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Effects of aerobic training on cardiopulmonary fitness in patients with long COVID-19: a randomized controlled trial

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Abstract

Background Long COVID-19 is characterized by systemic deterioration of the entire body, leading to significant physical and mental disorders. Exercise training has the potential to improve persistent symptoms and cardiopulmonary functions.

Method This was a single-center, randomized, controlled trial. Twenty-four patients aged 18 to 75 years who had a history of SARS-CoV-2 infection and long COVID symptoms. Patients were randomly allocated in a 1:1 ratio to receive either a 4-week exercise training program or an attention control group. The training group participated in 12 supervised aerobic sessions on a cycling ergometer over 4 weeks. The outcomes were to assess the impact of a 4-week aerobic exercise on the persistent symptoms and cardiopulmonary fitness, the surrogate endpoints of COVID-19 recovery and cardiopulmonary health.

Results After the 4-week intervention, significant reductions were observed in the total number of symptoms in the training group. Specifically, 67.8% of patients in the training group exhibited reduced or completely resolved symptoms, in comparison to 16.7% in the control group ($P=0.013$). After adjusting for gender, significant improvements in the training group were observed for exercise time ($P_{group*time}=0.028$), maximum load ($P_{group*time}=0.01$), and peak VO_2 ($P_{group*time}=0.001$), as well as O_2 pulse ($P_{group*time}=0.042$) and maximum heart rate ($P_{group*time}=0.007$). The score of Short Form-12, depression, anxiety, perceived stress, and insomnia did not show significant changes between groups ($P_{group*time}>0.05$).

Conclusion A supervised aerobic training program has the potential to alleviate persistent symptoms and improve exercise tolerance in patients with long COVID-19. Further research is necessary to confirm these effects in a large population. This intervention could be easily implemented in non-hospital settings, potentially benefiting a broader range of individuals.

Trial registration number ClinicalTrials.gov NCT05961462. Registered on July 25, 2023.

Keywords Long COVID-19, Exercise training, Persistent symptoms, Cardiopulmonary function

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Introduction

With the World Health Organization (WHO) declaring that COVID-19 is no longer a public health emergency of international concern, focus has shifted to the management of its long-term effects. Approximately 39 to 46% of individuals who contract COVID-19 may experience a range of new-onset or persistent symptoms, including fatigue, shortness of breath, cough, exercise intolerance, chest pain, and more [1]. These symptoms manifest within 3 months after infection and persist for over 2 months, significantly impacting daily life activities without any other identifiable cause, leading to the commonly recognized conditions referred to as "long COVID-19" [2].

Long COVID-19 is a systemic condition that affects multiple organ systems, leading to severe physical and functional impairments [3]. Psychological manifestations including depression, anxiety, post-traumatic stress disorder, and high perceived stress are also frequently reported [4]. These prevalent symptoms may be associated with the short- or long-term decline in exercise capacity caused by organ and tissue damage in the myocardium, lungs, nervous system, and peripheral muscle tissue [5–7]. It is worth noting that despite the availability of vaccines and medical treatments, effectively managing the adverse consequences of COVID-19 remains a challenging task.

Given the central role of exercise tolerance in patients with long COVID-19, exercise rehabilitation is emerging as a potentially vital intervention for this condition [8]. Aerobic exercise, in particular, has been shown to significantly enhance physical abilities and improve the quality of life in individuals with various chronic diseases [9]. It positively affects metabolism, pulmonary function, cardiovascular health, neurocognitive function, and musculoskeletal conditions [10–12]. Studies indicate that exercise rehabilitation can improve physical function and mental health and alleviate persistent symptoms in COVID-19 survivors [13, 14]. However, most studies on long COVID-19 patients have concentrated on pulmonary rehabilitation interventions and assessments such as pulmonary function tests, the 6-min walk test, or the sit-to-stand test, while rare studies conducted aerobic exercise training guided by oxygen uptake from CPET assessment [15–17]. Although it has been suggested that a 4-week exercise program may yield similar improvements in exercise capacity and quality of life as longer rehabilitation programs [18–21], the effectiveness of such short-term aerobic exercise training in improving long COVID-19 symptoms and cardiopulmonary function remains unclear. Therefore, we hypothesize that a tailored 4-week exercise training program can alleviate persistent symptoms and improve cardiopulmonary function in long COVID-19 patients.

Materials and methods

Study design and randomization

This was a single-center, parallel-group, open-label, randomized, controlled trial. This study was registered at ClinicalTrials.gov (NCT05961462), approved by an ethical review board by the Ethics Review Committee (No. KY2023-053), and was conducted according to the Consolidated Standards of Reporting Trials extension checklist: CONSORT-Surrogate [22].

Eligible and consenting patients were randomized to training or attention control groups in a 1:1 ratio (block randomization). An independent, blinded research used a computer to generate a random sequence. Sequentially numbered, opaque, sealed envelopes (SNOSE) were provided to the trial assistant who arranges patient attendance and appointments.

