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Evaluation of fitness in stroke survivors

Edited by
Felipe Cunha, Arthur Sá Ferreira and
Adrian Wayne Midgley

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Evaluation of fitness in stroke survivors

Topic editors

Felipe Cunha — Rio de Janeiro State University, Brazil

Arthur Sá Ferreira — University Center Augusto Motta, Brazil

Adrian Wayne Midgley — Edge Hill University, United Kingdom

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EDITED AND REVIEWED BY
Anthony Pak Hin Kong,
The University of Hong Kong,
Hong Kong SAR, China

*CORRESPONDENCE
Arthur de Sá Ferreira
✉ asferreira@unisuam.edu.br

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

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Editorial: Evaluation of fitness in stroke survivors

Felipe Cunha[1†], Arthur de Sá Ferreira[2*†] and Adrian Wayne Midgley[3†]

[1]Laboratory of Physical Activity and Health Promotion, Institute of Physical Education and Sports, Rio de Janeiro State University, Rio de Janeiro, Brazil, [2]Laboratory of Computational Simulation and Modeling in Rehabilitation, Postgraduate Program in Rehabilitation Sciences, Centro Universitário Augusto Motta, Rio de Janeiro, Brazil, [3]Department of Sport & Physical Activity, Edge Hill University, Ormskirk, United Kingdom

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Editorial on the Research Topic
Evaluation of fitness in stroke survivors

Stroke remains a leading cause of long-term disability worldwide, often resulting in impairments in cardiorespiratory and neuromuscular function (Tsao et al., 2023). These limitations contribute to decreased physical activity, increased fatigue, and heightened sedentary behavior, jeopardizing functional independence and increasing the risk of recurrence. This Research Topic showcase recent advances in evaluating key domains of physical fitness in stroke survivors, including cardiorespiratory fitness, muscular strength, and endurance, neuromotor control, fatigue tolerance, and body composition.

Cardiorespiratory fitness assessment remains a cornerstone of post-stroke evaluation. The cardiopulmonary exercise test (CPET) is recognized as the gold standard for determining maximal oxygen uptake (VO_{2max}), however, its validation, safety, and feasibility in stroke populations remain underexplored. Qu et al. addressed this gap by examining the decline in cardiorespiratory fitness post-stroke using resting-state functional magnetic resonance imaging, opening new perspectives for combining physiological and neuroimaging data in this population.

Accurate assessment of neuromuscular function and physical performance is equally critical. Pu et al. developed a nomogram to predict sarcopenia risk in stroke patients, incorporating anthropometric and biochemical markers, while Zhong et al. validated a Chinese version of the performance-oriented mobility assessment, ensuring reliability for use in chronic stroke survivors. Bi et al. further linked serum albumin levels to severe impairment in activities of daily living (ADLs), reinforcing the role of nutritional and metabolic markers in functional prognosis.

The interplay between physical health, psychological status, and functional independence also emerged as a key theme. Dan et al. demonstrated how depression mediates the link between stroke and fracture risk, highlighting the need for integrative assessments that include emotional and cognitive domains. Similarly, Lin and Liu proposed a predictive model for ADL dysfunction, offering clinicians a tool to anticipate limitations early in the recovery process.

Contributions addressed innovative assessment and rehabilitation strategies. Bian et al. performed a network meta-analysis comparing different physical stimulation therapies, offering evidence to guide upper limb motor rehabilitation strategies. Dai et al. explored

the concept of exercise preference in stroke survivors, emphasizing the value of patient-centered approaches when designing fitness evaluations and rehabilitation plans.

Lastly, Yin et al. analyzed thrombectomy timing by stroke subtype, and Chunjuan et al. applied machine learning clustering to inflammatory profiles, both enhancing our understanding of physiological factors influencing recovery potential.

These studies represent a multidisciplinary effort to improve the precision, relevance, and personalization of fitness assessment in stroke rehabilitation. Continued research must ensure that tools are accessible, scalable, and responsive to the specific needs of stroke survivors across the recovery continuum. We hope this Research Topic inspires further innovation and collaboration in optimizing fitness assessment and rehabilitation strategies in stroke care.

Author contributions

FC: Writing – original draft, Resources, Project administration, Validation, Funding acquisition, Conceptualization, Writing – review & editing. AF: Resources, Writing – original draft, Funding acquisition, Validation, Project administration, Writing – review & editing, Conceptualization. AM: Project administration, Writing – review & editing, Writing – original draft, Conceptualization, Resources, Validation.

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EDITED BY
Felipe Cunha,
Rio de Janeiro State University, Brazil

REVIEWED BY
Gelu Onose,
University of Medicine and Pharmacy "Carol Davila", Romania
Guilherme Fonseca,
Rio de Janeiro State University, Brazil

*CORRESPONDENCE
Qing Wang
ruoyiwangqing@163.com

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Exercise preference in stroke survivors: a concept analysis

Yuting Dai[1], Huiling Shi[1], Kangling Ji[1], Yuxin Han[2], Minerva De Ala[3] and Qing Wang[4]*

[1]Department of Neurology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China, [2]School of Nursing, Nanjing University of Chinese Medicine, Nanjing, China, [3]School of Nursing, Philippine Women's University, Manila, Philippines, [4]Department of Nursing, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Background: Exercise preference in stroke survivors is related to their adherence to long-term rehabilitation regimen and functional recovery. Although explored recently, the term exercise preference still lacks a clear definition.

Objective: The aim of this study is to conceptualize exercise preference in stroke survivors.

Methods: The Walker and Avant method was applied as a framework for the conceptual analysis of exercise preference. Data from 34 publications were collected using seven databases (PubMed, Web of Science, Embase, CINAHL, CNKI, Wanfang Data, and CBM) and applied in the analysis. The search period was from the inception of the database to April 30, 2023.

Results: Exercise preference in stroke survivors was defined according to four attributes: priority of choice, behavioral tendency, affective priming, and patience in adherence. The common antecedents of the concept of exercise preference in stroke survivors were classified into patient-related, therapy-related, and environmental-related categories and the consequences were classified into three categories: patient-related, rehabilitation provider–related, and rehabilitation service system–related.

Conclusion: Exercise preference in stroke survivors refers to the patient's choice, tendency, affective response, and attitude toward engagement in the recommended rehabilitation regimen. It is beneficial for understanding the essential attributes of exercise preference in stroke survivors by clarifying the concept. In addition, it will facilitate the development of instruments for assessing exercise preference in stroke survivors and the construction of theory-based intervention programs that can improve adherence to exercise rehabilitation.

KEYWORDS

stroke, exercise, rehabilitation, patient preference, concept analysis

1 Introduction

Stroke has become a major global public health problem, and loss of motor function is the main cause of patient disability. More than 80% of the stroke survivors have varying degrees of motor function loss, and approximately 50% of them experience motor dysfunction in 3 months after stroke onset, leading to dependence, limited mobility, and "hard return" (1, 2). The extreme challenge in motor recovery is to minimize motor impairment. Rehabilitation is key to promoting

motor recovery after a stroke, and much of the rehabilitation experience—whether inpatient, outpatient, or at home—as it relates to motor recovery after acute care discharge revolves around physical activity and exercise (3). However, motor recovery involves actively acquiring knowledge and skills through external support to promote physical, psychological, and social function improvement. Rehabilitation is a complex behavior regulated by automatic process (habit) and goal-directed control process (intention) (4, 5), and patient preference plays a crucial role in motivation and control (6). Therefore, exercise preferences in the rehabilitation process of stroke survivors, which will be closely related to their adherence to long-term rehabilitation processes and functional recovery, need to be studied.

Evidence suggests stroke patients may benefit more from earlier, more intensive rehabilitation (7, 8). Exercise is an integral component of rehabilitation after stroke onset and plays a crucial role in promoting functional independence (9). Exercise rehabilitation is a long-term, dynamic, multifactorial, and complex process, and stroke survivors present different exercise preferences over time (10). Patients want themselves, rather than the techniques, to be kept as the center of attention in the rehabilitation process, such as the exercise mode they are interested in, accessible, positive, and meaningful as they perceived it, confidence, external supervision and support, and so on (11–13). Exercise regimes need to be designed that keeping in mind exercise preferences that promote the affective response of stroke survivors so that they become engaged and motivated to be physically active (14, 15).

The term preference has been used for a long time in the fields of psychology and economics, which refers to weighing the risk and benefit for the individual (16, 17). It has mainly been studied in personal financial investment decisions, also reflecting choice tendency or behavioral intention (17, 18). As the patient-centered care was proposed, patient preference has been valued and recognized as a crucial element of best nursing practice (19). Patient preference (PP) information is defined as qualitative or quantitative assessments of the relative desirability or acceptability of patients among specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions (20). However, we cannot simply equate the concept of patient preference information with the concept of exercise preference in stroke survivors. The concept of exercise preference in stroke survivors is more focused on the personal preferences in the recommended rehabilitation regimen. Exercise preference in stroke survivors has been presented only as a fragmented information in several studies (13–15). But exercise preference of stroke survivors has not been extensively covered, including the heterogeneity of personal values and inclination for long-term rehabilitation (11, 13, 21).

Clarifying the concept of exercise preference in stroke survivors in the rehabilitation process can provide primary knowledge about preferences in rehabilitation in the selected population with similar traits and ensure consistency in its utilization and adoption. It can also enable scholars and researchers to develop assessment instruments for evaluating the exercise preference of stroke survivors and construct hypotheses that clearly mirror the relationships between and among the related concepts and factors. Furthermore, health care professionals designing the rehabilitation regimes for stroke survivors could adopt personalized strategies that can support adherence to exercise and improve self-management of the rehabilitation process. Hence, this study aims to provide a clear and evidence-based definition of exercise preference in patients with stroke and construct its antecedents, attributes, consequences, and empirical referents.

2 Materials and methods

2.1 The concept analysis approach

The Walker and Avant's method of analysis was be adopted to evaluate the concept of exercise preference in stroke survivors, which contained the following eight steps (22): (1) select a concept (2), determine the aims or purposes of analysis, (3) identify all the uses of the concept that you can discover, (4) determine the defining attributes (5), identify a model case (6), identify borderline, related, contrary, invented, and illegitimate cases (7), identify antecedents and consequences, and (8) define empirical referents.

2.2 Data sources

A comprehensive and broad search for the term "exercise preference of stroke survivors" was performed in PubMed, Web of Science, Embase, CINAHL, China National Knowledge Infrastructure (CNKI), Wanfang Data, and China Biology Medicine disc (CBM) from their inception to April 30, 2023 to confirm the basic elements of the concept. The keywords "stroke," "apoplexy," "cerebrovascular accident," "cerebrovascular apoplexy," "CVA," "rehabilitation," "exercise rehabilitation," "exercise," "physical activity," "preference," "value," "favor" were used as search terms individually or in combination with each other. The specific search strategy is shown in Supplementary material S1. In addition, references from the retrieved literature (especially review literature) were also reviewed to supplement and ensure a complete search. The inclusion criteria involved literature in English or Chinese, full-text publications, and academic journals that can confirm the concept of exercise preference using stroke survivors as a sample. Commentaries, editorials, and dissertations were excluded.

A total of 34 studies with full-text publications were included in this study (Figure 1). The process of the search conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) search strategy guidelines.

2.3 Data collection and management

Thirty-four studies were reviewed for systematic data collection and management, including study characteristics, as well as antecedents, attributes, and consequences of concepts. The information was extracted and tabulated (Table 1). Clear definitions of exercise preference in stroke survivors are relatively rare in the aforementioned studies. Thus, only some studies include all the antecedents, attributes, and consequences of exercise preference in stroke survivors.

3 Results

3.1 Definitions and uses of concept

The common and universal understanding and usage of the term should be captured for a concept analysis. Based on the framework proposed by Walker and Avant (22) and synthesizing

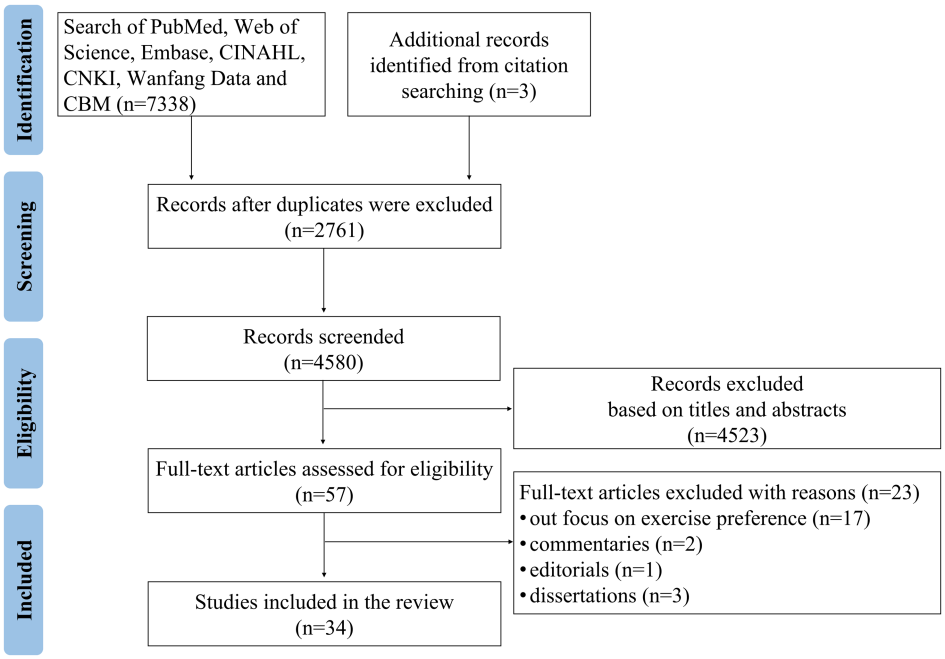

FIGURE 1
Flow diagram of the study selection.

the 34 included studies, the concept of exercise preference in stroke survivors refers to the patient's choice, tendency, affective response, and attitude toward engagement in the recommended rehabilitation regimen.

In 2001, Wu et al. (23) evaluated exercise preference for explaining the motor performance of the participants in performing a task and showed significant differences between the task preferences. In 2012, the Exercise Preference Questionnaire for stroke survivors was developed to capture exercise preferences and current exercise habits. The exercise preferences in stroke survivors contained five dimensions: (i) exercise with others, (ii) degree of structure of exercise program, (iii) independence, (iv) exercise location, and (v) intensity (24). In 2016, the Stroke Exercise Preference Inventory (SEPI) was constructed and consists of supervision support, confidence challenge, health and well-being, similar others, exercise context, home-alone, and music-TV (25). Furthermore, the concept of exercise preference has been developed both psychologically and theoretically. It addresses concerns that are relevant to people who require physical rehabilitation for conditions other than stroke. For medical professionals delivering exercise rehabilitation, especially in a home setting, the SEPI acts as a tool to promote specific discussion about choices and concerns and thus individualize the exercise regimes (14).

The studies mentioning concepts similar to exercise preference in stroke survivors have been found in the fields of nursing, medicine, psychology, physiology, and occupational therapy. Most of these are exploratory qualitative studies regarding experience (10), dilemma (26), expectation (27), facilitators, and barriers (11, 13, 26) in the rehabilitation process. Moreover, several quantitative studies have investigated the association between and among exercise preferences, potential barriers, and psychosocial factors such as self-efficacy and depression (14, 15, 21).

3.2 Attributes of exercise preference in stroke survivors

The exercise preference in stroke survivors were found to be the priority of choice, behavioral tendency, affective priming, and patience in adherence. Particulars of each attribute are described below.

3.2.1 Priority of choice

Priority of choice is a crucial attribute of exercise preference in stroke survivors. This is mainly reflected in the choice of exercise programs such as social situation, location, type of exercise, intensity, frequency, and duration (28). Choosing or refusing a certain mode of exercise depends on what they like or what they do not like when exercising (13). Individuals with stroke are more interested in a certain exercise mode and more likely to make corresponding choices and exhibit better adherence (13, 29). Of course, there are also pros and cons to weigh in this process (30).

3.2.2 Behavioral tendency

According to Caetano and colleagues (15), in the sphere of stroke rehabilitation, behavioral tendency reflects as the intention of individuals with stroke engaging in exercise. This often aligns with personal recovery goals and overall health goals. It usually presents as a willingness to make an effort to exercise to achieve a certain rehabilitation goal (26). As Bastos et al. (21) have observed, stroke survivors prefer exercises in controlled environments (gyms/rehabilitation centers) and those offered in groups (with family/friends, other individuals of similar age and health condition).

3.2.3 Affective priming

An analysis of the preferences of the stroke survivors shows that when they perceived the certain exercises as positive and meaningful

TABLE 1 Antecedents, attributes and consequences of exercise preference in stroke survivors.

Author	Year	Study design	Sample size	Antecedents	Attributes	Consequences
Abrahamson and Wilson	2019	Multiple case study design	74	/	Preferring exercises in controlled environments	/
Banks et al.	2012	Cross-sectional study	64	/	The choice of exercise with others, degree of structure of exercise program, independence, exercise location, and intensity	/
Bastos et al.	2021	Cross-sectional study	24	Motivation	Preferring exercises in controlled environments (gyms/rehabilitation centers) and those offered in groups (with family/friends, other individuals of similar age and health condition)	Personalized regimens providing; promoted the impeccable stroke rehabilitation service system construction
Bernhardt et al.	2020	Systematic review	/	/	/	Promoted the impeccable stroke rehabilitation service system construction
Blennerhassett et al.	2022	Mixed methods research	42	Capacity of mobility; cognitive and emotional status; self-efficacy; personality traits; painful; fatigue; financial and social support; convenience and accessibility	The choice of exercise programs such as location	Enhanced the level of physical activity; personalized regimens providing; promoted the impeccable stroke rehabilitation service system construction; decreased in costs; improved rehabilitation services
Bonifacio et al.	2022	Systematic review	/	/	/	Promoted motor recovery; promoted quality of life of individuals with stroke
Bonner et al.	2016	Cross-sectional study	134	Capacity of mobility; cognitive and emotional status; self-efficacy; personality traits; painful; fatigue; financial and social support; convenience and accessibility	The choice of exercise programs such as location	Improved adherence to rehabilitation
Caetano et al.	2020	Cross-sectional study	93	Self-efficacy; outcome expectancy	The intention of individuals with stroke engaging in exercise	Improved adherence to rehabilitation
Chen et al.	2020	Qualitative research	13	Motivation; diversity and individualized of exercise program; convenience and accessibility	Pros and cons to weigh in this process	/
Forgea and Lorenz	2021	Systematic review	/	Capacity of mobility; cognitive and emotional status; motivation; financial and social support	/	/
Gard et al.	2019	Qualitative research	20	/	Choosing or refusing a certain mode of exercise depend on what they like or what they do not like when exercising	/

(Continued)

TABLE 1 (Continued)

Author	Year	Study design	Sample size	Antecedents	Attributes	Consequences
Geidl et al.	2018	Cross-sectional study	103	/	The choice of exercise programs such as social situation, location, type of exercise, intensity, frequency, and duration	/
Hunter et al.	2018	Cross-sectional study	176	Present bias	/	/
Jones et al.	2021	Mixed methods research	156	/	/	Improved the convenience and accessibility of rehabilitation delivery
Khoshbakht Pishkhani et al.	2019	Qualitative research	20	Capacity of mobility; beliefs in the benefits of exercise; perception of meaningful; financial and social support; family support; emotional stimulus	Choosing or refusing a certain mode of exercise depend on what they like or what they do not like when exercising; immediate gratification comes from the comfort of low intensity and lower-level exercise of physical inactivity or delayed gratification such as motor functional improvement by adherence to the recommended exercise	/
Ko et al.	2020	cohort study	168	/	/	Promoted motor recovery; promoted quality of life of individuals with stroke
Last et al.	2022	Qualitative research	11	Perception of meaningful; adaption; therapeutic relationships with therapists; diversity and individualized of exercise program; trust in rehabilitation providers; convenience and accessibility; behavior habit	A willingness to make effort on exercising to achieve a certain rehabilitation goal	Personalized regimens providing; job satisfaction; communication promoting in patients and rehabilitation team
Lin et al.	2022	Cross-sectional study	208	Capacity of mobility; education; previous experience and habit; financial and social support	/	/
Lin et al.	2021	Systematic review	/	/	/	Improved the convenience and accessibility of rehabilitation delivery
Luker et al.	2015	Systematic review	/	Preceding experience	Preferring the certain exercises as positive and meaningful to improve performance or linked to a better activity of daily life	/
Mahmood et al.	2022	RCT	52	Self-efficacy; education; painful	/	Improved adherence to rehabilitation; enhanced the level of physical activity; promoted motor recovery; promoted quality of life of individuals with stroke; personalized regimens providing; decreased in costs; improved rehabilitation services

(Continued)

TABLE 1 (Continued)

Author	Year	Study design	Sample size	Antecedents	Attributes	Consequences
Mameletzi et al.	2021	Systematic review	/	/	Choosing or refusing a certain mode of exercise depend on what they like or what they do not like when exercising	/
Matchar et al.	2022	RCT	266	Cognitive and emotional status; special incentives	/	/
Mohd Nordin et al.	2014	Qualitative research	23	/	Preferring exercises in controlled environments; as the stroke became chronic, motivation level declined	/
O'Dell et al.	2023	Systematic review	/	/	/	Promoted the impeccable stroke rehabilitation service system construction
Schuster-Amft et al.	2022	Single-arm clinical trial	14	Diversity and individualized of exercise program	/	/
Stark et al.	2019	Qualitative research	22	/	Preferring the certain exercises as positive and meaningful to improve performance or linked to a better activity of daily life	/
Temehy et al.	2022	Systematic review	/	/	/	Improved the convenience and accessibility of rehabilitation delivery
Timme et al.	2022	Cohort study	53	/	The affective response during exercise	/
Tyagi et al.	2018	Qualitative research	37	/	The intention of individuals with stroke engaging in exercise	/
Vadas et al.	2021	Systematic review	/	Self-efficacy; cognitive and emotional status; beliefs in the benefits of exercise; fatigue; adaption; therapeutic relationships with therapists; diversity and individualized of exercise program; trust in rehabilitation providers; financial and social support; family support; convenience and accessibility	Choosing or refusing a certain mode of exercise depend on what they like or what they do not like when exercising; preferring the certain exercises as positive and meaningful to improve performance or linked to a better activity of daily life; immediate gratification comes from the comfort of low intensity and lower-level exercise of physical inactivity or delayed gratification such as motor functional improvement by adherence to the recommended exercise	Improved adherence to Rehabilitation
Wijma et al.	2017	Systematic review	/	Therapeutic relationships with therapists; trust in rehabilitation providers	/	Professional identify; communication promoting in patients and rehabilitation team
Wu et al.	2001	Cross-sectional study	27	/	/	Improved adherence to rehabilitation
Yao et al.	2017	Cross-sectional study	98	/	Immediate gratification comes from the comfort of low intensity and lower-level exercise of physical inactivity or delayed gratification such as motor functional improvement by adherence to the recommended exercise	/

to improve performance or linked to a better activity of daily life, they will like it (10, 13). Affective priming was modulated by the valence of the preceding experience (10), behavior habit (26), emotional stimulus (29), and present bias (31), and exhibit the trait of dynamic, changeable, reversible, and personalized.

3.2.4 Patience in adherence

It refers to the individual with stroke who is more concerned with immediate gratification that comes from the comfort of low-intensity and lower-level exercise of physical inactivity or prefers delayed gratification such as motor functional improvement by adherence to the recommended exercise (13, 29). As Bastos and colleagues have found, laziness leads to interrupting physical exercise (21). In other words, it means lack of patience in adherence to the exercise, and the stroke survivor is more likely to enjoy immediate gratification from "lying flat."

3.3 Cases

3.3.1 Model case

The model case is a real-life example involving all the defining attributes of the concept in a clinical context (22). A model case is the best example of concept application because it elaborates all of the defining attributes of the concept.

Mrs. Zhao, 62 years old, was suddenly affected by a stroke and was paralyzed on her left side. The rehabilitation regime was formulated before she was discharged as an acute inpatient. She engaged in the discussion actively and told the health professionals what exercises she prefers, such as walking, dancing, and swimming. She likes exercising in the park with other old friends, especially "square dancing." She does not like high-intensity exercise. As proposed by the rehabilitation facility and specialty health institutions, she could not accept intense exercises because of previous bad experiences, distance, and financial reasons. Based on the physical functional recovery, she likes to design short-term goals. She is more interested in new rehabilitation approaches and techniques and willing to accept the challenge of higher goals. She thinks they are all beneficial to enhancing the performance. Regarding adherence to exercise, she expressed nothing could interrupt exercise and she will not be lazy. Then the professionals tailored an individualized rehabilitation regimen and supervision schedule for her. This personalized program included her exercise preferences and had a satisfactory efficacy of adherence and motor recovery.

The case of Mrs. Zhao contains all the previously discussed defining attributes of exercise preference in stroke survivors.

3.3.2 Borderline case

Borderline cases are the scenarios that sit on the edge or boundary of a concept, making it difficult to definitively categorize. Those include most of the defining attributes, but one of them existing with a significant difference in time, intensity, or extent. Identifying borderline cases might reduce the ambiguity and inconsistencies between cases by clarifying attributes that are basic for the model (22).

Mr. Qian is 70 years old, has right hemiplegia and is living alone. Her right lower limb muscle strength was grade 2 at discharge. Walking or acquiring assistive devices to independently move were his main rehabilitation goals. After the acute care discharge, he was admitted to a rehabilitation facility. He has no particular preference for the exercise regimen. He faces various challenges in making decisions about his physical activity. He is open to trying various options but lacks strong motivation. He always wants to try the higher intensity exercises and repetitive exercise alone but falls into fatigue. He expressed the outcome expectation of motor recovery, but always felt lazy and unable to exercise. He lacks patience and prefers lying on the bed. Nursing staff paid more attention to him, including daily reminders, exercising in a direct supervision environment, and helping him visualize the restoration of motor function. After 2 weeks, he felt the guided exercises by professionals is effective to his motor recovery and perceived its meaningful outcome. Then he became active in exercising and his motor function gradually recovered, but the shoulder pain caused by high-intensity activities still affected him.

Mr. Qian's case involves the attributes of uncertainty about the type of exercise he prefers. He recognizes the potential benefits of regular physical activity, and sometimes lacks the motivation to engage in structured exercise due to feelings of frustration and fatigue. He is willing to explore different exercise options, but lacks patience in adherence. There is a contradiction between behavioral tendency and patience in adherence. Therefore, nursing staff should adopt nudging strategies to help him achieve exercise goals.

3.3.3 Related case

Related cases are instances that are in some way related to a concept but do not contain all the defining attributes. These help in understanding how the concept under study integrates into the network of concepts surrounding it (22).

Mrs. Sun is 52 years old and has right hemiplegia. Before stroke onset, she was a passionate "square dancing" lead dancer at their local community center square. After that, she was embarrassed by the disability caused by stroke and felt ashamed of meeting familiar people. In the initial phase, she refused to dance ever. She has been undergoing physiotherapy, and her therapist believes that dancing can be therapeutic if done with caution. Mrs. Sun modifies her dance mode to accommodate her post-stroke limitations. Instead of the fast-paced square dancing, she prefers slower dances like the ballroom dance, which requires less rapid movement and provides her with more stability. Her therapist introduced her to Tai Chi, emphasizing its benefits for balance and coordination, and she finds it meditative and beneficial, noticing that some of the movements remind her of dance.

The case of Mrs. Sun is related because it revolves around the attributes of priority of choice and behavioral tendency of a stroke survivor. Nevertheless, unlike the previous case where the individual was ambivalent about returning to a previous activity, Mrs. Sun actively seeks ways to adapt her zeal for dance to her current physical capabilities. The introduction of the exploration of Tai Chi as a complementary exercise adds layers to the concept of exercise preference in the population with stroke, emphasizing the affective priming and the potential for discovering new, beneficial activities post-stroke.

3.3.4 Contrary case

The contrary case, as opposed to the model case, does not contain any of the main attributes of the concept (22). The clear example of not reflecting the concept is described below.

Mr. Li is 72 years old and is affected by left hemiplegia. She lives in the rural area alone. He has a son who is working in a neighboring city. He feels like an burden for his son and has no sense about the motor functional recovery. After acute care discharge, he was transferred to home. He refused to engage in any form of exercise despite being aware of its benefits for him. He has a strong aversion to physical activity and prefers a sedentary lifestyle, sometimes reading books and watching television. Nurses and therapists emphasized the importance of exercise for his recovery and overall health. However, despite having the physical capability to engage in light exercises like walking or stretching, he shows no interest. He often states that he never exercised before the stroke and he does not see why he should start now. The idea of exercising, even mildly, brings up fears of another stroke or injuring himself. He is more comfortable staying in his familiar, sedentary routine.

Unlike the primary concept where stroke survivors have some form of exercise preference (whether clear, ambivalent, or adapted), the case of Mr. Li displays a complete lack of interest in any physical activity as he harbors deep-seated fears or beliefs against exercise post-stroke. No attributes of exercise preference were included in this case. In the daily life activity of Mr. Li's rehabilitation process, there is no choice, no effort to functional recovery, only the attitude of "1 day passes, 1 day counts."

3.4 Antecedents and consequences

3.4.1 Antecedents

Antecedents are incidents or events that must exist or occur prior to the concept's occurrence (22). Concept occurrence is always preceded by antecedents. Those events that occur before the concept's occurrence include patient-related antecedents, therapy-related antecedents, and environment-related antecedents. Patients' related antecedent includes individuals' capacity of mobility (11, 12, 14, 29), self-efficacy (9, 13–15), outcome expectancy (15), cognitive and emotional status (11, 13, 32), education (9, 12), beliefs in the benefits of exercise (13, 29), motivation (11, 21, 30), perception of meaningfulness (26, 29), pain (9), fatigue (13), personality traits (14), adaption (13, 26), and previous experience and habit (12). Therapy-related antecedents include therapeutic relationships with therapists (13, 26, 27), diversity and individualized exercise program (13, 26, 30, 33), and trust in rehabilitation providers (13, 26, 27). Environmental-related antecedents include financial and social support (11–13, 29), family support (13, 29), special incentives (32), and convenience and accessibility (13, 14, 26, 30).

3.4.2 Consequences

Consequences are those events that occur as an outcome of concept's occurrence (22). The consequences of exercise preference in stroke survivors are classified into the three categories: (i) patient-related, (ii) rehabilitation provider–related, and (iii) rehabilitation service system–related (3, 34, 35). Patient-related consequences include improved adherence to rehabilitation (9, 13, 15), enhanced the level of physical activity (9, 14), promoted motor recovery and quality of life of individuals with stroke (9, 36, 37). Rehabilitation provider–related consequences include providing a personalized regimen (9, 14, 21, 26), job satisfaction (26), professional identify (27), and communication promoting in patients and rehabilitation team (26, 27). Rehabilitation service system–related consequences include promoting the impeccable stroke rehabilitation service system construction (3, 14, 21), improved convenience and accessibility of rehabilitation delivery (34, 38, 39), and decreased in costs and improvement of rehabilitation services (9, 14).

The conceptual structure of the exercise preference in stroke survivors, including the relationships between antecedents, attributes, and consequences, is shown in Figure 2.

3.5 Empirical referents

The final step in concept analysis is defining empirical referents for the main attributes of the concept (22). Empirical referents are the categories of real phenomena that prove the occurrence of the concept itself. A problem must be proposed: How can I measure this concept or verify its existence in the real world? Empirical referents are the way in which defining attributes should be determined or assessed. They are not instruments for evaluating concepts (22). The purpose of the definitions of empirical referents is to accelerate the measurement of the concept, discern the concept, and to help the development of research instruments.

Exercise preference reflects value orientation and choice in the process of rehabilitation. Very few studies have been conducted on exercise preference in patients with stroke. Some of the studies only showed exercise preference as part of facilitators and barriers to engaging in exercise or rehabilitation (11, 13, 26), or has been proposed in formulating the rehabilitation regimes (9).

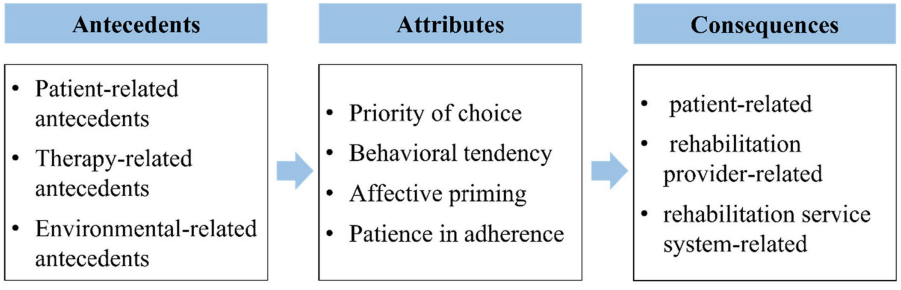

FIGURE 2
Conceptual structure of the exercise preference in stroke survivors.

The attributes of exercise preference in stroke survivors are measured using the tools for evaluating post-stroke conditions. Exercise Preference Questionnaire (*stroke*) (24) consists of 33 questions that are divided into three sections designed to capture exercise preferences and current exercise habits. There are 22 questions regarding different exercise preferences, which contain the domains of exercise with others, degree of structure of exercise program, independence, exercise location, and exertion. The Stroke Exercise Preference Inventory (SEPI) (25) consists of 13 preference items and an optional 9-item module on barriers to exercise participation after stroke. There are 7 exercise preference factors including supervision support, confidence challenge, health and well-being, similar others, exercise context, Home-alone, and music-TV. SEPI is the first stroke-specific tool for evaluating exercise preference in rehabilitation process and can be used in rehabilitation research and practice. Such large individual differences in exercise preference have been found in Bonner's investigation using SEPI, which may explain the poor uptake and adherence of one-size-fits-all exercise programs.

Based on literature review, the tools for measuring exercise preference in stroke survivors were more concerned with choice and behavior, focusing less on affective priming and patience in adherence. Exercise preference in stroke survivors is associated with not only their attitude and beliefs of patients but also emotional and psychological aspects. Therefore, attention to precise evaluation of this concept and construction of appropriate tools for stroke survivors become essential.

4 Discussion

There are four attributes as a result of the concept analysis derived from the critical literature review: (i) priority of choice, (ii) behavioral tendency, (iii) affective priming, and (iv) patience in adherence. We discuss the meaning and features of each attribute and analyze the antecedents and consequences in depth.

For individuals, engaging in exercise after a stroke is a long-term process that continues beyond hospital to discharge, highlighting the need to learn skills by stroke survivors and adhere to the prescribed rehabilitation regimen. The personalized exercise strategies have been effective in rehabilitation adherence and motor recovery (9, 29, 40). This means a specific exercise choice made by themselves based on what they like or more interested in (classified as "priority of choice" in this analysis). They are provided personalized education and supervision. Vadas et al. (13) showed that clinicians are advised to spend time learning about each individual's life circumstances, so they can tailor proposed exercise programs to patients' personal situations, preferences, and needs to have a positive effect on adherence. In an interpretive description qualitative study by Last et al. (26), the interviewed participants stated the following: "I enjoyed the therapy because I could have fun in there, and if the music was on I could dance … it was a happy place for me…," supporting this attribute. Participants want to be involved in planning and setting goals, which integrate their choice in it (41), so they enjoy and are motivated to engage in physical exercises. People who engaged in an exercise rehabilitation that they did not like show poor adherence and fall into bad mood. "They wanted me to work with the silly putty stuff there … I found that it hurt me more to use it…" (26) Priority of choice is a critical point in the development of stroke rehabilitation regimen and can have a significant impact on adherence.

The second attribute, "behavioral tendency," may emerge based on the "priority of choice" attribute. Task-specific exercise and repetition or mass practice is the critical principle of an effective exercise program for stroke survivors. How to design the task and exercise schedule to help them willing to be engaged and exercising? Individuals after suffering a stroke prefer exercising in controlled environments (21). In interviews described in the study by Mohd Nordin et al. (42) and Chen et al. (26), the participants gave the following statements: "I wanted to get moving because the physio was so good in hospital… but then when you come home there's nothing…" "I enjoy giving clarification on how to do the exercises. … she would watch, give some little corrections…," supporting this attribute. On the contrary, sometimes participants tend to refuse or lack motivation for a specific task of exercise. The interviews described in the study by Last et al. (26) and Tyagi et al. (43) show this: "… they got me to make a sandwich, use the toaster, make coffee—little things like that-they were not challenging at all for me." "A lot of it is setting up the equipment that we do not want to do. I hate doing it …" Behavioral tendency plays an important role in long-term rehabilitation process, which determines individuals' behavior intention in a certain exercise mode, including environments, supervision, and support. It also determines whom they want to exercise with, as well as if they want to engage in the exercise or adhere to the rehabilitation regimen (14, 15).

The affective response during exercise is an important factor for long-term exercise adherence (44). If the stroke survivors perceive the exercise or activity as positive and meaningful, they are more willing to perform that exercise or activity. This appeared as the third attribute, "affective priming." Repeated experiences of core affective reactions (i.e., the degree to which exercise or rehabilitation feels useful or useless) during exercise in stroke survivors and automatic affective valuations would be generated, which influence their decision to engage in exercise behavior (13, 15). In an interview described in the study by Stark et al. (45): "The first time … I managed (it) once, toward the end of the study I managed (it) 15 times in 30 s. It was the highlight of the study." "We had our fun and we were happy when things got better." Patients were motivated when they subjectively experienced progress or their caregivers observed the progress. Nevertheless, as the automatic affective valuations are negative, they tend to drop out, as a participant mentioned in an interview by Last, et al.: "No, because … it's not gonna do nothing for me. I'm not gonna get nothing out of it … I do not think it's helping me" (26).

The last attribute of exercise preference in stroke survivors was "patience in adherence." In the rehabilitation process, stroke survivors made a choice of exercise regimen that they like and accept. They engage in a series of activities with a sense of emotional involvement or commitment with a deliberate application of effort (11). As the stroke became chronic, their motivation level declined. Some of them act lazy, as described in a study by Mohd Nordin et al. (42) in focus group discussions: "Initially, I was motivated. After several months, I do not feel that excited anymore." "I feeling lazy at home…" Bastos et al. (21) pointed out that laziness is the crucial factor that leads to interruption in physical exercise. Some of the patients with more severe disability caused by stroke also weighed their current efforts

against future benefits, and thus choose to continue exercising or give up (46). More present-oriented individuals prefer an immediate, smaller reward, as observed by Forgea et al. (11) who reported that short-term conservative goals with an orientation toward physical functioning are preferred by stroke survivors. However, patients more concerned with their future were more likely to exhibit behaviors associated with positive recovery, as described by Chen et al. (30) in a qualitative study: "We wished to view their data in the long run."

5 Limitations

Exercise rehabilitation after stroke is a long-term, dynamic, and complex process involving many factors. Exercise preference varies between stroke survivors and changes over time (10). Therefore, future research could focus on the different stages of stroke rehabilitation to better understand the exercise preference in stroke survivors and thus provide a more in-depth exploration of exercise rehabilitation after stroke.

6 Conclusion

This study presented an evidence-based and operational definition of exercise preference in stroke survivors and its antecedents, attributes, consequences, and empirical referents. It helped clarify the ambiguous concepts that are used in the context of exercise instead of preference. The operational definition of exercise preference in stroke survivors reflects the patient's choice, tendency, affective response, and attitude toward engagement in the recommended rehabilitation regimen. Research regarding concept derivation of exercise preference in stroke survivors can help nurses and rehabilitation service providers to understand this concept better and pay more attention to it in the process of rehabilitation to promote individualized exercise regimen and enhance adherence to rehabilitation. In addition, this may facilitate the development of instruments for assessing exercise preference in stroke survivors and the construction of theory-based intervention programs that can improve adherence to exercise rehabilitation.

Author contributions

YD: Conceptualization, Data curation, Formal analysis, Writing – original draft. HS: Formal analysis, Writing – review & editing. KJ: Formal analysis, Writing – review & editing. YH: Formal analysis, Writing – review & editing. MA: Writing – review & editing. QW: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1326649/full#supplementary-material

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Adrian Wayne Midgley,
Edge Hill University, United Kingdom

REVIEWED BY
Mehmet Özkeskin,
Ege University, Türkiye
Ye Zhao,
Krirk University, Thailand

*CORRESPONDENCE
Chunping Du
✉ duchunping118@wchscu.cn
Yihao Liu
✉ yl531@exeter.ac.uk

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

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Evaluating the reliability and validity of a Chinese version of the performance-oriented mobility assessment among patients with chronic stroke

Ming Zhong[1†], Yongnan Jing[2†], Xiaofeng Zhao[2], Ying Gao[3], Yanju Jiang[2], Yihao Liu[4*] and Chunping Du[5,6*]

[1]Department of Sports Medicine, Sichuan Provincial Orthopedics Hospital, Chengdu, China, [2]Department of Rehabilitation, Shanghai MCC Hospital, Shanghai, China, [3]School of Acupuncture-Moxibustion and Tuina and School of Health Preservation and Rehabilitation, Nanjing University of Chinese Medicine, Nanjing, China, [4]School of Psychology, Faculty of Health and Life Sciences, University of Exeter, Exeter, United Kingdom, [5]Rehabilitation Medicine Center and Institute of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu, China, [6]Key Laboratory of Rehabilitation Medicine in Sichuan Province, West China Hospital, Sichuan University, Chengdu, China

Background: The Performance-Oriented Mobility Assessment (POMA) is a reliable instrument for evaluating the mobility (balance and gait) of patients with chronic stroke to manage their risk of falling; however, it has not been validated among Chinese patients with stroke. This study aimed to evaluate the reliability and validity of the Chinese POMA in patients with stroke.

Methods: The POMA was applied to volunteer patients with stroke from the Shanghai MCC Hospital. The patients underwent the Chinese POMA, Berg balance scale (BBS), and timed up and go (TUG) tests on the first day of inpatient treatment. The same physician repeated the tests the next day to assess test–retest reliability, and upon the patient's discharge from the inpatient department, two different physicians measured inter-rater reliability.

Results: The study involved 76 patients with stroke (age: 62.04 ± 9.76 years; 34.2% female). The results showed that the Chinese POMA had good overall internal consistency (σ=. 875), with a moderate consistency between its two subscales (balance $\sigma = 0.875$; gait $\sigma = 0.668$). The individual items showed high test–retest (ICC = 0.997) and inter-rater reliability (ICC = 0.988). The content validity test showed high correlations between the Chinese POMA, the BBS (rs = 0.70), and the TUG (rs = −0.75). However, the confirmatory factor analysis suggested that the two-factor model (balance and gait) was mediocre.

Conclusion: The Chinese POMA showed acceptable reliability and validity for evaluating mobility (balance and gait) in Chinese patients with stroke in terms of their risk of falling. However, further evaluation of the two-factor model (balance and gait) is required.

KEYWORDS

stroke, performance-oriented mobility assessment, risk-of-fall, balance, gait, reliability

1 Introduction

According to the latest reports estimating the global prevalence of stroke, the age-standardized prevalence of stroke in China is estimated to be 2% among the Chinese population, accounting for 40% of the world's stroke cases (1), and the incidence rate is estimated to be 14.48%. This indicates approximately 28 million active stroke cases in China that need treatment and medical care. One of the risk factors for stroke mortality is the risk of falls because patients with stroke often have impaired motor function (2). Consequently, instruments are required to assess mobility and manage the risk of falls in Chinese patients with stroke.

The Performance-Oriented Mobility Assessment (POMA) is suggested to be a reliable instrument for mobility (balance and gait) among patients with stroke (3); it was initially designed to measure mobility (balance and gait) among the elderly (4, 5). The POMA has also been translated and validated in other languages (6, 7). A validation investigation of Turkish and Persian POMA translations was conducted among healthy elderly individuals and yielded high reliability and validity. In both reliability and validity studies, the POMA was measured for internal consistency, test–retest reliability, inter-rater reliability, and content validity in correlation with the Berg Balance Scale (BBS) (8) and the Timed Up and Go test (TUG) (9). Specifically, the BBS is considered a useful instrument for measuring balance ability in patients with stroke (3, 10), and the TUG test is considered to reflect the functional ability and risk of falls in patients with stroke (3, 11). Consequently, these two measurements have been used in previous reliability studies of the POMA as an external reference for content validity.

The POMA has been widely used and translated into many languages and has been recommended by the Chinese Medicine Association to assess mobility for Chinese seniors (12). A formal validation of the Chinese POMA has not been conducted for patients with chronic stroke, which could be a potentially helpful instrument for determining the prevalence of Chinese patients with stroke. The current study aimed to translate the POMA into Chinese and evaluate its reliability and validity using a method similar to that used in relevant research.

2 Method

2.1 Participants

The inclusion criteria were participants who were (1) native Mandarin Chinese speakers, (2) diagnosed with chronic stroke based on brain imaging, (3) able to comprehend the (simplified) Chinese semantic context, and (4) able to walk with aid. The exclusion criteria were participants who (1) had any self-reported history of comorbidities that could not be mobilized, such as osteoarthritis, cerebellar atrophy, or heart disease, or (2) had hearing or cognitive impairment, including those with language comprehension screened with the post-stroke language assessment sets (13). The participants signed up for the experiment as volunteers and did not receive any payment for their participation.

2.2 Procedure and material

The procedure of the current experiment was similar to that of a previous study evaluating the reliability of the POMA among patients with stroke (3), following the COSMIN checklist. The target sample size was estimated using the formula by Bonett (14):

$$n = 8 \times z^2_{\alpha/2} \times \frac{\left\{(1-\tilde{\rho}_I)^2 \times \left[1+(k-1)\times\tilde{\rho}_I\right]^2\right\}}{\left[k\times(k-1)\times w^2\right]} + 1$$

Where (1) n is the target sample size; (2) σ is the significance level (default = 0.05); (3) $z_{\sigma/2}{}^2$ is the point on a standard normal distribution exceeded with probability at σ/2 (fixed at 1.96^2); (4) $\tilde{\rho}$ is the expected intraclass correlation coefficient (ICC); (5) k is the number of instrument scales; (6) w is the desired tolerance width. The calculation was conducted using an online sample size calculator developed for reliability studies (https://wnarifin.github.io/ssc/ssicc.html) based on the above formula (15). Accordingly, previous studies suggested the ICC ranged from 0.75 to 0.97 (6, 7), with no estimated dropping rate. Consequently, we would expect a similar ICC of approximately 0.85 with a 0.1 tolerance width. The calculator estimated a minimum sample size of 23 using the 3 instruments used in the current study. However, validation studies of questionnaires generally require a sample of 5 or 10 times the number of items. In this case, evaluating the 16-item POMA is expected to reach at least a sample of 80, which would be our target.

The participants were recruited from the Rehabilitation Department at Shanghai MCC Hospital based on the inclusion criteria, and they consented and were screened for eligibility by three physiatrists based on the exclusion criteria. Inpatients were registered with a code for their individual hospital beds at administration, and this code was used in the current study to identify participants' data. The physicians contacted the participants through their bedcode because there were multiple waves of measurements in the current study. Consequently, the researchers were blinded when accessing the data through bed codes and could not access the participants' personal information during or after the experiment.

The physicians conducting the ratings underwent a structured training program to ensure accurate and consistent administration of the Chinese POMA. The training began with a comprehensive introduction to the assessment tool, including detailed explanations of the balance and gait items. The physicians were then trained to administer each item task step-by-step, led by a senior physiotherapist (YJ). The physicians participated in practical demonstrations by the senior physiotherapist administering the assessment on patients, followed by hands-on practice. During this practice, each physician administered the POMA to individuals simulating stroke-related mobility impairments, receiving real-time feedback from the senior physiotherapist. The focus of the training was on understanding each item's criteria, correct task execution, and unbiased, objective scoring. Once the physicians and experiment settings were well-prepared, eligible participants underwent the measurements in the following order:

The participants' gait and balance were measured using the Chinese POMA on the first day of admission to the inpatient department. The Chinese POMA preserves the same structure as the original English version, containing 16 items assessing participants' gait and balance. The POMA ranges from 0 to 28,

including seven items assessing gait ranging from 0 to 12 and nine items assessing balance ranging from 0 to 16. A score of <24 indicates a potential impairment in balance, and a score of <15 indicates a potential risk of falls. An independent physiatrist conducted the assessment by instructing the participants to perform movements on the POMA and scored them from 0 to 2 based on the participants' performance. The participants rested for 10–15 min after each assessment. The Chinese POMA and the original English versions are attached in the Supplementary material.

Participants were then assessed using the BBS to re-evaluate balance by another independent physiatrist. The BBS consists of 14 items scored from 1 to 4 to assess balance in the elderly with good reliability (8, 16). The scale scores ranged from 0 to 56. Scoring from 0 to 20 indicates poor balance, potentially wheelchaired, and the risk of falls; scoring from 21 to 40 indicates some balance to mobilize with aid and the risk of falls; and scoring from 41 to 56 indicates a fair balance to mobilize without aid. An independent physiatrist instructed the participants to perform movements on the BBS and assessed their performance.

After the BBS, a third independent physiatrist measured the participants' balance using the TUG test (9, 17). The TUG required the participants to stand up from an armed chair with back support; the chair was 46 cm high, with an arm 21 cm high. Participants were instructed to sit on a chair with arms resting on the chair arms and back supported, stand up upon instruction, walk toward a marked position 3 meters in front of the chair, and walk back to sit on the chair again. An independent physiatrist recorded the participants' time spent on the test. The test was repeated three times with a 1 to 2-min break. The results are presented as the mean time spent on the three tests.

Each set of ratings takes a long time and requires considerable effort from the patients. Considering ethics and clinical practice, it is impractical to measure the patients twice on the same day, either to rapidly conduct multiple trials in the upcoming days, because it may develop the practice effect that patients would improve their performance with rapid physical assessments (18, 19) or bias the consistency in reliability tests. The same physiatrist measured the Chinese POMA the next day to estimate the test–retest reliability. Test–retest reliability aims to determine the extent to which unchanged scores are the same for repeated measurements (20). However, since the patients were receiving inpatient treatment, it would have been impossible to compare the POMA results from baseline with the results after some period of time because the POMA outcomes would have been improved with the treatment they received. Therefore, the current test–retest reliability used the outcome from the second day of administration to inpatient treatment, which is consistent with another POMA reliability study (3). To determine the inter-rater reliability, two independent physiatrists measured the Chinese POMA again on the first and second days after the participants were discharged from inpatient treatment. Consequently, as summarized in Figure 1, the Chinese POMA was measured four times by two raters (POMA T1, T2, T3, and T4), where two were measured before (POMA T1 and T2) and two after inpatient treatment (POMA T3 and T4), and The BBS and TUG were measured on the first day of administration to the inpatient treatment (after POMA T1).

2.3 Statistical analysis plan

Statistical analyses were conducted in SPSS v29 with AMOS (IBM Corp., Armonk, NY, USA). The pilot data were entered into the reliability test estimated using Cronbach's α coefficient to determine its internal consistency and Pearson bivariate correlation with BBS to check for its content validity quickly. Regarding the formal reliability test data, the individual POMA item ratings of four measurements were entered into the reliability test estimated using Cronbach's α coefficient to determine its internal consistency. Then, the POMA ratings measured by the same physiatrists on the first and second days of patient admission to the inpatient department were entered into the test–retest reliability test estimated using the ICC (POMA T1 vs. T2). ICC absolute agreement was used because the current measurements obtained their own mean score (21) for patients with different stroke severities. The ICC of the test–retest reliability and the standard error of the mean (SEM) were used to calculate the minimal detectable change (MDC) at a 95% confidence interval using the following formula (22):

$$MDC_{95\%} = 1.96 \times \sqrt{2} \times SEM$$

SEM was expressed using the following formula, where SDtrial 1 refers to the standard deviation of the first trial of POMA (POMA T1):

$$SEM = SD_{trial1} \times \sqrt{1 - ICC}$$

The POMA ratings measured by two independent physiatrists on the first and second days after patient discharge from the inpatient department were entered into an inter-rater reliability test estimated using the ICC (POMA T3 vs. T4).

