

How asthmatic children dealt with the coronavirus pandemic? Adherence to Controller Medications and Level of Control among Children with Asthma Registered in Mashhad University of Medical Sciences

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Abstract

Background: Coronavirus disease 2019 pandemic had a great effect on the lives of asthmatic children. In this study we assessed changes in medication adherence and asthma control rate among our registered children with pediatric asthma.

Methods: This cross-sectional study was conducted on 113 patients registered in our asthma and allergy clinic in Mashhad, Iran. We called them via phone and completed a questionnaire on the level of asthma medication adherence and the asthma control test (ACT) before and in the 6 months after COVID-19 emergence. We investigated the changes in medication adherence and asthma control due to COVID-19 pandemic.

Results: A total of 113 asthmatic children in the age range of 1 to 15 (mean, 7.02±3.24 years) were included in the study. There were zero confirmed positive cases among them since COVID-19 introduction. The minority of patients (8.8%) had weak adherence, most of the children (35.4%) completed one course of prescribed medications, 33% had longer adherence, and only 25 patients (22.1%) had full adherence during the pandemic. Overall, our patients experienced better asthma control with a 1.51 rise in ACT score to arrive in 23.64 points out of 25. They had no asthma exacerbation and emergency visit. Over half of the families compiled the national preventive measures; as 85% of children had followed the stay-at-home order during the first peak of the pandemic.

Conclusion: Our patients managed to come to a higher asthma control level despite their generally decreased adherence to medications during the pandemic. COVID-19 not only could not worsen asthma status in our children but surprisingly improved it. This shows that the preventive measures should be strongly applied for the asthmatic population.

Key Words: Asthma control, COVID-19, Medication adherence, Pediatric asthma.

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1- INTRODUCTION

The 2019 widespread respiratory infection presented disastrous for patients with impaired respiratory function. Coronavirus disease 2019 (COVID-19) pandemic, especially in its first months, put asthmatic children and their parents at great anxiety. The Centers for Disease Control and Prevention (CDC) identified asthma as the 4th risk factor in SARS-CoV-2 infection (1). Moreover, the World Health Organization and CDC encouraged asthmatic patients not to stop their medications, including inhaled corticosteroids (ICS) (1), (2). On the other hand, some unauthorized popular websites frightened patients to stop ICS for what they called decreasing immunity against coronavirus infection.

In the battle of opposing data in the COVID era, families with asthmatic children were concerned whether asthma or asthma medications make children more prone to coronavirus infection. There was little information regarding the rate of medication adherence among asthmatic children dealing with the pandemic.

In an early study (3), the adherence to preventive medications among an adult population of asthmatics was reported to be increased by about 14.5% two months after COVID-19 emergence. Another study by pediatric asthma providers (4) reported better medication adherence among their large pediatric asthmatic population. A third study in China (5) pointed to high medication compliance among asthmatic children. However, a study in September 2020 indicated that adherence to asthma controller medications decreased and adherence to asthma quick relief medications did not change compared with pre-COVID (6). The literature appears to contain little on the effects of Coronavirus pandemic on the medication adherence of asthmatic

children during the first months of the pandemic.

To help address this gap, we assessed adherence in our patients on telemedicine calls. Once asthma and allergy clinics were closed down to decrease exposure of asthmatic children to the virus, we programmed a tele-interview via phone with our registered families. We called the parents and assessed the level of adherence to medications in addition to the grade of asthma severity and control in their children. We also advised them to maintain prescribed medications, especially inhaled corticosteroids, reminded them of the technique of Metered Dose Inhalers (MDIs) utilization, and answered parents' questions. Additionally, occurrence of COVID symptoms in the preceding months was asked.

In this study, we aimed to measure medication adherence and asthma control among asthmatic children registered in MUMS Pediatric Asthma Registry during COVID-19 pandemic.

