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

Authors

Linda Rausch1, Bernhard Puchner2, Jürgen Fuchshuber3, 4, Barbara Seebacher2, Judith Löffler-Ragg5, Stephan Pramsohler6, Nikolaus Netzer6, 7, 8, Martin Faulhaber1

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

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, ω² = .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-
Rausch L et al. The Effects of Exercise ... Int J Sports Med 2022; 43: 1043–1051 | © 2022. The Author(s)

... weight(kg)) – 309 m; for women: 6MWD = (2.11 x height(cm)) – 2.29

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

... weight(kg)) – (5.78 x age(years)) = (1.76 x weight(kg)) – 309 m; for women: 6MWD = (2.11 x height(cm)) – 2.29

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-

... weight(kg)) – (5.02 x age (years) ) – (1.76 x height(cm) – (7.57 x

The difference in pre and post measurements of the 6MWT were compared to the min-
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 ≥ 25 kg/m²) 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 exercise 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 (FEV₁, FVC and IC\text{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

<table>
<thead>
<tr>
<th>Category</th>
<th>Females (n=94)</th>
<th>Males (n=139)</th>
<th>T(df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>M = 61.50</td>
<td>M = 61.69</td>
<td>−0.12(231)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight difference (kg)</td>
<td></td>
<td>−0.58</td>
<td>1.49</td>
<td>−0.36</td>
</tr>
<tr>
<td>BMI\text{pre} (kg/m²)</td>
<td>29.10</td>
<td>28.47</td>
<td>0.73(153.77)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI\text{post} (kg/m²)</td>
<td>28.93</td>
<td>28.39</td>
<td>0.65(152.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>2.61(2)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>51</td>
<td>63</td>
<td>45.32</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>2</td>
<td>1</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>40</td>
<td>71</td>
<td>51.08</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37</td>
<td>72</td>
<td>51.8</td>
<td>3.48(1) NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38</td>
<td>65</td>
<td>46.76</td>
<td>0.91(1) NS</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>35</td>
<td>55</td>
<td>39.57</td>
<td>0.13(1) NS</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6</td>
<td>7</td>
<td>5.04</td>
<td>0.19(1) NS</td>
</tr>
<tr>
<td>COPD</td>
<td>9</td>
<td>9</td>
<td>6.47</td>
<td>0.76(1) NS</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>17</td>
<td>17</td>
<td>12.23</td>
<td>1.54(1) NS</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>7</td>
<td>13</td>
<td>9.35</td>
<td>0.26(1) NS</td>
</tr>
<tr>
<td>COVID-19 Severity Scale*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale 2</td>
<td>35</td>
<td>28</td>
<td>20.14</td>
<td></td>
</tr>
<tr>
<td>Scale 3</td>
<td>28</td>
<td>30</td>
<td>21.58</td>
<td></td>
</tr>
<tr>
<td>Scale 4</td>
<td>10</td>
<td>20</td>
<td>14.39</td>
<td></td>
</tr>
<tr>
<td>Scale 5</td>
<td>9</td>
<td>28</td>
<td>20.14</td>
<td></td>
</tr>
<tr>
<td>Scale 6</td>
<td>12</td>
<td>33</td>
<td>23.74</td>
<td></td>
</tr>
</tbody>
</table>

Notes. BM\text{Pre} = Body Mass Index at rehabilitation entry, BM\text{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; χ²(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 but 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.
Lung Function Testing

Both male and female patients improved their maximal inspiration capacity (IC$_{\text{max}}$) during the three weeks of rehabilitation (T (229) = 15.97; p < 0.001; d = 1.05), however, the improvement was significantly superior in males as 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).

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

<table>
<thead>
<tr>
<th>Exercise Type</th>
<th>Female (n = 94)</th>
<th>Male (n = 139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory muscle</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>exercise *</td>
<td>6.82 (+ 2.08)</td>
<td>7.39 (+ 2.31)</td>
</tr>
<tr>
<td>Pulmonary group</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td>exercise</td>
<td>6.37 (+ 2.60)</td>
<td>6.71 (+ 2.57)</td>
</tr>
<tr>
<td>Strength exercise</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.40 (+ 2.79)</td>
<td>6.18 (+ 2.77)</td>
</tr>
<tr>
<td>Endurance exercise</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.84 (+ 3.49)</td>
<td>10.38 (+ 2.67)</td>
</tr>
<tr>
<td>Relaxation exercise</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.85 (+ 1.89)</td>
<td>4.58 (+ 2.13)</td>
</tr>
<tr>
<td>All training sessions</td>
<td>M (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34.29 (+ 7.74)</td>
<td>35.23 (+ 5.66)</td>
</tr>
</tbody>
</table>

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).

