Effects of computerized cognitive training combined with aerobic exercise on patients with early Post-Stroke Cognitive Impairment: a randomized controlled trial

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Abstract

Background: Previous studies have demonstrated that the combination of computerized cognitive training (CCT) and aerobic exercise produces more significant therapeutic effects on cognitive function compared to either intervention alone. However, its impact on specific cognitive domains remains unclear.

Objective: This study was aim to investigate the rehabilitative effects of computerized cognitive training combined with aerobic exercise on cognitive domains in patients with post-stroke cognitive impairment (PSCI) using objective indicators.

Methods: This randomized controlled trial was conducted at a tertiary hospital in northern China, recruiting 134 participants with PSCI who were randomly assigned to either the control group (n=67) or the intervention group (n=67) using an opaque envelope method. Both groups received 30-minute interventions five times a week. Changes in cognitive domains, global cognitive function, activities of daily living, stroke severity, and quality of life (QOL) were compared prior to the intervention, at 3 months, and at 6 months post-intervention.

Results: Of the 109 participants who completed the full intervention and follow-up, analysis of the 5 cognitive function variables revealed a significant group × time interaction for all variables except visuospatial ability, favoring the intervention group (global cognitive function [Wald c2=26.437, P<0.001], memory [Wald c2=67.781, P<0.001], attention [Wald c2=12.174, P=0.002], execution [Wald c2=136.341, P<0.001], visuospatial ability [Wald c2=3.755, P=0.153]). Additionally, both activities of daily living and QOL also showed significant group × time interactions, favoring the intervention group.

Conclusions: The combination of CCT and aerobic exercise effectively enhanced the cognitive function of patients with PSCI, particularly in the areas of memory, attention, and execution. Moreover, it improved activities of daily living and QOL. Clinical Trial: Clinical trial registration: ChiCTR2300076646.

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ABSTRACT

Background: Previous studies have demonstrated that the combination of computerized cognitive training (CCT) and aerobic exercise produces more significant therapeutic effects on cognitive function compared to either intervention alone. However, its impact on specific cognitive domains remains unclear.

Objective: The aim of this study was to investigate the effects of computerized cognitive training combined with aerobic exercise on cognitive function in patients with post-stroke cognitive impairment (PSCI).

Methods: This randomized controlled trial was conducted at a tertiary hospital in northern China, recruiting 134 participants with PSCI who were randomly assigned to either the control group (n=67) or the intervention group (n=67) using an opaque envelope method. Both groups received 30-minute interventions five times a week. Changes in cognitive domains, global cognitive function, activities of daily living, stroke severity, and quality of life (QOL) were compared prior to the intervention, at 3 months, and at 6 months post-intervention.

Result: Of the 109 participants who completed the full intervention and follow-up, analysis of the 5 cognitive function variables revealed a significant group × time interaction for all variables except visuospatial ability, favoring the intervention group (global cognitive function [Wald χ^2=26.437, P<0.001], memory [Wald χ^2=67.781, P<0.001], attention [Wald χ^2=12.174, P=0.002], execution [Wald χ^2=136.341, P<0.001], visuospatial ability [Wald χ^2=3.755, P=0.153]). Additionally, both activities of daily living and QOL also showed significant group × time interactions, favoring the intervention group. Participants who underwent CCT combined with aerobic exercise demonstrated enhanced global cognitive function, memory, attention, execution, activities of daily living and QOL performance compared to the control group.

Conclusion: The combination of CCT and aerobic exercise offers unique advantages in cognitive rehabilitation and achieving early adaptation to daily life after a stroke. This approach requires for trainers are low, trainers can be trained without a long training time, thereby holding great potential for widespread promotion. However, it is important to note that while this rehabilitation scheme has shown superior effectiveness, there is still a need to explore the reasons behind the lack of significant differences in visual spatial function recovery among stroke severity levels. Further research is necessary to enhance the overall effectiveness of the treatment.

Clinical trial registration: ChiCTR2300076646.
Key words: Stroke, Cognitive function, Computerized training, Aerobic exercise, Rehabilitation

Introduction

Stroke stands as the primary cause of death and disability globally, affecting approximately 17 million individuals each year. The recurrence rate of a first stroke within one year remains high at 17.1%[1,2]. Post-stroke patients often exhibit impaired activities of daily living due to physical or cognitive limitations[3], making it challenging for them to manage life events compared to the general population. Post-Stroke Cognitive Impairment (PSCI) refers to the impairment of cognitive function in the past, and there is still a cognitive impairment of cognitive function in the six months after the onset of stroke of stroke, with at least one cognitive domain function (memory, attention, etc.) is impaired[4], emerges between 3-6 months after a stroke. Unlike physical dysfunction, cognitive issues are often overlooked more frequently, and the field of clinical diagnosis and therapy for cognitive function is still evolving[5]. While advancements in medical detection and treatment technologies have led to a decline in stroke mortality, the number of PSCI patients has been steadily increasing[6].

Early cognitive therapy holds crucial importance for stroke patients[7]. Presently, cognitive training for stroke survivors in clinical neurology and rehabilitation departments heavily rely on traditional cognitive training methods and drug therapy. However, traditional cognitive training places significant demands on the professional qualifications of trainers in medical institutions, frequent hospital visits for training can also hinder patients from adhering to the training due to inconvenience[8]. Certain drugs like acetylcholinesterase inhibitors and memantine have demonstrated potential in improving the cognitive function of patients with vascular dementia and overall functional rehabilitation[9,10]. However, their effectiveness is inconsistent and often accompanied by side effects, leading to additional economic burdens on the patient's family[11,12]. Consequently, there is an urgent need to explore a rehabilitation program that is convenient, efficient, and has minimal side effects.

Over the past decade, there has been a burgeoning body of research confirming the effectiveness of computerized cognitive training (CCT)[13] and exercise therapy[14] as non-pharmacological interventions for enhancing cognitive function. CCT involves utilizing modern computer programs to offer targeted and repetitive practice in various cognitive domains through small games that simulate daily tasks. The cognitive function of stroke patients undergoes a dynamic process of change, tending to gradually stabilize over time[15]. Hence, early and effective intervention is crucial. CCT significantly contributes to rehabilitating memory and other cognitive domains [13]in the early stages of stroke, bolstering the self-confidence of survivors, mitigating anxiety and depression, reducing activity avoidance, and encouraging active participation in rehabilitation training(like aerobic exercise) and social adaptation, thereby fostering a positive feedback loop[16]. Unlike traditional cognitive training methods, CCT provides a user-friendly experience, with operators requiring only basic computer skills to adjust the training difficulty and target specific cognitive domains. This therapy can be conducted independently, in groups, under supervision, or even at home, offering versatility. Considering the increasing number of stroke survivors and the shortage of healthcare workers, promoting CCT as a self-directed rehabilitation training tool holds significant clinical practicality, in the author's view. However, although the results of the above studies suggest that cognitive function can be improved by CCT, the research is limited to overall cognitive function and does not explore specific cognitive domains. The use of measuring tools such as MoCA and MMSE provided relatively subjective results. Therefore, this study adopted the the Vienna Test System (VTS, Schuhfried Corp in Austria) to measure specific cognitive domains, the measurement results were scored based on the participants' correct response rate and response time, these results were more accurate and objective than those of previous studies.While CCT can enhance the biochemical processes in cognitive-related brain regions like the temporal lobe and frontal lobe[17], improving cognitive levels, its effectiveness is constrained by inherent neural plasticity, limiting further recovery of cognitive function after a stroke. Following a stroke, brain tissue is impacted by nutrient deprivation, oxygen deprivation, and inflammatory attacks, potentially leading to cell necrosis[18] and decreases in cognitive function. In contrast, aerobic exercise can enhance blood circulation in brain tissue[19], promote synaptic remodeling in the ischemic penumbra area, regulate neurotransmitters[20], improve connectivity between functional networks[21], and improve neuroplasticity in stroke patients, thereby enhancing the cognitive rehabilitative effects of CCT. Although CCT utilizes game simulations of daily tasks to aid participants in adjusting to post-rehabilitation life, transitioning from a game-simulated environment to real-life home settings poses a significant challenge in clinical work[22]. Therefore, regular aerobic exercise after CCT may help integrate healthy brain function and improve the ability of patients with PSCI to perform daily activities[23], which can ultimately lead to a higher quality of life for these patients in the future. Numerous studies have demonstrated the effectiveness of hyperbaric oxygen therapy and transcranial magnetic stimulation (TMS) in improving neurological function in stroke patients. Hyperbaric oxygen therapy not only increases oxygen supply to nerve cells damaged by hypoxia and improves cell function, but also inhibits the mechanism of cognitive function recovery through various pathways. These pathways include the inhibition of apoptosis, improvement of mitochondrial function, stimulation of stem cell proliferation, enhancement of antioxidant defense activity, reduction of neuroinflammation, and neuroprotection[24,25]. TMS is a physical therapy method that delivers electromagnetic pulses to the brain to improve cognitive function. High-frequency TMS can enhance the functional connectivity of distributed brain regions and networks involved in cognitive processing, regulate the excitability of the cerebral cortex, and enhance the neuroplasticity of individuals[26,27]. However, due to variations in medical resources and economic levels across different countries and regions, it may be impractical for patients to frequently return to medical institutions for treatment after rehabilitation and discharge. Furthermore, it remains uncertain whether such rehabilitation programs would be supported by local medical facilities. Comparatively, CCT combined with aerobic exercise appears to be a more feasible rehabilitation program in settings with limited medical resources compared to the aforementioned intervention plans.

