ORIGINAL RESEARCH

Clinical Features and Outcomes Associated with Bronchial Asthma Among COVID-19 Hospitalized Patients

Miguel Angel Diaz[1], Nelly Catalan-Caceres [ID][1], Thais C Beauperthuy [ID][2], Carlos Domingo[1], Ethel Ibañez[1], Carmen Morata[3], Alfredo De Diego[2]

[1]Allergy Department, Hospital Universitari I Politècnic La Fe, Valencia, Spain; [2]Respiratory Department, Hospital Universitari I Politècnic La Fe, Valencia, Spain; [3]Internal Medicine Department, Hospital Universitari I Politècnic La Fe, Valencia, Spain

Correspondence: Miguel Angel Diaz, Allergy Department, Hospital Universitari I Politècnic La Fe, Avinguda de Fernando Abril Martorell, 106, Valencia, 46026, Spain, Tel +34 961244084, Email diaz_mig@gva.es

Background: The impact of diagnosis treatment and bronchial asthma on coronavirus disease 2019 (COVID-19) associated outcomes remains unclear.

Objective: To identify the prevalence and outcomes associated with asthma among hospitalized patients with COVID-19.

Methods: Electronic health records of 130 patients with asthma among hospitalized patients with COVID-19 were reviewed. Two subgroups of asthmatic patients were compared according to clinical outcomes during hospitalization. Patients with death results, intubation, and/or need of intensive care unit (ICU) stay were grouped as asthmatic patients with severe COVID-19 outcomes, and the rest were grouped as asthmatic patients with non-severe COVID-19 outcomes. Multivariable analyses were conducted with logistic regression to identify independent risk factors for severe outcomes.

Results: The prevalence of asthma in COVID-19 hospitalized patients was 5%. The mean age was 59.4 years and 54% were women. 17% received treatment in GINA step 4–5 asthma at the time of admission. An allergic asthma phenotype was determined in 38%. There was no significant difference in hospital length of stay or need for intubation between asthmatic patients and global COVID-19 admitted patients. 17% of asthmatic patients developed a severe outcome, and 5% had a death result. Elevated Lactate Dehydrogenase (LDH) level, low transcutaneous pulse oximetry (SpO2), the coexistence of atrial fibrillation (AF), and need for moderate or high ICS at admission were independent risk factors for a worse outcome in asthmatics COVID-19 hospitalized patients.

Conclusion: The prevalence of asthma in COVID-19 hospitalized patients was 5%, consistent with the asthma prevalence in the general population. The asthmatic patients with the previous prescription of moderate or high doses of ICS and/or coexistence of atrial fibrillation at admission had a higher risk of the severe outcome.

Keywords: bronchial asthma, COVID-19, risk factors, outcomes

Introduction

There is no clear evidence so far that patients with asthma are more likely to be infected with COVID-19 or to become severely ill. Most of the prevalence studies agree in pointing out an underrepresentation of asthma as a risk factor for admission and/or morbi-mortality due to COVID-19,[1–4] and this risk would be even lower in patients with asthma with allergic phenotype when compared to patients with non-allergic phenotype.[5] Nevertheless, some studies contradict this general trend, reporting in asthmatic patients a higher risk of hospitalization[6] or intubation,[7] particularly in severe asthma or non-allergic asthma cases.[8]

Different hypotheses have been proposed to explain the low representation of asthma in COVID-19 complicated outcomes: better compliance of the social isolation measures in asthmatic patient population compared to other groups, a protective effect of T2 response in asthmatic patients[9,] or a protective effect of inhaled and/or systemic corticosteroids.[10,11]

Our study aimed to analyze the clinical features of asthmatic patients and SARS-CoV-2 pneumonia who required admission to a tertiary referral hospital in Valencia, Spain, and to identify the risk predictor factors of worse outcomes at admission.

Materials and Methods

Electronic medical records of patients admitted to COVID-19 Units of our hospital were reviewed (1st March 2020–28th February 2021). Asthmatic patients were determined based on ICD-10 coding in the discharge report. Asthma cases were only included when the diagnosis was confirmed in electronic clinical history and the patient required ongoing asthma medication at admission. Two groups of patients were compared according to clinical outcomes during hospitalization. Patients with death results, and/or need for intubation, and/or need of intensive care unit (ICU) stay were grouped as asthmatic patients with severe COVID-19 outcomes, and patients discharged without requiring invasive procedures were grouped as asthmatic patients with non-severe COVID-19 outcomes. The previous history of sensitization to aeroaller-gens detected by prick test and/or specific IgE were considered as an allergic asthma phenotype. Atopic dermatitis and/or food allergy were considered atopic comorbidity. Asthmatic exacerbation was considered if the patient had required at least a short course of oral or parental corticosteroids during the previous year to admission. Spirometry values were collected if an examination was available in electronic medical records within 2 years prior to admission.

