Long-Term Effects of COVID-19 on Respiratory Symptoms and Asthma Control in Pediatric Patients with Asthma

COVİD-19 Enfeksiyonu Olan Pediatrik Astımlı Hastaların Uzun Vadede Değerlendirilmesi

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ABSTRACT

Objective: After Covid-19 infection, many patients complain of persistent symptoms. There are limited studies evaluating the long-term consequences of COVID-19, in pediatric patients with asthma. The aim of this study is to evaluate the persistence of symptoms and asthma control in asthmatic children during follow-up after COVID-19 infection.

Material and Methods: Children with asthma who were admitted to our hospital between March 11, 2020, and August 31, 2021, for COVID-19 infection were included. Patients were evaluated for long- term symptoms and asthma control through phone interviews at least 6 months after infection.

Results: Eighty-five children with asthma were evaluated. The median duration of follow-up was 20 months. Patients experiencing symptoms after 1 month, 3 month and 6 month of COVID were 45.8% (n:39), 30.6% (n:26), and 23.5% (n:20) respectively. The most common symptom was cough. No significant relationship was found between time period from the date of COVID-19 to phone call and symptom persistence. Patients adopting a new pet and having stress were significantly higher in group of patients having symptoms at first month. Frequency of being well controlled was not different before and at 1 and 6 month of infection.

Conclusion: This study suggests that respiratory symptoms may persist in pediatric asthma patients for an extended period after COVID-19 infection.

Key Words: Asthma, Child, COVID-19

ÖZ

Amaç: Çalışmanın amacı, COVİD-19 enfeksiyonu sonrası astımlı çocukların persistan semptomlarını ve astım control durumlarını değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya 11 Mart 2020 ve 31 Ağustos 2021 arasında astım tanısı olan ve COVİD-19 enfeksiyonu olan çocuklar alınmıştır. Hastalara telefon görüşmesi aracılığıyla, COVİD-19 enfeksiyonundan en az 6 ay sonra, uzun dönem semptom ve astım kontrolü için değerlendirildi.

Bulgular: Astımlı 58 çocuk değerlendirildi. Ortanca izlem süresi 20 aydı. COVİD-19 enfeksiyonundan 1, 3 ve 6 ay sonra halen semptomu olan hastalar sırasıyla %45.8 (n:39), %30.6 (n:26), ve %23.5 (n:20) olarak saptandı. En sık saptanan semptom öksürüktü. COVİD-19 enfeksiyonu geçirdikleri tarihten telefon görüşmesine kadar olan süre ile semptom persistansı arasında anlamlı ilişki saptanmadı. COVİD-19 enfeksiyonu sonrası 1.ayında semptomu sebat edenlerde anlamlı olarak yeni evcil hayvan sahiplenme ve stresli olma daha fazla saptandı.

Astımda iyi kontrollü olma durumu enfeksiyon öncesi dönem, enfeksiyon sonrası 1. ve 6.ayda anlamlı olarak farklı olmadığı saptandı.

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital Ethics Committee (E2-22-1900). Parental consent was received.

Contribution of the Authors / Yazarların katkısı*: *TOYRAN M: Conceived of the presented idea. ***CİVELEK E, TOYRAN M and DİBEK MISIRLIOĞLU E:*** developed the theory and performed the computations. ***METBULUT AP, YILMAZ D and KÜLHAŞ ÇELİK İ:*** chose and directed the appropriate patients for the study. ***METBULUT AP and TOYRAN M:*** carried out literature review and verified the analytical methods. ***METBULUT AP:*** mainly wrote the article. ***METBULUT AP* and *TOYRAN M:*** supervised the findings of this study. All authors discussed the results and contributed to the final article.

How to cite / *Atıf yazım şekli* : Metbulut AP, Yılmaz D, Külhaş Çelik İ, Civelek E, Dibek Mısırlıoğlu E and Toyran M. Long-Term Effects of COVID-19 on Respiratory Symptoms and Asthma Control in Pediatric Patients with Asthma. Turkish J Pediatr Dis 2024;18:117-123.

