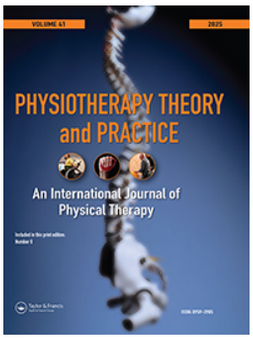

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RESEARCH REPORT

Oxygen consumption chronotropic response to maximal exercise and physical activity level in patients with post-COVID-19 and pulmonary involvement

Ece Baytok MSc, PT[a], Meral Boşnak Güçlü PhD, PT[a], Başak Kavalcı Kol PhD, PT[b], and Nilgün Yılmaz Demirci MD[c]

[a]Faculty of Health Sciences, Department of Cardiopulmonary Physical Therapy and Rehabilitation, Gazi University, Ankara, Türkiye; [b]Pilot Health Coordinatorship, Kırşehir Ahi Evran University, Kırşehir, Türkiye; [c]Faculty of Medicine, Department of Pulmonology, Gazi University, Ankara, Türkiye

ABSTRACT

Background: Pulmonary involvement due to coronavirus disease 2019 (COVID-19) is common. Pulmonary involvement may affect pulmonary function. Moreover, structural alterations in the lungs may impair the extrapulmonary functions.

Purpose: This study compared respiratory functions, peripheral muscle strength, maximal exercise capacity, chronotropic incompetence (CI) (< 80% of maximal heart rate), physical activity level, and dyspnea in patients with post-COVID-19 who had lung involvement and healthy controls.

Methods: Forty-seven patients and 60 healthy controls were compared. Pulmonary function (spirometry), respiratory muscle strength (maximal inspiratory-expiratory pressures – MIP, MEP) and endurance, peripheral muscle strength (dynamometry), exercise capacity (cardiopulmonary exercise test – CPET), CI, physical activity(metabolic holter), and dyspnea (modified Borg Scale) were evaluated.

Results: Pulmonary function test parameters, MIP, MEP, respiratory muscle endurance, peripheral muscle strength, oxygen consumption, CI during CPET, total and active energy expenditures, daily physical activity duration, metabolic equivalents, and the number of steps were significantly lower in patients compared to controls ($p < .001$). In contrast, lying down duration ($p = .027$) and dyspnea on exertion ($p < .001$) were significantly higher in patients compared with controls. The diffusing capacity for carbon monoxide (DLCO) was 77.2% in patients, indicating mild diffusion impairment.

Conclusion: Respiratory functions, peripheral muscle strength, exercise capacity, and chronotropic response are considerably impaired in patients with post-COVID-19 with pulmonary involvement. The majority of patients demonstrate sedentary lifestyle and reported higher levels of dyspnea during daily living activities. Therefore, these outcomes need to be evaluated in patients with pulmonary involvement, and patients should be referred to comprehensive pulmonary rehabilitation to prevent long-term impairments.

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COVID-19; exercise capacity; physical activity; pulmonary involvement

Introduction

The coronavirus disease 2019 (COVID-19) is a global health concern caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which primarily affects the respiratory system (Zhou et al, 2020). Following symptoms caused by the acute infection, some symptoms may persist in patients with COVID-19, referred to as "long COVID" or "post-COVID-19" (National Academies of Sciences and Medicine, 2024). The prevalence of post-COVID-19 is 43%, with fatigue being the most common symptom (Chen et al, 2022).

The COVID-19 virus causes alveolar damage, impairs the alveolar-capillary barriers, reduces surfactant production and infiltration into alveolar and interstitial spaces, and contributes to interstitial fibrosis (D'Agnillo et al, 2021). Abnormal lung injuries, particularly ground-glass opacity and interstitial fibrosis, were defined in chest computed tomography (CT) scans during the acute phase of COVID-19 infection (You et al, 2020). All of these changes in the lungs lead to a ventilation-perfusion mismatch, which results in hypoxemia. Furthermore, long-term CT scans may reveal persistent sequelae in the lungs (Zhou et al, 2021). Notably, a one-year follow-up study indicated that over 50% of patients with post-COVID-19 exhibited at least one abnormality on a chest CT scan (Huang et al, 2021). Additionally, it was found that the development of pulmonary involvement is independent of the severity of the acute phase (Tarraso et al, 2022).

CONTACT Ece Baytok ecebaytok@gazi.edu.tr Faculty of Health Sciences, Department of Cardiopulmonary Physical Therapy and Rehabilitation, Gazi University, Emek District, Bişkek Street, No: 2, Ankara 06490, Türkiye

Exercise intolerance and impaired chronotropic response are the long-term consequences of post-COVID-19 (Durstenfeld et al, 2022). While various mechanisms could explain the mechanism underlying exercise intolerance, chronotropic incompetence (CI), which is one of the reasons for exercise intolerance, is primarily based on symptoms, particularly dyspnea in post-COVID-19 (Durstenfeld et al, 2023). The majority of studies in the literature have primarily focused on patients who experienced lingering symptoms after COVID-19, with exercise intolerance often attributed to deconditioning (Durstenfeld et al, 2022). One study indicated that the reduction in oxygen consumption was not linked to pulmonary involvement; however, it's noteworthy that 60% of the patients included in the study did have pulmonary issues (Ali and Kunugi, 2021).

Respiratory and skeletal muscle atrophy were documented in COVID-19 (Ali and Kunugi, 2021; Mancuzo et al, 2021). Similar to other lung diseases, arterial hypoxemia related to pulmonary involvement in COVID-19 significantly contributes to muscle wasting through heightened oxidative stress and inflammation (Di Girolamo et al, 2022). Arterial hypoxemia may also hinder oxygen delivery to both respiratory and peripheral muscles. Peripheral muscle weakness also restricts exercise capacity and daily activities in COVID-19 (Van Aerde et al, 2020). Meanwhile, although the severity of the COVID-19 pandemic has diminished, most individuals infected with the COVID-19 virus remain physically inactive and find it challenging to return to their pre-pandemic physical activity levels (Taçalan and Kafa, 2023). Furthermore, dyspnea perception may further restrict physical activity levels in those recovering from COVID-19 (Romano et al, 2023).

It is evident that patients with post-COVID-19 have still intra- and extrapulmonary functional deficits. However, existing studies in the literature have predominantly focused on the impact of disease severity, hospitalization, or intensive care unit status rather than explicitly addressing pulmonary involvement and its effects on pulmonary and clinical functions in patients. Pulmonary complications associated with COVID-19 infection are likely to contribute to exercise intolerance and disrupt the chronotropic response by perpetuating ventilation-perfusion mismatch. Moreover, these pulmonary issues may directly or indirectly impact both intra- and extrapulmonary functions in patients experiencing post-COVID-19 symptoms resulting from pulmonary microcirculation injury and ventilatory insufficiency.

The understanding of the effects of COVID-19 on pulmonary function and related aspects such as maximal exercise capacity, heart rate response during maximum exercise testing, respiratory muscle strength and endurance, peripheral muscle strength, physical activity levels, and the experience of dyspnea is still incomplete. More information is needed to gain a comprehensive understanding of these impacts.