After evaluating the reliability, confirmatory factor analysis (CFA) was conducted to evaluate the validity of the two components (gait and balance) of the POMA using SPSS 29 AMOS. A lower Chi^2 value indicates a better fit. A value of Root Mean Square Error of Approximation with the 90% confidence interval (RMSEA[90%]) ≤ 0.05 indicates a close fit, RMSEA [90%] between 0.05 and 0.08 indicates a reasonable fit, and RMSEA [90%] between 0.08 and 0.10 suggests a mediocre fit. RMSEA[90%] > 0.10, indicative of a poor fit. Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) close to 1 indicate a good fit, with values ≥0.95 suggesting an excellent fit and values between 0.90 and 0.95 indicating an acceptable fit. Finally, Standardized Root Mean Square Residual (SRMR) ≤ 0.08 indicates a good fit. A lower SRMR suggests a model that better reproduces the observed covariances.

Finally, the POMA results were entered into a Pearson bivariate correlation with the BBS and TUG results to evaluate external construct validity. A Cronbach's α and ICC range from 0.6 to 0.75 is considered moderate, a Cronbach's α and ICC range from 0.75 to 0.9 is considered good, and a Cronbach's α and ICC greater than 0.9 is considered excellent (23, 24). Regarding the correlation between the Chinese POMA, BBS, and TUG, a coefficient range from 0.6 to 0.8 is considered strong, and a coefficient greater than 0.8 is considered very strong (25).

2.4 Ethics statement

The ethics application was submitted and approved by the ethics committee of the Shanghai MCC Hospital (Reference No:

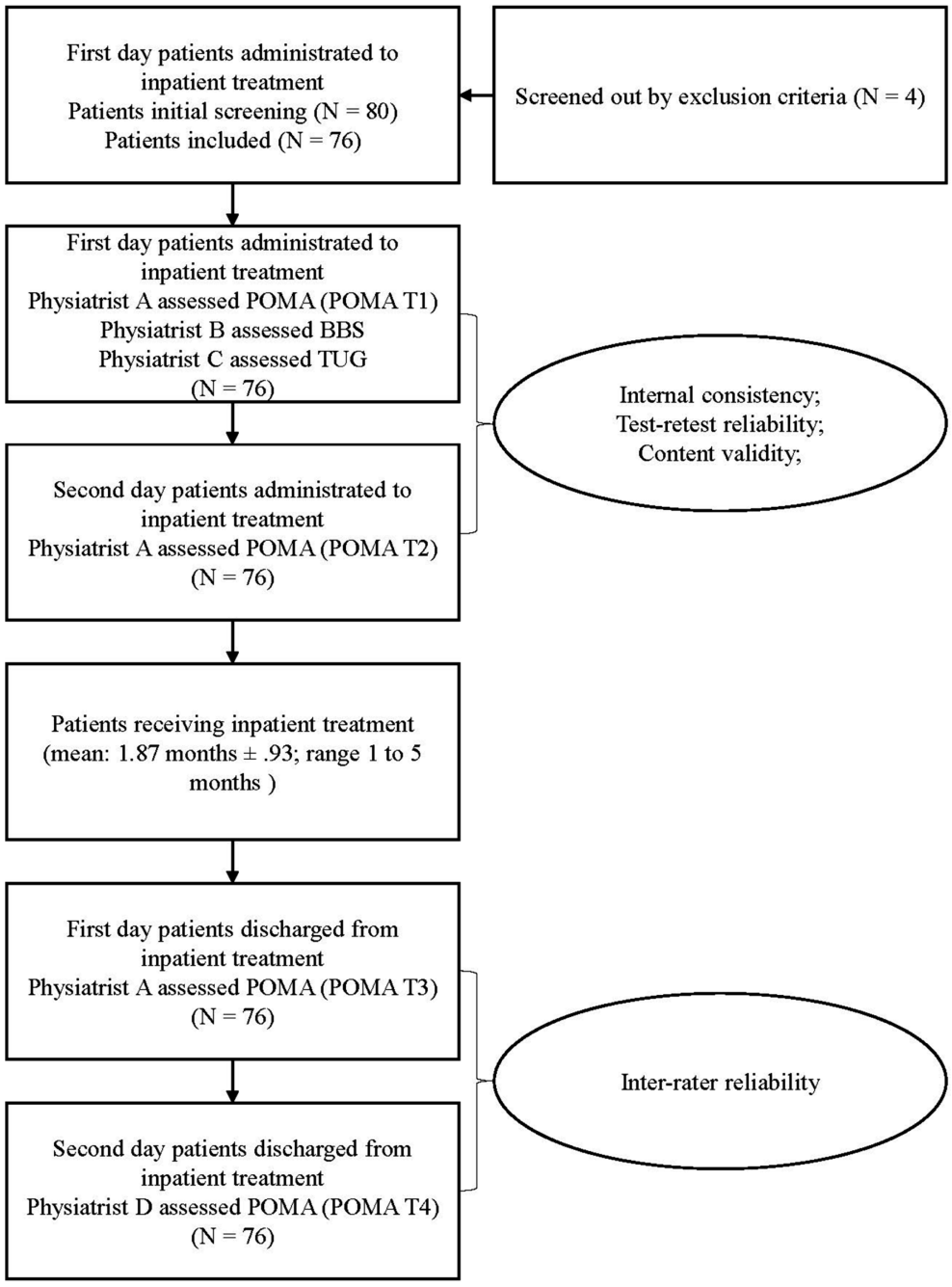

FIGURE 1
Experiment procedure flow.

ZYLS202001), where the data was collected. Participants provided written informed consent before enrolment in the experiment.

3 Results

3.1 Participants characteristic information

Eighty participants who met the inclusion criteria were recruited. Four participants violated the exclusion criteria and were excluded from the study, leaving 76 eligible participants for analysis, including 50 men and 26 women (34.2% women). Among these, 28 had left hemiplegia and 48 had right hemiplegia. Detailed characteristics of the participants are presented in Table 1.

3.2 Internal consistency

As shown in Table 2, the overall ratings of the Chinese POMA yielded Cronbach's α from 0.875 to 0.901, suggesting a good internal consistency across four measurements. The balance subscale yielded Cronbach's α ranged from 0.842 to 0.930, and gait subscales yielded Cronbach's α ranged from 0.668 to 0.736, suggesting a moderate to good internal consistency across four ratings.

3.3 Test–retest reliability

As shown in Table 3, the overall POMA scale yielded excellent test–retest reliability (ICC = 0.997), with an $MDC_{95\%}$ of 1. The balance and gait subscale scores also yielded excellent test–retest reliability (ICC = 0.997, ICC = 0.993, respectively). The individual POMA items yielded a high ICC from 0.878 to 983, suggesting good-to-excellent test–retest reliability.

TABLE 1 Participants' characteristic information.

	Mean (SD)	Range
Age	62.04 ± 9.76	29–82
Stroke duration	4.91 ± 2.65	1–12 (months)
Inpatient duration	1.87 ± 0.93	1–5 (months)
POMA T1	16.99 ± 5.45	4–27
POMA T2	17.05 ± 5.49	4–27
POMA T3	21.21 ± 5.72	4–28
POMA T4	21.12 ± 5.71	4–28

POMA T1 and POMA T2 refer to the POMA measured on the first and second day of administration to the inpatient, respectively, rated by the same physiatrist; POMA T3 and POMA T4 refer to the POMA measured on the first and second day of discharge from the inpatient by two independent physiatrists. Please contact the corresponding author for the detailed raw data of individual items.

3.4 Inter-rater consistency

As shown in Table 4, the inter-rater reliability tests between the ratings from the two individual physiatrists 2 days after inpatient treatment yielded high intraclass correlation coefficients of the overall POMA ratings (ICC = 0.996), POMA balance subscale (ICC = 0.999) and POMA gait subscale (ICC = 0.988), suggesting a high (post-treatment) inter-rater consistency.

3.5 Confirmatory factor analysis

The individual POMA items were entered into a confirmatory factor analysis with goodness-of-fit and maximum likelihood estimation to evaluate their content validity. The first question (item

TABLE 2 Internal consistency of the Chinese POMA scale.

Chronbach's σ	Day 1 on inpatient	Day 2 on inpatient	Day 1 post-inpatient	Day 2 post-inpatient
Balance	0.930	0.842	0.871	0.871
Gait	0.688	0.668	0.717	0.736
Overall	0.879	0.875	0.901	0.901

TABLE 3 Test–retest reliability test.

Item	POMA T1 mean	T1 SD	POMA T2 mean	T2 SD	Intraclass correlation coefficient	[95% CI]		$MDC_{95\%}$
Balance1	1.00	0.00	1.00	0.00	1.000			
Balance2	1.47	0.58	1.50	0.58	0.980	[0.969]	[0.987]	
Balance3	1.64	0.58	1.64	0.58	1.000			
Balance4	1.30	0.61	1.30	0.61	0.982	[0.971]	[0.988]	
Balance5	1.26	0.53	1.26	0.53	1.000			
Balance6	1.20	0.61	1.20	0.59	0.972	[0.975]	[0.983]	
Balance7	0.43	0.50	0.43	0.50	0.981	[0.970]	[0.988]	
Balance8	0.57	0.62	0.58	0.62	0.991	[0.986]	[0.994]	
Balance9	1.47	0.50	1.46	0.53	0.961	[0.939]	[0.975]	
Balance total	10.36	3.22	10.38	3.20	0.997	[0.995]	[0.998]	0.5
Gait1	0.83	0.38	0.83	0.38	1.000			
Gait2	2.84	1.11	2.82	1.13	0.978	[0.966]	[0.986]	
Gait3	0.14	0.35	0.17	0.47	0.872	[0.798]	[0.919]	
Gait4	0.38	0.49	0.41	0.50	0.942	[0.909]	[0.964]	
Gait5	1.16	0.59	1.16	0.59	0.980	[0.969]	[0.988]	
Gait6	1.12	0.65	1.12	0.65	0.984	[0.975]	[0.990]	
Gait7	0.16	0.37	0.17	0.41	0.878	[0.807]	[0.922]	
Gait total	6.63	2.54	6.67	2.57	0.993	[0.990]	[0.996]	0.5
POMA total	16.99	5.45	17.05	5.49	0.997	[0.996]	[0.998]	1

Test–retest reliability was conducted between the POMA ratings on the first and second days of patients' administration to inpatient treatment by the same physiatrist ($N = 76$).

TABLE 4 Inter-rater reliability test.

Item	Inter-rater intraclass correlation coefficient [95% CI]		
Balance	0.996	[0.994]	[0.998]
Gait	0.999	[0.998]	[0.999]
Overall	0.988	[0.981]	[0.993]

The inter-rater reliability test was conducted on the first and second days of patients' discharge from inpatient treatment by two independent physiatrists ($N = 76$).

1 for the balance subgroup) was excluded from the analysis for it had no variance, which all participants reported as "Steady, safe" and scored 1 on the item. As shown in Table 5, the two-factor model yielded a mediocre fit in the RMSEA model (0.095) and an acceptable fit in the CFI model (0.857) or the TLI model (0.831). An SRMR of 0.82 indicated a marginal fit. The CFA results suggested that the constructs of the two subscale components were acceptable. The maximum likelihood estimation is shown in Figure 2.

TABLE 5 Goodness-of-fit statistics for the two-factor models.

Fit model	Two-factor model
Chi (df)	149.407 (89)
RMSEA [90% CI]	0.095 [0.068 0.121]
AIC	211.407
BIC	283.660
CFI	0.857
TLI	0.831
SRMR	0.082

3.6 Construct validity

Finally, the Chinese POMA and its subscales were entered into the Pearson correlation coefficient with the BBS and TUG results to evaluate their construct validity. As shown in Table 6, the Chinese POMA and its subscales yielded strong positive correlations with the BBS and negative correlations with the TUG test, suggesting satisfactory construct validity.

4 Discussion

The current study tested the reliability and validity of the Chinese version of the Performance-Oriented Mobility Assessment (POMA) among 76 patients with chronic stroke (mean age: 62.04 ± 9.76 years; 34.2% female) with similar procedures and material to previous studies (3, 6, 7). The test–retest reliability was assessed on the first and second days of patient administration for inpatient treatment by the same physiatrist, and the inter-rater reliability was assessed on the first and second days of patient discharge from inpatient treatment by two independent physiatrists. The construct validity was measured based on external correlations with the BBS and TUG on the first day of inpatient treatment following the POMA. The results suggested that the Chinese POMA obtained a good overall internal consistency between 0.875 and 0.901 across the trials but a moderate internal consistency of its two subscales (balance and gait) between 0.688 and 0.930. The Chinese POMA showed high reliability between the test–retest trials (ICC = 0.872 to 0.997), an overall MDC95% of one score, and high inter-rater consistency (ICC = 0.988). However, the confirmatory factor analysis suggested a mediocre fit for the two-factor model (balance and gait). Finally, the correlation between the Chinese POMA, BBS, and TUG yielded satisfactory construct validity with moderate to high R coefficients. The details of this process are discussed below.

The overall internal consistency of the Chinese POMA among patients with stroke was good (0.901), consistent with the Turkish (0.88) (6) and Persian (0.94) versions of the POMA (7). Consistency may vary depending on stroke severity. Some motor functions were influenced more among some patients than others, which caused minor inconsistencies between the items. The internal consistency of the POMA in measuring mobility (balance and gait) in patients with stroke has not been reported in a previous reliability study of the original English version (3). Consequently, this study suggests a preliminary result that the Chinese POMA has good internal consistency. Further investigation is required to replicate the internal consistency of the POMA in both Chinese and the original English, measuring mobility (balance and gait) in patients with chronic stroke.

The Chinese POMA obtained good test–retest reliability (POMA overall ICC = 0.997; Balance ICC = 0.997; Gait ICC = 0.993), which is consistent with Turkish (POMA overall ICC = 0.94; Balance ICC = 0.88; Gait ICC = 0.92) and Persian versions of the POMA (POMA overall ICC = 0.97; Balance ICC = 0.95; Gait ICC = 0.96) (6, 7). The Chinese POMA also obtained good inter-rater reliability (POMA overall ICC = 0.996; Balance ICC = 0.999; Gait ICC = 0.988), which is consistent with Turkish (POMA overall ICC = 0.86; Balance ICC = 0.86; Gait ICC = 0.80) and Persian versions of the POMA (POMA overall ICC = 0.92; Balance ICC = 0.90; Gait ICC = 0.90) (6, 7). However, the overall MDC95% of the Chinese POMA was 1 with a standard deviation of 5.4, which was much smaller than the previously estimated English POMA among patients with stroke (3) of 6.0, with a standard deviation of 5.2 and also smaller than the Persian version of 3, with a standard deviation of 6.23 (7). Theoretically, MDC95% should mean a statistical meaning that patients rated the number of points not due to chance but due to an actual change in performance (26). The current results for MDC95% at 1 point should be interpreted with caution because we reported a high ICC of 0.997, which resulted in a very low standard error and led to a low MDC95%. Therefore, the results were likely caused by a bias in the statistical numbers despite all other results being comparable to those of reliability studies in different languages. Future studies should clarify this point by including larger sample sizes.

The construct validity measured using CFA showed a mediocre fit for the current two-factor model (balance and gait). This result is also in line with the previous Persian translation of the POMA (7), although the Turkish validation study did not conduct a factor analysis. The original development of the POMA did not engage in any factor analysis in the first place (4, 5), in which the factors of balance and gait were more theory-based than data-based. However, as Moulodi, Azad (7) suggested, the purpose of the POMA scale reliability is not to investigate a data-driven model with statistical figures but to determine whether it measures mobility. Future studies could investigate more fitted models to evaluate the POMA.

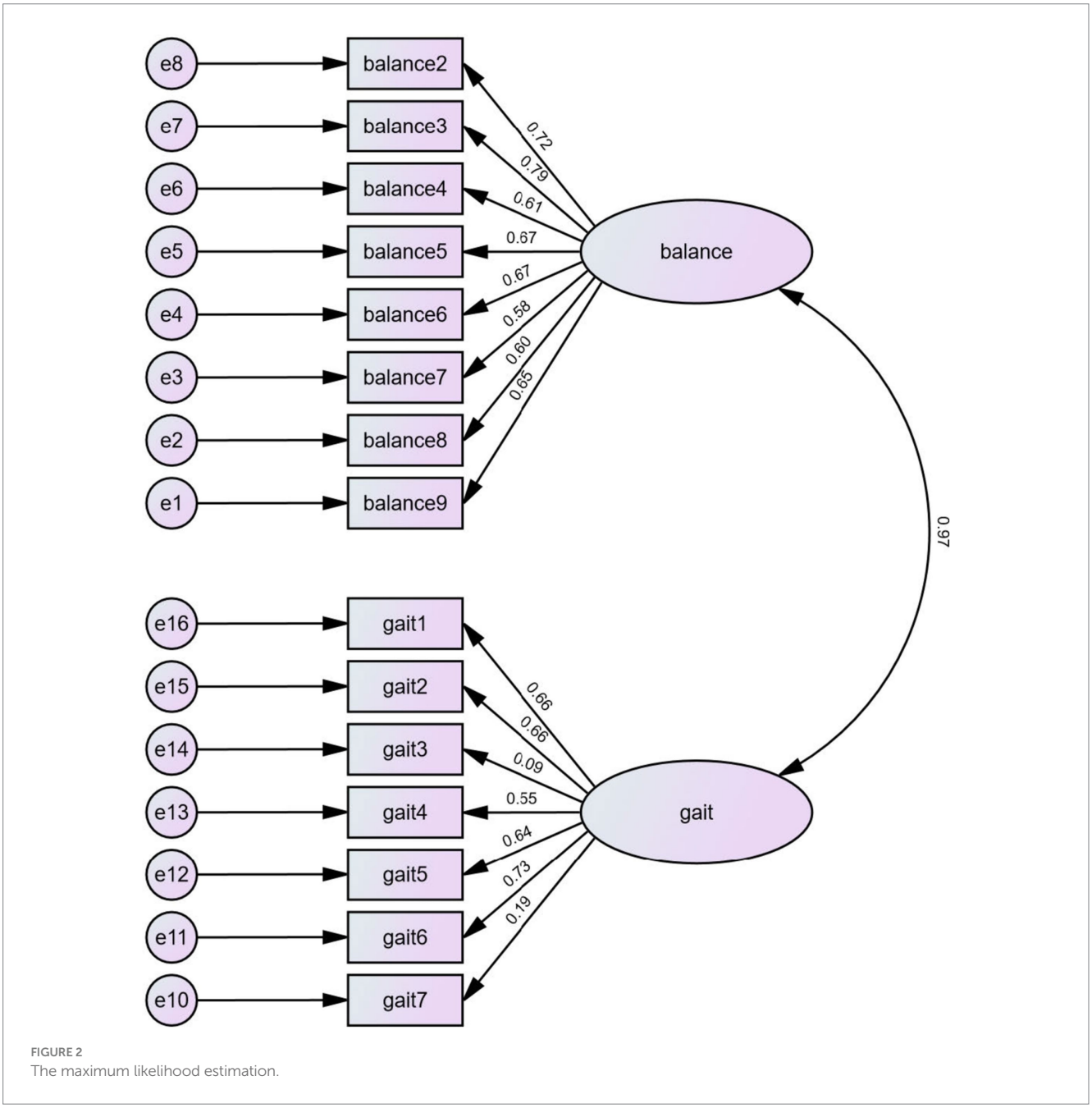

FIGURE 2
The maximum likelihood estimation.

TABLE 6 Correlation matrix of the Chinese POMA and subscales with BBS and TUGT.

	Berg Balance Scale		Timed Up and Go Test	
POMA Total T1	rs = 0.696	ps <0.001	rs = −0.752	ps <0.001
POMA Balance T1	rs = 0.762	ps <0.001	rs = −0.676	ps <0.001
POMA Gait T1	rs = 0.528	ps <0.001	rs = −0.757	ps <0.001

POMA Total T1, POMA Balance T1 and POMA Gait T1 refer to the total score of POMA, the balance and the gait subscale, respectively, measured on the first day of administration to inpatient treatment ($N = 76$).

Finally, the Chinese POMA showed moderate-to-high content validity in correlation with BBS (POMA overall rs = 0.696; Balance rs = 0.762; Gait rs = 0.528) and TUG scores (POMA overall rs = −0.752; Balance rs = −0.676; Gait rs = −0.757), similar with Turkish (BBS: POMA overall rs = 0.866; Balance rs = 0.840; Gait rs = 0.770; TUG: POMA overall rs = −0.759; Balance rs = −0.675; Gait rs = −0.772) and Persian versions of the POMA (BBS: POMA overall rs = 0.90; Balance rs = 0.89; Gait rs = 0.85; TUG: POMA overall rs = −0.75; Balance rs = −0.73; Gait rs = −0.73) (6, 7). This is consistent with the results of testing the validity of the original English POMA in patients with stroke (3). This result suggests that the Chinese POMA could provide a valid prediction of fall risk as well as other similar measurements.

This study had two important limitations. First, we included a limited sample size of 76 patients with chronic stroke. Validation studies of questionnaires generally require a sample of 5 or 10 times the number of items, which should be 80 in our case. This number was first reached but dropped 4 patients meeting exclusion criteria. From the statistical approach, the current results obtained high correlation coefficients ($r > 0.9$), indicating the high statistical power of the tests with a larger sample size than the estimated minimum (14, 15). All

available patients met our criteria during the past 2 years. However, 76 patients with stroke may not be enough to be generalized to all chronic stroke populations in terms of their characteristics, such as age (mean = 62.04 ± 9.76 years) and sex (34.2% female). Therefore, this study could not address solid conclusions on whether the POMA is valid among generalised patients with stroke or suggests a minimum score to detect performance changes, which requires future investigation. Second, as explained in the Methods section, considering clinical practice and ethics, the current study assessed inter-rater reliability after the patients were discharged from inpatient treatment. Consequently, the trial reflected post-treatment inter-rater reliability among patients with stroke, although it may diverge from pre-treatment inter-rater reliability. Although a previous study did not raise such a concern with a similar design (3), it would be better to clarify the pretreatment inter-rater reliability of the Chinese POMA in future studies.

In summary, this study examined the reliability and validity of the Chinese version of the POMA in patients with chronic stroke. The results demonstrated good internal consistency, test–retest reliability, inter-rater reliability, and content validity, supported by external correlations. However, the two-factor model of the balance and gait subscale structure revealed only moderate fit. Given these limitations, a cautious conclusion is warranted, defining the reliability of the Chinese POMA within the specific scope of the patient population tested. Future research should focus on further exploring the factorial structure, minimal detectable change (MDC95%), and pre-treatment inter-rater reliability using a more generalized and diverse sample of chronic stroke patients.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Shanghai MCC Hospital ethics committee (Reference No: ZYLS202001). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MZ: Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. YoJ: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – review & editing. XZ: Data curation, Investigation, Resources, Writing – review & editing. YiG: Data curation, Investigation, Writing – review & editing. YaJ: Data curation, Investigation, Writing – review & editing. YL: Formal analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. CD: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1461069/full#supplementary-material

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EDITED BY
Felipe Cunha,
Rio de Janeiro State University, Brazil

REVIEWED BY
Arthur Sá Ferreira,
University Center Augusto Motta, Brazil
Guilherme Fonseca,
Rio de Janeiro State University, Brazil

*CORRESPONDENCE
Xuejing Li
✉ lixuejing914@163.com

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Predicting sarcopenia risk in stroke patients: a comprehensive nomogram incorporating demographic, anthropometric, and biochemical indicators

Yufan Pu, Ying Wang, Huihuang Wang, Hong Liu, Xingxing Dou, Jiang Xu and Xuejing Li*

The Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an, Jiangsu, China

Objective: Although there is a strong correlation between stroke and sarcopenia, there has been a lack of research into the potential risks associated with post-stroke sarcopenia. Predictors of sarcopenia are yet to be identified. We aimed at developing a nomogram able to predict sarcopenia in patients with stroke.

Methods: The National Health and Nutrition Examination Survey (NHANES) cycle year of 2011 to 2018 was divided into two groups of 209 participants—one receiving training and the other validation—in a random manner. The Lasso regression analysis was used to identify the risk factors of sarcopenia, and a nomogram model was created to forecast sarcopenia in the stroke population. The model was assessed based on its discrimination area under the receiver operating characteristic curve, calibration curves, and clinical utility decision curve analysis curves.

Results: In this study, we identified several predictive factors for sarcopenia: Gender, Body Mass Index (kg/m^2), Standing Height (cm), Alkaline Phosphatase (ALP) (IU/L), Total Calcium (mg/dL), Creatine Phosphokinase (CPK) (IU/L), Hemoglobin (g/dL), and Waist Circumference (cm). Notably, female patients with stroke exhibited a higher risk of sarcopenia. The variables positively associated with increasing risk included Alkaline Phosphatase, Body Mass Index, Waist Circumference, and Hemoglobin, while those negatively associated with risk included Height, Total Calcium, and Creatine Phosphokinase. The nomogram model demonstrated remarkable accuracy in distinguishing between training and validation sets, with areas under the curve of 0.97 and 0.90, respectively. The calibration curve showcased outstanding calibration, and the analysis of the decision curve revealed a broad spectrum of beneficial clinical outcomes.

Conclusion: This study creates a new nomogram which can be used to predict pre-sarcopenia in stroke. The new screening device is accurate, precise, and cost-effective, enabling medical personnel to identify patients at an early stage and take action to prevent and treat illnesses.

KEYWORDS

sarcopenia, post-stroke, nomogram, risk, biochemical, hematological

Introduction

Sarcopenia, a musculoskeletal condition defined by the progressive loss of muscle mass and strength (1), particularly in elderly populations, is a phenomenon that has established itself as a significant medical issue (2). This disorder results in adverse consequences, including falls, functional decline, frailty, and mortality (3). Therefore, it is pivotal to understand sarcopenia's risk factors, strategies to cope, and potential treatments, thereby intensifying the importance of extensive research on this topic. To comprehend the significance of sarcopenia research, one must view this condition not merely as an individual health concern but indeed as a global issue (4). The diagnosis of sarcopenia encompasses decreased levels of muscle strength, muscle quantity or quality, and physical performance. Such musculoskeletal degeneration impairs daily activities and poses a real threat to individual autonomy. However, the disorder's full scope extends beyond the personal level, potentially straining healthcare systems due to the increased burden of care for the elderly (5). Hence, sarcopenia research is vital in mitigating these issues. Stroke and sarcopenia constitute two significant health issues with substantial impacts on older adults' health and quality of life (6). Dynamic is the relationship between stroke and sarcopenia—the loss of muscle mass and strength—commonly seen in the elderly population (7). Despite the growing body of scientific literature exploring these two conditions separately, comprehensive research examining their interplay is needed to fully grasp how they influence one another (8–10). Stroke often leads to varying degrees of disability due to motor impairments and can interfere with a patient's functional ability, both of which can exacerbate sarcopenia's progression (11). This sarcopenic progression following stroke has been associated with poorer recovery outcomes and increased disability (12). Substantial attention should be directed toward the stroke and sarcopenia relationship to fully understand and effectively address these underlying mechanisms (11). Patients who experienced stroke often exhibit significant muscle changes, including muscle atrophy and increased intramuscular fat on the side of the body affected by the stroke (13). Research by Aydin et al. (14) indicates that these muscle alterations might serve as a link to post-stroke sarcopenia and reinforces the importance of further research. Given that sarcopenia is characterized by functional deficits, it can substantially interfere with post-stroke rehabilitation (8). Limited muscle strength and mass may negatively influence a patient's ability to participate in rehabilitation activities, ultimately affecting recovery outcomes (15).

Recent research has indicated that sarcopenia can be reversed or prevented, implying that stroke patients suffering from sarcopenia are likely to experience positive outcomes from timely diagnosis and intervention, particularly during the initial phase of sarcopenia (16). Nevertheless, the assessment of skeletal muscle mass is exceedingly restricted, necessitating the utilization of specialized apparatus like dual-energy X-ray absorptiometry (DXA), bio-impedance analysis (BIA), X-ray computed tomography (CT), or magnetic resonance imaging (MRI) (17).

In recent years, predictive models have been developed to assess the risk of sarcopenia in general populations, often leveraging demographic, biochemical, and hematological parameters (18). Nomograms, for instance, have become increasingly valuable as visual prediction tools, translating complex statistical models into practical applications for clinicians (19). These models have demonstrated accuracy in estimating sarcopenia risk and guiding early interventions in general healthcare settings (20, 21).

However, in the context of stroke patients, research on sarcopenia prediction is relatively sparse, despite the high prevalence and impact of sarcopenia in this population. Stroke survivors are at particular risk due to the compounded effects of neurological impairments and prolonged immobility, which can accelerate muscle atrophy (22). While some studies have examined predictors of functional decline post-stroke (23), few have applied predictive modeling approaches, such as nomograms, specifically tailored to forecast sarcopenia risk in this group (24, 25). This gap indicates a need for targeted tools that could support timely interventions in stroke recovery settings.

In light of this, our study aimed to develop and validate a nomogram to predict sarcopenia risk in stroke patients using data from the National Health and Nutrition Examination Survey (NHANES). This tool incorporates key predictors identified through Lasso regression analysis, enabling clinicians to assess sarcopenia risk more effectively and personalize care in post-stroke management. The hypothesis of this study is that in stroke patients, sarcopenia risk can be effectively predicted based on specific demographic and biochemical indicators using a constructed nomogram model.

Methods

Data source and study population

In this study, we gathered data from NHANES, a comprehensive survey conducted by the esteemed National Center for Health Statistics (NCHS), which falls under the Centers for Disease Control and Prevention (CDC). It aims to assess the health and nutritional status of adults and children in the United States. NHANES uses a complex, multistage, probability sampling design to select a representative sample of about 5,000 participants each year from 15 counties across the country. The flowchart for the research is shown in Figure 1. From 2011 to 2018, the NHANES data encompassed a total of 29,902 individuals. With the exception of individuals who did not experience a stroke, a total of 913 individuals remained. The number of people linked using Respondent sequence number (SEQN) is 238 because there are fewer people with laboratory examinations in the NHANES database than those with questionnaires. After removing samples with a missing rate of more than 10%, 209 individuals were still present. Due to the fact that removing all samples with missing values will render the research unfeasible, multiple imputation techniques are employed to complete missing values for samples with fewer missing values. The effectiveness of random forests in multiple imputation methods has been confirmed by studies (26, 27), so this article uses multiple imputation methods. Utilizing a random forest methodology for interpolation. The process is shown in Figure 1.

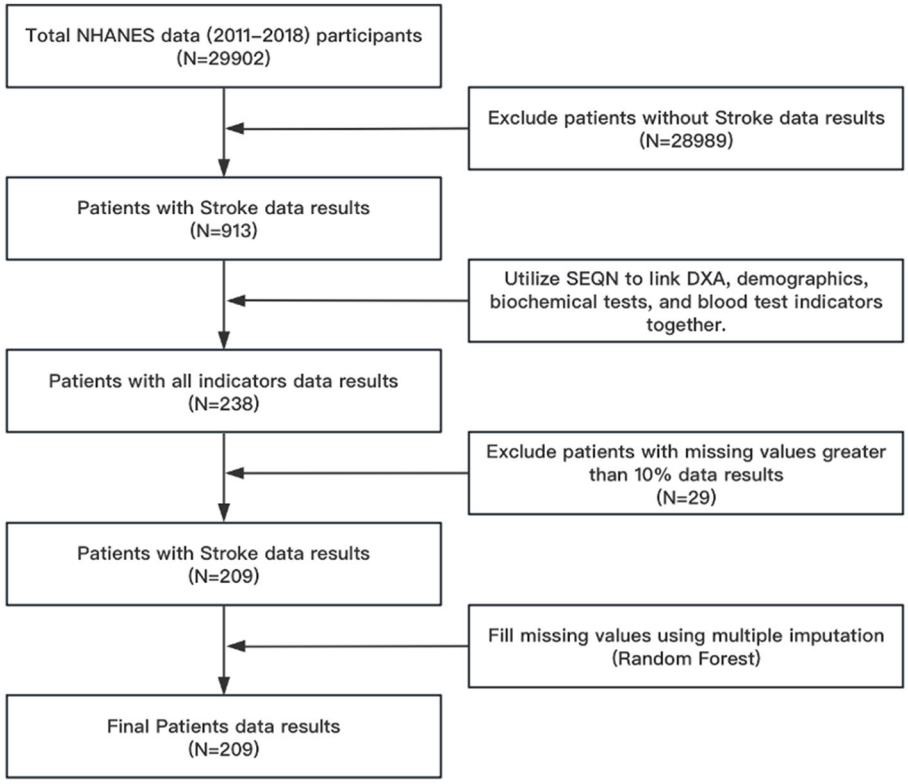

FIGURE 1
Flow chart for screening research samples. NHANES, National Health and Nutrition Examination Survey; DXA, Dual energy x-ray absorptiometry; SEQN, Respondent sequence number.

Measurements and definition of sarcopenia

The NHANES dataset utilized DXA to measure body composition, employing the Hologic QDR-4500 A fan beam densitometer, a dependable device produced by Hologic, Inc., situated in Bedford, MA, USA. To acquire a thorough collection of DXA findings, we amassed data files encompassing the period from 2011 to 2018 within NHANES. The metric of appendicular skeletal muscle mass (ASM), which measures the combined lean mass of the arms and legs, is widely accepted in clinical practice. In order to carry out our analysis, we utilized the skeletal muscle mass index (SMI), a metric endorsed by the Foundation for the National Institutes of Health (FNIH) Sarcopenia. SMI entails modifying ASM based on body mass index (BMI) (28). Our research revealed that men with a SMI of <0.789 or women with a SMI of <0.512 had a low muscle mass, thus satisfying the criteria for sarcopenia (29).

Procedure

The dataset was partitioned into training and validation sets using a random allocation method, ensuring an equitable split of 5:5 proportions. The judgment of stroke in patients in this study comes from a questionnaire in the NHANES database. The question is "Has a doctor or other health professional ever told {you/SP} that {you/s/he}...had a stroke?" Additional variables include gender, age, BMI, height, weight, waist circumference, race, complete blood cytology, and biochemical tests. Race is divided into four categories: Mexican American; non-Hispanic white; non-Hispanic black, and others. BMI is defined as body weight (kilograms) divided by height (meters) squared.

Statistical analysis

The descriptive statistics included both continuous and categorical variables. The continuous variables were subjected to group comparisons using either the *t*-test or the Wilcoxon rank-sum test. The chi-square test and Fisher's exact test were used to compare the categorical variables. Initially, the predictors underwent preliminary screening using LASSO regression in the development set. The LASSO analysis reduced the regression coefficient of variables to zero through the implementation of a penalized coefficient of Lambda. It disregarded variables that had no regression coefficients and chose variables that had no regression coefficients. The variables that were chosen were found to have the strongest association with post-stroke sarcopenia. Subsequently, the training set was used to create a prediction model through multivariate logistic regression analysis. The model was used to determine the score of each predictor. The model was visualized through the use of a nomogram. Lastly, the receiver operating characteristic (ROC) curve analysis was used to assess model discrimination. Area under the curve (AUC) values of 0.75 or higher were indicative of strong discrimination

TABLE 1 Baseline characteristics of study patients with stroke.

Variable	Non sarcopenia N = 176	Sarcopenia N = 33	P
Gender			1.000
Male	73 (41.5%)	14 (42.4%)	
Female	103 (58.5%)	19 (57.6%)	
Age	48.7 (9.54)	51.4 (7.69)	0.074
Race			0.003
Mexican American	18 (10.2%)	5 (15.2%)	
Other Hispanic	9 (5.11%)	6 (18.2%)	
Non-Hispanic White	62 (35.2%)	16 (48.5%)	
Non-Hispanic Black	69 (39.2%)	4 (12.1%)	
Other race	18 (10.2%)	2 (6.06%)	
BMI	30.1 (7.07)	37.7 (9.44)	<0.001
Weight	85.6 (22.8)	97.3 (27.1)	0.025
Height	168 (8.59)	161 (9.54)	<0.001
WAIST	103 (17.2)	116 (16.7)	<0.001

(30). The accuracy of the prediction was evaluated through the use of calibration plots. Calibration plots are a valuable tool for evaluating the accuracy of predictive models, including nomograms. They help determine how well predicted probabilities align with actual observed outcomes. A well-calibrated model will provide predicted probabilities that closely match the actual incidence of the event of interest (31). Decision curve analysis (DCA) was utilized to estimate the clinical utility (32). The test set was used to validate the nomogram. All tests employed a two-tailed approach, with a *p*-value of 0.05 or less indicating statistical significance. We used R statistical software (version 4.3.2) to carry out statistical analysis, and the nomogram was created with the help of the "nomogramFormula" package, authored by Zhi, J and Jing, Z.

Results

Patient characteristics

In this study, 209 people were included, with 33 having sarcopenia after stroke and 176 having non-sarcopenia after stroke, making up 15.8% of the total. The mean age of patients without sarcopenia (48.7 + 9.54) and those with sarcopenia (51.4 + 7.69) exhibited no significant statistical difference. Out of the non-sarcopenic population, 41.5% were female and 58.5% were male, whereas in the sarcopenic population, 42.2% were female and 57.6% were male. The sarcopenic and non-sarcopenic groups significant statistical differences in other demographic attributes such as race, BMI, weight, height, and waist circumference. Furthermore, Table 1 displays Baseline characteristics, and the biochemical analysis and a comprehensive array of blood test markers showed in the Supplementary material.

Predictors of post-stroke sarcopenia

This study established a LASSO regression model for 68 variables screened from the NHANES database. Variables were centralized and normalized by 10-fold cross-validation. According to Figure 1, we filter variables based on the binomial deviance of log (λ). Selected predictors were Gender, Race, Body Mass Index (kg/m**^{2}), Standing Height (cm), Alkaline Phosphatase (ALP) (IU/L), Total Calcium (mg/dL), Creatine Phosphokinase (CPK) (IU/L), Hemoglobin (g/dL), and Waist Circumference (cm). Secondly, to avoid the curse of dimensionality in the model, we eliminated the race variable and included the remaining eight variables to build a multiple logistic regression model (Figure 2).

Nomogram in patients with post-stroke sarcopenia

A nomogram was constructed to predict the risk of sarcopenia in patients with stroke. This model contained eight predictors: Gender, Body Mass Index (kg/m**2), Standing Height (cm), Alkaline Phosphatase (ALP) (IU/L), Total Calcium (mg/dL), Creatine Phosphokinase (CPK) (IU/L), Hemoglobin (g/dL), and Waist Circumference (cm) (Figure 3). For example, A man who is 1.55 meters tall has a BMI of 27 and a waist circumference of 110 centimeters. His blood laboratory tests were Total Calcium 8.9 mg/dL, Hemoglobin 16 g/dL, Alkaline Phosphatase 300 IU/L, and Creatine Phosphokinase 600 IU/L. The corresponding score of each predictor was 10 points, 15 points, 29 points, 40 points, 30 points, 78 points, 25 points, and 13 points respectively. His total score was 250 points. It indicated that the risk of sarcopenia was 70% in patients with stroke.

Performance and validation of the nomogram

The findings indicated that the anticipated results closely aligned with the observed outcomes. The ROC curve in the training set exhibited a strong ability to distinguish (AUC: 0.97; 95% CI: 0.94–0.99) (Figure 4A). The model's ability to discriminate was confirmed in the test set (0.90; 0.82–0.98) (Figure 4B). Additionally, the calibration curve analysis revealed a strong correlation between the anticipated probabilities and the observed sarcopenia after stroke in both the training and test sets (Figure 5). DCA demonstrated the clinical usefulness of this model (Figure 6).

Discussion

This study aimed to develop a nomogram to predict sarcopenia risk in post-stroke patients using demographic and biochemical factors. Key findings identified eight predictive factors: Gender, BMI, Standing Height, ALP, Total Calcium, CPK, Hemoglobin, and Waist Circumference. The model demonstrated high accuracy, with AUC values of 0.97 and 0.90 for the training and validation sets, respectively, showing strong predictive power. Calibration and

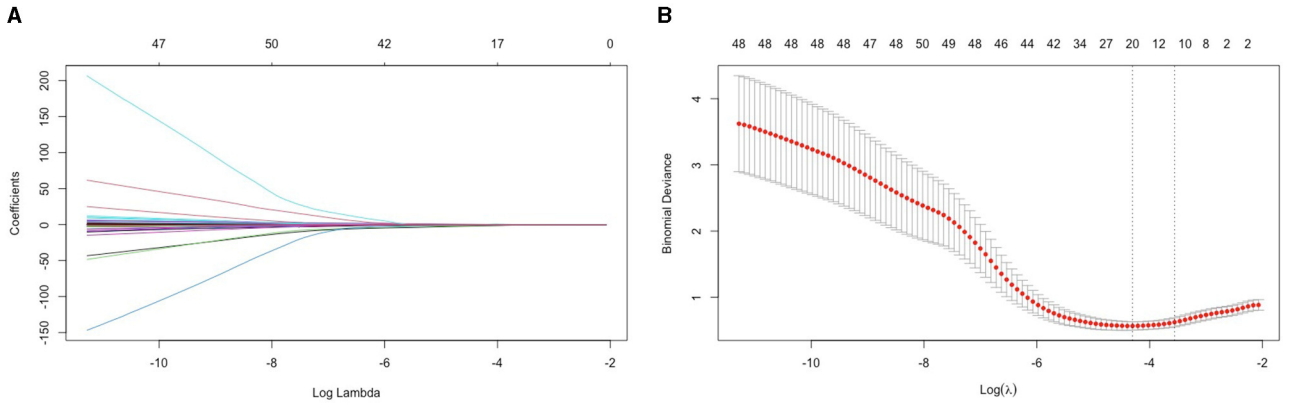

FIGURE 2
LASSO regression model for 64 variables. **(A)** The figure illustrates the variation in coefficient for each variable. The coefficient value is represented by the ordinate, while the lower abscissa corresponds to log (λ), and the upper abscissa signifies the count of non-zero coefficients in the current model. **(B)** After performing a 10-fold cross-cross validation fitting, the model was chosen. The best option is to select the lowest value with a standard deviation of one.

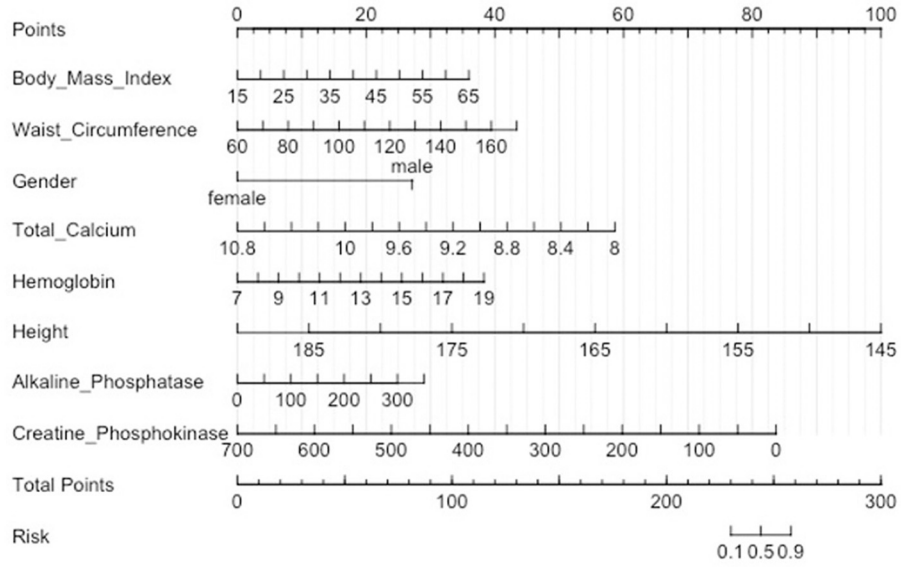

FIGURE 3
Nomogram for predicting sarcopenia in stroke patients. A certain score is indicated by each level of predictor. The score of each predictor was summarized to generate a total score. The overall score aligns with the likelihood of sarcopenia.

decision curve analyses further supported the model's reliability and clinical utility, suggesting it can aid in early sarcopenia intervention for stroke patients.

Personalized patient management in post-stroke care represents a core aspect of modern healthcare, particularly in the context of comorbidities such as sarcopenia, a progressive skeletal muscle disorder involving the accelerated loss of muscle mass and function (33). Current research on the development of a nomogram prediction model for sarcopenia risk in hemodialysis patients indicates promising avenues for post-stroke patients (34). The development of a nomogram predicting the risk of sarcopenia introduces a mathematical model than enhances clinical decision-making (35). This prediction model incorporates variables such as age, C-reactive protein, serum phosphorus, BMI, and mid-upper arm muscle circumference, thus offering a multidimensional risk assessment for sarcopenia in post-stroke patients (34). Such comprehensive data can aid in the early identification of high-risk patients, thus enhancing proactive patient management and potentially mitigating adverse outcomes. The introduction of a nomogram prediction model for post-stroke sarcopenia presents a potential paradigm shift in patient management. Early risk stratification and identification of sarcopenia can lead to early interventions, reducing the major complications associated with sarcopenia and improving stroke recovery outcomes (36). Further empirical research examining the statistical and clinical validity of the nomogram prediction model for post-stroke sarcopenia will offer significant contributions to stroke management. By aligning clinical practice with personalized

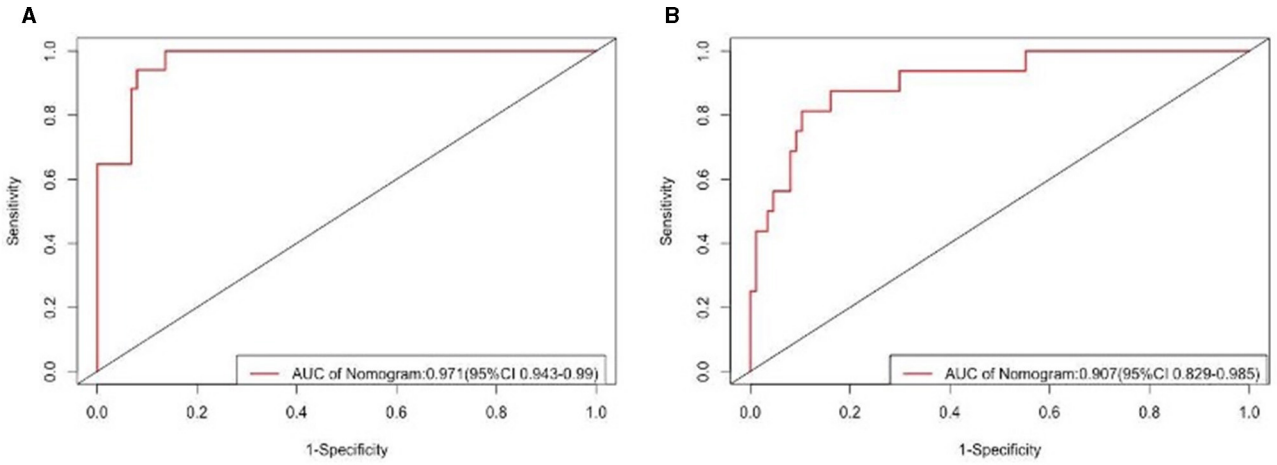

FIGURE 4
ROC curve and AUC of the predictive model. **(A)** The ROC in the development set. **(B)** The ROC in the validation set. ROC, receiver operating characteristic; AUC, area under the curve.

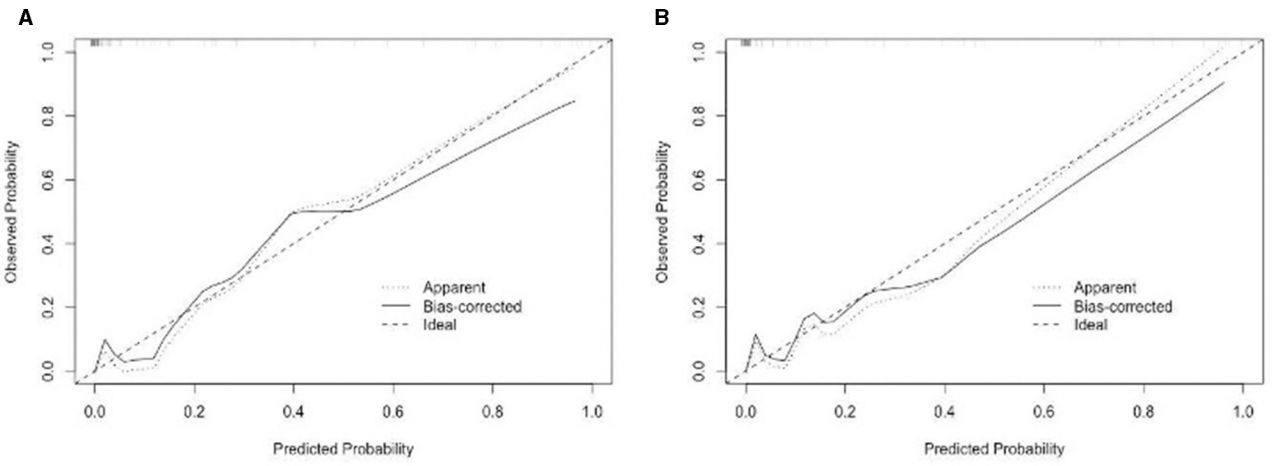

FIGURE 5
(A) The nomogram for sarcopenia in the training set was calibrated using a curve. **(B)** The nomogram for sarcopenia in the validation set was calibrated using a curve. The X-axis depicts the anticipated likelihood, while the Y-axis signifies the factual ratio. The ideal model's best prediction is denoted by the diagonal dotted line. The nomogram's uncorrected performance is depicted by the apparent line, whereas the bias-corrected performance is depicted by the solid line.

medicine insights, we can optimize post-stroke patient outcomes, particularly concerning comorbid sarcopenia.

These Asian studies have often found high rates of sarcopenia linked to lower physical activity levels, malnutrition, and metabolic factors, such as low serum albumin and hemoglobin, particularly among post-stroke patients. This aligns with our findings where factors like Hemoglobin and biochemical markers (e.g., ALP, CPK) were significant predictors of sarcopenia. Asian research has also identified sarcopenic obesity, which reflects the complex interaction between high BMI and muscle loss—similarly seen in our study where BMI was a predictor despite obesity traditionally being a protective factor (37).

However, specific gender-related factors influencing the development or progress of this condition remain a topic of interest. Due to gender-based differences in muscle mass and hormonal influences, the overall natural history of sarcopenia may vary (33). This discrepancy emphasizes the necessity to examine gender-based differences in the incidence and progression of post-stroke sarcopenia. To address gender-based hormonal differences in sarcopenia, researchers and clinicians should adopt gender-specific approaches. Prediction models should use gender-specific baselines for muscle mass and strength, and clinical evaluations may include hormone monitoring to understand individual risk better. Tailored exercise and nutrition programs—resistance training for men and estrogen-supportive interventions for postmenopausal women—can address these differences effectively. Additionally, more gender-specific longitudinal studies are needed, and clinician education should focus on recognizing and addressing these disparities, ensuring more personalized and effective sarcopenia management. Recognizing these differences can potentially foster enhanced rehabilitation strategies, promoting improved outcomes in stroke patients. This study confirms that

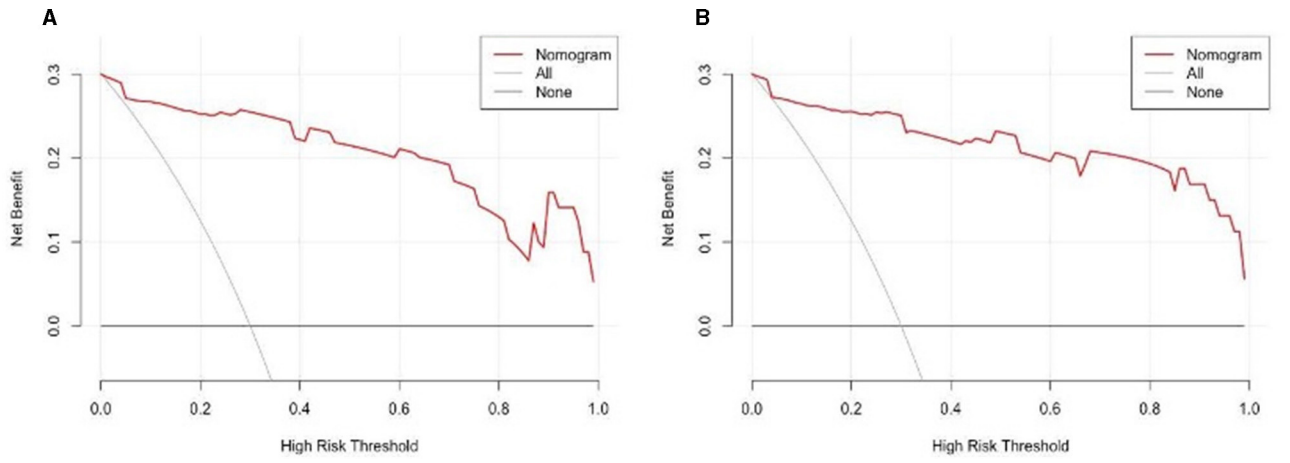

FIGURE 6
DCA of the nomogram. **(A)** The train set was occupied by the DCA. **(B)** The validation set includes DCA. The patient refrains from applying the nomogram, resulting in no net benefit, as depicted by the black-solid line; conversely, the gray-solid line indicates that all patients receive treatment based on the nomogram. The three lines enclosing the area demonstrate the practicality of the nomogram. Examining the Decision Curve of the Decision-Making Process.

gender is the main factor influencing the occurrence of sarcopenia in post-stroke patients.

