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Original Research

Preexisting cardiorespiratory comorbidity does not preclude the success of multidisciplinary rehabilitation in post-COVID-19 patients

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ABSTRACT

Patients recovering from coronavirus disease 2019 (COVID-19) may not return to a pre-COVID functional status and baseline levels of healthcare needs after discharge from acute care hospitals. Since the long-term outcomes of COVID-19 can be more severe in patients with underlying cardiorespiratory diseases, we aimed at verifying the impact of a preexisting cardiorespiratory comorbidity on multidisciplinary rehabilitation in post-COVID-19 patients. We enrolled 95 consecutive patients referring to the Pulmonary Rehabilitation Unit of Istituti Clinici Scientifici Maugeri Spa SB, IRCCS of Telesse Terme, Benevento, Italy after being discharged from the COVID-19 acute care ward and after recovering from acute COVID-19 pneumonia. Forty-nine of them were not suffering from underlying comorbidities, while 46 had a preexisting cardiorespiratory disease. Rehabilitation induced statistically significant improvements in respiratory function, blood gases and the ability to exercise both in patients without any preexisting comorbidities and in those with an underlying cardiorespiratory disease. Response to the rehabilitation cycle tended to be greater in those without preexisting comorbidities, but DLco %-predicted was the only parameter that showed a significant greater improvement when compared to the response in the group of patients with underlying cardiorespiratory comorbidity. This study suggests that multidisciplinary rehabilitation may be useful in post-COVID-19 patients regardless of the presence of preexisting cardiorespiratory comorbidities.

1. Introduction

An Italian study showed that 87.4% of patients recovering from COVID-19 reported persistence of symptoms, particularly fatigue and dyspnea, even two months after being discharged [1]. Furthermore, many patients after hospitalization, which is usually prolonged, have decreased respiratory movement, pain and weakness in lower limbs, skin lesions, decreased metabolism, joint stiffness, and venous stasis. In keeping with this, some manifestations of systemic dysfunction (e.g. respiratory impairment, muscle weakness, neuropathy, and psychological disorders) may still occur [2]. This delayed recovery of symptoms has been termed 'post-COVID-19 syndrome' or 'long COVID' [3].

An early bedside rehabilitation program is strongly recommended for these patients [4]. Unfortunately, much of the information we have on the effects of respiratory rehabilitation relates to the management of critically ill patients in acute care settings, while the rehabilitation of the

post-acute patient referring to a long-term care facility is very poor [5].

Taking into account these information gaps, the International Multiprofessional Steering Committee of Cochrane Rehabilitation REHCOVER (Rehabilitation for COVID-19: an Evidence-Based Response) action has recently highlighted that data on the efficacy of specific rehabilitation approaches in the acute and also post-acute phase are needed [6].

Since the long-term outcomes of COVID-19 can be more severe in patients with underlying cardiorespiratory diseases [7,8], we aimed at verifying the impact of preexisting cardiorespiratory comorbidities on multidisciplinary rehabilitation program in post-acute COVID-19 patients admitted to a Pulmonary Rehabilitation Unit. To this end, we compared the effects of rehabilitation in two groups of patients, one free of preexisting comorbidities and the other with an underlying cardiorespiratory disease.

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2. Patients and methods

2.1. Patients

In this study, we recruited 95 patients consecutively referring to the Pulmonary Rehabilitation Unit of the Istituti Clinici Scientifici Maugeri Spa SB, IRCCS of Telesse Terme, Benevento, Italy after being discharged from the COVID-19 acute care ward and after recovering from acute COVID-19 pneumonia (Table 1). Forty-nine of them were not suffering from underlying comorbidities, while 46 had a preexisting cardiorespiratory disease. The average age of those without any chronic disease, of which 41 were male and 8 female, was 61.5 (95% CI: 58.4–64.6) years, while that of subjects with an underlying cardiorespiratory disease, of which 39 were male and 7 female, was 65.3 (95% CI: 62.8–67.8) years. According to a recent meta-analysis, male patients with COVID-19 have almost three times the risk of requiring admission at intensive treatment unit (OR: 2.84; 95% CI: 2.06–3.92) as well as a higher risk of death (OR: 1.39; 95% CI: 1.31–1.47) compared to females [9]. This finding accounts for the high prevalence of male patients experiencing a more severe disease, thus requiring post-acute pulmonary rehabilitation. The most common preexisting illnesses were hypertension (27 patients), ischemic heart disease (11 patients) and chronic obstructive pulmonary disease (COPD) (9 patients).

