Effects of a 16-week home-based exercise training programme on health-related quality of life, functional capacity, and persistent symptoms in survivors of severe/critical COVID-19: a randomised controlled trial

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjsports-2022-106681).

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Accepted 8 April 2023
Published Online First 10 May 2023

To cite: Longobardi I, Goessler K, de Oliveira Júnior GN, *et al*. *Br J Sports Med* 2023;**57**:1295–1303.

ABSTRACT

Background Long-lasting effects of COVID-19 may include cardiovascular, respiratory, skeletal muscle, metabolic, psychological disorders and persistent symptoms that can impair health-related quality of life (HRQoL). We investigated the effects of a home-based exercise training (HBET) programme on HRQoL and health-related outcomes in survivors of severe/critical COVID-19.

Methods This was a single-centre, single-blinded, parallel-group, randomised controlled trial. Fifty survivors of severe/critical COVID-19 (5±1 months after intensive care unit discharge) were randomly allocated (1:1) to either a 3 times a week (~60–80 min/session), semi-supervised, individualised, HBET programme or standard of care (CONTROL). Changes in HRQoL were evaluated through the 36-Item Short-Form Health Survey, and physical component summary was predetermined as the primary outcome. Secondary outcomes included cardiorespiratory fitness, pulmonary function, functional capacity, body composition and persistent symptoms. Assessments were performed at baseline and after 16 weeks of intervention. Statistical analysis followed intention-to-treat principles.

Results After the intervention, HBET showed greater HRQoL score than CONTROL in the physical component summary (estimated mean difference, EMD: 16.8 points; 95% CI 5.8 to 27.9; effect size, ES: 0.74), physical functioning (EMD: 22.5 points, 95% CI 6.1 to 42.9, ES: 0.83), general health (EMD: 17.4 points, 95% CI 1.8 to 33.1, ES: 0.73) and vitality (EMD: 15.1 points, 95% CI 0.2 to 30.1, ES: 0.49) domains. 30-second sit-to-stand (EMD: 2.38 reps, 95% CI 0.01 to 4.76, ES: 0.86), and muscle weakness and myalgia were also improved in HBET compared with CONTROL ($p<0.05$). No significant differences were seen in the remaining variables. There were no adverse events.

Conclusion HBET is an effective and safe intervention to improve physical domains of HRQoL, functional capacity and persistent symptoms in survivors of severe/critical COVID-19.

Trial registration number NCT04615052.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ COVID-19 may cause multisystemic consequences that continue or develop after acute SARS-CoV-2 infection, which can negatively impact patients' health-related quality of life (HRQoL). In fact, multiple sequelae and life-threatening events have already been documented even months after infection, particularly in those who had severe/critical COVID-19. Exercise has a potential therapeutic role in a broad spectrum of diseases, with positive effects on different physiological and psychological systems; however, its ability to mitigate post-COVID-19 impact on HRQoL and health outcomes in survivors of severe/critical COVID-19 is unknown.

WHAT THIS STUDY ADDS

⇒ A home-based exercise training programme specifically tailored to patients with severe/critical COVID-19 was safe and able to improve physical domains of HRQoL. Of relevance, exercise also improved functional capacity and reduced the occurrence of persistent muscle weakness and myalgia in this population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Post-COVID-19 syndrome is a worldwide health issue. The bespoke exercise intervention herein emerges as an effective, safe and relatively easy to escalate therapeutic strategy for patients recovering from severe/critical COVID-19. Future multicentre studies with larger sample sizes should address the effectiveness of different exercise interventions, as well as barriers and facilitators to their implementation, in cohorts of patients experiencing persistent symptoms of COVID-19.

INTRODUCTION

COVID-19 pandemic has led to a growing number of survivors experiencing debilitating persistent symptoms long after infection. Post-COVID-19 syndrome, or long COVID, is a frequent condition, affecting approximately 39%–46% of survivors of COVID-19 worldwide.[1] It has been defined as newly occurring and persistent symptoms (eg, fatigue, dyspnoea, muscle weakness, etc) lasting more than 12 weeks that cannot be explained by an alternative diagnosis.[2] This

condition is usually associated with substantial health impairments, including poor cardiorespiratory fitness, exertional intolerance, reduced functional capacity, lower muscle mass and psychological morbidities (eg, anxiety and depression).[3–8] Available evidence suggests that patients who have had severe/critical COVID-19 (eg, those admitted to an intensive care unit) may present with even worse outcomes.[9] As a consequence, survivors of severe/critical COVID-19 commonly have poor health-related quality of life (HRQoL) scores, even several months after the infection.[8 10 11]

Therefore, there is an emergency for novel therapies capable of recovering overall health in these patients. Exercise training has been proven an effective non-pharmacological therapy for a broad spectrum of diseases, showing positive effects on cardiovascular, respiratory, skeletal muscle, metabolic and mental disorders.[12] In COVID-19, there is preliminary data to suggest that exercise may be of clinical value to individuals previously hospitalised (in wards) by improving cardiovascular (eg, pulse wave velocity) and respiratory (eg, maximal inspiratory and expiratory pressures) parameters.[13] However, little is known about the effects of exercise interventions on severe/critical patients, who may be prone to post-exertional symptoms exacerbation. We hypothesised that a home-based exercise training (HBET) programme would improve HRQoL, and physical and mental parameters in survivors of severe/critical COVID-19.

MATERIALS AND METHODS

Study design

This was a single-centre, single-blinded, parallel-group, randomised, controlled trial. The study was pre-registered at Clinicaltrials.gov (NCT04615052). The trial design is illustrated in the online supplemental figure S1. The manuscript was reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Randomisation

The allocation list was created using a specific software (https://www.random.org/sequences) with a computer-generated block design stratified by post-COVID-19 Functional Status (PCFS) score, which has five levels, ranging from Grade 0 to Grade 4. Participants who met the eligibility criteria were enrolled consecutively and those who successfully completed baseline assessments were randomly assigned to either HBET or standard of care (CONTROL) group in a 1:1 ratio. The randomisation process was performed by an independent researcher, who had no involvement in the trial.

