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Comparison of the exercise capacity, respiratory muscle strength, pulmonary function, muscle oxygenation, and dyspnea in patients with post-COVID-19 syndrome with mild and moderate functional limitations

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Abstract:

BACKGROUND AND AIM: Hypoxia, dyspnea, and respiratory function abnormalities take place in patients following coronavirus disease 2019 (COVID-19) due to pulmonary involvement. Moreover, abnormalities in skeletal and respiratory muscles negatively affect exercise capacity. In this study, exercise capacity, respiratory and peripheral muscle strength, pulmonary function, muscle oxygenation, and dyspnea were compared in patients with mild and moderate functional limitations who had post-COVID-19 syndrome.

METHODS: In this study, patients with moderate functional limitations with post-COVID-19 syndrome were included on the basis of the Post-COVID-19 Functional Status Scale (PCFS) score 2 mild (n=15) and PCFS score 3 (n=20). Respiratory muscle strength (mouth pressure device), exercise capacity (6-min walk test [6-MWT)], pulmonary function (spirometry), peripheral muscle strength (dynamometer) and muscle oxygenation (Moxy® device), dyspnea during daily living activity [London Chest Activity of Daily Living Scale [LCADL)] were evaluated.

RESULTS: Patients with moderate functional limitations with post-COVID-19 syndrome had statistically lower maximal inspiratory and expiratory pressures, 6-MWT distance, and pulmonary function parameters (peak expiratory flow, forced expiratory flow 25%–75%) when compared to those with mild functional limitations ($p<0.05$). Muscle oxygen saturation, quadriceps femoris muscle strength, LCADL total, and all sub-parameters scores were similar in both groups ($p>0.05$).

CONCLUSIONS: Patients with post-COVID-19 syndrome with moderate functional limitations have less respiratory muscle strength, exercise capacity, and more exertional dyspnea and airway obstruction than those with mild functional limitations. The effects on muscle oxygenation, lower extremity muscle strength, and dyspnea during activities of daily living are similar. Decreased exercise capacity and dyspnea in patients with moderate functional limitations may be associated with decreased respiratory muscle strength. Patients with post-COVID-19 syndrome should be evaluated according to their functional status, and exercise should be planned according to their limitations.

Keywords:

COVID-19, dyspnea, exercise tolerance, respiratory muscle

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Introduction

Coronavirus disease 2019 (COVID-19) is a multi-organ disease, and the severity of the disease can range from asymptomatic to severe symptoms.[1] COVID-19 infection impacts patients' physical and mental health, including those with mild illness.[2] Fatigue and dyspnea are the most prevalent symptoms in COVID-19 survivors.[3] After more than 1 year of follow-up, fatigue was detected in 41% of the patients and dyspnea in 31%.[4] These long-term symptoms encourage patients' sedentary lifestyles and cause limited exercise tolerance. Exercise intolerance and dyspnea have been found even in patients with COVID-19 in the long term with preserved lung function.[5] Exercise intolerance in patients with COVID-19 in the long term may be associated with pulmonary and cardiac problems and respiratory muscle dysfunction.

Avoiding activities that cause dyspnea leads to the deterioration of muscle functions. Inflammation of the interstitial tissue of the lungs can also affect the muscles.[6] While COVID-19 infection continues to cause significant morbidity in patients, it is essential to determine its long-term effects on exercise capacity and respiratory muscle strength in patients. A study found that 34% of patients with COVID-19 had a six-minute walk test (6-MWT) expected walking distance of less than 80% of predicted. [7] On chest computed tomography (CT) scans, patients with more severe pulmonary involvement had greater desaturation during the 6-MWT.[8] Furthermore, even in functionally independent patients, persistent symptoms may limit physical activity and affect activities of daily living.[9] Patients with COVID-19 may develop hypoxemia due to the systemic inflammatory response. Oxygenation of skeletal muscles is restricted due to arterial hypoxemia.[10] However, the effect of COVID-19-associated hypoxemia on peripheral muscle oxygenation has not been studied.

More than 60% of patients infected with COVID-19 have long-term symptoms.[11] A simple measurement method, the Post-COVID-19 Functional Status Scale (PCFS), has been developed to monitor the progression of symptoms and the impact of these symptoms on the functional status of affected patients. PCFS detects functional status at hospital discharge and long-term follow-up.[12] This study aimed to compare exercise capacity, respiratory and peripheral muscle strength, pulmonary function, muscle oxygenation, and dyspnea during activities of daily living in patients with post-COVID-19 syndrome with mild and moderate functional limitations.

Materials and Methods

Study design and subjects

In this study, 35 patients with pulmonary involvement post-COVID-19 syndrome[13] referred from Gazi University, Faculty of Medicine, Department of Chest Diseases for pulmonary rehabilitation to the Cardiopulmonary Rehabilitation Unit located in the Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, were recruited between June 2022 and July 2023.

