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# Comparison of clinical features of COVID-19 infection in children with asthma and their healthy peers

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## Abstract

**Aim:** We aimed to assess the impact of COVID-19 on asthma exacerbations and to compare the severity of symptoms of SARS-CoV-2 infection of asthmatic children with those of healthy children.

**Methods:** The clinical course of COVID-19 was compared among 89 children with asthma and 84 healthy children with age- and gender-matched. Demographic factors, severity of asthma, duration of asthma, presence of atopy, type of treatment, and compliance to treatment in asthmatic children on clinical course of infection and to determine the risk factors for severe course for asthma exacerbation during COVID-19 were evaluated retrospectively. Demographic characteristics, clinical symptoms, duration of complaints, and hospitalization rates were statistically compared between the two groups.

**Results:** Both groups had similar rates of symptomatic disease, hospitalization, and duration of fever. Among children with asthma mean age was 10.3 years, 59.6% were male, and 84.3% had mild asthma. Dyspnea was more prevalent in asthmatic children ($p$:0.012), but other clinical findings were not different from those of healthy controls. 12.4% ($n$:11) of asthmatic children had asthma exacerbation, 2.2% ($n$:2) of them were hospitalized; one (1.1%) of which was due to asthma exacerbation.

**Conclusion:** The course of COVID-19 in patients with mild to moderate asthma, who were followed up regularly and who were compliant with their treatment, was similar to their healthy peers. Since there was no severe asthma case in our study, the results could not have been generalized to all asthmatic patients. Further comprehensive and multicenter studies are required in pediatric population.

KEYWORDS

asthma, children, COVID-19

  

## 1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported on December 31st in Wuhan, China causing clinical symptoms of fever and difficulty in breathing. It was named the coronavirus disease (COVID-19) by the World Health Organization (WHO), and on March 11th, 2020, the disease course was announced to be pandemic.[1,2] Since then, over 280 million cases and 5 million deaths were reported due to COVID-19.[3] The first case in Turkey was identified on March 11th and over 9 million cases and over 80,000 deaths were recorded so far.[4]

COVID-19 tends to have a more severe course in advanced age groups with underlying medical conditions. Children at any age may be infected with COVID-19. In the United States of America (USA), approximately 13% of all laboratory-confirmed cases that were reported to The Center for Disease Control and Prevention Units (CDC) were children under 18 years of age.[5]

Although the disease course in children is reported to be asymptomatic or relatively mild in comparison to adults; the clinical course in children with chronic conditions evokes concern in both the families and the medical staff. Asthma is the most common chronic disease of childhood worldwide. Since asthma is a chronic inflammatory pulmonary disease and COVID-19 may progress with severe lung involvement and respiratory failure; the patients with asthma were initially regarded as a risk group for severe disease course. At the early stages of the pandemic, the CDC confirmed moderate to severe asthma as a risk factor for severe disease. However, in recent reports, asthma is classified as a risk factor supported by mixed evidence.[6] It was indicated by The Global Initiative for Asthma (GINA) that the patients with asthma do not have an increased risk of being infected with COVID-19.[7] A comprehensive research demonstrated no increase in the risk for COVID-19 related death in asthmatic patients in general, though it is high in the patients with severe asthma.[8]

In this study, we aimed to evaluate and compare the COVID-19 disease course in children with asthma and their healthy peers as well as to assess the effect of demographic factors and disease-related features of asthmatic children (such as type and severity of asthma, treatment received for asthma, and compliance to treatment) on clinical course of infection and to determine the risk factors for severe disease course.

## 2 | METHODS

### 2.1 | The study is designed as cross-sectional, case-control, and descriptive

The study group consisted of the children with asthma who were being followed up regularly by Pediatric Allergy Clinics of Bezmialem Vakıf University and Bakirkoy Dr Sadi Konuk Research and Training Hospital. Control group was chosen among children attending the Pediatric Outpatient Clinics of Bezmialem Vakıf University for any reason and did not have asthma or chronic disease. In both groups, there were children who were learned to have COVID-19 in their medical history during the outpatient clinic control.

