

Additive benefit of rehabilitation on physical status, symptoms and mental health after hospitalisation for severe COVID-19 pneumonia

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ABSTRACT

Introduction The potential additive benefits of rehabilitation beyond spontaneous recovery post-COVID-19 currently remain unknown.

Methods In this prospective, interventional, non-randomised parallel assignment two-arm study, we investigated the effects of an 8-week rehabilitation programme (Rehab, n=25) added to usual care (UC) versus UC (n=27) on respiratory symptoms, fatigue, functional capacity, mental health and health-related quality of life in patients with COVID-19 pneumonia, 6–8 weeks post-hospital discharge. The rehabilitation programme included exercise, education, dietary and psychological support. Patients with chronic obstructive pulmonary disease, respiratory and heart failure were excluded from the study.

Results At baseline, groups were not different in mean age (56 years), gender (53% female), intensive care unit admission (61%), intubation (39%), days of hospitalisation (25), number of symptoms (9) and number of comorbidities (1.4). Baseline evaluation was conducted at median (IQR) 76 (27) days after symptoms onset. Groups were not different regarding baseline evaluation outcomes. At 8 weeks, Rehab showed significantly greater improvement in COPD Assessment Test by a mean±SEM (95% CI) 7.07±1.36 (4.29–9.84), p<0.001 and all three fatigue questionnaires: Chalder-Likert: 5.65±1.27 (3.04–8.25), p<0.001; bimodal: 3.04±0.86 (1.28–4.79), p=0.001; Functional Assessment of Chronic Illness Therapy: 6.37±2.09 (2.08–10.65), p=0.005 and Fatigue Severity Scale: 1.36±0.433 (0.47–2.25), p=0.004. At 8 weeks rehab also showed significantly greater improvement in Short Physical Performance Battery: 1.13±0.33 (0.46–1.79), p=0.002; Hospital Anxiety and Depression Scale (HADS) Anxiety: 2.93±1.01 (0.67–5.18), p=0.013; Beck Depression Inventory: 7.81±3.07 (1.52–14.09), p=0.017; Montreal Cognitive Assessment: 2.83±0.63 (1.5–4.14), p<0.001; EuroQol (EQ-5D-5L) Utility Index: 0.21±0.05 (0.1–0.32), p=0.001 and Visual Analogue Scale: 6.57±3.21 (0.2–13.16), p=0.043. Both groups significantly improved 6-min walking distance by approximately 60 m and pulmonary function measures, whereas post-traumatic stress disorder measurement IES-R (Impact of Event Scale, Revised) and HADS-Depression score were not different between groups at 8 weeks. A 16% attrition rate was

WHAT IS ALREADY KNOWN ON THIS TOPIC

A significant proportion of patients post-COVID-19 suffers from persistent symptoms. Rehabilitation improves COVID-19 sequelae; however, the impact of natural recovery has not been determined.

WHAT THIS STUDY ADDS

The present study shows that rehabilitation is associated with significant additive benefits beyond spontaneous recovery and facilitates recovery of symptoms, impaired mental health and health-related quality of life post-COVID-19 that otherwise would remain incomplete with usual care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Randomised controlled trial studies are needed to confirm the benefits of rehabilitation post-COVID-19 compared to usual care.

observed in the rehabilitation group exhibiting a threefold increase in training workload. There were no adverse effects reported during exercise training.

Discussion These findings highlight the added value of rehabilitation post-COVID-19 to amplify the natural course of physical and mental recovery that otherwise would remain incomplete with UC.

INTRODUCTION

The COVID-19 pandemic has claimed worldwide more than half a billion of cumulative cases and 7 million deaths and numbers are still rising every day (<https://COVID-19.who.int/>). A significant proportion of these patients, ranging from 10% in the general population¹ up to 76% in hospitalised patients² suffer from a diversity of symptoms persisting for 5–12 months from disease onset.^{2–4} These symptoms include fatigue

and muscle weakness, mental health issues (anxiety, depression, sleeping difficulties),² cognitive impairment including memory loss and concentration disorders, shortness of breath, chest pain and poor health-related quality of life (HRQoL).^{5,6} Fatigue is a cardinal symptom of post-COVID-19 patients. The majority of patients report worse symptoms after hospitalisation³ that persist a year after.⁴ Even after discharge from an inpatient rehabilitation programme, post-COVID-19 patients suffer from a significant reduction in physical function, and the ability to perform daily activities⁷; however, fatigue and respiratory symptoms significantly improve.⁸ The National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network and the Royal College of General Practitioners in the UK defined this cluster of symptoms persisting for more than 12 weeks as 'post-COVID-19 syndrome'.⁹ NICE and the latest European Respiratory Society (ERS) statement integrate these definitions to describe patients with ongoing symptomatic or post-COVID syndrome using the term 'long-COVID'.^{9,10}

Among the factors associated with poor recovery are comorbidities and more severe acute illness.³ Patients hospitalised, especially those admitted to the intensive care unit (ICU), been intubated or receiving high oxygen mixtures have severe symptoms for several months on recovery.^{3,11} Advanced age and prolonged hospitalisation are predictors of poor recovery in patients admitted to the ICU due to respiratory failure.¹² Natural recovery from COVID-19 pneumonia varies among patients.¹³ Evans *et al* have shown a much slower recovery for patients hospitalised compared with those not requiring hospitalisation.^{3,4}