Contrary to the notion that higher BMI corresponds to a lower risk of sarcopenia, findings propose the existence of sarcopenic obesity, suggesting the complex interplay between BMI and sarcopenia (38). The concept of sarcopenic obesity highlights a paradox where individuals have both high body mass index (BMI) and low muscle mass (39). This can be explained by the fact that BMI does not differentiate between muscle and fat, meaning a person can appear to have adequate or excess weight while actually experiencing muscle depletion (40). Sarcopenic obesity often involves a high proportion of body fat with reduced muscle mass and quality, impacting physical function and metabolic health (41). In stroke patients, sarcopenic obesity is particularly relevant (42). Stroke survivors often experience decreased mobility, leading to muscle wasting and increased fat accumulation due to prolonged physical inactivity and metabolic disruptions (43, 44). Additionally, neurological impairments can hinder rehabilitation efforts, compounding muscle atrophy while promoting weight gain if caloric intake remains the same or increases due to stress-related eating patterns (45, 46). This combination may contribute to poor outcomes, as muscle loss impairs mobility and recovery, while excess fat increases the risk of cardiovascular complications and insulin resistance. These findings have implications for interpreting our results, as BMI alone may mask the underlying muscle loss in post-stroke patients. In our study, higher BMI was a predictor of sarcopenia, likely reflecting sarcopenic obesity. This reinforces the need to assess both muscle and fat composition in clinical settings to accurately evaluate sarcopenia risk in stroke patients, as BMI alone could misclassify at-risk individuals. Recognizing sarcopenic obesity allows for a more comprehensive approach to managing post-stroke recovery by targeting both muscle preservation and body composition improvements through tailored interventions.

While height's influence on post-stroke sarcopenia remains unclear, it forms part of the sarcopenia diagnosis, with height-based cut-off points established for muscle mass (47).

Waist Circumference, a proxy for abdominal adiposity, seems contradictory in the context of sarcopenia, with some research showing no significant association (38). Recognizing the associations between these physiological parameters and post-stroke sarcopenia may enhance our understanding of sarcopenia's multifaceted nature and broaden the horizon for therapeutic interventions. Future research should address these variables in a combined or sequential manner to uncover the overlapping and unique contributions each makes toward post-stroke sarcopenia.

The regulation of ALP, Total Calcium, CPK, and Hemoglobin within the body may influence post-stroke sarcopenia development. While aberrant ALP levels mark liver damage or bone disorders (48), their role in sarcopenia remains unexplored. Studies indicate that calcium signaling has a key role in muscle function (49), potentially influencing sarcopenic progression. Similarly, CPK, a measure of muscle destruction, may correlate with post-stroke sarcopenia (50). Lastly, Hemoglobin, indicative of anemia status, may affect sarcopenia as muscle oxygenation can impact muscle function (51).

This study presents several notable strengths. Firstly, the development of a nomogram for predicting sarcopenia in stroke patients fills a critical gap in the existing literature, addressing the correlation between these two conditions. The use of the NHANES dataset enhances the generalizability of the findings, as it reflects a diverse population. The employment of Lasso regression analysis allows for the identification of key predictive factors, ensuring a robust selection of variables. The model's high discrimination ability, indicated by area under the curve (AUC) values of 0.97 and 0.90 for training and validation sets respectively, demonstrates its potential clinical utility. Additionally, the study's calibration and decision curve analysis suggest that the nomogram could lead to significant improvements in clinical outcomes, making it a valuable tool for early identification and intervention in at-risk patients. Despite these advantages, the study does have some limitations. The reliance on a secondary data source may introduce biases associated with the dataset,

including potential confounding variables that were not accounted for. Furthermore, the study's cross-sectional design limits the ability to infer causation between the identified predictors and the onset of sarcopenia. The sample size, while adequate for a preliminary analysis, may not fully capture the complexity of the relationship between stroke and sarcopenia across different demographic groups, particularly in underrepresented populations. Additionally, the clinical applicability of the nomogram in real-world settings requires further validation through prospective studies.

Future research should focus on several key areas. Longitudinal studies are needed to establish causative relationships between the identified risk factors and sarcopenia in stroke patients. Expanding the research to include diverse populations will enhance the nomogram's applicability across different demographics. Investigating the biological mechanisms underlying the relationship between stroke and sarcopenia could provide deeper insights into effective prevention and treatment strategies. Finally, exploring the integration of the nomogram into clinical practice, alongside patient outcomes, would be essential for assessing its real-world impact on healthcare delivery, and patient management.

Conclusion

This study successfully developed and validated a nomogram for predicting sarcopenia risk in stroke patients based on key demographic and biochemical factors. The findings indicate that factors such as gender, BMI, and biochemical markers like ALP and hemoglobin significantly contribute to sarcopenia risk. By implementing this model in clinical practice, healthcare providers can identify at-risk patients earlier and tailor interventions to prevent or manage sarcopenia, thus enhancing overall recovery and quality of life for stroke survivors.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The data, physical examination, and survey results were acquired from the NHANES, the National Centre for Health Statistics Research Ethics Review Board approved the protocol. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

YP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YW: Conceptualization, Investigation, Writing – original draft. HW: Conceptualization, Writing – original draft. HL: Writing – review & editing. XD: Conceptualization, Writing – review & editing. JX: Writing – review & editing. XL: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1438575/full#supplementary-material

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EDITED BY
Arthur Sá Ferreira,
University Center Augusto Motta, Brazil

REVIEWED BY
Natalie M. Zahr,
Stanford University, United States
Oleh Kuzyk,
Drohobych Ivan Franko State Pedagogical University, Ukraine

*CORRESPONDENCE
Fang Cui
✉ fangcui200808@163.com

†These authors have contributed equally to this work

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Association between serum albumin and severe impairment of activities of daily living in patients with stroke: a cross-sectional study

Ranran Bi[1†], Yupeng Shi[2†], Manrong Li[1], Xiaochen Liu[1], Zhenchao Ma[1], Yiqing Huang[1], Bingyin Liang[1] and Fang Cui[1*]

[1]Department of Rehabilitation Medicine, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China, [2]Shandong Provincial Key Medical and Health Laboratory of Intensive Care Rehabilitation, Shandong Provincial Third Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

Purpose: The relationship between serum albumin levels and severe limitations in ADLs among stroke patients remains unclear. Specifically, the dose–response relationship between the two needs further exploration. This study aims to provide further results.

Materials and methods: This study examined cross-sectional data from patients aged 18 years or older with a diagnosis of stroke confirmed by cranial CT or MRI within 24 h of admission, gathered from January 2020 to August 2022. Data included serum albumin levels, Barthel Index scores recorded after admission, and other essential variables.

Results: The study comprised 2,393 stroke patients. After adjusting for confounding factors, the multivariate analysis revealed a 7% decrease in severe impairment of ADL after stroke for every unit (g/L) increase in serum albumin levels. Compared with individuals with lower serum albumin levels (Q1: ≤ 37.4 g/L), the adjusted odds ratios (OR) for severe of ADL impairment among stroke patients in Q2 (37.4–40.21 g/L), Q3 (40.21–42.80 g/L), and Q4 (≥42.8 g/L) were 0.68 (95% CI: 0.4–1.15, $p = 0.148$), 0.55 (95% CI: 0.32–0.97, $p = 0.04$), and 0.64 (95% CI: 0.37–1.15, $p = 0.139$), respectively. The relationship between serum albumin and severe impairment of ADLs in stroke patients showed an L-shaped curve (non-linear, $p = 0.002$), with an inflection point at 38.0 g/L. The OR for significant impairment of ADLs was 0.680 (95% CI: 0.568–0.814, $p < 0.001$) in participants with serum albumin levels <38.0 g/L. However, when serum albumin levels were greater than or equal to 38.0 g/L, the severe impairment of ADLs no longer decreased with rising serum albumin levels.

Conclusion: In summary, an L-shaped connection with an approximate inflection point of 38.0 g/L was found between blood albumin levels and significant ADL impairment in stroke patients. The results of this study suggest that increasing serum albumin levels can significantly help improve the severity of ADL impairment in stroke patients, particularly those with serum albumin levels below 38.0 g/L.

KEYWORDS

serum albumin, severe impairment, activities of daily living, stroke, L-shaped, cross-sectional study

Introduction

Stroke is the second most common cause of death globally, accounting for over 5.5 million deaths annually (1, 2). While significant advancements have been made in the treatment of stroke, the majority of patients continue to experience disability, significantly impacting their functional independence and quality of life (3). The China Stroke Surveillance Report 2021 estimates that 17.8 million adults in China had a stroke in 2020, with 2.2 million of them having disability as a result of the stroke (4). Stroke results in impairment-related functional limits that might make it difficult to do ADLs without guidance, support, or physical aid (5, 6). Thus, stroke has been the primary global cause of acquired disability in adults, and its prevalence is expected to rise (7).

Serum albumin level is a key biochemical marker of nutritional status (8–11). Lower serum albumin levels in patients indicate inadequate nutritional status and impaired physiological performance. Research suggests a connection between serum albumin and ADL (12). Specifically, Low serum albumin levels increase the risk of ADL limitation. Meanwhile, Serum albumin levels and the risk of stroke were negatively correlated (13). Zhou et al. found that hypoproteinemia was associated with neurological recovery status and mortality outcomes in patients with acute ischemic stroke or transient ischemic attack (14), but there were no outcome-related studies on ADL limitations. Improvements in nutritional status were independently associated with enhanced ADL performance during inpatient rehabilitation in older patients with malnutrition (15).

However, the association between serum albumin and severe ADL impairments in stroke patients has yet to be investigated. To fill this knowledge gap, we evaluated the relationship between severe ADL limits and serum albumin levels, as well as the dose–response relationship between the two, in stroke patients.

Materials and methods

Study population

This study used a cross-sectional design to gather stroke patients who were admitted to Shanghai East Hospital between January 2020 to August 2022. It comprised patients (18 years of age or older) whose diagnosis of stroke was verified by cranial CT or MRI within 24 h of admission.

Patients without a reported Barthel Index score at admission or those whose serum albumin levels were not tracked were excluded. Figure 1 illustrates the patient selection process. The cross-sectional study was reported concerning the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and approved by the Shanghai East Hospital Ethics Committee (No. 2024055). As a retrospective cross-sectional study with anonymous data collection, informed consent was not required. All procedures and methods followed the World Medical Association's Declaration of Helsinki on Human Experimentation ethics.

General data collection

Participants´ demographic and lifestyle data was gathered. Individual anthropometric information was entered into the hospital's electronic medical record system, including height, weight, sex, and age. In summary, these anthropometric measurements were taken at the time of the patient's hospital admission during their physical examinations. Weight and height assessments followed the World Health Organization's guidelines. Weight (kg) divided by height squared (m2) yielded the body

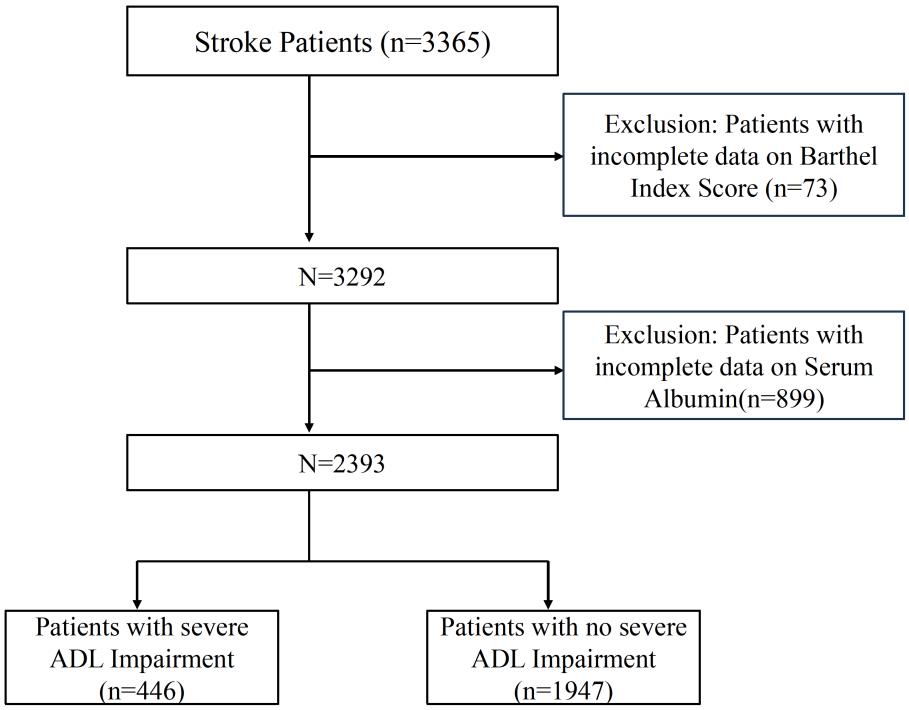

FIGURE 1
The study's flow diagram.

mass index (BMI). There were two categories for smoking status: "current or ever smoking" and "current or ever drinking" for drinking status. A history of documented hypertension or blood pressure of at least two instances of ≥140 mmHg (systolic) or ≥ 90 mmHg (diastolic) following the acute phase of a stroke was used to diagnose hypertension. Information on diabetes, coronary heart disease, atrial fibrillation, cancer, and previous stroke history was extracted from the electronic medical records.

The National Institute of Health Stroke Scale (NIHSS) was used to evaluate the severity of the stroke at the time of admission (16, 17). The TOAST criteria classified ischemic strokes into five subtypes: large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke with another identified etiology, and stroke with unknown etiology (18). Additionally, Serum albumin level was measured using a Roche analyser within 24 h of the onset of stroke. Serum albumin levels are measured using the bromocresol green (BCG) method, based on the principle that albumin specifically binds to the dye bromocresol green under acidic conditions, resulting in a color change that is quantified spectrophotometrically. The method is widely used and economical; when obtaining serum samples from patients, ensure that they are free from hemolytic, lipemic, or jaundiced interference to ensure the accuracy of the measurement.

Activities of daily living (ADL) comprise the basic actions that involve caring for one's self and body, including personal care, mobility, and eating. The Barthel Index (BI) is a widely used scale for assessing a patient's ability to perform basic activities of daily living (ADLs). It was first developed in 1965 by Dorothea Barthel and Florence Mahoney in the United States (19). The index evaluates ten functional areas, including feeding, bathing, dressing, toileting, mobility, walking, stair climbing, and bowel and bladder control (20, 21). The total score ranges from 0 to 100, with higher scores indicating greater independence in daily activities. The Barthel Index is extensively used to assess functional status in various conditions, particularly in the study of Stroke (22), Spinal Cord Injury (23), Dementia (24), and Parkinson's Disease (25). Several previous studies in China have also used BI to assess ADL capacity in stroke patients (26, 27).

Previous studies have further categorized subjects into two groups based on activities of daily living (ADL): those with a high ADL score of 40 or more and those with a low ADL score of 40 or less (28). When any patient's Barthel score is less than 40, it means that neither their mobility abilities nor ability to feed themselves, groom themselves, or control their sphincters are autonomous (29). The patient cannot perform daily tasks independently and relies on assistance from others. This level of impairment is defined as severe impairment of activities of daily living.

Statistical analysis

Every patient was the subject of a descriptive analysis. Numbers (percentages) were used to express categorical data, and depending on the distribution, continuous data were shown as the median (interquartile range) or the mean ± standard deviation. To evaluate differences among groups, one-way analysis of variance (for normally distributed data), Kruskal–Wallis tests (for non-normally distributed data), and chi-square tests (for categorical variables) were performed. The odds ratios (OR) and 95% confidence intervals (CIs) for the association between serum albumin and severe impairment of ADL in stroke patients were calculated using logistic regression models. Model 1 was calibrated for BMI, age, sex, drinking, and smoking status. Age, sex, BMI, drinking and smoking status, hypertension, diabetes, cancer, atrial fibrillation, coronary heart disease, and history of stroke were all taken into account while adjusting Model 2. All of the variables from Model 2 were included in Model 3, along with TOAST classification and NIHSS.

Additionally, after controlling for the factors in Model 3, we used restricted cubic spline (RCS) regression to analyze curvilinearity and investigate the dose–response association between serum albumin and severe ADL impairment. To evaluate the association threshold between serum albumin and severe ADL impairment after stroke, we employed a smoothed binary logistic regression model. Likelihood ratio tests and bootstrap regression were used to identify significant inflection points in this relationship.

Furthermore, we investigated several variables that could alter the association between serum albumin and severe ADL impairment following a stroke. The variables that were analyzed were sex; age (less than 60 years old versus more than 60 years old); BMI (less than 25, 25–29.9, versus more than 30 kg/m^2); smoking and drinking status (yes or no); hypertension (yes or no); diabetes (yes or no); and TOAST classification (large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke with another identified etiology, and stroke with unknown etiology).

Using multivariate logistic regression, we assessed subgroup heterogeneity, and the likelihood ratio test examine interactions between subgroups and serum albumin.

To examine the robustness of the results, we did a sensitivity analysis by interpolating the NIHSS, which had a high number of missing data, using median values. No, *a priori* statistical power analyses were carried out because the sample size was established exclusively using the data that were available data. R version 4.3.1[1] and Free Statistics version 1.8 were used for all analyses. A descriptive study was carried out on each individual. A two-tailed *p*-value of less than 0.05 was specified as statistically significant.

Results

Study population

The study initially included 3,365 stroke patients. Among these, 73 patients were eliminated due to missing data on ADL, whereas 899 patients were omitted due to missing albumin levels. As a result, this cross-sectional study comprised 2,393 patients from Shanghai East Hospital from 2020 to 2022. Figure 1 provides a detailed illustration of the selection process, depicting both inclusion and exclusion criteria.

Baseline characteristics

Table 1 summarizes all subjects′ baseline characteristics, classified by serum albumin quartiles.

The average age of the patients was 69.6 ± 11.6 years, with 1,538 (64.3%) being male. Patients with higher serum albumin

1 http://www.R-project.org, The R Foundation.

levels were younger, male, had a slightly higher BMI, higher BI scores, lower NIHSS scores, had a history of hypertension, no history of coronary heart disease and atrial fibrillation, were non-smokers, and had atherosclerosis according to the TOAST classification. The four groups had significant differences in sex, age, BMI, Barthel Index Score, NIHSS, Hypertension, Coronary heart disease, Atrial Fibrillation, Smoking Status, and TOAST (all $p < 0.05$).

TABLE 1 The baseline characteristics by categories of serum albumin.

Variables	Total	Q1 (<37.4)	Q2 (37.4–40.21)	Q3 (40.21–42.80)	Q4 (≥42.8)	*p*
No.	2,393	597	599	590	607	
Sex, n (%)						< 0.001
Male	1,538 (64.3)	347 (58.1)	365 (60.9)	388 (65.8)	438 (72.2)	
Female	855 (35.7)	250 (41.9)	234 (39.1)	202 (34.2)	169 (27.8)	
Age, Mean ± SD	69.6 ± 11.6	74.6 ± 11.0	71.5 ± 10.1	68.0 ± 10.8	64.3 ± 11.8	< 0.001
BMI, Mean ± SD	24.5 ± 3.4	23.7 ± 3.6	24.4 ± 3.5	24.8 ± 3.3	25.0 ± 3.2	< 0.001
Barthel Index Score, Mean ± SD	62.1 ± 26.9	49.2 ± 27.8	61.2 ± 26.0	68.2 ± 23.6	69.9 ± 25.1	< 0.001
NIHSS, Mean ± SD	3.9 ± 4.7	5.5 ± 5.7	3.7 ± 4.1	3.2 ± 3.5	3.4 ± 5.0	< 0.001
Hypertension, *n* (%)						0.028
No	472 (20.2)	139 (24.3)	119 (20.2)	109 (18.8)	105 (17.6)	
Yes	1867 (79.8)	434 (75.7)	470 (79.8)	471 (81.2)	492 (82.4)	
Diabetes, *n* (%)						0.27
No	1,257 (53.7)	328 (57.2)	309 (52.5)	302 (52.1)	318 (53.3)	
Yes	1,082 (46.3)	245 (42.8)	280 (47.5)	278 (47.9)	279 (46.7)	
Coronary heart disease, *n* (%)						< 0.001
No	1952 (83.5)	448 (78.2)	486 (82.5)	501 (86.4)	517 (86.6)	
Yes	387 (16.5)	125 (21.8)	103 (17.5)	79 (13.6)	80 (13.4)	
Atrial fibrillation, *n* (%)						< 0.001
No	2053 (87.8)	444 (77.5)	509 (86.4)	539 (92.9)	561 (94)	
Yes	286 (12.2)	129 (22.5)	80 (13.6)	41 (7.1)	36 (6)	
Cancer, *n* (%)						0.374
No	2048 (87.6)	498 (86.9)	507 (86.1)	518 (89.3)	525 (87.9)	
Yes	291 (12.4)	75 (13.1)	82 (13.9)	62 (10.7)	72 (12.1)	
History of stroke, *n* (%)						0.951
No	1934 (82.7)	471 (82.2)	490 (83.2)	477 (82.2)	496 (83.1)	
Yes	405 (17.3)	102 (17.8)	99 (16.8)	103 (17.8)	101 (16.9)	
Smoking status, *n* (%)						0.002
No	1,289 (58.7)	362 (64.9)	320 (59.1)	307 (57.1)	300 (53.8)	
Yes	906 (41.3)	196 (35.1)	221 (40.9)	231 (42.9)	258 (46.2)	
Drinking status, *n* (%)						0.562
No	1887 (82.7)	469 (83.3)	471 (82.8)	478 (83.9)	469 (80.9)	
Yes	395 (17.3)	94 (16.7)	98 (17.2)	92 (16.1)	111 (19.1)	
TOAST classification, *n* (%)						< 0.001
Large-artery atherosclerosis	865 (42.4)	209 (43.7)	211 (40.1)	212 (41.7)	233 (44)	
Small-vessel occlusion	802 (39.3)	133 (27.8)	212 (40.3)	231 (45.4)	226 (42.7)	
Cardioembolism	204 (10.0)	76 (15.9)	66 (12.5)	33 (6.5)	29 (5.5)	
Stroke of another determined etiology	55 (2.7)	20 (4.2)	12 (2.3)	9 (1.8)	14 (2.6)	
Stroke of unknown etiology	116 (5.7)	40 (8.4)	25 (4.8)	24 (4.7)	27 (5.1)	

Relationship between serum albumin and severe impairment of ADL among stroke patients

After adjusting for confounding factors, the multivariate analysis revealed a 7% decrease in severe impairment of ADL after stroke for every unit (g/L) increase in serum albumin levels. When blood albumin levels were analyzed using quartiles, a negative relationship was found between serum albumin levels and severe impairment of ADL after controlling for relevant variables. In comparison to patients with lower levels of serum albumin (<37.4 g/L), the adjusted odds ratio (OR) for severe impairment of ADL after stroke for those in the second quartile (Q2: 37.4–40.21 g/L), third quartile (Q3: 40.21–42.80 g/L), and fourth quartile (Q4: >42.8 g/L) were 0.68 (95% confidence interval [CI]: 0.40–1.15, $p = 0.148$), 0.55 (95% CI: 0.32–0.97, $p = 0.04$), and 0.65 (95% CI: 0.37–1.15, $p = 0.139$), respectively (Table 2).

In Figure 2, the link between serum albumin and severe impairment of ADLs after stroke displayed an L-shaped curve (nonlinear, $p = 0.002$). The link between serum albumin levels and severe impairment of ADLs among stroke patients shows an inflection point around 38.0 g/L. In the threshold analysis, the odds ratio (OR) for severe impairment of ADLs among stroke patients with serum albumin levels less than 38.0 g/L was 0.680 (95% CI: 0.568–0.814, $p < 0.001$). When serum albumin levels were greater than or equal to 38.0 g/L, the severe impairment of ADLs no longer decreased with rising serum albumin levels, indicating that the threshold had been reached (Table 3).

Subgroup analyses

Figure 3 illustrates the relationship between serum albumin levels and severe limitations in ADL, as analyzed across various subgroups. Serum albumin levels were associated with severely impaired ability to perform activities of daily living in male (OR, 0.92; 95% CI, 0.88–0.96), female (OR, 0.86; 95% CI, 0.81–0.92), more than 60 years (OR, 0.91; 95% CI, 0.87–0.94), with BMI less than 25 kg/cm^2 (OR, 0.9; 95% CI, 0.85–0.95), BMI 25–29.9 kg/cm^2 (OR, 0.91; 95% CI, 0.85–0.97), smoking (OR, 0.91; 95% CI, 0.86–0.96), non-smoking (OR, 0.89; 95% CI, 0.85–0.94), alcohol (OR, 0.88; 95% CI, 0.8–0.96), no alcohol (OR, 0.9; 95% CI, 0.86–0.94), hypertension (OR, 0.89; 95% CI, 0.86–0.93), diabetes (OR, 0.91; 95% CI, 0.85–0.97), no diabetes (OR, 0.92; 95% CI, 0.88–0.97), and those with TOAST classification large-artery atherosclerosis (OR, 0.91; 95% CI, 0.86–0.96), small-artery occlusion (OR, 0.89; 95% CI, 0.82–0.95), stroke of unknown etiology (OR, 0.81; 95% CI, 0.7–0.94). There was no significantly association among aged less than 60 years, BMI more than 30 kg/cm^2, or those without hypertension or in the Cardioembolism and Stroke of another determined etiology subgroups. After subgroup analysis according to sex, age, BMI, smoking status, alcohol status, hypertension, and diabetes, TOAST classification, no significant interactions were found in any subgroup (all p-values for interaction >0.05).

Sensitivity analysis

Due to the high rate of missing NIHSS and TOAST data, we found a more robust association between serum albumin and severely impaired ADL of stroke after the multiple interpolation of NIHSS and TOAST. After adjusting for confounding factors, multivariate analysis showed that for every 1 g/L increase in serum albumin levels, there was a 7% reduction in severe ADL impairment post-stroke. Compared with those with lower serum albumin levels (<37.4 g/L), the adjusted ORs for serum albumin and ADL in Q2 (37.4–40.21 g/L), Q3 (40.21–42.80 g/L), and Q4 (>42.8 g/L) were 0.57 (95% CI: 0.38–0.86, $p = 0.007$), 0.50 (95% CI: 0.32–0.77, $p = 0.002$), and 0.52 (95% CI: 0.33–0.81, $p = 0.004$), respectively (Supplementary Table S1).

TABLE 2 Association between serum albumin and severe impairment of ADL among stroke patients.

Variable	n. total	n. event_%	Crude model		Model 1		Model 2		Model 3	
			OR (95%CIs)	*p*-value	OR (95%CIs)	*p*-value	OR (95%CIs)	*p*-value	OR (95%CIs)	*p*-value
Albumin (g/L)	2,393	446 (18.6)	0.85 (0.83 ~ 0.87)	<0.001	0.9 (0.87 ~ 0.93)	<0.001	0.9 (0.87 ~ 0.94)	<0.001	0.93 (0.88 ~ 0.98)	0.004
Albumin Group (g/L)										
Q1 (<37.4)	597	212 (35.5)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (37.4–40.21)	599	108 (18)	0.4 (0.31 ~ 0.52)	<0.001	0.49 (0.34 ~ 0.71)	<0.001	0.5 (0.34 ~ 0.73)	<0.001	0.68 (0.4 ~ 1.15)	0.148
Q3 (40.21–42.80)	590	58 (9.8)	0.2 (0.14 ~ 0.27)	<0.001	0.43 (0.29 ~ 0.64)	<0.001	0.45 (0.3 ~ 0.68)	<0.001	0.55 (0.32 ~ 0.97)	0.04
Q4 (≥42.8)	607	68 (11.2)	0.23 (0.17 ~ 0.31)	<0.001	0.44 (0.29 ~ 0.66)	<0.001	0.48 (0.31 ~ 0.73)	0.001	0.65 (0.37 ~ 1.15)	0.139
Trend test				<0.001		<0.001		<0.001		0.116

Q, quartiles; OR, odds ratio; CI, confidence interval; Ref: reference. Model 1 was adjusted for Sex, Age, BMI, Smoking Status, and Drinking Status. Model 2 was adjusted for Sex, Age, BMI, Smoking Status, Drinking Status, Hypertension, Diabetes, Coronary heart disease, Atrial fibrillation, Cancer, and History of stroke. Model 3 was adjusted for Sex, Age, BMI, Smoking Status, Drinking Status, Hypertension, Diabetes, Coronary heart disease, Atrial fibrillation, Cancer, and History of stroke, NIHSS, TOAST classification.

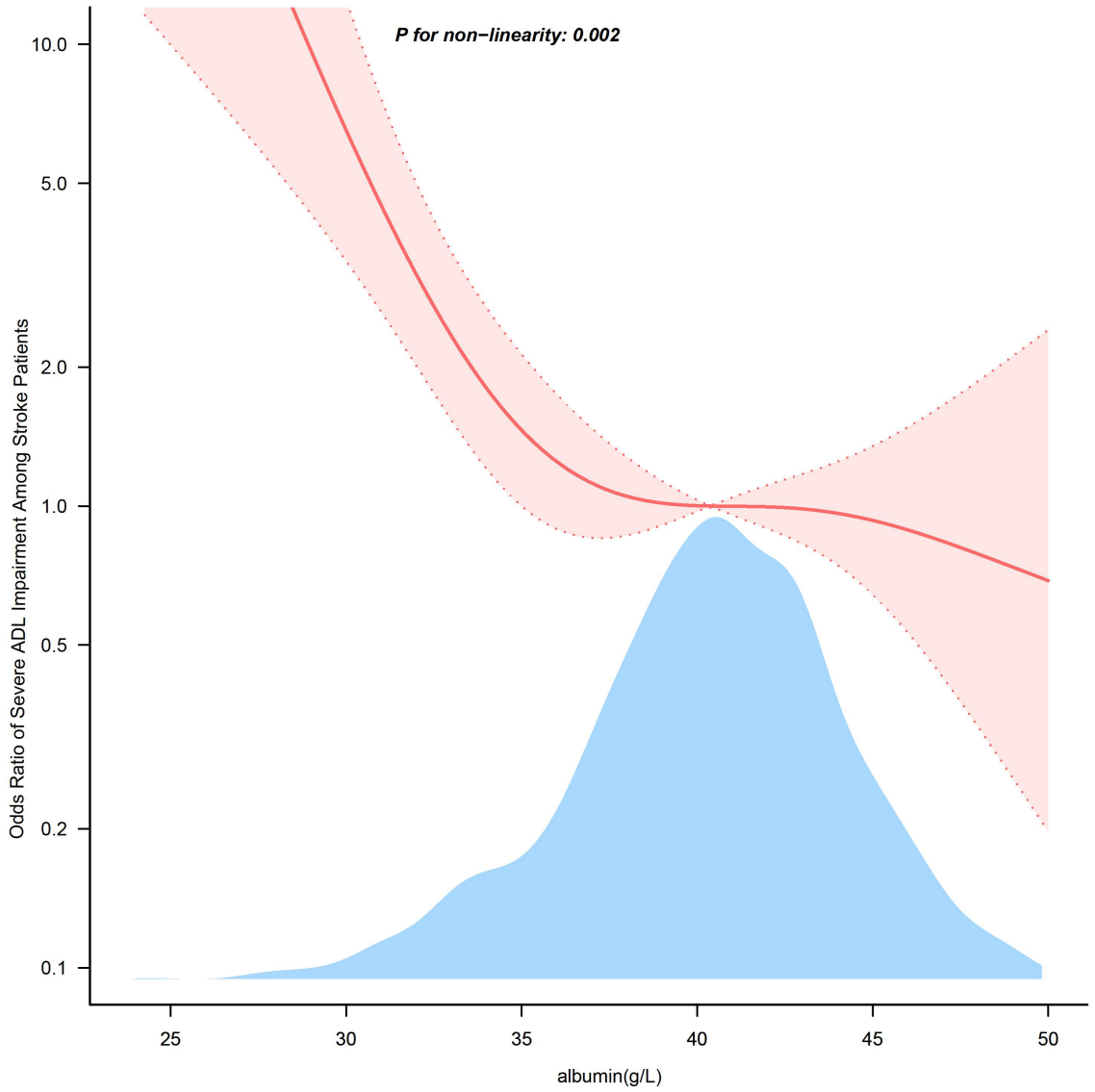

FIGURE 2
Association between serum albumin levels and the odds ratio of severe ADL impairment among stroke patients. Solid and dashed lines represent the predicted value and 95% confidence intervals. They were adjusted for Sex, Age, BMI, Smoking Status, and Drinking Status, Hypertension, Diabetes, Coronary heart disease, Atrial fibrillation, Cancer, and History of stroke, NIHSS, TOAST. Only 99% of the data is displayed.

TABLE 3 Threshold effect analysis of the relationship of serum albumin with severe impairment of ADL among stroke patients.

Serum albumin (g/L)	Adjusted Model	
	OR (95%CI)	*p*-value
<38.0	0.680 (0.568 ~ 0.814)	<0.001
≥38.0	0.961 (0.875 ~ 1.057)	0.4125
Likelihood Ratio test		0.001

OR, odds ratio; CI, confidence interval. Adjusted for Sex, Age, BMI, Smoking Status, and Drinking Status, Hypertension, Diabetes, Coronary heart disease, Atrial fibrillation, Cancer, and History of stroke, NIHSS, TOAST classification. Only 99% of the data is displayed.

Discussion

Serum albumin level significantly indicates an individual's ability to perform ADL (30). Studies have shown that serum albumin levels are associated with physical functioning disability among older adults (31). Additionally, higher serum albumin levels in ischemic stroke patients are associated with a lower likelihood of poor prognosis (32, 33). Due to its relatively long half-life, serum albumin reflects a patient's nutritional status before stroke onset. Albumin levels measured within 24 h of admission are less likely to be affected by the acute stress of stroke (34). Consequently, this study collected albumin levels within 24 h of admission. The results revealed an L-shaped relationship between serum albumin levels and severely impaired ADL in stroke patients, with an inflection point at 38.0 g/L. Subgroup analyses revealed that serum

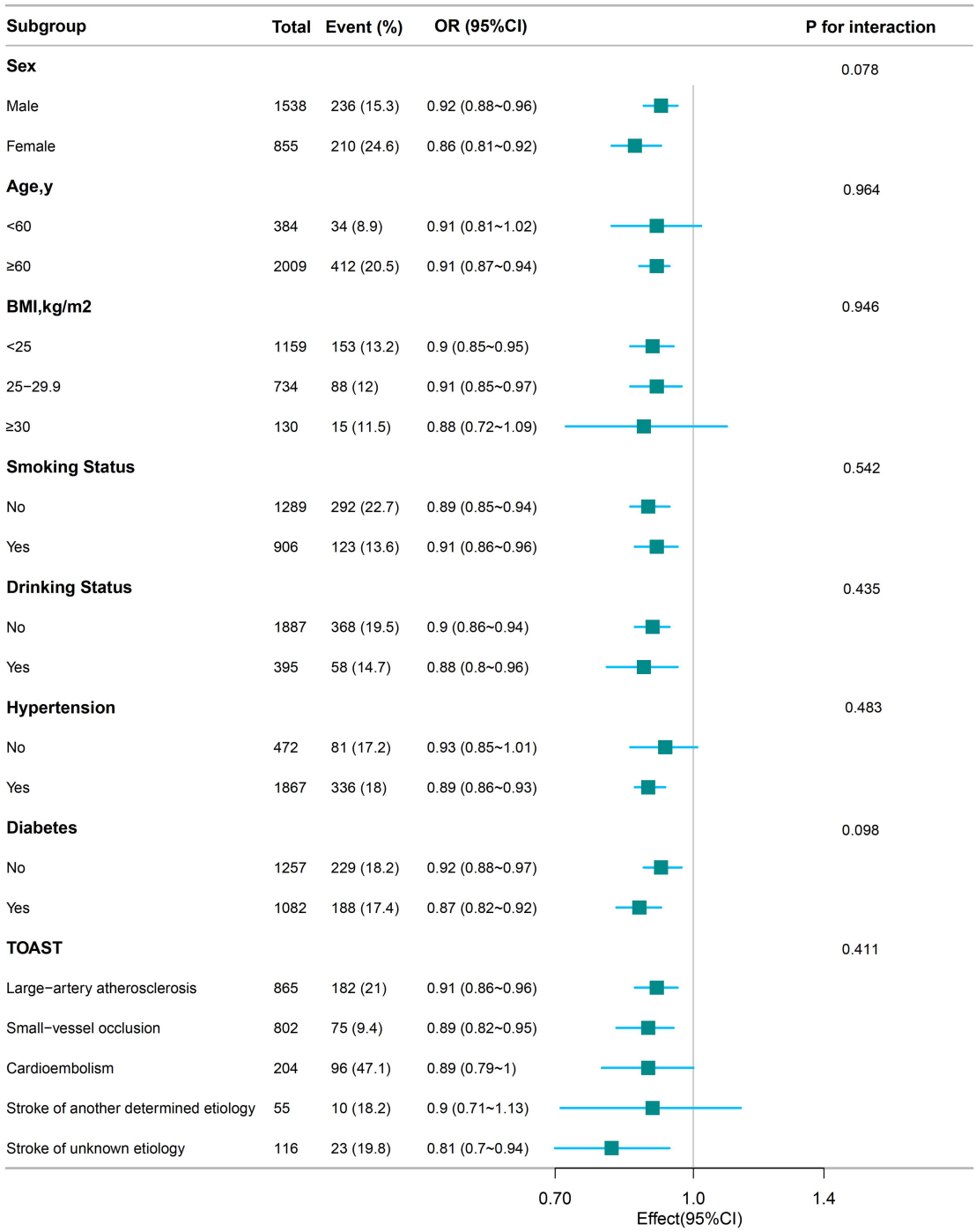

FIGURE 3
The relationship between serum albumin levels and the odds ratio of severe ADL impairment among stroke patients according to basic features. Except for the stratification component itself, each stratification factor was adjusted for all other variables (Sex, Age, BMI, Smoking Status, Drinking Status, Hypertension, Diabetes, Coronary heart disease, Atrial fibrillation, Cancer, History of stroke, NIHSS, TOAST).

albumin levels were inversely associated with severe ADL limitations following a stroke in different subgroups, consistent with the primary outcome. In this study, serum albumin was not significantly associated with severe ADL impairment in patients younger than 60 years, those with BMI greater than 30, individuals without hypertension, and with cardioembolism or stroke of another determined etiology. Given the limited sample size in these subgroups, caution is warranted in interpreting these findings, and further well-designed prospective studies are needed to confirm these results. Subgroup analysis stratified by sex, age, BMI, smoking status, alcohol status, hypertension, diabetes, and TOAST classification showed no significant interactions in any subgroup. Sensitivity analyses also reinforced the robustness of the observed relationship between serum albumin levels and severe ADL impairment after stroke.

Recent studies have confirmed a strong association between blood albumin levels and ADL in the general old population (9, 35–44). A

cross-sectional study of centenarians demonstrated that albumin levels were negatively associated with the likelihood of ADL disability. Higher albumin levels correlated with a lower likelihood of ADL disability, suggesting a protective effect of albumin against ADL decline in centenarians (45). However, the mechanisms connecting serum albumin to daily mobility after stroke remain unclear.

There are three possible mechanisms by which albumin enhances daily mobility after stroke. First, during the early reperfusion phase in acute ischemic stroke, albumin antagonizes stagnation, thrombosis, and leukocyte adhesion within the postcapillary microcirculation (8). Adequate serum albumin amounts increase microcirculatory flow, plasma viscosity, and oxygen transport capacity (46). Second, albumin may protect nerves by reducing cerebral edema or through its antioxidant or anti-apoptotic properties (47). Third, serum albumin levels have a favorable effect on the immune system (46), as protein energy deficiency after acute stroke impairs cellular immune function and further worsens prognosis, thereby increasing the risk of poor prognosis.

The strength of our study lies in its novel exploration of the association between serum albumin levels and severe ADL impairment following stroke, including the first discussion of their dose–response relationship. However, several limitations must be considered. Firstly, our data was exclusively obtained from 2020 to 2022. To ensure greater consistency, a larger dataset would be essential. Secondly, despite utilizing regression modeling, stratified analyses, and sensitivity analyses, residual confounding effects from unmeasured or unknown factors cannot be entirely excluded. Thirdly, our findings are based on a survey conducted with adults, necessitating further research to confirm their applicability to other populations. Finally, the cross-sectional nature of our study limits our ability to establish a causal relationship between serum albumin and severe ADL impairment after stroke, which requires further investigation through longitudinal studies. Additionally, future research could explore other biochemical markers that may influence ADL impairment post-stroke.

Conclusion

To summarize, our study found an L-shaped correlation between serum albumin levels and severe ADL impairment in stroke patients, with a critical threshold at around 38.0 g/L. These findings indicate that elevating serum albumin levels can notably reduce the severity of ADL impairment, especially in patients whose serum albumin levels are below the 38.0 g/L mark.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Shanghai East Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because as a retrospective cross-sectional study with anonymous data collection, informed consent was not required. 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

RB: Conceptualization, Data curation, Methodology, Writing – original draft. YS: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Writing – original draft. ML: Formal analysis, Investigation, Validation, Writing – original draft. XL: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. ZM: Formal analysis, Methodology, Project administration, Supervision, Writing – original draft. YH: Data curation, Formal analysis, Methodology, Writing – original draft. BL: Data curation, Formal analysis, Methodology, Writing – original draft. FC: Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1501294/full#supplementary-material

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EDITED BY
Felipe Cunha,
Rio de Janeiro State University, Brazil

REVIEWED BY
Hayk Petrosyan,
JFK Johnson Rehabilitation Institute, United States
Candela Diaz Canestro,
University of Zürich, Switzerland

*CORRESPONDENCE
Jie Jia
✉ shannonjj@126.com

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

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A resting-state fMRI cross-sectional study of cardiorespiratory fitness decline after stroke

Qingming Qu[1†], Kexu Zhang[2†], Hewei Wang[3,4], Jie Zhu[3,4], Yingnan Lin[5] and Jie Jia[3,4,6*]

[1]Department of Rehabilitation Medicine, Affiliated Hospital of Nantong University, Nantong, Jiangsu, China, [2]School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China, [3]Department of Rehabilitation Medicine, Huashan Hospital, Fudan University, Shanghai, China, [4]National Center for Neurological Disorders, Shanghai, China, [5]Department of General Medicine, Huashan Hospital, Fudan University, Shanghai, China, [6]National Clinical Research Center for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, China

Objective: The present study aimed to investigate alterations in neural activity and reorganization of functional networks within critical brain regions associated with reduced cardiorespiratory fitness (CRF) in stroke patients. By employing resting-state functional magnetic resonance imaging (fMRI), we sought to identify specific brain areas that may be implicated in CRF decline among this patient population.

Methods: A total of 22 patients with stroke and 15 healthy subjects matched for age, gender, and body mass index were recruited. Rehabilitation assessments included peak oxygen uptake (VO_2peak), peak work-rate, 10-meter walk test (10mWT), five times sit-to-stand test (FTSST), and 6-min walking distance (6MWD). Resting-state fMRI data were collected for the two groups, and correlation between changes in the amplitude of low-frequency fluctuations (ALFF) and CRF was analyzed to detect brain regions related to CRF and local neural activity in patients with stroke. On the basis of ALFF analysis, brain network analysis was performed, and the CRF-related brain regions in patients with stroke were selected as seed points. Functional connectivity (FC) analysis was the used to identify brain regions and networks potentially associated with CRF in patients with stroke.

Results: Patients with stroke exhibited significantly lower VO_2peak, peak work-rate, 10mWT, and 6MWD compared to healthy controls ($p < 0.001$). FTSST was significantly higher in patients with stroke than healthy controls ($p < 0.001$). ALFF analysis identified CRF-related brain regions in patients with stroke, including the ipsilesional superior temporal gyrus ($r = 0.56947$, $p = 0.00036$), middle frontal gyrus ($r = 0.62446$, $p = 0.00006$), and precentral gyrus ($r = 0.56866$, $p = 0.00036$). FC analysis revealed that the functional connectivity of brain regions related to CRF in patients with stroke involved the ipsilesional M1 to ipsilesional precentral gyrus and contralesional postcentral gyrus, and the correlation coefficients were $r = 0.54802$ ($p = 0.00065$) and $r = 0.49511$ ($p = 0.0025$), respectively. The correlation coefficients of ipsilesional middle frontal gyrus to contralesional middle frontal gyrus, angular gyrus and ipsilesional superior frontal gyrus were $r = 0.58617$ ($p = 0.00022$), $r = 0.57735$ ($p = 0.00028$), and $r = -0.65229$ ($p = 0.00002$), respectively.

Conclusion: This study observed that CRF levels were lower in stroke patients compared to those in healthy individuals. Resting fMRI analysis was applied to

identify CRF-related brain regions (ipsilesional superior temporal, middle frontal, precentral gyri) and networks in patients with stroke.

Clinical trial registration: https://www.chictr.org.cn/showproj.html?proj=151095.

KEYWORDS

cardiorespiratory fitness, resting-state fMRI, amplitude of low-frequency fluctuations, functional connectivity, brain network

1 Introduction

In China, a country with the largest stroke burden in the world, stroke (including ischemic stroke and hemorrhagic stroke) is the leading cause of mortality (1), and it is the third most common cause of disability-adjusted life years lost worldwide (2). It is well known that stroke is associated with many long-term complications, such as impairments in motor, language, and cognitive functions (3). Additionally, stroke can lead to a decline in cardiorespiratory fitness (CRF). CRF is the ability of the body to transport and use oxygen, usually expressed as maximal oxygen uptake (VO_2max) or peak oxygen uptake (VO_2peak) (4) and is considered a core component of health-related fitness (5). A low or unhealthy CRF is an independent and strong predictor of cardiovascular disease and adult all-cause mortality (6). The CRF of the stroke population, at an average level of 15.78 mL/kg/min (7), is approximately 53% of that of age-matched healthy populations (8). This CRF level is predictive of an inability to maintain daily activities and may be associated with a range of adverse outcomes, including frailty, reduced physical performance, an increased risk of cardiovascular events, and an increased rate of recurrent stroke (9).

Neuroplasticity, which can be defined as the ability of the brain to change its structure or function after exposure to new stimuli or environments (10), plays an important role in the recovery of patients with stroke (11). To the best of our knowledge, very little research has focused on whether CRF affects the recovery of stroke through neuroplasticity, and there have been no firm conclusions. Functional magnetic resonance imaging (fMRI), which can reflect the evolution of cortical functional remolding (12), has evolved rapidly in recent times, and resting state (rs)-fMRI especially has been applied to the study of many neurological disorders (13). Therefore, we used rs-fMRI to explore the brain regions associated with CRF to better understand the mechanisms affecting functional recovery in patients with stroke.

2 Methods

2.1 Study population

All stroke subjects were hospitalized in the department of rehabilitation medicine of Huashan Hospital Jing'an Branch of Fudan University from January to October 2022. A total of 58 patients with stroke with limb motor dysfunction were screened, and 22 patients (13 males and 9 females, with an average age of 57.2 ± 11.8 years) completed the trial and were ultimately included in the study. General patient information is shown in Table 1, and the superposition of lesions in the stroke subjects is shown in Figure 1. At the same time, 15 age-and sex-matched healthy volunteers (6 males and 9 females, mean age 57.3 ± 13.7 years) were recruited as healthy controls in Shanghai, and their general information is shown in Table 2.

All stroke subjects met the diagnostic criteria of "Diagnostic points for Major Cerebrovascular Diseases in China 2019" and were diagnosed as having stroke by computed tomography (CT) or magnetic resonance imaging (MRI). Inclusion criteria: (1) first onset, mainly subcortical injury; (2) 18 years ≤ age ≤ 80 years; (3) stable vital signs, clear consciousness, no obvious visual or hearing impairments, able to understand and execute commands; (4) unilateral limb movement disorder, Brunnstrom lower limb motor function grade IV; (5) mRS ≤ 3; (6) tolerance of cardiopulmonary exercise testing (CPET); (7) informed consent was obtained from patients or their immediate family members. Exclusion criteria: (1) history of heart, lung, or other diseases that seriously affect cardiopulmonary function; (2) severe spasticity (modified Ashworth Spasticity scale >2) or limited range of motion of the hemiplegic lower limb; (3) previous muscle, bone, and other serious diseases affecting power cycling pedaling; (4) patients with severe dementia or mental disorders; (5) patients with a cardiac pacemaker, metal joint replacement, claustrophobia, or other contraindications to MRI examination.

The inclusion criteria for the healthy subjects were as follows: (1) matched with the age, gender, and BMI of stroke subjects; (2) no major underlying diseases; (3) tolerance of MRI examination; (4) able to complete CPET; (5) fully understood the study and signed the informed consent form. Exclusion criteria were (1) history of stroke and (2) participants in other clinical trials.

This study was reviewed and approved by the Ethics Review Committee of Huashan Hospital, Fudan University. The Chinese clinical trial registry number is ChiCTR2200056043, and the registration time was January 31, 2022. All patients signed the written informed consent before enrolment, and the study was conducted in accordance with the Declaration of Helsinki.

2.2 Clinical outcome measurements and imaging data acquisition

Patients with stroke and healthy controls participated in 6-min walking distance (6MWD), 10-meter walk test (10mWT), five times stand-to-sit test (FTSST), VO_2peak, and peak work-rate assessments. VO_2peak and peak work-rate were assessed using CPET. Images of all subjects were collected with a 3.0-T MRI scanner (GE MR750, United States). MRI scanning included a T1-weighted scan, a T2-weighted scan, and a resting functional scan. Detailed information on the scanning and image preprocessing is included in the Supplementary material.

TABLE 1 Demographic and clinical information for stroke patients.

Number	Sex	Age	Ischemia (I)/ Hemorrhage (H)	Lesion	Days after stroke onset	Side of lesion, left/ right	Hemiplegic side
S1	M	45	H	BG	365	R	L
S2	M	58	I	BG	90	R	L
S3	F	53	I	BG	360	R	L
S4	M	68	I	CR	361	L	R
S5	M	38	I	BG	150	R	L
S6	M	53	I	Pon	120	L	R
S7	M	51	H	BG	120	R	L
S8	F	73	I	BG	30	L	R
S9	M	65	I	BG	60	R	L
S10	F	22	I	BG, IC	30	R	L
S11	F	65	I	CR	362	R	L
S12	M	52	I	CR	32	L	R
S13	F	57	H	BG	400	R	L
S14	F	72	I	Pon	60	L	R
S15	F	58	I	BG	181	L	R
S16	F	66	I	BG, IC	14	L	R
S17	M	52	H	Tha	35	L	R
S18	M	55	I	Pon	397	L	R
S19	M	72	I	BG	99	L	R
S20	F	71	I	BG	21	R	L
S21	M	70	I	BG	210	L	R
S22	M	49	I	BG	389	L	R

S, stroke; F, female; M, male; I, ischemia; H, hemorrhage; L, left; R, right; BG, basal ganglia; CO, centrum ovale; CR, corona radiate; Tha, thalamus; IC, internal capsule.

