Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Medicine 207 (2023) 107092

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Long COVID outcomes in an asthmatic cohort and its implications for asthma control

Daniel Laorden [a,*], Javier Domínguez-Ortega [b], Carlos Carpio [a], Pilar Barranco [b], Elena Villamañán [c], David Romero [a], Santiago Quirce [b], Rodolfo Álvarez-Sala [a], ASMA@COVIDHULP group

[a] Department of Pneumology, Hospital La Paz, Universidad Autónoma de Madrid, IdiPAZ, and CIBER of Respiratory Diseases, Madrid, Spain
[b] Department of Allergy, Hospital La Paz, IdiPAZ, and CIBER of Respiratory Diseases, Madrid, Spain
[c] Department of Pharmacy, Hospital La Paz, IdiPAZ, Madrid, Spain

ARTICLE INFO

Keywords:
Asthma
Long COVID
Inhaled corticosteroids
Oral systemic corticosteroids
Dyspnea
Chest pain
Cough
Eosinophils

1. Introduction

COVID-19 disease is an infectious entity caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that has spread throughout the world [1]. Some people who have recovered from the acute phase of COVID-19 have symptoms for weeks or months much longer than expected (long COVID). Several long-term symptoms, such as dyspnea, chronic fatigue, chest pain, or cognitive impairment, may persist after SARS-CoV-2 infection [2].

Asthma is a chronic inflammatory disease in the airways that affects over 300 million people [3]. Most studies worldwide do not consider asthma as a comorbidity associated with the risk of severe COVID-19 infection [3], particularly for allergic asthma [4]. However, a recent meta-analysis described being young and obese as risks factors [5].

It has been hypothesized that there could be a protective factor for eosinophils and T2 cytokines in COVID-19 disease. Warner et al. [6] and Muñoz et al. [7] pointed out the protective effect of eosinophils against COVID-19. Eosinophils have antiviral properties such as expression of Toll-Like Receptor-7 that recognizes RNA viruses such as SARS-COV2, antigen presentation function, secretion of Th1 cytokines such as interferon gamma and IL-12, and generation of superoxide and nitric oxide [6]. Airway eosinophils, however, have an inflammation-regulating activity that could protect against hyper-inflammatory conditions in COVID-19 infection [6]. Furthermore, innate immune responses to viral respiratory infections (e.g. COVID-19) are associated with innate lymphoid cells type 2 (ILC2) that release alarmins such as IL-23, IL-33 and thymic stromal lymphopoetin (TSLP) that fight COVID-19 infection. ILC2 release IL-4 and IL-5 cytokines that induce eosinophil proliferation and maturation [6]. Notwithstanding, there is a lack of information on post-COVID symptoms in patients with asthma in the long-term [7].

The aim of this study was to assess the long COVID outcomes after six to twelve months of an asthma population. We also attempted to identify clinical features during the acute episode of COVID-19 and their potential implications for asthma outcomes.

2. Material and methods

2.1. Study population

This is a one single-center, consecutive descriptive observational retrospective study. La Paz University Hospital is one of the largest

* Corresponding author.
E-mail address: laordendaniel1@gmail.com (D. Laorden).

https://doi.org/10.1016/j.rmed.2022.107092
Received 8 October 2022; Received in revised form 5 December 2022; Accepted 12 December 2022
Available online 16 December 2022

hospitals in this region and has developed one of the largest cohorts in Europe with more than 3500 patients collected during the pandemic [1].

We collected demographic, clinical and laboratory data from the medical history. The inclusion criteria were consecutive asthmatic patients older than 18 years-old admitted in Emergency Department in our hospital that presented firmly established COVID-19 infection (173 patients) confirmed by polymerase chain reaction during the first and second COVID-19 waves (March–December 2020), no patients were vaccinated at this point. The protocol was approved by local regulatory ethics committee (ethics committee La Paz University Hospital; Madrid, Spain (PI-4336), and respected the ethical principles of the Declaration of Helsinki.

2.2. Data collection

We employed a modified version of the electronic case record form (eCRF) for severe acute respiratory infections, developed by the World Health Organization/International Severe Acute Respiratory and Emerging Infection Consortium [8]. Our eCRF includes 94 variables, grouped into demographics, asthma medical history, COVID-19 infection clinical history, and post-COVID-19 clinical history.

We collected the clinical data directly extracting the information by a manual and individual review of the patients' electronic clinical records, including the clinical notes (DXC–HCIS– Healthcare Information System). The data collection effort was conducted by a volunteer team of resident doctors and medical doctors from La Paz University Hospital.