Therefore, this study aimed to compare pulmonary function, respiratory muscle strength and endurance, peripheral muscle strength, maximal exercise capacity, CI to maximal exercise, physical activity level, and dyspnea parameters above affect patients with post-COVID -19 who had pulmonary involvement and healthy controls.

Material and methods

Study design

This cross-sectional study was conducted in Gazi University, the Faculty of Health Sciences, Department of Cardiopulmonary Physiotherapy and Rehabilitation. The patients with post-COVID-19 referred for pulmonary rehabilitation from Gazi University, Faculty of Medicine, Department of Chest Diseases, were recruited between March 2022 and September 2023, and healthy controls were compared. This study was approved by the Gazi University Ethics Committee (Protocol ID: 2022–608) and was registered at Clinicaltrials.gov (ClinicalTrials number: NCT05381727). Written informed consent was obtained from each patient and healthy control. The current study was conducted according to the standards established by the Declaration of Helsinki (Harriss, MacSween, and Atkinson, 2017).

Participants

This study recruited patients with pulmonary involvement related to COVID-19 who were at least 12 weeks post-diagnosis and still had symptoms (National Academies of Sciences and Medicine, 2024). A pulmonologist determined pulmonary involvement using a chest CT (Hansell et al, 2008). The inclusion criteria were ages 18 to 75 and a negative COVID-19 PCR test. The exclusion criteria included acute respiratory infections and pulmonary exacerbation; orthopedic/neurological/neuro-muscular diseases affecting function; participation in a planned exercise program over the last three months; lung bullae observed on CT; uncontrolled hypertension, diabetes mellitus, heart failure, cardiovascular disease, cancer, renal or liver disease, aortic stenosis, arrhythmia, acute aneurysm; cognitive disorders affecting understanding of exercise test

instructions or contraindications for exercise testing (American Thoracic Society and American College of Chest Physicians, 2003). Healthy controls aged 18 to 75 and willing to participate were included. At the same time, those with a history of COVID-19, chronic/systemic diseases, acute pulmonary infections, and current or former smoking of over 10 pack years were excluded.

On the first day, demographic and clinical characteristics, pulmonary and respiratory muscle functions, and dyspnea perception were evaluated; on the second, cardiopulmonary exercise test (CPET) and peripheral muscle strength were assessed. An activity monitor was worn to measure each participant's physical activity level over five consecutive weekdays.

Pulmonary involvement

A chest CT scan is used to define pulmonary involvement severity following Fleischner Society recommendations (Hansell et al, 2008). Each lung lobe scored between 0 and 3. A total score of ≤ 7 indicated ≤ 50% involvement; > 7 indicated > 50% involvement (Pan et al, 2020).

Measurements

Pulmonary function and carbon monoxide diffusion capacity (DLCO) (Vmax 220 Sensormedics Corporation, Yorba Linda, California, USA) were assessed using a portable spirometer based on the American Thoracic Society (ATS) guideline (American Thoracic Society, 1991). Expected values below 75% were accepted as abnormal (Johnson and Theurer, 2014). Maximal inspiratory (MIP) and expiratory pressure (MEP), which indicate respiratory muscle strength, were measured using a mouth pressure device (Micro Medical MicroRPM, England) according to ATS and European Respiratory Society (ERS) guidelines (Evans and Whitelaw, 2009). Lista-Paz et al.'s (2023) cutoff values were used to determine respiratory muscle weakness. An incremental threshold loading test was performed via the POWERbreathe classic device to evaluate respiratory muscle endurance (Laveneziana et al, 2019). The test began at 30% of the highest MIP, increasing by 10% every 2 minutes until reaching 100% of MIP. Maximum pressure was sustained for at least 1 minute, and the total duration measured in seconds was multiplied (Basso-Vanelli et al, 2018). A handheld dynamometer (JTECH Power Track Commander) measured the isometric muscle strength of the quadriceps femoris (QF) and shoulder abductors (Andrews, Thomas, and Bohannon, 1996). An incremental, symptom-limited CPET was conducted on a treadmill (Trackmaster, 3017 Full Vision, Georgia, USA) to evaluate maximal exercise capacity. Following ATS/American College of Chest Physicians guidelines, an analyzer interface was used via a breath-by-breath (Carefusion, Oxycon Mobile Version 02.00, Germany) (American Thoracic Societyand American College of Chest Physicians, 2003). The 12-lead electrocardiography CareFusion Version 02.00 (Pulse Biomedical, Inc., 935 S, Pennsylvania, USA) monitored electrocardiography (ECG) while an earlobe probe was used to measure oxygen saturation during the test. The standard ramp protocol was used, gradually increasing the speed by 1 km/h and incline by 1% per minute, with total exercise lasting about 8–12 minutes, followed by a 3-minute recovery phase.

Oxygen consumption (VO_2), carbon dioxide output (VCO_2), anaerobic threshold-oxygen consumption ($ATVO_2$), respiratory exchange ratio (RER), metabolic equivalent (MET), heart rate (HR), heart rate reserve (HRR), load, oxygen pulse (VO_2/HR), minute ventilation (VE), breathing reserve (BR) and frequency (BF), ventilatory equivalent for VO_2 (VE/VO_2) and VCO_2 (VE/VCO_2), partial pressure of carbon dioxide ($PETCO_2$) were evaluated. Systolic (SBP) and diastolic blood pressure (DBP), dyspnea, and general fatigue were assessed before and after the CPET and at 1st minute of the end of the test.

The CPET was stopped upon reaching maximum heart rate (HR > 90% predicted), heart rate reserve (HRR) < 10 pulse/min, respiratory exchange ratio (RER) > 1.05, abnormal changes in ECG, or severe symptoms occurred like dyspnea or chest pain. Chronotropic incompetence (CI) was defined as a response of < 80% of age-predicted maximal heart rate during the CPET (Zweerink et al, 2018). A physical activity monitor (Sensewear, BodyMedia, Inc. Pittsburgh, USA) was used to evaluate physical activity levels. The device was worn on the patient's triceps brachii muscle of the non-dominant upper limb for five week-days after all assessments (Patel, Benzo, Slivka, and Sciurba, 2007). Dyspnea during daily activities was questioned using a modified Borg Scale (Wilson and Jones, 1989).

Statistical analysis

Statistical analyses were performed with the SPSS 26.0 statistical package (SPSS, Chicago, IL, USA). G*Power software was used to calculate the sample size. Utilizing the VO_{2peak} value (effect size = 1.76) following the pilot study, a sample size estimation with 95% power (α = 0.05) was calculated, and at least 10 patients were planned to be included in each group. The "Kolmogorov-Smirnov/Shapiro-Wilk" tests were employed to determine normality. Descriptive analyses

were expressed as mean±standard deviation (X±SD), mean difference, and 95% confidence interval for normally distributed data; median, interquartile range from 25% to 75%, and U values for non-normally distributed data. Categorical variables were analyzed using Chi-square tests. Student's *t* and Mann-Whitney U tests were used to compare normally distributed and undistributed variables, respectively. Power analysis was calculated using VO_{2peak} values. Statistical significance was admitted as $p < .05$.

