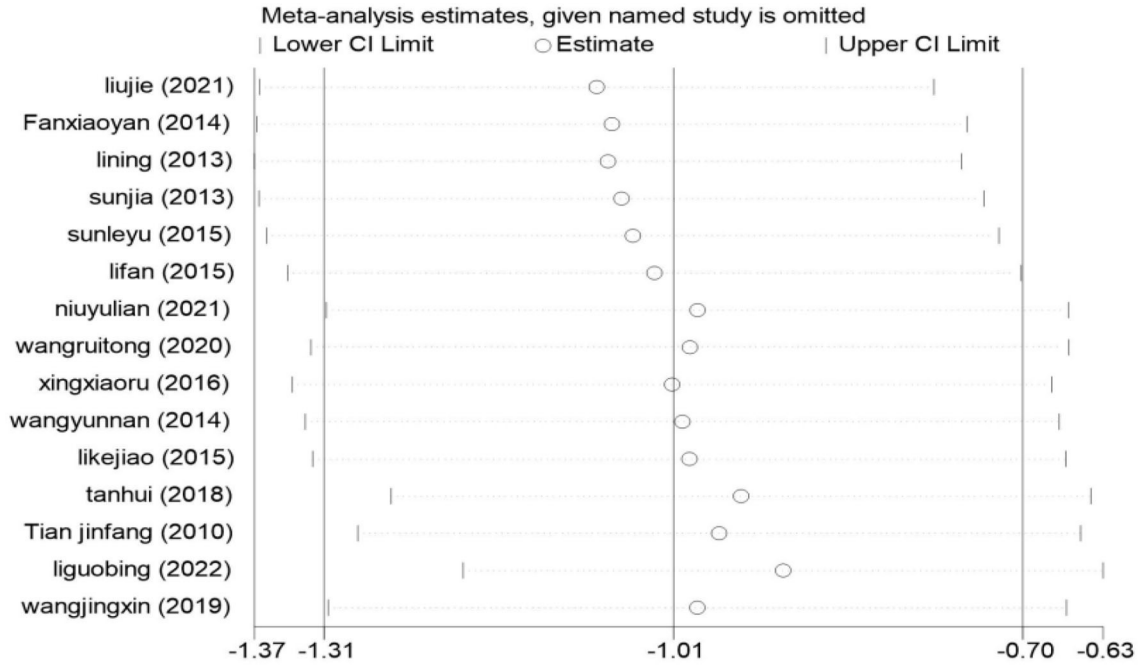


FIGURE 9
Result of sensitivity analysis.

```
. metareg _ES Time, wsse(_seES) bsest(reml)
Iteration 1: tau^2 = 0
Iteration 2: tau^2 = .13055639
Iteration 3: tau^2 = .25262345
Iteration 4: tau^2 = .28373423
Iteration 5: tau^2 = .28840491
Iteration 6: tau^2 = .28903937

Meta-analysis regression                        No of studies =    15
                                                tau^2 method       reml
                                                tau^2 estimate =   .2891

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
Time	-.6222725	.3090279	-2.01	0.044	-1.227956	-.016589
_cons	-.1283497	.4609588	-0.28	0.781	-1.031812	.7751129

FIGURE 10
Meta-regression results of the intervention period.

the results, the 16 included RCTs were shown to be at low risk (Figures 11, 12). Because we could not obtain the original study protocols of the included kinds of literature, other biases could not be determined and were evaluated as unknown risks after discussion by three researchers (JHP, YW, and YSW).

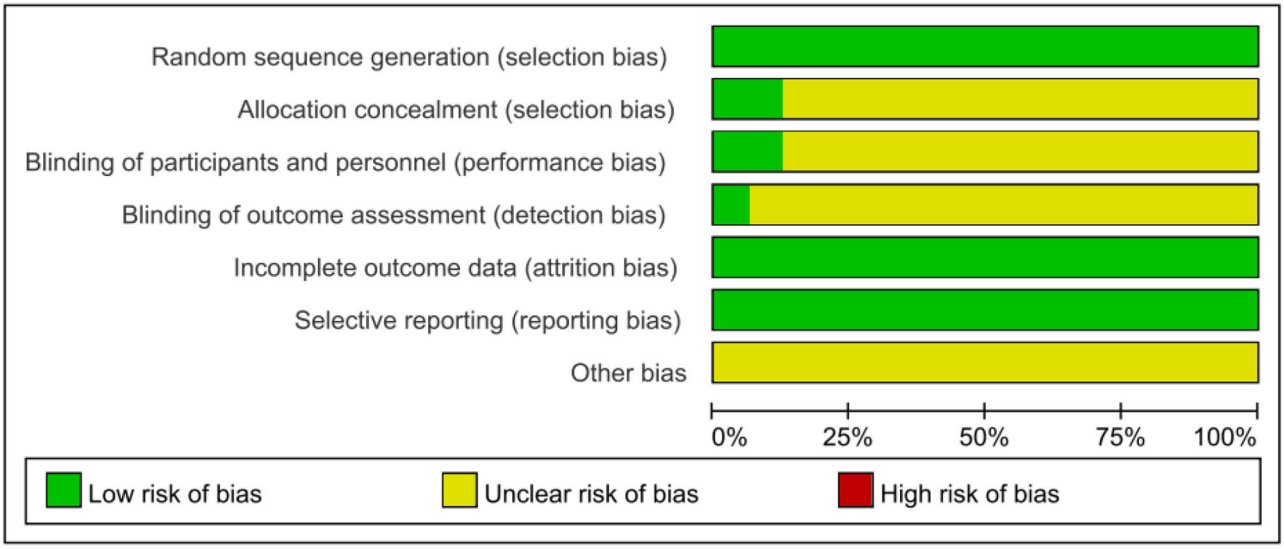


FIGURE 11
Risk of bias graph.

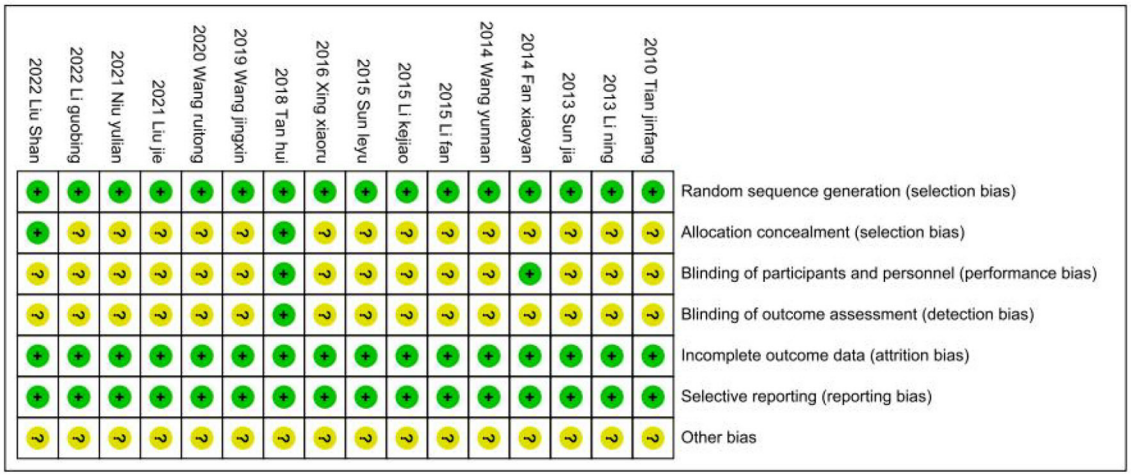


FIGURE 12
Risk of bias summary.

Publication bias

We used StataMP 17 to analyze the publication bias of the HAMD score and total effective rate by Egger's test (2). The results showed that the Egger's test of the HAMD score and the total effective rate was $p = 0.421 > 0.05$ and $p = 0.339 > 0.05$, showing no significant publication bias (Figures 13, 14).

Discussion

This meta-analysis included 16 studies with 1,463 patients with PSD. The experimental group used rTMS combined with antidepressants (such as fluoxetine, duloxetine, mirtazapine, paroxetine, or flupentixol melitracen), and the control group received antidepressants (Table 1). We used PEDro to assess the quality of the included studies, including two high-quality studies (eight scores) and 13 medium-quality studies (six scores). The risk of bias was evaluated as low because the 16 studies described the randomization method and reported the primary outcome measures. However, we did not have access to the original protocol and other risks of bias evaluations are unclear. We used Egger's test to analyze the publication bias of the HAMD score and the total response rate, and the results did not show a significant publication bias of the HAMD score and the total response rate ($p = 0.421 > 0.05$ and $p = 0.339 > 0.05$).

The results of the meta-analysis proved that rTMS combined with antidepressants could reduce the HAMD score of PSD patients compared to an antidepressant [SMD = −1.01, 95% CI (−1.31,

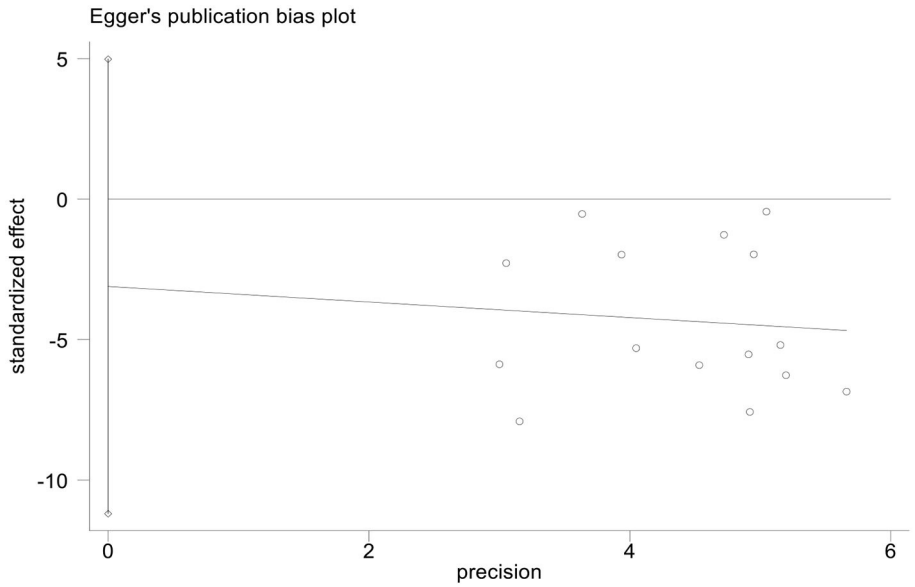


FIGURE 13
Egger's publication bias plot of HAMD scores.

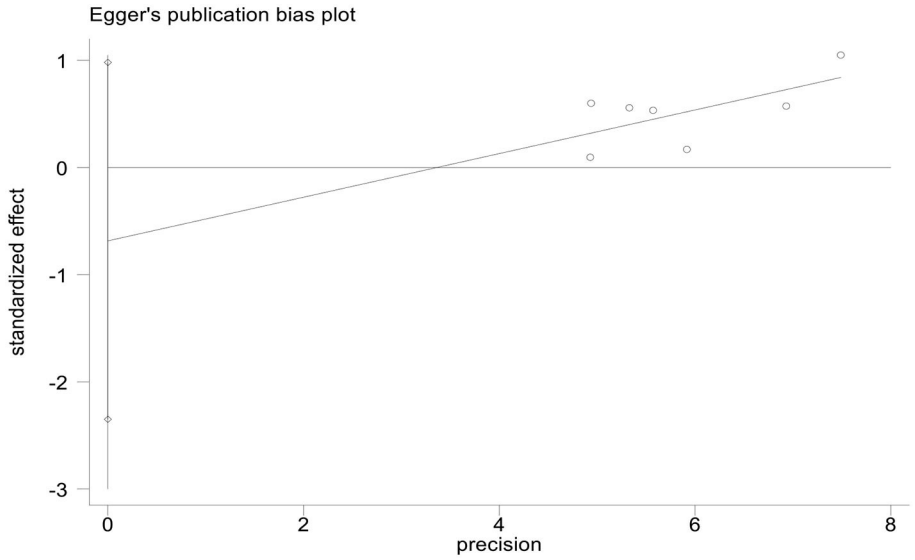


FIGURE 14
Egger's publication bias plot of effective rate.

−0.70), I^2 = 86.0%, p = 0.000]. However, there was significant heterogeneity. In order to find the source of heterogeneity, we conducted a meta-regression according to publication year, age, intervention frequency, intervention period, intervention site, and intervention drug. We also performed subgroup analyses according to the intervention period (≤4 and ≥8 weeks). The results show that SMD = 0.76, 95% CI (1.19, 0.32), I^2 = 87%, p = 0.001 < 0.05 (4 weeks) or less, and SMD = 1.33, 95% CI (1.31, 0.70), I^2 = 23.1%, p = 0.000 < 0.05 (≥8 weeks). Low rTMS combined with an antidepressant had a positive effect in improving the depression of PSD patients. In order to further verify the stability of the meta-results, we conducted a sensitivity analysis. The results showed that no matter which study was excluded, the combined results of the remaining studies were not statistically significant, consistent with the original combined results [SMD = −1.01, 95% CI (−1.31, −0.70)], and the results were stable.

Previous studies have shown that the pathological mechanism of PSD may be related to the inflammatory process caused by stroke, and serum levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), IL-10, interferon-γ, and the TNF-α level in PSD patients increased to varying degrees (40–42). Furthermore, it will increase with an increase in the degree of depression. The results of this

meta-analysis evidenced that rTMS combined with antidepressants could reduce the levels of serum inflammatory factors (IL-6 [WMD = −3.66, 95% CI (−4.29, −3.04), I^2 = 6.5%, p = 0.075]) and TNF-α [WMD = −5.41, 95% CI (−6.77, −4.05), I^2 = 3.0%, p = 356]). It could be seen that low-frequency repetitive transcranial magnetic stimulation could increase the protective factors of nerve cells. In contrast, the expression of factors IL-6 and TNF-α that damage nerve cells decreases. Therefore, there is evidence that low-frequency repetitive transcranial magnetic stimulation could somewhat protect nerve cells by inhibiting the production of inflammatory factors related to depression (43–45).

This study also demonstrated that low rTMS combined with antidepressants could reduce NIHSS scores [SMD = −0.67, 95% CI (−0.96, −0.38), p = 0.610] and increase the MMSE score [WMD = 4.19, 95% CI (2.11, 6.26)] in PSD patients. There is promising data that the low-rTMS combined with antidepressants possibly improve neurological function in stroke patients and the cognitive function of PSD patients to some extent.

Currently, research on the mechanism of PSD is not very detailed and most of the clinical treatments are symptomatic. However, some studies have also shown that the appearance of PSD may be related to the following factors. First, dysfunction of the central monoamine neurotransmitter system. The experiments of Whyte et al. (46) showed that the destruction of noradrenergic and serotonergic neurons led to varying degrees of decrease in norepinephrine and serotonin after PSD, which can lead to the occurrence of depression. Relevant experiments by Robinson et al. (47) also showed that the levels of 5-HT, NE, and DA neurotransmitters in the hippocampus and frontal cortex of PSD rats were significantly reduced, leading to the appearance of depression.

Meanwhile, the significant efficacy of SSRI and SNRI in treating PSD has confirmed this speculation. Second, the appearance of oxidative stress. Nabavi et al. (48) believed that reactive oxygen species produced in the stroke process could cause oxidative stress, lipid peroxidation, protein oxidation, and DNA damage in the nerve tissue, which induced post-stroke depression. The study of Nabnvi et al. (49) also provided favorable evidence for the hypothesis. Third, a decrease in neurotrophic factors. Xia et al. (50) showed that the occurrence of PSD negatively correlated with the level of neurotrophic factor (BDNF). The study of Moghbelinejad et al. (51) also proved that BDNF could effectively regulate the regeneration and apoptosis of neurons, mediate the growth and proliferation of nerve cells, and protect nerve tissues from the damage caused by neuronal death caused by ischemia or depression. Fourth, psychosocial changes. Brggimann et al. (52) showed that posttraumatic stress disorder was associated with changes in psychological status after stroke. Moreover, there are also relevant studies (53, 54) that the degree of social support at 3–6 months, 1 year, and 2 years after stroke is related to the severity of PSD.

A total of five studies (24, 26, 32, 34, 38) reported adverse effects, mainly including neurological and digestive abnormalities. Neurological abnormalities mainly included scalp discomfort, sweating, drowsiness, fatigue, and headache. Digestive abnormalities include nausea, vomiting, loss of appetite, and constipation. In the low-frequency rTMS combined with the antidepressant group, scalp discomfort occurred in three cases, headache in 20 cases (14 cases relieved after rest and six cases relieved after taking acetaminophen), fatigue in two cases, nausea in two cases, and vomiting in one case. In the antidepressant group, there were three cases of drowsiness, two cases of headache, four cases of constipation and loss of appetite, five cases of nausea, and five cases of vomiting. These adverse effects may be related to the administration of antidepressants.

This study also has some limitations. First, as shown in Table 2 and Figures 11, 12, most of the studies included in this study had methodological deficiencies and mostly did not blind participants, therapists, and assessors. These factors may affect the effect of low rTMS combined with antidepressants in the treatment of PSD, so more high-quality and large-sample studies are needed to confirm it in the future. Second, most of the intervention periods of the 16 included studies were between 4 weeks and 8 weeks, and there were no reports on long-term follow-up, thus, the long-term efficacy of these studies could not be analyzed, which may be an issue we should consider in the future. Third, only three studies were recovered according to the inclusion criteria and used the inflammatory factors IL-6 and TNF-α as outcome indicators. Although our conclusion is positive and supported by research, it is still necessary to verify this conclusion with more high-quality studies in the future. Finally, as shown in Table 1, there were differences in intervention sites and intervention frequencies in the 16 included studies. Unfortunately, in this meta-analysis, we only compared the efficacy of low-frequency rTMS and antidepressants and did not compare the efficacy between different sites. A new meta-analysis can be carried out in this regard in the future.

Conclusion

The results of this meta-analysis evidenced the efficacy and safety of low-rTMS combined with antidepressants in the treatment of depression in PSD patients. The combined therapy could reduce The depression state and the levels of IL-6 and TNF-α, and enhance the cognitive function of patients. In addition, low-rTMS had fewer adverse effects, proving safety. However, there are shortcomings, such as a lack of long-term follow-up, different intervention sites of low-rTMS, and different intervention frequencies (0.5 or 1 Hz). In the future, more large sample size, higher quality, and more extended observations of RCTs are needed to verify further effectiveness of low-rTMS combined therapy on PSD. A new meta-analysis could determine which intervention sites and frequency are more effective in treating PSD.

Data availability statement

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

Author contributions

JP, DZ, YW, LL, HL, YW, and SJ contributed equally to this meta-analysis. JP, DZ, and SJ conceived the study and drafted the first framework of the manuscript. JP, YW, LL, HL, and YW were responsible for data collection and verification. JP and DZ contributed significantly to the revision of the study. All authors contributed to the design, information gathering, data collection, analysis, writing, and final editing.

Funding

This review was funded by the Sichuan Provincial Administration of Traditional Chinese Medicine (Number: 2022CP0992).

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

References

1. Feigin VL, Stark BA, Johnson CO. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0

2. Liu S, Wang X, Yu R, Sun Y. Effect of transcranial magnetic stimulation on treatment effect and immune function. *Saudi J Biol Sci.* (2022) 29:379–84. doi: 10.1016/j.sjbs.2021.08.104

3. Juan W, Zhiwei L, Yu Y. Analysis on related factors of post-stroke depression. *Chongqing Med.* (2014) 43:3165–7.

4. Liu H, Zhao Q, Wang K, et al. Study on mediating role of family function between activity of daily living and post-stroke depression among stroke patients. *Chin Nurs Res.* (2019) 33:3350–5.

5. Zhong X, Hao Q, Wang Y, Yan Y, Zhong L, Zhou X. The evaluation and influencing factors of post-stroke depression in the elder patients. *Mod Prev Med.* (2020) 47:474–8.

6. Saxena A, Suman A. Magnitude and determinants of depression in acute stroke patients admitted in a rural tertiary care hospital. *J Neurosci Rural Pract.* (2015) 6:202–7. doi: 10.4103/0976-3147.153228

7. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis. *Ageing Res Rev.* (2019) 50:102–9. doi: 10.1016/j.arr.2019.01.013

8. Li H, Ma H, Zhang Z, et al. Research and progress on the related factors of post-stroke depression and social support. *Chin J Gerontol.* (2011) 31:4730–2.

9. Shaoshi W, Xinyu Z, Chunyan Z. Chinese expert consensus on clinical practice of post-stroke depression. *Chin J Stroke.* (2016) 11:685–93.

10. Yang L, Liu Y, Wu N, et al. Effect of low-frequency repetitive transcranial magnetic stimulation on serum neurotransmitters and cytokines in patients with ischemic poststroke depression. *J Hainan Med Univ.* (2017) 23:1434–7. doi: 10.13210/j.cnki.jhmu.20170406.009

11. Niu Y, Ma L, Wang L, et al. Expression and clinical significance of IL-1, IL-2, IL-6 and TNF-α in serum of patients with post-stroke depression. *Mod Med J.* (2016) 44:89–91.

12. Taylor D, Lenox-Smith A, Bradley A. A review of the suitability of duloxetine and venlafaxine for use in patients with depression in primary care with a focus on cardiovascular safety, suicide and mortality due to antidepressant overdose. *Ther Adv Psychopharmacol.* (2013) 3:151–61. doi: 10.1177/2045125312472890

13. Jie Y, Yueying L, Xin G, et al. Efficacy and safety of sertraline versus amitriptyline in the treatment of post-stroke depression in Chinese: a Meta-analysis. *Chin J Gerontol.* (2018) 38:6017–23.

14. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. *Cochrane Database Syst Rev.* (2008) CD003437. Update in: *Cochrane Database Syst Rev.* (2020) 1:CD 003437. doi: 10.1002/14651858.CD003437.pub3

15. O'Reardon JP. Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry.* (2007) 62:1208–16. doi: 10.1016/j.biopsych.2007.01.018

16. Tang Y, Wu Y, Wang J. Shanghai expert consensus on the clinical application and operation of repetitive transcranial magnetic stimulation. *Shanghai Med J.* (2022) 45:65–70.

17. Shiyi M, Bingyou L, Rui W. Efficacy of mirtazapine combined with repetitive transcranial magnetic stimulation in the treatment of post-ischemic stroke depression. *Chin J Phys Med Rehabil.* (2021) 43:520–2. doi: 10.3760/cma.j.issn.0254-1424.2021.06.008

18. Liu F. Effect of repetitive transcranial magnetic stimulation and paroxetine hydrochloride on the efficacy and complications of patients with post-stroke depression. *Reflexol Rehabil Med.* (2020) 1:133–5,146.

19. Xu W, Xiong L. Transcranial magnetic stimulation improves the effectiveness of psychological intervention in relieving post-stroke depression. *Chin J Phys Med Rehabil.* (2022) 44:348–52. doi: 10.3760/cma.j.issn.0254-1424.2022.04.014

20. Zhao X, Li X, Li J, Tian B, Wang G. Therapeutic effects of auricular points sticking with magnetic beads combined with repeated transcranial magnetic stimulation on post-stroke depression. *J Shandong Univ.* (2022) 60:65–70. doi: 10.6040/j.issn.1671-7554.0.2021.0508

21. Liang J, Feng J, He J, Jiang Y, Zhang H, Chen H. Effects of noninvasive brainstimulation combined with antidepressants in patients with poststroke depression: a systematic review and meta-analysis. *Front Pharmacol.* (2022) 13:887115. doi: 10.3389/fphar.2022.887115

22. Liang C, Jie C, Ge J, et al. Therapeutic efficacy of low-frequency repetitive transcranial magnetic stimulation in post-stroke depression: a Meta-analysis. *Chin J Med Phy.* (2019) 36:736–44.

23. Jie L. To investigate the effect of low frequency repetitive transcranial magnetic stimulation combined with rehabilitation training on the levels of 5-HIAA and 5-HT in patients with post-stroke depression. *Clin Res.* (2021) 29:92—4.

24. Niu Y, Wu H. Efficacy evaluation of low frequency repetitive transcranial magnetic stimulation in the treatment of post-stroke. *Chin Gen Pract.* (2021) 24:49–52.

25. Wang R, Zhao C, Qin X, et al. Low-frequency repetitive transcranial magnetic stimulation combined with paroxetine in the treatment of post-stroke depression Preliminary study of clinical efficacy and mechanism. *Neural Injury Funct Reconstr.* (2020) 15:349–351354.

26. Guobing L. Effects of low frequency repeated transcranial magnetic stimulation combined with fluoxetine on serum NPY, BDNF and CRF levels in patients with post-stroke depression. *Reflexol Rehabil Med.* (2022) 3:77–9.

27. Wang J, Wang Y, Li Y, et al. Effect of low-frequency repetitive transcranial magnetic stimulation on serum neurotransmitters and serum inflammatory factors in patients with post-stroke depression. *J Clin Psychosom Dis.* (2019) 25:5–8.

28. Li Y, Guo Z, Zhang X. Changes of levels of inflammatory factors and BDNF in patients with post-stroke depression and their correlations. *Med Pharm J Chin Peoples Liberation Army.* (2018) 30:101–4.

29. Leyu S, Lijun W. Efficacy of low frequency repetitive transcranial magnetic stimulation in the treatment of anxiety and depression comorbidity after stroke. *Chin J Pract Nerv Dis.* (2015) 18:75–6.

30. Tian J, Jia H. Effects of repetitive transcranial magnetic stimulation on functional recovery in patients with post-stroke depression. *Chin J Phys Med Rehabil.* (2010) 32:457−8. doi: 10.3760/cma.j.issn.0254-1424.2010.06.016

31. Fan X. Effect of duloxetine combined with repetitive transcranial magnetic stimulation on post-stroke depression. *Chin J Pract Nerv Dis.* (2014) 17:102–3.

32. Jia S, Hong W, Qingyang S, et al. Efficacy of repetitive transcranial magnetic stimulation in the treatment of post-stroke depression. *Chin J Integr Med Cardio-Cerebrovasc Dis.* (2013) 11:321–2.

33. Li N, Han Y, Pan W, et al. A study of efficacy mirtazapine merge rTMS to treatment of post-stroke depression. *Chin J Trauma Disabil Med.* (2013) 21:48–50.

34. Fan L. *Clinical Effect of Repetitive Transcranial Magnetic Stimulation Combined with Fluoxetine on Post-stroke Depression*. Kunming: Kunming Medical University. (2015).

35. Tan H, Zhang W, Zhu L. A clinical controlled trial of repeated transcranial magnetic stimulation combined with body acupuncture for treatment of post-stroke depression. *World Latest Med Inf.* (2018) 18:9–11.

36. Yunnan W, Xuan Y, Qianying W. Low frequency repetitive transcranial magnetic stimulation improves depression in stroke patients living ability and cognitive function were observed. *Mod J Integr Tradit Chin West Med.* (2014) 23:2311–3.

37. Xiaoru X, Xinchun Z, Kuien W, et al. Effects of low frequency repetitive transcranial magnetic stimulation on cognitive and daily life ability of patients with post stroke depression. *J Int Psychiatry*. (2016) 43:648-650+654.

38. Kejiao L. Effects of low-frequency repetitive transcranial magnetic stimulation on cognitive function and daily life ability in patients with post stroke depression. *Neural Injury Funct Reconstr*. (2015) 10:411–3.

39. Xu D, Tao T, Zhang J, He G. The effect of proprioceptive training on knee joint recovery among patients with total knee replacement: a meta-analysis of randomized controlled trials. *Chin J Geriatr.* (2018) 37:339–43.

40. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. (2011) 343:d4002. doi: 10.1136/bmj.d4002

41. Cai X, Wang X, Wu C, et al. The correlation between serum IL-1β, IL-2, IL-6 and TNF-α and post-stroke depression. *Heilongjiang Med J*. (2017) 41:1222–3.

42. Wang Z, Chen N. Depression and inflammation. *Acta Neuropharmacol.* (2013) 3:27–37. doi: 10.1007/s10753-013-9714-z

43. Wang SS, Chen HY, Sun H, Wang T, Guan JQ. Activation of TNF-α and signaling pathway in the hypothalamus of the rats subjected to chronic unpredictable mild stressors after middle cerebral artery occlusion. *Acta Physiol Sin.* (2014) 66:463–8. doi: 10.13294/j.aps.2014.0054

44. Howren M, Lamkin D, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6:a meta-an nalysis. *Psychos Med.* (2009) 71:171–3. doi: 10.1097/PSY.0b013e3181907c1b

45. Valkanova V, Ebmeier K, Allan C. CRPIL-6 and depression: a systematic review and meta-analysis of lonigitudinal studies. *J Affect Disord.* (2013) 150:736–44. doi: 10.1016/j.jad.2013.06.004

46. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. *Biol Psychiatry*. (2002) 52:253–64. doi: 10.1016/S0006-3223(02)01424-5

47. Robinson RG, Jorge RE. Post-stroke depression: a review. *Am J Psychiatry*. (2016) 173:221–31. doi: 10.1176/appi.ajp.2015.15030363

48. Nabavi SF, Dean OM, Turner A, Sureda A, Daglia M, Nabavi SM. Oxidative stress and post-stroke depression: possible therapeutic role of polyphenols? *Curr Med Chem.* (2015) 22:343–51. doi: 10.2174/0929867321666141106122319

49. Nabavi SF, Habtemariam S, DI Lorenzo A, et al. Post-Stroke depression modulation and *in vivo* antioxidant activity of gallic acid and its synthetic derivatives in a murine model system. *Nutrients.* (2016) 8:248. doi: 10.3390/nu8050248

50. Xia L, Wendong Y. Post-stroke depression level and the level of brain derived neurotrophic factor correlation studies. *Chin J Geriatric Care.* (2016) 14:21–3.

51. Moghbelinejad S, Nassiri-Asl M, Farivar TN, Abbasi E, Sheikhi M, Taghiloo M, et al. Rutin activates the MAPK pathway and BDNF gene expression on beta-amyloid induced neurotoxicity in rats. *Toxicol Lett*. (2014) 224:108–13. doi: 10.1016/j.toxlet.2013.10.010

52. Bruggimann L, Annoni JM, Staub F, von Steinbüchel N, Van der Linden M, Bogousslavsky J. Chronic posttraumatic stress symptoms after nonsevere stroke. *Neurology.* (2006) 66:513–6. doi: 10.1212/01.wnl.0000194210.98757.49

53. Altedomeburg M, Bereczki D. Post-stroke depression. *Orv Hetil.* (2014) 155:1335–43. doi: 10.1556/0H.2014.29968

54. Mei L, Jinling M, Yanfang Z, et al. The effect of low frequency repetitive transcranial magnetic stimulation on stroke induced depression and its effect on serum brain-derived neurotrophic factor and IL-6. *Chin J Gerontol.* (2018) 38:4711–3.

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 02 June 2023
DOI 10.3389/fneur.2023.1195915

OPEN ACCESS

EDITED BY
Haiqing Zheng,
Third Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Carlo Trompetto,
University of Genoa, Italy
Massimiliano Mangone,
Sapienza University of Rome, Italy

*CORRESPONDENCE
Shu-Yun Zhang
✉ John-lw@sohu.com
Xiang-Zhen Yuan
✉ yuanxiangzhen@163.com

RECEIVED 29 March 2023
ACCEPTED 10 May 2023
PUBLISHED 02 June 2023

CITATION
Jia F, Zhu X-R, Kong L-Y, Fan J-C, Zhu Z-J, Lin L-Z, Zhang S-Y and Yuan X-Z (2023) Stiffness changes in internal rotation muscles of the shoulder and its influence on hemiplegic shoulder pain. *Front. Neurol.* 14:1195915. doi: 10.3389/fneur.2023.1195915

Stiffness changes in internal rotation muscles of the shoulder and its influence on hemiplegic shoulder pain

Fan Jia[1], Xin-Rui Zhu[1], Ling-Yu Kong[2], Jie-Cheng Fan[3], Zong-Jing Zhu[3], Li-Zhen Lin[3], Shu-Yun Zhang[4]* and Xiang-Zhen Yuan[4]*

[1]Faculty of Rehabilitation Medicine, Weifang Medical University, Weifang, Shandong, China, [2]Physical Education and Sports School, Soochow University, Suzhou, Jiangsu, China, [3]Department of Rehabilitation Medicine, Weifang People's Hospital, Weifang, Shandong, China, [4]Department of Neurology, Weifang People's Hospital, Weifang, Shandong, China

Background: Hemiplegic shoulder pain (HSP) is a common complication in patients with stroke. The pathogenesis of HSP is complex, and muscle hypertonia, especially the hypertonia of internal rotation muscles of the shoulder, may be one of the important causes of shoulder pain. However, the relationship between muscle stiffness and HSP has not been well studied. The purpose of this study is to explore the correlations between the stiffness of internal rotation muscles and clinical symptoms in patients with HSP.

Methods: A total of 20 HSP patients and 20 healthy controls were recruited for this study. The stiffness of internal rotation muscles was quantified using shear wave elastography, and Young's modulus (YM) of the pectoralis major (PM), anterior deltoid (AD), teres major ™, and latissimus dorsi (LD) were measured. Muscle hypertonia and pain intensity were evaluated using the Modified Ashworth Scale (MAS) and Visual Analog Scale (VAS), respectively. The mobility of the shoulder was evaluated using the Neer score. The correlations between muscle stiffness and the clinical scales were analyzed.

Results: YM of internal rotation muscles on the paretic side was higher than that of the control group in the resting and passive stretching positions ($P < 0.05$). YM of internal rotation muscles on the paretic side during passive stretching was significantly higher than that at rest ($P < 0.05$). YM of PM, TM, and LD during passive stretching were correlated with MAS ($P < 0.05$). In addition, the YM of TM during passive stretching was positively correlated with VAS and negatively correlated with the Neer score ($P < 0.05$).

Conclusion: Increased stiffness of PM, TM, and LD was observed in patients with HSP. The stiffness of TM was associated with pain intensity of the shoulder and shoulder mobility.

KEYWORDS

hemiplegic shoulder pain, stroke, shear wave elastography, muscle stiffness, ultrasound

Introduction

Hemiplegic shoulder pain (HSP) is one of the most common complications after stroke, and patients with HSP often have shoulder pain and limited mobility (1). The prevalence of HSP in post-stroke patients has been reported to be 84% and remains elevated throughout recovery (2, 3). The etiology of HSP is multifactorial, and factors including impingement

syndrome, rotator cuff dysfunction, and muscle hypertonia may be related to HSP (4). The initial weakness and muscle hypertonia after stroke are mainly due to the injury of upper motor neurons, which change the muscle stiffness and cause pain by pulling the periosteal attachments (5, 6). As the clinical manifestations of HSP are variable, there is no universal treatment method at present. However, untreatable shoulder pain can cause secondary problems and limit upper limb function (7). Therefore, further research is needed to clarify the factors affecting HSP. It has been reported that muscle hypertonia was an important cause of shoulder pain in patients with hemiplegia during spasticity (1). In stroke patients, the shoulder girdle on the paretic side usually shows increased stiffness of the internal rotation muscles during the spastic phase, resulting in an abnormal pattern of internal rotation of the humerus and retraction of the scapula, which affects the normal humeral rhythm and squeezes soft tissues and causes shoulder pain (8). The internal rotation muscles with hypertonia included pectoralis major (PM), deltoid anterior (AD), teres major (TM), latissimus dorsi (LD), and subscapularis. These hypertonic muscles may be the main cause of pain and limited movement in HSP (1). Therefore, evaluation and rehabilitation of shoulder internal rotation muscles may be beneficial for patients with HSP.

Focal and characteristic muscle dysfunction is often observed in HSP patients (9). Investigations have shown that the overactivity of PM and subscapularis are obvious in HSP. With the increase in the activity of TM and LD, HSP patients have pain and limited activity (4). In addition, the incidence of disability in HSP is also high. In the Auckland stroke study, patients who were discharged home from a hospital had an increased risk of shoulder pain. Approximately 20% of patients have persistent shoulder pain for more than 6 months and the pain becomes permanent, affecting their activities of daily living (10). Thus, it is very important to find out the disabling factors and implement preventive intervention before HSP occurs. However, the changes in the stiffness of the shoulder's internal rotation muscles and the impact on HSP are still unclear.

The clinical evaluation of hypertonia mainly includes clinical scale evaluation, biomechanical evaluation, and electrophysiological evaluation. The commonly used clinical scale is the Modified Ashworth Scale (MAS), which can only assess the overall condition of the patient and is highly subjective with limited reliability and validity. Moreover, biomechanical evaluation and electrophysiological evaluation are complicated and expensive. Shear wave elastography (SWE), an emerging technique, has the advantages of non-invasive, simple, and timely detection. Most importantly, it has a certain pathological basis for muscle hypertonia assessment, monitoring the structure and viscoelasticity properties of hypertonic muscle. The principle of SWE is to generate shear waves by creating acoustic radio frequency force impulse, stimulating tissue vibration to quantify muscle stiffness (11). Muscle stiffness can be quantified by Young's modulus (YM) or shear wave velocity (SWV) (12). YM is the ratio of longitudinal stress to strain, which indicates the longitudinal deformation trend of the tissue and can directly reflect the change in muscle stiffness (13). YM increases with the increase in muscle stiffness (14). Currently, SWE is widely used to assess muscle stiffness with excellent reliability (15). In particular, it is possible to quantify the stiffness of individual muscle tissues and observe subtle changes in muscle properties in the early stages of the disease, providing clinicians with an objective indicator. In addition, measuring the stiffness of muscles in different states can help physical therapists design targeted, individualized treatment plans.

In this prospective observational study, we hypothesized that the stiffness of internal rotation muscles was related to the clinical symptoms of HSP. Using the SWE technique, we quantitatively measured the YM of internal rotation muscles and analyzed the relationship between muscle stiffness and hypertonia, pain intensity, and shoulder dysfunction.