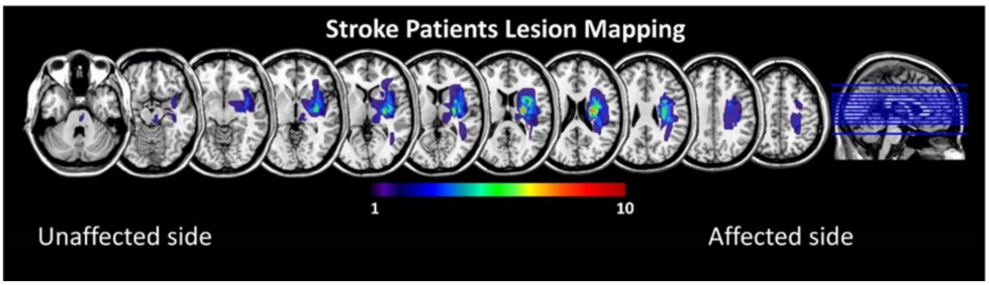

FIGURE 1
Lesion overlay maps for the stroke patients, all left lesions were flipped to the right side.

2.3 CPET

The study employed standardized CPET measuring equipment, utilizing a cycle ergometer, spirometry analysis, continuous gas exchange analysis (measuring oxygen consumption VO_2peak, ml/kg/min), and electrocardiogram monitoring for heart rate analysis to assess baseline fitness levels (PowerCube Ergo, Schiller, Switzerland). CPET was conducted under the supervision of a medical doctor with expertise in cardiopulmonary resuscitation.

The CPET involved a ramp protocol that incorporated a multistage incremental step test. Following a 3-min warm-up at a power output of 0 W and a pedal cadence of 50 revolutions per minute, the workload was increased by 15–20 W every 2 min until participants reached a state of self-perceived exhaustion, characterized by an inability to maintain the prescribed pedal cadence, cardiovascular or pulmonary distress, or fatigue. Objective exhaustion was verified when the respiratory exchange rate exceeded 1.05. Following peak exercise, a 3-min recovery phase was administered to all participants. The calculation of oxygen consumption at the anaerobic threshold (ml/kg/

TABLE 2 Demographic and clinical information for the participants.

	S (n = 22)	HC (n = 15)	Test statistics	P
	M (Q1–Q3)	M (Q1–Q3)		
Sex (M/F)	13/9	6/9	/	0.325
Age	57 (52, 68)	65 (48, 67)	$Z = -1.567$	0.117
BMI (kg/m^2)	24.0 (22.8, 26.0)	24.3 (20., 25.9)	$Z = -0.537$	0.592
Weight (kg)	63.5 (56.5, 72.5)	62.5 (51, 69)	$Z = -0.868$	0.386
FTSST (s)	13.0 (11.4, 15.0)	7.7 (6.4, 10.0)	Z = −21.791	0.000
VO_2 (ml/min)	895.7 (662.1, 1276.2)	1269.0 (1049.4, 1431.3)	$Z = -2.351$	0.019
VO_{2peak} (ml/kg/min)	14.3 (10.7, 18.7)	19.6 (16.3, 25.3)	$Z = -15.539$	0.000
Work-rate$_{peak}$ (W)	75 (60, 90)	80 (70, 100)	$Z = -7.218$	0.000
6MWD (m)	190 (128, 330)	535 (493, 553)	$Z = -24.835$	0.000
10mWT (m/s)	1.0 (0.5, 1.3)	1.8 (1.6, 2.0)	$Z = -19.934$	0.000

S, stroke; F, female; M, male; HC, healthy controls.

min) was carried out using the modified V-slope method, as outlined by Wasserman (14). The definition of VO_2peak was the highest level of oxygen consumption attained during the exercise test. It should be noted that this definition represents the maximum value, rather than an average of multiple breaths (15).

2.4 ALFF and FC analyses

The DPARSF toolbox was utilized to conduct the amplitude of low-frequency fluctuations (ALFF) analysis (16). The preprocessed image's time series for each voxel underwent fast Fourier transformation to convert it into the frequency domain. The ALFF value was calculated for each voxel in the slow-5 band by dividing the power in the 0.01–0.027 Hz frequency range by the power in the full frequency range (0–0.25 Hz). The resulting ALFF maps were transformed into Z-score maps using Fisher's Z-transformation.

Functional connectivity (FC) analysis was conducted using the CONN toolbox (17). The preprocessed images underwent band-pass filtering within the frequency range of 0.01–0.08 Hz. The voxel exhibiting the lowest p-value in the ALFF analysis (with detailed coordinates listed in the results) was designated as the center of a spherical seed (radius: 8 mm). The Pearson correlation coefficient was calculated for the relationship between the time series of each voxel and the seed to determine the FC.

2.5 Statistical analysis

We used SPSS (IBM SPSS 25.0, SPSS Inc.) to perform statistical analysis. The normality of function scores was assessed using the Shapiro–Wilk test, and measurement data are presented as mean ± SD for normally distributed data and median (Q1, Q3) for non-normally distributed data. The independent samples t-test or non-parametric Mann–Whitney U test was employed to determine statistically significant differences between groups. Categorical data were analyzed using the chi-square test, and the Fisher's exact test probability method was utilized. Pearson's correlation was utilized for correlation analysis. A p-value of $\leq$0.05 was deemed significant.

The SPM software was applied to analyze the resting fMRI data. In an effort to mitigate the occurrence of multiple comparison errors, threshold-free cluster enhancement (TFCE corrected $p < 0.01$, $H = 2$, $E = 0.5$, number of permutations = 5,000) with a cerebral gray matter mask was implemented. A statistically significant difference was established through line correction, with a p-value of less than 0.05. The results were presented using Xjview software. To further validate the relationship between the observed changes in brain activity and the patient's CRF, a Pearson correlation assay was employed to calculate the correlation between ALFF, FC, and VO_2peak change.

3 Results

3.1 Behavior

Statistical analysis revealed that patients with stroke exhibited significant differences in various physical performance measures compared to healthy controls. Specifically, patients with stroke demonstrated increased performance in the FTSST, while exhibiting decreased CRF, peak work-rate, 6MWD, and 10mWT performance (Table 2 and Figure 2).

3.2 ALFF

The brain regions exhibiting statistically significant differences in ALFF between the two groups were the middle frontal gyrus (MFG) and precentral gyrus (preCG), and superior temporal gyrus (STG) on the ipsilesional side, and the superior parietal lobule (SPL) on the bilateral side. Notably, patients with stroke demonstrated decreased ALFF value for their MFG and anterior central gyrus on the ipsilesional side, while an increased ALFF value was observed for their ipsilesional STG and bilateral SPL (Figure 3).

The brain regions that exhibited differences in ALFF between stroke-afflicted individuals and healthy controls, and those regions demonstrating a significant convergence between the ALFF and CRF correlation analyses of the two groups were associated with local neural activity in patients with stroke. The correlation coefficients for these regions were $r = 0.62446$ ($p = 0.00006$), $r = 0.56866$ ($p = 0.00036$),

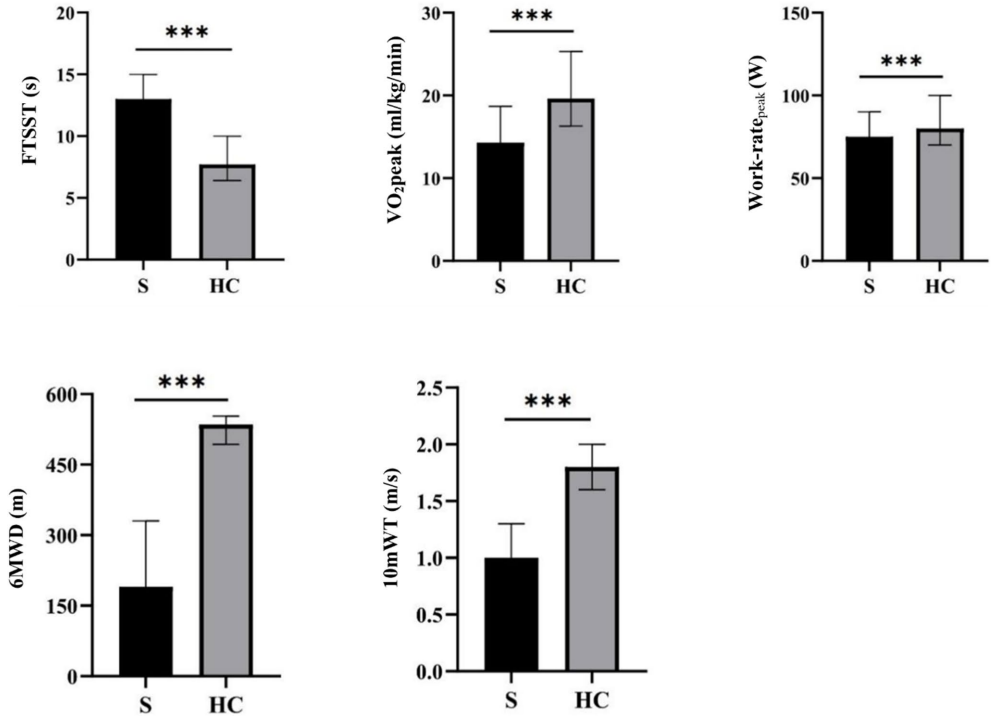

FIGURE 2
An analysis of behavioral data for stroke patients and healthy controls. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. FTSST, five times sit-to-stand test; VO_2peak, peak oxygen uptake; 6MWD, 6-min walking distance; 10mWT, 10-meter walk test.

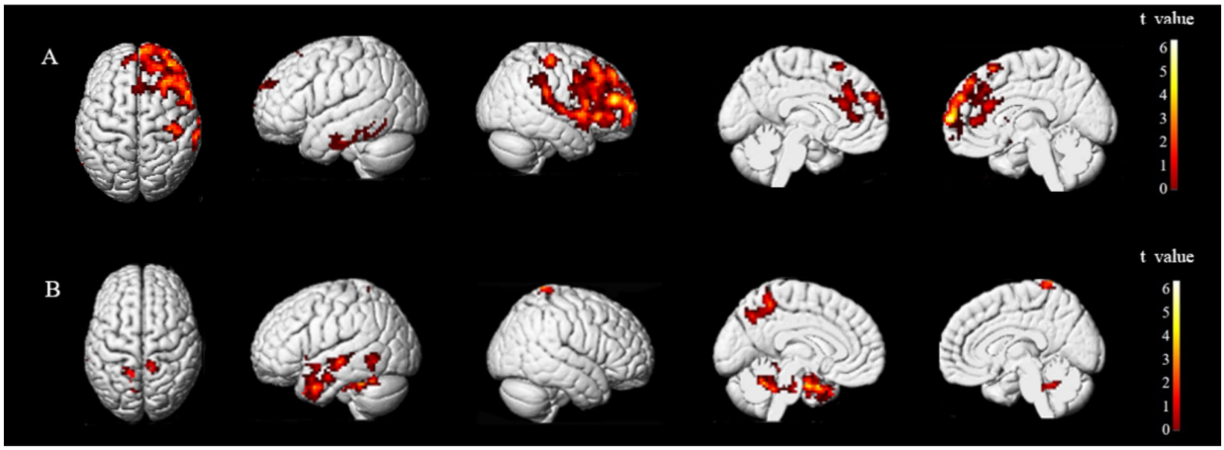

FIGURE 3
Brain regions with differences in ALFF between two groups. ALFF values were subjected to TFCE correction with a significance level of $p < 0.005$ and a cluster threshold of >30. Group A and Group B represent brain regions of stroke patients with reduced and increased ALFF values, respectively. The *t*-value is depicted in the color bar chart.

and $r = 0.56947$ ($p = 0.00036$), representing the MFG, preCG, and STG, respectively, on the ipsilesional side (Figure 4).

3.3 FC

Subsequent to the ALFF findings, further analysis of brain networks was conducted, whereby functional connections were established based on seed points. The seed points selected for this analysis were the primary motor cortex (M1), MFG, and STG, all located on the ipsilesional side. The MNI coordinates for the center of each seed point were as follows: ($X = -39$, $Y = -24$, $Z = 60$), ($X = 42$, $Y = 30$, $Z = 45$), and ($X = 69$, $Y = -15$, $Z = 9$) for M1, MFG, and STG, respectively. The entire brain was subjected to resting-state FC analysis (Figure 5).

The results showed a difference in the FC of stroke subjects. The overlapping brain network associated with the FC and CRF of all

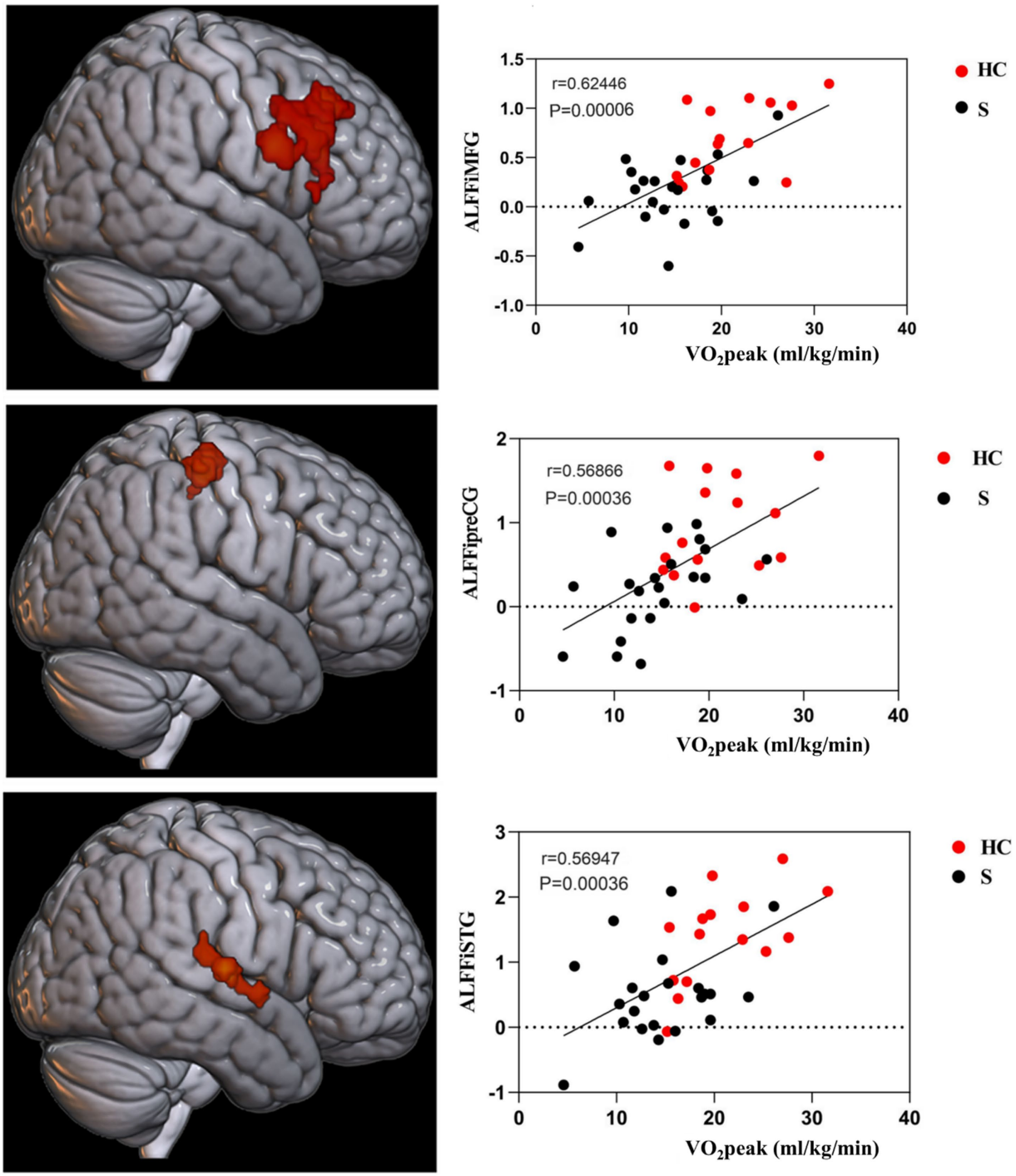

FIGURE 4
CRF-associated brain regions in stroke subjects. i, ipsilesional; MFG, middle frontal gyrus; preCG, precentral gyrus; STG, superior temporal gyrus.

subjects ran from the M1 of the ipsilesional side to the preCG of the ipsilesional side and the postcentral gyrus (poCG) of the contralesional side, the MFG of the ipsilesional side to the MFG of the contralesional side, the MFG of the ipsilesional side to the Angular Gyrus (ANG) of the contralesional side, and the MFG of the ipsilesional side to the superior frontal gyrus (SFG) of the ipsilesional side. The overlapping brain region seemed to be associated with CRF in stroke subjects (Figures 6, 7).

3.4 Schematic diagram of FC and CRF-related brain regions in patients with stroke

The FC between M1 and preCG on the ipsilesional side of stroke subjects was positively correlated with CRF ($r = 0.54802$, $p = 0.00065$). The FC of M1 on the ipsilesional side and poCG on the contralesional side were also positively correlated with CRF ($r = 0.49511$, $p = 0.0025$) (Figure 8).

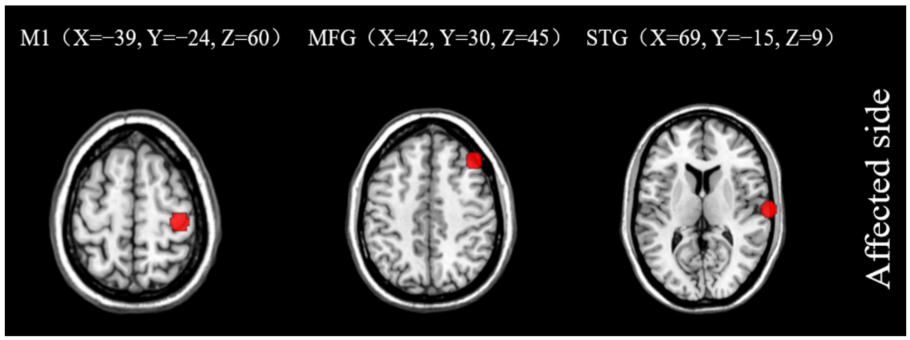

FIGURE 5
Seed points of interest coordinate diagram. M1, primary motor cortex; MFG, middle frontal gyrus; STG, superior temporal gyrus.

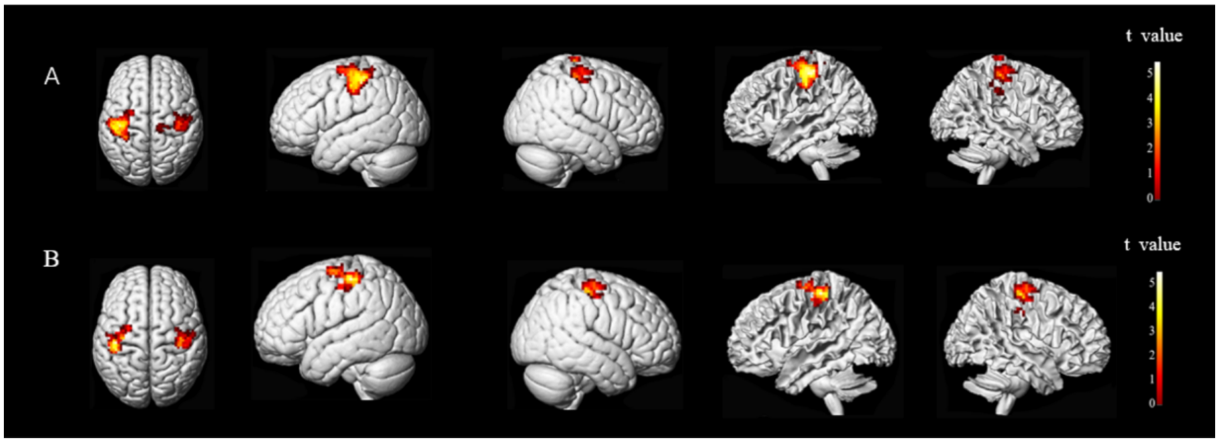

FIGURE 6
Different FC brain regions based on the M1 on the ipsilesional side of the two groups.

Based on the FC of the ipsilesional MFG in patients with stroke, the FC of the injured MFG and the contralesional MFG was positively correlated with CRF ($r = 0.58617$, $p = 0.00022$). Also positively correlated with CRF was the functional connection between the ipsilesional MFG and the contralesional ANG ($r = 0.57735$, $p = 0.00028$). Whereas the functional connection between the ipsilesional MFG and SFG was negatively correlated with CRF ($r = -0.65229$, $p = 0.00002$) (Figures 9, 10).

4 Discussion

In this cross-sectional study, rs-fMRI was used to identify potential CRF-related brain regions and networks in patients with stroke based on two levels of local neural activity. By comparing the ALFF values of healthy subjects with those of patients with stroke, we discovered increased ALFF values for the ipsilesional STG, MFG, and preCG regions in patients with stroke. Based on the ALFF analysis, brain regions related to CRF were selected as seed points for FC analysis. The results showed that the functional connection strength of stroke subjects was related to the ipsilesional preCG, contralesional poCG, contralesional MFG, contralesional ANG, and ipsilesional SFG.

First, by comparing the clinical indicators of patients with stroke and healthy subjects, we found that the 6MWD, 10mWT, CRF, and peak work-rate of patients with stroke were all far lower than those of healthy subjects, but not the FTSST, which demonstrated that stroke patients exhibit lower CRF levels compared to age-and sex-matched healthy controls. After stroke, motor function is impaired, and there is a decline in CRF closely related to motor function, which eventually results in patients being unable to carry out normally daily behavior and activities, leading to a further decline in their functional ability. CRF is one of the five vital signs (6) and plays a fundamental role in the recovery of various functions (including motor function and cognition). In this study, CPET was used to accurately measure CRF and peak work-rate, and the differences between the two groups were compared. Our results showed that the CRF of patients with stroke was reduced by about 28% compared with that of healthy people of the same age, which is consistent with previous studies (8).

Secondly, resting-state ALFF is an effective data-driven analysis technique based on fMRI (18) that effectively reflects changes in spontaneous neural activity after stroke (19). An elevated ALFF value suggests increased local neural activity. When we conducted a comparative analysis of ALFF values, we observed significantly higher ALFF values in the MFG and preCG of the ipsilesional side of healthy

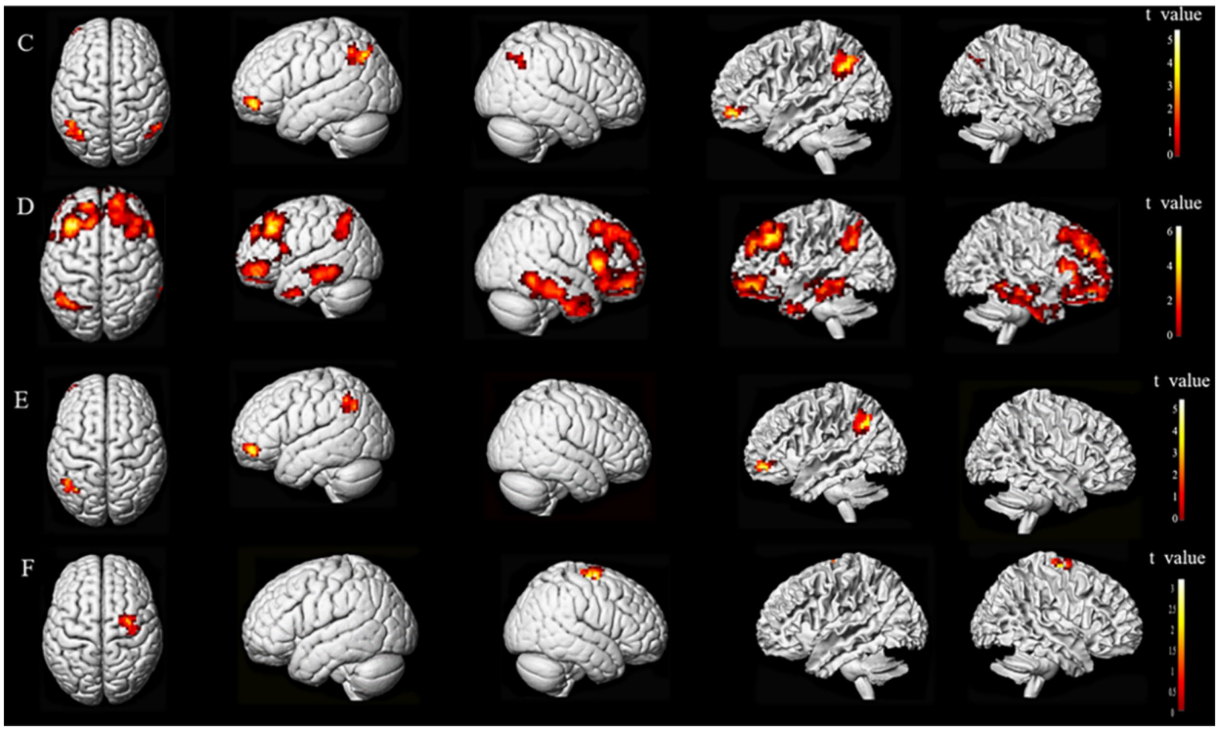

FIGURE 7
Brain regions with FC differences based on the MFG on the ipsilesional side.

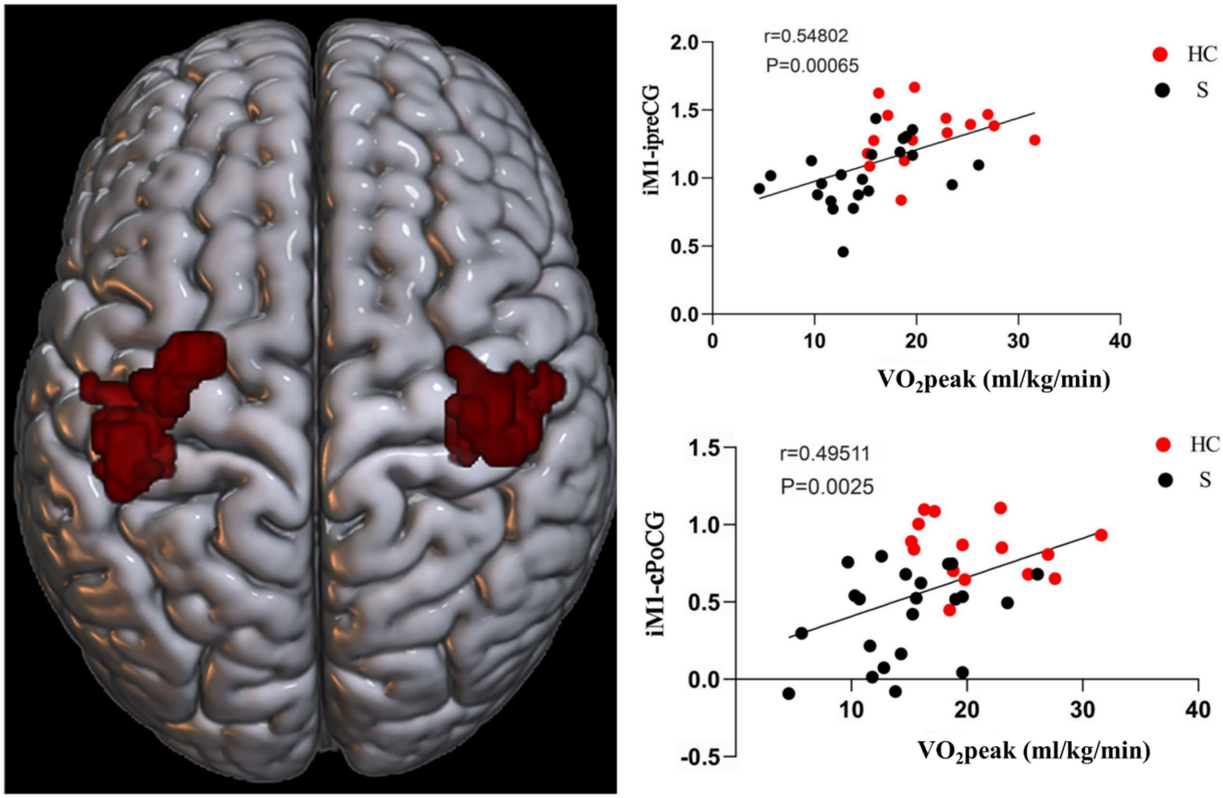

FIGURE 8
Functional connectivity (FC) of M1 on the ipsilesional side was positively correlated with CRF in stroke patients. i, ipsilesional; c, contralesional; preCG, anterior central gyrus; PoCG, postcentral gyrus.

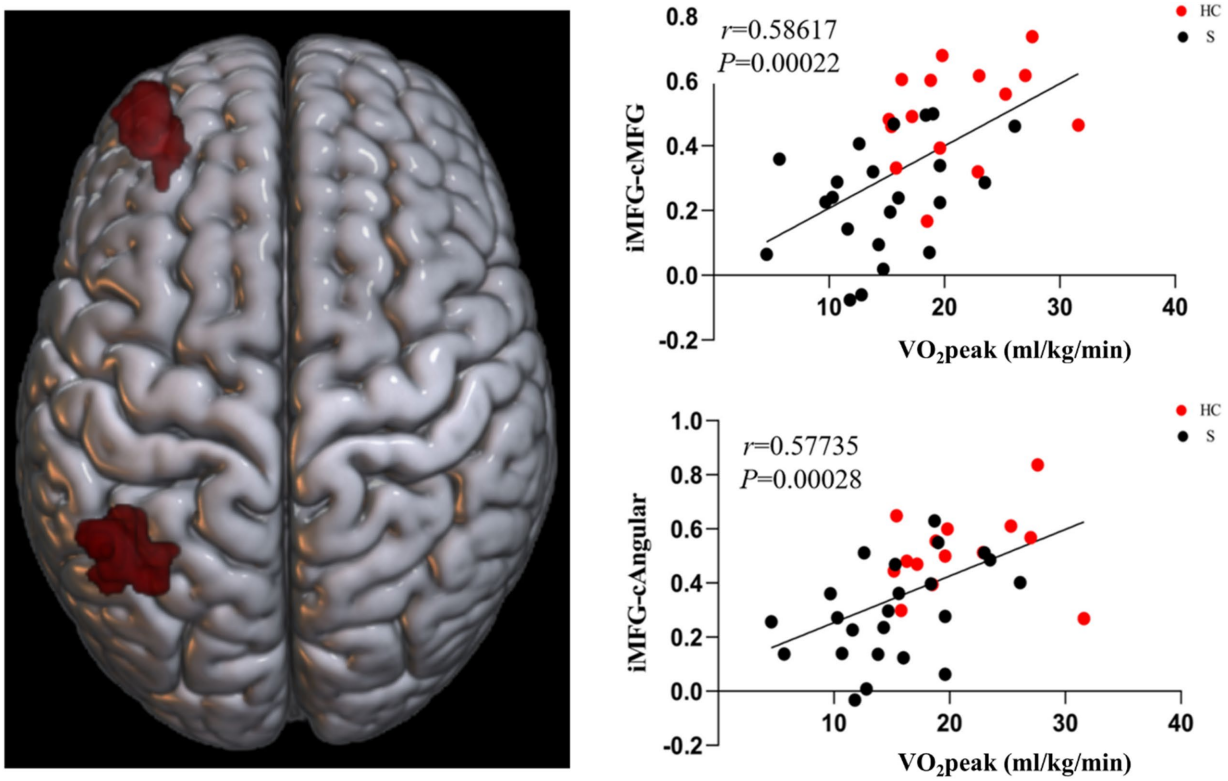

FIGURE 9
Functional connectivity of MFG on the ipsilesional side was positively correlated with CRF in stroke patients. c, contralesional; MFG, middle frontal gyrus; ANG, angular gyrus.

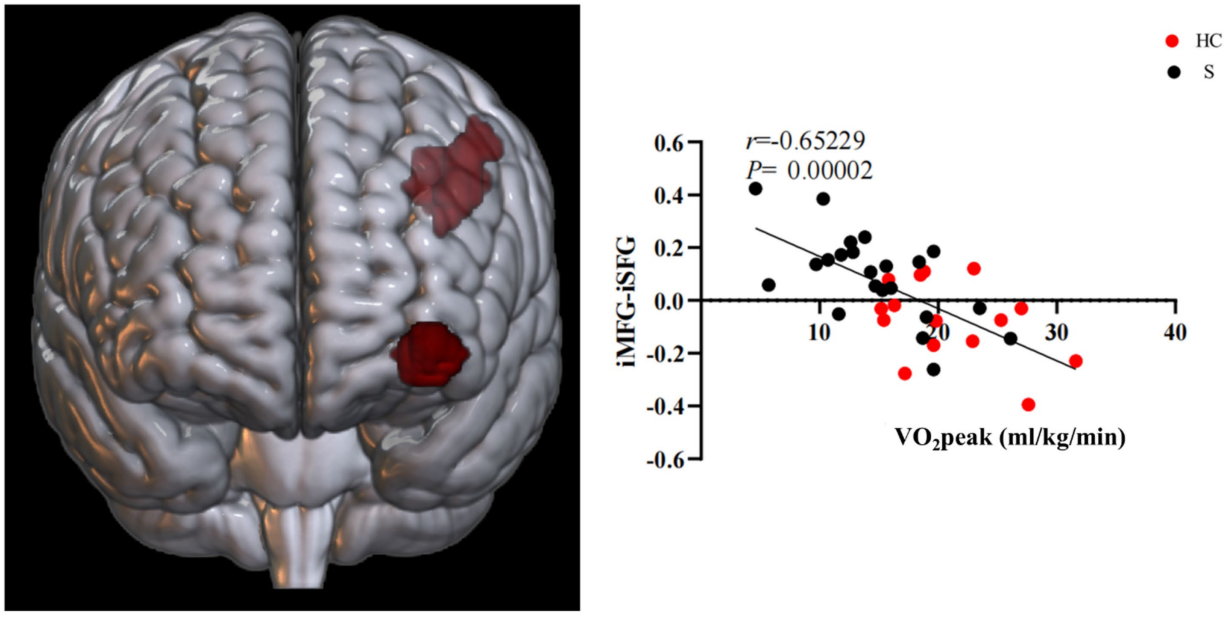

FIGURE 10
Functional connectivity of MFG on the ipsilesional side was negatively correlated with CRF in stroke patients. i, ipsilesional; MFG, middle frontal gyrus; SFG, superior frontal gyrus.

controls than those of patients with stroke. Conversely, the ALFF values of the bilateral SPL and MTG on the ipsilesional side were significantly higher in patients with stroke than healthy controls.

As a higher motor function center, the preCG is involved in alertness, selection, and preparation for performing tasks. The MFG is part of the prefrontal lobe, and previous studies have shown that it is

closely related to higher cognitive functions such as attention, executive function, and emotion (20, 21). After stroke, the excitability of the brain hemisphere on the ipsilesional side decreases due to the death of neurons, so the neuronal activity of the MFG and preCG on the ipsilesional side decreases, resulting in a decrease in ALFF. The SPL is part of the parietal lobe and plays a key role in many cognitive, perceptual, and motor related processes (22). The SPL is a component of the default network, and changes in this network affect the motor recovery of patients with stroke (23). Given the variability in the onset of stroke in subjects in this study and the known association between brain activity of patients with stroke and their onset course, it is plausible that the elevated ALFF values observed in the bilateral SPL of patients with stroke may have been attributable to compensatory mechanisms. The MTG, being a constituent of the temporal lobe, is associated with default, motor, memory, and auditory networks. Following impairments in related functions in patients with stroke, a compensatory elevation in brain activity ensues, which may account for the augmented ALFF value observed in the affected hemisphere of the MTG.

Analysis of ALFF values and CRF values in patients with stroke showed that the injured STG, MFG, and preCG were positively correlated with CRF in patients with stroke, and it is possible that CRF is associated with local nerve activity in these related brain regions in patients with stroke. The reduction in CRF in patients with stroke across all stages of the condition has a major impact on their ability to recover motor and other functions, as well as to varying degrees on their morbidity and stroke recurrence rates. An investigation conducted by Wittfeld and his team on an elderly population in good health demonstrated that CRF was linked to the majority of cortical networks, with the most notable correlations observed in the default mode network's prefrontal, middle temporal, and parahippocampal gyrus (24). Both the preCG and MFG are integral components of the frontal lobe and crucial constituents of the motor network. CRF and motor function are closely intertwined, which suggests there is an association. Despite the subjects in this study not being entirely congruent with those in Wittfeld et al.' (24) study, both studies have preliminarily substantiated that there is an intimate relationship between the frontal lobe and CRF. Hence, our conjecture posits that the frontal lobe has significance in relation to CRF. The STG, as a crucial component of the default network, may assume a relatively prominent function in the CRF of individuals with stroke. Nevertheless, the current dearth of pertinent research necessitates further empirical medical evidence to elucidate the mechanism by which the STG influences CRF.

Functional connectivity is a widely used method for examining brain network activity, with the strength of FC serving as an indicator of the level of connectivity between different regions of the brain. Based on the findings from the ALFF analysis, the ipsilesional STG, MFG, and primary motor cortex (M1) were identified as seed points for conducting a comprehensive FC analysis of patients with stroke, with the aim of identifying brain regions associated with CRF and brain network activity. FC analysis using the seed point of the ipsilesional STG revealed no discernible distinction between the two groups. However, when the analysis was conducted using the ipsilesional MFG as the seed point, the functional connection between the bilateral MFG and the ipsilesional ANG was observed to be significantly weakened. Conversely, the functional connection with the ipsilesional MFG was found to be enhanced. Patients with stroke exhibited a significant reduction in functional connection strength between ipsilesional M1 and ipsilesional preCG as well as contralesional poCG, as determined by their functional connectivity. The functional connections associated with CRF in patients with stroke were identified as contralesional MFG, ANG, and SFG, with the former two displaying a positive correlation with CRF, and the latter exhibiting a negative correlation. Furthermore, functional connections between ipsilesional preCG and contralesional poCG were positively correlated with CRF, as determined by their functional connectivity with ipsilesional M1.

The MFG is part of the motor network and plays an important role in attention control (25). The ANG, within the Inferior Parietal Lobule (IPL), is an important component of the frontal parietal motor network (26). In the present study, we observed a reduction in the functional connection strength of the ipsilesional MFG, contralesional MFG, and ANG, indicating a potential association between CRF and the motor network in individuals with stroke. Additionally, the functional connection strength of the MFG and SFG in the ipsilesional hemisphere was found to be augmented in patients with stroke, and it exhibited a negative correlation with CRF. One possible explanation is that the injury resulted in a decrease in the excitability of the cerebral hemispheres, leading to compensatory mechanisms being activated to sustain brain function. This over-compensation may disrupt functional equilibrium and the coherence between the hemispheres, which are fundamental for maintaining functional stability (26), and therefore, lead to a decline in CRF. M1 is a prominent brain region implicated in the motor network. Research has demonstrated a noteworthy association between a reduction in the strength of interhemispheric motor network functional connectivity and motor function recovery outcomes. Conversely, no correlation has been found between intra-hemispheric functional connectivity and motor function recovery outcomes (27). In this study, the functional connectivity strength of the motor network in the hemispheres of patients with stroke was positively correlated with CRF, and clinical observations indicate that motor function in patients with stroke is closely correlated with CRF. This suggests that the brain regions related to CRF in patients with stroke are similar and different from the brain regions of the motor network, which indirectly indicates that motor function is not the only factor affecting CRF. The functional connectivity strength of ipsilesional M1 and contralesional poCG was positively correlated with CRF. M1 and poCG are core components of the sensorimotor network and play crucial roles in human movement. Previous studies on motor function recovery after stroke found that the functional connection strength of ipsilesional M1 and the sensorimotor network on the contralesional side decrease after patients with stroke (28), and motor function is closely related to CRF; therefore, this also may be why the functional connection strength of ipsilesional M1 and contralesional poCG is positively correlated with CRF.

In general, we observed lower CRF levels in stroke patients compared to healthy individuals. However, our cross-sectional study design limits our ability to determine if the reduced CRF is a direct consequence of stroke or predated the event. Physical inactivity is known to increase stroke risk, suggesting that differences in CRF levels may have existed before the stroke. Therefore, we cannot exclude the influence of pre-stroke physical activity on post-stroke CRF. These findings highlight the need for longitudinal studies to better understand the causal relationships between physical activity, stroke, and CRF. Furthermore, most of the brain regions that correlated with CRF in patients with stroke, such as the MFG, preCG, and poCG, are components of the sensorimotor network. An important reason for

this may be that motor function is closely related to CRF, and sensory function affects the recovery of motor function. Various constituent brain regions of the default mode network (DMN) are also related to CRF, such as the ANG and STG. The basic function of the DMN is in maintaining the functions of other networks. Therefore, how it plays a role in brain networks related to CRF needs to be further dissected.

4.1 Conclusion

The CRF, peak work-rate, 10mWT and 6MWD of stroke subjects were lower than those of healthy controls, while the results for the FTSST were the opposite. Our rs-fMRI index ALFF analysis highlighted several brain regions and areas of local neural activity that appeared to be related to CRF in patients with stroke: the ipsilesional STG, MFG, and preCG. Additionally, FC showed several brain regions and networks were correlated with CRF in stroke patients, i.e., the ipsilesional M1 to ipsilesional preCG and contralesional postcentral gyrus, ipsilesional MFG to contralesional MFG, ANG and ipsilesional SFG.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Review Committee of Huashan Hospital, Fudan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

QQ: Writing – original draft, Writing – review & editing. KZ: Writing – original draft, Writing – review & editing. HW: Data curation, Formal analysis, Writing – original draft. JZ: Data curation, Validation, Writing – review & editing. YL: Data curation, Writing – review & editing. JJ: Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1465467/full#supplementary-material

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EDITED BY
Arthur Sá Ferreira,
University Center Augusto Motta, Brazil

REVIEWED BY
Shinsuke Hidese,
Teikyo University, Japan
Chi Chen,
Guizhou University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Gongchang Yu
✉ yugongchang@sdfmu.edu.cn
Li Li
✉ lily.jinan@163.com

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Association between stroke and fracture and the mediating role of depression: a cross-sectional study from NHANES 2017 to 2020

Yuqin Dan[1], Xuewen Pei[2], Danghan Xu[3], Zhaoxi Liu[4], Yuqi Wang[1], Meng Yin[5], Li Li[6]* and Gongchang Yu[5,7]*

[1]Shandong University of Traditional Chinese Medicine, Rehabilitation Medicine School, Jinan, China, [2]State University of New York at Buffalo, Albany, NY, United States, [3]The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Rehabilitation Center, Guangzhou, China, [4]Affiliated Traditional Chinese Medicine Hospital of Guangzhou Medical University, Guangzhou, China, [5]Neck-Shoulder and Lumbocrural Pain Hospital of Shandong First Medical University, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, China, [6]The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Rehabilitation Medicine Department, Jinan, China, [7]The Central Laboratory, Shandong Mental Health Center, Shandong University, Jinan, China

Background: Stroke is a significant health threat, and its complex interplay with fractures warrants further investigation. Depression, a critical psychological mediator in various health conditions, may also play a role. This study aims to clarify the intricate relationships among stroke, depressive symptoms, and fracture risk, potentially informing more holistic clinical strategies.

Methods: Utilizing the most recent data from the National Health and Nutrition Examination Survey (NHANES, 2017 to 2020), this study encompassed 4,979 valid samples. *T*-test and chi square test are conducted to compare the differences between fracture and non fracture subgroups. Subsequently, regression models were applied to assess the mediating impact of depression, with Sobel's test and the bootstrap method deployed to substantiate the mediation pathways.

Results: In this study, we conducted subgroup and regression analyses to investigate factors influencing fractures in stroke patients using NHANES data. Subgroup analysis revealed significant associations with gender, race, osteoporosis, and depression. Female stroke patients had a higher fracture rate (73.86% vs. 47.78%, $p < 0.001$), and those with post-stroke depression (29.67% vs. 13.16%, $p < 0.001$) or osteoporosis (33.33% vs. 15.81%, $p < 0.05$) were at increased risk of fractures. Logistic regression models showed a positive association between stroke and fractures in the unadjusted (OR = 1.862, 95% CI: 1.348–2.573, $p < 0.001$) and adjusted I models (OR = 1.789, 95% CI: 1.240–2.581, $p < 0.01$), but not in the adjusted II model. Depression was significantly correlated with fractures in all models (unadjusted OR = 2.785, 95% CI: 1.271–6.101, $p < 0.05$; Model 1 OR = 3.737, 95% CI: 1.470–9.498, $p < 0.01$; Model 2 OR = 3.068, 95% CI: 1.026–9.175, $p < 0.05$). Mediation analysis using Sobel and bootstrap tests indicated that depression mediates 7.657% of the relationship between stroke and fractures ($Z = 2.31$, $p < 0.05$), with significant indirect ($Z = 2.80$, $p < 0.01$), direct ($Z = 3.61$, $p < 0.001$), and total effects ($Z = 3.92$, $p < 0.01$). The direct effect of stroke on fracture was 0.079 (95% CI: 0.036–0.121), the total effect was 0.085 (95% CI: 0.043–0.128), and the indirect effect mediated by depressive symptoms was 0.007 (95% CI: 0.002–0.011). These results suggest that depressive symptoms following stroke may contribute to an increased risk of fractures.

Conclusion: Depressive symptoms serve as a critical mediator in the link between stroke and fracture risk. Consequently, our study concludes that holistic prevention strategies for fractures in stroke patients must incorporate a focus on mental health to effectively address this complex clinical challenge.

KEYWORDS

stroke, fracture, depression, association, NHANES, mediation

1 Introduction

Stroke is now the second leading cause of death and disability worldwide (1). Data indicates a concerning trend of stroke incidence shifting toward younger demographics (2). Moreover, a staggering 70% of stroke-related fatalities and 87% of resulting disabilities are concentrated in low- and middle-income nations (3). This alarming situation not only leads to a significant loss of labor force but also imposes a substantial financial and healthcare burden on these countries (4). Fracture represents a perilous complication arising from stroke (5). The occurrence of fractures in the stroke population can hinder functional recovery by leading to prolonged hospitalization, reduced independence and delays in rehabilitation (6). Therefore, prevention of fractures is important for the recovery of stroke patients.

Depression affects approximately 71% of stroke survivors within the critical three-month post-stroke period (7). This mental health condition is a significant contributor to the exacerbation of physical decline and the decline in cognitive-psychological performance among individuals who have experienced a stroke (8–10). Notably, a negative correlation exists between the depression severity and bone density, with severe depression contributing to osteoporosis, and increased fracture risk (11, 12). The mechanisms underlying these phenomena are likely closely related to the regulation of the "brain-neuro-musculoskeletal" axis, which involves the bidirectional interaction between the brain's neural control over the musculoskeletal system and the feedback regulation of brain function by the musculoskeletal system (13). For instance, the hypothalamic–pituitary–adrenal (HPA) axis, a critical pathway through which the nervous and endocrine systems interact, leads to the secretion of cortisol and other hormones upon activation (14). Depression often activates the HPA axis, increasing cortisol levels. Elevated cortisol not only exacerbates mood disorders like depression but also impairs musculoskeletal health by inhibiting osteoblast activity, reducing calcium absorption, and weakening bone structure. Cortisol plays a key role in stress responses, including fear, anxiety, and depression, while also inhibiting osteoblast activity, bone calcium absorption, and vascularization (15, 16). These effects indirectly disrupt bone microstructure and impedes bone turnover and metabolism (17). Therefore, depression, as a prevalent mood disorder, may significantly influence the link between stroke and fracture.

However, current research on the association between neuropsychiatric disorders and musculoskeletal diseases primarily focuses on adolescent and elderly populations (18–20). The relationship between depression and fracture incidence in stroke patients has not been well-defined. While previous studies have reported significant associations between depression and fall risk in stroke patients, most have been limited by small sample sizes and insufficient analytical depth, leaving the precise role of depression in the relationship between stroke and fracture poorly understood (21). To address these limitations, this study employs robust statistical methods, such as Sobel's test and bootstrap analysis, which enhance the reliability and validity of the mediation findings. This provides a solid foundation for future research and clinical practice, supporting the development of more effective strategies (22, 23).

In summary, to delve deeper into the association between stroke and fracture incidence risk, we used data from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 to (1) identify the influencing factors affecting fracture incidence in stroke and non-stroke populations; (2) investigate the relationship between stroke and fracture incidence and analyze the mediating role and extent of the influence of depression between stroke and fracture; (3) analyze stroke and fracture incidence-related Potential Mechanisms.

2 Materials and methods

2.1 Study population

A cross-sectional study was conducted using data from the National Health and Nutrition Examination Survey (NHANES) official website: https://www.cdc.gov/nchs/nhanes/NHANES. First, we included the entire 2017–2020 NHANES population (n = 15,560). Samples younger than 50 (n = 104,573) and those with missing fracture information (n = 8) were then excluded. We finally analyzed the remaining sample of 4,979 cases. Due to the fact that Mexican American persons were oversampled and all Hispanic persons from 2007 onwards were oversampled, we adjusted all analyses for the complex sample design of NHANES using the sample weights from NHANES (24).

2.2 Outcome variable

The primary outcome variable is fracture. Participants were asked, "Has the doctor ever told you about a hip/wrist/spine fracture or fracture?" A fracture in any of these three areas is considered a separate issue; a 'yes' to any one of them is indicative of a fracture (25).

2.3 Evaluation of exposures

The exposure variable is stroke, which was diagnosed through self reporting by doctors and patients in face-to-face interviews. A person who answers "Yes" to the question "Ever told you had a stroke?" is defined as having a stroke. With the NHANES database's limited

details on stroke types and severity, it is reasonable to deduce that most stroke participants in this study likely suffer from ischemic stroke, aligning with the prevailing research within the NHANES database (26).

Depression is the main covariate. The Patient Health Questionnaire (PHQ-9) is used to diagnose depression, which is a self reporting assessment based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) version, used to describe the nine signs and symptoms of depression. The scores were summed to give each participant a total score ranging from 0 to 27. As in previous studies, the present study defined depression as a total PHQ-9 score of ≥10 (27).

In addition, covariates also include: osteoporosis, dizziness, fasting glucose, alcohol, diabetes, High blood pressure, BMI, age, gender, race, marital status, education level, family monthly poverty level category, et al. An individual who affirms the query "Have you ever been diagnosed with osteoporosis or brittle bones?" is classified as having osteoporosis. Similarly, an individual who responds affirmatively to the question "Have you experienced dizziness or lightheadedness?" is categorized as experiencing dizziness. Furthermore, an individual who answers "Yes" to the question "Have you ever consumed any form of alcohol?" is identified as an alcohol consumer. Additionally, serum cotinine levels are a reliable biomarker for assessing tobacco exposure. Cotinine, a primary metabolite of nicotine, serves as an effective indicator of an individual's level of exposure to tobacco smoke (28). All variables were obtained through standardized clinical evaluation and laboratory testing, and were selected based on previous literature and clinical expert opinions to control for potential confounding factors.

2.4 Ethic statement

The study protocol was reviewed and approved by the Research Ethics Review Board of the National Center for Health Statistics.