The inclusion criteria for both groups were to have a history of COVID-19 and to be between 2 and 18 years of age. Children in the healthy group and asthma group with malnutrition, immunodeficiency, and chronic disease (only atopic disease were included in the asthma group) were not included in the study.

### 2.2 | Data collection

Children attending routine follow-up visits at Pediatric Allergy Clinics of Bezmialem Vakıf University and Bakirkoy Dr Sadi Konuk Research and Training Hospital between January 4 and April 30, 2021, with the suitable criteria were included. Asthma was diagnosed according to the GINA guidelines.[7] The parents of the study and control group were informed about the study and a face-to-face interview was carried on. The interview consisted of demographic features, signs, and symptoms during COVID-19, duration of fever, and the need for hospitalization or intensive care. Severity of asthma, disease duration, presence of atopy, concomitant atopic diseases, use of controller medicine for asthma, and whether the controller medicine was used during COVID-19 infection were also noted for the asthma group. Atopy was defined as a positive skin prick test and/or elevated specific IgE. The controller treatment for asthma was classified in accordance with current GINA guidelines.[7] The asthma patients were classified according to severity criteria of the current GINA guidelines. The asthma patients whose symptoms were under control with steps 1 and 2 treatment were classified as mild, those receiving step 3 treatment were accepted as moderate, and those requiring steps 4 and 5 treatment for asthma control were regarded as severe asthma.[7]

The medical data of the patients were obtained from the hospital automation system records, and the nasopharyngeal/oropharyngeal polymerase chain reaction (PCR) results were obtained by using the Public Health Information System.

### 2.3 | The evidence of COVID-19 infection

In accordance with The Guidelines of The Ministry of Health of Turkish Republic; the definite cases with positive nasopharyngeal/oropharyngeal SARS-CoV-2 PCR and probable cases meeting clinical criteria plus epidemiological evidence without any confirmatory laboratory test for COVID-19 were included.[9] Epidemiologic evidence was defined as contact with a person with COVID-19. The patients who were asymptomatic despite having family contact were not involved in the study if they were not tested or had a negative PCR test. According to the algorithm of the Ministry of Health in our country; children with two or more symptoms or signs (fever, cough, tachypnea, abnormal chest

osculation, and oxygen saturation below 92%); children with one symptom and a contact with COVID-19; children who do not have symptoms but have two or more family members with COVID 19 are being tested. However, PCR testing was not performed on a significant portion of pediatric patients with mild clinical findings or no symptoms, who did not apply to a health institution and were isolated and followed up at home.

### 2.4 | Statistical analysis

SPSS 20.0®IBM for Windows program was used for statistical analysis. Descriptive statistics were given as mean and standard deviation for numeric variables, and number and percentages for categorical variables. The ratios of the categorical variable among the groups were tested with Chi-square analysis with the Fisher's exact test. Student's *t*-test was used for two independent groups if the condition of normal distribution of numeric variables was provided, and one-way ANOVA for more than two independent groups was used to analyze relationships between numeric variables. The Mann–Whitney *U*-test was used for comparisons in nonparametric distribution parameters between two groups. *p* values of <0.05 were considered statistically significant.

### 2.5 | Ethical issues

The study was approved by both The Ethical Committee of Bezmialem Vakıf University (No: 02/37) and The Scientific Study Group of The Ministry of Health (No: 2020-12-31T11_43_52). The study was conducted in accordance with the principles stated in the Declaration of Helsinki. Informed consent was obtained from all parents and patients older than 16 years.

