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Evaluation of pulmonary function and exercise capacity after COVID-19 pneumonia

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A R T I C L E   I N F O

A B S T R A C T

Background: Individuals who suffer from coronavirus disease 2019 (COVID-19) pneumonia may experience pulmonary dysfunction during the chronic period due to pulmonary parenchymal damage after acute disease.
Objectives: The aim of the present study was to evaluate the pulmonary function and exercise capacity of patients treated for COVID 19 pneumonia after discharge.
Methods: In this cross-sectional study, 79 people who were hospitalized with COVID-19 between March and October 2020 were evaluated at least two months after discharge. A pulmonary function test and a six-minute walk test were administered to the individuals included in the study.
Results: Restrictive-type disorder was detected in 21.5% of the individuals who were evaluated at least two months after discharge. The forced expiratory volume in the first second (FEV1) and the forced vital capacity (FVC) values of the pulmonary function tests were significantly lower in the individuals with severe/critical clinical disease compared to those with moderate disease ($p = 0.004$ and $p = 0.001$, respectively). Although the six-minute walk test (6MWT) distances were lower in the severe/critical group than in the moderate group, the difference was not statistically significant ($p > 0.05$).
Conclusions: Individuals who are discharged after hospitalization for COVID-19 pneumonia may develop a restrictive type of pulmonary dysfunction. Therefore, survivors of COVID-19 pneumonia should be evaluated for pulmonary function and rehabilitation needs and should be provided with treatment as required.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) infection can be asymptomatic, but it can also have clinical manifestations called coronavirus disease 2019 (COVID-19), which can range from mild airway disease to severe illness that can cause respiratory failure and even death.[1] As of November 1, 2021, more than 251 million people worldwide had been infected with SARS-CoV-2, and more than five million people had died.[2] The most common cause of hospitalization for COVID-19 is interstitial pneumonia, which can lead to acute respiratory distress syndrome (ARDS), refractory

respiratory failure, and death.[3] Recent pathological studies have shown that the predominant pathological changes in early stage patients are edema, inflammatory infiltrate, and type II pneumocyte hyperplasia and organization, but some patients develop desquamation of pneumocytes and hyaline membrane formation, indicating acute respiratory distress syndrome.[4,5] In a meta-analysis that evaluated 38 studies involving 3062 COVID-19 patients, bilateral lung lesions were detected in most individuals who suffered from COVID-19 pneumonia, and the incident rate of respiratory failure or ARDS was 19.5% in hospitalized patients.[6] Cortés-Telles et al.[7] examined the physiological mechanisms of persistent dyspnea in COVID-19 survivors and found that about half of the patients who recovered from COVID-19 reported chronic dyspnea that persisted for two to three months after infection. Dyspnea is an independent predictor of morbidity and mortality in the general population and is linked to reduced functional capacity and poor health-related life quality.[8] Patients who survive acute COVID-19 pneumonia need health care support to identify and measure the consequences of the disease. It is unclear whether or to what extent COVID-19 causes permanent lung and/or physical damage.[9] It was reported that the diffusion capacity