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Received / Geliş tarihi : 16.09.2023
Accepted / Kabul tarihi : 29.11.2023
Online published : 15.01.2024
Elektronik yayın tarihi
DOI:10.12956/tchd.1354529

Sonuç: Bu çalışma, pediatrik astım tanısı olan çocuklarda semptomların uzun süre devam edebileceğini göstermektedir.
Anahtar Sözcükler: Asthma, Çocuk, COVİD-19

INTRODUCTION

SARS-CoV-2 is a coronavirus responsible for Coronavirus Disease 2019 (COVID-19), which HAS led to a global pandemic (1). COVID-19 causes serious acute respiratory syndromes that can cause significant morbidity and mortality. The spectrum of diseases caused by the coronavirus can range from the common cold to severe acute respiratory syndrome. Asystematic review reported that 1%–5% of individuals diagnosed with COVID-19 were children, and clinical findings were milder in children than in adults (2). According to the Centers for Disease Control and Prevention (CDC), 8.1% of patients infected with COVID-19 are children, and their mortality rate is <0.1% (3). Comorbidities, such as hypertension, chronic obstructive pulmonary disease, diabetes mellitus, and obesity, affect the prognosis of COVID-19 (4).

Asthma is one of the most common chronic conditions among children, and its prevalence in the US was increasing until recently (5). In two studies from Turkey, the prevalence of asthma in children was found to be 8.6%–12.6% between 1994 and 2004, and between March and June 1997 respectively (6,7). In a study conducted at our hospital, 54 (0.87%) of 6205 pediatric patients diagnosed with COVID-19 were found to have asthma (8). According to the CDC, individuals with moderate and severe asthma have an increased risk of being hospitalized for COVID-19 (9). COVID-19 may cause asthma attacks, pneumonia, and acute respiratory disease due to its effects on the nose, throat, and lungs (10).

Few studies have evaluated pediatric patients with asthma during follow-up after COVID-19 infection. As there is a lack of data on the long-term effects of COVID-19 infection on asthma control status and persistent symptoms among children with asthma, we believe that our data are important and can shed some light on this subject. Accordingly, the aim of this study is to evaluate persistence of symptoms and asthma control state of asthmatic children during follow up after Covid-19 infection.

MATERIALS and METHODS

This retrospective study included children with asthma who were admitted to our hospital between March 11, 2020, and August 31, 2021, and were diagnosed with COVID-19 based on reverse transcription-polymerase chain reaction (RT-PCR) tests using nasopharyngeal and throat swabs. The inclusion criteria were having asthma diagnosis, having COVID-19 and being below 18 years of ages.

We collected data from patients' medical records, including medical history, demographic information, asthma evaluation data, asthma medication usage during COVID-19, and asthma control according to the Global Initiative for Asthma Main Report (GINA) criteria (12). Partially controlled and uncontrolled patients were classified as not well controlled for better statistical analysis, and asthma maintenance was evaluated according to GINA criteria (12). Patients' symptoms and treatment at the time of COVID-19 infection were collected from hospital files. Patients who had undergone COVID-19 infection at least 6 months before the study were chosen and evaluation was done according to data at 1st month and data at 6th month, all patients had these data. Follow-up interviews were evaluated by interviewing the patient's parents. A questionnaire created by the authors was used however more detailed questions were asked when needed for a better definition of symptoms.The questions were open-ended. Symptoms occurring in a short time period as a worsening of asthma were defined as "asthma exacerbation" but other symptoms ongoing in most of the days were defined as "symptoms". They were asked whether they had persistent symptoms after their COVID-19 infection (Fever, nausea, headache, vomiting, weakness, abdominal pain, cough, diarrhea, shortness of breath, joint pain, sore throat, runny nose), how long their symptoms had lasted, whether they had any symptoms at the time of polyclinic control, if there were any changes in their asthma treatment following infection, whether they experienced asthma exacerbation, if they had undergone systemic steroid use, or if they had an emergency department visit or hospitalization for asthma after infection or within six months prior to infection. The presence of other possible risk factors for developing symptoms or exacerbation, such as exposure to tobacco smoke, new pet ownership, and differences in home and school environments, were also determined.

The study was approved by Ankara Bilkent City Hospital Ethics Committee (E2-22-1900). Parental consent was received.

