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Original Article

Comparison of cardiopulmonary fitness level with normal values after COVID-19 and evaluation of factors affecting physical capacity

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ABSTRACT

Objectives: This study aims to investigate whether exercise capacity changes following coronavirus disease 2019 (COVID-19), to clarify its relationship with age, sex, physical activity, disease severity, and comorbidities, and to identify the factors affecting exercise capacity.

Patients and methods: Between June 2021 and June 2022. A total of 132 participants (61 males, 71 females; mean age: 43.3±12.4 years; range, 24 to 74 years) who were older than 18 years and had a history of COVID-19 were included at least 30 days after the recovery of all COVID-19 symptoms. The International Physical Activity Questionnaire-Short Form, six-minute walk test, pulmonary function tests, and cardiopulmonary exercise test were performed.

Results: Of the study population, 23.1% had decreased exercise capacity 86 days after the COVID-19 diagnosis. Younger age (p=0.049), male sex (p=0.003), and disease severity (p=0.007) were related to lower VO_{2max} (adjusted R^2=0.132, p<0.001). Compared to individuals with normal exercise capacity, in those with decreased exercise capacity, vital capacity (p<0.001), forced vital capacity (p=0.002), forced expiratory volume in 1 sec (p=0.006), and maximum voluntary ventilation (p=0.027) were lower, and the anaerobic threshold was reached earlier (p<0.001).

Conclusion: The exercise capacity of certain individuals was low nearly three months after COVID-19. Younger age, male sex, and COVID-19 severity were related to low exercise capacity. Respiratory dysfunctions and physical inactivity-induced deconditioning were the factors affecting exercise capacity.

Keywords: Cardiopulmonary exercise test, COVID-19, exercise tolerance, pulmonary function tests, six-minute walk test.

In December 2019, a novel coronavirus strain was discovered in Wuhan, China. The World Health Organization (WHO) designated the novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused by SARS-CoV-2 was referred to as coronavirus disease 2019 (COVID-19).[1] On March 11th, 2020, the WHO declared a pandemic due to an abrupt increase in the number of cases across many different countries.[2]

Mostly affecting the upper and lower respiratory tracts, COVID-19 can also have an impact on other organs and systems. Particularly in hospitalized COVID-19 patients, neurological disorders, thromboembolic events, kidney, liver, and cardiac damage may occur. From upper respiratory tract infection and mild pneumonia to septic shock and multiple organ failure, COVID-19 has a broad clinical spectrum.[3] There are several factors affecting the prognosis of COVID-19. Older age, male sex, and physical inactivity have been associated with a poor prognosis.[4,5] Comorbidities which are linked to a poor prognosis include smoking, cardiovascular disorders, diabetes, hypertension, and chronic obstructive pulmonary disease (COPD).[6]

A different coronavirus strain called SARS-CoV is the cause of the disease known as severe acute respiratory syndrome (SARS), which led to a global

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outbreak at the beginning of this century. This disease has a similar clinical course to COVID-19.[7] A decline in exercise capacity that persists for one to two years after SARS was reported.[8] Certain individuals experience persistent symptoms and a limitation in their participation in the activities of daily living after COVID-19.[9] Considering the similar origin and clinical course of COVID-19 and SARS, functional impairments after COVID-19 suggest that there may be a similar decline in the exercise capacity of individuals following COVID-19, for whom rehabilitation interventions should be initiated.[10] Clarifying the traits of people with decreased exercise capacity may make it easier to identify, from the sizable COVID-19 patient pool, those who would be candidates for rehabilitation. Also, identifying the factors influencing exercise capacity may make it easier to create rehabilitation programs that are tailored to the needs of the patients.

In the light of previous studies,[8,9] we hypothesized that individuals experienced a decline in their exercise capacity affecting their functional levels following COVID-19. In the present study, we, therefore, aimed to investigate whether exercise capacity changed following COVID-19 and to clarify its relationship with age, sex, physical activity level, disease severity, and comorbidities. In addition, we also aimed to determine the causes of potential changes in exercise capacity and to define the objectives of rehabilitation programs.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at Ankara University Faculty of Medicine, Department of Physical Medicine and Rehabilitation Clinic between June 2021 and June 2022. A total of 132 participants (61 males, 71 females; mean age: 43.3±12.4 years; range, 24 to 74 years) who were older than 18 years and had a history of COVID-19 were included at least 30 days after the recovery of all COVID-19 symptoms. Exclusion criteria were as follows: first five days after myocardial infarction, unstable angina pectoris, active endocarditis, myocarditis, pericarditis, symptomatic severe aortic stenosis, decompensated heart failure, acute pulmonary embolism, pulmonary infarction, deep venous thrombosis, suspected dissecting aortic aneurysm, uncontrolled asthma, resting oxygen saturation of less than 85% in room air, respiratory failure, acute non-cardiopulmonary disorders that may affect exercise performance or be exacerbated by exercise, mental impairment, high grade atrioventricular block, uncontrolled arterial hypertension, orthopedic, neurological, or systemic impairments that may hamper the performance of assessments. Written informed consent was obtained from each individual. The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (Date: 10.12.2020, No: İ11-670-20). The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov with the number of NCT04753346.

