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Six-Minute-Walk Test Follow-Up In Post-Coronavirus Disease 2019 Patients

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Abstract

Objective: Since coronavirus disease 2019 (COVID-19) is a novel disease that involves the respiratory system, its long-term effect on respiratory functions is not exactly known. The complaint of dyspnea may contain for a long term in the patients with COVID-19. In this study, consecutive 6-minute-walk-test (6MWT) walking distance, spirometry and radiological findings of patients who continued to complain of dyspnea after COVID-19 were evaluated at the first and third months.

Methods: Two visits were performed at the first and third months in 34 patients with complaints of dyspnea in the post-COVID-19 period. Six-minute-walk-test and spirometry were performed. The Borg scale was used to evaluate dyspnea and leg fatigue before and after 6MWT. COVID-19 lesions in the lung parenchyma detected by thoracic computed tomography (CT) in the acute stage were divided into three groups using visual quantities as <30% involvement, 30%-50% involvement, and >50% involvement. The patients were grouped and compared according to lung involvement percentages in the thoracic CT scan.

Results: Thirty-four (27 females and 7 males) patients were included into this study. Six-minute-walk-test score was significantly higher in the third month than in the first month ($P = .001$). Similarly, 6MWT score was significantly higher in the third month than in the first month in the patients with <30% lung involvement ($P = .005$). There was no statistically significant difference was found between the spirometry values (FEV1, FVC, FEV1/FVC) of the different radiological involvement groups.

Conclusion: It was observed that the 6MWT distance of the patients increased in the third month, and the walking distance increased more in the third month in patients with less lung involvement. However, no difference was detected between spirometry values according to radiological groups. 6MWT is easily accessible and easily implemented. It may be considered for follow-up of patients after COVID-19.

Keywords: COVID-19, post-COVID-19 follow-up, 6-minute walk test, spirometry, lung function

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been defined as an infectious agent leading to acute atypical respiratory tract disease in a series of patients in December 2019 in Wuhan City of Hubei Province of China.[1]

SARS-CoV-2 is a multisystemic disease that may also affect other organ systems as well as the respiratory system.[2] It is accepted that coronavirus disease 2019 (COVID-19) is a disease that manifests a wide heterogeneity varying from mild symptoms to remarkable hypoxia with adult respiratory distress syndrome (ARDS).[3] These symptoms are associated with diffuse ground-glass opacities in thoracic computed tomography (CT) scans.[4]

The complaint of dyspnea may continue for a long time in patients detected with COVID-19 lung involvement, and its possible long-term consequences are not exactly known.[5] It has been shown that at the first-month follow-up of patients with a history of hospital admission for COVID-19, exercise capacity decreased and abnormal thoracic CT findings continued.[6] Long-term follow-up has been recommended after SARS-CoV-2 infection in patients, particularly those with a history of pneumonia.[7]

Six-minute-walk-test (6MWT) is an objective test that indicates the exercise capacity and measures the distance that a patient can walk in a 6-minute period to assess the cardiopulmonary reserve. It is widely used for objective assessment of functional exercise capacity in patients with moderate to severe pulmonary disease such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and pulmonary arterial disease. Its availability without the requirement of complicated equipment and technical specialization, as well as identification of extrapulmonary signs of chronic pulmonary diseases, are its superiority over pulmonary function tests.[8]

In the present study, the patients with COVID-19 lung involvement and complaints of dyspnea were evaluated with the 6MWT at the first and third months. The aim was to demonstrate the improvement in exercise capacity during follow-up and the compliance of 6MWT with radiology and spirometry.

Methods

Study Design and Settings

It was planned to include patients in the study who applied to the post-COVID outpatient clinic with a history of COVID-19 between 15 October and 30 December 2021. Our study is a prospective real-time study. Two visits were planned to be performed

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at the first and third months after SARS-CoV-2 polymerase chain reaction (PCR) positivity. The times of the visits and the tests they included were explained to each patient, and their consent was obtained. Spirometry and 6MWT were performed during these visits after confirmation of a negative SARS-CoV-2 PCR test result. Patients who did not accept any of the tests at the first or third month visit were excluded from the study. Chest CT scans that were already taken when the patients were diagnosed with Covid-19 were used in the study.

The study was approved by the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa (Approval No: E-237 86442-604.01.01-186328, Date: October 8, 2021).