Materials and methods

Subjects

A total of 20 stroke patients with HSP and 20 healthy controls participated in this study. The inclusion criteria for the stroke patients with HSP were as follows: (1) patients with cerebral hemorrhage or cerebral infarction confirmed by computer tomography or magnetic resonance imaging (16), (2) patients with first onset of stroke with unilateral involvement, (3) patients with the duration of stroke <6 months, (4) patients with shoulder pain and muscle hypertonia on the paretic side, (5) patients with the paretic side had no history of shoulder pain before the stroke, (6) patients who could cooperate with the examination and assessment, (7) patients with sitting balance ≥ 1 grade, (8) patients with the visual analog scale (VAS) scored >0, (9) patients with MAS graded 1–3, and (10) patients with shoulder pain lasting for 2 weeks or more (17). The exclusion criteria were as follows: patients with (1) impairment of consciousness, cognition, or language, (2) severe muscle or bone joint disease affecting upper limbs, (3) a history of shoulder surgery, and (4) VAS score $= 10$ or MAS grade $= 0$. The inclusion criteria for the control group were as follows: (1) patients with no history of stroke, (2) patients with normal range of motion of shoulder joint (18), (3) patients who could cooperate with inspection and evaluation, (4) patients who could tolerate ultrasound examination, and (5) patients who matched with HSP group for age, sex, weight, height, and BMI (19). The exclusion criteria for the control group were as follows: patients with (1) a history of shoulder trauma and surgery and (2) a history of shoulder disease.

The participants were recruited for this study from October 2021 to April 2022. This study was approved by the Ethics Committee of Weifang Medical College, and all participants provided written informed consent before participation.

Clinical evaluation

Before the ultrasonic measurement, all patients were evaluated by experienced physiotherapists using the MAS, VAS, and Neer scores for the evaluation of shoulder muscle hypertonia, pain, and function, respectively. MAS is one of the most commonly used scales to evaluate muscle hypertonia in clinics. The clinician

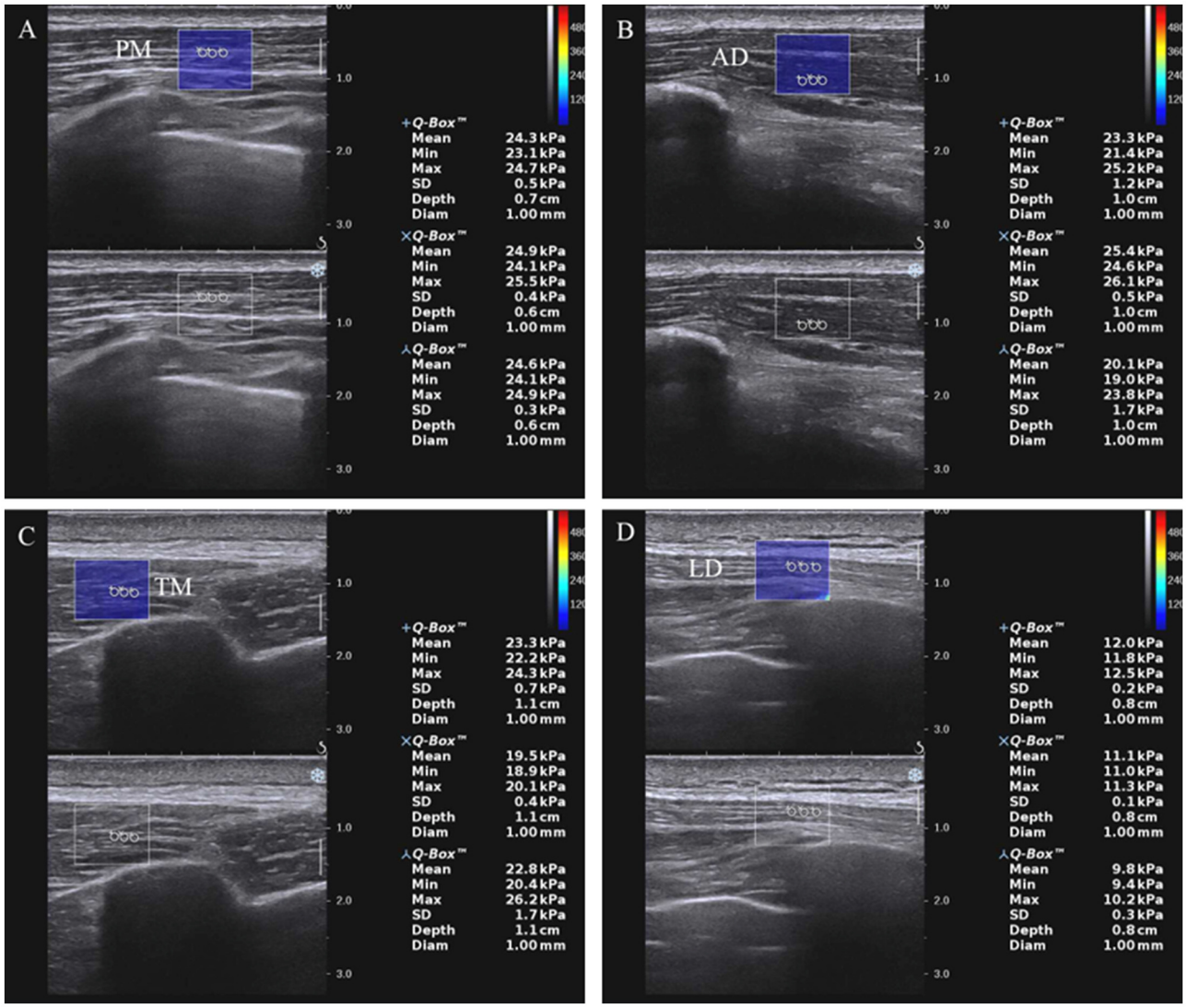


FIGURE 1
SWE images of the shoulder internal rotation muscles at rest **(A–D)** in patients with HSP. The dark blue area on the left is the elastic sampling frame. Three white circles are regions of interest. PM, pectoralis major; AD, anterior deltoid; TM, teres major; LD, latissimus dorsi.

passively moved the patient's upper limb in the 0° to 90° range of external rotation and rated the resistance from 0 (no increase in muscle tone) to 4 (the joint is rigid) (20), and the patients were asked to rate their sense of pain numerically (VAS) on a scale from 0 to 10, with 0 representing "no pain" and 10 indicating "very severe pain." The Neer score consists of four aspects, namely, numerical ratings of pain, function, range of motion, and anatomy, with a total score of 100 points. A higher score indicates a better shoulder function (21).

Experimental equipment

Ultrasound images were captured using the SWE ultrasound system (Supersonic Imagine, Aix-en-Provence, France) with a 2–10 MHz linear transducer array (Super Linear, 10-2, Vermon, France). All subjects were seated in a neutral position with the torso, shoulder abduction 0°, and upper limbs naturally relaxed on the legs. The probe was applied perpendicularly to the skin, paralleling the muscle bundle. First, the measurement position was determined by the B-mode grayscale. Thereafter, SWE was switched to establish the region of interest (ROI), set to an ROI of 1 mm diameter, and a depth of 0–2 cm (Figure 1 and Supplementary Figure S1). YM was measured three times at the same location, and the average value was taken for analysis. Participants were asked to hold their breath during the measurement to avoid muscle elongation by chest movement. The patient's upper limb was then passively stretched to shoulder abduction at 45° and maximum tolerable external rotation (4, 22, 23), which could induce muscle hypertonia and pain through this position, and YM of the muscle in the passive stretching position was measured.

The measurement sites were as follows: PM was measured at the midpoint between the greater tubercle of the humerus and sternoclavicular joint; anterior deltoid (AD) was measured at a site

2 to 3 cm below 1/3 lateral to the midpoint of the clavicle. The probe is perpendicular to the line between the inferior angle of the scapula and the acromion to measure TM; LD was measured at the position of the eighth thoracic vertebra parallel to the lower part of the inferior angle of the scapular.

Statistical analyses

The Mann–Whitney test or independent samples *t*-test was used for the comparisons as appropriate, and the Shapiro–Wilk test was used to check whether the data conformed to normal distribution. The gender distribution between HSP and healthy controls was compared using the chi-square test. The correlations between muscle stiffness and the MAS, VAS, and Neer score were analyzed using Spearman's rank test. The *p*-values of multiple comparisons and correlation analysis were corrected by controlling the false discovery rate (FDR) at a level of 0.05 (24). All calculations were performed in SPSS Statistics 26 (SPSS Inc, Chicago, IL, USA).

Results

Subject characteristics

The demographic data are summarized in Table 1. A total of 20 HSP patients (14 male and 6 female patients) and 20 healthy controls (13 male and 7 female patients) were included for further analysis. The average ages of HSP patients and the control group were 53.90 ± 7.17 years and 57.10 ± 3.51 years, respectively. The average body weight of HSP patients and control group were 66.37 ± 9.44 kg and 64.33 ± 9.45 kg, respectively. The mean height of HSP patients and the control group were 168.20 ± 6.22 cm and 165.10 ± 7.20 cm, respectively. The mean BMI of HSP patients and control group were 23.42 ± 2.78 kg/m^2 and 23.57 ± 2.60 kg/m^2, respectively. There was no statistical difference in age, height, weight, and BMI between the two groups (all $P > 0.05$).

The results of the clinical evaluation for the HSP group are summarized in Table 2. According to the MAS evaluation, six patients were in level 1, nine in level 1+, three in level 2, and two in level 3. On the VAS scale, the distribution of patients ranged from 1 to 8. In the Neer score, 15 patients scored below 70, and five scored 80–89.

TABLE 1 Clinical data of control and HSP groups.

	Control	HSP	*P*-value
Males: females	13:7	14:6	0.736
Age (years)	57.10 ± 3.51	53.90 ± 7.17	0.070
Body height (cm)	165.10 ± 7.20	168.20 ± 6.22	0.082
Weight (kg)	64.33 ± 9.45	66.37 ± 9.44	0.497
BMI (kg/m^2)	23.57 ± 2.60	23.42 ± 2.78	0.892
Infarction	—	15	—
Hemorrhage	—	5	—
paretic side (right: left)	—	11:9	—
Duration post-stroke (mo)	—	2.6 ± 1.27	—

BMI, body mass index; HSP, hemiplegic shoulder pain, $P < 0.05$ was considered statistical significance.

SWE evaluation

There was no significant difference in the stiffness of shoulder internal rotation muscles between the two sides of the control group in the resting and passive stretching positions (all $P > 0.05$) (Supplementary Table 1 and Supplementary Figure S2). The dominant side of the control group was used to compare with the HSP group. Compared with the control group, YM of PM, AD, TM, and LD on the paretic side of HSP patients were significantly increased in the resting and passive stretching positions (all $P < 0.001$) (Table 3 and Figure 2). Then, the YM of the paretic side was measured at shoulder abduction 45° and maximum tolerable external rotation, concluding that the YM of the paretic side under passive stretching was significantly higher than that at rest (all $P < 0.001$) (Table 3 and Figure 3).

Correlation between muscle stiffness and the MAS, VAS, and Neer scores

No correlation was found between stiffness and MAS in PM (r = 0.083, $P = 0.727$), AD (r = −0.051, $P = 0.832$), TM (r = −0.039, $P = 0.869$), and LD (r = 0.223, $P = 0.344$) at rest. However, YM of PM (r = 0.839, $P = 0.000$), TM (r = 0.491, $P = 0.044$), and LD (r = 0.478, $P = 0.044$) were correlated with MAS during passive stretching (Figures 4A–C). YM of AD (r = −0,030, $P = 0.901$) did not correlate with MAS. YM of TM was positively correlated with VAS (r = 0.562, $P = 0.039$) (Figure 4D). In addition, the YM of TM was also negatively correlated with the Neer score (r = −0.553, $P = 0.046$) (Figure 4E).

TABLE 2 Clinical evaluation information of HSP patients.

	N		N
MAS		VAS	
0	0	0	0
1	6	1	2
1+	9	2	3
2	3	3	3
3	2	4	2
4	0	5	4
Neer score		6	5
>90	0	7	0
80–89	5	8	1
71–79	0	9	0
≤70	15	10	0

MAS, modified Ashworth scale; VAS, visual analog scale; N, number.

TABLE 3 Comparison of the paretic side of the HSP group with the dominant side of the control group at rest and stretching position.

	Rest			Stretching		
	Paretic side (kPa)	Dominant side (kPa)	*P*-value	Paretic side (kPa)	Dominant side (kPa)	*P*-value
PM	22.26 ± 2.27	14.55 ± 1.53	0.000**	31.88 (29.79, 35.61)	21.90 (21.13, 23.20)	0.000**
AD	22.50 (21.29, 23.64)	15.90 (14.77, 16.51)	0.000**	32.58 (29.23, 35.15)	23.98 (22.49, 25.20)	0.000**
TM	22.76 ± 2.51	15.37 ± 1.10	0.000**	30.09 ± 4.68	22.10 ± 1.33	0.000**
LD	12.48 ± 1.82	8.41 ± 0.89	0.000**	14.85 ± 2.26	11.92 ± 0.95	0.000**

The data conforming to a normal distribution are expressed as mean and standard deviation, while data conforming to a non-normal distribution are expressed as median (quartiles). PM, pectoralis major; AD, anterior deltoid; TM, teres major; LD, latissimus dorsi. **indicates $P < 0.001$.

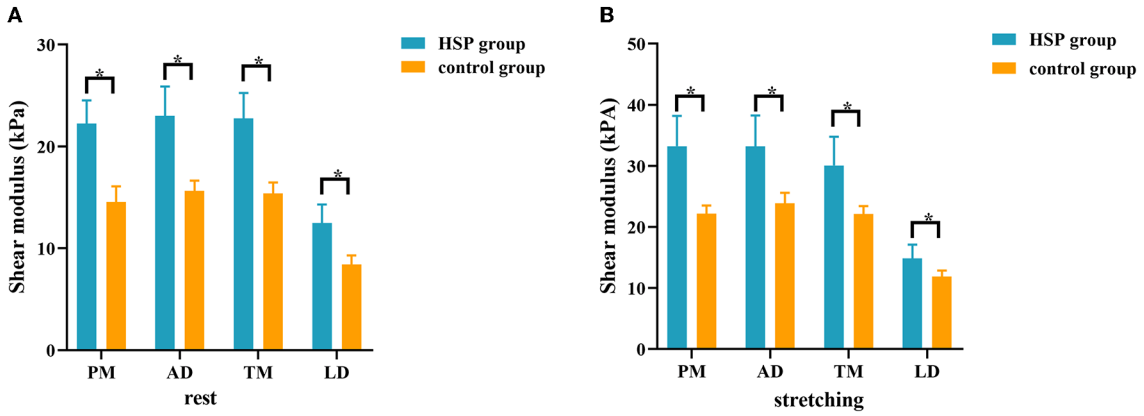


FIGURE 2
Comparison of the stiffness of shoulder internal rotation muscles between patients with HSP and healthy controls in the resting and passive stretching states. The stiffness of internal rotation muscles was higher in HSP patients than in healthy controls in both the resting **(A)** and passive stretching **(B)** positions. *$p < 0.05$. PM, pectoralis major; AD, anterior deltoid; TM, teres major; LD, latissimus dorsi.

Discussion

Using ultrasonic SWE, we found that the stiffness of shoulder internal rotation muscles was significantly increased on the paretic side of patients with HSP. Moreover, as to paretic side muscles, the muscle stiffness was significantly higher during passive stretching than at rest. The stiffness of PM, TM, and LD during passive stretching was correlated with MAS. We also found that the stiffness of TM was positively correlated with the VAS and negatively correlated with the Neer score. These results suggested that the increased stiffness of the shoulder's internal rotation muscles may be related to the severity of HSP.

In this study, SWE was used to evaluate the internal rotation muscles of the shoulder. The results of our study were consistent with the study of Lee et al. (19). They reported that stroke patients had higher SWV in the biceps on the paretic side than controls. This may be attributed to the change in muscle segment length. Fridén et al. (25) found that resting muscle segment length in spastic patients was shorter than that in normal ones. In addition, after nerve injury, the muscle structure was changed, with stiffer fibers (26), increased muscle collagen, and abnormal aggregation of extracellular matrix (27). These studies suggested that changes in the composition and structure of paretic muscles may cause increased passive stiffness (28). We also observed the stiffness of the paretic side muscles at shoulder abduction 45°, and maximum tolerable external rotation was significantly higher than that at rest position. As the muscle is stretched, the length of the muscle increases, creating greater passive resistance and increases in stiffness. Lee et al. (29) found that SWV was positively correlated

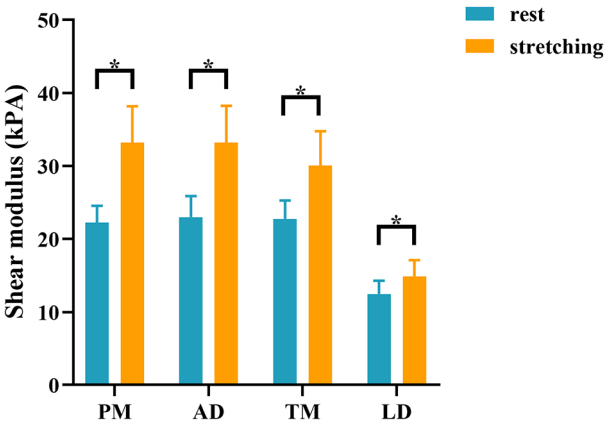


FIGURE 3
Comparison of the stiffness of shoulder internal rotation muscles in the resting and passive stretching positions in patients with HSP. The stiffness of internal rotation muscles in the HSP group was higher in the stretching position than in the resting position. *$p < 0.05$. PM, pectoralis major; AD, anterior deltoid; TM, teres major; LD, latissimus dorsi.

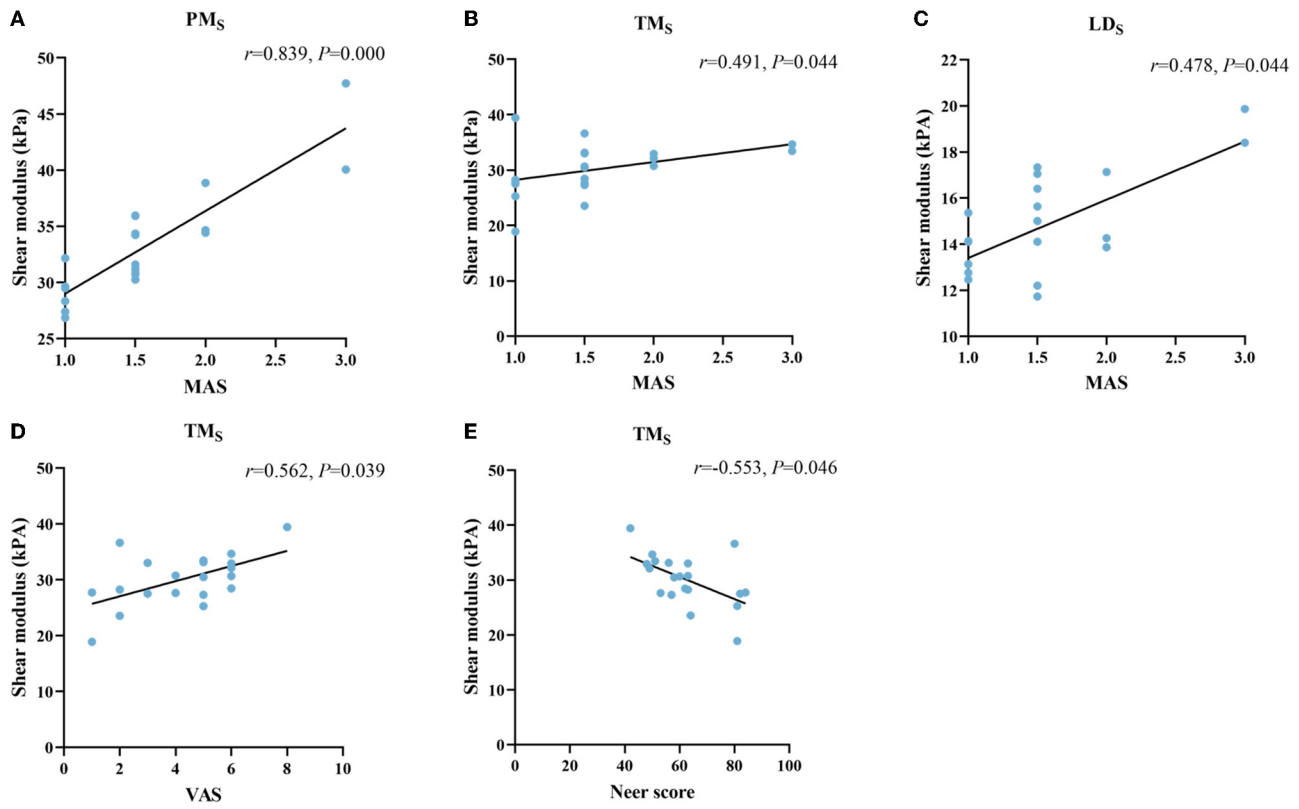


FIGURE 4
Correlation between the stiffness of shoulder internal rotation muscles with the MAS, VAS, and Neer score in patients with HSP. The stiffness of PM **(A)**, TM **(B)**, and LD **(C)** at stretched (S subscript) was positively correlated with MAS. The stiffness of TM **(D, E)** was positively correlated with the VAS and negatively correlated with the Neer score. PM, pectoralis major; TM, teres major; LD, latissimus dorsi.

with muscle length, and the changes in SWV were associated with an increase in passive tension. Moreover, passive muscle tension is related to titin (30), which bears the major load when the muscle is passively stretched (31). However, the role of titin in passive tension may vary considerably in different muscles (30), and whether titin isoform size was altered in stroke patients with hypertonia was still controversial (27, 32).

In stroke patients, it has been reported that shoulder pain was related to muscle hypertonia, motor, sensory disturbance, and musculoskeletal system problems (33). Previous studies using the SWE technique have reported a correlation between the stiffness of the upper limb hypertonic muscle and MAS in stroke patients (18, 34, 35). However, these studies have focused on the flexors of the upper extremity, and few studies have involved the girdle of the shoulder. In this study, we also found that the stiffness of PM, TM, and LD during passive stretching was correlated with MAS, and the stiffness of internal rotation muscles was not related to MAS at rest. This may be because the stiffness of the muscles in the stretched state better reflects the differences between pathological muscles (36). Our results showed that the stiffness of PM was highly correlated with MAS, and the stiffness of TM and LD was weakly correlated with MAS. This indicates that the stiffness changes of internal rotation muscles under passive stretching, especially PM, were consistent with MAS. The muscle hypertonia of PM was more predominant in the shoulder than in other muscles. With the muscle hypertonia of TM and LD, shoulder movement is inhibited. These results are consistent with clinical features. Many patients' families reported that muscle tension was increased only when the shoulder joint was passively moved. In chronic stroke patients, it has been reported that patients with higher MAS scores have longer shoulder pain duration, which often leads to secondary complications (7).

In this study, we analyzed the correlation between the stiffness of internal rotation muscles of the shoulder and VAS and Neer scores, finding that only the stiffness of TM was correlated with them. This is probably because TM is the main internal rotation muscle, and when TM hypertonia occurs, it leads to limited external rotation and shoulder abduction and causes pain. The results indicated that HSP patients with higher muscle stiffness may have more severe pain, and treatment to reduce muscle stiffness may relieve pain. This finding was consistent with the results of Itoigawa et al. (37). They also found a significant correlation between muscle stiffness and shoulder pain during exercise. In addition, the TM, as a deep muscle, may have a more significant dominant effect on the internal rotation of the shoulder joint. This result provides a new intervention idea for clinical practitioners that deep muscles may play an essential role in the development of HSP and focusing interventions on deep muscles of HSP patients may better

relieve their shoulder pain. Currently, botulinum toxin-A (BoNT-A) combined with rehabilitation treatment, such as passive muscle stretching and exercise therapy, is an effective method of treating HSP to relieve pain and increase joint mobility (38). Ashford et al. (39) conducted the intervention of BoNT-A combined with rehabilitation therapy on hypertonic muscles of 16 patients with shoulder pain, and the results showed that hypertonia and pain of patients were significantly improved. However, BoNT-A is rarely used in TM alone. Aksoy et al. (6) compared the efficacy of BoNT-A injections in PM and TM (Group 1) with a suprascapular nerve block (Group 2). They found that the two groups had the same effect in the short term (2 weeks), while the improvement in pain and range of motion was more significant in the medium term (6 weeks) in group 1. Many previous studies have chosen PM combined with TM for treatment possibly because the majority of patients treated with BoNT-A had moderate-severe muscle hypertonia. In this study, our results initially suggested that the stiffness of TM was associated with pain and impaired movement in patients with mild-moderate muscle hypertonia. However, the results still need to be confirmed in a larger cohort.

There are several limitations to this study. First, SWE cannot fully observe the stiffness of the subscapular due to the special anatomical position, which may affect the judgment of the author. Second, we only assessed the pain intensity of HSP patients using the VAS scale, but not the frequency and duration of pain, and the VAS had a large range, which could have influenced the results. At present, self-reporting is an effective method to measure pain. However, VAS can still be used as a method to evaluate pain due to the special population. Third, the SWE has some limitations. For example, transducer placement, muscle position, and the lack of a uniform measure have limited the development of SWE in the musculoskeletal field. Fourth, although we measured multiple times in order to reduce the error, we did not calculate intraclass correlation coefficients to evaluate the reliability of SWE in the HSP group. In addition, the relationship between MAS grade 4 and muscle stiffness could not yet be determined because patients with MAS grade 4 were unable to cooperate with passive stretching movement. Finally, due to the small sample size, the results of this study need to be validated in a larger cohort.

In conclusion, our study found increased stiffness of the internal rotation muscles in patients with HSP. The stiffness of the TM was associated with the pain intensity and function of the shoulder. The stiffness of internal rotation muscles can be used as a quantitative indicator for HSP evaluation.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Weifang Medical College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FJ, X-RZ, L-YK, and X-ZY developed the study concept and design. FJ and X-RZ collected clinical and imaging data and interpreted the data. S-YZ and X-ZY designed and revised this manuscript. J-CF, Z-JZ, and L-ZL analyzed the data. FJ wrote the first draft. All authors critically reviewed this manuscript, contributed to this article, and approved the submitted version.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1195915/full#supplementary-material

References

1. Yelnik AP, Colle FM, Bonan IV. Treatment of pain and limited movement of the shoulder in hemiplegic patients with botulinum toxin a in the subscapular muscle. *Eur Neurol.* (2003) 50:91–3. doi: 10.1159/000072505

2. Najenson T, Yacubovich E, Pikielni SS. Rotator cuff injury in shoulder joints of hemiplegic patients. *Scand J Rehabil Med.* (1971) 3:131–7.

3. Wilson RD, Chae J. Hemiplegic shoulder pain. *Phys Med Rehabil Clin N Am.* (2015) 26:641–55. doi: 10.1016/j.pmr.2015.06.007

4. Vasudevan JM, Browne BJ. Hemiplegic shoulder pain: an approach to diagnosis and management. *Phys Med Rehabil Clin N Am.* (2014) 25:411–37. doi: 10.1016/j.pmr.2014.01.010

5. Niessen M, Janssen T, Meskers C, Koppe P, Konijnenbelt M, Veeger D. Kinematics of the contralateral and ipsilateral shoulder: a possible relationship with post-stroke shoulder pain. *J Rehabilit Med.* (2008) 40:482–6. doi: 10.2340/16501977-0201

6. Kasapoglu-Aksoy M, Aykurt-Karlibel I, Altan L. Comparison of the efficacy of intramuscular botulinum toxin type-a injection into the pectoralis major and the

teres major muscles and suprascapular nerve block for hemiplegic shoulder pain: a prospective, double-blind, randomized, controlled trial. *Neurol Sci.* (2020) 41:2225–30. doi: 10.1007/s10072-020-04334-4

7. Lundström E, Terént A, Borg J. Prevalence of disabling spasticity 1 year after first-ever stroke. *Eur J Neurol.* (2008) 15:533–9. doi: 10.1111/j.1468-1331.2008.02114.x

8. Chuang LL, Chen YL, Chen CC, Li YC, Wong AM, Hsu AL, et al. Effect of EMG-triggered neuromuscular electrical stimulation with bilateral arm training on hemiplegic shoulder pain and arm function after stroke: a randomized controlled trial. *J Neuroeng Rehabil.* (2017) 14:122. doi: 10.1186/s12984-017-0332-0

9. Karaahmet OZ, Eksioglu E, Gurcay E, Karsli PB, Tamkan U, Bal A, et al. Hemiplegic shoulder pain: associated factors and rehabilitation outcomes of hemiplegic patients with and without shoulder pain. *Top Stroke Rehabil.* (2014) 21:237–45. doi: 10.1310/tsr2103-237

10. Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke.* (2004) 35:134–9. doi: 10.1161/01.STR.0000105386.05173.5E

11. Davis LC, Baumer TG, Bey MJ, Holsbeeck MV. Clinical utilization of shear wave elastography in the musculoskeletal system. *Ultrasonography.* (2019) 38:2–12. doi: 10.14366/usg.18039

12. Gennisson JL, Deffieux T, Fink M, Tanter M. Ultrasound elastography: principles and techniques. *Diagn Interv Imaging.* (2013) 94:487–95. doi: 10.1016/j.diii.2013.01.022

13. Bastijns S, De Cock AM, Vandewoude M, Perkisas S. Usability and pitfalls of shear-wave elastography for evaluation of muscle quality and its potential in assessing sarcopenia: a review. *Ultrasound Med Biol.* (2020) 46:2891–907. doi: 10.1016/j.ultrasmedbio.2020.06.023

14. Boulard C, Mathevon L, Arnaudeau LF, Gautheron V, Calmels P. Reliability of shear wave elastography and ultrasound measurement in children with unilateral spastic cerebral palsy. *Ultrasound Med Biol.* (2021) 47:1204–11. doi: 10.1016/j.ultrasmedbio.2021.01.013

15. Gao J, He W, Du LJ, Chen J, Park D, Wells M, et al. Quantitative ultrasound imaging to assess the biceps brachii muscle in chronic post-stroke spasticity: preliminary observation. *Ultrasound Med Biol.* (2018) 44:1931–40. doi: 10.1016/j.ultrasmedbio.2017.12.012

16. Huang YC, Liang PJ, Pong YP, Leong CP, Tseng CH. Physical findings and sonography of hemiplegic shoulder in patients after acute stroke during rehabilitation. *J Rehabilit Med.* (2010) 42:21–6. doi: 10.2340/16501977-0488

17. Uzdu A, Kirazli Y, Karapolat H, Unlu B, Tanigör G, Çaliş FA. Efficacy of platelet-rich plasma in the treatment of hemiplegic shoulder pain. *Neurol Sci.* (2021) 42:1977–86. doi: 10.1007/s10072-020-04710-0

18. Wu CH, Ho YC, Hsiao MY, Chen WS, Wang TG. Evaluation of post-stroke spastic muscle stiffness using shear wave ultrasound elastography. *Ultrasound Med Biol.* (2017) 43:1105–11. doi: 10.1016/j.ultrasmedbio.2016.12.008

19. Lee SSM, Jakubowski KL, Spear SC, Rymer WZ. Muscle material properties in passive and active stroke-impaired muscle. *J Biomech.* (2019) 83:197–204. doi: 10.1016/j.jbiomech.2018.11.043

20. Eby S, Zhao H, Song P, Vareberg BJ, Kinnick R, Greenleaf JF, et al. Quantitative evaluation of passive muscle stiffness in chronic stroke. *Am J Phys Med Rehabil.* (2016) 95:899–910. doi: 10.1097/PHM.0000000000000516

21. Brien H, Noftall F, MacMaster S, Cummings T, Landells C, Rockwood P. Neer's classification system: a critical appraisal. *J Trauma.* (1995) 38:257–60. doi: 10.1097/00005373-199502000-00022

22. Francisco-Martínez C, Padilla-Medina JA, Prado-Olivarez J, Pérez-Pinal FJ, Barranco-Gutiérrez AI, Martínez-Nolasco JJ. Kinect V2-assisted semi-automated method to assess upper limb motor performance in children. *Sensors.* (2022) 22:2258. doi: 10.3390/s22062258

23. Dean CM, Mackey FH, Katrak P. Examination of shoulder positioning after stroke: a randomised controlled pilot trial. *Aust J Physiother.* (2000) 46:35–40. doi: 10.1016/S0004-9514(14)60312-3

24. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B—Methodol.* (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

25. Fridén J, Lieber RL. Spastic muscle cells are shorter and stiffer than normal cells. *Muscle Nerve.* (2003) 27:157–64. doi: 10.1002/mus.10247

26. Lieber RL, Runesson E, Einarsson F, Fridén J. Inferior mechanical properties of spastic muscle bundles due to hypertrophic but compromised extracellular matrix material. *Muscle Nerve.* (2003) 28:464–71. doi: 10.1002/mus.10446

27. Smith LR, Lee KS, Ward SR, Chambers HG, Lieber RL. Hamstring contractures in children with spastic cerebral palsy result from a stiffer extracellular matrix and increased in vivo sarcomere length. *J Physiol.* (2011) 589:2625–39. doi: 10.1113/jphysiol.2010.203364

28. Lieber RL, Ward SR. Cellular Mechanisms of Tissue Fibrosis. 4 Structural and Functional Consequences of Skeletal Muscle Fibrosis. *Am J Physiol Cell Physiol.* (2013) 305:C241–52. doi: 10.1152/ajpcell.00173.2013

29. Lee SS, Gaebler-Spira D, Zhang LQ, Rymer WZ, Steele KM. Use of shear wave ultrasound elastography to quantify muscle properties in cerebral palsy. *Clin Biomech.* (2016) 31:20–8. doi: 10.1016/j.clinbiomech.2015.10.006

30. Prado LG, Makarenko I, Andresen C, Krüger M, Opitz CA, Linke WA. Isoform diversity of giant proteins in relation to passive and active contractile properties of rabbit skeletal muscles. *J Gen Physiol.* (2005) 126:461–80. doi: 10.1085/jgp.200509364

31. Magid A, Law DJ. Myofibrils bear most of the resting tension in frog skeletal muscle. *Science (New York, NY).* (1985) 230:1280–2. doi: 10.1126/science.4071053

32. Olsson MC, Krüger M, Meyer LH, Ahnlund L, Gransberg L, Linke WA, et al. Fibre type-specific increase in passive muscle tension in spinal cord-injured subjects with spasticity. *J Physiol.* (2006) 577:339–52. doi: 10.1113/jphysiol.2006.116749

33. Roosink M, Renzenbrink GJ, Buitenweg JR, Van Dongen RT, Geurts AC MJ IJ. Persistent shoulder pain in the first 6 months after stroke: results of a prospective cohort study. *Arch Phys Med Rehabil.* (2011) 92:1139–45. doi: 10.1016/j.apmr.2011.02.016

34. Galvão S, de Oliveira LF, de Lima R, Xerez D, Menegaldo LL. Shear wave elastography of the brachioradialis spastic muscle and its correlations with biceps brachialis and clinical scales. *Clin Biomech.* (2022) 97:105687. doi: 10.1016/j.clinbiomech.2022.105687

35. Liu J, Pan H, Bao Y, Zhao Y, Huang L, Zhan W. The value of real-time shear wave elastography before and after rehabilitation of upper limb spasm in stroke patients. *Biomed Res Int.* (2020) 2020:6472456. doi: 10.1155/2020/6472456

36. Dubois G, Kheireddine W, Vergari C, Bonneau D, Thoreux P, Rouch P, et al. Reliable protocol for shear wave elastography of lower limb muscles at rest and during passive stretching. *Ultrasound Med Biol.* (2015) 41:2284–91. doi: 10.1016/j.ultrasmedbio.2015.04.020

37. Itoigawa Y, Koga A, Morikawa D, Kubota A, Uehara H, Maruyama Y, et al. Posterior shoulder stiffness was associated with shoulder pain during throwing in college baseball players: assessment of shear wave elastography. *Eur J Orthop Surg Traumatol.* (2022) 33:1237–1244. doi: 10.1007/s00590-022-03286-z

38. Franceschini M, Iocco M, Molteni F, Santamato A, Smania N. Management of stroke patients submitted to botulinum toxin type a therapy: a delphi survey of an italian expert panel of specialist injectors. *Eur J Phys Rehabil Med.* (2014) 50: 525–33.

39. Ashford S, Turner-Stokes L. Management of shoulder and proximal upper limb spasticity using botulinum toxin and concurrent therapy interventions: a preliminary analysis of goals and outcomes. *Disabil Rehabil.* (2009) 31:220–6. doi: 10.1080/09638280801906388

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 02 June 2023
DOI 10.3389/fneur.2023.1139048

OPEN ACCESS

EDITED BY
Haiqing Zheng,
Third Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Christoph Stretz,
Brown University, United States
Xian-Hua Han,
Yamaguchi University, Japan

*CORRESPONDENCE
Xu Qiao
✉ qiaoxu@sdu.edu.cn
Hongfeng Shi
✉ 221170300422@stu.haut.edu.cn

†These authors have contributed equally to this work

RECEIVED 06 January 2023
ACCEPTED 08 May 2023
PUBLISHED 02 June 2023

CITATION
Yang G, Xu M, Chen W, Qiao X, Shi H and Hu Y (2023) A brain CT-based approach for predicting and analyzing stroke-associated pneumonia from intracerebral hemorrhage. *Front. Neurol.* 14:1139048. doi: 10.3389/fneur.2023.1139048

A brain CT-based approach for predicting and analyzing stroke-associated pneumonia from intracerebral hemorrhage

Guangtong Yang[1†], Min Xu[2†], Wei Chen[3], Xu Qiao[1*], Hongfeng Shi[2*] and Yongmei Hu[1]

[1]School of Control Science and Engineering, Shandong University, Jinan, China, [2]Neurointensive Care Unit, Shengli Oilfield Central Hospital, Dongying, China, [3]Department of Radiology, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Introduction: Stroke-associated pneumonia (SAP) is a common complication of stroke that can increase the mortality rate of patients and the burden on their families. In contrast to prior clinical scoring models that rely on baseline data, we propose constructing models based on brain CT scans due to their accessibility and clinical universality.