Participants

Survivors of COVID-19 from a tertiary referral hospital (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) were identified and screened from their medical records between November 2020 and April 2022. COVID-19 status followed the WHO severity classification.[2] Patients were categorised either as severe (severe pneumonia, resting oxygen saturation <90% on room air, signs of respiratory distress, eg, respiratory rate ≥30 breaths/min) or critical (defined by the criteria for acute respiratory distress syndrome, sepsis, septic shock, acute thrombosis or other conditions that would normally require life-sustaining therapies such as invasive or non-invasive mechanical ventilation or vasopressor therapy). Eligibility criteria for the study included patients aged 45 years or older, who had received a confirmed diagnosis of COVID-19 by RT-PCR testing for SARS-CoV-2 from nasopharyngeal swabs and had been discharged from the intensive care unit (ICU) between 3 months and 6 months prior to their enrolment into the study.

Patients who need oxygen supply or had resting oxygen saturation <85% on room air, anaemia, pulmonary hypertension, recent myocardial infarction (<12 months), severe valve disease, unstable angina, untreated heart failure, uncontrolled arrhythmias, active oncological disease or recent malignancy (<5 years), transplant history, uncontrolled hypertension, uncontrolled type-2 diabetes, autoimmune diseases, with inability to walk, with severe cognitive dysfunction that could compromise any assessments, considered unstable due to any other health condition, or already engaged in rehabilitation programmes and/or exercise training programmes at baseline were excluded.

All participants provided written consent after being informed of the purpose of the study, experimental procedures and potential risks. Our study included participants from diverse ethnicities, sexual orientations, social status and religions.

Outcomes

All outcomes of interest were assessed at baseline (ie, pre-intervention) and after 16 weeks (post-intervention) at the same intrahospital laboratory.

Health-related quality of life

We assessed HRQoL through the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[14] SF-36 yields an 8-scale profile of scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health). Physical component summary (primary outcome) and mental component summary were also calculated. Scores range from 0 to 100 (higher scores indicate better HRQoL).

Cardiorespiratory fitness and pulmonary function

We carried out a maximal a graded cardiopulmonary exercise testing on a treadmill (Centurion C200, Micromed, Brazil) using a modified Balke protocol to the limit of tolerance; each patient performed the same protocol pre-intervention and post-intervention. Heart rate (HR) was continuously recorded beat-by-beat from the R–R interval using a 12-lead electrocardiograph (ErgoPC Elite, Micromed, Brazil). Gas exchange and ventilatory parameters were recorded breath by breath by continuous sampling using a rapid response gas analyser (Metalyzer 3B, Cortex, Germany). System was calibrated immediately before each test following manufacturer's specifications. Outcome variables, including peak oxygen uptake (VO_{2peak}), oxygen uptake at ventilatory threshold (VO_{2VT}), oxygen uptake efficiency slope (OUES), respiratory exchange ratio (RER), pulmonary ventilation (V_E), ventilatory equivalent for carbon dioxide (V_E/V_{CO2}), O_2 pulse and chronotropic index were assessed as previously described.[3 15 16] Heart rate recovery was assessed during the first (HRR_{1min}), second (HRR_{2min}) and fourth minute (HRR_{4min}) of the recovery phase.

We assessed pulmonary function without bronchodilator, in the upright position, by using a computer-based spirometry system (Metalyzer 3B, Cortex, Germany) in accordance with recommendations.[17] Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC

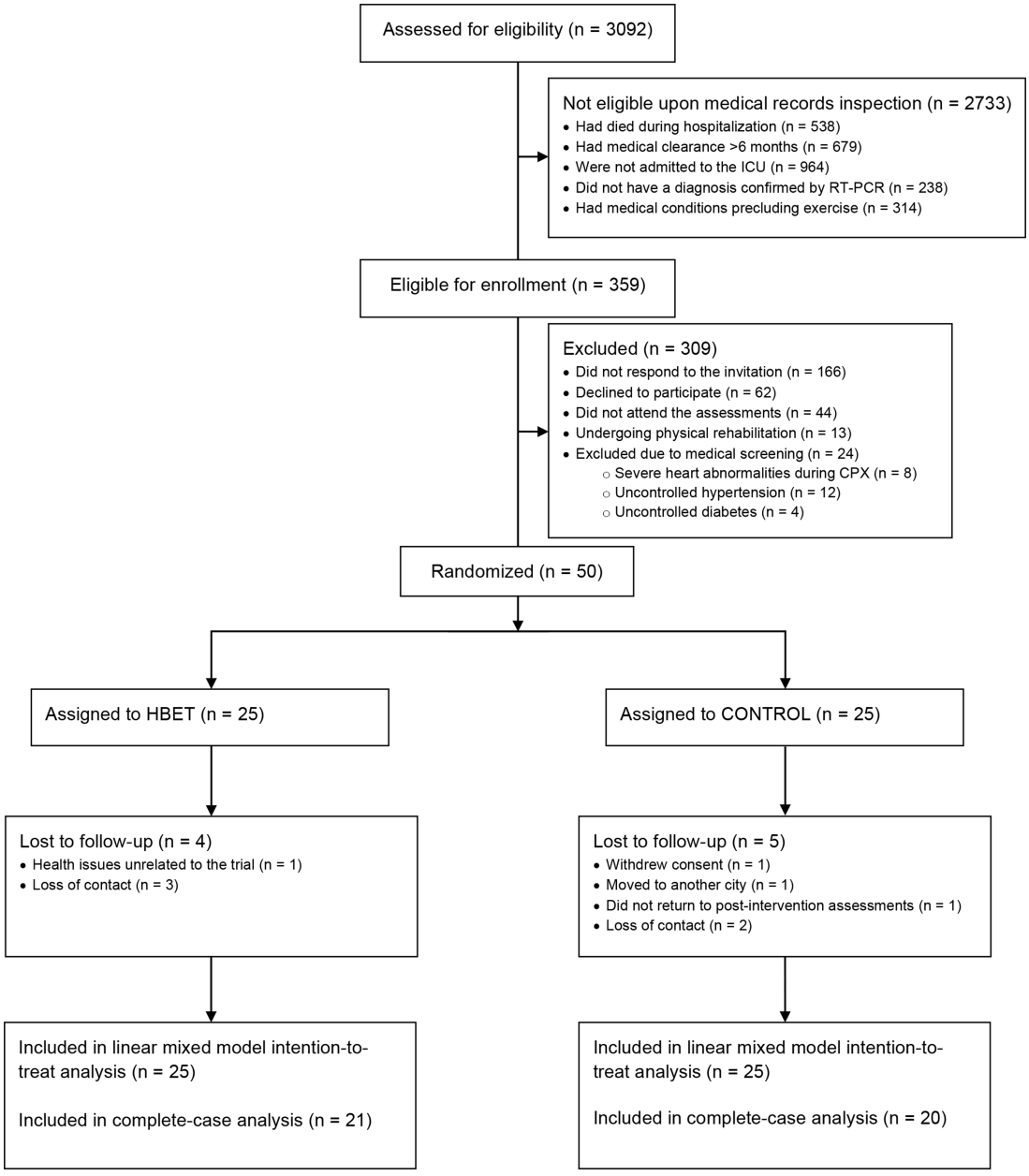


Figure 1 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; CONTROL, standard of care; CPX, cardiopulmonary exercise testing; HBET, home-based exercise training; ICU, intensive care unit.

ratio, peak inspiratory flow and peak expiratory flow were also assessed.[17]

An experienced physician blinded to the protocol conducted all tests.