Statistical analysis

SPSS 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Results were expressed as percentiles (absolute numbers), means and standard deviations, or as medians and interquartile ranges (IQRs) as required. A chi-square test was performed to compare the categorical variables. p-values < 0.050 were considered to be statistically significant.

Patients symptoms after one month, three months, six months, and at the time of the phone call were gathered from these data. Patients who did and did not have symptoms one month following infection were compared for possible risk factors. Asthma characteristics in the periods six months before and six months after COVID-19 infection were also compared. The Mac–Nemar test was used to determine if the patients had well-controlled or non-well- controlled asthma before COVID-19

infection, one month after infection, and at the time of the phone call. The relation of symptom presence and duration between the infection and phone interview were determined using a box-plot test.

RESULTS

Characteristics of the patients

There were 85 COVID-19 patients with asthma in our hospital between March 2020 and August 2021, who we could be reached by phone call for the study. Patients who still had symptoms were invited to the clinic; 35 (41.2%) of them came for evaluation and were examined and treated for their symptoms.

Of the 85 patients, 44 (51.8%) were male. The female/male ratio was 0.93. The median age of the patients was 13 years (IQR: 8–17 years). Forty-four (51.8%) of the patients had concomitant allergic disease, and allergic rhinitis (n:36, 42.4%) and atopy (n:42, 49.4%) were particularly common. The most commonly detected allergen was pollen (n:30, 35.3%). All of the patients had a follow-up period of at least six months.

COVID-19 symptoms and management of these patients during infection

The median age at the first diagnosis of COVID-19 was 12 years (IQR 7–15.5 years). Seventy-nine patients were diagnosed with COVID-19 once, five were diagnosed twice, and only one patient was diagnosed three times. The symptoms of the patients are shown in Table I. Of the patients, 12 (14.1%) were hospitalized, but none required treatment in the intensive care unit. The mean duration of hospitalization was four days (min–max:1–6 days). Only three (3.5%) patients needed oxygen treatment, and 18 (21.2%) were treated with antibiotics and/or antivirals. All of the patients have recovered.

Before contracting COVID-19, 69 (81.2%) of the patients had well-controlled asthma. Twenty-nine patients (34.1%) were on asthma maintenance therapy at step 1, 34 (40%) were at step 2, and 22 (25.9%) were at step 3.

Persistent symptoms after COVID-19 infection

The patients' symptoms after one month, three months, and six months are shown at Table I.

After one month of COVID-19

One month after the COVID-19 diagnosis, 39 (45.9%) of the patients still had symptoms: 29 (93.5%) had respiratory symptoms, while 17 (54.8%) had non-respiratory symptoms. The most common symptom was cough (n:20). The patients' symptoms one month after their COVID-19 diagnosis are shown in Table I.

Comparing patients who did and did not have symptoms one month after infection, the frequency of adopting a new pet and experiencing stress (e.g. due to an important exam) was higher in the patients with persistent symptoms (p=0.003 and p=0.021, respectively). There were no differences in age, gender, atopy status, concomitant allergic disease, asthma control status before infection, asthma treatment before COVID-19, and regular daily asthma maintenance between the groups (Table II).

After six months of COVID-19

Six months after the COVID-19 diagnosis, 20 (23.5%) patients still had symptoms: 19 (95%) had respiratory symptoms, and 12 (60%) had non-respiratory symptoms. The most common

Table I: Reported symptoms by duration of follow-up after COVID-19 diagnosis

Symptoms	During COVID-19 diagnosis, n(%) n:85	After 1st month of COVID-19, n(%) n:39 (45.8)	After 3th month of COVID-19, n(%) n:26 (30.6)	After 6th month of COVID-19, n:(%) n:20 (23.5)
Fever	39 (45.9)	0	0	0
Cough	48 (56.5)	22 (25.9)	16 (18.8)	11 (12.9)
Dyspnea	19 (22.4)	20 (23.5)	15 (17.6)	11 (12.9)
Chest pain	5 (5.9)	11 (12.9)	7 (8.2)	7 (8.2)
Chest palpitation	NA	5 (5.9)	5 (5.9)	4 (4.7)
Activity limiting symptom	NA	11 (12.9)	8 (9.4)	6 (7.1)
Headache	6 (7.1)	12 (14.1)	9 (10.6)	7 (8.2)
Fatigue	15 (17.6)	12 (14.1)	9 (10.6)	7 (8.2)
Loss of smell and taste	3 (3.5)	4 (4.7)	3 (3.5)	3 (3.5)
Anxiety	NA	3 (3.5)	3 (3.5)	2 (2.4)
Vertigo	1 (1.2)	2 (2.4)	1 (1.2)	1 (1.2)
Joint pain	11 (12.9)	1 (1.2)	1 (1.2)	1 (1.2)
Amnesia	NA	1 (1.2)	1 (1.2)	1 (1.2)
Nausea	8 (9.4)	1 (1.2)	1 (1.2)	1 (1.2)

