



Obesity is a risk factor for decrease in lung function after COVID-19 infection in children with asthma

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Abstract

Introduction: It is not clear whether asthma, the most frequent chronic disease in childhood, is a risk for severe SARS-CoV-2 infection in the pediatric population and how SARS-CoV-2 infection affects the lung functions in these patients.

Purpose: We aimed to investigate the course and the consequences of SARS-CoV-2 infection among children with asthma and determine the risk factors for the decline in lung function tests (LFTs).

Methods: In this retrospective study, asthmatic children with coronavirus disease 2019 (COVID-19) were compared with a random control group of asthmatic patients without COVID-19. In addition, the clinical course and the effect on LFTs of COVID-19 among children with asthma were also evaluated.

Results: One hundred eighty-nine patients who had COVID-19, and 792 who did not were included in the study. Fever, fatigue, and cough were the most frequent symptoms during COVID-19. Regarding the severity of COVID-19, 163 patients (87.6%) had a mild clinical condition, 13 (7%) had moderate disease, 1 (0.5%) had severe disease, and 2 had (1.1%) critically ill disease. Two patients were diagnosed with multisystem inflammatory syndrome in children (MIS-C), one patient suffered from pneumothorax. LFTs of the patients before and after COVID-19 infection were analyzed; no significant differences were found in FEV₁% (91.7% vs. 90.9%, $p = 0.513$), FVC% (89.8% vs. 90.8%, $p = 0.502$) and FEV₁/FVC (103.1% vs. 100.6%, $p = 0.056$), while FEF₂₅₋₇₅ values (107.6% vs. 98.4%, $p < 0.001$) were significantly lower after the COVID-19 infection. Obesity (odds ratio [OR]: 3.785, 95% confidence interval [CI]: 1.152–12.429, $p = 0.028$) and having a family history of atopy (OR: 3.359, 95% CI: 1.168–9.657, $p = 0.025$) were found to be the independent risk factors for $\geq 25\%$ decrease in FEF₂₅₋₇₅ after COVID-19 infection.

Conclusion: COVID-19 infection leads to dysfunction of the small airways in asthmatic children and obesity is an independent risk factor for a $\geq 25\%$ decrease in FEF₂₅₋₇₅. The long-term effects of COVID-19 infection especially on small airways require close monitoring in children with asthma.

KEYWORDS

asthma, childhood, COVID-19, obesity, small airway dysfunction

1 | INTRODUCTION

The novel coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome-CoV-2, has now become the most dangerous pandemic in over 100 years, with over 219 million cases and 4,550,000 deaths as of October 2021. Although COVID-19 is generally known as a mild disease in children compared to adults, children with certain underlying medical conditions might be at increased risk for severe illness from SARS-CoV-2 infection.^{1,2}

Asthma is the most frequent chronic disease in childhood, and a current concern exists concerning whether asthma is a risk factor for severe SARS-CoV-2 infection in the pediatric population.^{3,4} While there have been multiple published studies about the impact of COVID-19 on asthma, much remains conflicting. A survey evaluating data from 147 centers reported that, among the 49 children with asthma, 19 needed supplemental oxygen, and 4 required mechanical ventilation.⁵ A systematic review by Castro-Rodriguez stated that recurrent wheezing or asthma is a potential risk factor for COVID-19 in children.⁶ Recently, the Global Asthma Network group reported that asthmatic children did not have a high frequency of severe COVID-19.⁷

To date, to our knowledge, there has been no report of the effect of COVID-19 infection on lung function tests (LFTs) in asthmatic adults and children. However, in adult patients hospitalized with COVID-19 pneumonia, a mild to severe reduction in lung function tests has been experienced.^{8,9} In survivors from severe COVID-19, no improvement was reported in FEF25–75¹⁰ that was correlated with impairment of small airways.¹¹ Therefore, further larger-scale data are required in the field of COVID-19 in asthmatic patients.

This study aims to investigate the course and the consequences of SARS-CoV-2 infection among children with asthma and determine the risk factors for the decline in LFTs after infection.

