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LETTER TO THE EDITOR

WILEY

COVID-19 and childhood asthma: Analysis of a pediatric referral hospital

To the Editor,

Spain has been one of the epicenters of the SARS-CoV-2 pandemic. Children (0–14 years-old) account at least for 10.5% of all cases and usually develop mild severity of coronavirus disease 2019 (COVID-19).[1] Clinical observations point out allergy and/or asthma are not risky conditions in pediatric patients with COVID-19,[2] and hypothetically, allergic sensitization could be inversely related to the expression of COVID-19.[3] However, little is known about the effect of SARS-CoV-2 infection in allergic and/or asthmatic children and adolescents.

This study, approved by the Ethics Committee of Hospital Niño Jesús (Madrid, Spain), aimed to evaluate allergic comorbidities among symptomatic COVID-19 children attended at a referral pediatric hospital for this disease. The database of positive SARS-CoV-2 cases diagnosed based on reverse transcription polymerase chain reaction (RT-PCR) between 20 March and 13 July 2020 was retrospectively reviewed. Demographic information, COVID-19 symptoms, disease severity, clinical course, comorbidities, and blood biomarkers were obtained from electronic medical records. Eosinopenia was defined as absolute eosinophil counts $\leq 0.05 \times 10^9$ cells/L. Information on allergic disorders was obtained by telephone interview with parents and patients, who provided their oral consent to participate. The severity of COVID-19 was established according to Qiu's classification.[4] The criteria used to classify as allergic or asthmatic patients included a specialized physician's diagnosis. A modified questionnaire on allergy and asthma based on a survey from the Asthma Committee of the Spanish Society of Allergy and Clinical Immunology was used.

Qualitative variables are expressed as numbers and percentages, and the Fisher and chi-squared tests were used for comparison. Quantitative variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Normality of age distribution was confirmed using the Shapiro–Wilk test. The Student *T*, ANOVA, and least significant difference (LSD) tests were used as post hoc tests to compare normally distributed variables. The Wilcoxon, Mann–Whitney *U*, and Kruskal–Wallis tests were used to compare nonparametric variables. Statistical significance was set at 95% ($p < .05$).

Ninety-two children were identified as SARS-CoV-2–RT-PCR positive, two declined to participate. Asymptomatic patients were excluded. Fifty patients were diagnosed with symptomatic COVID-19 disease (52% male; mean age: 7 ± 7 years, IQR: 6 months–12 years) and finally enrolled (Figure 1). Regarding the severity, 37(74%) had mild-moderate COVID. The remainder developed a severe disease.

Demographics and clinical features of asthmatic and nonasthmatic children with symptomatic COVID-19 were collected (Table 1). Eight of 50 symptomatic children had asthma with or without RC (Figure 1 and Table 2). Asthmatic patients (8/50; 16%) developed more respiratory symptoms caused by COVID-19 than nonasthmatic patients (42/50; 84%) ($p = .018$). No statistical difference was found for fever, anosmia, ageusia, gastrointestinal or cutaneous symptoms, COVID severity, discharged, hospitalization or PICU admission.

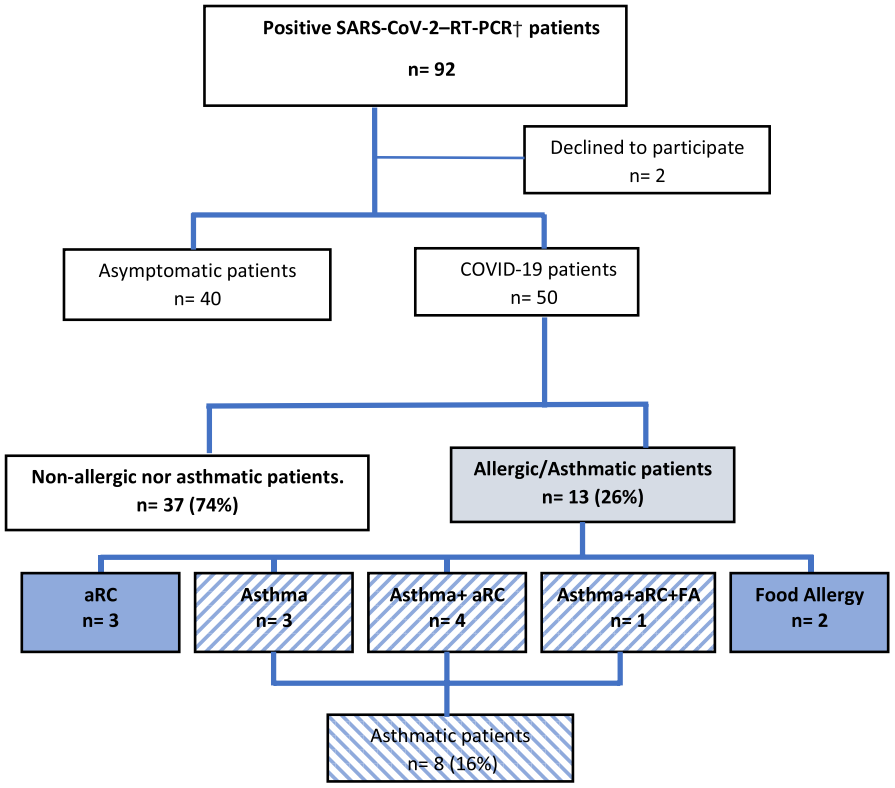
Regarding asthma control based on GINA guidelines, 75% had well-controlled asthma, 25% partially controlled, 37.5% had a mild exacerbation due to COVID-19 disease, and only 37.5% needed to escalate controller treatment (Table 2).