Demographics data included sex, age, comorbidities (smoking habit, COPD, obesity (body mass index $\geq$30), obstructive-sleep-apnoea syndrome, gastro-oesophageal reflux, chronic rhinosinusitis with nasal polyps, congestive heart failure, anxiety and depression) blood eosinophils, and immunoglobulin E (IgE).

We classified patients as having T2 or non-T2-asthma according to the 2021 Global Initiative for Asthma guidelines [9]. We collected previous asthma treatment, including inhaled therapy, use of oral corticosteroids (OCS), biological treatment, azithromycin and antileukotrienes. Pre-COVID-19 and post-COVID-19 asthma control measured by asthma control test (ACT) and number of previous exacerbations in one year and after the episode, were registered. Pre-COVID-19 and Post-COVID-19 pulmonary lung function, blood eosinophils, and IgE were also studied.

For the acute COVID-19, the presence of thoracic symptoms as chest pain, cough, expectoration, dyspnea, anosmia and ageusia were recorded and evaluated after 6 and 12 months post-disease. The presence of pneumonia, thromboembolism, need of hospitalization, admission to intensive care unit (ICU) or intermediate respiratory care units (IRCU) and mortality were also considered. Treatment during the acute episode was also analyzed.

We also collected the post-COVID-19 symptoms (chest pain, cough, expectoration, dyspnea). Both asthma control test (ACT) and the number of exacerbations during this period were collected. Other variables included were the treatment post-COVID-19, including inhaled therapy, use of OCS, biologic treatment and pulmonary lung function.

2.3. Statistical analyses

We analyzed qualitative data with absolute frequencies and percentages and quantitative data in mean and standard deviation, or median and ranks. The Kolmogorov-Smirnov test evaluated normality in continuous data. The chi-squared test, or the exact Fisher test, studied the association between categorical variables. The Mann-Whitney *U* test studied the association between categorical and continuous variables. We have applied logistic regression with multivariant regression models in order to assess the risk factors to have some acute and long-term outcomes. All statistical tests were bilateral and significant if $p < 0.05$. We analyzed data with SAS 9.3 program (SAS-Institute,Cary,NC, USA).

3. Results

The average age was 55 years, 67% were women, 22% were smokers. 60.7% had T2-asthma. We did not discontinue previous treatments with OCS, inhalers and omalizumab during COVID-19 disease. Table-1 lists baseline characteristics of 173 patients included.

Mortality at 12 months was 11%. 67% of patients suffered hospitalization and 5% was admitted to ICU. Pneumonia was present in 60% of patients diagnosed with thoracic X-ray or computerized tomography.

During COVID-19 disease, 75% of patients suffered dyspnea, 80% cough, 26% chest pain, 15% ageusia, 13% anosmia and 11% wheezing.

After a univariant model study, we found a significant association between COVID-19 pneumonia and male patients (odds ratio-OR = 2.828, p = 0.005), current smokers (OR = 2.568, p = 0.024), use of ICS + LABA pre-COVID-19 disease (OR = 3.119, p = 0.001) (table-2). COVID pneumonia was found as a risk factor for chest pain after 6–12 months post-COVID (OR = 5.625, p = 0.01) (Table 2). After a multivariant regression model study, we found a significant association between COVID-19 pneumonia and male patients (p = 0.02) and chest pain after 6–12 months (p = 0.019) (Table 2).

A lower risk of hospitalization was present in patients who suffered T2-asthma (OR = 0.32, p = 0.002) and were treated previously with ICS (OR = 0.272, p = 0.006) (table-2). A higher risk of hospitalization was found in males (OR = 2, p = 0.047), current smokers (OR = 4.803, p = 0.001), and patients treated previously with ICS + LABA (OR = 2.793, p = 0.002). Multivariant regression model found a significant association between hospitalization and smoking (p = 0.045), pre-COVID ICS treatment (p = 0.007), pre-COVID ICS + LABA treatment (p = 0.014)

Table 1
Baseline characteristics.

