Accepted Manuscript online: 2022-06-01 Article published online: 2022-07-19

The Effects of Exercise Therapy Moderated by Sex in Rehabilitation of COVID-19

OPEN ACCESS

Authors

Linda Rausch[1], Bernhard Puchner[2], Jürgen Fuchshuber[3, 4], Barbara Seebacher[2], Judith Löffler-Ragg[5], Stephan Pramsohler[6], Nikolaus Netzer[6, 7, 8], Martin Faulhaber[1]

Affiliations

1 Department of Sport Science, University of Innsbruck, Innsbruck, Austria
2 Department of Rehabilitation Research, Rehab Center Muenster, Muenster, Austria
3 Grüner Kreis Society, Center for Integrative Addiction Research (CIAR), Vienna, Austria
4 University Clinic for Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Graz, Austria
5 Department of Internal Medicine II, Medical University Innsbruck, Innsbruck, Austria
6 associated to University of Innsbruck, Hermann Buhl Institute for Hypoxia and Sleep Medicine Research, Lenggries, Germany
7 Department Medicine, Division Sports Medicine, University Hospital Ulm, Ulm, Germany
8 Institute of Mountain Emergency Medicine, EURAC Research, Bolzano, Italy

Key words

exercise therapy, rehabilitation, sex characteristics, COVID-19, respiratory function tests, six-minute walk test

accepted 19.05.2022
published online 19.07.2022

Bibliography

Int J Sports Med 2022; 43: 1043–1051
DOI 10.1055/a-1866-6092
ISSN 0172-4622

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Dr. Linda Rausch
University of Innsbruck, Sport Science, Fürstenweg 185
6020 Innsbruck
Austria
Tel.: 051250745848
linda.rausch@uibk.ac.at

ABSTRACT

Standardized exercise therapy programs in pulmonary rehabilitation have been shown to improve physical performance and lung function parameters in post-acute COVID-19 patients. However, it has not been investigated if these positive effects are equally beneficial for both sexes. The purpose of this study was to analyze outcomes of a pulmonary rehabilitation program with respect to sex differences, in order to identify sex-specific pulmonary rehabilitation requirements. Data of 233 post-acute COVID-19 patients (40.4 % females) were analyzed before and after a three-week standardized pulmonary rehabilitation program. Lung function parameters were assessed using body-plethysmography and functional exercise capacity was measured by the Six-Minute Walk Test. At post-rehabilitation, females showed a significantly smaller improvement in maximal inspiration capacity and forced expiratory volume ($F = 5.86$, $\omega^{2} = .02$; $p < 0.05$) than males. Exercise capacity improvements between men and women did not differ statistically. Females made greater progress towards reference values of exercise capacity ($T(231) = -3.04$; $p < 0.01$) and forced expiratory volume in the first second ($T(231) = 2.83$; $p < 0.01$) than males. Sex differences in the improvement of lung function parameters seem to exist and should be considered when personalizing standardized exercise therapies in pulmonary rehabilitation.

Introduction

Since the corona virus disease 2019 (COVID-19) was declared a pandemic in March 2020, healthcare providers have been globally challenged to manage disease spreading and maintain instant and long-term medical treatment for all affected individuals [1]. As the pandemic progresses, COVID-19-related sex disparities have been observed. The risk of a severe progression of COVID-19 has consistently been found two times greater for men than for women worldwide, measured by the number of deaths, hospitalizations, intensive care unit stays and intubations for mechanical ventilation [2–4]. Especially men between the ages of 65 and 85 have dominated the prevalence of COVID-19-related deaths [5], probably associated with chronic metabolic disease, such as obesity, type 2 diabetes and hypertension [6], or cardiovascular disease tending to affect men more frequently than women [6–8]. Potential reasons range from biological factors, including stronger female immune response to viral infections and protective properties of estrogen, to social factors e.g., higher alcohol consumption and enhanced smoking behavior in men [9–11].

A SARS-CoV-2 infection specifically affects the respiratory system and symptoms have been shown to be manifested six months to one year after hospital discharge [12, 13]. Patients, predominantly males, who were seriously ill during their hospital stay had more severely impaired lung function capacities whereas lung diffusion impairment and fatigue or muscle weakness were symptoms mainly observed in women six months after their hospital discharge [12, 13]. However, these patients may not have undergone inpatient rehabilitation following their acute hospital stay. Evidently, pulmonary rehabilitation has been promoted as a key treatment component after acute COVID-19 illness and applied successfully including standardized exercise therapy interventions connected to a multidisciplinary approach [14, 15]. This has been shown in improved lung function parameters and functional exercise capacity of post-acute COVID-19 patients after three to five weeks [16, 17]. Especially respiratory exercise has led to a significant improvement in lung function and physical performance in elderly patients [18]. These findings emphasize the effectiveness of pulmonary rehabilitation reducing recovery time after burden of COVID-19. So far however, it has not been investigated, if standardized pulmonary rehabilitation is equally efficacious in males and females in the post-acute stage after a COVID-19 infection. Therefore, based on sex disparities in former hospitalized COVID-19 patients [19, 20], we aimed to analyze the outcomes of standardized pulmonary rehabilitation in post-acute COVID-19 patients with respect to sex-specific differences. The purpose of the study is to initiate a discourse with other researchers evaluating the relevance of sex-specific approaches in standardized rehabilitation treatments of COVID-19 patients.