2.5 Statistical analysis

We conducted all statistical analyses using SAS version 9.4. Firstly, this study conducted a statistical description of the demographic characteristics and key variables of society. Categorical variables are described by frequency (percentage), while continuous variables are described by mean (standard deviation, SD). The differences between fractured and non fractured subgroups were compared using *t*-test or chi square test. Secondly, a univariate analysis was conducted on the fracture and non fracture subgroups of stroke patients using the aforementioned method. All samples were weighted to account for potential biases and to ensure that the study's findings are representative of the broader population. This approach is crucial for enhancing the accuracy and generalizability of the research results (29). Then, we employed weighted logistic regression models to estimate the adjusted odds ratios (aOR) for fracture occurrence, accounting for various covariates and adjusting for independent variables across different demographic groups. Model 1 focused on the influence of age, gender, and race, while Model 2 expanded the analysis to include education, marital status, family monthly poverty level category, cotinine levels, and history of alcohol consumption. These additional variables in Model 2 aimed to provide a more comprehensive understanding of the factors associated with fracture risk. Both models were designed to control for potential confounding effects, ensuring that the estimated odds ratios were adjusted for the influence of these independent variables (30). Next, Judd and Kenny's recommendations and Baron and Kenny's causal step approach were employed to investigate the relationship between stroke, depression, and fracture among the population aged 50 and above.Therefore, the three regression processes would estimate the follow ing effects: (1) the effect of stroke on fracture; (2) the effect of stroke on depressive symptoms; (3) the effect of depressive symptoms on fracture when stroke were controlled; and (4) the effect of stroke on fracture when depressive symptoms were controlled (31). In our analyses, covariates were adjusted to enhance model estimation precision. The Sobel test was applied to assess the significance of the indirect effect, with a Z-value surpassing 1.96 indicating significance. Effect sizes and 95% confidence intervals were determined using bootstrapping with 5,000 resamples, considering effects significant if their intervals did not span zero. Statistical tests were two-tailed, with $p < 0.05$ set as the threshold for significance (25) (Figure 1).

3 Result

3.1 Univariate analysis

The results of univariate analysis are shown in Table 1. We found significant association between participants with and without fractures in terms of age, race, marital status, education level, tobacco smoke exposure, alcohol consumption, bone density level, depression status, and stroke. Compared with the non fracture group, the fracture group had a higher proportion of patients diagnosed with stroke (10.93% > 6.18%, $p < 0.001$), depression (11.13% > 6.21%, $p < 0.05$), and osteoporosis (21.63% > 11.51%, $p < 0.001$). However, there is no significant association between dizziness and fractures(44.35% > 39.91%, $p > 0.05$).

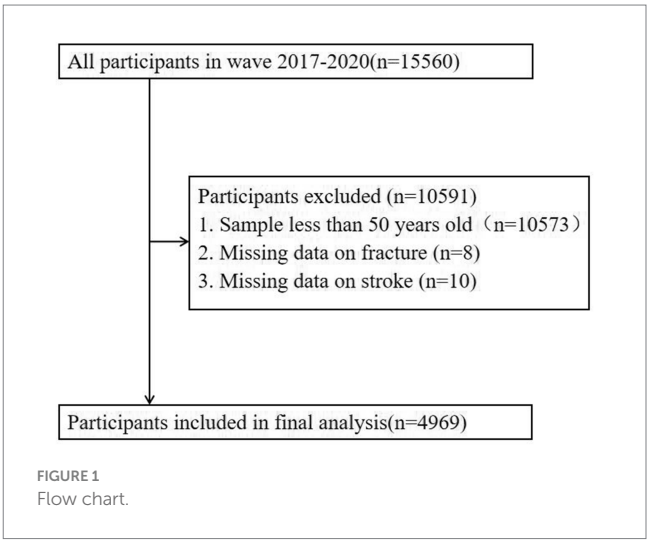

FIGURE 1
Flow chart.

TABLE 1 Weighted univariate analysis of factors affecting fractures.

Variable	Fracture		*p*-value
	Yes	No	
No. of participants	726	4,253	
Age, years	65.32 (0.58)	63.87 (0.29)	**0.0085**
Gender, %			0.7979
Male	366 (46.91)	2094 (46.19)	
Female	360 (53.09)	2,159 (53.81)	
Race, %			**<0.0001**
Mexican American	38 (2.30)	419 (5.37)	
Other Hispanic	73 (4.92)	432 (6.45)	
Non-Hispanic White	403 (80.71)	1,558 (67.33)	
Non-Hispanic Black	134 (5.42)	1,198 (11.40)	
Non-Hispanic Asian	35 (1.97)	494 (5.83)	
Other Race - Including Multi-Racial	43 (4.66)	152 (3.62)	
Marital status, %			**0.0053**
Married/Living with Partner	376 (58.64)	2,444 (64.94)	
Widowed/Divorced/Separated	291 (36.24)	1,435 (28.76)	
Never married	59 (5.12)	366 (6.30)	
Education level			**0.0441**
Less than 9th grade	55 (2.69)	448 (5.24)	
9-11th grade (Includes 12th grade with no diploma)	74 (5.95)	508 (7.77)	
High school graduate/GED or equivalent	199 (31.01)	1,060 (28.73)	
Some college or AA degree	249 (34.55)	1,234 (28.17)	
College graduate or above	148 (25.7880)	992 (30.08)	
Family monthly poverty level category			0.8509
Monthly poverty level index =1.30	177 (17.6039)	1,086 (18.85)	
1.30 < Monthly poverty level index = 1.85	100 (12.4898)	597 (12.61)	
Monthly poverty level index >1.85	363 (69.9063)	2009 (68.54)	
BMI (kg/m**2)	30.02 (0.4)	29.87 (0.16)	0.7253
High blood pressure	446 (54.09)	2,345 (49.41)	0.1472
Fasting Glucose (mg/dL)	114.926560 (2.09)	117.135401 (1.55)	0.3133
Diabetes	183 (20.27)	1,019 (19.19)	0.6496
Cotinine, Serum (ng/mL)	53.651996 (4.43)	40.818935 (2.63)	**0.0068**
Alcohol	592 (95.75)	3,263 (91.28)	**0.0028**
Osteoporosis	160 (21.63)	450 (11.51)	**<0.0001**
Depression	88 (11.13)	317 (6.21)	**0.0013**
Dizziness	133 (44.35)	567 (39.91)	0.2357
Stroke	101 (10.93)	334 (6.18)	**<0.0001**

Bolded text reads: $p < 0.05$.

3.2 Subgroup analysis

Subgroup analysis was conducted to confirm which factors affect fractures in the stroke population. The results of subgroup analysis are shown in Table 2. We found a significant association between gender, race, osteoporosis, depression, and fractures in stroke patients. Specifically, among stroke patients, the proportion of male fractures is lower (26.14% < 52.22%, $p < 0.001$), while the probability of female fractures is higher (73.86% > 47.78%, $p < 0.001$). In addition, stroke patients with depression(29.67% > 13.16%, $p < 0.001$) and osteoporosis(33.33% > 15.81%, $p < 0.05$) are more likely to experience fractures.

TABLE 2 Weighted univariate analysis of the impact on fractures in stroke patients.

Variable	Stroke		
	Fracture	Non-fracture	*p*
No. of participants	101	334	
Age, years	68.65 (1.53)	68.01 (0.83)	0.734
Gender, %			
Male	47 (26.14)	180 (52.22)	**<0.0001**
Female	54 (73.86)	154 (47.78)	
Race, %			
Mexican American	4 (1.65)	19 (4.33)	**0.0122**
Other Hispanic	8 (2.59)	24 (5.68)	
Non-Hispanic White	54 (77.69)	131 (64.51)	
Non-Hispanic Black	21 (7.94)	130 (18.16)	
Non-Hispanic Asian	4 (1.64)	15 (2.75)	
Other Race	10 (8.48)	15 (4.57)	
Marital status, %			
Married/Living with Partner	47 (55.34)	158 (56.42)	0.4007
Widowed/Divorced/Separated	44 (35.17)	148 (39.26)	
Never married	10 (9.49)	26 (4.32)	
Education level			
Less than 9th grade	10 (4.76)	30 (6.63)	0.2507
9-11th grade (Includes 12th grade with no diploma)	11 (6.51)	61 (13.46)	
High school graduate/GED or equivalent	35 (37.87)	107 (40.62)	
Some college or AA degree	27 (24.61)	88 (24.43)	
College graduate or above	18 (26.25)	48 (14.86)	
Family monthly poverty level category			
Monthly poverty level index =1.30	34 (31.55)	111 (25.51)	0.7839
1.30 < Monthly poverty level index = 1.85	15 (13.30)	45 (13.92)	
Monthly poverty level index >1.85	40 (55.15)	138 (60.57)	
BMI (kg/m**2)	30.72 (0.72)	29.85 (0.55)	0.316
High blood pressure			
Yes	76 (71.83)	261 (71.64)	0.9881
No	25 (28.17)	73 (28.36)	
Fasting Glucose (mg/dL)	120.71 (8.55)	127.59 (6.56)	0.5116
Diabetes			
Yes	43 (43.64)	106 (32.23)	0.3055
No	55 (54.43)	216 (66.46)	
Borderline	3 (1.92)	11 (1.31)	
Cotinine, Serum (ng/mL)	52.37 (13.87)	65.19 (13.71)	0.5708
Alcohol			
Yes	78 (87.44)	253 (93.2069)	0.2654
No	8 (12.55)	25 (6.7931)	
Osteoporosis			
Yes	34 (33.33)	46 (15.81)	**0.0167**
No	67 (66.67)	286 (84.19)	
Dizziness			
Yes	34 (56.58)	88 (54.98)	0.8836
No	15 (43.42)	75 (45.02)	
Depression			
Yes	25 (29.67)	48 (13.16)	**0.0028**
No	76 (70.33)	286 (86.84)	

Bolded text reads: $p < 0.05$.

3.3 Logistic regressive analysis

The associations between stroke, depression, and fracture risk were evaluated using Unadjusted, Model I, and Model II approaches. The effect sizes, ORs, and 95% CIs are presented in Table 3. The results showed that stroke was positively associated with fracture risk in both Unadjusted model (OR = 1.862, 95% CI: 1.348–2.573, $p < 0.001$) and Model I (OR = 1.789, 95% CI: 1.240–2.581, $p < 0.01$). However, there is no significant association in Model II. In the stroke population, using non depressed individuals as a reference, there was a significant positive association between depression and fractures among Unadjusted (OR = 2.785, 95% CI: 1.271–6.101, $p < 0.05$), Model I (OR = 3.737, 95% CI:1.470–9.498, $p < 0.01$) and Model II (OR = 3.068, 95% CI: 1.026–9.175, $p < 0.05$).

3.4 Mediation analysis

Regression analysis was utilized to explore the mediating role of depressive symptoms on the relationship between stroke and fracture. Meanwhile, we adjusted the covariate osteoporosis, age, gender, race, marital status, education level, family monthly poverty level category, tobacco exposure and alcohol. The Sobel and bootstrap tests were conducted to check for indirect, direct, and total effects. Table 4 shows that the percentage of depression mediated stroke and fracture is 7.657% ($Z = 2.31$, $p < 0.05$). As shown in Figure 2, Sobel test indicates that indirect effects ($Z = 2.80$, $p < 0.01$), direct effects ($Z = 3.61$, $p < 0.001$), and total effective rate ($Z = 3.92$, $p < 0.001$) are significant. This indicates that stroke can cause depressive symptoms, thereby increasing the risk of fractures. The boot strap method indicated that the direct effect of stroke on fracture was 0.079 (95% CI: 0.036–0.121), while the total effect was 0.085 (95% CI: 0.043–0.128). The indirect effect of stroke on fracture mediated by depressive symptoms was 0.007 (95% CI: 0.002–0.011).

4 Discussion

Using data from 2017 to 2020 in the National Health and Nutrition Examination Survey (NHANES), the study found a significant association between stroke and fractures, with depressive symptoms mediating the risk of fractures in stroke patients (32). Sobel and Bootstrap methods supported the results of fundamental analysis, demonstrating the robustness of the results (33).

The relationship between stroke and fracture is influenced by multiple factors. While stroke survivors are prone to dizziness, often leading to falls and fractures (34, 35). However, the present study found no significant association between dizziness and fracture risk in this population. This suggests that dizziness may not be a primary factor in stroke-related fractures (36). As is well known, osteoporosis is the primary factor leading to fractures (37). The study identified a significant association between osteoporosis and fractures in stroke patients, likely due to limited mobility, reduced mechanical load from paralysis (38), and oxidative stress from cerebral ischemia–reperfusion injury. This stress disrupts the dynamic balance of osteoblast differentiation, apoptosis, and metabolism, contributing to osteoporosis (39). At the same time, gender emerges as an important influencing factor (40). Table 2 shows that in the stroke population, women in the stroke population are more prone to fractures than men. Yao et al. (41) reveal that estrogen fluctuations during menopause disrupt neurotransmitter secretion, affecting osteoblast and osteoclast balance and leading to osteoporosis. Furthermore, estrogen may contribute to osteoporosis progression by inducing oxidative stress, triggering inflammatory responses, and modulating microRNA expression, further increasing fracture susceptibility (42).

Existing research confirms that depression plays a pivotal mediating role in stroke and its associated complications (43), with a significant association between stroke and depression (44). In addition, osteoporosis can be triggered by increased life stress and

TABLE 3 Multi-model regression analysis of fracture risk in stroke patients by depression status.

Variable	Unadjusted		Model I		Model II	
	aOR (95%CI)	*p*	aOR (95%CI)	*p*	aOR (95%CI)	*p*
Stroke						
Yes	1.862 (1.348,2.573)	**0.0005**	1.789 (1.240,2.581)	**0.0031**	1.624 (0.931,2.832)	0.0845
No	Referent		Referent		Referent	
Stroke						
With depression	2.785 (1.271,6.101)	**0.0125**	3.737 (1.470,9.498)	**0.0075**	3.068 (1.026,9.175)	**0.0453**
Without depression	Referent		Referent		Referent	

Bolded text reads: $p < 0.05$.

TABLE 4 Mediation analysis of depression on stroke and fracture.

	Estimate	Std. Error	95% Confidence interval		Z	*p*
			Lower	Upper		
Stroke→depression→fracture	7.657	3.314	2.21	11.83	2.31	**0.0209**

Adjusted covariates osteoporosis/age/gender/race/marital status/education level/family monthly poverty level category/tobacco smoke exposure/alcohol. Bolded text reads: $p < 0.05$.

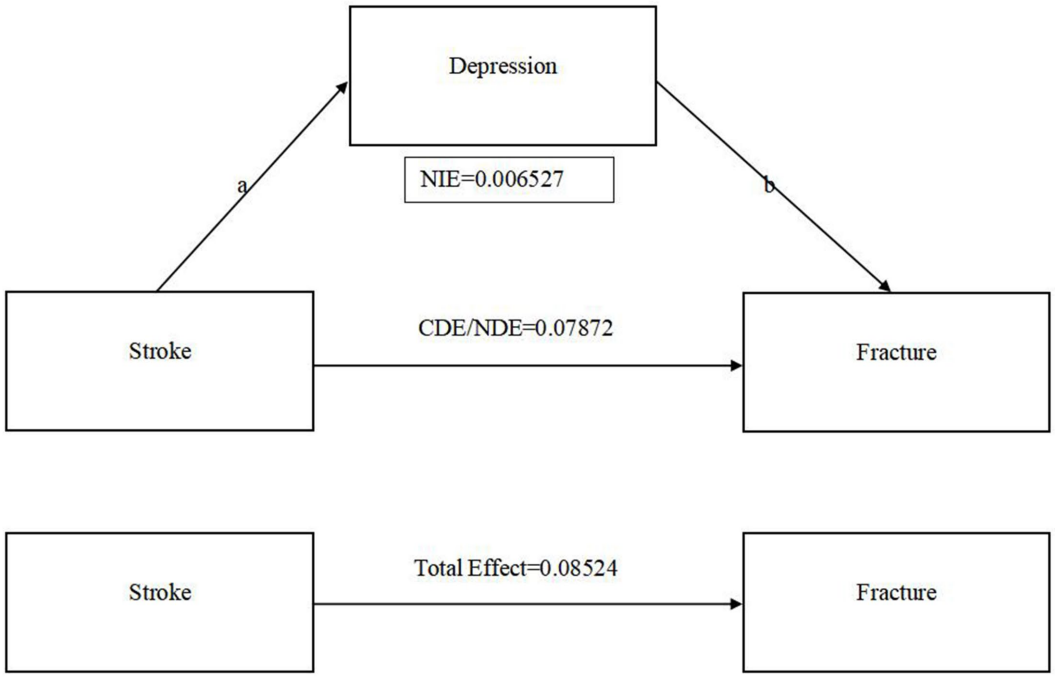

FIGURE 2
The relationship between stroke, depression and fracture. (a) CDE: Controlled Direct Effect; NDE: Natural Direct Effect; NIE(a*b): Natural Indirect Effect. (b) Adjusted covariates osteoporosis/age/gender/race/marital status/education level/family monthly poverty level category/tobacco smoke exposure/alcohol.

depression (45). Hence, we cautiously posit that depression could serve as a critical intermediary in the relationship between stroke and fractures. Table 3 shows that the stroke and unadjusted fracture models showed significant associations. Nonetheless, following the partial adjustment for confounding factors, the association observed between stroke and fracture models became non-significant. This indicates that the association between stroke and fractures is likely due to a complex interplay of various contributing elements (46). However, stratified regression analyses of the stroke population yielded a significant association between depressive status and the fracture model in the stroke population, whether or not confounders were excluded (47). Therefore, depression plays an important role in the relationship between stroke and fracture. Table 4 indicates that while the mediated association between depression and the occurrence of stroke-related fractures is modest (7.57%, $p < 0.05$) but statistically significant (48). The Sobel test results, as illustrated in Figure 2, confirm the statistical significance of the indirect effects ($Z = 2.80$, $p < 0.01$), direct effects ($Z = 3.61$, $p < 0.001$), and total effects ($Z = 3.92$, $p < 0.001$) of stroke on depressive symptoms and subsequent fracture risk. Bootstrap analysis provides a more nuanced view, pinpointing the direct effect of stroke on fractures at 0.079 (95% CI: 0.036–0.121) and the total effect at 0.085 (95% CI: 0.043–0.128). The indirect effect, mediated by depression, is a modest but significant 0.007 (95% CI: 0.002–0.011). These insights highlight the pivotal role of depression as a mediator in the relationship between stroke and fracture risk, underscoring the need for integrated approaches in managing these conditions (49).

In addition to exploring depression as a mediator between stroke and fracture risk, the underlying neurophysiological mechanisms warrant further investigation. Stroke induces structural and functional impairments in critical brain regions, which can precipitate negative emotional states such as depression (50). This emotional disturbance is associated with dysregulation of neurotransmitter secretions (51). Specifically, the HPA axis increases cortisol levels while decreasing serotonin levels (52). These imbalances impair osteoblast function, hinder calcium absorption in bones, and impede skeletal angiogenesis (53). Consequently, bone microarchitecture is compromised, and normal bone turnover and metabolism are disrupted, predisposing individuals to osteoporosis and an increased risk of fractures. Conversely, fractures also impact stroke recovery (47). Research indicates that fractures can enhance inflammation in the peri-infarct area, thereby exacerbating ischemic stroke (54). Furthermore, inadequate post-fracture care leading to lower extremity deep vein thrombosis also increases the risk of stroke (55). Thus, stroke and fractures may have a reciprocal causal relationship, with regulatory mechanisms based on the "brain-neuro-musculoskeletal" axis.

During the analysis, we searched for papers published on PubMed before September 2024 using the keywords "stroke," "fracture," and "depression." A total of 199 papers were retrieved, of which three were relevant to our study. Yeh et al. (56) found that post-stroke depression significantly contributes to hip fractures among stroke survivors, exerting a disproportionately negative effect on younger individuals, irrespective of gender and the presence of comorbid conditions. Kelly et al. (57) consider that the brain-bone axis plays a crucial role in the regulation of skeletal metabolism, sensory innervation, and endocrine crosstalk among these organs. Furthermore, a previous study

identified a notable association between stroke and fractures in elderly patients undergoing rehabilitation post-stroke (58). However, unlike our findings, no significant disparities in depressive symptoms and functional status were observed upon admission and discharge among the compared patient cohorts. This discrepancy may be related to the failure to exclude confounding factors (59). Additionally, the previous study did not quantify depression's influence on the stroke-fracture relationship. Moreover, it lacked an analysis of the underlying mechanisms at play.

Our research has to some extent overcome these shortcomings and has the following advantages. Firstly, we established a distinct association between stroke and fractures, particularly noting a significant association between fracture incidence and depression in stroke patients. Secondly, we employed a weighted regression model to scrutinize the relationship between depression and fractures in this patient population, effectively addressing the challenge of a limited sample size. Thirdly, through an in-depth analysis with depression as a mediating variable, we discovered that while depression's contribution is not substantial, its statistical significance is marked. Lastly, we propose an interactive relationship exists between brain neurotransmitters and bone cells, potentially regulated by the 'brain-bone' axis.

However, our study has some limitations. The sample size is relatively small and the data is restricted to the American demographic, primarily composed of Hispanic Americans, the elderly, and children, which may affect the generalizability of the findings. Additionally, the stroke situation is obtained through self-report, which could easily cause recall bias. Moreover, NHANES only records fracture data for individuals over 50 years old, preventing us from observing stroke and fracture incidence in younger populations.

The cross-sectional design of our study limits the ability to establish a temporal sequence among stroke, depression, and fracture occurrence. Future studies should incorporate multicenter and demographically diverse cohorts to further validate the intricate relationships among these variables. A prospective study design would be beneficial, as it would allow for a more accurate assessment of the temporal relationships between stroke, depression, and fracture risk (60). This approach would help in understanding the causal pathways and potential differences in outcomes across various stroke subtypes, such as ischemic and hemorrhagic strokes. Additionally, intervention studies could be recommended to evaluate the impact of targeted mental health interventions on reducing fracture risk in stroke patients. Such studies could include randomized controlled trials to assess the efficacy of depression management programs in improving bone health outcomes and reducing fall-related injuries. Moreover, animal experiments exploring the mechanisms of the brain-bone axis could provide valuable insights into the underlying physiological processes. Studies using animal models can help elucidate the bidirectional communication between the brain and bone, involving factors such as neuroendocrine signals and extracellular vesicles. Such research could advance our understanding of neuroendocrine signals and extracellular vesicles, ultimately contributing to the development of therapeutic strategies for treating both neurological and musculoskeletal disorders. By exploring these mechanisms, researchers may pave the way for developing novel therapeutic strategies that target both neurological and musculoskeletal disorders.

5 Conclusion

This study indicates a positive association between stroke and fractures, highlighting depression as a substantial mediating factor. It suggests that clinicians should consider both conditions concurrently in their assessments.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://www.cdc.gov/nchs/nhanes/NHANES.

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

YD: Conceptualization, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. XP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DX: Conceptualization, Data curation, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. ZL: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. YW: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. MY: Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. GY: Formal analysis, Funding acquisition, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing. LL: Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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EDITED BY
Arthur Sá Ferreira,
University Center Augusto Motta, Brazil

REVIEWED BY
Chaohua Cui,
Affiliated Liutie Central Hospital of Guangxi Medical University, China
Khuzeima Khanbhai,
Jakaya Kikwete Cardiac Institute (JKCI), Tanzania
Jorge Amaral,
Rio de Janeiro State University, Brazil

*CORRESPONDENCE
Zhang Chunjuan
✉ 18842656942@163.com
Ma Xiaodong
✉ 13666789996@163.com

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Machine learning consensus clustering for inflammatory subtype analysis in stroke and its impact on mortality risk: a study based on NHANES (1999–2018)

Zhang Chunjuan*, Wang Yulong, Zhou Xicheng and Ma Xiaodong*

Haiyan People's Hospital, Jiaxing, Zhejiang, China

Background: Our study aims to utilize unsupervised machine learning methods to perform inflammation clustering on stroke patients via novel CBC-derived inflammatory indicators (NLR, PLR, NPAR, SII, SIRI, and AISI), evaluate the mortality risk among these different clusters and construct prognostic models to provide reference for clinical management.

Methods: A cross-sectional analysis was conducted using data from stroke participants in the U.S. NHANES 1999–2018. Weighted multivariate logistic regression was used to construct different models; consensus clustering methods were employed to subtype stroke patients based on inflammatory marker levels; LASSO regression analysis was used to construct an inflammatory risk score model to analyze the survival risks of different inflammatory subtypes; WQS regression, Cox regression, as well as XGBoost, random forest, and SVMRFE machine learning methods were used to screen hub markers which affected stroke prognosis; finally, a prognostic nomogram model based on hub inflammatory markers was constructed and evaluated using calibration and DCA curves.

Results: A total of 918 stroke patients with a median follow-up of 79 months and 369 deaths. Weighted multivariate logistic regression analysis revealed that high SIRI and NPAR levels were significantly positively correlated with increased all-cause mortality risk in stroke patients ($p < 0.001$), independent of potential confounders; Consensus clustering divided patients into two inflammatory subgroups via SIRI and NPAR, with subgroup 2 having significantly higher markers and mortality risks than subgroup 1 ($p < 0.001$); LASSO regression analysis showed subgroup 2 had higher risk scores and shorter overall survival than subgroup 1 [HR, 1.99 (1.61–2.45), $p < 0.001$]; WQS regression, Cox regression, and machine learning methods identified NPAR and SIRI as hub prognostic inflammatory markers; The nomogram prognostic model with NPAR and SIRI demonstrated the best net benefit for predicting 1, 3, 5 and 10-year overall survival in stroke patients.

Conclusion: This study shows NPAR and SIRI were key prognostic inflammatory markers and positively correlated with mortality risk ($p < 0.001$) for stroke patients. Patients would been divided into 2 inflammatory subtypes via them, with subtype 2 having higher values and mortality risks ($p < 0.001$). It suggests that enhanced monitoring and management for patients with high SIRI and NPAR levels to improve survival outcomes.

KEYWORDS

stroke, machine learning, consensus cluster, inflammation subtype, neutrophil-percentage-to-albumin ratio, systemic inflammatory response index

1 Introduction

Stroke, also termed cerebrovascular accident (CVA), is characterized by rapidly developing neurological deficits due to sudden cerebral blood flow disruption, leading to long-term disability or mortality. As a leading global cause of disability and death (1), stroke affects approximately 15 million individuals annually, with a substantial proportion experiencing recurrent events or persistent functional impairments. The inflammatory cascade plays a dual role in post-stroke pathophysiology, mediating both secondary neuronal injury and repair processes (2). While inflammation has emerged as a promising therapeutic target, the clinical benefits of systemic anti-inflammatory interventions remain controversial. Consequently, stratifying acute ischemic stroke (AIS) patients based on inflammatory heterogeneity may enhance pathophysiological understanding and enable tailored therapeutic modulation of neuroinflammation, thereby optimizing cerebral protection and functional recovery.

Complete blood count (CBC)-derived inflammatory indices—including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil percentage-to-albumin ratio (NPAR), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), and aggregate index of systemic inflammation (AISI)—provide integrative prognostic insights by quantifying interactions among platelets, neutrophils, and lymphocytes. These indices have demonstrated diagnostic and prognostic utility across multiple diseases. In AIS, compelling evidence highlights their clinical relevance: NLR independently predicts 90-day functional outcomes (3), while NLR, PLR, lymphocyte-to-monocyte ratio (LMR), and SIRI correlate with in-hospital mortality, length of stay (4), and 3-month disability rates (5). Notably, these CBC-based biomarkers reflect real-time inflammatory dynamics through routine hematological testing, offering practical advantages over conventional cytokine assays. Their integration into AIS subtyping frameworks may thus facilitate precision medicine by identifying high-risk phenotypes amenable to targeted immunomodulation.

Unsupervised machine learning (ML), a statistical approach that identifies latent patterns by analyzing the underlying structures of unlabeled data, has demonstrated unique value in medical research for classification and risk stratification (6). As a pivotal branch of unsupervised ML, consensus clustering enables precise phenotypic classification by iteratively validating multidimensional feature heterogeneity across patient populations, independent of outcome variables. This methodology has been successfully applied to elucidate disease mechanisms and optimize therapeutic strategies across various conditions (7–10). Notably, its potential is emerging in stroke research. For instance, Yang et al. (11) classified AIS patients into three molecular subtypes based on peripheral blood monocyte transcriptomic profiles, revealing that the high-inflammatory-response subtype exhibited a significantly elevated risk of hemorrhagic transformation, providing critical insights for timing immunomodulatory therapies. Similarly, Cui et al. (12) integrated clinical and neuroimaging data using unsupervised ML to identify a subgroup showing superior therapeutic responses to a "statin combined with repetitive transcranial magnetic stimulation" regimen. However, existing studies have yet to systematically explore the role of CBC (complete blood count)-derived inflammatory indices (e.g., SIRI, NPAR) in AIS subtyping. These indices not only dynamically reflect key inflammatory pathways, such as neutrophil–platelet interactions, but also offer practical advantages for point-of-care testing.

This study applies consensus clustering to resolve inflammatory heterogeneity in AIS, aiming to achieve dual objectives: (1) identifying pathophysiologically meaningful stroke inflammatory subtypes based on CBC-derived inflammatory indices, and (2) constructing interpretable ML prognostic models to quantify mortality risk disparities across subtypes. Ultimately, this work seeks to provide evidence-based guidance for anti-inflammatory therapy optimization and monitoring frequency stratification (e.g., dynamic inflammation monitoring in high-risk subtypes), thereby facilitating the clinical translation of precision medicine in AIS management.

2 Methods

2.1 Data source

The National Health and Nutrition Examination Survey (NHANES) database is dedicated to the systematic collection of data pertaining to the health and nutritional status of households in the United States. It encompasses a wide array of information, including demographic characteristics, dietary assessments, results from physical examinations, responses to questionnaires, laboratory findings, and data with restricted access. The database utilizes a sophisticated stratified, multistage clustered sampling technique to ensure that the statistical sample accurately reflects the broader U.S. population. This research was sanctioned by the Ethics Review Committee of the National Center for Health Statistics, and informed consent was secured from all participants through signed consent forms. Comprehensive details regarding the publicly available NHANES research design and data can be found at https://www.cdc.gov/nchs/nhanes/.

2.2 Study population

This cohort study examined data from the continuous National Health and Nutrition Examination Survey (NHANES), which was conducted between 1999 and 2018. Participants under the age of 20, those with incomplete complete blood count (CBC) parameters, individuals lacking specific information regarding stroke, and those with missing critical covariate and follow-up data were excluded from the analysis. Consequently, the final sample comprised 918 patients diagnosed with stroke. Given the inclusion of hematological parameters in our study, we employed mobile examination center (MEC) weights for the data analysis. The weight calculation for the cohorts from 1999 to 2000 and 2001–2002 was determined using the formula $2/10 \times$ wtmec4yr, whereas for the cohorts from 2003 to 2018, the formula applied was $1/10 \times$ wtmec2yr.

2.3 Definition of inflammatory indices

The inflammatory markers evaluated in this research included the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil percentage-albumin ratio (NPAR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), and aggregate index of systemic inflammation (AISI), all of which are derived from standard complete blood count (CBC) tests. The formulas utilized for the computation of these ratios are as follows: NLR = Neutrophil count (NC) / Lymphocyte count (LC); PLR = Platelet count (PC) / Lymphocyte count (LC); SII = (Platelet count (PC) × Neutrophil count (NC)) / Lymphocyte count (LC); NPAR = (Neutrophil percentage of total white blood cell count (%) × 100) / Albumin (g/dL); SIRI = (Neutrophil count (NC) × Monocyte count (MC)) / Lymphocyte count (LC); AISI = (Neutrophil count (NC) × Platelet count (PC) × Monocyte count (MC)) / Lymphocyte count (LC).

2.4 Covariates

The covariates utilized in this research included age, race, and ethnicity, which were categorized into the following groups: Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other races. Educational attainment was classified into three distinct categories: individuals with less than a high school education, high school graduates, and those with education beyond high school. Family income was stratified into two categories: low income (less than 1.3 times the federal poverty level) and high income (greater than 3.5 times the federal poverty level). Smoking status was delineated between current smokers—defined as individuals who have smoked 100 or more cigarettes in their lifetime—and non-smokers, which included those who have smoked 100 cigarettes or fewer or who have never smoked. Alcohol consumption was operationally defined as the consumption of at least 12 alcoholic beverages within any year of the participant's life. The diagnosis of diabetes was established based on one or more of the following criteria: confirmation by a physician or healthcare professional; a fasting blood glucose level of 126 mg/dL or higher; an HbA1c percentage of 6.5% or greater; or the use of diabetes medications, including insulin.

2.5 Statistical analysis

All statistical analyses were conducted with consideration of the intricate design of the National Health and Nutrition Examination Survey (NHANES). In the table detailing baseline characteristics, continuous variables were presented as weighted means accompanied by 95% confidence intervals (CIs), while categorical variables were expressed as weighted percentages with corresponding 95% CIs. To evaluate differences between groups, weighted linear regression and weighted chi-square tests were employed.

To investigate the relationships between six inflammatory markers and the risk of all-cause mortality in stroke patients, three logistic regression models were utilized. NPAR and SIRI were selected for consensus clustering subtype analysis, and LASSO regression was applied to develop a risk score model aimed at analyzing the mortality risk associated with different subtypes. Consensus clustering was implemented using K-means clustering with Euclidean distance through the ConsensusClusterPlus package (1.64.0). Subsequently, weighted quantile sum (WQS) regression models were employed to estimate the combined effects of the six inflammatory markers, allowing for the identification of primary markers through the calculated WQS index. Additionally, methods such as XGBoost, random forest (RF) and support vector machine recursive feature elimination (SVMRFE) were utilized to select key prognostic inflammatory markers. Ultimately, a prognostic nomogram model was developed based on the identified key inflammatory prognostic markers. The predictive accuracy of this nomogram was evaluated using calibration curves, while decision curve analysis (DCA) was conducted to assess the potential benefits to patients derived from the model.

3 Results

3.1 Study cohort selection

Following the exclusion of participants lacking comprehensive primary variable data and mortality status information during the follow-up period from the NHANES database, a total of 918 individuals aged 20 years and older who had experienced a stroke were identified. The flowchart illustrating the study's inclusion and exclusion criteria is depicted in Figure 1.

3.2 Baseline characteristics of the study cohort

Table 1 presents the baseline characteristics of the study cohort. Over a median follow-up period of 79 months, a total of 369 deaths were recorded, with deceased individuals being a significantly older ($p < 0.001$). in addition to household income, smoking status, and diabetes status, there were marked differences in the distributions of sociodemographic, behavioral, and health-related characteristics between the two groups. Furthermore, among the six inflammatory

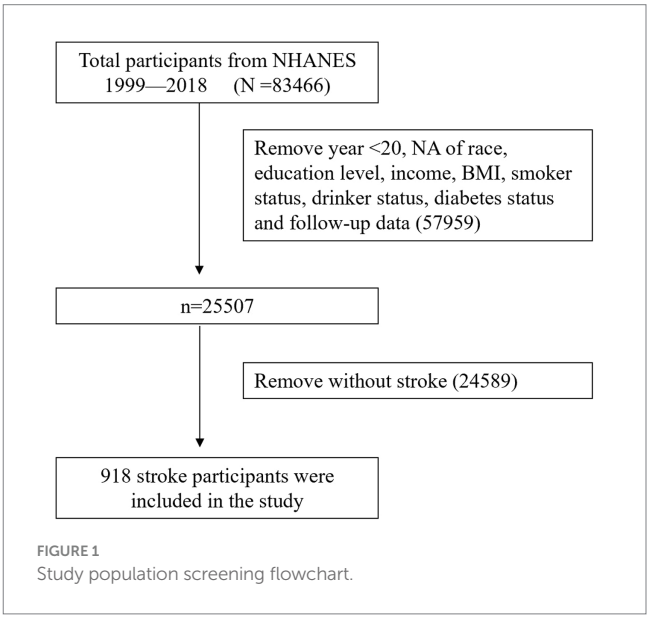

FIGURE 1
Study population screening flowchart.

TABLE 1 Baseline characteristics of study participants in stroke patients, weighted.

Characteristic	Stroke			
	Overall, *N* = 918[1]	Alive, *N* = 549[1]	Dead, *N* = 369[1]	*p* value[2]
Age	67.0 (56.0, 77.0)	62.0 (51.0, 69.0)	77.0 (68.0, 80.0)	<0.001
Gender				0.4
Female	465 (56%)	305 (57%)	160 (54%)	
Male	453 (44%)	244 (43%)	209 (46%)	
Race				<0.001
Mexican American	85 (4.4%)	60 (5.1%)	25 (3.1%)	
Non-Hispanic Black	234 (13%)	160 (15%)	74 (9.8%)	
Non-Hispanic White	494 (73%)	248 (67%)	246 (82%)	
Other Hispanic	56 (2.8%)	43 (3.6%)	13 (1.4%)	
Other Race	49 (6.9%)	38 (8.8%)	11 (3.4%)	
Education				0.002
Above high school	355 (45%)	234 (50%)	121 (37%)	
Below high school	141 (9.9%)	77 (8.0%)	64 (14%)	
High school	422 (45%)	238 (42%)	184 (50%)	
Income				0.2
Poverty	227 (20%)	151 (22%)	76 (17%)	
Richer	691 (80%)	398 (78%)	293 (83%)	
BMI	29 (25, 34)	30 (25, 34)	28 (24, 32)	0.001
Drinker	608 (69%)	372 (73%)	236 (60%)	0.005
Smoker	259 (28%)	176 (31%)	83 (22%)	0.050
Hypertension	704 (75%)	404 (71%)	300 (81%)	0.003
Diabetes				0.8
Diabetes	343 (33%)	197 (32%)	146 (35%)	
Normal	275 (33%)	168 (34%)	107 (32%)	
Prediabetes	300 (34%)	184 (34%)	116 (33%)	
NLR	2.19 (1.69, 3.06)	2.08 (1.65, 2.74)	2.42 (1.81, 3.45)	0.004
PLR	123 (94, 155)	122 (95, 151)	125 (92, 168)	0.5
NPAR	145 (128, 160)	141 (125, 157)	151 (132, 171)	0.001
SII	525 (361, 730)	501 (353, 711)	558 (384, 781)	0.12
SIRI	1.26 (0.86, 1.95)	1.20 (0.82, 1.82)	1.53 (1.00, 2.17)	<0.001
AISI	299 (187, 450)	279 (183, 427)	348 (200, 514)	0.004

[1]Median (Q1, Q3); *n* (unweighted) (%). [2]Design-based Kruskal-Wallis test; Pearson's X^2: Rao-Scott adjustment.

indicators assessed, the death group presented significantly greater NLR, NPAR, SIRI, and AISI values than the survival group ($p < 0.001$).

3.3 The associations between inflammatory markers and all-cause mortality in stroke patients

Table 2 presents the findings from the weighted multivariable logistic regression analysis. In Model 1, elevated levels of four inflammatory markers were found to be significantly correlated with an increased risk of all-cause mortality among stroke patients, particularly within the higher SIRI group, which exhibited an odds ratio (OR) of 1.49 (95% confidence interval [CI], 1.25–1.77). In Model 2, following adjustments for additional covariates including age, sex, race, education level, and alcohol consumption, the risk associated with three inflammatory markers remained significantly elevated, with SIRI demonstrating an OR of 1.29 (95% CI, 1.05–1.57). In Model 3, after controlling for all covariates, NPAR and SIRI, continued to exhibit a significant positive association with the risk of all-cause mortality in stroke patients ($p < 0.05$).

3.4 KM survival curve analysis

Figure 2 shows the results of the Kaplan–Meier plotter curve analysis, which demonstrated that higher expression levels of SIRI (hazard ratio [HR], 1.94 [1.57–2.39], $p < 0.001$) and NPAR (HR, 1.58 [1.29–1.95], $p < 0.001$) are associated with a significant reduction in the survival probability of patients who have experienced a stroke.

TABLE 2 Stepped logistic regression models showing the association between inflammation indicators and the odds of stroke patients.

Indicators	Model 1			Model 2			Model 3		
	OR[1]	95% CI[1]	*p*-value	OR[1]	95% CI[1]	*p*-value	OR[1]	95% CI[1]	*p*-value
NLR	1.24	1.06, 1.45	0.008	1.16	0.99, 1.35	0.066	1.14	0.99, 1.31	0.077
PLR	1.00	1.00, 1.00	0.200	1.00	1.00, 1.00	0.700	1.00	1.00, 1.00	0.600
NPAR	1.01	1.00, 1.02	0.002	1.01	1.00, 1.02	0.006	1.01	1.00, 1.02	0.010
SII	1.00	1.00, 1.00	0.120	1.00	1.00, 1.00	0.200	1.00	1.00, 1.00	0.300
SIRI	1.49	1.25, 1.77	<0.001	1.29	1.05, 1.57	0.015	1.24	1.02, 1.51	0.029
AISI	1.00	1.00, 1.00	0.003	1.00	1.00, 1.00	0.049	1.00	1.00, 1.00	0.090

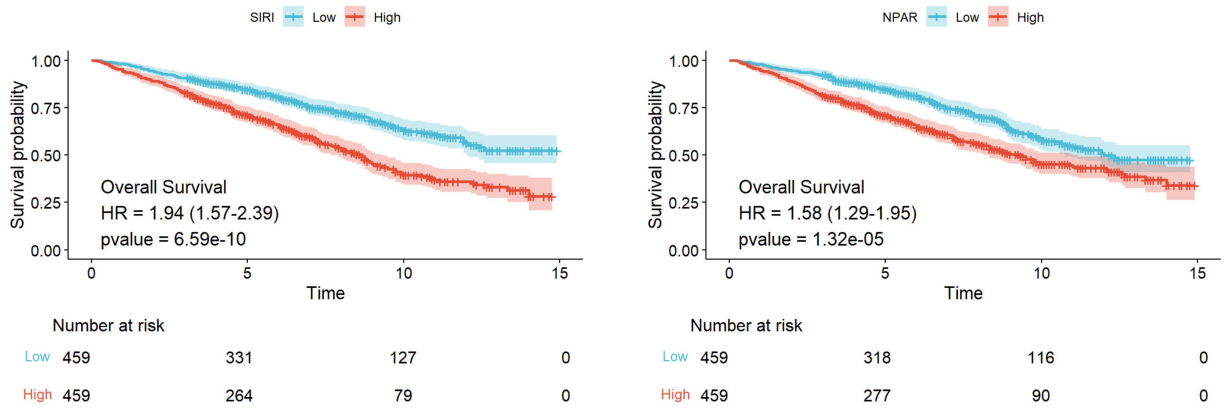

FIGURE 2
Kaplan–Meier plotter of SIRI and NPAR.

3.5 Construction of inflammation-related subtypes

The results of the consensus clustering analysis, which utilized the key inflammatory markers NPAR and SIRI, are illustrated in Figures 3A–C. The PAC metric identified the optimal number of clusters as k = 2, leading to the formation of two distinct clusters: C1 ($n = 491$) and C2 ($n = 427$). The principal component analysis (PCA) plot indicates a strong separation between cluster C2 and cluster C1, as depicted in Figure 3E. Furthermore, the Kaplan–Meier (KM) curve analysis assessing all-cause mortality risk for the two inflammatory subtypes revealed that the survival probability for subtype C2 was significantly lower than that for subtype C1 (Figure 3D). An examination of the baseline clinical characteristics for the two subtypes, presented in Table 3, indicated that both age and inflammatory markers were significantly elevated in subtype C2 compared to subtype C1 ($p < 0.05$).

3.6 Analysis of the subtype prognostic inflammation risk scoring model

A risk model was established utilizing LASSO-Cox regression analysis to evaluate the survival risk associated with various subtypes (Figures 4A,B). The risk score is computed using the following formula: Risk score = (0.1543 × NLR) + (0.0017 × PLR) + (0.0041 × NPAR) + (0.4874 × SIRI) − (0.0012 × SII). Subsequently, patients who experienced a stroke were categorized into high-risk and low-risk groups based on the median risk score. Figure 4C illustrates the distribution of risk scores alongside survival duration in stroke patients. The results of the KM analysis presented in Figure 4D indicate that the overall survival time for the high-risk group, characterized by elevated risk scores, is significantly shorter than that of the low-risk group (HR, 1.99 (1.61–2.45), $p < 0.001$), thereby suggesting a poorer prognosis for the high-risk cohort. Furthermore, Figure 4E displays the receiver operating characteristic (ROC) curve, revealing that the area under the curve (AUC) for the time-dependent ROC at 1, 3, and 5 years for the three cohorts is 0.706, 0.655, and 0.673, respectively, which indicates that the prognostic model exhibits commendable predictive performance. Additionally, Figure 4F indicates that Cluster 2 possesses a higher risk score, while Figure 4G presents a Sankey diagram that depicts the distribution of inflammation risk scores, encompassing both the risk scores and survival status across the two subtypes.

3.7 Screening of hub prognostic inflammation indicators based on WQS regression analysis and machine learning

The weighted quantile sum (WQS) model (Figure 5A) used to evaluate the relationships between six inflammatory markers and the risk of all-cause mortality among stroke patients, revealing a positive association between these inflammatory indicators and mortality risk (slope 0.36, $p < 0.001$). An analysis of the primary

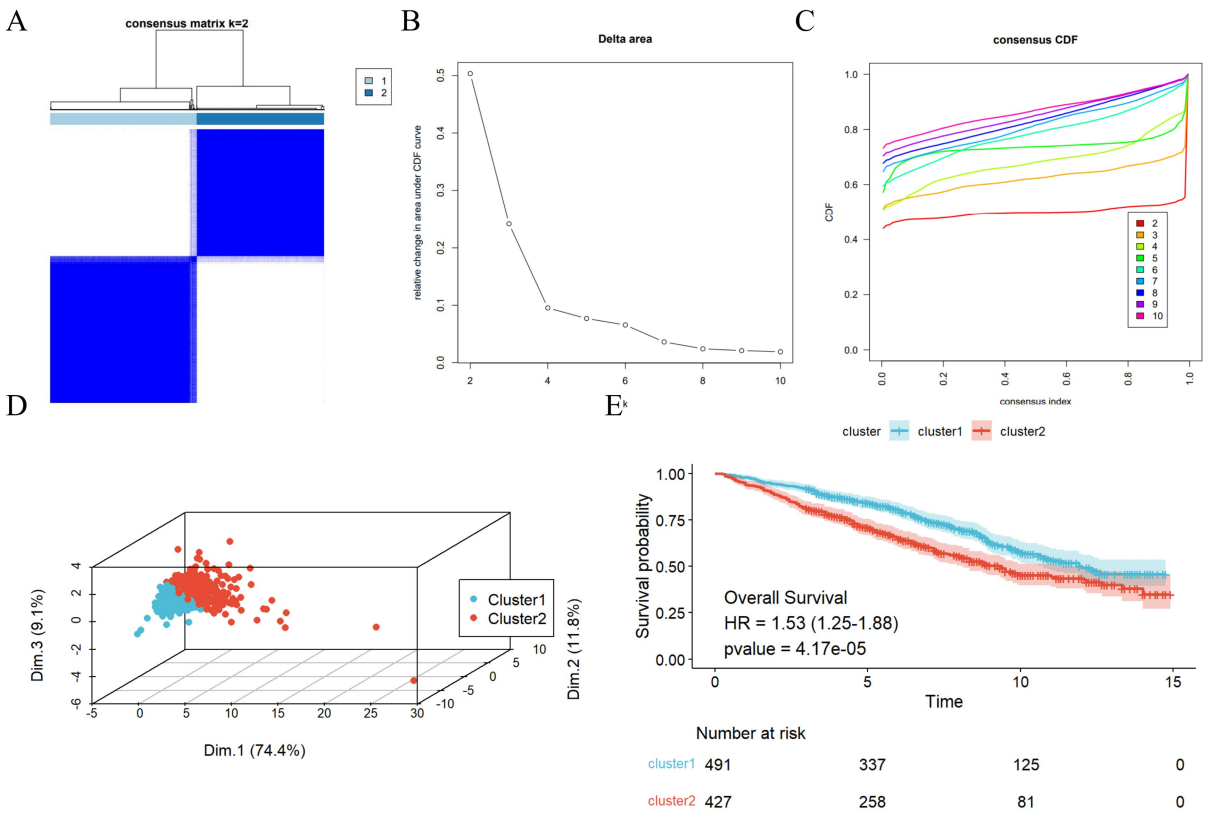

FIGURE 3
Two inflammation-cluster based NPAR and SIRI. **(A)** Unsupervised cluster analysis of SIRI and NPAR developed two clusters (k = 2); **(B)** Consensus CDF curves when k = 2 to 10; **(C)** Relative alterations in CDF delta area curves; **(D)** Kaplan–Meier plotter of two clusters. *$p < 0.05$, ***$p < 0.001$; **(E)** 3D Principal Component Analysis delineating the segregation between Cluster C1 and Cluster C2.

contributions of the inflammatory markers within the WQS model indicated that the SIRI had the most substantial effect (73.82%), followed by NPAR (12.42%), NLR (8.61%), and PLR (3.28%). The XGBoost algorithm identified the SIRI, NPAR, AISI, and NLR as the four most significant inflammatory indicators (Figure 5B), while the RF algorithm corroborated these findings, also ranking the SIRI, NPAR, AISI, and NLR as the top four indicators (Figure 5C). Furthermore, the Support Vector Machine Recursive Feature Elimination (SVMRFE) algorithm demonstrated that reducing the number of indicators to five minimized classification errors and maximized accuracy, identifying SIRI, AISI, NLR, NPAR, and SII as key indicators (Figure 5D). In summary, the NPAR and SIRI were ultimately recognized as central prognostic inflammatory indicators.

3.8 Construction of a prognostic model for all-cause mortality risk in stroke patients

Based on the evaluation of key prognostic inflammatory markers, NPAR and SIRI were identified for the development of a prognostic nomogram model (Figure 6A). The concordance index (C-index) for this prognostic model was determined to be 0.637 (95%CI, 0.627–0.647). Analysis of the calibration curve demonstrated a strong alignment between the observed and predicted overall survival rates at 1, 3, 5, and 10 years (Figure 6B). Furthermore, decision curve analysis (DCA) revealed that the integrated model, which incorporates these two inflammatory indices, offers the most favorable net benefit for overall survival across the same time intervals (Figure 6C).

4 Discussion

The present study investigated the relationship and prognostic significance of six novel inflammatory markers derived from CBC data in relation to all-cause mortality among patients who have experienced a stroke. Our findings revealed a statistically significant positive correlation between the inflammatory markers NPAR and SIRI and the risk of all-cause mortality in this patient population ($p < 0.001$). Consequently, we employed consensus clustering to categorize stroke patients into two distinct inflammatory subtypes. Notably, subtype 2 exhibited markedly elevated levels of inflammatory marker expression and a heightened risk of all-cause mortality when compared to subtype 1 ($p < 0.001$). These results offer valuable insights for the inflammatory risk stratification and management of clinical stroke patients, underscoring the necessity for intensified monitoring and intervention for individuals with elevated levels of SIRI and NPAR, which may ultimately contribute to improved survival outcomes.

This research initially utilized logistic regression and weighted multivariable Logit models to evaluate the associations between six novel inflammatory markers derived from complete blood counts

TABLE 3 Characteristics of the study population in two inflammation cluster.