## 3 | RESULTS

The study was completed with 89 children with asthma and 84 healthy controls. The flowchart for the asthmatic children to be included in the study is summarized in Figure 1. The mean age was 10.3 ± 4 and 9.5 ± 4.8 years, respectively, in the asthma and control groups and had similar distribution among the groups (*p*:0.262). 40.4% of the asthma group and 52.4% of the control group were female. There was no significant difference in terms of gender distribution between the groups (*p*:0.129).

There was no significant difference in terms of number of confirmed COVID-19 cases between both groups (*p*:0.280). The rate of confirmed cases was 53.9% in the asthma group and 63.1% in the control group (Table 1).

96.6% of the COVID-19 cases with asthma as well as 92.9% of the healthy children were symptomatic, and there was no significant difference between the groups. Although shortness of breath was reported more significantly in asthmatic COVID-19 cases in comparison to the control group (10% and 1.2%, respectively; *p*:0.012). There was no significant difference in terms of other symptoms (Table 1). None of the patients reported rash. The hospitalization rates were similar in both groups (*p*:0.595), two patients in the asthma group (2.2%) and one patient in the control group (1.2%) were hospitalized but none required intensive care unit admission. One of the asthmatic patients was hospitalized because of respiratory symptoms and asthma attack, and the other because of vomiting and insufficient oral nutrition.

Of the patients in the asthma group, 89.9% had atopy and 83.1% had other atopic diseases. Allergic rhinitis was the most prevalent concomitant atopic disease (94.6%, *n*:70), followed by atopic dermatitis (13.5%, *n*:10), and food allergy (2.7%, *n*:2). 84.3% of our patients had mild asthma and 15.7% had moderate asthma. There was no severe asthma case in our study group. 50.5% of the patients were taking their controller treatment regularly during COVID-19, while 36% were being followed up without any controller medicine.

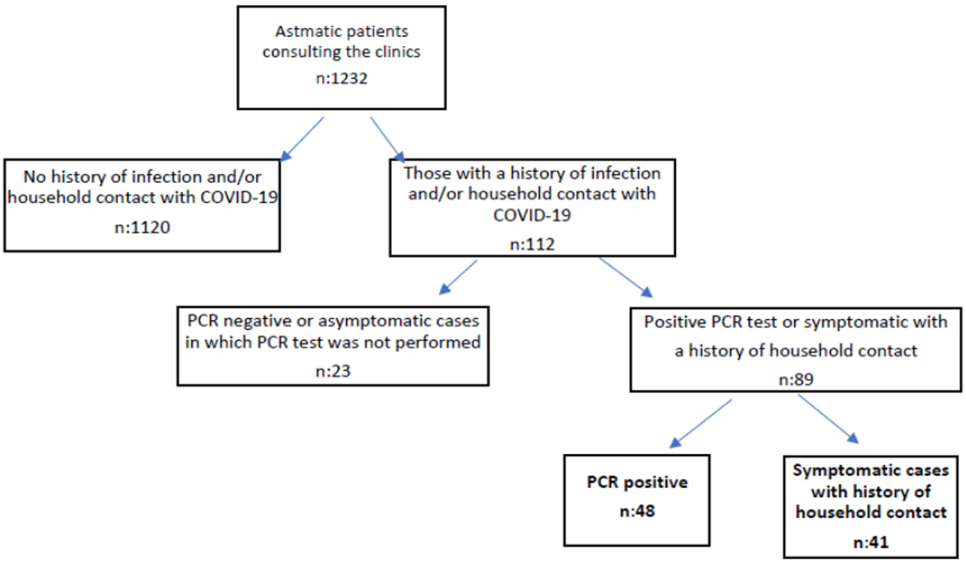


**FIGURE 1** The flowchart of the asthmatic patients to be recruited for the study. [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** The demographic features, the evidence status of COVID-19, and hospitalization rates in both asthma and healthy groups.

