

# Effect of combined aerobic exercise and cognitive training in older adults with post-stroke cognitive impairment

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**Abstract.** Cognitive impairment affects >50% of individuals who survive for 6 months following a stroke. Cognitive impairment not only reduces the ability of patients to relearn motor skills due to memory problems or poor judgment, but also significantly impairs daily living activities and quality of life. Early intervention in mild cognitive impairment (MCI) not only improves cognition, but also attenuates the progression to dementia. The present controlled prospective study included 38 older adults with post-stroke MCI, who were assigned to the intervention group (aerobic + cognitive exercise) and the control group (cognitive exercise). Both groups participated in 60-min sessions, three times per week, for 12 weeks (4 weeks in the hospital and 8 weeks at home). The intervention group exhibited a significant improvement in cognitive function (Montreal cognitive assessment and frontal assessment battery,  $P < 0.05$ ), as well as in physical function and quality of life, compared to the control group. On the whole, the present study demonstrates that the combination of aerobic and cognitive exercise is beneficial leading to improvements in the cognitive function, physical function and quality of life of individuals with post-stroke MCI.

## Introduction

Stroke is one of the main causes of mortality and permanent disability. The stroke rate doubles every decade and frequently affects individuals aged  $\geq 55$  years (1). Of note, ~90% of stroke survivors continue to suffer from chronic sequelae, and ~30% of these patients are unable to perform daily activities independently (2). Among these sequelae, cognitive impairment, a common consequence of stroke, affects >50% of individuals who survive for 6 months following a stroke (3). Another study found that 83% of patients had impairment

in at least one cognitive domain, while 50% had cognitive impairment across multiple domains (4). The American Heart Association/American Stroke Association (AHA/ASA) Guidelines for Stroke Rehabilitation and Treatment in Adults (2016) state that the majority of patients who suffer a clinical stroke undergo cognitive assessment prior to hospital discharge (5). Cognitive impairment and cognitive rehabilitation have been identified as top research priorities in stroke survivors (top 10). The majority of available treatments aim to either restore lost skills or to teach compensatory techniques; however, the evidence has not been persuasive yet (6,7).

A previous systematic review article found that targeted cognitive training in specific cognitive domains provides several positive effects (8). Starovasnik Žagavec *et al* (9) conducted a study with 11 stroke survivors who underwent intensive training in selective attention. The results of their study revealed a significant improvement from a moderate to strong level in divided attention, and a mild effect on alertness (9). Another study highlighted the functional connectivity of the hippocampus with the left frontal and parietal lobes through cognitive training, indicating a key mechanism in cognitive recovery following a stroke (10). Physical exercise is another effective approach for improving the cognitive function of patients. A previous systematic review examining the effects of physical activity on cognitive function following a stroke demonstrated that physical exercise exerted significant cognitive benefits (11). Aerobic exercise not only exerts beneficial effects in improving physical function and reducing the risk of developing secondary complications, but also reduces the risk of developing Alzheimer's disease and related cognitive disorders (12). Aerobic exercise has a positive effect on overall cognitive function, with potential benefits to memory, attention and the visuospatial domain in stroke survivors (13). The improvement in cognitive function following exercise is probably due to the regulation of angiogenic and neurotrophic growth factors, which may facilitate neurogenesis, circuitry and synaptic plasticity in the hippocampus and other cognitively relevant cortical regions (14).

There is mounting evidence to indicate that combining aerobic interventions with cognitive training may yield additional benefits to cognitive performance, surpassing the effects of a single type of training alone (15). Combining physical activity with cognitive training leads to significant cognitive improvements and reduces depression symptoms in older adults (16). A previous systematic review found that this combination enhanced overall cognitive function, memory,

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executive function and attention, in both cognitively impaired and non-impaired populations (17). In another study, in a population with cognitive impairment following a stroke, the combination of exercise and cognitive training exerted greater beneficial effects on cognitive function compared to exercise alone (18). In addition, a previous study posited that for exercise to effectively produce combined neurological and cognitive benefits, it needs to occur within a cognitively challenging environment (19). Performing aerobic sessions prior to cognitive training prepares the brain for compensatory recruitment during the subsequent cognitive training session (17). Aerobic exercise prior to cognitive exercise can increase arousal levels, facilitate neurogenesis and enhance memory consolidation, which may benefit memory retrieval and cognitive task performance afterwards (20).