Participants

The study recruited adult patients aged 18 to 75 years from January to July 2023 in the cardiac rehabilitation clinic. Eligible patients were those who had a history of SARS-CoV-2 infection, occurring 3 months from the onset of COVID-19, and presented with symptoms persisting for at least 2 months, without any alternative diagnosis to explain these symptoms. At least one of the following conditions is present: cough, dizziness, fatigue, cognitive impairment (memory loss, loss of concentration, and slow thinking), palpation, chest tightness or pain, muscle pain, vision disturbance, dyspnea, diarrhea, anosmia/ageusia, insomnia, hair loss, voice change, or other new symptoms after COVID-19 infection. Tested positive for COVID-19 quantitative RT-PCR or antigen kit and turned negative for at least 4 weeks before inclusion. Exclusion criteria included patients who have conditions that may be worsened by exercise, such as acute cardiac insufficiency, exercise-induced asthma, or epilepsy. Physical disabilities are caused by bone and joint or neuromuscular diseases. Patients are complicated with other serious diseases (such as unstable angina, resting oxygen saturation < 93%, untreated heart failure, uncontrolled arrhythmia, uncontrolled hypertension, and uncontrolled type 2 diabetes). Women are also ineligible if they are pregnant or lactating. Written informed consent was obtained from all patients.

Intervention

Tailored and supervised exercise training sessions were conducted 3 times per week at the cardiac rehabilitation center in Guangdong Provincial People's Hospital. The training group underwent a 4-week program consisting

of 12 supervised aerobic training sessions on a cycling ergometer, with continuous monitoring of heart rate, blood pressure, and blood oxygen saturation.

The exercise intensity was personalized based on individuals' peak VO_2 and peak power (peak WR), which were determined through cardiopulmonary exercise testing (CPET). Two aerobic training protocols were employed, moderate-intensity interval training (MIIT) and high-intensity interval training (HIIT). Both began with a 5-min warm-up. HIIT and MIIT protocols have been validated for their safety and efficacy in populations, which are common modalities for exercise training studies [21, 23–26].

In the MIIT protocol, the initial session's intensity was set at 40% of peak WR for 8 min, followed by a 2-min rest, repeated for 4 cycles (RPE12-14). Subsequently, intensity increased to 50% of peak WR for 4 sessions and 55% for the final 4 sessions (see Supplement Fig. S1A). In the HIIT protocol, the initial 4 sessions mirrored MIIT, followed by an intensity increase to 80% of peak WR for 30-s cycles with 30-s rest, totaling 20–25 cycles. After 4 sessions, intensity rose to 85% and then 90% of peak WR, maintaining the same cycle duration and intervals. Repetitions increased gradually from 20 to 25 (RPE15-17) (see Supplement Fig. S1B). Importantly, total energy expenditure remained consistent across both groups. A professional CR team with a cardiologist, a nurse, and a physician supervised the exercise program in the hospital, and patients received encouragement from team members via telephone or WeChat to ensure attendance.

Control patients were informed to follow the guideline-based recommendations for a healthy lifestyle and WHO guideline: Self-management after COVID-19 Related Illness [3, 27, 28]. Control patients were contacted by telephone or WeChat at 2 and 4 weeks to ensure a reassessment 4 weeks later. Patients in the intervention and control groups with cardiovascular risk factors or cardiovascular disease were treated by professional cardiologists following the guidelines for underlying disease.

Measurements and outcomes

All the interested outcomes were assessed in the same laboratory at baseline and 4 weeks later. The change of persistent symptoms and physical fitness were surrogate outcomes to evaluate the efficacy of exercise training.

Severity of symptoms

Improvements in persistent symptoms were defined as a reduction or disappearance of symptoms assessed using a designed questionnaire at 4 weeks compared to baseline [14, 29]. The total number of long COVID symptoms was quantified at baseline and 4 weeks.

Health-related quality of life (HRQoL) was measured with the Short Form-12 Health Survey, generating Physical Component Summary (PCS-12) and Mental Component Summary (MCS-12) scores, ranging from 0 (poor health) to 100 (excellent health) [30–33].

Depression and anxiety levels were evaluated by using the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) scales, respectively, with higher scores indicating greater severity [34, 35]. The Perceived Stress Scale was used to measure stress levels, with higher scores indicating elevated stress [36]. Insomnia severity was assessed by using the Insomnia Severity Index (ISI) scale, categorized as 0–7 points (normal sleep), 8–14 points (subclinical insomnia), 15–21 points (moderate insomnia), and 22–28 points (severe insomnia) [37].