3. Methods

The study was approved by the Institutional Review Board of Istituto Nazionale Tumori, Fondazione Pascale, Naples, Italy with reference number ICS 11/20, and all patients provided written informed consent to use their de-identified data for future research.

Upon entering the ward, pulmonary function test (PFT) and evaluation of carbon monoxide diffusion capacity (DL_{CO}) were performed whenever possible. Furthermore, always when the patient's clinical conditions allowed it, a 6-min walking test (6MWT) was performed.

PFTs were performed using an automated equipment (Vyasis, Milan,

Italy) according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [10]. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and the FEV_1 /FVC ratio were measured. Moreover, measurement of DL_{CO} using the single-breath method was performed according to ATS/ERS guidelines [11].

The 6MWT was also performed in accordance with the ATS/ERS guidelines [12]. The 6-min walking distance (6MWD) was measured in metres and the other outcomes that have been reported, such as symptoms of dyspnoea and fatigue, were measured at the beginning and at the end of the test. Each patient was asked to walk at his/her own pace to cover maximum distance possible in the allotted time.

Immediately afterwards, all patients began a 30-day respiratory rehabilitation program, in addition to the appropriate pharmacological treatment.

At the end of the rehabilitation program, patients underwent again PFT, DL_{CO} measurement and 6MWT.

In all patients, arterial blood gas levels were measured while breathing room air before and at the end of the rehabilitation cycle.

3.1. Pulmonary rehabilitation

All included patients underwent a 5-week pulmonary rehabilitation program with daily sessions (6 sessions/week). The program consisted of 30 sessions following the official ATS/ERS statement on pulmonary rehabilitation [13], including physical exercise training, dietary counselling, and psychosocial counselling. Physical exercise training was the cornerstone of the program, consisting of exercises to strengthen groups of muscles in the upper and lower extremities, treadmill walking and stationary cycling. All exercises were performed at moderate to high intensity to obtain an overload stimulus, and the training intensity was increased during the rehabilitation period, based on dyspnea and fatigue symptom scores. All patients underwent flexibility exercises, general physical exercise for lower and upper extremities, and daily supervised 30-min outdoor walks.

3.2. Statistical analysis

Statistical analysis was performed using Prism 8 software package (GraphPad Software Inc, USA). Data were expressed as mean and 95% confidence interval (CI) (standard errors have been reported in figures). Analysis of spirometric, 6MWT and blood gases changes collected before and after rehabilitation was performed using the Student's *t*-test for paired variables. Comparison between subjects with no previous pathology and those with preexisting cardiopulmonary comorbidity was made with unpaired *t*-test and Welch's correction. All results were expressed as 2-tailed values, *P* values < 0.05 being statistically significant.

4. Results

At the end of the rehabilitation program, during which no adverse events occurred, in the group of patients without underlying cardiorespiratory comorbidities and in which spirometry could also be performed at admission, there was a significant improvement in pulmonary function measurements, with FEV_1 increasing by 267.1 mL (95% CI: 161.3–372.9; *P* < 0.0001) and a mean increase in FVC of 415.0 mL (95% CI: 278.1–551.9; *P* < 0.0001) (Fig. 1). DL_{CO} %-predicted improved by 9.7% (95% CI: 6.0–13.5%; *P* = 0.016) (Fig. 1). The PFT data refer to 38 patients because the other 11 were unable to perform the PFT when they were admitted to our ward. Before starting rehabilitation, among the patients with no previous pathology, 30 had a DL_{CO} < 80% indicating the presence of a diffusion deficit [14], in 13 it was not possible to perform the test and only 6 had a value \geq 80%.

As a result of the rehabilitation program, the 6MWD increased by 149.2 m (95% CI: 128.3–170.2; *P* < 0.0001) (Fig. 2). In the 6MWT performed before starting rehabilitation, the dyspnea score was 1.8

Table 1
Patients' clinical characteristics.