	Cluster			
Characteristic	Overall, *N* = 918[1]	Cluster1, *N* = 491[1]	Cluster2, *N* = 427[1]	*p* value[2]
MORTSTAT				0.004
0	549 (64%)	321 (70%)	228 (57%)	
1	369 (36%)	170 (30%)	199 (43%)	
Age	67.0 (56.0, 77.0)	65.0 (54.0, 75.0)	68.0 (58.0, 78.0)	0.034
Gender				0.3
Female	465 (56%)	247 (54%)	218 (58%)	
Male	453 (44%)	244 (46%)	209 (42%)	
Race				0.042
Mexican American	85 (4.4%)	45 (4.8%)	40 (3.9%)	
Non-Hispanic Black	234 (13%)	147 (16%)	87 (11%)	
Non-Hispanic White	494 (73%)	238 (68%)	256 (78%)	
Other Hispanic	56 (2.8%)	34 (3.0%)	22 (2.6%)	
Other Race	49 (6.9%)	27 (8.7%)	22 (4.8%)	
Education				0.7
Above high school	355 (45%)	190 (47%)	165 (44%)	
Below high school	141 (9.9%)	76 (10%)	65 (9.8%)	
High school	422 (45%)	225 (43%)	197 (46%)	
Income				0.3
Poverty	227 (20%)	125 (19%)	102 (22%)	
Richer	691 (80%)	366 (81%)	325 (78%)	
BMI	29 (25, 34)	29 (25, 33)	29 (25, 35)	0.5
Drinker	608 (69%)	313 (67%)	295 (71%)	0.4
Smoker	259 (28%)	135 (26%)	124 (30%)	0.2
Hypertension	704 (75%)	368 (72%)	336 (78%)	0.2
Diabetes				0.8
Diabetes	343 (33%)	172 (32%)	171 (34%)	
Normal	275 (33%)	153 (34%)	122 (32%)	
Prediabetes	300 (34%)	166 (34%)	134 (34%)	
NLR	2.19 (1.69, 3.06)	1.75 (1.38, 2.06)	3.13 (2.40, 3.93)	<0.001
PLR	123 (94, 155)	106 (84, 131)	140 (114, 188)	<0.001
MLR	0.29 (0.22, 0.40)	0.26 (0.21, 0.33)	0.36 (0.27, 0.47)	<0.001
NPAR	145 (128, 160)	129 (119, 138)	162 (154, 175)	<0.001
SII	525 (361, 730)	390 (286, 510)	711 (564, 957)	<0.001
SIRI	1.26 (0.86, 1.95)	0.96 (0.67, 1.30)	1.82 (1.28, 2.48)	<0.001
AISI	299 (187, 450)	220 (141, 322)	419 (288, 606)	<0.001

[1]*n* (unweighted) (%); Median (Q1, Q3). [2]Pearson's X^2: Rao-Scott adjustment; Design-based Kruskal-Wallis test.

(CBC) and the risk of all-cause mortality among patients who have experienced a stroke. These inflammatory markers, derived from routine CBC tests, reflect the body's immune activation status and inflammatory burden. Our focus on NPAR, SIRI, and other CBC-based indices was motivated by their cost-effectiveness and universal availability in routine clinical practice and emerging evidence supporting their prognostic value in stroke patients. Our investigation, utilizing data from the NHANES database, assessed the cumulative effects of various novel combined inflammatory indicators, thereby enhancing our understanding of their influence on the prognostic outcomes for stroke patients. The findings indicated that inflammation is a significant factor in the prognosis of stroke patients, particularly highlighting a strong positive correlation between elevated levels of the SIRI and NPAR with an increased risk of all-cause mortality among this population ($p < 0.001$). These results imply that inflammation is a critical component in the pathophysiology of stroke and possesses substantial prognostic value in forecasting all-cause mortality in stroke patients, independent of potential confounding variables such as demographic factors, socioeconomic status, and lifestyle choices. This result aligns with prior studies (3–5). A study (13) involving 1,484 stroke patients indicated that an increased mitochondrial DNA copy number is correlated with a decrease in mortality rates, implying that inflammatory processes may influence the prognosis of individuals who have experienced a stroke. Collectively, these findings support the hypothesis that inflammatory markers can act as prognostic indicators of mortality among stroke patients. Nevertheless, the literature presents conflicting results. For example, a separate

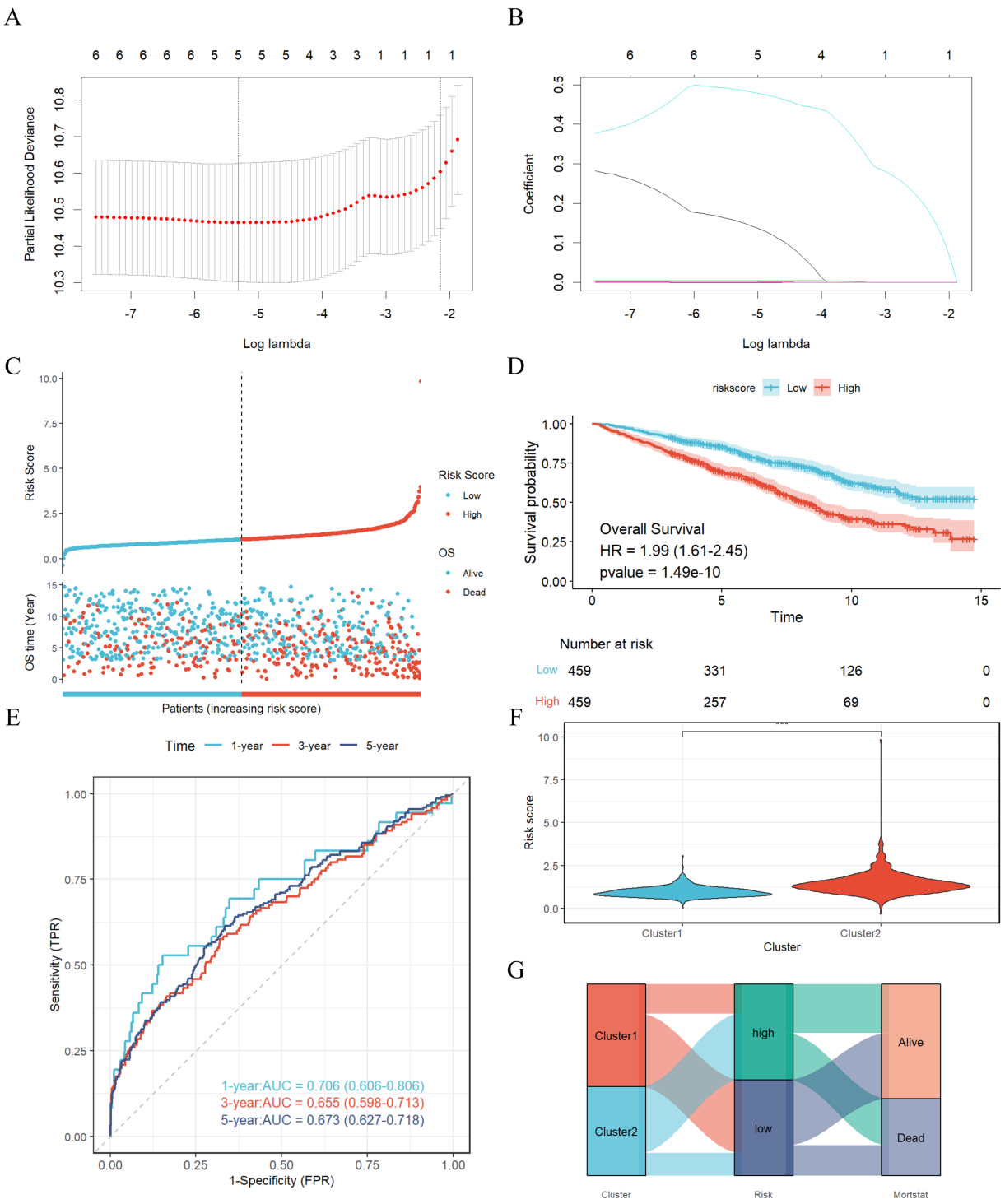

FIGURE 4
Construction and validation of the risk score model. **(A,B)** Constructed a prognostic model in the through LASSO COX regression analysis. **(C)** Risk scores distribution and survival status of each patient. **(D)** Kaplan–Meier curves for the survival probability of the two subtypes. **(E)** ROC curves illustrated the predictive efficacy of the risk score for 1-, 3-, and 5-year survival; **(F)** The difference in risk scores between two clusters; **(G)** Alluvial diagram of subtype distributions and prognosis of stroke patients.

investigation involving 1,316 stroke patients found no significant association between the systemic immune-inflammation index and mortality, suggesting that the relationship may differ based on specific patient demographics or the methodologies employed in the studies (14). Additionally, another study suggested that while inflammation is a key factor in stroke, its role in predicting mortality may not be as direct due to the complex interactions of various biological processes involved in stroke recovery (15). These discrepancies may arise from variations in study design, sample size, and the particular inflammatory markers evaluated.

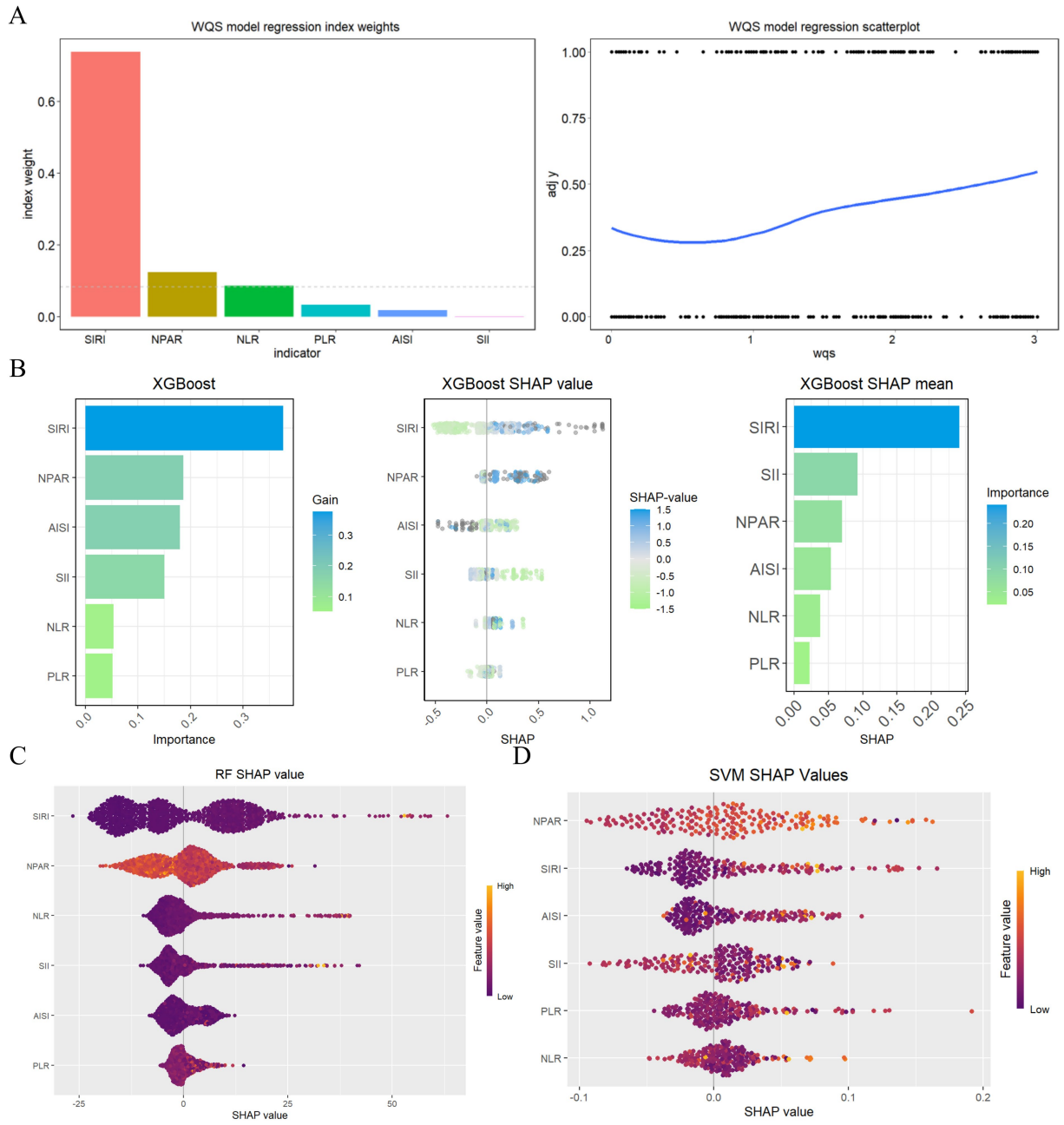

FIGURE 5
Evaluating the importance of indicators based on WQS analysis, XGBoost, RF, SVMRFE, and COX analysis **(A)** WQS model regression index weights for inflammation indicators on stroke patients; **(B)** Screening of prognostic biomarkers based on XGBoost algorithm; **(C)** Important features selected by random forest algorithm; **(D)** Through SVF-RFE algorithm selects the best indicators.

Utilizing the findings from model 3 of the weighted multivariable logistic regression, which accounted for all covariates, we identified the SIRI and NPAR as significant inflammatory indicators. We then employed consensus clustering to categorize stroke patients into distinct inflammatory subtypes. The results of the clustering analysis revealed two separate inflammatory subgroups, with subgroup 2 demonstrating markedly elevated levels of inflammatory markers and an increased risk of all-cause mortality in comparison to subgroup 1 ($p < 0.001$). Following this, we developed an inflammatory risk scoring model for stroke patients through LASSO regression analysis to evaluate survival risks across the identified subtypes. The findings indicated that the risk score for subgroup 2 was significantly greater than that for subgroup 1, with subgroup 2, classified as high-risk, exhibiting a notably reduced overall survival compared to the low-risk group (HR, 1.99 (1.61–2.45), $p < 0.001$). This suggests that the high-expression subtype 2 is associated with a poorer prognosis. These results provide a valuable reference for the inflammatory risk stratification management of clinical stroke patients, highlighting the necessity for enhanced monitoring and management of individuals with elevated levels of SIRI and NPAR, which may contribute to improved patient survival outcomes.

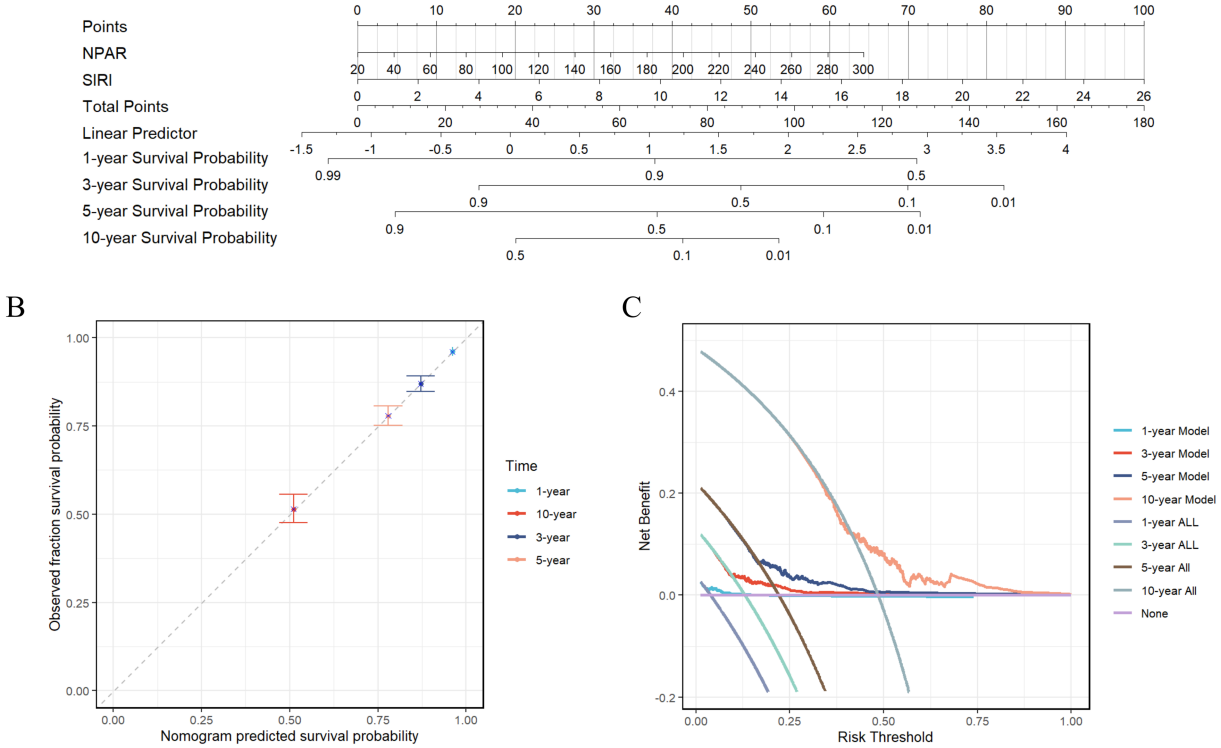

FIGURE 6
Construction of a prognostic model for all-cause mortality risk in stroke patients. **(A)** The Nomogram containing NPAR and SIRI; **(B)** The calibration plot of nomogram; **(C)** The DCA curves of nomogram.

Finally, we employed a variety of statistical methods—including weighted quantile sum (WQS) regression and three machine learning techniques—to identify key inflammatory markers that influence stroke prognosis. The WQS model demonstrated a significant association between six inflammatory markers and the risk of all-cause mortality in stroke patients, revealing a positive correlation between these inflammatory indicators and mortality risk (slope = 0.36, $p < 0.001$). Integrating these various statistical results, NPAR and SIRI were ultimately identified as hub prognostic inflammatory indicators. A prognostic nomogram model was subsequently constructed based on these indicators. Evaluation of the model's performance through calibration curves and decision curve analysis (DCA) revealed that the comprehensive model incorporating both NPAR and SIRI offered the best net benefit for predicting overall survival in stroke patients at 1, 3, 5, and 10 years. These statistical methods, from different analytical perspectives, enhanced the robustness of our conclusions and emphasized the importance of inflammatory markers as potential intervention targets in managing the mortality risk of stroke patients, providing a new perspective on the prognostic value of inflammatory markers in stroke patients. It reminds us to pay special attention to NPAR and SIRI, as both serve as reliable prognostic indicators, with their elevation often accompanying a high risk of mortality in stroke patients, consistent with previous studies. For example, Cui et al.'s (16) retrospective study found that NPAR was positively correlated with adverse functional outcomes (OR, 2.76 (1.52–5.03), $p = 0.001$); Yang et al.'s (17) study shown that NPAR was independently associated with the risk of recurrence within 3 months (OR 9.71 (3.05–31.62), $p < 0.001$); Chen et al.'s study (18) indicated that higher NPAR still had significant predictive ability for 30-day all-cause mortality (HR, 1.45 (1.05–2.00), $p < 0.05$); Huang et al.'s (19) research displayed that SIRI exhibited strong predictive ability in identifying adverse outcomes and stroke-associated pneumonia, with higher SIRI values typically associated with negative endpoints. However, two critical gaps are addressed in our work. Our study utilized the NHANES database to analyze not only the long-term prognostic outcomes of stroke patients but also to stratify patients based on inflammatory risk, providing a reference for healthcare professionals in identifying different inflammatory subtypes in stroke patients and offering personalized treatment.

Our inflammatory subtype prognostic model is positioned as a complementary decision-support tool to established stroke prognostic scores (e.g., ASTRAL, iScore), specifically designed to provide inflammation-enhanced risk stratification. We propose a stepped integration protocol in clinical practice—initial baseline risk assessment using conventional scores (e.g., THRIVE) followed by individualized adjustments based on inflammatory subtypes, including anti-inflammatory therapy intensification and

monitoring frequency stratification (6-month intervals for low-risk vs. monthly for high-risk subgroups). Nonetheless, it is important to recognize the limitations of this study. Firstly, the dependence on the NHANES database may introduce biases typical of observational studies, as there may be unmeasured confounding variables despite our comprehensive statistical adjustments. Secondly, single-timepoint biomarkers cannot capture post-stroke inflammatory dynamics. Third, the lack of stroke subtyping data prevented us from exploring potential differences in inflammatory profiles between ischemic and hemorrhagic stroke, which warrants further investigation in cohorts with detailed phenotyping. To address these limitations, we have initiated a prospective validation study (Haiyan Stroke Cohort) featuring with dynamic multi-timepoint monitoring. This protocol has been approved by Haiyan People's Hospital Ethics Committee (2024-52) and the preliminary results will be reported in 2026.

5 Conclusion

In conclusion, our study identified a significant positive correlation between the inflammatory markers NPAR and SIRI and all-cause mortality among stroke patients. Consequently, we developed various inflammatory subtypes and prognostic models based on these findings. This research not only underscores the relevance of these biomarkers as potential prognostic indicators but also establishes a comprehensive framework for clinical risk stratification and patient management. By integrating inflammation assessment into standard clinical practice, we can enhance patient outcomes and facilitate the development of targeted interventions, which are essential for addressing the morbidity and mortality challenges associated with stroke. Specifically, for patient populations at elevated risk of inflammation, personalized treatment strategies can markedly improve prognosis and mitigate the long-term burden related to stroke.

Data availability statement

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

Ethics statement

The NHANES database received approval from the NCHS Research Ethics Review Board and all participants provided their written informed consent. Given that the data disseminated by NCHS are de-identified and anonymous during the analytical process, no further ethical approval or informed consent is necessary for secondary analyses. Details concerning the approval from the NCHS Research Ethics Review Board can be found on the NHANES website at the following link: https://www.cdc.gov/nchs/nhanes/about/erb.html?CDC_AAref_Val=https://www.cdc.gov/nchs/nhanes/irba98.htm.

Author contributions

ZC: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. WY: Project administration, Supervision, Writing – review & editing. ZX: Data curation, Investigation, Writing – review & editing. MX: Conceptualization, Data curation, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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EDITED BY
Arthur Sá Ferreira,
University Center Augusto Motta, Brazil

REVIEWED BY
Yundong Shen,
Fudan University, China
Sukumar Shanmugam,
Gulf Medical University, United Arab Emirates

*CORRESPONDENCE
Fuyan Chen
ecfy_2005@163.com

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Comparison of the effects of different physical stimulation therapies on reducing upper limb spastic paralysis and motor dysfunction in stroke survivors after stroke: a network meta-analysis of randomized controlled trials

Mingtong Bian[1,2], Fuyan Chen[1,2,3]*, Huizhen Su[3], Zhiying Li[1,2], Xiaowei Sun[1,2], Yang Liu[1,2], Jinyuan Shi[1,2], Shuo Liu[1,2] and Ru Rong[1,2]

[1]Department of Acupuncture, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China, [2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China, [3]Qinghai Provincial Hospital of Traditional Chinese Medicine, Xining, Qinghai, China

Background: Upper limb spasticity is a common and disabling sequela of stroke, which significantly impairing motor function and the capacity to perform activities of daily living (ADL). The relative efficacy of different physical therapies and their combinations compared to monotherapies remains unclear.

Methods: A comprehensive database search was conducted to identify randomized controlled trials (RCTs) published from database inception to 2024 that evaluated physical therapies for post-stroke upper limb spasticity. Data were analyzed using RevMan and STATA/R software with a Bayesian framework for network meta-analysis. Evidence consistency was assessed via node-splitting approaches, and intervention efficacy was ranked using the surface under the cumulative ranking curve (SUCRA). Effect sizes were expressed as mean differences (MD) with 95% confidence intervals (CI), and study quality was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system.

Results: Forty-nine RCTs involving 3,219 patients were included. The combination of physical rehabilitation (PR) with repetitive transcranial magnetic stimulation (rTMS) and electro-acupuncture (EA) demonstrated the highest improvement in Fugl-Meyer Assessment for Upper Extremity (FMA-UE) scores (91.1%), outperforming PR alone (13.2%) or EA monotherapy (30.3%). PR combined with rTMS and body acupuncture (BA) shows the most significant improvement in the Modified Barthel Index (MBI) (83.1%), superior to PR (20.8%) or BA (23.8%) alone. Adverse events (e.g., minor bruising from EA) were infrequent and self-resolving.

Conclusion: Current evidence indicates that synergistic application of PR with rTMS and acupuncture (EA/BA) significantly enhances upper limb motor function and ADL capacity. However, GRADE evaluations rated most evidence as moderate quality, limited by implementation bias, insufficient subgroup analyses,

and lack of long-term follow-up data. Future studies should adopt standardized protocols and investigate efficacy variations across stroke subtypes.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/view/CRD42025633289, identifier [CRD42025633289].

KEYWORDS

spasticity, stroke, rehabilitation, review, network meta-analysis

1 Introduction

Upper limb dysfunction following a stroke represents a significant cause of long-term disability in patients, frequently occurring in conjunction with a range of injuries, including upper limb weakness and spasticity. The principal manifestation of upper limb spastic paralysis is an increase in muscle tone on the affected side, which is characterized by symptoms such as shoulder adduction and internal rotation, elbow flexion and pronation, wrist flexion and ulnar deviation, and finger clenching (1). This can result in a number of adverse effects, including pain, muscle contraction, changes in soft tissue structure, weakness, associated reactions, loss of passive function, limited active function, and a decrease in quality of life. This has a significant impact on the patient's activities of daily living (2). The pathological mechanism of upper limb spasticity is complex, involving damage to the corticospinal tract, peripheral mechanisms, extensor mechanisms, and potential spastic dystonia, among other factors (3). Furthermore, because the upper limb's role in more refined and diverse functions, the recovery of its dysfunction is more complex and slow, posing significant challenges to the patient's daily life and social participation.

Nevertheless, research has demonstrated that spasticity can be effectively managed in the chronic phase of stroke through appropriate intervention, thereby enhancing motor function and facilitating the restoration of limb function (4). It is therefore imperative to identify and investigate efficacious rehabilitation techniques to facilitate enhanced recovery of upper limb function in patients. At present, there is a general consensus on the rehabilitation treatment for this condition, both domestically and internationally. The aforementioned treatments are primarily comprised of physical exercise and occupational therapy. In recent years, the advancement of medical technology and the intensification of clinical research have given rise to a multitude of novel rehabilitation therapies, including acupuncture, massage, proprioceptive neuromuscular facilitation (PNF), repetitive transcranial magnetic stimulation (rTMS), and theta-burst stimulation (TBS). A number of studies (5–8) have demonstrated that these physical therapies can facilitate the improvement of post-stroke spastic paralysis to a certain extent. However, existing research has predominantly focused on monotherapies, with insufficient comparative investigations of multimodal therapeutic regimens, leaving the optimal therapeutic combinations poorly defined.

Network meta-analysis (NMA) overcomes the limitations of traditional pairwise meta-analyses, which are restricted to comparing two interventions at a time, by integrating direct and indirect evidence to systematically evaluate the synergistic effects of complex multimodal rehabilitation strategies within a unified framework (9). This study applied NMA to compare the efficacy of 21 intervention modalities for post-stroke upper limb spasticity, aiming to provide evidence-based insights for personalized, multimodal rehabilitation protocols. A total of 49 randomized controlled trials (RCTs) involving 3,219 participants, published between 2009 and 2024, were included. Outcomes were quantified using the Fugl-Meyer Assessment for Upper Extremity (FMA-UE) for motor function and the Modified Barthel Index (MBI) for activities of daily living (ADL). A Bayesian network meta-analysis (implemented in STATA/R) was conducted to comprehensively assess efficacy differences among rehabilitation therapies, neuromodulation techniques, and integrative traditional Chinese medicine (TCM) regimens. Interventions were ranked via the surface under the cumulative ranking curve (SUCRA). The results elucidated effectiveness hierarchies through probabilistic estimates and established indirect efficacy comparison pathways for interventions lacking direct comparative data. This framework provides clinicians and patients with a scientific foundation for optimizing combined strategies of rehabilitation, neuromodulation, and TCM therapies, while bridging critical evidence gaps in the current literature on post-stroke spasticity management.

2 Methods

2.1 Registration

The evaluation plan of this system has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024607022. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Network Meta-Analyses (PRISMA-NMA), as detailed in the Supplementary Appendix S1.

2.2 Search strategy

A systematic search of the following databases was conducted in order to identify eligible randomized controlled trials (RCTs): The following databases were searched: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), China Science and Technology Journal (VIP) database, and Wanfang Database. The search was conducted from the inception of the databases to October 2024, with the search terms limited to Chinese or English language sources. Furthermore, the reference lists of the retrieved relevant review articles were examined to ascertain whether any additional literature had been overlooked. The search strategy employed the following keywords: ("stroke" OR "cerebrovascular accident" OR "cerebral infarction" OR "cerebral haemorrhage") AND ("spastic paralysis" OR "rigid paralysis" OR "paralysis, spastic") AND ("upper extremity") AND ("acupuncture" OR "massage" OR "rTMS" OR "low-frequency electrical stimulation"). Additionally, the search was conducted in Chinese databases using Chinese characters with the same meanings (shown in Supplementary Appendix S2).

2.3 Literature selection criteria

The literature screening and adjustment were conducted in accordance with the inclusion and exclusion criteria set forth in Table 1.

2.4 Data collection and extraction

Two researchers (JY-S and S-L) conducted the preliminary search and excluded titles and abstracts that were not pertinent to the subject matter of this review, while also cross-verifying the screening results. Furthermore, two additional researchers (MT-B and XW-S) conducted independent evaluations of the remaining titles and abstracts, obtained the full texts of these studies, and determined whether they met the inclusion criteria. They also cross-checked these results. Only after confirming that the full-text literature met the inclusion criteria was it included in the study, and the relevant Data were analyzed were then extracted. The extracted content comprised the following elements: basic study information (first author, publication year, diagnostic criteria, number of participants), study design (including sample size, specific description of interventions, type of control group, duration of treatment, treatment cycle, frequency), participant characteristics (age, gender, type of stroke and duration of stroke), outcomes, and data on the quality of the studies (randomization method, allocation concealment, implementation of blinding, loss to follow-up or withdrawal, etc.). Subsequently, an additional researcher (FY-C) undertook an independent review of the extracted data. Any discrepancies were resolved through discussion with FY-C.

2.5 Quality assessment

The methodological quality of each study was evaluated by two researchers (MT-B and XW-S) using the Cochrane Risk of Bias tool (ROB2). The Cochrane tool identifies seven potential areas of bias, including sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other biases. The risk of bias and quality of evidence for each domain can be categorized as low risk, unclear risk (insufficient detail or not reported), or high risk of bias. In order to assess the quality of the included literature, the Consolidated Standards of Reporting Trials (CONSORT) guidelines (10) were adopted. Furthermore, the quality of evidence for each outcome measure was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (11), with ratings classified as high, moderate, low, or very low levels, respectively. Any discrepancies that arose during the assessment process were resolved by a third researcher (FY-C).

2.6 Statistical analysis

Pairwise meta-analyses were conducted utilizing RevMan 5.4 software (Cochrane Collaboration, Oxford, United Kingdom). In the case of continuous data, the mean difference (MD) and its 95% confidence interval (CI) were employed as a means of measuring the effect size. In the case of binary data, the effect size was evaluated using the odds ratio (OR) and its 95% confidence intervals (CIs). The extent of heterogeneity among the included studies was assessed using Cochran's Q test (p-value) and Higgins's I^2 statistic. If $p \geq 0.05$ and $I^2 \leq 50\%$, heterogeneity was considered acceptable, and a fixed-effect model was used. Otherwise, a random-effects model was selected.

In conducting the network meta-analysis, the STATA 14.0 (Stata Corp, College Station, Texas, United States) and the R 4.3.3 (maintained by the R Core Team, Vienna, Austria) were employed to perform the requisite analysis within a Bayesian framework. In the event of a closed loop of evidence, an initial assessment of the inconsistency of the evidence was conducted. An inconsistency model was constructed to ascertain whether the p-value exceeded 0.05. If the p-value is greater than 0.05, this indicates that there is no significant inconsistency and that a consistency model should be selected for subsequent effect size estimation. Conversely, if the p-value was less than or equal to 0.05, this indicated significant inconsistency across the studies. In such cases, it was necessary to investigate the sources of inconsistency and consider the use of an inconsistency model or the implementation of sensitivity analyses to assess the potential impact of this inconsistency on the study results. In view of the potential heterogeneity of the included studies, a random-effects model was employed for the synthesis of the data. As the outcome variables of the studies were continuous, the effect size was measured using mean differences (MDs) and 95% confidence intervals (CIs). Markov Chain Monte Carlo (MCMC) methods were employed to estimate the model, with four chains configured, 20,000 iterations, and a burn-in period of 5,000, setting a thinning interval of 1. To confirm model convergence, Brooks-Gelman-Rubin diagnostics plots, chain trace plots, and probability density plots were examined. The node-splitting method was employed to assess the consistency of direct and indirect comparisons. If the resulting p-value was greater than 0.05, it was inferred that there was a higher degree of consistency. In instances where closed-loop comparisons were present, the inconsistency factor (IF) was utilized for evaluation purposes. If the 95% CI encompassed 0, this indicated that there was consistency between the direct and indirect evidence. Furthermore, the Surface Under the Cumulative Ranking (SUCRA) was calculated to probabilistically rank the various treatment interventions, with SUCRA scores ranging from 0 to 100%, where higher scores indicated superior treatment effectiveness. In analyzing the result data, consideration was given to the potential impact of baseline differences by employing a correlation coefficient R value of 0.5 in the following formula (Equations 1, 2) for estimation.

$$\overline{MDs}_{Change} = \overline{MDs}_{Final} - \overline{MDs}_{Baseline} \tag{1}$$

$$SD_{Change} = \sqrt{\left(SD_{Baseline}\right)^2 + \left(SD_{Final}\right)^2 - \left(2 \times R \times SD_{Baseline} \times SD_{Final}\right)} \tag{2}$$

3 Results

3.1 Results of the search

In accordance with the established inclusion criteria, our preliminary search yielded a total of 1,466 published studies.

TABLE 1 Eligibility criteria for relevant studies.

Criteria	Inclusion	Exclusion
Population	• Patients diagnosed with a stroke through head CT or MRI scans, exhibiting increased muscle tone, brisk tendon reflexes, and the presence of pathological reflexes on the affected side of the upper limb, are classified as having negative or positive pathological reflexes. • Eligible study participants were adults over 18 years of age, with no limitations regarding gender or disease duration.	• Spastic paralysis due to etiologies such as head trauma. • Under the age of 18 years
Intervention	The physical therapy programme encompasses individual and combined treatments, including acupuncture (electroacupuncture and body acupuncture), massage, PNF techniques, ESWT, rTMS, cTBS, iTBS, and physical rehabilitation.	Other non-pharmacological treatments not covered by the study
Comparators	Physical rehabilitation (Traditional rehabilitation therapy without the use of mechanical aids, such as manual physical therapy and traditional exercise therapy)	Other non-pharmacological treatments not covered by the study
Outcomes	• Fugl-Meyer Assessment-Upper Extremity (FMA-UE) • Modified Barthel Index (MBI) • Adverse events (AEs)	Lack of valid outcome
Languages	Chinese and English	Other languages
Study designs	Randomized controlled trials (RCTs)	Non-randomized controlled trials (RCTs) and conference papers

Following the preliminary review, 581 studies were identified as duplicates and subsequently removed. The remaining 885 studies were then subjected to independent examination by two researchers, with their titles and abstracts analyzed. A total of 179 studies were excluded on the basis of their irrelevance to the research question. Subsequently, a comprehensive review was conducted on the 706 selected studies, with a detailed assessment of their study design, participant population, interventions, and outcome measurements. In conclusion, a total of 49 RCTs (12–60) were included in the final analysis. The process of study selection is outlined in detail in the PRISMA flow diagram (shown in Figure 1).

The studies included in the analysis spanned a period of approximately 15 years, from September 2009 to March 2024. The studies were distributed across a number of countries, including mainland China ($n = 44$), Taiwan, China ($n = 2$), Brazil ($n = 1$), Turkey ($n = 1$) and Iran ($n = 1$) Of the included trials, 42 RCTs (12, 13, 15–28, 30–35, 37, 38, 41, 42, 44–55, 57–60) were two-arm designs (85.71%), 6 RCTs (14, 29, 36, 39, 40, 56) were three-arm designs (12.24%), and 1 RCTs (43) was a four-arm experiment (2.04%). The studies exhibited considerable variation in terms of sample size, duration of treatment, and intervention measures. In total, the studies recruited 3,219 participants, with 1,697 allocated to the experimental group and 1,522 to the control group. The number of participants ranged from 12 (19) to 204 (45). The baseline characteristics of the participants in the two groups were generally similar, with the average age being 60.24 years (standard deviation 9.15). However, one study (16) did not provide data on the mean age. Seven studies (15, 22, 30, 36, 43, 44, 58) did not report the mean duration of disease. Among the remaining 42 studies, the mean duration of disease ranged from (8.2 ± 6.6) days (27) to (58.9 ± 27.2) months (18). Regarding disease phases, the majority of studies (12–14, 16, 17, 20, 21, 23–26, 28, 29, 31, 33–35, 37, 38, 40–42, 45, 46, 48–57, 59, 60) (75.5%, 37/49) involved patients in the subacute phase, whereas only 4 (18, 19, 32, 39) and 1 studies (27) focused on chronic and acute phases, respectively. With the exception of one study (19) that did not provide gender information, the proportion of male participants among those who had experienced a stroke was 59.34%. Four studies (23, 29, 38, 58) provided data on patient dropout and the specific reasons for this, with the number of dropouts ranging from one to five individuals.

The included RCTs employed seven physical rehabilitation treatment methods, including physical rehabilitation (PR, encompassing exercise training and functional activity training, among others). The remaining treatments were acupuncture therapy (including body acupuncture BA and electro-acupuncture, EA), massage (M), PNF, rTMS, extracorporeal shock wave therapy (ESWT), and TBS (including continuous theta burst stimulation cTBS and intermittent theta burst stimulation iTBS). These physical rehabilitation treatments may be applied either individually or in combination, forming a total of 21 distinct treatment strategies. The core operational parameters of the interventions exhibited limited overall heterogeneity (shown in Supplementary Table S1), with the following modality-specific patterns: In the 16 studies (18–20, 25, 28, 31, 37, 39, 40, 44, 48, 52, 54, 57, 58, 60) that employed rTMS, a low-frequency stimulation pattern of 1 Hz was frequently utilized. However, there was some variation in stimulation intensity thresholds, ranging from 60 to 120% of resting motor threshold (RMT) or active motor threshold (AMT). Furthermore, the target of stimulation in all studies focused on the primary motor cortex (contralesional M1) contralateral to the lesion. Among the 6 studies (43, 46, 47, 55, 56, 59) employing ESWT, five (46, 47, 55, 56, 59) opted for a frequency of 8 Hz, while one (43) selected 5 Hz. The energy intensity was modulated based on anatomical location, with the majority of upper limb treatment parameters ranging from 1.0 to 3.0 bar. For instance, Ai et al. (56) utilized a gradient strategy (1.0–2.0 bar for the upper limb and 2.0–3.0 bar for the elbow-shoulder complex) depending on the site, whereas Chen et al. (59) employed a uniform intensity program (3.0 bar). Of the 4 studies (20, 30, 38, 40) employing TBS, all utilized 80% AMT. In acupuncture treatments, the duration of a single stimulation of BA ranged from 15–30 min, and all studies (13, 16, 21, 23, 24, 27, 29, 32–35, 41–43, 46, 47, 50, 51, 53, 55, 56, 58, 60) using BA

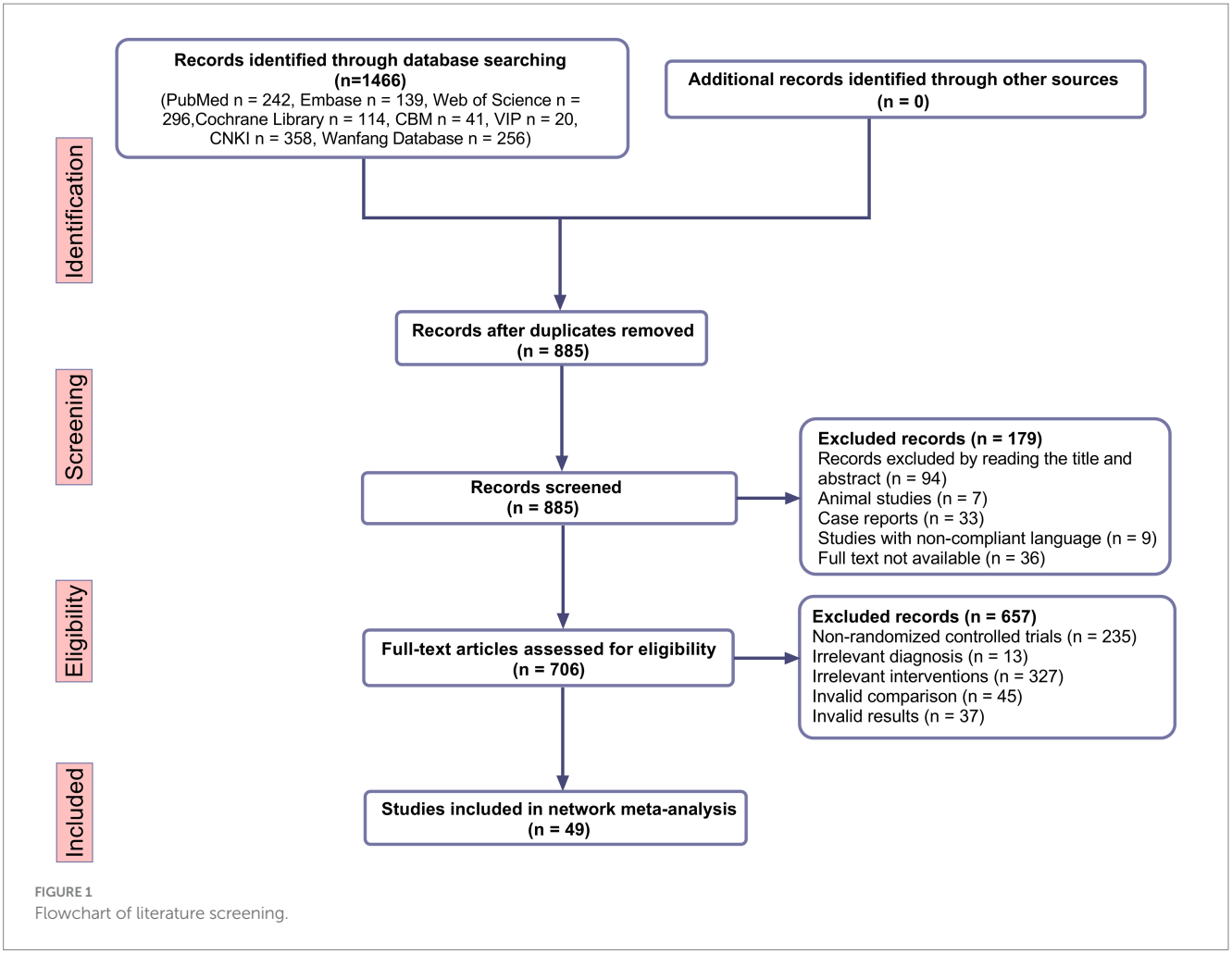

FIGURE 1
Flowchart of literature screening.

focused on upper limb acupoints. The frequency parameters of EA exhibited a bimodal distribution, with a low-frequency group (2–5 Hz) (14, 52) and a high-frequency group (50–100 Hz) (12). Among the 8 studies (15, 22, 26, 35, 36, 41, 45, 49) employing M therapy, the single-session intervention duration ranged from 10 to 40 min, with all protocols exclusively applied to the spastic upper limb.

In terms of outcomes, a total of 41 studies (14, 15, 18, 24, 26, 27, 30, 37, 39, 49, 52, 53, 56, 59–61) employed the Fugl-Meyer Assessment-Upper Extremity (FMA-UE) scale, a tool with a maximum score of 66 points, designed to assess patients' motor function, balance, joint pain, and range of motion. Furthermore, 34 studies (14, 19, 21–23, 25–28, 31, 32, 34–38, 40–44, 46–49, 51–53, 56–61) employed the Modified Barthel Index (MBI) scale to assess patients' abilities in activities of daily living. The MBI has a total score of 100 points and encompasses aspects such as self-care ability, mobility, and degree of dependence. In both assessment tools, a higher score indicates superior functional performance of the patient. Additional details regarding the characteristics of the studies are presented in Table 2.

Follow-up outcomes were reported in 7 studies (18, 20, 25, 39, 46, 48, 54), revealing time-dependent therapeutic effects: A study (48) conducted post-intervention revealed that patients in the low-frequency rTMS group exhibited a significantly higher MBI scores at the 2-week follow-up when compared to the conventional group ($p < 0.05$), thereby suggesting an early effect of enhanced ability in performing ADL. Three studies found that at 4-week follow-up, myotonia modified Ashworth scale (MAS) scores were reduced by ≥1 in the rTMS group by up to 55.5% (18) and that combined cTBS maintained upper limb motor function and improved carpal flexor spasticity (39), but did not significantly enhance ADL independence (25). Three-month follow-up data suggest that combined rTMS with an iTBS regimen resulted in sustained improvements in motor function (20), with a significantly lower relapse rate in the observation group than in the control group (54). Furthermore, Zhang et al. (46) reported a significant improvement in self-assessed outcome (PRO) scores from baseline in both groups ($p < 0.05$).

3.2 Risk-of-bias assessment

The results of the bias risk assessment for the included studies are presented in Supplementary Figure S1. Three studies (23, 29, 56, 58) were classified as exhibiting a high risk of bias, six (18, 25, 30, 34, 39, 43) were deemed to have a low risk of bias, and the remaining studies were situated between these two categories, indicating a certain level of bias risk. While the majority of studies adhered to the fundamental tenets of the CONSORT statement, the absence of certain essential information is a notable shortcoming. For example, deficiencies were identified in the description of intervention similarity, discussion of

TABLE 2 Characteristics of the included studies.

Author	Year	Sample (T/C) (M/F)	Age (year)	Stroke type (I/H)	Course of disease	Treatment	Intervention period	Outcome	Drop-out situation (T/C)
Ai YX	2023	19/11	55 ± 4	-	(4.56 ± 0.89) w	PR+ESWT+BA	4 w	FMA-UE MBI	None
		17/13	56 ± 5	-	(4.23 ± 0.93) w	PR+BA			
		14/16	57 ± 4	-	(4.16 ± 0.78) w	PR			
Bao YH	2012	23/23	67.39 ± 9.75	34/12	(2.63 ± 1.42) m	PR+EA	4 w	FMA-UE	None
		19/22	66.56 ± 9.65	32/9	(2.58 ± 1.46) m	EA			
		22/20	64.85 ± 8.90	31/11	(2.59 ± 1.41) m	PR			
Barros G	2014	6/4	57.4 ± 12.0	9/1	(47.8 ± 43.2) m	PR+rTMS	4 w	FMA-UE	None
		7/3	64.6 ± 6.8	8/2	(58.9 ± 27.2) m	PR			
Chen DY	2024	17/13	68.74 ± 5.23	18/12	(26.41 ± 4.29) d	PR+ESWT	4 w	FMA-UE MBI	None
		18/12	69.11 ± 6.14	20/10	(27.31 ± 5.64) d	PR			
Chen QF	2021	20/10	64.13 ± 13.20	26/4	(2.00 ± 1.34) m	PR+rTMS	4 w	FMA-UE MBI	None
		20/10	61.37 ± 11.90	23/7	(2.17 ± 11.1) m	PR			
Chen Y	2021	13/3	57.38 ± 8.04	10/6	(80.13 ± 35.19) d	PR+iTBS	2 w	MBI	2
		12/4	51.44 ± 9.19	8/8	(101.50 ± 54.15) d	PR			0
Chen YJ	2019	7/4	52.9 ± 11.1	2/9	-	PR+iTBS	2 w	FMA-UE	None
		7/4	52.6 ± 8.3	3/8	-	PR			
Chu GX	2009	18/12	60.37 ± 10.81	25/5	(42.33 ± 16.72) d	PR+EA	4 w	MBI	None
		16/14	60.77 ± 10.65	24/6	(40.20 ± 14.06) d	PR			
Dang YS	2020	20/15	55.23 ± 8.48	18/17	(50.28 ± 16.32) d	PR+BA	4 w	MBI	None
		19/16	55.26 ± 8.51	20/15	(50.24 ± 16.27) d	PR			
Gu YL	2018	26/14	58.01 ± 10.14	-	(48.50 ± 12.12) d	PR+M	3 w	FMA-UE MBI	None
		25/15	56.12 ± 11.06	-	(50.92 ± 12.03) d	PR			
Hao JB	2016	26/14	61.30 ± 9.33	28/12	-	PR+M	4 w	MBI	None
		24/16	60.96 ± 8.76	26/14	-	PR			
Jiang YY	2023	13/12	56.72 ± 10.50	-	(2.62 ± 1.18) m	PR+rTMS+EA	4 w	FMA-UE MBI	None
		17/8	54.56 ± 12.68	-	(2.66 ± 1.12) m	PR+EA			
Kuzu Ö	2021	4/3	56.3 ± 11.5	7/0	(16.4 ± 2.5) m	PR+rTMS	10 w	FMA-UE	None
		6/1	61.3 ± 9.8	7/0	(14.5 ± 1.6) m	PR+cTBS			
		4/2	65.0 ± 4.6	6/0	(14.5 ± 2.0) m	PR			

(Continued)

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TABLE 2 (Continued)

Author	Year	Sample (T/C) (M/F)	Age (year)	Stroke type (I/H)	Course of disease	Treatment	Intervention period	Outcome	Drop-out situation (T/C)
Lei JF	2024	18/2	58.90 ± 9.49	16/4	(1.82 ± 1.25) m	PR+rTMS+BA	4 w	FMA-UE MBI	None
		11/9	59.10 ± 11.92	12/8	(1.18 ± 0.63) m	PR+BA			
Lei M	2012	27/19	64.91 ± 8.85	31/15	-	PR+M	12 w	FMA-UE	None
		27/14	63.66 ± 9.02	26/15	-	PR			
Li B	2021	22/13	62.53 ± 2.75	-	(45.86 ± 1.54) d	BA+M	8 w	MBI	None
		19/16	62.46 ± 2.87	-	(45.93 ± 1.65) d	BA			
Li BJ	2017	32/28	55.7 ± 4.8	-	(15.2 ± 3.7) d	PR+BA	8 w	FMA-UE	None
		35/25	54.9 ± 5.2	-	(15.6 ± 3.3) d	PR			
Li D	2021	20/10	56.77 ± 8.58	24/6	(3.63 ± 1.85) m	PR+rTMS+cTBS	4 w	MBI	None
		19/11	57.60 ± 7.40	23/7	(3.80 ± 1.71) m	PR+rTMS			
		18/12	55.13 ± 7.90	24/6	(3.67 ± 1.84) m	PR+cTBS			
Li ZW	2022	18/12	60.27 ± 6.14	16/14	(8.97 ± 4.14) w	PR+M	4 w	FMA-UE MBI	None
		16/14	59.93 ± 7.15	19/11	(9.30 ± 4.55) w	PR			
Lin FY	2018	17/13	59 ± 5	25/5	(8.2 ± 6.6) d	PR+BA	4 w	FMA-UE MBI	None
		16/14	59 ± 7	26/4	(9.3 ± 6.3) d	PR			
Liu HJ	2023	18/12	55.23 ± 7.86	25/5	(3.83 ± 1.03) m	PR+BA	4 w	FMA-UE MBI	0
		17/12	54.83 ± 13.92	20/9	(3.99 ± 0.96) m	PR			1
Liu QQ	2021	19/12	55.51 ± 3.20	-	(45.78 ± 5.45) d	BA+PNF	4 w	FMA-UE MBI	None
		18/13	55.42 ± 3.19	-	(45.21 ± 5.23) d	PNF			
Liu SD	2023	28/22	73.05 ± 6.31	-	(21.41 ± 5.61) d	EA+rTMS	4 w	FMA-UE	None
		30/20	72.37 ± 5.63	-	(20.21 ± 5.44) d	EA			
Liu SH	2019	7/13	61.35 ± 9.43	-	(2.81 ± 1.27) m	PR+rTMS	4 w	FMA-UE MBI	None
		11/9	55.00 ± 11.86	-	(3.11 ± 1.37) m	PR			
Liu Y	2018	5/5	56.90 ± 9.02	-	(4.50 ± 1.90) m	PR+rTMS	8 w	FMA-UE MBI	None
		9/4	55.38 ± 8.40	-	(4.85 ± 2.08) m	PR			
Ma AF	2022	30/12	61 ± 6	32/10	(27.8 ± 3.8) d	PR++BA	4 w	FMA-UE	None
		32/10	60 ± 6	31/11	(27.3 ± 3.6) d	PR			
Ma JY	2020	17/13	60.47 ± 3.98	-	(49.13 ± 4.48) d	BA+M	8 w	MBI	None
		19/11	60.43 ± 3.73	-	(48.60 ± 2.88) d	BA			

(Continued)

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TABLE 2 (Continued)

Author	Year	Sample (T/C) (M/F)	Age (year)	Stroke type (I/H)	Course of disease	Treatment	Intervention period	Outcome	Drop-out situation (T/C)
Motamed V	2014	6	55.17 ± 5.42	-	(24.00 ± 8.29) m	PR+rTMS	3 w	FMA-UE MBI	None
		6	57.00 ± 8.67	-	(23.00 ± 8.94) m	PR			
Ni HH	2012	36/14	-	34/16	(35.02 ± 6.82) d	PR+BA	4 w	FMA-UE	None
		34/16	-	33/17	(35.20 ± 6.40) d	PR			
Qin Y	2023	9/6	55.87 ± 10.50	-	(3.20 ± 1.93) m	PR+rTMS	8 w	FMA-UE MBI	None
		11/3	59.43 ± 9.12	-	(2.85 ± 1.74) m	PR			
Shi J	2019	12/8	58.5 ± 9.5	-	(67.3 ± 45.9) d	BA+PNF	4 w	FMA-UE MBI	None
		13/7	55.2 ± 13.9	-	(72.3 ± 48.6) d	BA			
Sun X	2023	16/14	55.83 ± 11.05	-	(29.60 ± 6.48) d	PR+ESWT+BA	4 w	FMA-UE	None
		17/13	58.30 ± 10.95	-	(29.13 ± 5.50) d	PR+BA			
Sun YZ	2013	17/13	62.82 ± 7.93	-	(55.44 ± 8.30) d	PR+EA	4 w	FMA-UE	None
		15/15	63.50 ± 6.51	-	(59.67 ± 6.81) d	PR			
Tong JY	2022	32/26	60.62 ± 5.63	-	(58.35 ± 6.21) d	PR+BA	4 w	FMA-UE MBI	None
		31/27	60.45 ± 5.59	-	(58.27 ± 6.17) d	PR			
Wang CP	2014	14/3	62.2 ± 12	-	(4.6 ± 3.9) m	PR+rTMS+iTBS	4 w	FMA-UE	None
		11/5	62.5 ± 13.4	-	(4.4 ± 3.1) m	PR			
Wang J	2018	15/15	53.75 ± 7.97	18/12	(50.43 ± 16.93) d	PR+BA	4 w	FMA-UE	1
		17/13	55.17 ± 8.46	19/11	(50.26 ± 16.34) d	BA			1
		16/15	54.91 ± 8.76	17/14	(54.91 ± 8.76) d	PR			1
Wei CB	2021	10/10	56.7 ± 10.5	20/0	-	PR+ESWT+BA	4 w	FMA-UE MBI	None
		11/9	57.5 ± 9.4	20/0	-	PR+ESWT			
		13/7	56.3 ± 11.4	20/0	-	PR+BA			
		12/8	55.3 ± 10.4	20/0	-	PR			
Wen DG	2020	12/8	57.15 ± 11.04	-	-	PR+M	3 w	FMA-UE MBI	None
		14/6	62.60 ± 8.99	-	-	M			
		14/4	62.15 ± 8.97	-	-	PR			
Xie WX	2023	13/6	58.42 ± 12.76	14/5	-	PR+rTMS+BA	2 w	MBI	1
		10/7	54.47 ± 9.152	10/7	-	PR+BA			3
Xu SF	2016	28/8	60 ± 10	-	(50.39 ± 22.52) d	PR+BA	4 w	FMA-UE MBI	2
		24/11	65 ± 6	-	(47.75 ± 22.63) d	PR			3

(Continued)

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TABLE 2 (Continued)

Author	Year	Sample (T/C) (M/F)	Age (year)	Stroke type (I/H)	Course of disease	Treatment	Intervention period	Outcome	Drop-out situation (T/C)
Xu YL	2010	17/15	57 ± 7.3	17/15	(48.73 ± 19.52) d	BA	12 w	FMA-UE	None
		14/17	58 ± 4.7	16/15	(52.49 ± 21.65) d	PR			
Yang NY	2017	12/8	60.7 ± 12.2	16/4	(37.5 ± 26) d	PR+rTMS	2 w	FMA-UE MBI	None
		17/3	58.7 ± 12.7	13/7	(42.5 ± 30.6) d	PR			
Yang X	2021	8/6	60.86 ± 12.396	-	-	PR+rTMS	8 w	FMA-UE MBI	None
		4/7	66.09 ± 7.436	-	-	PR			
Zhang L	2015	22/18	51.6 ± 10.4	31/9	(2.7 ± 1.2) m	PR+BA	8 w	FMA-UE MBI	None
		24/16	52.1 ± 8.6	33/7	(2.5 ± 1.3) m	PR			
Zhang QF	2021	48/54	53.47 ± 3.81	-	(2.34 ± 0.75) m	PR+M	4 w	FMA-UE	None
		58/44	53.84 ± 3.29	-	(2.15 ± 0.63) m	PR			
Zhang X	2021	18/17	50.66 ± 8.77	29/6	(2.43 ± 1.32) m	PR+ESWT+BA	4 w	FMA-UE MBI	None
		19/16	52.63 ± 8.64	29/6	(2.31 ± 1.56) m	PR+BA			
Zhao J	2021	36/14	56.32 ± 7.83	-	(2.87 ± 0.82) m	PR+rTMS	4 w	FMA-UE MBI	None
		35/15	56.29 ± 7.88	-	(2.81 ± 0.79) m	PR			
Zhao JY	2021	18/12	66.1 ± 1.6	-	(29.8 ± 1.5) d	BA+ ESWT	3 w	FMA-UE MBI	None
		16/14	67.8 ± 1.8	-	(30.2 ± 2.0) d	BA			
Zhou P	2019	17/13	60 ± 9	12/18	(45.4 ± 21.1) d	PR+BA	4 w	FMA-UE MBI	None
		16/14	61 ± 8	14/16	(44.1 ± 20.2) d	BA			

T, Treatment group; C, Control group; M, Man; F, Female; I, Ischemic Stroke; H, Hemorrhagic stroke; PR, Physical rehabilitation; BA, Body acupuncture; EA, Electro-acupuncture; M, Massage; PNT, Proprioceptive Neuromuscular Facilitation; ESWT, Extracorporeal shock wave treatment; rTMS, Repetitive transcranial magnetic stimulation; iTBS, Intermittent theta burst stimulation; cTBS, Continuous theta burst stimulation; FMA-UE, The Fugl-Meyer Assessment-Upper Extremity scale; MBI, The Modified Barthel Index scale.