Cardiopulmonary fitness and pulmonary function

All patients completed a symptom-constrained maximum load exercise test on a cycle ergometer (JAEGER, Germany) while reporting their rate of perceived exertion (RPE). The test followed a Ramp protocol with power ergometer speed maintained at 55–65 r/min. Electrocardiogram (ECG), gas exchange, blood pressure, and SpO_2 were monitored during warm-up, exercise, and recovery phases. Calibration adhered to manufacturer specifications, and gas exchange and ventilatory parameters were continuously recorded.

Cardiopulmonary fitness, including peak oxygen uptake (peak VO_2), oxygen uptake of anaerobic threshold (AT VO_2), respiratory exchange ratio (RER), O_2 pulse, slope of ventilatory equivalent for carbon dioxide (VE/VCO_2), pulmonary ventilation (VE), and $\Delta VO_2/\Delta$work power ($\Delta VO_2/\Delta WR$), was assessed. Pulmonary function was evaluated by a computer-based spirometry system, including forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. The CPET procedures followed the American Thoracic Society (ATS) standard guideline [38].

Statistics

Based on the outcomes of a previous exercise training study, the sample size was calculated. After a 4-week exercise training, the peak oxygen uptake was improved significantly at 18.66 ± 2.26 mL/kg/min in the training group compared to 14.3 ± 2.22 mL/kg/min in the control group [39]. To minimize both false positive and false negative errors, the type-I error rate (α) is set at 0.01 and the type-II error rate is set at 0.1. The sample size of each group was estimated to be 10 per group. Taking a 20% drop-off rate into account, we finally recruited 12 patients per group ($N = 24$).

Analyses were performed on an intention-to-treat (ITT) basis. Descriptive data are presented as mean ± SD or median (1st, 3rd quartile) for continuous variables or as frequency and percentage for categorical variables. Changes in frequency outcomes were analyzed by using the X^2 test or Fisher's exact test. A linear mixed model using maximum likelihood was performed to investigate the group, time, and their interaction effects between the training and control groups from baseline to 4 weeks. Gender was included in the model as a covariate for adjustment. "Group" and "time" were designated as fixed factors and "patient" as a random factor. Missing values less than 5% were imputed using the sequence mean. The significance level was set at $P \leq 0.05$. Analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY).

Results

Patients

Twenty-four patients exhibiting long COVID-19 symptoms were randomized into the exercise group and control group. All the patients completed the baseline characteristics, pre to post-coropulmonary function, and mental status assessments. There was 1 patient who missed the baseline mental health assessment, for which the research team imputed the relevant data (Fig. 1). Patients in the intervention group finished a minimum of 12 exercise training sessions, with a median count of 12.5 (interquartile range = 2) sessions. Adverse events were recorded and shown in Supplemental Table S1. No patients withdrew from the study.

Overall, patients were 46.5 ± 15.1 years old, and 58.3% female sex ($n = 14$). The median time from COVID-19 diagnosis to study enrollment was 14 weeks. Table 1 shows demographic, clinical characteristics, and baseline COVID-19 symptoms. Each patient exhibited at least one long COVID-19 symptom and a maximum of six symptoms at baseline. Cough, fatigue, cognitive impairment, chest discomfort, and palpation were the most common symptoms. There were 9 (37.5%) patients who had the habit of regular exercise (except for stroll). All the patients in the training group did not drink or smoke. Training RPE and heart rate were recorded and shown in Supplemental Table S2.

Persistent symptoms

The distribution of the symptoms between the two groups pre-post training is depicted in Fig. 2. Notably,