According to supplementary tests, all asthmatic patients had a chest x-ray done and six (75%) had a blood test performed (Tables 1 and 2). No statistical difference was found comparing both groups regarding imaging test. However, laboratory tests demonstrated a significant eosinopenia in the asthmatic group ($p = .014$) as well as comparing the number of eosinophils in each group ($p = .008$). Moreover, the condition of eosinopenia and the total number of eosinophils was related to the severity of the disease (respectively, $p = .005$ and $p = .013$). Showing that in moderate and severe disease, eosinophils were lower than in patients with milder disease (three patients had a blood test analysis done with mild disease: median 960 (IQR: 130–960) cells/μl, 21 patients with moderate disease: median 170 (IQR: 70–320) cells/μl, and 13 patients had severe disease: median 40 (IQR: 25–105) cells/μl). A month later during the follow-up, eosinopenia was recovered in nine (81.8%) patients, and it was significantly higher in the nonasthmatic group ($p = .007$; Table 1).

Regarding evolution, three (37.5%) asthmatic patients remained with exercise-induced asthma; the remainder did not present any immediate sequelae at the time of writing this paper. None of the patients had issues to get access to medication or medical care during the pandemic.

At the current stage of knowledge, children develop less severe symptoms of COVID-19, although the concern about the importance of underlying respiratory diseases, such as asthma, is still widely spread.[2,5,6] Furthermore, it has been studied whether severe asthma should be classified as a risk factor.[5,7–9]

In our study, we found that 16% of the patients were asthmatic. These patients had more respiratory symptoms due to COVID-19



† RT-PCR reverse transcription-polymerase chain reaction
aRC: allergic rhinoconjunctivitis
FA: Food allergy

FIGURE 1 Flowchart of the study. †RT-PCR reverse transcription polymerase chain reaction. aRC, allergic rhinoconjunctivitis; FA, food allergy

disease. Comparing them with nonasthmatic patients, we could not find any other statistical difference regarding other variables, but this may be due to a reduce statistical power. However, the asthmatic group developed more eosinopenia, which was correlated with severity of the disease and also showed that recovery was lower compared to that of the nonasthmatic group.

The prevalence of allergy and asthma in this cohort was 26% higher than that in other series published to date.[2,6,7,10] The age of our population, similar to the studies previously mentioned, might play a part to this issue as normally younger patients have allergic asthma and other allergic comorbidities.

Papadopoulos et al[10] published similar data in a multicenter study in regards of asthma control. However, in their results, 10% of the asthmatic population studied needed to increase their controller treatment.

Our data showed that 76% of the total patients had mild-moderate COVID-19 disease. Similar findings have been published by the studies conducted in children.[2,6,8–11]

To our knowledge, this is the first study reporting comparisons between asthmatic and nonasthmatic pediatric patients with alterations in the chest x-ray. Literature is scarce on this topic as the major study performed in children used CT scan.[6] An Italian group showed 10% of patients with pneumonia, but neither this study nor others specify if these patients were asthmatic.[2,6]

Similar limitations are observed in the analysis of blood eosinophils. Eosinopenia is known to be a severity predictor in COVID-19 disease.[12,13] In our cohort, asthmatic patients developed more eosinopenia and their recovery was lower compared to that of the nonasthmatic group. To date, no other studies have published similar data, and no relationship has access between COVID-19 disease, asthma, and eosinopenia. However, our results are conditioned on the number of participants enrolled, not all were followed before in our center, nor had a recent blood test done, so we could not compare whether this condition was previously ongoing, and it should be taken into account that moderate-severe forms of COVID-19 are more prone to have a blood test done.

