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Effect of a home-based inspiratory muscle training programme on functional capacity in postdischarged patients with long COVID: the InsCOVID trial

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ABSTRACT

Background Fatigue and exercise intolerance are the most common symptoms in patients with long COVID.

Aims This study aimed to evaluate whether a home-based inspiratory muscle training (IMT) programme improves maximal functional capacity in patients' long COVID after a previous admission due to SARS-CoV-2 pneumonia.

Methods This study was a single-centre, blinded assessor, randomised controlled trial. Twenty-six patients with long COVID and a previous admission due to SARS-CoV-2 pneumonia were randomly assigned to receive either a 12-week IMT or usual care alone (NCT05279430). The physiotherapist and participants were not blinded. Patients allocated to the IMT arm were instructed to train at home twice daily using a threshold inspiratory muscle trainer and to maintain diaphragmatic breathing during the training session. The usual care arm received no intervention.

The primary endpoint was the change in peak oxygen consumption (peakVO2). Secondary endpoints were changes in quality of life (QoL), ventilatory efficiency and chronotropic response during exercise (evaluated by chronotropic index-CI_x- formula). We used linear mixed regression analysis for evaluating changes in primary and secondary endpoints.

Results The mean age of the sample and time to first visit after discharge were 50.4±12.2 years and 362±105 days, respectively. A total of 11 (42.3%) were female. At baseline, the mean of peakVO_2, ventilatory efficiency and Clx were 18.9±5 mL/kg/min, 29.4±5.2 and 0.64±0.19, respectively. The IMT arm improved their peakVO_2 significantly compared with usual care (+Δ 4.46 mL/kg/min, 95% CI 3.10 to 5.81; p<0.001). Similar positive findings were found when evaluating changes for CI_x and some QoL dimensions. We did not find significant changes in ventilatory efficiency.

Conclusion In long COVID patients with a previous admission due to SARS-CoV-2 pneumonia, IMT was associated with marked improvement in exercise capacity and QoL.

Trial registration number NCT05279430.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Little is known about the clinical utility of home-based rehabilitation programmes on maximal functional capacity and quality of life in patients with long COVID, particularly in those with a previous admission due to SARS-CoV-2 pneumonia.

WHAT THIS STUDY ADDS

⇒ Home-based inspiratory muscle training (IMT) improves maximal functional capacity and quality of life in patients with long COVID after a previous admission due to SARS-CoV-2 pneumonia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Home-based IMT seems to be a suitable, feasible and effective alternative to supervised exercise training programmes for improving exercise capacity and quality of life in patients with long COVID and may offer an accessible physical therapy model, requiring minimal infrastructure resources.

INTRODUCTION

The pathophysiology of long COVID conditions is complex and multifactorial. Patients with long COVID have long-lasting and heterogeneous symptoms with a non-accepted uniformed definition.[1 2] The most commonly reported symptoms among long COVID patients are muscular weakness, fatigue and breathlessness.[1 3] Indeed, compared with control individuals matched for age, sex and comorbidities, patients with long COVID showed significantly impaired exercise capacity.[4]

Current clinical recommendations from international societies[5] and evidence from supervised exercise training programmes[6–8] and unsupervised training programmes[8 9] support the beneficial effect

of physical therapies on COVID and post-COVID-19 conditions. Nevertheless, home-based programmes' feasibility and clinical utility on maximal functional capacity in long COVID are small or even absent, particularly in symptomatic postdischarged patients. Based on results in other clinical scenarios,[10–12] we hypothesised that a home-based IMT programme might significantly improve maximal functional capacity in long COVID patients. Accordingly, this randomised controlled study aimed to evaluate the effect of a 12-week home-based inspiratory muscle training (IMT) programme on maximal functional capacity and quality of life (QoL) in patients with long COVID recovering from a SARS-CoV-2 pneumonia requiring hospitalisation.