	All participants (n = 173)
Age, years	55.53 ± 18.2 (n = 173)
Gender	
Men	56/173 (32.0%)
T2 asthma	105/171 (60.7%)
Smoking habit	39/172 (22.5%)
Pack year index	11.7 ± 17.9 (n = 38)
Hospitalizations	116/173 (67.1%)
Mortality at 12 months	19/173 (11.0%)
ICU admission	9/119 (5.2%)
COVID acute pneumonia	105/171 (60.7%)
Pre-COVID ACT	23.8 ± 2.6 (n = 15)
Pre-COVID Number of exacerbations	0.16 ± 0.54 (n = 138)
Pre-COVID FEV1 (%)	87.89 ± 27.03 (n = 53)
Pre-COVID asthma treatment	
ICS	23/168 (13.3%)
ICS + LABA	117/172 (67.6%)
LAMA	25/172 (14.5%)
SABA	94/172 (54.3%)
Antileukotrienes	28/172 (16.2%)
Azithromycin	1/173 (0.6%)
Omalizumab	2/172 (1.2%)
OCS	8/172 (4.6%)
Symptoms during COVID-19	
Dyspnea	130/172 (75.1%)
Chest pain	45/172 (26.0%)
Cough	139/170 (80.3%)
Wheezing	19/165 (11.0%)
Anosmia	23/172 (13.3%)
Ageusia	26/172 (15.0%)
Co-existing disorders	
Obesity	30/173 (17.3%)
COPD	13/172 (7.5%)
Rhinosinusitis	44/173 (25.4%)
OSA	14/173 (8.1%)

ACT: asthma control test; COPD: chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in 1 s; ICU: intensive care unit; ICS: inhaled corticosteroids; LABA: long-acting beta agonists; LAMA: long-acting muscarinic antagonist; OCS: Oral systemic corticosteroid; OSA: obstructive sleep apnoea; SABA: short-acting beta agonists.

Table 2
Univariant and multivariant model study.

COVID ACUTE PNEUMONIA			
	p-value	**OR**	**CI 95%**
Gender	**0.005**		
- Men		**2.828**	**1.375–5.813**
- Women			
Current smokers	**0.024**	**2.568**	**1.130–5.836**
Obesity (BMI>30)	0.618		
T2 asthma	0.536		
Pre-COVID ICS treatment	0.557		
Pre-COVID ICS + LABA treatment	**0.001**	**3.119**	**1.597–6.092**
Pre-COVID OCS treatment	0.153		
Dyspnea 6–12 months post-COVID	0.645		
Chest pain 6–12 months post-COVID	**0.010**	**5.625**	**1.503–21.054**
Cough 6–12 months post-COVID	0.774		
Thromboembolism post-COVID	0.421		
Eosinophilic asthma	0.06		
HOSPITALIZATION			
	p-value	**OR**	**CI 95%**
Gender	**0.047**		
- Men		**2.000**	**1.008–3.967**
- Women			
Current smokers	**0.001**	**4.803**	**1.887–12.224**
Obesity (BMI >30)	0.054		
T2 asthma	**0.002**	**0.320**	**0.153–0.669**
Pre-COVID ICS treatment	**0.006**	**0.272**	**0.108–0.686**
Pre-COVID ICS + LABA treatment	**0.002**	**2.793**	**1.443–5.404**
Pre-COVID OCS	0.145		
Dyspnea 6–12 months post-COVID	0.411		
Chest pain 6–12 months post-COVID	0.415		
Cough 6–12 months post-COVID	0.665		
Thromboembolism post-COVID	0.830		
Eosinophilic asthma	**0.022**	**1.003**	**1.000–1.005**

BMI: body mass index; CI: confidence interval; ICS: inhaled corticosteroids; LABA: long-acting beta agonists; OCS: oral systemic corticosteroids; OR=Odds ratio.

and eosinophilic asthma (p = 0.032) (table-2).

After a multivariate regression analysis, we found no association between ICU admission and baseline characteristics (sex, obesity, T2 asthma, ICS pre-COVID-19, ICS + LABA pre-COVID-19, OCS pre-COVID-19). We also studied the association between ICU admission and dyspnea, chest pain and cough after 6–12 months, finding no significant associations.

Long-COVID outcomes were also studied at 12 months, dyspnea was present in 52 patients (30%), chest pain in 21 patients (12%) and cough in 21 patients (12%) (table-3). Mean asthma control test (ACT) after 12 months post-COVID was 21.6 ± 4.36, the average number of exacerbations was 0.12 ± 0.435, FEV_1 12 months post-COVID was 83.15% ± 21.23. We applied univariant and multivariant regression logistic models to different outcomes after 12 months post-COVID. Dyspnea, cough and corticosteroid requirement after 12 months were not statistically significant. However, chest pain at 12 months post-COVID was less prevalent in T2 asthma (OR = 0.319, p = 0.044) (table-3). There was also a lower necessity of LAMA in T2 asthmatic patients (OR = 0.122, p = 0.008) (table-3).

