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ORIGINAL ARTICLE

Time course of exercise capacity in patients recovering from COVID-19-associated pneumonia

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ABSTRACT

Objective: High prevalences of muscle weakness and impaired physical performance in hospitalized patients recovering from COVID-19-associated pneumonia have been reported. Our objective was to determine whether the level of exercise capacity after discharge would affect long-term functional outcomes in these patients. **Methods:** From three to five weeks after discharge from acute care hospitals (T_0), patients underwent a six-minute walk test (6MWT) and were divided into two groups according to the distance walked in percentage of predicted values: <75% group and ≥75% group. At T_0 and three months later (T_1), patients completed the Short Physical Performance Battery and the Euro Quality of Life Visual Analogue Scale, and pulmonary function and respiratory muscle function were assessed. In addition, a repeat 6MWT was also performed at T_1. **Results:** At T_0, 6MWD values and Short Physical Performance Battery scores were lower in the <75% group than in the ≥75% group. No differences were found in the Euro Quality of Life Visual Analogue Scale scores, pulmonary function variables, respiratory muscle function variables, length of hospital stay, or previous treatment. At T_1, both groups improved their exercise capacity, but only the subjects in the <75% group showed significant improvements in dyspnea and lower extremity function. Exercise capacity and functional status values returned to predicted values in all of the patients in both groups. **Conclusions:** Four weeks after discharge, COVID-19 survivors with exercise limitation showed no significant differences in physiological or clinical characteristics or in perceived health status when compared with patients without exercise limitation. Three months later, those patients recovered their exercise capacity.

Keywords: Exercise; Health status; Rehabilitation, Respiratory muscles; Dyspnea.

INTRODUCTION

The COVID-19 pandemic has been having impressive effects worldwide, with tens of million people infected and more than one million casualties.[1] Approximately 80% of the infected individuals are asymptomatic, whereas 15% and 5% of those present with moderate/severe and critical disease, respectively.[2] Pulmonary infection can cause alveolar damages that result in hypoxemic acute respiratory failure, requiring mechanical ventilation (MV).[3,4] Muscle impairment in patients admitted to the ICU can be associated with systemic inflammation, MV, sedation, and prolonged bed rest, among other causes.[5] Long-term physical, psychological, and cognitive impairment of both survivors and caregivers needs to be investigated.[6] A high prevalence of muscle weakness and impaired physical performance was described in hospitalized patients recovering from COVID-19 who had had no previous motor limitations.[7] COVID-19 survivors complain of fatigue, muscle weakness, sleep difficulties, anxiety, and depression six months after acute infection.[8] COVID-19 survivors with functional and muscular performance impairment, dyspnea, and poor perceived health status[9] can benefit from pulmonary rehabilitation.[10]

It is unclear whether the level of exercise capacity after discharge would affect long-term functional outcomes. Therefore, the aim of the present study was to evaluate the exercise capacity of patients four weeks after discharge from an acute care facility and after a three-month follow-up.

METHODS

This was an observational prospective controlled study. The study was approved by the Central Ethics Committee of *Istituti Clinici Scientifici Maugeri* (CEC no. 2435; May 26, 2020), and the participants signed the informed consent form.

Participants

Between May 27 and September 17 of 2020, consecutive patients recovering from COVID-19-associated pneumonia

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enrolled in a follow-up program at the *Istituti Clinici Scientifici Maugeri* outpatient clinic, in the city of Tradate, Italy, were included in the study. The clinic is part of the network of referral institutions for pulmonary rehabilitation, diagnosis, and care of post-acute and post-chronic patients.[11,12] All patients had previously been admitted to an ICU, an intermediate care unit, or a respiratory unit and had been discharged home or to an inpatient multidisciplinary program in accordance with the Italian Position Paper.[10,13,14] The patients were included in the follow-up program from three to five weeks after discharge.

Measurements

The following data were collected from patients at inclusion in the follow-up program (baseline: T_0): demographics; anthropometrics; number and type of comorbidities using the Cumulative Illness Rating Scale,[15] which includes a comorbidity index and a severity index; length of hospital stay; and use of invasive or noninvasive MV. According to the distance walked on the six-minute walk test (6MWT) at T_0, that is, six-minute walk distance (6MWD) at T_0, patients were divided into two groups: those with a 6MWD < 75% of the predicted values (<75% group) and those with a 6MWD ≥ 75% of the predicted values (≥75% group).

