Respiratory sequelae in patients with bronchial asthma after SARS-CoV-2 pneumonia: a retrospective study in a large academic centre in 2020

Received: 19 May 2024
Accepted: 1 Aug 2024

To the Editor:

The relationship between asthma and SARS-CoV-2 infection has not been clearly established. It has been suggested that patients with the T2 phenotype may be associated with lower rates of infection than others, and that the infection is less severe [1]. However, the consequences of SARS-CoV-2 infection in patients with asthma have not been assessed in previous research. The aim of the present study was to establish whether there are differences in the number and/or severity of respiratory sequelae in asthma and non-asthma patients who have suffered SARS-CoV-2 pneumonia.

A retrospective case–control study was designed that included all asthma patients treated for SARS-CoV-2 pneumonia at our unit for post-COVID-19 respiratory sequelae from May to December 2020. Patients were evaluated between 3 and 6 months after hospital discharge. All patients underwent a clinical interview, physical examination, chest computed tomography (CT), spirometry and carbon monoxide transfer test. For each asthma patient, two control patients were matched after adjustment for the date of hospital admission, sex, age and severity of SARS-CoV-2 pneumonia. The study was approved by the local ethics committee and all the subjects included gave informed consent prior to participation (PR(AG)222/2020).

All the included patients had a positive test for SARS-CoV-2 virus at the time of their hospital admission and a chest radiograph that confirmed pneumonia. In the study period, B lineages were the main circulating lineages in Catalonia. The severity of SARS-CoV-2 pneumonia was defined based on the ventilatory support that the patient required: mild, with inspiratory oxygen fraction <40%; moderate, with inspiratory oxygen fraction >40%; and severe when mechanical ventilation (invasive or non-invasive) was required. The severity of asthma was graded according to GINA (Global Initiative for Asthma) guidelines [2]. Patients were considered to have a T2-Th2 phenotype when they presented allergic symptoms with sensitisation to pneumoallergens, a T2-ILC2 phenotype when there was eosinophilia in blood or sputum without the presence of allergy, and a non-T2 phenotype when no sensitisation or allergic symptoms were found, nor eosinophilia in blood or sputum.

A descriptive statistical study of the variables recorded was carried out, as well as a comparative study between the groups to identify any differences in the number and/or severity of the sequelae. Continuous variables with a normal distribution were analysed using t-test and ordinal variables using the Mann–Whitney U-test; categorical variables were analysed using the Chi-square test or Fisher's exact test.

A total of 2457 patients attended our unit during the study period, 66 of whom had asthma (26 male, 39%), with a median age of 52 years (range 28–83 years) and a median body mass index of 29 $kg \cdot m^{-2}$ (range 17–48 $kg \cdot m^{-2}$). As for phenotype, 48 patients were T2-Th2, eight T2-ILC2 and 10 non-T2. No differences were found between the phenotypes in asthma severity (only 6% had severe asthma) or asthma treatment. The severity of pneumonia was lower in patients with the T2-Th2 phenotype (table 1).

With respect to the control population, asthma patients had more cough, fatigue and wheezing, but there were no clear differences in lung function. The chest CT did not reveal differences in terms of

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Patients with asthma do not present more respiratory sequelae than a control population after SARS-CoV-2 pneumonia. However, patients with asthma do seem to present more symptoms and a distinct involvement of the airway https://bit.ly/47E6Hze

Cite this article as: Espejo D, Pilia F, Romero-Mesones C, *et al*. Respiratory sequelae in patients with bronchial asthma after SARS-CoV-2 pneumonia: a retrospective study in a large academic centre in 2020. *ERJ Open Res* 2025; 11: 00510-2024 [DOI: 10.1183/23120541.00510-2024].

TABLE 1 Data at baseline, during hospital admission and at the post-COVID-19 visit recorded in asthmatic patients and controls; in asthma patients, data are differentiated according to phenotype

