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Early View

Original article

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Figure

Benefits of pulmonary rehabilitation in COVID-19 – a prospective observational cohort study

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Take home message: „Pulmonary rehabilitation is effective, feasible, and safe to improve exercise performance, lung function, and quality of life in patients with persistent impairments due to a mild to critical course of COVID-19."

Keywords: COVID-19, SARS-CoV-2, long COVID, post-COVID-19 syndrome, pulmonary rehabilitation, sequelae, quality of life, exercise

Abstract

Background: The new Corona-Virus disease (COVID-19) can result in a large variety of chronic health issues like impaired lung function, reduced exercise performance, and diminished quality of life. Our study aimed to investigate the efficacy, feasibility, and safety of pulmonary rehabilitation (PR) in COVID-19 patients and to compare outcomes between patients with a mild/moderate and a severe/critical course of the disease.

Methods: Patients in the post-acute phase of a mild to critical course of COVID-19 admitted to a comprehensive three-week inpatient PR were included in this prospective, observational cohort study. Several measures of exercise performance (6-minute walk distance, 6MWD), lung function (forced vital capacity, FVC), and quality of life (36 question short-form health survey, SF-36) were assessed before and after PR.

Results: Fifty patients were included in the study (24 with mild/moderate and 26 with severe/critical COVID-19). On admission, patients had a reduced 6MWD (mild: 509m [426-539]; severe: 344m [244-392]), an impaired FVC (mild: 80% [59-91]; severe: 75% [60-91]) and a low SF-36 mental health score (mild: 49pts [37-54]; severe: 39pts [30-53]). Patients attended a median of 100% [94-100] of all provided PR sessions. At discharge, patients in both subgroups improved in 6MWD (mild/moderate: +48m [35-113m]; severe/critical: +124m [75-145m], both $p<0.001$), FVC (mild/moderate: +7.7% [1.0-17.8], $p=0.002$; severe/critical: +11.3% [1.0-16.9], $p<0.001$) and SF-36 mental component (mild/moderate +5.6pts [1.4-9.2], $p=0.071$; severe/critical: +14.4pts [-0.6-24.5], $p<0.001$). No adverse event was observed.

Conclusion: Our study shows that PR is a feasible, safe, and effective therapeutic option in COVID-19 patients independent of disease severity.

Background

Disease severity in coronavirus disease 2019 (COVID-19) can be very heterogeneous. Forty percent of COVID-19 subjects develop mild disease (defined as symptomatic patients without evidence of viral pneumonia or hypoxia), another 40% have a moderate disease (with clinical signs of pneumonia). Approximately 15% suffer from a severe disease (with severe pneumonia) that requires oxygen therapy and 5% develop a critical disease with complications such as respiratory failure, acute respiratory distress syndrome, thromboembolism, sepsis, and/or multiorgan failure [1, 2]. Older age, smoking, and pre-existing comorbidities have been reported to be risk factors for a more severe course of COVID-19 and an increased mortality [3, 4].

Even two to three months after being “cured” from the severe acute respiratory syndrome corona virus type 2 (SARS-CoV-2) infection many patients are still affected with chronic, clinically relevant sequelae. Frequently reported health issues are a new illness-related fatigue (53 to 87%), breathlessness (43 to 71%), or neuropsychological impairments (47%) with a high prevalence of psychological disorders like increased levels of stress, anxiety, and depression [5-8]. According to recent NICE guidelines, signs and symptoms of COVID-19 from 4 to 12 weeks after the onset of first symptoms are defined as “ongoing symptomatic COVID-19” [9] whereas COVID-19 sequelae that last longer than 12 weeks are summarized in terms like “long-COVID” or “post-COVID-19 syndrome” [9, 10]. The latter are typically more pronounced in patients that needed treatment on an intensive care unit (ICU) compared to ward patients [5].

Based on the individual deficits in COVID-19 patients, comprehensive and multidisciplinary rehabilitation like pulmonary rehabilitation (PR) should be offered with attention for improving respiratory, physical, and psychological impairments, as suggested by various international expert groups [11-13]. Carda et al. suggested to provide PR treatment based on the content that is usually recommended in lung fibrosis since COVID-19 can also induce a restrictive lung disease [14].
So far, only few retrospective data and case series on PR in COVID-19 have been published. Therefore, the aim of our study was to prospectively investigate the efficacy, feasibility, and safety of PR in COVID-19 patients and to compare differences in PR outcomes between patients with a mild/moderate and a severe/critical course of the disease.

Methods

Study design

COVID-19 patients with persistent impairments following their SARS-CoV-2 infection were referred to PR from the hospital (severe/critical COVID-19) or by their general practitioner (mild/moderate COVID-19). Patients admitted to a comprehensive, inpatient PR program at the Schoen Klinik Berchtesgadener Land (Schoenau am Koenigssee, Germany) were screened for eligibility to participate in this prospective, observational cohort study. Patients were recruited between November 2020 and January 2021. This study was submitted to the Clinical Trials Registry (www.clinicaltrials.gov, NCT04649918) and approved by the Ethics Committee of the Philipps-University of Marburg (approval number: 85/20). This manuscript was written according to the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guideline.

Study population

Inclusion criteria were as follows: (a) patients in the post-acute phase of mild, moderate, severe or critical COVID-19 as defined by the world health organization [2] and (b) an obtained written informed consent. Patients unable to walk were excluded from the study.

Intervention

Patients participated in a three-week comprehensive multimodal and multidisciplinary inpatient PR. The PR program for COVID-19 patients was based on the PR content for patients with lung fibrosis (as suggested by Carda et al. [14]) and is described in detail in panel 1.

Panel 1: Description of the standardized pulmonary rehabilitation program in COVID-19

Pulmonary rehabilitation content	description
Diagnostics and medical treatment	- Initial physical check-up including bodyplethysmography, echocardiography, cardiac ultrasound,blood sampling - Continuous adaptation of drug treatment - initiation and adjusting of long-term oxygen therapy, if necessary - if necessary, patients received a high-resolution chest computed tomography, sleep lab diagnostics or an online consultation with a neurologist
Endurance training	Cycle endurance training was performed for 10 to 20 minutes per session at 60% to 70% of peak work rate on five days per week.
Strength training	Strength training was performed using resistance training machines. Following exercises were performed: leg press, knee extension, pull-down, and push-down. If possible, the following additional exercises were applied: butterfly forward/backward, rowing, back extension, and abdominal trainer. Patients performed three sets per exercise at an individual intensity to reach momentary muscular failure after 15 to 20 repetitions. Resistance training usually took about 30 minutes per session and was applied on five days per week.
Patient education	Patients visited two educational sessions per week about COVID-19 as well as on general topics like physical activity, oxygen therapy, smoking cessation etc.
Respiratory physiotherapy	Individually tailored chest physiotherapy using various techniques like breathing retraining, cough techniques, mucus clearance, connective tissue massage, energy conservation techniques, and others was applied two to four times per week for 30 minutes each.
Activities of daily living training	Activities of daily living training (calisthenics) was applied four to five times per week for 30 minutes. In Addition, Nordic walking or aqua fitness were applied two times per week for 30 minutes
Relaxation techniques	QiGong or progressive muscle relaxation according to Jacobsen were applied two times per week for 30 minutes
Occupational therapy	- Occupational therapy was treating individual neurological issues like i.e. limited motor ability in the hands or insecure gait (if needed). - Brain-performance training was performed to improve memory and concentration abilities
Psychological support	A psychologist supported COVID-19 patients individually as well as during a group therapy on aspects of disease management and coping with COVID-19 and its sequelae.

