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Pulmonary Rehabilitation in Patients Recovering from COVID-19

Elisabetta Zampogna[a] Mara Paneroni[b] Stefano Belli[c] Maria Aliani[d] Alessandra Gandolfo[e] Dina Visca[a, f] Maria Teresa Bellanti[c] Nicolino Ambrosino[g] Michele Vitacca[b]

[a]Respiratory Rehabilitation of the Institute of Tradate, Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Italy; [b]Respiratory Rehabilitation of the Institute of Lumezzane, Istituti Clinici Scientifici Maugeri, IRCCS, Brescia, Italy; [c]Respiratory Rehabilitation of the Institute of Veruno, Istituti Clinici Scientifici Maugeri, IRCCS, Veruno, Italy; [d]Respiratory Rehabilitation of the Institute of Bari, Istituti Clinici Scientifici Maugeri, IRCCS, Bari, Italy; [e]Respiratory Rehabilitation of the Institute of Pavia, Istituti Clinici Scientifici Maugeri, IRCCS, Pavia, Italy; [f]Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese-Como, Italy; [g]Respiratory Rehabilitation of the Institute of Montescano, Istituti Clinici Scientifici Maugeri, IRCCS, Montescano, Italy

Keywords
Exercise training · Exercise capacity · Dyspnoea · Pulmonary rehabilitation

Abstract
Background: In hospitalized patients recovering from the SARS-coronavirus-2 disease 19 (COVID-19), high prevalence of muscle weakness and physical performance impairment has been observed. ***Objectives:*** The aim of this study was to evaluate the effectiveness of pulmonary rehabilitation in these subjects in a real-life setting. ***Methods:*** Retrospective data analysis of patients recovering from COVID-19, including those requiring assisted ventilation or oxygen therapy, consecutively admitted to an in-patient pulmonary rehabilitation program between April 1 and August 15, 2020. Short Physical Performance Battery (SPPB: primary outcome), Barthel Index (BI), and six-min walking distance were assessed as outcome measures. ***Results:*** Data of 140 patients were analyzed. After rehabilitation, patients showed improvements in SPPB {from: (median [IQR]) 0.5 (0–7) to 7 (4–10), $p < 0.001$} and BI (from 55 [30–90] to 95 [65–100], $p < 0.001$), as well as in other assessed outcome measures. The proportion of patients unable at admission to stand, rise from a chair and walk was significantly reduced ($p < 0.00$). ***Conclusions:*** Pulmonary rehabilitation is possible and effective in patients recovering from COVID-19. Our findings may be useful to guide clinicians taking care of patients surviving COVID-19 infection.

Introduction

The SARS-coronavirus-2 disease 19 (COVID-19) pandemic has caused dramatic effects throughout the world, with tens of millions of people infected and >1 million casualties [1]. Approximately 80% of patients have mild to moderate, 15% severe disease, and 5% have critical illness [2]. The disease can cause major alveolar damage resulting in hypoxemic acute respiratory failure requiring mechanical ventilation in a high proportion of cases [3, 4]. The long-term physical, psychological, and cognitive impairment of both survivors and their caregivers remain to be described [5]. In hospitalized patients without any prior motor limitation, recovering from COVID-19, a

karger@karger.com
www.karger.com/res

Karger

Elisabetta Zampogna
Respiratory Rehabilitation of the Institute of Pavia
Istituti Clinici Scientifici Maugeri, IRCCS
via Maugeri, 10, 27100 Pavia, IT (Italy)
elisabetta.zampogna@icsmaugeri.it

high prevalence of muscle weakness and physical performance impairment has been observed [6]. Furthermore in patients requiring intensive care unit stay, the muscle impairment could be related, among others, to systemic inflammation, mechanical ventilation, sedation, and prolonged bed rest [7]. In addition, many authorities have forbidden for long-time travels and people moving, resulting also in prevention of attendance to in- or outpatient pulmonary rehabilitation programs.