	Patients without comorbidities (n = 49)	Patients with comorbidities (n = 46)
Age (years)	61.5 ± 1.6	65.3 ± 1.2
Sex		
Man	41	39
Woman	8	7
Smokers	3	7
Ex-smokers	20	21
FVC % predicted	76.7 ± 3.2†	72.6 ± 2.9 §
FEV_1 % predicted	79.9 ± 3.1†	73.2 ± 3.3 §
6MWT (meters)	242.5 ± 14.6	200.5 ± 16.6
Comorbidities		
hypertension		27
valvular heart disease		7
cardiac arrhythmia		9
heart failure		2
ischemic heart disease		11
hypertrophic cardiomyopathy		8
COPD		9
Asthma		3
Pulmonary fibrosis		2
Number of comorbidities		
one		11
two		28
three		5
four		2

† spirometry was not available in 11 patients; § spirometry was not available in 21 patients.

Values are expressed as mean ± ES.

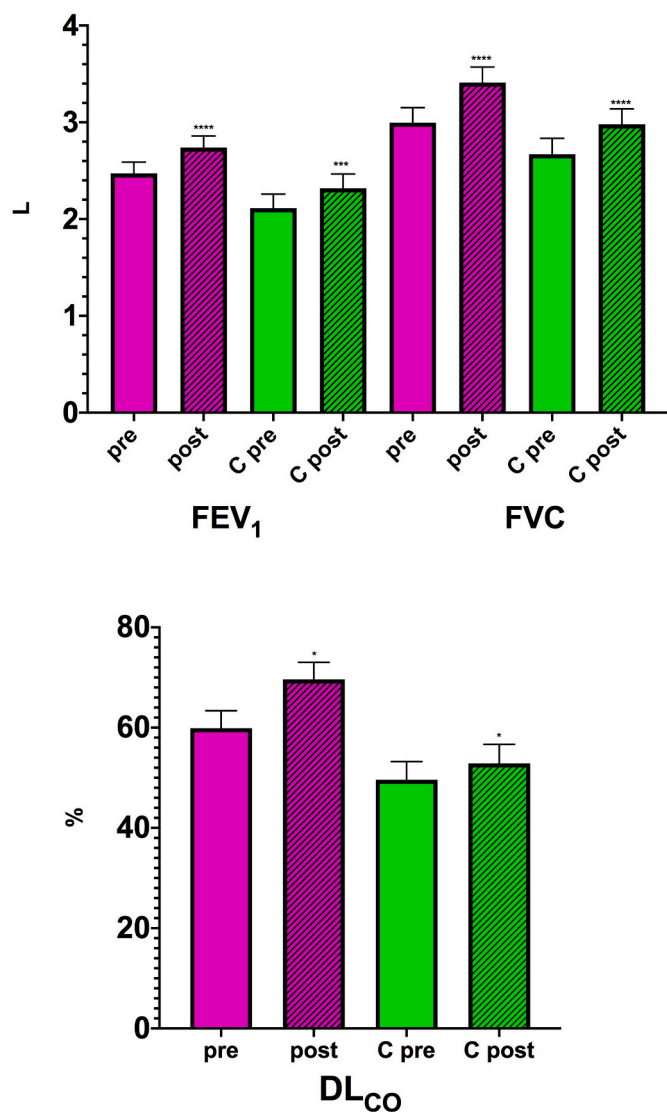


Fig. 1. – FEV₁, FVC and DL_{CO} %-predicted before (pre) and at the end of the rehabilitation program (post) in patients with no previous pathology (magenta) and those with preexisting cardiopulmonary comorbidity (C green). *P < 0.05, ***P < 0.001, ****P < 0.0001 post-rehabilitation vs pre-rehabilitation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(95% CI: 1.2–2.3) at resting (time 0) and 6.9 (95% CI: 5.9–7.8) the end of the test. Rehabilitation induced a significant reduction in this score. In fact, in the test performed at the end of the rehabilitation cycle the dyspnea score was reduced to 0.4 (95% CI: 0.03–0.8; P = 0.0003 vs pre-rehabilitation) at resting and to 1.6 (95% CI: 1.1–2.1; P < 0.0001 vs pre-rehabilitation) at the end of the test (Fig. 2). Muscle fatigue scores also dropped significantly thanks to rehabilitation, going from 2.2 (95% CI: 1.5–2.8) to 6.0 (95% CI: 4.7–7.3) on the test performed on admission and from 0.6 (95% CI: 0.1–1.1; P = 0.0004 vs pre-rehabilitation) to 1.4 (95% CI: 0.8–2.0; P < 0.0001 vs pre-rehabilitation) on the test performed before discharge (Fig. 2). The 6MWT was performed before and after rehabilitation in 34 patients. It was, however, possible to perform a 6MWT at the end of the rehabilitation program in 14 of the other 15 patients.