Results

The study analyzed 47 patients with post-COVID-19 who had pulmonary involvement and 60healthy controls (Figure 1). Both groups had similar demographics ($p > .05$) except for smoking exposure, which was higher in patients (63.8%) compared to controls (20%) (Table 1) ($p < .05$). Of patients, 46.8% had mild and 40.4% had moderate functional limitations according to the "Post-COVID-19 Functional Status" scale, while 25.5% had pulmonary involvement over 50% (Table 1). The average duration from COVID-19 diagnosis was 83.06 weeks. 57.4% of patients were hospitalized, and 42.6% had a history of corticosteroid usage. Body mass index (BMI) classification was similar in the two groups, with 17 patients (36.2%) and 16 controls (26.7%) having a BMI ≥30 kg/m^2 ($p > .05$).

The patients' DLCO was 77.2%, with 27 patients (57.4%) having a DLCO of less than 80%. The predicted forced expiratory volume in one second (FEV_1%), forced vital capacity (FVC%), and forced expiratory flow from 25 to 75% ($FEF_{25-75\%}$%) were statistically significantly decreased in patients than in controls ($p < .05$, Table 2). The MIP, MEP, respiratory muscle endurance, muscle strength of the QF, and shoulder abductor were significantly decreased in patients than in controls ($p < .05$, Table 3).

The VO_{2peak} [(1−β) = 100%], VO_{2peak}%, VCO_{2peak}, HR_{peak}, HR_{peak}%, $HRR_{recovery}$, VO_2/HR_{peak}, VO_2/HR_{peak} %, AT/VO_2%, MET_{peak}, V_{Epeak}, $load_{peak}$%, SpO_{2peak}, and difference between post and pretest (Δ) SBP were significantly decreased in patients than controls ($p < .05$, Table 4, Figure 2). The patients had significantly higher resting and peak VE/VO_2 and VE/VCO_2 values than controls; HRR, BR%, BF, Δdyspnea, and ΔSpO_2 at peak were significantly higher than controls ($p < .05$, Table 4, Figure 2). The predicted VO_{2peak}% was below 85% in 30 (63.8%) patients. The 12 (25.5%) patients and 3 (5.1%) controls did not reach 90% of maximal HR; 26 (55.3%) patients and 26 (44.1%) controls could not exceed RER > 1.05. Due to dyspnea, fatigue, and chest pain, 17 (36.2%)

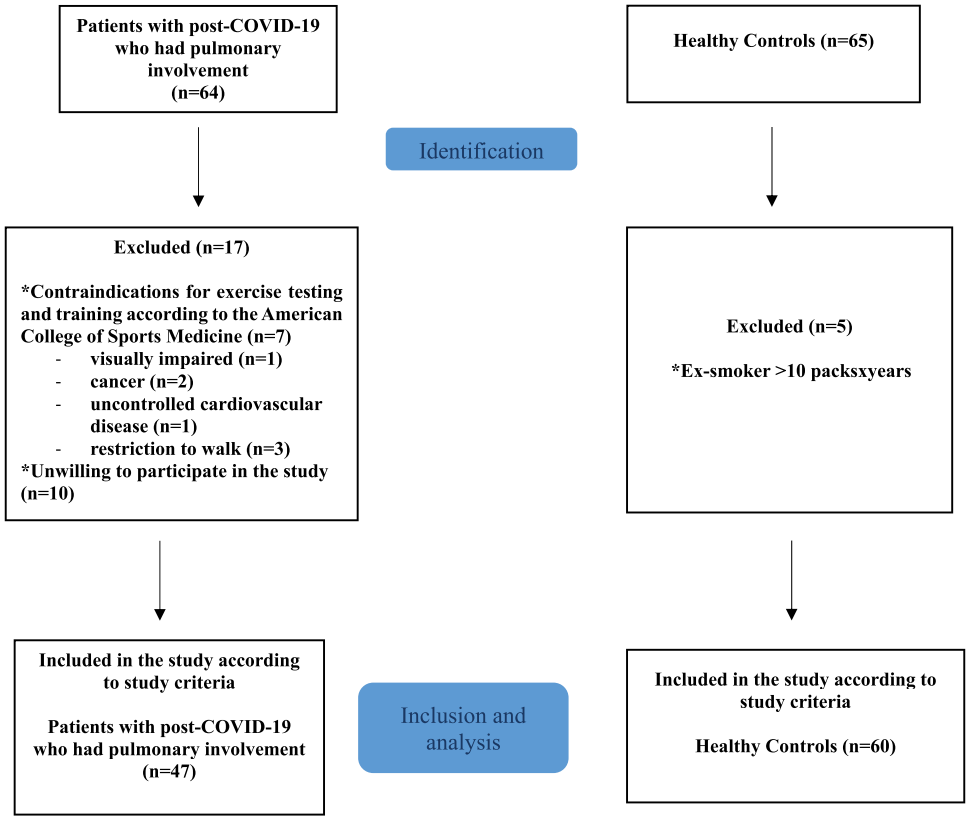

Figure 1. The STROBE flow diagram of the patients with post-COVID-19 with pulmonary involvement and healthy controls.

Table 1. Comparison of demographic data and pulmonary function in patients with post-COVID-19 with pulmonary involvement and healthy controls.

	Patients with post-COVID-19 ($n = 47$)	Healthy controls ($n = 60$)		
Characteristics	X±SD/Median ($IQR_{25-75\%}$)	X±SD/Median ($IQR_{25-75\%}$)	Mean difference (95%CI)/U	p
Age (years)	59 (52–66)	55 (52–60)	1158.50	0.114
Female/Male (n/%)	23/48.9%; 24/51.1%	27/45%; 33/55%		0.701
Height (cm)	165.11 ± 9.57	166.60 ± 8.69	−1.49 (−5.00 to 2.02)	0.401
Body weight (kg)	75 (67–87)	75 (69–85.50)	1405.00	0.975
BMI (kg/m^2)	28.25 ± 4.07	27.68 ± 3.10	0.57 (−0.85 to 1.99)	0.428
BMI classification (n/%)				0.196
Normal	14/29.8%	14/23.3%		
Overweight	16/34%	30/50%		
Obese class I	13/27.7%	15/25%		
Obese class II	4/8.5%	1/1.7%		
History of smoking (n/%)				
Smoker	9/19.1%	–		**< 0.001***
Ex-smoker	21/44.7%	12/20%		
Non-smoker	17/36.2%	48/80%		
Smoking (packxyear)	25 (10–40)	5 (5–8.50)	51.50	**< 0.001***
PCFS (0–4 score)				
PCFS 0	1/2.1%			
PCFS 1	5/10.6%			
PCFS 2	22/46.8%			
PCFS 3	19/40.4%			
PCFS 4	0			
Pulmonary involvement in CT ≤ 50%	35/74.5%			
Pulmonary involvement in CT > 50%	12/25.5%			
Time from COVID-19 diagnosis (weeks)	83.06 ± 37.60			
Hospitalization (n/%)	27/57.4%			
Hospitalization days	15.00 ± 10.33			
Mechanically ventilation (n/%)	7/14.9%			
Mechanical ventilation (days)	5.71 ± 3.20			
Corticosteroid usage (n/%)	20/42.6%			
Corticosteroid usage days	27.26 ± 30.61			
Corticosteroids dose (mg)	21.94 ± 22.10			
Charlson Comorbidity Index (0–37)	0.68 ± 0.72			
Very light (0)	21/44.7%			
Light (1–2)	21/44.7%			
Heavy (3–4)	4/8.5%			
Very heavy (≥5)	1/2.1%			