Nutritional counselling	If necessary, nutritional counselling or nutritional supplements were provided to recover body composition (after body weight loss during hospital stay)

Outcomes and measures

Exercise performance

The 6-minute walk test (6-MWT) was the primary outcome of this study. One 6MWT was performed on admission and one at discharge of PR, respectively [15].Thirty meters is regarded as the threshold of the minimal important difference (MID) [15].

Additionally, the following comprehensive exercise testing was performed only in the subgroup of patients with severe/critical COVID-19 to assess the complexity of severe/critical COVID-19 in more detail.

An endurance shuttle walk test (ESWT) was performed at 85% of the maximum walking speed derived from an incremental shuttle walk test [15]. Both tests were performed on a consecutive day following the 6MWT. Physiological parameters like oxygen saturation (SpO_2) and heart rate were measured continuously by Sentec Digital Monitor (SenTec AG, Therwil, Switzerland). Breathing frequency was assessed by Apnea Link (ResMed, Martinsried, Germany). To compare physiological changes after PR at an equal level of exercise performance, these outcomes were analysed at baseline and ESWT isotime (= end of the shortest ESWT).

Maximum isometric knee extension force at 90° knee angle (MicroFET 2 dynamometer) and handgrip force (JAMAR hand dynamometer) were assessed by dynamometry using the best out of three tests [16]. A five-repetition sit-to-stand test was performed from a 46 cm height chair with arms crossed in front of the chest [17] and the frailty phenotype was assessed by the Fried Frailty Index [18].

Respiratory parameters

Bodyplethysmography was performed in all patients to measure forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), total lung capacity (TLC), and diffusion lung capacity for carbon monoxide (DLCO). Capillary blood gas samples to assess the partial oxygen pressure (PaO_2) and partial carbon dioxide pressure ($PaCO_2$) were taken at rest, breathing ambient air.

The subjective effect of breathlessness on daily activities was assessed with the modified Medical Research Council (mMRC) [19].

Quality of life, psychological distress and (cognitive) impairment

- Generic quality of life was assessed by the physical and the mental component sum score of the short-form 36 question health survey (SF-36). The score ranges from 0 to 100 with higher scores indicating better quality of life.
- Anxiety symptoms were assessed by the generalized anxiety disorder-7 questionnaire (GAD-7). GAD-7 scores are interpreted as follows: no anxiety symptoms (0–4 points), mild symptoms (5–9 points), moderate (10–14 points), and severe symptoms (15–21 points) [20].

- Depressive symptomatology was assessed using the depression scale of the patient health questionnaire (PHQ-D). PHQ-9 scores are interpreted as follows: no depressive symptomatology (0 points), minimal symptoms of depression (1-4 points), mild symptoms (5-9 points), moderate symptoms (10-14 points), severe symptoms of depression (15-27 points) [21].
- The Montreal Cognitive Assessment (MoCA) is a widely used screening assessment for detecting cognitive impairment (score of <26 out of a maximum of 30 points) [22].

Sample size

Due to a lack of data we did not perform an a priori sample size calculation. However, a post-hoc power calculation based on the mean and standard deviation of the improvements in the primary outcome (6MWD) showed an effect size of 1.21 for the group of 24 mild/moderate COVID-19 patients and an effect size of 1.75 for the severe/critical COVID-19 group to analyze the changes in exercise performance.

Statistical methods

Results are presented as median and interquartile range. Non-parametric tests have been used for statistical analyses due to the small sample size. For comparing pre to post PR effects within the two groups, a two-tailed Wilcoxon rank-sum test or Chi^2-test was applied, as appropriate. The Mann-Whitney U-test was used to compare between-group differences and the Kruskal-Wallis test including a post-hoc U-test with Bonferroni correction was applied to compare results between three groups (data shown in the online supplementary material). The McNemar test was used to analyze categorial data. The significance level was set at $p<0.05$. Statistical analyses were performed using SPSS 26 (IBM, USA).

Results

Fifty out of 58 eligible patients were included in the study. Eight patients were excluded due to the following reasons: three were too weak to perform a walk test, one refused to participate, one had language difficulties, one was isolated due to a multi-resistant infection and two had other reasons.

Baseline characteristics

Twenty-four patients had a mild/moderate course of COVID-19 which was treated in an outpatient setting and 26 had severe/critical COVID-19 and were hospitalized for a median of 37 [IQR: 18-60] days (table 1). 85% of these severe/critical COVID-19 patients were treated on an intensive care unit for 28 [IQR:15-40] days and 58% needed mechanical ventilation for 18 [11-43] days.

On PR admission, patients with severe/critical COVID-19 had significantly lower exercise performance (6MWD: 344m versus 509m; p<0.001) and worse lung function (FVC: 75.1% versus 80.0%; p<0.004) compared to patients with mild/moderate COVID-19. Quality of life as assessed by SF-36 was reduced to a similar level in all outcomes in both subgroups (table 2).

Table 1. Baseline characteristics

	Mild/moderate COVID-19	Severe/critical COVID-19
n	24	26
Age, ys	52 [47 - 56]	66 [60 - 71]
Sex, female (%)	20 (83%)	8 (31%)
BMI, kg/m²	24.7 [22.0 – 29.8]	26.9 [24.2 – 29.2]
Smoking status, current/former/never/unknown	2 / 5 / 10 / 7	1 / 19 / 6 / 0
Hospitalization, n (%)	0 (0%)	26 (100%)
Duration of hospitalization, d	NA	37 [18 - 60]
ICU stay, n (%)	0 (0%)	22 (85%)
Duration of ICU stay, d	NA	28 [15 - 40]
O_2-therapy during hospitalization, n (%)	0 (0%)	24 (92%)
Mechanical ventilation during ICU, n (%)	0 (0%)	15 (58%)
Duration of mechanical ventilation, d	NA	18 [11 - 43]
Duration between first positive PCR-test and PR admission, d	178 [127 - 217]	61 [40 - 108]
Duration between hospital discharge and PR admission, d	NA	18 [5 - 40]
Comorbidities prior to COVID-19, n	2 [2 - 4]	3 [3 – 5]
Arterial hypertension, n (%)	5 (21%)	16 (62%)
Dyslipidemia, n (%)	3 (13%)	10 (38%)
Coronary heart disease, n (%)	1 (5%)	7 (27%)
Diabetes mellitus, n (%)	1 (5%)	6 (23%)
Chronic lung disease, n (%)	7 (30%)	5 (19%)
Obstructive sleep apnea, n (%)	9 (38%)	9 (35%)
Chronic kidney disease, n (%)	0 (0%)	6 (23%)
Obesity, n (%)	5 (21%)	5 (19%)
Stroke, n (%)	0 (0%)	1 (4%)

Data are presented as median and percentage or median and interquartile range
Abbreviations: BMI: Body Mass Index, O_2: oxygen, ICU: intensive care unit, COVID-19: corona virus disease 2019, NA – not applicable

PR outcomes

Post-COVID-19 patients attended a median of 100% [IQR 94% - 100%] of all provided PR sessions. At PR discharge, patients in both subgroups were able to improve exercise performance significantly by 48m (mild/moderate COVID-19 with 88% of patients exceeding the MID, p=0.001) and 124m (severe/critical COVID-19 with 92% of patients exceeding the MID, p<0.001), respectively (Figure 1). Also, measures of lung function like FVC or FEV_1 improved significantly in a range of 7.7% to 15.7% within both groups (see details in table 2). Quality of life improved significantly only in patients with severe/critical COVID-19 in the mental component sum score of the SF-36 (from 38.5 to 52.9 points; p<0.001).

