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Original Article

Impact of Long COVID on Lung Function in Children

Uzun Süreli COVID'in Çocuklarda Akciğer Fonksiyonlarına Etkisi

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ABSTRACT

Objective: While the coronavirus disease-2019 (COVID-19) pandemic has generally resulted in milder illness among children than adults, persistent respiratory symptoms have been increasingly reported in this population.

Methods: We conducted a prospective, single-center cohort study focusing on children experiencing prolonged respiratory symptoms after contracting COVID-19. Spirometry, 6- minute walk tests (6MWTs), and tests of lung volume, the diffusing capacity of the lungs for carbon monoxide (DLCO), and fractional exhaled nitric oxide (FeNO) were performed on COVID-19 survivors at least 4 weeks after infection and a group of healthy control subjects.

Results: Fifty-five children with long-term COVID and 55 healthy control subjects were recruited. The weight, height, and body mass index Z-scores were similar in the groups. Within a median duration of 85 days (minimum-maximum: 35-194) following COVID-19 infection, a restrictive pattern was observed to be more common in the study group (p=0.021). In children with long COVID, 6MWT distances, DLCO Z-scores, and the predicted values of spirometry and lung volume tests were found to be significantly lower but in the normal range. The average predicted values for DLCO, FeNO, and 6MWT were similar in the two groups.

Conclusions: Prolonged respiratory symptoms often persist long after COVID-19 infection, necessitating comprehensive evaluation of affected children. Close monitoring, including spirometry and lung volume assessments, is crucial for children with abnormalities in lung imaging. However, FeNO measurements were found to be ineffective in monitoring long COVID.

Keywords: Children, diffusing capacity, fractional exhaled nitric oxide, long COVID, 6-minute walk test

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) pandemisinin başlangıcından bu yana, çocuklarda hastalığın seyrinin yetişkinlerdeki kadar şiddetli olmadığı gözlemlenmiştir. Bununla birlikte, uzun vadeli solunum semptomları görülebilmektedir.

Yöntemler: Çalışmamız prospektif, tek merkezli kohort çalışması olarak tasarlandı. Spirometri, 6 dakika yürüme testi (6DYT), akciğer hacim ölçümleri, karbon monoksit için akciğerlerin difüzyon kapasitesi (DLCO) ve fraksiyonel nitrik oksit (FeNO) testleri, COVID-19 enfeksiyonu geçiren ve solunumsal semptomları en az dört haftadır devam eden çocuklar ile aynı sayıda sağlıklı kontrol grubuna uygulandı.

Bulgular: COVID-19 sonrası solunum semptomları devam eden 55 çocuk çalışma grubu olarak, herhangi bir akciğer hastalığı bulunmayan 55 çocuk ise kontrol grubu olarak çalışmaya dahil edildi. Ağırlık, boy ve vücut kitle indeksi Z-skorları gruplar arasında benzerdi. COVID-19 enfeksiyonunu takiben ortanca 85 günde (minimum-maksimum: 35-194 gün) restriktif solunum paternini çalışma grubunda daha fazla olduğu gözlendi (p=0,021). Uzun süreli COVID'e sahip çocuklarda, 6DYT mesafeleri, DLCO Z-skorları ve spirometri ile akciğer hacmi testlerinin tahmin edilen değerleri daha düşük bulundu, ancak ortalama değerler normal referans aralığındaydı. DLCO, FeNO ve 6DYT için ortalama tahmin edilen değerler iki grup arasında benzerdi.

Sonuçlar: COVID-19 enfeksiyonu sonrasında ısrarcı solunumsal semptomları devam eden çocukların solunum fonksiyon testleri ile detaylı değerlendirilmesi gerekir. Akciğer görüntülemesinde anormallikleri olan çocuklar, özellikle spirometri ve akciğer hacim ölçümleri ile ayrıntılı değerlendirilmelidir. FeNO ölçümlerinin uzun süreli COVID izleminde anlamlı olmadığı bulunmuştur.

Anahtar kelimeler: Çocuklar, difüzyon kapasitesi, fraksiyonel solunan nitrik oksit, uzun süreli COVID, 6 dakika yürüme testi

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic, caused by the novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been associated with significant morbidity and mortality. The prolonged process of the pandemic has brought with it many questions about long-term sequelae in patients and studies that seek answers to these questions. It has been strongly suggested that there are "long-term symptoms," as evidenced by adult studies[1]. Although the definition of long COVID is constantly changing, most studies define

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it as the persistence of symptoms or development of sequelae more than 3 or 4 weeks after the onset of acute symptoms of COVID-19[2].

A study from Australia reported that 8% of children aged 0-19 years, most with a mild history of COVID-19, had persistent symptoms 3-6 months after acute onset[2]. A cross-sectional study of 129 children in Italy noted that 42.6% had at least one persistent symptom after more than 60 days[3]. Reductions in spirometry values and the diffusing capacity of the lungs for carbon monoxide (DLCO) are the most frequently reported disorders in adults, but pediatric data on this issue are insufficient[4-6].

We aimed to investigate whether respiratory complaints impact pulmonary function test (PFT) findings in children with long-term COVID. Because pre-infection PFT values in this population are unknown, we excluded children with lung diseases and compared post-COVID individuals with healthy controls. In addition, we determined whether clinical and radiological findings from the acute period of COVID-19 affected the PFT results of post-COVID individuals. For this purpose, detailed PFTs [spirometry and tests of lung volume, DLCO, and fractional exhaled nitric oxide (FeNO)] and exercise capacity tests [the 6-minute walk test (6MWT), modified Borg dyspnea scale, and fatigue scale] were performed on children with long COVID and healthy controls.