Functional capacity and muscle strength

We performed a handgrip strength test using a handheld dynamometer (TKK 5101; Takei, Tokyo, Japan) on the dominant hand with subjects standing and their elbow fully extended.[18] We assessed lower-limb muscle function and strength through the 30-second sit-to-stand and the timed-up-and-go tests.[19 20] The same researcher blinded to the patients' assignment performed all tests.

We assessed functional status (broadly defines as the ability to independently perform self-care and instrumental activities of daily living)[21 22] through the Brazilian Portuguese version of the PCFS scale following previous recommendations.[23] It comprises 17 (yes/no) questions, with scores ranging between 0 and 4. Overall classification is based on the highest-scoring answer (higher scores indicate greater functional limitations).

Anthropometry and body composition

After an overnight fast, we performed a whole-body dual-energy X-ray absorptiometry scan using a Lunar iDXA equipment (GE Healthcare, Madison, WI, USA) to evaluate the body composition. We measured the body weight using a calibrated digital scale and the height using a stadiometer. We determined waist and hip circumferences by using an anthropometric measuring tape. The same trained technician blinded to the patients' assignment conducted all measurements.

Table 1 Characteristics of the participants

	HBET (n=25)	CONTROL (n=25)
Age, years	60.8±7.1	61.2±7.7
Women, n (%)	13 (52)	12 (48)
Height, cm	163.9±0.1	163.1±0.1
Weight, kg	84.9±16.4	84.0±13.56
BMI, kg/m^2	31.5±5.0	31.9±5.0
Overweight, n (%)	9 (36)	10 (40)
Obesity class I, n (%)	10 (40)	7 (28)
Obesity class II, n (%)	5 (20)	6 (24)
Obesity class III, n (%)	1 (4)	2 (8)
HR, bpm	75.8±9.4	75.0±11.0
Systolic blood pressure, mm Hg	125.6±16.1	125.0±14.5
Diastolic blood pressure, mm Hg	81.8±12.0	80.0±8.7
SpO_2, %	96.7±1.2	97.0±1.3
Smoking status		
Current smoker, n (%)	1 (4)	1 (4)
Former smoker, n (%)	12 (48)	12 (48)
Never smoked, n (%)	12 (48)	12 (48)
PAL, min/week	170 (160)	180 (155)
Comorbidities		
Hypertension, n (%)	15 (60)	13 (52)
Dyslipidaemia, n (%)	13 (52)	14 (56)
Rheumatic disease, n (%)	9 (36)	7 (28)
Diabetes mellitus, n (%)	8 (32)	10 (40)
CVD, n (%)	5 (20)	5 (20)
Psychological disease, n (%)	5 (20)	5 (20)
Pulmonary disease, n (%)	4 (16)	4 (16)
Hypothyroidism, n (%)	4 (16)	5 (20)
Others, n (%)	2 (8)	3 (12)
Medications		
AT1 inhibitor, n (%)	13 (52)	7 (28)
Diuretics, n (%)	7 (28)	3 (12)
CCB, n (%)	1 (4)	5 (20)
ACE inhibitor, n (%)	1 (4)	4 (16)
β-blockers, n (%)	1 (4)	3 (12)
Insulin, n (%)	2 (8)	5 (20)
Metformin, n (%)	6 (24)	7 (28)
Sulfonylureas, n (%)	4 (16)	6 (24)
Statins, n (%)	7 (28)	7 (28)
Levothyroxine, n (%)	4 (16)	4 (16)
NSAIDs, n (%)	3 (12)	3 (12)
SSRIs, n (%)	4 (16)	3 (12)
Atypical antidepressants, n (%)	3 (12)	1 (4)
Anticoagulants, n (%)	2 (8)	3 (12)
Others, n (%)	4 (16)	3 (12)
Severity of COVID-19 illness		
Severe, n (%)	6 (24)	6 (24)
Critical, n (%)	19 (76)	19 (76)
Hospital LoS, days	18 (13)	19 (12)
ICU LoS, days	9 (7)	7 (8)
IMV, n (%)	13 (52)	12 (48)
Time since discharge, days	160±35	157±33

Data expressed as mean±SD, median (IQR), or as frequency and percentage (%).
AT1, angiotensin-1; BMI, body mass index; CCB, calcium channel blocker; CVD, cardiovascular disease; HBET, home-based exercise training; ICU, intensive care unit; IMV, invasive mechanical ventilation; LoS, length of stay; NSAIDs, non-steroidal anti-inflammatory drugs; PAL, physical activity level; SpO_2, peripheral oxygen saturation; SSRI, selective serotonin reuptake inhibitors.

Laboratory analysis

We collected blood samples from the median or cephalic basilic vein after a 12-hour fast and analysed for complete blood count, glucose metabolism, lipid profile, skeletal and cardiac muscle damage and C reactive protein.