Methods: Our study aims to explore the mechanism behind the distribution and lesion areas of intracerebral hemorrhage (ICH) in relation to pneumonia, we utilized an MRI atlas that could present brain structures and a registration method in our program to extract features that may represent this relationship. We developed three machine learning models to predict the occurrence of SAP using these features. Ten-fold cross-validation was applied to evaluate the performance of models. Additionally, we constructed a probability map through statistical analysis that could display which brain regions are more frequently impacted by hematoma in patients with SAP based on four types of pneumonia.

Results: Our study included a cohort of 244 patients, and we extracted 35 features that captured the invasion of ICH to different brain regions for model development. We evaluated the performance of three machine learning models, namely, logistic regression, support vector machine, and random forest, in predicting SAP, and the AUCs for these models ranged from 0.77 to 0.82. The probability map revealed that the distribution of ICH varied between the left and right brain hemispheres in patients with moderate and severe SAP, and we identified several brain structures, including the left-choroid-plexus, right-choroid-plexus, right-hippocampus, and left-hippocampus, that were more closely related to SAP based on feature selection. Additionally, we observed that some statistical indicators of ICH volume, such as mean and maximum values, were proportional to the severity of SAP.

Discussion: Our findings suggest that our method is effective in classifying the development of pneumonia based on brain CT scans. Furthermore, we identified distinct characteristics, such as volume and distribution, of ICH in four different types of SAP.

KEYWORDS

image registration, intracerebral hemorrhage, stroke-associated pneumonia, machine learning, statistical analysis

1. Introduction

Stroke-associated Pneumonia (SAP) is a serious complication for patients with intracerebral hemorrhage (ICH), leading to increased hospitalization time, medical expenses, and mortality rates (1–4). The causes of SAP can be categorized as central or non-central factors, with the former including disturbance of consciousness and bulbar palsy, and the latter including bed rest, pulmonary edema, and pre-existing chronic respiratory conditions such as COPD, bronchiectasis, and pulmonary fibrosis (5, 6). While tracheal intubation can protect the airway, it also increases the risk of ventilator-associated pneumonia (VAP) (7, 8). To effectively identify high-risk groups of pneumonia in patients with acute and severe ICH, clinicians commonly use pneumonia CT scans to review lung infections (9). Accurately identifying pneumonia-prone patients is essential to guide clinical decisions regarding tracheal intubation and to provide timely interventions to reduce the risk of pneumonia in this vulnerable population, especially for inexperienced healthcare providers.

Risk factors associated with pneumonia include immunosuppression, dysphagia, age, sex, smoking, stroke severity, stroke type, hypertension, diabetes, history of chronic respiratory disease, and history of atrial fibrillation (10, 11), which are usually referred as baseline (clinical) data. Previous studies suggest that predicting the risk of a lung infection after stroke can help doctors select interventions to reduce morbidity in high-risk patients (4). Ji et al. (12) developed an SAP risk model "ICH-APS" based on the patients' baseline data, which could effectively predict pneumonia after ICH, especially for patients whose hospitalization time was more than 48 h. Yan et al. (13) used the permutation method to select the characteristics and finally constructed a logical regression model called "ICH-LR2S2" using nine patient characteristics, including dysphagia, age, sex, and fasting blood glucose. But baseline data is hard to collect and could not build a relationship with ICH distribution. If the ICH region corresponds to the relevant brain area, it will have a meaningful and positive effect on the study of the generation mechanism and progression of SAP (14). CT is the most common experimental method for ICH patients, and it is feasible to locate bleeding areas and distinguish between left and right hemispheres using CT images due to the different Hounsfield unit (Hu) values; however, CT images cannot accurately label the brain structure; therefore, high-quality brain MRI images are required. Brain MRI is being increasingly used in research and clinical medicine to obtain high-quality images of the brain's anatomical structure, providing detailed information for clinical diagnosis and biomedical research (15, 16). Medical image registration has important clinical application value: the registration of medical images obtained by various or the same imaging methods is used for medical diagnosis as well as in formulating surgical plans, formulating radiation therapy plans, tracking pathological changes, and evaluating treatment effects (17–20). However, thus far, no research on the relationship between ICH and pneumonia through medical image registration technology has been reported.

In this study, we propose a registration method to match brain CT images with MRI images representing the brain's anatomical structure. This allows us to obtain the anatomical distribution characteristics of the hemorrhage area, which we refer to as the "bleeding distribution feature". Since the hemorrhagic mass can squeeze the patient's brain tissue, we also determine the "bleeding squeezing feature" based on the relationship between the total bleeding magnitude and the patient's brain tissue. Using these features, we establish three machine learning models to predict the severity of SAP using brain CT instead of lung CT in clinical situations. We can further discuss important features by implementing feature selection. Additionally, we superimpose transformed binary bleeding area images from four pneumonia categories to build a statistical model and probability atlas. This visualization and analysis of the distribution of cerebral hemorrhages in different pneumonia categories can be beneficial for diagnosis and treatment. The flow chart of this study is shown in Figure 1.

2. Materials and methods

2.1. Datasets

Our dataset comprises 244 brain CT images, each with a corresponding segmented image of ICH. Experienced neurologists annotated the ICH area using ITK-Snap software, while the patient's name, gender, underlying disease, admission time, corresponding treatment, and other basic information were recorded in detail. Following a previous study (21), we assessed the extent of pneumonia in patients with early ICH (1–4 days of onset) by evaluating the lung involvement area on chest CT (classified as mild, moderate, or severe based on involvement percentages of 1–25, 26–50, and 51–100%, respectively). All chest CT images were independently reviewed by two radiologists with more than 10 years of experience, who were blinded to clinical and laboratory findings. The images were subsequently categorized into 19 cases of severe pneumonia, 47 cases of moderate pneumonia, 77 cases of mild pneumonia, and 101 cases of no pneumonia.

After obtaining informed consent from the local ethics committee (Q/ZXYY–ZY–YWB–LL202243), the CT images were used for further research.

2.2. MRI atlas

In this study, a normal human brain MRI image was chosen as the reference image for registration, and its corresponding anatomical structure image was used as a template for analysis. The MRI image used in this study was obtained from the OASIS project, which contains 35 anatomical structure divisions. Any area in the image with a grayscale value of 0 was considered a blank area (22). To process the MRI image, Hoopes et al. (23) utilized FreeSurfer software to remove the skull and align the images. The image was then divided into 35 brain anatomical regions, each assigned a grayscale value ranging from 1 to 35. Table 1 provides a list of the specific structure names and their corresponding gray values. Additionally, Figures 2A, B illustrates the brain MRI image and the corresponding brain anatomical structure MRI. Figure 2E

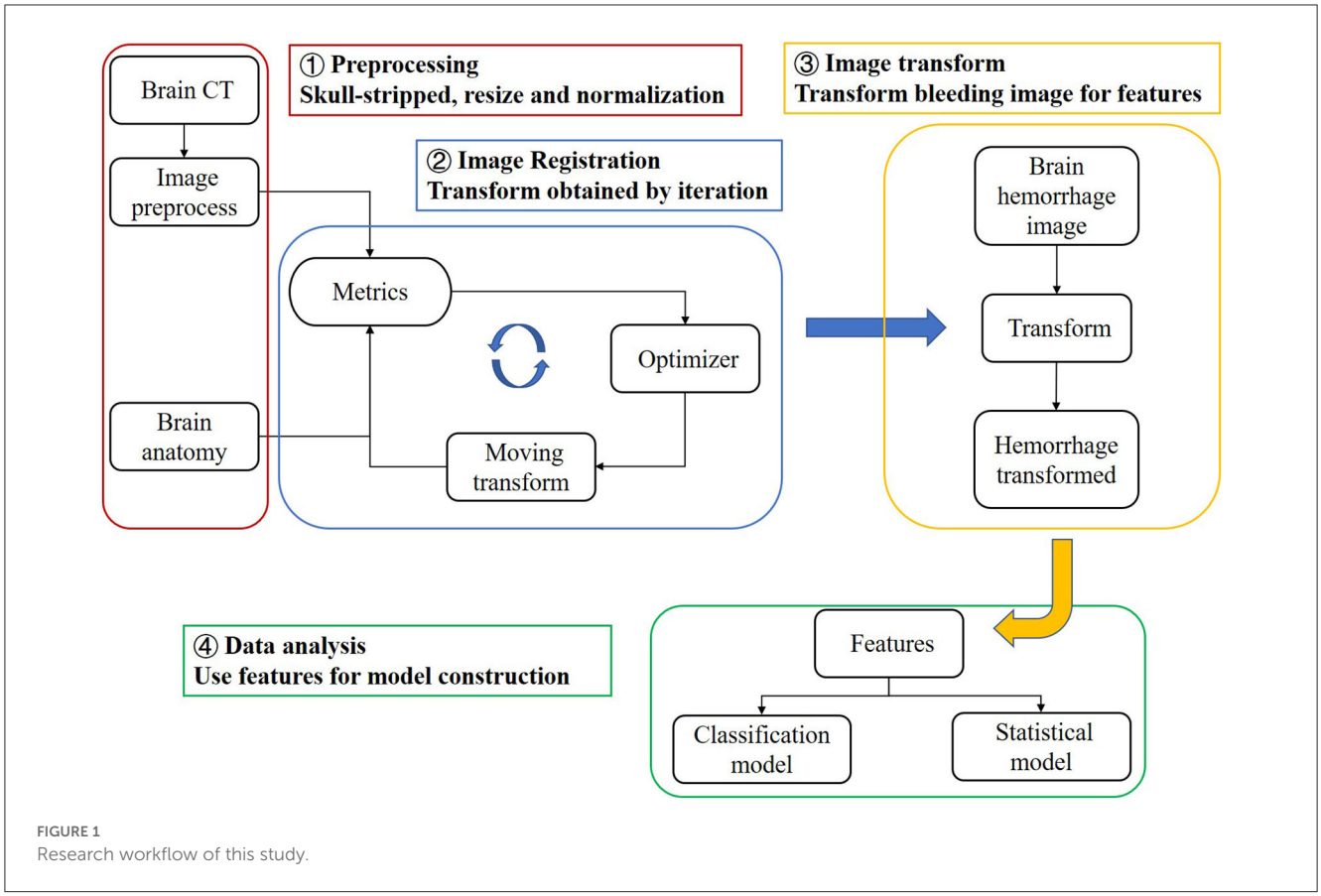


FIGURE 1
Research workflow of this study.

TABLE 1 Brain anatomical structure reference.

Gray value	Brain anatomy	Gray value	Brain anatomy	Gray value	Brain anatomy	Gray value	Brain anatomy
1	Left-Cerebral-White-Matter	10	Left-Pallidum	19	Left-Choroid-Plexus	28	Right-Putamen
2	Left-Cerebral-Cortex	11	3rd-Ventricle	20	Right-Cerebral-White-Matter	29	Right-Pallidum
3	Left-Lateral-Ventricle	12	4th-Ventricle	21	Right-Cerebral-Cortex	30	Right-Hippocampus
4	Left-Inf-Lat-Ventricle	13	Brain-Stem	22	Right-Lateral-Ventricle	31	Right-Amygdala
5	Left-Cerebellum-White-Matter	14	Left-Hippocampus	23	Right-Inf-Lat-Ventricle	32	Right-Accumbens
6	Left-Cerebellum-Cortex	15	Left-Amygdala	24	Right-Cerebellum-White-Matter	33	Right-Ventral-DC
7	Left-Thalamus	16	Left-Accumbens	25	Right-Cerebellum-Cortex	34	Right-Vessel
8	Left-Caudate	17	Left-Ventral-DC	26	Right-Thalamus	35	Right-Choroid-Plexus
9	Left-Putamen	18	Left-Vessel	27	Right-Caudate		

presents the 3D diagram of the anatomical structures resulting from the MRI images.

2.3. Acquisition of features

In this study, we used the bleeding distribution and extrusion features to construct our models. In order to obtain the bleeding distribution feature, we matched preprocessed brain CT to the brain MRI image to get the deformation field of the process and applied the deformation field to the corresponding ICH segmented image (binary bleeding image) of the patient to generate the transformed image. The transformed bleeding image was used to extract the bleeding distribution feature.

2.3.1. Image preprocessing

To improve the image registration results, several preprocessing steps, such as skull-stripping, image normalization, and resampling, were performed on the original brain CT image

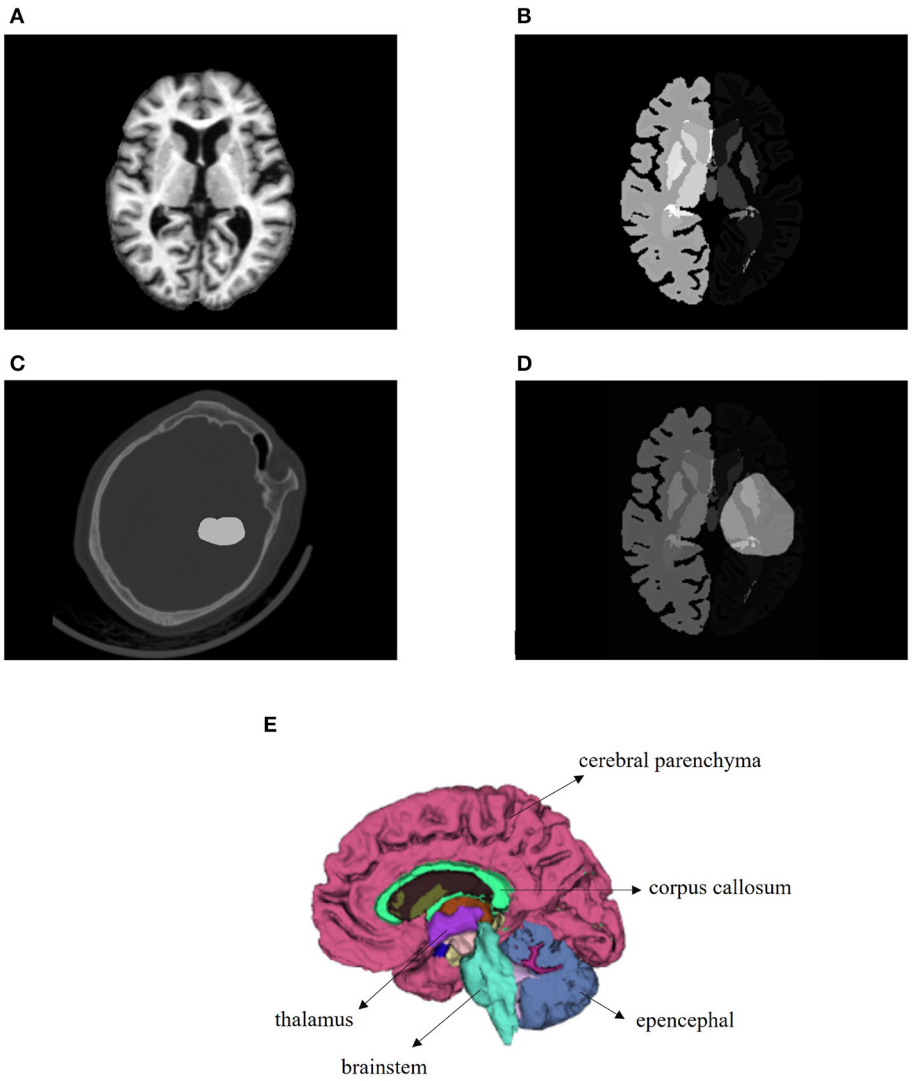


FIGURE 2
Images utilized in this paper. **(A)** Brain MRI used in the registration as a reference image. **(B)** Brain anatomical structure MRI having 35 regions. **(C)** One brain CT sample with ICH area labeled. **(D)** Transformed bleeding image shown with brain anatomical image. **(E)** Three-dimensional schematic diagram of the anatomical structure of the brain.

(24). Since the reference MRI image used as a fixed image only shows brain tissue, it was necessary to remove the skull from the patient's original CT image. To achieve this, we utilized the SegmentEditorExtraEffects and SurfaceWrapSolidify extension modules in the 3D Slicer software (25). Specifically, we created a new segment in the segmentation editor from the skull segmentation, determined the threshold to initially segment the skull, used the islands method to remove small spots caused by image noise, and applied the Wrap Solidify effect to segment the inner area of the skull as a mask. Finally, we used the mask as our output after removing the skull from the CT image. To process a large number of samples efficiently, we developed a Python script for the 3D Slicer to automate the skull-stripping operations for all samples, thereby reducing time and labor. Moreover, we used min-max normalization to preprocess the CT image after skull-stripping. The normalization equation used is as follows:

$$v = (v - min)/(max - min) \quad (1)$$

where v is the voxel value of the image and min and max are the minimum and maximum voxel values of the image, respectively. Since the obtained brain CT image and reference MRI image had different dimensions, we resampled the image to match the dimensions of the reference MRI image. The resulting images are depicted in Figure 3.

2.3.2. Image registration

According to the characteristics of our data, we performed image transformation by applying both rigid and non-rigid

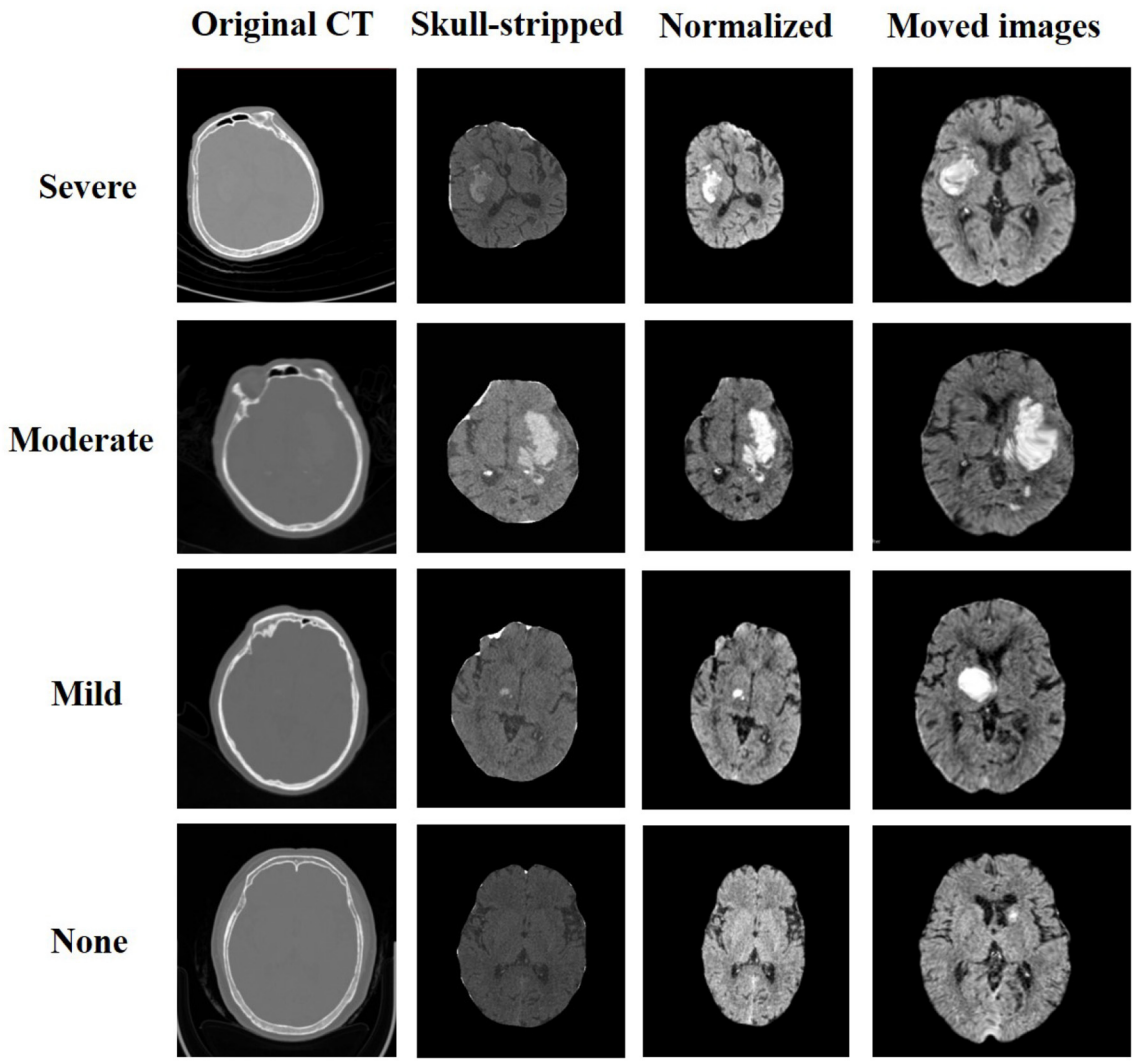


FIGURE 3
Resulted images of preprocess and registration.

registration methods (26). Rigid transform is a type of transformation that preserves the shape of an image by including translation, rotation, and scaling. It can be used to align images rigidly. Non-rigid transform refers to a type of transformation that can be used to deform, warp, or morph images. It can deform different regions of the image but cannot preserve the overall shape of the image. During the registration process, the CT image was considered as the moving image, denoted as $I_m(v)$, while the MRI image was regarded as the fixed image, denoted as $I_f(v)$, where v represents the voxel of the image. The moving image was iteratively transformed to find the most suitable transform $T(v)$ that matches the fixed image. The objective was to minimize the mutual information between the two images, which can be expressed as follows:

$$min_{x=3} MI\left(I_m(v), I_f(v)\right) \tag{2}$$

Here, the parameter $x = 3$ indicates that our image is three-dimensional. Since the moving and fixed images had different origins and orientations, we applied a rigid transformation to translate and rotate the original image without changing its size or internal structure. Next, we used non-rigid transformation to precisely match the CT image to the reference brain MRI image, using the "bspline" method and inputting the result into the previous image filter. In this process, we adopted a multi-resolution strategy to construct a resolution pyramid, and each resolution layer performed a maximum number of iterations to obtain the optimal result.

$$T = T_{rigid} + T_{nonrigid} \tag{3}$$

In our study, we utilized mutual information (MI) as the evaluation metric for each iteration of our registration process (27). MI is a versatile metric that calculates the mutual information between two images, based on the correlation of the probability density distribution (PDF) of the intensity from the fixed and moving images. MI measures the amount of information that a random variable (such as image intensity in one image) tells

another random variable (such as image brightness in another image), without requiring knowledge of the actual form of the correlation. Therefore, it is particularly suitable for multimodal image pairs and single-mode images. The output image was determined as the moving image with the highest MI score (28, 29). The images before and after the registration of one patient are presented in Figures 2C, D.

$$MI(X,Y) = I_{binned}(X,Y) = \sum_{ij} p(i,j) log(\frac{p(i,j)}{p_x(i)P_y(j)}) \quad (4)$$

Where $p_x(i) = \int_i dx\mu_x(X)$, $p_y(i) = \int_i dx\mu_x(X)$, and $p(i,j) = \int_i \int_j dxdy\mu(x,y)$ and $\int_i$ means the integral over bin I and μ means the marginal densities.

2.3.3. Bleeding area transformation

After completing the registration of the patients' CT images, we obtained the deformation field. The image of the bleeding area denoted by the doctor was binarized, where 1 and 0 represented the bleeding and non-bleeding areas, respectively. We performed the same preprocessing operations as for the CT images except for skull-stripping on the original bleeding area image, to make the transformed bleeding image consistent with the reference brain anatomy MRI. The transformed bleeding image was then overlayed on the MRI image, as shown in Figure 2D.

2.3.4. Obtaining bleeding distribution features

After transforming the bleeding area image, we obtained a binary image in which the value 1 represents bleeding and 0 represents non-bleeding. We then identified the position of each voxel with a value of 1 in the transformed image and determined the corresponding voxel value (ranging from 1 to 35) in the reference MRI image. Next, we identified the brain structures covered by the voxel points representing the hemorrhage area. By processing all voxel points, we obtained the number of voxels representing bleeding on a specific anatomical structure $BNum_i$. We then calculated the proportion of bleeding in all 35 anatomical structures partitioned for the patient, represented by $BNum_i$, relative to the total number of voxels in that structure, $AllNum_i$, using the following equation:

$$Bd_i = BNum_i / AllNum_i \quad (5)$$

This allowed us to quantitatively analyze the distribution of bleeding in different brain structures. The results of this analysis are presented in our study.

2.3.5. Obtaining bleeding extrusion features

We quantified the cerebrospinal fluid and brain parenchyma areas in the original CT image based on the Hu value during CT imaging of different tissues and represented them using the number of voxels. We also calculated the total volume of the bleeding area. Additionally, we constructed five specific proportional characteristics: cerebrospinal fluid to the brain parenchyma, cerebrospinal fluid to the brain parenchyma and cerebrospinal fluid, hemorrhage to cerebrospinal fluid, hemorrhage to the brain parenchyma, and hemorrhage to cerebrospinal fluid and the brain parenchyma. In total, we obtained eight bleeding volume and extrusion features that characterize the extent to which the hemorrhagic mass affects the surrounding brain tissue. These features are referred to as bleeding extrusion features.

We stored all the obtained features, the ICH distribution, and hemorrhage extrusion features in the file. The summary and meaning of all features can be roughly distributed into three classes, namely, L', which indicates the hemorrhagic volume, L/All' presented as "/", indicating the proportion of the bleeding volume to brain tissue, and numbers 1–35 indicating the proportion of the bleeding volume in the brain anatomical structure. Specific meanings are given in Supplementary Table 1.

2.4. Construction of classification and statistical models

The obtained features were used to construct machine learning models for classification prediction and feature selection. A probability map was then generated to analyze the distribution characteristics of bleeding areas for four types of pneumonia.

2.4.1. Classification model

To analyze the data, we combined the bleeding distribution feature and bleeding extrusion feature and trained three classical machine learning models, namely logistic regression, support vector machine (SVM), and random forest, to classify and predict whether patients have pneumonia symptoms. The labels referring to the degree of pneumonia progression were severe, moderate, mild, and no symptoms of pneumonia. We used several indicators to evaluate the model, including area under the curve (AUC), accuracy, sensitivity, and specificity. Sensitivity is defined as the ratio of true positives to all positive samples, and specificity is defined as the ratio of true negatives to all negative samples. For each model, we evaluated the average metric of 10-fold cross-validation.

The classification problem of with or without pneumonia (SAP) can be viewed as a typical binary classification problem based on the cerebral hemorrhage situation. The feature combinations could reflect the contribution of different characteristics to the classification problem. Before entering the model, data standardization was required to improve the classification effect of the model.

Furthermore, since moderate-to-severe pneumonia can lead to prolonged hospitalization and increase the risk of poor patient outcomes (30), we divided the patients into two categories: SAP above moderate level and the others and performed a two-category prediction problem. We used three different machine learning models, and the features were treated the same as the above classification task. Data standardization was performed, and the mean value of the metrics of the 10-fold cross-validation was used to instruct the classification problem.

2.4.2. Statistical model

In addition to the classification task, we developed a statistical model based on the pneumonia classification to present and analyze the data in the form of a probability map. The specific method for constructing the probability map for one category involved superimposing the transformed hemorrhagic area images of all patients with the same SAP type. During the registration process when matching the brain CT and brain MRI, a transformation was generated for each patient. Multiple binarized images were then superimposed to create the probability map, with a gray value of 0 in some places and the largest voxel not exceeding the number of people with the particular pneumonia type. We compared the gray value of all voxels in the final image to the number of people in the category to obtain the probability map. To visualize the distribution characteristics of the hemorrhagic areas of various types of pneumonia more intuitively, we used the 3D Slicer software to superimpose the obtained probability maps with the brain MRI image. The original hemorrhage area images were not directly added to obtain the probability map because they could not be correlated with the brain anatomy MRI.

Furthermore, we analyzed the bleeding volume of each type of patient and constructed a box plot to examine the relationship between the development of pneumonia and the bleeding volume.

3. Results

We extracted a total of 35 bleeding distribution features, which included bleeding extrusion features, as well as the volumes of the cerebrospinal fluid, brain parenchyma, and hemorrhage mass (represented by the number of voxels). The remaining five features were represented on a scale of 0 to 1. To ensure that each feature contributed equally to the analysis, we performed standardization operations on the features based on their eigenvalues. Figure 3 displays the samples that were selected from each category of pneumonia. For each sample, both the preprocessed image and the final image after registration are shown.

TABLE 2 Metrics of machine learning models for predicting SAP.

Model	AUC	Accuracy	Sensitivity	Specificity
Logistic regression	0.79	0.75	0.75	0.74
SVM	0.79	0.76	0.77	0.72
Random forest	0.82	0.73	0.76	0.70

3.1. Classification model

The evaluation metrics are AUC value, accuracy, sensitivity, and specificity. For predicting SAP, the logistic regression model achieved an AUC of 0.79, with all four indexes above 0.73, and the specificity index being the highest among the three classifiers. The SVM model achieved the highest accuracy and sensitivity of 0.76 and 0.77, respectively. The random forest model performed the best in terms of AUC, which was above 0.8, and all other indexes were greater than 0.7. It should be noted that the ICH-APS-A model (12) achieved an AUC of 0.76, while the ICH-LR2S2 model (13) obtained an AUC of 0.78 in their respective test cohorts. This suggests that our method has performed well. Table 2 presents the performance evaluation results of the three classification models for predicting the occurrence of SAP.

For predicting SAP above a moderate level, the logistic regression model achieved an AUC of 0.77, with accuracy and specificity above 0.7. The SVM model achieved the best performance on accuracy and sensitivity of 0.75 and 0.74, respectively. The random forest model had an AUC and specificity of 0.78, the highest among the three models. Figure 4 displays the ROC curve of the random forest model, which demonstrated the highest performance. The ROC curves of the other two models are available in Supplementary material. Table 3 shows the experimental results of the two-classification problems for differing SAP above the moderate level.

The obtained AUCs were all above 0.75 for both classification problems, demonstrating that the severity of pneumonia can be predicted by the features extracted from our method.

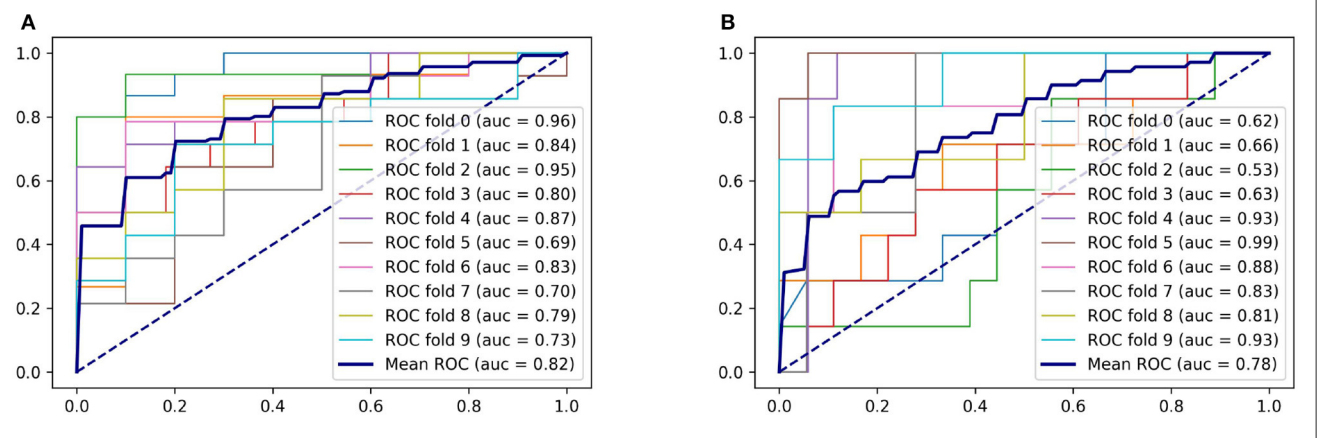


FIGURE 4
ROC curves of the random forest model. **(A)** For predicting SAP. **(B)** For predicting SAP above the moderate level.

TABLE 3 Metrics of machine learning models for predicting SAP above the moderate level.

Model	AUC	Accuracy	Sensitivity	Specificity
Logistic regression	0.77	0.72	0.67	0.74
SVM	0.77	0.75	0.74	0.74
Random forest	0.78	0.75	0.66	0.78

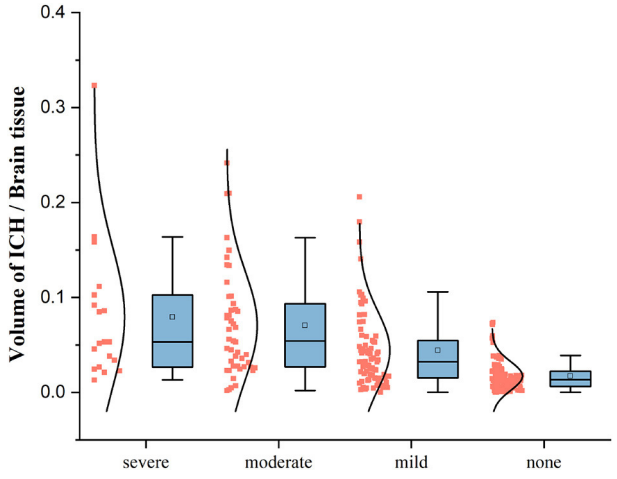


FIGURE 5
The box plot of the ratio of bleeding volume to total volume based on four SAP types.

3.2. Statistical model

The bleeding volume in patients with pneumonia symptoms is generally distributed below 20% of the brain tissue volume, with a higher density of patients having a bleeding volume ratio of less than 10%. However, patients without pneumonia symptoms also show bleeding volume ratios below 10% of the brain tissue volume. Thus, additional features are required to effectively classify pneumonia symptoms. The box plot in Figure 5 indicates that the bleeding volume alone is not a reliable indicator for classifying pneumonia symptoms.

For patients with severe pneumonia, there is an unbalanced distribution of hemorrhagic areas in the left and right cerebral hemispheres. The probability of hemorrhage in some areas of the left brain is high, with a probability above 0.6, while the probability of hemorrhage in some areas of the right brain is low, with a probability of approximately 0.3. In contrast, for patients with mild pneumonia or no pneumonia symptoms, there is no significant imbalance in the distribution of hemorrhagic areas between the left and right brain. The probability map can be a useful tool for analyzing the distribution characteristics of hemorrhagic areas in different types of pneumonia and can aid in diagnosing and treating patients with pneumonia. Figure 6 shows the probability map for the four pneumonia categories, which provides valuable insights into the distribution of hemorrhagic areas in different brain regions.

4. Discussion

We constructed classification and statistical models based on the obtained features and combined them with the clinical expertise of physicians to correlate the development of SAP in patients and the distribution of cerebral hemorrhages.

4.1. Novelty of our method

For predicting pneumonia infection after ICH, previous studies mostly focused on the patients' baseline data and aimed to build a risk model. Their risk model used AUC as an evaluation index and achieved good performance, ICH-LR2S2 (13) was constructed based on nine patient features and used an external validation cohort to evaluate the model. The overall performance of ICH-LR2S2 was AUC = 0.784. The ICH-APS (12) model achieved an AUC of 0.76 on its validation cohort and was also built by baseline data. Our logistic regression model was established on the features extracted by the registration method from the MRI atlas and achieved a good performance of AUC = 0.79 on the validation set for predicting SAP. There is a fact that the patients' baseline data is hard and time-consuming to collect and preprocess, such as data filling and cleaning, for our proposed method, the only input was the segmented ROI of brain CT which could rapidly offer risk score and the classified results after CT examination if an accuracy segmentation algorithm is matched with our model. It is worth mentioning that, ICH-LR2S2 and ICH-APS had a lot of data in the training phase, our database still needs to be expanded and methods should be improved and practiced in clinical situations.

4.2. Feature selection

Previous studies have shown that using L1 regularization to penalize the logistic regression model can significantly impact model performance by achieving critical factors (31, 32). In our study, we inputted two types of features and their combinations into the model and implemented 10-fold cross-validation. By considering the feature weights from the regression coefficients shown in Figure 7, we were able to determine the factors and brain regions that occupied important weights in our logistic model.

Among the bleeding distribution features, the left-hippocampus, left-choroid-plexus, right-choroid-plexus, third-ventricle, and right-hippocampus had larger weights than others, indicating that ICH in these regions is associated with a greater risk of pneumonia infection. The involvement of these areas can cause swallowing dysfunction or disturbance of consciousness in the patient (33). Among the bleeding extrusion feature, we found that hemorrhage and cerebrospinal fluid volume can contribute to the development of pneumonia. The weight of the cerebrospinal fluid is relatively large due to its liquid nature, and there is circulation and absorption of the cerebrospinal fluid (34). Figure 7A shows the feature weights for predicting SAP.