MATERIALS and METHODS

Study Design and Participants

This investigation was designed as an analytical, non-randomly controlled, prospective cohort study at a university hospital in Istanbul, Türkiye. The subjects were referred to a pediatric pulmonology clinic between January and July 2021 to evaluate persistent respiratory symptoms manifesting 6 weeks or more after acute SARS-CoV-2 infection. The inclusion criteria consisted of a history of positive SARS-CoV-2 RNA testing and, subsequently, the presence of persistent respiratory symptoms, such as cough, dyspnea, and chest pain, for 6 weeks. The medical data of the COVID-19-positive patients were obtained from the National Electronic Medical Record System (NEMRS)[7], which was also used to extract clinical data on demographics, comorbidities, SARS-CoV-2 polymerase chain reaction (PCR) test results, chest imaging [thorax computed tomography (CT) and chest X-rays], specific COVID-19 treatments, and hospitalization (if necessary).

All participants yielded negative results on SARS-CoV-2 PCR tests at our center. FeNO tests and then spirometry, lung volume, and DLCO measurements were performed. After the participants rested for 1 h, 6MWTs were initiated.

"Long COVID" was defined as the persistence of respiratory symptoms for at least 4 weeks after the completion of the acute infection period (two weeks). The time span from symptom onset to admission (the day PFTs were performed) was also recorded in days. Based on clinical data collected during the acute phase of the original COVID-19 infection, each participant's disease severity was classified in accordance with the World Health Organization criteria as asymptomatic, mild, moderate, severe, and critical infection[8].

Healthy children of approximately the same age who had no history of lung disease and applied to a general pediatric outpatient clinic for any reason were classified as the control group. None of the participants in the control group or their families had a history of COVID-19, which was confirmed by NEMRS data. The exclusion criteria ruled out participants with chronic lung diseases (including asthma and allergic rhinitis), smokers, and those who did not want to participate (Figure 1).

Demographic and Clinical Data

We recorded the age, gender, weight, height, and body mass index (BMI) Z-scores, oxygen saturation at room air, and comorbidities of each individual in both groups. We classified the comorbidities into organ-specific diseases (obesity; pulmonary, cardiac, connective tissue, metabolic, and endocrinological diseases; and hematologic diseases in patients predisposed to thromboembolism).

Chest X-rays and thorax CTs taken during the acute period were evaluated by the same pediatric pulmonologist. The quantitative radiological scoring system was used to define idiopathic pulmonary fibrosis due to SARS infection. This test, used in previous years, evaluates signs including ground glass opacities, consolidation, reticulosis, bronchiectasis, honeycombing, parenchymal bands, fibrosis, and air trapping. The five lobes in the lungs are scored between 0 and 5 according to the density of the lung area involved; a total score of 0 is considered normal, while <5% involvement for each lobe yields 1 point, 5-25% yields 2 points, 25-49% yields 3 points, 50-75% yields 4 points, and >75% involvement is scored as 5 points. The scores calculated for each segment and the total score were calculated from 0 to 25[9-12].

Pulmonary Function Tests

All PFT measurements were performed in the pulmonary function laboratory of a pediatric pulmonology department according to the guidelines

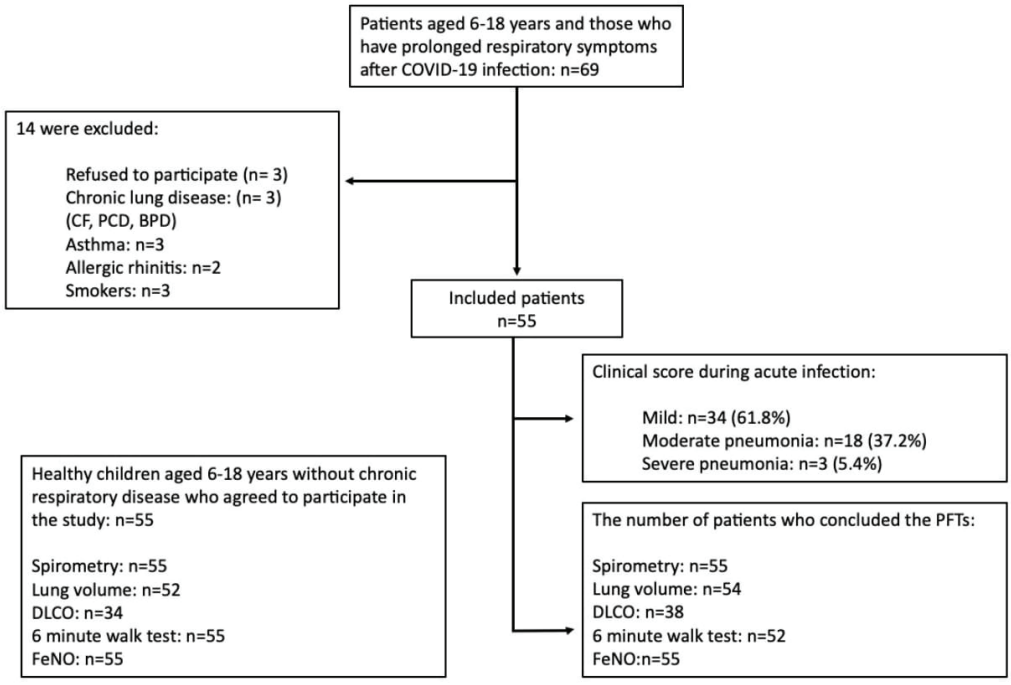

Figure 1. The participate diagram of the study.