Persistent symptoms

We evaluated newly occurring and persistent symptoms through a self-reported checklist recalling since the onset of acute SARS-CoV-2 infection, in accordance with WHO definition.[2] In addition, fatigue severity was assessed in-depth through the Fatigue Severity Scale (FSS). Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) were also used to properly classify patients with symptoms of anxiety and depression.[24]

Physical activity level

We used the International Physical Activity Questionnaire–Short Form to estimate physical activity level.[25]

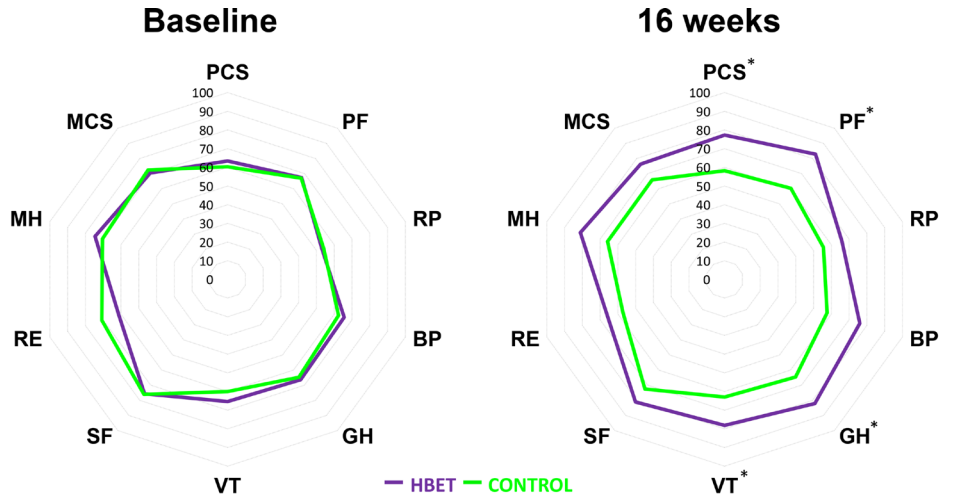
Intervention and control

The intervention was a 16-week, 3-times-a-week (~60–80 min/session), semi-supervised, HBET programme. One weekly session was individually supervised through online live video-calls with an experienced physical trainer. The patients received instructions to give feedback to the trainer immediately after completing the other 2 weekly unsupervised training session. In case of non-compliance, the missed training session was rescheduled within the same or next week. Supplementary materials containing exercise cards and videos, and educative information about how to rate their effort were provided (online supplemental figure S2). Patients were instructed to immediately communicate the research team of any symptoms (including post-exertional symptom exacerbation), or any adverse events potentially related to the intervention. Adherence to the training programme was verified by a training log.

Training volume and exercise complexity progressed as a function of patients' functional capacity (based on PCFS score), which was reassessed every 2 weeks. Exercise volume for the aerobic training sessions ranged from multiple bouts of 10 min/day of walking (PCFS Grade 4) to a single bout of ≥50 min/day of jogging (PCFS Grade 0) (online supplemental table S1). Strength training sessions comprised 3–5 sets (depending on PCFS grade) of 8–15 repetitions per exercise (online supplemental table S2). A set of six strengthening exercises was designed for each PCFS grade. Training intensity progressed every 2 weeks based on RPE, and ranged from 'very light' to 'fairly light' (Borg Scale score 9–11) within the first 2 weeks of the protocol toward 'hard' to 'very hard' (Borg Scale score 15–17) in the last 4 weeks (online supplemental table S3). Active stretching exercises for the major muscle groups were also prescribed. Online supplemental tables S1–S3 provides detailed information on training progression.

Patients with hypertension were instructed to measure their blood pressure immediately before training sessions (sessions were suspended if systolic or diastolic blood pressure were ≥160 mm Hg or ≥105 mm Hg, respectively). Patients with type-2 diabetes were instructed to measure their blood glucose, with acceptable values between 90 mg/dL and 250 mg/dL before the training session.

Standard of care included general advice for a healthy lifestyle (eg, guideline-based recommendations for healthy dieting and physical activity), which was provided at the beginning of the study. CONTROL patients were contacted by phone or text message every 2 months (unless they reached out to the research team sooner for any reason) for a general check-up on their well-being and any medical needs. Whenever necessary, patients from both groups received outpatient care, consultation with a specialised physician and additional diagnostic exams.



SF-36 Domain	PCS	PF	RP	BP	GH	VT	SF	RE	MH	MCS
ES	0.74	0.83	0.43	0.50	0.73	0.49	0.38	0.66	0.37	0.56

Figure 2 Radar chart of SF-36 health-related quality of life scores assessed pre-intervention (ie, baseline) and post-intervention (ie, 16 weeks) in survivors of severe/critical COVID-19. ESs calculated from between-group mean differences of pre-to-post changes divided by the pooled pre-intervention SD. BP, bodily pain; CONTROL, standard of care; ESs, effect sizes; GH, general health; HBET, home-based exercise training; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; VT, vitality. *Indicate significant between-group difference after 16 weeks (p≤0.05).

Deviations from the protocol

Inflammatory cytokines and inspiratory muscular strength analyses were originally planned, but sufficient financial resources were not available.

Statistics

Sample size was calculated a priori considering SF-36 physical component summary as the primary outcome. Analyses were conducted on G*Power (V.3.1.9.2) using a two-way analysis of variance with two repeated measures for group by time interaction. Data from our pilot study resulted in a partial eta squared (η^2_p) of 0.051 and an effect size (ES) *f* of 0.23. Power was set to 80% (β=0.2) and a two-sided α level of 0.05 was considered. Initial estimated sample size was 40 (n=20 per group); however, we aimed for 25 participants per group due to potential dropouts.

Statistical analysis was performed on SAS V.9.2 software using an intention-to-treat approach for the primary analysis. A linear mixed-model with repeated measures was performed for longitudinal data using a restricted maximum likelihood algorithm to compare changes of outcomes in time between experimental groups. 'Group' (HBET and CONTROL) and 'time' (pre-intervention and post-intervention) were included as fixed factors and 'patients' as a random factor with assumed normal distribution. Kenward-Roger degrees-of-freedom adjustment was used to adjust for data imbalance eventually generated by missing data. Data normality and homoscedasticity was visually checked with histogram of the studentized residuals and residual plots. Nonnormal data were log transformed. The absence of extreme observations (outliers) was guaranteed through standard visual inspection. For the primary outcome, baseline values were used as covariates. ESs were calculated from between-group mean differences of pre-to-post changes divided by the pooled pre-intervention SD, as previously described.[26] Changes in frequency outcomes were determined by using either χ^2 test or Fisher's exact test when necessary. Significance level was set at p ≤0.05. A post hoc test with Tukey's adjustment was performed in case of a significant F value. Data are presented as mean±SD for continuous variables or as frequency and percentage for categorical variables, except otherwise stated. Linear mixed-model's adjusted estimated mean difference (EMD) and 95% CI are provided whenever the post hoc analysis indicated between-group significant differences. An additional post hoc, complete-case (per protocol), sensitivity analysis comprising only those who did not drop out was performed using independent t-tests to compare between-group delta changes ($\Delta_{HBET} - \Delta_{CONTROL}$). The sensitivity analysis was conducted in order to assess the robustness of the findings based on our intention-to-treat primary analysis.