| | Asthma group, *n*:89 | Control group, *n*:84 | *p* |
|---|---|---|---|
| **Age, years (mean ± SD)** | 10.3 ± 4 | 9.5 ± 4.8 | 0.262 |
| **Range** | 2–18 | 2–18 | |
| **Age distribution, *n* (%)** | | | |
| 2 to ≤5 years | 13 (14.6) | 20 (23.8) | 0.303 |
| 6 to ≤11 years | 40 (44.9) | 33 (39.3) | |
| 12 to ≤18 years | 36 (40.4) | 31 (36.9) | |
| **Gender, *n* (%)** | | | |
| Female | 36 (40.4) | 44 (52.4) | 0.129 |
| Male | 93 (59.6) | 40 (47.6) | |
| **Evidence of COVID-19 infection, *n* (%)** | | | |
| Confirmed (PCR+) | 48 (53.9) | 53 (63.1) | 0.280 |
| Symptomatic with a history of domestic contact | 41 (46.1) | 31 (36.9) | |
| **Presence of symptoms, *n* (%)** | | | |
| Present | 86 (96.6) | 78 (92.9) | 0.319 |
| Absent | 3 (3.4) | 6 (7.1) | |
| **Fever, *n* (%)** | 49 (55.1) | 49 (58.3) | 0.759 |
| **Duration of fever, days (mean ± SD)** | 2.02 ± 1.33 | 1.92 ± 0.72 | 0.643 |
| **Range** | 1–8 | 1–3 | |
| **Sore throat, *n* (%)** | 26 (29.2) | 28 (33.3) | 0.623 |
| **Malaise, *n* (%)** | 41 (46.1) | 37 (44.1) | 0.879 |
| **Myalgia, *n* (%)** | 26 (29.2) | 19 (22.6) | 0.387 |
| **Cough, *n* (%)** | 26 (29.2) | 24 (28.6) | 0.926 |
| **Shortness of breath, *n* (%)** | 9 (10.1) | 1 (1.2) | **0.012** |
| **Wheezing, *n* (%)** | 5 (5.6) | 2 (2.4) | 0.280 |
| **GIS[a] symptoms, *n* (%)** | 26 (29.2) | 17 (20.2) | 0.218 |
| **Nasal symptoms, *n* (%)** | 7 (7.9) | 8 (9.5) | 0.698 |
| **Headache, *n* (%)** | 33 (37.1) | 24 (28.6) | 0.260 |
| **Loss of taste and smell, *n* (%)** | 19 (21.3) | 16 (19) | 0.707 |
| **Conjonctival hyperemia, *n* (%)** | 3 (3.4) | 5 (6) | 0.419 |
| **Others,[b] *n* (%)** | 12 (13.5) | 3 (3.6) | **0.021** |
| **Hospitalization, *n* (%)** | 2 (2.2) | 1 (1.2) | 0.595 |

[a]GIS (gastrointestinal system) syptoms: Vomiting, diarrhea, and abdominal pain.

[b]Other: Oral sore (*n*:1), dizziness (*n*:3), hypothermia (*n*:1), chest pain (*n*:2), loss of appetite (*n*:3), itching (*n*:1), nausea (*n*:2), sweating (*n*:1), and increased secretion of tear (*n*:1).

Noncompliance to asthma treatment (not using regularly as advised or not using at all) was determined as 13.5%. During COVID-19, 12.4% of children (*n*:11) in the asthma group had an exacerbation. Only two patients with asthma (2.2%) required hospitalization. One of these patients was hospitalized for vomiting and had no respiratory symptoms, the other had severe asthma exacerbation and respiratory symptoms. None of the children in both asthma and control groups needed intensive care.