Early in the course of the pandemic, medical associations worldwide issued guidance emphasising the necessity for rehabilitation programmes tailored to the needs of the growing number of post-COVID-19 patients with persistent symptoms and disabilities.^{14,15} Since then, an increasing number of prospective, single cohort studies have shown that rehabilitation is a feasible, safe and effective therapeutic intervention in post-COVID-19 patients with a range of severity and symptoms.^{16,17} Studies have shown clinically meaningful benefits in improving symptoms (including fatigue), exercise capacity, respiratory function and measures of HRQoL in these patients.^{8,17–19} However, the impact of natural recovery was not determined in these studies. Therefore, the additive benefits of rehabilitation beyond spontaneous recovery post-COVID-19 currently remain unknown. A certain degree of natural recovery in pulmonary and extrapulmonary disease sequelae has been reported to occur post-COVID-19.^{20,21} Therefore, it is important to evaluate the additive value of rehabilitation beyond spontaneous recovery to appreciate which aspects of the post-COVID-19 sequelae could be targeted through a rehabilitation programme. Accordingly, the aim of the present study was to investigate the effects of rehabilitation added to usual care (UC) versus UC on fatigue and respiratory symptoms, functional capacity, mental

health and HRQoL outcomes in patients with COVID-19 pneumonia as suggested by the British Thoracic Society (BTS) and joint ERS and American Thoracic Society (ATS) guidance.^{14,15} Based on the emerging evidence from a review of literature on rehabilitation studies,¹⁷ it was reasoned that rehabilitation would be more effective than UC in improving respiratory symptoms and fatigue post-COVID-19.

METHODS

Study design

This was a prospective, interventional, non-randomised parallel assignment two-arm study that was conducted from January until August 2021. Patients who recovered from severe/critical COVID-19 pneumonia (WHO score 6–9)²² with a COPD Assessment Test (CAT) score ≥ 10 ²³ and/or a Post-COVID-19 Functional Status Scale (PCFS) score ≥ 2 ²⁴ (both indicative of significant symptoms during daily activities^{23,24}) were considered eligible for enrolment. Eligible patients were encouraged to participate in a supervised, outpatient rehabilitation programme within 6–8 weeks post hospital discharge, according to BTS and joint ERS/ATS guidance.^{14,15} Patients who could participate in the supervised rehabilitation programme comprised the intervention group (Rehab, n=25), whereas patients who were unable to participate (due to logistical/transport issues) comprised the UC group (n=27). All patients were evaluated at study entry (baseline) and following 8 weeks from baseline.

Participants

Inclusion criteria

Patients who were hospitalised in a ward or ICU requiring high oxygen mixtures, non-invasive ventilation (NIV) or intubation were approached to enrol in rehabilitation as they were in need of supported recovery.^{3,12,14,15} All patients had positive molecular testing for COVID-19 infection, a CAT score ≥ 10 and/or a PCFS score ≥ 2 .

Exclusion criteria

Patients excluded from the study (not the post-COVID-19 rehabilitation service programme) were those with chronic obstructive pulmonary disease (COPD), chronic respiratory or heart failure. These patients even though particularly susceptible to severe complications from COVID-19³ were evidently expected to benefit from a rehabilitation programme.^{14,15} Exclusion of these comorbidities served to focus on the post-COVID sequelae in terms of baseline symptomatology and improvements after rehabilitation. Patients treated for COVID-19 infection where the main reason for hospitalisation was not the virus infection (eg, due to coronary heart disease, surgery, etc) and patients with active disease (until they stopped being infectious) were also excluded. Not ambulatory patients, suffering from dementia, chronically paralysed, with paraplegia, with multiple injuries or other serious orthopaedic problems that caused disability, and

patients suffering from very serious underlying diseases such as end-stage cancer and those with neurological diseases causing disability were also excluded.¹⁴

Patient and public involvement

The study design was dictated by the post-COVID-19 rehabilitation protocol of our clinic. Early in the pandemic, we designed and implemented a supervised post-COVID-19 rehabilitation service programme where the safety precautions, rehabilitation and evaluation procedures followed the ATS/ERS and BTS guidance.^{14 15} The experience from the programme informed the Hellenic Thoracic Society post-COVID-19 taskforce (<https://hts.org.gr/guidelines>)²⁵ guiding post-COVID-19 rehabilitation practice in Greece. Our post-COVID-19 rehabilitation service programme was available to all symptomatic patients 6–8 weeks post-hospital discharge, thereby precluding randomisation of patients to intervention and UC.

Given that the main complaints of patients post-COVID were persistent symptoms from the respiratory system and fatigue, the CAT and fatigue questionnaires were chosen as the primary outcomes of the study. Our rehabilitation centre is linked through the Ministry of Health to the Greek Association of patients with the long-COVID syndrome. The findings of the study are expected to provide more evidence for the effectiveness of post-COVID-19 rehabilitation and consequently the need to expand rehabilitation services and make them available to more patients.

Outcomes

The primary outcome of the present study was fatigue and respiratory symptoms. We used three questionnaires to assess fatigue in the last 7 days (Functional Assessment of Chronic Illness Therapy—FACIT), 2 weeks (Fatigue Severity Scale—FSS) and 1 month (Chalder Fatigue Scale—CFQ) to study short-term and long-term impact or change. The FACIT is a 13-item questionnaire designed to assess fatigue and tiredness with higher scores representing less fatigue.²⁶ The FSS is a nine-item questionnaire that rates the severity of fatigue symptoms.²⁷ The CFQ is a self-report questionnaire for measuring the extent and severity of tiredness and fatigue within both clinical and non-clinical, epidemiological populations. The bimodal score (CFQ-bim) is used to assess the number of symptoms with a threshold of 4 or more indicating severe fatigue.^{28 29} The Likert score (CFQ-Lik) is used to assess the intensity of symptoms.³⁰ Post-COVID-19 respiratory symptoms were assessed by the CAT. The CAT is an eight-item questionnaire that was developed to assess COPD symptoms and qualify health status impairment.³¹ In healthy subjects, the mean score is 6.9, in COPD 9.2³² and a score ≥ 10 indicates increased symptoms and is used as a threshold for treatment.³³ Clinically relevant improvements need to exceed 3 points in patients with COPD of similar age.³⁴