COVID-19: Coronavirus disease-2019, CF: Cystic fibrosis, PCD: Primary ciliary dyskinesia, BPD: Bronchopulmonary dyskinesia, FeNO: fractional exhaled nitric oxide, PFT: Pulmonary function test, DLCO: Diffusing capacity for carbon monoxide

of the American Thoracic Society (ATS) and European Respiratory Society (ERS) by a single qualified pulmonary function technologist[13]. During the measurements, the PFT technologist performed control measures against COVID-19. The flowmeter calibration was performed daily using a 3 L syringe. Forced expiratory maneuvers were performed on all participants while they sat comfortably in a chair.

Spirometry, Lung Volume and Pulmonary Diffusion Capacity

Pulmonary flow, lung volume, and diffusing capacity were evaluated using the Minibox+ (PulmOne Advanced Medical Devices, Ra'ananna, Israel) following the ATS/ERS guidelines[13]. Each subject underwent three accepted maneuvers for spirometry; the highest values were recorded and used in subsequent analyses. The DLCO single-breath technique was adjusted for each participant's hemoglobin concentration. The following parameters were measured: forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), forced expiratory flows at 25% and 75% of FVC (FEF_{25-75}), FEV_1/FVC, total lung capacity (TLC), residual volume (RV), RV/TLC, VC, and functional residual capacity (FRC). All spirometry measurements were expressed as percentages of predicted normal values, which were calculated automatically based on age, sex, height, and ethnicity[14]. The spirometry and plethysmography values and DLCO Z-scores of the measurements were calculated using the Global Lung Function Initiative Calculator according to age, gender, and height[15]. The criteria for classifying lung function abnormalities were based on the current ERS guidelines: starting from the FEV_1/FVC ratio, we determined whether an obstruction existed by checking whether the ratio was lower than the lower limits of normal (LLN, Z-score <-1.64). If an obstruction was present, the FVC was assessed to determine whether there was simply an obstruction or whether there might have been a restrictive pattern. TLC measurement was used to define the restriction. If the FEV_1/FVC ratio was normal, it was determined that there was no obstruction, and the FVC was evaluated again. If the FVC was normal, spirometry was considered normal; however, if the FVC was below the LLN, the TLC measurement was evaluated, and a possible restriction was considered. If the DLCO value was above the LLN in patients with a restrictive pattern, restriction by the chest wall or musculoskeletal system was considered. However, if the DLCO value was below the LLN, it was considered that there might be parenchymal damage (Figure 2)[16].

Fractional Exhaled Nitric Oxide

Airway inflammation was measured noninvasively and quantitatively using the NObreathe® FeNO analyzer. This process was performed according to the ATS/ERS recommendations[17].

Six-Minute Walk Test and Borg Scale

The 6MWT was performed by the same pulmonary functional technologist in accordance with the ATS guidelines[18]. The modified Borg dyspnea and fatigue scale was administered to the participants, who were requested to assess their respective conditions by responding to the following questions: "Please indicate the degree of your shortness of breath using this scale" and "Please indicate the degree of your fatigue using this scale." The participants were instructed to select a number on a scale ranging from 0 (representing no symptoms) to 10 (representing extremely severe symptoms)[18].

The 6MWT percentage values were determined by calculating the percentage of the distance walked as the ideal walking distance[19] [The ideal 6MWT distance equation for men is 1140 – (5.61 x BMI) – (6.94 x age); the equation for women is 1017 – (6.24 x BMI) – (5.83 x age)].

Ethical Committee Approval and Informed Consent

This study adhered to the revised Declaration of Helsinki and received approval from the Clinical Research Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital on January 27, 2021 (decision no: 2021/0068). Both participants and their parents provided informed consent before participation.

Statistical Analysis

The statistical analysis was performed using the Number Cruncher Statistical System (NCSS) 2007 software (Kaysville, Utah, USA). Descriptive statistics, including mean, standard deviation, median, frequency, ratio, minimum (min), and maximum (max), were employed to analyze the study data. Normal distribution of quantitative data was assessed via the Shapiro-Wilk test and graphical methods. Two-group comparisons of normally distributed quantitative data were conducted using Student's t-test, whereas non-normally distributed data were analyzed using the Mann-Whitney U-test. Qualitative data were compared using Pearson's chi-square test, Fisher's exact test, and Fisher-Freeman-Halton test. For group comparisons involving three