Materials and Methods

Design and Data Source

The retrospective case series contains data from post-acute COVID-19 patients who were admitted to a standardized three-week pulmonary rehabilitation program at the Clinic for Rehabilitation in Münster, Austria. They were admitted between the 1st of March 2020 and 31st of May 2021, due to a laboratory confirmed SARS-CoV-2 infection prior to rehabilitation, according to the definition of the Austrian Federal Ministry of Social Affairs & Health Care. Initially, data of all eligible patients who underwent rehabilitation in this time frame were screened by a physician. Before data evaluation, data were pseudonymized and then extracted from the clinic information system (MP2 IT-Solutions, Austria). Data pseudonymization and extraction were carried out by one physician and one research assistant. Data privacy was guaranteed by an in-house data protection agreement made by a commissioner for data protection. Steps of the retrospective data analyses are shown in ▶ **Figure 1**. The research ethics committee of the Medical University of Innsbruck approved the study protocol (1066/2021) and the study was registered at the German Clinical Trials Register (ID: DRKS00026936).

Characteristics of Patients' Data

Records from post-acute COVID-19 patients with the principal diagnosis ICD U.07.1 (COVID-19) were analyzed. Anthropometric data as well as secondary diagnoses which were present before the COVID-19 infection were included in the analyses. Secondary diagnoses included cardiovascular and cerebrovascular diseases, chronic kidney diseases, obstructive pulmonary disease (COPD), bronchial asthma, as well as diabetes and hypertension. These diagnoses were documented by the treating physician. Diabetes mellitus was defined by an elevated hemoglobin (Hb) A1c value of ≥ 6,5 % (≥ 48 mmol/mol) or prescribed anti-diabetic medication [21]. Hypertension was defined by > 130/80 mmHg or prescribed antihypertensive medication according to the International Society of Hypertension Guidelines [22]. Patients were admitted to pulmonary rehabilitation as soon as they were physically stable without the need of continuous supervision, invasive or non-invasive ventilation. They could be admitted after being tested negative twice by real-time polymerase chain reaction via swab. If patients terminated their stay before completing the three-week program or if admission and discharge measurements were incomplete, their data were excluded from analyses (see ▶ **Figure 1**).

After inclusion, patient's data were categorized according to Huang's COVID-19 severity scales (Huang, 2021):

Scale 1: not admitted to hospital before rehabilitation stay with resumption of normal activities

Scale 2: not admitted to hospital before rehabilitation stay, but unable to resume normal activities

Scale 3: admitted to hospital before rehabilitation stay and not requiring supplemental oxygen

Scale 4: admitted to hospital before rehabilitation stay, but requiring supplemental oxygen

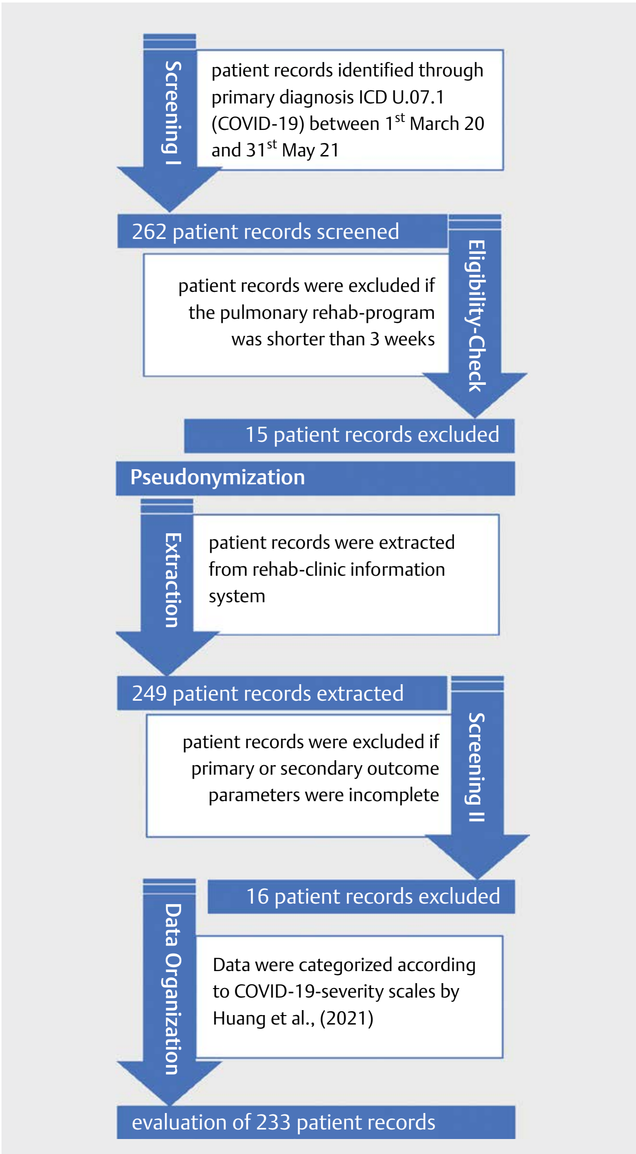
Scale 5: admitted to hospital before rehabilitation stay requiring high flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIV) or both

Scale 6: admitted to hospital before rehabilitation stay requiring extracorporeal membrane oxygenation, invasive mechanical ventilation (IMV) or both

Scale 7: death (not applicable)

Included Measurement Data

After their admission to rehabilitation, patients were assessed following a standardized clinical routine. As part of this clinical rou-



▶ **Fig. 1** Flow diagram of data extraction and processing.