2- MATERIALS AND METHODS

2-1. Study population

We included all the 119 patients registered in our pediatric asthma program. A checklist was scheduled for adherence to asthma medications, types of medications, causes of nonadherence, current and pre-COVID-19 grade of asthma control by measuring Asthma Control TestTM (ACT) score, COVID symptoms (including fever and chills, cough, dyspnea, sore throat, rhinorrhea, loss of smell or taste, headache, myalgia, exhaustion, gastrointestinal complications, red or dry eye and skin rash) with characterization of each, COVID infection in the family or near relatives, history of contact with infected people, being tested for COVID-19, compliance with national infection

prevention measures such as wearing facial masks, social distancing, and staying at home, and finally influenza vaccination in 2019 before COVID emergence.

One hundred and thirteen parents answered the call and were included in the study; of which 110 ones were glad of the telemedicine plan and fulfilled the checklist. However, 3 families refused to answer completely. Mean age of the patients was 7.02 ± 3.24 years; 40 of them were females and 73 males.

2-2. Study Variables

The core variables of our study are the level of medication adherence and the grade of asthma control among the registered asthmatic children during COVID-19 pandemic. Other variables include patients' gender and age groups, the level of medication adherence before COVID-19 pandemic, the causes of non-adherence to medications, and the relation between COVID-19 symptoms and any prescription adherence before and during the pandemic, the level of obeying preventive measures, influenza vaccination last year, and finally the parents' certification and job. The data was managed using the Excel software (Windows Corp. 2017).

2-3. Statistical Analysis

Kolmogorov-Smirnov test was used for assessing the normality of the distribution of the numerical parameters. We used the Kruskal-Wallis test to check for significance between adherences to treatment during COVID-19 pandemic and ACT score at this time. The significance of relations among different parameters of the checklist was calculated by the Chi-Square test. With Spearman's Correlation test, we assessed the correlation between numerical parameters.

Mann-Whitney test was also used to compare the numerical and scalar parameters. The statistical analyses were

performed by SPSS (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY). Differences were considered statistically significant at $p < .05$.

2-4. Outcomes

The primary outcome of interest in the present study was medication adherence of asthmatic children during the corona virus disease 2019 pandemic. Secondary outcomes were the effect of the pandemic on disease control, the rate and severity of COVID-19 infection among the pediatric asthmatics, the quality of infection prevention care, and the association between better adherence and personal factors; e.g., the educational level of the patients' parents.

3- RESULTS

A total of 113 children with pediatric asthma, aged 1 to 15 years old (mean, 7.02 ± 3.24 years), were included in the study; of which 40 (35.4%) were females and 73 (64.6%) males. The patients were 0.9% <1y, 6.2% 1-2y, 7.1% 2-3y, 23.9% 3-5y, and 61.9% >5 years old. Most of them (68.8%) lived in Mashhad city, Iran.

Duration of medication adherence after the last clinical visit varied considerably. The minority of patients (8.8%) had weak adherence, among whom 2.7% had not used at all and 6.2% had just used some days. Most children (35.4%) completed one course of prescribed medications (one-month adherence). Others who had stronger adherence more than 1 month comprised 33% of the population. Finally, 25 patients (22.1%) had full adherence later on during the COVID-19 pandemic.

The causes of incomplete adherence of 88 patients were asked. At most, 65% of non-adherence was because of removal of persistent symptoms. Running out of drugs and loss of access to clinical visits was the second cause by 19%. Others were personal refusal, asthma symptoms only during cold or flu, and not finding the

prescription anymore (11%, 5%, and 2%; respectively).

We used the Asthma Control Test™ (ACT) scoring to measure asthma control (Copyright 2002, by QualityMetric Incorporated). In the preceding month before COVID-19 introduction in Iran, the mean ACT score of the patients was

22.13±4.20 out of 25, meaning overall well-controlled asthma. Five months later, during the pandemic in June 2020, the mean ACT score increased by 1.51 to arrive at 23.64±2.60. The control rate was not significantly associated with better medication adherence among patients (p=0.33).