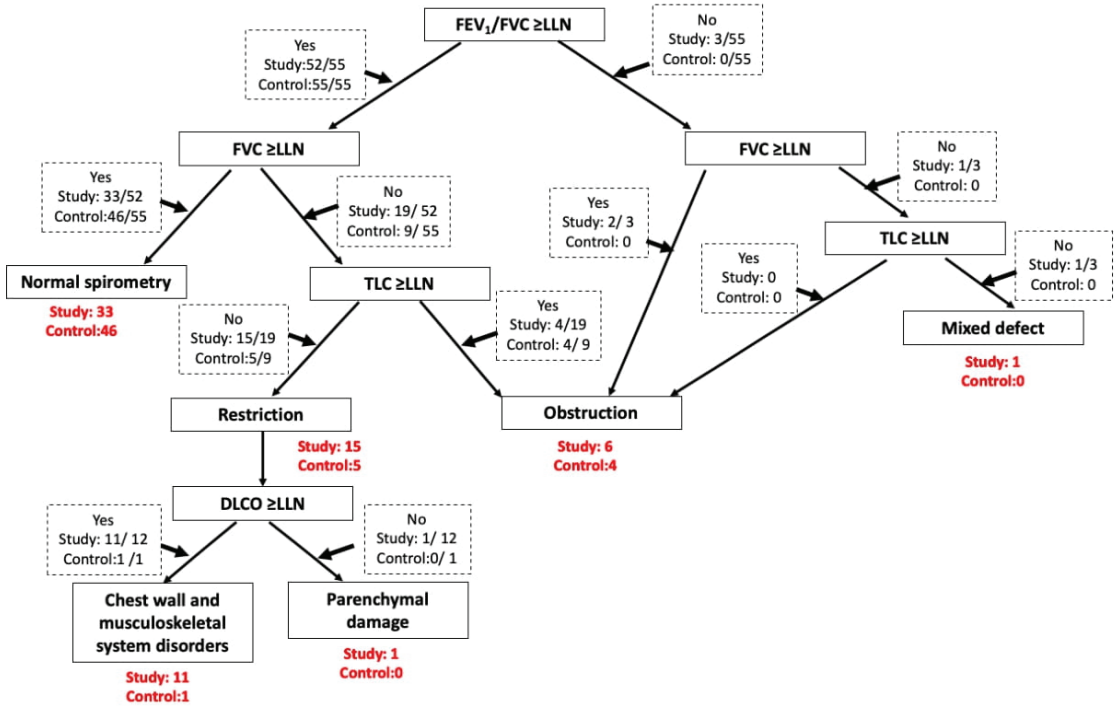

Figure 2. Pulmonary function test evaluation of the participants in both study and control groups.

FEV_1/FVC: The ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC), LLN: Lower limits of normal (Z-score <-1.64), FVC: Forced vital capacity, TLC: Total lung capacity, DLCO: Diffusing capacity of lungs for carbon monoxide

or more groups with non-normal distribution, the Kruskal-Wallis test was employed, followed by pairwise comparisons using the Bonferroni-Dunn test. Spearman's correlation analysis was used to assess the relationships between variables. The significance level was set at $p<0.05$.

RESULTS

General Characteristics of the Participants

Fifty-five of the 69 children with long COVID and 55 healthy controls participated in the study. Fourteen patients were excluded from the study group (three patients refused to participate, three had chronic lung disease, three had asthma, two had allergic rhinitis, and three were smokers). Figure 1 presents the participants' characteristics and results of the spirometry, lung volume, DLCO, 6MWT, and FeNO tests.

The mean age of the study group was 14.71±3.03 years (min: 7.1, max: 18.6), and that of the control group was 12.5±2.9 years (min: 6.8, max: 17.5) (p=0.001). Thirty-one patients (56.4%) in the study group and 27 patients (49.1%) in the control group were female (p=0.445). The weight, height, and BMI Z-scores were similar between the two groups (p=1.000 in all groups). In total, 14 of the 55 (25.5%) patients in the study group had comorbidities: one had experienced a total pulmonary venous return abnormality (that was operated upon), two had obesity, two had hematologic issues (Evans syndrome and polycythemia), two had connective tissue diseases (familial Mediterranean fever), and five had endocrine and metabolic system diseases (hypothyroidism, type IV glycogen storage disease, isovaleric acidemia, hypophosphatemic ricketss, and growth hormone deficiency). Three patients in the control group were obese.

Characteristics Associated with Acute COVID-19 Infection and Long COVID

In the study group, most of the participants (61.8%) had mild infections, approximately one-third (37.2%) had moderate pneumonia, and only 5.4% had severe pneumonia. More than one-third of the participants had a history of hospitalization, with an average stay of 10.11±4.48 days. When the treatments of 18 hospitalized patients were reviewed, it was observed that the most frequently used treatment options were favipiravir and antibiotics. Most patients had undergone more than one treatment method. Twenty-one of the patients showed consolidation on chest X-rays during acute infection, and all underwent thoracic CT. Seventeen participants had pulmonary involvement on thoracic CT, and the median CT score was 6.23. The average number of days from the onset of acute infection to admission to our clinic was 88.62±30.84. The clinical findings of the participants in the study group during the acute COVID-19 infection period are presented in Table 1.

In the acute phase of COVID-19 infection, the most common symptoms were cough (63.6%) and fever (50.9%). Other symptoms were fatigue (40%), myalgia (38.2%), headache (32.7%), chest pain (25.5%), dyspnea (23.6%), runny nose (18.2%), nausea and vomiting (14.5%), and sore throat (10.9%). The most common long COVID

Table 1. Clinical findings of the participants in the study group at the time of acute COVID-19 infection.

