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RESEARCH ARTICLE

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Effects of continuous aerobic training associated with resistance training on maximal and submaximal exercise tolerance, fatigue, and quality of life of patients post-COVID-19

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Abstract

Background and Purpose: Dyspnea, fatigue, and reduced exercise tolerance are common in post-COVID-19 patients. In these patients, rehabilitation can improve functional capacity, reduce deconditioning after a prolonged stay in the intensive care unit, and facilitate the return to work. Thus, the present study verified the effects of cardiopulmonary rehabilitation consisting of continuous aerobic and resistance training of moderate-intensity on pulmonary function, respiratory muscle strength, maximum and submaximal tolerance to exercise, fatigue, and quality of life in post-COVID-19 patients.

Methods: Quasi-experimental study with a protocol of 12 sessions of an outpatient intervention. Adults over 18 years of age ($N = 26$) with a diagnosis of COVID-19 and hospital discharge at least 15 days before the first evaluation were included. Participants performed moderate-intensity continuous aerobic and resistance training twice a week. Maximal and submaximal exercise tolerance, lung function, respiratory muscle strength, fatigue and quality of life were evaluated before and after the intervention protocol.

Results: Cardiopulmonary rehabilitation improved maximal exercise tolerance, with 18.62% increase in peak oxygen consumption (VO2peak) and 29.05% in time to reach VO_2peak. VE/VCO_2slope reduced 5.21% after intervention. We also observed increased submaximal exercise tolerance (increase of 70.57 m in the 6-min walk test, p = 0.001), improved quality of life, and reduced perceived fatigue after intervention.

Discussion: Patients recovered from COVID-19 can develop persistent dysfunctions in almost all organ systems and present different signs and symptoms. The complexity and variability of the damage caused by this disease can make it difficult to target rehabilitation programs, making it necessary to establish specific protocols. In this work, cardiopulmonary rehabilitation improved lung function, respiratory muscle strength, maximal and submaximal exercise tolerance, fatigue and quality of life. Continuous aerobic and resistance training of moderate intensity proved to be effective in the recovery of post-COVID-19 patients.

KEYWORDS
COVID-19, exercise tolerance, fatigue, long-COVID-19, quality of life, rehabilitation

1 | INTRODUCTION

Severe COVID-19 impairs lung, physical, and mental functions (Goërtz et al., 2020). Dyspnea, fatigue, and reduced exercise tolerance are also common in patients post-COVID-19 (Cortés-Telles et al., 2021). The long-term effects of these symptoms in patients with acute respiratory syndrome after hospital discharge are called long-COVID (Iqbal et al., 2021). The National Institute for Health and Care Excellence guideline defines long-COVID as signs and symptoms that continue or develop after acute COVID-19. Includes both ongoing symptomatic COVID-19 (4–12 weeks) and post-COVID-19 Syndrome (>12 weeks) (Excellence National Institute for Health and Clinical Excellence, 2022).

Decreased lung function is associated with damage caused by both mechanical ventilation and pathophysiology of virus response (Cortés-Telles et al., 2021). Also, prolonged immobility and use of sedatives are associated with respiratory and peripheral muscle weakness. All these factors reduce functional capacity and quality of life of patients post-COVID-19 (Torres-Castro et al., 2021).

In this context, rehabilitation is important for treating patients post-COVID-19, especially in those who have been hospitalized. The benefits of physical exercise in dependence and community reintegration of patients are well documented in other populations (Anderson et al., 2016; Araújo et al., 2019; Rugbjerg et al., 2015). In patients post-COVID-19, rehabilitation may improve functional capacity, reduce deconditioning after prolonged stay in the Intensive care unit (ICU), facilitate return to work, and improve quality of life (Wasilewski et al., 2021).

However, few studies addressed intensity, duration, and effects of aerobic and resistance training in patients post-COVID-19 (Daynes et al., 2021; Liu et al., 2020; Mayer et al., 2021). Thus, the present study verified the effects of a cardiopulmonary rehabilitation program consisting of continuous moderate-intensity aerobic and resistance training on lung function, respiratory muscle strength, maximal and submaximal exercise tolerance, fatigue, and quality of life of patients post-COVID-19.