Several studies have evaluated the effects of combining physical activity with cognitive training in older adults or those with cognitive impairment (16-18). However, evidence in older adults with mild cognitive impairment (MCI) after stroke remains limited. The present study aimed to evaluate a group of older adults for several reasons. First, the incidence of stroke is higher among older adults. Older adults with MCI following a stroke, if not addressed early, are at a risk of further cognitive decline due to the degenerative process, which may lead to the early onset of dementia and progress more severely. Additionally, older adults generally engage in less physical activity compared to younger individuals, rendering them more likely to benefit from participation in a structured exercise program, which can improve adherence to the training regimen.

In the present study, patient recruitment was conducted at the National Geriatric Hospital in Hanoi, Vietnam, with the target group primarily consisting of older adults. It was observed that older adults with cognitive impairment following a stroke often require long-term care, which places a notable burden on both families and society. It should be noted that the classification of the 'older adult' age group is not standardized across various organizations. The present study followed the definition provided by the National Institute on Aging (NIA) and the classifications used in numerous Western countries and studies, which define older adults as individuals aged  $\geq 65$  years. Furthermore, the methods of combining these interventions need to be carefully considered for optimal effectiveness. Patients residing at a marked distance from the hospital or those with limited access to prolonged in-hospital programs may derive fewer benefits from the intervention compared to others. Therefore, the present study not only evaluated the effectiveness of sequential aerobic exercise and cognitive training, but also proposed an intervention program with follow-up after hospital discharge. It was hypothesized that the combination of aerobic exercise and cognitive training would improve the cognitive function, physical health and quality of life of patients than cognitive intervention alone.

## Patients and methods

*Study type and population.* The present study was a controlled prospective study and adopted a convenience sampling method to evaluate the effectiveness of a combined aerobic exercise in treating mild cognitive impairment following a stroke.

The sample size formula for a two-independent-sample study, with a type I error probability of 5%, a two-tailed test, and 80% power, as proposed by Yeh *et al* (21), indicated a variance of  $\sigma^2=4.92$  for the intervention group. A mean difference of  $\Delta=4.7$  between the two groups was expected. The minimum sample size per group was 17, with a 10% increase to ensure adequacy, resulting in 19 participants per group.

Stroke survivors with MCI who met the inclusion criteria were randomly assigned at a 1:1 ratio to either the intervention or control group. Participants were first paired based on similar characteristics, and subsequently, within each pair, randomization was used to assign one participant to the intervention group and the other to the control group. One researcher was responsible for conducting the screening and assessments both before and after the intervention, while another researcher was assigned to randomize the participants and prescribe the corresponding exercise protocols.

There were no modifications to the intervention method following the recruitment of the participants. Each group practiced for 60 min per day, 3 days per week, for 12 weeks. A total of 36 sessions were divided into two phases as follows: The first 4 weeks in the hospital and the following 8 weeks at home. No interim analysis was performed during the study.

*Participation and recruitment.* The study was conducted at the Rehabilitation Department of the National Geriatric Hospital in Hanoi, Vietnam. Participants were provided with all information about the study and signed a consent form after understanding the details of the study.

The inclusion criteria were as follows: i) Patients with a confirmed diagnosis of MCI following an ischemic stroke [according to DSM-5 diagnostic criteria, Montreal cognitive assessment (MoCA) score  $< 26$ , mini-mental state examination score  $\geq 19$ ]; ii) patients with the first ischemic stroke occurring within the past 6 months; iii) those with an age  $\geq 65$  years; iv) those with the ability to participate in the program, including sufficient mobility, balance, cognitive capacity to engage in and adhere to the program, and the presence of a family member or caregiver to monitor and supervise self-practice process; v) those who agreed to provide informed consent and participate in the study.

The exclusion criteria were the following: i) Patients with other neurological disorders, such as Parkinson's disease, multiple sclerosis, etc.; ii) patients with injuries or musculoskeletal diseases that markedly impaired mobility, preventing participation in the program; ii) patients with acute or chronic respiratory or cardiovascular diseases that were not stably controlled or were at a risk of acute exacerbations during physical activity.

The present study was approved by Hanoi Medical University under Decision No. 3963/QĐ-ĐHYHN, dated September 26, 2022 and Hanoi Medical University Institutional Ethical Review Board under Decision No. 1259/GCN-HDDDNCYSH-DHYHN, dated May 7, 2024. All patients provided a written consent to participate in this study.