Outcome measures were assessed, using full protective measures,[16] both at T_0 and three months after T_0 (T_1). Exercise tolerance was assessed by means of the 6MWT.[17] 6MWD was expressed in meters and in percentage of the predicted values.[18] At the beginning and at the end of the test, the perception of dyspnea and leg fatigue were assessed by means of the modified Borg scale.[19] SpO_2 and HR were monitored with a pulse oximeter (8500M; Nonin Medical, Inc., Plymouth, MN, USA) and baseline SpO_2, baseline HR, SpO_{2nadir} and HR_{peak} were recorded. Exercise-induced desaturation was defined as baseline SpO_2 – SpO_{2nadir} (ΔSpO_2) > 4% during the 6MWT.[17,20] Lower extremity function was assessed by means of the Short Physical Performance Battery (SPPB)[21] using the values predicted by Bergland et al.[22] The total SPPB score results from the sum of three components: standing balance, four-meter walk test, and moving from a sitting to a standing position (five times). The total SPPB score ranges from 0 to 12 points: 1-2, severe disability; 3-8, moderate disability; and 9-12, no disability. The minimal clinically important difference for SPPB is considered to be 1 point.[23] Arterial blood gases were measured by means of an automated analyzer in samples collected from the radial artery with the patient breathing room air or oxygen in a sitting position for at least 1 h. Motor performance was assessed by the Barthel index[24]; the total score ranges from 0 (maximum level of dependency) to 100 (complete autonomy). A score ≤ 70 corresponds to severe dependency. Dyspnea was measured by the Barthel index dyspnea.[25] Total scores range from 0 (absence of dyspnea) to 100 (extremely severe dyspnea). A reduction of 9 and 12 points is considered as the minimal clinically important difference in COPD patients without and with chronic respiratory failure, respectively.[26] Perceived health status was measured by the Euro Quality of Life Visual Analogue Scale.[27] Total scores range from 0 to 100 (higher scores represent better quality of life). Dynamic lung volumes were assessed in accordance with standards[28] using the values predicted by Quanjer,[29] whereas MIP and MEP were assessed in accordance with international guidelines[30] using the values predicted by Bruschi et al.[31]

Statistical analysis

Qualitative variables were described as absolute and relative frequencies; quantitative variables were summarized as means and standard deviations or medians and interquartile ranges, depending on their parametric or nonparametric distribution. Between-group comparisons of qualitative variables were performed with the chi-square test or Fisher's exact test. To detect any statistical difference in the comparison of parametric and nonparametric quantitative variables, respectively, the Student's t-test and the Mann-Whitney test were used. We used the Student's t-test and Wilcoxon signed-rank test to evaluate paired differences. We used Spearman's and Pearson's correlations to detect the relationships between 6MWD measured during the follow-up and clinical variables. On the basis of previously published data,[10] a baseline 6MWD of 86.7 m and a pre- and post-intervention difference of 105 m, an alpha error of 0.05, and a statistical power of 0.9 estimated a sample size = 8. A two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed with the Stata statistical software package, version 16 (StataCorp LP, College Station, TX, USA).

RESULTS

Figure 1 shows the patient selection process. During the study period, 48 individuals were referred to our clinic, 33 met the inclusion criteria, and 3 were lost to follow-up; therefore, 30 patients were included in the analysis (Figure 1). According to 6MWD at T_0, 15 and 15 patients were included in the <75% group and in the ≥75% group, respectively. Eleven patients (73%) in the <75% group and 5 patients (33%) in the ≥75% group underwent pulmonary rehabilitation ($p = 0.03$).[14]

Demographic, anthropometric, physiological, and clinical characteristics of patients at T_0 are shown in Table 1. No significant differences were found between the groups. At T_0, all of the subjects had a BMI > 23.2 kg/m^2, 11 (33.3%) of whom had a BMI ≥ 30 kg/m^2 (4 and 7 in the <75% and ≥75% groups, respectively).