In order to ensure a well-balanced participant population for the study, a total of 40 subgroups were created depending on the combination of age (20-29, 30-39, 40-49, 50-59, and 60+), sex (male and female), and disease severity (mild, moderate, severe, and critical). The primary outcome of the study was maximum oxygen consumption (VO_{2max}), which is the gold standard indicator for exercise capacity.[11] The sample size for each subgroup was estimated to be six, assuming the mean ± standard deviation of the difference between the measured VO_{2max} in the study population and the predicted VO_{2max} for their healthy counterparts was 3±2, with $p<0.05$ and $1-\beta=0.80$. The study was intended to involve 240 participants in total, with six participants in each of the 40 subgroups.

The individuals' demographic data, comorbidities, COVID-19 symptoms, and treatments for COVID-19 were recorded. The time from the positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 to the assessment was also recorded. The severity of COVID-19 was classified into four categories, which are mild, moderate, severe, and critical, regarding the WHO's recommendations.[12] The Turkish version of the International Physical Activity Questionnaire-Short Form (IPAQ-SF), which is valid and reliable for assessment of physical activity, was utilized to classify physical activity levels before and after COVID-19 into three categories (low, moderate, and high).[13]

Pulmonary function tests (PFTs) were performed in accordance with the guidelines of the European Respiratory Society (ERS) and the American Thoracic Society (ATS).[14,15] The vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), FEV_1/FVC, and maximum voluntary ventilation (MVV) were measured using the Vyntus CPX Metabolic Cart (CareFusion-Vyaire, Hochberg, Germany) and additionally presented as a percentage of the predicted value (%pred) of healthy counterparts. In compliance with ATS standards, six-minute walk test (6MWT) was conducted, and walking distance was measured to evaluate functional capacity.[16]

Cardiopulmonary exercise test (CPET) was performed to assess the exercise capacity by following the American Heart Association's recommendations.[17] It was implemented on a treadmill (The Ars-Efor ECG Stress Test System, Kardinero Medical Systems, Ankara, Türkiye) with Bruce or modified Bruce protocols.[18] Maximum oxygen consumption (VO_{2max}), oxygen consumption at anaerobic threshold (VO_{2AT}), respiratory exchange ratio (RER), and maximum heart rate (HR_{max}) were measured using the Vyntus CPX Metabolic Cart (CareFusion-Vyaire, Hochberg, Germany). The ratio of measured VO_{2max} to predicted VO_{2max} of healthy counterparts (VO_{2max} [%pred]), the ratio of oxygen consumption at anaerobic threshold to predicted VO_{2max} of healthy counterparts (VO_{2AT} [%]), and the ratio of the maximum heart rate to the heart rate estimated from the “220-age” equation (HR_{max} [%]) were calculated. The VO_{2max} (%pred) >84 was regarded as normal exercise capacity.[11] Perceived exertion and dyspnea were measured using the Modified Borg Scale (MBS) at the end of the CPET.[19]

All assessments and tests were performed by the same researcher and completed on the same day for each individual.

Statistical analysis

Statistical analysis was performed using the R statistical software version 4.2.1 (R Foundation, Vienna, Austria). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The Kolmogorov-Smirnov test was utilized to analyze the distributions of the variables. The homogeneity of variances was evaluated using Levene's test. The Pearson chi-square test, one-way analysis of variance (ANOVA) test, and Kruskal-Wallis test were used to compare the sociodemographic features and CPET parameters of the individuals with varying COVID-19 severity. The Pearson chi-square test, Fisher exact test, Mann-Whitney U test, and independent sample t-test were used to compare the sociodemographic features, comorbidities, COVID-19 symptoms, physical activity level, alteration in physical activity level, and parameters of 6MWT, PFTs, and CPET of the individuals with decreased and normal exercise capacity. The Pearson or Spearman correlation analysis was utilized to analyze the relationship between disease severity, walking distance, and the parameters of PFTs and CPET. They were marked with superscripted a and b symbols in the main text, respectively. The correlation coefficient's magnitude was determined.[20] Multivariate linear regression analysis was performed to estimate the effect of various variables on VO_{2max} (%pred). A p value of <0.05 was considered statistically significant.