2 | METHODS

This is a quasi-experimental study performed between March and September 2021 and conducted with a convenience sample of patients post-COVID-19. Assessments and data collection, such as clinical history and associated comorbidities, were performed at the Laboratory of Cardiopulmonary Physiotherapy of the Federal University of Pernambuco. Interventions took place at Physical Therapy Outpatient Clinic (Post-ICU Rehabilitation) of Hospital das Clínicas in Pernambuco. The study was approved by the human research ethics committee of the Federal University of Pernambuco (number 4.598.136) and registered at clinicaltrials.gov (ID: NCT04767477). All participants signed the informed consent form following resolution 466/12 of the Brazilian National Health Council and Declaration of Helsinki. The study followed CONSORT and Standard Protocol Items: Recommendations for Interventional Trials Extension for RCTs Revised in Extenuating Circumstances (CONSERVE) guidelines (Orkin et al., 2021).

Adults aged over 18 years, diagnosed with COVID-19 using reverse transcription polymerase chain reaction test and without mental disorders. Patients were admitted with limiting sequelae from 15 days after hospital discharge or ongoing symptomatic COVID-19 up to 8 weeks of symptom permanence. Those with orthopedic limitations and unable to perform cardiopulmonary exercise tests were excluded.

2.1 | Instruments for data collection

2.1.1 | Manovacuometry

A digital manometer MVD-300 (Globalmed) assessed respiratory muscle strength. Patients used a nose clip and were instructed to sit with feet flat on floor, erect spine, and no upper limb support. Maximum inspiratory pressure (MIP) was assessed by performing a maximal and sustained inspiration from residual volume, whereas maximal expiration from total lung capacity was performed to assess maximum expiratory pressure (MEP). Predicted values for MIP and MEP were calculated according to Simões et al. (2010). Patients with MIP and MEP values of <70% of predicted were considered with inspiratory and expiratory muscle weakness, respectively (Dall'Ago et al., 2006).

2.1.2 | Spirometry

Lung function was assessed using a portable spirometer (Micro Medical Microloop MK8, England). At least three forced vital capacity (FVC) maneuvers were performed with a two-minute interval in between, according to reproducibility and acceptability criteria of the

American Thoracic Society (Graham et al., 2019). Forced vital capacity, forced expiratory volume in the first second (FEV_1) and, FEV_1/FVC were expressed as percentage of predicted for the Brazilian population (De Castro Pereira et al., 2007), while classification of ventilatory disorders followed Pereira (2002).

2.1.3 | Cardiopulmonary exercise test

Maximal functional capacity was assessed using a symptom-limited cardiopulmonary exercise test (CPET). Patients performed a ramp protocol (Weisman et al., 2003) on a treadmill (Centurium 300, Micromed, Brazil) associated with a 12-channel electrocardiogram (Micromed, Brazil). The following respiratory variables were assessed breath-by-breath using a gas analyzer (Cortex—Metalyzer II, Germany) under standard temperature, pressure, and humidity conditions: peak oxygen consumption (VO_{2peak}), VO_2 at first ventilatory threshold (VO_{2AT}), ventilatory equivalent of carbon dioxide (VE/VCO_2), slope of increase of ventilation relative to carbon dioxide production ($VE/VCO_{2\ slope}$), time to reach the first ventilatory threshold ($TVO_{2\ AT}$), time to reach VO_{2peak} ($TVO_{2\ peak}$), and recovery time of 50% of VO_{2peak} ($T_{1/2}$).

2.1.4 | Six-minute walk test

The six-minute walk test (6MWT) was performed according to the American Thoracic Society (Crapo et al., 2002). Patients walked as fast as possible in a 30 m corridor, without running, for 6 minutes. The test was interrupted if the patient reported dizziness, cramps, chest pain, severe dyspnea, sweating, or pallor.

2.1.5 | Fatigue Pictogram

Fatigue intensity and its impact after COVID-19 were assessed using the Fatigue Pictogram. This is an ordinal scale composed of two questions with five illustrations to assess fatigue intensity (I can do everything I usually do; I can do almost everything I usually do; I can do some of the things I normally do; I do what I have to do; I can do very little). Cutoff points for diagnosis or classification of fatigue intensity are not available in the literature (Mota et al., 2009).