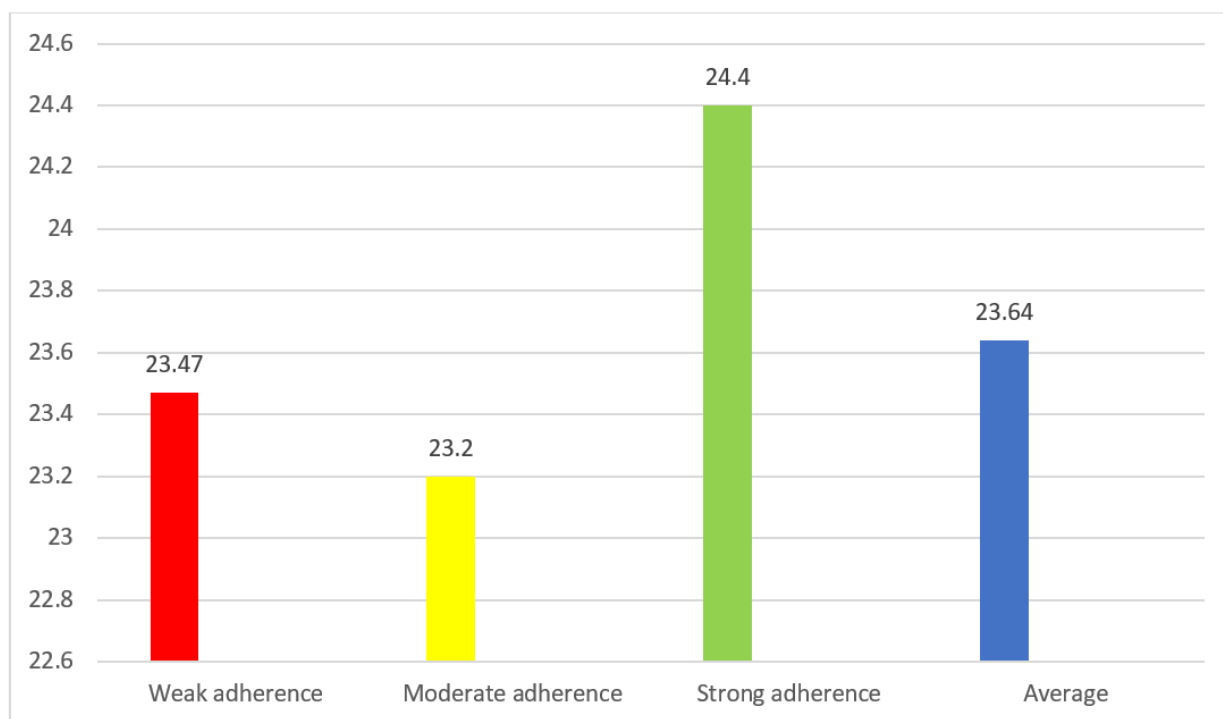


Fig. 1: Asthma Control Test® score in asthmatic children with weak, moderate, and strong medication adherence in the first 6 months of COVID-19 pandemic and their average score

Weak adherence is defined as ≤1 month asthma controller drug use, moderate adherence as 1 to 5 months drug use, and strong adherence as full-time drug use during the studied period.

Overall compliance with national preventive measures during the pandemic was favorable. The majority of children (85%) had followed the national stay at home order during the first peak of the pandemic. More than half of parents (56.6%) reported wearing masks by their children anywhere outside home. Most families never or hardly ever (69%) took their children outside home. Children had no contact with SARS-CoV-2 infected people; even in the 3 families of which one

parent had contracted COVID-19. Twenty-three children had been vaccinated for influenza in the last year.

None of the patients had a positive COVID-19 laboratory test. However, assessment of COVID-19 symptoms revealed probable viral infection in at least 18 children during the pandemic. The most prevalent symptom was cough (32.7%). Most parents of these patients (87.9%) reported it to be less severe than the chronic cough of asthma, 6.1% with the

same severity and 6.1% more severe. Gastrointestinal symptoms were the second most common symptoms (21.2%). Dyspnea, running nose, and skin rash prevalence rates were 17.7% each. Of 20 patients with dyspnea, 18 had previous dyspnea due to asthma. Eighteen children (15.9%) had experienced fever with a mean time of 0.41 days during the COVID-19 pandemic, among whom only 3 had a physician visit to control it. Other symptoms included sore throat, eye disturbance, headache, loss of smell or taste, myalgia, exhaustion, and chills (5.3%, 5.3%, 4.4%, 2.7%, 1.8%, 0.9%, and 0.9%; respectively).