In conclusion, we believe that CCT combined with aerobic exercise represents a beneficial program for patients with PSCI. This combined approach not only promotes treatment compliance among patients but also demonstrates positive efficacy. Further research is necessary to investigate the comprehensive impact of this program on various aspects of PSCI patients. While previous studies[28,29] have been conducted, they primarily focused on global cognitive function, and there is an urgent need to fill the gap bycomputerized cognitive assessment systems to objectively measure changes in domain-specific cognition. Furthermore, a substantial body of research consistently indicates the superiority of combining computerized cognitive training with aerobic exercise over using either intervention alone[29], making it less meaningful to re-evaluate the comparison between the combined intervention and single interventions again for us. In the present study, 108 subjects with PSCI were randomly assigned to an intervention group (combined intervention) or a control group (traditional cognitive intervention) to investigate the efficacy of combining computerized cognitive training with aerobic exercise on various cognitive domains. We hypothesized that the intervention group would demonstrate significant improvements in cognitive function, activities of daily living, stroke severity, and QOL compared to the control group.

Method

Study Design

This study employed a evaluator-blind randomized controlled trial, given the impracticality of blinding the interveners and participants due to specific intervention characteristics. Participants were categorized into five age groups: 18-50, 51-65, 66-80, and 80-100, with each age group corresponding to a specific envelope from which the group sequence number was extracted. This method ensured that age differences did not impact the assignment process and helped minimize the potential influence of age-related factors on the research, each group was randomly assigned with stratification by age in a 1:1 ratio to either the intervention group (involving CCT combined with aerobic exercise) or the control group (receiving conventional rehabilitation) using opaque envelopes containing concealed serial numbers representing treatment assignments. All randomization procedures were carried out by an investigator who was unaware of the group assignments. Assessments were conducted for both groups at baseline (T0), as well as at 3 months (T1) and 6 months (T2) after the intervention. The study was designed in accordance with the Declaration of Helsinki, approved by the institutional Human Ethics Research Subcommittee, and registered with the Chinese Clinical Trial Registry. Prior to commencing the study, all participants provided written informed consent.

Participants

Eligible participants were recruited through convenience sampling from a general hospital located in a northern city of China. Inclusion criteria consisted of: (1) patients aged ≥18 years old, capable of cooperation with the treatment; (2) patients meeting the diagnostic criteria proposed by the Chinese Expert Consensus on the Management of Post-Stroke Cognitive Impairment in 2021; (3) patients with a first stroke within a month of onset were identified by imaging; (4) patients experiencing cognitive decline after stroke or reported by caregivers, with mild or above cognitive impairment based on the Montreal Cognitive Assessment (MoCA) scale (□26); (5) patients who signed informed consent form. Exclusion criteria included: (1) patients with a history of cognitive impairment not caused by stroke; (2) patients with the presence of other serious diseases or diseases with a poor prognosis such as malignant tumor and organ failure; (3) patients unable to cooperate with rehabilitation training due to unstable condition after stroke or other reasons. The sample size was estimated using the formula and G*Power 3.1 software. According to the formula $N1=N2=2$ □□ $\mu_\alpha+\mu_\beta$ □ σ/δ □^{2}, Zhang S et al[30] reported that σ of 0.95, δ of 1.50, at least 9 participants per group were required given α of 0.05 ($\mu_\alpha=1.96$) and β of 0.1 ($\mu_\beta=1.282$). According to G*Power 3.1 software, previous studies[29] reported an effect size of 0.22 (95% CI 0.14 to 0.30) for cognitive training on cognitive function rehabilitation in patients, therefore, the effect size of this study was 0.25. Requiring a minimum of 43 subjects per group to achieve a statistical power of 0.9 and reject the null hypothesis at a significance level $\alpha=0.05$. Accounting for potential loss to follow-up, the sample size for each group was increased to 54 subjects, resulting in a total sample size of at least 108 for the study.

Intervention

A professional rehabilitation nursing team was assembled, comprising one primary nurse, two doctors, and a rehabilitation therapist. The control group received conventional cognitive training, passive exercise training, voluntary exercise, and the standard routine rehabilitation nursing, which included managing vascular risk factors such as hypertension, diabetes, and smoking. In contrast, the intervention group received a modified approach, replacing traditional cognitive training with CCT combined with aerobic exercise, specifically targeting memory, attention, executive functions, and visuospatial abilities.

Participants were assessed prior to enrollment to confirm their ability to complete the training and to prevent withdrawal due to physical issues. After participants and their families have a thorough understanding of the benefits and potential risks of the training, they are required to self-assess their ability to complete the training and follow-up in order to prevent subsequent loss to follow-up. To mitigate the risk of prolonged disconnection leading to loss to follow-up, investigators actively maintained communication with participants during both the training and follow-up periods. During hospitalization, participants received health monitoring from attending physicians and nurses. Following discharge, due to logistical constraints preventing real-time monitoring by the researchers, participants were monitored monthly via telephone to oversee and assess their health status. All participants will return to the hospital for a follow-up visit six months after the intervention to ensure their ongoing health and safety. Furthermore, in order to minimize dropout rates, researchers should continuous encouragement for both participants and their families and give small gifts at the end of the study.