2.1.6 | Short-form—36

The Short-form—36 was used to assess quality of life. It consists of 36 items divided into eight subscales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Final score ranges from 0 to 100, and high scores correspond to better general health status (Ciconelli et al., 1999).

2.1.7 | Patient global impression of change

The Patient Global Impression of Change (PGIC) was used to assess the degree of perceived satisfaction and importance of changes in health status. Patients can rate improvements associated with the intervention on a 7-item scale ranging from 1 (no change) to 7 (a great deal better and a considerable improvement that has made all the difference) (Dominges & Cruz, 2012).

2.1.8 | Intervention protocol

Aerobic training was prescribed between 60% and 80% of VO_2peak, assessed using CPET. Exercise was performed on a treadmill for 40 min: 5 min of warm-up, 30 min of conditioning, and 5 min of cool-down (Barker-Davies et al., 2020; Carvalho & Mezzani, 2011).

Resistance training consisted of exercises for upper (triceps, biceps, and shoulder abductors) and lower limb muscles (quadriceps, hip abductors, and sural triceps). Exercise load was 60% of one-repetition maximum, with load progression every six sessions. Exercises were performed twice a week in three sets of 8–12 repetitions, and patients were reassessed after 12 sessions.

2.1.9 | Statistical analysis

Data analysis was performed using SPSS® software (IBM Corp., USA), version 20. Shapiro-Wilk test verified data distribution. Paired *t*-test was used to analyze intragroup variables before and after intervention. McNemar's test analyzed categorical variables in both moments of the study. Cohen's d effect size was calculated and interpreted as very small (0.1), small (0.2), medium (0.5), and large (0.8) (Fritz et al., 2012). p-value < 0.05 (two-tailed) was considered significant.

3 | RESULTS

A total of 41 patients started the intervention protocol, however 26 patients completed the cardiopulmonary rehabilitation program (Figure 1). Mean age was 51.73 ± 10.41 years, and 46.20% of patients were hospitalized in the ICU. Sample characterization is presented in Table 1.

Table 2 presents lung function and respiratory muscle strength data. The percentage of patients with ventilatory disorders and respiratory muscle weakness reduced after cardiopulmonary rehabilitation program.

Maximal exercise tolerance improved with a significant increase of 18.62% in VO_2peak (19.11 ± 4.61 ml·kg^{-1}·min^{-1} vs. 22.67 ± 4.81 ml·kg^{-1}·min^{-1}; Cohen's d = 0.76, $p < 0.001$) and 29.05% in TVO_{2peak} (397.38 ± 165.60s vs. 512.85 ± 75.82s; Cohen's d = 0.96, $p = 0.001$). VE/VCO_2slope also reduced 5.21% (34.90 ± 5.13 L/min vs. 33.08 ± 4.44 L/min; Cohen's d = 0.38, p = 0.011) (Table 2), while