For predicting SAP above moderate level, the brain regions that contributed more to the model were the left-choroid-plexus, right-choroid-plexus, right-hippocampus, left-hippocampus, and

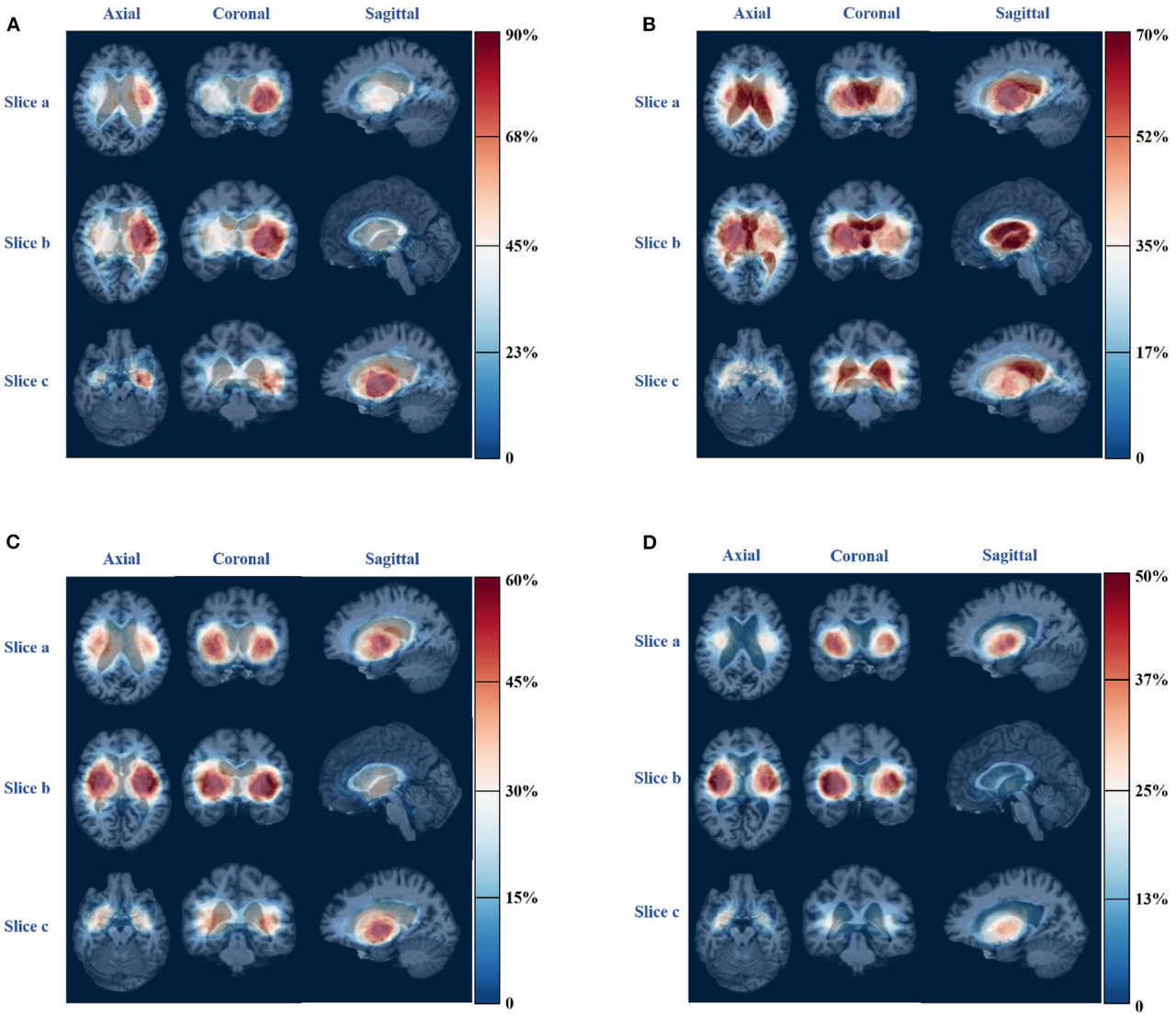


FIGURE 6
Bleeding probability map of four types of pneumonia. **(A)** Severe pneumonia. **(B)** Moderate pneumonia. **(C)** Mild pneumonia. **(D)** No pneumonia.

left-accumbens, usually located in the basal ganglia region. When involved, swallowing or conscious function will be affected (35), and the right cerebellar white matter involvement affects ataxia function (36). For the bleeding extrusion feature, the hemorrhage volume and cerebrospinal fluid and its proportion with the brain tissues play a significant role in the classification problem. The mass effect occurs during ICH due to the cerebrospinal fluid's nature and its circulation and absorption functions. The cerebrospinal fluid plays a major buffer function (37), and the image shows the shrinkage of the ventricular system, whereas the amount of bleeding and the mutual ratio of the cerebrospinal fluid and brain tissue change significantly. Figure 7B shows the feature weights for predicting SAP above the moderate level.

Through feature selection, we surprisingly found that some anatomical regions implemented by ICH cause higher risk scores of SAP, including the choroid-plexus, hippocampus, and third-ventricle. If the hemorrhage mass affected the basal ganglia region, it increased the risk of pneumonia developing to more than moderate. Additionally, whether the cerebrospinal fluid was affected by hemorrhage mass was a critical factor in the fact of feature selection.

4.3. The distribution of cerebral hemorrhage

The distribution of ICH in severe pneumonia shows a left-right imbalance, as shown in Figure 6A. More than 70% of patients with severe pneumonia had hemorrhage in regions such as left-cerebral-white-matter, left-pallidum, left-putamen, left-thalamus, left-ventral-dc, and left-cerebral-cortex, which are all located in the left half of the brain. Since the left hemisphere is mostly the dominant hemisphere,

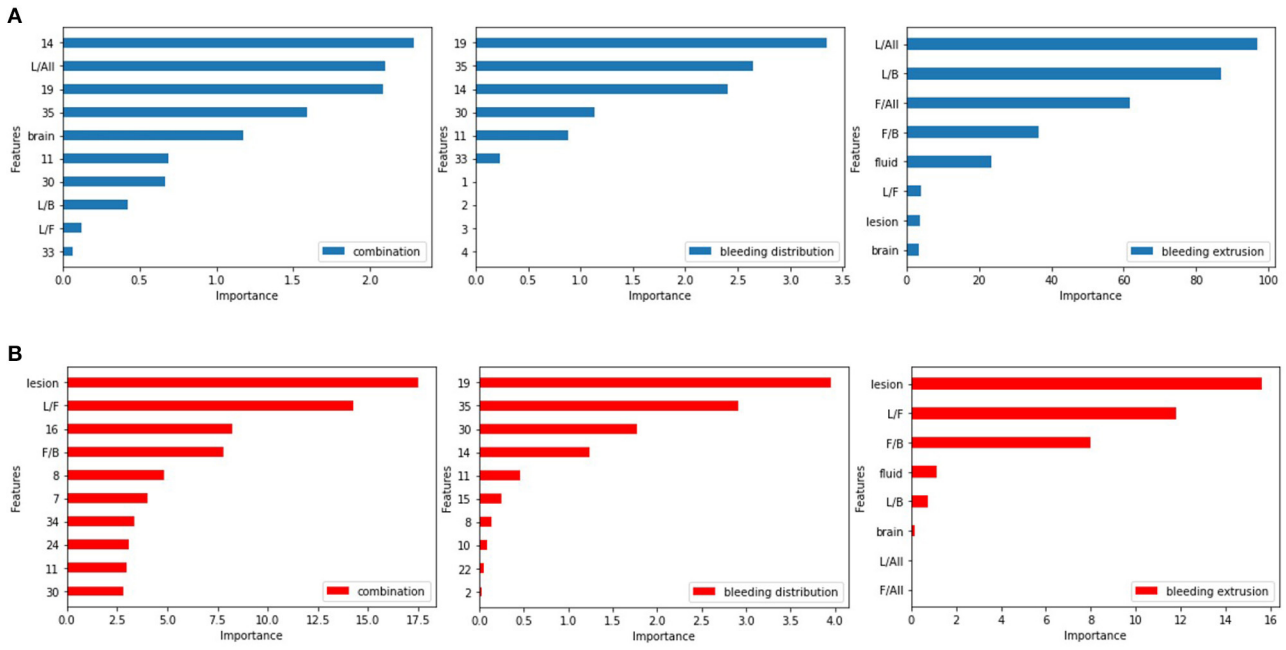


FIGURE 7
Feature weights of the logistic regression model. **(A)** For predicting SAP. **(B)** For predicting SAP above the moderate level.

involvement of this hemisphere results in more severe disease, combined with disturbance of consciousness, swallowing dysfunction, and inability to expectorate sputum, leading to poor airway protection and severe pulmonary infection (38).

For patients with moderate pneumonia, more than 50% had hemorrhagic clots in the right-cerebral-white-matter, right-lateral-ventricle, right-thalamus, right-pallidum, third-ventricle, left-lateral-ventricle, right-caudate, and left-choroid-plexus, which are mostly located in the right half of the brain. The volume of hemorrhage in the cerebrospinal fluid was also found to be greater in patients with this type of pneumonia compared to those with the other three types. The right hemisphere is the non-dominant hemisphere, which has little impact on the patient's consciousness and allows limited airway protection ability.

For patients with mild pneumonia, only a small portion of the probability map exceeds 0.5, indicating that there is no obvious clustering in the distribution of ICH in this category. More than 40% of the patients had bleeding clumps in regions, such as right-cerebral-white-matter, right-cerebral-cortex, left-cerebral-white-matter, left-cerebral-cortex, right-putamen, left-putamen, left-pallidum, right-pallidum, right-thalamus, and left-thalamus, and there was no apparent imbalance in the distribution of the left and right brains.

For patients without symptoms of pneumonia, hemorrhages were found in regions such as the right-cerebral-cortex, right-putamen, right-cerebral-white-matter, and right-pallidum in more than 40% of patients. Hemorrhages occurred in the right white matter and right cerebral cortex in more patients than in the left-brain matter.

4.4. Hemorrhage volume and pneumonia classification

According to the data box plot of the ratio of the bleeding volume to brain tissue in each category of patients, we found that the upper limit, upper quarter, mean and maximum value of the data exhibited an increasing trend according to the deepening of the development of SAP. Additionally, the data in the category without pneumonia symptoms are all lower than the three categories with pneumonia symptoms except for the lower limit point. There is a significant difference, indicating that if the patient does not show pneumonia symptoms, the probability of bleeding will not be higher than 10% of the brain tissue. If the ICH mainly occurs in a functional area, especially when the patient's consciousness, swallowing function, or expectoration reflex is affected, pulmonary infection is more likely to occur.

Moderate-to-severe pneumonia with cerebral hemorrhage significantly increases hospitalization and medical expenses and can aggravate brain damage and cause other complications (30). We divided the data into two types: SAP above moderate level and others. There are obvious differences in the box plot data of ICH between the two types. The maximum value, upper limit, upper quartile, mean, median, lower quartile, and lower limit in the data of patients with moderate and severe pneumonia are higher than those of no, mild pneumonia. This indicates that with the development of pneumonia, the volume of bleeding gradually increased. For the binary classification problem, according to the weights of the features and the deduction that patients in each category can have bleeding areas with volumes less than 10% of brain tissue, we cannot make an effective prediction using a single factor of the hemorrhage volume; we need to

consider multiple features to predict pneumonia. Protection of the airway is dependent on the level of consciousness and swallowing function. The functional areas affecting the patient's consciousness and swallowing function are mainly distributed in the ascending reticular activation system, bilateral basal ganglia, posterior cranial nerves, and other related areas (35). Therefore, the influence of the structure can better predict the risk of early pulmonary infection in patients by effectively combining the amount of bleeding with the bleeding site, evaluating the effect of mass on each area, and taking relevant measures in a timely manner for a better recovery effect and quality of life.

4.5. Technical limitations

The precision of the registration process is critical to the accuracy of our conclusion analysis, as the hemorrhage distribution feature we obtained is based on the image transformation of registration technology. We utilized non-rigid transformation based on continuous optimization iteration, and technical precision can be improved. In recent years, deep learning technology has significantly advanced the development of medical image registration, such as BIRNet. Fan et al. (39) proposed a fully convolutional network subject to dual guidance, including ground truth and image dissimilarity guidance, which demonstrated high registration accuracy and efficiency. For unsupervised learning, Balakrishnan et al. (40), Krebs et al. (41), Vos et al. (42), and Gierlichs et al. (28) proposed end-to-end networks that estimate deformable transformations by maximizing the similarity between image pairs without real deformations. Using deep networks to improve image registration in our study facilitated more accurate results and improved model accuracy.

While our data comes from only one hospital and is limited in size, our method needs to be validated on an external cohort and evaluated for clinical application. Thus, limitations are associated with a single center and species. Collecting data from multiple centers could yield more interesting results, especially considering that most Asians are right-handed.

5. Conclusion

To the best of our knowledge, no study has been reported on the prediction and analysis of SAP based on the distribution characteristics of the ICH area. In this study, we utilized an MRI atlas that could clearly represent 35 anatomical brain regions and creatively combined our data with MRI through medical image registration. We constructed machine learning models to detect the occurrence and development of SAP using patient brain CT scans, which to a certain extent, reduced dependence on lung CT and clinical doctors.

Our findings suggest that hemorrhage in specific brain regions, such as the left-choroid-plexus, right-choroid-plexus, right-hippocampus, and left-hippocampus, were more likely to affect the development of pneumonia. We determined the distribution characteristics of the ICH in patients with various types of pneumonia by using a probability map and box plot. Specifically, patients with severe pneumonia had more ICH in the left cerebral hemisphere (dominant side), whereas those with moderate pneumonia had more ICH in the right cerebral hemisphere and cerebrospinal fluid. The volume of the patients' ICH played an important role in the occurrence and development of pneumonia, as shown by significant differences in the amount of bleeding in different categories of patients in the box plot, which mainly displayed maximum, average, and median indicators.

In summary, our study presents a novel method for predicting and analyzing SAP based on the distribution characteristics of the ICH area in brain CT scans. We identified specific brain regions that were more closely related to the occurrence and development of SAP, and our probability map and box plot provided valuable insights into the distribution characteristics of ICH in patients with various types of pneumonia.

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 human participants were reviewed and approved by Shengli Oilfield Central Hospital. The patients/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

GY, MX, and XQ were responsible for the overall conception and supervision of the study. WC and XQ designed the study protocol. GY and MX conducted the experiments and drafted the initial manuscript. HS, YH, WC, and XQ contributed to critical revisions of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Funding

This work was supported by Shandong Provincial Natural Science Foundation (Grant No. ZR202103030517) and the National Natural Science Foundation of China (Grant Nos. U1806202 and 82071148).

Acknowledgments

The authors express their immense gratitude to all of the patients who participated in each of the individual studies as well as the many personnel who helped with recruitment, collection, curation, management, and processing of the samples and data.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1139048/full#supplementary-material

References

1. Li J, Zhang P, Wu S, Wang Y, Wang C. Stroke-related complications in large hemisphere infarction: incidence and influence on unfavorable outcome. *Therapeut Adv Neurol Disord.* (2019) 12:175628641987326. doi: 10.1177/1756286419873264

2. Montmollin ED, Ruckly S, Schwebel C, Philippart F, Timsit JF. Pneumonia in acute ischemic stroke patients requiring invasive ventilation: impact on short and long-term outcomes. *J Infect.* (2019) 79:220–7. doi: 10.1016/j.jinf.2019.06.012

3. Ho SW, Tsai MC, Teng YH, Yeh YT, Wang YH, Yang SF, et al. Population-based cohort study on the risk of pneumonia in patients with non-traumatic intracranial haemorrhage who use proton pump inhibitors. *BMJ Open.* (2014) 4:e006710. doi: 10.1136/bmjopen-2014-006710

4. Hannawi Y, Hannawi B, Rao CPV, Suarez JI, Bershad EM. Stroke-associated pneumonia: major advances and obstacles. *Cerebrovasc Dis.* (2013) 35:430–43. doi: 10.1159/000350199

5. Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, Di Napoli M, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. *Stroke.* (2015) 46:1202–9. doi: 10.1161/STROKEAHA.114.007843

6. Smith CJ, Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, et al. Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group. *Stroke.* (2015) 46:2335–40. doi: 10.1161/STROKEAHA.115.009617

7. Elliott J, Smith M. The acute management of intracerebral hemorrhage: a clinical review. *Anesthesia Anal.* (2010) 110:1419–27. doi: 10.1213/ANE.0b013e3181d568c8

8. Hinchey JA, Shephard T, Furie K, Smith D, Wang D, Tonn S. Formal dysphagia screening protocols prevent pneumonia. *Stroke.* (2005) 36:1972–6. doi: 10.1161/01.STR.0000177529.86868.8d

9. Alsumrain M, Melillo N, DeBari VA, Kirmani J, Moussavi M, Doraiswamy V, et al. Predictors and outcomes of pneumonia in patients with spontaneous intracerebral hemorrhage. *J Intens Care Med.* (2013) 28:118–23. doi: 10.1177/0885066612437512

10. Sui R, Zhang L. Risk factors of stroke-associated pneumonia in Chinese patients. *Neurol Res.* (2011) 33:508–13. doi: 10.1179/016164111X13007856084205

11. Eltringham SA, Kilner K, Gee M, Sage K, Bray BD, Smith CJ, et al. Factors associated with risk of stroke-associated pneumonia in patients with dysphagia: a systematic review. *Dysphagia.* (2020) 35:735–44. doi: 10.1007/s00455-019-10061-6

12. Ji R, Shen H, Pan Y, Du W, Wang P, Liu G, et al. Risk score to predict hospital-acquired pneumonia after spontaneous intracerebral hemorrhage. *Stroke.* (2014)45:2620–8. doi: 10.1161/STROKEAHA.114.005023

13. Yan J, Zhai W, Li Z, Ding L, You J, Zeng J, et al. ICH-LR2S2: a new risk score for predicting stroke-associated pneumonia from spontaneous intracerebral hemorrhage. *J Transl Med.* (2022) 20:1–10. doi: 10.1186/s12967-022-03389-5

14. Ikram MA, Wieberdink RG, Koudstaal PJ. International epidemiology of intracerebral hemorrhage. *Curr Atherosc Rep.* (2012) 14:300–6. doi: 10.1007/s11883-012-0252-1

15. Ardekani BA, Guckemus S, Bachman A, Hoptman MJ, Wojtaszek M, Nierenberg J. Quantitative comparison of algorithms for inter-subject registration of 3D volumetric brain MRI scans. *J Neurosci Methods.* (2005) 142:67–76. doi: 10.1016/j.jneumeth.2004.07.014

16. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al. Incidental findings on brain MRI in the general population. *N Engl J Med.* (2007) 357:1821–8. doi: 10.1056/NEJMoa070972

17. Hill DL, Batchelor PG, Holden M, Hawkes DJ. Medical image registration. *Phys Med Biol.* (2001) 46:R1. doi: 10.1088/0031-9155/46/3/201

18. Sotiras A, Davatzikos C, Paragios N. Deformable medical image registration: a survey. *IEEE Trans Med Imaging.* (2013) 32:1153–90. doi: 10.1109/TMI.2013.2265603

19. Maintz JA, Viergever MA. A survey of medical image registration. *Med Image Anal.* (1998) 2:1–36.

20. Maes F, Vandermeulen D, Suetens P. Medical image registration using mutual information. *Proc IEEE.* (2003) 91:1699–722. doi: 10.1109/JPROC.2003.817864

21. Zapata-Arriaza E, Moniche F, Blanca PG, Bustamante A, Escudero-Martínez I, Uclés O, et al. External validation of the ISAN, A2DS2, and AIS-APS scores for predicting stroke-associated pneumonia. *J Stroke Cerebrovasc Dis.* (2018) 27:673–6. doi: 10.1016/j.jstrokecerebrovasdis.2017.09.059

22. Marcus DS, Wang TH, Parker J, Csernansky JG, Morris JC, Buckner RL. Open Access Series of Imaging Studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. *J Cogn Neurosci.* (2007) 19:1498–507. doi: 10.1162/jocn.2007.19.9.1498

23. Hoopes A, Hoffmann M, Fischl B, Guttag J, Dalca AV. Hypermorph: amortized hyperparameter learning for image registration. In: *International Conference on Information Processing in Medical Imaging.* Springer (2021). p. 3–17.

24. Kuijf HJ, Biesbroek JM, Viergever MA, Biessels GJ, Vincken KL. Registration of brain CT images to an MRI template for the purpose of lesion-symptom mapping. In: *International Workshop on Multimodal Brain Image Analysis.* Springer (2013). p. 119–28.

25. Lassoan. *Segmentation Recipes for 3D Slicer* (2020).

26. Cocianu C-L, Uscata CR, Stan AD. *Evolutionary Image Registration: A Review, Vol. 23.* Multidisciplinary Digital Publishing Institute. p. 197.

27. Kraskov A, Stögbauer H, Grassberger P. Estimating mutual information. *Phys Rev E.* (2004) 69:066138. doi: 10.1103/PhysRevE.69.066138

28. Gierlichs B, Batina L, Tuyls P, Preneel B. Mutual information analysis. In: *International Workshop on Cryptographic Hardware and Embedded Systems.* Springer (2008). p. 426–42.

29. Belghazi MI, Baratin A, Rajeshwar S, Ozair S, Bengio Y, Courville A, et al. Mutual information neural estimation. In: *International Conference on Machine Learning.* PMLR (2018). p. 531–40.

30. Masiero S, Pierobon R, Previato C, Gomiero E. Pneumonia in stroke patients with oropharyngeal dysphagia: a six-month follow-up study. *Neurol Sci.* (2008) 29:139–45. doi: 10.1007/s10072-008-0925-2

31. Schmidt M, Niculescu-Mizil A, Murphy K. Learning graphical model structure using L1-regularization paths. In: *AAAI.* (2007). p. 1278–83.

32. Sporns O. Structure and function of complex brain networks. *Dialogues Clin Neurosci.* (2022) 15:247–62. doi: 10.31887/DCNS.2013.15.3/osporns

33. Sakka L, Coll G, Chazal J. Anatomy and physiology of cerebrospinal fluid. *Eur Ann Otorhinolaryngol Head Neck Dis.* (2011) 128:309–16. doi: 10.1016/j.anorl.2011.03.002

34. Graybiel AM. The basal ganglia. *Curr Biol.* (2000) 10:R509–11. doi: 10.1016/S0960-9822(00)00593-5

35. Della Nave R, Ginestroni A, Tessa C, Salvatore E, Bartolomei I, Salvi F, et al. Brain white matter tracts degeneration in Friedreich ataxia. An *in vivo* MRI study using tract-based spatial statistics and voxel-based morphometry. *Neuroimage.* (2008) 40:19–25. doi: 10.1016/j.neuroimage.2007.11.050

36. Brinker T, Stopa E, Morrison J, Klinge P. A new look at cerebrospinal fluid circulation. *Fluids Barriers CNS.* (2014) 11:1–16. doi: 10.1186/2045-8118-11-10

37. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere: an electrical stimulation mapping investigation in 117 patients. *J. Neurosurg.* (1989) 71:316–26.

38. Kumar RG, Kesinger MR, Juengst SB, Brooks MM, Fabio A, Dams-O'Connor K, et al. Effects of hospital-acquired pneumonia on long-term recovery and hospital resource utilization following moderate to severe traumatic brain injury. *J Trauma Acute Care Surg.* (2020) 88:491. doi: 10.1097/TA.0000000000002562

39. Fan J, Cao X, Yap PT, Shen D. BIRNet: brain image registration using dual-supervised fully convolutional networks. *Med Image Anal.* (2019) 54:193–206. doi: 10.1016/j.media.2019.03.006

40. Balakrishnan G, Zhao A, Sabuncu MR, Guttag J, Dalca AV. An unsupervised learning model for deformable medical image registration. In: *Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition*. (2018). p. 9252–60.

41. Krebs J, Delingette H, Mailhé B, Ayache N, Mansi T. Learning a probabilistic model for diffeomorphic registration. *IEEE Trans Med Imaging.* (2019) 38:2165–76. doi: 10.1109/TMI.2019.2897112

42. Vos BD, Berendsen FF, Viergever MA, Staring M, Išgum I. End-to-end unsupervised deformable image registration with a convolutional neural network. In: *Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support*. Springer (2017). p. 204–12.

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 15 June 2023
DOI 10.3389/fneur.2023.1190544

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
Roddy Hiram,
Université de Montréal, Canada
Xiaobin Gu,
First Affiliated Hospital of Zhengzhou University, China

*CORRESPONDENCE
Mingchao Fan
✉ fanmingchao@qdu.edu.cn
Huanting Li
✉ lihuanting26@163.com

†These authors have contributed equally to this work

RECEIVED 21 March 2023
ACCEPTED 31 May 2023
PUBLISHED 15 June 2023

CITATION
Xiao H, Li L, Zhang F, Cheng L, Li Y, Han W, Li H and Fan M (2023) Preoperative systemic immune-inflammation index may predict prolonged mechanical ventilation in patients with spontaneous basal ganglia intracerebral hemorrhage undergoing surgical operation. *Front. Neurol.* 14:1190544. doi: 10.3389/fneur.2023.1190544

Preoperative systemic immune-inflammation index may predict prolonged mechanical ventilation in patients with spontaneous basal ganglia intracerebral hemorrhage undergoing surgical operation

Huaming Xiao[1†], Lei Li[2†], Feng Zhang[2], Lei Cheng[2], Yang Li[2], Wenlan Han[2], Huanting Li[2*] and Mingchao Fan[2,3*]

[1]Department of Neurosurgery, Weihai Central Hospital, The Affiliated Hospital of Qingdao University, Weihai, Shandong, China, [2]Department of Neurosurgery, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China, [3]Department of Neurosurgical Intensive Care Unit, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

Background: Prolonged mechanical ventilation (PMV) has been proven as a risk factor for poor prognosis in patients with neurocritical illness. Spontaneous basal ganglia intracerebral hemorrhage (ICH) is one common subtype of hemorrhagic stroke and is associated with high morbidity and mortality. The systemic immune-inflammation index (SII) is used as a novel and valuable prognostic marker for various neoplastic diseases and other critical illnesses.

Objective: This study aimed to analyze the predictive value of preoperative SII for PMV in patients with spontaneous basal ganglia ICH who underwent surgical operations.

Methods: This retrospective study was conducted in patients with spontaneous basal ganglia ICH who underwent surgical operations between October 2014 and June 2021. SII was calculated using the following formula: SII = platelet count × neutrophil count/lymphocyte count. Multivariate logistic regression analysis and receiver operating characteristics curve (ROC) were used to evaluate the potential risk factors of PMV after spontaneous basal ganglia ICH.

Results: A total of 271 patients were enrolled. Of these, 112 patients (47.6%) presented with PMV. Multivariate logistic regression analysis showed that preoperative GCS (OR, 0.780; 95% CI, 0.688–0.883; $P < 0.001$), hematoma size (OR, 1.031; 95% CI, 1.016–1.047; $P < 0.001$), lactic acid (OR, 1.431; 95% CI, 1.015–2.017; $P = 0.041$) and SII (OR, 1.283; 95% CI, 1.049–1.568; $P = 0.015$) were significant risk factors for PMV. The area under the ROC curve (AUC) of SII was 0.662 (95% CI, 0.595–0.729, $P < 0.001$), with a cutoff value was 2,454.51.

Conclusion: Preoperative SII may predict PMV in patients with spontaneous basal ganglia ICH undergoing a surgical operation.

KEYWORDS

systemic immune-inflammation index, intracerebral hemorrhage, prolonged mechanical ventilation, lactic acid, surgical operation

Introduction

Spontaneous intracerebral hemorrhage (ICH) is one common subtype of hemorrhagic stroke and is associated with high morbidity and mortality (1, 2). The basal ganglia is the usual incidence area of spontaneous ICH, and the most common pathogenic factor is hypertension (3, 4). Postoperative respiratory failure is one of the complications following ICH and is the main cause of mechanical ventilation (5). Among patients with acute central nervous system injury, about 17–33% required endotracheal intubation and mechanical ventilation, and more than 10% of patients with stroke need mechanical ventilation (6), this percentage may be even higher in patients who underwent surgical intervention.

Prolonged mechanical ventilation (PMV) is significantly associated with poor prognosis in patients with critical illness (7, 8). Several risk factors, including old age, obesity, chronic obstructive pulmonary disease, atrial fibrillation, and severe comorbidity, have been identified to be associated with PMV in these patients (9, 10). For patients with hemorrhagic stroke, the risk factors additional include large hematoma volume, obstructive hydrocephalus, coma, brain hernia, and thalamic location of the bleeding (11, 12). PMV is associated with longer hospital stays, increased treatment costs, various mechanical ventilation-related complications, and a relatively high mortality rate (13, 14). Early prediction of PMV may provide useful information for making a comprehensive management plan, help the medical staff to anticipate the ICU course, and help the patient's families to adjust their emotions and live.

Systemic Immune-inflammation index (SII), calculated using lymphocyte, neutrophil, and platelet counts, is a novel comprehensive inflammatory index, and better reflects the state of immune and inflammation of the body. It was reported as a prognostic marker for hepatocellular carcinoma by Hu et al. in 2014 for the first time (15). Recently, many studies have reported that increased SII was associated with unfavorable prognoses in various types of cancers and other critical illnesses (16–18). Best to our knowledge, the SII has not been reported as a predictive factor for PMV, especially for patients with neurocritical illness. We hypothesized that SII can predict PMV in patients with spontaneous basal ganglia ICH who underwent surgical intervention. Thus, the present retrospective study was designed to analyze the predicted value of preoperative SII for PMV in patients with spontaneous basal ganglia ICH who underwent surgical operations.

Methods

The research protocol was approved by the Human Ethics Committee of the Affiliated Hospital of Qingdao University (QYFY-WZLL-26903) and was registered at the Chinese Clinical Trial Registry (ChiCTR2200056494). The study adhered to the tenets of the Declaration of Helsinki and the related laws and regulations. Informed consent for clinical record data to be used in the study was obtained from the patient's guardians. The privacy rights of human subjects always be observed.

Patient population

This retrospective cohort study of patients admitted to the Affiliated Hospital of Qingdao University from October 2014 to June 2021 with the diagnosis of spontaneous basal ganglia ICH who underwent surgical intervention. Spontaneous basal ganglia ICH was diagnosed by three senior neurosurgeons based on neuroimaging, history of present illness, and surgical operations results (3, 4).

Patients were included if they met the following criteria: (a) age $\geq$ 18 years old; (b) unilateral cerebral hemorrhage in the basal ganglia; (c) underwent surgical intervention; (d) the time from onset to surgical operations $\leq$ 72 h. The exclusion criteria are as follows: (a) with stroke, traumatic brain injury, or craniotomy history; (b) with a history of chronic inflammation status, hematologic (except iron deficiency anemia), or autoimmune diseases; (c) with malignant tumor; (d) need prehospital mechanical ventilation; (e) severe respiratory system diseases, such as chronic obstructive pulmonary disease; (f) non-invasive ventilation; (g) secondary ICH; (h) without complete data.

Data collection

Clinical data were acquired from the scientific research big data platform and the hospital information system. Surgical intervention was conducted within 72 h of the initial symptoms. All the patients received consistent necessary medical management. The laboratory and clinical data on admission were analyzed and calculated, including age, gender, body mass index, medical history, blood routine analysis, blood biochemical analysis, and Glasgow Coma Scale (GCS). Arterial blood was used for lactic acid analysis. The indications and procedures of operations were under the corresponding surgical guidelines and operating procedures (3, 19). The size of the hematoma was calculated with the following formula: "0.5 × a × b × c," where "a" and "b" are the largest diameters measured on the CT scans and "c" is the slice thickness (cm) (20).

All patients received general anesthesia and mechanical ventilation during surgical operations. Adjust mechanical ventilation modes and parameters according to actual requirements. The spontaneous breathing trial and weaning were performed based on adequate ventilation indices and oxygenation at the discretion of the neurocritical physician (11). Analgesics-sedatives were achieved with continuous intravenous pumping at the discretion of the treating physician. Depth of sedation was controlled at −1 – −2 score (Richmond Agitation Sedation Scale).

The SII was calculated using the following formula: SII = platelet count×neutrophil count/lymphocyte count (15). PMV was defined as mechanical ventilation lasting for more than 24 h after surgical operations (21, 22). Length of mechanical ventilation was defined as the time from initiation of ventilatory to the accomplishment of weaning. The prognosis of patients at 3 months was evaluated using the modified Rankin Scale (mRS). The score of 0–2 was a favorable prognosis, while 3–6 was defined as an unfavorable prognosis.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were summarized as means ± standard deviations (SD). The abnormal distribution of continuous variables was summarized as median and interquartile ranges (25^{th} to 75^{th} percentile). Categorical data were presented as frequency and percentage. The student's *t*-test and Kruskal-Wallis test were used to compare the normal distribution and abnormal distribution continuous variables respectively. The Chi-square test was used to compare the categorical data. Logistic regression analysis was conducted to identify the independent risk factors. Receiver operating characteristic curve (ROC) analysis was performed to define the differences in the area under the curves (AUC) and the cutoff value, then the sensitivity and specificity. A P value < 0.05 was considered statistically significant.

Due to SII being calculated by multiplying the neutrophil and platelet count and then dividing the result by the lymphocyte count, leukocyte count and neutrophil count were abandoned in the logistic regression models in order to avoid bias effect.

Results

Baseline characteristics

The demographics and details information of all patients was shown in Table 1. A total of 271 patients were enrolled. The median age of these patients was 56 years (interquartile range, 47–65 years), and 80 patients (29.52%) were women. Of these, 112 patients (47.6%) who presented PMV were allocated to the PMV group, and 159 (52.4%) patients without PMV were allocated to the non-PMV group (Figure 1). Percutaneous tracheotomy was performed in 67 (59.82%) of 112 patients with PMV. The median time of tracheotomy was 6 (5–9) days after surgical operation. Of these 271 patients, 106 patients had a favorable prognosis (39.1%), and 165 patients (60.9%) had an unfavorable prognosis.

The association of PMV with prognosis

Among these 112 patients with PMV, 9 cases (8.04%) had good prognosis and 103 patients (91.96%) had poor ($\chi^2 = 77.422$, $P < 0.001$). The duration of PMV was 120 (48–258) h. A total of 22 patients (8.12%) died during hospitalization and follow-up, 18 patients (16.07%) were in the PMV group, and 4 patients (2.52%) were in the non-PMV group ($\chi^2 = 16.189$, $P < 0.001$). The length of ICU stay ($P < 0.001$) and total hospital stay ($P < 0.001$) in PMV group patients were significantly longer than those in the non-PMV group. PMV was a risk factor for poor prognosis of patients with spontaneous basal ganglia ICH who underwent surgical operations [Odds Ratio (OR), 17.905; 95% confidence interval (CI), 8.440–37.985; $P < 0.001$].

Univariate analysis of pre-operations risk factors for PMV

The results of the univariate analysis of risk factors for PMV are presented in Table 1. Univariate analysis revealed that systolic pressure ($P = 0.043$), GCS ($P < 0.001$), hematoma volume ($P < 0.001$), serum Potassium ($P < 0.001$), blood glucose ($P < 0.001$), serum albumin ($P = 0.016$), and lactic acid ($P < 0.001$) on admission were significantly correlated with PMV. There was no relationship between age ($P = 0.550$), gender ($P = 0.714$), Body Mass Index ($P = 0.656$), history of smoking ($P = 0.502$), history of drinking ($P = 0.850$), history of diabetes ($P = 0.287$), serum sodium ($P = 0.477$), intraventricular hematoma ($P = 0.215$), Analgesics-sedatives ($P = 0.071$), and PMV.

Of these 271 patients, 121 patients (44.65%) underwent craniectomy, 86 patients (31.73%) underwent endoscopic evacuation of hematoma, and 64 patients (23.62%) underwent directional burr hole hematoma aspiration. There was no significant difference in postoperative prolonged mechanical ventilation among different surgical operations ($P = 0.056$).

Of the peripheral blood cells analysis, neutrophil ($P < 0.001$) and WBC ($P < 0.001$) were significantly correlated with PMV. And monocyte ($P = 0.287$), lymphocyte ($P = 0.077$), hemoglobin ($P = 0.906$), and platelet ($P = 0.130$) didn't find a significant correlation with PMV. The SII of PMV group patients was significantly higher than that of non-PMV patients ($P < 0.001$).

Logistic regression analysis of predictive factors for PMV

The results of univariate and multivariate Logistic regression analysis were presented in Table 2. These risk variables, except the neutrophil and WBC, were analyzed using univariate Logistic regression, and all of them were statistically significant. Then these factors with statistical significance in univariate logistic regression were brought into a multivariate logistic regression analysis to establish the PMV risk prediction model. We found that GCS (OR, 0.780; 95% CI, 0.688–0.883; $P < 0.001$), hematoma size (OR, 1.031; 95% CI, 1.016–1.047; $P < 0.001$), lactic acid (OR, 1.431; 95% CI, 1.015–2.017; $P = 0.041$), and SII (OR, 1.283; 95% CI, 1.049–1.568; $P = 0.015$) were significant in multivariate logistic regression (Figure 2).

ROC curves analysis of predictive factors for PMV

ROC curves were performed to evaluate the predictive ability of SII, lactic acid, hematoma size, and GCS (Figure 3; Table 3). The corresponding AUC of SII was 0.662 (95% CI, 0.595–0.729, $P < 0.001$), and the cutoff value was 2,454.51, with sensitivity and specificity of 51.8% and 76.1%, respectively. The corresponding AUC of lactic acid was 0.645 (95% CI, 0.575–0.715, $P < 0.001$), and the cutoff value was 1.55 with sensitivity and specificity of 55.4% and 74.8%, respectively. The corresponding AUC of hematoma size was 0.709 (95% CI, 0.645–0.773, $P < 0.001$), and the cutoff

TABLE 1 The demographic and baseline characteristics of patients in the PMV and non-PMV groups.