METHODS

Study design

This study was a single-centre, blinded assessor, randomised clinical trial designed to evaluate the effect of a home-based IMT programme on maximal functional capacity in long-term symptomatic patients (>3 months) after hospital admission due to SARS-CoV-2 pneumonia (InsCOVID trial). The patients received a concealed allocation 1:1 to either a 12-week programme of IMT (IMT group) or usual care (UC) alone by a computer-generated randomisation scheme. At the baseline visit, demographic, echocardiographic and laboratory data were collected, and baseline primary and secondary endpoint measures were recorded for all participants. All participants underwent these measures after 12 weeks. The study design was previously published.[13]

Study population

The eligibility of candidate patients was based on the following inclusion criteria: (a) symptomatic adult >18 years old with a previous admission due to SARS-CoV-2 pneumonia; (b) at least 3 months after discharge; and (c) provide informed consent. In addition, exclusion criteria were: (a) inability to perform a maximal baseline exercise test; (b) structural heart disease, valve heart disease or diastolic dysfunction estimated by two-dimensional echocardiography; (c) previous ischaemic heart disease, heart failure, myocardiopathy or myocarditis; (d) effort angina or signs of ischemia during cardiopulmonary exercise testing (CPET); (e) significant primary pulmonary disease, including a history of pulmonary arterial hypertension, chronic thromboembolic pulmonary disease or chronic obstructive pulmonary disease; (f) treatment with digitalis, calcium channel blockers, β-blocker or ivabradine; (g) chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m^2); (h) patients with pacemakers or previous history of atrial fibrillation; (i) autoimmune, inflammatory or active neoplastic disease; (j) anaemia; and (k) pregnancy.

The intervention sessions were conducted by a single physiotherapist with more than 20 years of respiratory physiotherapy experience and no contact with the assessors or the participants' results.

Intervention

Eligibility assessment, randomisation and baseline visit

Patients who met the inclusion–exclusion criteria and signed the informed consent form were randomised (1:1) into two arms: (1) a home-based 12-week programme of IMT (IMT group) or (2) UC. At the baseline visit (day 0), a comprehensive medical history, physical examination, anthropometry and examination tests were performed by one pulmonologist and two cardiologists blinded to the patients' allocation arm. The examination tests included: an ECG, two-dimensional transthoracic echocardiography, CPET, QoL assessment by the European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L) questionnaire, pulmonary function test and blood samples for a panel of baseline biomarkers. Researchers performing the CPET and the other study procedures, excluding physiotherapist visits, were also blinded to treatment assignment.

Treatment intervention and physiotherapist visits

Following screening and baseline visit (day 0), patients received the following physiotherapist visits:

1. UC arm: Patients allocated to this arm were checked by a physiotherapist at the first visit (at day 1±3) and last visit (at day 90±5), who measured their maximal inspiratory pressure (MIP). MIP was obtained using a handheld respiratory mouth pressure metre (electronic manometer-ELKA, PM15). With a nose clip, patients were instructed to breathe through a mouthpiece only during inspiration. Patients repeated this manoeuvre within a 1 min interval until three technically satisfactory and reproducible measurements were obtained (variation of −10%). The MIP values were obtained standing by inspiration from residual volume.

Patients allocated to this arm did not receive any physical therapy.

2. IMT group arm: patients allocated to this arm were checked by a physiotherapist at visit 1 (at day 1±3), weekly and at the last visit (at day 90±5). MIP was measured at each visit. Also, on visit 1 (day 1±3), a physiotherapist instructed and educated patients to perform diaphragmatic breathing during the training sessions. After visit 1, the patients started home-based inspiratory training at a resistance of 25%–30% of measured MIP, twice daily, for 20 min each session, for 12 weeks, using a threshold inspiratory muscle trainer (Threshold IMT, Respironics).

The physiotherapist examined the patients weekly by checking the diary card and measuring their MIP. The resistance was modified each session according to 25%–30% of their weekly MIP measured.