1 Computerized cognitive training (CCT)

The study utilized the CogniPlus cognitive ability training system developed by Schuhfried Company[31]. All training programs were designed around daily life scenarios, involving interactive sessions generating dynamic pictures, which will change depending on whether the subject input the commands correctly or incorrectly. These life-like simulations formed the basis for subsequent aerobic exercises and the participants' future daily life. CogniPlus is an intelligent system capable of assessing participants' cognitive ability levels based on their performance during the training process. It automatically adjusts the difficulty of the training, if the participant often makes the wrong operation during the training, the difficulty will be reduced, on the contrary, if the participant's correct rate is maintained at a high level, the difficulty will increase, and the requirements for attention, memory and so on will be higher to ensure it is neither too easy nor too challenging, thereby maintaining participant enthusiasm and optimizing the training outcome. To accommodate participants with limited upper limb movement, a more convenient and universal response panel was selected as the input device, compared with the computer keyboard, the response panel has only a few simple keys with bright colors, which helps participants' enter instructions more clearly. The training comprised four programs: (1) Attention Training (FOCUS), many animals will appear from both sides of the river, the participants' task is to respond to them, if they press buttons too slowly to the correct animal or make a wrong choice for another animal, they will receive a feedback with red alert. (2) Memory Training (VISP), participants will see ships arranged in a particular spatial order and must replicate this arrangement within a limited time frame on a separate interface, the system will provide prompts if the order is incorrect. As the difficulty level increases, boats will movement and number will increase, while the training cue will decrease, we requiring participants to actively repeat and reproduce the boat positions, it could enhance participants' memory. (3) Executive Function Training (PLAIN), the participants' task was to arrange the various actions in the game in their optimal order. At the outset of the task, participants were simulated placed in a street environment (complete with signage), and surrounded by numerous buildings. They were required to strategize the order of visiting these buildings based on various task requirements before initiating their actions. As the difficulty level increases, the complexity of the task also rises. (4) Visuospatial Ability Training (SPACE), participants will act as photographers, and necessitating participants to track a moving picture with their eyes, press the corresponding button following the dynamic image changes. As the difficulty increases, the movement trajectory of the viewing angle will be increasingly difficult to discern and difficult to follow, as detailed in Figure 1. Each training session was conducted five times per week, lasting approximately 30 minutes each time for 4 weeks (week 1-4).

2 Conventional cognitive training

The control group underwent conventional cognitive training administered by professional rehabilitation personnel in the hospital. This training program encompassed various techniques such as the associative memory method, picture recall method, life task assignment, error-free learning method, and others. To ensure comparability between the two groups, the duration and frequency of these training sessions matched those of computerized cognitive training.

3 Aerobic exercise

The exercise program was constructed based on preliminary research and expert consultation, participants will formally commence aerobic exercise after completing 4 weeks of cognitive training. The primary forms of aerobic exercise include walking and gymnastics, the target training intensity was determined based on the heart rate reserve (HRR) and the talk test, and it was gradually increased. HRR = 220- age- resting heart rate, our plan is to increase the HRR by 5% to 10% every 1 to 4 weeks, gradually reaching a training intensity of 40% to 70% HRR. Participants will be evaluated and followed up during this period by smart devices in order to guarantee the validity and application of the exercise program, with specific intervention details outlined in Table 1. The exercise regimen took place 3-4 times per week (week 5-8), with each session lasting 20 to 40 minutes.

Figure 1 The procedure for CCT: FOCUS, VISP, PLAIN and SPACE.

Table 1 Intervention protocol for CCT combined with aerobic exercise.

Stage	Theme	Intervention content	Time
First stage	Educating participants to comprehend the role that training in stroke recovery, for rehabilitation to increase compliance	1. Patients were invited to attend. The purpose of providing the patients and their families with the exercise rehabilitation training introduction manual was to improve patient compliance, foster a positive nurse-patient relationship, and educate them about post-stroke cognitive impairment. 2. In order to provide thorough early exercise rehabilitation assessment, plan creation, and inspection, a multidisciplinary team comprising medical, nursing, and rehabilitation specialists was formed.	Week 1 (Admission to hospital)
Second stage	The CCT was conducted, along with the necessary preparation before the aerobic exercises training.	1. Prior to the CCT, participants received verbal instructions and performed manipulation exercises. Formal training began after they completed the practice task. 2. CCT was carried out simultaneously, the CCT program adjusted the difficulty and intensity of training in real time based on the participant' feedback during the training process. The training programs covered four cognitive domains: memory, attention, executive function, and visuospatial abilities. 3. Prior to being given instructions to exercise, patients had their exercise tolerance evaluated. Participants and their families were also told about the heart rate ranges for low- and moderate-intensity exercise, as well as the technique used to measure heart rate.	Week 1-4 (In the hospital)
Third stage	Gradually increase the intensity of the patient's training.	1. Patients are guided to initial exercise training, and the frequency and duration of aerobic exercise (walking, doing exercises, etc.) are adjusted according to the results of exercise testing, health status, and exercise capacity. 2. Assign informal homeworks and engage in 20-40 minutes of aerobic activity 4-5 times each week. To guarantee the validity and application of the exercise program, researchers conducted follow-up studies and a dynamic and comprehensive review of the entire process. During the follow-up, they also kept an eye on the exercise rehabilitation's development and promptly fixed any anomalies.	Week 5-8 (In the home)
Fourth stage	Consolidate the knowledge.	Consolidate and strengthen the knowledge they have gained via cognitive exercise, and assist patients in forming wholesome exercise routines.	Week 8

Outcome measure

Participants will be assessed at baseline (T0), as well as at 3 months (T1) and 6 months (T2) after the intervention.

Level of domain-specific cognition (objective indicators)

The study employed four main objective outcome indicators representing cognitive domains: memory, attention, executive function, and visuospatial abilities. To measure these subjects, the Vienna Test System (VTS) for Psychologische Diagnostik (Schuhfried Corp in Austria) was used, employing the following programs. (1) FGT, assessment of memory, the test assessed memory through guided recall of picture shapes. Participants were presented with 9-12 figures and subsequently asked to recall their shapes. This method allows for evaluation of both short-term and long-term memory abilities, making it suitable for clinical neuropsychological assessment. Numerous studies[32] have confirmed the effectiveness, reliability, and repeatability of the figure test. (2) WAF, assessment of attention, participants were presented with circles, triangles, and squares on the screen, and asked to press the green button as quickly as possible when they saw the specified figure, the system measured their reaction time (which visually quantified the patient's attention level). (3) PLAND, assessment of executive function using the Tower of London–Freiburg version, the system will ask participants to arrange the rings in a specific order, assess both the accuracy and time required for the test, providing an overall score. The Tower of London was recognized by many clinic staff members in the practicality and effectiveness[33]. (4) TMT, functional assessment, which was developed by Partington and Leiter in 1938, and Jordi Llinàs-Reglà's study[34] demonstrated the effectiveness of TMT in evaluating the visual scanning and visuomotor processing speed[35], researchers used TMT-A with only numbers and no letters considering that the participants may not be familiar with English letters. Compared to traditional paper questionnaires, VTS provided more objective and accurate measurement results[36,37].

Level of global cognitive function

Cognitive function was evaluated using the MoCA, scored out of a total of 30 points[38]. Additionally, if the individual’s education level was less than 12 years, one additional point was added to the total score, while the maximum score remained 30 points. A score of 26 or above was considered normal, whereas a score lower than 26 indicated cognitive impairment.

Activities of daily living

The Functional Independence Measure (FIM) was utilized to assess participants' functional abilities[39], encompassing both motor and cognitive function. The FIM score is based on a total of 18 items, with scores ranging from 18 to 126.

Severity of stroke

Assessment of various aspects of neurological function[40], including consciousness level, limb muscle strength, ataxia, and sensory disturbance, among others, was carried out using the National Institute of Health Stroke Scale (NIHSS). The scale comprises 15 items in total with scores ranging from 0 to 42, the higher the total score, the more severe the damage to the patient's neurological function.`

Quality of life

To evaluate functional abilities, emotional well-being, and social aspects across 12 dimensions, the Stroke-Specific Quality of Life Scale (SS-QOL) was applied[41]. The scores ranging from 49 to 245, a higher score on the scale indicates a better QOL.

Adverse events

In order to monitored, recorded, and managed throughout the trial to assess the intervention's safety, researchers should provide participants with supportive guidance and protection during training, as well as conduct regular follow-up and guidance after discharge. At the final assessment of outcome measures, evaluators will administer a questionnaire related to adverse events to comprehensively assess the participants' overall situation.