Variable	Total ($n = 271$)	PMV		*P*-value
		YES ($n = 112$)	NO ($n = 159$)	
Gender (female, %)	80 (29.52)	32 (28.57)	48 (30.19)	0.714
Age (years)	56 (47–65)	56 (47–67)	57 (47–65)	0.513
BMI	25.40 (23.30–27.68)	25.40 (23.40–27.70)	25.40 (22.90–27.55)	0.656
Smoking (%)	71 (26.20)	32 (28.57)	39 (24.53)	0.502
Drinking (%)	76 (28.04)	31 (27.68)	45 (28.30)	0.850
Cardiac insufficiency (%)	30 (11.07)	17 (15.18)	13 (8.18)	0.070
Hypertension (%)	176 (64.94)	78 (69.64)	98 (61.64)	0.234
Diabetes mellitus (%)	23 (8.49)	12 (10.71)	11 (6.92)	0.287
Systolic pressure (mmHg)	158 (140–180)	163 (142–190)	155 (140–179)	**0.043**
Diastolic pressure (mmHg)	92 (80–105)	94 (80–110)	92 (80–101)	0.782
Length of ICU stay (days)	3 (1–9)	9 (3–19)	1 (0–3)	**<0.001**
Length of stay (days)	16 (11–25)	23 (14–36)	14 (11–18)	**<0.001**
GCS	9 (7–12)	8 (5–9)	10 (8–13)	**<0.001**
Hematoma size (ml)	50 (40–80)	70 (50–80)	50 (40–60)	**<0.001**
Intraventricular hematoma	121 (44.65)	55 (49.11)	57 (35.85)	0.215
Surgical Operation				0.056
Craniectomy (%)	121 (44.65%)	59 (52.68%)	62 (38.99%)	
Endoscopic (%)	86 (31.73%)	33 (29.46%)	53 (33.33%)	
Burr hole aspiration (%)	64 (23.62%)	20 (17.86%)	44 (27.67%)	
Serum potassium (mmol/L)	3.77 ± 0.52	3.64 ± 0.55	3.86 ± 0.49	**<0.001**
serum sodium (mmol/L)	140 (137–142)	140 (137–142)	140 (137–142)	0.477
Serum albumin (g/L)	39.20 ± 5.30	38.26 ± 5.62	39.86 ± 4.98	**0.016**
Monocyte ($\times 10^9$/L)	0.54 (0.38–0.75)	0.57 (0.39–0.82)	0.54 (0.38–0.73)	0.583
Neutrophil ($\times 10^9$/L)	9.86 (7.10–13.01)	11.53 (8.37–14.55)	8.61 (6.43–11.37)	**<0.001**
Lymphocyte ($\times 10^9$/L)	1.11 (0.78–1.66)	1.07 (0.71–1.56)	1.21 (0.85–1.76)	0.077
WBC ($\times 10^9$/L)	11.93 (9.31–14.95)	13.00 (10.47–16.39)	10.56 (8.18–13.35)	**<0.001**
Hemoglobin (g/L)	146 (132–157)	147 (131–159)	146 (134–157)	0.906
Platelet ($\times 10^9$/L)	211 (178–251)	214 (184–255)	207 (170–248)	0.130
SII	1,796.35 (1,093.86–3,047.16)	2,463.14 (1,369.03–3,516.28)	1,538.17 (980.51–2,432.10)	**<0.001**
Blood glucose (mmol/L)	7.8 (6.8–9.3)	8.3 (7.3–10.2)	7.4 (6.3–8.6)	**<0.001**
Lactic acid (mmol/L)	1.5 (1.0–2.0)	1.7 (1.1–2.4)	1.2 (1.0–1.5)	**<0.001**
Uric acid (μmol/L)	226.5 (170.1–285.0)	225 (174–301)	228 (168–264)	0.234
Lactate dehydrogenase (u/L)	196.5 (164.0–249.0)	205 (168–258)	194 (158–243)	**0.046**
Postoperative analgesics-sedatives	142 (52.40)	66 (58.93)	76 (47.80)	0.071

BMI, body mass index; GCS, Glasgow coma scale; SII, systemic immune inflammation index; WBC, white blood cells. The significance of bold data: $P < 0.05$.

value was 75 ml with sensitivity and specificity of 47.3% and 88.1%, respectively. The corresponding AUC of GCS was 0.775 (95% CI, 0.720–0.830, $P < 0.001$), and the cutoff value was 8.5 with sensitivity and specificity of 73.6% and 61.9%, respectively.

Based on the SII cutoff value, these 271 patients were then dichotomized into 2 groups, SII < 2,454.51 group ($n = 182$, 67.16%) and SII > 2,454.51 group ($n = 89$, 32.84%). The prognosis was poorer for SII > 2,454.51 group patients than for SII < 2,454.51 group patients ($\chi^2 = 50.502$, $P < 0.001$). However, there was no statistically significant difference in mortality between these two groups ($\chi^2 = 3.196$, $P = 0.074$).

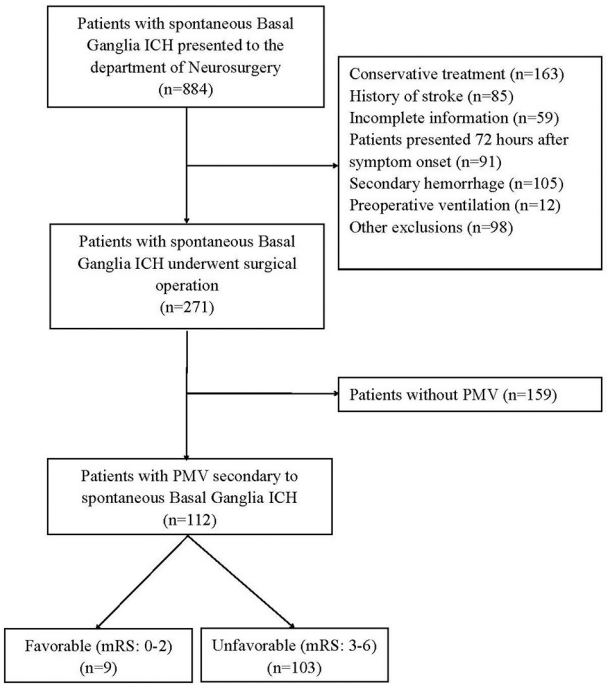


FIGURE 1
The study flow chart. ICH, Intracerebral Hemorrhage; PMV, Prolonged Mechanical Ventilation; mRS, the Modified Rankin Scale.

TABLE 2 Univariate and multivariate regression analysis of factors related to PMV.

Predictors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Systolic pressure	1.008 (1.000–1.016)	0.043	0.998 (0.987–1.008)	0.679
GCS	0.685 (0.616–0.762)	<0.001	**0.780 (0.688–0.883)**	**<0.001**
Hematoma size	1.041 (1.028–1.055)	<0.001	**1.031 (1.016–1.047)**	**<0.001**
Serum potassium	0.415 (0.251–0.687)	0.001	0.566 (0.303–1.056)	0.074
Serum albumin	0.942 (0.898–0.988)	0.013	0.965 (0.908–1.026)	0.249
Blood glucose	1.150 (1.051–1.258)	0.002	1.028 (0.930–1.136)	0.594
Lactic acid	1.848 (1.375–2.482)	<0.001	**1.431 (1.015–2.017)**	**0.041**
Lactate dehydrogenase	1.005 (1.001–1.008)	0.006	1.004 (1.000–1.008)	0.067
SII	1.471 (1.235–1.752)	<0.001	**1.283 (1.049–1.568)**	**0.015**

GCS, Glasgow coma scale; SII, systemic immune inflammation index. The significance of bold data: $P < 0.05$.

Discussion

In this retrospective study, We retrieved and analyzed the clinical data of patients with spontaneous basal ganglia ICH who underwent surgical operations in a single center during an 8-year period using the hospital's scientific research big data platform. For the first time, we examined the risk factors of postoperative PMV after spontaneous basal ganglia ICH and analyzed the association between SII and PMV. We found that preoperative SII may predict PMV in patients with spontaneous basal ganglia ICH who underwent surgical operations. These findings may be helpful for the medical staff to anticipate the therapy course, and help the patient families to adjust their emotions and face the challenge of life.

The time definition of PMV is still uncertain, ranging from 24 h to 21 days (11, 12, 14, 21–23). This is mainly based on the evaluation criteria of each clinical center, and the actual needs of the prognosis estimate (24). The length of PMV defined by the surgical department was shorter, while the PMV time defined by the rehabilitation medicine department tended to be longer. PMV was defined as mechanical ventilation for more than 24 h in this study, and the clinical prognostic differentiation was satisfactory. PMV has been proven to harm the prognosis. A high incidence of PMV (47.6%) was shown in our cohort, and more than 90% of them had unfavorable prognoses. The length of ICU stay and total length of stay in PMV patients were significantly longer, and the mortality was higher.

Acute persistent disturbance of consciousness and the related inability to protect the airway, and abnormal respiratory mechanics were secondary to severe intracranial lesions are the most frequent reasons for initiating mechanical ventilation and postoperative weaning difficulty (6, 25–27). Among the factors associated with unfavorable prognosis of neurocritical ill patients, GCS and hematoma size are general acceptance predictors (12, 13). Decreased consciousness was often significantly associated with increased intracranial hematoma volume (28). The surgical operation usually signifies large intracranial bleeding and severe disease progression. In the present study, initial GCS < 9 and hematoma size > 75 ml were identified as significant and independent predictors of PMV in patients with spontaneous basal ganglia ICH who underwent surgical operations.

The inflammation is implicated in the pathogenesis of stroke, and the inflammatory response following acute brain injury has been demonstrated (27, 29). The extent of the systemic inflammatory response and count of circulating neutrophils were significant correlation with hematoma size (30). Increased circulating neutrophil is recruited directly due to the inflammatory environment and high level of the stress state. Catecholamine released from sympathetic activation also leads to neutrophil increase and lymphopenia (31). Lymphopenia on admission is one of the characteristics of neurogenic immunosuppression, independently associated with the severity and extension of brain injury, and reflects the functional frailty status of the patient (32, 33). In our study, the lymphocyte count of patients in the PMV group was lower than those in the non-PMV group (1.07×10^9/L vs. 1.21×10^9/L), but the difference was not statistically significant ($P = 0.077$). In addition to preventing bleeding and promoting hemostasis, the platelet participates in post-stroke immune-inflammatory responses by releasing chemokines and cytokines (34, 35). In the present study, we found that the platelet

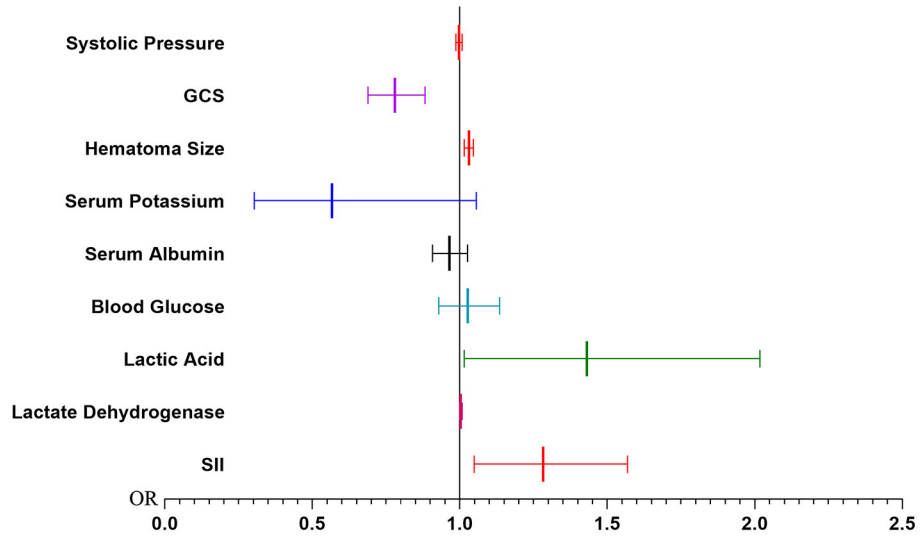


FIGURE 2
Forest map of multivariate logistic regression. SII, Systemic Immune Inflammation Index.

TABLE 3 Diagnostic values of factors related to PMV.

Variable	AUC (95% CI)	*P*-value	Cutoff value	Sensitivity	Specificity
SII	0.662 (0.595–0.729)	<0.001	2,454.51	0.518	0.761
GCS	0.775 (0.720–0.830)	<0.001	8.5	0.736	0.619
Lactic acid	0.645 (0.575–0.715)	<0.001	1.55	0.554	0.748
Hematoma size	0.709 (0.645–0.773)	<0.001	75	0.473	0.881

count of patients in the PMV group was higher than those in the non-PMV group (214×10^9/L vs. 207×10^9/L), but the statistical results were not significant too ($P = 0.130$).

The systemic production of inflammatory mediators induces inflammatory responses not only in the brain environment but also in a systemic inflammatory environment. Excessive systemic inflammatory response participates in the pathogenesis of acute lung injury (36, 37). Sympathetic overstimulation and large amounts of catecholamines release into the systemic circulation increase pulmonary vascular hydrostatic pressure and endothelial permeability, causing neurogenic pulmonary edema (38, 39). SII, which was obtained by combining neutrophils, lymphocytes, and platelets in a single index, has been confirmed as a novel predictive inflammation marker of PMV in our cohort, and the cut-off value was 2,454.51. To our knowledge, the present report may be the first study to show that pre-operation increased SII can be a risk factor for PMV in patients with spontaneous basal ganglia ICH who underwent surgical operations.

In this study, another risk factor identified for PMV was lactic acid. Elevated lactic acid underscores the systemic impact of intracranial pathology, and predicts the disease's systemic severity in patients with devastating neurologic diseases (40). Due to excessive catecholamine release could induce increased glucose metabolism with a rapid output of lactate in the systemic circulation, and enhanced renal perfusion may lead to negative liquid equilibrium (41, 42). In addition, a sharp increase in intracranial pressure leads to the use of large doses of osmotic diuretics, which may cause subsequential hypovolemia. Other potential causes of elevated lactic acid include neurogenic pulmonary edema and acute lung injury (43). But lactic acidosis is multifactorial, a prospective study with other causes excluded may be useful.

In the present study, We found that pre-operation SII predicted PMV quite well in patients with spontaneous basal ganglia ICH who underwent surgical operations. The incorporation of these cheap and readily available markers into clinical treatment may simplify prediction procedures and strengthen the predictive power. However, this article also has some limitations. First, it is a single-center retrospective study with a relatively small scale and may have potential biases. Second, although we excluded comorbidities that might affect inflammation, immunity, and breathing, some potential confounders may not be easily detected. Third, the purpose of this study was to analyze the predictive value of preoperative factors for PMV, but some factors after surgery were also affecting PMV (such as acute respiratory distress syndrome or hypostatic pneumonia), and no further comparison was made in this study. Fourth, we only validated the effectiveness of preoperative SII in predicting PMV after surgical operations

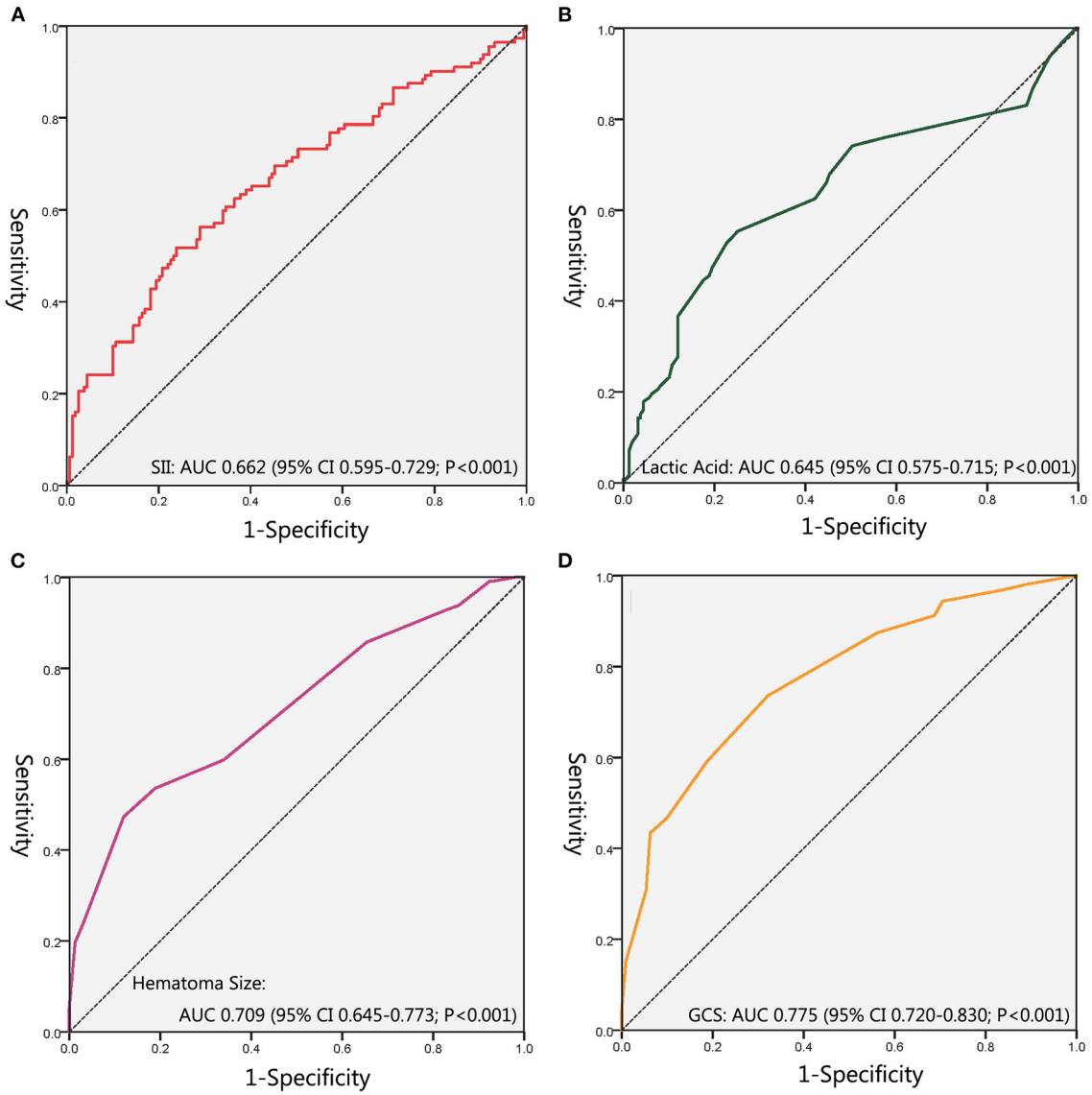


FIGURE 3
The receiver-operating characteristic curves. **(A)** ROC for SII; **(B)** ROC for Lactic Acid; **(C)** ROC for Hematoma Size; **(D)** ROC for GCS. SII, Systemic Immune Inflammation Index; ROC, Receiver Operating Characteristics Curve; GCS, Glasgow Coma Scale.

for spontaneous basal ganglia ICH but did not cross-compare SII with other inflammatory indices. Fifth, only these patients with spontaneous basal ganglia intracerebral hemorrhage who underwent surgical treatment were included and analyzed, so the information on patients who underwent conservative treatment could not be presented. Finally, we only observed the baseline SII on admission, the relationship between the dynamic changes of SII and the occurrence of PMV worthy of further study.

Conclusion

Preoperative SII may predict PMV in patients with spontaneous basal ganglia ICH who undergo surgical operations.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Human Ethics Committee of the Affiliated Hospital of Qingdao University (QYFY-WZLL-26903). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HX: conceptualization, data curation, formal analysis, investigation, methodology, visualization, and writing—original draft. MF: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing—original draft, and writing—review and editing. HL: conceptualization, formal analysis, investigation, methodology, visualization, and writing—review and editing. WH and YL: data curation and writing—review and editing. LC: data curation, formal analysis, and writing—review and editing. FZ: data curation, visualization, and writing—review and editing. LL: conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing—original draft, and writing—review and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

References

1. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH, Kong LZ. Stroke in China: epidemiology, prevention, and management strategies. *Lancet Neurol.* (2007) 6:456–64. doi: 10.1016/S1474-4422(07)70004-2

2. Li K, Ding X, Wang Q, Fan G, Guo W, Li C, et al. Low-Cost, accurate, effective treatment of hypertensive cerebral hemorrhage with three-dimensional printing technology. *Front Neurol.* (2021) 12:608403. doi: 10.3389/fneur.2021.608403

3. Kim JY, Bae HJ. Spontaneous intracerebral hemorrhage: management. *J Stroke.* (2017) 19:28–39. doi: 10.5853/jos.2016.01935

4. Shi J, Liu Y, Wei L, Guan W, Xia W. Admission neutrophil-to-lymphocyte ratio to predict 30-day mortality in severe spontaneous basal ganglia hemorrhage. *Front Neurol.* (2023) 13:1062692. doi: 10.3389/fneur.2022.1062692

5. Cote DJ, Karhade AV, Burke WT, Larsen AM, Smith TR. Risk factors for post-operative respiratory failure among 94,621 neurosurgical patients from 2006 to 2013: a NSQIP analysis. *Acta Neurochir (Wien).* (2016) 158:1639–45. doi: 10.1007/s00701-016-2871-8

6. Pelosi P, Ferguson ND, Frutos-Vivar F, Anzueto A, Putensen C, Raymondos K, et al. Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med.* (2011) 39:1482–92. doi: 10.1097/CCM.0b013e31821209a8

7. de Montmollin E, Terzi N, Dupuis C, Garrouste-Orgeas M, da Silva D, Darmon M, et al. One-year survival in acute stroke patients requiring mechanical ventilation: a multicenter cohort study. *Ann Intensive Care.* (2020) 10:53. doi: 10.1186/s13613-020-00669-5

8. Schmidt SB, Boltzmann M, Bertram M, Bucka C, Hartwich M, Jöbges M, et al. Factors influencing weaning from mechanical ventilation in neurological and neurosurgical early rehabilitation patients. *Eur J Phys Rehabil Med.* (2018) 54:939–946. doi: 10.23736/S1973-9087.18.05100-6

9. Ghiani A, Paderewska J, Sainis A, Crispin A, Walcher S, Neurohr C. Variables predicting weaning outcome in prolonged mechanically ventilated tracheotomized patients: a retrospective study. *J Intensive Care.* (2020) 8:19. doi: 10.1186/s40560-020-00437-4

10. Tseng YH, Ko HK, Tseng YC, Lin YH, Kou YR. Atrial fibrillation on intensive care unit admission independently increases the risk of weaning failure in non-heart failure mechanically ventilated patients in a medical intensive care unit: a retrospective case-control study. *Medicine (Baltimore).* (2016) 95:e3744. doi: 10.1097/MD.0000000000003744

11. Rass V, Ianosi BA, Lindlbauer M, Lindner A, Kofler M, Schiefecker AJ, et al. Factors associated with prolonged mechanical ventilation in patients with subarachnoid hemorrhage-the raise score. *Crit Care Med.* (2022) 50:103–13. doi: 10.1097/CCM.0000000000005189

12. Lehmann F, Schenk LM, Ilic I, Putensen C, Hadjiathanasiou A, Borger V, et al. Prolonged mechanical ventilation in patients with deep-seated intracerebral hemorrhage: risk factors and clinical implications. *J Clin Med.* (2021) 10:1015. doi: 10.3390/jcm10051015

13. Huang HY, Lee CS, Chiu TH, Chen HH, Chan LY, Chang CJ, et al. Clinical outcomes and prognostic factors for prolonged mechanical ventilation in patients with acute stroke and brain trauma. *J Formos Med Assoc.* (2022) 121:162–69. doi: 10.1016/j.jfma.2021.02.011

14. Saber H, Palla M, Kazemlou S, Navi BB, Yoo AJ, Simonsen C Z, et al. Prevalence, predictors, and outcomes of prolonged mechanical ventilation after endovascular stroke therapy. *Neurocrit Care.* (2021) 34:1009–16. doi: 10.1007/s12028-020-01125-9

15. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res.* (2014) 20:6212–22. doi: 10.1158/1078-0432.CCR-14-0442

16. Fu F, Deng C, Wen Z, Gao Z, Zhao Y, Han H, et al. Systemic immune-inflammation index is a stage-dependent prognostic factor in patients with operable non-small cell lung cancer. *Transl Lung Cancer Res.* (2021) 10:3144–54. doi: 10.21037/tlcr-21-267

17. Agus HZ, Kahraman S, Arslan C, Yildirim C, Erturk M, Kalkan AK, et al. Systemic immune-inflammation index predicts mortality in infective endocarditis. *J Saudi Heart Assoc.* (2020) 32:58–64. doi: 10.37616/2212-5043.1010

18. Geraghty JR, Lung TJ, Hirsch Y, Katz EA, Cheng T, Saini NS, et al. Systemic immune-inflammation index predicts delayed cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurgery.* (2021) 89:1071–9. doi: 10.1093/neuros/nyab354

19. Zhang Y, Qin XY, Chen XC. Modern Neurosurgery. 2nd ed, Shanghai: Zhou LF, 2015.

20. Liu L, Shen H, Zhang F, Wang JH, Sun T, Lin ZG. Stereotactic aspiration and thrombolysis of spontaneous intracerebellar hemorrhage. *Chin Med J (Engl).* (2011) 124:1610–5.

21. Schuss P, Lehmann F, Schäfer N, Bode C, Scharnböck E, Schaub C, et al. Postoperative prolonged mechanical ventilation in patients with newly diagnosed glioblastoma-an unrecognized prognostic factor. *Front Oncol.* (2020) 10:607557. doi: 10.3389/fonc.2020.607557

22. Suarez-Pierre A, Fraser CD, Zhou X, Crawford TC, Lui C, Metkus TS, et al. Predictors of operative mortality among cardiac surgery patients with prolonged ventilation. *J Card Surg.* (2019) 34:759–766. doi: 10.1111/jocs.14118

23. Huang C, Chen JC. The long-term survival of intracranial hemorrhage patients successfully weaned from prolonged mechanical ventilation. *Int J Gen Med.* (2021) 14:1197–203. doi: 10.2147/IJGM.S287529

24. Higgins AM, Neto AS, Bailey M, Barrett J, Bellomo R, Cooper DJ, et al. Predictors of death and new disability after critical illness: a multicentre prospective cohort study. *Intensive Care Med.* (2021) 47:772–81. doi: 10.1007/s00134-021-06438-7

25. Borsellino B, Schultz MJ, Gama de Abreu M, Robba C, Bilotta F. Mechanical ventilation in neurocritical care patients: a systematic literature review. *Expert Rev Respir Med.* (2016) 10:1123–32. doi: 10.1080/17476348.2017.1235976

26. Koutsoukou A, Perraki H, Raftopoulou A, Koulouris N, Sotiropoulou C, Kotanidou A, et al. Respiratory mechanics in brain-damaged patients. *Intensive Care Med.* (2006) 32:1947–54. doi: 10.1007/s00134-006-0406-0

27. Robba C, Bonatti G, Battaglini D, Rocco PRM, Pelosi P. Mechanical ventilation in patients with acute ischaemic stroke: from pathophysiology to clinical practice. *Crit Care.* (2019) 23:388. doi: 10.1186/s13054-019-2662-8

28. Wang WJ, Lu JJ, Liu LP, Jia J K, Zhao XQ. Ultraearly hematoma growth in acute spontaneous intracerebral hemorrhage predicts early and long-term poor clinical outcomes: a prospective, observational cohort study. *Front Neurol.* (2021) 12:747551. doi: 10.3389/fneur.2021.747551

29. Parikh NS, Merkler AE, Iadecola C. Inflammation, autoimmunity, infection, and stroke: epidemiology and lessons from therapeutic intervention. *Stroke.* (2020) 51:711–718. doi: 10.1161/STROKEAHA.119.024157

30. Tapia-Pérez JH, Karagianis D, Zilke R, Koufuglou V, Bondar I, Schneider T. Assessment of systemic cellular inflammatory response after spontaneous intracerebral hemorrhage. *Clin Neurol Neurosurg.* (2016) 150:72–9. doi: 10.1016/j.clineuro.2016.07.010

31. Chu YW, Chen PY, Lin SK. Correlation between immune-inflammatory markers and clinical features in patients with acute ischemic stroke. *Acta Neurol Taiwan.* (2020) 29:103–13.

32. Morotti A, Marini S, Jessel MJ, Schwab K, Kourkoulis C, Ayres AM, et al. Lymphopenia, infectious complications, and outcome in spontaneous intracerebral hemorrhage. *Neurocrit Care.* (2017) 26:160–6. doi: 10.1007/s12028-016-0367-2

33. Adiguzel A, Arsava EM, Topcuoglu MA. Temporal course of peripheral inflammation markers and indexes following acute ischemic stroke: prediction of mortality, functional outcome, and stroke-associated pneumonia. *Neurol Res.* (2022) 44:224–31. doi: 10.1080/01616412.2021.1975222

34. Yilmaz Y, Kelesoglu S, Kalay N. A novel predictor of contrast-induced nephropathy in patients with carotid artery disease; the systemic immune inflammation index. *Angiology.* (2022) 73:781–7. doi: 10.1177/00033197211061919

35. Ali RA, Wuescher LM, Worth RG. Platelets: essential components of the immune system. *Curr Trends Immunol.* (2015) 16:65–78.

36. D'Alessio FR. Mouse models of acute lung injury and ARDS. *Methods Mol Biol.* (2018) 1809:341–50. doi: 10.1007/978-1-4939-8570-8_22

37. Song D, Zhao M, Feng L, Wang P, Li Y, Li W. Salidroside attenuates acute lung injury via inhibition of inflammatory cytokine production. *Biomed Pharmacother.* (2021) 142:111949. doi: 10.1016/j.biopha.2021.111949

38. Ziaka M, Exadaktylos A. Brain-lung interactions and mechanical ventilation in patients with isolated brain injury. *Crit Care.* (2021) 25:358. doi: 10.1186/s13054-021-03778-0

39. Elmer J, Hou P, Wilcox SR, Chang Y, Schreiber H, Okechukwu I, et al. Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage. *Crit Care Med.* (2013) 41:1992–2001. doi: 10.1097/CCM.0b013e31828a3f4d

40. Aisiku IP, Chen PR, Truong H, Monsivais DR, Edlow J. Admission serum lactate predicts mortality in aneurysmal subarachnoid hemorrhage. *Am J Emerg Med.* (2016) 34:708–12. doi: 10.1016/j.ajem.2015.12.079

41. Lehmann F, Schenk LM, Schneider M, Bernstock JD, Bode C, Borger V, et al. Predictive relevance of baseline lactate and glucose levels in patients with spontaneous deep-seated intracerebral hemorrhage. *Brain Sci.* (2021) 11:633. doi: 10.3390/brainsci11050633

42. Oh CH, Kim JW, Kim GH, Lee KR, Hong DY, Park SO, et al. Serum lactate could predict mortality in patients with spontaneous subarachnoid hemorrhage in the emergency department. *Front Neurol.* (2020) 11:975. doi: 10.3389/fneur.2020.00975

43. Satoh E, Tagami T, Watanabe A, Matsumoto G, Suzuki G, Onda H, et al. Association between serum lactate levels and early neurogenic pulmonary edema after non-traumatic subarachnoid hemorrhage. *J Nippon Med Sch.* (2014) 81:305–12. doi: 10.1272/jnms.81.305

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 15 June 2023
DOI 10.3389/fneur.2023.1205487

OPEN ACCESS

EDITED BY
Wenqiang Chen,
Harvard Medical School, United States

REVIEWED BY
Alicia Zha,
The Ohio State University, United States
Pamel Duncan,
Wake Forest Baptist Medical Center, United States

*CORRESPONDENCE
Adalia H. Jun-O'Connell
✉ adalia.junoconnell@umassmed.edu

RECEIVED 13 April 2023
ACCEPTED 22 May 2023
PUBLISHED 15 June 2023

CITATION
Jun-O'Connell AH, Grigoriciuc E, Gulati A, Silver B, Kobayashi KJ, Moonis M and Henninger N (2023) Stroke nurse navigator utilization reduces unplanned 30-day readmission in stroke patients treated with thrombolysis. *Front. Neurol.* 14:1205487. doi: 10.3389/fneur.2023.1205487

Stroke nurse navigator utilization reduces unplanned 30-day readmission in stroke patients treated with thrombolysis

Adalia H. Jun-O'Connell[1]*, Eliza Grigoriciuc[1], Akanksha Gulati[1], Brian Silver[1], Kimiyoshi J. Kobayashi[2], Majaz Moonis[1] and Nils Henninger[1,3]

[1]Departments of Neurology, University of Massachusetts Chan Medical School, Worcester, MA, United States, [2]Departments of Internal Medicine, University of Massachusetts Chan Medical School, Worcester, MA, United States, [3]Departments of Psychiatry, University of Massachusetts Chan Medical School, Worcester, MA, United States

Background: Unplanned 30-day hospital readmissions following a stroke is a serious quality and safety issue in the United States. The transition period between the hospital discharge and ambulatory follow-up is viewed as a vulnerable period in which medication errors and loss of follow-up plans can potentially occur. We sought to determine whether unplanned 30-day readmission in stroke patients treated with thrombolysis can be reduced with the utilization of a stroke nurse navigator team during the transition period.

Methods: We included 447 consecutive stroke patients treated with thrombolysis from an institutional stroke registry between January 2018 and December 2021. The control group consisted of 287 patients before the stroke nurse navigator team implementation between January 2018 and August 2020. The intervention group consisted of 160 patients after the implementation between September 2020 and December 2021. The stroke nurse navigator interventions included medication reviews, hospitalization course review, stroke education, and review of outpatient follow-ups within 3 days following the hospital discharge.

Results: Overall, baseline patient characteristics (age, gender, index admission NIHSS, and pre-admission mRS), stroke risk factors, medication usage, and length of hospital stay were similar in control vs. intervention groups ($P > 0.05$). Differences included higher mechanical thrombectomy utilization (35.6 vs. 24.7%, $P = 0.016$), lower pre-admission oral anticoagulant use (1.3 vs. 5.6%, $P = 0.025$), and less frequent history of stroke/TIA (14.4 vs. 27.5%, $P = 0.001$) in the implementation group. Based on an unadjusted Kaplan–Meier analysis, 30-day unplanned readmission rates were lower during the implementation period (log-rank $P = 0.029$). After adjustment for pertinent confounders including age, gender, pre-admission mRS, oral anticoagulant use, and COVID-19 diagnosis, the nurse navigator implementation remained independently associated with lower hazards of unplanned 30-day readmission (adjusted HR 0.48, 95% CI 0.23–0.99, $P = 0.046$).

Conclusion: The utilization of a stroke nurse navigator team reduced unplanned 30-day readmissions in stroke patients treated with thrombolysis. Further studies are warranted to determine the extent of the results of stroke patients not treated with thrombolysis and to better understand the relationship between resource utilization during the transition period from discharge and quality outcomes in stroke.

KEYWORDS

stroke, TPA, stroke nurse navigator, 30-day readmission, quality improvement

Introduction

Unplanned hospital readmission following a stroke is a costly and common problem in the United States (1). Reported unplanned readmission rates after a stroke have been reported to be as high as 12–21% within 30 days, reaching up to 55% within 1 year (2–6). The use of intravenous tissue plasminogen activator (tPA) improves long-term outcomes (7–12). Moreover, it has shown 11 to 23% lower odds of 30-day unplanned readmission (6), indicating that there is a significant subset of tPA-treated patients that is at risk for unplanned 30-day readmission. Therefore, quality improvement measures are needed to further reduce readmission risk. Specifically, the transition period between the hospital discharge and subsequent ambulatory follow-up following an ischemic stroke is a critical period during which medication errors, failed hand-offs, inadequate post-discharge support, and loss of follow-up can occur, which may increase the risk for complications and unplanned readmission (13–15). Thus, there is a critical need to optimize systems of care in clinical practice to improve post-stroke outcomes (16, 17).

One strategy to improve patient care during the transition period may include post-discharge phone calls, which have been shown to reduce unplanned hospital readmission rates within 6 months in a pragmatic, randomized control trial (18). However, little is known whether such an intervention reduces readmission rates in patients treated with thrombolysis and whether this translates to improved long-term outcomes (16).

To address this issue, we sought to determine whether the utilization of a stroke nurse navigator team reduces 30-day stroke unplanned readmission of tPA-treated patients during the transition period. Comparisons between tPA-treated patients vs. non-tPA-treated patients were made as we recognize the concern that there remains a significant subset of tPA-treated patients that is at risk for unplanned 30-day readmission. The tPA-treated patients offer an additional advantage in the study, considering that all patients with acute ischemic strokes undergo a similar work-up and treatment paradigm in the acute setting due to the standardization of stroke care. A secondary objective was to determine whether this intervention was associated with a reduced risk of major adverse cardiovascular events (MACE), functional deficit severity defined by the modified Rankin scale (mRS), and neurological status defined by the National Institutes of Health Stroke Scale (NIHSS) at 90-days from discharge.

Methods

Study cohort

We retrospectively analyzed prospectively accrued adult patients (age 18 years and older) who were admitted to our academic tertiary care center for an acute ischemic stroke between January 2018 and December 2021. Electronic medical records and relevant ICD codes were used to identify the principal diagnosis of stroke. Patients who were determined to have had a planned 30-day readmission as identified by our hospital readmission committee were excluded from this search. We excluded patients who did not receive intravenous thrombolysis, died during the index admission, were discharged to hospice, had a hospital length of stay exceeding 30 days, or were lost to follow-up (19). The Institutional Review Board (IRB) approved the study, and the Health Insurance Portability and Accountability Act (HIPPA) waiver of informed consent was granted. We prepared our manuscript according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (http://www.strobe-statement.org).

All diagnoses were first established by the treating board-certified neurologist and confirmed by abstracting physicians (EG and AG). Conflicting diagnoses were resolved by consensus after adjudication by board-certified vascular neurologists (AJ-O and NH).

Intervention

We compared patients treated before nurse navigator implementation (between January 2018 and August 2020) with those treated after nurse navigator implementation (between September 2020 and December 2021). The stroke nurse navigator team consisted of two trained nurses (RN) experienced in stroke care. After the nurse navigator implementation, each patient received a standardized follow-up transition plan as follows. On the day of the discharge, introduction to the transition process, ambulatory follow-up appointments, and ambulatory testing were confirmed. Between days 3 and 7 after discharge, nurses conducted phone interviews with the patients and/or their health caregiver to review discharge summaries, verify medications, confirm the follow-up plans for outpatient-based testing and appointments, and address patient satisfaction and any outstanding questions. The flow process was such that each stroke nurse navigator had access to the inpatient stroke admission team list, and they attended daily huddles twice a week on Monday and Wednesday. On the day of the discharge, the inpatient team notifies the stroke nurse navigator for disposition follow-up plans. To prevent potential missed errors, the stroke nurse navigator reviewed the inpatient stroke team census each morning to identify potential discharge candidates and verified the discharge plan with the stroke team *via* electronic communication. To determine whether our goal to have the nurse navigator call patients within 3–7 days was met, we spot-checked every other patient ($n = 81$). Among these, the median time to patient call was 3 days (interquartile range 2–7 days) after discharge. Any issues that the nurse navigator could not resolve were escalated to the discharging physicians and neurology quality officer (AJ-O) for resolution.

Data collection

Patient age, gender, insurance information, total admission cost in dollars, index admission length of stay (LOS), co-morbidities, pre-admission medications, admission National Institutes of Health Stroke Scale (NIHSS), admission modified Rankin Score (mRS), and discharge status were collected for all patients by review of the medical records through the electronic medical record system. In addition, we assessed COVID-19 status (confirmed

infection within 30 days of the index admission) in all patients that were admitted between 2020 and 2021.