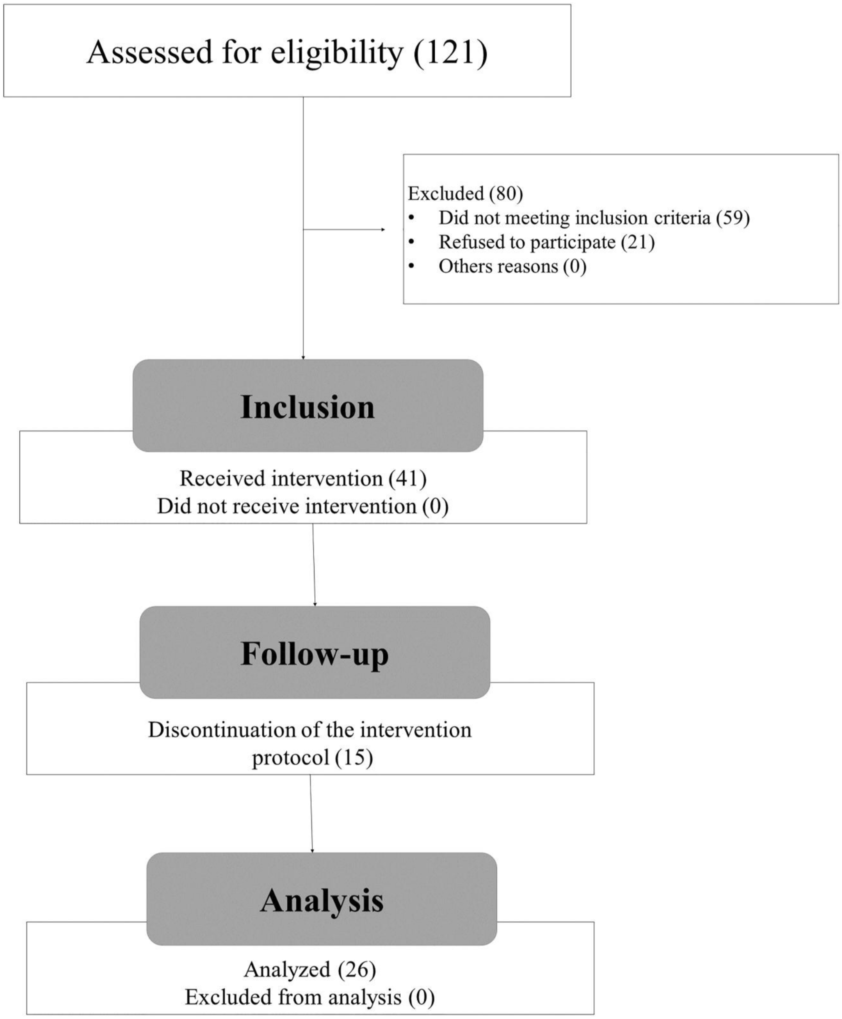

FIGURE 1 Flowchart of study sample

submaximal exercise tolerance increased 70.57 m (419.47 ± 119.72 vs. 490.04 ± 7 1.66; Cohen's d = 0.74, p = 0.001) (Figure 2).

Quality of life increased in all subscale scores. Physical functioning increased 59.37%, role emotional improved 69.49%, and total SF-36 score increased 49.53% (Table 3).

Regarding fatigue after COVID-19, 36% of patients reported being “A little bit tired” and 32% “Moderately tired”, whereas only 12% reported “I can do everything I normally do”. After cardiopulmonary rehabilitation program, 36% of patients reported being “Not at all tired” and 28% reported “I can do everything I normally do” (Figure 3).

According to PGIC, 65.4% of patients reported “Better, and a definitive improvement that has made a real and worthwhile difference“.

4 | DISCUSSION

This is the first study investigating the effects of a cardiopulmonary rehabilitation program consisting of continuous moderate-intensity aerobic and resistance training in patients post-COVID-19. This program improved respiratory muscle strength, lung function, exercise tolerance, fatigue, and quality of life. We highlight the significant improvement in VO_2peak, TVO_2peak, and quality of life and reduction in VE/VCO_2slope and fatigue after the intervention.

In this study, 39.10% of patients had restrictive and 21.70% obstructive ventilatory disorder in the initial evaluation. After intervention, this percentage was reduced due to improvements in FVC and predicted percentage of FEV_1. Respiratory muscle weakness was also reduced, with significant increase in MEP. Lung function improved after 6 weeks of respiratory rehabilitation in a clinical trial conducted with older adults post-COVID-19 (Liu et al., 2020). Moreover, similar effects have been reported in patients with chronic obstructive pulmonary disease, indicating aerobic and resistance training improve respiratory muscles strength (Chiu et al., 2020; Lee & Kim, 2019). Therefore, increased ventilation provided by physical training may affect respiratory muscles, increasing oxidative fibers and oxidative enzyme activity (Decramer, 2009).