tine, the Six-Minute Walk Test (6MWT) and pulmonary function testing were carried out at the beginning and at the end of the three-week rehabilitation stay. The 6MWT is a well-documented standardized assessment used to assess walking endurance and functional exercise capacity and has been used to assess the response to medical interventions in diverse patient groups [23]. It was executed by an experienced and well-instructed physiotherapy staff member according to the guidelines of the American Thoracic Society (ATS) [24]. 6MWT outcome values were compared to 6MWT reference values for recovered healthy adults according to Enright et al., [25]. The corresponding reference values for each participant were calculated according to reference equations for men: $6MWD = (7.57 \times height_{(cm)}) - (5.02 \times age_{(years)}) - (1.76 \times weight_{(kg)}) - 309\,m$; for women: $6MWD = (2.11 \times height_{(cm)}) - 2.29 \times weight_{(kg)}) - (5.78 \times age_{(years)}) + 667\,m$ [25]. The difference in pre and post measurements of the 6MWT were compared to the minimal clinically important difference across multiple patient groups [26] and to reference values for patients suffering from acute respiratory distress syndrome or having survived acute respiratory distress syndrome [27]. After the 6MWT, maximal inspiratory capacity (IC_{max}) was measured using a manometer connected to a PEP-RMT-System (Positive Expiratory Pressure- Respiratory Muscle Training- System) (Mediplast, Malmö, Sweden). Further pulmonary functions were tested using body-plethysmography (Master Screen Body, Traeger GmbH, Hoechberg, Germany). Measurements were carried out by an experienced physician according to recent updated guidelines by the ATS [28] and the European Respiratory Society (ERS) [29, 30].

Primary outcomes included the 6MWT, IC_{max} measured by the PEP-RMT-System as well as Forced Vital Capacity (FVC) and Forced Expiratory Volume in the first second (FEV_1) assessed by body-plethysmography. FVC and FEV_1 were compared to calculated reference values of body-plethysmography. Secondary outcomes included the number and type of exercise therapy sessions throughout the patients' rehabilitation visit.

Exercise Therapy Interventions

All post-acute COVID-19 patients admitted to pulmonary rehabilitation followed a standardized program with a duration of at least three weeks, including exercise therapy sessions on 5–6 weekdays. Each week, patients participated in a maximum of 3 exercise therapy sessions per day (Monday to Friday). The exercise therapy sessions consisted of individual respiratory muscle training, pulmonary group exercises, individual strength exercises (3 to 5 exercises for large muscle groups in three series of 8 to 12 repetitions per exercise with or without weight machines), individual endurance training (cycling, treadmill, in and outdoor walking) and relaxation group exercises. Intensities and intervals of endurance training were based on the results of the 6MWT performance. For respiratory muscle training, a hand-held resistance device was used (PEP-RMT-System, Mediplast, Malmö, Sweden) for 3 sets of 10 breaths each and a 1-min rest between sets. Each exercise session lasted for 30–45 min and was supervised by a exercise therapist or a physiotherapist. The amount and type of the group exercise therapy sessions and the amount of individual physiotherapy sessions were determined by the physicians in charge.

Statistical Analyses

Descriptive characteristics and secondary diagnoses of males and females were presented as mean with standard deviation or percentages. Spearman's rank correlations between COVID-19 severity and secondary diagnoses were calculated, as COVID-19 severity was categorized by the ordinally scaled COVID-19 Severity Scale (Huang et al., 2021). Spearman's rank correlations were also calculated between the number of respiratory muscle training sessions and lung function parameters (FEV_1, FVC and IC_{max}) as well as the 6MWT. For the comparison of functional exercise capacity (6MWT) and lung function parameters (FEV_1, FVC and IC_{max}) by sex, Welch-ANOVA was used, as results of Levene's test suggested significant heteroscedasticity regarding the investigated parameters ($p > 0.05$). When comparing post-treatment 6MWT, FEV_1 and FCV to corresponding reference values, paired t-tests were used.

Results

In total, 233 previously confirmed COVID-19 cases were included in the analyses i.e., 94 (40.4 %) females and 139 (59.6 %) males. The mean number of rehabilitation days was 21.51 (± 2.22) for females and 21.86 (± 3.75) for males with no significant differences between groups. Baseline characteristics such as body mass index (BMI), smoking status or comorbidities also did not differ significantly between groups as seen in ▶ **Table 1**. Considering the previous COVID-19 infection, females were significantly less affected by COVID-19 severity according to Huang's severity stages than males ($p = 0.004$). COVID-19 severity and the comorbidity of bronchial asthma exhibited a weak negative correlation ($r = -0.16$; $p < 0.05$), while cerebrovascular diseases showed a weak positive correlation with COVID-19 severity ($r = 0.16$; $p < 0.05$). No further significant correlations between secondary diagnoses and COVID-19 severity were found (all $p > 0.05$). Furthermore, neither smoking status nor overweight or obesity ($BMI \geq 25\,kg/m^2$) was significantly associated with a more severe COVID-19 history ($p > 0.05$). Details about the COVID-19 severity, patients' characteristics and secondary diagnoses are shown in ▶ **Table 1**.

Exercise Therapy Sessions

Within the 3 weeks of pulmonary rehabilitation, females completed an average of 34.29 and males an average of 35.23 exercise therapy sessions, with no significant differences between sexes ($p = 0.284$). The different types of exercise therapy (i.e. strength, endurance and relaxation exercises and respiratory muscle training) were equally distributed between sexes, except for a trend ($p = 0.056$) in males receiving more sessions of respiratory muscle training when compared to females. A detailed description of exericse therapy sessions is provided in ▶ **Table 2.** Additionally, females received 6.88 and males 7.42 individual physiotherapy sessions on average. No significant correlations were found between the number of respiratory muscle training sessions and lung function parameters (FEV_1, FVC and IC_{max}) as well as the 6MWT (all $p > 0.05$).