In the asthma group, the mean duration of asthma was 5.7 ± 3.2 years (range: 1–15 years), and there was no statistically significant relationship between asthma duration and exacerbation of asthma during COVID-19 (*p*:0.625). There was no statistically significant relation between having asthma exacerbation during the COVID-19 infection with gender, severity of asthma, presence of atopy, concomitant atopic disease, use of controller medicine during COVID-19 infection, type of controller medicine, and use of inhaled corticosteroids (Table 2). There

**TABLE 2** The relation between asthma exacerbation rates and demographic factors, presence of atopy, severity of asthma, and treatment features in asthma patients.

| Asthma group, *n* (%) | Total patients (*n*:89) | Without exacerbation (*n*:78) | With exacerbation (*n*:11) | *p*[a] |
|---|---|---|---|---|
| **Gender** | | | | |
| Female | 36 (40.4) | 31 (39.7) | 5 (45.5) | 0.718 |
| Male | 53 (59.6) | 47 (60.3) | 6 (54.5) | |
| **Evidence of COVID-19** | | | | |
| Confirmed | 48 (53.9) | 42 (53.8) | 6 (54.5) | 0.965 |
| Probable | 41 (46.1) | 36 (46.2) | 5 (45.5) | |
| **Age group** | | | | |
| 2 to ≤5years | 13 (14.6) | 10 (12.8) | 3 (27.3) | 0.204 |
| 6 to ≤11 years | 40 (44.9) | 34 (43.6) | 6 (54.5) | |
| 12–18 years | 36 (40.5) | 34 (43.6) | 2 (18.2) | |
| **Presence of atopy** | | | | |
| Present | 80 (89.9) | 71 (91.0) | 9 (81.8) | 0.343 |
| Absent | 9 (10.1) | 7 (9.0) | 2 (18.2) | |
| **Severity of asthma** | | | | |
| Mild | 75 (84.3) | 67 (85.9) | 8 (72.7) | 0.261 |
| Moderate | 14 (15.7) | 11 (14.1) | 3 (27.3) | |
| **Concomitant atopic disease** | | | | |
| Present | 74 (83.1) | 66 (84.6) | 8 (72.7) | 0.271 |
| Absent | 15 (16.9) | 12 (15.4) | 3 (27.3) | |
| **Compliance to asthma treatment** | | | | |
| Compliant | 77 (86.5) | 68 (87.2) | 9 (81.8) | 0.626 |
| Noncompliant | 12 (13.5) | 10 (12.8) | 2 (18.2) | |
| **Controller medicine**[b] | | | | |
| Step 1 | 23 (25.8) | 20 (25.6) | 3 (27.3) | 0.488 |
| Step 2 | 52 (58.4) | 47 (60.3) | 5 (45.5) | |
| Step 3 | 14 (15.7) | 11 (14.1) | 3 (27.3) | |
| **Inhaled corticosteroids** | | | | |
| Present | 37 (41.6) | 32 (41) | 5 (45.5) | 0.780 |
| Absent | 52 (58.4) | 46 (59) | 6 (54.5) | |

[a]Statistical comparison between the two groups.

[b]Treatment is classified according to current GINA guidelines.[7]

was no significant relation between presence of fever and having asthma exacerbation ($p$ : 0.971).

## 4 | DISCUSSION

Although children with COVID-19 have been reported to be asymptomatic or to have mild symptoms, it is still a debate whether asthma, the most common chronic disease of childhood, causes susceptibility to infection or more severe disease. Our study is valuable in terms of comparing the course of COVID-19 in children with asthma and their healthy peers.

The rates of asymptomatic infection in both asthma and control groups were similar in our study. The rate of asymptomatic patients is lower than that reported in the literature. This is due to the fact that PCR testing is not usually ordered for asymptomatic children despite having risky contact. Asymptomatic children (either healthy or with asthma) who did not have PCR test were not included in our study even if they had domestic contact with COVID-19 due to lack of evidence for infection. So, the rate of asymptomatic infection is less

than expected in our study. Asymptomatic COVID-19 rate was reported as 22.7% among 1156 children in a multicenter study from Turkey.[10] A review of 61 observational studies involving all age groups as well as children states reported that at least one third of all children with COVID-19 are asymptomatic.[11] In a multicenter study conducted in the pediatric age group in Europe, the rate of asymptomatic cases was found to be 16%. It represents individuals at the more severe end of the disease spectrum since it was conducted in tertiary healthcare institutions.[12] Asymptomatic infection rate was reported to be 12.7% in a retrospective study in the USA, involving PCR-positive pediatric patients.[13] In a retrospective study conducted in our country, the presence of COVID-19 symptoms in asthmatic and non-asthmatic pediatric patients was found to be 94.4% and 85.8%, respectively, and no statistically significant difference was found between the two groups.[14]