*Clinical intervention, part 1: Training program in the hospital (first 4 weeks)*

*Aerobic exercise.* Patients in the intervention group performed a 30-min treadmill exercise, including 3 min of warm-up, and

25 min of main exercise (walking on the treadmill) and ending with 2 min of cool-down. The target intensity of the exercise was moderate, assessed by aiming for a target heart rate during the aerobic period that was 40% of the reserve heart rate of the patient, calculated using the Karvonen formula. Additionally, the Borg Perceived Exertion Scale was recorded during each session. Depending on the ability and the physical activity level of each individual, the 25-min main exercise was divided into 2-3 intervals, interspersed with short 2-min rest periods, to achieve the target after 4 weeks. Achieving the target meant reaching the target heart rate and completing 25 min of sustained exercise. All sessions were conducted by physical therapists. The exercise was fully monitored by rehabilitation doctors and physiotherapists to observe the symptoms of the patient and adjust the intensity as needed (Fig. 1).

**Cognitive training.** The cognitive training program was conducted on paper, focusing on cognitive domains commonly impaired in patients who have suffered a stroke, including executive function, processing speed, concentration and attention, memory, etc. Participants performed various tasks and the level was gradually increased until an improvement was observed. Occupational therapists conducted and monitored the sessions. The duration of cognitive training was 30 min per day for the intervention group and 60 min per day for the control group. The following exercises were performed: i) Memory exercises: Interventions for memory retrieval (mnemonic methods for language memory recovery; organizing information into categories; using visual imagery to enhance semantic memory; linking new information with previously known information, etc.) and compensatory memory interventions (using devices, schedules, etc.). ii) Attention, concentration and processing speed exercises: Applying attention process training to improve sustained, selective, alternating and divided attention. iii) Executive function exercises: Applying metacognitive strategy training to process tasks.

**Clinical intervention, part 2: Home training program (8 weeks).** The program was continued at home following the instructions provided at the hospital. The duration of training was 8 weeks, comprising 24 sessions in total.

Aerobic exercise consisted of brisk walking on a flat surface to achieve the target intensity. Cognitive exercises involved instructing patients to prepare comic strips, images and various objects related to different topics, similar to the tasks practiced during their hospital sessions. In addition, patients were provided with a document that recorded the exercises, along with illustrative images of previously taught tasks. This allowed patients to continue practicing at home with the support of family members or caregivers.

**Compliance monitoring.** Groups of patients were created on the phone app with 3-5 patients per group. All participants were required to exercise within a specified time frame each day and on specific days of the week. Researchers were aware of the training schedules for each group and regularly monitored and supervised each the training sessions of group via video using phone software. A tracking sheet was used for each patient. The evaluators verified the exercise sessions of the patients according to the exercise schedule of each group and marked the tracking sheet accordingly.



Figure 1. Aerobic exercise training.

**Outcome assessment.** The outcomes were evaluated at two-time points as follows: Once before the intervention began and again at 12 weeks following the commencement of the intervention.

**Primary outcome measures.** Primary outcome measures were cognitive functions, including the MoCA and the frontal assessment battery (FAB). The MoCA is a brief screening tool with a high sensitivity and specificity for detecting mild cognitive impairment, assessing six domains: Memory, executive function, attention, language, visuospatial ability and orientation. The FAB includes six subdomains related to frontal lobe function and is a simple tool for assessing frontal lobe function.

**Secondary outcome measures.** Secondary outcomes included measures of physical function and quality of life. Physical functions were assessed using the Fugl-Meyer Assessment Lower Extremity (FMA-LE) and the 6-min walk test (6MWT). The FMA-LE is designed to evaluate motor function, balance, sensation and joint function in patients of all ages with post-stroke hemiplegia. The 6MWT measures the distance a patient can walk in 6 min and is used as an indicator of walking endurance. It is an important predictor of mobility and community integration in stroke survivors.

Quality of life was assessed using the European Quality of Life-5 Dimension-5 Level (EQ-5D-5L) instrument. This tool evaluates five health aspects: Mobility, self-care, usual daily activities, pain or discomfort and anxiety or depression. Each aspect is rated on a five-level severity scale: No problems, slight problems, moderate problems, severe problems and extreme problems.