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trial limitations, and assessment of external validity. The reporting of blindness and allocation concealment, two fundamental methods for controlling bias, was inadequate, thereby further undermining the reliability of the trial results. Furthermore, the majority of studies did not indicate whether they had been registered, which restricts the capacity to evaluate the transparency and reliability of the trials. Further detailed assessment information can be found in Supplementary Appendix S3.

3.3 Pairwise meta-analysis

In order to evaluate the impact of different interventions on the improvement of patients' upper limb function, a comprehensive analysis was conducted on studies utilizing the same treatment and observing the same outcome indicators. This analysis was employed to facilitate direct paired meta-analyses for the FMA-UE and MBI, with 25 and 22 studies, respectively. For the FMA-UE scores, the following interventions were compared to PR: BA (two RCTs; MD = 5.6, 95% CI: 0.90, 10, p = 0.39), PR+rTMS (ten RCTs; MD = 7.2, 95% CI: 4.4, 9.9, p < 0.00001), PR+ESWT (two RCTs; MD = 7.2, 95% CI: 2.4, 12, p < 0.00001), PR+EA (two RCTs; MD = 12, 95% CI: 5.6, 18, p < 0.00001), PR+BA (eleven RCTs; MD = 6.1, 95% CI: 4.0, 8.2, p = 0.68), PR+M (five RCTs; MD = 7.2, 95% CI: 3.9, 11, p < 0.00001), PR+ESWT+BA (five RCTs; MD = 7.5, 95% CI: 2.8, 12, p = 0.15), all showing superior effects to PR. BA+ESWT (one RCT; MD = 11, 95% CI: 3.1, 19, p < 0.00001) was more effective than BA alone, EA+rTMS (one RCT; MD = 8.3, 95% CI: 1.0, 16, p < 0.00001) was more effective than EA alone, PR+M (one RCT; MD = 16, 95% CI: 5.1, 27, p < 0.00001) had a better effect than M alone. In addition, PR+ESWT+BA (one RCT; MD = 4.4, 95% CI: 1.6, 7.2, p = 0.51) was more effective than PR+ESWT, and PR+ESWT+BA (four RCTs; MD = 4.6, 95% CI: 1.1, 8.1, p < 0.00001) was superior to PR+BA. With regard to the MBI scores, the following interventions were observed to yield enhanced outcomes in comparison to PR: PR+rTMS (eight RCTs; MD = 6.6, 95% CI: 0.074, 13, p < 0.00001), PR+BA (eight RCTs; MD = 9.0, 95% CI: 2.9, 15, p < 0.00001), PR+M (four RCTs; MD = 18, 95% CI: 9.5, 27, p < 0.00001), PR+ESWT+BA (two RCTs; MD = 16, 95% CI: 2.9, 30, p = 0.80) all demonstrated statistically significant superiority over PR. Furthermore, no statistically significant differences were identified in the comparisons between the remaining treatment measures. For further details, please refer to Table 3.

3.4 Network meta-analysis

The transferability hypothesis was evaluated by means of a comparison of the FMA-UE baseline data. The results demonstrated MD = −0.0609, with 95% CI [−0.2749; 0.1531], and p = 0.5772 > 0.05. This indicates that there was no statistically significant difference in the baseline FMA-UE scores among the included studies, and thus no heterogeneity. Similarly, a comparison of the MBI baseline data revealed MD = −0.1220, with 95% CI [−0.5859; 0.3419], and p = 0.6063 > 0.05. This indicates that no significant heterogeneity was detected between the MBI baseline data. In light of these findings, it can be concluded that the transferability hypothesis is supported, indicating that the baseline characteristics across different studies are comparable. This provides support for the reliability of the study outcomes.

The inconsistency tests for the FMA-UE and MBI scores yielded p-values of 0.7784 and 0.6056, respectively, both greater than 0.05. Consequently, a consistency model was selected for subsequent analysis. To further investigate the potential for internal distribution inconsistency, a node-splitting method was employed for additional testing. The forest plots demonstrate that there are no statistically significant differences between the direct and indirect comparisons at each split node (p > 0.05), indicating that there is no evidence of inconsistency (shown in Supplementary Figure S2). In the closed-loop inconsistency test, all 95% CIs were found to include 0, indicating a high degree of consistency in the closed-loop comparisons (shown in Supplementary Table S2). Furthermore, the Brooks-Gelman-Rubin diagnostic plots indicated that the median and 97.5th percentile of the shrinkage factor exhibited a tendency toward 1 and reached a stable state after 5,000 iterations. Subsequently, the Bayesian model computations were completed with 20,000 iterations, as illustrated in Supplementary Figure S3. Furthermore, the trajectory and density plots of the model were analyzed (shown in Supplementary Figure S4). These results consistently indicate that the model exhibited excellent convergence.

Figures 2A,B present the NMA diagrams for the impact of different treatments on FMA-UE and MBI scores, respectively. The size of the nodes in the diagrams is proportional to the number of participants in each intervention, while the thickness of the lines between nodes is proportional to the number of studies that have been conducted to make the corresponding comparisons. The largest sample sizes were observed for the PR, PR+BA, and PR+M interventions. The most frequently compared pairs were PR vs. PR+rTMS and PR vs. PR+BA.

A league table (Supplementary Table S7) provides a summary of the comparative results of different treatment methods. The table presents the treatment effects based on FMA-UE scores in the lower triangular area and the results related to MBI scores in the upper triangular area. In order to evaluate the efficacy of treatments in improving upper limb motor function, this study compared the effects of standalone PR with various combined treatment. The findings demonstrate that the combined treatments, when compared to the standalone PR, yielded significantly enhanced outcomes in terms of FMA-UE scores. The combined treatments BA+ESWT (MD = −15.15, 95% CI: −23.75, −6.48), EA+rTMS (MD = −12.11, 95% CI: −23.18, −1.07), PR+EA (MD = −11.66, 95% CI: −17.69, −5.56), and PR+rTMS+EA (MD = −17.57, 95% CI: −27.15, −7.97) were able to increase the scores by more than 10 points. Further analysis indicates that, in comparison to the BA treatment alone, the treatments of BA+ESWT (MD = −10.76, 95% CI: −18.7, −3.09) and PR+rTMS+EA (MD = −13.12, 95% CI: −23.51, −2.78) demonstrated more pronounced improvements in FMA-UE scores. Similarly, the combination of PR+ rTMS+EA (MD = −13.68, 95% CI: −24.84, −2.75) also demonstrated superior therapeutic efficacy in comparison to EA treatment alone. Furthermore, the treatments of BA+ESWT (MD = −23.16, 95% CI: −35.43, −10.96), BA+PNF (MD = −21.79, 95% CI: −40.12, −2.79), EA+rTMS (MD = −20.04, 95% CI: −33.92, −6.17), PR+rTMS (MD = −15.11, 95% CI: −24.11, −5.86), PR+rTMS (MD = −14.97, 95% CI: −24.64, −5.16), PR+EA (MD = −19.58, 95% CI: −30.17, −8.97), PR+BA (MD = −14.15, 95% CI: −22.88, −5.13), PR+M (MD = −15.21, 95% CI: −23.7, −6.52), PR+rTMS+BA (MD = −16.69, 95% CI: −27.91, −5.3), PR+ESWT+BA (MD = −17.86, 95% CI: −27.17, −8.45), and PR+rTMS+EA (MD = −25.48, 95% CI: −38.2, −12.58) all showed significant improvements in FMA-UE

TABLE 3 The results of the paired meta-analysis.

Comparison	MD (95% CI)	Number of studies	Number of patients	I^2 (%)	*p*-value
FMA-UE					
B-A	**5.6 (0.90, 10)**	2	124	43.7%	0.39
C-A	2 (−8.0, 12)	1	83	-	-
D-A	−7.3 (−19, 5.1)	1	40	-	-
J-A	2.3 (−19, 24)	1	14	-	-
K-A	7.7 (−10, 25.)	1	22	-	-
L-A	**7.2 (4.4, 9.9)**	10	362	61.7%	-
M-A	**7.2 (2.4, 12)**	2	100	40.0%	-
N-A	**12 (5.6, 18)**	2	148	62.4%	-
O-A	**6.1 (4.0, 8.2)**	11	851	90.9%	0.68
P-A	**7.2 (3.9, 11)**	5	472	38.9%	-
R-A	−3.2 (−20, 14)	1	33	-	-
T-A	**7.5 (2.8, 12)**	2	100	88.6%	0.15
F-B	**11 (3.1, 19)**	1	60	-	-
G-B	9.7 (−6.1, 26)	1	40	-	-
O-B	3.4 (−1.5, 8.2)	2	120	72.8%	0.30
I-C	**8.3 (1.0, 16)**	1	100	-	-
N-C	6.0 (−3.6, 15)	1	87	-	-
P-D	**16 (5.1, 27)**	1	40	-	-
G-E	5.3 (−2.4, 13)	1	62	-	-
L-J	−2.5 (−19., 14)	1	14	-	-
O-M	−0.92 (−8, 6.1)	1	40	-	0.97
T-M	**4.4 (1.6, 7.2)**	1	40	-	0.51
U-N	5.9 (−1.3, 13)	1	50	-	-
S-O	2.5 (−4.5, 9.3)	1	40	-	-
T-O	**4.6 (1.1, 8.1)**	4	230	0.0%	-
MBI					
D-A	−2.8 (−21, 16)	1	40	-	-
K-A	−9.2 (−29, 10)	1	32	-	0.70
L-A	**6.6 (0.074, 13)**	8	329	78.4%	-
M-A	11 (−2.7, 24)	2	100	44.6%	-
N-A	0.70 (−16, 18)	1	60		-
O-A	**9.0 (2.9, 15)**	8	557	86.4%	-
P-A	**18 (9.5, 27)**	4	260	99.9%	-
T-A	**16 (2.9, 30)**	2	100	91.4%	0.80
F-B	12 (−5.9, 30)	1	69	-	-
G-B	10 (−11, 31)	1	40	-	-
H-B	8.3 (−3.7, 20)	2	130	0.0%	-
O-B	8.7 (−8.3, 26)	1	60	-	-
P-D	8.4 (−9.8, 26)	1	40	-	-
G-E	8.3 (−8.9, 26)	1	62	-	-
L-J	−2.8 (−25., 19)	1	60	-	-
Q-J	10 (−11, 32)	1	60	-	-
Q-L	13 (−8.5, 34)	1	60	-	-

(Continued)

TABLE 3 (Continued)

Comparison	MD (95% CI)	Number of studies	Number of patients	I^2 (%)	*p*-value
O-M	−6.7 (−30, 16)	1	40	-	0.59
T-M	8.9 (−17, 34)	1	40	-	0.81
U-N	10 (−7.4, 28)	1	50	-	-
S-O	11 (−1.8, 23)	2	76	0.0%	-
T-O	9.3 (−1.5, 20)	3	170	14.5%	-

A, Physical rehabilitation; B, Body acupuncture; C, Electro-acupuncture; D, Massage; E, Proprioceptive Neuromuscular Facilitation; F, Body acupuncture plus extracorporeal shock wave treatment; G, Body acupuncture plus proprioceptive neuromuscular facilitation; H, Body acupuncture plus massage; I, Electro-acupuncture plus repetitive transcranial magnetic stimulation; J, Physical rehabilitation plus continuous theta burst stimulation; K, Physical rehabilitation plus intermittent theta burst stimulation; L, Physical rehabilitation plus repetitive transcranial magnetic stimulation; M, Physical rehabilitation plus extracorporeal shock wave treatment; N, Physical rehabilitation plus electro-acupuncture; O, Physical rehabilitation plus body acupuncture; P, Physical rehabilitation plus massage; Q, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus continuous theta burst stimulation; R, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus intermittent theta burst stimulation; S, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus body acupuncture; T, Physical rehabilitation plus extracorporeal shock wave treatment plus body acupuncture; U, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus electro-acupuncture; FMA-UE, The Fugl-Meyer Assessment-Upper Extremity scale; MBI, The Modified Barthel Index scale. Bold values indicate statistically significant results (95% CI excluding zero).

scores compared to M. Similarly, the combination of PR+rTMS+EA (MD = −10.41, 95% CI: −20.38, −0.45) demonstrated superior efficacy compared to PR+rTMS. The combination of PR+rTMS+EA (MD = −11.36, 95% CI: −21.23, −1.57) demonstrated a superior therapeutic effect compared to PR+BA. The combination of PR+rTMS+EA (MD = −10.3, 95% CI: −20.29, −0.1) demonstrated superior efficacy compared to PR+M, while the combination of PR+rTMS+EA (MD = −20.21, 95% CI: −39.79, −0.81) exhibited enhanced effectiveness compared to PR+rTMS+ITBS. However, when compared to BA, M was observed to have a slightly lesser impact on the total FMA score (MD = 12.33, 95% CI: 2.72 to 21.78). Similarly, PR+BA was less effective in increasing the FMA-UE score than BA+ESWT (MD = 9.01, 95% CI: 0.32 to 17.66).

In terms of enhancing patients' capacity to perform activities of daily living, combined treatment exhibited greater efficacy than did the use of PR alone. Specifically, PR+M (MD = 18.12, 95% CI: 9.33, 26.7), PR+rTMS+BA (MD = 19.7, 95% CI: 5.77, 33.59), and PR+ESWT+BA (MD = 17.32, 95% CI: 7.32, 27.63) were all significantly more efficacious than PR alone. Further comparison revealed that the PR+M (MD = 27.19, 95% CI: 5.68, 48.22), PR+rTMS+cTBS (MD = 28.88, 95% CI: 0.29, 57.68), PR+rTMS+BA (MD = 28.75, 95% CI: 4.79, 53.01), and PR+ESWT+BA (MD = 26.42, 95% CI: 4.16, 48.75) all demonstrated superiority over the PR+iTBS. Furthermore, the PR+M (MD = 11.51, 95% CI: 0.3, 22.18) exhibited superior outcomes in comparison to the PR+rTMS.

The SUCRA values for each intervention method were calculated in order to facilitate a probabilistic ranking. The specific data can be found in Supplementary Table S3 and Supplementary Figure S5. A probability rank histogram was constructed for the purpose of visually presenting these rankings. As illustrated in Figure 3A, the three most efficacious treatment modalities for enhancing FMA-UE scores were PR+rTMS+EA (91.1%), BA+ESWT (84%), and BA+PNF (74.8%). Figure 3B illustrates that the most efficacious three treatment protocols for enhancing patients' activities of daily living and increasing MBI scores were PR+rTMS+BA (83.1%), PR+M (80.6%), and PR+rTMS+cTBS (79.0%). Furthermore, probability rank graphs and tables were constructed, and their outcomes corroborated those of the probability rank histograms, thus providing additional validation of the analytical findings.

3.5 Adverse effect

A total of 16 studies (32.65%) reported adverse reactions among the 49 included studies. Twelve of the studies indicated that no adverse reactions were observed during the course of treatment. One study reported that a very small number of patients developed mild subcutaneous bruising following electroacupuncture therapy. However, these cases resolved spontaneously without the need for specialized treatment. Additionally, three studies indicated that patients experienced discomfort at the site of treatment during extracorporeal stimulation physical therapy. However, no further adverse reactions of a serious nature were reported (shown in Supplementary Table S5). Overall, extracorporeal stimulation physical therapy appears to have a favorable safety profile. Nevertheless, given the paucity of current research data, a cautious evaluation of its long-term safety and efficacy is still warranted.

3.6 Publication bias

To further investigate the potential publication bias and the impact of small sample sizes on the FMA-UE and MBI scores, corresponding funnel plots were constructed for analysis. As can be observed in Figures 4A,B, the adjusted funnel plots for the comparison of the FMA-UE and MBI scales both demonstrate a symmetrical distribution, with the majority of study points situated equidistant from the central guiding line on either side. This suggests that the included studies have moderate sample sizes and a low risk of publication bias.

3.7 Evidence assessment of outcome measures

Following an assessment of the pertinent outcomes using the GRADE scoring system, it was determined that the strength of evidence for the two scales under discussion ranges from very low to moderate. The principal factors responsible for the reduction in the quality of the evidence are the limitations of the study design and the considerable statistical heterogeneity. The detailed information can be found in the Supplementary Table S6.

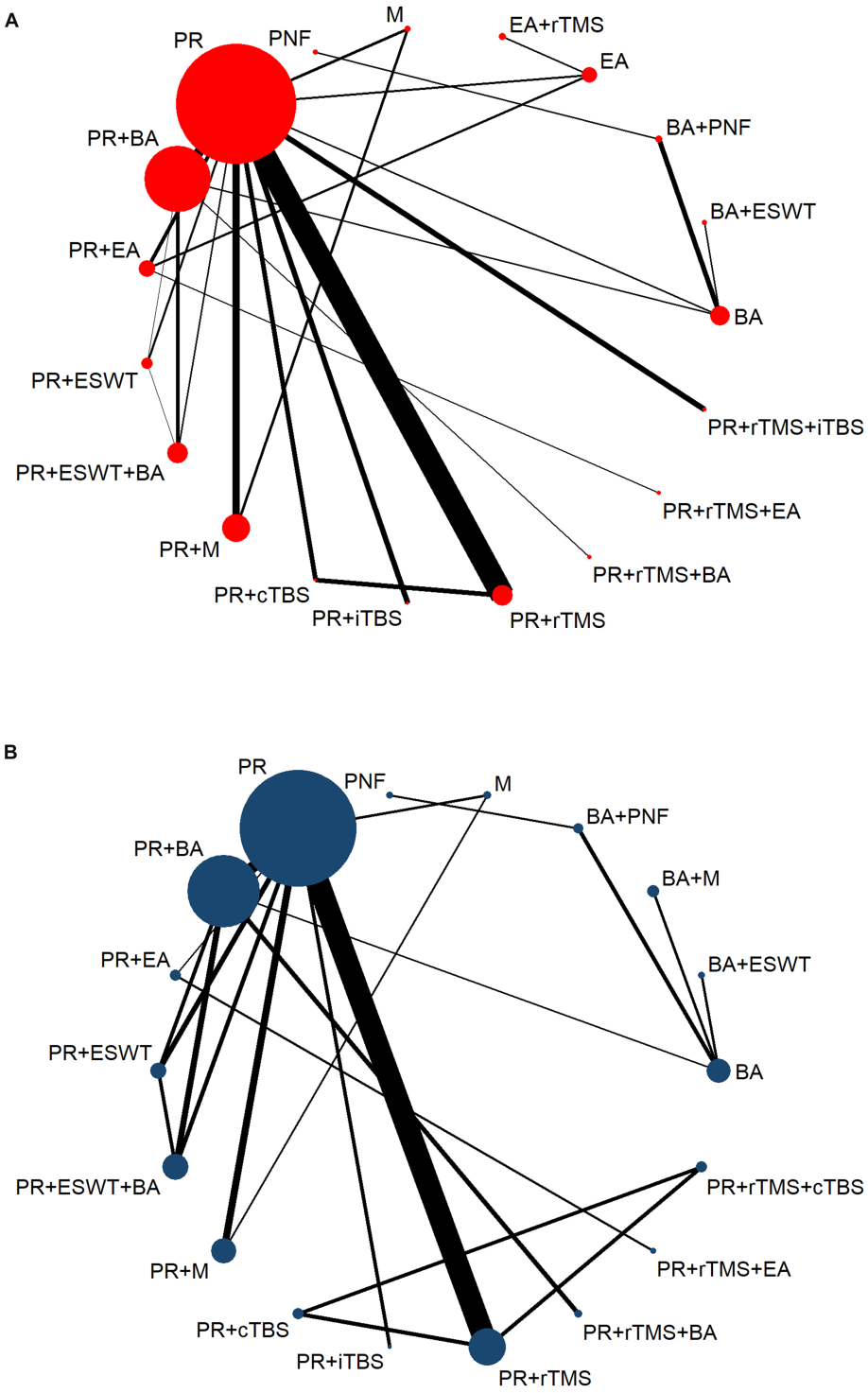

FIGURE 2
Network evidence diagram. PR, Physical rehabilitation; BA, Body acupuncture; EA, Electro-acupuncture; M, Massage; PNF, Proprioceptive Neuromuscular Facilitation; BA+ESWT, Body acupuncture plus extracorporeal shock wave treatment; BA+PNF, Body acupuncture plus proprioceptive neuromuscular facilitation; BA+M, Body acupuncture plus massage; EA+rTMS, Electro-acupuncture plus repetitive transcranial magnetic stimulation; PT+cTBS, Physical rehabilitation plus continuous theta burst stimulation; PT+iTBS, Physical rehabilitation plus intermittent theta burst stimulation; PT+rTMS, Physical rehabilitation plus repetitive transcranial magnetic stimulation; PT+ESWT, Physical rehabilitation plus extracorporeal shock wave treatment; PT+EA, Physical rehabilitation plus electro-acupuncture; PT+BA, Physical rehabilitation plus body acupuncture; PT+M, Physical rehabilitation plus massage; PT+rTMS+cTBS, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus continuous theta burst stimulation; PT+rTMS+iTBS, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus intermittent theta burst stimulation; PT+rTMS+BA, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus body acupuncture; PT+ESWT+BA, Physical rehabilitation plus extracorporeal shock wave treatment plus body acupuncture; PT+rTMS+EA, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus electro-acupuncture; FMA-UE, The Fugl-Meyer Assessment-Upper Extremity scale; MBI, The Modified Barthel Index scale. **(A)** The Fugl-Meyer Assessment-Upper Extremity scale (FMA-UE). **(B)** The Modified Barthel Index scale (MBI).

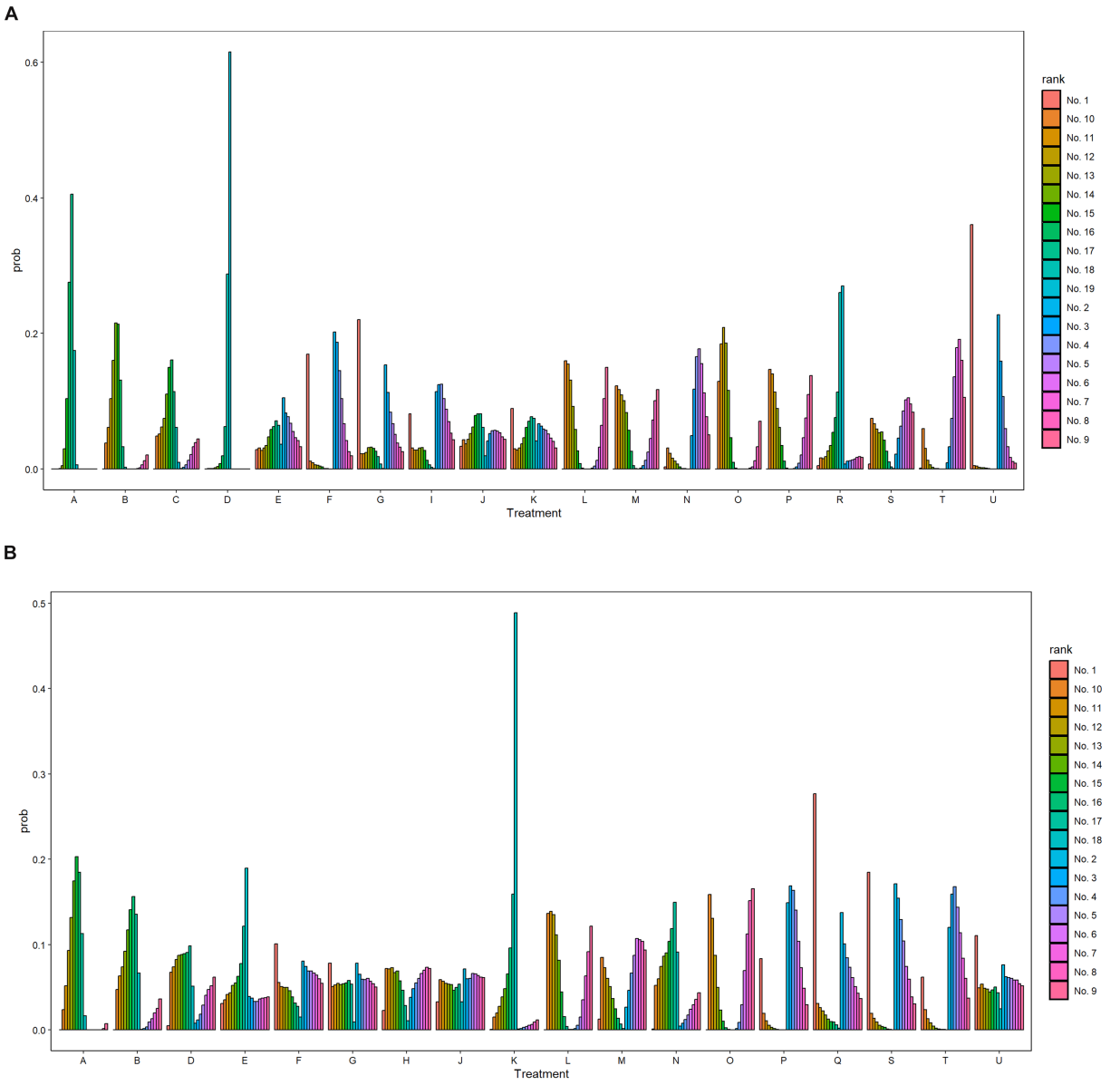

FIGURE 3
Probability ranking diagram. A, Physical rehabilitation; B, Body acupuncture; C, Electro-acupuncture; D, Massage; E, Proprioceptive Neuromuscular Facilitation; F, Body acupuncture plus extracorporeal shock wave treatment; G, Body acupuncture plus proprioceptive neuromuscular facilitation; H, Body acupuncture plus massage; I, Electro-acupuncture plus repetitive transcranial magnetic stimulation; J, Physical rehabilitation plus continuous theta burst stimulation; K, Physical rehabilitation plus intermittent theta burst stimulation; L, Physical rehabilitation plus repetitive transcranial magnetic stimulation; M, Physical rehabilitation plus extracorporeal shock wave treatment; N, Physical rehabilitation plus electro-acupuncture; O, Physical rehabilitation plus body acupuncture; P, Physical rehabilitation plus massage; Q, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus continuous theta burst stimulation; R, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus intermittent theta burst stimulation; S, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus body acupuncture; T, Physical rehabilitation plus extracorporeal shock wave treatment plus body acupuncture; U, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus electro-acupuncture; FMA-UE, The Fugl-Meyer Assessment-Upper Extremity scale; MBI, The Modified Barthel Index scale. **(A)** The Fugl-Meyer Assessment-Upper Extremity scale (FMA-UE). **(B)** The Modified Barthel Index scale (MBI).

4 Discussion

This study used systematic review and meta-analysis methods to thoroughly investigate the impact of different interventions on improving upper limb function in stroke patients. The results showed that a variety of combined treatment regimens significantly outperformed PR alone in improving FMA-UE scores and MBI scores.

In terms of improving upper limb motor function, the efficacy of combined treatments such as PR in conjunction with rTMS, ESWT, and EA, among others, is superior to that of standalone PR. This indicates that combined treatment strategies have significant

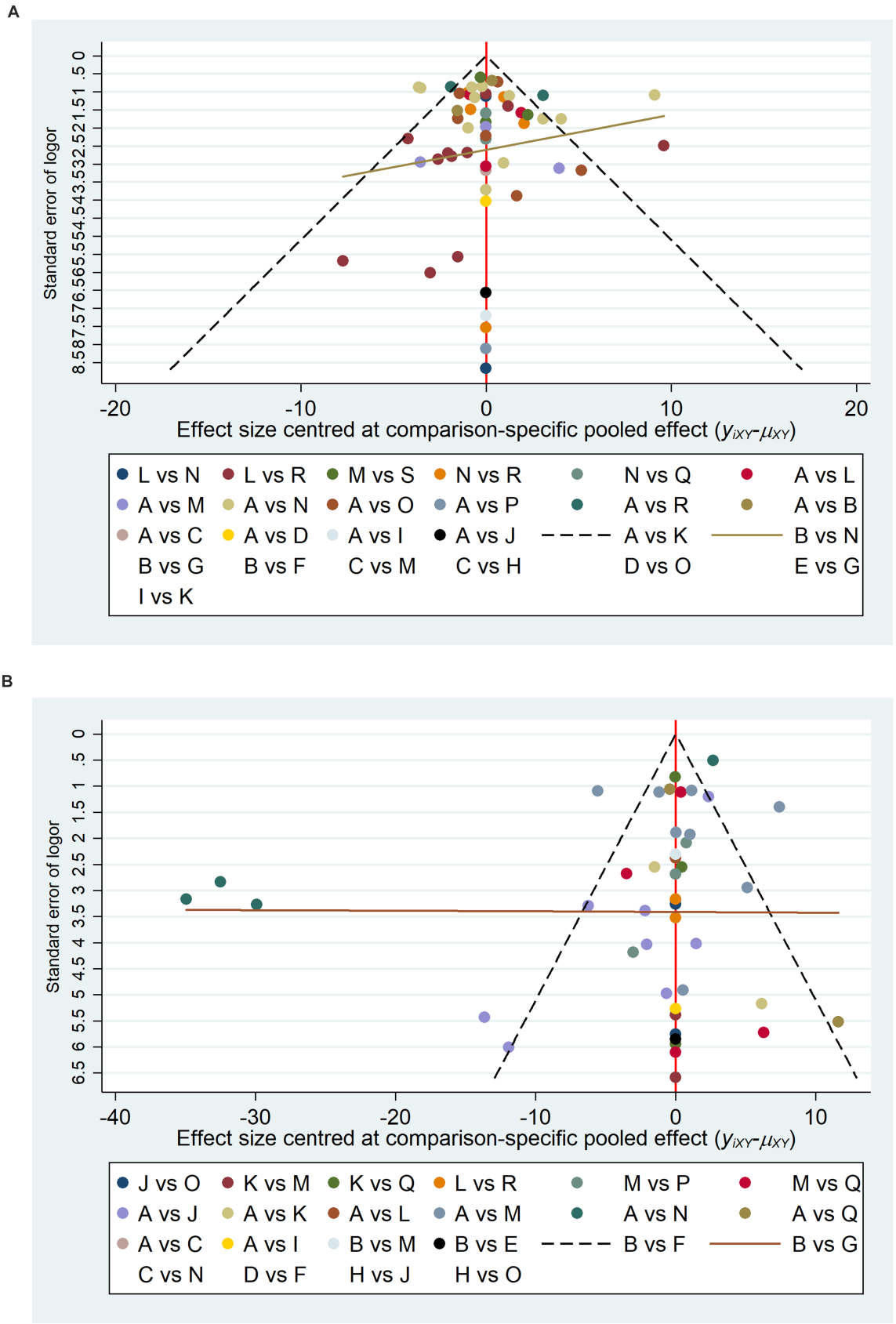

FIGURE 4
Comparative adjustment funnel plots. A, Physical rehabilitation; B, Body acupuncture; C, Electro-acupuncture; D, Massage; E, Proprioceptive Neuromuscular Facilitation; F, Body acupuncture plus extracorporeal shock wave treatment; G, Body acupuncture plus proprioceptive neuromuscular facilitation; H, Body acupuncture plus massage; I, Electro-acupuncture plus repetitive transcranial magnetic stimulation; J, Physical rehabilitation plus

(Continued)

FIGURE 4 (Continued)
continuous theta burst stimulation; K, Physical rehabilitation plus intermittent theta burst stimulation; L, Physical rehabilitation plus repetitive transcranial magnetic stimulation; M, Physical rehabilitation plus extracorporeal shock wave treatment; N, Physical rehabilitation plus electro-acupuncture; O, Physical rehabilitation plus body acupuncture; P, Physical rehabilitation plus massage; Q, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus continuous theta burst stimulation; R, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus intermittent theta burst stimulation; S, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus body acupuncture; T, Physical rehabilitation plus extracorporeal shock wave treatment plus body acupuncture; U, Physical rehabilitation plus repetitive transcranial magnetic stimulation plus electro-acupuncture; FMA-UE, The Fugl-Meyer Assessment-Upper Extremity scale; MBI, The Modified Barthel Index scale. **(A)** The Fugl-Meyer Assessment-Upper Extremity scale (FMA-UE). **(B)** The Modified Barthel Index scale (MBI).

advantages in enhancing upper limb motor function in stroke patients. Among these, the PR+rTMS+EA (MD = −17.57, 95% CI: −27.15, −7.97, SUCRA = 91.1%) regimen has demonstrated the most outstanding performance in increasing the FMA-UE score. This regimen incorporates three distinct treatment modalities: PR, rTMS, EA. These three approaches may act on the central and peripheral nervous systems through different mechanisms, resulting in additive or synergistic effects that promote the recovery of upper limb motor function. rTMS can modulate the release and expression of neurotransmitters, regulate the excitability of the cerebral cortex, and improve neural inflammation by modulating the activation and polarization of astrocytes and microglia (61). This may facilitate the reorganization of damaged neural networks and enhance motor control abilities. Electroacupuncture has been demonstrated to enhance the area of cerebral infarction and downregulate the expression of various inflammatory factors by stimulating specific acupoints, thereby further promoting neural repair and regeneration (62). Furthermore, a meta-analysis (63) has demonstrated that the combination of EA and rehabilitation training represents an efficacious approach to the reduction of post-stroke limb spasticity.

The NMA also demonstrated that the combination of PR with rTMS and BA yielded the most favorable outcomes for improving activities of daily living (MD = 19.7, 95% CI: 5.77, 33.59, SUCRA = 83.1%). Concurrently, combined treatment regimens, including PR+M (MD = 18.12, 95% CI: 9.33, 26.7, SUCRA = 80.6%) and PR+rTMS+cTBS (MD = 28.88, 95% CI: 0.29, 57.68, SUCRA = 79.0%), demonstrated remarkable efficacy, exhibiting superior outcomes compared to standalone physical therapy. This may be due to the fact that these combined treatment strategies can facilitate functional recovery through a number of different mechanisms. To illustrate, rTMS has been demonstrated to stimulate the cerebral cortex (61), thereby promoting neural remodeling. Meanwhile, BA has been shown to alleviate muscle spasticity and improve joint mobility (64). M has been demonstrated to enhance blood circulation and relieve muscle tension (65). Furthermore, the combination of rTMS+cTBS has the capacity to stimulate multiple brain regions simultaneously, thereby producing a broader neural effect (66, 67). It can therefore be concluded that these combined treatment strategies can complement each other, generating a synergistic effect and thus more effectively improving activities of daily living.

The results clearly demonstrate that combined treatments have a significant impact on patients' motor function and also markedly enhance their activities of daily living. The combined treatment strategies have a positive impact on patients through multifaceted functional improvements, including but not limited to increasing muscle strength, improving joint mobility, enhancing coordination and balance, as well as promoting neuroplasticity and functional recovery. In contrast, a standalone physical therapy program may not address all the issues that patients face in a comprehensive manner. It can therefore be concluded that combined treatment regimens, which adopt a more comprehensive approach, represent a superior choice for enhancing patients' activities of daily living.

It is notable that this study did not identify any significant heterogeneity during the analysis phase. This suggests that the baseline characteristics across the various studies were comparable, thereby reinforcing the reliability of the research findings. Furthermore, inconsistency tests and closed-loop inconsistency tests revealed that the model demonstrated a high degree of consistency, thereby providing additional validation for the stability of the analysis results.

Adverse events were infrequent and generally mild. Only one study reported subcutaneous bruising associated with EA, while three studies utilizing ESWT or rTMS noted transient discomfort at the stimulation site. No serious or persistent adverse events were documented, underscoring the safety of these interventions.

Follow-up outcomes demonstrated short-term rTMS efficacy (improved MBI/MAS at 2–4 weeks) and sustained motor benefits at 3 months with lower relapse rates, though ADL gains were inconsistent; PRO scores improved significantly across groups. The inconsistent ADL improvements may reflect differences in rehabilitation intensity or patient-specific functional goals.

Nevertheless, given the limited nature of the current research data, further investigation is required to evaluate the long-term safety and effectiveness of this approach.

4.1 Limitations and future directions

This study has several limitations that warrant consideration. First, the generalizability of findings may be constrained by geographic bias, as over 85% of included trials were conducted in China. Regional variations in rehabilitation paradigms—such as the prevalent integration of acupuncture in Chinese practice (68, 69) versus Western preferences for botulinum toxin or robotic-assisted training (70)—may introduce cultural specificity. Future multinational studies are needed to validate the cross-cultural applicability of these interventions.

Methodological shortcomings in primary studies further limit evidence quality, including inadequate allocation concealment, insufficient blinding of assessors, and incomplete reporting of prospective protocols. To address this, future studies should prioritize rigorous methodologies, including robust allocation concealment, blinded outcome assessment, and adherence to CONSORT guidelines.

Heterogeneity in intervention parameters (e.g., rTMS intensity thresholds, acupuncture session duration) complicates direct

comparisons. Standardization of intervention protocols—particularly for multimodal combinations—is critical to enhance reproducibility and cross-study comparability. Additionally, the predominance of short-term interventions (≤4 weeks in 85.7% of trials) and paucity of longitudinal follow-up data (≥6 months) constrain assessment of sustained treatment effects. Prolonged observation periods are essential to evaluate durability of therapeutic benefits and monitor potential late-onset complications.

The rehabilitation process following stroke is categorized into three distinct phases—acute, subacute, and chronic—each necessitating tailored therapeutic strategies. However, this study was unable to conduct stratified analyses across these phases or specific patient subgroups due to insufficient raw data, which may partially explain the observed heterogeneity in outcomes. This limitation likely stems from a paucity of clinical trials investigating personalized, advanced rehabilitation techniques optimized for distinct recovery stages. Future research should address this gap by conducting granular analyses stratified by stroke phase, etiology (ischemic vs. hemorrhagic), and spasticity severity to identify phase-specific optimal interventions. Such stratified investigations are critical for advancing precision rehabilitation protocols in stroke care.

Mechanistically, the neuroplastic effects of combined therapies remain incompletely understood. Multicenter trials integrating advanced neuroimaging techniques (e.g., fMRI, DTI) and biomarker profiling are warranted to map neural reorganization pathways and optimize synergistic mechanisms.

Consequently, a cautious approach should be employed when interpreting the results of this NMA.

5 Conclusion

The findings of this study suggest that, in comparison to single treatment modalities, combined therapies are more efficacious in improving motor dysfunction and markedly enhancing the daily living abilities of patients with upper limb spasticity following a stroke. The combined physical rehabilitation and rTMS and EA appear to offer a notable advantage in terms of increasing FMA-UE scores and alleviating upper limb spasticity. The combination of physical rehabilitation with rTMS and BA may represent the optimal treatment approach for enhancing functional outcomes as measured by the MBI and improving patients' daily living abilities. Nonetheless, it is imperative to exercise caution when interpreting these findings, given the limited number and questionable quality of the extant studies. A future imperative is to undertake additional high-quality studies that will facilitate the validation of the findings and the further exploration of the long-term efficacy and safety of combination therapies.

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

MB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FC: Data curation, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. HS: Data curation, Methodology, Supervision, Writing – review & editing. ZL: Data curation, Methodology, Supervision, Writing – review & editing. XS: Conceptualization, Writing – review & editing. YL: Data curation, Formal analysis, Writing – review & editing. JS: Validation, Visualization, Writing – review & editing. SL: Validation, Visualization, Writing – review & editing. RR: Validation, Visualization, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

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EDITED BY
Arthur Sá Ferreira,
University Center Augusto Motta, Brazil

REVIEWED BY
Jan Hendrik Schaefer,
Goethe University, Germany
Ozge Altintas Kadirhan,
Kırklareli University, Türkiye

*CORRESPONDENCE
Yiming Deng
✉ parkerdeng@163.com
Zhongrong Miao
✉ zhongrongm@126.com

†These authors have contributed equally to this work

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Time dependency of thrombectomy for large artery atherosclerosis versus cardioembolic stroke subtypes: evidence from the ANGEL-ACT registry

Yue Yin[1†], Hanlin Chen[1†], Anxin Wang[2,3,4], Xiaoli Zhang[2,3,4], Miao Li[1], Ligang Song[1,2,3], Baixue Jia[1,2,3], Ning Ma[1,2,3], Dapeng Mo[1,2,3], Xuan Sun[1,2,3], Feng Gao[1,2,3], Yiming Deng[1,2,3*†] and Zhongrong Miao[1,2,3*†] on behalf of the ANGEL-ACT Study Group

[1]Department of Interventional Neuroradiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [2]China National Clinical Research Center for Neurological Diseases, Beijing, China, [3]Center of Stroke, Beijing Institute for Brain Disorders, Beijing, China, [4]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Introduction: In this study, we investigated the differences in clinical outcomes following endovascular thrombectomy among ischemic stroke subtypes caused by large artery atherosclerosis (LAA) versus cardioembolism (CE) and the time-dependent nature of these clinical outcomes based on the stroke subtypes. Methods: Study participants were selected from the Endovascular Treatment Key Technique and Emergency Workflow Improvement of Acute Ischemic Stroke Registry to conduct a post-hoc analysis of a prospective, observational study. We included 1,046 patients, who had either LAA or CE stroke subtypes based on the Trial of Org 10172 in Acute Stroke Treatment criteria, drawn from the thrombectomy cohort. The association between clinical outcomes and time from stroke onset-to-recanalization time (ORT) was analyzed using a logistic regression model.

Results: Overall, 545 (52.6%) and 491 (47.4%) patients were included in the LAA and CE groups, respectively. No significant difference was found in the 90-day clinical functional outcome between the LAA and CE patients when ORT was achieved within 240 min. Beyond 240 min, the rate of achieving a modified Rankin Scale score of 0–2 in patients with LAA was higher than that of patients with CE [48.17% versus 38.66%; odds ratio (OR) = 0.678, 95% confidence interval (CI) = 0.521–0.884, p = 0.0040], and after adjustment, the OR was 0.732 (95% CI: 0.537–0.998, p = 0.0486).

Conclusion: In cases where the ORT exceeded 240 min, the clinical outcomes of patients with LAA were better than those of patients with CE, demonstrating a stronger time-dependency for achieving a favorable prognosis in patients with cardioembolic stroke.

KEYWORDS

thrombectomy, time dependency, large artery atherosclerosis, cardioembolism, stroke subtypes

1 Introduction

Mechanical thrombectomy (MT) has become the gold standard treatment for patients with acute large-vessel occlusion stroke, as demonstrated by multiple clinical studies (1–7). Guidelines recommend that patients with circulation occlusion undergo endovascular treatment (EVT) within 24 h of symptom onset, provided rigorous imaging screening is performed (8–10). Numerous studies have identified that surgical complications and clinical outcomes vary among patients with different stroke subtypes, suggesting that thrombectomy strategies should be tailored to the specific stroke subtype to optimize patient outcomes. Among patients with acute large vessel occlusion, cardioembolism (CE) is associated with an increased risk of hemorrhagic transformation within 24 h following EVT compared to large artery atherosclerosis (LAA) (11). For patients with vertebrobasilar occlusion stroke undergoing EVT, those with embolic stroke of undetermined origin have poorer outcomes and higher mortality rates compared to those with LAA or cardioembolic stroke (12). Additionally, in the cardioembolic group, the proportion of patients achieving a modified Rankin Scale (mRS) score of 0–2, indicative of good functional recovery, decreased as the onset-to-puncture time increased, a trend not observed in the LAA group (13).

Additionally, most current research focuses on the time window for patient selection but neglects the timing of surgical recanalization, including onset-to-door time, door-to-puncture time, puncture-to-recanalization time, and onset-to-recanalization time (ORT). Research on these times would be more beneficial for establishing better quality control metrics for thrombectomy. In this study, we aimed to explore the relationship between thrombectomy effectiveness and the ORT in patients with LAA and CE stroke.

2 Materials and methods

2.1 Study population

Data used in this study were obtained from the Endovascular Treatment Key Technique and Emergency Workflow Improvement of Acute Ischemic Stroke (ANGEL-ACT), a prospective nationwide registry comprising 2004 consecutive adult patients diagnosed with acute ischemic stroke (AIS) who underwent EVT across 111 hospitals in China between November 2017 and March 2019. Detailed methods of the registry, including inclusion and exclusion criteria as well as data collection standards, have been previously documented (14). The study protocol was approved by the ethics committee of each center, and all participants (or legal representatives) provided written informed consent. The study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

This study included patients aged ≥18 years diagnosed with AIS who underwent initiation of EVT. Of the 2004 patients registered in the ANGEL-ACT database, 211 were excluded for the following reasons: 83 had isolated extracranial large-vessel occlusion, 98 had no evidence of large-vessel occlusion on digital subtraction angiography, and 30 had missing baseline data. Among the remaining 1793 patients, we further excluded those who did not undergo thrombectomy ($n = 186$), those with tandem lesions ($n = 318$), those with Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria for stroke of other determined etiology ($n = 40$), those with stroke of undetermined etiology ($n = 203$), and those whose 90-day mRS scores were missing ($n = 10$). Ultimately, 1,036 patients met the inclusion criteria for this analysis, comprising 545 with LAA and 491 with CE (Figure 1).

2.2 Data collection

Information regarding baseline demographic characteristics (age and sex), medical history (presence of hypertension, hyperlipidemia, or diabetes mellitus; prior stroke; mRS score ≥ 1 before stroke; use of GP IIb/IIIa receptor inhibitors; pretreatment with anti-platelets, intravenous thrombolysis, and anticoagulants), clinical features [systolic blood pressure (SBP), Alberta Stroke Program Early Computed Tomography Score (ASPECTS), National Institutes of Health Stroke Scale (NIHSS) score, onset-to-door time, door-to-puncture time, puncture-to-recanalization time, and ORT], location of the intracranial occlusion [anterior circulation included internal carotid artery, anterior cerebral artery (A1/A2), and middle cerebral artery (M1/M2); posterior circulation included vertebral, basilar, and posterior cerebral arteries (P1)], anesthesia type, and successful recanalization after the final attempt was documented.