RESULTS

Participants

Fifty survivors of severe/critical COVID-19 were randomised. Four patients in HBET and five in CONTROL group were lost during follow-up, none of them due to reasons related to the trial or training protocol (figure 1).

Table 1 shows demographic and clinical characteristics of the participants. Half of the patients required invasive mechanical ventilation, while the other half required non-invasive mechanical ventilation (eg, continuous positive airway pressure or high flow nasal cannula oxygen therapy). No patient included in this study required extracorporeal membrane oxygenation. All patients met current diagnostic criteria for the various case definitions in use for post-COVID-19 syndrome.[27] The proportion of patients classified in PCFS scale as having severe (Grade 4), moderate (Grade 3), mild (Grade 2), very mild (Grade 1) or absence (Grade 0) of functional limitations were: 20%, 24%, 28%, 20% and 8%, respectively.

At baseline, laboratory markers were within normal range on average, except for blood glucose, total cholesterol and triglycerides levels which were slightly altered; there were no between-group differences after 16 weeks (online supplemental table S4). Physical activity level increased in HBET but not

Table 2 Effects of HBET intervention and standard of care (CONTROL) on cardiorespiratory fitness and pulmonary function parameters in survivors of severe/critical COVID-19 pre-intervention (ie, at baseline) and post-intervention (ie, after 16 weeks)

	HBET		CONTROL		Post-intervention between-group differences			
	Baseline	16 weeks	Baseline	16 weeks	EMD	95% CI	P value	ES
Cardiorespiratory fitness	n=25	n=21	n=25	n=20				
Time to exhaustion, s	640.2±145.8	715.2±157.0	605.4±197.7	631.1±186.6	81.6	(–58.9 to 222.2)	0.406	0.24
VO_{2peak}, L/min	1.72±0.57	1.91±0.61	1.76±0.61	1.79±0.62	0.12	(–0.34 to 0.58)	0.892	0.27
VO_{2peak}, mL/kg/min	20.5±5.2	22.2±4.3	20.6±6.0	21.3±6.0	1.57	(–2.71 to 5.86)	0.757	0.32
VO_{2peak}, % pred.	70.9±17.9	78.5±16.1	71.5±18.4	74.6±19.5	4.06	(–10.2 to 18.3)	0.869	0.20
VO_{2VT}, L/min	1.07±0.33	1.13±0.34	1.01±0.28	1.09±0.34	0.03	(–0.24 to 0.30)	0.991	–0.17
VO_{2VT}, mL/kg/min	12.5±2.1	13.4±3.1	11.8±3.0	12.5±3.9	0.53	(–2.12 to 3.17)	0.951	0.25
VO_{2VT}, % pred VO_{2peak}	44.6±9.2	46.6±10.8	44.5±14.1	45.4±15.0	0.74	(–10.5 to 12.0)	0.998	0.21
OUES, L/min	2.06±0.60	2.19±0.69	1.94±0.57	1.90±0.56	0.34	(–0.13 to 0.82)	0.239	0.41
RER_{peak}	1.06±0.07	1.07±0.11	1.07±0.08	1.07±0.09	0.00	(–0.07 to 0.07)	1.000	0.13
$V_{E,}$ L/min	70.5±25.5	72.9±27.3	68.9±19.8	68.2±23.2	6.89	(–12.0 to 25.8)	0.762	0.25
V_E/VCO_2 slope	34.6±4.9	33.2±5.3	34.6±6.0	33.5±4.0	–0.11	(–4.49 to 4.27)	0.999	0.11
V_E/VCO_{2nadir}, L/min	32.0±3.2	30.7±4.1	31.5±4.8	30.5±4.2	0.11	(–3.59 to 3.80)	0.999	0.07
O_2 pulse, mL/bpm	11.6±3.7	12.3±3.6	11.4±2.2	11.7±3.1	0.69	(–1.88 to 3.25)	0.888	0.20
O_2 pulse, % pred.	73.3±13.9	81.8±19.2	76.3±13.7	79.1±17.6	2.74	(–10.7 to 16.2)	0.946	0.47
HR_{max}, bpm	144±14	154±17	143±19	143±14	10.5	(–3.16 to 24.14)	0.183	0.52
ΔHR, bpm	60±18	76±17	61±19	66±20	7.95	(–6.67 to 22.56)	0.470	0.41
Chronotropic index, %	80.4±18.7	94.0±19.2	80.0±22.2	80.2±16.7	11.1	(–5.02 to 27.25)	0.266	0.46
HRR_{1min}, bpm	9.5 (11)	20 (10)	13 (11)	17 (6)	1.55	(–5.29 to 8.41)	0.929	0.19
HRR_{2min}, bpm	26±10	40±13	31±9	35±13	5.11	(–4.45 to 14.68)	0.488	0.85
HRR_{4min}, bpm	44±10	53±11	47±11	47±12	4.33	(–5.25 to 13.91)	0.621	0.61
Pulmonary function test	n=25	n=21	n=25	n=20				
FEV_1, L	2.56±0.84	2.51±0.81	2.73±0.73	2.63±0.77	–0.16	(–0.77 to 0.44)	0.881	0.06
FVC, L	2.75±0.84	2.71±0.81	2.86±0.77	2.78±0.81	–0.16	(–0.79 to 0.46)	0.893	0.05
FEV_1/FVC, %	93.8±3.5	93.8±4.3	95.5±3.2	94.8±3.9	–0.71	(–4.01 to 2.60)	0.938	0.20
Peak inspiratory flow, L/s	5.27±2.59	5.91±1.93	5.17±1.88	6.03±2.66	–0.08	(–1.97 to 1.81)	0.999	–0.09
Peak expiratory flow, L/s	7.34±3.15	7.48±2.80	6.84±1.96	7.08±2.52	0.20	(–1.88 to 2.28)	0.994	–0.04

Data expressed as unadjusted mean±SD or median (IQR).
bpm, beats per minute; EMD, adjusted estimated mean difference; ES, effect size; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HBET, home-based exercise training; HRR, heart rate recovery; OUES, oxygen uptake efficiency slope; pred, predicted; RER_{peak}, peak exercise respiratory exchange ratio; V_E/VCO_2, ventilatory equivalent for carbon dioxide; VO_{2peak}, peak oxygen uptake; VO_{2VT}, oxygen uptake at the ventilatory threshold.

in CONTROL after the intervention (EMD: 328 min/week; 95% CI 161 to 494; p<0.001; ES: 2.78).