Definitions

The transition of care was defined as the movement of a patient from the admitted hospital to another healthcare setting (20). The index admission was defined as the admission of the starting point for studying repeat hospital visits (21). The 30-day unplanned readmission was defined as a subsequent unplanned admission, occurring within 30 days of the discharge date from the index admission (22). For dyslipidemia, two definitions were used: LDL higher than 100 based upon AHA/ASA ischemic stroke guideline (23) and LDL higher than 189 based upon ACC/AHA guideline (24).

Study outcomes

The primary outcome of interest was the 30-day unplanned readmission. Secondary outcomes of interest were the rate of MACE, including death within 90 days from discharge as well as the 90-day mRS and NIHSS. Medical records were independently reviewed by two investigators to confirm the qualifying index diagnosis and the outcomes of interest.

Statistical analyses

Data are reported as median (interquartile range) unless otherwise stated. Univariate comparisons were performed using the χ^2 test, Fisher's exact test, and Mann-Whitney U-test as appropriate. A two-sided p-value of <0.05 was considered to be statistically significant in all analyses. The Kaplan–Meier analysis, log-rank test, and multivariable Cox regression analysis (with backward elimination) were used to determine whether stroke nurse navigator implementation was associated with a reduction of the 30-day unplanned readmission rate. We calculated adjusted hazard ratios (aHR) with corresponding 95% confidence intervals (CI). Models were adjusted for age, gender, admission NIHSS, pre-admission mRS, treatment with mechanical thrombectomy, oral anticoagulant use, history of stroke/TIA, COVID-19 diagnosis within the 30 days of index admission, and total cost of the index hospitalization. All statistical analyses were performed using IBM SPSS Statistics version 28.0.1 (IBM, Armonk, NY).

Results

The study flowchart is depicted in Figure 1. We included 447 consecutive stroke patients treated with thrombolysis ($n = 287$ before and $n = 160$ after the implementation of stroke nurse navigator transition care implementation).

Table 1 shows the baseline characteristics of the studied population as stratified by a stroke nurse navigator transition care implementation status. Overall, patient characteristics were similar between groups except for higher mechanical thrombectomy utilization ($P = 0.016$), lower pre-admission oral anticoagulant use ($P = 0.025$), less frequent history of stroke/TIA ($P = 0.001$), more frequent COVID-19 diagnosis ($P = 0.001$), and higher total cost of hospitalization ($P < 0.001$) in the implementation vs. the control group.

Reasons for 30-day unplanned readmission in ischemic stroke

Among the 447 stroke patients, 50 (11.2%) had 30-day unplanned readmission. In total, 16 (32%) readmissions were due to neurological causes (such as seizure or recurrent stroke), and 34 (68%) readmissions were due to medical issues. In the subgroup of readmissions due to medical issues, 12 (24%) were due to infections.

Association between stroke nurse navigator implementation and 30-day unplanned readmission risk

Based on an unadjusted analysis, the 30-day readmission rate was significantly higher prior to stroke nurse navigator implementation as compared to post-implementation (13.6% vs. 6.9%, $P = 0.041$) with the Kaplan–Meier analysis indicating continued separation of the readmission rates throughout the 30-day transition period (log-rank $P = 0.029$, Figure 2). The implementation of the nurse navigator transition care remained independently associated with a lower adjusted hazard rate (aHR) of unplanned 30-day readmission based on a multivariable Cox regression analysis (aHR 0.48, 95% CI 0.23–0.99, $P = 0.046$, Table 2). Overall, patients with the stroke nurse implementation had a 67.6% reduced probability (defined as 1-[aHR/(1+aHR)]) of 30-day unpreventable stroke readmission compared to patients without the implementation.

90-day MACE

Table 3 summarizes the univariate comparison of 90-day outcomes between groups. Overall, we found no significant differences in the unadjusted 90-day mortality, MACE, 90-day NIHSS, and 90-day mRS ($P > 0.05$, each).

Discussion

Despite improvements in stroke prevention and acute stroke care processes, many patients and their caregivers face significant gaps in post-stroke care during the post-stroke recovery period (16). A recent systemic review and meta-analysis of qualitative studies focusing on hospital-to-home transition care in stroke showed the importance of patient and caregiver engagement in discharge preparation, along with the need for the implementation of post-discharge support to help stroke patients adjust to post-stroke rehabilitation and the need for integrated transitional

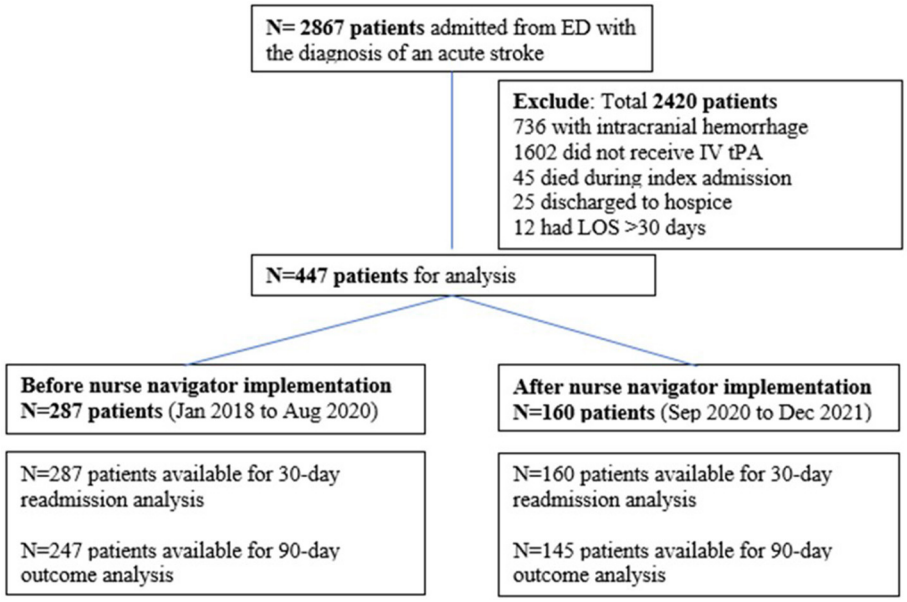


FIGURE 1
Patient flowchart.

support for post-stroke adjustment (25). However, the potential impact of stroke nurse navigator implementation on unplanned readmissions in patients treated with thrombolysis is unknown.

We now show that in the studied cohort, the utilization of a stroke nurse navigator for transition care was independently associated with a reduced rate of unplanned 30-day readmission in ischemic stroke patients treated with thrombolysis. This is an important finding as the Centers for Medicare and Medicaid Services (CMS) defined 30-day unplanned readmission as an indicator of poor hospital care, connecting to hospital penalties and payment determination (2, 26). The utilization of stroke nurse navigator teams for the transition period may thus represent an effective tool to improve stroke care by both engaging patients and caregivers to improve support as well as reduce unplanned readmission risk. This is important as stroke nurse navigators during the transition period are also known to improve self-efficacy, quality of life, and stroke-relevant knowledge, as well as reduce caregiver burnout (27). Further studies aimed at identifying patients at high risk for unplanned readmission have the potential to address precipitating factors and create an opportunity to recognize and mitigate issues surrounding patient care during the transition period (1).

Our study also showed a 67.6% reduced probability of 30-day unplanned readmission with transition care utilization. Although the previous Transition Coaching for Stroke (TRACS) trial showed a potential reduction of 30-day unplanned readmissions following stroke by 48% with transition care, the study called for further replicable studies due to its size of 510 patients in a single center setting, and the study intervention focused only on patients that were discharged home (17). Contrary to TRACS, our study also included patients that were discharged to facilities.

Previous studies showed that unplanned 30-day readmission after stroke is associated with increased mortality and significant societal financial burden, costing up to 17 billion dollars in the United States alone (2). Therefore, we sought to determine whether stroke nurse navigator utilization could improve the risk of MACE including mortality as well as functional outcomes by 90 days after stroke. We found no significant difference in these outcomes between studied cohorts. This observation is similar to the COMPASS (Comprehensive Post-Acute Stroke Services) trial, which failed to show that post-acute stroke transitional care services had a significant effect on the 90-day functional outcome as assessed by the Stroke Impact Scale (primary outcome) as well as the mRS and mortality outcome (secondary outcomes). This may have been in part related to the pragmatic trial design with incomplete case ascertainment (16). Nevertheless, our results should be interpreted cautiously as subjects were not randomly assigned to the intervention, and comparison groups were not measured during concurrent time periods introducing the possibility of unmeasured confounding. Thus, further prospective studies in larger cohorts are required to determine the possible beneficial effects of stroke nurse navigator implementation on long-term outcomes.

The CMS created the Bundled Payments of Care Improvement (BPCI) initiative, which created incentives for cost and quality care (28). Although there is limited data, the impact of stroke bundle programs is being studied on patient outcomes, and stroke nurse navigators are starting to be recognized to provide support for BPCI initiatives (28, 29). From a patient perspective, there is a demand and need for having a dedicated care coordinator or point of contact during the transition period to guide through expectations of post-stroke adjustment and transition (30–33).

Further future studies are needed to investigate the cost-effectiveness of stroke nurse navigators in stroke BPCI initiative, quality improvements, and overall patient satisfaction. Patients that are specifically discharged home with home healthcare have been

10.3389/fneur.2023.1205487

TABLE 1 Patient characteristics stratified by absence vs. presence of stroke nurse navigator implementation in ischemic strokes that received alteplase.

Characteristics	Before implementation ($n = 287$)	After implementation ($n = 160$)	*P*-value
Age [Years; Median (IQR)]	**71 (58–80)**	**69 (59–78)**	0.54
Gender			0.37
Female	128 (44.6%)	79 (49.4%)	
Male	159 (55.4%)	81 (50.6%)	
Total cost of hospitalization ($), median (IQR)	$22,989 ($17,192–$34,571)	$27,096 ($21,896–$53,208)	<0.001
Index admission NIHSS, median (IQR)	6 (3–12)	7 (3–14)	0.53
Pre-admission mRS, median (IQR)	0 (0–1)	0 (0–1)	0.2
Length of stay, median (IQR)	3 (2–6)	4 (2–6)	0.54
Mechanical thrombectomy	71 (24.7%)	57 (35.6%)	0.02
Dyslipidemia			
LDL > 100	99 (34.9%)	61 (38.1%)	0.54
LDL > 189	5 (1.8%)	3 (1.9%)	1
History of prior stroke or TIA	79 (27.5%)	23 (14.4%)	0
Hypertension	212 (73.9%)	114 (71.3%)	0.58
Diabetes mellitus	72 (25.1%)	43 (26.9%)	0.74
Atrial fibrillation	85 (29.6%)	40 (25%)	0.32
Coronary artery disease	64 (22.3%)	28 (17.5%)	0.27
CHF	43 (15%)	17 (10.6%)	0.25
Peripheral arterial disease	77 (26.8%)	40 (25%)	0.74
Tobacco use hx	141 (49.1%)	70 (43.8%)	0.28
Statin use	129 (44.9%)	76 (47.5%)	0.62
Anti-hypertensives	191 (66.6%)	101(63.1%)	0.47
Anti-diabetic med	56 (19.5%)	25 (15.6%)	0.37
Antiplatelet use	123 (42.9%)	59 (36.9%)	0.23
Oral anticoagulant	16 (5.6%)	2 (1.3%)	0.03
Insurance			0.5
Medicare	165 (57.5%)	89 (55.6%)	
Medicaid	24 (8.4%)	20 (12.5%)	
Commercial	89 (31.0%)	50 (31.3%)	
Military	3 (1.0%)	0 (0%)	
Others	5 (1.7%)	1 (0.6%)	
Uninsured	1 (0.3%)	0 (0%)	
Discharge status			0.56
Home	147 (51.2%)	77 (48.1%)	
Facility	140 (48.8%)	83 (51.9%)	
COVID-19 diagnosis within 30 days of index admission	1 (0.4%)	8 (5.4%)	0.001

Data are median (IQR) or *n* (%). IQR, Interquartile Range; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Score; TIA, Transient ischemic attack; Facilities (acute rehabilitation center, short-term or long-term nursing facility).

shown to have a higher 30-day unplanned readmission rate and significantly lower Medicare payment reimbursements for overall care within the first 60 days after index admission (34). Thus, the optimization and standardization of transition care services also need to be further considered in the future for better patient support (1). Future studies are warranted to further understand the association between stroke nurse navigators, patient outcomes, and barriers to improvement in care. Specifically, it will be important

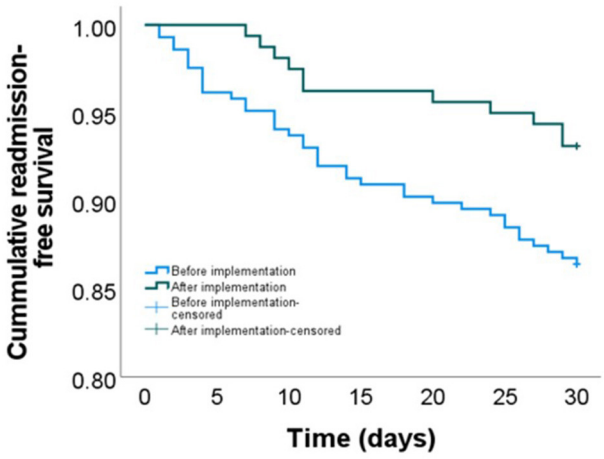


FIGURE 2
Cumulative unpreventable 30-day readmission-free survival stratified by a stroke nurse navigator implementation period. Log-rank $P = 0.029$; adjusted HR 0.48, 95% CI (0.23–0.99).

TABLE 2 Variables associated with 30-day unplanned readmission on multivariable Cox regression.

Study variable	Hazard ratio (95% CI)	*p*-value
Nurse navigator implemented	0.48 (0.23–0.99)	0.046
NIHSS	1.04 (1–1.08)	0.052
Thrombectomy	0.47 (0.22–1.01)	0.053
Total admission cost (per $10,000)	1.12 (1.02–1.23)	0.021
History of stroke and or TIA	1.93 (1.07–3.45)	0.028

CI, confidence interval. Variables not retained in the final step of the model included age, gender, history of stroke/TIA, oral anticoagulant use, pre-admission mRS, and COVID-19 infection within 30 days.

TABLE 3 Outcome events.

Characteristics	Before implementation ($n = 287$)	After implementation ($n = 160$)	*P*-value
30-day Readmission	39 (13.6%)	11 (6.9%)	0.041
90-day Outcome			0.313
Death	16 (5.6%)	11 (6.9%)	
Cardiovascular event	31 (10.8%)	11 (6.9%)	

to study the associative relationship between patient outcomes and medication compliance, access to ambulatory services and treatments, follow-up appointments, and issues surrounding patient-nurse navigator communications. It is also not known if families used other outpatient services more after implementation. One may hypothesize that patients were less willing to bring loved ones to the hospital due to the pandemic or other concerns and utilized outpatient services more. Future studies are needed to further address the question of potential increased usage of resource utilization after stroke nurse navigator implementation.

There are limitations to this study. As discussed, comparison groups were not measured during concurrent time periods, which may have introduced the possibility that unmeasured factors may have played a role in the differences seen. Furthermore, the sample sizes and time frame of the pre-vs. post-implementation phase differed. While this approach may have introduced additional bias, it allowed us to increase the overall sample size and, thus, the power of our analyses. Second, the study population was obtained from a single tertiary care center limiting the generalizability of our findings. Nevertheless, the observed unplanned 30-day readmission rate was 13.6% prior to stroke nurse navigator implementation, which is in line with previously reported rates of 12 to 21% (1), suggesting that our results likely translate to other hospital settings. Furthermore, although we adjusted our analyses for COVID-19 status, we cannot exclude the possibility that our results are biased by unmeasured factors related to the COVID-19 pandemic. Finally, there were differences in the total cost of care in the intervention vs. non-intervention despite the similar length of stay. The difference may be explained by the greater number of thrombectomies in the intervention, which could potentially increase the hospital cost. This could confound our results and therefore should be interpreted with caution. However, it also attests to the operational strength, in which the volume of thrombectomy cases did not decrease during the COVID-19 pandemic.

Conclusion

The utilization of a stroke nurse navigator team was associated with reduced unplanned 30-day readmissions in stroke patients treated with thrombolysis. Further prospective studies are warranted to determine the extent of the results of stroke patients not treated with thrombolysis and to better understand the relationship between resource utilization during the transition period from discharge and quality outcomes in stroke.

Data availability statement

The raw data supporting the conclusions of this article will be made available on reasonable request. Access requests should be directed to the corresponding author(s).

Ethics statement

The studies involving human participants were reviewed and approved by IRB at UMass Chan Medical School. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AJ-O'C: study concept and design, data acquisition, interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. EG: data acquisition, interpretation of data, and critical revision of the manuscript for important intellectual content. AG: data

acquisition and critical revision of the manuscript for important intellectual content. BS: study concept, interpretation of data, and critical revision of the manuscript for important intellectual content. KK and MM: critical revision of the manuscript for important intellectual content. NH: study concept and design, interpretation of data, drafting of the manuscript, data analysis, and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors would like to thank Karin Assad, Kelsey Donahue, Robert Flade, Carolyn Griffin, and Akanksha Gulati.

Conflict of interest

AJ-O'C receives compensation for adjudication of stroke outcomes in the Women's Health Initiative (WHI). BS receives compensation for the review of medicolegal malpractice cases, for adjudication of stroke outcomes in the Women's Health Initiative, and for the authorship of Ebix Medlink, Medscape. NH received support from CDMRP/DoD W81XWH-19-PRARP-RPA, NINDS NS131756, and the ALS foundation during the conduct of the study.

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.

Publisher's note

References

1. Jun-O'Connell AH, Grigoriciuc E, Silver B, Kobayashi KJ, Osgood M, Moonis M, et al. Association between the lace+ index and unplanned 30-day hospital readmissions in hospitalized patients with stroke. *Front Neurol.* (2022) 13:963733. doi: 10.3389/fneur.2022.963733

2. Nouh AM, McCormick L, Modak J, Fortunato G, Staff I. High mortality among 30-day readmission after stroke: Predictors and etiologies of readmission. *Front Neurol.* (2017) 8:632. doi: 10.3389/fneur.2017.00632

3. Fehnel CR, Lee Y, Wendell LC, Thompson BB, Potter NS, Mor V, et al. Post-acute care data for predicting readmission after ischemic stroke: A nationwide cohort analysis using the minimum data set. *J Am Heart Assoc.* (2015) 4:e002145. doi: 10.1161/JAHA.115.002145

4. Kind AJ, Smith MA, Frytak JR, Finch MD. Bouncing back: Patterns and predictors of complicated transitions 30 days after hospitalization for acute ischemic stroke. *J Am Geriatr Soc.* (2007) 55:365–73. doi: 10.1111/j.1532-5415.2007.01091.x

5. Fonarow GC, Smith EE, Reeves MJ, Pan W, Olson D, Hernandez AF, et al. Hospital-level variation in mortality and rehospitalization for medicare beneficiaries with acute ischemic stroke. *Stroke.* (2011) 42:159–66. doi: 10.1161/STROKEAHA.110.601831

6. Vahidy FS, Donnelly JP, McCullough LD, Tyson JE, Miller CC, Boehme AK, et al. Nationwide estimates of 30-day readmission in patients with ischemic stroke. *Stroke.* (2017) 48:1386–88. doi: 10.1161/STROKEAHA.116.016085

7. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet.* (2014) 384:1929–35. doi: 10.1016/S0140-6736(14)60584-5

8. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochr Datab System Rev.* (2014) 2014:1–144. doi: 10.1002/14651858.CD000213.pub3

9. Ist-3 collaborative group. Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third international stroke trial [ist-3]): 18-month follow-up of a randomised controlled trial. *Lancet Neurol.* (2013) 12:768–76. doi: 10.1016/S1474-4422(13)70130-3

10. Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, Lu M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National institute of neurological disorders and stroke recombinant tissue plasminogen activator stroke study group. *New England J Med.* (1999) 340:1781–87. doi: 10.1056/NEJM199906103402302

11. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA.* (2013) 309:2480–8. doi: 10.1001/jama.2013.6959

12. Man S, Xian Y, Holmes DN, Matsouaka RA, Saver JL, Smith EE, et al. Association between thrombolytic door-to-needle time and 1-year mortality and readmission in patients with acute ischemic stroke. *JAMA.* (2020) 323:2170–84. doi: 10.1001/jama.2020.5697

13. Cortelyou-Ward K, Swain A, Yeung T. Mitigating error vulnerability at the transition of care through the use of health it applications. *J Med Syst.* (2012) 36:3825–31. doi: 10.1007/s10916-012-9855-x

14. Roy CL, Poon EG, Karson AS, Ladak-Merchant Z, Johnson RE, Maviglia SM, et al. Patient safety concerns arising from test results that return after hospital discharge. *Ann Intern Med.* (2005) 143:121–8. doi: 10.7326/0003-4819-143-2-200507190-00011

15. Alper E, O'Malley T, Greenwald J. Hospital discharge and readmission. Available online at: https://www.uptodate.com/contents/hospital-discharge-and-readmission#H19 (accessed June 1, 2023).

16. Duncan PW, Bushnell CD, Jones SB, Psioda MA, Gesell SB, D'Agostino RB, et al. Randomized pragmatic trial of stroke transitional care: The compass study. *Circ Cardiovasc Qual Outcomes.* (2020) 13:e006285. doi: 10.1161/CIRCOUTCOMES.119.006285

17. Condon C, Lycan S, Duncan P, Bushnell C. Reducing readmissions after stroke with a structured nurse practitioner/registered nurse transitional stroke program. *Stroke.* (2016) 47:1599–604. doi: 10.1161/STROKEAHA.115.012524

18. Liss DT, Ackermann RT, Cooper A, Finch EA, Hurt C, Lancki N, et al. Effects of a transitional care practice for a vulnerable population: A pragmatic, randomized comparative effectiveness trial. *J Gen Intern Med.* (2019) 34:1758–65. doi: 10.1007/s11606-019-05078-4

19. Lin KH, Lin HJ, Yeh PS. Determinants of prolonged length of hospital stay in patients with severe acute ischemic stroke. *J Clin Med.* (2022) 11:3457. doi: 10.3390/jcm11123457

20. Agency for healthcare research and quality. *Transitions of care*. Available online at: www.ahrq.gov/research/findings/nhqrdr/chartbooks/carecoordination/measure1.html (accessed November 3, 2022).

21. U. S. Department of health and human services, agency for healthcare research and quality. *Hcup methods series: Overview of key readmission measures and methods, report#2012-04.* Available online at: https://www.hcup-us.ahrq.gov/reports/methods/2012_04.pdf#:$\sim$:text=The%20index%20admission%20is%20the%20starting%20point%20for,of%20cancer%3B%20an%20initial%20hospitalization%20is%20not%20required (accessed June 1, 2023).

22. Center for medicare & medicaid services. *"Hospital readmissions reduction program" (hrrp)*. Available onlinea t: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/HRRP/Hospital-Readmission-Reduction-Program (accessed June 1, 2023).

23. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the american heart association/american

stroke association. *Stroke.* (2021) 52:e364–467. doi: 10.1161/STR.0000000000000375

24. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. (2018) aha/acc/aacvpr/aapa/abc/acpm/ada/ags/apha/aspc/nla/pcna guideline on the management of blood cholesterol: Executive summary: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* (2019) 73:3168–209. doi: 10.1161/CIR.0000000000000624

25. Chen L, Xiao LD, Chamberlain D, Newman P. Enablers and barriers in hospital-to-home transitional care for stroke survivors and caregivers: A systematic review. *J Clin Nurs.* (2021) 30:2786–807. doi: 10.1111/jocn.15807

26. Lichtman JH, Leifheit-Limson EC, Jones SB, Wang Y, Goldstein LB. Preventable readmissions within 30 days of ischemic stroke among medicare beneficiaries. *Stroke.* (2013) 44:3429–35. doi: 10.1161/STROKEAHA.113.003165

27. Lin S, Xiao LD, Chamberlain D, Ullah S, Wang Y, Shen Y, et al. Nurse-led health coaching programme to improve hospital-to-home transitional care for stroke survivors: A randomised controlled trial. *Patient Educ Couns.* (2022) 105:917–25. doi: 10.1016/j.pec.2021.07.020

28. Gzesh D, Murphy DA, Peiritsch H, MacCracken T. Benefit of a stroke management program. *Popul Health Manag.* (2020) 23:482–86. doi: 10.1089/pop.2019.0123

29. Murphy D, Boyle C, Della Monica E, Peiritsch H, Schmidt L, Gzesh D, et al. Abstract tp278: Positive impact of a stroke bundle program. *Stroke* (2017) 48:ATP278. doi: 10.1161/str.48.suppl_1.tp278

30. Cobley CS, Fisher RJ, Chouliara N, Kerr M, Walker MF. A qualitative study exploring patients' and carers' experiences of early supported discharge services after stroke. *Clin Rehabil.* (2013) 27:750–7. doi: 10.1177/0269215512474030

31. Lutz BJ, Young ME, Creasy KR, Martz C, Eisenbrandt L, Brunny JN, et al. Improving stroke caregiver readiness for transition from inpatient rehabilitation to home. *Gerontologist.* (2017) 57:880–89. doi: 10.1093/geront/gnw135

32. White CL, Korner-Bitensky N, Rodrigue N, Rosmus C, Sourial R, Lambert S, et al. Barriers and facilitators to caring for individuals with stroke in the community: The family's experience. *Can J Neurosci Nurs.* (2007) 29:5–12. Available online at: https://pubmed.ncbi.nlm.nih.gov/18240626/

33. White CL, Brady TL, Saucedo LL, Motz D, Sharp J, Birnbaum LA, et al. Towards a better understanding of readmissions after stroke: Partnering with stroke survivors and caregivers. *J Clin Nurs.* (2015) 24:1091–100. doi: 10.1111/jocn.12739

34. Werner RM, Coe NB, Qi M, Konetzka RT. Patient outcomes after hospital discharge to home with home health care vs to a skilled nursing facility. *JAMA Intern Med.* (2019) 179:617–23. doi: 10.1001/jamainternmed.2018.7998

frontiers | Frontiers in Neurology

TYPE Brief Research Report
PUBLISHED 04 July 2023
DOI 10.3389/fneur.2023.1205256

OPEN ACCESS

EDITED BY
Yinong Huang,
Sun Yat-sen University, China

REVIEWED BY
Tiina Sairanen,
Hospital District of Helsinki and Uusimaa, Finland
Luis Rafael Moscote-Salazar,
Colombian Clinical Research Group in Neurocritical Care, Colombia

*CORRESPONDENCE
Victor Dumas
✉ victor.dumas@chu-poitiers.fr

†These authors have contributed equally to this work and share first authorship

RECEIVED 13 April 2023
ACCEPTED 12 June 2023
PUBLISHED 04 July 2023

CITATION
Dumas V, Martin K, Giraud C, Prigent J, Bloch W, Soualmi K, Herpe G, Boucebci S, Neau JP, Guillevin R and Velasco S (2023) Functional outcome in low-ASPECTS (0–5) acute ischemic stroke treated with mechanical thrombectomy: impact of laterality explored in a single-center study.
Front. Neurol. 14:1205256.
doi: 10.3389/fneur.2023.1205256

Functional outcome in low-ASPECTS (0–5) acute ischemic stroke treated with mechanical thrombectomy: impact of laterality explored in a single-center study

Victor Dumas[1,2*†], Killian Martin[2†], Clément Giraud[1], Julia Prigent[3], William Bloch[3], Karim Soualmi[2], Guillaume Herpe[1,2], Samy Boucebci[2], Jean Philippe Neau[3], Rémy Guillevin[1,2] and Stéphane Velasco[2]

[1]LabCom I3M, DACTIM-MIS Team, LMA CNRS 7348, Poitiers University Medical Center, Poitiers, France, [2]Department of Radiology, Poitiers University Medical Center, Poitiers, France, [3]Department of Neurology, Poitiers University Medical Center, Poitiers, France

Background: There is no consensus regarding the influence of infarct laterality in patients with acute ischemic stroke due to anterior large vessel occlusion (AIS-LVO) treated with mechanical thrombectomy (MT), particularly in low-ASPECT (0–5) patients who were excluded from the initial MT studies and that participated in dedicated randomized-controlled trials that do not consider the side of the occlusion. We aimed to evaluate the role of infarct laterality on the clinical outcome in low-ASPECT AIS patients treated with MT.

Material and methods: We retrospectively analyzed our institutional stroke database in our Thrombectomy-Capable Stroke Center (TCSC), including patient characteristics, procedural variables, and outcomes, between January 2015 and January 2022. Patients with acute intracranial ICA and/or proximal MCA occlusions with ASPECT $\leq$ 5 either on CT or MRI were included and divided into 2 groups according to the location of ischemia. The primary endpoint was a good clinical outcome at 90 days (modified Rankin Scale (mRS) score of 0–3).

Results: Between January 2015 and November 2021, 817 MT were performed, of which 82 were low-ASPECT (10.0%): 41 left-sided and 41 right-sided strokes. The rates of good clinical outcome were 30.8% (12/41) for the left-sided group and 43.6% (17/41) for the right-sided group, with a p-value of 0.349. The morality rate showed no significant difference between the two groups: 39.0% (16/41) in the right stroke group and 36.6% (15/41) in the left stroke group.

Conclusion: The clinical outcome was not significantly influenced by stroke laterality. The results of this single-center retrospective study indicate either a lack of strength or equal value in performing mechanical thrombectomy regardless of stroke laterality.

KEYWORDS

stroke, mechanical thrombectomy, low-ASPECT, AIS-LVO, laterality

1. Introduction

Acute ischemic stroke due to large vessel occlusion (AIS-LVO), whose therapeutic strategy has recently been revolutionized by the emergence of mechanical thrombectomy (MT), is one of the leading causes of death and disability worldwide (1, 2). Large-volume AIS-LVO represents a significant proportion of all strokes and is correlated with higher mortality and higher post-stroke disabilities. ASPECTS is the main score used both in computed tomography (CT) and magnetic resonance imaging (MRI) to evaluate the extent of AIS-LVO, and large core volume strokes are commonly considered with ASPECTS ranging from 0 to 5 (3). Since few of these patients were enrolled in the first randomized controlled clinical trials (RCTs), the benefit of MT in this setting was uncertain until recently (4–10); however, three recent RCTs have demonstrated the positive outcomes of MT in this context, and additional trial results are expected in the near future, placing these patients at the forefront of current challenges in stroke management (11–14). In this context, the influence of stroke laterality, which was historically a major and early subject of stroke studies and much studied in the post-thrombolysis era, is unclear (15–17). This study aimed to evaluate the impact of infarct laterality in patients with low-ASPECTS AIS-LVO who underwent MT.

2. Materials and methods

2.1. Patient selection and characteristics

We retrospectively analyzed all consecutive patients with AIS-LVO who underwent MT at a single Thrombectomy-Capable Stroke Center (TCSC) from January 2015 to November 2021. The inclusion criteria were acute occlusion of the intracranial ICA and/or proximal middle cerebral artery, including a proximal branch of the M2 segment on CT or MRI, treatment with thrombectomy, and an ASPECT score of $\leq$ 5 either on CT or MRI. Individuals younger than 18 years, patients with posterior circulation strokes, or those who experienced spontaneous recanalization were not included in the analysis (Figure 1).

2.2. Clinical and radiological data

For each patient, the recorded data included age, gender, medical history, baseline NIHSS, presence of major deficits such as aphasia and neglect, pre-stroke mRS, antiplatelet and anticoagulant treatments, stroke etiology, and symptomatic bleeding events (defined by a neurologic worsening, an increase in an NIHSS score of 4 or more, and evidence of intracranial hemorrhage on imaging). NIHSS and pre-stroke mRS were conducted by neurologists at the stroke center. The clinical outcome was based on the 90-day follow-up period, which could take place either at the same hospital where the mechanical thrombectomy was performed or at the center to which the patient was transferred. The neurologists conducted the assessment through physical examination or a telephone conversation. Technical success was evaluated by the radiologist who conducted the procedure and documented the assessment in the MT report. Radiological characteristics, including diagnostic and angiographic imaging, were retrieved from the local PACS and analyzed. Concerning radiological imaging, we assessed modality, thrombus location, supra-aortic trunk imaging, ASPECT, and stroke volume. The 10 brain regions (caudate, lentiform nucleus, internal capsule, insula, and six cortical regions) used to calculate the ASPECT score were inspected using the image set from each study. Out of a possible total score of ten, one point was deducted for each affected region. The images were evaluated independently by a senior neuroradiologist and a radiology resident. In cases of disagreement, a consensus was reached with the help of Rapid AI software. Stroke volumes were determined using Rapid AI software in the case of MRI and with semi-automatic contouring via Vitrea software in the case of CT scans.

2.3. Definition of outcomes

Successful reperfusion was defined as achieving a modified thrombolysis in cerebral infarction (mTICI) score of $\geq$ 2b. A good clinical outcome was determined by a modified Rankin Scale (mRS) score ranging from 0 to 3.

2.4. Study endpoint

Good clinical outcome according to stroke laterality was the study endpoint.

2.5. Statistical analysis

The characteristics of the population were obtained using different tests: the Student *t*-test or the Wilcoxon–Mann–Whitney test for continuous variables and the chi-squared and Fisher's exact test for categorical variables. Continuous variables were presented as the mean +/− standard deviation (SD). Categorical variables were presented as numbers (the corresponding percentage). These variables allowed us to determine whether patients had similar characteristics in the two groups. For all analyses, we considered the commonly used threshold of 005 for the type 1 error risk. The effect of stroke laterality and affected hemisphere on radiological, clinical, and hemorrhagic risks was studied using the chi-squared test. We compared the modified Rankin Score at 90 days in the right and left stroke groups using the chi-squared test. Then, adjustments were made with quantile regression models. The adjustment factors were the stroke volume and the major symptoms, i.e., the presence of aphasia and neglect at the onset.

3. Results

3.1. Study sample

Between January 2015 and January 2022, 817 MT were performed, of which 82 were low-ASPECT (10.0%): 41 left-sided strokes (50.0%) and 41 right-sided strokes (50.0%) (Table 1). The mean age of study subjects was 69 years old (±SD 15). A total of 46 patients were women (34.1%). In our sample, 96.7% of the

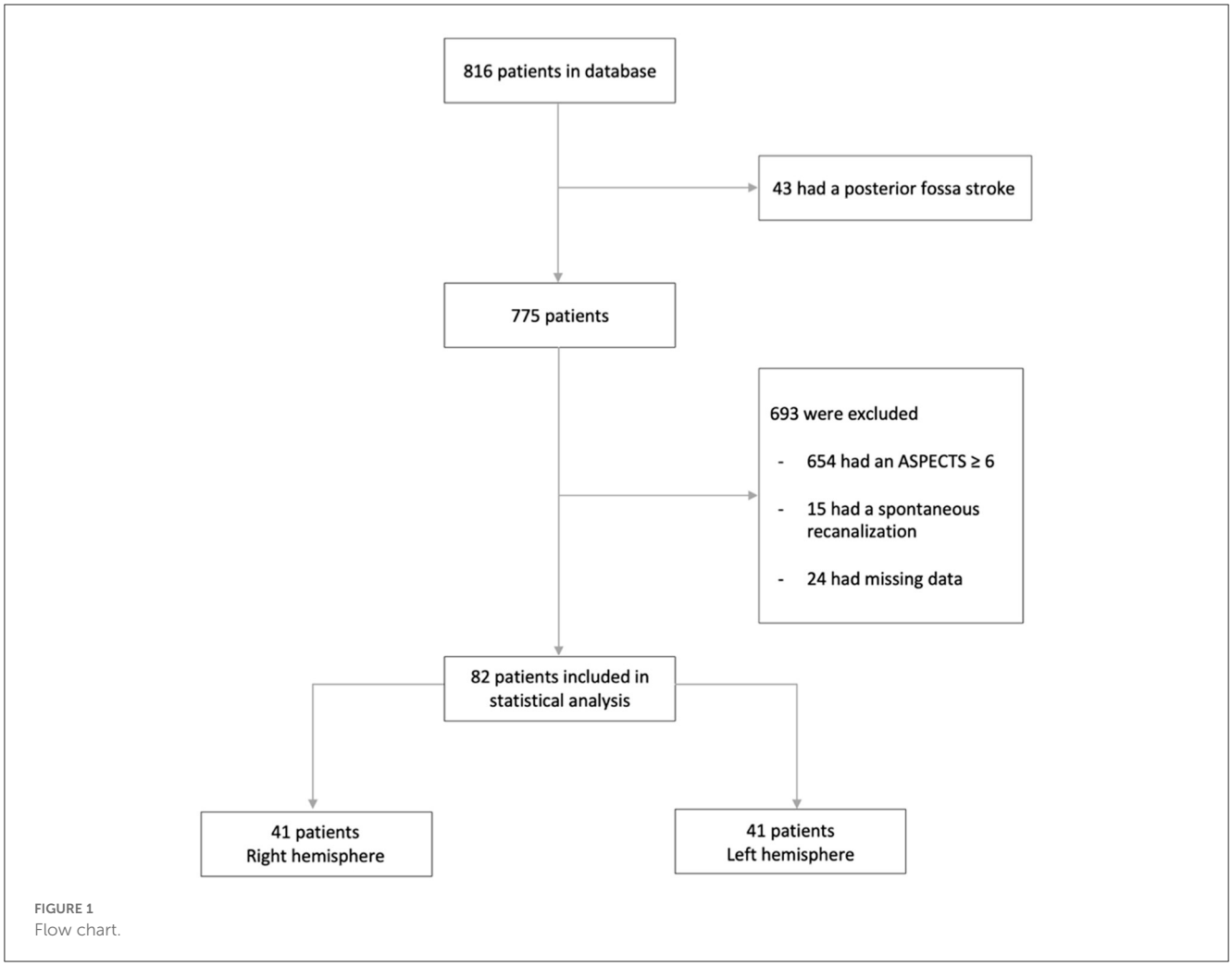


FIGURE 1
Flow chart.