**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$_{\text{max}}$ 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$_{\text{max}}$. 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$_{\text{max}}$ 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...
to assist the diaphragm work. This might result in less efficient gene-
ral activation of respiratory muscles as well as to a conditioned re-
response to respiratory muscle exercise [37, 38]. However, these
functional implications of sex differences in respiratory muscle ac-
tivation remain to be fully investigated [35].

In this regard, the trend of a greater number of respiratory mus-
cle exercise sessions in men has to be mentioned. The overall num-
ber of exercise therapy sessions did not differ between sexes how-
ever. A reason for this uneven, yet not significantly different distri-
bution could be the greater need of respiratory muscle exercise in
men, due to their more severe COVID-19 symptoms when com-
pared to women. In inpatient pulmonary rehabilitation, an individ-
ual 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 pa-
tient male and female cohort were similar with regard to pre-exist-
ing cardiorespiratory pathologies.

The significant improvement in the 6MWT as a performance meas-
ure 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]. How-
ever, when the 6MWD was compared to corresponding normative

---

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

<table>
<thead>
<tr>
<th>Measures</th>
<th>Female (n = 94)</th>
<th>Male (n = 139)</th>
<th>F</th>
<th>df</th>
<th>ω²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>405.80</td>
<td>435.47</td>
<td>2.43</td>
<td>1</td>
<td>215.65</td>
<td>0.14</td>
</tr>
<tr>
<td>Post</td>
<td>477.29</td>
<td>498.08</td>
<td>1.27</td>
<td>1</td>
<td>215.53</td>
<td>0.29</td>
</tr>
<tr>
<td>Difference</td>
<td>71.49</td>
<td>62.61</td>
<td>1.09</td>
<td>1</td>
<td>164.21</td>
<td>0.33</td>
</tr>
<tr>
<td>FVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.80</td>
<td>3.68</td>
<td>1.00</td>
<td>1</td>
<td>56.68</td>
<td>0.24</td>
</tr>
<tr>
<td>Post</td>
<td>2.95</td>
<td>3.90</td>
<td>0.98</td>
<td>1</td>
<td>69.47</td>
<td>0.29</td>
</tr>
<tr>
<td>Difference</td>
<td>0.14</td>
<td>0.22</td>
<td>0.46</td>
<td>1</td>
<td>2.03</td>
<td>0.17</td>
</tr>
<tr>
<td>FEV₁</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.29</td>
<td>2.98</td>
<td>0.81</td>
<td>1</td>
<td>51.47</td>
<td>0.22</td>
</tr>
<tr>
<td>Post</td>
<td>2.37</td>
<td>3.17</td>
<td>0.83</td>
<td>1</td>
<td>69.80</td>
<td>0.30</td>
</tr>
<tr>
<td>Difference</td>
<td>0.09</td>
<td>0.19</td>
<td>0.39</td>
<td>1</td>
<td>5.86</td>
<td>0.02</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>82.42</td>
<td>81.72</td>
<td>9.57</td>
<td>1</td>
<td>180.45</td>
<td>0.62</td>
</tr>
<tr>
<td>Post</td>
<td>80.82</td>
<td>81.67</td>
<td>10.17</td>
<td>1</td>
<td>154.74</td>
<td>0.59</td>
</tr>
<tr>
<td>Difference</td>
<td>1.60</td>
<td>13.22</td>
<td>1.39</td>
<td>1</td>
<td>145.93</td>
<td>0.24</td>
</tr>
<tr>
<td>Icmax</td>
<td>Female (n = 94)</td>
<td>Male (n = 136)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>33.09</td>
<td>50.06</td>
<td>20.69</td>
<td>1</td>
<td>55.75</td>
<td>0.24</td>
</tr>
<tr>
<td>Post</td>
<td>49.02</td>
<td>72.99</td>
<td>24.34</td>
<td>1</td>
<td>69.99</td>
<td>0.30</td>
</tr>
<tr>
<td>Difference</td>
<td>15.94</td>
<td>22.93</td>
<td>21.44</td>
<td>1</td>
<td>8.93</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Notes. 6MWT = Six-Minute-Walk Test in meters; FVC = Forced vital capacity in liters; FEV₁ = Forced expiratory volume in the first second in liters; Icmax = maximal inspiration capacity in mbar; pre = measures at rehabilitation admission; post = measures at rehabilitation discharge

---

**Fig. 2** Changes in FEV₁ values at rehabilitation entry and dis-
charge in female and male patients. Legend: FEV₁ (liter) = forced
expiratory volume in the first second; pre-treatment: measurement
before start of rehabilitation; post-treatment: measurement at the
derend of rehabilitation

---

**Fig. 3** Table 3 Sex differences (Welch-ANOVA) in outcome measures.
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 intersubject 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 physical 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 retrieving 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