Study group	Data
Severity of disease, n (%)	55 (100)
Mild infection	34 (61.8)
Moderate pneumonia	18 (32.7)
Severe pneumonia	3 (5.4)
Number of hospitalized patients, n (%)	18 (32.7)
Hospitalization days, mean ± SD	10.11±4.48
Treatments administered during hospitalization among 18 patients, n (%)	
Favipiravir	13 (72.2)
Antibiotics	10 (55.6)
Anticoagulants	5 (27.8)
Oral steroids	5 (27.8)
IVIG	3 (16.7)
Hydroxychloroquine	2 (11.1)
Azithromycin	2 (11.1)
Follow-up without treatment	1 (5.6)
PICU admission, n (%)	2 (3.6)
Supportive treatment, n (%)	
Oxygen	3 (5.5)
HFNC	1 (1.8)
Consolidation on chest X-ray, n (%)	21 (38.2)
Number of patients who underwent thorax CT, n (%)	21 (38.2)
Number of patients with normal thorax CT findings, n (%)	4 (19)
Number of patients with abnormal thorax CT findings, n (%)	17 (81)
Thorax CT score, median (min-max) (n=17)	6.23 (1-14)
Number of days to PFT date after COVID-19 infection, median (min-max)	85 (35-194)

COVID-19: Coronavirus disease-2019, SD: Standard deviation, IVIG: Intravenous immunoglobulin, PICU: Pediatric intensive care unit, HFNC: High flow nasal cannula, CT: Computed tomography, PFT: Pulmonary function test, min-max: Minimum-maximum

symptoms when our study began were cough (52.7%), dyspnea (32.7%), and chest pain (14.5%).

Pulmonary Function Tests

There were significant differences between the study and control groups in FEV_1, FVC, and FEF_{25-75} percentages and Z-scores; average FEV_1/FVC and z-scores; TLC, RV, and FRC percentages and Z-scores; RV/TLC ratios and Z-scores; and VC Z-scores. The values were higher in the control group. No differences were detected in the average DLCO or FeNO values across the two groups, whereas the DLCO Z-scores were significantly lower in the study group (p=0.007). There was no difference between the two groups in exercise test results and modified Borg scale scores (Table 2).

The spirometry results of the children participating in our study were classified as normal, restrictive, obstructive, or mixed based on the ERS recommendations[16], as shown in Figure 3. In total, 33 children in the study group (60%) and 46 (83.6%) in the control group had normal spirometry results. Fifteen patients (27.2%) in the study group and five (9.1%) in the control group had restrictive PFTs. Thirteen out of 20 children with restrictive PFTs had DLCO data; one had a DLCO value below the LLN, whereas the other 12 had DLCO values above the LLN.

Table 2. Spirometry, lung volume, DLCO, FeNO, and exercise test results of the two groups.

Pulmonary function test		Study group	Control group	p-value
FEV_1	% predicted, mean ± SD	87.20±12.92	100.26±10.92	**0.001**[a]
	Z-score, Q2 (Q1-Q3)	-0.92 (-1.46-0.04)	0.37 (-0.59-1.38)	**0.001**[b]
FVC	% predicted, mean ± SD	84.98±13.80	91.09±12.04	**0.015**[a]
	Z-score, Q2 (Q1-Q3)	-1.17 (-1.91-0.03)	-0.31 (-1.30-1.18)	**0.001**[b]
FEV_1/FVC	Mean ± SD	101.93±9.17	110.02±6.27	**0.001**[a]
	Z-score, Q2 (Q1-Q3)	0.70 (-0.04-1.30)	1.50 (0.66-2.55)	**0.001**[b]
FEF_{25-75}	% predicted, mean ± SD	89.73±20.36	114.35±23.22	**0.001**[a]
	Z-score, Q2 (Q1-Q3)	-0.12 (-1.03-0.31)	0.75 (-0.31-1.23)	**0.001**[b]
TLC	% predicted, mean ± SD	82.02±16.89	90.40±19.06	**0.019**[a]
	Z-score, Q2 (Q1-Q3)	-2.99 (-3.96- -1.21)	1.16 (-1.17-3.04)	**0.001**[b]
RV	% predicted, mean ± SD	53.46±49.00	74.33±43.29	**0.003**[a]
	Z-score, Q2 (Q1-Q3)	-1.72 (-2.73-0.16)	-0.28 (-1.0-0.87)	**0.001**[b]
RV/TLC	mean ± SD	59.04±45.08	78.75±33.38	**0.012**[a]
	Z-score, Q2 (Q1-Q3)	-1.0 (-2.19-0.49)	-0.35 (-0.95-0.34)	**0.001**[b]
VC	% predicted, mean ± SD	86.78±11.51	91.04±15.39	0.109[a]
	Z-score, Q2 (Q1-Q3)	-2.94 (-3.88- -1.01)	0.47 (-1.57-4.22)	**0.001**[b]
FRC	% predicted, mean ± SD	70.95±42.06	93. 45±43.17	**0.022**[a]
	Z-score, Q2 (Q1-Q3)	-2.30 (-4.48- -1.20)	0.06 (-1.20-2.75)	**0.001**[b]
DLCO	%, mean ± SD	97.13±18.40	103.76±14.87	0.099[a]
	Z-score, Q2 (Q1-Q3)	-0.48 (-1.33-0.20)	0.23 (-0.66-0.89)	**0.007**[b]
FeNO	ppb, mean ± SD	9.58±6.75	7.55±5.79	0.070[b]
sPO_2	%, mean ± SD	98.13±0.82	98.00±0.94	0.340[b]
6MWT	meter, mean ± SD	568.69±107.47	588.51±44.20	**0.013**[b]
	%, mean ± SD	66.45±12.70	67.31±7.25	0.183[b]
Borg dyspnea score	Median (min-max)	0.5 (0-5)	0 (0-6)	0.258[b]
Borg fatigue score	Median (min-max)	0.5 (0-5)	0.5 (0-5)	0.691[b]