Table 2. Outcomes of a comprehensive inpatient pulmonary rehabilitation in 50 post-acute COVID-19 patients

	mild/moderate COVID-19 (n=24)			severe/critical COVID-19 (n=26)			Between-group difference
	Pre PR	**Post PR**	**Δ**	**Pre PR**	**Post PR**	**Δ**	**p-value**
Exercise performance							
6MWD, m	509 [426-539]	557 [463-633]	48§ [35-113]	344 [244-392]	468 [374-518]	124§ [75-145]	**0.009**
6MWD, %predicted	70.1 [57.8-80.2]	81.0 [67.9-90.7]	10.9§ [4.7-14.6]	52.5 [42.4-58.3]	70.5 [59.5-82.6]	18.0§ [11.2-23.1]	**0.002**
6MWT SpO_2 nadir, %	95.5 [94.0-97.0]	95.5 [93.0-97.0]	0.0 [-2.0-1.0]	92.0 [87.8-94.2]	93.0 [85.5-94.5]	1.0 [-1.0-2.5]	0.19
End-6MWT dyspnea, Borg scale	4 [3-5]	4 [2-6]	0 [-1-1]	5 [4-6]	5 [3-6]	0 [-2-1]	0.83
General							
O_2-therapy at rest, n (%)	0 (0%)	0 (0%)	0	5 (19%)	3 (11%)	-2§ (-7%)	0.16
O_2-therapy during exertion, n (%)	0 (0%)	0 (0%)	0	8 (31%)	7 (27%)	-1§ (-4%)	0.33
Respiratory parameters							
PaO_2, mmHg (at rest and ambient air)	73.1 [63.6-77.4]	75.8 [71.0-80.2]	2.7* [-0.9-10.8]	73.2 [62.7-77.6]	75.7 [71.0-80.2]	2.5* [-1.2-10.5]	0.95
$PaCO_2$, mmHg (at rest and ambient air)	35.0 [32.6-38.5]	34.8 [31.1-36.5]	-1.2 [-2.7-2.5]	35.5 [31.8-36.9]	35.3 [31.8-36.9]	-0.2 [-2.9-2.7]	1.00
DLCO, %predicted	57.0 [50.0-65.5]	61.5 [50.0-76.3]	4.5 [-1.8-16.5]	55.8 [37.2-63.0]	59.5 [37.8-70.9]	3.7§ [-0.5-12.7]	0.92
KCO, %predicted	67.6 [41.5-91.1]	77.9 [55.6-95.1]	10.3 [-3.0-11.8]	85.0 [81.5-99.5]	89.0 [80.0-102.5]	4.0 [-4.5-9.5]	0.38
TLC, %predicted	82.2 [65.3-88.9]	81.1 [69.3-95.1]	-1.1 [-4.7-10.7]	80.9 [64.4-88.6]	81.0 [68.8-93.3]	0.1 [-4.3-10.5]	0.91
FVC, %predicted	80.0 [59.2-90.9]	87.7 [67.0-98.9]	7.7# [1.0-17.8]	75.1 [59.8-90.6]	86.4 [67.6-96.3]	11.3§ [1.0-16.9]	0.97
FEV_1, %predicted	83.3 [65.5-101.1]	95.1 [84.0-106.8]	11.8§ [3.3-18.1]	79.1 [65.8-99.7]	94.8 [80.9-106.2]	15.7§ [3.7-17.5]	0.95
Quality of life							
SF-36 physical component sum score, points	31.8 [26.2-35.7]	31.7 [31.7-42.0]	-0.1 [-4.0-9.9]	30.2 [22.7-36.8]	34.7 [30.2-41.3]	4.5 [0.5-9.5]	0.59
SF-36 mental component sum score, points	48.6 [37.2-53.8]	54.2 [52.5-56.7]	5.6 [1.4-9.2]	38.5 [30.1-52.8]	52.9 [32.0-58.2]	14.4§ [-0.6-24.5]	**0.036**
Laboratory parameters							
CRP, mg/l	1.4 [0.6-3.9]	1.0 [0.6-2.2]	-0.4 [-1.2-0.1]	2.6 [1.5-5.4]	2.0 [1.3-3.9]	-0.6 [-1.6-0.4]	0.95
Leucocytes, g/l	5.9 [5.3-6.4]	5.6 [4.9-6.3]	-0.3 [-1.1-0.1]	7.2 [6.0-9.7]	7.0 [6.0-9.7]	-0.2 [-0.8-1.1]	0.19
D-Dimer, µg/ml	292 [196-498]	291 [210-537]	-1 [-25-30]	726 [367-982]	428 [307-807]	-298§ [-639- -14]	**0.001**
Pro-BNP, pg/ml	72 [56-106]	56 [33-91]	-16* [-28-7]	130 [59-335]	147 [74-361]	17 [-91-39]	0.44

Data are presented as median and percentage or median and interquartile range.
*p<0.05 from pre to post PR; #p<0.01 from pre to post PR; §p<0.001 from pre to post PR
Abbreviations: 6MWD – 6-minute walk distance, 6MWT – 6-minute walk test, BNP – brain natriuretic peptide, CRP – c-reactive protein, DLCO – diffusion lung capacity for carbon monoxide, FEV_1 – forced expiratory volume in 1 second, FRC – functional residual capacity, FVC – forced vital capacity, $PaCO_2$ – partial carbon dioxide pressure, PaO_2 – partial oxygen pressure, SpO_2 – oxygen saturation, TLC – total lung capacity

Furthermore, in the group of severe/critical COVID-19 patients, there was a significant improvement in frailty status (Table 3). ESWT duration improved from 460sec to 1200sec (p=0.001) with 14 patients (54%) reaching the test duration maximum of 20 minutes. Also severe desaturations (oxygen saturation <85%) during ESWT were significantly less common at PR discharge (5 versus 1 patient; p<0.001) and breathing frequency at isotime reduced from 50 to 45 breaths per minute (p=0.005) (Table 4). No adverse event was observed during the PR period. However, patients with severe/critical COVID-19 reported persistent COVID-19-related impairments at PR discharge for symptoms like dyspnea (73%), fatigue (58%) or cough (35%) (Figure S3).