The secondary outcomes of the study included functional capacity, mental health, pulmonary function and HRQoL. Functional capacity was assessed by the 6-min walking test (6MWT) and the Short Physical Performance Battery (SPPB) test. The SPPB is an established test for measuring physical performance. In people of 60–69 years of age, the mean \pm SD reference score is 11.7 \pm 0.8 for men and 11.4 \pm 1.1 for women.³⁵ Mental health was assessed by the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), the Impact of Event Scale, Revised (IES-R) for post-traumatic stress disorder (PTSD) and the Montreal Cognitive Assessment (MoCA). The HADS is a 14-item questionnaire that measures anxiety and depression in the general medical population³⁶ with a threshold of 8 for substantial symptoms of anxiety or depression.³⁷ The BDI is a self-reported inventory of 21 questions that is used to measure the severity of depression.³⁸ The IES-R is a 22-item tool for assessing the extent of symptoms the past 7 days caused by a traumatic life event.³⁹ MoCA is a brief (10-min) screening tool for clinicians to detect mild cognitive impairment (MCI).⁴⁰ HRQoL was assessed using the EuroQol (EQ-5D-5L), and pulmonary function was evaluated by spirometry (forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC)) and diffusing capacity of the lungs for carbon monoxide (TL_{co}). The EQ-5D-5L is a simple, five-dimension, self-reported instrument for the assessment of HRQoL that has been widely used in patients with COPD to estimate health changes after rehabilitation. The EQ-5D-5L comprises the Utility Index (UI)—a single number that is obtained by applying a formula that assigns values to each of the levels in each dimension. The EQ-VAS, a Visual Analogue Scale (VAS), is used by patients to rate their own health.⁴¹

Adverse effects evaluation

Patients' medical records were thoroughly checked before enrolling to the study for possible complications of COVID-19 infection including thromboembolic disease, complications from the heart, mainly myocarditis and the detection of hypoxaemia during exertion. At every rehabilitation session, patients completed a checklist of newly related symptoms (leg swelling, chest pain, arrhythmia, etc) according to BTS guidance.¹⁴ Patients with symptoms were referred for further evaluation including a complete cardiological assessment. The safety precautions that were followed have been described by the Hellenic Thoracic Society post-COVID-19 taskforce (<https://hts.org.gr/guidelines>)²⁵ and are detailed in the online supplement file.

Rehabilitation programme

The programme was multidisciplinary and included supervised exercise training, education, breathing control, dietary advice and psychological support. The programme consisted of two sessions per week over an 8-week period.

Cycle ergometer peak work capacity

Patients assigned to the Rehab group performed a maximum incremental test on an electromagnetically braked cycle ergometer (Ironman M3; Garland, Texas, USA) to determine peak work rate (WR_{peak}) (see online supplement file). Heart rate (HR) and percentage of arterial oxygen saturation (%SpO₂) were determined using a pulse oximeter (Onyx, NONIN), and symptoms of dyspnoea and leg discomfort were assessed by the 0–10 Borg scale.⁴²

Exercise prescription

At the beginning of the programme, exercise intensity was equivalent to 50% of WR_{peak}, alternating 30 s of work by 30 s of rest periods for a total duration of 30 min/session.^{43 44} The workload was increased weekly by 10% of the baseline work rate, based on patients' Borg Scale symptoms of breathlessness and leg discomfort. The workload was increased when Borg dyspnoea and/or leg discomfort was reduced by 1 unit for a given workload. During training, the HR was recorded by a pulse oximeter and the Borg (0–10) scale was used for the evaluation of breathlessness and leg discomfort. The programme also included resistance training for upper and lower limbs using fitness equipment. Details of the programme are provided in the online supplement file.

Statistical analysis

Analyses were performed using SPSS (V.25, IBM). Prior to analysis, the assumption of normality for outcomes was assessed using the Shapiro-Wilk test. Descriptive statistics included mean (\pm SD or SE) or median (IQR) as appropriate. Comparisons of baseline characteristics between the intervention and UC groups were made using independent sample *t*-test or Mann-Whitney *U* tests for non-parametric data. Within-group differences were assessed by paired *t*-tests for parametric data or Wilcoxon signed rank tests for non-parametric data. Fisher's exact test was used for categorical data. Univariate analysis of covariance (ANCOVA) was used to compare Rehab and UC groups at 8 weeks using baseline values (including patients who were lost at follow-up) as covariate to compensate for potential baseline differences and missing data. Multiple comparisons were adjusted using the Bonferroni method. Non-parametric ANCOVA (Quade's) was used for non-parametric data.⁴⁵ Statistical significance was set at $p < 0.05$ for all analyses.

RESULTS

Participant recruitment

From January until August 2021, 133 patients hospitalised with severe COVID-19 pneumonia were identified as potential candidates for the study. Of the 133 hospitalised patients, 72 were assessed for enrolment in the study; the remaining 61 were not assessed for various reasons detailed in figure 1. From those 72 assessed, 3 were excluded due to previously undiagnosed COVID-19

complications (see figure 1), 52 had a CAT score ≥ 10 and/or a PCFS ≥ 2 and agreed to be enrolled into the study; the remaining 17 had a CAT score < 10 and PCFS < 2 and therefore were deemed ineligible for the study. Only 25/52 were able to participate to the rehabilitation programme (Rehab), whereas 27/52 were unable to participate due to transport/logistic reasons thereby comprising the UC group. Of the 25 patients in the Rehab group, 4 did not complete the programme due to professional commitments ($n=3$) and new-onset pulmonary embolism ($n=1$). In the UC group, four patients failed to attend the re-evaluation visit at 8 weeks (figure 1). No adverse effects were found or reported in the UC group.

Patient demographics

There were no significant differences in gender, age, comorbidities, number of symptoms, ICU admission, days of hospitalisation and intubation between the two groups. Groups did not differ in the number of days from discharge and symptoms onset until the baseline assessment. The rehabilitation centre–home distance was significantly greater in the UC group (table 1). Baseline evaluation was conducted at median (IQR) 76 (27) days after symptoms onset.

Outcome measures

Primary outcomes

Baseline measurements were not different between groups. At 8 weeks, Rehab showed significantly greater improvement for CAT by mean \pm SEM (95% CI) 7.07 \pm 1.36 (4.29–9.84), $p < 0.001$ and for all three fatigue questionnaires: Chalder-Likert: 5.65 \pm 1.27 (3.04–8.25), $p < 0.001$ and bimodal score: 3.04 \pm 0.86 (1.28–4.79), $p=0.001$, FACIT: 6.37 \pm 2.09 (2.08–10.65) points, $p=0.005$ and FSS: 1.36 \pm 0.433 (0.47–2.25) points, $p=0.004$. Mean values and 95% CI of primary outcomes at baseline and after 8 weeks are shown in figure 2.

Secondary outcomes

Baseline measurements were not different between groups. Both groups significantly improved 6MWT by approximately 60 m at 8 weeks, whereas Rehab showed significantly greater improvements in SPPB (by 1.13 \pm 0.33 (0.46–1.79) points, $p=0.002$), HADS anxiety (by 2.93 \pm 1.01 (0.67–5.18), $p=0.013$), BDI (by 7.81 \pm 3.07 (1.52–14.09), $p=0.017$), MoCA (by 2.83 \pm 0.63 (1.5–4.14), $p<0.001$), EQ-5D-5L UI (by 0.21 \pm 0.05 (0.1–0.32), $p=0.001$) and VAS (by 6.57 \pm 3.21 (0.2–13.16), $p=0.043$). IES-R (PTSD) and HADS-Depression scores were not significantly different between groups at 8 weeks. Mean or median values at baseline and 8 weeks and differences are presented in table 2. In both groups, pulmonary function tests (PFTs) revealed a significant increase in mean \pm SEM FEV₁ (by 8.5 \pm 2.65% predicted), FVC (8.53 \pm 2.22% pred.) and TL_{co} (8.96 \pm 2.9% pred.) after 8 weeks reaching normal values ($>90\%$ pred) in FEV₁ and FVC and remaining mildly impaired in TL_{co} (72 \pm 15% pred) regardless of

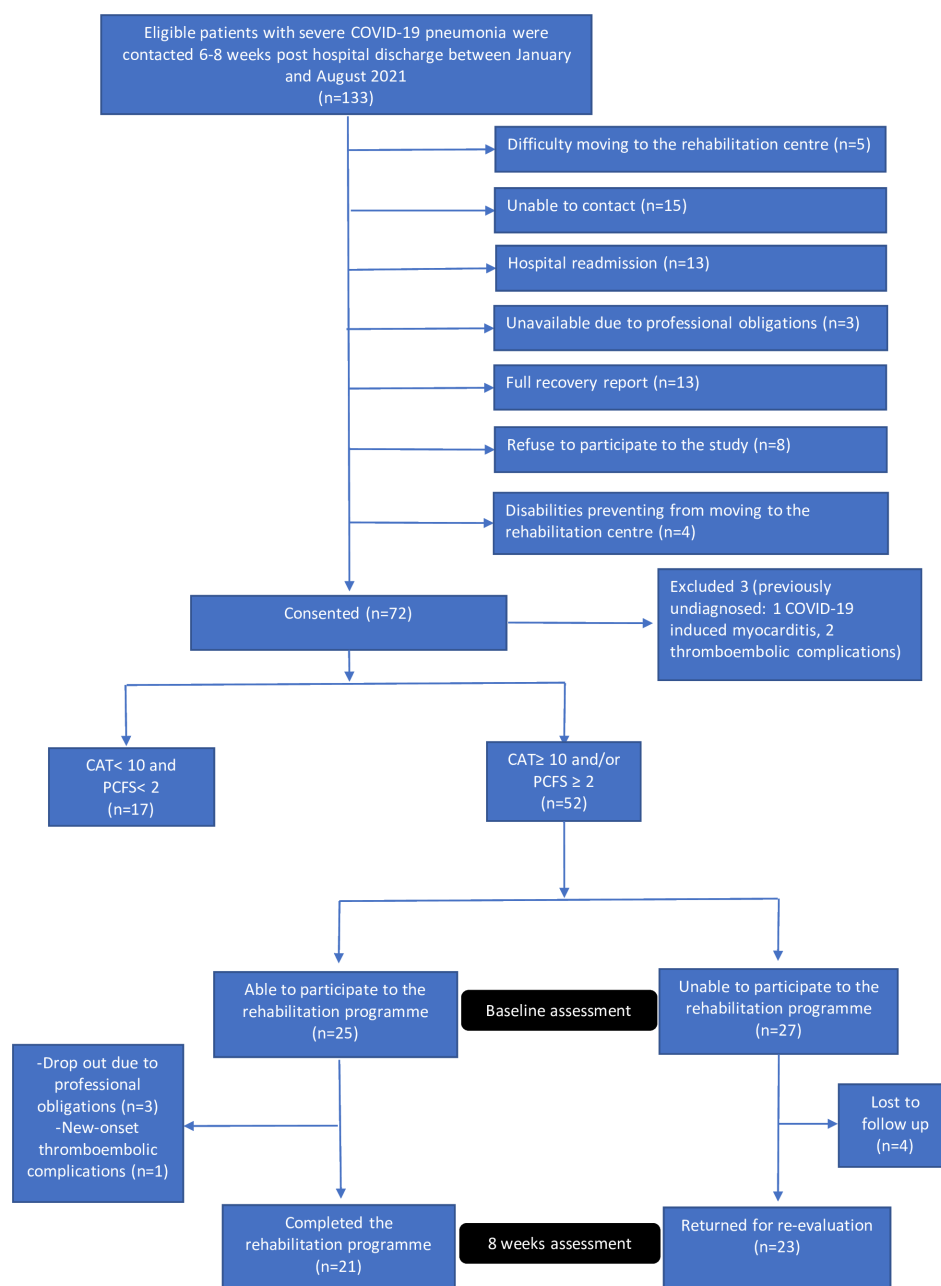


Figure 1 Participant flowchart. CAT, COPD Assessment Test; PCFS, Post-COVID-19 Functional Status Scale.

rehabilitation participation ($p=0.9$). Detailed PFTs outcomes are presented in the online supplement file.

Exercise training

Patients adhered to their exercise regimens reasonably well. The attendance rate during the 16 exercise sessions averaged $90\pm13\%$. Examination of the group's mean training intensity throughout the programme revealed that training intensity increased threefold from the first to the last training session (figure 3). Despite the progressive increase in work rate during cycling, $\%SpO_2$, symptoms of dyspnoea and leg discomfort and HR remained stable throughout the exercise programme (figure 3). The average HR was equivalent to $73\pm11\%$ of maximal

HR. There were not any adverse effects reported throughout the exercise training programme.

DISCUSSION

The main finding of the present study is that compared with UC, outpatient rehabilitation in post-COVID-19 patients with severe/critical pneumonia is associated with significantly greater improvements in measures of fatigue, respiratory symptoms, functional capacity, mental health and HRQoL. Interestingly, we found that UC was associated with significant improvements in measures of functional capacity and pulmonary function 8 weeks after the initial evaluation. However, at (mean \pm SD) 133 ± 20 days following symptoms onset, patients assigned to UC still

Table 1 Baseline characteristics

Group	Median (IQR)	Comparison between groups
Age (years)		
Rehab	55 (11)	p=0.156
UC	60 (15)	
Gender		
Rehab	47% ♂	p=0.611
UC	48% ♂	
ICU admission		
Rehab	67%	p=0.732
UC	57%	
Intubation		
Rehab	47%	p=0.499
UC	33%	
Days of hospitalisation		
Rehab	25 (28)	p=0.279
UC	20 (18)	
Initial evaluation from hospital discharge (days)		
Rehab	49 (31)	p=0.480
UC	42 (22)	
Initial evaluation from symptoms onset (days)		
Rehab	78 (33)	p=0.214
UC	72 (32)	
Symptoms (n)		
Rehab	9 (6)	p=0.897
UC	9 (5)	
Comorbidities (n)		
Rehab	1 (1)	p=0.634
UC	2 (2)	
Distance of rehab centre from home (km)		
Rehab	3.6 (3)	p=0.002*
UC	6.3 (9.9)	
Data are presented as median (IQR). Comparisons between groups were performed with independent sample <i>t</i> -tests for parametric or Mann-Whitney <i>U</i> tests for non-parametric data, and Pearson's χ^2 tests for categorical data.		
*Denotes statistical significance between groups (p<0.05). ICU, intensive care unit; Rehab, rehabilitation group; UC, usual care group .		

suffered from increased fatigue, respiratory symptoms, cognitive and psychological impairment and reduced quality of life. These findings highlight the added value of rehabilitation post-COVID-19 to amplify the natural course of physical and mental recovery.

The novelty of our study is the inclusion of a UC group with comparable baseline characteristics to the rehabilitation group. A challenge in appreciating the potential benefit of rehabilitation post-COVID-19 has been the limited knowledge of the long-term trajectory of

persisting COVID-19 symptoms. It is therefore unclear to what extent natural recovery occurs over time after hospital admission with COVID-19.⁴⁶ Emerging evidence from large multicentre studies indicates that more than 50% of patients perceive that they have not fully recovered 5 and 12 months post-hospital discharge. These patients present with persistent symptoms of fatigue, breathlessness, anxiety, depression, poor cognition and physical dysfunction.³⁴ The long COVID-19 sequelae may persist for several months with minimal signs of recovery.

Little more than half (52%) of patients recovering from COVID-19 pneumonia 32 days after discharge had a mean CAT score ≥ 10 .²³ One year after discharge, the percentage dropped to 6.6%.⁴⁷ Daynes *et al* have found a moderate mean decrease in CAT score (3 points) after 6 weeks of rehabilitation in patients of similar age with less severe disease and baseline scores compared with our cohort.⁸ In the present study, patients after rehabilitation returned to scores close to those observed in healthy subjects (95% CI 5.03–10.35). UC still suffered from increased symptoms (95% CI 10.71–15.52) more than 4 months after disease onset.

In the cohort of Evans *et al*, 56.9% of patients reported worse symptoms of fatigue compared with before hospitalisation.³ Fatigue was still present a year after as measured with the FACIT score.⁴ In the cohort of Daynes *et al*, post-COVID-19 patients after rehabilitation improved FACIT significantly,⁸ a finding confirmed by our study. The FSS baseline score (mean \pm SD) of 4.33 \pm 1.17 in Rehab and 4.02 \pm 2.01 in UC was well above the score in healthy subjects (3.00 \pm 1.08) and comparable to patients with multiple sclerosis, sleep problems and after ischaemic stroke.²⁷ Following rehabilitation, scores (2.57 \pm 1.42) were in accordance with normal subjects while UC remained impaired (3.88 \pm 1.27). In the present study, patients in Rehab showed a significant reduction in both the number of symptoms and intensity of fatigue after rehabilitation. UC scores remained unchanged and above the threshold of 4 in CFQ-bim indicating that patients remained severely fatigued more than 4 months after symptoms onset. In a cohort of patients with diabetes 92 days after COVID-19 infection (41.5% hospitalised, 15% ICU admission), the mean CFQ-bim score was 3.9, significantly different from the score (2.98) of a matched control population without COVID-19 infection.⁴⁸ In a cohort of 128 post-COVID-19 patients with a mean age of 50 years, half of whom were hospitalised, and 72 days after hospital discharge, the mean CFQ-Lik was 15.8 and the mean CFQ-bim was 4.2 (figures similar) to our baseline values.⁴⁹

Improvements in functional capacity are a common finding after rehabilitation^{18 50 51} and our findings concur. However, in our study both groups achieved an increase of around 60 m in 6MWT, whereas other investigators found larger improvements¹⁸ or better performance compared with control.^{50 51} Significant differences in programme structure and exercise intensity, timing of rehabilitation implementation and degree of patient's impairment led

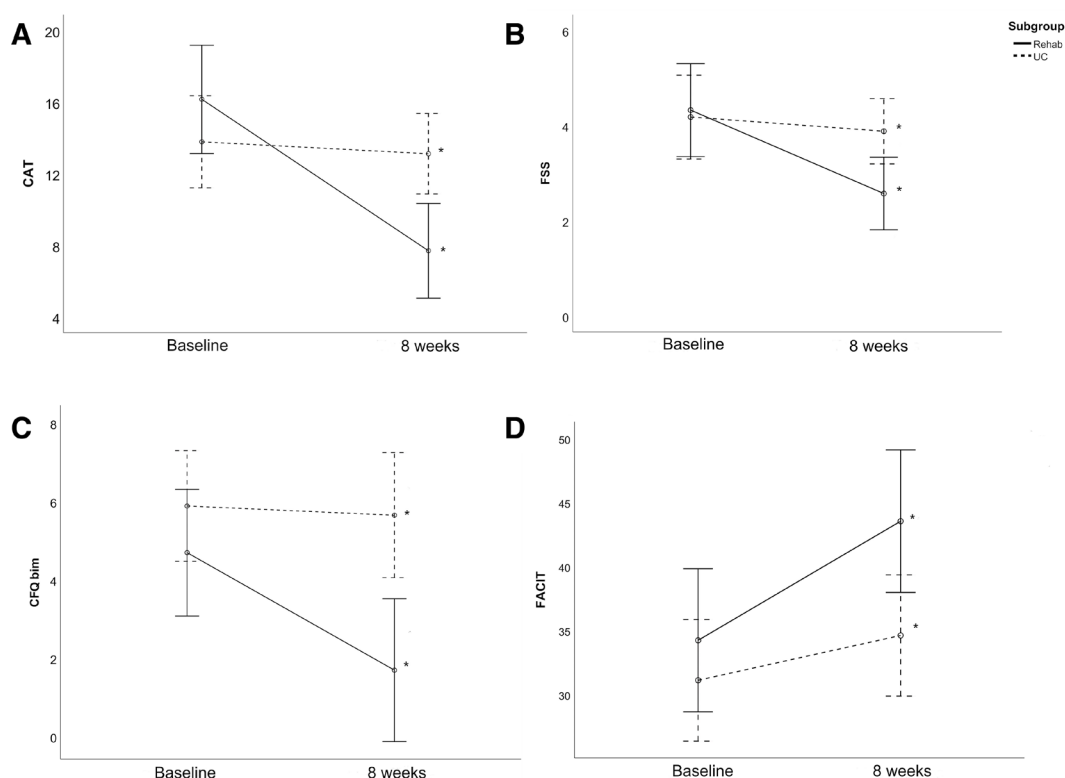


Figure 2 Mean values and 95% CI of primary outcomes at baseline and after 8 weeks in (A) CAT, (B) FSS, (C) CFQ bim and (D) FACIT. *Denotes significant difference between mean values ($p<0.05$). Bim, bimodal scoring; CAT, COPD Assessment Test; CFQ, Chalder Fatigue Scale; Error bars, 95% CI; FACIT, Functional Assessment of Chronic Illness Therapy; FSS, Fatigue Severity Scale; UC, usual care.

to different outcomes. On the other hand, the SPPB score increased two times more in Rehab compared with UC. Only 7% of patients scored ≤ 10 points (a threshold of functional impairment³) after rehabilitation, whereas the majority of UC (70%) remained impaired. A score ≤ 10 was reported by Evans *et al* in 46.2% of post-COVID-19 patients 6 months after hospital discharge, increasing to 51% for post-ICU patients.³

Following rehabilitation, patients significantly improved anxiety, depression, PTSD symptomatology and cognitive function, whereas UC remained impaired. In patients surviving acute lung injury and treated in the ICU, average HADS scores remained unchanged over 2 years of follow-up and were accompanied by significant PTSD symptoms.³⁷ We have shown that rehabilitation can significantly improve anxiety symptoms measured by HADS in post-COVID-19 patients. That was not the case with depression where no change was found in both groups. However, when depression was measured with BDI, the Rehab group improved significantly achieving a mean value <10 (scores 0–9 indicate minimal depression and 10–18 mild depression³⁸). Moreover, 56% of all patients had a score >10 at baseline, whereas after rehabilitation the percentage dropped to 23%. UC showed no improvement, and the median score remained above 10 after 8 weeks. Discrepancies between BDI and HADS-D in depression assessment have been reported before,⁵²

and BDI is considered a more robust instrument.⁵³ The average score of IES-R in our cohort was elevated compared with Acute Respiratory Distress Syndrome (ARDS) survivors at 3 months of follow-up (1.2 vs 0.9)³⁷, however, lower than the cut-off point for diagnosing PTSD (1.6 measured 1–5 years after ARDS).⁵⁴ In the post-COVID cohort of Mazza *et al* where 75% of patients were hospitalised, 1 month after discharge the mean score was 1.08. PTSD symptoms were inversely correlated to hospitalisation duration and subsequent severity.⁵⁵ In the present study, although Rehab significantly improved PTSD symptomatology (IES-R score) at 8 weeks, no difference was found when compared with UC. Baseline mean scores of MoCA in our cohort were below 26, the threshold of MCI,⁴⁰ and UC mean score remained below the MCI threshold after 8 weeks. In contrast, none of the patients who followed rehabilitation showed an impaired MoCA after 8 weeks (median value 29, minimum value 26). Daynes *et al* also demonstrated a significant increase in mean MoCA score (from 25 to 27) in post-COVID-19 patients after rehabilitation.⁸

A recent review and meta-analysis¹⁹ of post-COVID rehabilitation studies concluded that the effects on pulmonary function were inconsistent across studies. In our study, we report significant improvements in pulmonary function in both groups, which are likely due to natural recovery. Significant improvements between 60

Table 2 Initial evaluation and outcome measurements of functional capacity, mental health and health related quality of life

Group	Baseline	8 weeks	Pre-post difference	Pre-post significance	Between-groups significance at 8 weeks
6MWT (m)					
Rehab	451.5±109.2	513.3±102.7	61.77±39.11	p<0.001*	p=0.501
UC	408.3±85.7	466.2±83.4	57.95±67.09	p<0.001*	
SPPB					
Rehab	9.85±1.95	11.46±0.88	1.62±1.26	p=0.001*	p=0.002*
UC	9.15±1.57	9.95±1.51	0.80±1.11	p=0.004*	
HADS-A					
Rehab	7.08±4.03	5.0±3.87	−2.08±1.71	p=0.001*	p=0.013*
UC	6.06±3.56	7.06±4.65	1.00±3.65	p=0.261	
HADS-D					
Rehab	5.31±1.97	4.23±3.22	−1.08±2.29	p=0.105	p=0.627
UC	6.39±5.37	5.44±4.49	−0.94±4.14	p=0.319	
IES-R (PTSD)					
Rehab	1.25±0.79	0.97±0.71	−0.29±0.42	p=0.028*	p=0.135
UC	1.14±0.87	1.22±1.02	0.08±0.74	p=0.660	
BDI					
Rehab	9 (15)	3 (10)	−8 (7)	p=0.001*	p=0.017*
UC	12 (14)	11 (17)	0 (5)	p=0.938	
MoCA					
Rehab	25 (5)	29 (2)	3 (4)	p=0.008*	p<0.001*
UC	25 (6)	25 (6)	1 (2)	p=0.046*	
EQ-5D-5L (UI)					
Rehab	0.59±0.18	0.85±0.11	0.26±0.19	p<0.001*	p=0.001*
UC	0.62±0.25	0.66±0.23	0.04±0.17	p=0.372	
EQ-5D-5L (VAS)					
Rehab	68.46±16.63	81.1±10.4	12.6±12.1	p=0.003*	p=0.043*
UC	69.44±15.99	75.0±11.7	5.5±12.8	p=0.084	

Data are presented as mean±SD for parametric or as median (IQR) for non-parametric data. Baseline evaluation was within 6–8 weeks post-hospital discharge. Pre-post significance within groups was evaluated by paired *t*-tests for parametric data or Wilcoxon signed rank tests for non-parametric data. Outcome comparisons at 8 weeks between groups were performed with univariate analysis of covariance using baseline values as covariates.

*Denotes statistical significance between groups (p<0.05).

BDI, Beck Depression Inventory; EQ-5D-5L UI, EuroQol Utility Index; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Event Scale, Revised; MoCA, Montreal Cognitive Assessment; 6MWT, 6-min walking test; PTSD, post-traumatic stress disorder; Rehab, rehabilitation group; SPPB, Short Physical Performance Battery; UC, usual care group; VAS, Visual Analogue Scale.

and 100 days after COVID-19 diagnosis in chest CT and PFTs (including FEV₁, FVC and TL_{co}) have been shown in post-COVID-19 patients.²¹

Patients with long-COVID at 3 and 6 months after symptoms onset showed some improvement in EQ-VAS (mean increase of 7 points).¹³ Enrolment in rehabilitation accelerates improvement as shown in the cohort of Daynes *et al* (mean increase of 8 points in 6 weeks)⁸ and in our study (13 points in 8 weeks).

In line with BTS guidance,¹⁴ healthcare workers involved in post-COVID-19 rehabilitation programmes should screen patients for possible complications of

COVID-19 infection. Indeed, during the initial evaluation three patients were excluded due to previously undiagnosed complications and one stopped rehabilitation due to new onset of pulmonary embolism (figure 1). Rigorous adherence to safety precautions is of paramount importance (see online supplement file).

Exercise training is the cornerstone of rehabilitation. Official guidance on exercise training post-COVID-19 suggested low-grade exercise with gradual increases in intensity.^{14 15} In line with this official guidance and considering that exercise programmes at relatively high intensity could be harmful in patients with postviral

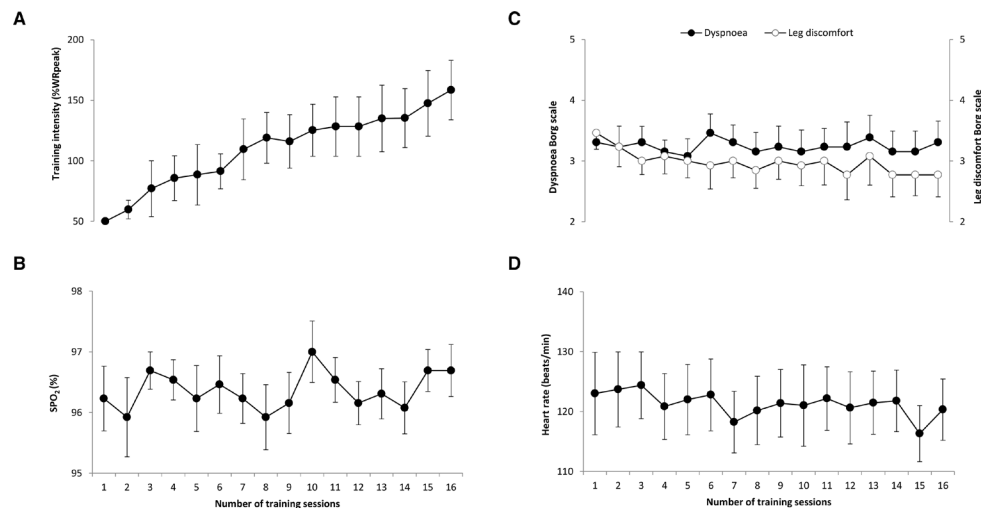


Figure 3 Exercise training outcomes throughout the rehabilitation programme: (A) training intensity (WRpeak), (B) %SpO₂, (C) dyspnoea and leg discomfort scores (Borg scale) and (D) heart rate. Data are presented as mean±SEM. %SpO₂, percentage of arterial oxygen saturation; WRpeak, % peak work rate.

‘chronic fatigue syndrome’, we implemented intermittent exercise training on the cycle ergometer starting at 50% of peak work rate. Intermittent exercise has been shown to be safe and well tolerated by COVID-19 survivors post-hospital discharge.^{16 56} Intermittent exercise, consisting of repeated bouts of exercise that are alternated with short periods of rest, has shown to be effective in respiratory patients with profound symptoms of exertional breathlessness and leg discomfort.⁵⁷ Accordingly, intermittent exercise may be better suited to COVID-19 survivors than continuous exercise because it is associated with moderate exertional symptoms without significant arterial oxygen desaturation (figure 3).⁵⁷ Moreover, there were not any adverse effects reported throughout the exercise training programme, thereby highlighting the safety aspect of progressively advancing the intensity of intermittent exercise throughout a rehabilitation programme in this population (figure 3). Importantly, despite a threefold increase in training workload throughout the 8-week programme, symptoms of dyspnoea and leg discomfort as well as HR remained unchanged. This indicates true physiological training effects compatible with those seen in healthy individuals following aerobic exercise training.⁵⁸

A limitation of the present study is the lack of patient randomisation. The investigators as well as the ethical committee considered it unethical to deprive post-COVID-19 patients of the opportunity to participate in a structured rehabilitation programme designed to operate in conditions of lockdown and social distancing where rehabilitation resources were disrupted worldwide. Therefore, patients who were unable to undertake rehabilitation comprised the UC arm of the study and the programme was still available to them after the 8-week follow-up assessment visit. Patients who declined rehabilitation did so for reasons beyond their willingness (figure 1). Indeed,

the mean distance to reach the rehabilitation centre in the UC group was twice as long compared with that in the Rehab group (table 1). Transportation issues along with competing obligations and poor perception of rehabilitation’s benefits are long been considered major factors for declining pulmonary rehabilitation.⁵⁹ This highlights the difficulties of implementing a supervised rehabilitation programme during a pandemic. Another limitation is the absence of longer-term follow-up, which would be informative about the possibility of a long-term effect (or not) of pulmonary rehabilitation. Two scenarios can be envisioned, one in which the effects of pulmonary rehabilitation would decline over time and one in which patients would naturally improve over time.

Future studies should investigate the feasibility and acceptability of hospital and community-based rehabilitation programmes and any perceived barriers and facilitators of delivery of such programmes from both the participant and healthcare worker perspectives. The long-term benefits of rehabilitation are also important areas of future research.

In conclusion, rehabilitation facilitates recovery of respiratory symptoms, fatigue, depression/anxiety, cognitive impairment and HRQoL that otherwise would remain incomplete with usual care. Intermittent exercise training in post-COVID-19 patients is safe and effective in facilitating progressive improvements in work capacity post-COVID-19.

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