Despite clinical indications and modalities of pulmonary rehabilitation have been proposed by international guidelines and recommendations [8–10], the tolerance to and the effects of such programs in patients recovering from COVID-19 remain to be elucidated. However, we cannot wait for well-designed randomized controlled trials to be published before starting these interventions in daily clinical practice, as the number of COVID-19 patients increases rapidly every day. Therefore, the aim of this multicenter retrospective study was to report the effectiveness of pulmonary rehabilitation in subjects recovering from COVID-19 in a real-life setting.

Methods

The study was approved by the Istituti Clinici Scientifici (ICS) Maugeri Ethics Committee (CEC 2279; March 12, 2020). At admission to ICS institutions, patients gave their informed consent for the scientific use of their data. As a retrospective analysis, the study was not registered.

Patients

This study was conducted on the Automated Integrated Health Care Record database of patients recovering from COVID-19 with negative RT-PCR test for SARS-CoV-2, consecutively admitted for inpatient pulmonary rehabilitation between April 1 and August 15, 2020, to ICS Maugeri hospitals in Italy (Bari, Lumezzane, Tradate, Pavia, and Veruno) and referral institutions for pulmonary rehabilitation, diagnosis, and care for post-acute and chronic subjects [11, 12]. Patients were transferred from intensive and subintensive care units, pneumology units, or general wards where they had been managed, including for COVID-19 induced acute respiratory failure requiring or not either invasive or noninvasive ventilation (NIV). Patients were admitted to selected areas and received drug therapy according to the evolving information and current research [13]. One or more of the following drugs – chloroquine, steroids, and anticoagulants – had been prescribed in addition to therapy for patients' underlying comorbidities. Exclusion criteria were persistent positive RT-PCR test and reported prior clinical conditions preventing active mobilization.

Measurements

At admission the following data were collected: demographics, anthropometrics, number, and diagnosis of comorbidities by the Cumulative Illness Rating Scale (CIRS), including the Cumulative Illness Rating Score Comorbidities Index (CI) and the Cumulative Illness Rating Score Severity Index (SI) [14]. CIRS-CI was calculated assigning to each item a score between 0 (none) and 4 (extremely severe), total score reflecting the mean value of the first 13 items. CIRS-CI was obtained by the sum of the items with score ≥3. Length of stay (LoS) in referring hospitals, use of mechanical ventilation, either invasive or NIV, and arterial blood gases were recorded as well.

With the safety procedures and wearing appropriate personal protective equipment [15], the following outcome measures were assessed when allowed by patients' clinical conditions and safety or organizational issues.

- Motor performance was assessed by the Barthel Index (BI) [16]. The total BI score ranges from 0 (maximum level of dependency) to 100 (complete autonomy). A score ≤70 corresponds to severe dependency.
- The lower extremity function was assessed by means of the Short Physical Performance Battery (SPPB) [17, 18] with the predicted normal values of Bergland et al. [19]. The SPPB total score results from the sum of 3 components: standing balance, 4-m walking test (4MWT) and standing from sitting position 5 times (5-STS). The total SPPB score ranges from 0 to 12: 1–2: severe; 3–8 moderate disability; 9–12 normal. One point is considered as the minimal clinically important difference (MCID) for SPPB [20]. i.For tests of standing balance included side-by-side, semi-tandem, and tandem standing, the subjects were timed until they moved or 10 s had elapsed. The subjects were given a score of 0 if bedridden, 1 if they could hold only the side-by-side standing position, a score of 2 if they could hold a semi-tandem position but were unable to hold a tandem position for >2 s, a score of 3 if they could stand in the tandem position for 3–9 s, and a score of 4 if they could stand in the tandem position for 10 s. ii. The 4MWT was performed twice. The faster time spent to complete the test was used for scoring as follows: unable to walk a score: 0; >8.7 s: 1; 8.7–6.2 s: 2; 6.2–4.8 s: 3; <4.8 s: 4 [21]. iii. Quartiles of time required to complete the 5-STS were used for scoring as follows: unable to rise: 0, ≥16.7 s: 1; 13.7–16.6 s: 2; 11.2–13.6 s: 3; and ≤11.1 s: 4 [22].
- Exercise tolerance was assessed by the 6-m walking test (6MWT) [23] using the predicted values of Enright et al. [24]. The baseline value of patients unable to perform the test was considered as 0 for analysis.