2 | METHODS

2.1 | Patients' enrollment and data collection

Patients who were followed at Hacettepe University, Department of Pediatric Allergy with a diagnosis of asthma and had a COVID-19 infection between March 2020 and March 2021, were included in the study. Asthma was diagnosed by a history of intermittent wheezing and/or the presence of reversible airway obstruction as defined by at least a 12% improvement in final expiratory volume in 1 (FEV₁) following bronchodilator administration.¹²

A random control group of 792 asthmatic patients without COVID-19 who were followed at the same clinic during the same period were also included in the analysis. This retrospective study was approved by the institutional ethics board of the Hacettepe University Ihsan Dogramaci Children Hospital (approval no: 2021/06-46).

Patients with a positive COVID-19 real-time reverse transcriptase-polymerase chain reaction or serum-specific antibodies

against 2019-nCoV were accepted as confirmed cases. Patients who had direct exposure to a confirmed COVID-19 patient and were presenting symptoms suggesting COVID-19 (cough, shortness of breath, or any other respiratory symptoms with fever) with no confirmatory laboratory testing performed for SARS-CoV-2 were accepted as probable cases.¹³

Data, regarding the demographic and clinical feature of patients, in particular, the information of age at asthma onset, the duration of follow up, presence of atopy, medical history and comorbidities, laboratory results including LFTs chest X-ray (CXR) and computed tomography (CT) images (if performed), treatments and outcomes were obtained from hospital or national electronic medical reports. Due to the COVID-19 pandemic, routine LFTs were not performed on the control group, and pre-COVID-19 LFTs were evaluated. Obesity was defined as having a body mass index \geq 95th percentile for age and sex.

The severity of the pediatric COVID-19 cases was categorized according to the classification of Dong et al.¹⁴ as follows: (a) Patients with a positive diagnosis but without any clinical or radiological findings were defined as asymptomatic. (b) Patients who had only mild symptoms of acute upper respiratory tract infections but without clinical and radiological pneumonia were defined as having a mild disease. (c) Moderate disease was identified in patients with pneumonia and symptoms of respiratory tract infection. (d) Patients with progressive respiratory disease, dyspnea, and central cyanosis were defined as having a severe disease. (e) Patients who presented with acute respiratory distress syndrome or respiratory failure, shock, and organ dysfunction, including encephalopathy, myocardial injury, coagulation abnormalities, and acute kidney injury, were defined as critically ill.

2.2 | Laboratory tests

Certain routine laboratory test results were collected from the clinical reports, including complete blood count, and serum levels of biomarkers, coagulation tests, myocardial injury markers, liver function tests, and renal function tests if performed.

Genscript SARS-CoV-2 Surrogate Virus Neutralization Test Kit was used for the detection of SARS-CoV-2 N-Abs. Patient samples were thawed and mixed and diluted 1:9 in sample buffer for Genscript SARS-CoV-2 Surrogate Virus Neutralization Test Kit. All the steps were carried out according to the instructions suggested by the manufacturer by trained research laboratory staff. Serum samples from 89 patients were analyzed and the results of the test, based on antibody-mediated blockage of ACE2–spike protein–protein interaction, were interpreted as positive when inhibition was $>20\%$ and negative when inhibition was $<20\%$.

2.3 | LFTs and radiological images

LFTs were performed with a median time interval of 72 weeks (50–105 weeks) after the COVID-19 infection by children older than 5 years of

age, and under supervision with the participant in the sitting position with nose-clip fixed on the nose, following American Thoracic Society guidelines.¹⁵ Lung function was evaluated using a calibrated spirometer (Zan 100 USB; Zan). Patient-specific FVC, FEV₁, PEF, FEV₁/FVC, and FEF25%–75% and the percentage of the predicted values based on the participant-specific sex, age, height, and weight were recorded. CXR and CT images were reviewed by experienced thoracic radiologists, blinded to the participants' clinical history.

2.4 | Asthma control measurement

All children and their parents filled in the Turkish version of the Childhood Asthma Control Test (C-ACT; 4–11 years old) or ACT (≥ 12 years old).^{16,17} The ACT score ranges between 5 and 25, with a score of less than 20 corresponding to uncontrolled asthma, whereas C-ACT score may range from 0 to 27, and a score of < 19 indicates uncontrolled asthma.