Statistical Analysis

Continuous variables are presented as mean ± SD and compared using the Student's *t*-test. Discrete variables are presented as percentages (proportions), and compared with the Chi-square test, using Fisher correction when needed. Statistical analysis was done using the SPSS statistical package (Chicago, Illinois). Associations were considered statistically significant when $p < 0.05$, although all p values are presented. Multivariable analyses were conducted with logistic regression to identify independent risk factors for severe outcomes. Variables with $p<0.1$ in the univariate analysis were included in multivariable analysis.

Results

130 patients with asthma were identified, representing 5.03% of the global population admitted for COVID-19 (n=2585) during the period of the study. Table 1 shows comparative data of asthmatics admitted patients and global admitted patients with COVID-19 in our hospital. There was no significant difference in mean age, hospital length of stay, or need for intubation between asthmatic patients and global COVID −19 admitted patients. Of note, patients with asthma and COVID-19 had a mortality rate of 5% vs 14% in the global admitted COVID-19 patients (p<0.001). Table 2 summarizes the demographic and clinical characteristics of the study population. The mean age of asthma patients was 59.4±17.5 years. Women were 54%. An allergic asthma phenotype was determined in 38% of the patients. At admission, 17% of asthmatic patients received treatment in GINA step 4 or 5, 46% in GINA step 2 or 3, and 37% were not treated with regular ICS (GINA step 1). Previous $FEV_1\%$ and FEV_1/FVC were 90.3±24 (1/m) and 75±14 respectively (n= 52). Table 3 shows laboratory findings on admission, COVID19- therapy, and length of hospital stay.

Table 1 Comparative Data of Asthmatic Admitted Patients and Global Admitted Patients with COVID-19

Variables	Asthma COVID-19 (n=130)	Non-Asthma COVID-19 (n=2585)	p-value
Female (%)	53.8	46	0.08
Age, years	59.4±17.5	61.4 ±19.1	0.24
Length of hospital stay (days)	12± 11.3	12.6± 12.9	0.56
ICU (%)	15.4	11.5	0.27
Death (%)	4.6	14.8	<0.001

Note: Data are presented as percentages or as mean ±SD.
Abbreviation: ICU, intensive care unit.

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Table 2 Demographics and Clinical Features of Asthmatic COVID-19 Admitted Patients

