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Early View

Research letter

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Is asthma a risk factor for COVID-19? Are phenotypes important?

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Dear Editor,

Asthma is a major health problem all over the world (1). Since SARS-COV-2 is a respiratory pathogen, it is important to quantify the risk that the current COVID-19 pandemic may represent for asthma patients.

Relatively few data are available on the relationship between SARS-COV-2 and patients with bronchial asthma. The first published studies from China suggested that asthma was not a risk factor for severe SARS-COV-2 disease. Indeed, a study carried out in a cohort of 140 patients with COVID-19 found no infected asthma patients (2), and in a larger study of 1,099 hospitalized patients, asthma was not identified as a risk factor (3). Data from Korea also indicate that asthma is not a relevant comorbidity (4). However, the first study of critically ill patients in the United States found that five out of 24 patients with severe COVID-19 requiring ICU admission were asthmatic (5) and a recent report for 393 patients admitted in a quaternary referral center in New York, establish a prevalence of asthma in this population of 12% (6).

In this climate of uncertainty, the aim of the study was to estimate the prevalence of asthma in patients hospitalized with severe pneumonia due to SARS-COV-2, in a region where the prevalence of asthma is around 6% (7). In the study, a cross-sectional analysis was performed of all the patients admitted with SARS-COV-2 infection confirmed by PCR to an asthma reference center in a hospital serving a population of 500,000 inhabitants, from March 1 to June 30. Age, sex, asthma status and the presence of comorbidities were recorded from the electronic medical records. In patients with asthma, data on the phenotype, severity and treatment received were also compiled. The severity of COVID-19 was recorded based on the needs of oxygen and ventilatory support and the chest x-ray findings. Disease was defined as severe if the patient needed FiO_2 <40%, very severe if they needed FiO_2> 40%, and critical if they needed ventilatory support. The patients were divided into two groups: T2 (with the subgroups T2-Th2 and T2-ILC2) and Non-T2 (Table 1). Patients were considered to have a T2-Th2 phenotype if, according to clinical history, they were allergic, a T2-ILC2 phenotype if they were not allergic and if an absolute eosinophil count of more than 300 cells per cubic millimeter

were found in peripheral blood, and a non-T2 phenotype if the above criteria were not met. Patients with elevated IgE and a positive prick test or specific IgE to some of the usual pneumoallergens were considered to be allergic. The study was approved by the local Ethics Committee and all the subjects included gave informed consent prior to participation (PR(AG)222/2020).

Until June 30, 2226 patients with SARS-COV-2 pneumonia were admitted to our center. Of these, 71 (3.2%) were asthmatic according to clinical history (Table 1). Of these 71 patients, in 42 (59%) patients the phenotype was non-T2, while 20 (28%) were allergic (T2-Th2) and 9 (13%) eosinophilic (T2-ILC2). Nineteen patients (27%) had mild asthma, 29 (41%) moderate, and 23 (32%) severe, according to the need for medication to achieve control of the disease. Eight patients (11%) were not receiving any regular treatment; 52 (73%) patients were taking inhaled corticosteroids (six as monotherapy). No correlation was observed between the dose of inhaled corticosteroids and COVID-19 severity. Chest x-ray indicated multilobar pneumonia in 45 (63%) patients, unilobar in 14 (20%) and diffuse interstitial involvement in nine (13%). Eighteen patients (25%) did not require oxygen therapy during admission. In 39 (55%) patients, the level of FiO_2 required was below 40%, and 14 (20%) patients presented a very severe or critical infection (ten were admitted to the Intensive Care Unit). In patients with a Non-T2 phenotype, a greater severity of COVID-19 disease is observed ($p = 0.018$). In 17 (24%) patients asthma was the sole chronic disease (11 presented a non-T2 and 6 a T2-Th2 phenotypes). In the 54 (76%) patients who presented a comorbidity, the most frequent was hypertension in 35 patients, followed by obesity (BMI> 30) (n = 23), cardiomyopathy (n = 19) and diabetes (n = 16). In the group of patients without comorbidity; asthma was mild in 7 patients, moderate in 6 and severe in 4 patients. Evolution was satisfactory in all 17 patients. In fact, in the total population, the evolution with standard treatment was good in 67 (94%) patients, while four died.

Our results support the idea that asthma does not appear to be a risk factor for the development of COVID-19, at least in hospitalized patients with more serious forms of infection. The question arises as to whether it might even be a protective factor. In the present study we found that only 3.2 % of hospitalized patients with severe disease had asthma – a prevalence lower than that in

the general population in our setting, which is around 6% (6). If we also bear in mind that 54 (76%) of the 71 affected patients had comorbidities which have been shown to be directly related to the involvement of SARS-COV-2 (8). The prevalence of asthmatics without other alterations suffering from severe disease falls to only 0.8%, a rate similar to that reported by 0.9% by LI et al in Wuhan, where the prevalence of asthma is also 6% (8).

