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Coronavirus Pandemic

Evaluation of long-term pulmonary functions after COVID-19 infection in children: a longitudinal observational cohort study

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Abstract

Introduction: We aimed to present the changes that may occur in pulmonary functions in children who experienced more severe coronavirus disease 2019 (COVID-19) during long-term follow-up.

Methodology: A prospective longitudinal observational cohort study was conducted with 34 pediatric patients (7–18 years) who were hospitalized with COVID-19 infection (moderate n = 25, severe n = 9), and followed up at our Pediatric Infection Outpatient Clinic for approximately two years. Pulmonary function tests (PFTs) were performed using spirometry.

Results: Data from the hospitalization period revealed no significant differences between the severity groups in terms of demographic, clinical, laboratory, radiological, treatment, and outcome ($p > 0.05$). The median time interval between COVID-19 infection and PFTs was 15 months (range 11–29 months), and there was no significant difference between severity groups ($p = 0.878$). Eight patients (24%) had abnormal pulmonary functions; among them, seven had an obstructive pattern (21%) and one had a restrictive pattern (3%). The severity groups had no statistical difference in pulmonary functions ($p = 0.105$). While forced expiratory volume in 1 second (FEV1) %, FEV1/forced vital capacity (FVC)%, and forced expiratory flow during the middle half of FVC (FEF25–75%) ratios were lower in the severe patient group, Z-scores were similar. Among the patients continuing polyclinic follow-up, 41% had persistent respiratory symptoms before PFTs. No differences were observed in PFTs when compared based on the presence of symptoms ($p > 0.05$).

Conclusions: We observed no significant long-term differences in pulmonary function between moderate and severe COVID-19 cases in children.

Key words: COVID-19; long-COVID; children; pulmonary function; spirometry.

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Introduction

It has been reported that children experience the novel coronavirus disease 2019 (COVID-19) infection in a milder form, often being asymptomatic or having mild symptoms compared to adults [1,2]. Common clinical symptoms in children with COVID-19 infection include persistent fever, cough, nasal congestion, shortness of breath, phlegm, myalgia, joint pain, headache, nausea, abdominal pain, and diarrhea [3]. Although COVID-19 tends to have milder symptoms in children, severe respiratory failure has been reported in some cases. However, the short-term and long-term effects of COVID-19 on the lungs still need to be fully understood [4].

Some adult and pediatric patients have been observed to have long-lasting symptoms following symptomatic or asymptomatic acute infection. Long COVID-19 includes all symptoms that continue or emerge within 4 to 12 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [5]. Adult studies examining the impact of prolonged symptoms on respiratory function have shown obstructive defects, impaired diffusion capacity, and decreased total lung capacity using pulmonary function tests (PFTs) [6–8]. There are limited studies on

pediatric patients investigating the effects of COVID-19 on pulmonary function, and most of the patient groups are asymptomatic or have mild disease severity, with relatively short follow-up periods.

Our study aimed to evaluate pulmonary functions in children who experienced more severe (moderate–severe) COVID-19 infection during long-term follow-up.

Methodology

Study design and population

Our study was conducted prospectively in a single center (Health Sciences University, Bursa Faculty of Medicine City Health Practices and Research Center, Department of Pediatrics) as a longitudinal observational cohort study between June 2022 and June 2023.

Children aged 7–18 years who were hospitalized with COVID-19 infection between March 2020 and May 2022, and after being followed up in our Pediatric Infection Outpatient Clinic for approximately two years, were included in the study. The diagnosis of COVID-19 infection was based on positive combined naso-oropharyngeal COVID-19 reverse transcriptase polymerase chain reaction (RT-PCR) swab samples. Combined naso-oropharyngeal samples were sent to the laboratory in a virus transport medium (Bio-Speedy vNAT Transfer Tubes, Bioeksen, İstanbul, Türkiye) at 4 °C. After nucleic acid extraction, the samples were tested using the Bio-Speedy severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) kit (Bioeksen, İstanbul Türkiye) in a real-time Rotor-Gene Q PCR device (Qiagen, Hilden, Germany), following the manufacturer's instructions.

Children with neurological diseases, heart diseases, pulmonary hypertension, cystic fibrosis, immunodeficiency, and asthma, which could cause chronic respiratory pathology were excluded from the study. The study also excluded those who had an acute upper respiratory tract infection during the previous month or who could not perform PFT, as well as adolescents who had smoked.