Variables	Total Cohort (n= 130)	Asthma with Non-Severe Outcome (n=108)	Asthma with Severe Outcome. (n= 22) (ICU Stay 20; Intubation 9; Death 6)	p-value
Demographics				
Age, years	59.4 ± 17.5	59.4 ± 17.9	58.7 ± 15.6	0.938
Sex, n (%)				0.645
Male	60 (46.2)	51 (47.2)	9 (40.9)	
Female	70 (53.8)	57 (52.8)	13 (59.1)	
BMI	30± 5.8	29.7± 5.4	31.4 ±7.6	0.222
Smoking, n (%)				0.509
Current smokers	6 (4.6)	4 (3.7)	2 (9.1)	
Former smokers	29 (22.3)	25 (23.1)	4 (18.2)	
Non-smokers	95 (73.1)	79 (73.1)	16 (72.7)	
Respiratory/allergy comorbidities				
Respiratory allergy, n (%)	50 (38.5)	43 (39.8)	7 (31.8)	0.632
Atopy, n (%)▲	20 (15.4)	18 (16.7)	2 (9.1)	0.369
Nasal Polyposis, n (%)	22 (16.9)	19 (17.6)	3 (13.6)	0.652
AERD, n (%)	6 (4.6)	5 (4.6)	1 (4.5)	0.986
OSA, n (%)*	15 (11.5)	14 (13.0)	1 (4.5)	0.260
Bronchiectasis, n (%)	9 (6.9)	5 (4.6)	4 (18.2)	0.022
COPD, n (%)	5 (3.8)	5 (4.6)	0 (0.0)	0.303
Previous pneumonia, n (%)	13 (10.0)	9 (8.3)	4 (18.2)	0.160
Onset of asthma, years	23.3 ± 14.9	24.1 ± 15.2	19.5 ± 13.3	0.192
Previous exacerbation, n (%)▲▲	14 (10.8)	12 (11.1)	2 (9.1)	0.781
FEV1%▲▲▲	90.3 ± 21.1	88.3± 23.8	99.7± 24.8	0.201
FEV1/FVC	74.9 ± 14	74.5 ± 13.7	77.2 ± 15.9	0.602
Asthma therapy				
GINA steps				0.048
Step 1	48 (36.9)	44 (40.7)	4 (18.2)	
Step 2–3	60 (46.1)	49 (45.4)	11 (50.0)	
Step 4–5	22 (16.9)	15 (13.8)	7 (31.8)	
ICS				0.001
Without or low ICS doses	92 (70.7)	83 (76.8)	9 (40.9)	
Moderate or high ICS doses	38 (29.3)	25 (23.2)	13 (59.1)	
OCS	2 (1.5)	2 (1.9)	0 (0.0)	0.520
Biologics	0 (0)	0 (0)	0 (0)	
Other comorbidities				
Arterial hypertension, n (%)	56 (43.1)	47 (43.5)	9 (40.9)	1.000
Diabetes mellitus, n (%)	25 (19.2)	21 (19.4)	4 (18.2)	0.891
Dyslipidaemia, n (%)	37 (38.5)	31 (28.7)	6 (27.3)	1.000
Obesity, n (%)▲▲▲▲	46 (35.4)	36 (33.3)	10 (45.5)	0.330
Heart failure	9 (6.9)	7 (6.5)	2 (9.1)	0.660
Renal insufficiency, n (%)	8 (6.2)	7 (6.5)	1 (4.5)	0.731
AF, n (%)	7 (5.4)	4 (3.7)	3 (13.6)	0.060
Severe congenital disease, n (%)	2 (1.5)	2 (1.9)	0 (0.0)	0.520
Haematological disease, n (%)	2 (1.5)	1 (0.9)	1 (4.5)	0.209
Immunodeficiency, n (%)	1 (0.8)	0 (0.0)	1 (4.5)	0.026
Autoimmune disease, n (%)	1 (0.8)	1 (0.9)	0 (0.0)	0.650
Stroke, n (%)	5 (3.8)	5 (4.6)	0 (0.0)	0.303
Dementia, n (%)	8 (6.2)	7 (6.5)	1 (4.5)	0.731

(Continued)

Table 2 (Continued).

Variables	Total Cohort (n= 130)	Asthma with Non-Severe Outcome (n=108)	Asthma with Severe Outcome. (n= 22) (ICU Stay 20; Intubation 9; Death 6)	p-value
Malignant neoplasm, n (%)	5 (3.8)	5 (4.6)	0 (0.0)	0.303
Hypothyroidism, n (%)	7 (5.4)	6 (5.6)	1 (4.5)	0.848
Chronic liver disease, n (%)	1 (0.8)	1 (0.9)	0 (0.0)	0.650

Notes: Data are presented as percentages or as mean ±SD. [▲]Atopy: food allergy and/or atopic dermatitis, [▲▲]Patients with at least 1 exacerbation in previous 12 months, [▲▲▲]Spirometric values obtained in 52 patients. [▲▲▲▲]Obesity =BMI ≥30 kg h^2.
Abbreviations: AERD, Aspirin–Exacerbated Respiratory Disease; AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV$_1$/FVC ratio, forced expiratory volume/forced vital capacity; GINA, Global Initiative for Asthma (2020); ICS inhaled corticosteroid; OCS, oral corticosteroid; OSA, obstructive sleep apnea; VEF$_1$, forced expiratory volume in one second.

Out of the asthmatic patients, 17% presented a severe outcome. Considering all data examined, significant differences for a poor prognosis were detected in comorbidities (bronchiectasis, AF), prescribed treatments (GINA step 4 or 5, moderate or high ICS doses), and laboratory findings (LDH, CRP, SpO$_2$).

In the multivariable regression analysis, 4 predictive independent factors were identified: AF comorbidity, need for moderate or high ICS doses, lower SpO$_2$, and higher LDH (Table 4). In laboratory findings, the best cut-off values for predicting severe outcome were LDH >300 U/L (p<0.001), CRP >90 mgrs./L(p=0.003) and SpO2≤94% (p=0.013).