Outcome measurement

Cardiopulmonary exercise testing

Maximal functional capacity was evaluated using incremental and symptom-limited CPET on a bicycle ergometer, beginning with a workload of 10 W and increasing gradually in a ramp protocol at 10 W increments every 1 min. We defined maximal functional capacity as when the patient stops pedalling because of symptoms and the respiratory exchange ratio (RER) was ≥1.1. During exercise, patients were monitored with 12-lead ECG and blood pressure measurements every 2 min. Gas exchange data and cardiopulmonary variables were averages of values taken every 10 s. PeakVO_2 was defined as the highest value of VO_2 during the last 20 s of exercise. Once peakVO_2 was obtained, we calculated its per cent of predicted peakVO2 (pp-peakVO2), defined as the percentage of predicted peakVO2 adjusted for sex, age, exercise protocol, weight and height according to the Wasserman/Hansen standard prediction equation for the healthy and sedentary population. The ventilatory efficiency was determined by measuring the slope of the linear relationship between minute ventilation (VE) and carbon dioxide production (VCO2) across the entire course of the exercise (VE/VCO_2 slope).

The heart rate (HR) response during CPET was evaluated following the chronotropic index (CIx) formula=peak HR-rest HR/ [(220-age)-restHR)].[14]

Each subject underwent two tests (at baseline and 12 weeks).

Health-related QoL assessment

EQ-5D-3L instrument was used to assess the impact of the IMT on health-related QoL.[15] The EQ-5D-3L evaluates five dimensions and uses a simple score (1–3) for evaluating each dimension, with 11 111 representing the best health state and 33 333 representing the worst health state. Furthermore, the EQ-5D-3L instrument introduces a visual analogue scale, which provides a self-rated health status, with 0 representing the worst imaginable health and 100 representing the best imaginable health.[15] Each subject underwent two tests (at baseline and 12 weeks).

Endpoints

The study's primary endpoint was the average change from baseline in mean peakVO_2. The secondary endpoints were: (a) absolute changes in VE/VCO_2 slope, (b) absolute changes in chronotropic response during CPET and (c) absolute changes in different QoL dimensions assessed by the EQ-5D-3L tool.

Statistical analysis

All statistical comparisons were made under an intention-to-treat principle.

Descriptive analysis

Continuous variables are expressed as means (±1 SD) or medians (IQR), and discrete variables are as percentages. At baseline, the means, medians, and frequencies among treatment groups were compared using the t-test, Wilcoxon and χ^2 test.

Sample size

The primary efficacy endpoint null hypothesis stated no differences in the mean peakVO_2 among the IMT group and UC arm patients. Based on previous studies in other clinical scenarios,[10–12] IMT would be associated with a significant increase of at least a mean peakVO_2 of 3 mL/kg/min, with an SD of ±2.5.

Assuming an allocation ratio of 1:1, 22 patients (11 patients per group) would provide 80% of power at a significance alpha level <0.05. In addition, we assumed 15% of withdrawals or losses to follow-up. Thus, 13 patients per arm (26 patients) were estimated. The software used for sample size calculation was GRANMO.

Inferential analyses

A linear mixed regression model (LMRM) was used to analyse the primary and secondary continuous endpoints. All analyses included the baseline value of the endpoint as a covariate (mixed model within the framework of analysis of covariance). In addition, the period effect was tested by modelling the interaction between the treatment group and the period. LMRMs are presented as least square means with 95% CIs and p values. All analyses were performed with STATA V.15.1. (Stata Statistical Software, Release 15 (2017); StataCorp LP).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our post hoc analysis.

RESULTS

Compliance with the trial protocol

Recruitment accomplished the sample size calculation estimated in the registered protocol. In addition, all enrolled participants met the eligibility criteria. Therefore, all of the outcome measures in the registered protocol are reported.