Clinical data of COVID-19 related hospitalization

Hematological, serum biochemical tests (including kidney and liver functions, lactate dehydrogenase [LDH], and electrolytes), myocardial enzymes, coagulation profile, erythrocyte sedimentation rate, C-reactive protein (CRP), and procalcitonin (PCT) levels were analyzed.

The patients were divided into two groups according to the clinical findings and outcomes during hospitalization based on the severity classification of COVID-19 in pediatric patients, as recommended by the World Health Organization (WHO) in its most recent bulletin [1]. Chest X-rays taken at the time of initial admission and thorax computed tomography (CT) scans administered to patients with unexplained respiratory symptoms or poor clinical prognosis was later evaluated by an experienced pediatric radiologist unaware of the patient's current clinical information.

Follow-up visit and pulmonary function testing

Spirometry (COSMED Pony FX, Rome, Italy) was performed to evaluate the pulmonary function of patients who continued their outpatient follow-up after COVID-19 infection. Spirometric procedures were performed as recommended by the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines [9]. The Quark SPIRO-OMNIA software was utilized for the testing. A pediatric-trained physician conducted forced spirometry. PFTs measured forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC, and forced expiratory flow during the middle half of FVC (FEF25–75) on at least three acceptable maneuvers. Tests that did not meet the ATS-ERS guidelines were rejected. Within the Global Pulmonary Function Initiative (GLI) framework, the Z score has been regarded as the most significant measure in evaluating pulmonary function in recent years. Spirometric measurements were assessed using Z-scores based on reference values from the GLI powered by the European Respiratory Society. Abnormal pulmonary function was defined as the result of at least one of the parameters: FEV-1 Z-score, FVC Z-score, and FEF25-75 Z-score ≤ 1.96.

Statistical analysis

During statistical analysis of the data, n (%) was used for categorical variables, and mean ± standard deviation (SD) values were used for continuous variables in case of conformity to normal distribution, and median (minimum–maximum) values were used when conformity was not achieved. When evaluating categorical data, Fisher's exact test was used in the presence of an expected frequency of less than 5 patients and in more than 20% of the cells; otherwise, the Chi-square test was used. Data normality was confirmed for each continuous variable using the Kolmogorov–Smirnov test ($p > 0.05$). Independent t-test was used for the comparison of severity groups, if parametric data were available. Mann Whitney U test was used for non-parametric data.

Data analysis was carried out using the IBM SPSS 25.0 (IBM SPSS Statistics for Windows, version 25.0. IBM Corp., Armonk, NY, USA). All tests were two-tailed, and a p value of <0.05 was considered statistically significant.

Results

Characteristics of the study group

There was a total of 56 pediatric patients during the follow-up after COVID-19 infection. Of these, 22 were not included in the study due to the exclusion criteria. Figure 1 shows the patients selected for the study and the groupings.

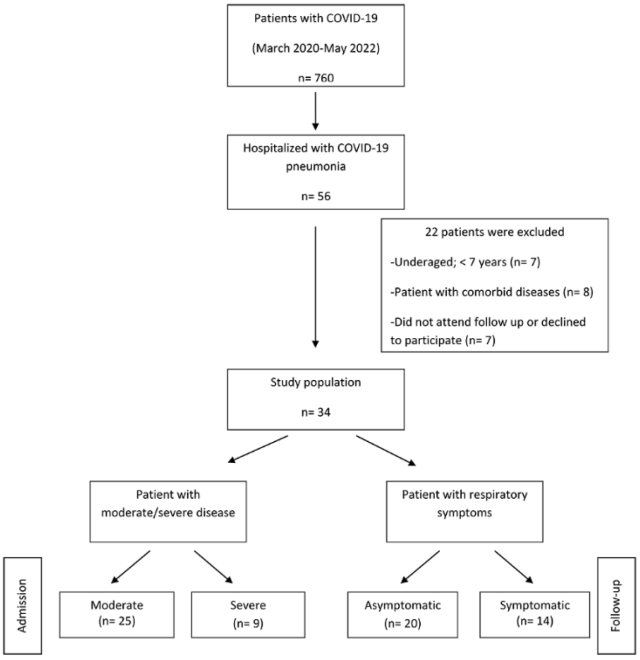
The median age of the patients included in the study was 15.75 years (min–max, 7.83–17.83 years) and 56% were male. Two (6%) patients had comorbidities: one patient had type 1 diabetes mellitus and one patient was being followed for juvenile idiopathic arthritis. The most common complaint at initial presentation was fatigue or myalgia (94%). Other common complaints included cough (91%) and fever (79%).