2.5 | Asthma severity

Asthma severity was assessed retrospectively from the level of treatment required to control symptoms and exacerbations according to the Global Initiative for Asthma 2019.¹⁸

2.6 | Statistical analysis

Statistical analyses were performed using SPSS version 22.0 statistical software package (IBM SPSS Statistics). First normality tests for continuous variables were performed and as all of the continuous variables were distributed non-normally, the results were given as median (interquartile range [IQR]). The χ^2 and Mann–Whitney *U*-tests were used to compare nonparametric values. For the risk analysis of drop-outs variables were selected if the *p* value was less than 0.20 in the univariate analysis (obesity, family history of atopy, and allergic rhinitis) and included in multivariate analysis. Odds ratios (ORs) with relevant 95% confidence intervals (CIs) were calculated to evaluate potential associations. Values of $p < 0.05$ were accepted as significant.

3 | RESULTS

A total of 979 asthmatic patients were enrolled in the study, including 187 patients who had COVID-19, and 792 without (Table 1). COVID-19 diagnosis was confirmed in 80 patients by COVID-19 PCR, and in 69 patients by SARS-CoV-2 N-Abs. The remaining 38 patients were diagnosed as probable COVID-19.

When patients were classified according to asthma severity, there were no significant differences between the COVID-19 and control groups ($p = 0.253$; Table 1). Asthmatic children with

COVID-19 were mainly male (57.2%), the median age was 8.6 years (IQR = 5.8–12.5). Atopic sensitization was more common in the COVID-19 group ($p = 0.027$), and pollen, dust mite, mold, and food sensitization were significantly higher (Table 1). Prematurity (21%) and obesity (21.8%) were the most common comorbid conditions. Most of the children were infected by family members (91.4%).

Fever, fatigue, and cough were the most frequent symptoms, followed by sore throat, dyspnea, and diarrhea during COVID-19 (Figure 1). The duration of fever at admission was mainly less than 3 days in 73.3% of patients. When the patients were classified into three groups according to age (< 6 , 6–11, and ≥ 12 years), the frequency of fever was significantly higher in patients younger than 6 years old (78%), whereas dyspnea (27%) and myalgia (36%) were significantly more frequent in the adolescent age group (Figure 2). Cough frequency was similar in all age groups.

Regarding the severity of COVID-19, 163 patients (87.6%) had a mild clinical condition and 13 (7%) had a moderate disease. Eight (4.3%) of the patients were asymptomatic.

Three children (1.6%) had severe ($n = 1$) and/or critically ill ($n = 2$) disease. Among these, two were diagnosed with multisystem inflammatory syndrome in children (MIS-C), and received favipiravir, intravenous immunoglobulin (2 g/kg), methylprednisolone (2 mg/kg/day), and anakinra (4 mg/kg/day) for 3–5 days, and were discharged after 1 week. The third patient, 15-year-old boy, suffered from pneumothorax, and subsequent respiratory arrest, followed by cardiac arrest, and was intubated at home by paramedics. A tube thoracostomy was performed, then mechanical ventilatory support was administered in the PICU. He was discharged uneventfully on the 9th day of hospitalization.

When the LFTs of the patients before COVID-19 infection were compared with control group, there was no statistical difference in FEV₁% (91.7 ± 13.4 vs. 89.4 ± 14.7 , $p = 0.137$), FVC% (89.8 ± 14.1 vs. 86.9 ± 13.5 , $p = 0.058$) and FEF25%–75% (107.6 ± 28.3 vs. 105.5 ± 29.9 , $p = 0.515$; Table 1).

LFTs of the patients before and after COVID-19 infection were also analyzed. Compared with the previous test, no significant differences were found in FEV₁% (91.7% vs. 90.9% , $p = 0.513$), FVC% (89.8% vs. 90.8% , $p = 0.502$) and FEV₁/FVC (103.1% vs. 100.6% , $p = 0.056$), while MEF25%–75% values were significantly lower after the COVID-19 infection (107.6% vs. 98.4% , $p < 0.001$; Table 2). Bronchodilator responsiveness was assessed in 31 patients and observed in 14 patients. The frequency of patients with moderate asthma increased after COVID-19 infection (34% vs. 45% , $p < 0.001$).

We further performed univariate and multivariate logistic regression analyses for the risk factors of decrease in FEF25–75 after COVID-19 infection. Patients were divided into two groups as those who had a $\geq 25\%$ fall in FEF25%–75% after COVID-19 infection and those who did not. Obesity (OR: 3.785, 95% CI: 1.152–12.429, $p = 0.028$) and having a family history of atopy (OR: 3.359, 95% CI: 1.168–9.657, $p = 0.025$) were found to be the independent risk factors for $\geq 25\%$ decrease in FEF25–75 due to COVID-19 infection (Table 3).