	Asthma (n=66)	No asthma (n=132)	p-value	T2-Th2 (n=48)	T2-ILC2 (n=8)	Non-T2 (n=10)	p-value
Age, years, median (IQR)	52 (17.25)	58 (15.00)	0.14	49 (10.75)	67 (9.00)	58 (24.00)	0.07
Sex, male, n (%)	26 (39)	54 (41)	0.48	19 (39)	4 (50)	3 (30)	0.45
Smoking habit, n (%)			0.38				0.97
Non-smoker	45 (68)	78 (59)		32 (67)	5 (63)	8 (80)	
Smoker	1 (2)	5 (4)		1 (2)	0	0	
Ex-smoker	20 (30)	49 (37)		15 (31)	3 (37)	2 (20)	
Pack-years[#]	14.5 (2–35)	30 (3–60)	0.24				
BMI, kg·m^{-2}, median (IQR)	29 (7.50)	30 (7.81)	0.09	30 (6.00)	26 (7.00)	30 (10.00)	0.19
Comorbidities[+]**, n (%)**	53 (80)	89 (67)	0.09	37 (77)	6 (75)	10 (100)	0.54
Atopy, n (%)	48 (73)			48 (100)	0	0	**0.0001**
Rhinitis, n (%)	35 (53)			32 (67)	3 (37)	0	**0.0001**
Rhinosinusitis, n (%)	6 (9)			4 (8)	2 (25)	0	0.17
Rhinopolyposis, n (%)	7 (11)			4 (8)	3 (37)	0	**0.023**
Asthma severity, n (%)							0.73
Intermittent	13 (20)			11 (23)	0	2 (20)	
Mild persistent	19 (29)			14 (29)	2 (25)	3 (30)	
Moderate persistent	30 (45)			21 (44)	5 (62)	4 (40)	
Severe persistent	4 (6)			2 (4)	1 (13)	1 (19)	
Eosinophils, ×10^9, median (IQR)	300 (200)			200 (275.00)	350 (275)	100 (150.00)	**0.05**
Total IgE, KU·L^{-1}, median (IQR)	88 (228.50)			118 (243.50)	48 (55)	9 (54.50)	0.67
Asthma medication, n (%)							
SABA on demand	39 (59)			30 (62)	4 (50)	5 (50)	0.65
LABA on demand	4 (6)			4 (8)	0	0	0.45
Inhaled corticosteroids	52 (79)			37 (77)	8 (100)	7 (70)	0.26
LABA	49 (87)			34 (71)	8 (100)	7 (70)	0.21
LAMA	17 (26)			8 (17)	5 (62)	4 (40)	**0.012**
No treatment	3 (4)			2 (4)	0	1 (10)	0.58
Oral corticosteroids	0			0	0	0	1.00
Montelukast	15 (23)			11 (23)	3 (37)	1 (10)	0.38
Azithromycin	2 (3)			0	2 (25)	0	**0.001**
Biological treatment	1 (1)			1 (2)	0	0	0.83
Data collected during admission							
COVID-19 severity, n (%)			1.00				**0.002**
Mild: F_{IO_2}<40%,	39 (59)	78 (59)		32 (67)	3 (37)	4 (40)	
Moderate: F_{IO_2} >40%	5 (8)	10 (8)		0	3 (37)	2 (20)	
Severe: NIVM or NIV	22 (33)	44 (33)		16 (33)	2 (25)	4 (40)	
COVID-19 medication, n (%)							
Lopinavir/ritonavir	32 (48)	54 (41)	0.19	22 (46)	5 (62)	5 (50)	0.68
Remdesivir	1 (1)	6 (4)	0.26	1 (2)	0	0	0.82
Tocilizumab	5 (8)	24 (18)	**0.034**	1 (2)	3 (37)	1 (10)	**0.002**
Hydroxychloroquine	35 (53)	70 (53)	0.56	24 (50)	5 (62)	6 (60)	0.72
Azithromycin	36 (54)	71 (54)	0.51	23 (48)	6 (75)	7 (70)	0.21
Dexamethasone	21 (32)	50 (38)	0.25	17 (35)	1 (12)	3 (30)	0.43
Duration of ventilatory support, median (IQR)	12 (13)	10 (8.00)	0.31	12 (12.00)	11 (10.00)	14 (23.50)	0.13
Days of stay in the ICU, median (IQR)	13 (16)	8 (19.50)	0.81	13 (17.50)	17 (10.00)	10 (10.00)	0.25
Control after COVID-19							
Dyspnoea, n (%)	30 (45)	58 (44)	0.48	21 (44)	4 (50)	5 (50)	0.90
mMRC			0.47				0.59
0	32 (48)	75 (57)		24 (50)	4 (50)	4 (40)	
1	24 (36)	35 (26)		18 (37)	2 (25)	4 (40)	
2	10 (16)	22 (17)		6 (13)	2 (25)	2 (20)	
Cough	10 (15)	8 (6)	**0.04**	8 (17)	1 (12)	1 (10)	0.84
Fatigue	12 (18)	0	**0.0001**	9 (19)	1 (12)	2 (20)	0.90
Expectoration	1 (1)	1 (1)	0.56	1 (2)	0	0	0.83
Chest pain	4 (6)	5 (4)	0.35	2 (4)	0	2 (20)	0.12
Wheezing, n (%)	5 (8)	0	**0.004**	4 (8)	1 (12)	0	0.57