n: frequency, %: percentage, cm: centimeter, kg: kilogram, kg/m^2: kilogram/meter square, mg: milligram, BMI: body mass index, CT: computed tomography, PCFS: Post-COVID-19 Functional Status scale, X: mean, SD: standard deviation, IQR: interquartile range, CI: confidence interval, U: U value, *$p < .05$.

patients and four controls (5.1%) failed to complete the test. No abnormal ECG changes or adverse events occurred throughout the tests. The median CI of patients and controls during CPET was 84.52% and 99.96%, respectively ($p < .05$, Table 4, Figure 2). Total and active energy expenditure, daily physical activity duration, average METs, and number of steps were significantly decreased in patients versus controls, while lying down duration increased ($p < .05$), and sleep duration was similar in the groups ($p > .05$, Table 5, Figure 3). Patients experienced significantly more exertional dyspnea than controls, with a ratio of 45 (95.7%) and 16 (29.1%), respectively ($p < .05$).

Discussion

The most important findings of the present study are that pulmonary function, respiratory muscle strength, and endurance, peripheral muscle strength – especially in large groups – maximal exercise capacity, chronotropic response to maximal exercise, and physical activity levels are impaired in patients with post-COVID-19 who had pulmonary involvement. Pulmonary function abnormalities, mainly obstructive and affecting small airways, are prevalent in the patients. Most patients are physically inactive or low-active and experience higher dyspnea perception during daily living activities.

Residual pulmonary function abnormalities are common in COVID-19 (Chaiwong et al, 2023; Zhou et al, 2021). The meta-analysis on COVID-19 indicated that patients with impaired DLCO and restrictive lung impairment had rates of 39% and 15%, respectively (Torres-Castro et al, 2021). Our study, consistent with the meta-analysis, found that patients with post-COVID-19 had decreased DLCO (57.44%) with mild

Table 2. Comorbidities and comparison of pulmonary function in patients with post-COVID-19 with pulmonary involvement and healthy controls.

	Patients with post-COVID-19 ($n = 47$)	Healthy controls ($n = 60$)		
	X±SD/Median ($IQR_{25–75\%}$)	X±SD/Median ($IQR_{25–75\%}$)	Mean difference (95%CI)/U	p
Comorbidity (n/%)	35/79.5%			
Hypertension	16/45.7%			
Coronary artery disease	11/32.4%			
Diabetes mellitus	8/22.9%			
Asthma	7/20%			
COPD	3/8.6%			
Heart failure	2/5.7%			
Cancer	2/5.7%			
Psoriasis	2/5.7%			
ILD	1/2.8%			
FEV_1 (%)	91.14 ± 20.51	105.35 ± 13.58	−14.22 (−21.12 to −7.31)	**< 0.001***
FVC (%)	98 (90–109)	109.48 (100–115)	889.00	**0.001***
FEV_1/FVC	77.89 ± 8.50	79.60 ± 4.40	−1.71 (−4.43 to 1.02)	0.216
PEF (%)	92.66 ± 22.21	96.74 ± 23.26	−4.09 (−12.89 to 4.72)	0.360
$FEF_{25–75\%}$ (%)	70 (42–90)	88.50 (80–106.35)	724.50	**< 0.001***
$FEF_{25–75\%}$%≤50% (n/%)	14/29.8%	-		
Pulmonary function abnormalities				
Obstructive type	11/23.4%	10/16.7%		**0.039***
Restrictive type	5/10.6%	1/1.7%		
Mixed type	2/4.3%	-		
DLCO (%)	77.21 ± 19.28			

n: frequency, %: percentage, cm: centimeter, 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: diffusing capacity of the lung for carbon monoxide, COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, X: mean, SD: standard deviation, IQR: interquartile range, CI: confidence interval, U: U value, *$p < .05$

Table 3. Comparison of respiratory muscle strength and endurance, peripheral muscle strength in patients with post-COVID-19 with pulmonary involvement and healthy controls.

	Patients with post-COVID-19 ($n = 47$)	Healthy controls ($n = 60$)		
	X±SD/Median ($IQR_{25–75\%}$)	X±SD/Median ($IQR_{25–75\%}$)	Mean difference (95%CI)/U	p
MIP (cmH_2O)	87.34 ± 25.93	109.70 ± 29.58	−22.36 (−33.02 to −11.70)	**< 0.001***
MIP (%)	74.78 (61.72–86.75)	87.80 (79.15–110.49)	759.00	**< 0.001***
MEP (cmH_2O)	125.98 ± 38.00	167.70 ± 47.98	−41.72 (−58.20 to −25.24)	**< 0.001***
MEP (%)	69.25 ± 16.70	90.04 ± 19.45	−20.79 (−27.85 to −13.72)	**< 0.001***
Inspiratory muscle weakness (n/%)	14/29.8%	1/1.7%		**< 0.001***
Expiratory muscle weakness (n/%)	8/17%			**0.001***
Respiratory muscle endurance (min*cmH_2O)	4566.00 (1795.50–9825.60)	20057.00 (10566.40–47808.00)	370.00	**< 0.001***
Quadriceps femoris (N) (ND)	231.00 (206.00–268.00)	310.96 (310.96–353.50)	406.00	**< 0.001***
Quadriceps femoris (%)	65.63 (56.66–74)	86.62 (72.90–95.96)	493.00	**< 0.001***
Shoulder abductor (N) (ND)	151 (118–187)	182.50 (160.34–205.95)	804.50	**< 0.001***
Shoulder abductor (%)	83.82 ± 21.70	103.31 ± 29.67	−19.49 (−29.34 to −9.64)	**< 0.001***
Quadriceps femoris muscle weakness (n/%)	37/78.7%	23/38.3%		**< 0.001***
Shoulder abductor muscle weakness (n/%)	21/44.7%	12/20%		**0.011***

MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure, N: Newton, ND: non-dominant, n: frequency, cmH_2O: centimeter water pressure, %: percentage, min: minute, X: mean, SD: standard deviation, IQR: interquartile range, CI: confidence interval, U: U value, ***$p < .05$**.

diffusion impairment (Pellegrino et al, 2005). Conversely, 38.3% of the patients in the current study had pulmonary function abnormalities, predominantly of the obstructive type. Zhou et al. (2021) demonstrated that FEV_1% and FVC% were in normal ranges in patients with COVID-19 who had lung involvement and found no relation between residual lesions on CT and obstructive ventilatory parameters, unlike DLCO (Zhou et al, 2021).