Pulmonary Rehabilitation

Health-care operators experienced in pulmonary rehabilitation were trained to manage patients with COVID-19 wearing appropriate personal protective equipment [15]. A multidisciplinary program according to the Italian Position Paper was applied in all centers involved [9]. Type, intensity, timing and modality of intervention were tailored to the individual patient according to age, clinical severity, length of immobilization, comorbidities, starting from a minimum of one, 20-min daily session up to two-three, 30-min daily sessions.

According to the SPPB total score, patients were allocated either to individual (level A if SPPB < 6 with a physiotherapist/patient ratio 1:1) or group (level B if SPPB ≥ 6 with a physiotherapist/patient ratio 1:4–5) sessions. The level A program might include or be limited to one or more of the following: mobilization, active exercises and free walking, peripheral limb muscle activities, shoulder, and full arm circling. The level B program might include

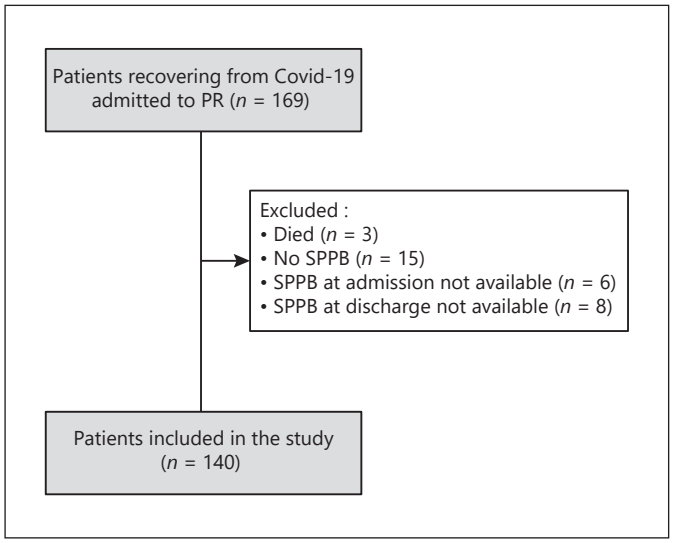

Fig. 1. CONSORT diagram of patient selection. SPBB, Short Physical Performance Battery; BI, Barthel Index.

Table 1. Demographic, anthropometric, physiological, and clinical characteristics of patients in study

Age, years	71.0 (61.5–78.0)
Male, *n* (%)	95 (67.8)
BMI, kg/m^2	25.2 (23.2–29.3)
LoS in acute hospitals, days	47.0 (33.5–64.0)
Previous invasive ventilation, *n* (%)	56 (40.0)
Previous NIV, *n* (%)	70 (50.0)
Previous oxygen need, *n* (%)	117 (83.6)
PaO_2/FiO_2 (*n* = 130)	338.1 (310.5–371.4)
PaO_2, mm Hg (*n* = 130)	72.4 (67.1–84.0)
$PaCO_2$, mm Hg (*n* = 130)	37.8 (34.00–42.1)
pH (*n* = 130)	7.43 (7.40–7.45)
CIRS-SI, score	1.6 (1.60–2.1)
CIRS-CI, score	4.0 (3.0–5.0)

Data are expressed as *n* (%) or median (IQR). BMI, body mass index; LoS, length of stay; NIV, noninvasive ventilation; PaO2, arterial oxygen tension; PaCO2, arterial carbon dioxide tension; FiO2, inspired oxygen fraction; CIRS-SI, Cumulative Illness Rating Score Severity Index; CIRS-CI, Cumulative Illness Rating Score Comorbidities Index; IQR, interquartile range.

or be limited to one or more of the following: callisthenic, strengthening, balance exercise, and paced walking. All exercises could be performed without devices or using gymnastic tools such as balls, canes, balance boards, or light weights bands [9].