**Statistical analysis.** The data were analyzed using SPSS 20.0 software (IBM Corp.). The Kolmogorov-Smirnov test was used to assess the normality of the data. The basic characteristics of the participants were compared using the Chi-squared ( $\chi^2$ ) test and Fisher's exact test. The Wilcoxon signed rank test was used to compare pre- and post-intervention values within each group. To compare the differences between the two groups, the Mann-Whitney U test was applied. To evaluate the strength of the difference, the effect size was calculated using the  $r$

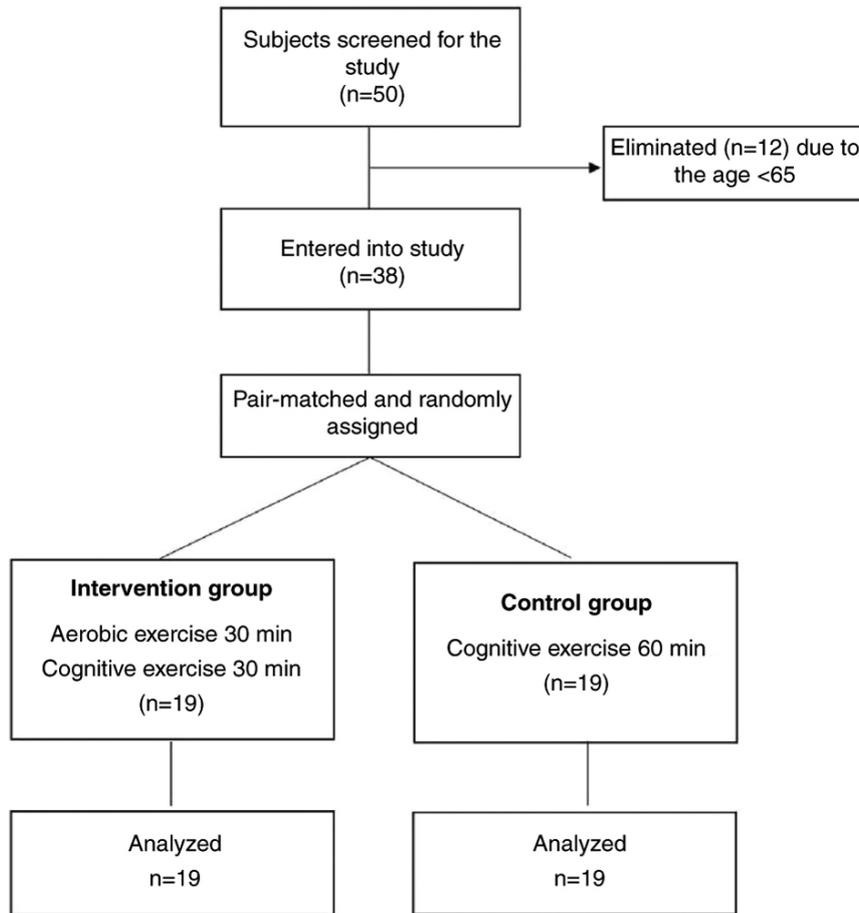


Figure 2. Flowchart of the study design.

coefficient for each outcome:  $r \leq 0.1$ , small effect size;  $0.1 < r \leq 0.3$ , moderate effect size; and  $r > 0.3$ , large effect size. A value of  $P < 0.05$  was considered to indicate a statistically significant difference. The Bonferroni correction was applied to adjust the P-values, thereby controlling the overall type I error rate at 0.05 across all statistical tests conducted in the study.

## Results

Initially, 50 ischemic stroke survivors were selected, of whom 12 did not meet the age eligibility criteria. Therefore, 38 stroke survivors with MCI were randomly assigned to two groups as follows: An intervention groups (n=19) and a control group (n=19) (Fig. 2). The selection and follow-up period took place concurrently from November 1, 2022, to May 31, 2023. During this period, participants were enrolled, trained, and followed-up. The follow-up continued until July 31, 2023. No changes were made to the study outcomes after the study commenced. No adverse events were reported during the study, and the study was conducted according to the planned protocol until its completion. The results revealed that no significant difference was observed in the demographic characteristics between the two groups ( $P > 0.05$ ), apart from sex ( $P < 0.05$ ; Table I).

*Primary outcome measures.* After applying the Bonferroni correction, the MoCA score results indicated that both groups

exhibited a significant improvement following treatment, for the intervention group ( $P = 0.003$ ) and the control group ( $P = 0.014$ ). However, the difference in MoCA score changes between the intervention and control groups was not statistically significant ( $P = 0.041$ ). As regards the FAB scores, the intervention group exhibited a significantly greater improvement compared to the control group ( $P = 0.008$ ). The FAB score in the intervention group improved significantly ( $P = 0.001$ ); by contrast, the improvement in the control group was not statistically significant ( $P = 0.068$ ) (Table II).