This study is single-center, cross-sectional by design. Patients who had at least 12 weeks after diagnosis and had long-term COVID-19 symptoms were included in this study. The patients were divided into two groups based on their PCFS scores: those with mild and moderate functional limitations. The pulmonary involvement of the patients was determined by a pulmonologist based on the computed tomography results.[14] Patients with post-COVID-19 syndrome were divided into two groups according to the PCFS score: 15 patients with mild functional limitations (PCFS score: 2) and 20 patients with moderate functional limitations (PCFS score: 3). The following inclusion criteria were employed: patients with pulmonary involvement post-COVID-19, those between 18 and 75 years old, those with current negative COVID-19 PCR test results, and volunteers to participate in the study. Exclusion criteria included the following: body mass index of ≥35 kg/m^2, suffering from acute pulmonary exacerbation and acute upper or lower respiratory tract infection; serious neurological, neuromuscular, and orthopedic diseases affecting physical functions; participation in a planned exercise program in the last 3 months; cognitive impairment causing difficulty in understanding and following exercise test instructions, contraindication for exercise testing and/or exercise training based on the American College of Sports Medicine;[15] cancer; renal or hepatic disease; aortic stenosis; complex arrhythmia; acute aneurysm; uncontrolled hypertension; diabetes mellitus; heart failure; and cardiovascular diseases. During the revision of this study, the authors employed Grammarly's artificial intelligence writing assistance to improve language and readability. The Gazi University Ethics Committee approved this study (Protocol ID: 2022-608). The patients were informed beforehand regarding the study and provided written informed consent. The study conformed to the standards outlined by the Declaration of Helsinki.

Post-COVID-19 functional status scale

To evaluate the functional status of patients after COVID-19, the Turkish version of PCFS was utilized.[12,16] The Post-COVID-19 Functional Status Scale is a questionnaire that evaluates all functional limitations, including changes in lifestyle and social activities. Based on the functional status limitation of the PCFS scale, the scores are as follows: score 0 = none, score 1 = negligible, score 2 = slight, score 3 = moderate, and score 4 = severe functional limitations.

Pulmonary function test

Dynamic lung volumes were measured using a spirometer (Vmax 220 Sensormedics Corporation, Yorba Linda, California, USA). Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow (PEF), and forced expiratory flow from 25% to 75% ($FEF_{25\%-75\%}$). Diffusing capacity of the lungs for carbon monoxide (DLCO), total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV), RV/TLC (DLCO; Vmax 220; Sensormedics Corporation, Yorba Linda, California, USA) were recorded from the patient's medical reports. The percentage of predicted FEV_1/FVC and FVC were defined as obstructive and restrictive lung function abnormality.[17]

Computed tomography

The chest CT images of the patients were evaluated via teleradiology to determine the characteristics based on Fleischner Society nomenclature recommendations.[18] Each of the five lung lobes was visually scored on a scale of 0–3 (0=no lesion, 1=<1/3 of the lobe volume involved, 2= >1/3 and <2/3 of the lobe volume involved, and 3 = >2/3 of the lobe volume involved). The total CT score for each case was the sum of the scores for the five lobes, with a maximum possible score of 5×3 = 15. A total score of ≤7 was considered to be ≤50% involvement, and >7 was considered to be >50% involvement.[19,20]

Respiratory muscle strength

Respiratory muscle strength was evaluated utilizing a mouth pressure device (Micro Medical MicroRM, England, UK) based on ATS/ERS guidelines.[21] Maximal inspiratory pressure (MIP) and maximal expiratory pressures (MEP) were evaluated. Measurements were repeated at least seven times, and the highest values for MIP and MEP were recorded for analysis. The percent of the predicted value of MIP and MEP was calculated with the reference equation of Evans et al.[22] Lista-Paz et al. cut-off points were used to define respiratory muscle weakness.[23]

Exercise capacity

Functional exercise capacity was evaluated using 6-MWT. It was implemented based on the criteria of the ATS.[24] Patients were requested to walk as fast as possible within 6 min in a closed, quiet corridor, 30 m long. During the test, the patients were stopped and rested if symptoms such as dyspnea and chest pain occurred. Heart rate (HR) (Polar FT I00, China), systolic (SBP) and diastolic blood pressure (DBP), breathing frequency (BF), oxygen saturation (SpO_2) (Model 9590 Oximeter Nonin Medical, Inc, Plymouth, MN, USA), dyspnea, fatigue, and leg fatigue were questioned before and after the test (modified Borg scale) and at the first minute of recovery. The test was repeated twice on the same day, with a minimum interval of 30 min between tests. The best distance between the two tests was selected for the statistical analysis.[24] Additionally, the differences (Δ) between the posttest and pretest values of cardiorespiratory parameters were calculated. The percent of the predicted value of 6-MWT distance was calculated with the reference equation of Gibbons et al.[25]