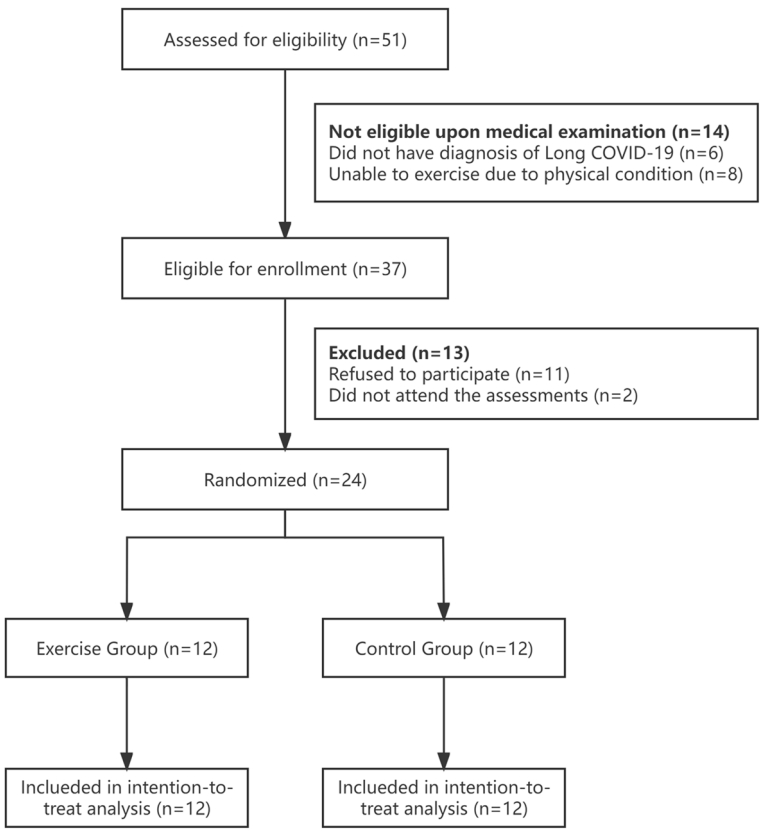

Fig. 1 CONSORT flow diagram

Table 1 Baseline characteristics of the patients

Characteristics	Exercise $N=12$	Control $N=12$
Age, years	46.85 ± 15.26	43.42 ± 14.96
Women, *n* (%)	4 (33.3)	10 (83.3)
Height, cm	167.13 ± 9.17	160.13 ± 7.57
Weight, kg	69.54 ± 16.83	59.04 ± 8.45
BMI, kg/m^2	23.46 ± 9.47	23.05 ± 3.01
Work state, *n* (%)		
Employment	6 (50)	5 (41.7)
Unemployment	6 (50)	7 (56.3)
Marriage state, *n* (%)		
Married or living with partner	10 (83.3)	6 (50)
Never married	1 (8.3)	4 (33.3)
Widowed, divorced, separated	1 (8.3)	2 (16.7)
Education level, *n* (%)		
Below high school	2 (16.7)	1 (8.3)
High school graduate or GED	2 (16.7)	0 (0)
Some college or above	8 (66.7)	11 (91.7)
Comorbidity, *n* (%)		
HBP	2 (16.7)	2 (16.7)
DM	1 (8.3)	0 (0)
Hyperlipidemia	4 (33.3)	2 (16.7)
CVD	10 (83.3)	8 (67.8)
Other	2 (16.7)	2 (16.7)
Lifestyle, *n* (%)		
Regular exercise (except for stroll), *n* (%)	4 (33.3)	5 (41.7)
Non-drinker, *n* (%)	12 (100)	12 (100)
Non-smoker, *n* (%)	12 (100)	11 (91.7)
COVID-19 infection symptom, *n* (%)		
Total number	20	17
Cough	2 (16.7)	3 (25.0)
Fatigue	3 (25.0)	3 (25.0)
Insomnia	1 (8.3)	1 (8.3)
Cognitive impairment	4 (33.3)	3 (25.0)
Palpitation	2 (16.7)	4 (33.3)
Chest pain/tightness	4 (33.3)	2 (16.7)
Dyspnea	1 (8.3)	0
Muscular pain	1 (8.3)	1 (8.3)
Anosmia/ageusia	1 (8.3)	0
Voice change	1 (8.3)	0
Exercise mode		
HIIT	6 (50.0)	–
MIIT	6 (50.0)	–

Data displayed as mean ± SD, or as frequency and percentage (%)

BMI body mass index, *HBP* high blood pressure, *DM* diabetes mellitus, *CVD* cardiovascular disease, *HIIT* high-intensity interval training, *MIIT* moderate-intensity interval training

the total number of symptoms in the training group was significantly reduced after 4 weeks, with improvements in fatigue, chest discomfort, and cognitive impairment (Table 2). There were 8 (67.8%) patients in the training group who had reduced or disappeared symptoms after 4 weeks, compared with only 2 (16.7%) patients in the control group ($X^2=6.17$, $P=0.013$) (Fig. 2).

After 4 weeks, the score of SF-12, depression, anxiety, perceived stress, and insomnia did not show any significant change between groups (all $P_{group*time}>0.05$), while the depression score significantly decreased in the training group ($P<0.05$) (Table 2).

Cardiopulmonary fitness and pulmonary function

Patients in exercise and control groups performed their best during the pre and post-CPET, in which the average RER was greater than 1.1. Following the 4-week supervised program, we identified significant differences in cardiopulmonary function between the training and control group. Exercise time increased by 80.34s and 20.83 s in the training and control groups ($P_{group*time}=0.028$). Maximum load also increased in both groups (mean change, watt: 20.25 vs. 3.83; $P_{group*time}=0.01$) (Table 3). Significant improvement between groups was observed for peak VO_2 in the training group (mean change, mL/kg/min: 4.64 vs. − 1.06; $P_{group*time}=0.001$) and AT VO_2 (mean change, mL/kg/min: 2.33 vs. − 0.37; $P_{group*time}=0.041$). O_2 pulse (mean change, %: 6.92 vs. 2.58; $P_{group*time}=0.042$) and maximum heart rate (mean change, bpm: 12 vs. 4; $P_{group*time}=0.007$) also revealed a significant increase in the training group from baseline to 4 weeks. No significant differences in changes between groups were detected for pulmonary function (Table 3). In the exercise group, no significant difference in the change of peak VO_2 was found between HIIT and MIIT intervention from baseline to 4 weeks ($P_{mode*time}>0.05$).