Regarding maximal exercise tolerance, VO_2peak, TVO_2peak, and VE/VCO_2slope increased after rehabilitation. These are considered significant predictors of mortality and hospitalization related to heart disease (Arena et al., 2004). Clavario et al. (2021) highlighted the importance of evaluating VO_2peak and TVO_2peak in a study that assessed patients with COVID-19 3 months after hospital discharge. Authors observed that VO_2peak was below 85% of predicted (mean

TABLE 1 Clinical variables of patients post-COVID-19

Variables[a]	*n* = 26
Age (years)	51.73 ± 10.41
Sex (% males)	53.80
Weight (kg)	86.51 ± 20.18
Height (m)	1.64 ± 0.07
BMI (kg/m^2)	31.72 ± 6.51
Comorbidities	
Hypertension (%)	61.50
Diabetes (%)	23.10
Obesity (%)	53.80
Lung diseases (%)	26.90
CKD (%)	7.70
Hospitalized	
Nursery (%)	23.10
ICU (%)	46.20
Not hospitalized (%)	30.80

Abbreviations: BMI, Body mass index; CKD, Chronic kidney disease; ICU, Intensive care unit.
[a]Variables presented as mean ± standard deviation.

TABLE 2 Lung function, respiratory muscle strength, and cardiopulmonary exercise test (CPET) before and after cardiopulmonary rehabilitation

Variables[a]	Pre-rehabilitation (*n* = 26)	Post-rehabilitation (*n* = 26)	*p*
Pulmonary function			
FEV_1 (%)	68.50 ± 15.18	84.32 ± 19.17	0.008
FVC (%)	81.27 ± 18.64	84.73 ± 17.09	0.249
FEV_1/FVC (%)	88.86 ± 21.84	99.32 ± 18.00	0.090
Ventilatory disorder			
Obstructive (%)	21.70	4.50	0.102
Restrictive (%)	39.10	36.40	0.102
Respiratory muscle strength			
MIP (cmH_2O)	78.20 ± 25.14	85.36 ± 27.29	0.111
Inspiratory muscle weakness (% of patients)	26.90	4.00	0.070
MEP (cmH_2O)	87.56 ± 34.09	102.28 ± 43.65	0.009
Expiratory muscle weakness (% of patients)	3.80	0	*
Cardiopulmonary exercise test			
VO_{2peak} (ml·kg^{-1}·min^{-1})	19.11 ± 4.61	22.67 ± 4.81	<0.001
VO_{2AT} (ml·kg^{-1}·min^{-1})	13.96 ± 3.35	15.13 ± 3.57	0.850
VE/VCO_2 (L/min)	31.18 ± 3.98	29.08 ± 5.45	0.650
$VE/VCO_{2\ slope}$ (L/min)	34.90 ± 5.13	33.08 ± 4.44	0.011
$TVO_{2\ peak}$ (s)	397.38 ± 165.60	512.85 ± 75.82	0.001
$TVO_{2\ AT}$ (s)	228.50 ± 120.12	269.44 ± 71.50	0.061
$T_{1/2}$ (s)	135.95 ± 45.50	139.77 ± 28.18	0.626

Note: * Computed only for a PxP table, where *p* must be greater than 1.
Abbreviations: AT, anaerobic threshold; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; MEP, maximal expiratory pressure; MIP, Maximal inspiratory pressure; T1/2, time for a 50% drop in VO2 measured at peak exercise; time, to oxygen consumption at anaerobic threshold; TVO2, AT; TVO2peak, time to peak oxygen consumption; VE/VCO_2, ventilation to carbon dioxide production; VE/VCO_2slope, ventilation to carbon dioxide production slope; VO_2, oxygen consumption.
[a]Variables presented as mean ± standard deviation.

of 17.7 ml·kg^{-1}·min^{-1}) in almost one-third of patients and increased significantly in approximately half of survivors (Clavario et al., 2021). Patients in our study also presented mean VO_2peak below 20 ml·kg^{-1}·min^{-1} in the initial assessment, which increased 3.56 ml·kg^{-1}·min^{-1} (18.62%) after intervention. In adult males, an increase of 3.5 ml·kg^{-1}·min^{-1} (1 Metabolic Equivalent) may correspond to a 12% improvement in survival (Arena et al., 2004; Myers et al., 2002; Trevizan et al., 2021).