Table 3. Additional outcome measures for the subgroup of 26 patients with severe to critical COVID-19 following pulmonary rehabilitation

	Pre PR	**Post PR**	**Δ**	**p-value**
Fried frailty index				
Non-frail, n (%)	0 (0%)	3 (12%)	-3 (-12%)	**<0.001**
Pre-frail, n (%)	8 (31%)	16 (62%)	8 (31%)	0.060
Frail, n (%)	18 (69%)	7 (27%)	-11 (-42%)	0.060
Endurance shuttle walk test				
ESWT, m	430 [195-758]	980 [390-1385]	550 [50-725]	**<0.001**
ESWT, sec	460 [217-625]	1200 [312-1200]	740 [143-789]	**0.0001**
ESWT baseline SpO_2, %	97 [95-97]	97 [96-98]	0 [-1-2.5]	**0.021**
ESWT isotime SpO_2, %	94 [87-96]	95 [91-96]	1 [-1-3]	0.053
ESWT SpO_2 <90%, n	9 (35%)	7 (27%)	-2 (-8%)	**<0.001**
Duration to ESWT SpO_2 <90%, sec	50 [18-122]	163 [32-276]	113 [13-262]	0.028
ESWT SpO_2 <85%, n	5 (19%)	1 (4%)	-4 (15%)	**<0.001**
Duration to ESWT SpO_2 <85%, sec	89 [62-199]	319 [319-319]	230 [NA]	-
ESWT baseline HR, bpm	86 [77-98]	85 [75-95]	-1 [-8-4]	0.35
ESWT isotime HR, bpm	114 [99-126]	108 [97-119]	-6 [-12-5]	0.52
ESWT baseline BF, 1/min	24 [18-30]	19 [15-25]	-5 [-5-0]	**0.001**
ESWT isotime BF, 1/min	50 [42-56]	45 [37-55]	-5 [-5-0]	**0.005**
Muscle function				
Handgrip strength, kg	25 [18-35]	30 [20-39]	5 [3-7]	**0.002**
Peak quadriceps strength, %predicted	78.4 [48.6-98.1]	99.6 [68.4-103.3]	21.2 [5.7-31.0]	**0.008**
5-rep STST, sec	13.3 [10.5-15.5]	10.3 [8.5-13.2]	-3.0 [-4.3- -0.3]	**0.001**
Psychological distress and (cognitive) impairment				
PHQ-9, points	7 [4-12]	4 [2-10]	-3 [-4-0]	**0.002**
Signs of at least mild depression according to PHQ-9 score ≥5	15 (58%)	9 (35%)	-6 (-23%)	**0.031**
GAD-7, points	4 [2-8]	5 [1-7]	1 [0-2]	**0.021**
Signs of at least mild anxiety according to GAD-7 score ≥5	10 (38%)	10 (38%)	0 (0%)	1.00
MoCA, points	25 [23-28]	28 [25-28]	3 [1-3]	**0.038**
Cognitive impairment according to MoCA score <26 points, n (%)	12 (46%)	6 (23%)	-6 (-23%)	**0.005**
mMRC, points	2 [2-2]	2 [1-2]	0 [-1-0]	**0.003**
mMRC score ≥1	24 (92%)	23 (88%)	-1 (-4%)	1.00
mMRC score ≥2	20 (77%)	14 (54%)	-6 (-23%)	**0.031**

Data are presented as median and percentage or median and interquartile range. Significance level: p<0.05 Abbreviations: ESWT – Endurance Shuttle Walk Test; SpO_2 – oxygen saturation; HR – heart rate; BF – breathing frequency; STST – sit-to-stand test; mMRC – modified Medical Research Council; PHQ-9 – patient health questionnaire (depression); GAD-7 – generalized anxiety disorder scale; MoCA – Montreal cognitive assessment

Discussion

Our study shows, that PR is feasible (with a very high adherence rate of PR sessions), safe (no adverse events), and beneficial to improve exercise performance, lung function, and quality of life in patients with persistent sequelae due to a mild to critical course of COVID-19. To the best of our knowledge, this is the first prospective study investigating the effects of a comprehensive PR in post-acute COVID-19 patients. In a recent systematic review, Negrini et al. determined the level of evidence of PR in COVID-19 patients to be low [23]. Searching the PubMed library with the terms "pulmonary rehabilitation" AND "COVID-19" on February 7th, 2021 yielded that only four studies have investigated the effects of PR in COVID-19 patients so far. Two studies were case series reports describing seven [24] and three [25] cases of COVID-19 PR. One study was conducted as a randomized, controlled trial in 72 patients with a severe acute course of COVID-19 [26]. However, this study provided home-based respiratory muscle training as the main content and should therefore not be considered as PR which is defined as a much more comprehensive intervention according to the current ATS/ERS PR statement [27]. Only Hermann et al. investigated the effects of a comprehensive inpatient PR similar to ours by retrospectively analyzing data from 28 patients with severe/critical COVID-19 [28]. In line with our findings, they concluded that PR following COVID-19 was effective to improve physical performance and subjective health status in these patients with severe disease.

In our study, not only patients with severe/critical COVID-19 suffered from persistent physical impairments, but also patients with a mild/moderate course of the disease. Despite significantly improving exercise performance, mild/moderate COVID-19 patients were still discharged with an impaired 6MWD (81% predicted). From experiences with SARS-CoV-1, it is known that the 6MWD could remain significantly lower compared to normal reference values even one-year after the acute SARS-CoV-1 infection phase [29]. However, mild/moderate COVID-19 patients in our study improved 6MWD by 48m what is clearly beyond the suggested MID of 30m in patients with respiratory diseases (88% of patients exceeded this threshold) [15]. Even though a certain natural recovery effect cannot be ruled out, we suggest that these improvements seem to be related to the impact of PR because patients reached this significant increase in 6MWD only within three weeks of PR, although their acute SARS-CoV-2 infection phase was already six months ago. Furthermore, a recent study by Daher et al. in patients with severe COVID-19 has shown, that exercise performance is still severely impaired six weeks after hospital discharge in patients who did not perform a PR (6MWD median 380m) [30]. This implies a slow natural recovery in severe COVID-19 patients following hospitalization. Severe/critical COVID-19 patients in our study were able to increase 6MWD substantially from 344m to 468m (with 92% of patients exceeding the MID) at PR discharge which was also six weeks after hospital discharge. A study by Huang et al. investigated 1733 hospitalized COVID-19 patients and found a median 6MWD of 495m [440m - 538m] at a six months follow-up after hospital discharge [31]. COVID-19 patients in our study reached a comparable range of 6MWD at PR discharge only 6 weeks after hospital discharge. It seems that the recovery of exercise performance can be accelerated when COVID-19 patients are referred to PR after the acute phase of the disease. Despite this large improvement following PR, patients with severe/critical COVID-19 still reached only 70.5% of their predicted 6MWD. This might be more related to the persisting impairments in respiratory capacity

rather than to skeletal muscle weakness because patients regained a normal level (99.6% predicted) of their quadriceps strength at PR discharge.

Up to now, it is not clear whether COVID-19 will leave permanent lung damage and, if so, to what extent [12]. In our study, COVID-19 patients showed a restrictive lung function pattern, a severely impaired gas exchange and an increased breathing rate during exertion.
Although lung function, gas exchange, and breathing frequency improved significantly following PR, patients were discharged with a persistent impaired respiratory function. From a 2005 study in 97 SARS-CoV-1 survivors, it is known that 24% had persistent reduced lung diffusion compared to healthy control subjects even at a one-year follow-up [29]. Furthermore, 28% to 62% of SARS-CoV-1 survivors exhibited decreased lung function and increased lung fibrosis [32]. Currently, there is some evidence that suggests that the development of a fibrotic lung disease as an outcome of COIVD-19 is also a serious concern [33, 34]. Since our study was not randomized and does not contain a COVID-19 control group without PR we would like to draw an indirect comparison by using a group of idiopathic pulmonary fibrosis (IPF) patients from a former study of our working group where the same outcome measures were assessed [35]. This IPF comparison group did not perform PR and had a comparable impairment in lung function (see online supplementary material table S1 and S2). However, at PR admission, COVID-19 patients with a severe/critical course showed even a significantly lower 6MWD and mental health summary score compared to IPF patients. COVID-19 patients were able to improve all mentioned outcomes following PR whereas IPF patients in our non-PR comparison group did not change in any of these outcomes at a two months follow-up assessment. In the lack of a COVID-19 non-PR control group, this comparison to non-PR IPF patients may give a further clue that PR in COVID-19 is beneficial beyond the natural recovery. However, although COVID-19 patients had a restrictive lung function pattern, this comparison must be interpreted with caution, since COVID-19 is an acute damage, whereas IPF is a chronic progressing disease.