Fever and runny nose in patients were significantly more prevalent with compatible COVID symptoms in the family members ($P = .045$ and $.031$; respectively).

The pandemic prevented 30 families from following up the scheduled physician visits in the asthma and allergy clinic. However; the majority of these parents (66.1%) did not face any need for a clinical visit.

4- DISCUSSION

The overall medication adherence among our registered patients was not appropriate with respect to being in danger of a global respiratory infectious disease. Most of the patients (77.9%) experienced a substantial decline in adherence through the first months of the pandemic and only 22.1% remained adherent until the tele-interview. This finding is inconsistent with the study by Kaye et al. which reports a 14.5% increase in adherence among patients with asthma and COPD in the first 3 months of the pandemic (3). Another study in Majmaah City, Saudi Arabia on 152 asthmatic children shows concordant results as the majority of the patients had poor adherence to asthma controller medication (83.6%) while the remaining minority had good adherence (16.4%) (7). Ullmann et al.'s study on 85 preschool

asthmatics revealed a significant drop in the use of salbutamol and Oral Corticosteroids (OCS) ($p < .0001$) and shows that 95% of patients needed no ICS bursts during the lockdown (8). Furthermore, an urban health network study on medical records of 18,912 pediatric patients with asthma from 2017 to 2020 in California demonstrated significant reductions in albuterol and ICS use ($P < .05$) (9).

Despite the decline in medical adherence, the control rate increased within the COVID-19 pandemic in our study population. To our surprise, five months post-COVID, the mean ACT score increased by 1.51 to arrive in 23.64. It was so that 65% of medication non-adherents reported removal of persistent symptoms as the cause of non-adherence. Other researchers report the same pattern of asthma control during the pandemic. A multicenter survey reported better than expected disease control in 20% (10%-40%) of patients, whereas control was negatively affected in only 10% (7.5%-12.5%) (4). Ferraro et al. report significantly better asthma control in their pediatric asthma population in April and March 2020 compared to the same time in 2019 (10). Furthermore, a questionnaire-based study and an interview-based one reported increased asthma control in a number of asthmatic children (11, 12). In a multinational cohort study on 1,054 children with asthma, 66% percent of asthmatic children had improved asthma control while in 33% the improvement exceeded the minimal clinically important difference (13). Another work on 85 preschool asthmatics revealed higher ACT score post- compared with pre-COVID (mean 25 vs. 23); along with significant reduction in medication adherence (8). Similarly, we did not find a significant relation between better medication adherence and higher asthma control ($p=0.33$). This may be due to allergen protection in children sensitized to outdoor

allergens, e.g., pollens; while not applying to others with indoor allergens, e.g., mites.

The rate of asthma exacerbations mirrors the level of asthma control (14). Our asthmatic children had no emergency department (ED) visits during the studied month of the pandemic. Likely, multiple studies show that asthmatics experienced significantly less ED visits during the pandemic compared with the same time of year before it. Sheehan et al. found that the annual fall spike of asthma ED visits was absent in 2020 in Washington (mean \pm SD, 125 ± 23 vs. 421 ± 29 ED visits/month, $p < .001$) (15). Other researchers studied 10,109 pediatric ED visits due to respiratory causes from 2018 to 2020 in Porto Alegre, Brazil and indicated a 64% decrease in asthma exacerbations in 2020 compared with 2018 and 2019 (16). A survey study in the Netherlands reported that in the summer of 2020, mean exacerbation frequency per asthma patient was significantly lower ($p=0.019$) in comparison to summers in the previous years (17). Guijon et al. in their urban health network study demonstrated 90%, 78%, and 68% reductions in ED visits, hospitalization, and exacerbations, respectively, after comparing post- and pre-COVID-19 2020, with significantly greater changes in comparison to the same time period during 2017 to 2019 (9). The ED in Bronx, which has the highest prevalence of asthma in the United States (US), experienced a 5% decline in asthma visits (2% vs. 7%, $p < 0.0001$) between March-July 2020 and in the same interval in 2019 (18). The PeARL multi-national cohort on 1054 children with asthma and 505 children without asthma indicated that asthmatics had fewer acute events; including upper respiratory tract infections, episodes of pyrexia, asthma attacks, ED visits, and hospital admissions during the pandemic, compared to the preceding year (13). Additionally, Simoneau et al. and Ulrich et al. found a