The mean changes in PaO₂ and PaCO₂ measured on ambient air are shown in Fig. 3.

In the group of patients with underlying cardiorespiratory diseases, FEV₁, FVC and DL_{CO} %-predicted (Fig. 1) improved by 205.5 mL (95%

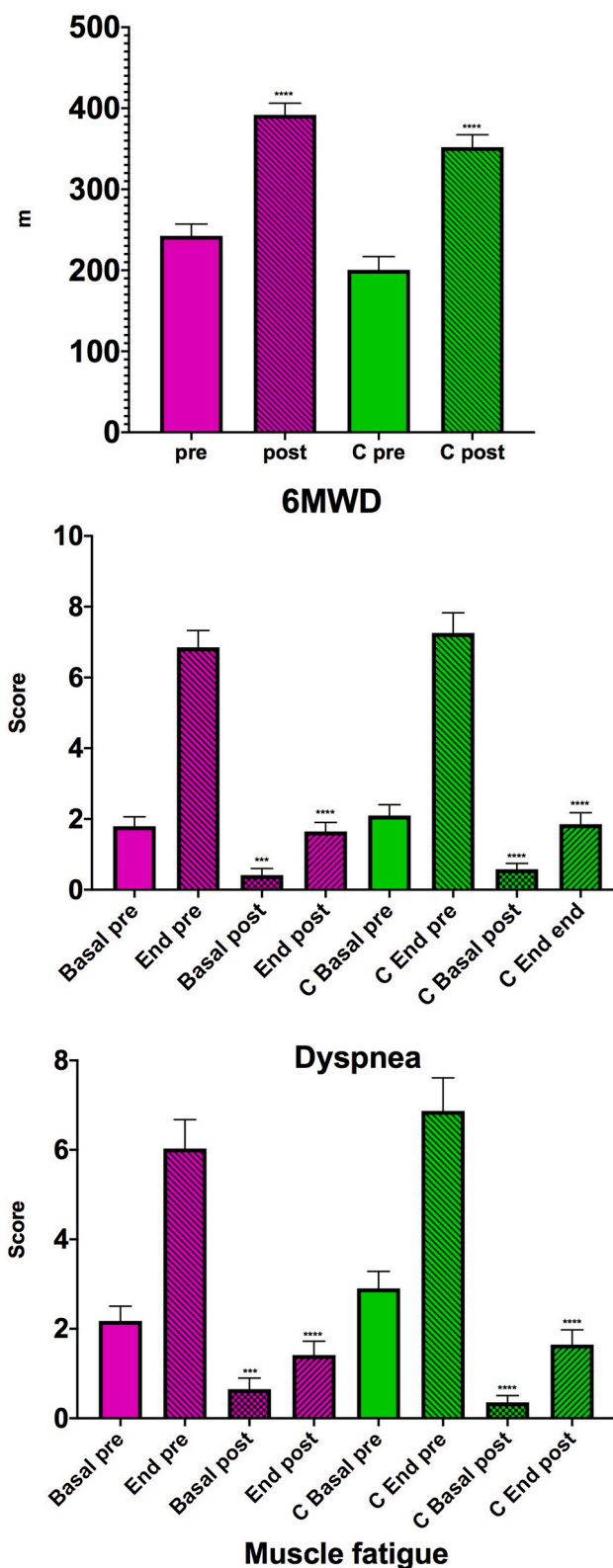


Fig. 2. – 6MWD, dyspnea and muscle fatigue scores before (pre) and at the end of the rehabilitation program (post) in patients with no previous pathology (magenta) and those with preexisting cardiopulmonary comorbidity (C green). ***P < 0.001, ****P < 0.0001 post-rehabilitation vs pre-rehabilitation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