RESULTS

Fatigue (90.2%), myalgia (70.5%), headache (67.4%), cough (67.4%), and fever (57.6%) were the most common COVID-19 symptoms experienced in the study population. Treatments for COVID-19 that were most frequently used were favipiravir (62.9%), corticosteroids (27.3%), and hydroxychloroquine (11.4%). The most common comorbidities were obesity (21.2%), hypertension (17.4%), smoking (11.4%), diabetes mellitus (type 2) (9.1%), and atherosclerotic cardiac disease (8.3%). The median time frame between the positive RT-PCR test for SARS-CoV-2 and the assessments was 86 (range, 31 to 272) days.

Sociodemographic features, PFTs parameters, 6MWT, and CPET parameters of the individuals with mild, moderate, severe, and critical disease severity are shown in Table 1 and Table 2. There were no statistically significant differences in age (p=0.258), sex (p=0.173), or time (p=0.547) between the groups with varying disease severity. In terms of VO_{2max} (%pred), there was no statistically significant difference between the individuals with different disease severity categories. A weak negative correlation was identified between disease severity and walking distance (r=−0.252, p^b=0.004). There was a weak negative correlation between disease severity and VC (%pred) (r=−0.279, p^b=0.001), FVC (%pred) (r=−0.331, p^b<0.001), and FEV_1 (%pred) (r=−0.256, p^b=0.003). There was a weak positive correlation between disease severity and FEV_1/FVC (%pred) (r=0.207, p^b=0.017). No correlation was found between disease severity and MVV (%pred) (r=−0.089, p^b=0.309).

TABLE 1
Descriptive statistics of sociodemographic features, pulmonary function tests parameters, and 6MWT of the individuals with mild, moderate, severe, and critical disease severity

Disease severity	Mild (n=53)	Moderate (n=44)	Severe (n=26)	Critical (n=9)	Total (n=132)
Sociodemographic features					
Age (year) (mean±SD)	41.7±12.5	42.6±12.1	46.1±12.1	48.7±12.9	43.3±12.4
Sex					
Male, n (%)	26 (49.1)	23 (52.3)	14 (53.8)	8 (88.9)	61 (46.2)
Time (day), median (min-max)	86 (35-272)	81 (31-247)	85 (33-196)	126 (66-156)	86 (31-272)
	Mild (n=53)	Moderate (n=44)	Severe (n=26)	Critical (n=9)	Total (n=132)
Pulmonary function tests					
VC (liter), median (min-max)	4.2 (2.2-6.6)	4.0 (2.1-6.1)	3.8 (2.0-6.2)	2.8 (1.7-5.3)	3.9 (1.7-6.6)
VC (%pred), median (min-max)	104 (79-135)	101.5 (75-133)	101 (57-136)	82 (30-101)	102 (30-136)
FVC (liter) (mean±SD)	4.1±1.1	3.9±1.1	3.7±1.0	3.1±1.4	3.8±1.1
FVC (%pred), median (min-max)	102 (82-128)	96.5 (73-123)	93.5 (57-129)	83 (28-101)	98 (28-129)
FEV_1 (liter) (mean±SD)	3.6±0.9	3.2±0.9	3.1±0.8	2.7±1.1	3.2±0.9
FEV_1 (%pred) (mean±SD)	101±11	95±16	95±14	75±27	96±16
FEV_1/FVC, median (min-max)	83.7 (68.4-97.8)	83.8 (59.2-90.9)	85.1 (68.0-96.5)	86.9 (78.8-98.8)	84.3 (59.2-98.8)
FEV_1/FVC (%pred), median (min-max)	105 (84-120)	103 (74-117)	106 (85-122)	113 (103-122)	105 (74-122)
MVV (liter) (mean±SD)	126.3±37.4	119.6±38.5	117.1±40.6	130.2±38.4	122.5±38.3
MVV (%pred) (mean±SD)	103±17	98±21	97±23	99±25	100±20
	Mild (n=53)	Moderate (n=44)	Severe (n=25)	Critical (n=9)	Total (n=131)
6MWT					
Walking distance (meter), median (min-max)	600 (420-786)	583 (180-726)	561 (120-705)	438 (174-653)	584 (120-786)

6MWT: Six-minute walk test; SD: Standard deviation; Time: from positive RT-PCR test for SARS-CoV-2 to the assessment; %pred: Percentage of predicted; VC: Vital capacity; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 sec; MVV: Maximum voluntary ventilation.