The patients included in our study were evaluated according to WHO's COVID-19 severity classification in pediatric patients. Our study included inpatients and we had no patients without evidence of viral pneumonia or hypoxia. Therefore, we did not have any asymptomatic or mild severity class patients. We defined the patients as moderate (n = 25, 74%) and severe COVID-19 infection (n = 9, 26%). When our patients were compared in terms of demographic and clinical characteristics, and disease severity during hospitalization, no statistically significant difference was found between the groups ($p > 0.05$) (Table 1).

Laboratory and radiological findings

No difference was found between the severity groups in terms of the laboratory results during the hospitalization period ($p > 0.05$). Chest X-ray reports of the patients indicated peribronchial-interstitial infiltration in 13 patients (38%) and consolidation was observed in 11 (32%) patients. Thorax CT was performed in 27 patients (79%). Fourteen (51%) patients had ground glass opacities. There was no difference in radiologic results between the severity groups ($p > 0.05$). The treatment and outcome

Figure 1. Study flow chart.



COVID-19: coronavirus disease 2019.

Table 1. Demographic and clinical features of patients during hospitalization.

Demographics	Total (n = 34)	Moderate (n = 25)	Severe (n = 9)	p value
Age (years)	15.75 (7.83–17.83)	16.50 (11.17–17.83)	14.16 (7.96–16.83)	0.094[a]
Gender				
Female	15 (44)	11 (44)	4 (44)	0.640[b]
Male	19 (56)	14 (56)	5 (56)	
Weight (kg)	73.59 ± 22.70	75.60 ± 21.79	68.00 ± 25.55	0.397[c]
Height (cm)	166 (120–186)	170 (140–186)	160 (120–170)	0.086[a]
BMI (kg/m^2)	26.21 ± 5.95	26.24 ± 5.31	26.14 ± 7.82	0.966[c]
Comorbidities present	2 (6)	2 (8)	0 (0)	NA
Signs and symptoms				
Fatigue or myalgia	32 (94)	24 (96)	8 (89)	0.465[b]
Cough	31 (91)	22 (88)	9 (100)	0.384[b]
Fever (body temperature > 37.3 °C)	27 (79)	22 (88)	5 (56)	0.061[b]
Dyspnea or tachypnea	20 (59)	14 (56)	6 (67)	0.070[b]
Sore throat	17 (50)	13 (52)	4 (44)	0.500[b]
Headache	16 (47)	10 (40)	6 (67)	0.660[b]
Runny nose	12 (35)	8 (32)	4 (44)	0.390[b]
Vomiting or diarrhea	6 (18)	4 (16)	2 (22)	0.616[b]

BMI: body mass index; NA: not applicable. Data are presented as n (%), mean ± standard deviation, and median (minimum– maximum values). [a] Mann Whitney U test; [b] Chi-square and Fisher's exact tests; [c] independent t-test.

information of the patients are detailed in Table 2. There was no difference between the severity groups in terms of treatment and outcomes ($p > 0.05$).

Pulmonary function tests (PFTs)

When the median time from COVID-19 infection to PFT application was evaluated, the median value was 15 months (min–max, 11–29 months). No difference was observed between the severity groups in this respect ($p = 0.878$). Pulmonary function was abnormal in 8 (24%) of the patients included in the study group. An obstructive pattern (FEV1 or FEF25–75 Z-score ≤ 1.96) was observed in 7 patients, while a restrictive pattern (FVC Z-score ≤ 1.96 but FEV1/FVC Z-score normal) was observed in one patient. Pulmonary functions were not statistically different in severity groups ($p = 0.105$).

When PFT results were evaluated in terms of disease severity groups, it was observed that FEV1% was lower in the severe group ($p = 0.013$). When 4 patients with FEV1 < 80% were analyzed; it was observed that 3 of these patients were in the severe severity group. However, there was no difference between the groups in terms of FEV1 Z score ($p = 0.079$). While no difference was observed between the groups regarding FVC results, FEV1/FVC% was lower in the severe patients' group ($p = 0.079$). When the groups were compared in terms of FEF25–75%, low values were again observed in the severe patients'

Table 2. Laboratory, radiological, and clinical outcome features of patients during hospitalization.