TABLE 1 Demographic and clinical characteristics of the asthmatic patients with/without COVID-19.

	All patients (n = 979)	Patients with COVID-19 (n = 187)	Patients without COVID-19 (n = 792)	p value
Age ^a (years)	8.6 (6.2–11.6)	8.6 (5.8–12.5)	8.5 (6.3–11.5)	0.565
Gender (male)	551 (56.3)	107 (57)	444 (56)	0.806
Atopy (%)	304 (31.1)	70 (37.4)	234 (30)	0.027
Pollen	137 (13.9)	36 (19.2)	101 (12.7)	0.021
Mold	51 (5.2)	16 (8.5)	35 (4.4)	0.022
Dust mite	74 (7.5)	21 (11.2)	53 (6.6)	0.035
Animal dander	56 (5.7)	10 (5.3)	46 (5.8)	0.554
Food	30 (3.0)	16 (8.5)	14 (1.7)	<0.001
Age at onset of asthma symptoms ^a (years)	3 (1–5)	2.5 (1–5)	3 (1–5)	0.343
Age at asthma diagnosis ^a (years)	4 (2–6)	3.5 (2–6)	4 (2–6)	0.415
Duration of follow-up ^a (years)	4 (2–6)	4 (2–6)	3.5 (2–6)	0.937
Mild asthma (%)	627 (64)	514 (64.9)	113 (60.4)	0.253
Moderate asthma (%)	344 (35.1)	273 (34.5)	71 (38.0)	
Severe asthma (%)	8 (0.8)	5 (0.6)	3 (1.6)	
Asthma control level ^b				>0.05
Well-controlled (%)	950 (97)	182 (97.3)	768 (96.9)	
Uncontrolled/partly controlled	29 (3)	5 (2.7)	24 (3)	
FEV ₁ % ^c	89.8 ± 14.5	91.7 ± 13.4	89.4 ± 14.7	0.137
FVC% ^c	87.1 ± 13.9	89.8 ± 14.1	86.9 ± 13.5	0.040
FEV ₁ /FVC ^c	103.1 ± 8.9	103.1 ± 13.2	103.1 ± 7.6	0.983
FEF _{25%–75%} ^c	105.9 ± 29.5	107.6 ± 28.3	105.5 ± 29.9	0.515
Maintenance therapy				
SABA	93 (9.5)	50 (26.9)	43 (5.4)	<0.001
ICS	458 (46.8)	54 (29.0)	404 (51.0)	
Montelukast	81 (8.3)	7 (3.8)	74 (9.3)	
ICS + LABA	235 (24.0)	47 (25.3)	188 (23.7)	
ICS + montelukast	74 (7.6)	16 (8.6)	58 (7.3)	
ICS + LABA + montelukast	37 (3.8)	12 (6.4)	25 (3.3)	

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist.

^aMedian, interquartile range.

^bControl levels based on childhood asthma control test and asthma control test scores (well-controlled ≥ 20).

^cLung function tests within last year.

3.1 | Radiological features

Eighteen patients (9%) with fever and respiratory symptoms underwent CXR imaging during the COVID-19 infection, and pathological lung findings were detected in 12 (66%) of the patients (Table 4). Findings were bilateral in five (41%) patients, and unilateral (five patients with right lung, and two patients with left lung findings) in seven (59%) patients. The middle and lower zones were the most

commonly affected areas. When the density characteristics of the lesions were evaluated, interstitial reticular opacity was observed in seven (58%) cases, ground-glass appearance in six cases (50%), and peribronchial wall thickening in one case (8%). Pneumothorax was observed in one case. Pleural effusion, consolidation, and lymphadenopathy were not identified.

CXR was performed on 55 patients due to persistent or intermittent respiratory symptoms after the COVID-19 infection.