The explanation for this finding is not clear. Some authors have suggested that inhaled corticosteroid treatment may protect these patients from the disease, or may reduce the severity (9). In favor of this hypothesis is the *in vitro* finding that inhaled corticosteroids alone or in combination with bronchodilators can suppress the replication of the coronavirus and decrease the production of cytokines (10). However, it is striking that in the present study we did not find a relationship between the dose of inhaled corticosteroids and the severity of COVID-19.

The T2 response is basically characterized by eosinophilic inflammation (7). The presence of activated eosinophils may protect individuals from infection by this virus, in a similar way to that already described for other viruses (11), although a relationship between the level of eosinophils and the possible protection against the virus has not been found in the present study. Another possible explanation is the interrelation between asthma and the renin-angiotensin system. Activation of the ACE2 receptor, the gateway for the virus into cells, regulates the asthmatic response in a rat asthma model (12). One might speculate that the reduced activity of this receptor that favors the development of asthma might also prevent the expression of the virus. In this sense, it has been documented that atopic asthmatics have a decreased expression of ACE2 levels (13) and this process may be mediated by IL-13 (14). In fact, in the present study, we have observed a less severity of COVID-19 disease in patients with a T2 phenotype. It may seem counter-intuitive that, although excessive T2 inflammation is known to facilitate viral exacerbations of asthma (15), in these patients it is a protective element and that the presence of a cellular environment in which there is a T2 response with an increased presence of cytokines in the Th2 pathway may protect against SARS-COV-2 infection. Therefore, the results of the present study suggest that SARS-COV-2, like SARS or MERS but unlike other coronaviruses (16), has not been found to exacerbate asthma.

Although the present study has inherent limitations due to its design, the results suggest that asthma could be a protective factor against infection by the SARS-COV-2 virus, especially in asthmatic patients with a T2 phenotype. If they are reproduced in studies with larger numbers of patients, they may open up a new avenue of research in the fight against SARS-COV-2.

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Table 1: Characteristics of asthmatic patients admitted since the onset of the COVID-19 pandemic until June 30.

	Asthma phenotype		
	T2 n = 29	**Non-T2 n = 42**	**p**
Age, yrs, median (range)	56 (15 - 85)	63 (28 - 93)	0.258
Gender, Male (%)	9 (31)	18 (43)	0.313
Smoking habit, n (%)			
Smoker	2 (7)	2 (5)	
Non-smoker	20 (69)	32 (76)	0.790
Ex-smoker	7 (24)	8 (19)	
BMI, median (range)	30 (15 - 38)	29 (16 - 43)	0.839
Comorbidities, n (%)			
No comorbidities	6 (21)	11 (26)	
AHT	15 (52)	20 (48)	
Cardiomyopathy	6 (21)	13 (31)	
Diabetes	6 (21)	10 (24)	
Obesity	10 (34)	13 (31)	0.632
Nephropathy	1 (3)	5 (12)	
Cancer	2 (7)	2 (5)	
Other pneumopathy	3 (10)	4 (9)	
Other	7 (24)	7 (17)	
Atopy, n (%)	20 (69)	0	**0.0001**
Asthma severity, n (%)			
Mild persistent	8 (28)	11 (26)	
Moderate persistent	11 (38)	18 (43)	0.990
Severe persistent	10 (34)	13 (31)	
Blood eosinophils, median (range)	300 (0 - 1400)	100 (0 -200)	**0.0001**
IgE levels, kU/L, median (range)	160 (10 - 1299)	36 (10 – 269)	**0.001**
FEV1 % predicted, median (range)	81 (58 – 133)	72 (35 – 112)	0.129
Asthma medication, n (%)			
No treatment	3 (10)	5 (12)	
SABA	5 (17)	1 (2)	
IC	1 (3)	5 (12)	
IC + LABA	17 (59)	29 (69)	
Oral corticoesteroids	0	1 (2)	
Antileukotrienes,	3 (10)	4 (9)	0.875
Antihistamines,	3 (10)	0	
Anti-IgE	1 (3)	0	
Anti-IL5	0	0	
Others	0	0	
IC µg / 24 h, median (range)	800 (320 – 1600)	800 (200 – 1600)	0.961
COVID-19 severity, n (%)			
Mild	13 (45)	5 (12)	
Severe	10 (35)	29 (69)	**0.018**

Very severe Critical	1 (3) 5 (17)	3 (7) 5 (12)	
Radiology pattern, n (%) Without alteration Unilobar pneumonia Multilobar pneumonia Diffuse interstitial disease	 1 (3) 7 (24) 18 (62) 3 (11)	 2 (5) 7 (17) 27 (64) 6 (14)	 0.854
Follow-up, death, n (%)	2 (7)	2 (5)	0.762

AHT: arterial hypertension; BMI: Body mass index; IC: Inhaled corticosteroid; SABA: Short-acting β2-agonist LABA: Long-acting β2-agonist; FEV1: forced expiratory volume in one-second. Dose of corticosteroids expressed as budesonide equivalent.

Comparison of the demographic and clinical variables was performed using the Fisher exact test for qualitative variables and Mann-Whitney U test for continuous variables. Spearman's rank correlation test was applied to determine correlations between the various parameters studied.

COVID-19 severity: Severe: FiO2 < 40%; Very severe: FiO2 >40%; Critical: need for ventilatory support.