Six-Minute Walk Test

Both males and females showed a statistically significant improvement in walking distance after the 3 week rehabilitation ($T(232) = -16.67$; $p < 0.001$; $d = 0.48$). The difference was not sex dependent

▶ **Table 1** Comparison of descriptive measures of patients by sex

Category	**Females (n = 94)**		**Males (n = 139)**		**T(df)**	**p**
	M	**SD**	**M**	**SD**		
Age (years)	61.50	12.81	61.69	11.55	− 0.12(231)	NS
Weight difference (kg)				− 0.58	1.49	− 0.36
BMI_{Pre} (kg/m^2)	29.10	7.04	28.47	5.09	0.73(153.77)	NS
BMI_{Post} (kg/m^2)	28.93	6.91	28.39	5.00	0.65(152.01)	NS
	Females (n = 94)		Males (n = 139)		χ^2(df)	p
	M	%	M	%		
Smoking status					2.61(2)	NS
Non-smoker	51	54.26	63	45.32		
Current smoker	2	2.13	1	0.72		
Former smoker	40	42.55	71	51.08		
Comorbidities						
Hypertension	37	39.4	72	51.8	3.48(1)	NS
Diabetes	38	40.4	65	46.76	0.91(1)	NS
Cardiovascular disease	35	37.2	55	39.57	0.13(1)	NS
Cerebrovascular disease	6	6.4	7	5.04	0.19(1)	NS
COPD	9	9.6	9	6.47	0.76(1)	NS
Bronchial asthma	17	18.1	17	12.23	1.54(1)	NS
Chronic kidney disease	7	7.4	13	9.35	0.26(1)	NS
COVID-19 Severity Scale *					15.63(4)	0.004
Scale 2	35	37.2	28	20.14		
Scale 3	28	29.8	30	21.58		
Scale 4	10	10.6	20	14.39		
Scale 5	9	9.6	28	20.14		
Scale 6	12	12.8	33	23.74		

Notes. BMI_{Pre} = Body Mass Index at rehabilitation entry, BMI_{Post} = Body Mass Index at rehabilitation discharge; M (SD) = mean ± standard deviation; T(df) = t-distribution with degrees of freedom; NS = level of significance > 0.05; χ^2(df) = chi-square value with degrees of freedom; COPD = Chronic Obstructive Pulmonary Disease; * defined as Scale 2 = not admitted to hospital before rehabilitation stay, but unable to resume normal activities; Scale 3 = admitted to hospital before rehabilitation stay and not requiring supplemental oxygen; Scale 4 = admitted to hospital before rehabilitation stay but requiring supplemental oxygen; Scale 5 = admitted to hospital before rehabilitation stay requiring HFNC, NIV or both; Scale 6 = admitted to hospital before rehabilitation stay requiring invasive mechanical ventilation.

▶ **Table 2** Number of exercise therapy sessions by females and males

		Female (n = 94)	**Male (n = 139)**
Respiratory muscle exercise *	M (SD)	6.82 (± 2.08)	7.39 (± 2.31)
Pulmonary group exercise	M (SD)	6.37 (± 2.60)	6.71 (± 2.57)
Strength exercise	M (SD)	6.40 (± 2.79)	6.18 (± 2.77)
Endurance exercise	M (SD)	9.84 (± 3.49)	10.38 (± 2.67)
Relaxation exercise	M (SD)	4.85 (± 1.89)	4.58 (± 2.13)
All training therapy sessions	M (SD)	34.29 (± 7.74)	35.23 (± 5.66)

Notes. * T(df) = –1.92(231), p = 0.056; M (SD) = mean ± standard deviation

($p > .05$; see ▶ **Table 3**). When comparing the 6-minute walking distance (6MWD) at rehabilitation discharge to corresponding reference values for healthy persons (Enright et al., 1998), males showed significantly reduced walking distances compared to females ($T(231) = –3.04$; $p < 0.01$; $d = 0.41$). In correspondence to that, males exhibited an actual average distance of 498.08 meters (m) vs. a reference average distance of 573.66 m ($p < 0.01$), as compared to female patients whose actual and reference [6]MWD values were not significantly different (average 477.29 m vs. 493.93 m; $p = 0.259$).

Lung Function Testing

Both male and female patients improved their maximal inspiration capacity (IC_{max}) during the three weeks of rehabilitation ($T(229) = 15.972$; $p < 0.001$; $d = 1.05$), however, the improvement was significantly superior in males as compared to females ($F(1,227.46) = 8.93$; $p > 0.01$; $\omega^2 = 0.03$). While no sex-related differences were found regarding the ratio of FEV_1/FVC ($p > 0.05$), male patients exhibited higher pre ($F(1,226.52) = 56.68$, $p < 0.001$; $\omega^2 = 0.24$) and post treatment FVC ($F(1,226.43) = 69.47$; $p < 0.001$; $\omega^2 = 0.29$;). However, no significant sex-interaction was observed ($p > 0.05$). Similarly, the results suggested higher pre ($F(1,223.33) = 51.47$; $p < 0.001$; $\omega^2 = 0.22$) as well as post treatment FEV_1 ($F(1,228.26) = 69.80$; $p < 0.001$; $\omega^2 = 0.30$) in males compared to females. Moreover, female patients showed a significantly smaller difference regarding the improvement in FEV_1 than males ($F(1,230.81) = 5.86$; $p < 0.05$; $\omega^2 = 0.02$ see ▶ **Figure 2**). The results of primary outcome measures are detailed in ▶ **Table 3**.