[a]Student's t-test, [b]Mann-Whitney U test. FEV_1: Forced expiratory volume in the first second, Q1: First-quarter value, Q2: Median, Q3: Third-quarter value, FVC: Forced vital capacity, FEF_{25-75}: Forced expiratory flows at 25 and 75% of FVC, TLC: Total lung capacity, RV: Reserve volume, VC: Vital capacity, FRC: Functional residual capacity, DLCO: Diffusing capacity of lungs for carbon monoxide, FeNO: Fractional exhaled nitric oxide, PPB: Parts per billion, sPO_2: Peripheral oxygen saturation, 6MWT: 6-minute-walk test, SD: Standard deviation, min-max: Minimum-maximum

Comparing the PFT results in two groups, a restrictive pattern was observed significantly more often in the study group (p=0.021). While six patients in the study group had low DLCO values (four had mild and two had moderate diffusing impairments), none of the participants in the control group had low DLCO results (p=0.015). When the six patients in the study group whose DLCO Z-scores were found to be below the LLN were examined, it was detected that two of them presented as normal, two suffered obstruction, one suffered restriction, and one had mixed PFT findings.

The FEV_1, FVC, TLC, and VC values of the group with consolidation on chest X-rays were found to be significantly lower than those of the group without consolidation (p=0.018, p=0.044, p=0.035, p=0.014, and p=0.018, respectively) (Table 3). No significant correlation was found between CT scores and spirometric values, but a negative correlation was found with TLC (p=0.026, r=-0.497), RV (p=0.027, r=-0.495), RV/TLC (p=0.021, r=-0.513), and FRC (p=0.002, r=-0.707) values (Table 4). No significant differences were found between clinical scores (mild and moderate/severe) and PFT values. Furthermore, no statistically significant relationship was found between clinical scores and FeNO levels (p=0.083).

No significant difference was found between the current symptoms (cough, chest pain, and dyspnea) of the COVID-19 survivors and their spirometry and plethysmography values. A significant difference was found between current symptoms and DLCO and

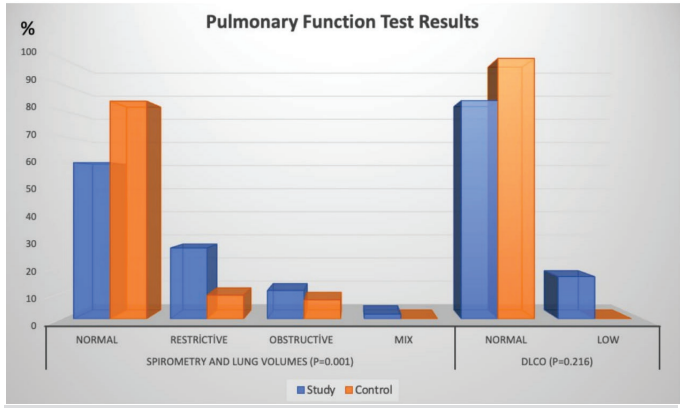

Figure 3. The comparisons of pulmonary function test results between study and control groups.

Table 3. Relationships between PFTs, presence of consolidation on chest X-rays, severity of disease, and long COVID symptoms among children with long COVID.

	Presence of consolidation on chest X-ray		Severity of disease			Current symptoms			
	Yes n=21	p	Mild n=34	Moderate-severe n=21	p[b]	Cough	Chest pain	Dyspnea	p[c]
FEV_1, %, mean ± SD	82.0±14.3	**0.018**[a]	88.6±10.7	81.8±19.2	0.467	89.2±13.2	87.9±11.1	83.7±13.1	0.322
FVC, %, mean ± SD	80.2±15.1	**0.044**[a]	86.2±12.2	80.1±18.7	0.377	85.6±14.1	85.0±12.6	84.0±14.5	0.801
FEV_1/FVC, mean ± SD	102.2±10.8	0.869[a]	102.3±9.1	100.6±9.6	0.577	103.0±9.3	103.5±3.6	99.5±10.4	0.471
TLC, %, mean ± SD	86.1±20.1	0.182[a]	82.4±17.7	80.7±13.2	0.982	79.0±13.9	90.4±17.4	83.2±20.2	0.280
RV, %, mean ± SD	67.8±59.9	0.162[b]	55.8±52.3	43.3±30.6	0.902	46.7±46.3	69.0±52.2	57.0±52.5	0.353
FeNO, ppb, mean ± SD	11.6±7.9	0.086[b]	8.5±5.2	13.7±10.3	0.083	8.9±6.1	9.0±4.6	10.9±8.5	0.812
DLCO, %, mean ± SD	96.5±18.6	0.874[a]	96.0±17.9	100.7±20.2	0.259	106.9±17.5	92.3±13.2	86.6±15.1	**0.008**
6MWT, %, mean ± SD	70.3±15.9	0.240[b]	64.8±11.6	74.2±15.3	0.100	62.1±9.9	78.7±16.0	68.9±12.3	**0.018**