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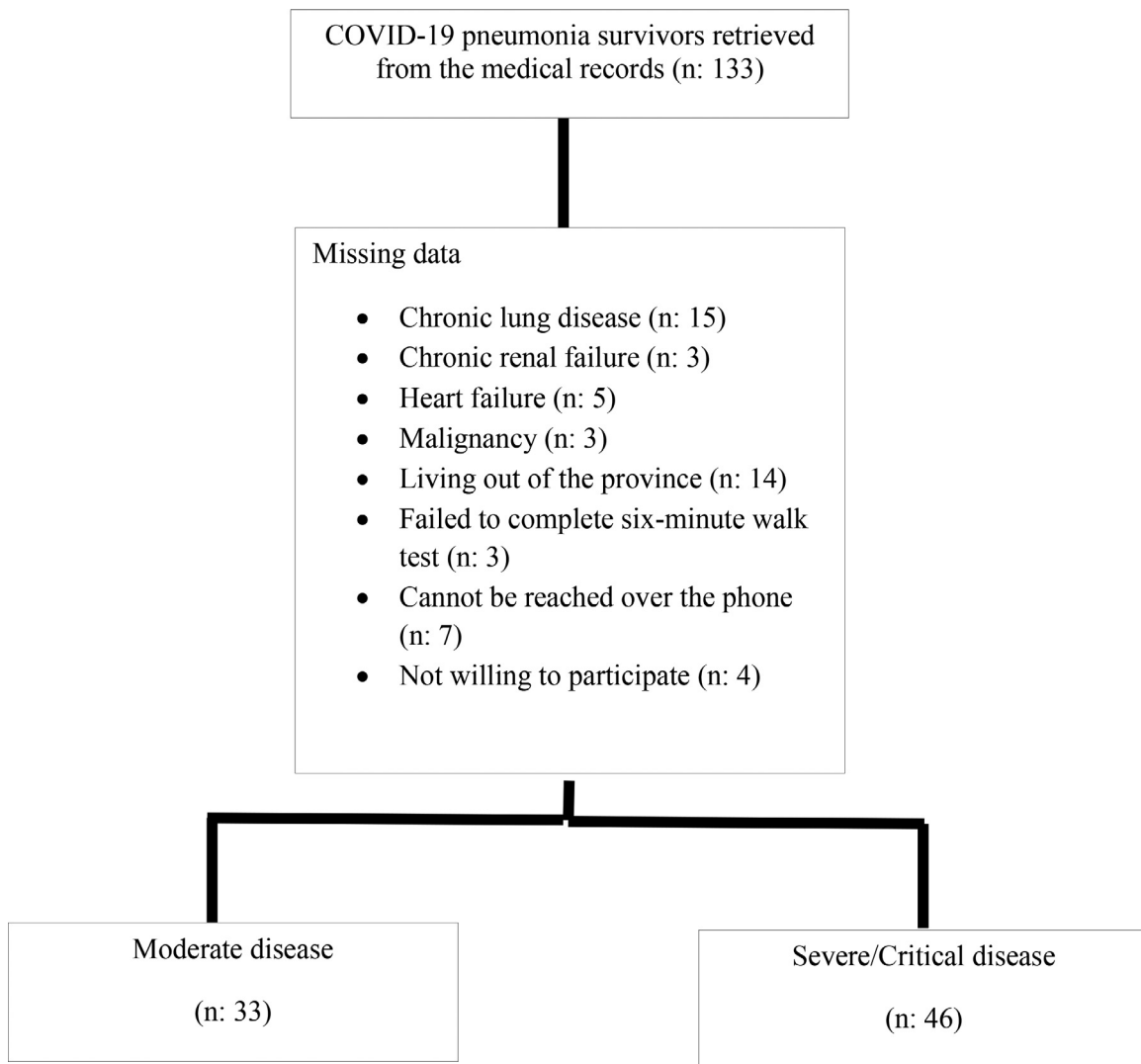*E-mail address:* doctorsevil@yahoo.com (S. Okan).

Fig. 1. The study flowchart.

of the lungs for carbon monoxide (DLCO) is frequently affected in patients recovering from COVID-19.[10] This situation was also observed in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), in which the deterioration in lung function lasted months and even years.[11,12] Impairment in exercise capacity is usually accompanied by in line with DLCO reduction. It was reported that the distances achieved in a six-minute walk test (6MWT) and the scores on the 36-point Short Form General Health Survey of patients recovering from SARS pneumonia were lower than those of the general population.[11]

The aim of the present study was to evaluate the lung function and exercise capacity of individuals discharged after being hospitalized with COVID-19 pneumonia.

Methods

Study design

In this cross-sectional study, 133 people 18 years of age and older who were hospitalized with polymerase chain reaction−confirmed COVID-19 and who had computed tomography findings during hospitalization consistent with COVID-19 were evaluated two months after their discharge. After applying the exclusion criteria, the study was carried out with 79 patients (moderate disease: $n = 33$; severe/critical disease: $n = 46$).