About 75% of hospitalized COVID-19 patients show abnormal patient-reported outcome measures three months after symptom onset, with 33% of patients reporting at least moderate impairments in major dimensions of quality of life [36]. Consistently, patients in our study also showed impairments in physical and mental quality of life. Notably, these patients in our study with severe/critical COVID-19 course experienced even a significantly lower mental quality of life than a comparison group of IPF-patients (table S1). Within our subsample of severe/critical COVID-19 patients, 58% showed at least mild depression and 38% at least mild anxiety symptoms. Notably, this group showed much more psychological distress than comparable cohorts of severe/critical COVID-19 three months after symptom onset (24% mood-impairment) [36] or six months after symptom onset (32% anxiety *or* depression) [31]. We found that mental quality of life and depression improved significantly in patients with severe/critical COVID-19 (although 35% of patients were still reporting at least mild depression symptoms after PR). We acknowledge that these effects could also be interpreted as spontaneous remission. However, the patients´ symptom onset in our cohort was two months ago. Therefore, we

attribute these improvements mainly to the impact of the PR program, which also included specific interventions focusing on disease management as well as on coping with COVID-19 and its sequelae. Interestingly, PR was not associated with a change in the number of patients reporting at least mild anxiety symptoms. However, patients' anxiety scores increased slightly but significantly. Potentially, patients only began during PR to reflect on daily life challenges as a result of their COVID-19 disease. Specifically, the increasing focus on day-to-day functioning along with patients' awareness of their persistent impairments (e.g. in cognitive function) may have resulted in higher anxiety scores. Of course, this finding needs replication before further interpretation. However, a potential area for future research could be that PR and possible interventions that take place after PR, should monitor and focus on patients´ disease-specific- and future related anxieties and help, to cope with their ongoing impairments after PR.

The most relevant limitation of our study is the absence of a randomized COVID-19 control group which was not possible due to ethical issues. However, the known COVID-19 sequelae from other studies without PR, the comparison to a non-PR group of IPF patients, and the large gains that mild/moderate COVID-19 patients reached during three weeks of PR (even six months after their acute SARS-CoV-2 infection) suggest, that these benefits are more related to PR rather than to only a natural convalescence. A second limitation of our study might be a specific selection bias because mainly COVID-19 patients with a focus on lung disease were referred to our PR program. However, it is known that there are COVID-19 patients in which neural, cardiac, renal, gastrointestinal, or coagulative disorders dominate [37]. This limits the generalizability of our findings. A third limitation might be that we did not perform a practice 6MWT.

A strength of our study is the inclusion of patients with the full spectrum of disease severity and the collection of a comprehensive data set that provides an important insight into the benefits of PR in COVID-19 patients.

Conclusion

Our study shows that PR is effective, feasible, and safe to improve exercise performance, lung function, and quality of life in patients with persistent impairments due to a mild to critical course of COVID-19. Further randomized controlled trials including follow-up assessments are needed to assess PR long-term benefits.

Figure legend

Figure 1. (A) Changes in 6-minute walk distance pre to post comprehensive pulmonary rehabilitation in patients with mild/moderate (circles; n=24) and severe/critical (triangles; n=26) COVID-19. (B) Changes in forced vital capacity (FVC). (C) Development of oxygen saturation during endurance shuttle walk test (ESWT) from baseline to isotime in patients with severe to critical COVID-19 before and after pulmonary rehabilitation (PR). Data are presented as median and interquartile range. (D) Development of breathing rate during ESWT from baseline to isotime in patients with severe to critical COVID-19 before and after pulmonary rehabilitation (PR). Data are presented as median and interquartile range.

*p<0.05, **p<0.01; ***p<0.001

Contributors

RG, DL, TS, IJ, KK and ARK designed the study. RG, DL, TS, IJ and ARK were involved in recruiting patients and collecting the data. DL and RG have verified the underlying data. RG and CN performed statistical analyses. RG and DL drafted the manuscript. RG, DL, TS, IJ, CN, NS, CFV, KK and ARK provided scientific discussion and revised the initial draft. All authors had full access to all the data in the study and accept responsibility to submit for publication. All authors approved the final version of the manuscript.

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Declaration of interests

All authors declare no competing interests.

Data sharing

A pseudonymized dataset will be made available upon reasonable request to the corresponding author. The request must include a statistical analysis plan.

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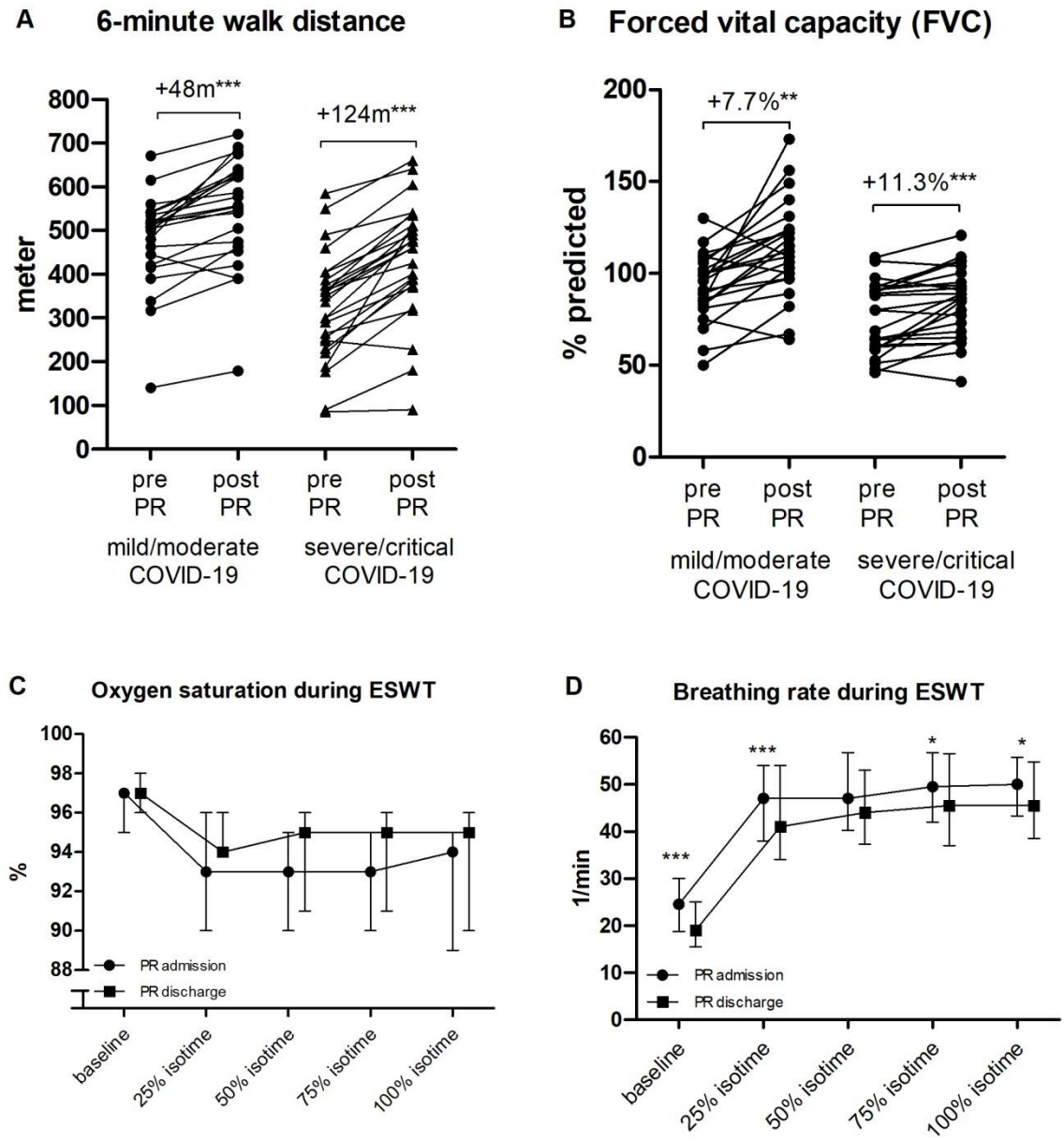
References