2.3 EVT and stroke subtype

Prior to MT, intravenous thrombolysis was administered to eligible patients without contraindications. The choice between local and general anesthesia depended on the patient's cooperation and condition. Following digital subtraction angiography, the neurointerventionist determined the optimal strategy and materials for the EVT. The surgical approach was determined based on the surgical situation and the personal experience of the neurointerventionist. To address *in situ* stenosis, several strategies were employed, including balloon expansion angioplasty alone (using Kalamazoo, MI, USA, Gateway, Stryker; or Neuro-RX SINOMED, Tianjin, China), balloon-mounted stents alone (such as Apollo, MicroPort, Shanghai, China), or a combination of balloon-mounted

Abbreviations: AIS, Acute ischemic stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CE, Cardioembolism; CI, Confidence interval; EVT, Endovascular treatment; ANGEL-ACT, Endovascular Treatment Key Technique and Emergency Workflow Improvement of Acute Ischemic Stroke; LAA, Large artery atherosclerosis; MT, Mechanical thrombectomy; mRS, Modified Rankin Scale; NHISS, National Institutes of Health Stroke Scale; OR, Odds ratio; ORT, Onset-to-recanalization time; SBP, Systolic blood pressure; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

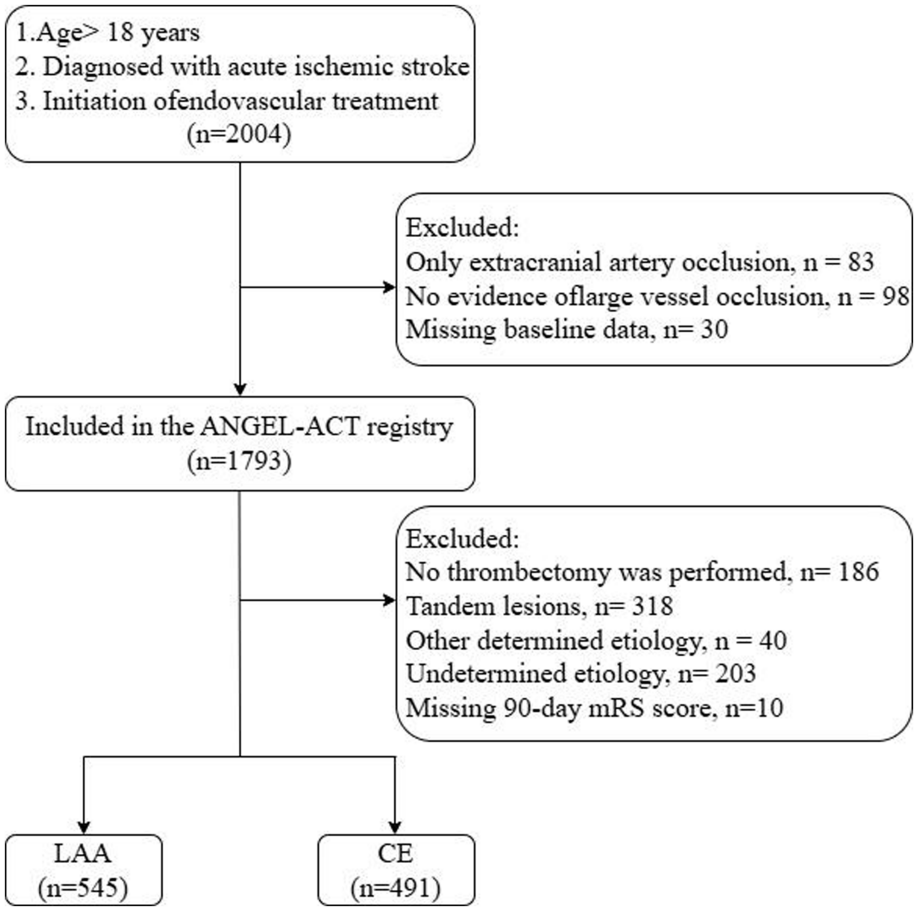

FIGURE 1
Patient selection flowchart. ANGEL-ACT, endovascular treatment key technique and emergency work flow improvement of acute ischemic stroke; LAA, large artery atherosclerosis; CE, cardioembolism.

and self-expanding stents (Enterprise, Codman & Shurtleff Inc., Miami, FL, USA; Wingspan or EZ, Stryker, Kalamazoo, MI, USA; or Solitaire AB, Medtronic, Minneapolis, Minnesota, USA), following balloon expansion.

Stroke subtype classification was performed by two separate neurologists or onsite investigators using the 1993 version of the TOAST criteria (15). Prior to patient enrollment, all evaluators underwent training by committee-assigned stroke specialists and were provided with a manual containing detailed descriptions of the TOAST subtyping system and operational guidelines for determining the etiological subtype. Diagnosis of CE stroke typically requires identification of at least one cardiac source of embolism (via electrocardiogram or echocardiogram), characterized by clinical symptoms and brain imaging findings demonstrating occlusion of a major cerebral or branch cortical artery. Using a standardized diagnostic process, trained evaluators reviewed the patients' clinical history, imaging findings, and laboratory features and categorized them into LAA or CE stroke subtypes according to the TOAST system.

2.4 Outcome measurement

Experienced investigators meticulously recorded all data. We considered a favorable functional recovery outcome at 90 days post-procedure (defined as a 90-day mRS score of 0–2) as the efficacy endpoint. We also recorded the onset-to-door time, door-to-puncture time, puncture-to-recanalization time, and ORT.

2.5 Statistical analysis

Data are presented as the median (interquartile range) or frequency (percentage). A comparison of baseline characteristics between patients with LAA and those with CE was performed using the Kruskal–Wallis test or chi-square test, as appropriate. A multivariate logistic regression model was used to examine the association between the stroke subtypes (LAA vs. CE) and ORT. Variables including age; sex; presence of hypertension, diabetes mellitus, or hyperlipidemia; SBP; baseline NIHSS score; ASPECTS; and pretreatment with antiplatelet agents (aspirin and clopidogrel) were adjusted for in the analysis. The adjusted odds ratio (OR) with 95% confidence intervals (CIs) was calculated to measure the strength of the association.

The cumulative percentage of good prognoses was used to determine the point at which the prognosis in the LAA group surpassed that in the CE group (Figure 2).

According to the statistical data, we analyzed the proportion of mRS scores of 0–2 across various time segments and identified

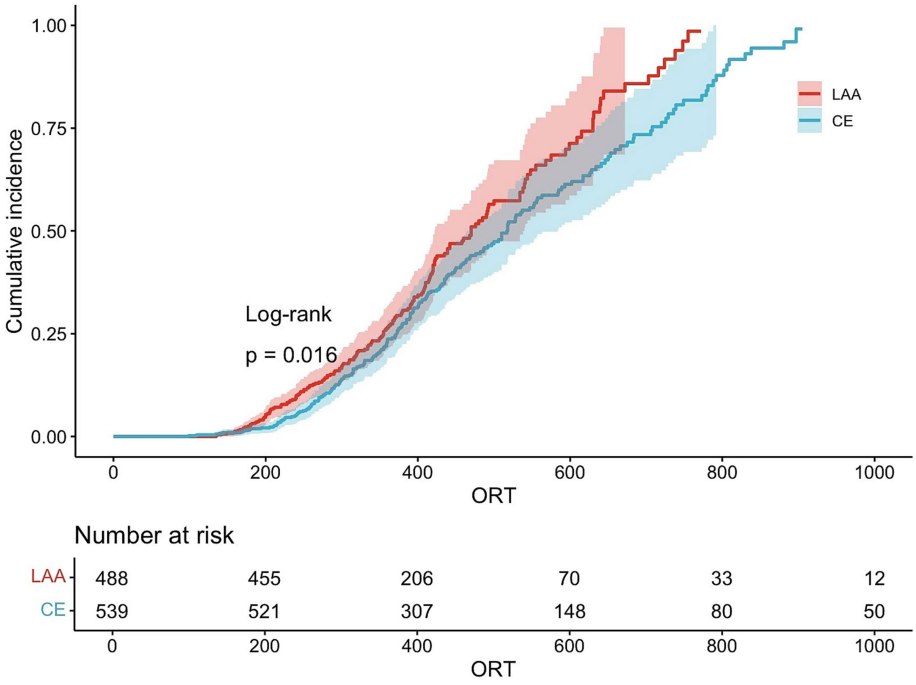

FIGURE 2
Cumulative percentage of good prognoses. LAA, large artery atherosclerosis; CE, cardioembolism.

240 min as the optimal cutoff. The correlation between good functional outcomes and ORT in the two groups was analyzed separately for cases occurring before and after 240 min.

Mediation models were used to examine whether the relationship between stroke subtype and ORT was mediated by the following factors: NIHSS score, site of occlusion, prior use of anticoagulants, type of thrombectomy (stent retriever alone or stent retriever plus aspiration), number of thrombectomy passes, and emergency angioplasty/stenting. The detailed methods of mediation analysis can be found in Supplementary Material. All statistical analyses were conducted using SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant.

3 Results

3.1 Baseline characteristics of patients with LAA versus CE

Of the 1,036 patients included in this study, 545 with LAA and 491 with CE were compared for baseline characteristics. As shown in Table 1, several baseline variables differed significantly between the two groups. Compared with the LAA group, the CE group exhibited the following characteristics: (1) a higher mean age (69 vs. 63 years); (2) a higher median NIHSS score (17 vs. 16); (3) a higher median ASPECTS (10 vs. 8); (4) a significantly larger proportion of women (52.55% vs. 23.12%); (5) a greater percentage of anterior circulation strokes (87.78% vs. 70.28%); and (6) a greater percentage of pretreatment with anticoagulants (8.35% vs. 1.47%). Meanwhile, the CE group had a smaller proportion of patients with hypertension (54.38% vs. 60.92%), diabetes mellitus (14.66% vs. 20.18%), and those who received antiplatelet agents before the procedure (12.83% vs. 17.25%). The CE group used GP IIb/IIIa receptor inhibitors less frequently during the procedure (35.23% vs. 72.11%). However, the CE group experienced shorter onset-to-door times (135 vs. 170 min), shorter door-to-puncture times (114 vs. 127 min), and shorter ORTs (367 vs. 432 min) than the LAA group. No significant difference was found between the two groups regarding the presence of hyperlipidemia, prior stroke, mRS scores ≥ 1 before stroke, initiation of intravenous thrombolysis pretreatment, type of anesthesia, puncture-to-recanalization time, or complete recanalization after the final attempt (Table 1).

3.2 Distribution of mRS scores across ORT categories and stroke subtypes

Among all enrolled participants, patients with LAA stroke had a higher percentage of favorable functional outcomes (mRS score of 0–2) than those with CE stroke. In the subgroup with an ORT < 240 min, 54.72% of patients with LAA stroke and 59.72% of patients with CE stroke achieved mRS scores of 0–2. In the subgroup with an ORT ≥ 240 min, 48.17% of patients with LAA stroke and 38.66% of patients with CE stroke achieved mRS scores of 0–2 (Table 2).

3.3 Logistic regression analysis of ORTs and mRS scores of 0–2 in patients with LAA and CE

Table 3 presents the results of the single and multifactor analyses examining the association between the ORTs and favorable functional outcomes (as indicated by mRS scores of 0–2). For cases with an

TABLE 1 Baseline characteristics of the patients with LAA and CE stroke.

	LAA (*n* = 545)	CE (*n* = 491)	*p* value
Age, y, median [IQR]	63 [54–71]	69 [62–77]	<0.0001
Hypertension, *n* (%)	332 (60.92)	267 (54.38)	0.0333
Male, *n* (%)	419 (76.88)	233 (47.45)	<0.0001
Hyperlipidemia, *n* (%)	62 (11.38)	41 (8.35)	0.1041
Diabetes Mellitus, *n* (%)	110 (20.18)	72 (14.66)	0.0197
Prior stroke, *n* (%)	103 (18.90)	100 (20.37)	0.5524
mRS ≥ 1 before stroke, *n* (%)	65 (11.93)	64 (13.03)	0.5988
SBP, mmHg, median [IQR]	149 [133–165]	145 [130–160]	0.0040
Baseline NIHSS, median [IQR]	16 [11–21]	17 [13–21]	0.0013
ASPECTS, median [IQR]*	8 [7–10]	10 [7–10]	<0.0001
Occlusion site, *n* (%)			<0.0001
Anterior circulation	383 (70.28)	431 (87.78)	
Posterior circulation	162 (29.72)	60 (12.22)	
Anesthesia type, *n* (%)			0.6245
General anesthesia	208 (38.17)	176 (35.85)	
Local anesthesia only	238 (43.67)	229 (46.64)	
Local anesthesia plus sedation	99 (18.17)	86 (17.52)	
Pretreatment with anti-platelets, *n* (%)	94 (17.25)	63 (12.83)	0.0477
Pretreatment with IVT, *n* (%)	145 (26.61)	144 (29.33)	0.3293
Pretreatment with anticoagulants, *n* (%)	8 (1.47)	41 (8.35)	<0.0001
Complete recanalization after the final attempt†	376 (68.99)	364 (74.13)	0.0673
GP IIb/IIIa receptor inhibitor, *n* (%)	393 (72.11)	173 (35.23)	<0.0001
Onset-to-Door time, min, median [IQR]	170 [78–330]	135 [61–260]	0.0058
Door to Puncture time, min, median [IQR]	127 [90–191]	114 [74–159]	<0.0001
Puncture-to -recanalization time, min, median [IQR]	83 [50–127]	80 [50–117]	0.5803
Onset-to-recanalization time (ORT), min, median [IQR]	432 [315–628]	367 [277.5–492.5]	<0.0001

LAA, large artery atherosclerosis; CE, cardioembolism; IQR, interquartile range; mRS, modified rankin scale; SBP, systolic blood pressure; mTICI, modified thrombolysis in cerebral infarction; NIHSS, national institutes of health stroke scale; ASPECTS, alberta stroke program early CT score; pc-ASPECTS, posterior circulation alberta stroke program early CT score; IVT, intravenous thrombolysis.
*ASPECTS for anterior circulation stroke and pc-ASPECTS for posterior circulation stroke.
†Defined as an mTICI score of 3.

TABLE 2 mRS scores of 0–2 for different ORT categories in patients with LAA and CE stroke.

Variable	LAA		CE	
	mRS score 0–2	mRS score 0–6	mRS score 0–2	mRS score 0–6
Total	266 (48.81%)	545	205 (41.75%)	491
ORT = 0–240 min	29 (54.72%)	53	43 (59.72%)	72
ORT> = 240 min	237 (48.17%)	492	162 (38.66%)	419
ORT = 241–480 min	138 (50.18%)	275	106 (37.19%)	285
ORT = 481–720 min	47 (39.17%)	120	30 (35.71%)	84
ORT> = 721 min	52 (53.61%)	97	26 (52.00%)	50

ORT < 240 min, there was no statistically significant difference in the rate of favorable functional outcomes between the LAA and CE groups (OR: 1.227; 95% CI: 0.599–2.514; $p = 0.5759$). Similar results were observed in the adjusted models, with $p > 0.05$. After adjusting for age, sex, high blood pressure, presence of diabetes mellitus, presence of hyperlipidemia, SBP, baseline NIHSS score, ASPECTS score, pretreatment with anti-platelets,

TABLE 3 Odds ratio of mRS scores distribution in LAA versus CE stroke.

mRS scores of 0–2		OR	*P*-value	OR (Adjusted MODEL)	*P*-value
LAA vs. CE	ORT<240 min	1.227 (0.599–2.514)	0.5759	1.633 (0.700–3.810)	0.2564
	ORT≥240 min	0.678 (0.521–0.884)	0.0040*	0.732 (0.537–0.998)	0.0486*

Adjusted Model: Logistic regression adjusted for age, gender, high blood pressure, presence of diabetes mellitus, presence of hyperlipidemia, systolic blood pressure, baseline NIHSS score, ASPECTS score, pretreatment with anti-platelets, and pretreatment with anticoagulants.
*Statistically significant.

and pretreatment with anticoagulants in the adjusted model, the OR was 1.633 (95% CI: 0.700–3.810, $p = 0.2564$).

For cases with an ORT ≥ 240 min, there was a statistically significant difference in favorable functional outcomes between the LAA and CE groups. The unadjusted OR was 0.678 (95% CI: 0.521–0.884; $p = 0.0040$), indicating that CE stroke is a risk factor compared to LAA stroke. Similar results are obtained for the adjusted model. After adjustment, the OR was 0.732 (95% CI: 0.537–0.998, $p = 0.0486$).

4 Discussion

To the best of our knowledge, this is the first study to investigate the association between the ORT and favorable clinical functional recovery (defined as mRS scores of 0–2) in patients with CE and LAA stroke subtypes. The study indicated no significant difference in clinical outcomes between patients with LAA and CE stroke within 240 min of stroke onset. However, beyond 240 min, the clinical outcomes of patients with LAA stroke were better than those of patients with CE stroke, demonstrating a stronger time dependency for favorable prognosis in patients with CE stroke. A possible reason for this is that patients with LAA stroke tend to have better collateral recruitment due to the chronic process of ischemic preconditioning (16). Researchers have found that patients with stroke due to cervical carotid atherosclerosis had better cerebral collateral circulation and slightly better median mRS scores at 90 days compared to those with CE stroke (17).

The findings suggest that CE stroke patients have a stronger time-dependent aspect. While early recanalization remains critical for both subtypes, CE strokes exhibit a stronger decline in favorable outcomes with delayed reperfusion, likely due to shortage of collateral circulation. Therefore, we recommend shortening the time from symptom onset to recanalization in patients with CE. Understanding the implications of these findings can significantly impact various aspects of stroke management.

Firstly, CE stroke was associated with a higher risk of any hemorrhagic transformation compared to LAA stroke (11). One possible explanation is that the difference in thrombus composition between stroke subtypes may account for the higher number of thrombectomy passes associated with CE stroke. These findings underscore the importance of accurately identifying the stroke subtype.

Secondly, given the time-sensitive nature of CE stroke outcomes, the choice of devices that can facilitate quicker and more efficient reperfusion is crucial to optimize the chances of favorable outcomes within the critical time window. Moreover, We found that the CE group experienced shorter onset-to-door times, shorter door-to-puncture times, and shorter ORTs than the LAA group. We hypothesize that CE patients presented with more severe symptoms (e.g., higher NIHSS due to abrupt vessel occlusion), prompting faster triage (18).

Finally, establishing stringent quality control standards for CE patients is essential for ensuring optimal clinical outcomes. Stringent medical quality control is crucial for a country like China with an uneven healthcare distribution.

This study has some limitations. Firstly, this was not a randomized study, and thus can only partly illustrate the issue. This study is a real-world investigation with a large sample size. However, due to the relatively early timeframe, the efficiency of thrombectomy was not very high, possibly because of insufficient thrombectomy experience and equipment. During the study period, researchers found that a subset of the population underwent direct aspiration as the primary thrombectomy approach, which was linked to lower rates of successful recanalization with the initial device, indicating the need for employing additional rescue treatments, and a higher risk of intracranial hemorrhage compared to using a stent retriever as the primary thrombectomy approach (19). Secondly, there is a high portion of patients with intracranial athero-occlusive disease in China, which decreases the external validity or generalizability of the findings.

In conclusion, this study suggests that patients with LAA stroke had better clinical outcomes compared to those with CE stroke when the ORT ≥ 240 min, demonstrating a stronger time-dependency for favorable prognoses in CE stroke. Further research is necessary to elucidate the factors mediating the relationship between stroke subtypes and the ORT and to inform the development of clinical management strategies.

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/s.

Ethics statement

The studies involving humans were approved by the IRB of Beijing Tiantan Hospital, Capital Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YY: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. HC: Software,

Writing – original draft. AW: Methodology, Software, Writing – review & editing. XZ: Methodology, Software, Writing – review & editing. ML: Data curation, Writing – review & editing. LS: Data curation, Supervision, Writing – review & editing. BJ: Data curation, Formal analysis, Writing – review & editing. NM: Supervision, Writing – review & editing. DM: Resources, Supervision, Writing – review & editing. XS: Resources, Supervision, Writing – review & editing. FG: Resources, Supervision, Writing – review & editing. YD: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. ZM: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1574948/full#supplementary-material

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EDITED BY
Arthur Sá Ferreira,
University Center Augusto Motta, Brazil

REVIEWED BY
Ting Peng,
Central South University, China
Yan-Jing Chen,
Central South University, China

*CORRESPONDENCE
Nan Liu
✉ xieheliunan1984@sina.com

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Development and validation of a risk prediction model for activities of daily living dysfunction in stroke survivors

Fangbo Lin and Nan Liu*

Neurology Department, Fujian Medical University Union Hospital, Fuzhou, China

Objective: Stroke is a leading cause of disability worldwide, imposing a significant burden on patients, families, and society. To create and verify a prediction model for activities of daily living (ADL) dysfunction in stroke survivors, pinpoint key predictors, and analyze the traits of those at risk.

Methods: Data from the China Health and Retirement Longitudinal Study wave 5 was used in this cross-sectional study. 1,131 stroke survivors were included and split into training and testing sets. The least absolute shrinkage and selection operator regression and multivariate logistic regression were applied for model development. Model performance was evaluated using the area under the receiver operating characteristic curve(AUC), calibration plots, and decision curve analysis. SHapley Additive exPlanations values were calculated to understand predictor importance.

Results: Six variables (age, the 10-item Center for Epidemiologic Studies Depression Scale score, memory disorder, self-rated health, pain count, and heavy physical activity) were identified as significant predictors. The model showed good discriminatory power (training set AUC = 0.804, testing set AUC = 0.779), accurate calibration, and clinical utility.

Conclusion: A prediction model for ADL dysfunction in stroke survivors was successfully developed and validated. It can help in formulating personalized medical plans, potentially enhancing stroke survivors' ADL ability and quality of life.

KEYWORDS

stroke survivors, ADL dysfunction, prediction model, LASSO regression, nomogram

1 Introduction

Stroke is a leading cause of disability worldwide, imposing a significant burden on patients, families, and society (1). Despite advancements in acute phase stroke treatment, a large number of stroke survivors experience limitations in activities of daily living (ADL) (2), which severely impacts their quality of life. Understanding the factors associated with ADL dysfunction in stroke survivors and predicting its occurrence at an early stage is crucial for developing targeted interventions.

Previous studies have investigated various factors related to post-stroke ADL dysfunction (3, 4), but there is still a lack of a comprehensive and accurate prediction

model. Identifying individuals at high risk of ADL dysfunction early can enable timely implementation of rehabilitation strategies and management plans, potentially improving their functional outcomes and quality of life (5, 6).

In this study, we aimed to develop and validate a prediction model for ADL dysfunction in stroke survivors. By analyzing data from a large scale dataset, we aimed to identify key predictors, understand the characteristics of stroke survivors at risk of ADL dysfunction, and provide a basis for personalized medical care and improved management of this patient population.

2 Methods

2.1 Study design

This study adopted a cross-sectional design, which is suited for exploring associations between risk factors and functional outcomes in stroke survivors. Cross-sectional studies are advantageous for identifying potential predictors of post-stroke disability, providing a basis for future longitudinal investigations. Data were obtained from wave 5 of the China Health and Retirement Longitudinal Study (CHARLS). The dataset is publicly accessible via the official CHARLS website (http://CHARLS.pku.edu.cn). The study adhered to ethical norms and received approval from the Biomedical Ethics Committee of Peking University, China (IRB00001052-11,015) (7). All procedures followed the principles outlined in the Declaration of Helsinki, and informed consent was obtained from all participants. In this study, patients and the public were not involved in the design, conduct, reporting, or dissemination plans of the research. This study adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) (8).

2.2 Study population

In the CHARLS database, stroke status was determined through self-reported responses to the question: "Have you ever been diagnosed with a stroke by a doctor?" This self-reported approach may lead to potential misclassification, which was considered in the study's limitations. ADL in two main categories: Basic ADL (BADL), which includes six essential tasks: dressing, bathing, eating, transferring (getting in and out of bed), toileting, and controlling urination and defecation. Instrumental ADL (IADL), which involves more complex activities, such as managing housework, cooking, shopping, financial management, and medication adherence. We used a questionnaire-based survey method to assess ADL dysfunction. If a stroke survivor was unable to independently complete any of the tasks listed under BADL or IADL, they were classified as having ADL dysfunction. Inclusion criteria: History of stroke; Ability to cooperate in completing the ADL screening. Exclusion criteria: No history of stroke or uncertain stroke diagnosis; Missing key variables; Pre-existing ADL dysfunction before stroke. Initially, 1,381 individuals with a self-reported history of stroke were identified. After excluding individuals with more than 30% missing data, the final analysis included 1,131 stroke survivors.

2.3 Candidate predictor variables

Predictor selection was based on prior literature and clinical expertise (9–11). Although stroke characteristics (e.g., lesion location, infarct size) influence prognosis, these variables were not recorded in CHARLS. Instead, we examined demographic, behavioral, health, and socioeconomic factors available in the dataset. Basic factors: age, gender, residence (urban/rural), education level, marital status, and life satisfaction (five-point Likert scale). Behavioral factors: sleep duration, smoking, alcohol consumption, social activity participation (eight categories), and physical activity levels (light, moderate, heavy). Total energy expenditure from physical activity was calculated using metabolic equivalent (MET) scores. Health status and medical conditions: self-rated health (five levels), hypertension, diabetes, cancer, cardiac disease, mental disorders, and the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10). Family and economic factors: household size, financial support from children/parents, and number of surviving children.

2.4 Statistical analysis

All statistical analyses were conducted using R software. Continuous variables were reported as medians and interquartile ranges, while categorical variables were presented as proportions. Between-group comparisons were performed using the Wilcoxon rank-sum test for continuous data and the Chi-square test or Fisher's exact test for categorical data. To develop the ADL dysfunction prediction model, the dataset was randomly split (6:4) into a training set ($n = 678$) and a testing set ($n = 453$). We applied the least absolute shrinkage and selection operator (LASSO) regression to identify key predictors while addressing multicollinearity. Optimal tuning parameters (λ) were selected via ten-fold cross-validation. Selected variables were incorporated into a multivariate logistic regression model, with predictors retained at $P < 0.05$. Model performance was assessed using the area under the receiver operating characteristic (ROC) curve (AUC) for discrimination, calibration plots for agreement between predicted and observed outcomes, and decision curve analysis (DCA) for clinical utility. SHapley Additive exPlanations (SHAP) values were computed to interpret predictor importance.

3 Results

3.1 Flow chart

The study flow chart is presented in Figure 1.

3.2 Baseline characteristics

A total of 1,131 stroke survivors were included in this study. The demographic and clinical characteristics of the participants are summarized in Table 1. The cohort consisted of 473 male participants (41.8%) and 658 female participants (58.2%), with an average age of 67 years. Among these stroke survivors, 57.3% experienced difficulties with ADL. Several factors showed

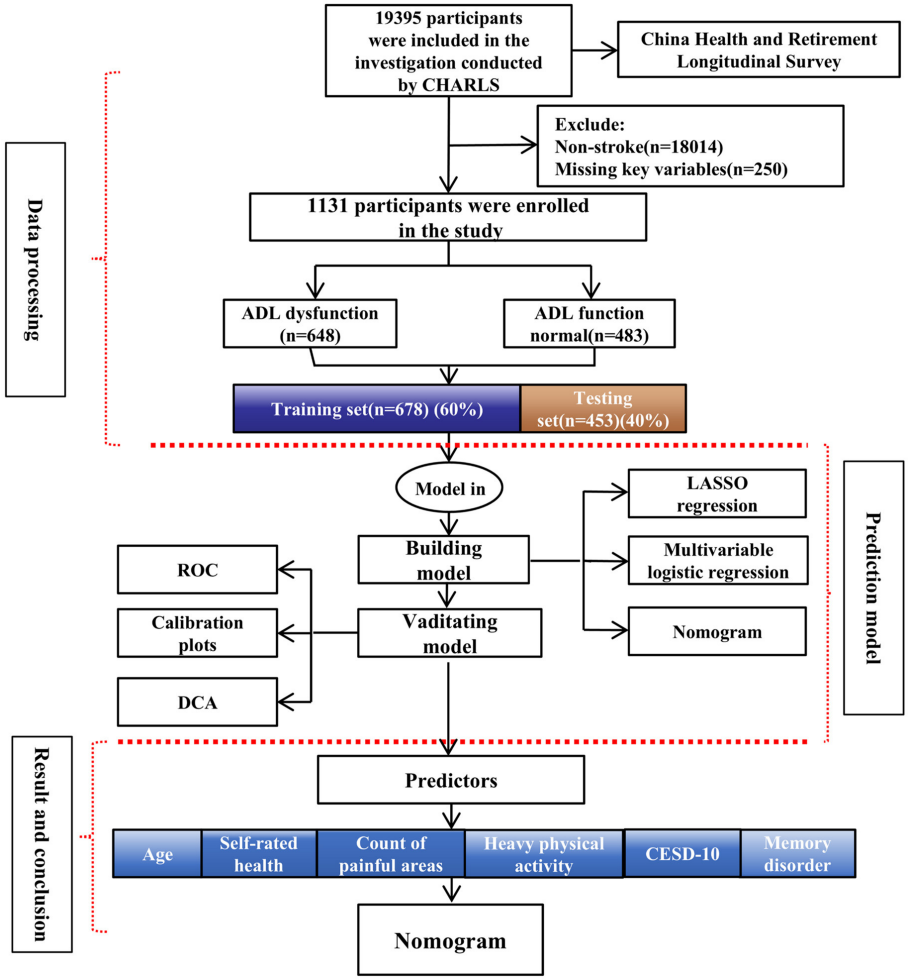

FIGURE 1
Flow chart of the study.

significant differences ($p < 0.05$) between stroke survivors with normal and impaired ADL function, including age, gender, education level, life satisfaction, CESD-10 score, and health status factors (e.g., hypertension, lung disease, arthritis). Additionally, factors such as social activity, sleep duration, pain count, and physical activity levels were also significantly associated with ADL dysfunction.

3.3 Prediction model development

LASSO regression was applied to identify the best predictors for ADL dysfunction, with predictors selected based on 10-fold cross-validation. The 11 significant variables identified included gender, age, hip fracture, CESD-10 score, memory disorder, pain areas, and levels of physical activity (Figure 2). These variables were then used in a multivariate logistic regression model, which selected the following significant predictors ($P < 0.05$): age, CESD-10 score, memory disorder, self-rated health, pain count, and heavy physical activity. The resulting predictive model was visualized through a nomogram, which allows for the quantitative assessment of ADL dysfunction risk in stroke survivors (Figure 3).

3.4 Prediction model validation

The predictive model's performance was assessed using the AUC. In the training set, the AUC value was 0.804 (95% CI: 0.772–0.837), and in the testing set, it was 0.779 (95% CI: 0.736–0.821), indicating good discriminatory power (Figures 4A, B). The nomogram's calibration curves (Figures 4C, D) showed alignment between predicted and observed probabilities of ADL dysfunction, confirming the model's accuracy and reliability. Clinical validity was assessed using DCA, shown in Figures 4E, F. The DCA demonstrated that the prediction model provided net benefits compared to the two extreme scenarios, suggesting its clinical utility in predicting ADL dysfunction.

3.5 Explanation of model characteristic variables

SHAP values were calculated for six key variables in the model. The global importance plot and swarm plot (Figures 5A, B) demonstrated the predictive importance of these variables across the dataset. To further understand their impact at the individual

TABLE 1 Participant characteristics.

Subject	ADL function normal	ADL dysfunction	*p* value
N	483	648	
Family size	2.00 (2.00–3.00)	2.00 (2.00–3.00)	0.487
Health child	2.00 (2.00–3.00)	3.00 (2.00–4.00)	0.028
Children's economic support	2500.00 (500.00–6500.00)	2515.00 (687.50–7000.00)	0.229
Parent's economic support	100.00 (0.00–2000.00)	100.00 (0.00–1200.00)	0.667
CESD-10	7.00 (3.50–12.00)	14.00 (9.00–19.00)	<0.001
Life satisfaction	3.00 (3.00–4.00)	3.00 (3.00–4.00)	<0.001
Count of painful areas	1.00 (0.00–4.00)	3.00 (1.00–7.25)	<0.001
Sleep duration	6.00 (5.00–7.50)	5.00 (4.00–7.00)	<0.001
Total categories of social activities	1.00 (0.00–1.00)	0.00 (0.00–1.00)	<0.001
Age	67.00 (60.00-71.00)	69.00 (62.75-74.00)	<0.001
Education level	2.00 (1.00–3.00)	1.00 (1.00–3.00)	<0.001
Total metabolic output from physical activity	3814.00 (1485.00–7068.00)	1732.50 (462.00–4764.00)	<0.001
Episodic memory (0–10)	4.00 (3.00–5.50)	3.50 (2.00–5.00)	<0.001
Self-rated health	3.00 (2.00–3.00)	2.00 (1.00–3.00)	<0.001
Gender			
0	195 (40.37%)	363 (56.02%)	<0.001
1	288 (59.63%)	285 (43.98%)	
Marry			
0	91 (18.84%)	142 (21.91%)	0.206
1	392 (81.16%)	506 (78.09%)	
Residence			
0	200 (41.41%)	240 (37.04%)	0.136
1	283 (58.59%)	408 (62.96%)	
Hip fracture			
0	483 (100.00%)	630 (97.22%)	<0.001
1	0 (0.00%)	18 (2.78%)	
Hypertension			
0	166 (34.37%)	169 (26.08%)	0.003
1	317 (65.63%)	479 (73.92%)	
Diabetes			
0	360 (74.53%)	456 (70.37%)	0.122
1	123 (25.47%)	192 (29.63%)	
Cancer			
0	471 (97.52%)	629 (97.07%)	0.648
1	12 (2.48%)	19 (2.93%)	
Lung disease			
0	410 (84.89%)	491 (75.77%)	<0.001
1	73 (15.11%)	157 (24.23%)	
Cardiac disease			
0	318 (65.84%)	335 (51.70%)	<0.001
1	165 (34.16%)	313 (48.30%)	
Mental disorder			
0	461 (95.45%)	590 (91.05%)	0.004
1	22 (4.55%)	58 (8.95%)	
Arthritis			
0	251 (51.97%)	260 (40.12%)	<0.001
1	232 (48.03%)	388 (59.88%)	
Dyslipidemia			
0	261 (54.04%)	308 (47.53%)	0.030
1	222 (45.96%)	340 (52.47%)	
Liver disease			
0	434 (89.86%)	551 (85.03%)	0.017
1	49 (10.14%)	97 (14.97%)	
Kidney disease			
0	406 (84.06%)	485 (74.85%)	<0.001
1	77 (15.94%)	163 (25.15%)	
Digestive disease			
0	309 (63.98%)	382 (58.95%)	0.086
1	174 (36.02%)	266 (41.05%)	
Asthma			
0	452 (93.58%)	569 (87.81%)	0.001
1	31 (6.42%)	79 (12.19%)	
Memory disorder			
0	432 (89.44%)	506 (78.09%)	<0.001
1	51 (10.56%)	142 (21.91%)	
Intense exercise			
0	319 (66.05%)	506 (78.09%)	<0.001
1	164 (33.95%)	142 (21.91%)	

(Continued)

TABLE 1 (Continued)

Subject	ADL function normal	ADL dysfunction	*p* value
Moderate exercise			
0	233 (48.24%)	402 (62.04%)	<0.001
1	250 (51.76%)	246 (37.96%)	
Light exercise			
0	114 (23.60%)	156 (24.07%)	0.854
1	369 (76.40%)	492 (75.93%)	
Alcohol consumption			
0	318 (65.84%)	505 (77.93%)	<0.001
1	165 (34.16%)	143 (22.07%)	
Smoking			
0	239 (49.48%)	365 (56.33%)	0.022
1	244 (50.52%)	283 (43.67%)	

level, waterfall and force plots (Figures 5C, D) were used to visualize the contribution of each variable to the model's predictions in selected samples, highlighting the practical significance of these variables in specific cases.

4 Discussion

The medical community has made significant progress in ensuring timely and effective stroke treatment during the acute phase. However, the high disability rate following a stroke remains a critical concern (12). Despite initial treatment, many stroke survivors continue to face challenges with ADL once the acute phase has passed (13). In our analysis of stroke survivors in CHARLS Wave 5, we found that 57.3% of participants exhibited ADL dysfunction. Compared to those with normal ADL function, stroke survivors with ADL dysfunction were generally older, reported shorter sleep durations, experienced higher levels of depressive symptoms, and suffered from poorer physical health. They were also more likely to have multiple chronic conditions, experience bodily pain, and engage in unhealthy habits such as smoking and alcohol consumption. Furthermore, these survivors had lower participation in social activities and physical exercise.

Older stroke survivors are particularly vulnerable to ADL dysfunction (14). Age-related declines in physical, cognitive, and sensory functions can impair one's ability to perform daily tasks independently (15). Research has shown that SRH is closely associated with ADL functioning, with those reporting poorer SRH (e.g., "fair" or "poor") more likely to experience ADL impairments (16–19). Chronic pain, whether acute or long-term, also plays a significant role in ADL dysfunction, as it can severely hinder daily activities (20, 21). Additionally, chronic pain may exacerbate psychological distress, including depression and anxiety, which can further impair ADL (22). Depression itself, a common mental health issue, contributes to reduced functional capacity and increases the risk of ADL dysfunction (23). Moreover, memory disorders, such as Alzheimer's disease or Parkinson's

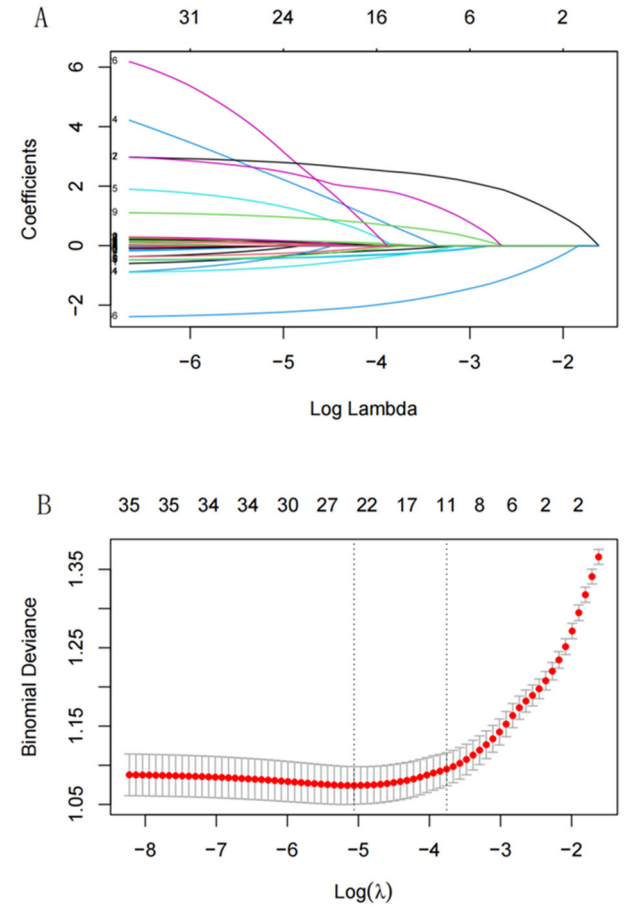

FIGURE 2
The LASSO plot.

disease, typically cause gradual cognitive decline, further impairing ADL (24, 25). Conversely, engaging in heavy physical activity has been shown to reduce the likelihood of chronic conditions and can enhance cognitive functioning, which may help prevent age-related cognitive decline (26–29). Therefore, regular physical exercise appears to be a beneficial strategy to improve ADL in stroke survivors. This indicates that heavy physical activities have potential benefits for ADL.

Based on our analysis, we identified six characteristic variables that are commonly observed in stroke survivors. These include age, SRH, heavy physical activity, depression, pain, and memory disorders. Among these variables, age, memory disorders, pain, and depression are known to exacerbate ADL dysfunction, making them significant risk factors for its development. Conversely, ADL dysfunction itself can also contribute to the onset or worsening of limb joint pain and depressive mood in stroke patients, thereby creating a cycle of increasing ADL dysfunction (30). While most stroke survivors experience some degree of ADL dysfunction after the stroke, the severity and progression of this dysfunction can vary (31). For some individuals, improper self-management or the lack of targeted rehabilitation can trigger or intensify ADL dysfunction (32). To address this, the model we developed is designed to identify, at an early stage, the factors closely associated

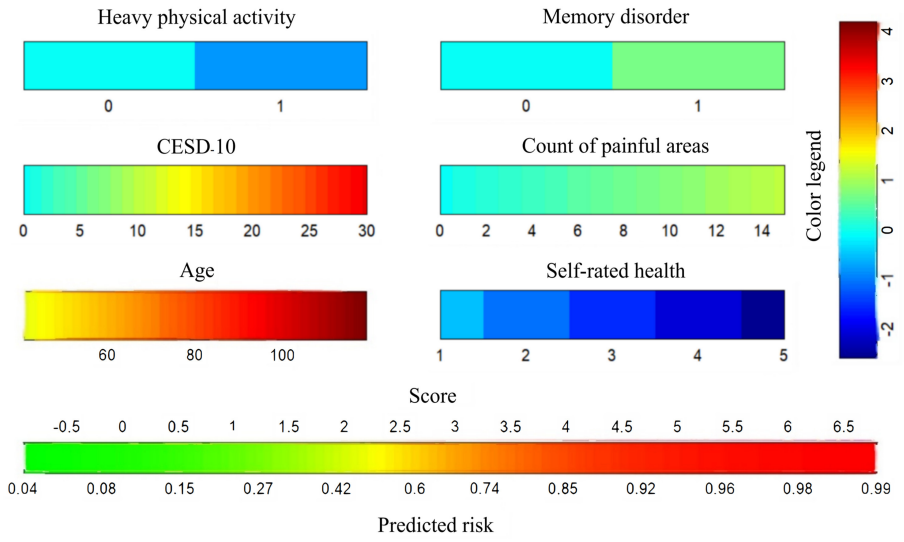

FIGURE 3
Nomogram to predict the probability of ADL dysfunction in stroke survivors.

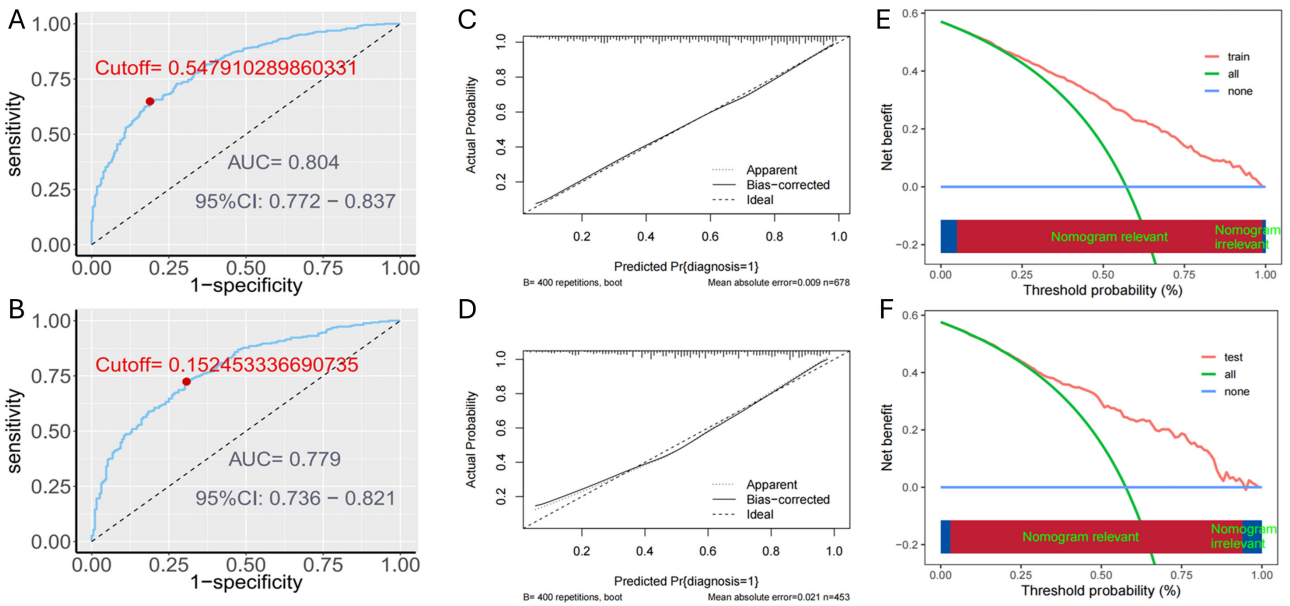

FIGURE 4
Assessment of the predictive accuracy of the nomogram: **(A)** ROC for the training set; **(B)** ROC for the testing set. Assessment of the predictive accuracy of the nomogram: **(C)** Calibration plot for the training set; **(D)** Calibration plot for the testing set. DCA curves of the nomogram: **(E)** The training set; **(F)** The testing set.

with the onset of ADL dysfunction in this group. Early intervention in these factors is crucial. For example, while direct intervention on age and self-rated health may be challenging, strengthening physical training and improving the management of pain and depression could help prevent or delay the progression of ADL dysfunction. These interventions may also lead to improvements in ADL function, ultimately enhancing the prognosis and quality of life for stroke survivors.

However, our study has several limitations. The CHARLS dataset lacks detailed information on important predictors such as walking pace, grip strength, waist circumference, body mass index (BMI), and certain biochemical markers, which were not captured in Wave 5. Additionally, data on stroke-specific factors such as lesion type, location, size, onset time, and treatment methods are not available in the CHARLS database. Moreover, as the data is specific to our country, the external validity of our findings may be limited, and the models may not be fully applicable to populations in other countries. Internal validation methods were used in this study, but further validation in diverse populations is needed to enhance the generalizability of our predictive models.

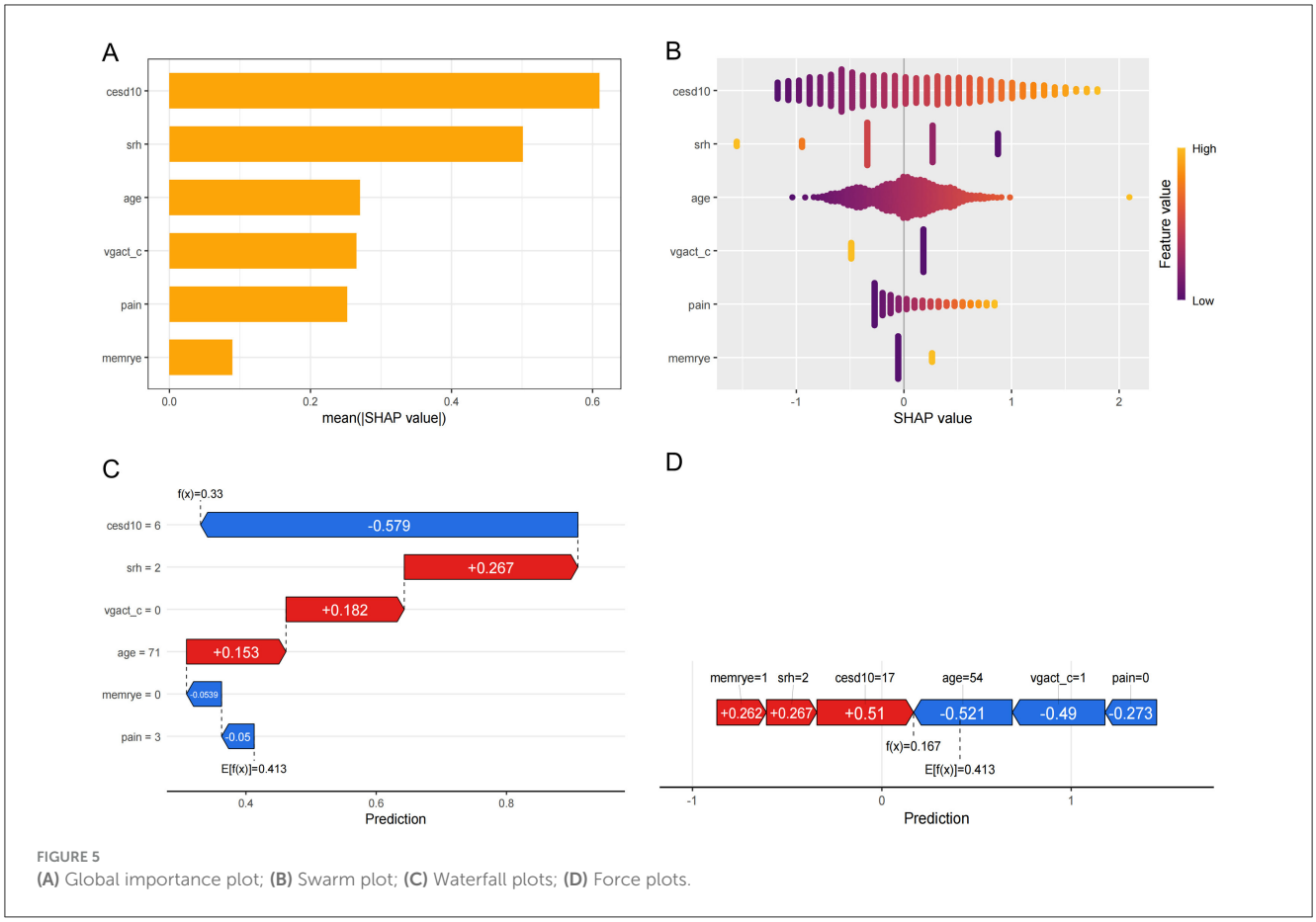

FIGURE 5
(A) Global importance plot; **(B)** Swarm plot; **(C)** Waterfall plots; **(D)** Force plots.

5 Conclusions

In summary, we developed and validated a prediction model for ADL dysfunction in stroke survivors. The model includes crucial factors like age, SRH, heavy physical activity, depression, pain, and memory disorders. It provides insights into the group's characteristics. Although the study has limitations, the model can guide personalized medical strategies. By implementing these, we can potentially enhance stroke survivors' ADL ability and, consequently, improve their quality of life.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Utilizing publicly accessible data from the CHARLS, which can be retrieved from the official website at http://CHARLS.pku.edu.cn.

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

FL: Writing – original draft. NL: Writing – review & editing.

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Conflict of interest

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

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1529724/full#supplementary-material

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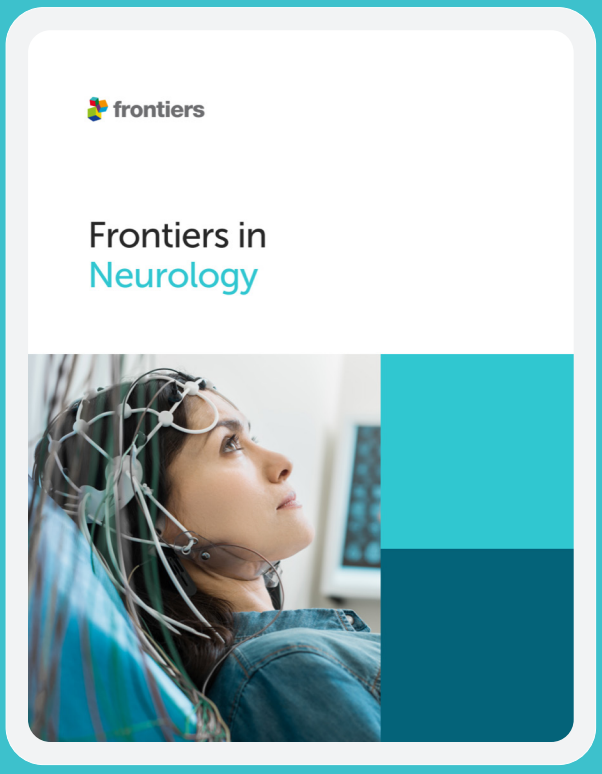

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