*Secondary outcome measures.* The data collected using the sub-measures in FMA-LE, 6MWT and EQ-5D-5L (Table III) revealed that both groups experienced significant physical improvement following treatment, with the intervention group demonstrating a significant change compared to the control group. After applying the Bonferroni correction, the intervention group exhibited significant improvements in both FMA-LE and 6MWT, whereas in the control group, only the 6MWT exhibited significant improvements. As regards quality of life, only the intervention group exhibited a significant improvement ( $P = 0.002$ ) (Table III).

## Discussion

The results of the present study demonstrated that the group participating in aerobic exercises experienced positive

Table I. General characteristics of the study participants.

Variables	Intervention group (n=19)	Control group (n=19)	P-value
Age (years)	71.42±5.10	73.95±7.04	0.278
Sex			0.036
Male	16 (84.2)	10 (52.6)	
Female	3 (15.8)	9 (47.4)	
BMI	20.75±1.55	20.32±1.56	0.365
NIHSS score	6.47±1.98	5.68±1.89	0.218
Side of brain lesion			0.103
Right	6 (31.6)	11 (57.9)	
Left	13 (68.4)	8 (42.1)	
Education			0.201
I (primary school)	8 (42.1)	3 (15.8)	
II (middle school)	5 (26.3)	7 (36.8)	
III (secondary school)	6 (31.6)	9 (47.4)	

Values are presented as the mean ± standard deviation or n (%). NIHSS, National Institute of Health Stroke Scale; BMI, body mass index.

Table II. Primary outcome measures.

Outcome	Pre-training		Post-training		Wilcoxon signed rank test P-value <sup>a</sup>		Mann-Whitney U test (Δ)	
	Intervention group (n=19)	Control group (n=19)	Intervention group (n=19)	Control group (n=19)	Intervention group (n=19)	Control group (n=19)	P-value <sup>b</sup>	Effect size (r)
MoCA	18.21±3.87	16.79±4.19	19.02±4.23	17.11±4.54	0.003	0.014	0.041	0.331
FAB	10.84±4.25	8.74±4.57	11.95±4.03	9.21±4.98	0.001	0.068	0.008	0.429

Values are presented as the mean ± SD. <sup>a</sup>Values for within-group comparisons; <sup>b</sup>values for between-group (intervention group vs. control group) comparisons. MoCA, Montreal cognitive assessment, FAB, frontal assessment battery.

Table III. Secondary outcome measures.

Outcome	Pre-training		Post-training		Wilcoxon signed rank test P-value <sup>a</sup>		Mann-Whitney U test (Δ)	
	Intervention group (n=19)	Control group (n=19)	Intervention group (n=19)	Control group (n=19)	Intervention group (n=19)	Control group (n=19)	P-value <sup>b</sup>	Effect size (r)
FMA-LE	17.58±3.50	17.42±3.61	20.21±3.77	17.74±3.86	<0.001	0.034	<0.001	0.759
6MWT (meters)	41.47±12.28	38.84±11.62	71.42±14.97	52.16±16.16	<0.001	<0.001	<0.001	0.797
EQ-5D-5L	0.78±0.04	0.77±0.04	0.81±0.41	0.78±0.05	0.002	0.128	0.011	0.41

Values are presented as the mean ± SD. <sup>a</sup>Values for within-group comparisons; <sup>b</sup>values for between-group (intervention group vs. control group) comparisons. FMA-LE, Fugl-Meyer Assessment Lower Extremity; 6MWT, six-minute walk test; EQ-5D-5L, European Quality of Life-5 Dimension-5 Level.

improvements in general cognition compared to the group that received cognitive training only. This supports the initial hypothesis that incorporating aerobic exercise would lead to

greater overall cognitive improvement. The intervention group also demonstrated notable improvements in physical function and quality of life outcomes.

Aerobic exercise positively enhances cognitive performance in patients who have suffered a stroke, both in general cognitive function as measured using the MoCA scale and in specific cognitive domains, including concentration, attention, visual-spatial and executive function (18,21,22,23). The findings of the present study are also partly in accordance with the results of previous studies (13,21,22,23). The findings indicate that combined aerobic exercise can help patients enhance general cognitive function and improves executive function, as assessed using FAB. In addition, aerobic exercise can regulate angiogenic and neurotropic growth factors, which likely facilitate neurogenesis, angiogenesis and synaptic plasticity. Aerobic exercise combined with cognitive exercise likely has synergistic or complementary effects on cognition at both the neurobiological and behavioral levels (17,20). The present study illustrated that the intervention of aerobic exercise exerted a synergistic effect on improving cognitive function in patients who had suffered a stroke.