1. China CDC Weekly: Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. 2020; 2: 113-122.
2. *World Health Organisation: Clinical Management of COVID-19; available at: https://www.who.int/publications/i/item/clinical-management-of-covid-19 from May 27, 2020*.
3. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-232.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062.
5. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, Walshaw C, Kemp S, Corrado J, Singh R, Collins T, O'Connor RJ, Sivan M. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol 2021; 93: 1013-1022.
6. Carfi A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. Jama 2020; 324: 603-605.
7. Goertz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, Houben-Wilke S, Burtin C, Posthuma R, Franssen FME, van Loon N, Hajian B, Spies Y, Vijlbrief H, van 't Hul AJ, Janssen DJA, Spruit MA. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res 2020; 6:
8. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, Ho RC. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int J Environ Res Public Health 2020; 17:
9. COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE-guideline. published on December 18, 2020. Available at: https://www.nice.org.uk/guidance/ng188.
10. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. Bmj 2020; 370: m3026.
11. 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;
12. Polastri M, Nava S, Clini E, Vitacca M, Gosselink R. COVID-19 and pulmonary rehabilitation: preparing for phase three. Eur Respir J 2020; 55:
13. Vitacca M, Lazzeri M, Guffanti E, Frigerio P, D'Abrosca F, Gianola S, Carone M, Paneroni M, Ceriana P, Pasqua F, Banfi P, Gigliotti F, Simonelli C, Cirio S, Rossi V, Beccaluva CG, Retucci M, Santambrogio M, Lanza A, Gallo F, Fumagalli A, Mantero M, Castellini G, Calabrese M, Castellana G, Volpato E, Ciriello M, Garofano M, Clini E, Ambrosino N, Arir Associazione Riabilitatori dell'Insufficienza Respiratoria Sip Societa Italiana di Pneumologia Aifi Associazione Italiana F, Sifir Societa Italiana di Fisioterapia ERO. Italian suggestions for pulmonary rehabilitation in COVID-19 patients recovering from acute respiratory failure: results of a Delphi process. Monaldi Arch Chest Dis 2020; 90:
14. Carda S, Invernizzi M, Bavikatte G, Bensmail D, Bianchi F, Deltombe T, Draulans N, Esquenazi A, Francisco GE, Gross R, Jacinto LJ, Moraleda Perez S, O'Dell MW, Reebye R, Verduzco-Gutierrez M, Wissel J, Molteni F. The role of physical and rehabilitation medicine in the COVID-19 pandemic: The clinician's view. Ann Phys Rehabil Med 2020; 63: 554-556.
15. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciurba FC, Pitta F, Wanger J, MacIntyre N, Kaminsky DA, Culver BH, Revill SM, Hernandes

NA, Andrianopoulos V, Camillo CA, Mitchell KE, Lee AL, Hill CJ, Singh SJ. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014; 44: 1428-46.
16. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R, Dekhuijzen PN, Franssen F, Gayan-Ramirez G, Gea J, Gosker HR, Gosselink R, Hayot M, Hussain SN, Janssens W, Polkey MI, Roca J, Saey D, Schols AM, Spruit MA, Steiner M, Taivassalo T, Troosters T, Vogiatzis I, Wagner PD. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014; 189: e15-62.
17. Jones SE, Kon SS, Canavan JL, Patel MS, Clark AL, Nolan CM, Polkey MI, Man WD. The five-repetition sit-to-stand test as a functional outcome measure in COPD. Thorax 2013; 68: 1015-20.
18. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146-56.
19. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54: 581-6.
20. Lowe B, Decker O, Muller S, Brahler E, Schellberg D, Herzog W, Herzberg PY. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 2008; 46: 266-74.
21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16: 606-13.
22. Ihle-Hansen H, Vigen T, Berge T, Einvik G, Aarsland D, Ronning OM, Thommessen B, Rosjo H, Tveit A. Montreal Cognitive Assessment in a 63- to 65-year-old Norwegian Cohort from the General Population: Data from the Akershus Cardiac Examination 1950 Study. Dement Geriatr Cogn Dis Extra 2017; 7: 318-327.
23. Negrini F, De Sire A, Andrenelli E, Lazzarini SG, Patrini M, Ceravolo MG. Rehabilitation and COVID-19: a rapid living systematic review 2020 by Cochrane Rehabilitation Field. Update as of October 31st, 2020. Eur J Phys Rehabil Med 2020;
24. Ferraro F, Calafiore D, Dambruoso F, Guidarini S, de Sire A. COVID-19 related fatigue: Which role for rehabilitation in post-COVID-19 patients? A case series. J Med Virol 2020;
25. Wootton SL, King M, Alison JA, Mahadev S, Chan ASL. COVID-19 rehabilitation delivered via a telehealth pulmonary rehabilitation model: a case series. Respirol Case Rep 2020; 8: e00669.
26. 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.
27. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Molken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013; 188: e13-64.
28. Hermann M, Pekacka-Egli AM, Witassek F, Baumgaertner R, Schoendorf S, Spielmanns M. Feasibility and Efficacy of Cardiopulmonary Rehabilitation After COVID-19. American journal of physical medicine & rehabilitation 2020; 99: 865-869.
29. Hui DS, Wong KT, Ko FW, Tam LS, Chan DP, Woo J, Sung JJ. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest 2005; 128: 2247-61.

30. Daher A, Balfanz P, Cornelissen C, Muller A, Bergs I, Marx N, Muller-Wieland D, Hartmann B, Dreher M, Muller T. Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. Respir Med 2020; 174: 106197.
31. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Zhong J, Wang C, Wang J, Zhang D, Cao B. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;
32. McDonald LT. Healing after Covid-19: Are Survivors at Risk for Development of Pulmonary Fibrosis? Am J Physiol Lung Cell Mol Physiol 2020;
33. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Casa GD, Sverzellati N, Maher TM. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med 2020; 8: 750-752.
34. Guler SA, Ebner L, Beigelman C, Bridevaux PO, Brutsche M, Clarenbach C, Garzoni C, Geiser TK, Lenoir A, Mancinetti M, Naccini B, Ott SR, Piquilloud L, Prella M, Que YA, Soccal PM, von Garnier C, Funke-Chambour M. Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. Eur Respir J 2021;
35. Jarosch I, Schneeberger T, Gloeckl R, Kreuter M, Frankenberger M, Neurohr C, Prasse A, Freise J, Behr J, Hitzl W, Koczulla AR, Kenn K. Short-Term Effects of Comprehensive Pulmonary Rehabilitation and its Maintenance in Patients with Idiopathic Pulmonary Fibrosis: A Randomized Controlled Trial. J Clin Med 2020; 9:
36. Wong AW, Shah AS, Johnston JC, Carlsten C, Ryerson CJ. Patient-reported outcome measures after COVID-19: a prospective cohort study. Eur Respir J 2020; 56:
37. Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, Terpos E, Dimopoulos MA. Organ-specific manifestations of COVID-19 infection. Clin Exp Med 2020; 20: 493-506.