Participants

Inclusion Criteria of the Study

- Giving written informed consent for each visit and tests to be performed.
- Having an age between 17 and 70 years.
- Being diagnosed with COVID-19 according to SARS-CoV2 PCR positivity 1 month (30-40 days) ago.
- Having applied to the hospital in the first 40 days due to continuing complaints of dyspnea and exercise intolerance.

Exclusion Criteria of the Study

- Patients who withdraw consent and refuse to attend any visit or undergo testing.
- Having concomitant orthopedic, neurological, or peripheral vascular diseases that may prevent undergoing the 6-minute walk test or may cause confusion in the interpretation of the test results.
- Currently receiving oxygen therapy for prolonged type 1 respiratory failure after COVID-19.
- Having experienced COVID-19 more than 40 days beforehand.
- Having a chronic pulmonary disease such as asthma, COPD, bronchiectasis, or interstitial lung disease.
- Patients diagnosed with malignancy, heart failure, and kidney failure.
- Pregnancy.
- Patients with a hemoglobin level <12.0 g/dL.
- Patients with a body mass index (BMI) >35.
- Patients detected with COVID-19-related pulmonary thromboembolism.
- Detection of COVID-19 PCR test positivity within 24 hours before the day of spirometry and the 6-minute walk test

Data Collection and Variables

The detailed anamnesis was taken from the study patients. The demographic characteristics (e.g., age, gender), anthropometric data, and chronic diseases of the patients were questioned. The history of cigarette smoking was recorded as pack-years. The weight and length of the patients in terms of kg and cm, respectively. The weight and height of the patients were measured in kilograms and centimeters, respectively. BMI was calculated by dividing the weight in kilograms by the height in centimeters squared (kg/m^2). Baseline assessment of dyspnea was performed using the Modified Medical Research Council Dyspnea Scale (mMRC) in the range of 0-4.[9,10]

Spirometry was performed in both visits with confirmation of SARS-CoV2 PCR negativity 24 hours before (ZAN 100 Flow Handy II Germany). All procedures were carried out according to the guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS).[11,12]

The 6MWT was performed involving only the patient and performer using personal protective equipment in a long, straight, and well-aerated corridor measured to be 30 m at the end of working hours during the patient visits at the first and third months in accordance with ATS 2002 guidelines.[13] Before and after the test, oxygen saturation (SaO_2), systolic and diastolic blood pressure levels, and heart rate were measured, dyspnea and leg fatigue were recorded according to the Modified Borg Dyspnoea Scale (range of 0-10).[14] At the end of the test, the heart rate recovery (HRR) time was recorded in seconds.

Study Size

All the patients who were selected according to the inclusion and exclusion criteria, and who gave consent were included in the study. Patients were divided into 3 groups according to the ground glass densities in thorax CT taken at the time of the COVID diagnosis. This was based on the following criteria: less than 30% lung involvement; 30%-50% lung involvement; greater than 50% lung involvement.[15,16]

Statistical Analysis

All analyses were performed on The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA). For the normality check, the Shapiro–Wilk test was used. Data are given as mean ± SD or median (minimum–maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Continuous variables were analyzed with the Wilcoxon signed ranks test for repeated measurements. Between groups comparisons of these variables were performed with the Kruskal–Wallis test. Categorical variables. were analyzed with the McNemar test for repeated measurements. Between groups comparisons of these variables were performed with the chi-square test. Pairwise comparisons were performed with the Bonferroni correction method. Multiple linear regression analysis (stepwise selection method) was performed to determine related factors with the 6-minute walk test score. Two-tailed *P*-values of less than .05 were considered statistically significant.

Results

We included 34 patients (27 females and 7 males) in our study. 34 patients attended the first visit but 7 patients did not attend the second visit. The demographic characteristics of the patients as well as their follow-up, treatment, and CT involvement were presented in Table 1.

Six-minute walk test score was significantly higher in the third month than in the first month ($P = .001$). Similarly, 6MWT score was significantly higher in the third month than in the first month in the patients with <30% lung involvement ($P = .005$). There was no statistically significant difference found between the spirometry values (FEV1, FVC, FEV1/FVC) of the different radiological involvement groups ($P > .005$) (Table 2).