Chaiwong et al. (2023) showed that $FEF_{25–75\%}$%, an obstructive parameter, was within normal ranges in patients with COVID-19 who had pulmonary involvement, in contrast to our findings (Chaiwong et al, 2023). Chaiwong et al. (2023) did not report the severity of pulmonary involvement. However, the prevalence of smokers among patients was higher in our study, and Chaiwong et al. (2023) excluded patients with chronic respiratory diseases. However, 79.5% of the patients had

Table 4. Comparison of cardiopulmonary exercise test in patients with post-COVID-19 with pulmonary involvement and healthy controls.

	Patients with post-COVID-19 ($n = 47$)	Healthy controls ($n = 60$)		
	X±SD/Median ($IQR_{25-75\%}$)	X±SD/Median ($IQR_{25-75\%}$)	Mean difference (95%CI)/U	p
VO_{2peak} (ml/kg/min)	18.35 ± 4.37	27.64 ± 4.77	−9.28 (−11.06 to −7.50)	**< 0.001***
VO_{2peak} (%)	80.25 ± 20.38	115.68 ± 18.24	−35.42 (−42.87 to −27.97)	**< 0.001***
VO_{2peak} (ml/min)	1422.04 ± 433.26	2123.42 ± 392.53	−701.38 (−862.75 to −540.01)	**< 0.001***
VCO_{2peak} (ml/min)	1471.32 ± 533.43	2247.77 ± 477.92	−776.45 (−973.31 to −579.60)	**< 0.001***
RER_{peak}	1.04 (0.94–1.13)	1.06 (1.03–1.13)	1156.50	0.143
HR_{peak} (beats/min)	154 (138–163)	165 (156–169)	789.50	**< 0.001***
HR_{peak} (%)	95 (90–100)	99 (97–102)	748.00	**< 0.001***
HRR_{peak} (beats/min)	7 (1–14)	1 (−2–5)	748.50	**< 0.001***
$HRR_{recovery}$ (beats/min)	18.63 ± 10.83	36.48 ± 21.53	−17.85 (−25.66 to −10.04)	**< 0.001***
CI	84.52 ± 19.35	99.96 ± 13.67	−15.44 (−21.81 to −9.07)	**< 0.001***
CI < 80%	12/25.5%	5/8.5%		
MET_{peak}	5.22 ± 1.25	7.81 ± 1.39	−2.60 (−3.11 to −2.08)	**< 0.001***
VO_2/HR_{peak} (ml/beats)	9.60 ± 2.69	13.04 ± 2.49	−3.44 (−4.44 to −2.44)	**< 0.001***
VO_2/HR_{peak} (%)	82.12 ± 23.80	110.19 ± 20.25	−28.07 (−36.56 to −19.59)	**< 0.001***
$ATVO_{2peak}$ (% predicted)	57.02 ± 17.52	78.19 ± 17.82	−21.17 (−28.10 to −14.24)	**< 0.001***
BR_{peak} (%)	27.06 ± 15.41	18.14 ± 13.11	8.93 (3.32 to 14.53)	**0.002***
BF_{peak} (breaths/min)	42.19 ± 7.04	35.14 ± 8.06	7.05 (4.13 to 9.98)	**< 0.001***
$Load_{peak}$ (%)	265.85 ± 92.26	320.30 ± 73.12	−54.45 (−87.22 to −21.69)	**0.001***
SpO_{2peak}(%)	95 (92–98)	99 (98–99)	676.50	**< 0.001***
V_{Epeak} (l/min)	70.06 ± 20.52	82.05 ± 20.13	−11.99 (−19.86 to −4.11)	**0.003***
V_E/VO_2				
Resting	36.78 ± 9.48	31.99 ± 5.25	4.79 (1.71 to 7.87)	**0.003***
Peak workload	45.50 (40.40–53.00)	36.80 (32.60–40.80)	548.00	**< 0.001***
V_E/VCO_2				
Resting	48.19 ± 8.75	41.01 ± 4.84	7.18 (4.30 to 10.05)	**< 0.001***
Peak workload	45.65 ± 8.29	35.00 ± 4.69	10.64 (7.93 to 13.345)	**< 0.001***
$PETCO_2$				
Resting	22.42 (3.74–25.42)	3.75 (3.52–4.01)	623.00	**< 0.001***
Peak workload	27.75 (4.65–30.60)	4.38 (3.89–4.77)	528.50	**< 0.001***
Δ SpO_2 (%)	−4 (−8 – (−1)	0 (−1–1)	482.50	**< 0.001***
Δ SBP (mmHg)	30 (20–40)	42.50 (30–70)	823.50	**< 0.001***
Δ DBP (mmHg)	10 (10–20)	10 (0–20)	1126.50	0.118
Δ Dyspnea (m. Borg Scale 0–10 points)	4 (2–5)	1.75 (0–3)	743.50	**< 0.001***
Δ General fatigue (m. Borg Scale 0–10 points)	3 (1–4)	2.50 (0–3.50)	1178.00	0.227

RER: respiratory exchange ratio, MET: metabolic equivalent, VO_{2peak}: peak oxygen uptake, VCO_{2peak}: peak carbon dioxide output, V_{Epeak}: peak minute ventilation, HR: heart rate, HRR: heart rate reserve, VO_2/HR: oxygen pulse, BF: breathing frequency, SpO_2: peripheral oxygen saturation, $PETCO_2$: partial pressure of carbon dioxide, BR: breathing reserve, SBP: systolic blood pressure, DBP: diastolic blood pressure, m. Borg Scale: modified Borg Scale, Δ: difference between post and pre test value, CI: Chronotropic incompetence, ml: milliliter, min: minutes, kg: kilogram, %: percentage, X: mean, SD: standard deviation, IQR: interquartile range, CI: confidence interval, U: U value, *$p < .05$.

comorbidities, predominantly with chronic lung diseases (31.4%) in our study.

A chest CT reveals that air-trapping, known as small airway disease, is a persistent consequence of COVID-19 (Cho et al, 2022). Small airways, characterized by non-cartilaginous with an internal diameter under 2 mm, provide minimal support for overall airway resistance (Burgel et al, 2013). As a result, small airway disease often remains undetected by spirometry until more than 75% of the small airways are occluded (Hogg, 2004). Upon reviewing CT scans of patients with COVID-19, acute lung lesions associated with the virus gradually disappeared, while fibrotic lesions emerged during the recovery phase. Furthermore, airway remodeling and fibrosis during recovery can last over 12 months (Zhou et al, 2021). In the present study, the duration of COVID-19 diagnosis among the patients was 83.06 ± 37.60 weeks. The prolonged timeframe for airway remodeling may explain why most patients exhibit obstructive-type pulmonary function abnormalities in our study, which warrants further investigation.