Muscle oxygenation

The oxygen saturation of the quadriceps femoris (QF) muscle was measured using a near-infrared spectroscopy device, a noninvasive method (Moxy®, Fortiori, Desing LLC, Minnesota, USA). The Moxy® monitor measures the local oxygen saturation and total hemoglobin in the muscle capillaries below the motor point of the muscle.[26] Before the 6-MWT, the Moxy® monitor was placed on the 1/3 lower motor point of the QF muscle with the help of an anti-allergic plaster. The data of resting, testing, and recovery were recorded with the device. Muscle oxygen saturation (SmO_2), minimum (SmO_{2min}), and maximum muscle oxygen saturation (SmO_{2max}), total hemoglobin (THb), minimum (THb_{min}), and maximum (THb_{max}) total hemoglobin values were measured.

Peripheral muscle strength

The digital pressure dynamometer (JTECH Power Track Commander, Baltimore, MA, USA) was employed for quadriceps muscle strength. The device was fixed on the distal portion of the tibia, and the patient was sitting with the hips and knees flexed at 90°. The QF muscle strength was tested three times. For statistical analysis, the highest value of the highest strength measurement, expressed in Newton, and the percentage of predicted was adopted.[27]

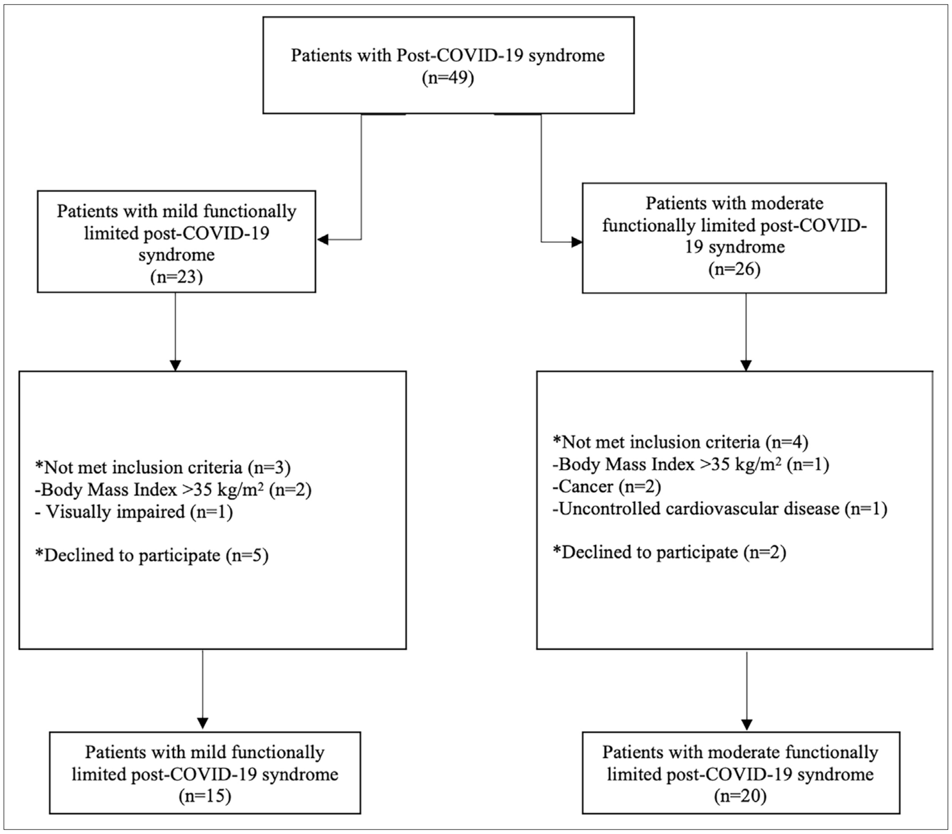

Figure 1: The STROBE flow diagram in the patients with mild and moderate functional limitations with post-COVID-19 syndrome

STROBE: The Strengthening the Reporting of Observational Studies in Epidemiology

London chest activity of daily living scale

The London Chest Activities of Daily Living Scale (LCADL) was utilized to evaluate dyspnea during activities of daily living.[28,29] The scale has a total of four components and 15 items, such as self-care (four items), domestic activities (six items), physical activities (two items), and leisure activities (three items). Each item is scored between 0 and 5 points. The total score is a maximum of 75. As the total score increases, dependency on daily living activities increases.