Compared to individual corresponding reference values, patients showed significantly reduced FVC (pretreatment: $T(232) = –11.19$; $p < 0.001$; $d = 0.73$; posttreatment: $T(232) = –4.05$; $p < 0.001$; $d = 0.27$) and FEV_1 (pretreatment: $T(232) = -10.22$; $p < 0.001$; $d = 0.67$; posttreatment: $T(232) = –7.00$; $p < 0.001$; $d = 0.46$) before and after the three-week rehabilitation program.

While there was no sex-related difference in posttreatment FVC ($p > 0.05$), female patients exhibited significantly lower differences between actual and corresponding reference values regarding pretreatment FVC ($T(228.51) = 5.05$; $p < 0.001$; $d = 0.67$) and pre- as well as posttreatment FEV_1 (pretreatment: $T(228.85) = 4.36$; $p < 0.001$; $d = 0.58$; posttreatment: $T(231) = 2.83$; $p < 0.01$; $d = 0.38$). Details about FEV_1 reference value and actual value changes are shown in ▶ **Figure 3**.

Discussion

This study highlights sex disparities in positive outcomes of lung function parameters after a standardized 3-week pulmonary rehabilitation in a cohort of 233 post-acute COVID-19 patients. Male patients showed significantly greater improvements in specific lung function parameters i.e. FEV_1 and IC_{max} than female patients. Furthermore, values from female patients corresponded more closely with FEV_1 normative values than male patients.

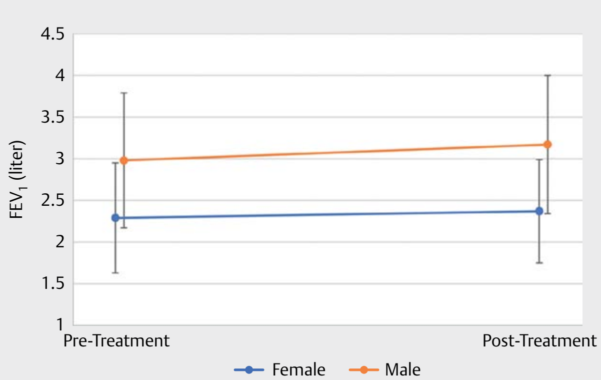
These sex disparities could be associated with the clinical representation of the investigated COVID-19 cohort. Male patients were significantly more affected by COVID-19 during their acute hospital stay prior to pulmonary rehabilitation than female patients, matching the results of other studies that have investigated COVID-19 hospital cohorts [2, 3, 31]. As a possible consequence, baseline FEV_1 and FVC values in men were poorer than those of women prior to their rehabilitation, with respect to individual normative values. As a possible consequence, specifically respiratory exercise sessions could have been enhanced in male patients as part of exercise therapy interventions compared to female patients which might have contributed to their greater improvements. Furthermore, standardized exercise therapy interventions in pulmonary rehabilitation might have had a greater effect in men as compared to women, due to a standard exercise principle: there is a greater likelihood of a pulmonary function improvement during a training period in the more untrained and the more disease affected people than in the more trained and less disease affected cohort, respectively [32]. A similar effect could also be observed by others showing greater improvements in patients with higher hyperglycaemia or hypertension levels at baseline after lifestyle interventions as compared to those with lower levels at baseline [33]. Furthermore, skeletal muscle mass, physical fitness as well as the amount of physical activity could represent confounding variables which positively influence exercise training outcomes as recently shown in a SARS-CoV-2-positive study population of athletes [34] In addition, patients with comorbidities such as chronic obstructive pulmonary disease (COPD) and bronchial asthma are suggested to lead to reduced values of FEV_1 and IC_{max}. However, in our study cohort, the same number of women (n = 9) and men (n = 9) were affected by these comorbidities, which possibly hampered the evaluation of sex differences.

Further, morphological differences between men and women need to be considered when interpreting the greater improvement in FEV_1 and IC_{max} in men. Smaller lung size and proportionally smaller airways in women, as well as different size and shapes of the lung and rib cage tend to lead to functional differences. For example, an expiratory flow limitation and greater cost of breathing has been observed during exercise in women, including particular activation of inspiratory muscles [35, 36]. At a given minute ventilation women have to perform greater respiratory work due to smaller airways, which may also induce different patterns of respiratory muscle activation in order to distribute the ventilation load [37]. Therefore, muscles such as sternocleidomastoid or the scalene muscles could be activated to a greater extent by women in order

▶ **Table 3** Sex differences (Welch-ANOVA) in outcome measures.

Measures	**Female (n = 94)**		**Male (n = 139)**		**F**	**df**		**ω²**	**p**
	M	**SD**	**M**	**SD**					
6MWT									
Pre	405.80	134.70	435.47	153.19	2.43	1,	215.65	–	0.14
Post	477.29	130.76	498.08	148.55	1.27	1,	215.53	–	0.32
Difference	71.49	69.75	62.61	53.50	1.09	1,	164.21	–	0.33
FVC									
Pre	2.80	0.77	3.68	1.00	56.68	1,	226.52	0.24	0.00
Post	2.95	0.76	3.90	0.98	69.47	1,	226.43	0.29	0.00
Difference	0.14	0.35	0.22	0.46	2.03	1,	228.15	–	0.17
FEV_1									
Pre	2.29	0.66	2.98	0.81	51.47	1,	223.33	0.22	0.00
Post	2.37	0.62	3.17	0.83	69.80	1,	228.26	0.30	0.00
Difference	0.09	0.25	0.19	0.39	5.86	1,	230.81	0.02	0.02
FEV_1/FVC									
Pre	82.42	0.04	81.72	9.57	0.25	1,	180.45	–	0.62
Post	80.82	0.04	81.67	10.17	0.30	1,	154.74	–	0.59
Difference	1.60	0.04	0.04	13.22	1.39	1,	145.93	–	0.24
IC_{max}	Female (n = 94)		Male (n = 136)						
Pre	33.09	13.78	50.06	20.69	55.75	1,	227.72	0.24	0.00
Post	49.02	19.03	72.99	24.34	69.99	1,	224.48	0.30	0.00
Difference	15.94	14.07	22.93	21.44	8.93	1,	227.46	0.03	0.00