The study was conducted according to the Declaration of Helsinki and was approved by the Ethical Board of Tokat Gaziosmanpasa University (20-KAEK-186). All subjects were informed about the study aims, and written consent was obtained from each participant.

Study participants

The excluded patients were as follows: 15 patients with chronic lung disease, three patients with chronic kidney failure, five patients with heart failure, three patients with malignancy, 14 patients living outside the province, three patients who did not complete the six-minute walk test, seven patients who could not be reached over the phone, and four patients who did not want to participate in the study; thus, the study was carried out with 79 patients (Fig. 1). The medical records of individuals who were admitted due to a COVID-19 diagnosis during the study period were screened from the hospital information system, and those who met the study criteria were invited to the hospital, where they were given a pulmonary function test and a six-minute walk test by the researchers. Following the tests, the patients were asked to fill out the questionnaire by themselves. Patients under the age of 18 and those with chronic lung disease, malignancy, active infection, moderate or severe heart failure, chronic kidney failure, a history of hemorrhagic or ischemic cerebrovascular disease, and those with diseases that could restrict mobility were not included in the study.

Table 1
Clinical and demographic data of individuals.

	% (n)
Age (mean±SD)	52.53±12.42
Body mass index (mean±SD)	31.63±5.01
Gender	
Female	48.1 (38)
Male	51.9 (41)
Comorbid disease	
Yes	57 (45)
No	43 (34)
Smoking	
Yes	10.1 (8)
No	89.9 (71)
Clinical stage	41.8 (33)
Moderate	58.2 (46)
Severe	
Pulmonary function test	
Restrictive pattern	21.5 (17)

The patients were divided into two groups according to the clinical severity of their disease (based on four severity grades described by the World Health Organization) during hospitalization: 1 = mild or moderate disease with clinical signs of pneumonia and $SpO_2 \geq$ 90% (mild/moderate); 2 = severe disease with pneumonia, $SpO_2 <$ 90%, and a respiratory rate > 30 min^{-1} or critical disease (i.e., ARDS, sepsis, septic shock, or multi-organ failure) (severe/critical).[15]

Study outcomes

Physical performance was assessed using the 6MWT, which was measured using a standardized protocol.[13] The 6MWT distances achieved by the patients were calculated as a percentage of the 6MWT reference values of healthy adults of the same sex, age, and height.[14] A walking distance of <0.26 miles (<1400 feet or <427 m) is defined as the anomaly and is associated with the anaerobic threshold.[16]

All pulmonary function tests (PFT) were performed at the Pulmonary Function Laboratory, where forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) measurements were performed. The FEV1/FVC ratio, forced expiratory flow at 25 and 75% of the pulmonary volume (FEF25−75%), and maximum voluntary ventilation (MVV) measurements were calculated. All PFT measurements were expressed as absolute values and as a percentage of predicted normal values (% predicted). The criteria for classifying lung function abnormalities based on ATS guidelines were as follows: normal = both FVC and the FEV1/FVC ratio were in the normal range; obstructive pattern = the FEV1/FVC ratio was <70% of the normal predicted value, and FEV1 was <80% of the normal predicted value; restrictive pattern = the FEV1/FVC ratio was $\geq$ 70% of the normal predicted value. Because the total lung capacity (TLC) was not available, a FVC value less than 80% was considered a restrictive pattern; small airway disease = FEF25−75% was <65% of normal predicted value.[17]

Statistical analyses

Statistical analyses of the data were carried out using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are reported as mean ± standard deviation for continuous data, while frequency distributions of categorical data are given as numbers and percentages (%). The distribution of normality was examined using the Kolmogorov−Smirnov test. The means of two independent samples of continuous variables were compared using independent sample tests. The chi-square test was used for ratio comparisons of categorical variables between the study groups. A p value <0.05 was considered to be statistically significant.