Statistical analysis

Statistical Package for Social Science (SPSS) 26.0 (SPSS Inc., Chicago, USA) statistical analysis program was employed for statistical analysis. Normality was evaluated using the Shapiro–Wilk test. Descriptive statistics were expressed as mean±standard deviation (mean±SD) and median (interquartile range, 25^{th} to 75^{th} percentile) or number (%), as appropriate. Chi-square tests examined categorical variables. Student's t-test for normal distributed data and Mann–Whitney U test for non-normal distributed data were used to compare statistical differences between groups. Univariate analysis of covariance (ANCOVA) was carried out to measure the effect of gender. Statistical significance was set at $p<0.05$.[30] G*Power (3.0.10 system) program was utilized for post-hoc power analysis. Power analysis was performed using 6-MWT distance (m) values.

Results

This study included 15 patients with mild and 20 with moderate functional limitations with post-COVID-19 syndrome [Fig. 1]. Demographic characteristics were similar in both groups ($p>0.05$, Table 1). Table 2 shows the comparisons of static and dynamic lung volumes of the groups. PEF% and $FEF_{25\%-75\%}$ of patients with moderate functional limitations were lower than those with mild functional limitations ($p<0.05$, Table 2). Of the patients with moderate functional limitation, one (5%) had restrictive, eight (40%) had mixed type respiratory dysfunction, and 11 (55%) patients had no abnormality in respiratory function. Of the patients with mild functional limitation, one (6.7%) had obstructive, two (13.3%) had

Table 1. Comparison of demographic and clinical characteristics in patients with mild and moderate functionally limited post-COVID-19 syndrome

	Mild functionally limited post-COVID-19 (n=15)			Moderate functionally limited post-COVID-19 (n=20)			
	n	Mean±SD Median ($IQR_{25–75\%}$)	%	n	Mean±SD Median ($IQR_{25–75\%}$)	%	p
Female	4		26.7	14		70	0.011*
Male	11		73.3	6		30	
Age (years)		57.07±9.3			61.75±9.53		0.156
Height (cm)		167.2±8.67			162.25±9.63		0.126
Weight (kg)		77.66±13.46			73.5±13.22		0.367
Body mass index (kg/m²)		27.75±4.49			27.76±4.36		0.997
Hypertension	6		40	11		55	0.380
Coronary artery disease	2		13.3	6		30	0.281
Diabetes mellitus	3		20	6		30	0.419
Asthma	2		13.3	4		20	0.680
COPD	0		0	3		15	0.244
Heart failure	0		0	2		10	0.496
ILD	3		13.3	0		0	0.070
Charlson comorbidity index score (0–37 points)		0 (0–1)			0.5 (0–1)		0.831
Very light (0)	8		53.3	10		50	
Light (1–2)	7		46.7	8		40	
Heavy (3–4)	0		0	2		10	
Very heavy (≥5)	0		0	0		0	
Time from COVID-19 diagnosis (weeks)		83.46±41.51			80.20±34.97		0.802
Lung infiltrates on CT							0.051*
≤50%	9		60	18		90	
>50%	6		40	2		10	
Hospitalization	11		73.3	9		45	0.094
Duration of hospitalization (days)		10 (8–19)			9 (7–10)		0.412
Intensive care stay	4		26.6	5		25	0.911
Duration of intensive care stay (days)		15.25±6.94			10.20±7.52		0.336
Mechanically ventilation	2		13.3	4		20	0.680
Duration of mechanical ventilation (days)		9.5±0.71			6.5±3.69		0.343
Corticosteroids use	10		66.6	8		40	0.176
Duration of corticosteroids (days)		14.5 (10–60)			16.0 (3–40)		0.492
Corticosteroids dose (mg)		25 (6–40)			6 (5.5–9.5)		0.139

*:p<0.05. n: Frequency, %: Percentage, SD: Standard deviation, IQR: Interquartile range, cm: Centimeter, kg: Kilogram, kg/m²: Kilogram/square meter, COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung disease, CT: Computed tomography, mg: milligram

mixed-type respiratory dysfunction, and twelve (80%) patients had no abnormality in respiratory function.

The measured and percentage of predicted 6-MWT distance values were significantly decreased in patients with post-COVID-19 syndrome with moderate functional limitations compared with those with mild functional limitations ($p<0.05$, Table 3). Resting values before 6-MWT and delta (Δ: end-baseline) cardiorespiratory parameters (HR, SpO_2, BF, SBP, DBP, general fatigue, and leg fatigue) were similar in both groups ($p>0.05$). The 6-MWT distance was less than 80% of the predicted in 14 (70%) patients with moderate functional limitations and six (40%) with mild functional limitations. In the test, Δ dyspnea was more common in patients with moderate functional limitations than in those with mild functional limitations ($p=0.036$) (Table 3). According to 6-MWT distance (m) values the power (1-ß) of this study is 80.03%.