Notes. 6MWT = Six-Minute-Walk Test in meters; FVC = Forced vital capacity in liters; FEV_1 = Forced expiratory volume in the first second in liters; IC_{max} = maximal inspiration capacity in mbar; pre = measures at rehabilitation admission; post = measures at rehabilitation discharge

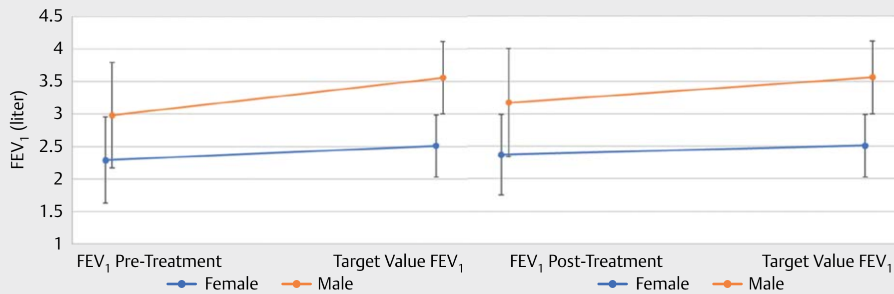


▶ **Fig. 2** Changes in FEV_1 values at rehabilitation entry and discharge in female and male patients. Legend: FEV_1 (liter) = forced expiratory volume in the first second; pre-treatment: measurement before start of rehabilitation; post-treatment: measurement at the end of rehabilitation

to assist the diaphragm work. This might result in less efficient general activation of respiratory muscles as well as to a conditioned response to respiratory muscle exercise [37, 38]. However, these functional implications of sex differences in respiratory muscle activation remain to be fully investigated [35].

In this regard, the trend of a greater number of respiratory muscle exercise sessions in men has to be mentioned. The overall number of exercise therapy sessions did not differ between sexes however. A reason for this uneven, yet not significantly different distribution could be the greater need of respiratory muscle exercise in men, due to their more severe COVID-19 symptoms when compared to women. In inpatient pulmonary rehabilitation, an individual approach is primarily used, with applying exercise programs as needed by each patient for their individual physical improvement [15, 16]. The significant FEV_1 and non-significant FVC improvement only in men could be related to the previous finding of a significant FEV_1 reduction in patients with cardiorespiratory pathologies; for these diseases, a higher prevalence has been reported in males compared to females [8, 39]. However, the present COVID-19 patient male and female cohort were similar with regard to pre-existing cardiorespiratory pathologies.

The significant improvement in the 6MWT as a performance measure of exercise capacity in both sexes was in line with Liu et al., and Spielmanns et al., who reported similar improvements in severe post-COVID-19 patients and elderly patients with COVID-19 [17, 18]. The majority of investigated patients of this study's cohort exceeded the threshold of 54 m for a clinically significant change, as well as the newly proposed 14 to 30.5 m across multiple patient groups [26, 40]. For patients suffering from acute respiratory distress syndrome or survivors of acute respiratory distress syndrome, a minimal clinically important difference (MCID) of 20 to 30 m was proposed [27]. However, when the 6MWD was compared to corresponding normative



▶ **Fig. 3** Comparison of actual pre-/post-treatment FEV_1 values and reference FEV_1 values for female and male patients. Legend: FEV_1 (liter) = forced expiratory volume in the first second; pre-treatment: measurement before start of rehabilitation and post-treatment: measurement at the end of rehabilitation; target values: calculated from body-plethysmography

values for healthy people [25] at rehabilitation discharge, there was a discrepancy between male and female patients, with significantly poorer walking endurance in males. From this could be derived that it is women rather than men who may be closer to a healthy status of functional exercise capacity after a three-week pulmonary rehabilitation program.

The effectiveness of a three to six-week standardized pulmonary rehabilitation after COVID-19 has been shown in previous studies and the number and type of comorbidities of this study's COVID-19 patient cohort are in line with others, as well as the improvement of total values of lung function parameters [17, 18, 41, 42]. Despite the demonstrated effectiveness, the failure of lung function parameters and functional exercise capacity reaching normative values at rehabilitation discharge majorly underlines the necessity of long-lasting pulmonary rehabilitation in former COVID-19 patients. The usual publicly financed time frame for inpatient pulmonary rehabilitation in Austria does not exceed five to six weeks [43]. Further gains in lung function and exercise capacity could probably be promoted through longer pulmonary rehabilitation programs offered in health care settings.