Discussion

To our knowledge, this study is the first to evaluate the effects of a 4-week supervised aerobic training on persistent symptoms and cardiopulmonary capacity in long-term COVID-19 patients. The main findings demonstrated the positive effects of this intervention on alleviating long COVID-19 symptoms and enhancing exercise capacity compared to the control group engaged in self-management. Nevertheless, no significant differences were observed in the improvement of SF-12, mental health, insomnia, or pulmonary function parameters.

Exercise training can alleviate persistent long COVID-19 symptoms, particularly fatigue, chest discomfort, and cognitive impairment. Fatigue and "brain fog" are the most common long-term symptoms after a COVID-19 infection [40]. SARS-CoV-2 infection induces chronic neuroinflammation and the accumulation of toxic substances within the central nervous system while simultaneously infecting skeletal muscles and neuromuscular

Table 2 Effects of aerobic training and usual care on quality of life and mental health in patients with long COVID-19

	Training ($N=12$)			Control ($N=12$)			*P* value	
	Baseline (mean ± SD)	4 weeks (mean ± SD)	Mean within-group difference (95% CI)	Baseline (mean ± SD)	4 weeks (mean ± SD)	Mean within-group difference (95% CI)	Time	Group*time
MCS	43.19 ± 8.10	43.06 ± 3.83	−0.13 (−5.76, 5.50)	38.12 ± 5.67	37.63 ± 5.67	−0.50 (−5.62, 4.63)	0.846	0.910
PCS	41.82 ± 3.00	42.37 ± 3.91	0.55 (−2.13, 3.23)	43.83 ± 5.50	43.83 ± 5.98	0.01 (−4.78, 4.79)	0.819	0.831
PHQ-9	4.75 ± 2.99	3.25 ± 3.28	−1.50 (−2.76, −0.24)*	7.75 ± 4.39	6.67 ± 4.74	−1.09 (−3.42, 1.25)	0.035	0.721
GAD-7	3.50 ± 3.34	1.67 ± 2.46	−1.83 (−4.07, 0.40)	6.33 ± 4.81	5.42 ± 4.03	−0.92 (−3.47, 1.63)	0.076	0.540
Perceived stress	11.42 ± 4.42	9.33 ± 4.42	−2.08 (−4.31, 0.14)	15.33 ± 7.27	14.58 ± 5.52	−0.75 (−3.24, 1.74)	0.067	0.367
Insomnia status	8.25 ± 5.08	7.00 ± 5.17	−1.25 (−4.26, 1.76)	11.75 ± 4.61	10.50 ± 6.14	−1.25 (−3.76, 1.26)	0.165	> 0.99
Persistent symptoms[a], No	20	7		17	18		0.153	0.097
Cough	2 (16.7)	1 (8.3)	–	3 (25.0)	2 (16.7)	–	–	–
Fatigue	3 (25.0)	0		3 (25.0)	2 (16.7)			
Insomnia	1 (8.3)	1 (8.3)		1 (8.3)	1 (8.3)			
Cognitive impairment	4 (33.3)	3 (25.0)		3 (25.0)	4 (33.3)			
Palpitation	2 (16.7)	1 (8.3)		4 (33.3)	4 (33.3)			
Chest pain/ tightness	4 (33.3)	0		2 (16.7)	2 (16.7)			
Dyspnea	1 (8.3)	0		0	0			
Muscular pain	1 (8.3)	0		1 (8.3)	1 (8.3)			
Anosmia/ ageusia	1 (8.3)	0		0	0			
Voice change	1 (8.3)	0		0	0			
Vision disturbance	0	1 (8.3)		0	2 (16.7)			
Symptom improvement[b], No	8 (67.8%)			2 (16.7%)				

Data displayed as mean ± SD, or as frequency and percentage (%)

Values were displayed as mean ± SD unless noted after the parameters

MCS mental component summary, *PCS* physical component summary, *PHQ-9* Patient Health Questionnaire-9, *GAD-7* Generalized Anxiety Disorder-7

* Significant difference from baseline, $P<0.05$

[a] Persistent symptoms has been shown as total numbers

[b] Number of patients whose persistent symptoms decreased or disappeared after 4 weeks

junctions. These factors may collectively contribute to the occurrence of fatigue, muscular pain, cognitive impairment, and psychological disorders [41–43]. Aerobic training may mitigate these issues through the synergistic effects of mitochondrial function boost, cardiorespiratory system, central nervous system function, and peripheral muscle fiber repair [9, 44]. Research indicates that a 6-week home-based rehabilitation program has shown improvements in dyspnea and fatigue among individuals with persistent COVID-19 symptoms [45]. A systematic review of exercise therapy for chronic fatigue syndrome suggests that exercise therapy does not worsen symptoms and leads to improvements in fatigue, sleep, and physical function [46]. Additionally, exercise plays a role in enhancing various neurocognitive abilities, such as memory and learning, attention, inhibitory control, and cognitive flexibility [47]. After 4 weeks of exercise training in the intervention group, the number of physical symptoms such as fatigue and muscular pain symptoms significantly improved, and there was a tendency