A
6-minute walk distance
+48m***
+124m***
meter
800
700
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400
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200
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pre PR
post PR
pre PR
post PR
mild/moderate COVID-19
severe/critical COVID-19
B
Forced vital capacity (FVC)
+7.7%**
+11.3%***
% predicted
200
150
100
50
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pre PR
post PR
pre PR
post PR
mild/moderate COVID-19
severe/critical COVID-19
C
Oxygen saturation during ESWT
%
100
98
96
94
92
90
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PR discharge
baseline
25% isotime
50% isotime
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100% isotime
D
Breathing rate during ESWT
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25% isotime
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- ONLINE SUPPLEMENTARY MATERIAL -

Benefits of pulmonary rehabilitation in COVID-19 – a prospective observational cohort study

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Additional information on the comparison group of idiopathic pulmonary fibrosis (IPF) patients:

The comparison group consisted of 17 IPF patients that were recruited for a randomized, controlled trial, investigating the benefits of pulmonary rehabilitation. These 17 patients belonged to the control group and received usual care (without pulmonary rehabilitation). Results from this study were recently published by our working group (Jarosch et al. J Clin Med 2020; 9, 1567). COVID-19 patients in the current study showed restrictive lung pattern similar to patients with chronic fibrotic lung diseases. Since the current study was not a randomized, controlled trial we draw an indirect comparison by using these IPF patients as a non-PR comparison group.

Description of baseline characteristics can be found in table S1. Furthermore, a comparison of changes following 3-weeks of rehabilitation in COVID-19 patients versus the outcomes of usual care in IPF patients after 2 months can be found in table S2.

Table S1. Baseline characteristics post-COVID-19 patients on admission of pulmonary rehabilitation (PR) and the comparison group of non-PR-patients with idiopathic pulmonary fibrosis (IPF)

	Mild/moderate COVID-19	Severe/critical COVID-19	Non PR IPF group	p-value
General				
n	24	26	17	
Age, ys	**52***** [47 - 56]	66 [60 - 71]	**65** [58 - 75]	**<0.001**
Sex, female (%)	**20** (83%)***	8 (31%)	**3** (18%)	**<0.001**
BMI, kg/m²	24.7 [22.0 - 29.8]	26.9 [24.2 - 29.2]	26.8 [24.8 - 28.8]	0.13
Oxygen therapy, n (%)	**0*** (0%)	7 (27%)	**6** (35%)	**0.007**
Respiratory parameters				
PaO_2, mmHg	73.1 [63.6 - 77.4]	73.2 [62.7 - 77.6]	65.0 [74.0 - 47.1]	0.10
$PaCO_2$, mmHg	35.0 [32.6 - 38.5]	35.5 [31.8 - 36.9]	37.4 [34.6 - 40.3]	0.25
DLCO, %predicted	**57.0*** [50.0 - 65.5]	55.8 [37.2 - 63.0]	**32.0** [20.0 - 48.0]	**0.043**
TLC, %predicted	82.2 [65.3 - 88.9]	80.9 [64.4 - 88.6]	65.5 [58.1 - 78.5]	0.24
FVC, %predicted	80.0 [59.2 - 90.9]	75.1 [59.8 - 90.6]	71.1 [62.2 - 88.5]	0.91
FEV_1, %predicted	83.3 [65.5 - 101.1]	79.1 [65.8 - 99.7]	82.9 [61.0 - 91.2]	0.65
FRC, %predicted	**113.0***** [95.0 – 127.0]	82.6 [70.3 – 97.4]	73.2 [55.3 – 100.1]	**<0.001**
Exercise performance				
6MWD, m	509 [426 - 539]	**344*** [244 - 392]	**416** [278 - 483]	**<0.001**
6MWD, %predicted	70.1 [57.8 - 80.2]	52.5 [42.4 - 58.3]	51.5 [40.4 - 70.5]	**0.003**
6MWT SpO_2 nadir, %	**96***** [94 - 97]	**92*** [88 - 94]	**81** [71 - 90]	**<0.001**
End-6MWT dyspnea, Borg scale	4 [3 - 5]	5 [4 - 6]	3 [2 - 7]	0.16
Quality of life				
SF-36 physical component sum score, points	31.8 [26.2 - 35.7]	**30.2* **[22.7 - 36.8]	**39.7** [30.5 - 46.9]	**0.023**
SF-36 mental component sum score, points	48.6 [37.2 - 53.8]	38.5 [30.1 - 52.8]	49.0 [35.4 - 52.8]	0.35

Data are presented as median and percentage or median and interquartile range.
Significance between COVID-subgroup and IPF comparison group: *p<0.05; **p<0.01; ***p<0.001
Abbreviations: 6MWD – 6-minute walk distance, 6MWT – 6-minute walk test, BMI: Body Mass Index, COVID-19: Corona Virus Disease 2019, DLCO – diffusion lung capacity for carbon monoxide, FEV_1 – forced expiratory volume in 1 second, FVC – forced vital capacity, O_2: oxygen, $PaCO_2$ – partial carbon dioxide pressure, PaO_2 – partial oxygen pressure, SpO_2 – oxygen saturation, TLC – total lung capacity

Table S2. Outcomes of a comprehensive inpatient pulmonary rehabilitation (PR) in 50 post-acute COVID-19 patients and a comparison group of 17 non-PR patients with idiopathic pulmonary fibrosis (IPF)

	mild/moderate COVID-19 (n=24)	*severe/critical COVID-19 (n=26)*	*non-PR IPF group (n=17)*	*p-value*
Respiratory parameters				
PaO_2, mmHg	2.7 [-0.9 - 10.8]	2.5 [-1.2 - 10.5]	0.6 [-6.5 - 5.7]	0.38
$PaCO_2$, mmHg	- 1.2 [-2.7 - 2.5]	- 0.2 [-2.9 - 2.7]	1.3 [-1.9 - 2.0]	0.37
DLCO, %predicted	4.5 [-1.8 - 16.5]	**3.7*** [-0.5 - 12.7]	**- 1.0** [-3.6 - 3.5]	**0.038**
TLC, %predicted	- 1.1 [-4.7 - 10.7]	0.1 [-4.3 - 10.5]	0.0 [-4.0 - 1.8]	0.69
FVC, %predicted	7.7 [1.0 - 17.8]	11.3 [1.0 - 16.9]	1.0 [-4.1 - 7.3]	0.06
FEV_1, %predicted	**11.8**** [3.3 - 18.1]	**15.7**** [3.7 - 17.5]	**0.5** [-4.0 - 4.5]	**0.002**
FVC, %predicted	0.0 [-5.0 – 11.0]	2.0 [-6.5 – 9.1]	-1.6 [-9.3 – 9.6]	0.882
Exercise performance				
6MWD, m	**48**** [35 - 113]	**124***** [75 - 145]	**-8** [-40 - 30]	**<0.001**
6MWD, %predicted	**10.9**** [4.7 - 14.6]	**18.0***** [11.2 - 23.1]	**- 4.1** [-5.9 - 4.5]	**<0.001**
6MWT SpO_2 nadir, %	0.0 [-2.0 - 1.0]	1.0 [-1.0 - 2.5]	0.5 [-3.0 - 7.3]	0.45
End-6MWT dyspnea, Borg scale	0 [-1 - 1]	0 [-2 - 1]	0 [-2 - 1]	0.98
Quality of life				
SF-36 physical component sum score, points	-0.1 [-4.0 - 9.9]	**4.5*** [0.5 - 9.5]	**- 1.4** [-4.2 - 3.2]	**0.019**
SF-36 mental component sum score, points	5.6 [1.4 - 9.2]	14.4 [-0.6 - 24.5]	- 6.3 [-1.0 - 4.4]	0.099