Table II: Evaluating the risk factors in terms of having symptoms after 1 and 6 month of COVID-19

	Having symptoms after 1 month of COVID-19	Not having symptoms after 1 month of COVID-19	p	Having symptoms after 6 month of COVID-19	Not having symptoms after 6 month of COVID-19	p
Age of the patients, mean, years	13.8	10.8	0.148	12.9	10.2	0.599
Male gender, n(%)	17 (43.6)	27 (58.7)	0.195	9 (45)	35 (53.8)	0.489
Having atopy, n(%)	22 (56.4)	20 (43.5)	0.542	9 (45)	33 (50.8)	0.662
Having additional allergic disease, n(%)	22 (56.4)	22 (47.8)	0.822	10 (50)	34 (52.3)	0.857
Patients using asthma maintenance therapy every day regularly, n(%)	17 (43.6)	24 (52.2)	0.321	9 (45)	32 (49.2)	0.926
Patients GINA control assessment before COVID-19, n(%)						
Well controlled asthma	29 (74.4)	40 (87)	0.139	16 (80)	53 (81.5)	1.00
Not well controlled asthma	10 (25.6)	6 (13)		4 (20)	12 (18.5)	
Asthma treatment Step before COVID-19						
Step 1	12 (30.8)	17 (37)	0.147	6 (30)	23 (35.4)	0.002*
Step 2	13 (33.3)	21 (45.7)		3 (15)	31 (47.7)	
Step 3	14 (35.9)	8 (17.4)		11 (55)	11 (16.9)	
Additional risk factors, n(%)						
Patients having school's closed	25 (64.1)	34 (73.9)	0.418	3 (15)	5 (7.7)	0.385*
Patients changing their homes	2 (5.1)	3 (6.5)	0.461*	1 (5)	3 (4.6)	1.00*
Patients adopting new pet	7 (17.9)	0	0.003*	1 (5)	6 (9.2)	0.682*
Patients having a family member smoking at home	7 (17.9)	2 (4.3)	0.073*	4 (20)	5 (7.7)	0.205*
Patients having increased family member living at home	2 (5.1)	1 (2.2)	0.591*	2 (20)	1 (1.5)	0.137*
Patients changing home heating system	1 (2.6)	0	0.459*	1 (5)	0	0.235*
Patients changing school	6 (15.4)	3 (6.5)	0.290*	2 (10)	7 (10.8)	1.00*
Patients changing class at school	6 (15.4)	3 (6.5)	0.290*	2 (10)	7 (10.8)	1.00*
Patients having stress	7 (17.9)	1 (2.2)	0.021*	5 (25)	3 (4.6)	0.16*

*Chi-square test, *Fisher test*

symptoms were cough and dyspnea (n:11). The patients' symptoms six month after their COVID-19 diagnosis are shown in Table I.

Comparing patients who did and did not have symptoms six months after infection, the frequency of experiencing stress (e.g. due to an important exam) and treatment at step 3 before COVID were higher in the group of patients with persistent symptoms (p=0.160 and p=0.002, respectively). There were no differences in age, gender, atopy status, concomitant allergic disease, adopting a pet, asthma control status before infection, asthma treatment step before COVID-19, and regular daily asthma maintenance between the groups (Table II).