Recovery was full in all patients, as other studies have published.[2,6,10,11] Although, 37.5% of our asthmatic patients remained with exercise exacerbated asthma after COVID-19 disease. Pulmonary function tests were not performed afterwards, leading to limited information on the baseline pulmonary capacity in our population. Furthermore, despite being standardized tools, these could not be performed due to the risk of generating aerosols.

Our study has limitations due to its retrospective nature and the age of the participants enrolled, which at the time this study was conducted, little was known about COVID-19 in this age group.

In summary, to our knowledge, this is the first report describing asthma and other allergic comorbidities in children with confirmed COVID-19 disease. In our study, asthma has a low prevalence among COVID-19 pediatric patients with some differences related to their clinical manifestations of their disease and laboratory findings. Nevertheless, more studies are needed to assess the influence of

TABLE 1 Demographics and clinical features of asthmatic and nonasthmatic children with symptomatic COVID-19

COVID−19 +	Asthmatic patients	Nonasthmatic patients	*p*
	8/50 (16%)	42/50 (84%)	
Demographic features			
Mean age (years)	10.9 ± 2.41	6.32 ± 5.77	.001
Sex (male)	6 (75%)	20 (47.6%)	.25
Rhinoconjunctivitis	6 (75%)	3 (7.14%)	<.0001
Food allergy	1 (12.5%)	2 (4.76%)	.414
Allergic sensitization	5 (62.5%)	3 (7.1%)	.001
COVID19 symptoms			
Respiratory symptoms[a]	8 (100%)	23 (54.76%)	.018
Pneumoniae	5 (62.5%)	9 (21.42%)	.215
Fever	6 (75%)	27 (64.28%)	.699
Anosmia	1 (12.5%)	4[b] (13.79%)	>.99
Ageusia	1 (12.5%)	7[b] (24.13%)	.391
Gastrointestinal symptoms	5 (62.5%)	28 (66.67%)	>.99
Cutaneous symptoms	5 (62.5%)	17/(40.47%)	.277
COVID19 severity[c]			.58
Mild	1/(12.5%)	11/(26.2%)	-
Moderate	5 (62.5%)	21/(50%)	-
Severe	2 (25%)	10/(23.8%)	-
Management			
Inpatient	2/(25%)	18/(42.85%)	.45
PICU	3/(37.5%)	11/(26.19%)	.67
Medical discharge	3/(37.5%)	13/(30.95%)	.69
Chest x-ray[d]	*N* = 8	*N* = 21	.215
Abnormal	6 (75%)	9 (42.85%)	-
Laboratory test	*N* = 6	*N* = 31	
Eosinopenia (≤0.05 × 10^9 cells/L)	5 (83.33%)	8 (25.80%)	.014
Total number of eosinophils cells/μl (median)	10 (IQR:0–88)	130 (IQR: 40–310)	.008
Recovery of the total number of eosinophils (median)	90 (IQR: 40–90)	140 (IQR: 60–225)	.007

Abbreviations: IQR, interquartile range; PICU, pediatric intensive care unit; SD, standard deviation.

[a]Respiratory symptoms included dyspnea, cough, shortness of breath, and thoracic pain.

[b]Anosmia and Ageusia were only measured in 29 nonasthmatic patients.

[c]From reference 4, Qiu C, et al. Qiu classification for COVID-19 grade of severity: mild (low fever, mild cough, slight fatigue, and no evidence of pneumonia on imaging), moderate (fever and respiratory symptoms and evidence of pneumonia on imaging), severe (dyspnea, tachypnea, desaturation or radiologic worsening over 24–48 h) and critical (respiratory failure, septic shock, and/or multiple organ dysfunction).

[d]Chest x-ray description made by a radiologist. Abnormalities: 5 pneumonia and 1 indeterminate (doubtful diffuse infiltrates).

TABLE 2 Clinical characteristics of asthmatic children with COVID-19 in a referral hospital