Eleven patients (HBET: n=6; CONTROL: n=5) required outpatient care during the follow-up period due to malnutrition, osteonecrosis, bedsores, gout crisis, suspected peripheral arterial disease, hypertensive crisis, depressive crisis, household accident and acute infection (common cold and non-specified respiratory tract infection). No adverse events potentially associated with the intervention were reported according to our medical staff. Among patients who completed the study, adherence to HBET protocol was 71.2% (81.0% in supervised and 66.5% in non-supervised sessions).

Health-related quality of life

After 16 weeks, the score of physical component summary (primary outcome) was higher in HBET compared with CONTROL (EMD: 16.8 points; 95% CI 5.8 to 27.9; p<0.001; ES: 0.74) (figure 2). Further analysis also revealed other between-group differences in favour of HBET for physical functioning (EMD: 22.5 points; 95% CI 6.1 to 42.9; p=0.005; ES: 0.83), general health (EMD: 17.4 points; 95% CI: 1.8 to 33.1; p=0.024. ES: 0.73) and vitality (EMD: 15.1 points; 95% CI 0.2 to 30.1; p=0.015; ES: 0.49). No statistically significant between-group differences could be observed for any other SF-36 domain (all p>0.05).

Cardiorespiratory fitness, pulmonary function, functional capacity and muscle strength

No significant between-group differences were detected for cardiorespiratory or pulmonary function variables (all p>0.05; table 2). Significant between-group differences were observed for 30-second sit-to-stand performance at post-intervention (EMD: 2.38 repetitions; 95% CI 0.01 to 4.76; p=0.048; ES: 0.86; table 3). There were no between-group differences in handgrip strength, timed-up-and-go or PCFS (all p>0.05) after 16 weeks.

Anthropometry and body composition

No significant between-group differences were detected for any measurement after 16 weeks (all p>0.05) (table 3).

Persistent symptoms

Self-reported presence of persistent symptoms was similar between groups at baseline (all p>0.05, table 4). After 16 weeks, the proportion of patients with muscle weakness (4.8% vs 35.0%) and myalgia (19.0% vs 55.0%) was significantly different in HBET versus CONTROL (p<0.05). No significant between-group differences could be observed in total number of symptoms per patient or the presence of any other persistent symptom (all p>0.05). However, the proportion of

Table 3 Effects of HBET intervention and standard of care (CONTROL) on functional capacity, anthropometry and body composition in survivors of severe/critical COVID-19 pre-intervention (ie, at baseline) and post-intervention (ie, after 16 weeks)

	HBET		Control		Post-intervention between-group differences			
	Baseline	16 weeks	Baseline	16 weeks	EMD	95% CI	P value	ES
Functional capacity	n=25	n=21	n=25	n=20				
Handgrip strength, kg*	30.0 (19.5)	32.0 (15.0)	28.5 (19.5)	29.2 (17.5)	2.42	(−6.33 to 11.15)	0.879	0.17
30-second sit-to-stand, repetitions	12.2±2.3	14.9±3.4	12.2±2.9	12.4±3.2	2.38	(0.01 to 4.76)	0.048	0.86
Timed-up-and-go, s*	7.33 (2.37)	6.79 (1.41)	6.81 (1.47)	6.88 (1.10)	−0.04	(−1.10 to 1.03)	0.997	0.36
PCFS	2.0 (2.0)	1.0 (1.0)	2.0 (2.0)	2.0 (3.0)	−0.66	(−1.63 to 0.31)	0.275	0.55
Anthropometry	n=25	n=21	n=25	n=20				
Waist circumference, cm	104.0±11.0	101.9±10.3	103.8±10.6	105.3±9.4	−4.49	(−13.91 to 4.93)	0.579	0.34
Hip circumference, cm	105.9±10.2	105.7±9.9	105.9±9.8	106.9±9.9	−0.99	(−8.67 to 6.67)	0.985	0.14
WTH circumference, cm	0.98±0.07	0.97±0.08	0.99±0.07	1.01±0.06	−0.03	(−0.09 to 0.02)	0.342	0.26
Body composition	n=25	n=17	n=22	n=12				
Lean body mass, kg	48.7±10.8	49.4±10.1	47.8±6.7	49.1±6.8	0.71	(−6.66 to 8.08)	0.993	−0.03
Leg lean mass, kg	16.6±4.3	17.0±4.4	15.8±2.4	16.6±2.5	0.56	(−2.38 to 3.49)	0.935	−0.06
Arms lean mass, kg	6.1±1.9	6.1±1.7	5.6±1.1	5.8±1.2	0.31	(−0.98 to 1.60)	0.909	−0.07
Appendicular lean mass, kg	22.6±6.1	23.0±5.9	21.4±3.4	22.4±3.5	0.87	(−3.22 to 4.96)	0.934	−0.07
Body fat mass, kg	33.1±8.8	32.2±8.9	31.9±9.4	31.2±9.2	−1.17	(−8.59 to 6.24)	0.927	0.27
Android fat mass, kg*	2.89 (1.56)	2.98 (1.15)	2.83 (1.61)	2.84 (1.53)	−0.18	(−0.99 to 0.63)	0.929	0.31
Gynoid fat mass, kg	5.2±1.6	5.0±1.7	4.9±1.8	4.7±1.7	−0.12	(−1.52 to 1.28)	0.995	0.21
Visceral adipose tissue, kg*	1.71 (0.99)	1.58 (0.87)	1.82 (0.86)	1.97 (0.69)	−0.19	(−0.71 to 0.32)	0.732	0.34

Data expressed as unadjusted mean±SD or median (IQR).
*Indicate that statistical analysis was performed on log-transformed data due to nonnormal distribution.
EMD, adjusted estimated mean difference; ES, effect size; HBET, home-based exercise training; PCFS, post-covid functional status; WTH, waist-to-hip.

patients with fatigue (76.0% vs 28.6%) and dyspnoea (36.0% vs 9.5%) remarkably decreased in HBET, although it did not reach between-group statistical significance. Symptoms of anxiety and depression (either self-reported or assessed by BAI/BDI) were comparable between the two groups at baseline, with no significant changes in either group after 16 weeks (all p>0.05).