Statistical Analysis

All statistical analyses were conducted using SPSS (version 26.0, IBM Corp.). Normality of the outcomes were tested. Categorical variables were presented as frequency (n) and percentage (%); continuous variables were shown as mean ± standard deviation (M ± SD) and Median and quartiles. Wilcoxon rank sum test, *t*-test, and chi-square test were used to compare baseline (T0), three months after training (T1), and six months after training (T2) between the two groups for cognitive function and secondary outcome indicators. We did not conduct an intention-to-treat (ITT) analysis for missing data due to the significant variations in outcome indicators that stroke patients may experience at adjacent time points over time. To assess the influence of missing data, we compared the differences in demographic data and baseline characteristics between participants who completed the study and those who did not, as well as between the two groups after excluding the missing data. The generalized estimating equation (GEE) was employed to analyze the effects on primary outcome measures (global cognitive function, cognitive domains) and secondary outcome indices at different treatment time points, between-group and within-group comparisons were used to explore the effects of CCT combined with aerobic exercise on the outcome measures of the participants. Statistical significance was set at $P \leq 0.05$ (two-tailed). The trend graph of each outcome variable over time was plotted using GraphPad Prism software (version 9.4, GraphPad software Corp).

Result

A total of 134 subjects were initially enrolled in the study, with 14 participants dropping out due to physical illnesses or distance and 11 participants lost to follow-up. Ultimately, 109 participants successfully completed the 8-week study course, as detailed in Figure 2 (Consolidated Standards of Reporting Trials [CONSORT] flowchart). The control group (n=67), comprising 42 males and 25 females, with 59 cases of cerebral infarction and 8 cases of cerebral hemorrhage, had an average age of 62.52±8.158 years. Meanwhile, the intervention group (n=67), consisting of 51 males and 16 females, with 61 cases of cerebral infarction and 6 cases of cerebral hemorrhage, had an average age of 65.42±9.423 years. Demographic data are presented in Table 2, the data of participants who were missing in Table 3, it is evident that the attrition of participants in the two groups is roughly balanced. No significant differences were found between the two groups in demographic variables, no significant differences were found between the participants who completed the entire study and those who did not (P>0.05).

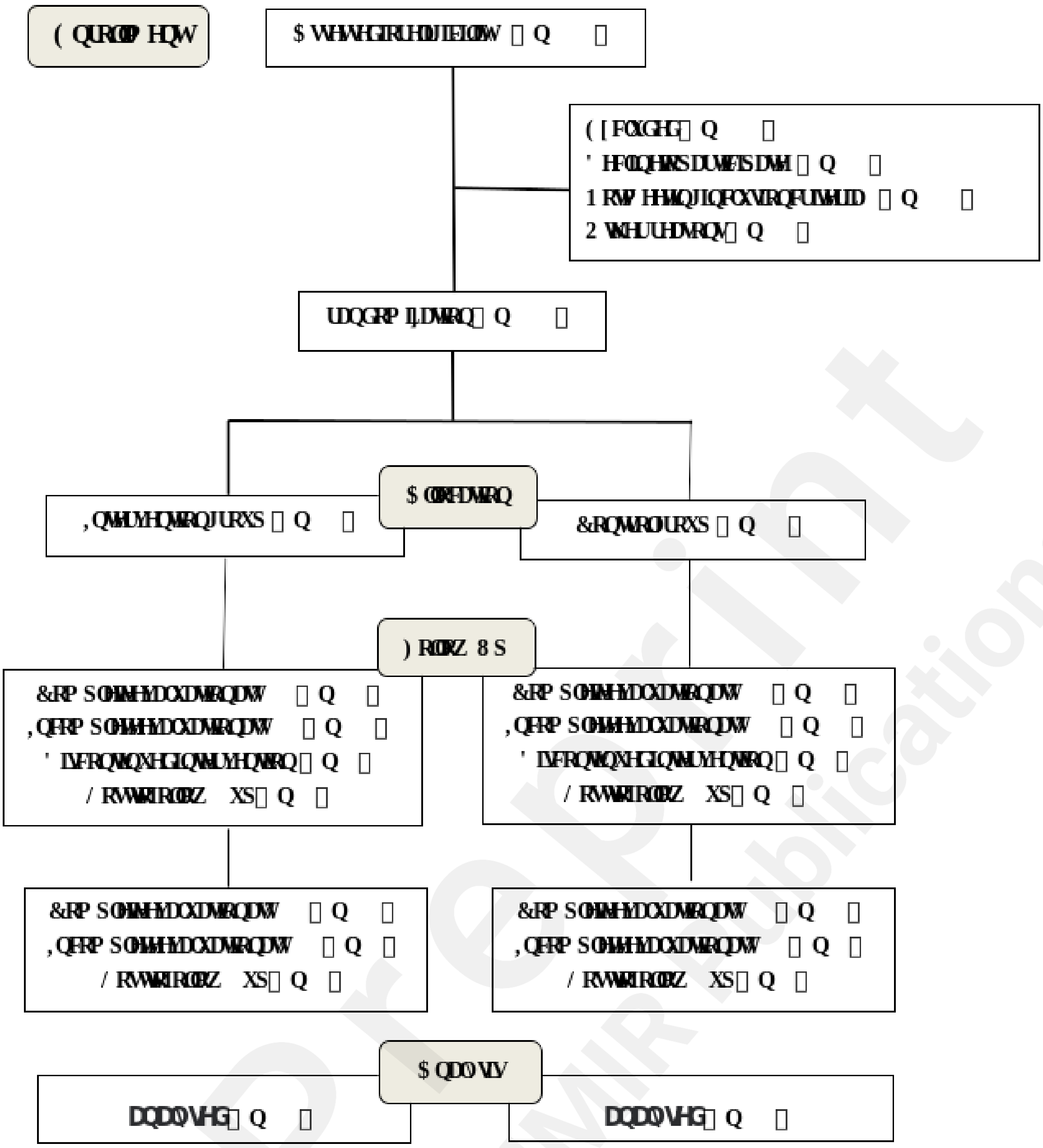

Figure 2 Enrollment and randomization.

	Control (n=67□	Intervention (n=67)	t/χ²	*P*
Age (years, x̄±s)	62.52±8.158	65.42±9.423	-1.902	0.059
Gender (n, □□				
Male	42□62.7□	51□76.1□	2.847	0.092
Female	25□37.3□	16□23.9□		
BMI (x̄±s)	24.04±1.673	23.88±1.721	0.529	0.597
Marital status (n, □)				
Married	53□79.1□	56□83.6□	0.443	0.506
Unmarried or divorced	14□20.9□	11□16.4□		
Education (n, □□				
Primary and below	18□26.9□	28□41.8□	3.482	0.175
Junior high school	21□31.3□	15□22.4□		
High school and above	28□41.8□	24□35.8□		
Medical expense (n, □□				
Self-funded	5□7.5□	4□6.0□	0.131	0.937
Resident medical insurance	37□55.2□	37□55.2□		
Employee medical insurance	25□37.3□	26□38.8□		
Monthly income per capita □CNY□x̄±s)	2874.63±2345.553	2507.46±2390.151	0.897	0.371
Address (n, □□				
Village	12□17.9□	11□16.4□	0.052	0.819
City	55□82.1□	56□83.6□		
Smoking (cigarettes/day□x̄±s)	4.93±7.359	5.07±6.825	-0.122	0.903
Alcohol consumption (ml/week□x̄±s)	236.57±379.252	230.60±312.608	0.099	0.921
Stroke type (n, □□				
Cerebral infarction	59□88.1□	61□91.0□	0.319	0.572
Cerebral hemorrhage	8□11.9□	6□9.0□		
Course of illness† (day□x̄±s)	4.69±1.699	4.45±1.861	0.776	0.439
Blood pressure H (x̄±s)	134.60±10.122	135.03±11.731	-0.229	0.819
Blood pressure L (x̄±s)	83.24±10.679	82.72±10.108	0.291	0.772
Glycosylated hemoglobin (x̄±s)	6.05±1.226	5.89±1.219	0.771	0.442
HDL (x̄±s)	1.35±0.210	1.28±0.255	1.566	0.120
LDL (x̄±s)	3.05±0.470	2.92±0.635	1.324	0.188
Total cholesterol (x̄±s)	4.54±0.589	4.46±0.575	0.779	0.437
Triglycerides (x̄±s)	1.28±0.247	1.33±0.323	-0.996	0.321
Days of intervention (x̄±s)	43.28±8.769	42.91±8.454	0.251	0.802

Table 2 The demographic data of participants in intervention and control groups.