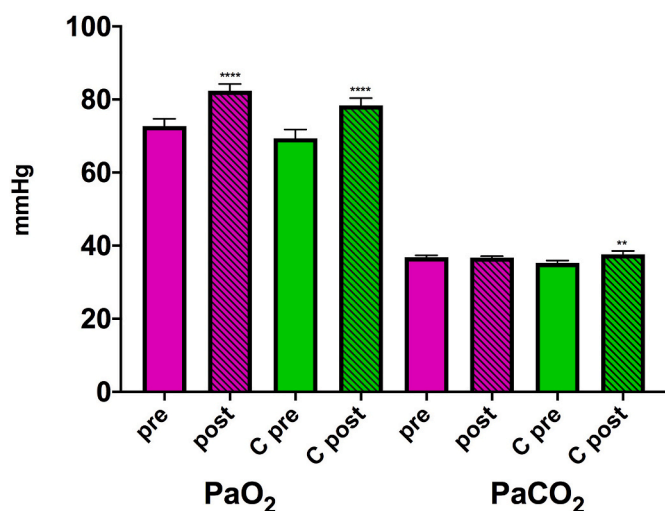


Fig. 3. – PaO₂ and PaCO₂ before (pre) and at the end of the rehabilitation program (post) in patients with no previous pathology (magenta) and those with preexisting cardiopulmonary comorbidity (C green). ****P < 0.0001 post-rehabilitation vs pre-rehabilitation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

CI: 106.3–304.9; P = 0.0003), 310.4 mL (95% CI: 176.0–444.8; P < 0.0001) and 3.3% (95% CI: 0.7–5.9; P = 0.016), respectively. In this group, the PFT data refer to 25 patients because the other 21 were unable to perform the PFT upon entering the ward, while only 2 had a DL_{CO} ≥ 80% and in other 19 patients clinical conditions did not allow performing this test.

The rehabilitation program significantly (P < 0.0001) increased the walking distance as assessed by the 6MWT (151.5 m, 95% CI: 121.9–181.1) (Fig. 2). The dyspnea score in the 6MWT performed at entry went from 2.1 (95% CI: 1.5–2.7) at time 0 to 7.3 (95% CI: 6.1–8.4) at the end of the test, while that of muscle fatigue went from 2.9 (95% CI: 2.1–3.7) to 6.9 (95% CI: 5.4–8.4) (Fig. 2). The dyspnea scores measured before (0.6, 95% CI: 0.2–0.9) and after (1.9, 95% CI: 1.2–2.5) the 6MWT at the end of the rehabilitation program were significantly lower (both P < 0.0001) than those measured before and after the test performed on admission to the ward. Muscle fatigue scores showed trends similar to those of dyspnea being 0.3 (95% CI: 0.04–0.7) before and 1.6 (95% CI: 1.0–2.3) after the 6MWT performed at the end of the rehabilitation program (Fig. 2). The scores measured before and after the test carried out at the end of the rehabilitation program were significantly lower (both P < 0.0001) than those measured before rehabilitation. The 6MWT was performed before and after rehabilitation in 31 patients, while in 11 other subjects it was possible to perform the 6MWT at the end of the planned hospitalization. Three patients were unable to perform any 6MWT, and 1 patient who had performed the test at admission was unable to perform it at the end of rehabilitation due to a worsening of his clinical status.

It should be noted that patients without a previous comorbidity started the rehabilitation program with better functional parameters (Table 2). The mean difference in FEV₁ between those without a previous pathology and those suffering from an underlying cardiopulmonary pathology was 359.4 mL (95% CI: -15.2–734.1; P = 0.06), whereas that in FVC was 326.3 mL (95% CI: -130.6–783.3; P = 0.158) and difference in DL_{CO}%-predicted was 10.3% (95% CI: 1.4–20.4; P = 0.037). Furthermore, they also suffered from less dyspnea (1.8, 95% CI: 1.2–2.3 vs. 2.1, 95% CI: 1.5–2.7), although the difference between the two groups was not statistically significant (P = 0.463). Also the 6MWD was greater in those without a previous pathology with a difference of 42.0 m (95% CI: -1.9–85.8), although even in this case the difference between the two groups was not statistically significant (P = 0.061), nor was the

Table 2

Differences in changes of examined parameters between patients with no underlying disease and those with preexisting cardiopulmonary comorbidity before and after rehabilitation.