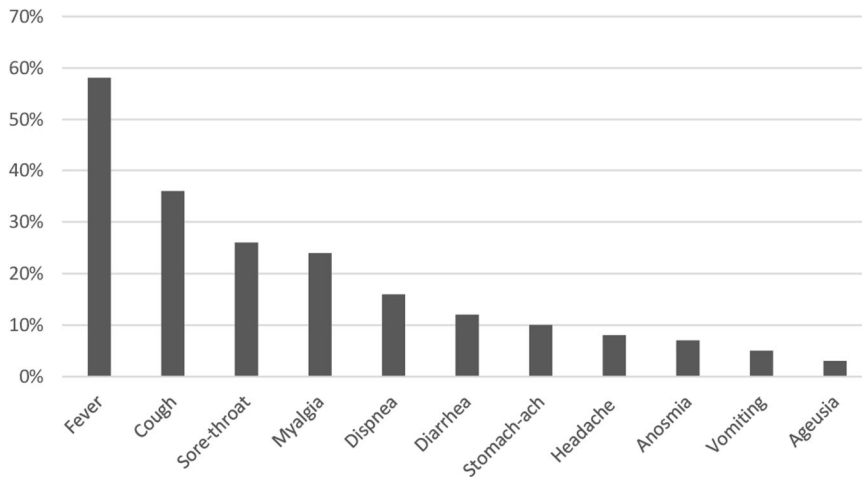


FIGURE 1 COVID-19 symptoms of the patients.

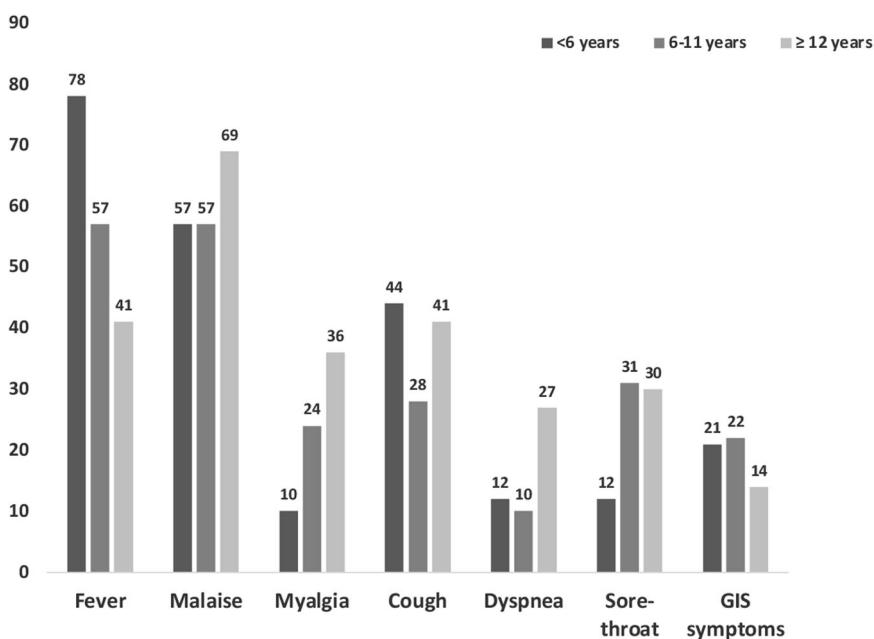


FIGURE 2 Comparison of the symptoms of the patients with COVID-19 according to ages.

TABLE 2 Lung function tests and asthma control test scores of the asthmatic patients before and after COVID-19.

	Before COVID-19	After COVID-19	p value
C-ACT ^a	25 (22.25–27)	25 (22–27)	0.001
ACT ^a	23 (22–25)	22.5 (21–25)	0.035
FEV ₁ % ^b	91.7 ± 13.4	90.9 ± 16.01	0.513
FVC% ^b	89.8 ± 14.1	90.8 ± 16.4	0.502
FEV ₁ /FVC ^b	103.1 ± 13.2	100.6 ± 8.4	0.056
FEF25%–75% ^b	107.6 ± 28.3	98.4 ± 27.3	<0.001

Abbreviations: ACT, asthma control test; C-ACT, childhood asthma control test.

^aMedian, interquartile range.

^bMean.

Forty-three patients had no findings on the CXR (76%). Perihilar bronchial wall thickening was observed in 10 patients (Supporting Information: Table 2). Less common findings included linear atelectasis ($n = 1$) and diffuse bilateral interstitial reticular densities ($n = 1$).

4 | DISCUSSION

This study describes the clinical and radiological characteristics and outcomes of 187 asthmatic children with COVID-19 and compares them with asthmatic children without COVID-19 infection. According to our findings, 95.7% of the asthmatic patients were symptomatic. In LFTs, MEF25%–75% values were significantly reduced, and asthma severity worsened after COVID-19 infection in some patients.