Results

The mean age of the individuals included in the study was 52.55 ± 12.42 years; 48.1% (n = 38) were female, and 51.9% (n = 41) were male. Forty-five participants (57%) had comorbidities (diabetes mellitus, hypertension, coronary artery disease, and/or hypothyroidism). It was found that during hospitalization, 41.8% of the individuals had mild/moderate and 58.2% had severe/critical clinical disease. Based on the pulmonary function test results two months after discharge, a restrictive pattern was observed in 21.5% (n = 17) of the individuals (Table 1).

When the individuals were divided into two groups according to the clinical severity of their disease (mild/moderate vs. severe/critical), the mean age (56.57 ± 9.45 vs. 46.91 ± 13.94 years, respectively; p = 0.001) and body mass index (32.94 ± 4.18 vs. 29.81 ± 5.55, respectively; p = 0.005) were significantly higher in the severe/critical

Table 2
Comparison of demographic and clinical data of individuals in moderate and severe/critical clinical stage groups.

	Moderate (n: 33)% (n)	Severe/critical (n: 46)% (n)	P
Gender female	50.0 (19)	50.0 (19)	0.177
Male	34.2 (14)	65.8 (27)	
Age (years) (Mean±SD)	46.91±13.94	56.57±9.45	0.001
Body mass index (Mean±SD)	29.81±5.55	32.94±4.18	0.005
Hospital stay (days) (Mean±SD)	6.21±4.74	12.75±5.23	0.001
Duration after diagnosis (days) (Mean±SD)	110±32.25	108.96±30.68	0.884
Steroid use Yes	20.0 (7)	80.0 (28)	0.001
No	59.1 (26)	40.9 (18)	
Immune plasma use Yes	10.0 (1)	90.0 (9)	0.028
No	46.4 (32)	53.6 (37)	
Dyspnea Yes	36.6 (19)	63.4 (33)	0.145
No	53.9 (14)	46.1 (12)	
Pulmonary function test			
Restrictive pattern	11.8 (2)	88.2 (15)	0.040

Table 3

Comparison of PFT and 6MWT values of individuals with moderate and severe/critical clinical stage.

	Moderate (*n*: 33)Mean±SD	Severe/critical (*n*: 46)Mean±SD	*P*
FEV1 %pred	95.88±12.52	86.17±15.29	0.004
FVC %pred	92.58±10.38	82.30±14.71	0.001
FEV1/FVC	103.67±7.59	104.8±7.25	0.502
FEF 25/75	108.30±28.60	106.28±33.46	0.780
MVV%pred	80.58±16.97	83.93±20.42	0.442
6MWT (m)	428.64±73.06	416.50±85.53	0.511
6MWT %pred*	79.24±12.07	81.61±15.37	0.508

* Eight individuals who were younger than 40 years of age were excluded from the analysis

Table 4

Comparison of clinical and demographic data of individuals with restrictive pattern and normal PFT Values.

	Normal (*n*: 62)Mean±SD	Restrictive disorder (*n*: 17)Mean±SD	*P*
Age (years)	50.84±12.81	58.71±8.60	0.020
BMI	31.64±5.39	31.61±3.44	0.987
Duration of hospital stay (days)	9.06±5.33	13.47±6.94	0.006
MVV %pred	84.21±18.85	76.41±18.90	0.135
6MWT (m)	430.24±77.45	389.94±84.89	0.660
6MWT %pred*	81.35±12.44	78.94±19.28	0.547

* Eight individuals who were younger than 40 years of age were excluded.

group compared to the moderate group. In the severe/critical group, the use of steroids and immune plasma was higher, and the hospital stay was longer compared to the moderate group (12.75 ± 5.23 vs. 6.21 ± 4.74 days, respectively; *p* = 0.001). There was no significant difference between the two groups in terms of complaints of dyspnea after discharge (*p* = 0.145). A restrictive pattern was observed after discharge in two individuals in the moderate group and in 15 individuals in the severe/critical group (*p* = 0.04) (Table 2).

FEV1%pred and FVC%pred values in the pulmonary function tests were significantly lower in the severe/critical group (*p* = 0.004 and *p* = 0.001, respectively). Other PFT parameters showed no significant differences between the two groups (*p* > 0.05). Although the 6MWT distances achieved by the moderate group were longer, the difference was not significant (*p* > 0.05) (Table 3).