Assessing the respiratory muscles' strength and endurance is crucial for understanding their function (Laveneziana et al, 2019). Anastasio et al. (2021) observed a reduction in respiratory muscle strength in patients with COVID-19 pneumonia after four months. This study revealed that the impairment of inspiratory muscle strength was more significant in patients without lung injury than in those with lung injury (Anastasio et al, 2021). Another study found that patients with long-COVID-19, particularly those hospitalized in an intensive care unit, experience inspiratory muscle dysfunction linked to reduced neural drive activity (Hennigs et al, 2022). In contrast to previous studies (Anastasio et al, 2021; Hennigs et al, 2022), Sirayder, Inal-Ince, Kepenek-Varol, and Acik (2022)

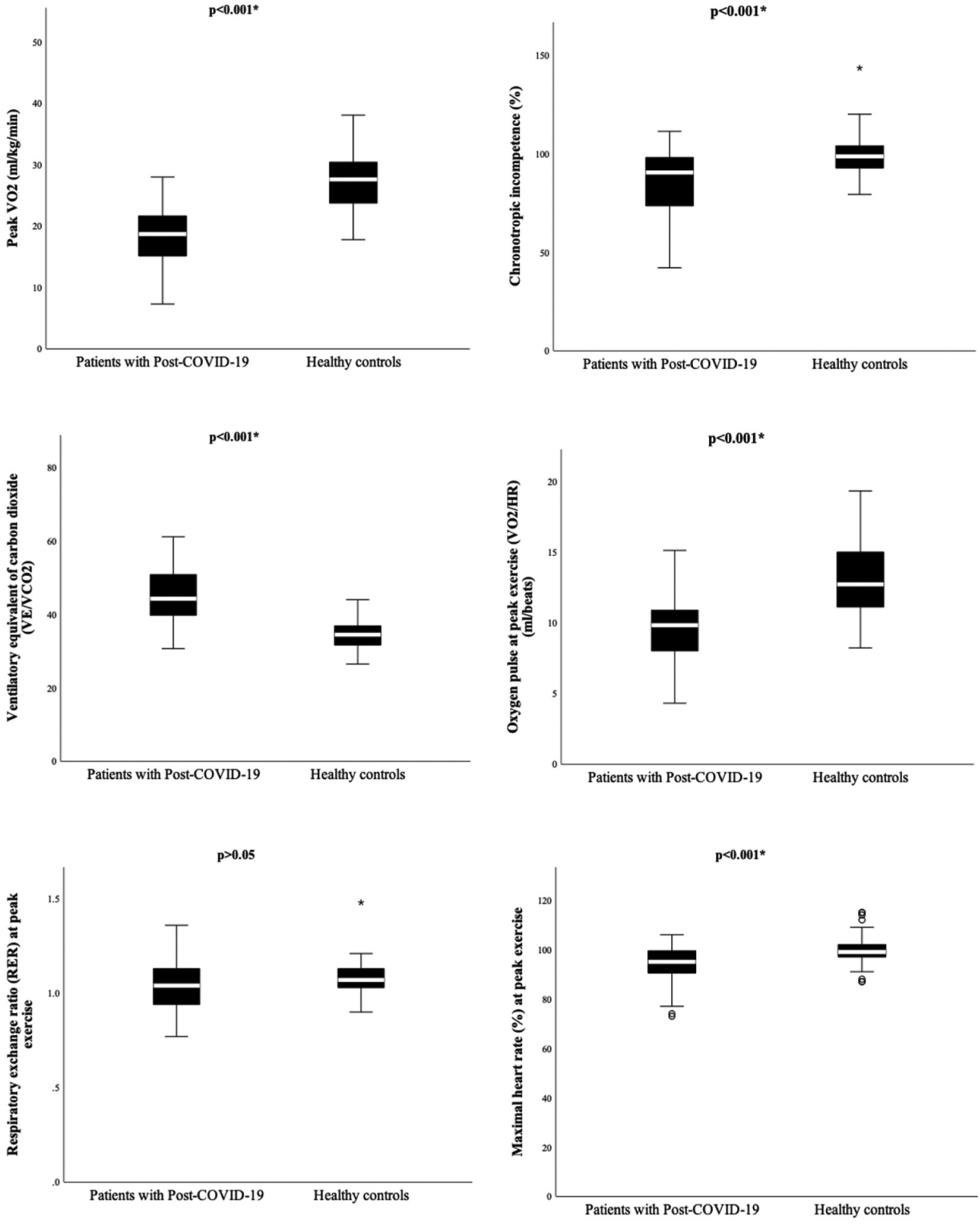

Figure 2. Comparison of cardiopulmonary exercise test parameters at peak exercise in patients with post-COVID-19 with pulmonary involvement and healthy controls.

demonstrated that although half of the patients with COVID-19 pneumonia received corticosteroid therapy or invasive mechanical ventilation, patients' respiratory muscle strength was preserved at 6 months (Sirayder, Inal-Ince, Kepenek-Varol, and Acik, 2022).

The current literature provides no information about respiratory muscle endurance in patients following COVID-19. The present study reveals that patients with post-COVID-19 who had pulmonary involvement exhibit impaired respiratory muscle strength and endurance,

Table 5. Comparison of physical activity level and dyspnea in patients with post-COVID-19 with pulmonary involvement and healthy controls.

	Patients with post-COVID-19 ($n = 47$)	Healthy controls ($n = 60$)		
	X±SD/Median ($IQR_{25-75\%}$)	X±SD/Median ($IQR_{25-75\%}$)	Mean difference (95%CI)/U	p
Total energy expenditure (J/d)	9576.00 (8412.00–10746.00)	10795.50 (9550.00–12427.00)	825.00	**< 0.001***
Active energy expenditure (> 3 METs) (J/d)	953.00 (491.00–1774.00)	1859.50 (1231.00–2781.00)	778.00	**< 0.001***
Daily physical activity duration (> 3 METs) (min/d)	47 (29–90)	85 (64–143.50)	815.00	**< 0.001***
Average metabolic equivalent (METs/d)	1.30 (1.10–1.40)	1.40 (1.30–1.50)	819.50	**< 0.001***
According to average METs				
Inactive	45 (95.7%)	48 (80%)		**0.020***
Low active	2 (4.3%)	12 (20%)		
Number of steps (steps/d)	5776.81 ± 2783.82	8883.67 ± 3783.19	−3106.86 (−4413.07 to −1800.65)	**< 0.001***
According to the number of steps				
Inactive	22 (46.8%)	11 (18.3%)		**0.001***
Low active	10 (21.3%)	12 (20%)		
Somewhat active	11 (23.4%)	15 (25%)		
Active	4 (8.5%)	9 (15%)		
Highly active	-	13 (21.7%)		
Lying down (min/d)	498.00 (444.00–557.00)	459.00 (396.50 to 521.00)	1058.50	**0.027***
Sleep duration (min/d)	396.89 ± 105.90	370.43 ± 99.56	26.46 (−13.08 to 66.00)	0.187
Dyspnea on exertion (m. Borg Scale 0–10 points)	3 (3–5)	0 (0–0.50)	154.50	**< 0.001***

METs: metabolic equivalent of the task, J: joule; d: day, min: minute, m. Borg Scale: modified Borg Scale, X: mean, SD: standard deviation, IQR: interquartile range, CI: confidence interval, U: U value, *$p < .05$.