TABLE 2
Cardiopulmonary exercise test parameters of the individuals with mild, moderate, severe, and critical disease severity

Disease severity	Mild (n=53)	Moderate (n=43)	Severe (n=24)	Critical (n=6)	Total (n=126)	*p*
Cardiopulmonary exercise test						
VO_{2max} ($mL.kg^{-1}.min^{-1}$) (mean±SD)	28.6±5.3	27.6±6.1	24.4±5.7	22.7±8.5	27.2±6.1	&
VO_{2max} (%pred) (mean±SD)	97±13	94±17	96±15	91±24	95±15	0.782[a]
VO_{2AT} ($mL.kg^{-1}.min^{-1}$) (mean±SD)	20.6±4.0	19.6±4.2	17.3±3.5	15.9±5.8	19.4±4.3	&
VO_{2AT} (%) (mean±SD)	70±12	68±15	68±10	64±17	69±13	0.685[a]
RER (mean±SD)	1.08±0.07	1.08±0.08	1.04±0.08	1.10±0.11	1.07±0.08	0.130[a]
HR_{max}, median (min-max)	170 (116-205)	164 (119-194)	161 (81-187)	157.5 (133-174)	166 (81-205)	&
HR_{max} (%), median (min-max)	95 (75-115)	94 (67-114)	91 (55-100)	91 (87-98)	93 (55-115)	0.130[b]
$MBS_{perceived\ exertion}$, median (min-max)	5 (0.5-8)	4 (0-10)	4 (0-10)	5 (3-8)	5 (0-10)	0.447[b]
$MBS_{dyspnea}$, median (min-max)	3 (0-9)	4 (0-8)	2 (0-9)	3.5 (1-10)	3 (0-10)	0.486[b]

SD: Standard deviation; VO_{2max}: Maximum oxygen consumption; %pred: Percentage of predicted; VO_{2AT}: Oxygen consumption at anaerobic threshold; VO_{2AT} (%): Ratio of oxygen consumption at anaerobic threshold to predicted maximum oxygen consumption; RER: Respiratory exchange ratio; HR_{max}: Maximum heart rate; HR_{max}(%): Ratio of the maximum heart rate to the heart rate estimated from the "220-age" equation; kg: kilogram; MBS: Modified Borg Scale; [a] One-way ANOVA test; [b] Kruskal-Wallis test; & Statistical analysis was not conducted between groups since these values differ by age and sex; comparison between groups was analyzed by using %pred values.

TABLE 3
Sociodemographic features, comorbidities, and physical activity level of the individuals with decreased and normal exercise capacity

Exercise capacity	Normal (n=100)	Decreased (n=30)	Total (n=130)	*p*
Sociodemographic features				
Age (year) (mean±SD)	43.6±12.2	41.3±12.5	43.1±12.2	0.384[a]
Sex				
Male, n (%)	51 (51)	19 (63.3)	70 (53.8)	0.235[b]
Time (day), median (min-max)	86 (33-271)	88.5 (31-272)	86.5 (31-272)	0.982[c]
Disease severity (mild and moderate), n (%)	75 (75)	21 (70)	96 (73.8)	0.585[b]
	Normal (n=100)	Decreased (n=30)	Total (n=130)	*p*
Comorbidities				
Asthma, n (%)	2 (2)	1 (3.3)	3 (2.3)	0.548[d]
Atherosclerotic cardiac disease, n (%)	8 (8)	2 (6.7)	10 (7.7)	1.000[d]
Cancer, n (%)	1 (1)	1 (3.3)	2 (1.5)	0.410[d]
Chronic kidney disease, n (%)	4 (4)	0 (0)	4 (3.1)	0.573[d]
Chronic liver disease, n (%)	0 (0)	1 (3.3)	1 (0.8)	0.231[d]
Diabetes mellitus (type 2), n (%)	10 (10)	1 (3.3)	11 (8.5)	0.455[d]
Hypertension, n (%)	18 (18)	4 (13.3)	22 (16.9)	0.749[b]
Immune deficiency, n (%)	0 (0)	1 (3.3)	1 (0.8)	0.231[d]
Obesity, n (%)	24 (24)	4 (13.3)	29 (21.5)	0.213[b]
Pulmonary fibrosis, n (%)	1 (1)	0 (0)	1 (0.8)	1.000[d]
Smoking, n (%)	11 (11)	4 (13.3)	15 (11.5)	0.748[d]
Number of comorbidities, median (min-max)	1 (0-4)	0 (0-3)	0 (0-4)	0.285[c]
	Normal (n=98)	Decreased (n=30)	Total (n=128)	*p*
Physical activity level before COVID-19				
Low, n (%)	26 (26.5)	7 (23.6)	33 (25.8)	
Moderate, n (%)	45 (45.9)	15 (50.0)	60 (46.9)	0.914[b]
High, n (%)	27 (27.6)	8 (26.7)	35 (27.3)	
	Normal (n=89)	Decreased (n=22)	Total (n=111)	*p*
Physical activity level after COVID-19				
Low, n (%)	36 (40.4)	13 (59.1)	49 (44.1)	
Moderate, n (%)	37 (41.6)	4 (18.2)	41 (36.9)	0.122[b]
High, n (%)	16 (18.0)	5 (22.7)	21 (18.9)	