Laboratory parameters	Total (n = 34)	Moderate (n = 25)	Severe (n = 9)	*p* value
White blood cells (× 10^9 per L)	4.92 (2.31–14.91)	4.92 (2.46–14.91)	4.83 (2.31–14.54)	0.994[a]
Neutrophil count (×10^9 per L)	3.18 (1.26–11.95)	3.19 (1.31–11.95)	2.91 (1.26–10.76)	0.818[a]
Lymphocyte count (×10^9 per L)	1.42 (0.61–3.32)	1.43 (0.61–3.25)	1.40 (0.85–3.32)	0.701[a]
Hemoglobin (g/dL)	12.2 (10.3–15.5)	12.5 (10.5–15.5)	11.9 (10.3–14.8)	0.683[a]
MCV (fL)	78.5 (64.1–93.2)	80.3 (69.4–93.2)	77.6 (64.1–88.2)	0.755[a]
RDW (%)	13.7 (12.5–18.0)	13.1 (12.5–17.6)	14.5 (12.9–18.0)	0.546[a]
Platelet count (×10^9)	200 ± 71	221 ± 76	190 ± 57	0.469[b]
C-reactive protein mg/L	13 (0–196)	13 (0–196)	28 (0–169)	0.376[a]
Procalcitonin, ng/mL	0.06 (0.02–2.08)	0.06 (0.02–0.83)	0.06 (0.03–2.08)	0.939[a]
D-dimer, µg/mL	0.50 (0.20–3.78)	0.48 (0.20–6.09)	0.40 (0.20–6.09)	0.701[a]
Radiological features				
X-ray	34 (100)	25 (100)	9(100)	0.308[b]
Normal	10 (30)	9 (36)	1 (11)	
Peribronchial-interstial infiltration	13 (38)	8 (32)	5 (56)	
Consolidation	11 (32)	8 (32)	3 (33)	
Chest computed tomography	27 (79)	20 (49)	7 (49)	0.354[b]
Normal	2 (6)	1 (4)	1 (12)	
Consolidation	11 (32)	8 (32)	3 (44)	
Ground-glass opacities	14 (51)	11 (64)	3 (44)	
Treatments				
Antibiotics	32 (94)	23 (92)	9 (100)	0.535[b]
Antiviral treatment	14 (41)	10 (40)	4 (44)	0.560[b]
Corticosteroids	8 (24)	5 (20)	3 (33)	0.198[b]
Intravenous immunoglobin	1 (3)	0 (0)	1 (11)	NA
Oxygen supplementation	9 (27)	4 (16)	5 (56)	0.162[b]
Inhaled corticosteroids	13 (38)	8 (32)	5 (56)	0.238[b]
Mechanical ventilation	1 (3)	0 (0)	1 (11)	NA
Outcomes				
Intensive care	3 (9)	1 (4)	2 (22)	0.164[b]
Total duration of hospitalization, days	5 (2–14)	5 (2–14)	5 (4–13)	0.316[a]
Total duration in intensive care unit, days	4 (2–5)	2	4.5 (4–5)	NA
Total duration of fatigue or myalgia, days	2 (1–10)	2 (1–10)	3 (1–5)	0.780[a]
Total duration of cough, days	3 (1–8)	3 (1–8)	3 (2–5)	0.833[a]
Total duration of fever, days	2 (1–7)	3 (1–7)	1	NA
Total duration of dyspnea or tachypnea, days	4 (1–8)	4 (1–8)	4 (3–5)	0.840[a]
Total duration of sore throat, days	3 (1–8)	4 (1–8)	2 (1–3)	0.327[a]
Total duration of headache, days	2 (1–8)	4 (1–8)	2 (1–2)	0.287[a]
Total duration of runny nose, days	3 (1–6)	4 (1–6)	2 (1–3)	0.381[a]
Total duration of vomiting or diarrhea, days	2 (1–7)	2 (1–7)	2 (1–5)	0.863[a]

NA: non applicable; MCV: mean corpuscular volume; RDW: red cell distribution width. Data are presented as n (%), mean ± standard deviation, and median (minimum–maximum values). [a] Mann Whitney U test; [b] Chi-square and Fisher's exact tests.