	Pre-rehabilitation	P value	Post-rehabilitation	P value
FEV ₁	359.4 mL (95% CI: -15.2–734.1)	0.06	420.9 mL (95% CI: 36.7–805.2)	0.0324
FVC	326.3 mL (95% CI: -130.6–783.3)	0.158	430.9 mL (95% CI: -20.6–882.5)	0.06
DL _{CO}	10.3% (95% CI: 1.4–20.4)	0.037	16.7% (95% CI: 6.5–27.0)	0.0019
6MWD	42.0 m (95% CI: -1.9–85.8)	0.06	39.7 m (95% CI: -2.5–81)	0.06
PaO ₂	3.3 mmHg (95% CI: -2.8–9.5)	0.284	4.0 mmHg (95% CI: -1.4–9.4)	0.145
PaCO ₂	1.5 mmHg (95% CI: -0.1–3.2)	0.07	-0.9 mmHg (95% CI: -2.9–1.2)	0.400

DL_{CO} carbon monoxide diffusion capacity %-predicted; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; partial pressure of carbon dioxide (PaCO₂); partial pressure of oxygen (PaO₂); 6MWD, 6-min walking distance.

difference in 6MWT-induced dyspnea significant (0.4, 95% CI: -1.1–1.9; P = 0.587).

At the end of the rehabilitation program, the mean difference in FEV₁ between the two groups became 420.9 mL (95% CI: 36.7–805.2; P = 0.032), while that in FVC was 430.9 mL (95% CI: -20.6–882.5; P = 0.06), and DL_{CO}%-predicted differed between those without a preexisting pathology and those suffering from an underlying cardiopulmonary comorbidity by 16.7% (95% CI: 6.5–27.0; P = 0.0019). The difference in the distance walked in the 6 min was not significant between the groups (39.7 m, 95% CI: -2.5–81; P = 0.06) and very similar to that recorded before rehabilitation. Pre-test dyspnea was mildly (-0.2, 95% CI: -0.7–0.3) but not significantly (P = 0.505) less in the group without prior disease, difference that was substantially unchanged at the end of the test (-0.2, 95% CI: -1.0–0.6; P = 0.616).

The differences between the two groups in the changes in muscle fatigue scores were also modest and not statistically significant both before starting rehabilitation and at its end.

5. Discussion

Our study shows that a multidisciplinary rehabilitation program is extremely useful in post-COVID-19 patients, regardless of the presence of an underlying cardiorespiratory comorbidity. In particular, the significant increase in 6MWD values regardless of the health status before the onset of COVID-19 deserves a specific mention because it was indicative of a noteworthy improvement in physical function. Rehabilitation greatly reduced dyspnea and muscle fatigue in both groups. This leads us to believe that there are no substantial differences in the response to physical effort between those with preexisting cardiorespiratory comorbidities and those initially healthy, even if the latter, as expected, tended to have a better performance in terms of walking distance.

It could be argued that in order to understand whether the results of this study are specific to COVID-19 and really due to the rehabilitation program, it would have been necessary to also consider specific groups of patients without COVID-19 and post-COVID-19 patients who were not been undergoing rehabilitation. Our study focused solely on post-COVID patients because currently it is preferred not to admit patients who have not contracted SARS-CoV-2 infection to reduce risk of contracting COVID-19 and spreading the virus. In any case, our centre, as well as most of the rehabilitation centres around the world, as correctly highlighted by the Assembly on pulmonary rehabilitation of the American Thoracic Society [15], has temporarily suspended its centre-based, face-to-face programs for COVID free subjects due to concerns of infection and the need for physical distancing.

On the other hand, even following outpatient patients who do not need rehabilitation is currently extremely difficult. As also stated by the 2020 GOLD Science Committee Report on COVID-19 and COPD [16], during periods of high prevalence of COVID-19 in the community, spirometry (and we also add the other exams of our study) should be restricted to patients requiring urgent or essential tests for the diagnosis of COPD and/or to assess lung function status for interventional procedures or surgery. Adding a control group in a COVID era by entering data from groups treated in the past should be an alternative, but in our opinion it would be wrong because the protocol would be completely different.

Great importance should be given to the improvements in 6MWD, which provides an assessment of exercise capacity and can better reflect daily activity than laboratory tests [17]. The 54 m threshold for 6MWD is considered representative of a clinically significant change [18]. The majority of our patients largely exceeded this value at the end of the rehabilitation program, although it has been highlighted that a statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient [19]. The fact that a large number of patients who were unable to walk upon arrival in our facility and, consequently did not perform the 6MWT before rehabilitation, were able to do it at the end of the multidisciplinary rehabilitation program even in the presence of a cardiorespiratory comorbidity reinforces our view that all patients hospitalized for COVID-19 should undergo a multidisciplinary rehabilitation cycle.