The flow of participants through the study

A total of 32 patients were assessed for eligibility, of whom 26 met the inclusion criteria and agreed to participate in the study. A detailed flow chart is presented in figure 1. All patients allocated to the control group completed the two physiotherapist visits. Among 13 patients assigned to the IMT group, 12 completed all weekly physiotherapist visits and one interrupted their weekly physiotherapist visit for 2 weeks due to SARS-CoV-2 reinfection.

Baseline characteristics

Patient baseline characteristics are presented in table 1. At baseline, the mean age was 50.4±12.2 years, 42.3%

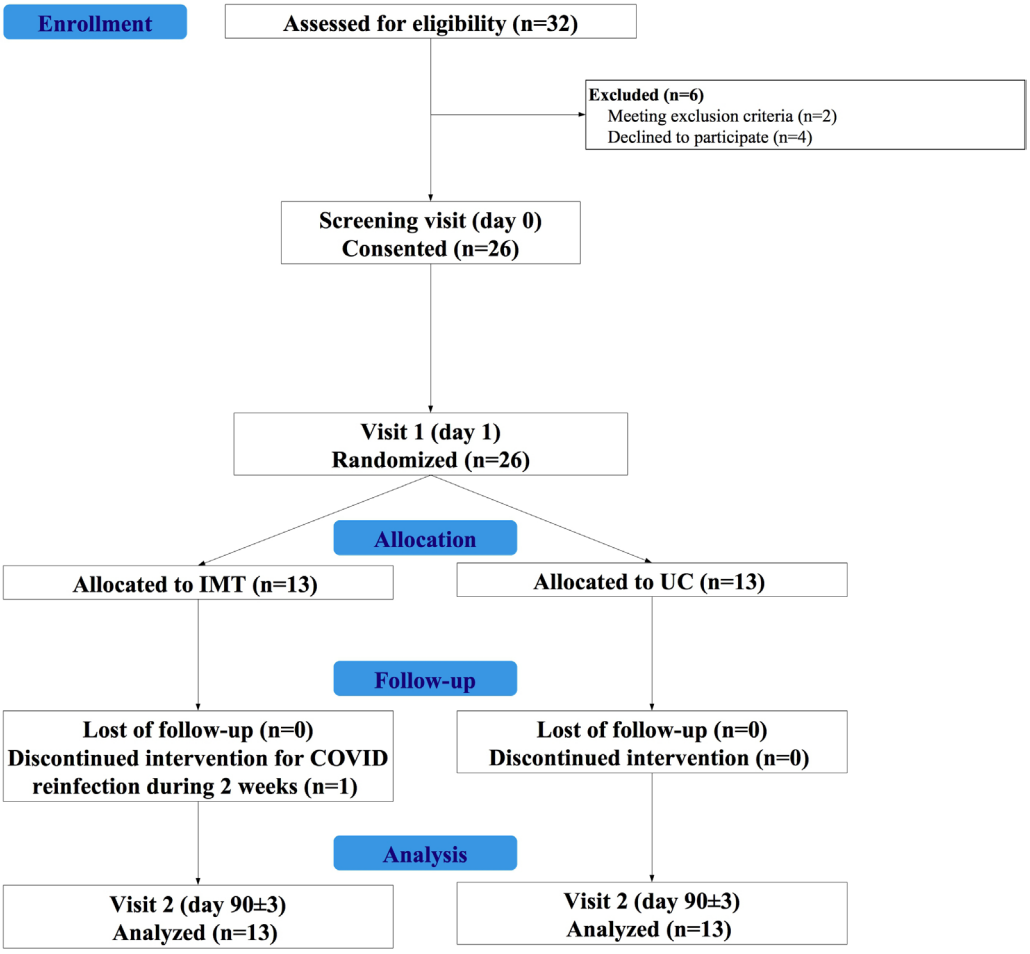

Figure 1 Flow chart for patient's inclusion and follow-up. IMT, inspiratory muscle training; UC, usual care.

were women, 11.5% had a history of hypertension and the mean time to the first CPET from hospital discharge was 362±105 days. Patients included showed a moderately reduced functional capacity (mean pp-peakVO_2 was 74.9±15%). There were no significant differences in clinical, echocardiographic, functional tests or laboratory data across randomisation arms.

