ORIGINAL RESEARCH LETTER

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

To the Editor:

Asthma is a major health problem all over the world [1]. Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory pathogen, it is important to quantify the risk that the current coronavirus disease 2019 (COVID-19) pandemic may represent for patients with asthma.

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 1099 hospitalised patients, asthma was not identified as a risk factor [3]. Data from the Republic of 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 intensive care unit admission were asthmatic [5], and a recent report for 393 patients admitted in a quaternary referral centre 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 hospitalised 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 for all patients admitted with SARS-CoV-2 infection confirmed by PCR to an asthma reference centre in a hospital serving a population of 500 000 inhabitants, from 1 March to 30 June 2020. 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 radiograph findings. Disease was defined as severe if the patient needed inspiratory oxygen fraction (F_{IO_2}) <40%, very severe if they needed F_{IO_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 >300 cells·mm^{-3} was recorded 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 subjects gave informed consent prior to participation (PR(AG)222/2020).

Up to June 30, 2020, 2226 patients with SARS-CoV-2 pneumonia were admitted to our centre. Of these, 71 (3.2%) were asthmatic according to clinical history (table 1), 42 (59%) of whom had the non-T2 phenotype, while 20 (28%) were allergic (T2-Th2) and nine (13%) eosinophilic (T2-ILC2). Nineteen patients (27%) had mild asthma, 29 (41%) moderate asthma and 23 (32%) severe asthma, 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 radiograph 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%)

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These results reaffirm the idea that asthma does not appear to be a risk factor for the development of #COVID19. However, most of the asthma patients in this study had a non-T2 phenotype. https://bit.ly/38hIp18

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TABLE 1 Characteristics of asthmatic patients admitted since the onset of the coronavirus disease 2019 (COVID-19) pandemic until 30 June 2020

	Asthma phenotype		p-value
	T2	Non-T2	
Subjects n	29	42	
Age years	56 (15–85)	63 (28–93)	0.258
Male sex	9 (31)	18 (43)	0.313
Smoking habit			
Smoker	2 (7)	2 (5)	
Nonsmoker	20 (69)	32 (76)	0.790
Ex-smoker	7 (24)	8 (19)	
BMI kg·m^{-2}	30 (15–38)	29 (16–43)	0.839
Comorbidities			
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	20 (69)	0	**0.0001**
Asthma severity			
Mild persistent	8 (28)	11 (26)	
Moderate persistent	11 (38)	18 (43)	0.990
Severe persistent	10 (34)	13 (31)	
Blood eosinophils per mm^3	300 (0–1400)	100 (0–200)	**0.0001**
IgE levels kU·L^{-1}	160 (10–1299)	36 (10–269)	**0.001**
FEV_1 % predicted	81 (58–133)	72 (35–112)	0.129
Asthma medication			
No treatment	3 (10)	5 (12)	
SABA	5 (17)	1 (2)	
IC	1 (3)	5 (12)	
IC+LABA	17 (59)	29 (69)	
Oral corticosteroids	0	1 (2)	
Antileukotrienes	3 (10)	4 (9)	0.875
Antihistamines	3 (10)	0	
Anti-IgE	1 (3)	0	
Anti-IL-5	0	0	
Others	0	0	
IC µg per 24 h	800 (320–1600)	800 (200–1600)	0.961
COVID-19 severity			
Mild	13 (45)	5 (12)	
Severe	10 (35)	29 (69)	**0.018**
Very severe	1 (3)	3 (7)	
Critical	5 (17)	5 (12)	
Radiology pattern			
Without alteration	1 (3)	2 (5)	
Unilobar pneumonia	7 (24)	7 (17)	0.854
Multilobar pneumonia	18 (62)	27 (64)	
Diffuse interstitial disease	3 (11)	6 (14)	
Follow-up, death	2 (7)	2 (5)	0.762

Data are presented as median (range) or n (%), unless otherwise stated. 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, inspiratory oxygen fraction (F_{IO_2}) <40%; very severe, F_{IO_2} >40%; critical, need for ventilatory support. Dose of corticosteroids expressed as budesonide equivalent. T2: type 2; BMI: body mass index; AHT: arterial hypertension; FEV_1: forced expiratory volume in 1 s; SABA: short-acting β_2-agonist; IC: inhaled corticosteroid; LABA: long-acting β_2-agonist; IL: interleukin. Bold indicates statistical significance.

patients, the level of F_{IO_2} required was below 40%, and 14 (20%) patients presented with a very severe or critical infection (10 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 with a non-T2 and six a T2-Th2 phenotype). In the 54 (76%) patients who presented with a comorbidity, the most frequent was hypertension in 35 patients, followed by obesity (body mass index >30) (n=23), cardiomyopathy (n=19) and diabetes (n=16). In the group of patients without comorbidity, asthma was mild in seven patients, moderate in six and severe in four 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 hospitalised 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 hospitalised patients with severe disease had asthma – a prevalence lower than that in the general population in our setting, which is around 6% [6]. It should also be borne in mind that 54 (76%) of the 71 affected patients had comorbidities that have been shown to be directly related to the involvement of SARS-CoV-2 [8]. The prevalence of patients with asthma without other comorbidities suffering from severe disease falls to only 0.8%, a rate similar to the 0.9% reported by Li *et al.* [8] in Wuhan, where the prevalence of asthma is also 6%.

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 favour 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 characterised 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 favours the development of asthma might also prevent expression of the virus. In this sense, it has been documented that patients with atopic asthma have decreased expression of ACE2 receptors [13], and this process may be mediated by interleukin (IL)-13 [14]. In fact, in the present study, we have observed less severe COVID-19 in patients with the 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 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 severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (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. Reproduction of these results in studies with larger numbers of patients could open up a new avenue of research in the fight against SARS-CoV-2.

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