Table 3. Comparison of spirometry values associated with moderate and severe disease.

	Total (n = 34)	Moderate (n = 25)	Severe (n = 9)	*p* value
Time from hospitalization to spirometry (months)	15 (11–29)	15 (11–22)	15 (12–29)	0.878[c]
Abnormal PFTs	8 (24)	4 (16)	4 (44)	0.105[b]
FEV1, %	92.08 ± 15.11	95.84 ± 13.56	81.66 ± 14.99	0.013[a]
FEV1 < 80%	4 (12)	1 (4)	3 (33)	0.048[b]
FEV1, Z-Score	–0.72 (–2.55–1.60)	–0.35 (–2.55–1.60)	–1.07 (–2.34–0.02)	0.079[c]
FVC, %	97.58 ± 13.35	99.24 ± 12.62	93.00 ± 15.01	0.235[a]
FVC < 80%	1 (3)	0 (0)	1 (12)	NA
FVC, Z-Score	–0.13 (–2.27–2.31)	–0.18 (–2.10–2.31)	–0.09 (–2.27–0.72)	0.539[c]
FEV1/FVC, %	82.49 ± 8.11	84.18 ± 6.73	77.78 ± 10.07	0.040[a]
FEV1/FVC < 80%	9 (26)	5 (25)	4 (44)	0.162[b]
FEV1/FVC, Z-Score	–0.73 (–3.20–2.23)	–0.61 (–2.81–2.23)	–2.29 (–3.20–0.62)	0.066[c]
FEF_{25-75}, %	83.47 ± 20.06	87.84 ± 18.24	71.33 ± 20.91	0.032[a]
FEF_{25-75} < 70%	8 (24)	2 (32)	6 (10)	0.001[b]
FEF_{25-75}, Z-Score	–0.71 (–3.05–1.72)	–0.70 (–3.00–1.72)	–1.96 (–3.05–0.16)	0.072[c]

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}, forced expiratory flow during the middle half of FVC; NA: not applicable; PFT: pulmonary functional test. The values are presented as n (%), mean ± standard deviation, and median (minimum–maximum values). Bold value indicates $p < 0.05$; [a] independent t-test; [b] Chi-square and Fisher's exact tests; [c] Mann Whitney U test.

group ($p = 0.032$). Of the 8 patients with FEF25–75% < 70%, 2 were in the moderate and 6 in the severe disease group. However, FEV1/FVC% and FEF25–75% Z scores were similar in both groups ($p > 0.05$). The comparison of PFTs according to the severity groups of the patients is detailed in Table 3.

Of the patients who continued outpatient follow-up, 14 (41%) had persistent respiratory symptoms before PFT. The frequency of persistent symptoms was cough 50%, dyspnea 29%, and exercise tolerance 21%. When the hospitalization information of the patients with symptoms was analyzed, it was observed that 11 (79%) of them were in the moderate and 3 (21%) in the severe severity group. When the patients were compared in terms of symptom status and disease severity, no difference was observed between the two conditions ($p = 0.440$). PFT results of the patients were compared in detail according to symptom status and no difference was found between the two groups ($p > 0.05$; Table 4).

Discussion

To the best of our knowledge, this is the first study that evaluated pulmonary function in children who experienced a more severe course of COVID-19 infection after long-term follow-up. Among the children hospitalized due to COVID-19 infection in our center, we encountered ongoing respiratory symptoms in 41% of patients during our outpatient follow-up, and abnormal pulmonary functions in 24% of them.

Many studies related to COVID-19 infection in children have focused on the epidemiological and clinical characteristics of the disease. It is also known that COVID-19 infection in children tends to be milder compared to adults. However, our knowledge regarding the long-term effects of COVID-19 still needs to be

Table 4. Comparison of spirometry values in asymptomatic and symptomatic patients during outpatient follow-up.