significant decrease in pediatric asthma ED visits between 2020 lockdown and the same time in 2019 (6, 19). Finally, a forecast modeling to identify the pattern of pediatric ED visits throughout the US based on 2010 through 2019 data detected that asthma ED visits in 2020 occurred below the predicted 95% CI (20).

We assume that the higher asthma control and fewer exacerbations in the COVID era are because of 2 main profits of COVID-19: 1) better respiratory infection protection and 2) lower outdoor allergen exposure; in spite of the decline in medication adherence. These two are due to personal protective measures esp. masks, long periods of staying-home orders, and online schooling of children. Nonetheless, decreased emergency visits does not admittedly show better asthma control; as Sheehan et al., who reported fewer ED visits, also found that the ratios of asthma-related hospitalizations and PICU admissions to ED visits were higher in fall 2020 as compared with the pre pandemic years (15). It represents that the exacerbations tended to be more severe than before, showing that there would have been a fear among asthmatics to go to the ED until they get more ill (15). In contrast, Ulrich et al. suggest that the decline in asthma-related ED utilization involved factors specific to asthma and was not due solely to avoidance of health care facilities because it was greater than the reduction of overall ED use during the same time period (6).

There has been a discussion on asthma as being a risk factor for coronavirus infection or disease severity. An initial study from Wuhan, China on asthmatics among 961 hospitalized COVID-19 patients showed low prevalence of asthma as a comorbidity (2.3%). Asthma was more frequent in non-severe cases than in severe cases (2.9% vs. 0.4%; $p=0.02$) (21). In a study directed in Korea, the prevalence of asthma in 7,590 COVID

patients was only 2.9%, but it is reported to be a significant risk factor for increased mortality ($p < 0.001$). However, it was not a significant factor after adjustment for age, sex, and underlying conditions (OR, 1.317; 95% CI, 0.708–2.451) (22). Despite a substantial prevalence of asthma in Chhiba and Gayatri COVID cohort (14%) among 1,526 patients, asthma was not associated with increased risk of hospitalization (relative risk, 0.96; 95% CI, 0.77–1.19) (23). Two systematic reviews and meta-analyses in August 2020 did not identify asthma as a risk factor for increased COVID mortality, (OR=1.03, 95% CI: 0.55–1.93, $I^2=76\%$, $p=0.92$) (24) and morbidity (OR=0.96; 95% CI 0.70–1.30; $I^2=0\%$; $p=0.79$) (25), respectively. Also, one of them did not find significant relation for COVID severity ($p=0.27$) (24). An original article on 241 asthmatics over 18 years among 1003 COVID patients reported a significantly longer intubation time in asthma patients ($p=0.002$); but there was neither a higher rate of death ($p=0.22$) nor the acute respiratory distress syndrome ($p=10.92$) (26). Yet it was early to conclude the exact impact of coronavirus infection on asthma and vice versa (27).