Evaluation of persistent symptoms in terms of time between time of assessment and diagnosis of COVID-19 were shown in Figure 1. 25 patient's schools were open during pandemic. Patients having persistent symptomw after 1 and 6 month of COVID-19, were 11 (44%) and 7 (28%) of them respectively. There was no significant differences in terms of having symptoms after 1 and 6 month of COVID-19, and school attendance (p=0.302 and 0.557 respectively).

Assessment of asthma control after COVID-19

Before COVID-19, and one month after COVID-19 infection, there were 69 (81.2%), and 60 (70.6%) well-controlled patients, respectively. Meanwhile, there were 16 (18.8%), and 15 (29.4%) non-well-controlled patients before COVID-19, and one month after infection, respectively.

Of the 69 patients who were well controlled before infection, 71% were still well controlled one month after infection, and 84.1% were still well controlled six months after infection. All of the patients who were not well controlled before COVID-19 were well controlled at the final assessment (p=0.012) (Table III).

Evaluation of the patients' characteristics six months before and after COVID-19

Regular asthma maintenance treatment was more frequent in the six months following COVID-19 infection than in the six months preceding it (p=<0.001). There were no significant differences in terms of hospitalization due to asthma, asthma attacks, or receiving systemic steroid treatment between the groups (Table IV).

Table III: Evaluating the GINA assesment of patients at 1st, 6th and at last assesment

GINA assesment	After 1 month of COVID *Well controlled n(%)	After 1 month of COVID *Not well-controlled n(%)	Total n(%)	p	After 6 month of COVID *Well controlled n (%)	After 6 month of COVID *Not well-controlled n (%)	Total n (%)	p	At phone call at last follow-up of COVID *Well controlled n(%)	At phone call at last follow-up of COVID * Not well-controlled n(%)	Total n(%)	p
Before COVID diagnosis *Well-controlled n(%)	49 (71)	20 (29)	69	0.150***	58 (84.1)	11 (15.9)	69	0.557***	65 (94.2)	4 (5.8)	69	0.012***
Before COVID diagnosis *Not well controlled n(%)	11(68.8)	5 (31.3)	16	0.150***	15 (93.8)	1 (6.1)	16	0.557***	16 (100)	0 (0)	16	0.012***
Total, n(%)	60 (70.6)	25 (29.4)	85	0.150***	73 (85.9)	12 (14.1)	85	0.557***	81 (95.3)	4 (4.7)	85	0.012***

***McNemar test*

Table IV: Comparison of characteristics of patients 6 months before and after the diagnosis of COVID-19

	6 month before COVID-19	6 month After COVID-19	p
Having hospitalization due to asthma, n(%)	12 (14.1)	13 (15.3)	0.585*
Having asthma attack, n(%)	8 (9.4)	14 (16.3)	0.494
Having systemic steroid treatment, n(%)	3 (3.5)	1 (1.2)	0.964*
Patients taking asthma maintenance theraphy regularly everyday, n(%)	41 (48.2)	46 (54.1)	<0.001

*Chi-square test, *Fisher test*

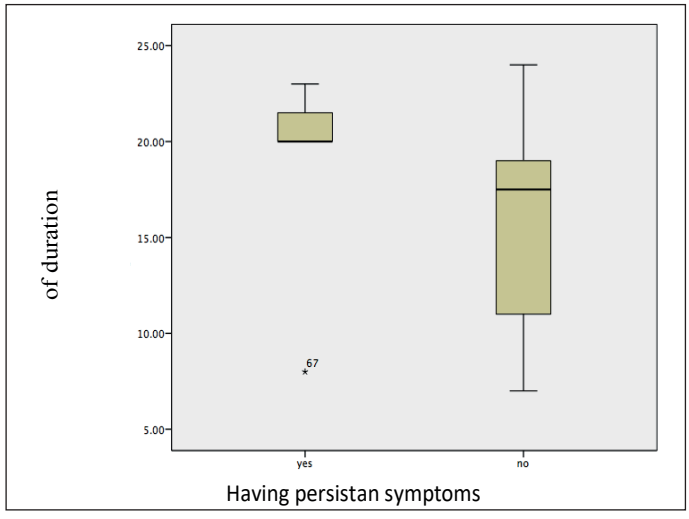

Figure 1: Evaluation of persistent symptoms in terms of time between time of assessment and diagnosis of COVID-19

DISCUSSION

In our study, 85 pediatric COVID-19 patients with asthma were evaluated for persistent symptoms after COVID-19 infection. The mean symptom duration was 4.1 months. Twenty (23.5%) of the patients were observed to have persistent symptoms at the sixth month of COVID-19 recovery. The most common symptom was cough and dyspnea. The frequency of well-controlled asthma did not differ before and one month after infection.