SD: Standard deviation; Time: From positive RT-PCR test for SARS-CoV-2 to the assessment; COVID-19: Coronavirus disease 2019; [a] Independent sample t test; [b] Pearson chi-square test; [c] Mann-Whitney U test; [d] Fisher exact test.

Sociodemographic features, comorbidities, and physical activity levels of the individuals with decreased and normal exercise capacity are summarized in Table 3. There was no statistically significant difference between the groups in terms of sociodemographic features, comorbidities, and physical activity levels. There was a statistically significant difference in the frequency of anosmia-ageusia (55.0% *vs.* 80.0%, p=0.014) and fatigue (87.0% *vs.* 100.0%, p=0.038) during COVID-19 in favor of the individuals with decreased exercise capacity. Similar frequencies were observed for other COVID-19 symptoms.

The 6MWT, PFTs, and CPET parameters of the individuals with decreased and normal exercise capacity are presented in Table 4. No statistically significant difference in walking distance between individuals with decreased and normal exercise capacity was detected. VC (%pred), FVC (%pred),

TABLE 4
6MWT, pulmonary function tests, and cardiopulmonary exercise test parameters of the individuals with decreased and normal exercise capacity

Exercise capacity	Normal (n=99)	Decreased (n=30)	Total (n=129)	*p*
6MWT				
Walking distance (meter), median (min-max)	588 (240-726)	556 (174-786)	584 (174-786)	0.113[a]
	Normal (n=100)	Decreased (n=30)	Total (n=130)	*p*
Pulmonary function tests				
VC (liter), median (min-max)	4.2 (2.0-6.6)	3.6 (1.7-6.1)	4.0 (1.7-6.6)	&
VC (%pred), median (min-max)	104 (72-136)	92 (30-121)	102 (30-136)	<0.001[a]**
FVC (liter) (mean±SD)	3.9±1.1	3.7±1.3	3.9±1.1	&
FVC (%pred), median (min-max)	101 (69-129)	90 (28-120)	98.5 (28-129)	0.002[a]*
FEV_1 (liter) (mean±SD)	3.2±0.9	3.1±1.0	3.2±0.9	&
FEV_1 (%pred) (mean±SD)	99±12	87±21	96±16	0.006[b]*
FEV_1/FVC, median (min-max)	83.8 (64.3-97.8)	84.9 (59.2-98.8)	84.3 (59.2-98.8)	&
FEV_1/FVC (%pred), median (min-max)	104 (81-122)	105.5 (74-122)	105 (74-122)	0.370[a]
MVV (liter) (mean±SD)	123.8±38.0	119.5±40.6	122.8±38.5	&
MVV (%pred) (mean±SD)	102±19	93±23	100±20	0.028[b]*
	Normal (n=99)	Decreased (n=27)	Total (n=126)	*p*
Cardiopulmonary exercise test				
VO_{2max} ($mL.kg^{-1}.min^{-1}$) (mean±SD)	27.9±5.5	24.3±7.2	27.6±6.1	&
VO_{2max} (%pred) (mean±SD)	101±11	75±9	95±15	<0.001[b]**
VO_{2AT} ($mL.kg^{-1}.min^{-1}$) (mean±SD)	20.0±3.9	17.4±5.0	19.4±4.3	&
VO_{2AT} (%) (mean±SD)	73±10	54±10	69±13	<0.001[b]**
RER (mean±SD)	1.08±0.07	1.05±0.09	1.07±0.08	0.115[b]
HR_{max}, median (min-max)	168 (116-205)	163 (81-194)	166 (81-205)	&
HR_{max} (%), median (min-max)	95 (75-115)	89 (55-110)	93 (55-115)	0.005[a]*
MBS perceived exertion, median (min-max)	5 (0-10)	4 (0-9)	5 (0-10)	0.724[a]
MBS dyspnea, median (min-max)	3 (0-10)	4 (0-8)	3 (0-10)	0.746[a]