TABLE 3 Risk factors associated with decrease in MEF25–75 after COVID-19.

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Obesity	2.312	0.804–6.648	0.120	3.785	1.152–12.429	0.028
Family history of atopy	2.554	0.961–6.786	0.060	3.359	1.168–9.657	0.025
Allergic rhinitis	0.448	0.151–1.329	0.148	0.330	0.102–1.066	0.064

Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 4 Chest X-ray findings of children with respiratory symptoms during COVID-19 infection (n = 18).

Findings	Number	%
Pulmonary lesions		
Normal	6	33
Pathological	12	66
Affected lung side		
Unilateral	7	58
Bilateral	5	42
Affected lung zone		
Right middle	6	50
Left middle	3	25
Right lower	9	75
Left lower	7	58
Density characteristics		
Interstitial reticular opacity	7	58
Ground glass opacity	6	50
Peribronchial thickening	1	8
Pneumothorax	1	8

Most of our patients exhibited symptoms during the course of COVID-19, whereas asymptomatic cases have been reported to be more common (15.8%–43.1%) in healthy populations.^{1,6,19,20} In the current study among symptomatic patients, most of the cases were mild (87.2%) and 1.1% of the children had critically ill disease. The distribution of severity of COVID-19 was similar in our cohort of asthmatic children and the general pediatric population.²¹ Only 6.4% of the children required hospitalization. Encouragingly, mechanical ventilation was required in one patient. Our data suggest that children with asthma were more likely to have a symptomatic illness from COVID-19.

Fever and cough were the most frequent symptoms in our study population. Fever was significantly more frequent in children younger than 6 years, whereas myalgia and dyspnea were more common in the ≥12-year group. Cough frequency was similar in all age groups (28%–44%). Unfortunately, we were not able to compare the frequency of symptoms of COVID-19 with a healthy population. However, in a large pediatric cohort of COVID-19 reported over 1000 children from Turkey, the frequency of cough was reported as

46.9%.²¹ In a subgroup of children with asthma (n = 38, 3.2% of the cohort), the frequency of cough was shown as 80.0%. Unexpectedly, the rate of cough exhibited in our patients with asthma during COVID-19 was similar to the general pediatric population and much lower than the subgroup with asthma. Metbulut et al.²² noted cough frequency as 59.3% in children with asthma during the course of COVID-19, which was more often than observed in our patients. Nearly 40% of their patients were using prophylactic asthma medications, while 31.4% of their study population were on inhaled corticosteroids (ICS) treatment and 66.7% of patients were well-controlled.²² The lower rate of cough during COVID-19 in our patients might be due to the higher frequency of use of ICS (68.9%) at the time of COVID-19 and better control level (well-controlled, 97.3%). Use of ICS was shown to be associated with lower expression of angiotensin-converting enzyme 2 receptor, responsible for virus attachment to host cell membranes.²³ Not only in our patient cohort but also in other pediatric populations with asthma, asthma control was shown to improve during the first wave of the COVID-19 pandemic, due to reduced exposure to asthma triggers and increased treatment adherence.²⁴

Most asthmatic children with COVID-19 experienced mild disease, however, two patients developed MIS-C that led to hospitalization, use of immunosuppressive agents, and IVIG. In one report from New York State, the incidence of MIS-C was 2 per 100,000,²⁵ whereas in our study, it was 1.07%. Previously, in children who developed MIS-C, being overweight (10%–39%) and having a prior history of asthma (5%–18%) were reported as the most common comorbidities.^{26–29} Although the pathophysiology of MIS-C is not well-understood, the latest studies suggest that the syndrome results from an abnormal postinfectious immune dysregulation.^{30–32} In asthma pathogenesis, in addition to genetic and environmental influences, defective antiviral immunity also plays a role.³³ Plasmoid dendritic cells from patients with asthma and allergic sensitization secrete less IFN-α on exposure to viruses compared with patients without asthma which is an important innate antiviral response. Moreover, regulatory T cells (Tregs), that act to suppress the immune response, thereby maintaining homeostasis and self-tolerance, are lower and functionally impaired in patients with asthma.^{34–36} Therefore, impaired antiviral immunity and immune dysregulation might contribute to the development of MIS-C in asthmatic children.