[a]Student's t-test, [b]Mann-Whitney U test, [c]Kruskal-Wallis test. FEV_1: Forced expiratory volume in the first second, FVC: Forced vital capacity, FEF_{25-75}: Forced expiratory flow at 25% and 75% of FVC, TLC: Total lung capacity, RV: Reserve volume, DLCO: Diffusing capacity of lungs for carbon monoxide, FeNO: Fractional exhaled nitric oxide, PPR: Parts per billion, 6MWT: 6-minute-walk test, SD: Standard deviation, COVID: Coronavirus disease, PFT: Pulmonary function test

6MWT percentages (p=0.008 and p=0.018, respectively). DLCO values were found to be lower in the group with dyspnea (p=0.008), and 6MWT percentages were found to be lower in the group with cough symptoms (p=0.018) (Table 3).

DISCUSSION

In our study, 16.2% of patients with long COVID had diffusion impairments and 27.2% had restrictive respiratory disorders. We found that clinical scores in the acute period did not affect long-term PFTs. Decreases in lung volume and expiratory flow were observed in patients with consolidation on chest X-rays and high thorax CT scores. The DLCO values of patients with dyspnea were found to be lower than those of individuals with coughing and chest pain. Exercise capacity was found to be the lowest in those with cough symptoms.

At the end of the first year of the pandemic, the National Institute for Health and Care Excellence published a rapid guideline for managing long-term COVID[20]. In children, long COVID was first reported in the literature in November 2020 by Ludvigsson[21] when the long-term symptoms of five pediatric patients were noticed. The first study to examine the pulmonary manifestations of long COVID in children was conducted by Bottino et al.[5] In this study, forced spirometry, DLCO, and lung ultrasound results were examined, and it was emphasized that pulmonary sequelae did not develop in the children in the follow-up.

Table 4. Correlations between CT scores and pulmonary function test values.

	CT score*	
	p	**r**
FEV_1, %	0.285	-0.245
FVC, %	0.098	-0.371
FEV_1/FVC	0.964	-0.011
FEF_{25-75}, %	0.795	-0.06
TLC, %	**0.026**	-0.497
RV, %	**0.027**	-0.495
VC, %	0.940	0.018
FRC, %	**0.002**	-0.707
FeNO, ppb	0.679	0.096
DLCO, %	0.302	-0.297
6MWT, meter	0.640	-0.108
6MWT, %	0.591	-0.124
Borg dyspnea score	0.895	0.031
Borg fatigue score	0.739	-0.077

*Based on the lung involvement of the disease, CT scores were assigned from 0-25. As the CT score increases, lung involvement increases. FEV_1: Forced expiratory volume in the first second, FVC: Forced vital capacity, FEF_{25-75}: Forced expiratory flows at 25% and 75% of FVC, TLC: Total lung capacity, RV: Reserve volume, VC: Vital capacity, FRC: functional residual capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, FeNO: Fractional exhaled nitric oxide, PPB: Parts per billion, 6MWT: 6-minute-walk test, r: Spearman's correlation coefficient, CT: Computed tomography

COVID-19 appears to harm the lungs the most, causing a variety of pathophysiological events in parts of the alveolar structure, including the alveolar epithelium, hyaline membrane, capillary, and alveolar septum[22,23]. It may impede gas diffusion due to damage to the alveolar epithelium and endothelial cells and eventually lead to restrictive respiratory conditions. In addition, secondary fibroproliferation, starting from the terminal bronchioles accompanying this pathway mentioned in the first sentence, may also cause airway obstruction and create obstructive respiratory conditions[23]. In Salem et al.[1], reductions were found in TLC, FVC, FEV_1, and DLCO on the long-term PFTs of adult COVID-19 survivors. Half of the COVID-19 survivors they studied suffered from restrictive lung impairment, and more than one-third of the patients had diffusion impairments[1]. Bottini et al.[5] prospectively investigated 16 children with asymptomatic or mild infections for at least 1 month after COVID-19 infection and found that none of the participants had any abnormalities on spirometry, DLCO, airway resistance, and lung ultrasonography tests. Öztürk et al.[6] retrospectively evaluated 50 children with and without respiratory symptoms using PFTs 3 months after acute infection. They found that the spirometry values were similar in children with and without respiratory symptoms and were all within the normal range. However, diffusion impairment was found to be significantly more common in children with severe COVID-19 infections than in those with mild infections[6]. In our study, it was found that expiratory flow and lung volume were lower in children with long COVID; 10.9% had obstructive, 27.2% had restrictive, and 1.8% had mixed respiratory patterns, whereas 16.2% had diffusion impairments. We found that DLCO Z-scores were slightly impaired in children with long COVID. Nevertheless, it should be noted that although the spirometry results and DLCO Z-scores of the healthy children were lower than those of the afflicted children, the latter's mean values were within the normal range. Because there was no long-term radiological evaluation of the COVID-19 survivors, we cannot offer sufficient commentary on this subject. In our study, contrary to that of Öztürk et al.[6], no significant relationship was found between diffusion impairment and clinical scores. This may be because most of the patients had mild to moderate infections in the acute phase of COVID-19. In the existing literature, the extent to

which a DLCO decrease is expressed in symptoms is not yet clear. Histopathologically speaking, alveolocapillary membrane involvement, impaired gas exchange, and inadequate oxygenation can lead to dyspnea during exercise, as assessed by DLCO measurement[23]. In addition, functional loss of respiratory muscle due to overuse because of symptoms such as cough and dyspnea may also cause restrictive lung disease[24]. In this study, parenchymal damage was identified due to decreased DLCO in only one participant, who had restrictive PFT results; because the DLCO values were above the LLN in the other 12 patients, it was thought that there might be a restriction for a reason other than the lungs. In cases where the DLCO is normal and the patient suffers from dyspnea, other systemic conditions that may cause symptoms in patients should be investigated.