Continued

TABLE 1 Continued

	Asthma (n=66)	No asthma (n=132)	p-value	T2-Th2 (n=48)	T2-ILC2 (n=8)	Non-T2 (n=10)	p-value
Pulmonary function							
FEV_1 (%), median (IQR)	83 (20.75)	87 (28.17)	0.20	83 (19.50)	76 (33.00)	88 (29.00)	0.20
FEV_1 <80%, n (%)	19 (29)	35 (26)					
FVC (%), median (IQR)	88 (18.00)	87 (25.88)	0.10	88 (15.00)	94 (23.50)	93 (34.50)	0.56
FVC <80%, n (%)	14 (21)	36 (27)					
FEV_1/FVC, median (IQR)	77 (8.00)	80 (8.38)	0.32	77 (9.50)	73 (15.75)	76 (8.00)	0.37
FEV_1/FVC <70%, n (%)	10 (15)	8 (6)					
D_{LCO} (%), median (IQR)	76 (20.00)	79 (22.38)	0.33	79 (20.00)	72 (28.25)	70 (27.50)	0.51
D_{LCO} <80%, n (%)	21	70					
K_{CO} (%), median (IQR)	85 (25.75)	83 (17.93)	0.26	86 (22.50)	84 (21.25)	76 (18.50)	0.62
Chest computed tomography							
Pathological, yes, n (%)	52 (79)	103 (78)	0.98	35 (73)	8 (100)	9 (90)	0.14
Principal, n (%)			0.09				0.23
None	38 (57)	51 (39)		30 (62)	3 (37)	5 (50)	
Ground glass	10 (15)	36 (27)		6 (13)	1 (13)	3 (30)	
Consolidation	1 (2)	2 (2)		0	0	1 (10)	
Linear opacities	2 (3)	3 (2)		2 (4)	0	0	
Reticulation	1 (2)	6 (4)		1 (2)	0	0	
Mixed type[¶]	14 (21)	34 (26)		9 (19)	4 (50)	1 (10)	
Interstitial, n (%)			0.67				0.67
None	62 (94)	121 (90)		45 (94)	8 (100)	9 (90)	
Septal thickening	4 (6)	8 (6)		3 (6)	0	1 (10)	
Crazy paving	0	1 (2)		0	0	0	
Fibrosis	0	2 (2)		0	0	0	
Bronchial involvement, yes, n (%)	40 (61)	71 (54)	0.24	27 (56)	5 (62)	8 (80)	0.37
Bronchial involvement, n (%)			**0.007**				0.81
Bronchiectasis	11 (17)	40 (30)		7 (15)	2 (25)	2 (20)	
Bronchial thickening	22 (33)	25 (19)		14 (29)	2 (25)	6 (60)	
Bronchiolitis	3 (4)	7 (5)		3 (6)	0	0	
Tracheobronchomalacia	4 (7)	0		3 (6)	1 (12)	0	

BMI: body mass index; SABA: short-acting beta-agonist; LABA: long-acting beta agonist; LAMA: long-acting muscarinic-antagonist; IQR: interquartile range; F_{IO_2}: inspiratory oxygen fraction; NIVM: non-invasive mechanical ventilation; NIV: non-invasive ventilation; ICU: intensive care unit; mMRC: modified Medical Research Council scale; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide. Bold text indicates statistical significance. [#]: information available on 46 patients (asthma: 12; no asthma: 32); [¶]: combination of more than one alteration; [+]: no differences were found regarding the different comorbidities (gastro-oesophageal reflux, heart disease, rheumatic disease, arterial hypertension, dyslipidaemia, diabetes, psychiatric disease, obesity).

parenchymal involvement, with mixed interstitial involvement being the most frequent sequela. Although no differences were found in terms of the incidence of airway involvement, the type of involvement did vary: patients with asthma had more tracheomalacia, more bronchial thickening and less bronchiectasis than the control population (table 1). The sequelae in asthma patients were independent of their asthma phenotype. Regarding the treatment received during admission, the percentage of patients treated with tocilizumab was higher in the controls. In asthma patients, this treatment was greater in the T2-ILC2 group (table 1).