When patients were classified according to asthma severity before and after COVID-19 infection, a significant increase in the

moderate asthma frequency was observed, supporting the notion that COVID-19 might be associated with disease progression in asthmatic children. We also evaluated the LFTs of the asthmatic children after COVID-19 infection. Compared with prior LFTs, no significant difference was observed in FEV₁% and FVC% while MEF25%–75% values were significantly reduced in some patients. Obesity was found to be the independent risk factor for a $\geq 25\%$ decrease in FEF25–75. Similarly, in adult patients who were hospitalized for COVID-19 pneumonia, small airway dysfunction, impaired gas-blood exchange, and reduced diffusing capacity of the lung for carbon monoxide (DLCO) were reported after discharge.^{37–40} Small airway dysfunction may result from the infection of the small airways with SARS-COV-2. Moreover, obesity may also contribute to airway dysfunction both with systemic inflammation and interstitial edema from elevated capillary hydrostatic pressure^{41,42} leading to a further decrease in LFTs in terms of FEF25%–75%. Family history of atopy was also another independent risk factor for a $\geq 25\%$ decrease in FEF25–75. In previous reports, family history of atopy was reported to be associated with severe asthma, severe atopic dermatitis, severe RSV infection suggesting that the presence of atopic background in family members is a risk factor for disease severity.^{43–45}

Abnormal CXR findings have been reported in 25%–33% of children in the general population with COVID-19.^{21,46} However, there are only a few studies evaluating radiological imaging in asthmatic children with COVID-19. Rabha et al.⁴⁷ reported data from 72 asthmatic children with confirmed COVID-19. CXR was performed in 56% of their patients, and abnormal findings were observed in 17.1% of them.⁴⁷ According to Metbulut et al.,²² CXR was performed in 77% of their patients and abnormal findings were observed in nearly half of them. In our study, CXR was performed in 9.6% of the patients and 66% had pathological findings. The higher prevalence of abnormal radiological findings in our study may be because we were more selective when it came to ordering imaging. In this study, interstitial opacities were the most common radiologic findings, which were also predominantly reported in children with MIS-C.⁴⁶

Pneumothorax is an uncommon complication of COVID-19. To date, there have been few reports of pneumothorax, mostly in adult patients without any underlying pulmonary disease.^{48,49} Oterino Serrano et al.⁵⁰ reported a 6-year-old child with systemic sclerosis and severe pulmonary involvement who developed pneumothorax and died due to respiratory failure. To the best of our knowledge, our patient is the first case of pneumothorax reported in asthmatic children with COVID-19, this indicates the importance of considering pneumothorax when acute deterioration occurs with persistent hypoxia in asthmatic patients during the COVID-19 pandemic.

The main limitation of the study is the lack of a healthy control group to compare LFTs. However, we had the opportunity to compare the clinical and radiological features of confirmed COVID-19 cases in a large pediatric cohort from Turkey using the current literature. Second, LFTs could not be performed in the

control group during the study period due to the COVID-19 precautions. Therefore, previous LFTs were evaluated. Finally, most patients had normal LFTs, although 48% of the patients had moderate and severe asthma. This could be explained by the fact that concerns about asthma control during the COVID-19 pandemic have led to an increase in daily controller adherence.⁵¹ Moreover, staying at home prevented exposure to viruses and outdoor allergens, and decreased asthma exacerbations.⁵² The strength of the present study is, to the best of our knowledge, being the first study with a large sample to assess the effect of COVID-19 on LFTs in asthmatic children.

In conclusion, the COVID-19 infection leads to small airway dysfunction in asthmatic children, and obesity and familial atopy are independent risk factors for a $\geq 25\%$ decrease in FEF25%–75. The long-term effects of COVID-19 infection especially on small airways require close monitoring in children with asthma. Moreover, the higher incidence of MIS-C than the general population deserves attention and further investigation.

AUTHOR CONTRIBUTIONS

Elif Soyak Aytekin collected the data and wrote the article; Sevda Tuten Dal, Hilal Unsal, and Ozan Hakverdi collected the data; Berna Oguz evaluated the radiological findings; Yasemin Ozsurekci managed the diagnosis, and follow-up of the patients; Umit M. Sahiner made the statistical analysis; Bulent E. Sekerel contributed in the study design and the discussion; Ozge Soyer planned the study and supervised the whole manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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