Patients in level B with higher physical autonomy were also trained on cycle-ergometer at low-intensity exercises (<3.0 METs). The initial training workload was chosen starting from 0 and progressively increasing until patients scored their dyspnea and/or leg fatigue as 4 or 5 on a modified 10-point Borg Scale [25]. Thereafter the progression of intensity was according to Maltais et al. [26]: the workload was increased by 5 W when patients scored less or equal to 3, was unchanged when the Borg score was 4 or 5, and was reduced by 5 W for scores of >5. Also, chest physiotherapy such as bronchial hygiene techniques by using disposable devices with self-management in order to avoid the risk of environmental contamination [15, 27], and lung expansion procedures were performed when required.

Subjects were re-assessed on a daily base in order to adjust the type, intensity, timing and modality of the intervention. According to patient's individual conditions, the program might include also nutritional and psychological assessment.

Statistical Analysis

Statistical analysis was performed using STATA 11 (StataCorp LLC). Data for continuous variables were expressed as median (interquartile range; IQR) and binary outcomes were described as percentage (%). SPPB total score and 6MWT were also defined as mean ± standard deviation (SD). The change in SPPB total score was the primary outcome. The pre-to-post outcome measure changes were evaluated by Wilcoxon signed rank test or by χ^2 tests. Odd ratio analysis was performed to evaluate the risk of improvement in SPPB above the MCID (1 point) [22] according to the baseline characteristics. $p < 0.05$ was considered as statistically significant.

Results

The study flow chart is shown in Figure 1. Out of 169 patients admitted, 140 (Bari: 5, Lumezzane: 51, Pavia: 5, Tradate: 56, Veruno: 23), with assessments of SPPB both before and after the program, were included. Demographics, anthropometrics, physiological, and clinical characteristics of patients are shown in Table 1. Sixteen 1 % and 4.4% of patients suffered from chronic obstructive pulmonary disease and asthma, respectively.

Patients had suffered from long LoS in acute care hospitals, and a high proportion of patients had undergone mechanical ventilation either invasive (including some tracheostomized) or NIV. At admission, 6.2% of patients still had a tracheostomy, 7.1% were still under NIV, and 23.8% still used oxygen supplementation (mean fraction of inspired oxygen [FiO_2] = 0.23 ± 0.05). LoS in our institutions was 24.0 (19.0–34.0) days.

Patient performed 60 (38–84) sessions corresponding to 2.8 (1.0–3.8) daily sessions. Thirty-one percent of patients performed only level A interventions, 7% only level B, and 62% shifted from level A to level B. About 70% of patients completed their program into level B. None of patients had to step down from level B to A. Eighty-five patients (61.0%) underwent 14.0 (8.0–19.0) sessions of cycle-ergometer endurance training with an initial workload of 5.0 (1.2–10.0) up to 30.0 (20.0–40.0) W. Additional physiotherapy other than endurance training was

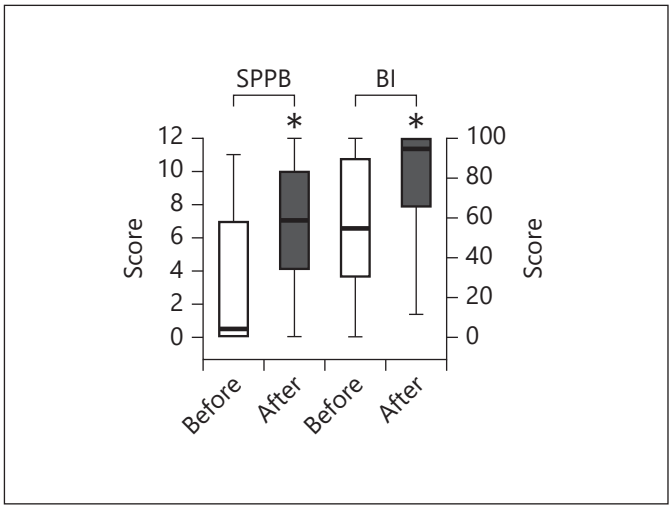

Fig. 2. Changes in SPPB and BI scores before and after pulmonary rehabilitation. SPBB, Short Physical Performance Battery; BI, Barthel Index.