Primary endpoint

At baseline and 3 months, all patients performed a maximal CPET (RER>1.1).

Between-person comparisons

At 3 months, the mean of peakVO_2 was higher in those in the IMT group (22.2 mL/kg/min, 95% CI 21.3 to 23.2 vs 17.8 mL/kg/min, 95% CI 16.8 to 18.7; p<0.001 (Δ+4.46 mL/kg/min)) as shown in figure 2A. Similar findings were found when pp-peakVO_2 was analysed. At 12 weeks, the mean of pp-peakVO_2 was also higher in patients allocated to the IMT group (89.1 %, 95% CI 85.2 to 92.9 vs 71.1 %, 95% CI 67.2 to 74.9; p<0.001 (Δ+18.03 %)) (figure 2B).

Within-person comparisons

The precomparisons and postcomparisons within groups showed a significant increase in mean peakVO_2 values for the IMT group (3.4 mL/kg/min, 95% CI 2.1 to 4.6, p<0.001). Conversely, the UC group decreased in mean peakVO_2 (−1.09 mL/kg/min, 95% CI −1.8 to −0.384, p=0.006).

Secondary endpoints

Effect of IMT on VE/VCO_2 slope

VE/VCO_2 slope did not significantly differ between the IMT group versus UC at 12 weeks (Δ −1.92, 95% CI −4.69 to 0.85, p=0.165) (figure 3A).

The precomparisons and postcomparisons within groups did not show a significant change for the IMT group (−1.03 mL/kg/min, 95% CI −2.75 to −0.69, p=0.214) or UC group (−0.24 mL/kg/min, 95% CI −2.14 to 1.66, p=0.784) at 12 weeks.

Effect of IMT on HR response to maximal exercise

At 12 weeks, the mean of CIx significantly increased in those patients allocated to the IMT group (0.75, 95% CI 0.66–0.84 vs 0.62, 95% CI= 0.53–0.71; p=0.046 (Δ+0.13)) (figure 3B).