6MWT: Six-minute walk test; SD: Standard deviation; %pred: Percentage of predicted; VC: Vital capacity; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 sec; MVV: Maximum voluntary ventilation; VO_{2max}: Maximum oxygen consumption; VO_{2AT}: Oxygen consumption at anaerobic threshold; VO_{2AT}(%): Ratio of oxygen consumption at anaerobic threshold to predicted maximum oxygen consumption; RER: Respiratory exchange ratio; HR_{max}: Maximum heart rate; HR_{max} (%): Ratio of the maximum heart rate to the heart rate estimated from the "220-age" equation; kg: kilogram; MBS: Modified Borg Scale; [a] Mann-Whitney U test; [b] Independent sample t test; * p<0.05; ** p<0.001; & Statistical analysis was not conducted between groups since these values differ by age and sex; comparison between groups was analyzed by using %pred values.

and FEV_1 (%pred), MVV (%pred), and VO_{2AT} (%) were statistically significantly lower in individuals with decreased exercise capacity compared to those with normal capacity.

There was a moderate positive correlation between walking distance and VC (r=0.663, $p^b<0.001$), FVC (r=0.672, $p^b<0.001$), and MVV (r=0.637, $p^b<0.001$). There was a strong positive correlation between walking distance and FEV_1 (r=0.706, $p^b<0.001$). There was no correlation between walking distance and FEV_1/FVC (r=−0.027, $p^b=0.763$). A moderate positive correlation was demonstrated between VO_{2max} and VC (r=0.687, $p^b<0.001$), FVC (r=0.695, $p^a<0.001$), and MVV (r=0.603, $p^a<0.001$). A strong positive correlation was demonstrated between VO_{2max} and FEV_1 (r=0.719, $p^a<0.001$). No correlation was observed between VO_{2max} and FEV_1/FVC (r=−0.031, $p^b=0.727$). There was a strong positive correlation between VO_{2max} and walking distance (r=0.792, $p^b<0.001$).

There was a decline in the physical activity level of individuals after COVID-19 (p<0.001). Before COVID-19: low (26.8%), moderate (46.4%),

TABLE 5
Multivariate linear regression analysis for VO_{2max} (%pred)

	Unstandardized coefficients		95% CI			
	B	SE	Lower limit	Upper limit	Standardized coefficients	*p*
Age	0.240	0.121	0.001	0.479	0.165	0.049*
Disease severity	−4.375	1.589	−7.519	−1.230	−0.231	0.007*
Male sex	−8.963	2.942	−14.785	−3.141	−0.253	0.003*

VO_{2max}: Maximum oxygen consumption; %pred: Percentage of predicted; SE: Standard error; CI: Confidence interval; * p<0.05.

and high (26.8%); after COVID-19: low (44.6%), moderate (36.6%), and high (18.8%). The ratio of individuals with declined physical activity was 45.5% and 23.9% in individuals with decreased and normal exercise capacity, respectively (p=0.131). Multivariate linear regression analysis demonstrated that younger age, male sex, and disease severity were related to lower VO_{2max} (%pred) ($p<0.001$, adjusted $R^2=0.132$) (Table 5). Pre-COVID-19 physical activity level and the number of comorbidities were removed from the model since they had no effect on VO_{2max} (%pred). The model explains 13.2% of the variance in VO_{2max} (%pred) by three variables: age, sex, and disease severity.

Post-hoc power of the study was analyzed through the results of the multivariate regression analysis, and it was 96% with $R^2=0.132$, $\alpha=0.05$, total sample size=128, and number of predictors=3.