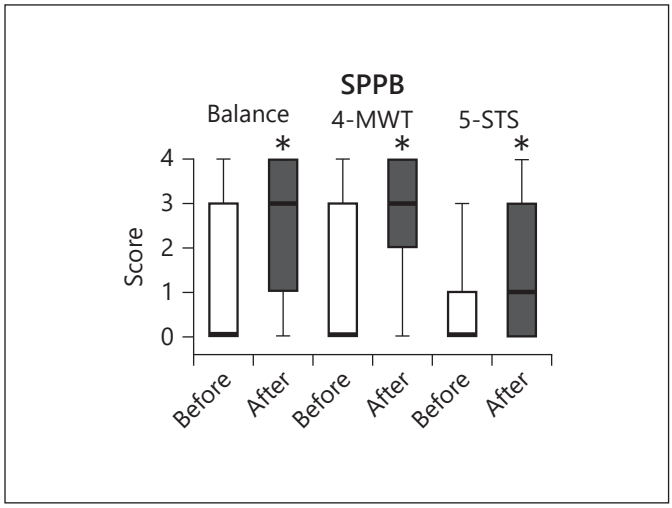

Fig. 3. Change of SPPB components (balance, 4MWT, and 5-STS) before and after rehabilitation. The lines indicating the medians of before rehabilitation data correspond to zero. SPBB, Short Physical Performance Battery; BI, Barthel Index; 4MWT, 4-m walking test; 5-STS, sitting position 5 times.

performed in 62% of patients (strengthening exercise, balance exercises, and chest physiotherapy). Educational sessions were performed in 50% of patients.

The physical conditions of our patient at admission were very severe as assessed by the values of baseline outcome measures and the high proportion of patients unable to perform the tests. Values of SPPB and BI before and after pulmonary rehabilitation are shown in Figure 2. At admission, the SPPB score was 0.5 (0–7) (mean ± SD = 3.2 ± 3.7). Eighty-two (58.6%) patients showed a SPPB score <3, indicating severe disability. Seventy-one (50.7%), 76 (54.3%), and 94 (67.1%) patients were unable to stand, walk, or rise from a chair without help, respectively. Among patients able to walk and rise from a chair, the time to complete the 4MWT and the 5-STS were 5.7 (4.1–9.0) and 16.7 (12.0–22.9) seconds, respectively.

Change in the SPPB total score after the program was 3.0 (1.0–6.0), and 89 patients (63.6%) reached the MCID. Final SPPB score was 7 (4–10) (6.9 ± 3.8). The SPPB, % predicted improved from 4.2 (0.0–58.3) to 66.7 (37.8–107.1) (p = 0.00). After the program, the number of patients reporting score ≤2 was reduced to 23 (16.4%). Figure 3 shows the SPPB components (balance, 4MWT, and 5-STS) before and after rehabilitation.

After the program, components of SPPB improved significantly in all subjects. The proportion of patients unable at admission to stand, walk and rise from a chair was significantly reduced after rehabilitation (p < 0.00). The odd ratio analysis showed that an improvement above 1 point in SPPB total score was significantly associated with the median baseline SPPB total score <3 (odds ratio [OR] 3.5 [SE 1.3], p = 0.00), previous use of NIV (OR 3.0 [SE 1.1] p = 0.002) and baseline inability to perform 6MWT (OR 2.3 [SE 0.9], p = 0.001).

The BI improved after the program from 55.0 (30.0–90.0) to 95.0 (65.0–100.0) (p = 0.00). Forty-two (30.0%) subjects were able to perform the 6MWT at admission as compared to 81 (57.8%) post treatment. The distance walked during the 6MWT by these 81 patients was 285.0 (232.0–370.0; mean ± SD 298.2 ± 116.7 m). Data for 6MWT improvement in 42 patients able also at admission to perform the test are shown on Table 2.