NOTE:
†: Course of illness, time from stroke onset to enrollment.

ID	age	sex	Stroke type	Time of data loss	Reason
C1	64	Woman	Cerebral infarction	T_1	Training is overly burdensome
C2	61	Man	Cerebral infarction	T_1	Lost to follow up
C3	75	Man	Cerebral infarction	T_1	strokes recurrence
C4	47	Man	Cerebral infarction	T_2	Lost to follow up
C5	63	Woman	Cerebral hemorrhage	T_1	Too distant from home
C6	42	Man	Cerebral infarction	T_1	Lost to follow up
C7	72	Man	Cerebral infarction	T_1	Training is overly burdensome
C8	54	Woman	Cerebral infarction	T_1	Training is overly burdensome
C9	66	Man	Cerebral infarction	T_1	Too distant from home
C10	57	Man	Cerebral hemorrhage	T_1	Lost to follow up
C11	70	Man	Cerebral infarction	T_1	Too distant from home
C12	51	Woman	Cerebral infarction	T_1	Lost to follow up
T1	65	Man	Cerebral infarction	T_1	Too distant from home
T2	73	Man	Cerebral infarction	T_1	Lost to follow up
T3	58	Man	Cerebral infarction	T_1	Too distant from home
T4	74	Man	Cerebral infarction	T_2	Lost to follow up
T5	66	Man	Cerebral hemorrhage	T_1	Training is overly burdensome
T6	59	Woman	Cerebral infarction	T_1	Lost to follow up
T7	73	Woman	Cerebral infarction	T_1	Too distant from home
T8	54	Man	Cerebral infarction	T_1	Lost to follow up
T9	76	Man	Cerebral infarction	T_1	strokes recurrence
T10	68	Woman	Cerebral infarction	T_2	Lost to follow up
T11	74	Man	Cerebral infarction	T_1	Training is overly burdensome
T12	63	Man	Cerebral infarction	T_1	Too distant from home
T13	54	Man	Cerebral hemorrhage	T_2	Lost to follow up

Table 3 The data of participants who were missing.

NOTE:
C1-12, Participants in the control group; T1-13, Participants in the intervention group.

Cognitive function

Assessment of cognitive function using the MoCA scale and Vienna Test System indicated improvements in global cognitive function over time. At T1, the intervention group exhibited greater improvement than the control group (Cohen's d=0.483, 95%CI=0.101~0.863, *P*=0.011). At T2, the difference was no longer statistically significant (Cohen's d=0.371, 95%CI=-0.001~0.748, *P*=0.051). Participants demonstrated satisfactory recovery in memory, attention, and executive cognition. Additionally, the intervention group outperformed the control group in memory (T1: Cohen's d=0.989, 95%CI=0.589~1.385, *P*<0.001. T2: Cohen's d=0.617, 95%CI=0.230~0.999, *P*=0.001), attention (T1: Cohen's d=-0.406, 95%CI=-0.784~-0.025, *P*=0.032. T2: Cohen's d=-0.550, 95%CI=-0.932~-0.167, *P*=0.004), and execution (T1: Cohen's d=0.993, 95%CI=0.591~1.387, *P*<0.001. T2: Cohen's d=0.629, 95%CI=0.241~1.011, *P*=0.001). However, our findings indicated that the combined CCT with aerobic exercise did not yield superior effects on visuospatial ability. Both groups showed improvement in visuospatial performance after treatment, which then stabilized during follow-up. There was no significant difference observed between groups at T1 (Cohen's d=-

0.240, 95%CI=-0.617~0.137, *P*=0.204) or T2 (Cohen's d=-0.323, 95%CI=-0.700~0.055, *P*=0.088. Figure 3, Figure 4 and Table 4). GEE analysis revealed significant group × time effects on global cognitive function, memory, attention, and execution (*P*<0.05), but not visuospatial ability (*P*=0.513, Table 5).

Severity of stroke

There was a trend toward better stroke severity over time. However, no significant difference in stroke severity was found between the two groups (Figure 3 and Table 4). Significant group × time interaction (Wald χ^2=15.033, *P*=0.001) and time effects(Wald χ^2=201.693, *P*<0.001, Table 5) were revealed by GEE.

Activities of daily living

After treatment, both groups showed improvement in activities of daily living. *t*-test results indicated that FIM scores were higher in the intervention group than in the control group at T1 (Cohen's d=0.755, 95%CI=0.363~1.141, *P*<0.001) and T2 (Cohen's d=0.692, 95%CI=0.304~1.077, *P*<0.001, Figure 3 and Table 4). GEE analysis revealed significant group × time (Wald χ^2=49.39, *P*<0.001) and time effects (Wald χ^2=581.074, *P*<0.001, Table 5).

Quality of life

Both intervention and control groups exhibited significant improvements in QOL over time. At T1, there was no significant difference between the two groups (Cohen's d=0.316, 95%CI=-0.062~0.693, *P*=0.096). However, the intervention group demonstrated significantly better QOL compared to the control group at T2 (Cohen's d=0.418, 95%CI=0.038~0.797, *P*=0.025, Figure 3 and Table 4). GEE analysis revealed significant time effects (Wald χ^2=212.209, *P*<0.001) and group × time effects (Wald χ^2=8.557, *P*=0.014, Table 5) on participants' QOL.

Adverse events

One patient experienced recurrent stroke in both the intervention and control groups; otherwise, no other adverse events were observed. There was no significant difference in the incidence of adverse events between the two groups (*F*<0.001, *P*=1.000).

Table **4** Outcome measures for each variable.

Variables	**Time**	**Intervention (n=54)**	**Control (n=55)**	**Cohen's d**	***P***
MoCA †	T0	20.59±2.359	20.76±2.560	-0.069	0.714
	T1	24.33±2.599	23.09±2.541	0.483	0.011
	T2	25.67±2.713	24.71±2.455	0.371	0.051
Memory †	T0	16.26±6.710	16.27±7.223	-0.001	0.992
	T1	23.93±5.362	18.40±5.804	0.989	<0.001

	T2	24.69±5.135	21.38±5.576	0.617	0.001
Attention †	T0	474.45±92.279	481.90±90.566	-0.081	0.668
	T1	349.28±96.701	391.34±110.00	-0.406	0.032
	T2	325.82±87.211	379.59±106.98	-0.550	0.004
Execution †	T0	10.80±5.007	12.64±5.762	-0.341	0.064
	T1	17.78±4.513	13.25±4.608	0.993	<0.001
	T2	17.56±4.082	14.87±4.460	0.629	0.001
Visuospatial ability †	T0	42.11±11.597	41.23±15.320	0.065	0.734
	T1	29.87±8.570	31.98±9.016	-0.240	0.204
	T2	28.88±6.501	31.47±9.276	-0.323	0.088
NIHSS ‡	T0	3 (1,4)	2 (1,3)	0.149	0.423
	T1	1 (0,1)	1 (0,2)	-0.348	0.067
	T2	1 (0,1)	0 (0,1)	-0.121	0.517
FIM †	T0	106.00±6.898	108.25±6.899	-0.326	0.085
	T1	118.69±4.295	114.69±6.128	0.755	<0.001
	T2	121.26±3.432	118.22±5.166	0.692	<0.001
SS-QOL †	T0	178.48±15.258	178.13±16.496	0.022	0.906
	T1	196.39±21.628	190.11±17.942	0.316	0.096
	T2	200.11±27.937	196.51±20.819	0.418	0.025

NOTE:
MoCA, Montreal Cognitive Assessment; NIHSS, the National Institutes of Health Stroke Scale; FIM, Functional Independence Measure; SS-QOL, Stroke Scale-Quality Of Life.
† Continuous variables in normally distributed are presented by Mean±SD.
‡ Continuous variables in not normally distributed are denoted by Median (P_{25},P_{75}).
* $P<0.05$, ** $P<0.01$.