patients were right-handed, with two left-handed people in the left stroke group and no left-handed people in the right stroke group. The groups were comparable regarding history, including high blood pressure, diabetes, and atrial fibrillation. We also determined that seven patients in each group had a history of stroke. The NIHSS score was higher in the left group without being significantly different (19 vs. 18 on the right, $p = 0.064$). The median time from symptom onset to reperfusion was 375 min in the left stroke group and 373 min in the right stroke group ($p = 0.178$). The median ASPECT score was 5, and the mean volume was 96.4mL; neither were significantly different between groups.

3.2. Procedural metrics

The median time of onset-recanalization was 373 min (IQR 253–493) in the right-sided group and 375 min (IQR 245-505) in the left-sided group. Intravenous thrombolysis was administered to more than half of the patients in each group: 26 patients (56.1%) in the left stroke group and 23 patients (63.4%) in the right stroke group. MT was performed under general anesthesia for 15 patients in the right stroke group (36.6%) and 16 patients in the left stroke group (39.0%).

3.3. Outcomes

A total of 71 patients (86.6%) had an mTICI reperfusion score of 2b or higher with no significant difference between groups: 36 out of 41 (87.8%) for the left location and 35 out of 41 (85.4%) for the right location ($p = 1$) (Table 2). There was less than 25% hemorrhagic transformation in each group (nine patients in the left stroke group and seven patients in the right stroke group).

3.4. Study endpoint

The number of patients with a score of 0 to 3 on the modified Rankin scale at 90 days was 12 (30.8 %) in the left stroke group and 17 (43.6%) in the right stroke group, $p = 0.349$ (Figure 2). There were 15 deaths (36.6%) at 3 months in the left stroke group and 16 deaths (39.0%) in the right stroke group ($p = 1$).

4. Discussion

In this series, the percentage of patients with good functional outcomes at 90 days was not significantly different between patients

10.3389/fneur.2023.1205256

TABLE 1 Demographic and clinical characteristics of the patients at baseline.

Laterality	Left ($N = 41$)	Right ($N = 41$)	Overall	Unknown	*P* value
Age—*yr*	68 ± 17	70 ± 14	69 ± 15	0	0.438
Hand—*no (%)*					
Left Handed	2 (6.5)	0 (0)	2 (3.3)	25.6	0.492
Right Handed	29 (93.6)	30 (100)	59 (96.7)	25.6	
Male Sex—*no (%)*	28 (68.3)	26 (63.4)	54 (65.9)	0	0.816
History—*no (%)*					
Hypertension	24 (58.5)	22 (53.7)	46 (56.1)	0	0.824
Diabetes	6 (14.6)	4 (9.8)	10 (12.2)	0	0.736
Active smoking	15 (36.6)	7 (17.1)	22 (26.9)	0	0.081
Hyperlipidaemia	10 (24.4)	11 (26.8)	21 (25.6)	0	1
Previous ischemic stroke	7 (17.1)	7 (17.1)	14 (17.1)	0	1
BMI	26.3 ± 4.9	26.0 ± 5.0	26.2 ± 4.9	2.4	0.784
Obesity (BMI > 29.9)	6 (14.6)	8 (20.5)	14 (17.5)	2.4	0.691
Atrial fibrillation	17 (41.5)	17 (41.5)	34 (41.5)	0	1
Chronic renal failure	4 (9.8)	5 (12.2)	9 (11.0)	0	1
Myocardial infarction	9 (22.0)	7 (17.1)	16 (19.5)	0	0.781
Pre-stroke mRS (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0	0.641
NIHSS	19 (13–25)	18 (14–22)	18 (13–23)	8.5	0.064
Interval between time of stroke onset and time of reperfusion					
Median (IQR)—min	375 (245–505)	373 (253–493)	374 (249–499)	4.9	0.178
<6.0 hr	17 (41.5)	12 (32.4)	29 (37.2)		0.488
6.0 to 24 hr	24 (58.5)	25 (67.6)	49 (62.8)		0.488
Occlusion site—*no (%)*				0	
M1	24 (58.5)	26 (63.4)	46 (61.0)		
M2	3 (7.3)	5 (12.2)	8 (9.8)		
ICA terminus	12 (29.3)	7 (17.1)	19 (23.2)		
Tandem	2 (4.9)	2 (4.9)	4 (4.9)		
Extracranial ICA	0 (0)	1 (2.4)	1 (1.2)		
ASPECT					
Median value (IQR)	5 (5–3)	5 (5–4)	5 (5–4)	0	0.341
0—no (%)	1	0	1		
1—no (%)	1	0	1		
2—no (%)	3	4	7		
3—no (%)	7	4	11		
4—no (%)	7	9	16		
5—no (%)	22	24	46		
Volume (mL)	95.1 (77.4–120.2)	97.7 (78.1–121.0)	96.4 (78.9–121.8)	0	0.490
General anesthesia—*no (%)*	16 (39.0)	15 (36.6)	31 (37.8)	0	1
Intravenous rt-PA use—*no (%)*	23 (56.1)	26 (63.4)	49 (59.8)	0	0.652

with right and left hemispheric strokes. Nevertheless, a visual analysis of the arrangement of mRS scores 2, 3, and 4 at 3 months indicates that the prognosis may be more favorable for people with right-sided strokes. The lack of statistical significance does not allow us to draw any definitive conclusions, and further studies are needed to ascertain whether this effect exists, as we

10.3389/fneur.2023.1205256

TABLE 2 Outcomes.

	Laterality		
	Left stroke (41)	Right stroke (41)	*P* value
Radiological			
mTICI reperfusion grade ≥ 2b—*no (%)*	36 (87.8)	35 (85.4)	1
Clinical			
mRs *médian* at 3 months *(IQR)*	4 (3–6)	4 (2–6)	0.291
mRS median *(IQR)* adjusted with infarct size (mL)	4 (3–6)	4 (2–6)	0.958
mRS median *(IQR)* adjusted with the presence of neglect at J0	5 (4–6)	3 (2–6)	0.282
mRS median *(IQR)* adjusted if aphasia is present at J0	4 (3–6)	6 (6–6)	0.092
mRS median *(IQR)* adjusted with full adjustment	3 (2–6)	5 (4–6)	0.151
mRS ≤ 3 at 3 months—no (%)	12 (30.8)	17 (43.6)	0.349
Mortality at 3 months—*no (%)*	15 (36.6)	16 (39.0)	1
Symptomatic hemorrhagic transformation—*no (%)*	9 (22.0)	7 (17.1)	0.781

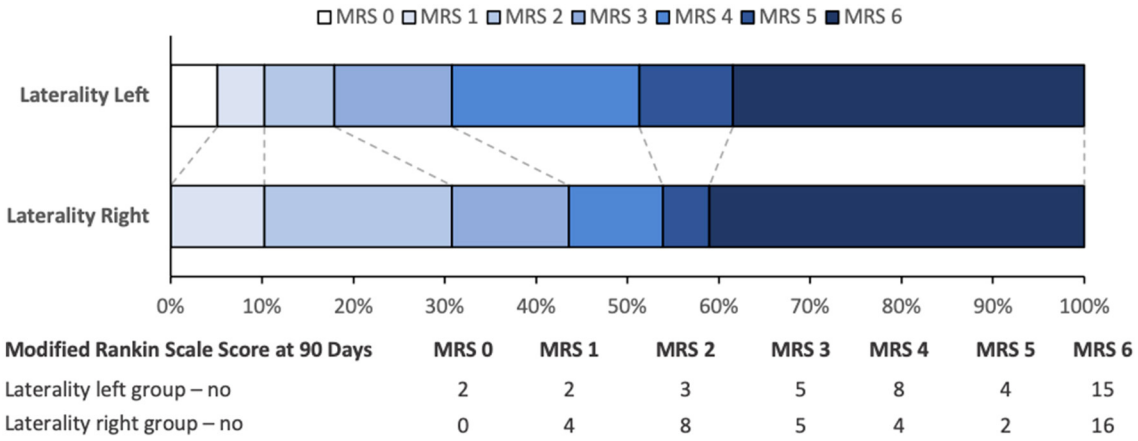


FIGURE 2
Modified Rankin scale scores at 90 days according to stroke laterality, A modified Rankin sclare score of 0 indicates no disability, 1 no clinically significant disability, 2 slight disability, 3 moderate disability but able to walk unassisted, 4 moderately severe disability, 5 severe disability, and 6 death.

assumed before conducting this study. In particular, we believe that conducting a meta-analysis of patients included in previously published randomized trials (11–14) as well as upcoming trials is essential (TESLA, LASTE, and TENSION) to provide the necessary statistical power and the level of evidence needed to definitively address this question.

In our study, we chose a threshold of a good clinical outcome with an mRS score of 0 to 3. It is worth noting that the more traditional threshold for good clinical outcomes is an mRS score of 0 to 2. However, we chose the broader threshold of 0 to 3 to align with the focus on severe strokes, which is consistent with recently conducted RCT studies on low-ASPECT AIS-LVO patients (11–13). The use of the mRS in our study could have been problematic, as patients with low ASPECT scores are more likely to exhibit significant cortical region damage. Indeed, this score can be used to assess limitations in autonomy and daily activities, but it lacks specificity, and domains such as cognition, language, visual function, emotional disturbance, and pain are not directly measured. However, we believed that it was essential to use it as the primary endpoint for three main reasons: (1) The mRS is extensively used in the post-MT era, including among patients with low-ASPECT AIS-LVO (11–13), which strengthens the intrinsic and extrinsic validity of the study; (2) it has previously been shown to have correct concurrent validity with regard to infarct volumes, and its construct validity has been shown to have excellent concordance with other rating scales (18, 19); and (3) mRS endpoints generally require significantly smaller sample sizes to achieve adequate statistical power, and the odds of obtaining a statistically significant result increase by 89% with an mRS endpoint compared with a Barthel index endpoint (18).

The absence of any significant difference in clinical outcome at 3 months is consistent with subgroup analyses performed in a previously published meta-analysis (20) but is at odds with some others that described a better clinical outcome in patients

with left-hemisphere stroke (16, 17). This association has been attributed to a larger infarct volume in right-vs.-left-hemisphere stroke patients (21) and a long time from the onset of stroke to its manifestation (22). Several studies have indeed highlighted that neglect increases the delay in stroke recognition and management (17, 23), but in our database, there was no longer a delay for right hemispheric stroke patients. This could be explained by the fact that low-ASPECT patients generally present a massive deficit that cannot be neglected.

On a similar note, neglect is often a determining marker that negatively influences functional recovery (24, 25), but this was not a finding in the mRS at 3 months in our sample.

Left-stroke patients in our trial had a non-statistically significant tendency to have a higher NIHSS score at admission, a notion that is concordant with other studies (21, 26). Thus, left hemispheric damage is often accompanied by language disorders that raise the NIHSS score compared with right hemispheric damage, associated with neglect, which is less weighted for the NIHSS score (27).

There were the same number of patients in each group. Thus, the laterality of stroke was not a factor influencing thrombectomy selection. We also observed no difference in the reperfusion rate between left and right strokes, thus laterality was not a factor in the failure of MT.

We failed to dichotomize our study population as having a major or minor hemisphere involvement because our sample included only two left-handers, which was insufficient for conducting a statistical analysis. We could have relied on clinical examination, which includes assessing aphasia and neglect; however, in the emergency setting, there is a higher likelihood of clinical examination errors. Identifying neglect can be particularly difficult, and distinguishing between aphasia and dysarthria can lead to misinterpretations. Furthermore, determining hemispheric dominance (major/minor) has become increasingly complex since Broca's study in the second half of the 19th century (28), as well as studies by Geschwing and Levitsky (29), Rasmussen and Milner (30), and Ringo et al. (31). This complexity has arisen owing to recent advancements in functional activation MRI, which have revealed a multitude of patterns that challenge the concept of hemispheric dominance (32).

This study has several limitations, including the retrospective nature of the analysis, the small sample due to a monocentric design, the overrepresentation of ASPECT 5 patients in both groups due to the lack of consensus in the indication of MT in lower ASPECT patients during the study period, and the absence of clinical assessments at 3 months to evaluate associative functions in detail (beyond what is possible with the mRS score).

The main strength of this study is that it is the first in the post-thrombectomy era to specifically examine the role of stroke laterality as it relates to the primary endpoint in patients with low-ASPECTS AIS-LVO.

5. Conclusion

The clinical outcome in our population of low-ASPECT AIS-LVO strokes was not significantly influenced by stroke laterality. The results of this single-center retrospective study indicate either a lack of strength or equal value in performing mechanical thrombectomy regardless of stroke laterality. A meta-analysis of upcoming RCTs dedicated to low-ASPECT patients might answer the question.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Anonymized and coded dataset can be made available upon request. Requests to access these datasets should be directed to victor.dumas@chu-poitiers.fr.

Author contributions

SB, JN, RG, and SV participated in the proofreading and validation of the article. GH, JP, KS, and WB participated in the data collection. CG conducted the statistical analysis.

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

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *The Lancet.* (2006) 367:1747–57. doi: 10.1016/S0140-6736(06)68770-9

2. Hankey GJ. Stroke. *The Lancet.* (2017) 389:641–54. doi: 10.1016/S0140-6736(16)30962-X

3. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *The Lancet.* (2000) 355:1670–4. doi: 10.1016/S0140-6736(00)02237-6

4. Román LS, Menon BK, Blasco J, Hernández-Pérez M, Dávalos A, Majoie CBLM, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *The Lancet Neurol.* (2018) 17:895–904. doi: 10.1016/S1474-4422(18)30242-4

5. Sarraj A, Hassan AE, Savitz S, Sitton C, Grotta J, Chen P, et al. Outcomes of endovascular thrombectomy vs medical management alone in patients with

large ischemic cores: a secondary analysis of the optimizing patient's selection for endovascular treatment in acute ischemic stroke (SELECT) study. *JAMA Neurol.* (2019) 76:1147. doi: 10.1001/jamaneurol.2019.2109

6. Panni P, Gory B, Xie Y, Consoli A, Desilles JP, Mazighi M, et al. Acute stroke with large ischemic core treated by thrombectomy: predictors of good outcome and mortality. *Stroke.* (2019) 50:1164–71. doi: 10.1161/STROKEAHA.118.024295

7. Soize S, Barbe C, Kadziolka K, Estrade L, Serre I, Pierot L. Predictive factors of outcome and hemorrhage after acute ischemic stroke treated by mechanical thrombectomy with a stent-retriever. *Neuroradiology.* (2013) 55:977–87. doi: 10.1007/s00234-013-1191-4

8. Inoue M, Olivot JM, Labreuche J, Mlynash M, Tai W, Albucher JF, et al. Impact of diffusion-weighted imaging alberta stroke program early computed tomography score on the success of endovascular reperfusion therapy. *Stroke.* (2014) 45:1992–8. doi: 10.1161/STROKEAHA.114.005084

9. Broocks G, Flottmann F, Schönfeld M, Bechstein M, Aye P, Kniep H, et al. Incomplete or failed thrombectomy in acute stroke patients with alberta stroke program early computed tomography score 0–5—how harmful is trying? *Eur J Neurol.* (2020) 27:2031–5. doi: 10.1111/ene.14358

10. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. "Guidelines for the early management of patients with acute ischemic stroke: 2019," In: *Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke [Internet]*. (2019). Disponible sur: https://www.ahajournals.org/doi/10.1161/STR.0000000000000211 doi: 10.1161/STR.0000000000000215 (cité 11 avr 2023).

11. Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS, et al. Trial of endovascular thrombectomy for large ischemic strokes. *N Engl J Med. 6 avr.* (2023) 388:1259–71. doi: 10.1056/NEJMoa2214403

12. Huo X, Ma G, Tong X, Zhang X, Pan Y, Nguyen TN, et al. Trial of endovascular therapy for acute ischemic stroke with large infarct. *N Engl J Med.* (2023) 388:1272–83. doi: 10.1056/NEJMoa2213379

13. Yoshimura S, Sakai N, Yamagami H, Uchida K, Beppu M, Toyoda K, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med.* (2022) 386:1303–13. doi: 10.1056/NEJMoa2118191

14. Li Q, Abdalkader M, Siegler JE, Yaghi S, Sarraj A, Campbell BCV, et al. Mechanical thrombectomy for large ischemic stroke: a systematic review and meta-analysis. *Neurology.* (2023) 10:7536. doi: 10.1212/WNL.0000000000207536

15. Deb-Chatterji M, Flottmann F, Meyer L, Brekenfeld C, Fiehler J, Gerloff C, et al. Side matters: differences in functional outcome and quality of life after thrombectomy in left and right hemispheric stroke. *Neurol Res Pract.* (2022) 4:58. doi: 10.1186/s42466-022-00223-7

16. Aszalós Z, Barsi P, Vitrai J, Nagy Z. Lateralization as a factor in the prognosis of middle cerebral artery territorial infarct. *Eur Neurol.* (2002) 48:141–5. doi: 10.1159/000065515

17. Di Legge S, Fang J, Saposnik G, Hachinski V. The impact of lesion side on acute stroke treatment. *Neurology.* (2005) 65:81–6. doi: 10.1212/01.wnl.0000167608.94237.aa

18. Kasner SE. Clinical interpretation and use of stroke scales. *Lancet Neurol.* (2006) 5:603–12. doi: 10.1016/S1474-4422(06)70495-1

19. Banks JL, Marotta CA. Outcomes validity and reliability of the modified rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke.* (2007) 38:1091–6. doi: 10.1161/01.STR.0000258355.23810.c6

20. Almekhlafi MA, Hill MD, Roos YM, Campbell BCV, Muir KW, Demchuk AM, et al. Stroke laterality did not modify outcomes in the hermes meta-analysis of individual patient data of 7 trials. *Stroke.* (2019) 50:2118–24. doi: 10.1161/STROKEAHA.118.023102

21. Fink JN, Selim MH, Kumar S, Silver B, Linfante I, Caplan LR, et al. Is the association of national institutes of health stroke scale scores and acute magnetic resonance imaging stroke volume equal for patients with right- and left-hemisphere ischemic stroke? *Stroke.* (2002) 33:954–8. doi: 10.1161/01.STR.0000013069.24300.1D

22. Legge SD, Saposnik G, Nilanont Y, Hachinski V. Neglecting the difference: does right or left matter in stroke outcome after thrombolysis? *Stroke.* (2006) 37:2066–9. doi: 10.1161/01.STR.0000229899.66019.62

23. Foerch C, Misselwitz B, Sitzer M, Berger K, Steinmetz H, Neumann-Haefelin T. Difference in recognition of right and left hemispheric stroke. *The Lancet.* (2005) 366:392–3. doi: 10.1016/S0140-6736(05)67024-9

24. Tarvonen-Schröder S, Niemi T, Koivisto M. Comparison of functional recovery and outcome at discharge from subacute inpatient rehabilitation in patients with right or left stroke with and without contralateral spatial neglect. *J Rehabil Med.* (2020) 52:jrm00071. doi: 10.2340/16501977-2698

25. Ween JE, Alexander MP, D'Esposito M, Roberts M. Factors predictive of stroke outcome in a rehabilitation setting. *Neurology.* (1996) 47:388–92. doi: 10.1212/WNL.47.2.388

26. Woo D, Broderick JP, Kothari RU, Lu M, Brott T, Lyden PD, et al. Does the national institutes of health stroke scale favor left hemisphere strokes? *Stroke.* (1999) 30:2355–9. doi: 10.1161/01.STR.30.11.2355

27. Lyden P, Claesson L, Havstad S, Ashwood T, Lu M. Factor analysis of the national institutes of health stroke scale in patients with large strokes. *Arch Neurol.* (2004) 61:1677. doi: 10.1001/archneur.61.11.1677

28. West S. Case of aphasia in which the chief lesion was seated in the supramarginal and angular gyri, broca's convolution being unaffected. *BMJ.* (1885) 1:1242–4. doi: 10.1136/bmj.1.1277.1242

29. Geschwind N, Levitsky W. Human brain: left-right asymmetries in temporal speech region. *Science.* (1968) 161:186–7. doi: 10.1126/science.161.3837.186

30. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. *Ann NY Acad Sci.* (1977) 299:355–69. doi: 10.1111/j.1749-6632.1977.tb41921.x

31. Ringo JL, Doty RW, Demeter S, Simard PY. Time is of the essence: a conjecture that hemispheric specialization arises from interhemispheric conduction delay. *Cerebral Cortex.* (1994) 4:331–43. doi: 10.1093/cercor/4.4.331

32. Greve JM. "The BOLD Effectm" In: Schröder L, Faber C, éditeurs. *In vivo NMR Imaging [Internet]. Totowa, NJ: Humana Press;.* (2011). p. 153-69. Disponible sur: https://link.springer.com/10.1007/978-1-61779-219-9_8 doi: 10.1007/978-1-61779-219-9_8 (accessed 11 avr 2023).

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 17 July 2023
DOI 10.3389/fneur.2023.1096911

OPEN ACCESS

EDITED BY
Haiqing Zheng,
Third Affiliated Hospital of Sun Yat-sen University, China

REVIEWED BY
Yiqun Jiang,
Hunan Normal University, China
Gaurav Kandoi,
Invaio Sciences, United States

*CORRESPONDENCE
Yiming Mao
✉ mym19850126@163.com
Ying Shen
✉ shenying@njmu.edu.cn

RECEIVED 22 December 2022
ACCEPTED 06 June 2023
PUBLISHED 17 July 2023

CITATION
Qiu H, Shen L, Shen Y and Mao Y (2023) Identification of a miRNA–mRNA regulatory network for post-stroke depression: a machine-learning approach. *Front. Neurol.* 14:1096911. doi: 10.3389/fneur.2023.1096911

Identification of a miRNA–mRNA regulatory network for post-stroke depression: a machine-learning approach

Huaide Qiu[1], Likui Shen[2], Ying Shen[3]* and Yiming Mao[4]*

[1]Faculty of Rehabilitation Science, Nanjing Normal University of Special Education, Nanjing, China, [2]Department of Neurosurgery, Suzhou Kowloon Hospital, Shanghai Jiao Tong University School of Medicine, Suzhou, Jiangsu, China, [3]Rehabilitation Medicine Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [4]Department of Thoracic Surgery, Suzhou Kowloon Hospital, Shanghai Jiao Tong University School of Medicine, Suzhou, Jiangsu, China

Objective: The study aimed to explore the miRNA and mRNA biomarkers in post-stroke depression (PSD) and to develop a miRNA–mRNA regulatory network to reveal its potential pathogenesis.

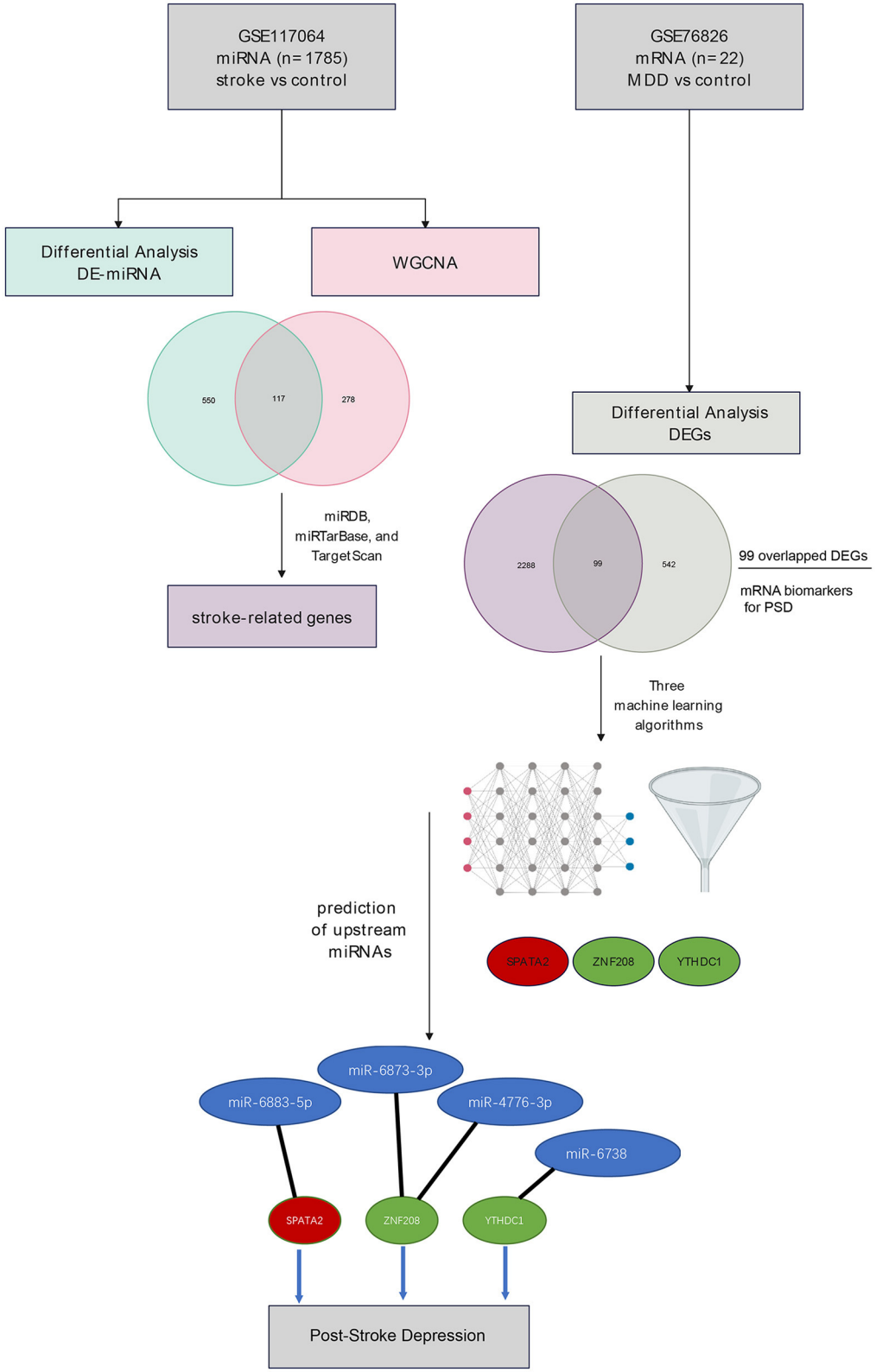
Methods: The transcriptomic expression profile was obtained from the GEO database using the accession numbers GSE117064 (miRNAs, stroke vs. control) and GSE76826 [mRNAs, late-onset major depressive disorder (MDD) vs. control]. Differentially expressed miRNAs (DE-miRNAs) were identified in blood samples collected from stroke patients vs. control using the Linear Models for Microarray Data (LIMMA) package, while the weighted correlation network analysis (WGCNA) revealed co-expressed gene modules correlated with the subject group. The intersection between DE-miRNAs and miRNAs identified by WGCNA was defined as stroke-related miRNAs, whose target mRNAs were stroke-related genes with the prediction based on three databases (miRDB, miRTarBase, and TargetScan). Using the GSE76826 dataset, the differentially expressed genes (DEGs) were identified. Overlapped DEGs between stroke-related genes and DEGs in late-onset MDD were retrieved, and these were potential mRNA biomarkers in PSD. With the overlapped DEGs, three machine-learning methods were employed to identify gene signatures for PSD, which were established with the intersection of gene sets identified by each algorithm. Based on the gene signatures, the upstream miRNAs were predicted, and a miRNA–mRNA network was constructed.

Results: Using the GSE117064 dataset, we retrieved a total of 667 DE-miRNAs, which included 420 upregulated and 247 downregulated ones. Meanwhile, WGCNA identified two modules (blue and brown) that were significantly correlated with the subject group. A total of 117 stroke-related miRNAs were identified with the intersection of DE-miRNAs and WGCNA-related ones. Based on the miRNA-mRNA databases, we identified a list of 2,387 stroke-related genes, among which 99 DEGs in MDD were also embedded. Based on the 99 overlapped DEGs, we identified three gene signatures (SPATA2, ZNF208, and YTHDC1) using three machine-learning classifiers. Predictions of the three mRNAs highlight four miRNAs as follows: miR-6883-5p, miR-6873-3p, miR-4776-3p, and miR-6738-3p. Subsequently, a miRNA–mRNA network was developed.

Conclusion: The study highlighted gene signatures for PSD with three genes (SPATA2, ZNF208, and YTHDC1) and four upstream miRNAs (miR-6883-5p, miR-6873-3p, miR-4776-3p, and miR-6738-3p). These biomarkers could further our understanding of the pathogenesis of PSD.

KEYWORDS

post-stroke depression, gene signatures, miRNA–mRNA network, machine-learning, diagnostics-clinical characteristic



GRAPHICAL ABSTRACT

1. Introduction

Post-stroke depression (PSD) is a common complication after a stroke, affecting up to one-third of stroke survivors (1). It compromises individual functional recovery, impairs the quality of life, and increases the burden on the healthcare system (2). It was observed that depressive symptoms were negatively correlated with functional recovery (3) and related to higher mortality (4). However, the pathogenesis of PSD remains elusive to date.

MicroRNAs (miRNAs) are a group of small non-coding RNAs with downregulative activity on post-transcriptional gene expression by binding to the 3′ untranslated regions of target mRNAs (5, 6). Profiles of miRNA expression could be as useful as mRNA in diagnosis and prognosis (7). Of note, miRNAs can be secreted into body fluids, including peripheral blood and urine, which can be non-invasively accessed for detection (8). As such, serum miRNAs have been widely studied in various diseases, including stroke as potential biomarkers (9–12). With the development of RNA sequencing technology, data sharing, and machine-learning methods, the identification of feature serum miRNAs and the construction of related signatures in a large number of subjects have become practical. According to previous studies, serum miRNA-based signatures could effectively predict the risk of strokes in healthy individuals (13) and clinical outcomes (14, 15) in patients with neurological tumors. Moreover, miRNAs are functionally involved in numerous biological processes, including cellular metabolism (16), cell-cycle regulation (17), and immune response (18). Therefore, we hypothesized that miRNAs and their target mRNAs could be potential biomarkers implicated in the pathogenesis of PSD.

With the advancement of the machine-learning methods, the identification of relevant biomarkers becomes practical in the big data era. The least absolute shrinkage and selection operator (LASSO), a regression analysis algorithm, uses regularization to improve prediction accuracy (19). The support vector machine (SVM) is a supervised machine-learning technique widely utilized for both classification and regression (20). Random forest (RF) is considered the most accepted group classification technique because of having excellent features such as variable importance measure and out-of-bag error (21). In this study, we aimed to explore the miRNA as well as mRNA biomarkers in PSD and to construct a miRNA–mRNA regulatory network to reveal its potential pathogenesis using a machine-learning approach.

2. Materials and methods

2.1. Data source

The miRNAs expression profile was obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/) using the accession number GSE117064, while mRNA expressions of blood samples from patients with late-onset MDD and controls were embedded in GSE76826. A total of 1,785 serum samples were incorporated into the dataset, which consists of 173 samples of patients with stroke and 1,612 controls. Extraction, detection, and data processing of serum miRNAs were provided in the previous report (13). Stroke was diagnosed based on physical and neurological examinations supplemented with brain imaging data, including computed tomography and/or magnetic resonance imaging, while healthy controls were defined as having no history of stroke and negative on medical checkup in a clinic (13). In GSE76826, there were 12 blood samples of late-onset MDD and 10 samples of controls. Late-onset MDD was defined according to the DSM-IV diagnosis and age of $\geq$ 50 years (22).

2.2. Differential analysis, WGCNA, and identification of stroke-related genes

The linear models for microarray data (LIMMA) package (23) in R software was applied to extract differentially expressed miRNAs (DE-miRNAs) between stroke and control samples. The *p*-value was adjusted with the false discovery rate (FDR) (24). An FDR of < 0.05 and $|FC|$ of > 1 were set as the threshold for DE-miRNAs. The visualization of differential analysis was presented with a heatmap and a volcano plot. Using GSE117064, the weighted gene correlation network analysis (WGCNA) (25, 26) was performed to construct a co-expression network to identify hub miRNA modules using the "WGCNA" package. Filtered miRNAs were employed to construct a scale-free network by calculating the connection strength between miRNAs. We assessed the correlation among miRNA modules as well as their correlations to the clinical group (stroke vs. control). Subsequently, DE-miRNAs incorporated in the stroke-related modules were identified as stroke-related miRNAs, and their target genes were predicted using miRDB (https://mirdb.org/), miRTarBase (https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/index.php), and TargetScan (https://www.targetscan.org/vert_80/).

2.3. Identification of overlapped DEGs in post-stroke depression

Overlapped DEGs for post-stroke depression were defined as aberrantly expressed mRNAs in the blood sample collected from stroke patients as well as late-onset MDD. In other words, these overlapped DEGs were implicated in two diseases simultaneously. Differentially expressed mRNAs (DE-mRNAs) for late-onset MDD were defined in a similar manner with an FDR of < 0.05 and $|FC|$ of > 0.5. Among these DE-mRNAs, stroke-related genes were selected to identify overlapped DEGs for post-stroke depression. With these overlapped DEGs, the *clusterProfiler* R package (27) was utilized to perform the gene ontology (GO) terms and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis on the predicted target genes. Three categories were included in the GO enrichment analysis, i.e., biological process (BP), cellular component (CC), and molecular function (MF).

2.4. Gene signatures and a miRNA–mRNA regulatory network for PSD

The least absolute shrinkage and selection operator (LASSO), random forest (RF), and support vector machine (SVM) algorithms

10.3389/fneur.2023.1096911

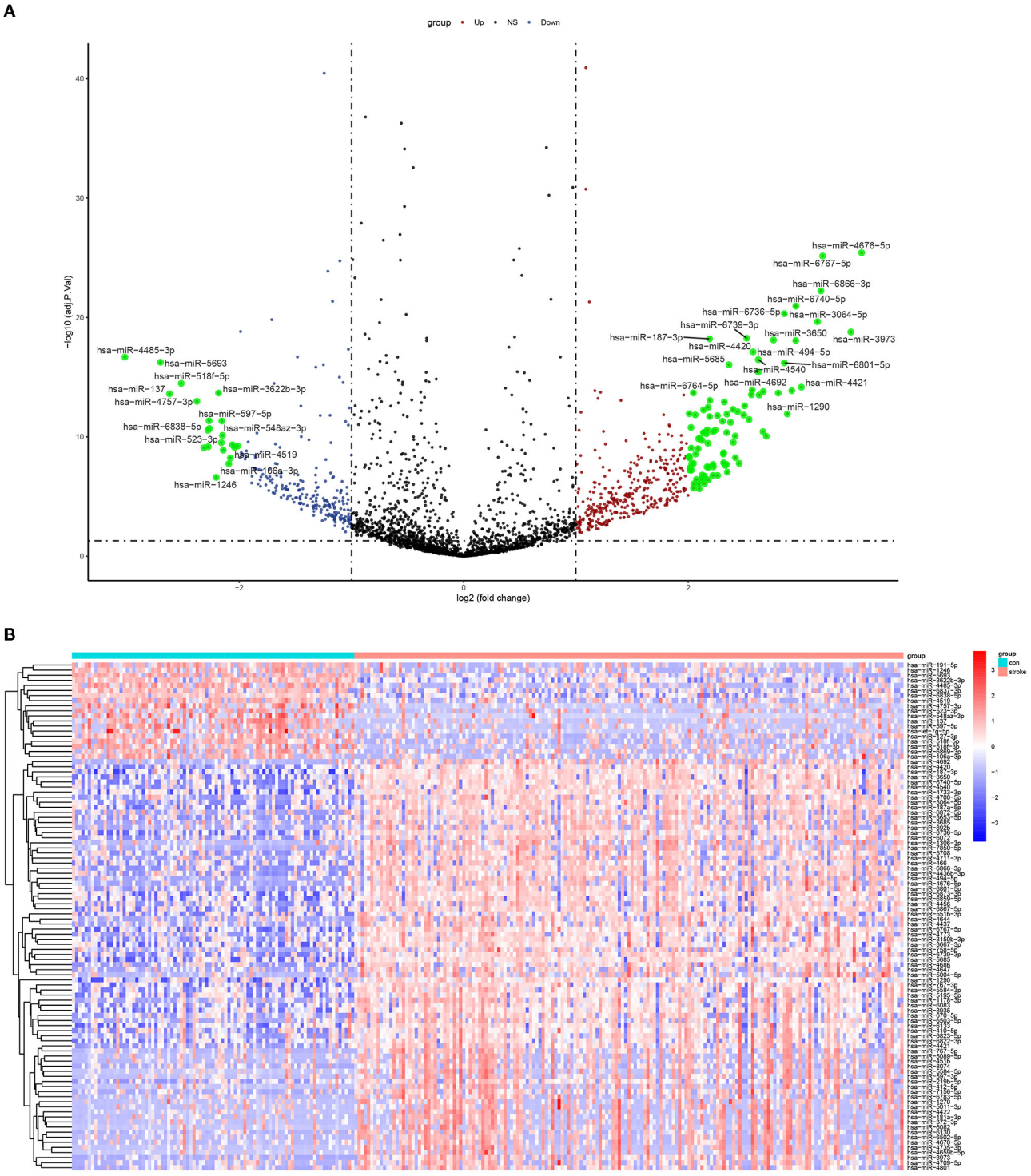


FIGURE 1
Differential analysis of miRNA expression profiles in stroke vs. control: **(A)** a volcano plot and **(B)** a heatmap with top 100 DE-miRNAs.

were utilized to build gene signatures for PSD using the overlapped DEGs. Gene signatures were established with the intersection of gene sets identified by each algorithm. The receiver operating characteristic (ROC) curves were mapped for the identified gene signatures, where the area under curves (AUCs) was calculated as an indicator of classification. The AUCs of > 0.8 were considered excellent classification, while AUCs of > 0.7 were considered acceptable. By matching miRNA–mRNA pairs in multiple databases (miRDB, miRTarBase, and TargetScan), the upstream miRNAs were predicted using the gene signatures for PSD. Subsequently, a potential miRNA–mRNA regulatory network for PSD was established.