Table 2 shows the exercise capacity and functional status of the patients at T_0. As expected, when compared with patients in the ≥75% group, those in the <75% group had reduced exercise capacity

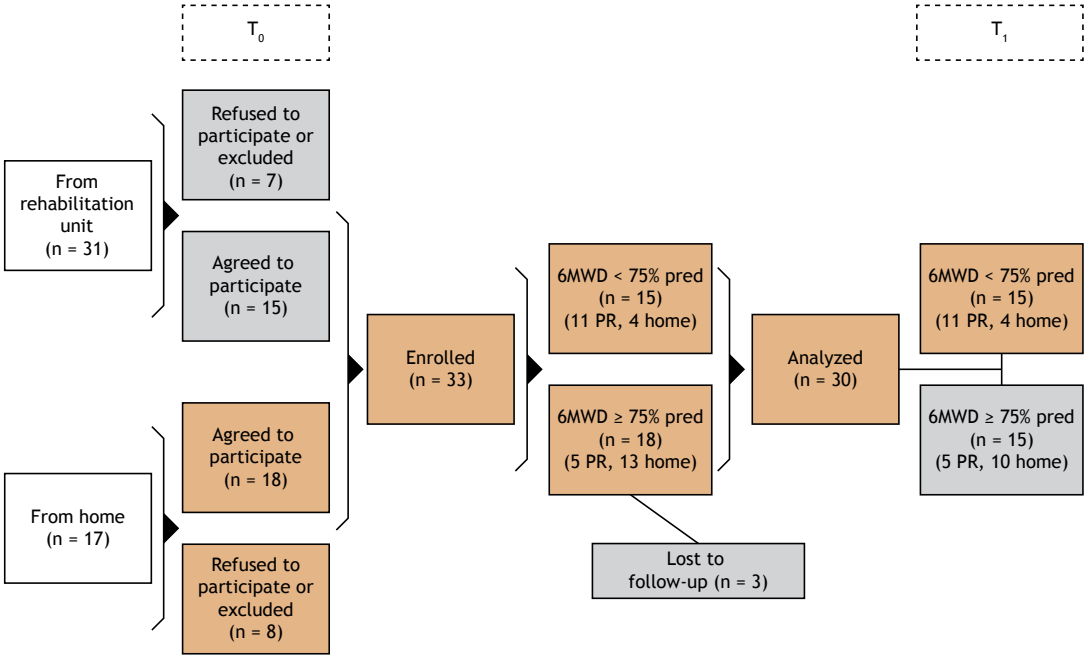

Figure 1. Flow chart of the patient selection process. T_0: enrolment visit; T_1: follow-up visit; 6MWD: six-minute walk distance; pred: of predicted; and PR: pulmonary rehabilitation.

and more severe dyspnea and had lower scores on the SPPB, but not on the Euro Quality of Life Visual Analogue Scale.

Table 3 shows the values of demographic, physiological, and functional variable results at T_1, as well as the differences ($T_1 - T_0$) regarding exercise capacity, dyspnea, and lower extremity function. No significant differences between the groups were found in anthropometric or physiological variables at T_1. However, 6MWD values and SPPB scores were higher in the ≥75% group than in the <75% group. Both groups showed improvement in exercise capacity, but only the <75% group showed significant improvements in dyspnea and in lower extremity function. As also shown in Table 3, exercise capacity and functional status results returned to predicted values in all of the patients in both groups.

Table 4 shows the correlations of demographic, physiological, and clinical characteristics at T_0 with 6MWD at T_1. Being older, having longer length of hospital stay, having comorbidities, and having needed invasive MV correlated with having lower 6MWD values at T_1. Having lower 6MWD values and lower SPPB scores at T_0 correlated with having higher 6MWD values at T_1. Because of the small sample, participating in the pulmonary rehabilitation program was not significantly correlated with exercise capacity at T_1.

DISCUSSION

The present study shows that half of the patients recovering from COVID-19-associated pneumonia may present with exercise limitation four weeks after discharge from acute care hospitals. Patients with exercise limitation and worse functional status, when compared with those without them, showed no significant differences in terms of demographic, anthropometric, physiological, or clinical characteristics, or in perceived health status. Three months after T_0, exercise capacity and functional status results returned to predicted values in both groups.

Our results confirm that COVID-19 survivors can have impaired physical functioning when they are discharged home, even after early mobilization.[32] The absence of differences at baseline highlights that the decline in physical performance cannot be attributed to lung impairment or respiratory muscle dysfunction.