Discussion

As occurred in phase one of COVID-19, when international scientific societies and professionals released practical recommendations to be followed [8–10], further insights into the most profitable and therapeutic trajectories including pulmonary rehabilitation have been advocated also for post-acute phase of the disease [28–31]. Our real life multicentric study is one of the first answers to these needs showing that pulmonary rehabilitation is

Table 2. Changes in 6MWT in 42 patients able to perform the test at admission and at the end of rehabilitation

	Before	After	*p* value
6MWT, m			
Median (IQR)	205.0 (160.0–280.0)	295.0 (250.0–370.0)	0.00
Mean ± SD	229.0±102.5	327.9±97.8	
6MWT, % predicted			
Median (IQR)	46.0 (32.0–55.0)	70.0 (56.7–75.2)	0.00
Mean ± SD	47.7±18.9	68.4±15.3	

Data are expressed as median (IQR) and mean ± SD and range. 6MWT, 6-m walking test; IQR, interquartile range.

possible and effective in patients recovering from COVID-19 infection, including those requiring assisted ventilation or oxygen therapy.

It has been reported that post-COVID patients can have an impaired physical functioning when they are discharged home, even after early mobilization [32]. Our results confirm those observations and extend to more severe patients directly transferred from acute care hospitals. As compared to that study [32], our patients suffered from more severe acute conditions as assessed by longer LoS in acute care hospitals and by the very high proportion of patients undergoing mechanical ventilation either invasive (including some tracheostomized) or NIV.

Among our patients, there were 16.1 and 4.4% with chronic obstructive pulmonary disease and asthma, respectively. The level and severity of comorbidities of our patients, as assessed by the CIRS indexes, were similar to those of patients reported outside the COVID conditions and likewise they did not influence the results of pulmonary rehabilitation [12].

Our pulmonary rehabilitation program was according to the Italian Position Paper [9]. Type, intensity, timing, and modality of intervention were tailored to the individual patient. Although the physical, cognitive, and emotional problems associated to prolonged LoS and/or mechanical ventilation are well-established in non-COVID-19 patients, their treatment is still under development [33–35].

Only patients with RT-PCR test for SARS-CoV-2 were included in our study. In the absence of such evaluation, there is no consensus on how long patients should be self-isolating. It has been suggested that local infection prevention recommendations should be followed with significant adaptation of the program, eventually with the adoption of "tele-rehabilitation" [36].

Limitations of the Study

For safety reasons, it was impossible to perform standard respiratory muscle or lung function tests, including the assessment of diffusion capacity. Hence, we are unable to define to what extent the decline in physical performance observed at admission can be ascribed to impairment in lung or respiratory muscle function. The results of an uncontrolled study may be difficult to interpret because we can suppose a positive effect in the long-term follow-up of these patients without a rehabilitative intervention. A control population not performing any activity would be unethical given the undisputed benefits of pulmonary rehabilitation or simple physical activity. One possible solution to this dilemma could be a trial with early versus delayed rehabilitation in post-COVID-19 patients. Our study could suffer from low external validity due to our restrictive inclusion criteria that limited the study to patients without functional limitations prior to COVID-19 so as to focus on the direct effect of the virus on muscle and functional ability, reducing confounding effects.

Conclusion

Pulmonary rehabilitation is possible and effective in patients recovering from COVID-19, including those requiring assisted ventilation or oxygen therapy. Our findings may be useful to guide clinicians taking care of patients surviving COVID-19.

Statement of Ethics

The research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts to declare.

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Author Contributions

The authors gave substantial contributions to the following: Zampogna E.: conception, interpretation, and drafting of the work; Paneroni M.: analysis, interpretation, and drafting of the work. Belli S.: conception and acquisition of the work; Aliani M.: conception and acquisition of the work; Gandolfo A.: conception and acquisition of the work; Visca D.: conception and acquisition of the work; Bellanti MT.: conception and acquisition of the work; Ambrosino N.: conception, interpretation, drafting of the work and revising it critically; Vitacca M: conception, interpretation, and revising it critically.

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