On the other hand, high VE/VCO_2slope values, especially ≥34, may indicate worse prognosis (Arena et al., 2004; Arena et al., 2003). In our study, mean VE/VCO_2slope was 34.90 before intervention and reduced 5.21% after 12 training sessions. A decrease in these variables was also observed in patients with heart failure after 4 weeks of physical training (Gademan et al., 2008) and after 12 weeks of aerobic training (Fu et al., 2013).

A change of 14–30.5 m in the 6MWT is considered clinically important in patients with cardiopulmonary diseases (Bohannon & Crouch, 2017). In our study, patients increased 70.57 m in the distance walked after 12 sessions of aerobic and resistance training. A 6-week pulmonary rehabilitation program also improved distance walked in older adults with post-COVID-19 (Liu et al., 2020). A case study with one patient post-COVID-19 showed an increase of 199 m in the distance walked in the 6MWT after 15 rehabilitation sessions (Mayer et al., 2021). These results demonstrate the benefits of aerobic training, which improves skeletal muscle properties and increase physical fitness (Nambi et al., 2021).

Adaptations caused by exercise may impact fatigue and activities of daily living of patients post-COVID-19. Fatigue, insomnia, anxiety, and depression are common after COVID-19 and may persist for 6 months after COVID-19 infection (Huang et al., 2021). In our study, most patients reported slight or moderate tiredness before rehabilitation. A total of 36% of patients also answered "I can do some of the things that I usually do". After intervention, a higher percentage of patients reported feeling "not tired at all" and "I can do almost everything that I usually do". Similarly, a 6-week supervised rehabilitation program improved fatigue symptoms (Daynes et al., 2021). The same was observed in a case series with patients post-COVID-

19, in which most did not report fatigue or only reported very light exertion after the exercise program (Ferraro et al., 2021).

Manifestations presented by patients post-COVID-19, such as reduced lung function, exercise intolerance, fatigue, and difficulties in daily activities, may impact quality of life (Halpin et al., 2021). All SF-36 domains improved after rehabilitation, indicating better quality of life. Similar results were observed after a 6-week pulmonary rehabilitation program in patients post-COVID-19 (Liu et al., 2020) and an 8-week aerobic training program in elderly adults with sarcopenia after COVID-19 infection (Nambi et al., 2021).

Regarding perception of clinical change, a higher percentage of patients chose an answer to number six on the scale, which considers "Better, and a definite improvement that has made a real and worthwhile difference". Another study found an association between clinical improvement and reduced risk of future clinical events in patients with heart failure (Luo et al., 2019). The findings on clinical perception reinforce the benefits of physical training for patients included in rehabilitation programs.

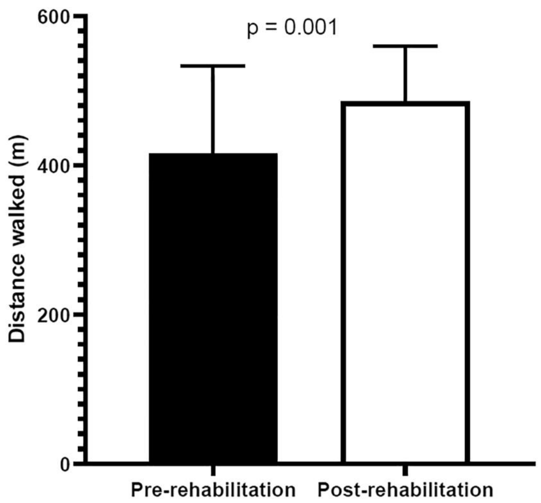

FIGURE 2 Distance walked before and after cardiopulmonary rehabilitation

4.1 | Limitations

Strenuous circumstances changed the study design during the COVID-19 pandemic. Functional impairments of many patients during initial screening, reduced number of patients, and insecurity of patients in attending to or using public transport to reach the hospital affected sample size and limited randomization and recruitment