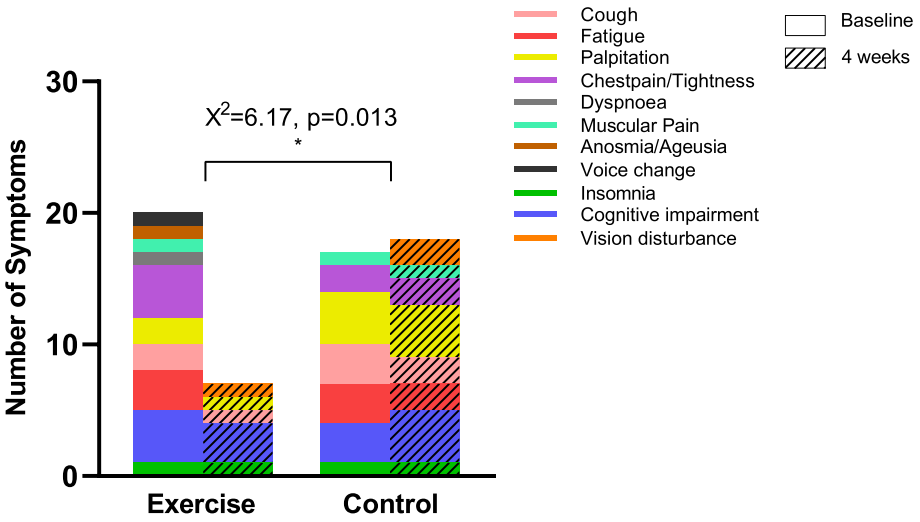

Fig. 2 Distribution and changes in persistent symptoms pre to post exercise training. *Significant difference in symptom improvement or disappearance pre to post exercise training between the exercise and control group

towards reduced cognitive impairment compared to the control group. Other symptoms were less prevalent in either group, but the overall number of symptoms decreased after exercise intervention.

Chest discomfort is a common symptom among long COVID-19 patients in this study. Notably, some patients had underlying cardiovascular disease, yet the chest discomfort and palpitation investigated in this study were newly developed after COVID-19 infection. Potential pathological responses include acute cardiac injury, viral myocarditis, and autonomic dysfunction in individuals with COVID-19 [48]. In our study, the training group showed reduced chest discomfort, but palpitations did not significantly change due to the sample size limitation. Non-pharmacological measures should be considered as first-line treatment options, especially aerobic progressive exercise training [49]. Aerobic training may help regulate autonomic function to improve heart rate variability, enhance mitochondrial function, improve endothelial function, and release myokines from skeletal muscles to enhance cardiovascular function [50, 51]. Additionally, the multidimensional improvements achieved through exercise therapy may reduce patients' focus on persistent symptoms.

Exercise-trained patients did not exhibit greater improvement in quality of life and mental health compared to the control group. However, the depression symptoms have been relieved in the training group over the exercise duration. In line with a similar study, it observed improvements only in depression after exercise [13]. Evidence supports that aerobic exercise improves depression and anxiety-related outcomes compared with attention control conditions [52]. Potential mechanisms could involve enhanced neural plasticity through neurobiological processes and behavioral learning of self-regulation skills [53]. A study of the effects of home-based exercise in patients with long COVID showed patients in the training group had higher scores in the physical component summary of SF-36 than those in the control group [14]. Our study showed similar results in physical function. In contrast to our results, a 4-week short-term rehabilitation study demonstrated significant improvements in anxiety, depression, and quality of life among patients with cardiac disease [18]. These benefits were likely attributable to the higher intensity and frequency of the exercise program, which involved 3-h daily sessions and 5.5 days per week.