Data are presented as median and percentage or median and interquartile range.
Abbreviations: 6MWD – 6-minute walk distance, 6MWT – 6-minute walk test, DLCO – diffusion lung capacity for carbon monoxide, FEV_1 – forced expiratory volume in 1 second, FVC – forced vital capacity, $PaCO_2$ – partial carbon dioxide pressure, PaO2 – partial oxygen pressure, SpO_2 – oxygen saturation, TLC – total lung capacity

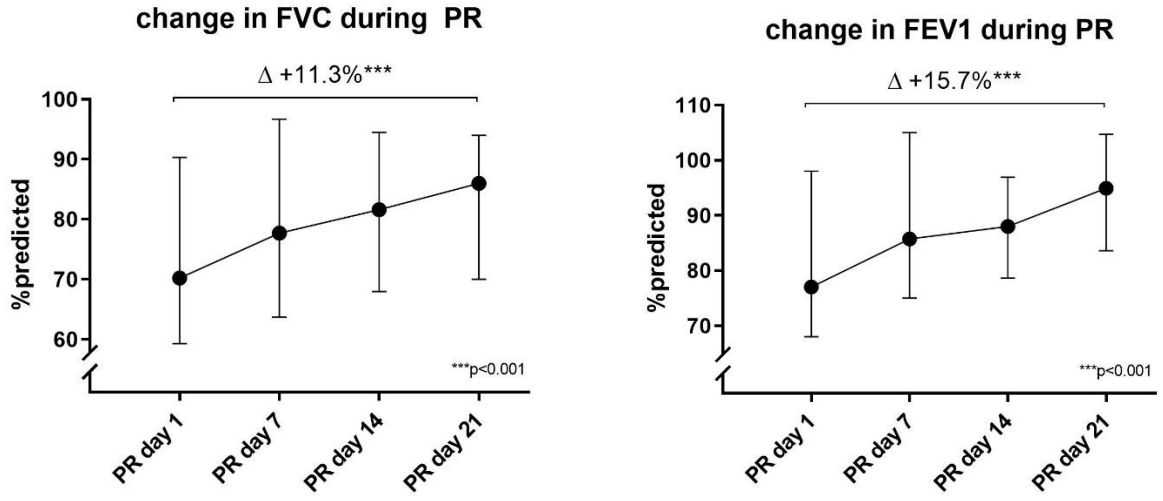

Figure S1. Change in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) during pulmonary rehabilitation (PR) in 26 patients with post-acute severe to critical COVID-19. Data are presented as median and interquartile range.

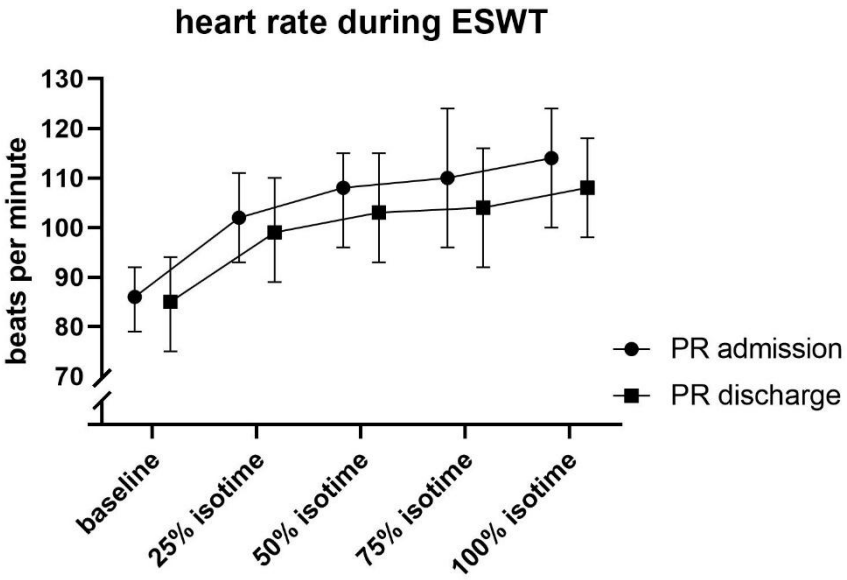

Figure S2. Development of heart rate during endurance shuttle walk test (ESWT) from baseline to isotime in 26 patients with post-acute severe to critical COVID-19 before and after pulmonary rehabilitation (PR). Data are presented as median and interquartile range.

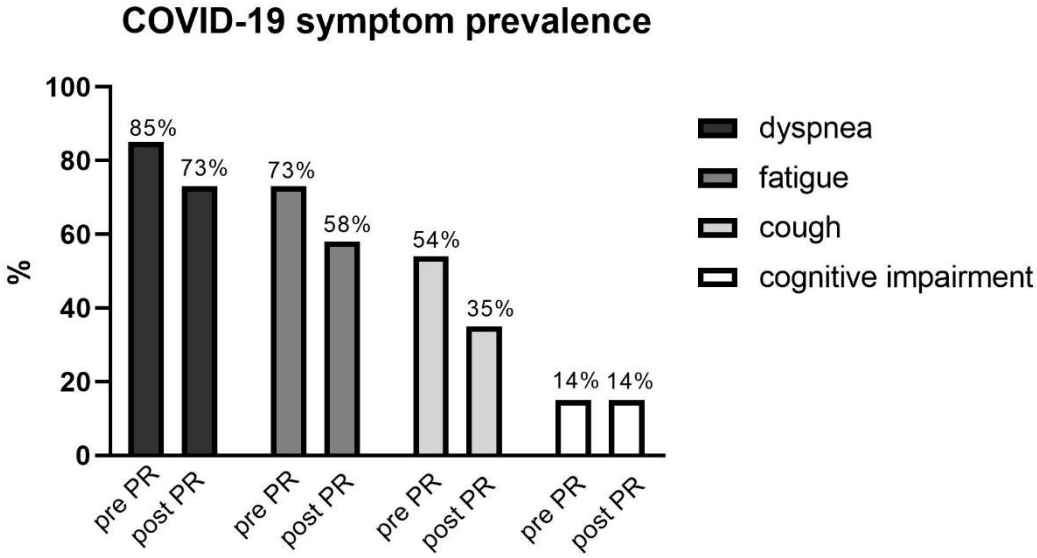

Figure S3. Prevalence of COVID-19 symptoms in 26 patients with severe to critical COVID-19 pre and post a 3-week comprehensive inpatient pulmonary rehabilitation. Symptoms were assessed by interviewing patients. Therefore, a list of typical COVID-19 symptoms was read to them and patients were asked to rate yes or no if they perceive any of the symptoms. None of the changes was significantly different.