The MIP, MEP, and MEP (%) of patients with post-COVID-19 with moderate functional limitations were significantly decreased when compared with those with mild functional limitations ($p<0.05$), and MIP (%) was similar in both groups ($p>0.05$, Table 4). All sub-

Table 2. Comparison of pulmonary function in patients with mild and moderate functionally limited post-COVID-19 syndrome

	Mild functionally limited post-COVID-19	Moderate functionally limited post-COVID-19	Mean difference %95 CI	p
	Mean±SD Median ($IQR_{25\%–75\%}$)	Mean±SD Median ($IQR_{25\%–75\%}$)		
FEV_1 (%)	92.36±18.48	81.95±24.04	10.41 (–4.75–25.60)	0.172
FVC (%)	93.56 ±19.03	87.05±24.50	6.51 (–9.01–22.04)	0.399
FEV_1/FVC (%)	79 (76.77–87)	78 (72.01–81.07)	–	0.330
PEF (%)	97.40±21.63	82.50±22.18	15.48 (1.57–29.39)	0.056*
$FEF_{25\%–75\%}$ (%)	82.52±28.05	54.40±22.50	28.12 (10.74–45.49)	0.002*
DLCO (%)	65 (58–83)	65 (55–82.5)	–	0.842
DLCO (%) <80%, n (%)	14 (70)	9 (60)	–	–
DLCO (%) ≥80%, n (%)	6 (30)	6 (40)	–	–
TLC (%)	78.07±20.56	69.85±18.62	8.22 (–5.86–22.32)	0.243
FRC (%)	84.92±22.77	72.60±19.87	12.32 (–2.97–27.61)	0.170
RV (%)	84.92± 22.18	77.7±22.37	7.22 (–8.98–23.42)	0.370
RV/TLC (%)	42.0 (40–49)	41.0 (39–55)	–	0.530

*: p<0.05. CI: Convidence interval, FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak expiratory flow, $FEF_{25\%–75\%}$: Forced expiratory flow from 25% to 75%, DLCO: Pulmonary diffusion capacity, TLC: Total lung capacity, FRC: Functional residual capacity, RV: Residual volume, %: Percentage, n: Frequency

Table 3. Comparison of exercise capacity in patients with mild and moderate functional limitations with post-COVID-19 syndrome

	Mild functional limitations with post-COVID-19	Moderate functional limitations with post-COVID-19	Mean difference %95 CI	p
	Mean±SD Median ($IQR_{25\%–75\%}$)	Mean±SD Median ($IQR_{25\%–75\%}$)		
6-MWT (m)	543.5 (490.5–595.8)	435.75 (323.25–489.25)	–	0.003*
6-MWT (%)	80.07 (70.84–86.80)	68.47 (58.09–80.98)	–	0.055*
Resting				
HR (beats/min)	82.33±11.87	77.80±13.31	4.53 (–4.30–13.37)	0.304
SpO_2 (%)	96 (95–98)	96 (93–97.50)	–	0.908
SBP (mmHg)	120 (110–130)	120 (105–130)	–	0.633
DBP (mmHg)	78.66±11.25	74.25±12.27	4.41 (–3.82–12.65)	0.283
Breathing frequency (breaths/min)	20 (16–28)	20 (20–28)	–	0.700
Dyspnea (MBS: 0–10 points)	0 (0–0)	0 (0–0.75)	–	0.214
General fatigue (MBS: 0–10 points)	0 (0–0)	0 (0–0.3)	–	0.214
QF fatigue (MBS: 0–10 points)	0 (0–0)	0 (0–0)	–	0.633
HR peak (%)	124 (115–147)	117.58 (102–128)	–	0.099
Δ HR (beats/min)	47.60±14.88	38.85±13.18	8.75 (–0.93–18.43)	0.075
Δ SpO_2 (%)	3 (0–6)	4.5 (1.5–5)	–	0.542
Δ SBP (mmHg)	20±13.62	17±12.71	3.0 (–6.10–12.10)	0.507
Δ DBP (mmHg)	0 (0–10)	10 (0–10)	–	0.240
Δ Breathing frequency (breaths/min)	12 (8–12)	12 (11–15)	–	0.086
Δ Dyspnea (MBS: 0–10 points)	3 (1–4)	4 (3–5)	–	0.036*
Δ General fatigue (MBS: 0–10 points)	2 (0–2)	2.5 (0–3)	–	0.107
Δ QF fatigue (MBS: 0–10 points)	0 (0–3)	1 (0–2)	–	0.610

*: p<0.05. 6-MWT: Six-minute walk test, min: minute, HR: heart rate, SpO_2: Peripheral oxygen saturation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, m: meter, mmHg: Millimeters of mercury, MBS: Modified Borg Scale, QF: Quadriceps femoris, Δ: difference between post and pre test value

scales and total LCADL scores of groups were similar between the groups (p>0.05, Table 4). Table 5 presents the QF muscle oxygenation during 6-MWT. SmO_2 rest, minimum, maximum, recovery averages and ΔSmO_2 and Thb rest, minimum, maximum, and recovery ΔThb were similar in both groups (p>0.05).