Later on, in the last season of 2020, a multi-center retrospective study on 502 COVID hospitalized patients with 14.3% asthma prevalence concluded that asthma is neither associated with increased severity nor worse outcomes (28). Another multicenter retrospective work on 71,182 Spanish asthmatics revealed that the 1.41% who contracted COVID-19 were significantly older than others (55 vs. 42 years) (29). Also, the prevalence of COVID was shown to be significantly higher in asthmatic people than that in the general population (0.86%, $P < 0.001$). The article stated that the proportion of inhaled corticosteroid users was lower in hospitalized patients (OR 0.58, 95% CI: 0.44–0.77) (29). At the same time, an editorial article indicated that due to more

recent reports from the United States and from several European countries, asthma is more prevalent among COVID patients than what previously reported in Asia and in the first European surveys (30). In addition, a review article on comorbidities in coronavirus infected children based on reports by health authorities like WHO and CDC introduced asthma as a strong predictor for the development of severe COVID-19, irrespective of age (31).

The beginning of the year 2021 became the checkpoint for established studies on COVID-19 and pediatric asthma. Beken et al. studied 107 coronavirus infected children aged 1 month to 18 years in Turkey and reported an asthma rate of 6.5% among patients (32). They concluded that pediatric asthma does not seem to be a risk factor for COVID-19 hospitalization. A review indicated that asthmatic children show less severe disease manifestations when infected with SARS-CoV-2, compared with adults (33). A single-center study on 38 pediatric COVID inpatients, of which 34.2% were asthmatic, stated that inpatient asthmatics did not have a more severe course and required a lower level of care. Additionally, 41% of their 95 asthma outpatients reported improved asthma control and decreased rescue medication use, with no COVID-19 hospitalizations (34). A study by Philadelphia health system on 979 polymerase chain reactions confirmed that among COVID-19 cases with ≤ 21 years of age, an asthma rate of 21% was observed. However, asthma was negatively associated with COVID-19-related hospitalization (OR: 0.34; 95% confidence interval (CI): 0.16–0.65; $p=0.001$) (35). In contrast, analysis of the data of 454 confirmed pediatric cases in Colorado showed that asthma is among predictors for admission at presentation ($p=0.04$) (36). Another study on 588 children with COVID introduced asthma as a risk factor for more severe outcomes ($p < 0.001$) but not with a higher risk for hospitalization ($p=0.48$) (37). Roland et al.

followed another point of view and showed that SARS-CoV-2 was not playing a role in the annual spike in viral wheeze and asthma admissions in their locality (38). Timberlake et al. compared COVID outcome between children with and without atopy and found no significant difference in ICU admission, 43% versus 44.7% (atopic versus no atopic disease, respectively; $p=0.84$); supplemental oxygen use, 79.1% versus 73.6% ($p=0.36$); intubation rate, 35.8% versus 36.5% ($p=0.92$); and mortality rate, 13.4% versus 20.7% ($p=0.19$) (39).

As mentioned above, there is substantial controversy among different research studies and different localities about asthma being a risk factor for coronavirus infection or severity. Herein, a number of articles are denoted to lower expression of ACE-2, coronavirus entry receptor, in asthmatic and atopic patients and its resultant lower infection rate among them (40, 41).

4-1. Limitations of the study

Our analysis is drawn from a single metropolitan area; there may be different findings in other cities or in rural areas. In addition, the rate of medication adherence is approximate, as many parents reported a rough date of discontinuing prescriptions. Also, lack of SARS-CoV-2 testing in symptomatic children makes infection estimates inaccurate.

5- CONCLUSION

Our asthmatic children experienced a period of surprisingly better asthma control during the COVID-19 pandemic. They upgraded guarding against respiratory infections including COVID-19 through the use of masks, social distancing and online schooling. This shows that the preventive measures are promising in protecting asthmatic children against the current pandemia and must be applied for future ones. However, the fault was the decreased medication adherence observed

among children during the pandemic; a fact that necessitates widespread guidance programs for the asthmatic community in the state of a pandemic. We tried to capture this purpose of education and guidance through the calls with the families, but it is not adequate and mass training programs are needed. We could not find a significant relation between better medication adherence and better asthma control in this setting. Precise surveys are required to clarify this relationship.

Our study does not show that pediatric asthma is a risk factor for COVID-19, at least not a strong risk factor. There is a great controversy on this issue in the literature and research on huge international populations of asthmatics should be conducted to clarify the relationship between asthma and COVID-19.

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7- CONFLICT OF INTEREST

None.

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