Table 3
Long-COVID outcomes.

Dyspnea 12 months post-COVID	52 (30.1%)
Chest pain 12 months post-COVID	21 (12.1%)
Cough 12 months post-COVID	21 (12.1%)
ACT 12 months post-COVID	21.6 ± 4.36
Number of exacerbations 12 months post-COVID	0.12 ± 0.435
FEV_1 12 months post-COVID	83.15% ± 21.23

Univariant and multivariant regression logistic model

Dyspnea at 12 months Post-COVID

	p-value	OR	CI 95%
Gender	0.225		
- Men			
- Women			
Current smokers	0.437		
Obesity (BMI>30)	0.262		
T2 asthma	0.324		
Pre-COVID ICS treatment	0.123		
Pre-COVID ICS + LABA treatment	0.836		
Pre-COVID OCS treatment	0.606		
Eosinophilic asthma	0.342		

Chest pain at 12 months Post-COVID

	p-value	OR	CI 95%
Gender	0.964		
- Men			
- Women			
Current smokers	0.088		
Obesity (BMI>30)	0.505		
T2 asthma	**0.044**	**0.319**	**0.105–0.968**
Pre-COVID ICS treatment	0.416		
Pre-COVID ICS + LABA treatment	0.310		
Pre-COVID OCS treatment	0.999		
Eosinophilic asthma	0.572		

LAMA necessity 12 months post-COVID

	p-value	OR	CI 95%
Gender	0.314		
- Men			
- Women			
Current smokers	0.067		
Obesity (BMI>30)	0.999		
T2 asthma	**0.008**	**0.122**	**0.026–0.581**
Pre-COVID ICS treatment	0.773		
Pre-COVID ICS + LABA treatment	0.404		
Pre-COVID OCS treatment	**0.005**	**13.8**	**2.192–86.877**
Eosinophilic asthma	0.995		

ACT: asthma control test; BMI: body mass index; CI: confidence interval; ICS: inhaled corticosteroids; LABA: long-acting beta agonists; LAMA: long-acting muscarinic antagonist; OCS: oral systemic corticosteroids; OR: odds ratio.

4. Discussion

The findings observed in this study help us better understand post-acute COVID-19 complications in patients with asthma. Patients with T2-asthma had less chest pain after 12 months post-COVID (OR = 0.319) (table-3). These results are consistent with previous studies, suggesting the potential protection of T2-asthma against acute COVID infection [8–11].

Viral infections clearly affect asthma outcomes [3,8,11]. Interestingly, and consistent with previous papers, we have not found that COVID-19 infection had an influence on asthma outcomes at the time of observation in our investigation. Exacerbations, asthma control (measured by ACT), and lung function parameters appeared to be unaffected by COVID-19, at least in most patients (table-3). Unfortunately, we could not perform spirometry on all the study patients because of the pandemic situation.

Given that the severity of acute COVID-19 was associated with the development of worse long-term outcomes of COVID-19, it is noteworthy that we found an increased risk of pneumonia in men (OR = 2.828), smokers (OR = 2.568) and subjects previously treated with ICS + LABA (OR = 3.119), it was confirmed by multivariant regression model) (table-2). In line with these findings, we have also observed a higher risk of hospitalization among patients with the same clinical characteristics: men (OR = 2), smokers (OR = 4.803) and treated with ICS + LABA (OR = 2.793). We found less risk in patients previously treated with ICS alone (OR = 0.272) than with an ICS + LABA combination (OR = 2.793), probably explained by severity of asthma in the acute phase of COVID-19, since more severe asthma has been associated

with a worse prognosis [11]. In contrast, and, as expected, T2-asthma patients had a lower risk of acute SARS-CoV-2 pneumonia (OR = 0.320), which probably influenced the clinical presentation of prolonged COVID.

The major drawback of this study is its retrospective design, in several waves of evolution of the pandemic. These circumstances make up the major limitation of the study, which is the absence of a prospective design that allows greater validation of these results. We also believe that some trends seen in our results might have been confirmed by a larger sample, which could have helped to better explore the impact of COVID-19 on asthma outcomes. However, it seems difficult to design this type of study because of the evolution of the pandemic after vaccination.

Among the strengths of this study, it includes many non-vaccinated patients with asthma and COVID infection. To our knowledge, this is the first study with a longitudinal evaluation after at least 6 months from the acute infection, including data from interviews and current physical examinations that others studies do not include [10].