	Case 1	Case 2	Case 3
Age (years)	12	12	10
Sex	Male	Male	Male
Allergy and asthma history			
Rhino conjunctivitis	No	Yes	Yes
Food allergy	No	No	No
Allergic sensitization	No	No	Pollen
Maintenance treatment	No	Antileukotriene and ICS+LABA	INS and ICS
PRN treatment	SABA	Ocular and oral antihistamine and SABA	Oral antihistamine and SABA
Rescue treatment for asthma exacerbations not related to COVID−19	No	No	No
Asthma management during COVID−19 pandemic			
Exacerbations	Yes	Yes	Yes
Rescue treatment	SABA PRN 7 days +ICS 7 days	SABA PRN 4 days	SABA PRN 7 days
Personal perception (2020 vs. 2019)	Worse	Worse	Same
Symptoms of COVID−19 disease			
Respiratory[a]	Cough	Pneumonia	Shortness of breath and thoracic pain
Gastrointestinal	Abdominal pain	No	No
Cutaneous	No	No	No
Fever	No	Yes	No
Anosmia	No	No	No
Ageusia	No	No	No
Grade of severity[b]	Mild	Moderate	Moderate
Hospitalization and treatment used			
Management	Home	Inpatient	Home
N° of days of hospitalization	N/A	3	N/A
Oxygen therapy	N/A	Yes	N/A
Radiology findings[c]	Normal	Unilateral pneumonia	Indeterminate (doubtful diffuse infiltrates)
Laboratory Findings	Not performed	Lymphopenia Eosinopenia Elevated D dimer Elevated LDH PCR not done	Not performed
Problems related to asthma disease due to COVID−19	Asthma exacerbation	Asthma exacerbation	Asthma exacerbation
Severity of asthma exacerbation based on GINA	Mild	Mild	Mild
Treatment after discharge	ICS 1 week +SABA 7 days PRN	Continue its maintenance treatment +SABA 4 days PRN	Continue its maintenance treatment SABA 7 days PRN
Recovery	Complete	Complete	Complete
Personal problems			
Of health care during the pandemic (not related to underlying allergic disease)	No	No	No
Respiratory sequelae after recovery	Not affected	Not affected	Exercise exacerbated asthma

Abbreviations: ICS, inhaled corticosteroids; INS, intranasal steroids; IQR, interquartile range; LABA, long-acting beta agonist; N/A, non applicable; PICU, pediatric intensive care unit; PRN, pro re nata (treatment as needed); SABA, short-acting beta agonist; SCIT, subcutaneous immunotherapy; SD, standard deviation.

[a]Respiratory symptoms included dyspnea, cough, shortness of breath, and thoracic pain.

[b]From reference 4 Qiu C, et al.

[c]Chest x-ray description made by a radiologist.

Case 4	Case 5	Case 6	Case 7	Case 8
15	12	7	10	9
Female	Male	Female	Male	Male
Yes	Yes	No	Yes	Yes
No	No	No	No	Yes
Pollen	Pollen	No	Pollen	Pollen, Nuts tree, legumes, fruit, and fish.
No	SCIT	Antileukotriene	No	No
Oral antihistamine and SABA	Oral antihistamine and SABA	SABA	Oral antihistamine and SABA	Oral antihistamine and SABA
SABA during 5 days in spring	No	No	SABA during 4–5 days in spring	No
No	No	No	No	No
No	No	No	No	No
Worse	Same	Same	Better	Better
Cough and shortness of breath	Pneumonia	Pneumonia	Pneumonia	Pneumonia
No	Vomiting and diarrhea	Vomiting and abdominal pain	Vomiting	Vomiting
Rash in upper extremities	Local rash perianal and knees	Perniosis	Generalized rash	Generalized rash
Yes	Yes	Yes	Yes	Yes
No	No	No	No	Yes
No	No	No	No	Yes
Moderate	Severe	Moderate	Severe	Moderate
Home	PICU	PICU	PICU	Inpatient
N/A	23	11	2	9
N/A	Yes	Yes	Yes	Yes
Normal	Bilateral pneumonia	Bilateral pneumonia	Unilateral pneumonia	Bilateral pneumonia
Normal	Lymphopenia Eosinopenia Elevated D dimer Elevated LDH Elevated PCR	Lymphopenia Eosinopenia Elevated D dimer Elevated LDH Elevated PCR	Eosinopenia Elevated LDH	Lymphopenia Eosinopenia Elevated D dimer Elevated LDH Normal PCR
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No
Complete	Complete	Complete	Complete	Complete
No	No	No	No	No
Not affected	Not affected	Not affected	Exercise exacerbate asthma	Exercise exacerbate asthma

asthma and allergy in COVID-19 disease due to the low number of patients included in all series.

KEYWORDS

allergy, asthma, children, COVID-19, pediatric population

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CONFLICT OF INTEREST

All authors declare no conflict on interests related to this manuscript.

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AUTHOR CONTRIBUTION

Irene Bartha: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing – original draft (lead); Writing – review & editing (lead). **Marta Bernaola:** Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Project administration (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing – original draft (lead); Writing – review & editing (lead). **Carmelo Escudero:** Conceptualization (supporting); Data curation (equal); Formal analysis (supporting); Investigation (supporting); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Pablo Rodriguez del Rio:** Conceptualization (supporting). **Raphaëlle Bazire:** Conceptualization (supporting). **Maria Dolores Ibañez:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (lead); Supervision (lead); Validation (lead); Writing – original draft (equal); Writing – review & editing (lead).

PEER REVIEW

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