Table 4 Effects of HBET intervention and standard of care (CONTROL) on persistent symptoms in survivors of severe/critical COVID-19 pre-intervention (ie, at baseline) and post-intervention (ie, after 16 weeks)

	HBET		CONTROL		Post-intervention between-group differences			
	Baseline	16 weeks	Baseline	16 weeks				
	(n=25)	(n=21)	(n=25)	(n=20)	EMD	95% CI	P value	ES
Self-reported persistent symptoms								
Symptoms per patient	6.0 (5.0)	3.0 (5.0)	7.0 (4.0)	5.0 (6.0)	−2.19	(−4.79 to 0.41)	0.126	0.90
Fatigue, n (%)	19 (76.0)	6 (28.6)	17 (68.0)	10 (50.0)			0.159	
Anxiety/depression, n (%)	16 (64.0)	10 (47.6)	17 (68.0)	13 (65.0)			0.262	
Muscle weakness, n (%)	13 (52.0)	1 (4.8)	14 (56.0)	7 (35.0)			0.020	
Myalgia, n (%)	13 (52.0)	4 (19.0)	13 (52.0)	11 (55.0)			0.025	
Loss of memory, n (%)	11 (44.0)	12 (57.1)	12 (48.0)	10 (50.0)			0.646	
Joint pain, n (%)	10 (40.0)	8 (38.1)	12 (48.0)	12 (60.0)			0.161	
Headache, n (%)	11 (44.0)	4 (19.0)	6 (24.0)	4 (20.0)			1.000	
Dry mouth/eyes, n (%)	11 (44.0)	5 (23.8)	5 (20.0)	7 (35.0)			0.431	
Dyspnoea, n (%)	9 (36.0)	2 (9.5)	8 (32.0)	6 (30.0)			0.123	
Paresthesia, n (%)	9 (36.0)	8 (38.1)	8 (32.0)	8 (40.0)			0.900	
Anosmia/ageusia, n (%)	8 (32.0)	5 (23.8)	4 (16.0)	2 (10.0)			0.410	
Dizziness, n (%)	6 (24.0)	6 (28.6)	6 (24.0)	3 (15.0)			0.454	
Palpitations, n (%)	5 (20.0)	1 (4.8)	5 (20.0)	4 (20.0)			0.184	
Chest discomfort/pain, n (%)	4 (16.0)	1 (4.8)	5 (20.0)	1 (5.0)			1.000	
Others, n (%)	13 (52.0)	4 (19.0)	11 (44.0)	6 (30.0)			0.484	
FSS, score	3.85±1.61	2.59±1.60	3.45±1.90	3.46±1.95	−1.08	(−2.47 to 0.30)	0.173	0.71
BAI >7 points, n (%)	8 (32.0)	5 (23.8)	8 (32.0)	7 (35.0)			0.431	
BDI >13 points, n (%)	6 (24.0)	3 (14.3)	6 (24.0)	6 (30.0)			0.224	

Data expressed as unadjusted mean±SD, median (IQR), or frequency and percentage (%).
BAI, Beck anxiety inventory; BDI, Beck depression inventory; EMD, adjusted estimated mean difference; ES, effect size; FSS, Fatigue Severity Scale; HBET, home-based exercise training.

Complete-case (per protocol), sensitivity analysis

HBET resulted in greater pre-to-post changes in scores than CONTROL for the primary outcome (physical component summary) and the following SF-36 domains: physical functioning, bodily pain, general health, vitality, role-emotional, mental health and mental component summary (all $p<0.05$). Changes in absolute and relative $VO_{2peak,}$ OUES, V_E, ΔHR and HRR_{2min} were also significantly different across groups (all $p<0.05$) in favour of HBET. Improvements in 30-second sit-to-stand performance and in PCFS scores were also greater in HBET than in CONTROL (both $p<0.05$). HBET also showed greater decreases in waist circumference and total and android fat mass, as well as in the total number of persistent symptoms and FSS (both $p<0.01$) (online supplemental table S5).

DISCUSSION

To the best of our knowledge, this is the first randomised controlled trial to investigate the effects of an HBET programme on health outcomes in patients previously admitted to ICU due to COVID-19. The main finding was the positive effect of the intervention on the physical domains of HRQoL, namely, physical functioning, general health, vitality and physical component summary (the primary outcome). In addition, 30-second sit-to-stand performance and some persistent symptoms (ie, muscle weakness and myalgia) were also improved following HBET. In contrast, our primary analysis did not show statistically significant improvements in the mental domains of HRQoL, cardiorespiratory fitness, pulmonary function and body composition.

HRQoL is determined by a variety of physical (eg, symptoms and functional status) and mental (eg, psychological status) factors that influence self-perceived health status.[28] Truffaut *et al* observed that decreased HRQoL 3 months after ICU discharge was associated with a variety of COVID-19 severity parameters during hospital stay.[29] In line with this, at baseline, our patients had scores below normative values for the Brazilian population in almost all SF-36 domains.[30] HBET had heterogenous ES (ranging from 0.43 to 0.83) on multiple domains of SF-36 related to physical health, indicating that it can be an effective strategy in enhancing HRQoL in survivors of severe/critical COVID-19. Importantly, the effect of HBET on the physical component summary of SF-36 (ES: 0.74) was beyond the minimally important difference,[31] supporting the potential clinical relevance of the intervention. This could be explained, at least partly, by the meaningful improvements observed in the secondary outcomes.