Fatigue, dyspnea, cough, and chest pain have been observed to persist two to six months after COVID-19 infection (13-15). Although it is well known that many patients have persistent symptoms after COVID-19 infection, data on symptom prolongation and asthma control after COVID-19 infection among asthmatic patients are scarce. As far as we could find, Dobkin et al. (15) conducted the only relevant study on children with asthma. They evaluated 29 pediatric patients, 11 of whom were asthmatic, 1.3–6.7 months after post-acute COVID-19 infection (15). Dyspnea, cough, and exercise intolerance were observed in 96.6%, 51.7%, and 48.3% of the patients respectively (16). In our study, 31 (36.5%) patients had persistent symptoms one month after infection, 20 (23.5%) had symptoms six months after infection.

Pet ownership and stress have been found to be higher during the COVID-19 pandemic (16,17). In our study, the numbers of patients who adopted a new pet and experienced stress were significantly higher in the group with symptoms one month after COVID-19 infection. Psychological effects can worsen asthma, and thus life stresses added to pandemic- related stress could negatively affect asthma. The number of patients experiencing additional stress in this study was limited, but individuals with additional stressors and pet owners should be monitored more closely.

COVID-19-related coughing may result from involvement of vagal sensory neurons and/or a neuro-inflammatory response to SARS-CoV-2, resulting in peripheral and central hypersensitivity

of the cough pathways. It is hypothesized that post-COVID syndrome results from a neuro-inflammatory response that affects various regions of the brain, causing chronic fatigue, pain, shortness of breath, and cough (18). A few studies have observed an association between mast cell activation syndrome and the resultant cytokine storm in long COVID. The organ damage caused by such excessive inflammatory response takes much longer to heal and is responsible for the symptoms of long COVID (14,19). The respiratory symptoms of children with asthma after infection may also be exacerbated by the infection.

In a meta-analysis of pediatric patients conducted by Yang et al. (20) , the level of asthma control according to ACT was observed to be significantly improved after COVID-19 infection. Further, a systematic review found increased therapeutic compliance of pediatric asthma patients during the COVID-19 pandemic (21). In our study, the number of well-controlled patients (according to GINA assessment) was observed to be significantly higher at the last follow-up than before COVID-19 infection. Further, regular asthma maintenance treatment was more frequent in the six months following COVID-19 infection than in the six months preceding it. This is likely due to the fact that patients tend to take their medications more regularly during the pandemic because they fear developing a more severe infection as a result of their chronic illness. It is thought that the increased use of masks by these patients and the decreased frequency of exacerbations due to the decrease in viral infections related to compliance with social isolation rules also contribute to the improvement of the control conditions. In our study, while there was no statistically significant difference one month after COVID-19 infection, the status of one-third of the patients changed from well controlled to not

well controlled. Although most children with asthma appear to tolerate COVID-19 infection well in terms of asthma control, this one-third must be considered, and it is crucial to monitor children with asthma closely following COVID-19 infection. This may be due to the long-term effects of COVID-19. More studies are needed on this subject.

The main limitation of this study is that it was a retrospective study. This may have caused errors due to patients' memory. However, during the pandemic, patients were reluctant to come to the hospital for follow-up. Other infections that patients may have had during this period and the symptoms that develop due to these may be confused with post-COVID period symptoms are also the limiting factor of our study. Since there is a limited data on this subject in the literature, our study will contribute to the literature.

CONCLUSIONS

Physicians must be aware of the long-term effects of COVID-19. This study shows that respiratory symptoms may persist for pediatric patients following COVID-19 infection, and one-third of children with asthma may lose control of their asthma. However, with close follow-up these patients can achieve better GINA control than before COVID-19 infection due to improved adherence to their asthma maintenance therapy. Further studies are needed to establish the prognosis of COVID-19 in pediatric asthma patients.

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