The presence and duration of fever did not differ significantly between the two groups. In retrospective studies in childhood, fever was reported to be 50.4% in our country and 51.2% in the USA which are similar to our study.[10,13] In the multicenter study in Europe presence of fever was reported as 65% though it should be emphasized again that more severe patients were included in this study.[12]

The second most common symptom in our study was malaise with a rate of 47%, with no significant difference between asthma and control groups. In a study in the pediatric group, the rate of fatigue was reported as 6.1%.[13] In a study evaluating 29 asthmatic children with probable COVID-19, asthenia was reported with a rate of 52%.[15]

Asthmatic children and their healthy peers had similar clinical course of COVID-19 in our study. Distribution of the clinical symptoms and the rates of hospitalization were similar in both groups. In a meta-analysis evaluating the data of 131 studies to compare COVID-19 infection of asthmatic and non-asthmatic patients; the prevalence of asthma was determined to be 1.1%–16.9% as a comorbidity. Asthma was not associated with more severe course of COVID-19 or worse prognosis. Moreover, asthmatic patients had lower risk for death compared to non-asthmatic patients.[16] The prevalence of asthma was not reported to be high in fatal cases of COVID-19 or in those patients requiring more intensive treatment (hospitalization, intensive care admission, intubation, or mechanical ventilation).[16] Asthma prevalence was 12.6% in 1298 COVID-19 patients under the age of 65 who did not have chronic obstructive pulmonary disease in a study in the USA. However, in a subgroup of 55 patients under the age of 21, it was more prevalent (23.6%). There was no significant difference in terms of length of hospital stay, need, and duration of intubation, need for tracheostomy, hospital readmission, or mortality between asthmatic and healthy children.[17] A review evaluating the interaction of SARS-CoV-2 and childhood asthma reported that available data support a favorable outlook for children with asthma infected by the novel coronavirus furthermore the way innate and acquired immunity responds to the virus in children with asthma, the reduction in the number of virus host-receptors, and the down-regulation of these receptors by Th2 inflammation and steroid therapy may play a role in the way SARS-CoV-2 is infected.[18] A multicenter study conducted with 1156 children with COVID-19 infection in our country, the prevalence of asthma was reported as 3.2%.[10] In contrast to our study, symptomatic disease (87.6%) and presence of cough (80%) were significantly higher in asthmatic patients.[10] Nevertheless in this study having asthma was not found to be significantly associated with disease severity.[10] The relationship between the severity of asthma and the severity of SARS-CoV-2 infection was investigated in a retrospective study of 212 children with asthma in Spain. Of the 29 patients who were considered as possible COVID-19 cases among these children, all developed mild symptoms related to COVID-19, similar to our study.[15]

The rate of exacerbation during COVID-19 in the asthma group was 12.4% in our study. Viral respiratory tract infections are among the most important causes of asthma exacerbations in the pediatric age group. Although in a meta-analysis evaluating respiratory viruses that cause asthma exacerbation, human coronavirus as a viral agent was detected in 8.4% of the pediatric age group.[19] There is not enough data yet on the rate of SARS-CoV-2 infection causing asthma exacerbation. In a multicenter study evaluating COVID-19 infection in children with underlying chronic respiratory disease, 20% of 49 children with asthma presented with an asthma exacerbation.[20] In a study conducted in Spain, the rate of bronchospasm was reported as 24% in children with asthma during COVID-19.[15] The rates in both studies were higher than in our study.