Table 4. Comparison of respiratory and peripheral muscle strength and daily living activity in patients with mild and moderate functionally limited post-COVID-19 syndrome

	Mild functionally limited post-COVID-19	Moderate functionally limited post-COVID-19	Mean difference %95 CI	p
	Mean±SD Median ($IQR_{25-75\%}$)	Mean±SD Median ($IQR_{25-75\%}$)		
MIP (cmH_2O)	101.93±25.05	76.15±19.70	25.78 (10.4–41.16)	0.002*
MIP (%)	124.20 (84.42–129.92)	92.81 (84.05–115.32)	–	0.139
Inspiratory muscle weakness, n (%)	3 (15)	7 (35)	–	–
MEP (cmH_2O)	145.26±35.62	108.6±23.84	36.66 (16.22–57.11)	0.001*
MEP (%)	114.30±26.06	88.67±20.01	25.63 (9.80–41.46)	0.002*
Expiratory muscle weakness, n (%)	3 (20)	3 (20)	–	–
QF strength (N) (ND)	242.0 (209–275)	218.5 (167–248)	–	0.080
QF strength (%) (ND)	66.13 ±14.63	70.07±14.84	–3.93 (–14.18–6.32)	0.441
QF strength (%) (ND) <80%	11 (73.3%)	16 (80%)	–	–
QF strength (%) (ND) ≥ 80%	4 (26.7%)	4 (20%)	–	–
$LCADL_{self\ care}$ (0–20 points)	4 (4–7)	5 (4–6.5)	–	0.882
$LCADL_{domestic\ activities}$ (0–30 points)	6 (1–14)	5 (3.5–8.5)	–	0.780
$LCADL_{physical\ activities}$ (0–10 points)	4 (3–7)	6 (3.5–7)	–	0.330
$LCADL_{leisure\ activities}$ (0–15 points)	3 (3–5)	3.5 (3–5)	–	0.831
$LCADL_{total\ score}$ (0–75 points)	17 (13–33)	18 (15.5–26.5)	–	0.587

*: p<0.05. SD: Standard deviation, $IQR_{25-75\%}$: Interquartile range, CI: Confidence interval, MIP: Maximal inspiratory pressure, MEP: Maximal expiratory pressure, QF: quadriceps femoris, N: Newton, ND: Non-dominant, LCADL: London Chest Activity of Daily Living, cmH_2O: Centimeter water pressure

Given the gender distribution difference between the groups, the effect of gender on the research results was evaluated via ANCOVA. The MIP (cmH_2O) and MEP (%) values of the groups were determined to be affected by the gender factor (F(1, 32)=8.273 p=0.007; F(1, 32)=5.942, p=0.021, respectively); however, when gender was controlled, the difference was due to functional status (F(1, 32)=5.084, p=0.031; F(1, 32)=4.60, p=0.040, respectively). The MEP (cmH_2O), 6-MWT distance and 6-MWT(%) values of the groups were not affected by the gender factor (F(1, 32)=3.377, p=0.075; F(1, 32)=0.027, p=0.870; F(1, 32)=2.998 p=0.093, respectively), and when the gender factor was controlled, the statistical differences resulted from the difference in functional status (F(1, 32)=6.884, p=0.013; F(1, 32)=7.019 p=0.012; F(1, 32)=5.638, p=0.024, respectively). It was determined that QF muscle strength and muscle oxygenation measurements, which did not vary between groups, were not affected by the gender difference (p>0.05, ANCOVA).

Discussion

This study revealed that patients with post-COVID-19 syndrome with pulmonary involvement have moderate functional limitations during physical activities, impaired respiratory muscle strength, exercise capacity, and increased airway obstruction in comparison to those with mild functional limitations. Moreover, more than half of the patients have decreased diffusion capacity and peripheral muscle strength. Although dyspnea during daily living activities of the patients in both groups increased similarly, dyspnea experienced during exercise was greater in patients with moderate functional limitations. Patients with moderate functional limitations with post-COVID-19 syndrome walked less distance during the exercise test and exhibited the same muscle oxygen responses as those with mild functional limitations at lower workloads.