In Table 3, heart rate recovery times, oxygen saturation levels, heart rates, Borg dyspnea severity scores, and Borg leg fatigue severity scores recorded before and after the 6MWT were compared. Heart rates, Borg dyspnea severity score, and Borg leg fatigue severity score were significantly higher in the after test than in the before test both in the first and third month. There was no significant difference between the before and after test with regard to oxygen saturation (Table 3). Heart rates, Borg dyspnea severity score, and Borg leg fatigue severity scores were significantly

Table 1. Summary of Patients' Characteristics

	N (%)/Mean ± SD
Age	45.26 ± 12.88
Gender	
Female	27 (79.41%)
Male	7 (20.59%)
Height (cm)	161.44 ± 9.62
Weight (kg)	76 (50-136)
Body mass index (kg/m^2)	29.23 ± 6.53
Comorbidity	12 (35.29%)
Diabetes mellitus	1 (2.94%)
Hypertension	3 (8.82%)
Coronary artery disease	2 (5.88%)
Others	8 (23.53%)
Smoking status	
Non-smoker	25 (73.53%)
Ex-smoker	3 (8.82%)
Smoker	6 (17.65%)
Smoking (pack-years)	0 (0 – 60)
mMRC	
Grade 1	18 (52.94%)
Grade 2	16 (47.06%)
Follow-up status	
Home	26 (76.47%)
Hospital service	6 (17.65%)
Intensive care unit	2 (5.88%)
Lung involvement, CT	25 (0 – 90)
<30%	17 (50.00%)
30%-50%	12 (35.29%)
>50%	5 (14.71%)

Data are given as mean ± SD or median (minimum–maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

higher in the after test than in the before test both in the first and third month in the patients with <30% lung involvement. Heart rates, Borg dyspnea severity score, and Borg leg fatigue severity scores were significantly higher in the after test than in the before test both in the first and third month in the patients with 30% to 50% lung involvement. first month heart rates, first month Borg dyspnea severity score, and first month Borg leg fatigue severity scores were significantly higher in the after test than in the before test in the patients with >50% lung involvement. We found no significant differences between lung involvement groups with regard to 6-minute walk test related measurements (Table 3).

We evaluated changes in measurements after a 6-minute walk test. Increase in Borg dyspnea severity score ($P = .001$) and increase in Borg leg fatigue severity score ($P < .001$) were significantly higher in the first month than in the third month. Increase in Borg dyspnea severity score ($P = .009$) and increase in Borg leg fatigue severity score ($P = .026$) were significantly higher in the first month than in the third month in the patients with <30% lung involvement. Increase in Borg leg fatigue severity score was significantly higher in the first month than in the third month in the patients with 30%-50% lung involvement ($P = .036$). We found no significant differences between lung involvement groups with regard to changes in measurements after a 6-minute walk test (Table 4).

Discussion

In this real-time prospective study, the follow-up processes of the patients diagnosed with COVID-19 showed that dyspnea regressed at the third month according to the Borg Scale and an elevation was encountered in 6MWT distances. Similarly, the 6MWT distance was higher in the third month than in the first month in the patients with <30% lung involvement. However, no difference was found between the spirometry values (FEV1, FVC, FEV1/FVC) of the different radiological involvement groups. It has been demonstrated that cardiopulmonary exercise capacity increased accompanied by clinical and radiological improvement.

The change in 6MWT is used to assess the treatment response and to predict the morbidity and mortality in chronic respiratory tract diseases.[17] The 6MWT can be helpful in predicting the potential hypoxia that may develop due to exercise in a comfortable patient at rest and without hypoxia in the post-COVID-19 early term. This simple diagnostic tool has reliable clinical applicability in providing safe health care for COVID-19 patients.[18] According to our study data, clinical and radiological improvement were found to be correlated with increased 6MWT distance.

Eksombatchai et al[7] have evaluated lung imaging at the second month, spirometry, and 6MWT in the post-COVID-19 patients, and determined a lower 6MWT distance in the patients with abnormal lung radiology according to the comparison between patients with and without lung involvement. On the other side, all the study patients had lung involvement, and a significant improvement was identified in 6MWT distances 2 months later in the control visit. It can be concluded that 6MWT decreases in the patients with COVID-19 lung involvement at the early term and that 6MWT distance improved by time together with radiological improvement.

In a study including patients discharged from the intensive care unit and patients discharged from the internal medicine department with pneumonia due to COVID-19 infection, the 6MWT and respiratory function parameters of the patients were examined at 4-6 months. One follow-up visit was planned after COVID-19. Unlike the group of patients discharged from the Internal Medicine department, it was observed that these parameters were within normal limits in only one-third of the patients discharged from the intensive care unit. It was emphasized that pulmonary function tests and 6-MWT can be used as a reliable and cost-effective tool that can accurately identify the sequelae of possible lung damage as a follow-up strategy after COVID-19 infection causing pneumonia.[19] In our study, patients were scheduled for two visits with 6MWT and respiratory function tests, and a similar improvement was observed in these parameters. It is recommended that these reliable, easy, and cheap tools be used in follow-up.