Table **5** The generalized estimated equation model effect test.

Outcome	Wald c^2	df	*P*
Global cognitive function			
Group	2.315	1	0.128
Time	531.541	2	<0.001
Group×Time	26.437	2	<0.001
Memory			
Group	7.802	1	0.005
Time	210.296	2	<0.001
Group×Time	67.781	2	<0.001
Attention			
Group	4.06	1	0.044
Time	313.476	2	<0.001
Group×Time	12.174	2	0.002
Execution			
Group	4.447	1	0.035
Time	297.446	2	<0.001
Group×Time	136.341	2	<0.001
Visuospatial ability			
Group	0.515	1	0.473
Time	186.363	2	<0.001
Group×Time	3.755	2	0.153
Severity of stroke			
Group	0.281	1	0.596
Time	201.693	2	<0.001
Group×Time	15.033	2	0.001
Activities of daily living			
Group	2.843	1	0.092
Time	581.074	2	<0.001
Group×Time	49.390	2	<0.001
Quality of life			
Group	2.558	1	0.110
Time	212.209	2	<0.001
Group×Time	8.557	2	0.014

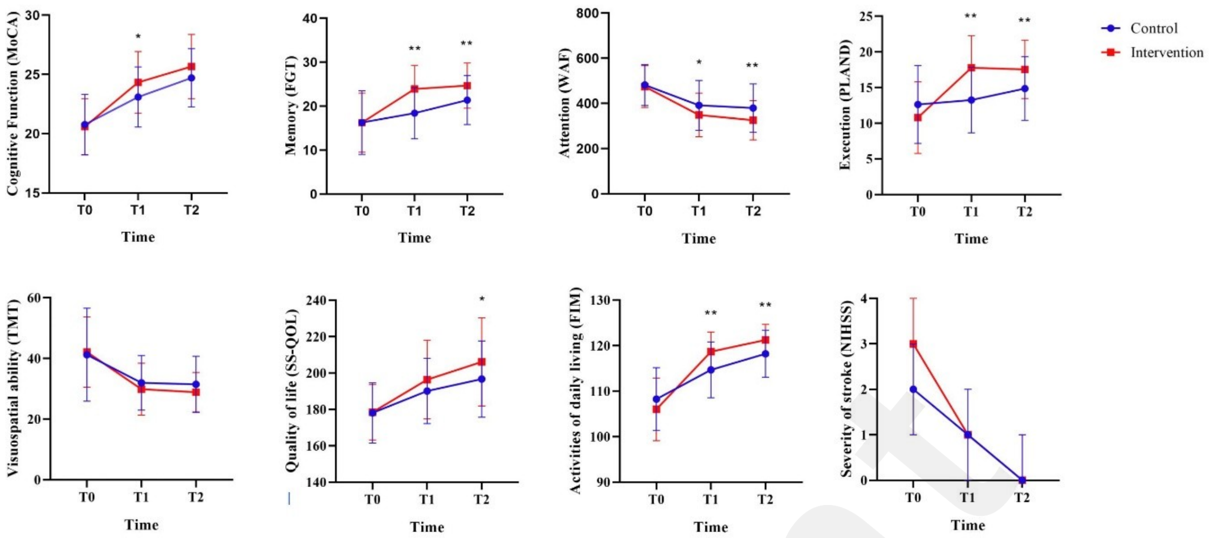

Figure 3 The change trend of each study variable between the intervention group and the control group during the follow-up time (*P < 0.05, **P < 0.01).

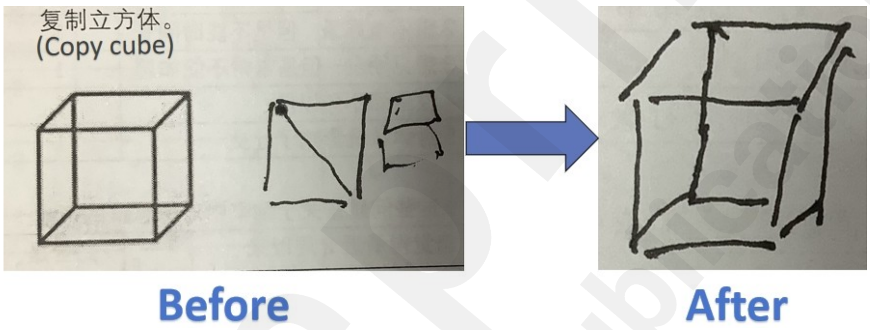

Figure 4 Participants' progress in MoCA.

Discussion

This study represented the first randomized controlled trial aimed at objectively measuring changes in domain-specific cognition by combining CCT with aerobic exercise in patients with PSCI. The findings demonstrated the effectiveness of this intervention program in rehabilitating these patients. The 8-week intervention has exhibited promising clinical benefits, only requiring a small amount of energy from medical workers, thus rendering it highly feasible for implementation and promotion.

Computerized cognitive training combined with aerobic exercise has been shown to effectively promote the rehabilitation of cognitive function in patients with PSCI

Post-stroke patients commonly face secondary impairments in attention, memory, execution, and visuospatial ability, significantly impacting their physical and mental health while potentially delaying the rehabilitation process[42]. Results from this study revealed that the intervention group displayed improved performance in attention, memory, and execution compared to the control group after training, consistent with previous research[43]. At the initial post-intervention stage (T1), the intervention group showed enhanced global cognitive function compared to the control group.

However, over time, post discontinuation of training, the difference between the two groups was no longer statistically significant ($P > 0.05$). It is hypothesized that the measured results of the MoCA scale may underestimate the actual outcomes due to potential limitations in visuospatial ability, possibly leading to a ceiling effect in the scale where higher levels of performance cannot be accurately captured[44]. This speculation arose because the Vienna Test System still indicated differences in domain-specific cognition between the two groups. Moreover, the duration of the intervention may have contributed to the between-group differences at T2[45], a longer period of CCT might prove to be more effective. Further studies are necessary to demonstrate the advantages of CCT for both long-term and home-based treatments in comparison to previous interventions, thereby supporting the promotion of computerized cognitive training systems in home training.

Computerized cognitive training provides personalized and targeted training based on the specific cognitive domain impairments and cognitive levels of patients [16], offering advantages such as controllable training intensity, reduced subjective influence of rehabilitation therapists, and time-saving for medical staff compared to traditional cognitive therapy. Aerobic exercise can alleviate nerve tissue damage caused by ischemia and hypoxia by increasing cerebral blood flow[46], regulating the concentrations of brain-derived neurotrophic factor[47,48] and nerve growth factor, consequently reducing nerve injury and inflammatory responses caused by cerebral hypoperfusion, which is one of the most significant factors contributing to cognitive impairment[49]. Numerous studies indicate that cognitive training can enhance biochemical processes in the brain's temporal lobe and elevate cognitive functioning [29]. However, its efficacy is constrained by inherent neuroplasticity limitations, resulting in suboptimal outcomes. Therefore, integrating aerobic exercise into cognitive training holds higher clinical value for ameliorating nerve tissue damage. Since some aspects of CCT training content overlap with aerobic exercise, engaging in aerobic exercise can better reinforce the training outcomes of CCT following hospitalization compared to other therapies.