	Total (n = 34)	Asymptomatic (n = 20)	Symptomatic (n = 14)	*p* value
Time from hospitalization to spirometry (months)	15 (11–29)	15 (11–29)	15 (12–22)	0.998[c]
Abnormal PFTs	8 (24)	3 (15)	5 (35)	0.065[b]
FEV1, %	92.08 ± 15.11	93.15 ± 14.24	90.57 ± 16.71	0.632[a]
FEV1 < 80%	4 (12)	2 (10)	2 (14)	0.551[b]
FEV1, Z-Score	–0.72 (–2.55–1.60)	–0.38 (–2.34–1.20)	–0.92 (–2.55–1.60)	0.321[c]
FVC, %	97.58 ± 13.35	98.30 ± 12.44	96.57 ± 14.98	0.716[a]
FVC < 80%	1 (3)	1 (5)	0 (0)	NA
FVC, Z-Score	–0.13 (–2.27–2.31)	0.01 (–2.27–1.22)	–0.54 (–2.10–2.31)	0.231[c]
FEV1/FVC, %	82.49 ± 8.11	82.80 ± 8.10	82.05 ± 8.40	0.794[a]
FEV1/FVC < 80%	9 (26)	5 (25)	4 (28)	0.560[b]
FEV1/FVC, Z-Score	–0.73 (–3.20–2.23)	–0.69 (–3.08–2.23)	–0.73 (–3.20–1.52)	0.849[c]
FEF_{25-75}, %	83.47 ± 20.06	84.25 ± 18.02	82.35 ± 23.34	0.791[a]
FEF_{25-75} < 70%	8 (24)	4 (20)	4 (28)	0.428[b]
FEF_{25-75}, Z-Score	–0.71 (–3.05–1.72)	–0.71 (–3.05–1.50)	–0.79 (–3.02–1.72)	0.743[c]

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF_{25-75}, forced expiratory flow during the middle half of FVC; NA: not applicable; PFT: pulmonary functional test. The values are presented as n (%), mean ± standard deviation, and median (minimum–maximum values). [a] independent t-test; [b] Chi-square and Fisher's exact tests; [c] Mann Whitney U test

improved [10–12]. While initial reports indicated near-complete recovery in children with almost no observation of long-COVID symptoms, recent information suggests that more than 25% of children may experience ongoing symptoms after COVID-19 [13]. Respiratory symptoms are frequently encountered among these persistent symptoms and are reported by approximately 30–35% of affected children. Various proportions of symptoms were reported within the category of respiratory symptoms, with the most common being dyspnea, exercise intolerance, and cough [14–16]. Our study observed persistent respiratory symptoms in 14 patients (41%) during their outpatient follow-up. The frequency of these symptoms was as follows: cough 50%, dyspnea 29%, and exercise tolerance 21%.

Possible risk factors for persistent respiratory symptoms after COVID-19 infection in children include older age, increased body mass index, and allergic diseases, among others [17,18]. In our study, we did not observe a relationship between older age and symptom status. Among the 8 patients with abnormal pulmonary function, only 1 had obesity, and we did not observe a significant difference in this regard. Allergic diseases were excluded from the study since we aimed to assess the effects of COVID-19 alone on pulmonary functions.

Complications after viral pneumonia such as prolonged cough, chronic bronchitis, asthma, and bronchiectasis can cause obstructive and restrictive lung diseases, leading to respiratory dysfunction. COVID-19 infection interacts with the angiotensin-converting enzyme 2 receptor on the surface of alveolar cells, causing epithelial damage and disrupting microcirculation. Early COVID-19-related alterations include edema, capillairitis, microthrombosis, exudative diffuse alveolar damage, hyaline membrane development, pneumocyte type 2 hyperplasia, and superinfections, which proceed to the fibrotic stage of diffuse alveolar damage. Alveolar gas transport is reduced in severe illness cases due to widespread alveolar injury. Furthermore, increased airway inflammation and mucus plugs in the peripheral airways might impede breathing [19–21]. The expected pathophysiology, in this case, suggested a higher probability of a restrictive pattern. A recent meta-analysis shows that the abnormal diffusing capacity of the lungs for carbon monoxide (DLCO), which correlates with the severity of acute illness, is observable in the PFTs of patients after acute illness [22].