Reduced exercise capacity is a prevalent feature following COVID-19. Possible reasons for the decrease may involve changes in both central (including cardiac, pulmonary, and autonomic functions) and peripheral factors (metabolic parameters). This study identified that compared to the control group, cardiopulmonary fitness and peak VO_2/predicted of patients in the training group showed a substantial improvement. Peak VO_2 is a robust predictor of mortality and a risk factor for the progression of various diseases [54]. Exercise rehabilitation programs can decrease mortality rates, readmission rates, and enhance cardiopulmonary health and functional status by improving blood circulation, increasing oxygen delivery to tissues, and enhancing pulmonary capacity [55–57]. Given the research that suggests that peripheral limitation in oxygen extraction is the main determinant of peak VO_2 in patients with long COVID-19 [58, 59], the significant improvement in peak VO_2 in our population is possibly the main mechanism that explains symptomatic

Table 3 Effects of aerobic training and usual care on cardiorespiratory fitness and pulmonary function parameters in patients with long COVID-19

	Training ($N=12$)			Control ($N=12$)			*P* value	
	Baseline (mean ± SD)	4 weeks (mean ± SD)	Mean within-group difference (95% CI)	Baseline (mean ± SD)	4 weeks (mean ± SD)	Mean within-group difference (95% CI)	Time	Group*time
Cardiopulmonary fitness								
Exercise time	493.33 ± 123.24	573.67 ± 83.72	80.33 (40.69, 119.97)*	475.83 ± 104.05	496.66 ± 101.83	20.83 (− 22.30, 63.97)	< 0.001	0.028
Max. load	120.25 ± 42.58	140.50 ± 44.95	20.25 (9.64, 30.86)*	111.75 ± 42.52	115.58 ± 41.36	3.83 (− 4.45, 12.11)	< 0.001	0.010
RER	1.33 ± 0.15	1.29 ± 0.13	− 0.04 (− 0.17, 0.10)	1.19 ± 0.10	1.25 ± 0.075	0.06 (0.003, 0.11)	0.816	0.126
Peak VO_2, mL/min	1400.92 ± 417.59	1713.75 ± 544.19	312.83 (158.61, 467.06)*	1488.585 ± 497.32	1407.58 ± 392.00	− 81.00 (− 228.52, 66.52)	< 0.001	0.019
Peak VO_2, mL/kg/min	20.49 ± 3.28	25.13 ± 5.12	4.65 (2.21, 7.08)*	25.30 ± 7.83	24.24 ± 6.47	− 1.07 (− 3.60, 1.46)	< 0.001	0.001
Peak VO_2, %pred	68.67 ± 15.92	85.67 ± 19.58	17.00 (7.10, 26.90)*	85.25 ± 20.87	83.83 ± 18.92	− 1.42 (− 12.76, 9.92)	0.001	0.010
AT VO_2, mL/min	778.25 ± 174.56	963.00 ± 357.75	184.75 (11.12, 358.38)*	869.42 ± 270.09	832.75 ± 222.99	− 36.67 (− 157.58, 84.24)	0.009	0.024
AT VO_2, mL/kg/min	11.71 ± 2.34	14.03 ± 3.13	2.33 (0.02, 4.63)*	14.60 ± 3.09	14.23 ± 3.15	− 0.37 (− 2.42, 1.69)	0.189	0.056
AT VO_2, %pred	39.75 ± 12.17	47.75 ± 10.62	8.00 (− 0.54, 16.54)	50.08 ± 10.72	49.67 ± 10.36	− 0.42 (− 8.28, 7.45)	0.168	0.109
VE, L/min	56.67 ± 21.52	64.71 ± 21.37	8.04 (− 0.31, 16.39)	50.51 ± 14.07	50.81 ± 12.92	0.31 (− 5.39, 6.00)	0.087	0.091
VE/VCO_2 slope	28.57 ± 3.77	26.90 ± 4.13	− 1.66 (− 4.09, 0.76)	27.42 ± 3.50	28.09 ± 4.08	0.90 (− 1.65, 3.45)	0.671	0.107
O_2 pulse, mL/bpm	10.14 ± 3.22	10.95 ± 3.00	0.81 (− 0.11, 1.72)	9.48 ± 3.23	9.17 ± 2.49	− 0.32 (− 1.42, 0.79)	0.466	0.084
O_2 pulse, % pred	81.33 ± 14.72	88.25 ± 10.49	6.92 (− 4.87, 18.70)	84.83 ± 34.55	93.17 ± 22.59	2.58 (− 9.53, 14.70)	0.359	0.042
$\Delta VO_2/\Delta WR$	9.56 ± 1.80	10.10 ± 1.65	0.44 (− 1.13, 2.17)	10.66 ± 1.25	10.20 ± 1.56	− 0.56 (− 1.02, − 0.12)	0.960	0.159
HRmax, bpm	140 ± 16	152 ± 19	12 (3, 21)*	160 ± 22	156 ± 25	− 4 (− 12, 4)	0.001	0.007
RPE 6–20, median	18 (16.5, 18)	18 (16, 18)	–	18 (18, 18)	18 (16, 18)	–	0.075	0.212
Pulmonary function test								
FVC, L	3.58 ± 1.07	3.59 ± 1.03	0.01 (− 0.14, 0.16)	2.88 ± 0.20	2.94 ± 0.17	0.07 (− 0.19, 0.32)	0.258	0.305
FVC, %	96.40 ± 12.68	95.00 ± 11.8	− 1.39 (− 6.39, 3.61)	92.18 ± 17.42	95.46 ± 10.15	3.64 (− 4.57, 11.84)	0.607	0.241
FEV1, L	3.12 ± 0.92	3.09 ± 0.90	− 0.03 (− 0.10, 0.05)	2.54 ± 0.51	2.55 ± 0.53	0.12 (− 0.17, 0.43)	0.520	0.307
FEV1, %	100.97 ± 11.72	98.83 ± 11.13	− 2.14 (− 5.36, 1.08)	95.82 ± 16.62	97.18 ± 10.35	2.37 (− 5.29, 10.04)	0.951	0.224
FEV1/FVC	87.18 ± 5.22	86.24 ± 4.21	− 0.94 (− 4.02, 2.13)	88.67 ± 2.52	85.17 ± 3.51	− 3.12 (− 5.86, − 0.39)	0.037	0.235
FEV1/FVC,%	107.75 ± 7.55	108.17 ± 5.37	0.41 (− 5.76, 6.59)	108.64 ± 6.73	105.46 ± 2.52	− 2.52 (− 6.94, 1.91)	0.518	0.369