We acknowledge that the present study has several limitations. First, we cannot report on the causality of the observed findings due to the observational study design. Second, caution is advised when claiming an overall improvement in lung function parameters and functional exercise capacity without an appropriate non-COVID-19 control group. The main focus of this study is the inter-subject comparison between sexes. Third, we cannot exclude an impact of additional medical treatment measures on the outcome of functional exercise capacity and lung function parameters in regard to the multidisciplinary rehabilitation plan. Fourth, it was not possible to extract and interpret diffusion capacity of the lungs due to missing data, associated with the nature of retrospective data collection. Additionally, baseline characteristics such as diet, alcohol consumption, HbA1c values and current as well as past physical activity levels limit the description of the study population. It has been shown that promoting physical activity in COVID-19 patients is connected to more positive outcomes, therefore the physcial activity behavior should be regarded when assessing future clinical populations [44]. This study exclusively investigated physical function of rehabilitated COVID-19 patients whereas psychological aspects such as quality of life could not be evaluated, which contribute essentially to the recovery of COVID-19 [45, 46]. Finally, long-term results of inpatient pulmonary rehabilitation on sex differences cannot be derived from this data.

In summary, pulmonary rehabilitation programs have shown to be beneficial in the recovery from COVID-19, however, men appear to benefit more than women, with respect to particular lung function parameters (FEV_1 and IC_{max}). Furthermore, women who previously suffered from COVID-19 and subsequently underwent rehabilitation treatment, seem to have better lung function parameters and functional exercise capacity than men compared to corresponding reference values. This knowledge could be of importance when designing pulmonary rehabilitation programs or when conducting respiratory muscle exercise sessions in a group setting, where an individual approach to each patient cannot be as guaranteed as in an one-on-one exercise session. However, further studies are needed to explore the effects of pulmonary rehabilitation programs for both sexes in the long-term. Therefore, a follow-up study from the same cohort will be conducted including former COVID-19 patients after six months of their rehabilitation stay.

Acknowledgements

We want to thank employees of the Rehab Clinic Muenster under the leadership of Dr. Christian Brenneis for the cooperation and technical support in retreiving the data.

Funding

The study is supported by the Early-Stage-Funding-Program of the University of Innsbruck financing travel expenses to and from the Clinic for Rehabilitation in Münster, Austria.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020; 91: 157–160. doi:10.23750/abm.v91i1.9397

[2] Richardson S, Hirsch JS, Narasimhan M et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 2020; 323: 2052–2059. doi:10.1001/jama.2020.6775

[3] Grasselli G, Zangrillo A, Zanella A et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020; 323: 1574–1581. doi:10.1001/jama.2020.5394

[4] Guan W-J, Ni Z-Y, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708–1720. doi:10.1056/NEJMoa2002032

[5] Nasiri MJ, Haddadi S, Tahvildari A et al. COVID-19 clinical characteristics, and sex-specific risk of mortality: systematic review and meta-analysis. Front Med (Lausanne) 2020; 7: 459. doi:10.3389/fmed.2020.00459

[6] Mauvais-Jarvis F. Aging, male sex, obesity, and metabolic inflammation create the perfect storm for COVID-19. Diabetes 2020; 69: 1857–1863. doi:10.2337/dbi19-0023

[7] Alberca RW, Oliveira LdMBranco, Anna Cláudia Calvielli Castelo et al. Obesity as a risk factor for COVID-19: an overview. Crit Rev Food Sci Nutr 2021; 61: 2262–2276. doi:10.1080/10408398.2020.1775546

[8] Banfi P, Garuti G, Diaz de Teran T et al. Differences between sexes concerning COVID-19-related pneumonia. Panminerva Med 2021. Online ahead of print. doi:10.23736/S0031-0808.21.04165-3

[9] Capuano A, Rossi F, Paolisso G. Covid-19 kills more men than women: an overview of possible reasons. Front Cardiovasc Med 2020; 7: 131. doi:10.3389/fcvm.2020.00131

[10] Channappanavar R, Fett C, Mack M et al. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol 2017; 198: 4046–4053. doi:10.4049/jimmunol.1601896

[11] Elgendy IY, Pepine CJ. Why are women better protected from COVID-19: Clues for men? Sex and COVID-19. Int J Cardiol 2020; 315: 105–106. doi:10.1016/j.ijcard.2020.05.026

[12] Huang C, Huang L, Wang Y et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220–232. doi:10.1016/S0140-6736(20)32656-8

[13] Huang L, Yao Q, Gu X et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet 2021; 398: 747–758. doi:10.1016/S0140-6736(21)01755-4

[14] Simpson R, Robinson L. Rehabilitation after critical illness in people with COVID-19 infection. Am J Phys Med Rehabil 2020; 99: 470–474. doi:10.1097/PHM.0000000000001443

[15] Sonnweber T, Sahanic S, Pizzini A et al. Cardiopulmonary recovery after COVID-19 – an observational prospective multi-center trial. Eur Respir J 2020; 57: 200–214. doi:10.1183/13993003.03481-2020

[16] Puchner B, Sahanic S, Kirchmair R et al. Beneficial effects of multi-disciplinary rehabilitation in post-acute COVID-19 – an observational cohort study. Eur J Phys Rehabil Med 2021; 57: 189–198. doi:10.23736/S1973-9087.21.06549-7

[17] Spielmanns M, Pekacka-Egli A-M, Schoendorf S et al. Effects of a comprehensive pulmonary rehabilitation in severe post-COVID-19 patients. Int J Environ Res Public Health 2021; 18: 26–35. doi:10.3390/ijerph18052695

[18] Liu K, Zhang W, Yang Y et al. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Clin Pract 2020; 39: 101–166. doi:10.1016/j.ctcp.2020.101166

[19] Quaresima V, Scarpazza C, Sottini A et al. Sex differences in a cohort of COVID-19 Italian patients hospitalized during the first and second pandemic waves. Biol Sex Differ 2021; 12: 45. doi:10.1186/s13293-021-00386-z