Table 1 Baseline characteristics of the patients stratified by randomisation arm

Variables	All patients	Training	Control	P value
n (%)	26 (100)	13 (50)	13 (50)	
Demographic and medical history				
Age, years	50.4±12.2	49.9±11.6	50.8±13.2	0.664
Women, n (%)	11 (42)	7 (54)	4 (31)	0.234
BMI, kg/m^2	29 (26–32)	29 (26–32)	30 (27–32)	0.643
Hypertension, n (%)	3 (12)	1 (8)	2 (15)	0.536
Current smoker, n (%)	1 (4)	1 (8)	0 (0)	0.232
Prior smoker, n (%)	8 (31)	4 (31)	4 (31)	1
Length of hospital stay, days	8 (5-15)	6 (5-15)	8 (7-11)	0.877
Received steroids, n (%)	25 (96)	12 (92)	13 (100)	0.232
Time to the first CPET from discharge, days	362±105	385±97	340±105	0.638
Vital signs				
Heart rate at rest, bpm	77±11	78±12	77±10	0.443
Systolic blood pressure at rest, mm Hg	117±12	116±10	118±13	0.357
Diastolic blood pressure at rest, mm Hg	61±5	63±5	60±6	0.434
Laboratory values, echocardiography parameters and pulmonary function test				
Haemoglobin, g/dL	14.6±1.1	14.6±1.4	14.5±0.9	0.801
CRP, mg/L	1.6 (0.8–3.2)	1.8 (0.8–3)	1.4 (0.8–3.2)	0.939
NT-proBNP, pg/mL	28 (14–43)	30 (18–36)	26 (11–50)	0.939
LVEF, %	65.6±6.1	65.2±5.8	66.1±6.6	0.680
PASP, mm Hg*	27.7±4.7	26.8±5.9	28.7±2.9	0.105
DLCO, %	72.5±13.3	72.8±13.2	72.1±13.9	0.868
MIP, cmH_2O	83 (62–105)	80 (66–101)	86 (60–110)	0.858
CPET variables				
Workload, W	119.5±36	122±34.2	117.1±39	0.659
Exercise time, s	684.8±218.7	669.5±237.3	700±207	0.644
Peak heart rate, bpm	139±20	144±20	135±20	1
Chronotropic index†	0.64±0.19	0.72±0.19	0.64±0.18	0.855
Peak systolic blood pressure, mm Hg	157±20	158±20	155±20	0.918
RER	1.12 (1.1–1.16)	1.12 (1.1–1.16)	1.1 (1.1–1.15)	0.708
PeakVO_2, mL/kg/min	18.9±5	18.8±5.8	18.9±4.4	0.323
pp-peakVO_2, %	74.9±15	76.9±17	72.9±14	0.494
VE/VCO_2 slope	29.4±5.2	28.2±4.6	30.5±5.6	0.480
Health-related QOL: EQ-5D-3L questionnaire				
Mobility dimension	1 (1–1)	1 (1–1)	1 (1–1)	0.149
Self-care dimension	1 (1–1)	1 (1–1)	1 (1–1)	1
Usual activities dimension	1 (1–2)	1 (1–2)	1 (1–1)	0.193
Pain/discomfort dimension	1 (1–2)	1 (1–2)	1 (1–2)	1
Anxiety/depression dimension	1 (1–2)	2 (1–2)	1 (1–1)	0.098
Visual analogue scale	70 (60–80)	70 (50–80)	79 (70–87)	0.073

Continuous variables are presented as median (IQR), and categorical variables are as percentages.
*Data available in 15 patients (eight in the training arm and seven in the control arm).
†Cronotropic index formula=peak HR-rest HR/ [(220-age)-restHR)].
BMI, body mass index; CPET, cardiopulmonary exercise testing; CRP, C reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; LVEF, left ventricle ejection fraction; MIP, maximal inspiratory pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; PASP, pulmonary artery systolic pressure; peakVO_2, peak oxygen consumption; pp-peakVO_2, percent of predicted peak oxygen consumption, RER, respiratory exchange ratio; QoL, quality of life; VE/VCO_2 slope, ventilatory efficiency.

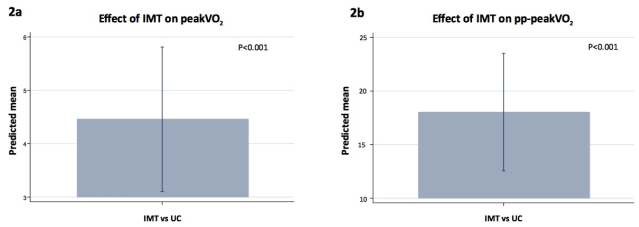

Figure 2 Change in mean $peakVO_2$ and $pp\text{-}peakVO_2$. IMT, inspiratory muscle training; $peakVO_2$, peak oxygen consumption; $pp\text{-}peakVO_2$, percent predicted peak oxygen consumption; UC, usual care.

The precomparisons and postcomparisons within groups did not show a significant change for the IMT group (0.06, 95% CI −0.17–0.13, p=0.122) or UC group (−0.04, 95% CI −0.15 to 0.072, p=0.447).

Effect of IMT on health-related QoL

A significant improvement in usual activities (−0.31, 95% CI −0.54 to −0.07, p=0.013) and anxiety/depression (−0.53, 95% CI −0.67 to −0.40, p<0.001) dimensions was found in IMT group (figure 4A,E), with no significant changes in UC. IMT resulted in a non-significant improvement in both groups' mobility, self-care and pain/discomfort dimensions (figure 4B,C,D). A significant change in the patient's self-rated health on a vertical visual analogue scale dimension in those patients allocated to the IMT group (21.1, 95% CI 12.9 to 29.4, p<0.001) (figure 4F).