There are relatively few studies examining the long-term impact of COVID-19 infection on pulmonary functions in children. These studies have reported that COVID-19 infection rarely leads to pulmonary function impairment, similar to other viral infections [13]. The first study in this area was reported by Bottino *et al.* who found no difference in spirometry and DLCO measurements in 16 asymptomatic and pauci-symptomatic children during infection and 1month after [23]. Knoke *et al.* also reported no significant difference in PFTs of 73 children with a history of COVID-19 infection after 6 months of follow-up, compared to a healthy control group [24]. However, this study was designed and presented at the beginning of the COVID-19 pandemic. It divided the patients into groups according to WHO's first severity classification criteria (non-severe to severe), and included adolescents who smoked and comorbid patients who may have had chronic respiratory pathologies such as asthma.

Ozturk *et al.* found abnormal PFT results in 14% of 50 children 3 months after COVID-19 infection but suggested that ongoing respiratory symptoms were not related to the severity of acute COVID-19 infection [25]. Chiara *et al.* reported that PFTs in 61 children who had asymptomatic or mild infections were similar to those of healthy children during their average 10-month follow-up [26]. Bogulawski *et al.* assessed the PFTs of 42 children 3 months after COVID-19 infection and found no difference compared to a healthy control group [13]. In this study, the patients were also grouped according to WHO's latest severity classification criteria, but there were only 3 patients in the severe group, and the study included comorbid patients with chronic respiratory pathologies as well.

Iovine *et al.* reported a large series study involving 589 children. They did not observe any impairment in pulmonary function after COVID-19 infection, and there was no difference in pulmonary function between those with respiratory symptoms during infection and those without [27]. However, this study also included asymptomatic or mildly affected patient groups (with only two hospitalizations) and comorbid patient groups. Kumari *et al.* did not report any impairment in pulmonary function in 20 children who underwent PFT an average of 8 months after COVID-19 infection [28]. In this study, only 2 patients were in the moderate/severe severity group, while 18 had mild infection.

In light of the existing studies, we assessed the impact of COVID-19 infection on pulmonary function in children with more severe illness. We did not observe a difference in the time elapsed until PFT application

among severity groups in our patients, followed for 11 to 29 months after COVID-19 infection. When PFT results were evaluated according to disease severity groups, it was observed that FEV1% was lower in the severe group. Among the 4 patients with FEV1 < 80%, 3 were in the severe severity group. However, there was no statistically significant difference in terms of FEV1 Z scores. Although there was no difference in FVC results between severity groups, FEV1/FVC% and FEF25–75% were lower in the severe group. Eight patients with FEF25–75% < 70% included 2 in the moderate and 5 in the severe disease group. However, there was no difference in FEF25–75 Z scores between groups. While 8 patients (24%) in the study group were found to have abnormal pulmonary functions, 7 of them had an obstructive pattern, and 1 had a restrictive pattern. However, when pulmonary functions were evaluated based on Z scores, there was no statistical difference between severity groups.

A recent meta-analysis by Bakhtiari and Moazzen [22] reviewed 8 articles on long-term pulmonary function effects in children after COVID-19. There was no documented change in PFT results with the severity of illness. Likewise, no difference was observed between symptomatic and asymptomatic patients in terms of PFT results. These results suggest that future studies with longer follow-up periods and evaluating patients with more severe respiratory presentations are needed.

This study has some limitations, including its single-center design and the relatively small sample size due to strict exclusion criteria. Another important limitation is the absence of DLCO measurements and total lung capacity as part of this study, which prevents the presentation of basic data on respiratory functions for each of these patients for serial comparison. Nevertheless, the data we present from the long-term follow-up of children who were more severely affected by COVID-19 provide valuable insights into our study's strengths.

Conclusions

Our study observed that the severity of the disease and the presence of ongoing respiratory symptoms did not lead to changes in pulmonary functions in pediatric patients after COVID-19 infection. Further extensive studies with larger and more representative cohorts are needed to clarify the long-term respiratory consequences of COVID-19 in the pediatric age group.

Ethics statement

All studies were carried out following the relevant recommendations and regulations and conducted according to the guidelines of the Declaration of Helsinki. The study protocol was approved by the local ethics committee (Approval No: 2022-KAEK-8/2, Approval Date: 25 May 2022). Written informed consent was obtained from all the patients.

Authors' contributions

MFK: conceptualization, methodology, data curation, investigation, formal analysis, writing – original draft, and supervision; GEŞ: data curation and writing – original draft; ŞEB: conceptualization, data curation, and writing – review and editing; MK, İK: data curation and investigation; BO: data curation, investigation, and visualization.

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