The minimal clinically important difference (MCID) for the MoCA score in patients who have suffered a stroke is estimated to range from 1.22 to 2.15, based on both anchor-based and distribution-based methods (24). In the present study, the changes in MoCA scores before and after the intervention for each group were as follows: Intervention group, from 18.21 to 19.02; difference=0.81; control group, from 16.79 to 17.11; difference=0.32). Neither group exceeded the MCID according to both methods. It was deemed that the small sample size was a limitation. Furthermore, the participants had MCI, which may explain the limited change in the MoCA scores.

Aerobic intervention led to multiple positive outcomes simultaneously. The difference from previous studies (18,21,22), is that the present study evaluated various outcomes related to physical health and quality of life. The results indicated significant improvements in both motor function and endurance in patients who have suffered a stroke following aerobic intervention, as assessed using the FMA-LE and 6MWT. Yeh *et al* (21) conducted a similar study with 56 patients assigned to three groups: Aerobic exercise, cognitive exercise and a combination of aerobic and cognitive exercise. The of their study results revealed improvements in endurance and mobility (6MWT); however, their study did not evaluate quality of life, daily functioning, or social engagement (21). Yeh *et al* (21) suggested that sequential training may improve both general and specific cognitive domains, although the effects were insufficient to transfer to activities of daily living, quality of life or social participation. A previous systematic review suggested that cognitive improvements appeared to be limited to trained cognitive functions and do not generalize to activities of daily living (25). It was hypothesized that, once the aerobic effects are achieved at the neurobiological level, they not only have a synergistic effect on cognitive function, but also on other domains, specifically physical function and daily living functions. The results of the present study support this hypothesis. Incorporating aerobic exercise was shown to improve cognitive function, lower limb function, mobility and endurance, which, in turn enhances quality of life. Quality of life was assessed using the EQ-5D-5L instrument, which measures five dimensions. Improvements were observed in two of these dimensions: Mobility and usual daily activities.

The present study has several limitations which should be mentioned. Firstly, the sample size was relatively small, which limits generalizability and may have been influenced by various confounding factors. The present study involved an unequal sex distribution between the two groups. Considering that this is an intervention study incorporating physical activity, the sex imbalance may have influenced both the intervention process and the outcomes. Future research with larger sample sizes is thus required, along with the further exploration of how patient characteristics may affect the results of the intervention. Secondly, the cognitive training conducted on paper may have more limitations compared to similar studies conducted on computers. Lastly, the present study only evaluated the outcomes at the end of the intervention. The present study did not monitor or assess whether the effects of the sequential training could be maintained over time. This remains an unknown factor that warrants further investigation.

When comparing the findings of the present study with those of previous studies (18,21,22), it was observed that while these studies support the combined approach of cognitive and physical training, the present study differs in several ways: It focused on older adults, utilized a paper-based cognitive intervention instead of a computer-based program, and implemented a 4-week hospital program followed by 8 weeks of home-based intervention, rather than a 12-week hospital-based program. These modifications were made to better align with practical intervention programs commonly available at most healthcare facilities, as numerous patients may find it difficult to adhere to a 3-month hospital program. The home-based approach, with monitoring, helps patients establish a routine that can be maintained after the intervention ends. Nevertheless, similar findings in cognitive and physical outcomes highlight the consistency of the combined training approach across various settings.

In conclusion, MCI following a stroke is prevalent and significantly affects the recovery of patients. The present study found that a sequential combination of aerobic and cognitive exercise improved general cognitive function and frontal lobe executive function, physical function and quality of life. However, further studies with larger sample sizes are required to investigate the factors influencing the effectiveness of intervention in order for patients with MCI to fully benefit from the intervention.

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#### **Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

#### **Authors' contributions**

TNAN and VMP were involved in the conception and design of the study, and performed the statistical analysis of the data.

TNAN and VMP were involved in the investigative aspects of the study. TNAN and VMP were involved in the interpretation of the data. TNAN and VMP were involved in the writing of original draft of the manuscript, and the writing, reviewing and editing of the manuscript. Both authors read and agreed to the published version of the manuscript. TNAN and VMP confirm the authenticity of all the raw data.

### Ethics approval and consent to participate

The present study was approved by Hanoi Medical University under Decision No. 3963/QĐ-DHYHN, dated September 26, 2022 and Hanoi Medical University Institutional Ethical Review Board under Decision No. 1259/GCN-HDDDDNCYSH-DHYHN, dated May 7, 2024. All patients provided a written consent to participate in this study.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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