DISCUSSION

In the present study, we investigated whether exercise capacity changed following COVID-19 and determined its relationship with age, sex, physical activity level, disease severity, and comorbidities. Our study results demonstrated that there was a decrease in the exercise capacity of certain individuals following COVID-19. Decreased exercise capacity was associated with younger age, male sex, and increasing disease severity. Pulmonary functions also declined, as the severity of COVID-19 increased. Deterioration of pulmonary functions and deconditioning after COVID-19 were predicted causes of a decrease in exercise capacity. In patients with a history of COVID-19, there was a significant relationship between walking distance in 6MWT and VO_{2max} in CPET.

The results of trials with varying evaluation times revealed that the VO_{2peak} (%pred) of those who recovered from COVID-19 ranged from 59 to 100.4% and was lower than that of the control groups.[21-23] The VO_{2peak} (%pred) was higher in studies, when the assessment was conducted later. In our study, 23.1% of the individuals had decreased exercise capacity after three months following COVID-19. In a study, the rate of individuals with VO_{2peak} (%pred) levels below 80% following COVID-19 was 54.9% between the second and third months and 31% at six months.[24] It can be concluded that after COVID-19, exercise capacity gradually increases. It still remains low in some individuals, though, which highlights the necessity of rehabilitation after COVID-19.

By defining the traits of those who require rehabilitation after contracting COVID-19, it is be easier to distinguish them from the sizable COVID-19 community and to successfully steer them toward rehabilitation. Therefore, it is helpful to reveal the impact of disease severity and factors associated with poor COVID-19 prognosis on exercise capacity. In our study, regression analysis showed that COVID-19 severity was independently related to lower exercise capacity. In a study, individuals with more severe COVID-19 had lower VO_{2peak} (%pred) values.[23] Nevertheless, in two more studies, there were no differences in the VO_{2peak} (%pred) of individuals with different COVID-19 severity levels.[25,26] In our study, younger age and male sex were found to be related to lower exercise capacity. In several studies, the ages of those with low and normal exercise capacity were similar and, also, there was a greater male ratio among those with poor exercise capacity, but this difference was not statistically significant.[25,27,28] In line with our findings, individuals with low and normal exercise capacity were shown to have comparable rates of comorbidities such as hypertension, smoking, dyslipidemia, cardiovascular disease, cardiac failure, COPD, and cancer.[25,28,29] However, in some studies, the prevalence of diabetes[28,29] and chronic kidney disease (CKD).[29] was found to be higher in those with low exercise capacity. Our findings are in contrast with a study that reported a favorable connection between pre-COVID-19 physical activity level and exercise capacity as measured by 6MWT.[30] In this regard, we believe that our results are more precise since exercise capacity was determined directly by VO_{2max}. Despite the discrepancies in the protocols, methodologies, and study outcomes, the findings of the research suggest that low exercise capacity may be associated with COVID-19 severity, male sex, diabetes, and CKD, and individuals with these characteristics should be evaluated for rehabilitation needs. Meta-analyses should, therefore, be carried out to provide a more definitive conclusion.

In COVID-19, the respiratory system was the most affected system. It was shown that individuals with a history of more severe COVID-19 had lower FVC (%pred), diffusing capacity for carbon monoxide (DLCO) (%pred), and total lung capacity (TLC) (%pred).[31] Our investigation showed that respiratory functions deteriorated and a restrictive dysfunction occurred as the severity of COVID-19 increased, as evidenced by a decline in FEV_1 and FVC and an increase in FEV_1/FVC. After COVID-19, restrictive and obstructive patterns in PFTs were found in 15% and 7% of the subjects, respectively. It was suggested that underlying pulmonary problems could be the cause of this disparity.[32] Comorbidities, including obesity, smoking, and asthma, that may impair the respiratory functions were also present (21.2%, 11.4%, and 2.3%, respectively) in a certain percentage of our study participants. This should be taken into account while evaluating our results. A systematic review and meta-analysis showed that while some individuals' respiratory functions improved, restrictive dysfunction and impaired diffusion capacity persisted in 5% and 31% of them, respectively, until 12 months after COVID-19.[33] In a case series, the improvement in respiratory functions after COVID-19 was more pronounced six months after recovery than it was six weeks after recovery.[34] Without a doubt, some people experience a persistent decline in their respiratory function after COVID-19, which calls for rehabilitation. Given the presence of diverse respiratory dysfunctions due to underlying conditions and COVID-19, an evaluation of respiratory functions in order to properly design a rehabilitation program may be beneficial.