[20] Yoshida Y, Gillet SA, Brown MI et al. Clinical characteristics and outcomes in women and men hospitalized for coronavirus disease 2019 in New Orleans. Biol Sex Differ 2021; 12: 20. doi:10.1186/s13293-021-00359-2

[21] Unwin N, Shaw J, Zimmet P, Alberti K G M M. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabet Med 2002; 19: 708–723. doi:10.1046/j.1464-5491.2002.00835.x

[22] Mancia G, Dominiczak A. The new international society of hypertension guidelines on hypertension. J Hypertens 2020; 38: 981. doi:10.1097/HJH.0000000000002490

[23] Mänttäri A, Suni J, Sievänen H et al. Six-minute walk test: a tool for predicting maximal aerobic power (VO(2) max) in healthy adults. Clin Physiol Funct Imaging 2018. Online ahead of print. doi:10.1111/cpf.12525

[24] ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111–117. doi:10.1164/ajrccm.166.1.at1102

[25] Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998; 158: 1384–1387. doi:10.1164/ajrccm.158.5.9710086

[26] Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. J Eval Clin Pract 2017; 23: 377–381. doi:10.1111/jep.12629

[27] Chan KS, Pfoh ER, Denehy L et al. Construct validity and minimal important difference of 6-minute walk distance in survivors of acute respiratory failure. Chest 2015; 147: 1316–1326. doi:10.1378/chest.14-1808

[28] McCormack MC, Bascom R, Brandt M et al. Electronic health records and pulmonary function data: developing an interoperability roadmap. An official American Thoracic Society workshop Report. Ann Am Thorac Soc 2021; 18: 1–11. doi:10.1513/AnnalsATS.202010-1318ST

[29] Graham BL, Steenbruggen I, Miller MR et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019; 200: 70–88. doi:10.1164/rccm.201908-1590ST

[30] Quanjer PH, Stanojevic S, Cole TJ et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40: 1324–1343. doi:10.1183/09031936.00080312

[31] Sha J, Qie G, Yao Q et al. Sex differences on clinical characteristics, severity, and mortality in adult patients with COVID-19: a multicentre retrospective study. Front Med (Lausanne) 2021; 8: 60–70. doi:10.3389/fmed.2021.607059

[32] Segizbaeva MO, Aleksandrova NP. Respiratory muscle strength and ventilatory function outcome: differences between trained athletes and healthy untrained persons. Adv Exp Med Biol 2021; 1289: 89–97. doi:10.1007/5584_2020_554

[33] Myers J, Kokkinos P, Nyelin E. Physical activity, cardiorespiratory fitness, and the metabolic syndrome. Nutrients 2019; 11: 1652. doi:10.3390/nu11071652

[34] Siopis G. Elite athletes maintain peak performance after testing positive for SARS-CoV-2. J Sci Med Sport 2022; 25: 195–196. doi:10.1016/j.jsams.2021.08.010

[35] Dominelli PB, Molgat-Seon Y, Sheel AW. Sex differences in the pulmonary system influence the integrative response to exercise. Exerc Sport Sci Rev 2019; 47: 142–150. doi:10.1249/JES.0000000000000188

[36] Torres-Tamayo N, García-Martínez D, Lois Zlolniski S et al. 3D analysis of sexual dimorphism in size, shape and breathing kinematics of human lungs. J Anat 2018; 232: 227–237. doi:10.1111/joa.12743

[37] Molgat-Seon Y, Dominelli PB, Ramsook AH et al. Effects of age and sex on inspiratory muscle activation patterns during exercise. Med Sci Sports Exerc 2018; 50: 1882–1891. doi:10.1249/MSS.0000000000001648

[38] Mitchell RA, Schaeffer MR, Ramsook AH et al. Sex differences in respiratory muscle activation patterns during high-intensity exercise in healthy humans. Respir Physiol Neurobiol 2018; 247: 57–60. doi:10.1016/j.resp.2017.09.002

[39] Wang B, Zhou Y, Xiao L et al. Association of lung function with cardiovascular risk: a cohort study. Respir Res 2018; 19: 214. doi:10.1186/s12931-018-0920-y

[40] Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997; 155: 1278–1282. doi:10.1164/ajrccm.155.4.9105067

[41] Hayden MC, Limbach M, Schuler M et al. Effectiveness of a three-week inpatient pulmonary rehabilitation program for patients after COVID-19: a prospective observational Study. Int J Environ Res Public Health 2021; 18: 9001. doi:10.3390/ijerph18179001

[42] Maniscalco M, Fuschillo S, Ambrosino P et al. Preexisting cardiorespiratory comorbidity does not preclude the success of multidisciplinary rehabilitation in post-COVID-19 patients. Respir Med 2021; 184: 106–470. doi:10.1016/j.rmed.2021.106470

[43] Glöckl R, Buhr-Schinner H, Koczulla AR et al. Recommendations from the German Respiratory Society for Pulmonary Rehabilitation in patients with COVID-19. DGP-Empfehlungen zur pneumologischen Rehabilitation bei COVID-19. Pneumologie 2020; 74: 496–504. doi:10.1055/a-1193-9315

[44] Siopis G. The case for promoting physical activity amidst the COVID-19 pandemic. An update. J Sci Med Sport 2021; 24: 900–901. doi:10.1016/j.jsams.2021.03.014

[45] Barker-Davies RM, O'Sullivan O, Senaratne KPP et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med 2020; 54: 949–959. doi:10.1136/bjsports-2020-102596

[46] Wang TJ, Chau B, Lui M et al. Physical medicine and rehabilitation and pulmonary rehabilitation for COVID-19. Am J Phys Med Rehabil 2020; 99: 769–774. doi:10.1097/PHM.0000000000001505