In conclusion, patients with severe asthma are at an increased risk of developing long COVID, while eosinophilic and T2-asthma could protect against complications of prolonged COVID.

Funding

No funding has been received for this study.

Ethics

The research was conducted ethically in accordance with the https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Klicken oder tippen Sie, wenn Sie diesem Link Vertrauen.">World Medical Association Declaration of Helsinki. Information revealing the patient's identity has been avoided. All patients have been identified by numbers or aliases and not by their real names.

Study approval statement

Ethics approval was not required because it was a retrospective and observational study. We did not change our daily clinical practice.

Consent to publish statement

The study participants have given their written informed consent to publish their case (including publication of images).

The protocol was approved by local regulatory ethics committee (PI-4336).

CRediT authorship contribution statement

Daniel Laorden: Conceptualization, Methodology, Investigation, Writing – original draft. **Javier Domínguez-Ortega:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Carlos Carpio:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Pilar Barranco:** Writing – review & editing. **Elena Villamañán:** Writing – review & editing. **David Romero:** Investigation, Writing – review & editing. **Santiago Quirce:** Methodology, Investigation, Writing – review & editing. **Rodolfo Álvarez-Sala:** Methodology, Investigation, Writing – review & editing.

Declaration of competing interest

The authors certify that none of them have any conflicts of interest.

Acknowledgements

We thank the support of the Universidad Autonoma Madrid students and members of the ASMA@COVIDHULP group that have made substantial contributions by data collection and María Jiménez-González and Itsaso Losantos for statistical analysis and processing.

References

[1] A.M. Borobia, A.J. Carcas, F. Arnalich, R. Álvarez-Sala, J. Monserrat-Villatoro, M. Quintana, et al., A cohort of patients with COVID-19 in a major teaching hospital in Europe, J. Clin. Med. 9 (2020) E1733.
[2] W.-J. Song, C.K.M. Hui, J.H. Hull, S.S. Birring, L. McGarvey, S.B. Mazzone, et al., Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses, Lancet Respir. Med. 9 (2021) 533–544.
[3] D. Howell, H. Verma, K.S. Ho, B. Narasimhan, D. Steiger, L. Rogers, Asthma and COVID-19: lessons learned and questions that remain, Expet Rev. Respir. Med. 15 (2021) 1377–1386.
[4] A. Habernau Mena, I. García-Moguel, M. Vazquez de la Torre Gaspar, V. Mugica, M.I. Alvarado Izquierdo, M.A. Jimenez Blanco, et al., COVID-19 course in allergic asthma patients: a Spanish cohort analysis, J. Asthma Allergy 15 (2022) 257–264.
[5] J.H. Choi, S.H. Choi, K.W. Yun, Risk factors for severe COVID-19 in children: a systematic review and meta-analysis, J. Kor. Med. Sci. 37 (5) (2022) e35.
[6] J.O. Warner, J.A. Warner, D. Munblit, Hypotheses to explain the associations between asthma and the consequences of COVID-19 infection, Clin. Exp. Allergy 52 (2022) 7–9.
[7] X. Muñoz, F. Pilia, I. Ojanguren, C. Romero-Mesones, M.J. Cruz, Is asthma a risk factor for COVID-19? Are phenotypes important? ERJ Open Res 7 (1) (2021), 00216-2020.
[8] Novel coronaviris (nCoV) acute respiratory infection clinical characterisation data tools. nCoV case records form version 1.3. 24, Feb 2020. Adapted from Sprint Sari Case Report form by ISARIC. Available online: https://media.tghn.org/medialibrary/2020/03/ISARIC_COVID19_CRF_V1.3_24Feb2020.pdf. (Accessed 28 September 2022).
[9] H.K. Reddel, L.B. Bacharier, E.D. Bateman, C.E. Brightling, G.G. Brusselle, R. Buhl, et al., Global initiative for asthma (GINA) strategy 2021 - executive summary and rationale for key changes, Am. J. Respir. Crit. Care Med. 205 (1) (2022) 17–35.
[10] C. Fernández-de-Las-Peñas, J. Torres-Macho, M. Velasco-Arribas, J.A. Arias-Navalón, C. Guijarro, V. Hernández-Barrera, et al., Similar prevalence of long-term post-COVID symptoms in patients with asthma: a case-control study, J. Infect. 83 (2021) 237–279.
[11] P.A. Palmon, D.J. Jackson, L.C. Denlinger, COVID-19 infections and asthma, J. Allergy Clin. Immunol. Pract. 10 (2022) 658–663.