Safety and adherence

There were no reports of adverse effects following or during exposure to IMT. All patients in the IMT group reported two daily sessions of IMT. Patients allocated in the IMT group significantly improved the maximal inspiratory pressure (+79.4 cmH_2O, 95% CI 68.7 to 98.1, p<0.001) at 12 weeks, with no significant change in the UC group (+17.3cmH_2O, 95% CI −2.1 to 36.7.1, p=0.075).

DISCUSSION

The main finding of the InsCOVID trial is that a 12-week home-based IMT programme in symptomatic postdischarged patients with long COVID resulted in a substantial improvement in physical performance and QoL. To our knowledge, this is the first randomised controlled study that evaluated the effect of a home-based IMT programme on maximal functional capacity over a middle-aged postdischarged population with long COVID and reduced aerobic capacity.

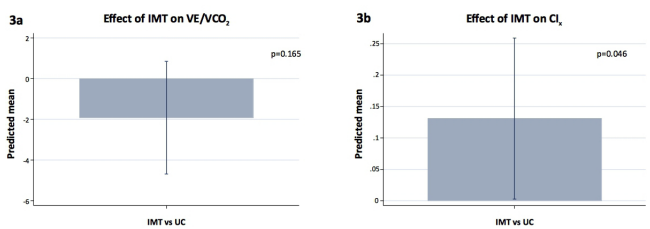

Figure 3 Change in mean ventilatory efficiency and chronotropic index. CIx, chronotropic index; IMT, inspiratory muscle training; UC, usual care; VE/VCO_2 slope, ventilatory efficiency.

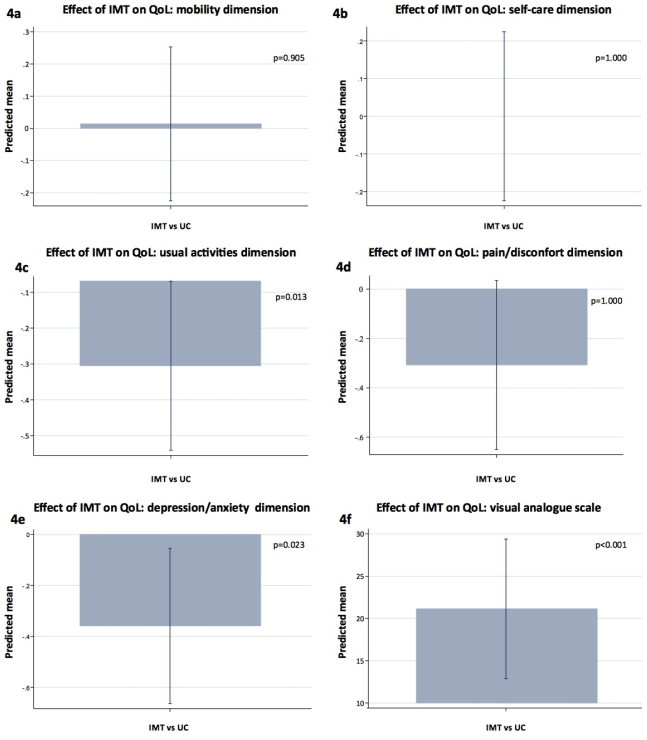

Figure 4 Change in the score of different QoL dimensions assessed by the EQ-5D-3L tool. IMT, inspiratory muscle training; QoL, quality of life; UC, usual care.