It has been reported that muscle wasting and dynapenia occur rapidly in ICU patients with severe COVID-19.[32] We have recently demonstrated that survivors of COVID-19 who suffered the greatest muscle wasting during hospital care present with persistent reduction in muscle cross-sectional area and handgrip strength 6 months after hospital discharge.[6] These parameters have already been shown to be determining factors for patients' prognosis.[33 34] Even though HBET was unable to increase muscle lean mass and strength during follow-up, presumably due to insufficient training volume load,[35] we observed improvements in some functional capacity parameters. HBET yielded a large effect on 30-second sit-to-stand performance (ES: 0.86), whereas PCFS also improved (only in the complete-case analysis) with a moderate magnitude (ES: 0.55). Our results contrast with a previous randomised controlled trial which did not observe any effect of HBET on functional capacity in individuals recovering from COVID-19 hospitalisation.[13] Discrepancies in results may be related to the lower severity of the disease during the acute phase, better functional state at baseline and differences in the training protocol, with a less active supervision and unreported adherence in Amaral *et al*'s study when compared with the present one.[13]

Exertional intolerance is a common feature following COVID-19, especially in severe forms of the disease.[3 4] Potential mechanisms for reduced exercise capacity include altered central (cardiac, pulmonary and autonomic) and peripheral (metabolic) parameters. In general, intention-to-treat analysis did not reveal between-group differences for cardiopulmonary exercise testing variables. These results could indicate either a low efficacy of our HBET or an insufficient power for these secondary outcomes. Our sensitivity analysis considering only completers suggest that the latter might be the case, by showing greater improvements in several cardiopulmonary exercise testing parameters (eg, VO_{2peak}, OUES, V_E and chronotropic responses) in favour of HBET. Importantly, these variables were previously found to be impaired in survivors of COVID-19.[3 36 37] Increments in VO_{2peak} (~8.3%) following HBET were slightly lower than mean improvements reported for individuals with chronic diseases undergoing exercise training.[38–40] This is not unexpected as we opted for a less intensive aerobic component within the programme considering the known and unknown potential risks associated with remotely training survivors of severe/critical COVID-19. Although VO_{2VT} and V_E/VCO_2 did not change in the sensitivity analysis either, HBET increased oxygen uptake efficiency (as indicated by OUES), which is related to pulmonary and metabolic factors.[16 38] These findings collectively suggest that HBET may have a therapeutic value to improve cardiorespiratory fitness in these patients, although further interventions primarily focused on improving cardiorespiratory parameters are warranted.

An association between physical conditioning and post-COVID-19 syndrome seems to exist.[41] Notably, HBET decreased the presence of persistent muscle weakness and myalgia. As seen in previous studies,[8 41] fatigue was the major persistent symptom reported by our patients. Despite the lack of between-group difference, the proportion of patients with self-reported fatigue and dyspnoea remarkably diminished among exercised patients. Furthermore, our exercise intervention was found to have a moderate-to-large effect on the total number of persistent symptoms and fatigue severity (ES: 0.90 and 0.79, respectively), corroborated by our complete-case sensitivity analysis showing greater reductions in both parameters following training. These improvements may have been translated into better SF-36 scores, especially in physical domains (eg, vitality and general health). These results are of clinical relevance considering the still growing number of individuals with post-COVID-19 syndrome worldwide.

Conversely, between-group differences were not found in any psychological symptoms (eg, anxiety and depression), which may account for the somewhat smaller ES (ranging from 0.37 to 0.66 in favour of HBET) observed in the mental domains of SF-36. The proportion of patients classified as having anxiety/depression symptoms when assessed by specific psychometric tools (ie, BAI and BDI) was in line with values reported in the literature following critical illness and COVID-19[7 42]; however, the presence of self-reported anxiety/depression symptoms was much higher, suggesting a mismatch between these inductive, and self-reported questionnaire methods. One may not rule out the possibility that exercise training programmes performed in groups or other environments (eg, outdoors) according to individual preference may have more positive results on psychological symptoms.[43]

The strengths of this study include the assessment of a well-characterised sample of individuals who had severe/critical COVID-19 (all patients with confirmed RT-PCR for SARS-CoV-2 test and admitted to the ICU of a tertiary referral hospital according to WHO criteria), the delivery of a well-monitored HBET intervention, and the use of broad, valid and gold-standard measures to assess primary and secondary outcomes. Nevertheless, this study is not without limitations. It was not possible to identify SARS-CoV-2 variant during acute phase infection; still, most patients were recruited during the first and second waves of COVID-19 in Brazil, during which Gamma P.1 prevailed and vaccines against SARS-CoV-2 were not available. We cannot extrapolate our results to other clinical populations; for instance, patients who had milder disease (eg, ward patients or outpatients) could respond differently to this type of intervention. Furthermore, it was not possible to blind the participants to the intervention; therefore, the benefits may be partially explained by placebo effects. Adherence to the training programme was suboptimal, which may have mitigated the magnitude of change in some outcomes. Measurement bias in intention-to-treat estimates, selection bias due to missing outcome data and random confounding could be limitations in our models, which were unable to be further adjusted owing to potential insufficient power. In fact, our sample size may be considered relatively small (although adequately powered for the primary outcome), which may have hindered our power to detect potentially clinically relevant differences in secondary outcomes. However, altogether, our primary (intention-to-treat) and secondary (complete-case) analyses suggest that there is enough of a signal to justify undertaking a larger study, which might yield more definitive results.

In conclusion, HBET improves physical domains of HRQoL in survivors of severe/critical COVID-19 as well as increases functional capacity and reduces some persistent symptoms in this population. This model of exercise emerges as an effective and safe therapeutic strategy in recovering patients recovering from severe/critical COVID-19. Future multicentre studies with larger sample sizes should address the effectiveness of different exercise interventions, as well as barriers and facilitators to their implementation, in cohorts of patients experiencing persistent symptoms of COVID-19.

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Acknowledgements The authors thank the patients and their families for participating in the study. We are also grateful to Alice Erwig Leitão, Fabiula Isoton Novelli, Ítalo Ribeiro Lemes and Kamila Meireles for the assistance in patients' training.

Contributors Designed research: IL, KG, DCOdA, SG, FRL, BG and HR. Conducted the research: IL and KG. Contributed to data collection: IL, KG, GNdOJ, DMLdP, JVPS, MMM and JASdOB. Analysed data/statistical analysis: IL and HR. Drafted the manuscript: IL, BG and HR. Guarantor: HR. All authors reviewed the manuscript critically and approved the final version. The corresponding author attests that all listed authors meet authorship criteria.

Funding This study was supported by grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (#2021/13580-1, #2019/18039-7, #2020/15678-6, #2020/07540-4, #2020/08091-9 and #2017/13552-2 for IL, KG, MMM, GNOJ, SG and BG) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; #308307/2021-6 for HR).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants. This study was performed in line with the principles of the 1964 Declaration of Helsinki. Ethics approval was obtained from the local Ethical Review Board (CAPPesq; No. 31303720.7.0000.0068). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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