Functional status is the individual's ability to perform normal daily activities that are necessary to meet basic needs, and decreased functional status includes difficulty in performing basic tasks or leisure activities.[31] PCFS is an assessment tool developed by Klok et al.[12] that detects symptoms in survivors of COVID-19 and its impact on the functional status of patients. In the literature, persistent functional limitations of patients recovering from COVID-19 infection have been identified and classified using PCFS.[32] To our knowledge, this study is the first to compare the pulmonary and extrapulmonary characteristics of patients with post-COVID-19 syndrome who have different functional status.

Table 5. Comparison of muscle oxygenation during 6-MWT in patients with mild and moderate functional limitations with post-COVID-19 syndrome

	Mild functional limitations with post-COVID-19	Moderate functional limitations with post-COVID-19	Mean difference %95 CI	p
	Mean±SD Median ($IQR_{25\%–75\%}$)	Mean±SD Median ($IQR_{25\%–75\%}$)		
$SmO_{2resting}$ (%)	52.60±15.39	48.0±16.77	4.60 (–6.66–15.86)	0.412
$SmO_{2maximum}$ (%)	55.0 (37.0–65.0)	46.0 (37.5– 55.09)	–	0.382
$SmO_{2minimum}$ (%)	32.73±17.14	23.95±16.52	8.78 (–2.88–20.45)	0.135
ΔSmO_2 (%)	19.0 (11.0–27.0)	21.5 (13.5–30.0)	–	0.364
$SmO_{2average\text{-}min}$ (%)	34.06±17.39	24.75±16.15	9.31 (–2.28–20.91)	0.112
$SmO_{2average\text{-}max}$ (%)	56.0 (37.0–67.0)	44.5 (38.0–55.0)	–	0.438
$SmO_{2recovery}$ (%)	50.86±21.16	43.36±14.97	7.49 (–5.12–20.12)	0.235
$SmO_{2recovery\text{-}average}$ (%)	50.40±21.18	42.60±14.77	7.80 (–4.55–20.15)	0.208
$THb_{resting}$ (g/dl)	12.32±0.44	12.21±0.38	–0.10 (–0.17–0.39)	0.440
$THb_{maximum}$ (g/dl)	12.26±0.40	12.18±0.34	–0.08 (–0.17– –0.33)	0.527
$THb_{minimum}$ (g/dl)	11.86±0.37	11.80±0.37	–0.05 (–0.20–0.31)	0.656
ΔTHb (g/dl)	0.30 (0.22–0.43)	0.38 (0.23–0.47)	–	0.657
$THb_{recovery}$ (g/dl)	12.15±0.45	12.11±0.43	–0.03 (–0.27– –0.34)	0.824

$p<0.05$. SD: Standard deviation, $IQR_{25\text{-}75\%}$: Interquartile range, CI: Confidence interval, SmO_2: Muscle oxygen saturation, Thb: Total hemoglobin, %: Percentage, min: Minimum, max: Maximum, g: Gram, dl: Deciliter, Δ: Difference between post and pre test value

The 6-min walk test is essential in evaluating, prognosis, and determining exercise programs, especially in cardiopulmonary diseases. It has also been utilized in the literature for the evaluation of exercise capacity in patients with COVID-19.[33,34]

Zhang et al.[33] reported that after an average of 8 months of hospital discharge of survivors of COVID-19, those with severe clinical disease had lower 6-MWT distances than those with moderate ones. In this study, more than half of the patients had reduced functional exercise capacity. Furthermore, the 6-MWT distance attained by patients with moderate functional limitations was shorter than that obtained by those with mild functional limitations. The decrease in exercise capacity may be due to several factors. Pulmonary parenchymal involvement and muscle dysfunction may be associated with exercise intolerance in patients with COVID-19 in the long term.[35] In survivors of SARS, decreased exercise capacity after hospital discharge was reported to be related to impaired respiratory function and extrapulmonary causes including physical deconditioning and muscle weakness.[36] In our study, the decreased respiratory muscle strength in patients with moderate functional limitations may explain their reduced exercise capacity. Moreover, 77% of the patients had QF muscle weakness. Furthermore, decreased exercise capacity may be due to muscle wasting and myopathy. A systematic review found that pulmonary rehabilitation increased exercise capacity in patients with COVID-19.[37] Comprehensive pulmonary rehabilitation programs may help improve the decreased exercise tolerance of patients with post-COVID-19 syndrome.

Based on the pathological findings, viral infiltration of the SARS-CoV-2 virus was detected in the diaphragm of the patients hospitalized in the intensive care unit. Additionally, an increase in the expression of genes that cause diaphragmatic fibrosis was detected histologically.[38]

It has been revealed that respiratory muscle strength deteriorates following COVID-19 infection.[39] This study determined that the inspiratory muscles of patients with moderate functional limitations weakened when compared to those of patients with mild functional limitations. As our study shows, respiratory muscle weakness was prevalent in approximately one-third of the patients, possibly due to myopathy in the diaphragm caused by the COVID-19 virus. Whether these effects are persistent in the long term necessitates investigation.