Different opinions exist regarding the causes of the decrease in exercise capacity following COVID-19. In two studies, deconditioning was found to be the main cause of exercise limitation.[27,35] In another study, decrease in respiratory functions, skeletal muscle mass, and function were thought to be related to decline in exercise capacity.[29] According to Ambrosino et al.,[36] decreased exercise capacity might be primarily caused by alterations in the functions of the endothelial barrier in the systemic and pulmonary circulation. According to our results, the individuals with decreased exercise capacity had lower VC (%pred), FVC (%pred), FEV_1 (%pred), and MVV (%pred) compared to those with normal capacity. This suggests that respiratory function impairment is one of the causes of the decrease in exercise capacity. Also, individuals with lower exercise capacity achieved the anaerobic threshold earlier, suggesting deconditioning. Deconditioning may be caused by direct viral damage to muscles or a decrease in oxygen delivery to the muscles, both of which are also possible causes of myalgia.[27,37] Although muscle function was not specifically tested in our study, the frequency of myalgia experienced during COVID-19 was similar in groups with diminished and normal exercise capacity. Immobilization due to prolonged hospitalization may lead to deconditioning as well.[27,35] The duration of hospital stay was not documented or evaluated in our research, yet disease severity, which has an impact on hospital stay, was similar for patients with diminished and normal exercise capacity. In our study, the proportion of individuals with decreased physical activity after COVID-19 was higher in those with limited exercise capacity, even if the difference did not reach statistical significance. Our findings indicate that decreased physical activity after COVID-19 leads to deconditioning and diminishes exercise capacity, while other potential causes of deconditioning cannot be ruled out completely.

Rehabilitation programs should focus on improving cardiovascular endurance and functional lung capacities following COVID-19, taking into account the underlying reasons for the decrease in exercise capacity. The physical activity levels of individuals should be increased. The relationship between MVV and VO_{2max} shows that enhancing respiratory muscle endurance and strength is also required in order to improve exercise capacity.

The 6MWT is a simple, low-cost test and provides insight on whether exercise capacity is sufficient for performing activities of daily living. If CPET cannot be carried out, 6MWT enables a simple assessment of exercise capacity.[16] In our study, walking distance at

6MWT was significantly correlated with VO_{2max} and respiratory functions. Consistent with our findings, it was reported that shorter walking distances after COVID-19 were observed in individuals with more severe disease.[38] It was observed that those having a history of COVID-19 had lower walking distances than the controls.[21] The association between walking distance and respiratory functions, VO_{2max}, and disease severity validates the use of 6MWT after COVID-19 for assessing exercise capacity and identifying candidates for rehabilitation in situations where CPET is not feasible. It should be emphasized that 6MWT evaluates submaximal capacity and does not completely replace CPET, which can test maximum capacity and reveal several causes of reduction in exercise capacity.

Nonetheless, our study has some limitations. We had no clue regarding the individuals' exercise capacity prior to COVID-19. Thus, it was unable to ascertain if COVID-19 directly contributed to the individuals' diminished exercise capacity, as the study relied on the estimated values of peers who were in good health. Due to the decline in the number of patients during the study as a result of an efficient immunization campaign[39] and the predominance of COVID-19 variants that cause less severe disease, the targeted participant number could not be attained, particularly in the severe and critical disease subgroups.[40,41] Yet, not much is known about the individuals who are most seriously affected by COVID-19. This limits the generalization of our findings. Despite reports of impairment in DLCO after COVID-19,[31,33] we were unable to conduct DLCO measurements in this study. Therefore, no conclusions could be drawn regarding the effect of DLCO on exercise capacity after COVID-19. The DLCO should be evaluated in the presence of ongoing respiratory problems and a limitation in exercise capacity which cannot be explained by other reasons.

In conclusion, some individuals end up with diminished exercise capacity after COVID-19. Male sex, younger age, and COVID-19 severity are related to low exercise capacity. Low exercise capacity may also be linked to diabetes and CKD. The respiratory functions and exercise capacity of individuals with these characteristics should definitely be evaluated to determine rehabilitation requirements. Deconditioning due to decreased physical activity and limitations of respiratory functions, including respiratory muscle strength and endurance, leads to decrease in exercise capacity after COVID-19. Rehabilitation interventions should be designed to improve cardiovascular endurance, functional lung capacities, respiratory muscle endurance, and strength. Of note, 6MWT can be used to determine exercise capacity after COVID-19, if CPET is not applicable.

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