Recent clinical practice recommendations and regulatory agencies have increasingly recognised patients' symptoms and physical function as important therapeutic targets in long COVID.[5 16–18] Among them, exercise intolerance and breathlessness are cardinal clinical features. $PeakVO_2$ during a maximal symptom-limited CPET is the most reliable parameter to assess maximal functional capacity in long COVID and provides relevant information about potential mechanisms of exercise limitation among people with long COVID.[19] Paradoxically, however, evidence regarding the effects of exercise-based rehabilitation programmes on improving maximal exercise capacity (measured as $peakVO_2$) in long COVID comes from observational studies and remains scarce.[20 21]

IMT in long COVID

Home-based IMT programmes demonstrated significant improvement in $peakVO_2$ in other clinical scenarios.[12 22] However, regarding the long COVID setting, only a previously published randomised study evaluated the effect of an 8-week home-based IMT programme versus UC on reported QoL (primary endpoint), perceived dyspnoea (secondary endpoint) and an indirect evaluation

of fitness (secondary endpoint) in a non-selected population of outpatients with long COVID.[23] The authors reported improved perceived dyspnoea with no differences in the primary endpoint. Furthermore, although the authors did not directly measure the maximal functional capacity, they reported a significant improvement in the trained group's indirect measurement of peakVO_2 (using a step test). Interestingly, the increase in estimated peakVO_2 was similar to the present study (Δ~+4 mL/kg/min). Likewise, in concordance with the current study, a home-based IMT seems to be a safe, feasible and efficacious approach for improving functional capacity in patients with long COVID.

Biological plausibility

Although it was not the aim of this study to analyse the physiological mechanisms underlying the effects of IMT on patients with long COVID, several potential mechanisms have been postulated to explain the beneficial effects of IMT on functional capacity: (1) decreases the rating of perceived exertion and improves respiratory muscle economy,[24 25] improving exercise tolerance; (2) improves ventilatory efficiency and improves breathing patterns during exercise hyperpnoea[24 26] and (3) attenuates the respiratory muscle metaboreflex,[24 27] which leads to sympathetic attenuation and autonomic regulation.

Interestingly, 12-week IMT significantly improved blunted HR response to exercise, which has been associated with autonomic dysfunction in long COVID patients.[28] Similarly, IMT enhanced patients' self-reported health-related QoL or anxiety. Finally, although VE/VCO_2 decreased in patients allocated to the IMT arm, the magnitude of this change was not significant. Two main reasons may partially explain this last fact. The first, and most likely reason, is the short follow-up, which may underestimate potential benefits that can take longer to emerge. Second, considering that the sample size was calculated for the primary endpoint, some of the negative results in secondary outcome measures could be explained by insufficient statistical power (type II error).

Clinical implications

Home-based IMT is a simple, low-cost and safe intervention that could be implemented after a short physiotherapeutic training period. According to present findings, home-based IMT is a suitable, feasible and effective alternative for improving exercise capacity and QoL in patients with long COVID and may offer an accessible physical therapy model, requiring minimal infrastructure resources.

Study limitations

Several limitations need to be acknowledged. First, as a single-centre study, the generalisability of our results to other populations may be limited. Second, this study has the inherent limitations of being a trial with a relatively small number of participants. As such, we cannot discard that the trial findings on secondary endpoints may be due to low statistical power (type II error). Third, we have exclusively evaluated patients with long COVID after hospital admission due to SARS-CoV-2 pneumonia. Therefore, whether home-based IMT improves short-term maximal exercise capacity in patients with other post-COVID-19 conditions remains elusive. Finally, with the current data, we cannot unravel the biological mechanism behind these findings.

CONCLUSIONS

Among postdischarged patients with long COVID and reduced aerobic capacity, home-based IMT resulted in a significant improvement in exercise capacity and QoL. However, further studies must confirm these results and elucidate the underlying pathophysiological mechanisms responsible for these benefits.

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Contributors Conceptualisation and design: PP, ED, CG and LL. Acquisition, analysis or interpretation of data for the work: all authors. Drafting protocol manuscript: all authors. A critical review of protocol manuscript: all authors. Guarantor: PP

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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 and was approved by Comité Ético de Investigación Clínica (CEIC) del Hospital Clínico Universitario de Valencia. This study was registered at http://clinicaltrials.gov (NCT05279430). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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