The lung is the most affected organ in COVID-19 infection, with different pathological mechanisms, including alveolar epithelial, capillary destruction, and alveolar septal fibrous proliferation.[40] In COVID-19, small airway obstruction was shown[41] and patients' diffusion and TLC deteriorated.[40] In this study, DLCO decreased in 66% of the patients, and

TLC decreased in 51%. Fibrotic changes in the lung following COVID-19 infection may cause restrictive deterioration in pulmonary function.[42] The decrease in DLCO and TLC of the patients in this study may be associated with lung fibrosis. Whether the parenchymal damage in these patients is permanent or not must be evaluated by a pulmonologist with advanced imaging techniques after a long period.

Arterial hypoxemia due to pulmonary involvement in COVID-19 may reduce the amount of oxygen uptake to the muscles. The 6-MWT is a practical, simple, and readily applicable test that detects hypoxia during exercise in patients who are not hypoxic at rest. A study proved that this test enables COVID-19 hypoxia detection.[39] Desaturation occurs during exercise, especially in patients with post-COVID-19.[10] Mild and moderate limited patients' peripheral oxygen saturation decreased similarly during exercise. In our study, muscle oxygen saturations and total hemoglobin of patients with mild and moderate functional limitations were similar at rest, during exercise, and recovery. Nevertheless, patients with moderate functional limitations walked a shorter distance during the submaximal exercise test, and the same muscle oxygen response was observed at lower workloads.

Muscle oxygen responses may vary during maximal exercise, which should be explored in future studies. Additionally, since muscle oxygen saturation was not compared with healthy controls in this study, how muscle oxygenation was affected in patients with post-COVID-19 syndrome could not be revealed. Comparison with healthy controls in future studies will provide additional information to the literature.

Dyspnea and fatigue are common in patients with COVID-19 in the long term.[3] Yaman et al.,[3] in their study, evaluated the dyspnea of patients who had COVID-19 and found that dyspnea was the most common symptom in patients (94.6%) and increased as the severity of the disease increased. In this study, the perception of dyspnea of patients with mild and moderate functional limitations during self-care, domestic, physical, and leisure activities increased similarly. By contrast, moderate patients' perception during exercise was more. A symptom with a complex pathophysiology, such as exertional dyspnea, may have a multifactorial origin. In this study, decreased respiratory muscle strength in patients with moderate functional limitations with post-COVID-19 syndrome may cause exercise dyspnea, which should be explored.

Limitations and future directions

The study grouped the patients based on their functional status using a subjective evaluation method. This grouping is independent of the severity of radiological lung involvement and is based entirely on the patient's subjective responses. Impairment of respiratory muscle strength and exercise capacity may be due to ongoing inflammation in the muscles, the cause of which has not yet been explained, independent of lung involvement. In patients in the PCFS 2 group with more lung involvement, symptoms may improve because of the decrease in inflammation in multiple systems over a long period from the date of COVID-19 infection. All the information provided here depends on the researchers' clinical experience and judgment. Nevertheless, these hypotheses must still be tested. To investigate the long-term effects of COVID-19, more studies are required.

Additionally, this study evaluated muscle oxygenation of post-COVID-19 syndrome at various functional grades during submaximal exercise. How the disease affects muscle oxygen saturation will be described better if the muscle oxygenation of patients with COVID-19 is compared with healthy controls in future studies. Furthermore, increased vaccination rates and the emergence of less transmissible variants were reduced during the COVID-19 pandemic, which limited the number of patients included in the study. Although the strength of this study is high, the sample size may require revision for some parameters in future studies.

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Ethics Committee Approval

The study was approved by the Gazi University Ethics Committee (No: 2022-608, Date: 10/05/2022).

Authorship Contributions

Concept – M.B.G., B.K.K., E.B., N.Y.D.; Design – B.K.K., E.B., N.Y.D., M.B.G.; Supervision – M.B.G., B.K.K., E.B., N.Y.D.; Funding – M.B.G.; Materials – B.K.K., E.B., N.Y.D.; Data collection &/or processing – B.K.K., E.B.; Analysis and/or interpretation – B.K.K., M.B.G.; Literature search – B.K.K., M.B.G.; Writing – B.K.K., M.B.G.; Critical review – B.K.K., E.B., N.Y.D., M.B.G.

Conflicts of Interest

There are no conflicts of interest.

Use of AI for Writing Assistance

Yes declared.

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