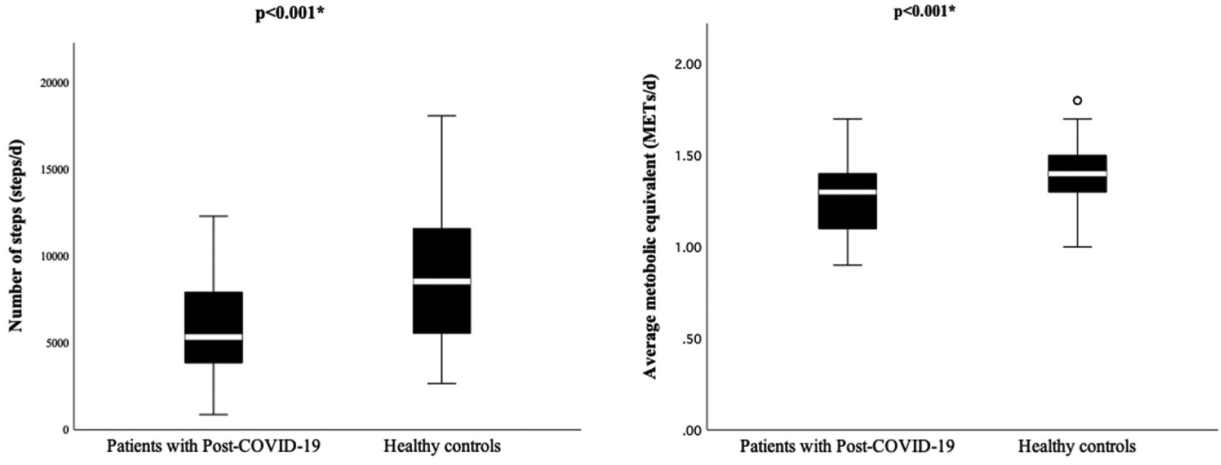

Figure 3. Comparison of physical activity levels in patients with post-COVID-19 with pulmonary involvement and healthy controls.

with 29.8% and 17% of patients having inspiratory and expiratory muscle weakness, respectively. This deterioration may be attributable to myopathy of the respiratory muscles following COVID-19. Diaphragm myopathy, caused by the elevated expression of genes associated with fibrosis, has been observed in patients with COVID-19 (Shi et al, 2021). Vonbank et al. (2024) demonstrated that systemic inflammation and immune cell infiltration into muscles can lead to pathological changes in muscle fibers, thereby impairing their ability to contract despite normal nerve conduction (Vonbank et al, 2024). Lung involvement related to COVID-19 may impair respiratory muscle function. Radiological changes in COVID-19 begin with interstitial thickening and progress to alveolar destruction, resulting in a decreased alveolar space (Spagnolo et al, 2020). Reduced alveolar volume may alter the configuration of the respiratory muscles and the chest wall (Anastasio et al, 2021). Nonetheless, the impact of the severity of lung involvement following post-COVID-19 on respiratory muscle functions remains unclear. Therefore, this requires further investigation.

Prior research documented skeletal muscle weakness in COVID-19 (Gérard et al, 2021; Ramírez-Vélez et al, 2023a; Tanriverdi, Savci, Kahraman, and Ozpelit, 2022). Ramírez-Vélez et al. (2023a) revealed that impairment in peripheral muscle strength is associated with a decline in skeletal muscle mass in non-hospitalized patients with long COVID-19 (Ramírez-Vélez et al, 2023a). Tanriverdi, Savci, Kahraman, and Ozpelit (2022) reported that patients with post-COVID-19 with moderate disease exhibited more significant muscle weakness compared to those with mild disease (Tanriverdi, Savci, Kahraman, and Ozpelit, 2022). Ramírez-Vélez et al. (2023b) reported lower extremity muscle weakness in patients with post-COVID-19, even in the absence of lung pathology and hospitalization, despite preserved hand grip strength (Ramírez-Vélez et al, 2023b). Unlike our study, Ramírez-Vélez et al. (2023b) evaluated upper extremity strength using a small muscle group, rather than shoulder abduction. The present study found that patients with post-COVID -19 who had pulmonary involvement experienced muscle weakness in both the upper and lower extremities, especially in larger muscle groups.

Muscle loss may arise from COVID-19 infection, which elevates levels of angiotensin-converting enzyme 2 (Ferrandi, Alway, and Mohamed, 2020). Subsequently, this causes an overproduction of cytokines, which disrupts muscle homeostasis. Additionally, muscle weakness may be linked to malnutrition, prolonged bed rest, physical inactivity, and corticosteroid use (Welch et al, 2020). The clinical characteristics and physical inactivity levels of the patients in our study support this hypothesis. However, the mechanisms underlying the effects of pulmonary involvement on muscle strength remain unknown. Thus, further studies are needed to compare muscle strength in patients with lung impairment to that of patients without it.

Decreased oxygen consumption has been reported in patients with post-COVID-19 who had lung involvement (da Silveira et al, 2024; Rinaldo et al, 2021). The present study reported that 63.8% of the patients with lung involvement related to COVID-19 had predicted VO_{2peak} below 85%. Rinaldo et al. (2021) found no correlation between lower VO_2 and lung involvement, despite 60% of patients having lung involvement due to COVID-19 (Rinaldo et al, 2021). da Silveira et al. (2024) attributed the decline in oxygen consumption to damage in the cardiocirculatory system and insufficiency in peripheral muscle function in patients with post-COVID-19 who had lung involvement. However, Rinaldo et al. (2021) and da Silveira et al. (2024) did not report the extent of lung involvement severity. In contrast to those (da Silveira et al, 2024; Rinaldo et al, 2021), our study showed that the ventilatory, cardiovascular, and gas exchange systems are insufficient during exercise in patients with lung involvement. A $VE/VO_2 > 40$ indicates an inadequate ventilation-perfusion ratio, suggesting mitochondrial myopathy; meanwhile, $VE/VCO_2 > 34$ at peak exercise in COPD signifies an abnormal exercise response, likely due to increased dead space (Neder et al, 2019; Taivassalo et al, 2003). The median VE/VO_2 at peak exercise was 45.50, suggesting that the patients with post-COVID-19 who had pulmonary involvement have oxidative defects, while VE/VCO_2 at peak exceeded 34, indicating an impaired exercise response in the current study. Moreover, the $PETCO_2$ was also elevated, suggesting a potential link to increased dead space in our study (Wasserman et al, 1987).

Diminished oxygen consumption, ventilatory insufficiency, and worse physiological responses at the CPET may be attributed to pulmonary involvement. Furthermore, residual impairment of the alveolar-capillary barrier due to COVID-19 may lead to a ventilation-perfusion mismatch (Dhont et al, 2020). Damaged lung endothelium from COVID-19 may activate inflammatory markers through cytokines and adhesion molecules, potentially causing scar tissue in the lung during recovery (Evans et al, 2020). Future studies need to investigate the effects of the severity of pulmonary involvement on exercise capacity and physiological responses in patients with post-COVID-19.