Length of hospital stay and mean age were significantly higher in individuals with restrictive pattern based on their PFT values compared to individuals who did not have any PFT abnormalities (*p* = 0.006 and *p* = 0.020, respectively). No significant differences were found between the two groups in terms of body mass index (BMI), MVV, and 6MWT values (*p* > 0.05) (Table 4).

When the individuals with severe (*n* = 40) and critical (*n* = 6) clinical disease were compared, no significant difference was found in their FEV1, FVC, FEV1/FVC, and MVV values (FEV1: 86.58 ± 15.28 and 83.50 ± 16.48; FVC: 82.90 ± 14.53 and 78.33 ± 16.76; FEV1/FVC: 104.53 ± 7.41 and 106.67 ± 6.37; MVV: 81.35 ± 19.55 and 101.17 ± 18.96, respectively) (*p* > 0.05). The 6MWT distances of the two groups were similar (411.63 ± 88.64 and 449.00 ± 55.73 m, respectively) (*p* > 0.05) (data not shown). Since the number of patients in the critical group was small, and no significant differences were found between the two groups, the individuals at severe and critical stages were combined into a single group for the other analyses.

Discussion

In the present study of individuals who had been hospitalized with moderate and severe/critical clinical COVID-19, a restrictive pattern was detected in 21.5% of the individuals at least eight weeks after their discharge from hospital. In a previous study in which COVID-19 patients who had been treated in the intensive care unit of the University of Virginia Medical Center were evaluated approximately six weeks after discharge, 61.54% (*n* = 16) of the individuals

were normal, while 15.38% (*n* = 4) had obstructive, 19.23% (*n* = 5) had restrictive, and 3.85% (*n* = 1) had mixed-type disorder.[18] However, it was not stated whether patients with known pulmonary disease were included in this study. Patients with obstructive or mixed-type disorder may have had lung disease before being diagnosed with COVID-19. In a prospective longitudinal cohort study conducted in the Netherlands in which 101 patients with moderate or severe COVID-19 pneumonia were evaluated six weeks after their discharge, reduced diffusion capacity in the lung was found in 92 people (71.7%), obstruction in 26 people (25.7%), and restriction in 21 people (21.2%). However, 34.7% of the individuals in that study had comorbid lung disease.[19] In another study evaluating 13 patients with COVID-19 diagnosis, it was observed that at the time of discharge, 10 patients had a restrictive pattern, and that after six weeks, the pulmonary function had improved, but some restrictive changes remained.[20] Similar studies reported that a restrictive pattern was frequently observed in the post-COVID-19 period.[10,21] In individuals followed up after influenza A (H7N9) infection, it was observed that restrictive ventilation dysfunction and dyspnea continued even in the sixty-fourth month after the onset of the disease.[22] It was found that in 80% of the individuals evaluated in the first year after ARDS, the diffusion capacity of their lungs was reduced, 20% of them had an obstructive pattern, and 20% had a restrictive pattern.[23] Long-term lung function disorders after COVID-19 and other viral pneumonias were also supported by the findings of our study.

Epidemiological studies found that 7−13% of adults had FVC%pred values below 80% when FEV1/FVC ratios were ≥70%. It was reported that these individuals were at high risk for all-cause and cardiovascular mortality. This restrictive spirometry pattern was also associated with various comorbid conditions, such as major functional impairment, diabetes mellitus, metabolic syndrome, hypertension, stroke, and cardiovascular diseases.[24] In the present study, FEV1 and FVC values were significantly lower in severe/critical individuals compared to indidviduals with moderate clinical disease. Similar results were obtained in the national prospective observational study conducted by Guler et al.[25] In this cross-sectional study involving 41 patients who were followed up after severe pneumonia or ARDS in Brazil, the pulmonary function of the individuals was evaluated 15−30 days after discharge. It was observed that FVC had decreased in 54% of the patients, but the FEV1/FVC rate had not changed.[26] Patients should be evaluated for pulmonary function in the post-

COVID-19 pneumonia period to detect the presence of a restrictive pattern that could be associated with mortality and various comorbid conditions. In this way, treatment and follow-up plans can be made to reduce mortality and morbidity risks.