Data displayed as mean ± SD, median (IQR), or as frequency and percentage (%)

Values were displayed as mean ± SD unless noted after the parameters

RER respiratory exchange ratio, *VO_2* oxygen uptake, *AT* anaerobic threshold, *WR* work rate, *HR* heart rate, *RPE* rate of perceived exertion, *FVC* forced vital capacity, *FEV1* forced expiratory volume in the first second, *PIF* peak inspiratory flow, *PEF* peak expiratory flow

* Significant difference from baseline

improvement in the number of patients who reported dyspnea, fatigue, and chest discomfort.

After 4 weeks, the training group exhibited significant improvements in both maximum heart rate, load time, and power during the CPET test, indicating an enhancement in patients' exercise capacity. At the same time, O_2 pulse demonstrated an improvement in the training group, while O_2 uptake and heart rate can directly impact the calculation of O_2 pulse. The capacity of mitochondria to utilize O_2 is enhanced after exercise training, resulting in a higher O_2 pulse, even though stroke volume might not have changed.

Based on the assessment of each patient's CPET and clinical symptoms, we implemented either HIIT or MIIT protocols. Both training modalities have been demonstrated to be safe and effective in improving patients' physical function [24, 25, 60, 61]. While patients undergoing MIIT may not tolerate the high-intensity demands of HIIT, the overall energy expenditure between the HIIT and MIIT groups remained consistent.

A secure and effective 4-week aerobic training program may alleviate persistent symptoms and enhance cardiopulmonary fitness in individuals with long COVID-19. However, this study is not without limitations. The sample size may be considered relatively small (although adequately powered for the main outcome). We did not conduct intergroup comparisons for individual persistent symptoms separately. Additionally, we conducted a 4-week short-term training program which has been shown to have the potential to improve physical function [21], but further long-term monitoring of changes in physical function, mental health, and quality of life is needed. However, altogether, the overall reductions in symptoms and improvement in cardiopulmonary function suggest that there is a noteworthy indication to conduct a larger study, which potentially leads to more conclusive results. Besides, although we did not use a detailed scale assessment, the baseline exercise habits were relatively balanced between the two groups. Finally, we did not conduct stratified analysis for patients combined with comorbidity, which could potentially modify our findings.

Conclusions

The tailored and supervised 4-week aerobic training program alleviated persistent symptoms and improved exercise tolerance in patients with long COVID-19. However, no significant improvements were found in pulmonary function and quality of life. Exercise may play a substantial role in the recovery of cardiopulmonary functions and mental health when suffering long COVID-19. In the future, multicenter studies with larger sample sizes should confirm these effects and address the efficacy of different exercise modes among populations enduring long COVID-19 symptoms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08473-3.

Supplementary Material 1. Supplemental Fig. S1. Exercise intervention protocol. A: Moderate-intensity interval training (MIIT) protocol; B: High-intensity interval training (HIIT) protocol.

Supplementary Material 2. Supplemental Table S1. Adverse events during exercise training. Supplemental Table S2 Exercise intensity during 4 weeks.

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Authors' contributions
BQB, MYX, YYY, HM, and QSG contributed to the study design. BQB, HFZ, YXL, and FYL contributed to the study conduction. BQB, MYX, and YTL contributed to data collection. BQB, and YYY contributed to the data analysis. BQB, MYX, QSG, and HM contributed to the manuscript draft. All authors reviewed the data analyses and approved the final version of the submitted research, and were responsible for the decision to submit the manuscript.

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Availability of data and materials
The datasets obtained and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was given by the medical ethics committee with the following reference number: GDER: KY2023-053. All patients gave written informed consent.

Consent for publication
All authors agree to the submission and publication of the article.

Competing interests
The authors have no conflicts of interest relevant to this article.

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