This study found no significant difference in visuospatial ability between the two groups after the intervention. We speculated that this might be related to the measurement method, patients need to integrate bottom-up visual information and top-down signals when completing the assessment task. Participants with impaired vision may struggle to complete the test due to the high bottom-up visual demands of the visuospatial exam[50]. Additionally, the possibility of poor intervention program effectiveness cannot be excluded. Previous studies[51] have highlighted distinct neural pathways for visuospatial perception and integration, observing that impairment in either pathway significantly impacts a patient's visuospatial ability. Further research into the underlying mechanisms is necessary to establish a foundation for the design of effective visuospatial rehabilitation programs.

CCT combined with aerobic exercise improved the activities of daily living and QOL in patients with PSCI

A diminished cognitive function significantly impedes physical rehabilitation after a stroke, and physical impairments have been found to worsen cognitive decline. In line with previous findings[7], the intervention group displayed considerably higher levels of daily functioning and QOL compared to the control group ($P > 0.05$). Unlike traditional cognitive training, computerized cognitive training utilizes multi-sensory human-computer interaction to replicate real-life scenarios[27,52], aiding patients in adapting more rapidly to social life and laying the groundwork for post-discharge adherence to aerobic exercise. Simultaneously, aerobic exercise enhances the daily living ability of PSCI patients by improving muscle strength, ameliorating negative emotions, and enhancing attention[53], thereby amplifying the efficacy of computerized cognitive training and ultimately improving QOL.

The study also indicated no significant difference in stroke severity between the two groups after the intervention. Similarly, a multicenter randomized controlled study[54] reported that aerobic exercise did not exhibit superiority over other forms of exercise in the treatment of subacute stroke. Therefore, despite some previous studies [55] confirming the positive impact of aerobic exercise on post-stroke recovery, this aspect remains a topic of debate. Stroke rehabilitation encompasses various facets, including nerve function, muscle strength, and hemodynamics, leading us to posit that different exercise modalities may produce diverse effects on the functional recovery of patients. Due to the limited availability of medical resources in many countries, rehabilitation programs with stringent professional requirements and high costs, such as hyperbaric oxygen therapy and repetitive transcranial magnetic stimulation, may not be feasible for most patients after discharge. In contrast, exercise prescriptions are more accessible and boast higher compliance rates. Hence, it is significant to explore the optimal exercise content and frequency to develop effective rehabilitation strategies for stroke patients in the future.

A total of 25 cases of data were lost in this study, but we not present the results of the intention-to-treat (ITT) analysis. The reason for this is that outcome measures in stroke patients often undergo significant changes over time. Therefore, using data prior to loss to follow-up and dropouts instead of the T2 time point in the analysis could introduce a considerable bias. In the later we conducted a further ITT analysis, the results indicated no significant differences when comparing the statistics from the ITT analysis with those without ITT analysis, only the global cognitive function showed a slightly larger effect size in the statistics with ITT analysis. On the other hand, data that exclude individuals declined to participate, lost to follow-up and dropouts may be more relevant to clinical staff and patients, they are interested in understanding the potential outcomes of persisting in training. Finally, no significant differences were observed in baseline and general data between the two groups after excluding data from individuals lost to follow-up and dropouts, no differences were found in baseline and general data between the participants who completed the study and those who did not, as well as between the two groups after excluding the missing data. After comprehensive consideration, we believe that the statistical results without ITT analysis are more consistent with the actual clinical situation and more reliable, so we have decided to present the statistical results without ITT analysis.

Study limitations

Blinding participants and investigators was difficult due to the nature of the intervention, despite participants in the intervention group being trained in separate rooms, there was still potential for communication between the two groups, which could have introduced bias into our study outcomes. Sixty-two participants declined to participate in the study due to living far from the hospital and perceiving the intervention and subsequent follow-up as inconvenient.This suggests that the generalizability of our study outcomes may be affected, and caution should be exercised when applying these results to non-Chinese stroke patients. Further multi-center studies with larger sample sizes are necessary to ensure the generalizability of the outcomes in the future. Considering the varying physical fitness levels among participants, exercise intensity was determined based on their reserve heart rate, resulting in some variability in their exercise intensity. In the future, further research is needed to determine the optimal exercise intensity and duration. Additionally, we were unable to measure the brain-derived neurotrophic factor and other related brain indicators in the participants, nor did we compare changes in each brain region before and after three months using imaging. Future research should focus on exploring non-invasive, cost-effective, and widely applicable objective assessment methods to further investigate the intrinsic rehabilitation mechanism of cognitive impairment post-stroke.

Conclusion

In summary, our study illustrated that combining CCT with aerobic exercise could enhance global cognitive function, attention, memory, executive cognitive domains, activities of daily living and QOL in patients with post-stroke cognitive impairment. These findings provided both theoretical and practical support for rehabilitation interventions in patients suffering from cognitive decline due to stroke.

Data availability statement

The raw data for this study will be available upon contacting the corresponding author or the first author.

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Statement

No LLM (large language model) was used to supplement this writing.

Conflicts of Interest

This study has no potential conflicts of interest.