TABLE 3 Quality of life before and after cardiopulmonary rehabilitation

Variables[a]	Pre-rehabilitation (n = 26)	Post-rehabilitation (n = 26)	p
Physical functioning	40.00 ± 24.58	63.75 ± 24.14	<0.001
Role physical	10.42 ± 19.38	39.58 ± 39.64	0.004
Bodily pain	47.50 ± 29.99	61.96 ± 24.22	0.006
General health	44.50 ± 24.83	65.25 ± 23.94	<0.001
Vitality	46.88 ± 27.21	65.63 ± 20.17	<0.001
Social functioning	48.88 ± 31.05	71.25 ± 27.79	0.001
Role emotional	31.96 ± 42.28	54.17 ± 40.36	0.015
Mental health	63.00 ± 25.76	76.67 ± 21.02	<0.001
Total score	333.13 ± 182.10	498.13 ± 159.21	<0.001

[a]Variables presented as mean ± standard deviation.

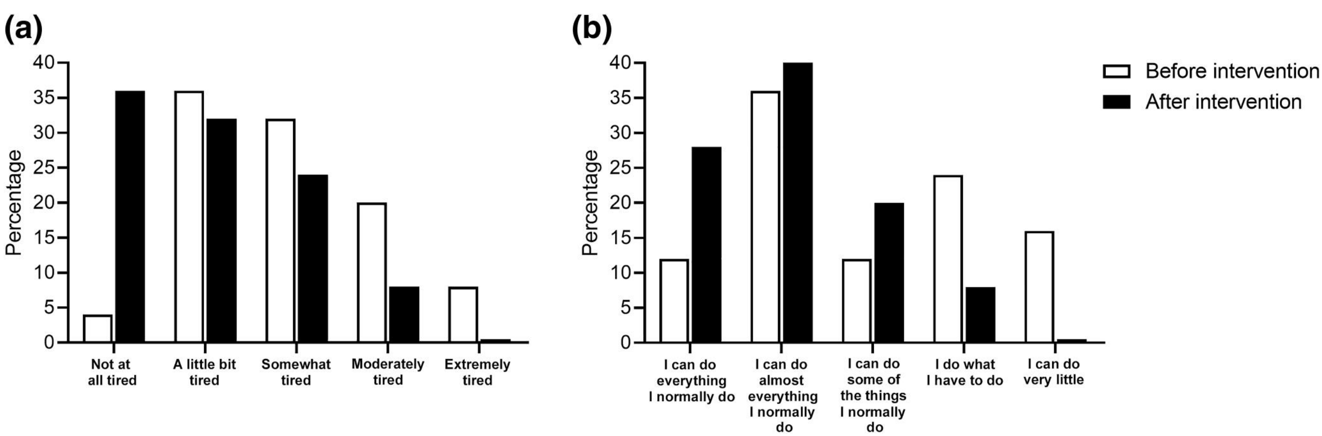

FIGURE 3 Comparison between feeling of fatigue (a) and impact of fatigue (b) before and after intervention

of a control group. Therefore, we extended the data collection period, provided financial assistance for patients to reach the outpatient clinic, and modified the data analysis plan. Furthermore, length of hospital stay could not be stratified.

Although we know that COVID-19 can have repercussions on lung function, the sample of the present study showed a percentage of obese individuals and individuals with lung diseases. These data may be a limitation to determine the real impacts of COVID-19 on the initial characterization of the sample.

Several issues regarding COVID-19, including symptoms and post-COVID-19 repercussions, are still poorly understood and need further studies for better clarification. The exercise program performed in the present study probably contributed to the improvement of the patients, but other factors should also be taken into account, such as the functional adaptations and the natural evolution of the condition presented by the patients.

5 | CONCLUSION

A cardiopulmonary rehabilitation program consisting of continuous moderate-intensity aerobic and resistance training is effective for patients post-COVID-19. Rehabilitation improved lung function, respiratory muscle strength, maximal and submaximal exercise tolerance, fatigue, and quality of life of patients post-COVID-19. Furthermore, most patients perceived positive clinical improvements after rehabilitation.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

The study was approved by the human research ethics committee of the Federal University of Pernambuco (number 4.598.136).

PATIENT CONSENT STATEMENT

All participants signed the informed consent form following resolution 466/12 of the Brazilian National Health Council and Declaration of Helsinki.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

STUDY REGISTRATION

The study was registered at clinicaltrials.gov (ID: NCT04767477).

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