We are fully aware that using a more demanding exercise capacity test, such as a cardiopulmonary exercise test, would have been more helpful in documenting that the rehabilitation cycle did not really impact differently in the two patient groups we examined, but the initial conditions of the patients discouraged the execution of this test.

Although the 6MWT can better reflect daily activity than laboratory tests, these also provide important information. As expected, the improvements in FEV₁, FVC and DL_{CO}% observed in those who were healthy prior to COVID-19 tended to be greater, but a statistically significant difference between the two groups was observed only in the FEV₁ and DL_{CO}%-predicted changes.

While the more substantial improvement in FEV₁ is not surprising because this parameter is substantially reduced in subjects with cardiorespiratory pathologies [20–23], particular attention should be paid to the differences in the DL_{CO} values. DL_{CO}%-predicted is the strongest independent factor associated with previous severe/critical COVID-19 [24].

More than 90% of our patients had a known or presumed diffusion deficit, although the deficit tended to be greater in those with history of cardiorespiratory comorbidities potentially affecting lung diffusing capacity. Alterations of gas transport occurs in more than half of the COVID-19 patients [25] and may be present even in subjects who had mild COVID-19 pneumonia and no or minimal persisting computed tomography (CT) abnormalities [26]. Although a reduced DL_{CO} may reflect parenchymal lung disease, it has been suggested that a low DL_{CO} is mainly determined by a reduced alveolar volume and not by the residual interstitial lung abnormalities or pulmonary vascular abnormalities [27]. However, COVID-19 specifically impacts the pulmonary circulation [28]. To determine whether the reduction in DL_{CO} in patients who have recovered from COVID-19 is caused by interstitial or pulmonary vascular abnormalities, it would be desirable to use more specific measures of the alveolar-capillary membrane, such as combined DL_{CO} and diffusion capacity of the lung for nitric oxide (DL_{NO}) measurements or advanced imaging techniques [29]. It has been suggested that an impairment of DL_{NO} exceeding standard DL_{CO} may be present during the recovery from COVID-19, possibly due to loss of alveolar units with alveolar membrane damage, but relatively preserved capillary volume [26].

Having not performed this type of test, we are not able to tell if the low DL_{CO} values we recorded were dependent on a parenchymal damage

rather than a vascular involvement. However, we have noticed a remarkable improvement of this parameter that has even normalized in 7 subjects without preexisting comorbidity.

While it is relatively simple to explain the improvements in PTF and 6MWT parameters induced by rehabilitation with the positive effects elicited by the respiratory muscle training [26], it is difficult to give explanation on its effect on the diffusion deficit. It has been suggested that the severity of pulmonary inflammation may be the reason for impaired DL_{CO} in COVID-19 patients [30]. Since there is evidence that exercise training represents a strategy to elicit an anti-inflammation effect, which may help to decrease the risk or progression of several disorders of an inflammatory nature [31], as are the parenchymal and vascular sequelae of COVID-19, we wonder if the improvement observed is linked to an anti-inflammatory effect induced by the rehabilitation cycle, an effect that in our patients was more evident in the absence of a previous cardiorespiratory damage. One could speculate that the effect should be different because of the systemic inflammation that characterises the cardiorespiratory diseases [32]. However, the impossibility of including in this study groups of patients without preexisting comorbidities or suffering from cardiorespiratory comorbidities but not been affected by COVID do not allow us to formulate solid conclusion.

Obviously, this is a hypothesis to be verified when it will be possible to compare groups with different characteristics. The study will have to use more sophisticated diagnostic tests and also consider the biomarkers of inflammation. In the meantime, as already pointed out, we strongly believe that multidisciplinary rehabilitation cycles must always be prescribed in patients who have a slow recovery from COVID-19 and this regardless if they are suffering from cardiorespiratory comorbidities.

Author contribution

M. Maniscalco: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing - review and editing. **S. Fuschillo:** Investigation. **P. Ambrosino:** Data curation, Investigation, Methodology, Writing - review and editing. **M. Martucci:** Investigation. **A. Papa:** Investigation. **M.G. Matera:** Formal analysis, Validation, Writing - review and editing. **M. Cazzola:** Conceptualization, Formal analysis, Validation, Writing - original draft, Writing - review and editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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