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Abbreviations

PSCI: Post-Stroke Cognitive Impairment

CCT: Computerized cognitive training

QOL: Quality of life

MoCA: Montreal Cognitive Assessment

VTS: Vienna Test System

FIM: Functional Independence Measure

NIHSS: National Institute of Health Stroke Scale

SS-QOL: Stroke-Specific Quality of Life Scale

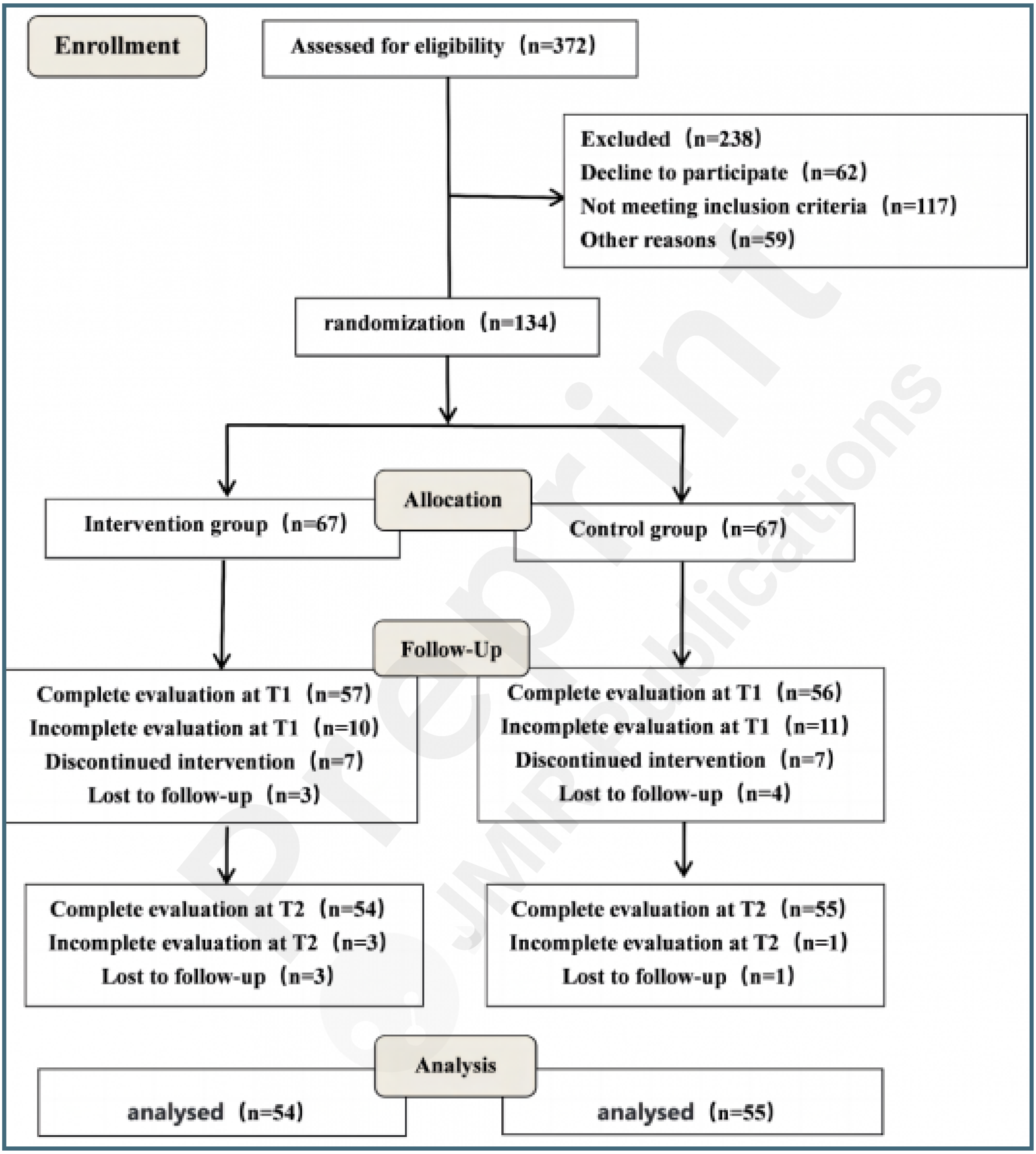
GEE: Generalized estimating equation

Supplementary Files

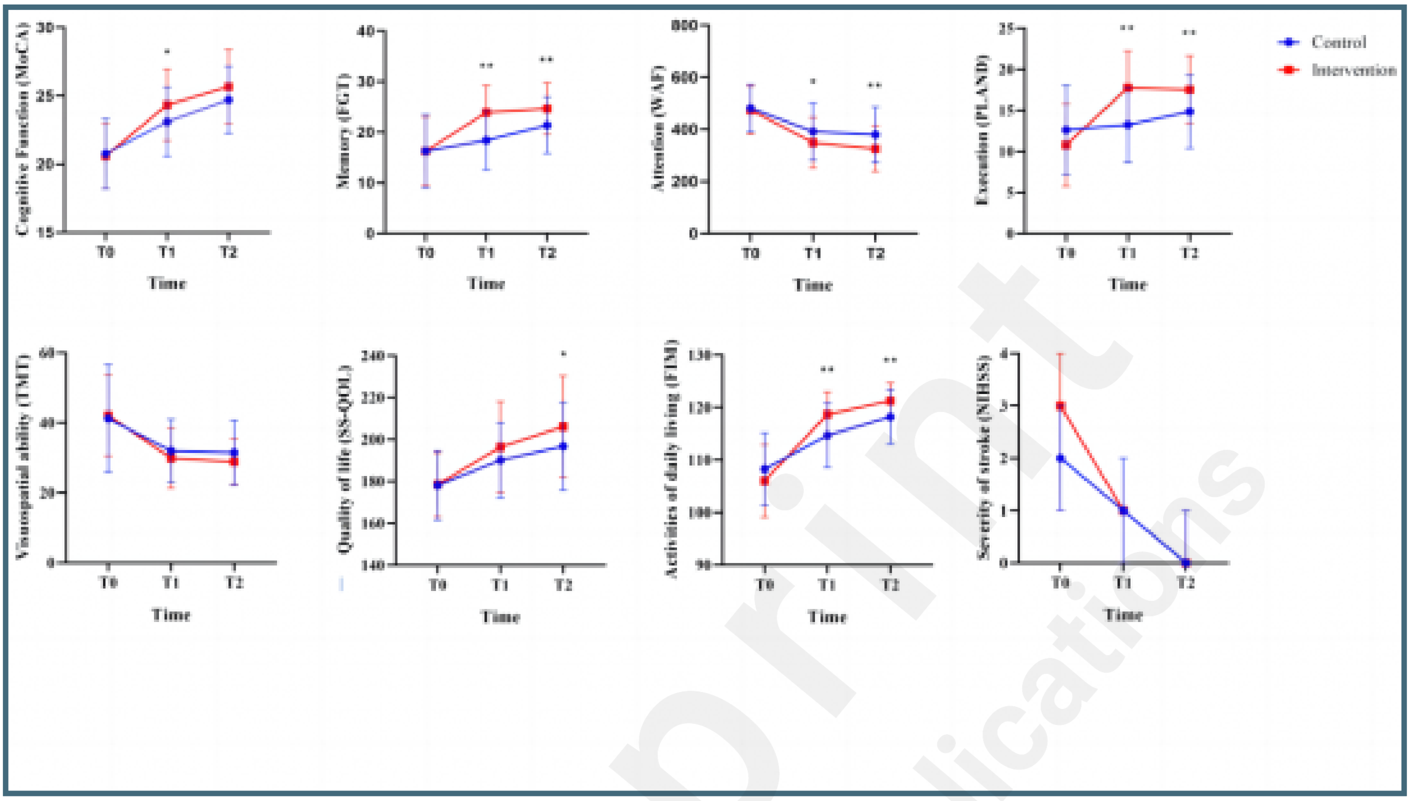
Figures

The procedure for CCT: FOCUS, VISP, PLAIN and SPACE.

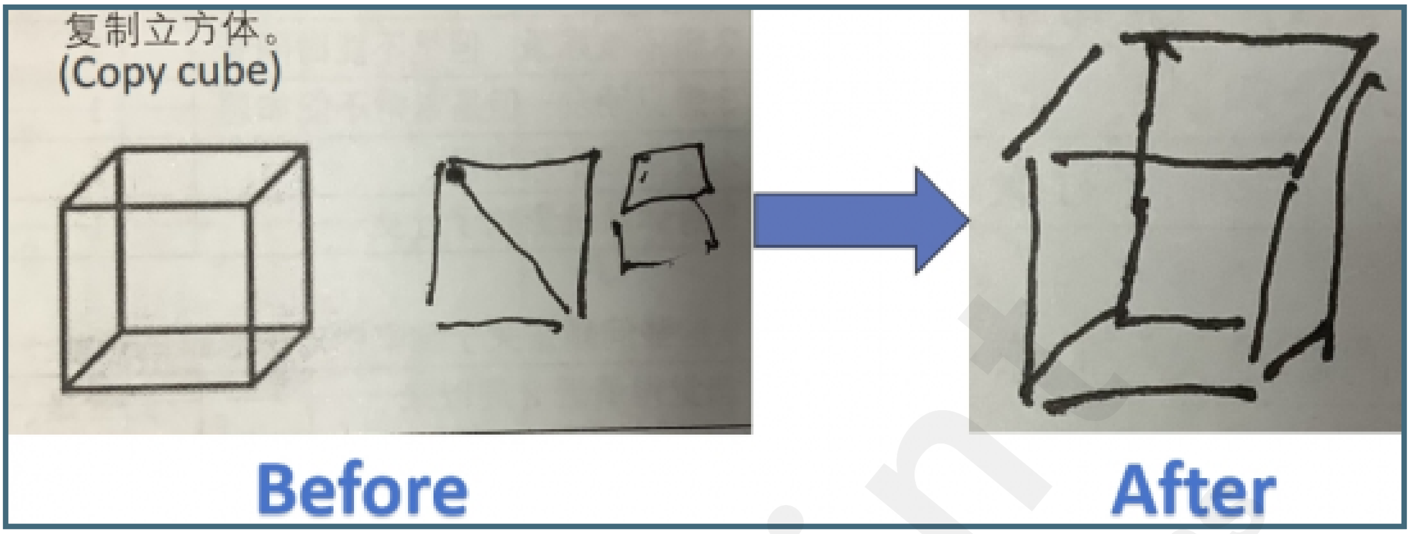
Enrollment and randomization (CONSORT flow diagram).



The change trend of each study variable between the intervention group and the control group during the follow-up time.



Participants' progress in MoCA.



CONSORT (or other) checklists

CONSORT checklist.
URL: http://asset.jmir.pub/assets/12bb1e2ae73d8ab82e8acf6626e7db2c.pdf