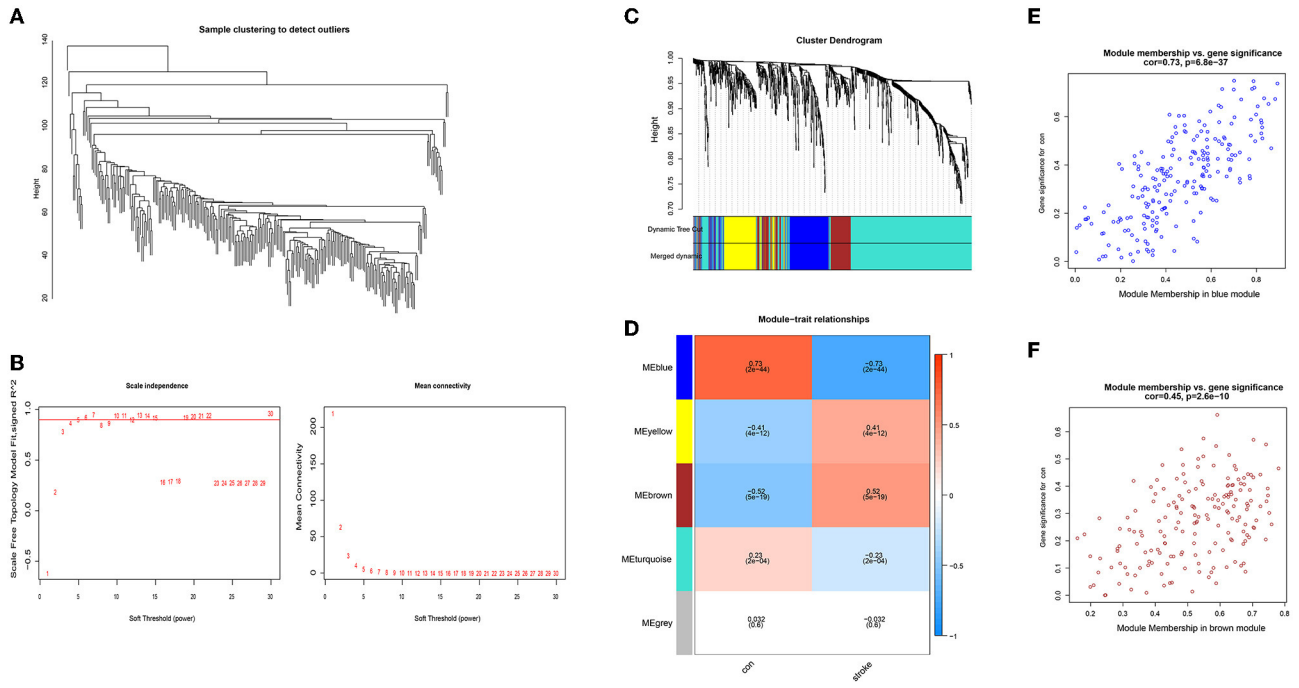


FIGURE 2
WGCNA identified two stroke-related miRNA modules: **(A)** a sample clustering tree; **(B)** soft threshold determination; **(C)** cluster dendrogram; **(D)** a module-trait correlation heatmap; **(E)** a scatter plot presenting correlation of module membership vs. gene significance in the blue module; and **(F)** a scatter plot presenting correlation of module membership vs. gene significance in the brown module.

3. Results

3.1. Differential analysis, WGCNA, and identification of stroke-related genes

The overall analysis of the study was presented in the Graphical abstract. Using the LIMMA package, we retrieved a total of 667 DE-miRNAs, which included 420 upregulated and 247 downregulated ones. The feature DE-miRNAs with the absolute value of logFC of >2 were marked in green in the volcano plot (Figure 1A). Meanwhile, a heatmap showing the top 100 DE-miRNAs is presented in Figure 1B. The details of these DE-miRNAs can be found in Supplementary material 1.

We performed the hierarchical clustering of the samples (Figure 2A), and the soft-thresholding power was set at 5 with the cutoff score of Scale-free R^2 being 0.9 (Figure 2B). The clustering dendrograms of the sample identified five modules (Figure 2C) and their correlations with clinical groups were presented in the heatmap plot (Figure 2D). Subsequently, we selected the blue and brown modules with the highest correlation coefficient for downstream analysis. The scatter plots in Figures 2E, F show a significant correlation between gene significance and module memberships in the aforementioned modules, while the details can be accessed in Supplementary material 2.

Stroke-related miRNAs were identified with the intersection of DE-miRNAs and modules of interest found in WGCNA, leading to the identification of 117 miRNAs (Figure 3A). A total of 2,387 target mRNAs were predicted with these stroke-related miRNAs according to the databases. Thus, these mRNAs were identified as stroke-related genes.

3.2. Identification of overlapped DEGs in post-stroke depression

Using mRNA expression profiles in GSE76826, we identified 641 DEGs with 10 samples from late-onset MDD and 12 controls. To find potential biomarkers in PSD, we intersected stroke-related genes with DEGs observed in MDD patients. As a result, 99 DEGs were identified (Figure 3B). The list of the 99 DEGs can be accessed in Supplementary material 3.

Thereafter, using *clusterProfiler* in R, GO functional and KEGG enrichment analyses were performed on the 99 DEGs to further understand their biological functions. As represented in Figure 3C, the biological process (BP) was significantly enriched in T cell differentiation in the thymus, mononuclear cell differentiation, cellular response to glucose starvation, regulation of striated muscle cell differentiation, regulation of lymphocyte apoptotic process; the cellular component (CC) was particularly enriched in the cytoplasmic side of the plasma membrane, cytoplasmic side of the membrane, nuclear speck, podosome, heterotrimeric G-protein complex; and molecular function (MF) was mainly enriched in DNA-binding transcription activator activity, RNA polymerase II-specific, DNA-binding transcription activator activity, cytokine receptor binding, platelet-derived growth factor receptor binding, and mitogen-activated protein (MAP) kinase activity.

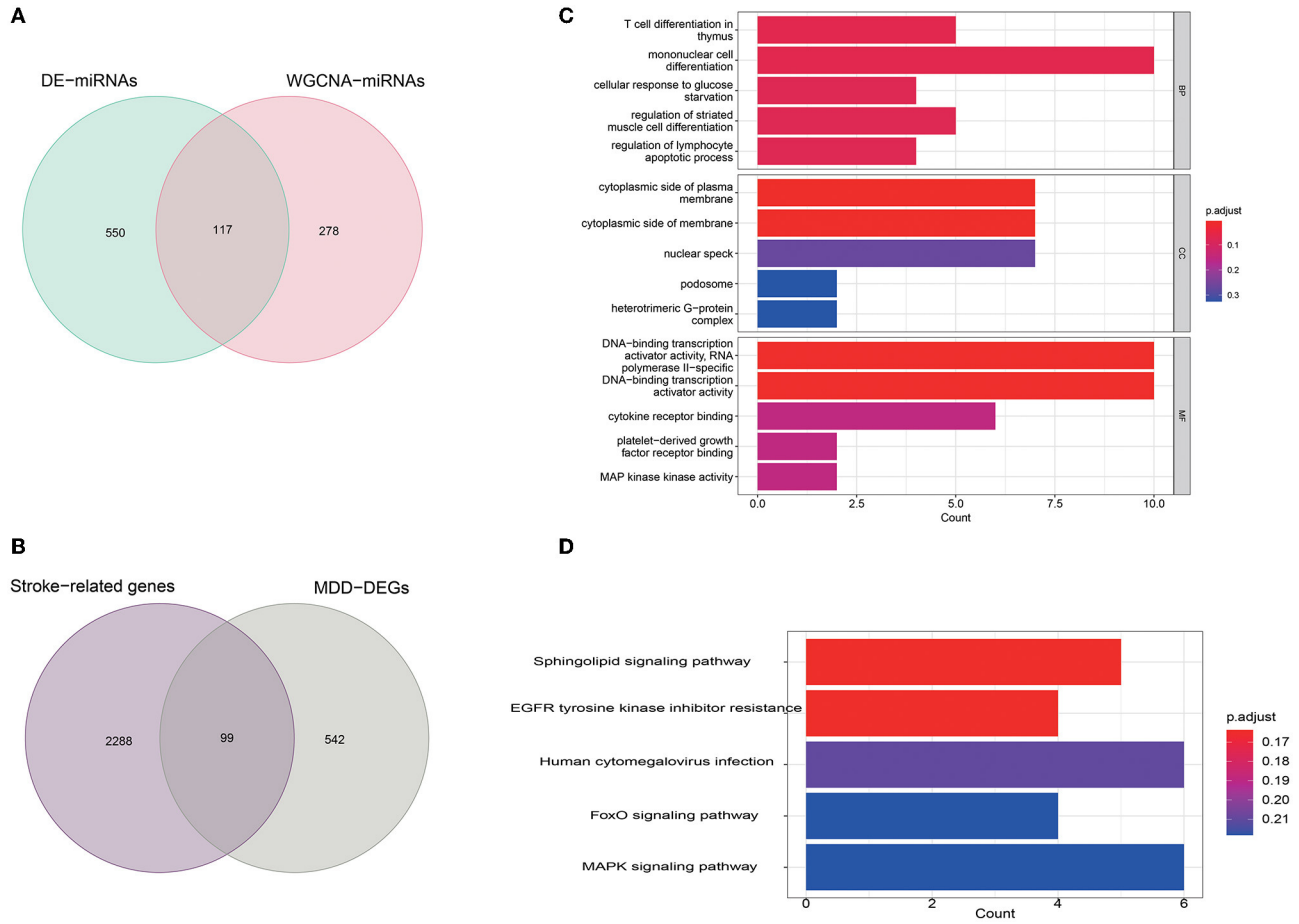


FIGURE 3
Identification of potential DEGs in PSD and enrichment analysis: **(A)** identification of stroke-related miRNAs; **(B)** identification of overlapped DEGs in PSD; **(C)** GO enrichment analysis; and **(D)** KEGG pathway analysis.

Furthermore, the KEGG pathway analysis of the 99 DEGs is shown in Figure 3D. Among all the pathways enriched, the top five most significant pathways were as follows: sphingolipid signaling pathway, EGFR tyrosine kinase inhibitor resistance, human cytomegalovirus infection, FoxO signaling pathway, and MAPK signaling pathway. Among them, MAPK signaling pathways have been associated with the pathophysiology of PSD in several studies (28–30).

The PPI network of the 99 DEGs was constructed by the STRING online database with high confidence of >0.4 applied. The disconnected nodes (genes) were removed from the PPI network (Figure 4A). The network was then presented using the cytoHubba tool in Cytoscape (Figure 4B); the top 10 hub genes were as follows: TP53, MAPK14, VEGFA, GPR29, CD40LG, SMAD3, GNAQ, PTEN, IL7R, and IL6R.

3.3. Selection of feature mRNA by machine-learning algorithms and construction of a miRNA–mRNA network

For a further selection of the mRNA features for post-stroke depression, we used the LASSO algorithm to identify a set of 13 mRNAs (Figure 5A), the SVM algorithm to select a set of 10 mRNAs (Figures 5B, C), and the RF algorithm to select a set of 23 mRNAs (Figure 5D). Specifically, a total of 99 genes were selected by the SVM algorithm to construct the classification model using a 10-fold cross-validation. When 10 genes were selected, the accuracy of the model was the highest (Figures 5B, C). The RF algorithm screened out a total of 99 genes, and the top 23 genes with positive values of importance were selected (Supplementary material 4).

RF: The RF algorithm screened out a total of 99 genes, and the top 23 genes with positive values of importance were selected (datasheet attached). After combining the mRNAs screened out via the LASSO, SVM, and RF algorithms, three diagnostic mRNAs (SPATA2, ZNF208, and YTHDC1) were identified for post-stroke depression (Figure 5E). These genes were also validated using the ROC curves with AUCs > 0.89 (Figures 6A–C). The prediction of these genes revealed a panel of four miRNAs, with which the genes form a miRNA–mRNA regulatory network, as presented in Figure 6D.

4. Discussion

In the present study, we identified stroke-related genes through differential analysis, WGCNA, as well as target

10.3389/fneur.2023.1096911

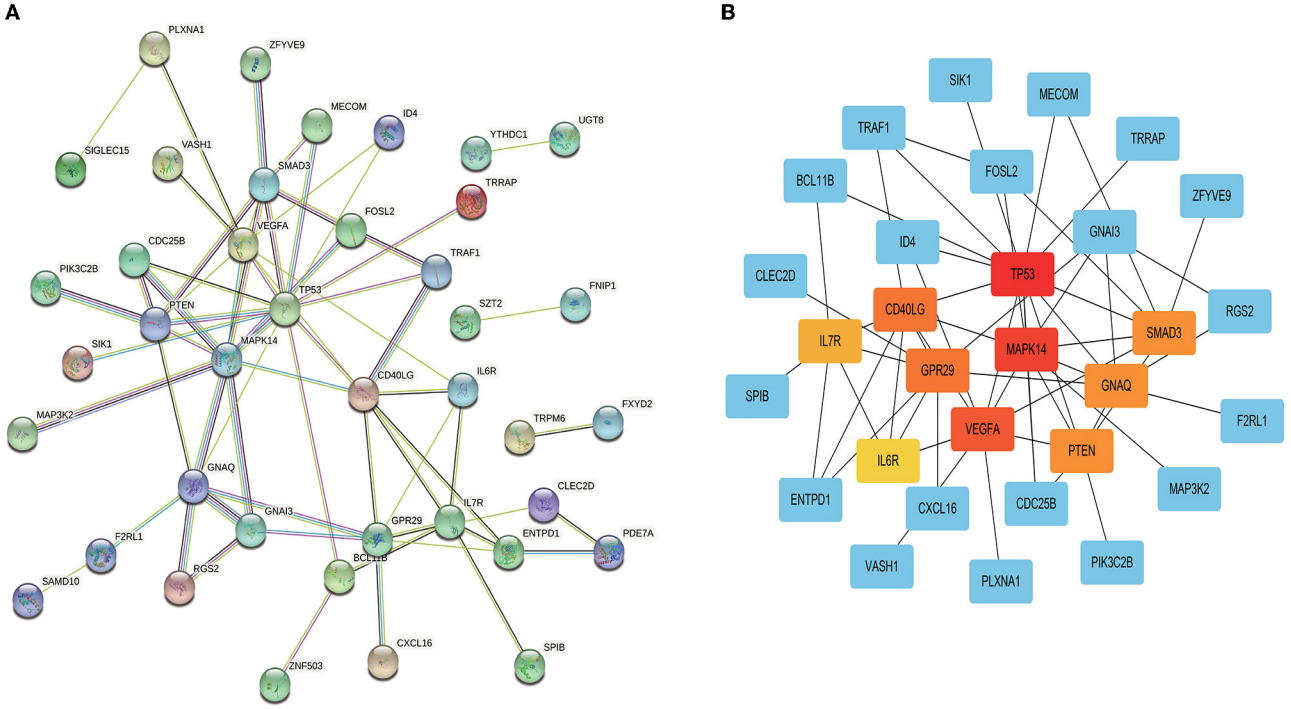


FIGURE 4
Protein–protein interaction (PPI) network using the overlapped DEGs. **(A)** PPI network based on the STRING database; **(B)** representation of the network using Cytoscape.

prediction via miRNAs. Subsequently, 99 overlapped DEGs were identified in late-onset MDD to reveal potential biomarkers in PSD. Enrichment analysis revealed that these genes were implicated in pathways related to sphingolipid signaling, EGFR tyrosine kinase inhibitor resistance, human cytomegalovirus infection, FoxO signaling, and MAPK signaling. Furthermore, three machine-learning algorithms were employed to explore gene signatures for PSD, which was validated with the ROC curves. At last, a miRNA–mRNA network was constructed.

Our study highlighted gene signatures for PSD with three genes: SPATA2, ZNF208, and YTHDC1. However, there were no reports on their role in PSD. SPATA2 enables signaling receptor complex adaptor activity and ubiquitin-specific protease binding activity (31). SPATA2 is involved in several processes, including protein deubiquitination, necroptotic process, and tumor necrosis factor-mediated signaling pathway (32, 33). The knockdown of SPATA2 leads to the activation of P38MAPK and NLRP3 inflammasome and the enhancement of NF-κB signaling, indicating that SPATA2 plays a protective role against brain inflammation induced by ischemia/reperfusion injury (34). ZNF208 polymorphisms were observed to be associated with ischemic stroke in a Chinese Han population (35); however, no other reports concerning its role in stroke or depression were reported. An increasing number of studies have shown that YTHDC1, an important N6-methyladenosine (m6A) reader, plays a key role in multiple biological functions as well as in disease progression. It was observed that YTHDC1 could be protective against ischemic stroke by enhancing Akt phosphorylation via destabilizing PTEN mRNA (36). Therefore, it could be a potential therapeutic target for ischemic stroke. With the gene signatures for PSD, we predicted a list of four miRNAs (miR-6883-5p, miR-6873-3p, miR-4776-3p, and miR-6738-3p) based on the databases. Subsequently, a miRNA–mRNA network was developed, and it could shed light on the pathogenesis of PSD.

Emerging studies have investigated the role of miRNA–mRNA networks in the pathogenesis and progression of diseases, such as HBV-related hepatocellular carcinoma (37), stroke due to atrial fibrillation (38), and MDD in ovarian cancer patients (39). These studies revealed potential mechanisms by which the existing risk factor or disease contributes to the development of specific complications. In the case of PSD, datasets were exploited to find overlapped DEGs in stroke and late-onset MDD. Using three machine-learning classifiers, we further selected three feature genes and four upstream miRNAs, which could be potential targets for PSD treatment. To the best of our knowledge, the present study was the first to depict a miRNA–mRNA network for PSD; further investigations with a focus on the biological functions of these miRNAs and mRNAs are necessary. Our study suffered from a lack of wet lab validation, which may be the major limitation. However, the role of the miRNAs and mRNAs on PSD was first reported in our study, which could be of interest to further studies.

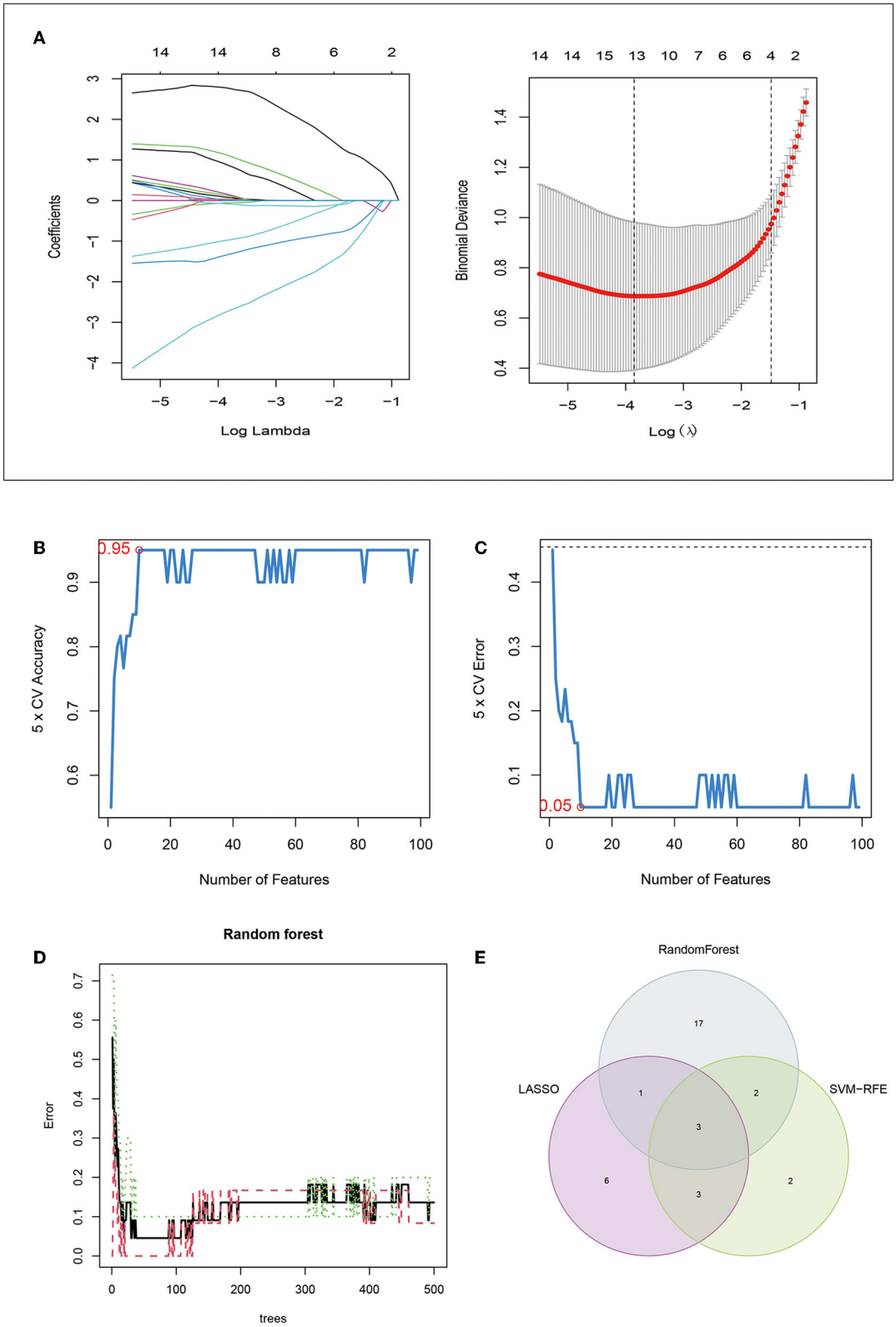


FIGURE 5
Machine-learning methods identified three hub genes in PSD: **(A)** 10-fold cross-validation for tuning parameter selection in the LASSO model, where LASSO identified 13 mRNAs; **(B)** accuracy of the SVM algorithm; **(C)** error of the estimate generation for the SVM algorithm; **(D)** relationship between model error rate and number of trees for the RF algorithm; and **(E)** feature selection with the intersection of results from LASSO, SVM, and RF algorithms.

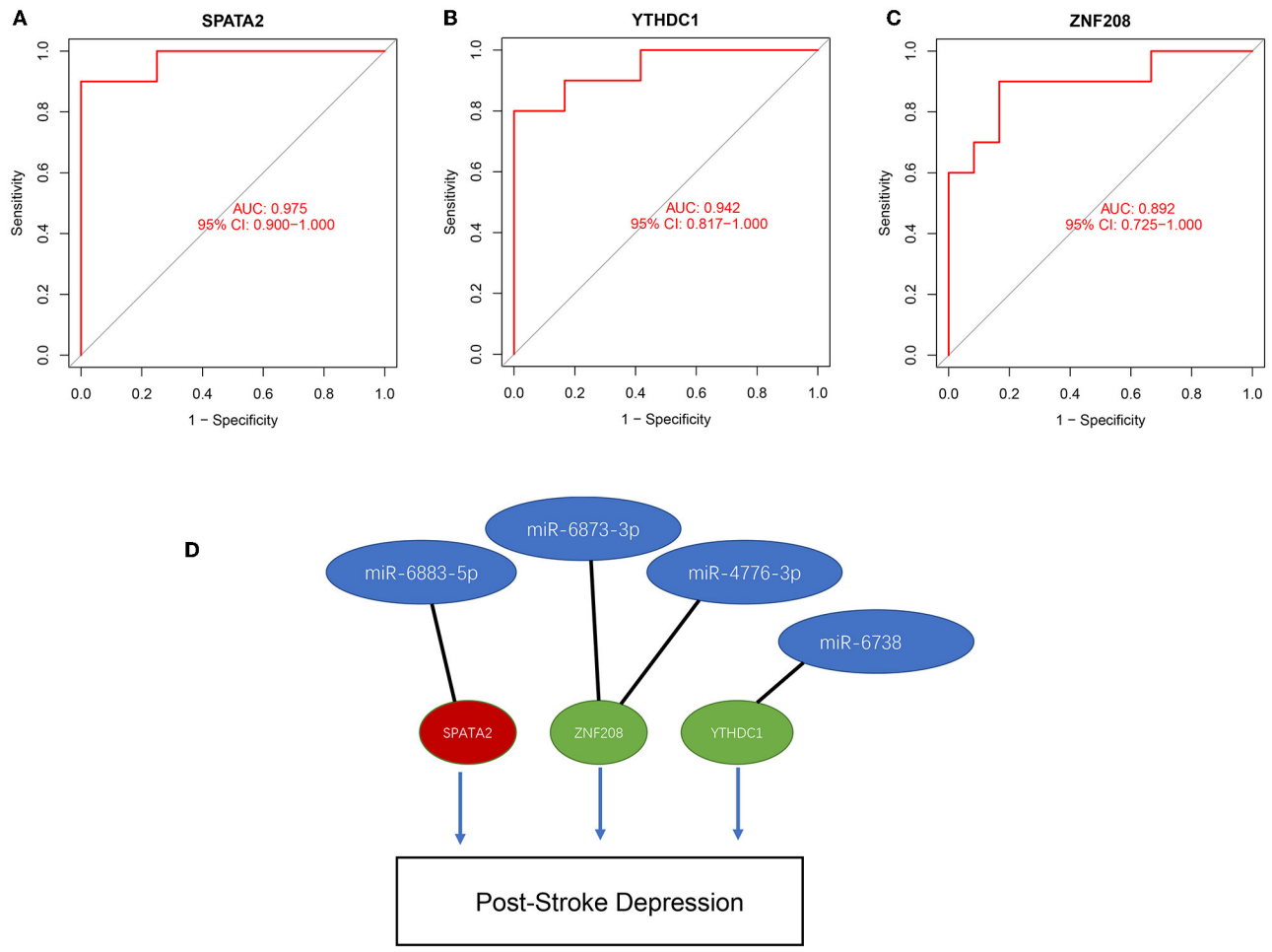


FIGURE 6
ROC validation of three hub genes **(A)** SPATA2, **(B)** YTHDC1, **(C)** ZNF208 and construction of a miRNA–mRNA network **(D)**.

5. Conclusion

Our study highlighted gene signatures for PSD with three genes: SPATA2, ZNF208, and YTHDC1; their upstream miRNAs were predicted as follows: miR-6883-5p, miR-6873-3p, miR-4776-3p, and miR-6738-3p. The miRNA–mRNA network was constructed, and these biomarkers could further our understanding of the pathogenesis of PSD.

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

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

HQ, YM, and YS: data curation, formal analysis, roles/writing—original draft, and writing—review and editing. LS: data curation. YM and YS: conceptualization, design, and methodology. All authors contributed to the article and approved the submitted version.

Funding

The study was funded by the National Key R&D Program of China (2022YFC2009700 and 2022YFC2009701) and Basic Science (Natural Science) Research Project of Higher Education Institutions in Jiangsu Province (No. 23KJB320001).

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1096911/full#supplementary-material

SUPPLEMENTARY MATERIAL 1
DE-miRNA list retrieved from GSE117064.

SUPPLEMENTARY MATERIAL 2
Correlations between gene significance and module membership.

SUPPLEMENTARY MATERIAL 3
List of 99 DEGs implicated in PSD.

SUPPLEMENTARY MATERIAL 4
Gene list generated by the RF algorithm.

References

1. Villa RF, Ferrari F, Moretti A. Post-stroke depression: mechanisms and pharmacological treatment. *Pharmacol Ther.* (2018) 184:131–44. doi: 10.1016/j.pharmthera.2017.11.005

2. Guo J, Wang J, Sun W, Liu X. The advances of post-stroke depression: 2021 update. *J Neurol.* (2022) 269:1236–49. doi: 10.1007/s00415-021-10597-4

3. Herrmann N, Black SE, Lawrence J, Szekely C, Szalai JP. The Sunnybrook Stroke Study: a prospective study of depressive symptoms and functional outcome. *Stroke.* (1998) 29:618–24. doi: 10.1161/01.STR.29.3.618

4. Ayerbe L, Ayis S, Crichton SL, Rudd AG, Wolfe CD. Explanatory factors for the increased mortality of stroke patients with depression. *Neurology.* (2014) 83:2007–12. doi: 10.1212/WNL.0000000000001029

5. Ambros V. The functions of animal microRNAs. *Nature.* (2004) 431:350–5. doi: 10.1038/nature02871

6. Eulalio A, Huntzinger E, Izaurralde E. Getting to the root of miRNA-mediated gene silencing. *Cell.* (2008) 132:9–14. doi: 10.1016/j.cell.2007.12.024

7. Liu DZ, Tian Y, Ander BP, Xu H, Stamova BS, Zhan X, et al. Brain and blood microRNA expression profiling of ischemic stroke, intracerebral hemorrhage, and kainate seizures. *J Cerebr Blood Flow Metabol.* (2010) 30:92–101. doi: 10.1038/jcbfm.2009.186

8. Matsuzaki J, Ochiya T. Circulating microRNAs and extracellular vesicles as potential cancer biomarkers: a systematic review. *Int J Clin Oncol.* (2017) 22:413–20. doi: 10.1007/s10147-017-1104-3

9. do Amaral AE, Rode MP, Cisilotto J, da Silva TE, Fischer J, Matiollo C, et al. MicroRNA profiles in serum samples from patients with stable cirrhosis and miRNA-21 as a predictor of transplant-free survival. *Pharmacol Res.* (2018) 134:179–92. doi: 10.1016/j.phrs.2018.06.019

10. Dieckmann KP, Radtke A, Spiekermann M, Balks T, Matthies C, Becker P, et al. Serum levels of microRNA miR-371a-3p: a sensitive and specific new biomarker for germ cell tumours. *Eur Urol.* (2017) 71:213–20. doi: 10.1016/j.eururo.2016.07.029

11. Ji D, Qiao M, Yao Y, Li M, Chen H, Dong Q, et al. Serum-based microRNA signature predicts relapse and therapeutic outcome of adjuvant chemotherapy in colorectal cancer patients. *EBioMedicine.* (2018) 35:189–97. doi: 10.1016/j.ebiom.2018.08.042

12. Rink C, Khanna S. MicroRNA in ischemic stroke etiology and pathology. *Physiol Genom.* (2011) 43:521–8. doi: 10.1152/physiolgenomics.00158.2010

13. Sonoda T, Matsuzaki J, Yamamoto Y, Sakurai T, Aoki Y, Takizawa S, et al. Serum MicroRNA-based risk prediction for stroke. *Stroke.* (2019) 50:1510–8. doi: 10.1161/STROKEAHA.118.023648

14. Zhi F, Shao N, Wang R, Deng D, Xue L, Wang Q, et al. Identification of 9 serum microRNAs as potential noninvasive biomarkers of human astrocytoma. *Neuro Oncol.* (2015) 17:383–91. doi: 10.1093/neuonc/nou169

15. Zhao H, Shen J, Hodges TR, Song R, Fuller GN, Heimberger AB. Serum microRNA profiling in patients with glioblastoma: a survival analysis. *Mol Cancer.* (2017) 16:59. doi: 10.1186/s12943-017-0628-5

16. Ouimet M, Ediriweera HN, Gundra UM, Sheedy FJ, Ramkhelawon B, Hutchison SB, et al. MicroRNA-33–dependent regulation of macrophage metabolism directs immune cell polarization in atherosclerosis. *J Clin Invest.* (2015) 125:4334–48. doi: 10.1172/JCI81676

17. Bueno MJ, Malumbres M. MicroRNAs and the cell cycle. *Biochim Biophys Acta.* (2011) 1812:592–601. doi: 10.1016/j.bbadis.2011.02.002

18. Saba R, Sorensen DL, Booth SA. MicroRNA-146a: a dominant, negative regulator of the innate immune response. *Front Immunol.* (2014) 5:578. doi: 10.3389/fimmu.2014.00578

19. Ranstam J, Cook J. LASSO regression. *J Br Surg.* (2018) 105:1348. doi: 10.1002/bjs.10895

20. Mahesh B. Machine learning algorithms-a review. *Int J Sci Res.* (2020) 9:381–6. doi: 10.21275/ART20203995

21. Abdulkareem NM, Abdulazeez AM. Machine learning classification based on Radom Forest Algorithm: a review. *Int J Sci Bus.* (2021) 5:128–42. doi: 10.5281/zenodo.4471118

22. Miyata S, Kurachi M, Okano Y, Sakurai N, Kobayashi A, Harada K, et al. Blood transcriptomic markers in patients with late-onset major depressive disorder. *PLoS ONE.* (2016) 11:e0150262. doi: 10.1371/journal.pone.0150262

23. Ritchie ME, Belinda P, Di W, Hu Y, Law CW, Wei S, et al. In limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucl Acids Res.* (2015) 7:gkv007. doi: 10.1093/nar/gkv007

24. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal Stat Soc Ser B.* (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

25. Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. *Stat Appl Genet Mol Biol.* (2005) 4:17. doi: 10.2202/1544-6115.1128

26. Oldham MC, Konopka G, Iwamoto K, Langfelder P, Kato T, Horvath S, et al. Functional organization of the transcriptome in human brain. *Nat Neurosci.* (2008) 11:1271–82. doi: 10.1038/nn.2207

27. Yu G, Wang LG, Han Y, He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. *Omics.* (2012) 16:284–7. doi: 10.1089/omi.2011.0118

28. Feng Y, Li X, Wang J, Huang X, Meng L, Huang J. Pyruvate kinase M2 (PKM2) improve symptoms of post-ischemic stroke depression by activating VEGF to mediate the MAPK/ERK pathway. *Brain Behav.* (2022) 12:e2450. doi: 10.1002/brb3.2450

29. Verma R, Harris NM, Friedler BD, Crapser J, Patel AR, Venna V, et al. Reversal of the detrimental effects of post-stroke social isolation by pair-housing is mediated by activation of BDNF-MAPK/ERK in aged mice. *Sci Rep.* (2016) 6:1–13. doi: 10.1038/srep25176

30. Zhang Y, Cheng L, Chen YG, Yang Y, Liu J, Zeng L. Clinical predictor and circulating microRNA profile expression in patients with early onset post-stroke depression. *J Affect Disord.* (2016) 193:51–8. doi: 10.1016/j.jad.2015.12.061

31. Schlicher L, Brauns-Schubert P, Schubert F, Maurer U. SPATA2: more than a missing link. *Cell Death Differ.* (2017) 24:1142–7. doi: 10.1038/cdd.2017.26

32. Elliott PR, Leske D, Hrdinka M, Bagola K, Fiil BK, McLaughlin SH, et al. SPATA2 links CYLD to LUBAC, activates CYLD, and controls LUBAC signaling. *Mol Cell.* (2016) 63:990–1005. doi: 10.1016/j.molcel.2016.08.001

33. Yang XD, Li W, Zhang S, Wu D, Jiang X, Tan R, et al. PLK4 deubiquitination by Spata2-CYLD suppresses NEK7-mediated NLRP3 inflammasome activation at the centrosome. *EMBO J.* (2020) 39:e102201. doi: 10.15252/embj.201902201

34. Ren Y, Jiang J, Jiang W, Zhou X, Lu W, Wang J, et al. Spata2 knockdown exacerbates brain inflammation via NF-κB/P38MAPK signaling and NLRP3 inflammasome activation in cerebral ischemia/reperfusion rats. *Neurochem Res.* (2021) 46:2262–75. doi: 10.1007/s11064-021-03360-8

35. Yu J, Zhou F, Luo D, Wang N, Zhang C, Jin T, et al. ZNF208 polymorphisms associated with ischemic stroke in a southern Chinese Han population. *J Gene Med.* (2017) 19:1–2. doi: 10.1002/jgm.2937

36. Zhang Z, Wang Q, Zhao X, Shao L, Liu G, Zheng X, et al. YTHDC1 mitigates ischemic stroke by promoting Akt phosphorylation through destabilizing PTEN mRNA. *Cell Death Dis.* (2020) 11:977. doi: 10.1038/s41419-020-03186-2

37. Lou W, Liu J, Ding B, Chen D, Xu L, Ding J, et al. Identification of potential miRNA-mRNA regulatory network contributing to pathogenesis of HBV-related HCC. *J Transl Med.* (2019) 17:7. doi: 10.1186/s12967-018-1761-7

38. Zou R, Zhang D, Lv L, Shi W, Song Z, Yi B, et al. Bioinformatic gene analysis for potential biomarkers and therapeutic targets of atrial fibrillation-related stroke. *J Transl Med.* (2019) 17:45. doi: 10.1186/s12967-019-1790-x

39. Wu C, Zhao Y, Liu Y, Yang X, Yan M, Min Y, et al. Identifying miRNA-mRNA regulation network of major depressive disorder in ovarian cancer patients. *Oncol Lett.* (2018) 16:5375–82. doi: 10.3892/ol.2018.9243

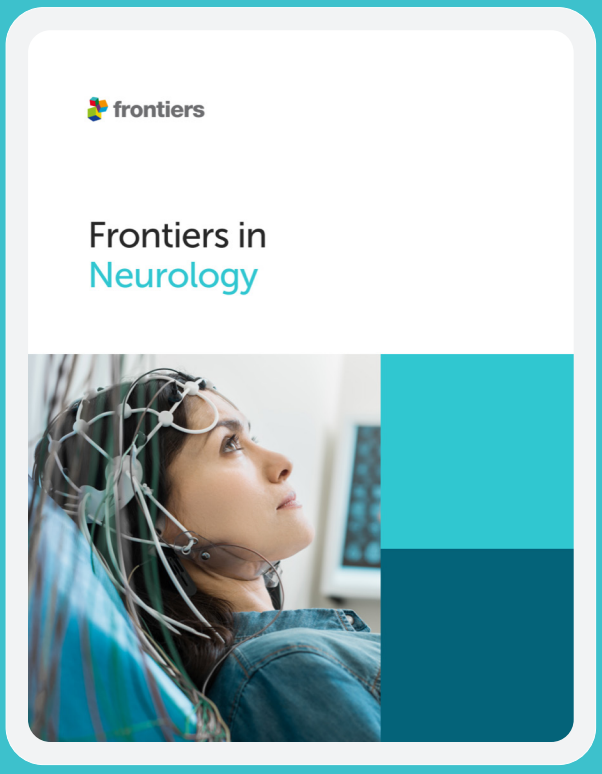
Frontiers in Neurology

Explores neurological illness to improve patient care

The third most-cited clinical neurology journal explores the diagnosis, causes, treatment, and public health aspects of neurological illnesses. Its ultimate aim is to inform improvements in patient care.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact