

# Rehabilitation Is Associated With Improvements in Post–COVID-19 Sequelae

Andreas Asimakos, Stavroula Spetsioti, Spyros Mentzelopoulos, Ioannis Vogiatzis, Alice G Vassiliou, Pantelis Gounopoulos, Archontoula Antonoglou, Dimitrios Spaggoulakis, Sofia Pappa, Spyros Zakynthinos, Ioanna Dimopoulou, and Paraskevi Katsaounou

**BACKGROUND:** Post–COVID-19 syndrome has affected millions of people, with rehabilitation being at the center of non-pharmacologic care. However, numerous published studies show conflicting results due to, among other factors, considerable variation in subject characteristics. Currently, the effects of age, sex, time of implementation, and prior disease severity on the outcomes of a supervised rehabilitation program after COVID-19 remain unknown. **METHODS:** This was a non-randomized case-control study. Subjects with post–COVID-19 sequelae were enrolled. Among study participants, those who could attend an 8-week, supervised rehabilitation program composed the intervention group, whereas those who couldn't the control group. Measurements were collected at baseline and 8 weeks thereafter. **RESULTS:** Study groups ( $N = 119$ ) had similar baseline measurements. Participation in rehabilitation ( $n = 47$ ) was associated with clinically important improvements in the 6-min walk test (6MWT) distance, adjusted (for potential confounders) odds ratio (AOR) 4.56 (95% CI 1.95–10.66); 1-min sit-to-stand test, AOR 4.64 (1.88–11.48); Short Physical Performance Battery, AOR 7.93 (2.82–22.26); health-related quality of life (HRQOL) 5-level EuroQol-5D (Visual Analog Scale), AOR 3.12 (1.37–7.08); Montreal Cognitive Assessment, AOR 6.25 (2.16–18.04); International Physical Activity Questionnaire, AOR 3.63 (1.53–8.59); Fatigue Severity Scale, AOR 4.07 (1.51–10.98); Chalder Fatigue Scale (bimodal score), AOR 3.33 (1.45–7.67); Modified Medical Research Council dyspnea scale (mMRC), AOR 4.43 (1.83–10.74); Post–COVID-19 Functional Scale (PCFS), AOR 3.46 (1.51–7.95); and COPD Assessment Test, AOR 7.40 (2.92–18.75). Time from disease onset was marginally associated only with 6MWT distance, AOR 0.99 (0.99–1.00). Prior hospitalization was associated with clinically important improvements in the mMRC dyspnea scale, AOR 3.50 (1.06–11.51); and PCFS, AOR 3.42 (1.16–10.06). Age, sex, and ICU admission were not associated with the results of any of the aforementioned tests/grading scales. **CONCLUSIONS:** In this non-randomized, case-control study, post–COVID-19 rehabilitation was associated with improvements in physical function, activity, HRQOL, respiratory symptoms, fatigue, and cognitive impairment. These associations were observed independently of timing of rehabilitation, age, sex, prior hospitalization, and ICU admission. *Key words:* post–COVID-19 syndrome; 6-min walk test (6MWT); pulmonary rehabilitation; physical function; respiratory symptoms; fatigue; mental health; health-related quality of life (HRQOL). [Respir Care 2024;69(11):1361–1370. © 2024 Daedalus Enterprises]

## Introduction

Post–COVID-19 sequelae are emerging as a new public health issue, with more than 65 million people affected worldwide. More than 200 symptoms have been recorded, with multiple organ systems affected, thereby frequently resulting in functional capacity impairment, fatigue, mental health issues, respiratory symptoms, and poor health-related quality of life (HRQOL).<sup>1</sup> Emerging evidence places

rehabilitation at the heart of non-pharmacologic interventions that improve multiple parameters of post–COVID-19 sequelae.<sup>2–4</sup> However, the numerous studies that have been published are characterized by heterogeneity and increased risk of bias due to differences in rehabilitation programs, study design elements, and diversity of subject populations.<sup>3</sup>

A certain degree of natural recovery in post–COVID-19 sequelae has been noticed early in the pandemic.<sup>5</sup> Con-

sequently, the outcome measurements of patients participating in rehabilitation during or immediately after hospitalization<sup>6,7</sup> may differ from patients recruited weeks or months after discharge,<sup>8</sup> due to the effect of natural recovery. Prior dis-

---

SEE THE RELATED EDITORIAL ON PAGE 1477

---

ease severity may impact outcome measurements as well. Critical illness is associated with an increased risk of subsequent post-COVID-19 complications<sup>1</sup> in addition to more severe post-discharge health impairments, thus providing the potential for greater improvements.<sup>7</sup> Disease severity, middle age, and female sex have also been linked to poor recovery after COVID-19.<sup>9,10</sup> A recent review and meta-analysis highlighted significant improvement in functional status in elderly subjects after rehabilitation.<sup>11</sup>

Despite heterogeneity of the studies, physical function, mental health, HRQOL,<sup>3</sup> and respiratory symptoms are consistently the outcomes with moderate-to-large improvements.<sup>2</sup> However, with few exceptions, rehabilitation studies lack outcome control for confounding factors.<sup>3</sup> The aim of the present study was to investigate whether the implementation of a supervised rehabilitation program in a mixed population of post COVID-19 patients with varying degrees of prior disease severity, time of rehabilitation intervention in relation to the onset of symptoms of COVID-19, age and sex were associated with potential improvements in post COVID-19 symptoms/sequelae.

### Methods

This was a prospective, non-randomized case-control study conducted from June 2022–September 2023. Early in the pandemic our center designed and implemented a supervised rehabilitation program for patients suffering from persistent post-COVID-19 symptoms. The program structure was based on the guidelines for post-COVID-19 rehabilitation issued by the American Thoracic Society

---

Dr Asimakos is affiliated with 1st Department of Critical Care and Pulmonary Services, Evangelismos General Hospital, Athens, Greece. Drs Mentzelopoulos, Antonoglou, Zakyntinos, Dimopoulou, and Katsaounou are affiliated with 1st Department of Critical Care and Pulmonary Services, Evangelismos General Hospital, Athens, Greece; and National and Kapodistrian University of Athens, School of Medicine, Athens, Greece. Mrs Spetsioti and Mr Spaggoulakis are affiliated with 1st Department of Critical Care and Pulmonary Services, Evangelismos General Hospital, Athens, Greece; and National and Kapodistrian University of Athens, School of Medicine, Athens, Greece. Dr Vogiatzis is affiliated with Sport, Exercise and Rehabilitation, University of Northumbria at Newcastle, Newcastle upon Tyne, United Kingdom. Dr Vassiliou is affiliated with 1st Department of Critical Care and Pulmonary Services, Evangelismos General Hospital, Athens, Greece; National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; and GP Livanos and M Simou Laboratories, Athens, Greece. Dr Gounopoulos is affiliated with 2nd Cardiology Department, Evangelismos General Hospital, Athens,

### QUICK LOOK

#### Current knowledge

Rehabilitation services have been suggested to ameliorate post-COVID-19 sequelae, including decline in physical fitness, impairments in mental health and health-related quality of life (HRQOL), as well as respiratory symptoms. However, the possible importance of various confounding factors, including patient demographics and prior disease severity, remains unexplored.

#### What this paper contributes to our knowledge

Rehabilitation was associated with improvements in physical function, HRQOL, respiratory symptoms, fatigue, and cognitive impairment post COVID-19. These associations were independent of, age, sex, timing of rehabilitation, prior hospitalization, and ICU admission.

(ATS), European Respiratory Society (ERS), and the British Thoracic Society (BTS)<sup>12,13</sup> and was subsequently adopted by the Hellenic Thoracic Society.<sup>14</sup> At the beginning of the pandemic, the patients recovering from severe COVID-19 pneumonia were given priority since they needed supported recovery.<sup>9</sup> Our rehabilitation program has been associated with improvements in physical function and symptoms.<sup>8</sup> However, as the pandemic progressed, so did the number of patients with post-COVID-19 symptoms who recovered after mild illness at home.<sup>1</sup> Consequently, rehabilitation services were made available to all symptomatic patients who were referred to the Long COVID day clinic of our hospital, irrespective of previous hospitalization (for COVID-19). Subjects who were able to attend our 8-week supervised program composed the intervention (rehab) group, whereas those who could not (eg, due to transportation issues along with professional or other competing obligations) the control group. Subject evaluation was conducted at study enrollment (baseline) and after 8 weeks

---

Greece. Dr Pappa is affiliated with Department of Brain Sciences, Faculty of Medicine, Imperial College, London, United Kingdom.

The authors have disclosed no conflicts of interest.

A version of this paper was presented at the 32nd Panhellenic Pulmonology Congress, held December 7–10, 2023, in Athens, Greece.

Dr Asimakos and Ms Spetsioti share first authorship.

Supplementary material related to this paper is available at <http://www.rcjournal.com>.

Correspondence: Andreas Asimakos MD PhD, Ypsilantou Street 45–47, 10676, Athens, Greece. E-mail: [silverakos@gmail.com](mailto:silverakos@gmail.com).

DOI: 10.4187/respcare.11863

of either rehabilitation or usual care (control). Following their first visit to our clinic, all study participants signed an informed consent form to participate in the study, according to the protocol approved by the Scientific Council of Evangelismos General Hospital, Athens, Greece (approval number 09-06-2022/188).

## Participants

**Inclusion criteria.** Patients > 18 y of age who suffered from persistent symptoms after COVID-19 infection confirmed by real-time polymerase chain reaction (PCR) were eligible for enrollment. Patients with prior hospitalization had to have persistent symptoms for > 8 weeks after hospital discharge, and patients with mild disease had to have persistent symptoms for at least 12 weeks from disease onset to become eligible for enrollment.<sup>12,13,15</sup>

**Exclusion criteria.** Patients who were not ambulatory, chronically paralyzed, with paraplegia, multiple injuries or other serious orthopedic problems that caused disability, and those suffering from dementia or very serious underlying diseases such as end-stage cancer were excluded. Patients treated for COVID-19 infection while being hospitalized for another reason (eg, coronary heart disease, elective surgery) and patients with active disease were also excluded.<sup>13</sup>

## Measurements and Clinically Relevant Thresholds

Subject improvement was assessed with tests that measured physical function, symptoms, HRQOL, and mental health. Thresholds of impairment or improvement were pre-specified for each test. Thresholds of impairment were cutoff score points indicating impairment (eg, COPD Assessment Test [CAT] score  $\geq 10$ ). The below-defined minimum clinically important difference was used to define an improvement threshold. Subject clinical status was considered as improved when a test's improvement threshold was exceeded at 8 weeks post enrollment. In tests with thresholds of impairment, subjects with normal baseline measurements that remained unchanged or deteriorated were considered as not improved.

Physical function was evaluated with the 6-min walk test (6MWT), the Short Physical Performance Battery (SPPB), the 1-min sit-to-stand test (STS), and the Activities-Specific Balance Confidence (ABC) Scale. Physical activity was evaluated with the International Physical Activity Questionnaire-Short Form (IPAQ-SF). The 6MWT is the most widely used exercise field test for assessing functional exercise capacity, and a walking distance improvement threshold of 30 m is established for patients with chronic respiratory disease.<sup>16</sup> A minimum clinically important difference for patients with Long COVID has not been established, however, given the younger age, the fewer comorbidities, and

the spontaneous improvement;<sup>8</sup> therefore, we adopted a more conservative threshold of 50 m.<sup>17</sup> The SPPB is an established test for measuring physical performance, with a threshold of functional impairment of  $\leq 10$  points.<sup>9</sup> The 1-min STS is an easy-to-perform test of lower muscle strength and endurance that measures the number of times a person can sit down and stand up on a chair in 1 min. A minimum clinically important difference after rehab of 3 repetitions was specified.<sup>18</sup> The IPAQ-SF is a 7-item questionnaire exploring the frequency and the duration of physical activity performed in the last 7 d and estimating energy expenditure/week. Low physical activity profile corresponds to a total physical activity score of < 600 metabolic equivalent of task (MET) min/week; accordingly, the threshold for functional impairment was set at 600 MET min/week.<sup>19</sup>

Respiratory symptoms were assessed with the CAT and the Modified Medical Research Council (mMRC) dyspnea scale. Fatigue was assessed with 3 questionnaires covering short- and long-term impact or change. The Functional Assessment of Chronic Illness Therapy (FACIT), the Fatigue Severity Scale (FSS), and the Chalder Fatigue Scale (CFQ) were used to assess fatigue in the last 7 d, 2 weeks, and 1 month, respectively. General post-COVID-19 functional status was assessed with the Post-COVID Functional Scale (PCFS). The CAT, an 8-item questionnaire that was initially developed to assess COPD symptoms and qualify health status impairment,<sup>20</sup> was used to assess rehabilitation outcomes in post-COVID-19 patients early in the pandemic.<sup>21</sup> A score of  $\geq 10$  indicates increased symptoms and is used as a threshold for treatment.<sup>22</sup> The mMRC scale is a 4-point scale based on the sensation of dyspnea during a patient's daily activities, with a cutoff point of  $\geq 2$  used as a commonly accepted threshold of breathlessness.<sup>22</sup> The FSS consists of 9 questions designed to assess the severity of fatigue symptoms. A scoring threshold of  $\geq 36$  may suggest severe fatigue or the need for further assessment.<sup>23</sup> 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  $\geq 4$  indicating severe fatigue.<sup>24</sup> For evaluating post-COVID-19 functional status, we used the PCFS, which correlates with quality of life, dyspnea, and mental health. A score of  $\geq 2$  on this scale indicates impairment in daily life.<sup>25</sup>

Mental health was assessed with the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), and the Impact of Event Scale - Revised (IES-R) for depression, anxiety, and posttraumatic stress disorder evaluation, respectively. The Montreal Cognitive Assessment (MoCA) was used as a brief screening tool for detecting mild cognitive impairment in subjects with a score of  $\leq 25$ .<sup>26</sup>

HRQOL was evaluated using the 5-level EuroQol-5D (EQ-5D-5L) and the 36-Item Short Form Health Survey (SF-36) questionnaire. The EQ-5D-5L assesses HRQOL

using a utility index (UI) and an EQ Visual Analog Scale (EQ-VAS). The minimum clinically important difference of the UI and EQ-VAS was set to 0.051 and 6.9, respectively.<sup>27</sup> The SF-36 is a widely used instrument for assessing HRQOL, measuring 8 scales that represent physical and mental dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). A score of 50 is considered normative for all scales and represents average health.<sup>28</sup> The ABC scale, FACIT, BDI, IES-R, and SF-36 are described in the supplementary material (see related supplementary materials at <http://www.rcjournal.com>).

### Rehabilitation Program

The program was multidisciplinary, including supervised interval aerobic and resistance training, education, physiotherapy, dietary advice, and psychological support twice a week for 8 weeks. Subjects assigned to the rehabilitation group performed a maximum incremental test on an electromagnetically braked cycle ergometer (Ironman M3, Key Fitness Products, Garland, Texas) to determine the peak work rate ( $WR_{peak}$ ). The procedure included 3 min of rest measurements, 3 min of unloaded pedaling, followed by an increase in work rate every minute by 5–20 W to the limit of tolerance, while subjects maintained a pedaling frequency of 60 RPM. Heart rate and  $S_{pO_2}$  were determined using a pulse oximeter (Onyx, Nonin Medical, Plymouth, Minnesota) as well as symptoms of dyspnea and leg discomfort using the 0–10 Borg scale.<sup>29</sup> Subjects performed intermittent exercise on an electromagnetically braked cycle ergometer. Intensity at the beginning of the program was equivalent to 50% of  $WR_{peak}$  (measured at baseline), with 30 s of work alternated by 30 s of rest periods for 30 min/session.<sup>30</sup> The work load was increased weekly by 10% of baseline work rate based on subject's Borg scale symptoms of breathlessness and leg discomfort. The work load was increased when Borg dyspnea and/or leg discomfort were reduced by 1 unit for a given work load. During training, heart rate was recorded by a pulse oximeter, and the Borg (0–10) scale was used for the evaluation of breathlessness and leg discomfort. The rehabilitation program also included upper- and lower-limbs resistance training sessions using fitness equipment. In particular, subjects performed 4 resistance exercises, namely knee extension, seated chest press, peck deck, and lateral pulldown, at an intensity equivalent to 60–70% of one repetition maximum (performed at baseline) with 3 sets of 10 repetitions/exercise.<sup>31</sup> The duration of each rehabilitation session was 1 h.

Safety precautions included infection prevention and control measures, exclusion of active infection, and control of disease-related complications. In brief, necessary protection measures were taken into consideration to avoid the spread of the virus in the facilities where the evaluation of

subjects and delivery of rehabilitation services took place. These measures are described in detail by the Hellenic National Public Health Organization (HNPHO).<sup>32</sup> Subjects upon arrival at the rehabilitation center were screened for active disease according to the guidance issued by the HNPHO for discontinuation of precautionary measures in a patient with (life threatening) COVID-19 infection following hospital discharge.<sup>32</sup> Evaluation and rehabilitation of subjects took place in properly ventilated facilities, with each subject individually, and a time separation of 1 h between assessments and rehabilitation sessions was implemented. According to BTS guidance, a series of possible complications of COVID-19 infection were taken into account during the initial evaluation including thromboembolic disease; complications from the heart, mainly myocarditis; and the detection of hypoxemia during exertion.<sup>33</sup> The safety precautions that were followed have been described in detail by the Hellenic Thoracic Society.<sup>14,34</sup>

### Study Outcomes

Our primary objective was to determine whether increases in the 6MWT distance of  $\geq 50$  m at 8 weeks post enrollment was associated with rehab, while concurrently controlling for potential confounders such as time from COVID-19 symptoms onset to rehab initiation or study enrollment as control, age, sex, and preceding hospitalization and ICU admission for COVID-19. Our secondary objectives comprised the determination of potential associations of the above-defined, clinically relevant improvements in measurements of physical function, symptoms, mental health, and HRQOL at 8 weeks post enrollment with rehab, while concurrently controlling for all of the aforementioned potential confounders.

### Statistical Analysis and Sample Size Estimation

Analyses were performed using SPSS version 25 (IBM, Armonk, New York). Distribution normality was tested by the Kolmogorov-Smirnov test. Descriptive statistics are presented as median (interquartile range). Depending on distribution normality, comparisons of baseline characteristics between the rehab and control groups were conducted using the independent samples *t* test or the Mann-Whitney U test. The Fisher exact test was used for between-group comparisons of proportions. All tests were 2 tailed.

The primary outcome analysis comprised multivariate logistic regression with improvement or no improvement in the 6MWT as the binary dependent variable; the explanatory variables included in the model were rehab (yes vs no), time from COVID-19 symptoms onset to study enrollment (d), age (y), sex (male vs female), preceding hospital admission due to COVID-19 (yes vs no), and ICU admission (yes vs no) due to COVID-19. Secondary outcome analyses comprised the fitting of logistic regression models using

Table 1. Baseline Characteristics

Group	Median (IQR)	Comparison Between Groups
Age, y		<i>P</i> = .83
Rehab	55 (48–59)	
Control	54 (40–63)	
Male		<i>P</i> = .84
Rehab	42.6	
Control	44.4	
Hospitalization		<i>P</i> = .07
Rehab	68.1	
Control	51.4	
ICU admission		<i>P</i> = .051
Rehab	40.4	
Control	23.6	
Disease onset to study enrollment, d		<i>P</i> = .59
Rehab	173 (100–258)	
Control	158 (93–259.75)	
Symptoms, no.		<i>P</i> = .22
Rehab	11 (8–13.25)	
Control	10 (7.25–12)	
Comorbidities, no.		<i>P</i> = .27
Rehab	1 (1–2)	
Control	1 (0–2)	
Distance of rehab center from home, km		<i>P</i> = .039
Rehab	4.8 (3.3–7.7)	
Control	6.65 (3.65–13)	

Data are presented as median (interquartile range) or %.  
 Comparisons between groups were performed with the Mann-Whitney U test and the Fisher exact tests for categorical data.

the same explanatory variables and having as dependent variables the improvement or no improvement in each one of the abovementioned tests of physical function, symptoms, HRQOL, and mental health (besides the 6MWT). Results of logistic regression analyses are presented as adjusted odds ratios (aORs) (95% CI). To prevent overfitting of logistic regression models, at least 20 measurements (observations) per independent variable were required.<sup>35</sup> As there were 6 pre-specified independent variables, the study was scheduled to end on the completion of the follow-up of 120 subjects. Statistical significance was set at *P* < .05 for all analyses.

**Results**

**Subject Participation and Demographics**

One hundred thirty-four subjects were initially recruited, of whom 9 in the control group were lost at follow-up and 5 in the rehab group who couldn't complete the program due to transportation and logistics reasons. In total, 120 subjects completed the study; 47 participated in the rehabilitation program, and 72 composed the control

group. One subject withdrew the informed consent and was excluded from the analysis, thus reducing the study population to 119 subjects. No adverse effects were reported during rehabilitation.

The subjects age ranged from 24–79 y, of whom 21 subjects (17.5%) exceeding 65 y. There were no significant between-group differences in sex, age, comorbidities, and number of symptoms between the 2 groups. Furthermore, rehab subjects and control subjects had similar numbers of days from COVID-19 symptoms onset until study enrollment. Hospitalization and ICU admission for COVID-19 were arithmetically (but not significantly) more frequent in the rehab group versus control (68% vs 51% and 40% vs 24%, respectively, *P* = .051 and .07). The rehabilitation center-to-home distance was significantly greater in the control group. Subjects' demographics are reported in Table 1.

**Between-Group Comparisons**

The baseline test measurements did not differ between groups, besides mMRC, which was significantly higher in rehab versus control (2 [1–3] vs 1 [1–2], respectively, *P* = .01) and IPAQ-SF, which was significantly higher in control versus rehab (930 [200–1,893] vs 636 [132–1,440], *P* = .03; e-Table 2, see related supplementary materials at <http://www.rcjournal.com>). Between-group comparisons of proportions are presented in the Fig. 1 and e-Table 1 (see related supplementary materials at <http://www.rcjournal.com>).

**Results of Multivariate Analyses**

Table 2 displays the main results of the primary and secondary outcomes logistic regression analyses. Participation in rehab versus control was 4.6 times more likely to increase the 6MWT distance more than 50 m, 7.9 times to restore physical performance (SPPB > 10), 4.6 times to perform > 3 repetitions in 1-min STS, 3.6 times to increase physical activity (IPAQ > 600), 7.4 times more likely to decrease the burden of respiratory symptoms (CAT < 10), 4.4 times to reduce dyspnea (mMRC < 2), 4.1 times to alleviate severe fatigue recorded over the past 2 weeks (FSS < 36) and 3.3 times over the past month (Chalder-bim < 4), 3.5 times to improve post-COVID-19 functional status (PCFS < 2), 6.3 times to restore cognitive function (MoCA ≥ 26), and 3.1 times to increase HRQOL (EQ-VAS ≥ 6.9). Neither rehab nor control subjects reached average health measured with SF-36 after 8 weeks (e-Table 3, see related supplementary materials at <http://www.rcjournal.com>).

The probability of increase in the 6MWT distance by ≥ 50 m decreased slightly with time from COVID-19 symptoms onset to study enrollment (AOR 0.996 [95% CI 0.993–1.000]). Subject hospitalization increased 3.4 times the

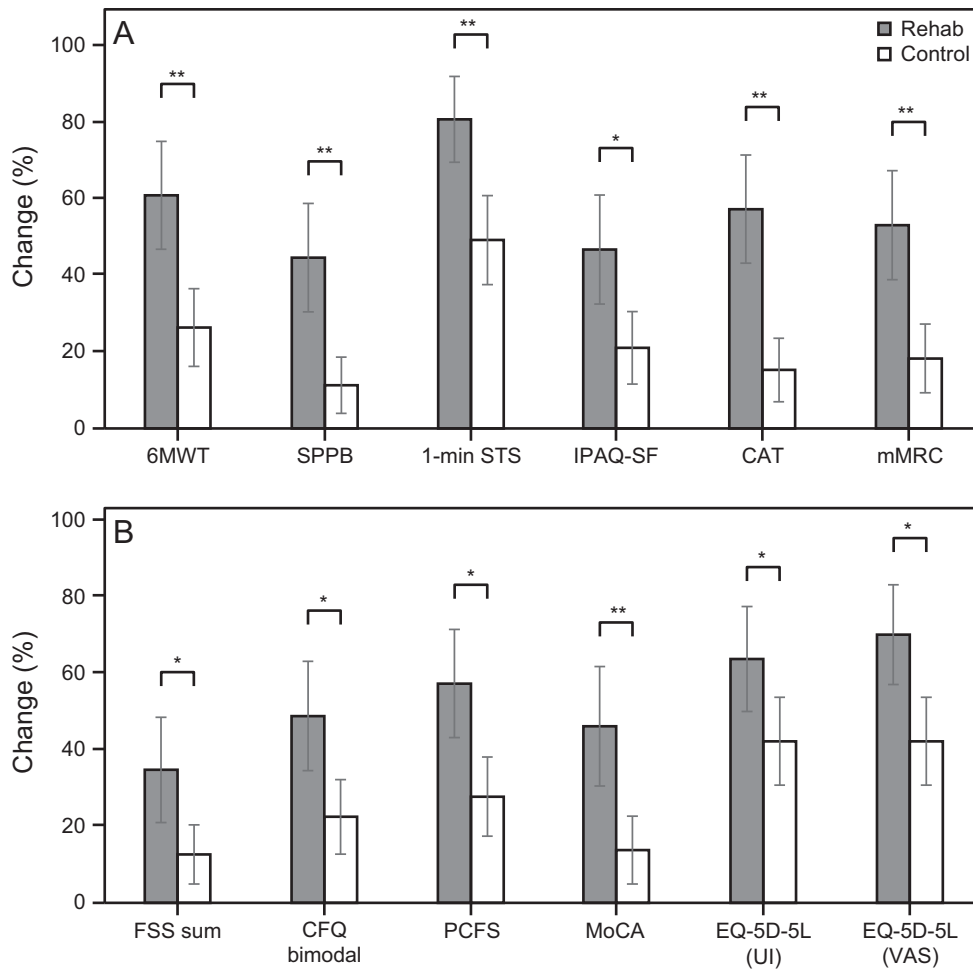


Fig. 1. Between-group comparisons of proportions (expressed as percentages) after 8 weeks of A: 6-min walk test (6MWT), Short Physical Performance Battery (SPPB), 1-min sit-to-stand test (1-min STS); International Physical Activity Questionnaire - Short Form (IPAQ-SF), COPD Assessment Test (CAT), and Modified Medical Research Council dyspnea scale (mMRC); and B: Fatigue Severity Scale (FSS) sum, Chalder Fatigue Scale (CFQ) bimodal score, Post-COVID-19 Functional Status Scale (PCFS), Montreal Cognitive Assessment (MoCA), and 5-level EuroQol-5D (EQ-5D-5L) (utility index [UI] and visual analog scale [VAS]). Comparisons between groups were performed using Fisher exact test for categorical data. \* $P < .05$ . \*\* $P < .001$ . Error bars = 95% CI.

probability of improving the post-COVID-19 functional status and 3.5 times the probability of dyspnea reduction after 8 weeks. Descriptive statistics and logistic regression models for HADS, SF-36, FACIT, ABC, BID, and IES-R as dependent variables are reported in the supplemental material (e-Table 3 and e-Table 4, see related supplementary materials at <http://www.rcjournal.com>).

### Discussion

In the present study, rehabilitation was associated with concurrent, multiple improvements in the measures of physical and cognitive function, fatigue, respiratory symptoms, dyspnea, and HRQOL. These improvements were clinically important and not associated with age, sex, and ICU admission. Prior hospitalization was associated only with dyspnea and post-COVID-19 functional

scale improvement. Days from disease onset to enrollment were marginally associated with not exceeding the 50-m distance threshold in 6MWT. These findings support the hypothesis that rehabilitation may substantially contribute to the reversal of multiple components of post-COVID-19 impairment in a population with substantially variable age, disease severity, and time elapsed from disease onset.

A strength of our study pertains to the adjustment of the multivariate analyses for potential confounders. The sole moderating effect on improved, rehabilitation-associated functional outcomes of elderly subjects who McCarthy et al<sup>11</sup> were able to examine in their review and meta-analysis was the length of stay in rehabilitation units. Meta-regression showed that the length of stay was not associated with functional outcomes ( $P = .30$ ). In another systematic review and meta-analysis of 14 observational studies, only

## POST-COVID-19 REHABILITATION

Table 2. Main Results of the Primary and Secondary Outcomes Logistic Regression Analyses

Test Cutoff Points or Minimum Clinically Important Difference	Group Rehab/Control	Sex Male/Female	Age, y	ICU Admission Yes/No	Hospitalization Yes/No	Time From Disease Onset, d	AOR
							Exp(B) (95% CI)
6MWT	4.560*	0.829	0.996	0.975	1.410	0.996†	
≥ 50 m	(1.950–10.664)	(0.340–2.023)	(0.961–1.033)	(0.333–2.855)	(0.463–4.297)	(0.993–1.000)	
SPPB	7.925*	0.749	1.035	0.838	1.115	0.997	
> 10	(2.821–22.264)	(0.265–2.117)	(0.990–1.081)	(0.262–2.673)	(0.298–4.171)	(0.992–1.001)	
1-min STS	4.638*	0.558	0.987	0.788	1.081	1.000	
≥ 3 repetitions	(1.875–11.476)	(0.229–1.358)	(0.953–1.022)	(0.261–2.378)	(0.365–3.205)	(0.997–1.003)	
IPAQ	3.627†	1.651	1.003	0.533	1.293	0.998	
≥ 600	(1.532–8.586)	(0.657–4.151)	(0.967–1.040)	(0.174–1.637)	(0.429–3.902)	(0.995–1.002)	
CAT	7.403*	0.559	1.000	1.300	2.201	1.001	
< 10	(2.923–18.752)	(0.208–1.497)	(0.961–1.041)	(0.422–4.008)	(0.651–7.439)	(0.998–1.005)	
mMRC	4.431*	1.192	0.983	1.140	3.499†	1.003	
< 2	(1.829–10.737)	(0.457–3.106)	(0.946–1.022)	(0.378–3.438)	(1.063–11.512)	(1.000–1.006)	
FSS sum	4.065†	0.627	1.014	1.034	0.827	0.998	
< 36	(1.505–10.980)	(0.223–1.761)	(0.972–1.057)	(0.316–3.383)	(0.216–3.170)	(0.993–1.002)	
CFQ-bim	3.334†	1.221	1.016	1.042	0.998	1.001	
< 4	(1.448–7.674)	(0.495–3.014)	(0.980–1.053)	(0.356–3.050)	(0.334–2.980)	(0.998–1.004)	
PCFS	3.461†	0.752	1.002	0.589	3.419†	1.000	
≤ 1	(1.506–7.954)	(0.313–1.807)	(0.968–1.038)	(0.208–1.663)	(1.162–10.056)	(0.997–1.003)	
MoCA	6.249*	0.407	0.998	1.778	0.599	1.000	
≥ 26	(2.164–18.041)	(0.132–1.253)	(0.957–1.041)	(0.451–7.004)	(0.143–2.515)	(0.996–1.004)	
EQ-5D-5L VAS	3.119†	1.940	1.011	1.092	1.251	1.001	
> 6.9	(1.374–7.080)	(0.815–4.616)	(0.978–1.044)	(0.384–3.106)	(0.438–3.577)	(0.998–1.004)	

Improvement or not in each measure (binary dependent variable) at 8 weeks was associated with 6 independent variables (age, sex, ICU, hospital admission, rehabilitation, and time after COVID-19 symptoms onset) using binary logistic regression. The cutoff points or minimum clinically important difference (threshold of improvement) for each test are marked below them.

\* $P < .001$

† $P < .05$

AOR = adjusted odds ratios

Exp (B) = exponential value of B

6MWT = 6-min walk test

SPPB = Short Physical Performance Battery

1-min STS = 1-min sit-to-stand test

IPAQ-SF = International Physical Activity Questionnaire - Short Form

CAT = COPD Assessment Test

mMRC = Modified Medical Research Council dyspnea scale

FSS sum = Fatigue Severity Scale sum

CFQ-bim = Chalder Fatigue Scale bimodal score

PCFS = Post-COVID-19 Functional Status Scale

MoCA = Montreal Cognitive Assessment

EQ-5D-5L (VAS) = 5-level EuroQol-5D (Visual Analog Scale)

two adjusted their analyses for potentially confounding factors (ie, ICU admission/length of stay and preexisting comorbidities), highlighting this absence as the most important risk of bias.<sup>3</sup>

Prior disease severity and time from disease onset to rehab might affect rehabilitation-associated outcomes due to the intervening natural recovery. Severely affected patients (lower baseline values) may have the potential of greater improvement, toward the predicted pre-disease values of population of similar age and comorbidities. In our previous study, post-COVID-19 subjects with severe pneumonia recruited 42 d after hospital discharge and following usual care increased the 6MWT distance from

a mean  $\pm$  SD of  $408.3 \pm 85.7$  m to  $466.2 \pm 83.4$  m in 8 weeks, not differing from rehab.<sup>8</sup> Gloeckl et al<sup>7</sup> recruited subjects with prior severe/critical and mild/moderate COVID-19 into a supervised rehabilitation program. Subjects with severe prior disease had a median increase in the 6MWT distance of 124 m, starting from a baseline median value of 344 m; subjects were recruited in the program at a median time of 18 d after hospital discharge. In contrast, subjects with mild-to-moderate COVID-19 who were recruited 178 d after positive PCR testing had a higher baseline exercise performance (ie, median 6MWT distance of 509 m) and achieved a smaller median increase of just 48 m at the end of the rehabilitation. This finding can be explained by the

interaction of disease severity and natural recovery.<sup>7</sup> In the present study, subjects' mean baseline 6MWT distance was 490 m and increased by 62 m in rehab versus 11.5 m in the controls ( $P < .001$ , e-Table 3, see related supplementary materials at <http://www.rcjournal.com>).

An interesting finding of our study was that prior hospitalization was associated with improvements in dyspnea and post-COVID-19 functional status after 8 weeks. Dyspnea is a persistent symptom in patients with post-COVID-19 sequelae. In a large survey of post-COVID-19 subjects, over half of them (ie, 395 of 769 or 51.4%) suffered from breathlessness at 1 y after disease onset.<sup>10</sup> Subjects with severe COVID-19 had worse mMRC scores at 14 d and 6 months after discharge compared to subjects with moderate disease.<sup>36</sup> A small mean decrease in mMRC (ie, from 1.1 to 0.9) has been reported in a small series of subjects recovering from COVID-19 in just 15 d after hospital discharge.<sup>37</sup> In the present study, rehabilitation was associated with amelioration of dyspnea since more than half (ie, 53%) of the rehab subjects had mMRC score 0 or 1 after 8 weeks of participation in the program.

Rehabilitation in elderly post-COVID-19 patients is challenging due to multiple comorbidities, frailty, immunosenescence, and an increased probability of more severe prior disease and accelerated functional decline.<sup>11</sup> The understanding of the risk profiles of older patients and the development of individualized treatment regimens are of paramount importance.<sup>38</sup> Improvements in functional outcomes,<sup>11</sup> respiratory function, HRQOL, and mental health<sup>39</sup> after rehabilitation in elderly patients are promising; however, there is lack of evidence regarding long-term effects.<sup>38,11</sup> In the present study, age was not associated with changes in functional status, HRQOL, mental health, or symptoms after 8 weeks. However,  $< 1/5$  of the study population was  $> 65$  y of age; consequently, multivariable analytic determination of associations between rehabilitation and pre-specified study outcomes was not feasible in this small subgroup.

The current study is limited by the absence of randomization. Post-COVID-19 rehabilitation services are still limited in Greece, and with the number of symptomatic post-COVID-19 patients on the rise, it was considered as unethical to deny participation in a potentially effective and safe therapeutic intervention.<sup>3,4</sup> The majority of controls couldn't participate in the program, mainly for reasons beyond their will. Indeed, the mean distance to reach the rehabilitation center in the control group was significantly longer compared to the rehab group (Table 1). Logistic and transportation issues, along with inflexible obligations and poor perception of rehabilitation's benefits have been previously identified as major factors for declining pulmonary rehabilitation.<sup>40</sup> Although subject characteristics and most baseline measurements did not differ significantly between the 2 groups, we adjusted our analyses for several potential

confounders.<sup>41</sup> Therefore, our results strongly support the hypothesis that rehabilitation may effectively address post-COVID-19 sequelae, independently from confounders such as the timing of intervention relative to disease onset and disease-related hospital and/or ICU admission.

Another limitation of our study is the low frequency of supervised rehabilitation sessions (twice a week). The ERS/ATS,<sup>31</sup> the American College of Sports Medicine,<sup>42</sup> and American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR)<sup>43</sup> recommend a frequency of 3–5 times/week of endurance training. However, our post-COVID-19 rehabilitation program was designed and implemented during the pandemic when lockdown measures were enforced, and transmission precautions were strictly followed. Consequently, rehabilitation sessions were held individually and 1 h apart between subjects to properly ventilate facilities and disinfect equipment, thereby significantly decreasing program capacity. Reducing session frequency to a minimum (supervised sessions twice a week according to BTS<sup>44</sup>) and keeping a total program duration of 8 weeks within recommendations (4–12 weeks according to AACVPR<sup>43</sup> and 6–8 weeks according to BTS<sup>44</sup>) were seen as an unavoidable compromise in order to continue providing rehabilitation services during the pandemic to as many patients as possible. The duration of 30 min of aerobic training and 1 h total session duration was as recommended.<sup>45</sup> The efficiency of our post-COVID-19 rehabilitation program has been proven,<sup>8</sup> and there was no adjustment in duration and frequency after the end of the pandemic. Finally, an additional limitation pertains to the absence of long-term follow-up, which might have been informative as regard to any potential long-term effects of pulmonary rehabilitation.<sup>11</sup>

New randomized control studies aim to investigate the long-term effects of rehabilitation and compare directly supervised with non-directly supervised programs utilizing new supportive technologies.<sup>46</sup> Such trials will provide valuable knowledge on the feasibility and effectiveness of new rehab programs in the context of personalized medicine.<sup>47</sup>

## Conclusions

In the current non-randomized study, rehabilitation of subjects with post-COVID-19 sequelae was associated with improvements in physical function, respiratory symptoms, severe fatigue, cognitive impairment, and HRQOL. These improvements were clinically important and were not associated with preceding disease severity, time from disease onset to rehab, age, and sex.

## REFERENCES

1. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms, and recommendations. *Nat Rev Microbiol* 2023;21(3):133-146.



2. Singh SJ, Baldwin MM, Daynes E, Evans RA, Greening NJ, Jenkins RG, et al. Respiratory sequelae of COVID-19: pulmonary and extrapulmonary origins and approaches to clinical care and rehabilitation. *Lancet Respir Med* 2023;11(8):709-725.
3. Meléndez-Oliva E, Martínez-Pozas O, Cuenca-Zaldívar JN, Villafañe JH, Jiménez-Ortega L, Sánchez-Romero EA. Efficacy of pulmonary rehabilitation in post-COVID-19: a systematic review and meta-analysis. *Biomedicine* 2023;11(8):2213.
4. Reinert G, Müller D, Wagner P, Martínez-Pozas O, Cuenca-Zaldívar JN, Fernández-Carnero J, et al. Pulmonary rehabilitation in SARS-CoV-2: a systematic review and meta-analysis of post-acute patients. *Diagn Basel Switz* 2022;12(12):3032.
5. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multi-center trial. *Eur Respir J* 2021;57(4):2003481.
6. Carvalho AC, Moreira J, Cubelo P, Cantista P, Aguiar Branco C, Guimarães B. Multidisciplinary rehabilitation in intensive care for COVID-19: randomized controlled trial. *ERJ Open Res* 2023;9(1):00350-02022.
7. Gloeckl R, Leitl D, Jarosch I, Schneeberger T, Nell C, Stenzel N, et al. Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. *ERJ Open Res* 2021;7(2):00108-02021.
8. Asimakos A, Spetsioti S, Mavrousou A, Gounopoulos P, Siousioura D, Dima E, et al. Additive benefit of rehabilitation on physical status, symptoms, and mental health after hospitalisation for severe COVID-19 pneumonia. *BMJ Open Respir Res* 2023;10(1):e001377.
9. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, Sereno M, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multi-center, prospective cohort study. *Lancet Respir Med* 2021;9(11):1275-1287.
10. PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med* 2022;10(8):761-775.
11. McCarthy A, Galvin R, Dockery F, McLoughlin K, O'Connor M, Corey G, et al. Multidisciplinary inpatient rehabilitation for older adults with COVID-19: a systematic review and meta-analysis of clinical and process outcomes. *BMC Geriatr* 2023;23(1):391.
12. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society-and American Thoracic Society-coordinated international task force. *Eur Respir J* 2020;56(6).
13. Singh SJ, Barradell AC, Greening NJ, Bolton C, Jenkins G, Preston L, et al. British Thoracic Society survey of rehabilitation to support recovery of the post-COVID-19 population. *BMJ Open* 2020;10(12):e040213.
14. Αναθεωρημένες οδηγίες Long-Post Covid/Ενήμερωση Ιατρών & ασθενών. Available at: <https://www.hts.org.gr/news/newsid510/1369>. Accessed March 20, 2022.
15. Antoniou KM, Vasarmidi E, Russell A-M, Andrejak C, Crestani B, Delcroix M, et al. European Respiratory Society statement on long COVID-19 follow-up. *Eur Respir J* 2022;60(2).
16. Singh SJ, Puhan MA, Andrianopoulos V, Hernandez NA, Mitchell KE, Hill CJ, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44(6):1447-1478.
17. Li J, Xia W, Zhan C, Liu S, Yin Z, Wang J, et al. A telerehabilitation program in post-discharge COVID-19 patients (TERECO): a randomized controlled trial. *Thorax* 2022;77(7):697-706.
18. Crook S, Büsching G, Schultz K, Leibert N, Jelusic D, Keusch S, et al. A multi-center validation of the 1-min sit-to-stand test in patients with COPD. *Eur Respir J* 2017;49(3).
19. Papatheanasiou G, Georgoudis G, Papandreou M, Spyropoulos P, Georgakopoulos D, Kalfakakou V, et al. Reliability measures of the short International Physical Activity Questionnaire (IPAQ) in Greek young adults. *Hellenic J Cardiol* 2009;50(4):283-294.
20. Jones PW, Harding G, Berry P, Wiklund I, Chen W-H, Leidy NK. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34(3):648-654.
21. Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity, and cognition - A cohort study. *Chron Respir Dis* 2021;18:14799731211015691.
22. Global Initiative for Chronic Obstructive Lung Disease. 2023 GOLD Report, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at: <https://goldcopd.org/2023-gold-report-2>. Accessed October 19, 2023.
23. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46(10):1121-1123.
24. Jackson C. The Chalder fatigue scale (CFQ 11). *Occup Med (Lond)* 2015;65(1):86.
25. Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JMM, Knauss S, et al. The Post-COVID-19 Functional Status (PCFS) Scale: a tool to measure functional status over time after COVID-19. *Eur Respir J* 2020;56(1).
26. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-699.
27. Nolan CM, Longworth L, Lord J, Canavan JL, Jones SE, Kon SSC, et al. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness, and minimum important difference. *Thorax* 2016;71(6):493-500.
28. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-483.
29. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-381.
30. Sawyer A, Cavalheri V, Hill K. Effects of high-intensity interval training on exercise capacity in people with chronic pulmonary conditions: a narrative review. *BMC Sports Sci Med Rehabil* 2020;12(1):22.
31. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al; ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188(8):e13-64-e64.
32. Νέος κορωνοϊός Covid-19-Οδηγίες. Εθνικός Οργανισμός Δημόσιας Υγείας. Available at: <https://eody.gov.gr/neos-koronaio-covid-19>. Accessed March 21, 2021.
33. Singh Sally, Bolton Charlotte, Nolan Claire, Harvey-Dunstan Theresa, Connolly Bronwen, Man William, Walker Paul. Delivering rehabilitation to patients surviving COVID-19 using an adapted pulmonary rehabilitation approach – BTS guidance.
34. Boutou AK, Asimakos A, Kortianou E, Vogiatzis I, Tzouveleki A. Long COVID-19 pulmonary sequelae and management considerations. *J Pers Med* 2021;11(9):838.
35. Stoltzfus JC. Logistic regression: a brief primer. *Acad Emerg Med* 2011;18(10):1099-1104.
36. Wu Q, Hou X, Li H, Guo J, Li Y, Yang F, et al. A follow-up study of respiratory and physical function after discharge in patients with re-detectable positive SARS-CoV-2 nucleic acid results following recovery from COVID-19. *Int J Infect Dis* 2021;107:5-11.
37. Santus P, Tursi F, Croce G, Di Simone C, Frassanito F, Gaboardi P, et al. Changes in quality of life and dyspnoea after hospitalization in

- COVID-19 patients discharged at home. *Multidiscip Respir Med* 2020;15(1):713.
38. van Haastregt JCM, Everink IHJ, Schols JMGA, Grund S, Gordon AL, Poot EP, et al. Management of post-acute COVID-19 patients in geriatric rehabilitation: EuGMS guidance. *Eur Geriatr Med* 2022;13(1):291-304.
  39. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study. *Complement Ther Clin Pract* 2020;39:101166.
  40. Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al; ATS/ERS Task Force on Policy in Pulmonary Rehabilitation. An Official American Thoracic Society/European Respiratory Society policy statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. *Am J Respir Crit Care Med* 2015;192(11):1373-1386.
  41. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. *Gastroenterol Hepatol Bed Bench* 2012;5(2):79-83.
  42. Ferguson B. ACSM's guidelines for exercise testing and prescription 9th ed. 2014. *J Can Chiropr Assoc* 2014;58(3):328.
  43. American Association of Cardiovascular and Pulmonary Rehabilitation. Guidelines for pulmonary rehabilitation programs, 5th edition. Champaign, Illinois: Human Kinetics, Inc; 2020.
  44. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al; British Thoracic Society Standards of Care Committee. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. *Thorax* 2013;68 Suppl 2(Suppl 2):ii1-i30.
  45. Garvey C, Bayles MP, Hamm LF, Hill K, Holland A, Limberg TM, et al. Pulmonary rehabilitation exercise prescription in chronic obstructive pulmonary disease: review of selected guidelines: an official statement from the American Association of Cardiovascular and Pulmonary Rehabilitation. *J Cardiopulm Rehabil Prev* 2016;36(2):75-83.
  46. Daynes E, Baldwin M, Greening NJ, Yates T, Bishop NC, Mills G, et al. The effect of COVID rehabilitation for ongoing symptoms Post HOSPitalisation with COVID-19 (PHOSP-R): protocol for a randomized parallel group controlled trial on behalf of the PHOSP consortium. *Trials* 2023;24(1):61.
  47. Holland AE, Cox NS, Houchen-Wolloff L, Rochester CL, Garvey C, ZuWallack R, et al. Defining modern pulmonary rehabilitation. An official American Thoracic Society Workshop report. *Ann Am Thorac Soc* 2021;18(5):e12-e29.

This article is approved for Continuing Respiratory Care Education credit. For information and to obtain your CRCE (free to AARC members) visit [www.rcjournal.com](http://www.rcjournal.com)