As shown by the comparison with predicted values, three months after T_0, all patients recovered their exercise capacity and functional status. A large study reported that, six months after the acute infection, COVID-19 survivors complained of fatigue or muscle weakness, sleep difficulties, and anxiety or depression.[8] The length of hospital stay in acute care facilities in our sample was similar to that in the aforementioned study[8] with patients on invasive MV, noninvasive ventilation, or high flow nasal cannula (mean: 43 vs. 35 days). Exercise capacity as assessed by 6MWD three months after discharge was similar to that in the aforementioned study with patients assessed six months after discharge from acute care hospitals (mean: 94% vs. 88 % of the predicted values).[8]

The vast majority of patients (73%) with exercise limitation (<75% group) underwent pulmonary rehabilitation in accordance with the Italian Position

Table 1. Demographic, anthropometric, physiological, and clinical characteristics of patients at baseline (T_0).[a]

Characteristic	Whole sample	Group		p
		<75%	≥75%	
	(N = 30)	(n = 15)	(n = 15)	
Male gender, n (%)	21 (70.0)	11 (73.3)	10 (66.7)	1.00
Age, years	63.6 ± 12.2	65.2 ± 12.5	62.0 ± 12.0	0.48
BMI, kg/m^2	27.0 (25.3-31.0)	26.7 (23.9-30.1)	28.4 (25.5-35.2)	0.15
Current or former smoker, n (%)	12 (42.9)	9 (60.0)	3 (23.1)	0.07
Length of hospital stay, days	43.0 ± 20.1	44.1 ± 23.7	41.6 ± 15.4	0.76
Previous IMV, n (%)	6 (20.0)	4 (26.7)	2 (13.3)	0.65
Previous NIV, n (%)	13 (43.3)	9 (60.0)	4 (26.7)	0.14
Previous oxygen therapy, n (%)	23 (76.7)	11 (73.3)	12 (80.0)	1.00
COPD, n (%)	2 (6.7)	1 (6.7)	1 (6.7)	1.00
Asthma, n (%)	3 (10.0)	1 (6.7)	2 (13.3)	1.00
Pulmonary embolism, n (%)	1 (3.3)	1 (6.7)	0 (0.0)	1.00
Diabetes, n (%)	5 (17.2)	2 (13.3)	3 (21.4)	0.65
FiO_2	0.21 (0.21-0.24)	0.21 (0.21-0.28)	0.21 (0.21-0.21)	0.21
PaO_2, mmHg	83.3 ± 9.3	81.6 ± 9.5	84.7 ± 9.2	0.43
PaO_2/FiO_2	394.7 ± 45.4	388.7 ± 45.2	399.7 ± 46.8	0.57
SaO_2, %	96.5 ± 1.4	96.4 ± 1.46	96.5 ± 1.40	0.87
$PaCO_2$, mmHg	36.1 ± 2.8	36.5 ± 3.2	35.8 ± 2.4	0.56
pH	7.412 ± 0.026	7.401 ± 0.180	7.420 ± 0.280	0.06
CIRS-SI	1.5 ± 0.2	1.6 ± 0.2	1.4 ± 0.2	0.07
CIRS-CI	2.4 ± 1.5	2.6 ± 1.6	2.1 ± 1.4	0.40
MIP, cmH_2O	90.0 ± 26.3	93.3 ± 21.2	88.7 ± 29.1	0.78
MIP, % predicted	113.3 ± 40.0	96.5 ± 19.7	120.0 ± 44.8	0.34
MEP, cmH_2O	142.4 ± 48.5	147.5 ± 48.2	140.4 ± 51.1	0.82
MEP, % predicted	128.0 ± 34.5	116 ± 37.7	132.8 ± 34.0	0.43
FEV_1, L	3.0 ± 1.2	3.5 ± 1.3	2.8 ± 1.1	0.27
FEV_1, % predicted	97.1 ± 23.4	103.8 ± 38.4	94.4 ± 16.5	0.52
FVC, L	3.7 ± 1.3	4.4 ± 1.3	3.4 ± 1.3	0.20
FVC, % predicted	96.9 ± 21.3	104.5 ± 37.4	93.9 ± 12.4	0.42
FEV_1/FVC, %	77.4 (74.3-80.4)	78.6 (75.7-83.2)	76.4 (70.0-78.7)	0.37

IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; CIRS-SI: Cumulative Illness Rating Scale severity index; and CIRS-CI: Cumulative Illness Rating Scale comorbidity index. [a]Values expressed as mean ± SD or median (IQR), except where otherwise indicated.