In follow-up studies on long-term COVID, the 6MWT and modified Borg scale are commonly used to evaluate functional capacity in adults. In one study conducted with 29 children who had protracted respiratory findings, 9 who completed the 6MWT walked 66.7% of the predicted distance (4). In a study conducted by Cortes-Telles et al.[25], both Borg fatigue and dyspnea scores were significantly higher among adults with both dyspnea and fatigue observed 30-90 days after acute COVID-19 infection. In our study, the 6MWT percentage and Borg scale values were similar in the patients and healthy controls, whereas the 6MWT distances were lower in the study group. For interpreting the 6MWT results in children, the use of estimated percentages based on age, BMI, and gender is crucial, and using similar estimated percentages is more valuable than using different 6MWT distances in both groups. In some studies, the low exercise capacity of patients with long COVID may be an effect of muscle weakness due to COVID-19 infection[26,27]. In our study, based on persistent complaints, it was observed that the 6MWT percentages of patients afflicted by coughing were lower than those of patients with chest pain and dyspnea. Even if the respiratory parameters of children with long COVID are within normal limits, they should be closely monitored in terms of exercise capacity.

Fractionally exhaled NO is mostly used for diagnosing asthma exacerbations in clinical practice[28]. Although prolonged inflammation may persist in long COVID, most studies have shown that FeNO measurement is not a useful method for detecting it[29,30]. However, FeNO has been accepted as a useful biomarker for assessing airway inflammation and oxidative stress in the lungs[29]. Lior et al.[28] found that lower levels of FeNO were associated with more severe disease, and Cameli et al.[31] reported increased FeNO values in post-COVID patients, which supports its correlation with pulmonary inflammation. Betancor et al.[30] found FeNO levels to be within the normal range during the acute phase of COVID-19, with some increase during the recovery phase. Although there is no consensus on FeNO measurement in adult studies, we did not find FeNO particularly useful in the long-term follow-up of COVID-19 in children.

Some adult studies have attempted to identify the relationship between the long-term effects of COVID-19 and demographic, clinical, and laboratory findings upon diagnosis[1]. In our study, we observed decreases in both the expiratory flows of patients with consolidation on chest X-rays and the lung volumes of patients with consolidation on thorax CT. We believe that it is important to follow up on children exhibiting consolidation on chest X-rays and thorax CT to detect other long-term symptoms using spirometry and lung volume tests. We also found that their clinical scores did not affect the long-term PFTs of children with long COVID. Diffusion impairment was more common in children with dyspnea than in those with other symptoms. Moreover, children with cough had lower functional capacity than children with other symptoms. It is important to monitor children with dyspnea carefully for DLCO and to follow-up on children with persistent coughing through 6MWTs after COVID-19.

To the best of our knowledge, in the limited body of literature on PFTs in long COVID during childhood, our study is the first to have recruited a healthy control group. It also used the highest number of children in the evaluation of PFTs. Moreover, the modified Borg dyspnea and fatigue scale was used for the first time to evaluate the long-term effects of COVID-19 on children's functional capacity. However, our study had some limitations. Although the mean age of the healthy children in the control group (who were selected randomly) was different from that of the study group, their heights, weights, and BMI Z-scores were similar. We believe that this limitation can be accepted because their body proportions were similar. In addition, there was no comparison of thorax imaging between the acute phase and the long-term follow-up stage. Despite these limitations, we believe that our data, along with the comparison with healthy control subjects, provide enlightening insights into the long-term monitoring of COVID-19 patients.

CONCLUSION

In conclusion, it is important to follow-up long COVID symptoms in children. In particular, in children with long COVID and respiratory complaints, expiratory flow and lung volume may decrease, and restrictive patterns may

be obvious. Where COVID symptoms such as cough, dyspnea, or chest pain emerge, spirometry and DLCO results may provide valuable insights into assessing functional capacity and determining potential chronic lung damage. There is a need for future studies in which longer-term PFTs are conducted to determine the duration of respiratory disorders.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital on January 27, 2021, with the decision number 2021/0068.

Informed Consent: Both participants and their parents provided informed consent before participation.

Author Contributions

Surgical and Medical Practices: Z.R.O., S.C.O., D.M.T., G.B., Y.A., F.D., S.G., Concept: Z.R.O., S.G., Design: Z.R.O., S.G., Data Collection and/or Processing: Z.R.O., S.C.O., D.M.T., G.B., Y.A., F.D., S.G., Analysis and/or Interpretation: Z.R.O., S.C.O., D.M.T., G.B., Y.A., F.D., S.G., Literature Search: Z.R.O., S.C.O., D.M.T., G.B., Y.A., F.D., S.G., Writing: Z.R.O., S.G.

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