Lerum et al[5] have followed up the patients for 3 months after discharge who were admitted to the hospital and intensive care unit due to COVID-19 in their study and noted that self-reported dyspnea by exercise continued at the third month using the

Table 2. Summary of Patients' Findings with Regard to Lung Involvement

		Lung Involvement, CT			
	Total (n = 34)	**<30% (n = 17)**	**30%-50% (n = 12)**	**>50% (n = 5)**	***P* (Between Groups)**
Six-minute walk test					
First month	455 (270-600)	410 (270-600)	460 (420-510)	460 (300-530)	.769
Third month	490 (60-660)	462.5 (360-660)	510 (60-540)	445 (420-645)	.923
P (within groups)	**.001**	**.005**	.051	.465	
FEV1/FVC					
first month	94 (84-100)	92.5 (84-100)	92 (90-98)	96 (94-98)	.667
third month	92 (70-100)	90.5 (70-100)	94 (83-100)	94 (92-100)	.532
P (within groups)	.959	.461	.465	1.000	
FEV1, mL					
First month	2960 (1830-3730)	3240 (1830-3730)	2830 (2520-2960)	2920 (2340-3500)	.262
Third month	2920 (1860-4660)	3070 (1860-4660)	2900 (1960-4000)	2885 (2370-3720)	.994
P (within groups)	.209	.500	.686	.180	
FEV1, %					
First month	114 (66-138)	115 (66-138)	108 (70-137)	111.5 (104-119)	.981
Third month	112 (71-139)	114 (71-139)	111 (89-138)	115 (93-133)	.988
P (within groups)	.222	.416	.680	.180	
FVC, mL					
First month	3230 (1950-4090)	3660 (1950-4090)	3040 (2580-3270)	3060 (2390-3730)	.375
Third month	3230 (2270-4900)	3290 (2290-4900)	3010 (2270-4210)	3075 (2580-3720)	.943
P (within groups)	.213	1.000	.225	.655	
FVC, %					
First month	101 (60-120)	105 (60-119)	101 (63-120)	96.5 (91-102)	.831
Third month	101 (74-136)	102.5 (74-119)	99 (81-136)	99.5 (79-123)	.785
P (within groups)	.591	.461	.221	.655	

Data are given as a median (minimum–maximum) for continuous variables according to normality of distribution. Same letters denote the lack of statistically significant difference between groups. Bold values indicate statistical significance.

Modified Medical Research Council Dyspnea Scale. In addition, our results support their study; dyspnea at the first month was significantly higher than dyspnea at the third month according to the Borg Scale, and dyspnea by exercise continued at the third month in the patients.

In another study that carried out a 1-month follow-up of patients with a history of hospital admission due to COVID-19, it has been demonstrated using 6MWT that exercise capacity decreased and abnormal thoracic CT evidence continued.[6] Similarly, in our study, radiological involvement was encountered in all the patients in the first month and 6MWT distances at the first month were significantly lower than those at the third-month control examination.

Our study has some limitations. The limited number of patients was one of the limitations. No control group constituted by patients without lung involvement was present.

The strengths of this study were its prospective real-time study design and multicentric structure. In addition, our study is valuable as the first study in which 6MWT monitoring was performed in the patient follow-up process. It is the first study that demonstrated that exercise capacity also increased, accompanied by improved radiology, in the patients with lung involvement. Our study has supported the fact that post-COVID follow-up of patients can be performed using a simple diagnostic tool such as 6MWT.

Conclusion

In this study, it was observed that the 6MWT distance of the patients increased in the third month, and the walking distance increased more in the third month in patients with less lung involvement. The 6MWT is an easily accessible and simply applicable test, and it can be used for follow-up of patients after being diagnosed with COVID-19 in health-care centers. Since the 6MWT

Table 3. Summary of Six-Minute Walk Test Related Measurements with Regard to Lung Involvement