In the present study, the decrease in pulmonary function in the patients appeared to show a restrictive pattern, which could be related to fibrosis in the lung. In both groups, the mean MVV pred% values were over 80%, which is considered the normal value. MVV measurement is a method that indicates the endurance of the respiratory muscles.[27] Previous studies have noted that fibrotic changes after COVID-19 infection can cause restrictive impairment of pulmonary function.[28] Although the restrictive pattern was thought to be due to the involvement of pulmonary parenchyma, the evaluation of respiratory muscle endurance supported our view that the problem could be due to pulmonary parenchymal damage because the mean MVV values were normal in both groups. Indeed, in another study evaluating COVID-19 patients in severe/critical stages, no change was observed in respiratory muscle strength. It was reported that lung dysfunction may result from lung parenchymal damage during the disease process rather than from respiratory muscle problems.[25] Whether the parenchymal damage is permanent in these patients could be evaluated at the end of a long follow-up period with the support of imaging studies.

The 6MWT is a simple test that investigates inducible hypoxia in non-hypoxic patients at rest, enables the early detection of hypoxia, and is useful in initiating early care. This test has broad clinical applicability in ensuring good-quality care for COVID 19 patients.[29] In the present study, the six-minute walk test distance achieved by the severe/critical stage patients was shorter than the distance achieved by the moderate-stage individuals, though the difference was not significant. The average 6MWT distance was less than 427 m in the severe/critical individuals. In a study in which COVID-19 survivors were evaluated an average of eight months after discharge from hospital, it was reported that individuals with severe clinical disease had lower 6MWT distances (558 ± 80 vs. 543 ± 88 m, respectively; $p = 0.583$) and poorer exercise tolerance compared to the moderate-stage individuals.[30] It was observed that the 6MWT evaluated in the first month after COVID-19 was also significantly shorter in individuals at the severe clinical stage compared to individuals at the moderate stage.[31] The mean 6MWT distance was less than 427 m in severe/critical individuals. This situation may also have been caused by the deconditioning of the critical/severe patients due to long hospital stays. Therefore, the validity of the 6MWT in terms of demonstrating isolated lung damage in COVID-19 patients should be tested. Because their exercise tolerance was also poor, it was concluded that these patients needed a comprehensive pulmonary rehabilitation program.

In our study, while there was no significant gender difference between the severe/critical group and the moderate group, it was found that the mean age and BMI of the severe/critical group were significantly higher than those of the moderate group. Similar to our findings, a multicenter Swiss prospective cohort COVID-19 lung study found that the severe/critical clinical stage group was older and had a higher average BMI.[24] Previous SARS and MERS experience also indicate that older age may be a risk factor for the development of lung fibrosis and for poor outcome.[32,33]

This study is the first in Turkey to evaluate lung function and exercise capacity in patients after they were diagnosed with COVID-19 pneumonia. However, the study has some limitations. These include the fact that all the individuals in the study population could not be reached, either because they lived in another province or because they could not be contacted by telephone, and the fact that the PFT and 6MWT values of the individuals prior to their COVID-19 diagnosis were not known. Also, DLCO measurements could not be taken due to limitations in the facility where the study was conducted. Multicenter studies that include long-term follow-up data of COVID-19 patients supported by imaging methods are needed.

Our study found that individuals who had been discharged following hospitalization due to COVID-19 pneumonia could develop a restrictive type of pulmonary dysfunction identified by PFT and the 6MWT. In particular, individuals assessed at the severe or critical clinical stages could have limited respiratory function, although the 6MWT was unable to distinguish between patients with severe/critical and those with moderate COVID-19. Therefore, survivors of COVID-19 pneumonia should be examined for pulmonary function to assess their rehabilitation needs and should subsequently be monitored and treated for clinically relevant sequelae during the follow-up period.

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Declarations of Competing Interest

None

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