Previous studies indicated that chronotropic response worsens in patients with post-COVID-19 (Durstenfeld et al, 2023; Ladlow et al, 2022), suggesting that CI restricts oxygen consumption .Jimeno-Almazán et al. (2021) noted that patients with COVID-19 often exhibit autonomic dysfunction (Jimeno-Almazán et al, 2021). Patients with autonomic dysfunction struggle to elevate heart rate and cardiac output during exercise, resulting in reduced peripheral muscle perfusion (Zweerink et al, 2018). In the present study, 12 (25.5%) of the 47 patients could not proceed with the test due to dyspnea, and 7 (58.3%) of those patients displayed CI. Ladlow et al. (2022) reported that patients with post-COVID-19 who had CI showed slower heart rate recovery at one minute after CPET and found a significant link between CI and reduced ventilatory efficiency (Ladlow et al, 2022). Our findings indicated that patients with post-COVID-19 who had lung involvement exhibited impaired ventilatory efficiency and heart rate recovery, similar to that reported by Ladlow et al. (2022) (Ladlow et al, 2022). Unfortunately, the studies mentioned above did not provide transparent information about lung damage in patients (Durstenfeld et al, 2023; Ladlow et al, 2022). Pulmonary involvement

following COVID-19 may indirectly lead to CI during CPET in patients with post-COVID-19 by resulting in ventilation-perfusion mismatch. Nevertheless, the impact of pulmonary involvement on CI in COVID-19 remains to be fully understood, and further studies are required.

In the literature, questionnaires were the most commonly used tool to assess physical activity levels in COVID-19 (Hennigs et al, 2022; Tanriverdi, Savci, Kahraman, and Ozpelit, 2022). The study showed that reduced physical activity is linked to ongoing symptoms, particularly increased dyspnea after post-COVID-19 (Hennigs et al, 2022). Tanriverdi, Savci, Kahraman, and Ozpelit (2022) employed the International Physical Activity Questionnaire, indicating that as COVID-19 severity increased, physical activity levels decreased and sitting duration increased (Tanriverdi, Savci, Kahraman, and Ozpelit, 2022). The present study utilized a metabolic holter, the most valid and reliable method (Segura-Jimenez et al, 2013), and included healthy controls, contrasting with earlier studies that relied on questionnaires (Hennigs et al, 2022; Tanriverdi, Savci, Kahraman, and Ozpelit, 2022). In the current study, 46.8% of patients had fewer than 5000 steps daily (Tudor-Locke and Bassett, 2004), and 95.7% of patients and 80% of controls were inactive based on MET values (Ainsworth et al, 2011). Our findings suggest that patients with post-COVID-19 who had pulmonary involvement were either inactive or less active and also chose to spend less time in moderate-to-vigorous intensity activities, primarily remaining seated throughout the day. In our study, the average daily physical activity duration was 47 minutes, while the duration of sitting exceeded 8 hours in the patients (Stamatakis et al, 2019). The results of our study clearly demonstrate the predominantly sedentary lifestyles in patients with post-COVID-19 who had lung involvement. A study confirmed that our findings regarding physical activity levels, measured via questionnaire, decreased in patients with severe post-COVID-19 lung involvement after six months (Sirayder, Inal-Ince, Kepenek-Varol, and Acik, 2022). Pulmonary involvement leading to pulmonary microcirculatory impairment may result in a high dead space fraction of tidal volume during maximal exercise tests. This could lead to physical inactivity by exacerbating dyspnea perception in patients with post-COVID-19 (Lafetá et al, 2023).

Dyspnea on exertion improved over time in post-COVID-19; however, certain patients with lung involvement still experienced dyspnea at six months (Özmen et al, 2024). Similar to our findings, Huang et al. (2021) reported that patients with lung involvement due to COVID-19 continue to suffer from dyspnea during daily living activities at 1-year follow-up (Huang et al, 2021). Dyspnea in patients with lung involvement after COVID-19 may result from endothelial injury, diffuse alveolar damage, and pulmonary fibrosis. These alterations in the lung can lead to reduced diffusion capacity (Xu et al, 2020). In COVID-19, inflammation also contributes to dyspnea by affecting lung parenchyma and muscle structure, which decreases lung compliance, diminishes respiratory muscle strength, and disrupts the balance between muscle force and the effort required for breathing (Silva et al, 2021).

Limitations and future directions

Patients with pulmonary involvement related to COVID-19 were included in our study. Furthermore, evaluating the maximal exercise capacity and physical activity through objective methods provided more detailed and accurate knowledge. Another strength of the current study is the high power calculated using VO_{2peak} [$(1-\beta) = 100\%$]. However, there were no restrictions regarding the severity of pulmonary involvement that could potentially impact the findings of this study. Further studies are necessary to understand how lung involvement in post-COVID-19 affects pulmonary and clinical outcomes. Therefore, intra-and extrapulmonary functions should be compared in future studies in patients with and without pulmonary involvement due to COVID-19.

Conclusions

Patients with post-COVID-19 who had pulmonary involvement showed deteriorated maximal exercise capacity and chronotropic response, impaired pulmonary and respiratory functions, weakened peripheral muscle strength, decreased physical activity level, and higher dyspnea on exertion. A sedentary lifestyle and higher dyspnea perception during daily living activities were typical in these patients. Our findings highlight that patients with pulmonary involvement resulting from COVID-19 have severe intra- and extrapulmonary impairments, and that these impairments will possibly worsen in the long term. Therefore, a comprehensive evaluation should be considered to define impairments in patients with post-COVID-19 syndrome who have known pulmonary involvement. These patients should be included in individualized and comprehensive pulmonary rehabilitation programs, including aerobic and resistance exercises, respiratory muscle strength and endurance training, and physical activity counseling, as

soon as possible to prevent or improve long-term impairments.

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Author contributions

CRediT: **Ece Baytok MSc, PT:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing; **Meral Boşnak Güçlü PhD, PT:** Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing; **Başak Kavalcı Kol PhD, PT:** Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing; **Nilgün Yılmaz Demirci MD:** Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing.

Disclosure statement

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ORCID

Ece Baytok MSc, PT http://orcid.org/0000-0003-0745-4251
Meral Boşnak Güçlü PhD, PT http://orcid.org/0000-0002-3861-9912
Başak Kavalcı Kol PhD, PT http://orcid.org/0000-0002-5346-8753
Nilgün Yılmaz Demirci MD http://orcid.org/0000-0001-6160-3778

Availability of data and materials

Due to concerns about sensitivity and patient privacy, the data from this study are not freely accessible. However, the corresponding author can provide the data upon reasonable request.

Ethics approval and consent to participate

This cross-sectional study was approved by the Ethics Committee of the Gazi University Clinical Research (2022--608) and performed by the Declaration of Helsinki. All the participants provided written informed consent.

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