		Lung Involvement, CT			
	Total (n = 34)	**<30% (n = 17)**	**30%-50% (n = 12)**	**>50% (n = 5)**	***P* (Between Groups)**
Heart rate recovery time (seconds)					
First month	56.5 (16-404)	76 (35-182)	55 (16-404)	54 (49-126)	.654
Third month	93 (35-515)	69 (35-298)	113 (41-515)	139 (84 -371)	.090
P (within groups)	**.017**	.638	.075	.068	
Oxygen saturation, first month					
Before test	97.5 (96-99)	98 (96-99)	98 (97-99)	97 (96-99)	.335
After test	98 (92-99)	98 (94- 99)	98 (96-99)	96 (92-99)	.171
P (within groups)	.347	.650	.705	.197	
Heart rate, first month					
Before test	88.5 (69-109)	90 (69-108)	86 (76-100)	90 (79-109)	.614
After test	108 (80-137)	108 (80-137)	106 (91-126)	122 (100-125)	.498
P (within groups)	**<.001**	**<.001**	**.002**	**.043**	
Borg dyspnea severity, first month					
Before test	2 (1-4)	2 (1-3)	2.5 (1-4)	3 (1-3)	.860
After test	6 (1-9)	6 (3-9)	6 (1-8)	6 (4-9)	.623
P (within groups)	**<.001**	**<.001**	**.003**	**.042**	
Borg fatigue severity, first month					
Before test	2 (1-8)	2 (1-4)	2 (1-8)	3 (1-3)	.985
After test	6 (3-9)	6 (3-9)	6 (3-9)	6 (4-9)	.999
P (within groups)	**<.001**	**<.001**	**.003**	**.042**	
Oxygen saturation, third month					
Before test	98 (96- 99)	98 (96 - 99)	98 (96 - 99)	97 (97 - 99)	0.659
After test	98 (94 - 99)	98 (97 - 99)	98 (96 - 99)	96.5 (94 - 99)	0.221
p (within groups)	0.959	0.102	0.679	0.180	
Heart rate, third month					
Before test	85 (64-107)	87 (64-106)	80 (66-95)	90 (78-107)	.410
After test	107 (82-138)	98.5 (82-138)	107 (87-136)	113.5 (90-132)	.340
P (within groups)	**<.001**	**.002**	**.003**	.068	
Borg dyspnea severity, third month					
Before test	2 (1-5)	1.5 (1-5)	2 (1-3)	2 (2-4)	.293
After test	4 (2-7)	5 (2-6)	4 (2-7)	4.5 (4-7)	.463
P (within groups)	**<.001**	**.002**	**.003**	.063	
Borg fatigue severity, third month					
Before test	2 (1-4)	2 (1-4)	2 (1-4)	2.5 (2-4)	.532
After test	4 (2-8)	5 (2-8)	4 (2-6)	4 (4-6)	.715
P (within groups)	**<.001**	**.002**	**.003**	.059	

Data are given as a median (minimum–maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Bold values indicate statistical significance.

Table 4. Summary of Changes in Measurements Before and After 6-Minute Walk Test with Regard to Lung Involvement

		Lung Involvement, CT			
	Total (n = 34)	**<30% (n = 17)**	**30%-50% (n = 12)**	**>50% (n = 5)**	***P* (Between Groups)**
Oxygen saturation					
First month	0 (−5-3)	0 (−2-3)	0 (−1 - 1)	−1 (−5- 1)	.364
Third month	0 (−3-2)	0 (0-2)	0 (−2-1)	−0.5 (−3-0)	.107
P (within groups)	.891	.541	.763	.414	
Heart rate					
First month	19.5 (3-47)	19 (5-47)	20.5 (3-44)	16 (10-40)	.974
Third month	21 (5-50)	16 (5-49)	22 (14-50)	23 (12-26)	.081
P (within groups)	.195	.859	.184	.197	
Borg dyspnea severity					
First month	3.5 (0-7)	4 (1-7)	3 (0-6)	3 (2-6)	.471
Third month	2 (1-4)	2.5 (1-4)	2 (1-4)	2.5 (2-3)	.839
P (within groups)	**.001**	**.009**	.143	.180	
Borg leg fatigue severity					
First month	3.5 (0-7)	4 (1-7)	3.5 (0-7)	3 (2-6)	.941
Third month	2 (1-4)	2.5 (1-4)	2 (1-4)	2 (1-2)	.371
P (within groups)	**<.001**	**.026**	**.036**	.063	

Data are given as a median (minimum–maximum) for continuous variables according to normality of distribution. Negative values represent a decrease and positive values represent an increase in measurements. Bold values indicate statistical significance.

is a cardiopulmonary exercise tool, it may provide data related to both the recovery process and increased cardiopulmonary reserve of the patient. It can be concluded that the decrease in exercise capacity developing due to COVID-19 may improve over time.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa (Approval No: E-23786442-604.01.01-186328, Date: October 8, 2021).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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