Table 2. Exercise capacity and functional status at baseline (T_0).

Variable	Whole sample	Group		p
		<75%	≥75%	
	(N = 30)	(n = 15)	(n = 15)	
BI score	100 (100-100)	100 (95-100)	100 (100-100)	0.41
BI-d score	5 (2-16)	16 (5-12)	2 (0-5)	0.0004
SPPB total score	11 (9-12)	8.5 (6-11)	11 (10-12)	0.006
SPPB, % predicted	92.3 (76.0-101.4)	74.3 (54.5-91.7)	99.9 (92.3-102.6)	0.001
6MWD, m	406.5 (318.0-521.0)	318.0 (250.0-380.0)	510.0 (433.0-570.0)	< 0.0001
6MWD, % predicted	77.0 (64.0-98.0)	64.0 (57.0-70.0)	98.0 (85.0-109.0)	< 0.0001
SpO_{2mean}, %	93.8 ± 2.4	92.7 ± 2.9	94.6 ± 1.7	0.04
SpO_{2nadir}, %	92.0 (89.0-94.0)	89.5 (87.5-92.0)	93.0 (92.0-95.0)	0.01
ΔSpO_2 (baseline/nadir), %	−4.8 ± 3.4	−6.8 ± 3.9	−3.3 ± 1.9	0.005
Borg dyspnea scale score	2.9 ± 1.9	3.4 ± 1.9	2.6 ± 1.9	0.29
Borg leg fatigue scale score	2 (0.5-3.0)	2.0 (0.5-3.5)	3.0 (1.0-3.0)	0.69
EuroQoL-VAS score	80.3 ± 12.7	79.1 ± 15.0	81.5 ± 10.2	0.61

BI: Barthel index; BI-d: Barthel index dyspnea; SPPB: Short Physical Performance Battery; 6MWD: six-minute walk distance; and EuroQoL-VAS: Euro Quality of Life Visual Analogue Scale. [a]Values expressed as mean ± SD or median (IQR).

Table 3. Anthropometric, physiological, and functional variables at T_1 and p-values of the differences between T_1 and T_0 within the groups[a] and between the groups.[b,c]

Variable	<75% group	p[a]	≥75% group	p[a]	p[b]
BMI, kg/m²	28.0 (24.0-30.0)	0.87	27.8 (25.2-35.0)	0.68	0.32
PaO_2, mmHg	84.3 ± 8.1	0.22	83.4 ± 6.4	0.29	0.76
$PaCO_2$, mmHg	36.8 ± 2.9	0.46	37.6 ± 2.9	0.17	0.49
pH	7.421 ± 0.03	0.005	7.417 ± 0.03	0.85	0.69
SaO_2, %	96.8 ± 1.1	0.29	96.8 ± 0.8	0.55	0.95
PaO_2/FiO_2	401.7 ± 38.8	0.22	397.2 ± 30.6	0.29	0.76
MIP, cmH_2O	84.5 ± 25.6	0.91	93.5 ± 21.8	0.01	0.31
MIP, % predicted	103.7 ± 28.1	0.87	121.6 ± 40.3	0.02	0.17
MEP, cmH_2O	133.3 ± 46.5	0.03	144.7 ± 47.3	0.29	0.51
MEP, % predicted	119.9 ± 28.9	0.03	134.3 ± 35.7	0.35	0.24
FEV_1, L	2.8 ± 0.8	0.66	3.0 ± 1.0	0.01	0.63
FEV_1, % predicted	101.3 ± 21.9	0.72	103.5 ± 18.4	0.04	0.77
FVC, L	3.3 (2.7-4.7)	0.12	3.6 (2.7-5.0)	0.02	1.00
FVC, % predicted	106 (77-123)	0.48	96 (88.127)	0.02	1.00
FEV_1/FVC	75.0 ± 9.1	0.13	78.1 ± 6.7	0.56	0.30
BI-d score	2 (0-5)	0.0007	0 (0-2)	0.20	0.09
ΔBI-d score	−10.9 ± 9.5	-	−1.0 ± 4.6	-	0.002
SPPB total score	10 (10-12)	0.003	12 (12-12)	0.06	0.007
ΔSPPB total score	+2.3 ± 2.4	-	+0.7 ± 1.3	-	0.03
SPPB, % predicted	94.4 (90.8-102.2)	0.002	101.9 (100.1-102.6)	0.06	0.02
6MWD, m	479.4 ± 65.9	0.0001	545.2 ± 95.2	0.004	0.04
Δ6MWD, m	+158 (100-200)	-	+43 (5-97)	-	0.0001
6MWD, % predicted	94.1 ± 12.2	0.0005	109.5 ± 10.8	0.003	0.001
Δ6MWD, % predicted	+28.0 (19.0-44.0)	-	+9.0 (3.0-19.0)	-	0.0005
SpO_{2mean}, %	93.8 (90.0-95.1)	0.94	95.2 (94.5-96.1)	0.90	0.05
SpO_{2nadir}, %	92 (88-93)	0.23	94 (93-96)	0.52	0.04
ΔSpO_2 baseline/nadir, %	−4 (−8.3 to −2.6)	0.15	−3 (−4.3 to −0.5)	0.97	0.15
EuroQoL-VAS score	78.7 ± 14.2	0.91	85.7 ± 11.5	0.06	0.15