The results of the present study demonstrate that patients with asthma (regardless of severity), do not appear to have a higher incidence of respiratory sequelae after experiencing SARS-CoV-2 pneumonia that required hospital admission. However, there were differences in airway involvement: bronchiectasis was more common in non-asthma patients, and bronchial thickening and/or tracheomalacia in asthma patients, regardless of asthma phenotype.

The relationship between asthma and SARS-CoV-2 infection throughout the pandemic has been the subject of multiple studies, which have reached a variety of conclusions. Currently, there seems to be a consensus that SARS-COV-2 infection in patients with asthma is less common than in the general population [1] and less severe in those who present a T2-Th2 asthma phenotype [3, 4]. As a result, we might surmise that the appearance of sequelae in patients with SARS-CoV-2 infection could also be

influenced by whether they have asthma, and, if they do, whether they present a particular phenotype. In general, 1 year after infection ∼29% of patients severely affected by SARS-CoV-2 present fatigue and 19% present dyspnoea [5]. At a radiological level, it has been reported that ∼45% of patients present ground glass opacities on chest CT, 28% fibrosis and ∼21% reticulations [6]. There are hardly any data regarding airway involvement, although the appearance of bronchiectasis seems to be the predominant form [6].

Around 40% of the patients included in this study had dyspnoea between 3 and 6 months after hospital discharge, regardless of whether or not they had asthma. Asthma patients had more fatigue, cough and wheezing than controls. This finding contrasts with the only related study reported to date, in which no differences were found between patients with and without asthma in terms of the evolution of symptoms [7]. More significant is the fact that no differences were found between the two populations in terms of parenchymal involvement, highlighting that neither the presence of asthma, nor the presence of a particular phenotype, is a risk factor for lung injury in the case of SARS-CoV-2 infection. Another interesting point is the fact that asthma could prevent the appearance of bronchiectasis after SARS-CoV-2 infection. Bronchiectasis is common after severe lung infections, regardless of the causative agent [8], and SARS-CoV-2 infection does not appear to be an exception; Han *et al.* [9] reported bronchiectasis in 7% of patients with SARS-CoV-2 infection at the time of admission, but the rate had risen to 24% in a control CT scan 6 months after hospital discharge. The administration of inhaled corticosteroids in patients with asthma may prevent the appearance of bronchiectasis due to their anti-inflammatory effect, in the same way as they reduce the severity of SARS-CoV-2 infection [10, 11].

We observed that patients with asthma had more bronchial thickening than controls. This finding is difficult to attribute to the viral infection itself, since practically all patients with asthma present this type of alteration [12]. The presence of tracheomalacia in these patients may have a different explanation; although it may be due to their asthma, it has also been attributed to the SARS-CoV-2 infection [13].

The present study is not without limitations. It is a single-centre, retrospective study in which lung function tests and chest CT were not available prior to SARS-CoV-2 pneumonia. However, the confirmation that there were no differences in respiratory sequelae between asthma patients and controls lends support to the notion that asthma is not a risk factor in SARS-CoV-2 pneumonia. Moreover, although patients were adjusted for severity, the percentage of patients treated with tocilizumab was higher in the controls. However, this difference does not seem to affect the respiratory sequelae between both groups.

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Provenance: Submitted article, peer reviewed.

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Ethics statement: The study was approved by the local ethics committee (Hospital Vall d'Hebron Ethics Committee approval PR(AG)219/2020) and all subjects signed an informed consent document prior to their participation.

Conflict of interest: X. Muñoz has received fees as a speaker, scientific advisor or participant of clinical studies from (in alphabetical order): AstraZeneca, Boehringer Ingelheim, Chiesi, Faes, GlaxoSmithKline, Menarini, Mundifarma, Novartis and Teva. M-J. Cruz is an associate editor of this journal. The other authors have nothing to disclose.

Support statement: This project received funding from the Instituto de Salud Carlos III (PI21/01046) and Fondo Europeo de Desarrollo Regional (FEDER). D. Espejo is a researcher supported by the Rio Hortega programme from the Instituto de Salud Carlos III (CM23/00174) and F. Pilia is a researcher supported by the PFis Programme from the Instituto de Salud Carlos III (FI22/00262). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Funding information for this article has been deposited with the Crossref Funder Registry.

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