We could not demonstrate any relation between severity of asthma and the rate of asthma exacerbation during COVID-19 infection. Similarly, in the study conducted in our country, no significant difference was found between the asthma-controlled and uncontrolled groups in terms of having symptoms of COVID-19, being hospitalized due to COVID-19, prescribing COVID-19 treatment, and requiring oxygen and steroid treatment.[14] In a study conducted in Spain, it was reported that asthma severity and control status were not associated with a worse clinical course.[15] All our patients had mild or moderate asthma, and we did not have any severe asthma cases. So our results can not be generalized for all asthma patients. Multicentric adult studies from the United Kingdom and Korea and the USA postulates that not mild but severe asthma is associated with COVID-19-related mortality.[8,21,22]

We did not find any significant correlation between the exacerbation rate during COVID-19 infection and use of inhaled corticosteroids or the step of asthma controller treatment. There is no data supporting the effect of inhaled corticosteroids on severity of COVID-19 infection.[23] A systematic review on inhaled corticosteroids (ICS) and COVID-19 found no evidence to support asthmatic patients to discontinue the use of ICS, and it was warned that discontinuation of ICS would cause exacerbation.[24] The current GINA guideline recommends that asthma patients continue inhaled corticosteroid therapy in the presence of COVID 19 infection.[7]

There was no difference between atopic and nonatopic asthmatic children in terms of having an exacerbation during COVID-19. SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) for entering the cell. ACE2 gene expression is significantly decreased in patients with allergic asthma compared to nonallergic

asthmatics.[25] During the course of COVID-19 infection, the secretion of interferon stimulates ACE2 gene and increases its production.[25] In asthma, there is insufficient interferon response to viral infection which is speculated to decrease the increased expression of ACE2 gene and the disease severity.[23]

### 4.1 | Limitations of the study

Our study population consisted of children with mild to moderate asthma most of which comply to the controller treatment. There were no individuals with severe asthma and there were few non-atopic patients. Therefore, we cannot generalize our results to all asthmatic children. Although the symptoms and their durations in both asthma and control groups were determined retrospectively by questioning the parents and/or patients, and some patients had considerable time lapse from the disease course, all parents were able to clearly express the presence of symptoms since the COVID-19 process is very worrying for families and they have been observing their children carefully. As we did not include asymptomatic patients who did not have a PCR test or those patients with negative PCR test despite having a household of contact, our study does not accurately reflect the rate of asymptomatic infection. Finally, our study is designed as cross-sectional on a small population. More comprehensive, multicentric studies are needed to evaluate the propensity for COVID-19 and the clinical course of the infection in children with asthma.

## 5 | CONCLUSION

In our study, we found that children with mild to moderate asthma experienced COVID-19 with similar clinical manifestations to their healthy peers. There was no relationship between the severity of asthma, the presence of atopy, the type of asthma treatment, and the rate of exacerbation. Further comprehensive, multicentric studies are required in the pediatric population on this subject.

### AUTHOR CONTRIBUTIONS

**Mustafa A. Nursoy**: Methodology (supporting); project administration (equal); supervision (equal); visualization (supporting). **Lida Bülbül**: Data curation (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Mebrure Yazıcı**: Conceptualization (supporting); data curation (equal); resources (equal). **Nazan Altinel**: Data curation (supporting); methodology (equal); resources (equal); writing – review and editing (equal). **Feyza Ustabas Kahraman**: Data curation (equal); methodology (equal); validation (equal). **Neslihan Ozkul Saglam**: Conceptualization (equal); methodology (equal); resources (equal). **Burcu Bursal Duramaz**: Data curation (equal); methodology (equal); supervision (equal). **Ozden Türel**: Conceptualization (equal); methodology (equal); writing–original draft (equal); writing–review and editing (equal). **Erkan Çakır**: Investigation (equal); project administration (equal); resources (equal); supervision (equal).

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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.

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