BI-d: Barthel index dyspnea; SPPB: Short Physical Performance Battery; 6MWD: six-minute walk distance; and EuroQoL-VAS: Euro Quality of Life Visual Analogue Scale. [a]Values expressed as mean ± SD or median (IQR).

Table 4. Correlations of demographic, physiological, and clinical characteristics at T_0 with the six-minute walk distance at T_1.

Characteristic	rho	p
IMV	-0.39	0.03
NIV	-0.36	0.05
Oxygen therapy	-0.27	0.14
Exposure to rehabilitation	-0.30	0.11
Age	-0.62	0.0002
Previous LoS in acute phase	-0.58	0.002
BMI, kg/m²	-0.10	0.61
CIRS-SI	-0.61	0.0004
CIRS-CI	-0.52	0.003
BI-d	-0.45	0.01
SPPB total score	0.65	0.0001
6MWD at T_0	0.75	< 0.0001
VC, %	-0.28	0.37

IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; LoS: Length of hospital stay; CIRS-SI: Cumulative Illness Rating Scale severity index; CIRS-CI: Cumulative Illness Rating Scale comorbidity index; BI-d: Barthel index dyspnea; SPPB: Short Physical Performance Battery; and 6MWD: six-minute walk distance.

Paper,[14] in comparison with 33% of the patients in the ≥75% group. The small sample size impedes a reliable comparison between patients who did and did not undergo pulmonary rehabilitation. However, our results confirm those of another study[10] that showed that a pulmonary rehabilitation program could improve but not fully recover exercise capacity. Furthermore, in our study, due to the small sample size, participation in a pulmonary rehabilitation program was not associated with exercise capacity at T_1.

There was no difference in perceived health status between patients with or without exercise limitation. In other words, at least in this sample of patients, there was a dissociation between exercise capacity and health status. This observation has been also reported in other studies about other diseases[33] and probably reflects the fact that health status does not depend on exercise capacity only. This underlines the importance of evaluating this parameter specifically.

The present study has limitations. Standard respiratory muscle or lung function tests, including assessment of diffusing capacity at discharge from acute care hospitals, could not be performed for safety reasons. The small sample size impedes a reliable

comparison between patients who did and did not undergo pulmonary rehabilitation.

In conclusion, patients recovering from COVID-19-associated pneumonia may present with exercise limitation four weeks after discharge from acute care hospitals. No significant differences were found in any demographic, anthropometric, physiological, or clinical characteristics or in perceived health status between patients with or without exercise limitation. However, three months later, the measurements of exercise capacity and functional status returned to the predicted values in both groups. Despite the small sample size and the possible lack of external validity, our findings may guide clinicians who treat COVID-19 survivors to design suitable rehabilitation programs.

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AUTHOR CONTRIBUTIONS

All authors participated in the drafting and revision of the manuscript, as well as in the approval of the final version.

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