Table 3 Laboratory Findings on Admission, COVID-19 Therapy, and Length of the Hospital Stay

Variables	Total Cohort (N = 130)	Asthma with Non-Severe Outcome (N=108)	Asthma with Severe Outcome (N = 22)	p-value
Clinical and Laboratory				
Lymphocytes, cells/µL	4429 ± 1261	1284.1 ± 698.1	1147.8 ± 589.4	0.394
AEC, cells/µL	50.4 ± 110.3	49.9 ± 98.4	53.3 ± 161.5	0.896
LDH, U/L	321.1 ± 235.5	280.5 ± 166.6	526.2 ± 388.5	0.010
D-dimer, ng/dl	735 ± 713	693.3± 688.1	947.6 ± 813.7	0.136
Temperature, Celsius	36.9 ± 0.9	36.6 ±0.9	36.9 ± 1	0.990
SpO2, %	93.5 ± 5.2	94.3 ± 4	90 ± 8.6	0.034
Ferritin, µg/L[▲]	499.5 ± 541.9	499 ± 549.8	496.8± 5534	0.991
CRP, mg/L	66.7± 68.6	57.7 ± 60	109.8± 89.8	0.015
IL-6, pg/mL[▲▲]	71.4 ± 242.1	43.6 ± 145.1	218.2 ± 500.3	0.277
Therapy				
Hydroxychloroquine, n (%)	24 (18.5)	20 (18.5)	4 (18.2)	0.970
Remdesivir, n (%)	13 (10.0)	10 (9.3)	3 (13.6)	0.533
Bariticinib, n (%)	25 (19.2)	15 (13.9)	10 (45.5)	0.001
Tocilizumab, n (%)	17 (13.1)	11 (10.2)	6 (27.3)	0.030
Corticosteroids, n (%)	105 (80.8)	83 (76.8)	22 (100)	0.012
Lopinavir/Ritonavir, n (%)	9 (6.9)	4 (3.7)	5 (22.7)	0.001
Antibiotics, n (%)	124 (95.4)	102 (94.4)	22 (100)	0.258
Oxygen therapy, n (%)	53 (40.8)	37 (34.2)	16 (72.7)	0.001
High-flow oxygen, n (%)	21 (16.2)	8 (7.4)	13 (59.1)	<0.001
Length of hospital stay, days	12± 11.3	9.5± 5.5	24.3± 21.4	0.005
ICU, n (%)			20 (15.4)	
Intubation, n (%)			9 (6.9)	
Death, n (%)			6 (4.6)	

Notes: Data are presented as mean±SD or (%), [▲]Data obtained in 34 patients. [▲▲]Data obtained in 69 patients.
Abbreviations: AEC, absolute eosinophil count; CRP, C-reactive protein; IL-6, interleukin 6; ICU, intensive care unit; LDH, lactate dehydrogenase; SpO2, pulse oximetry signal.

Table 4 Clinical Factors Independently Associated with Severe Outcomes Among Asthmatic Patients Hospitalized with COVID-19

Variables	Univariate	p-value	Multivariable	p-value
	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
LDH	1.002 (1.000–1.005)	0.05	1.003 (1.001–1.005)	0.01
AF	11.474 (1.803–73.032)	0.01	5.626 (1.048–30.195)	0.04
SpO2	0.937 (0.860–1.021)	0.14	0.899 (0.814–0.993)	0.04
Moderate or high ICS doses	2.5 (0.472–13.235)	0.28	3.255 (1.019–10.4)	0.05
4 or 5 GINA step	1.175 (0.369–3.744)	0.78		
CRP	1.007 (0.998–1.015)	0.11		
Bronchiectasis	3.584 (0.593–21.673)	0.16		

Abbreviations: AF, atrial fibrillation; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GINA, Global Initiative for asthma (2020); ICS, inhaled corticosteroid; LDH, lactate dehydrogenase; OR, odds ratio; SpO2, pulse oximetry signal.

Discussion

Previous research reveals significant differences in the prevalence of asthma among patients with COVID-19 according to geographical origin. Multiple factors possibly determine this variability: social and political customs, health system organization, genetic factors, or assessment period (an earlier or more advanced phase of the pandemic), among others.

The overall prevalence of asthmatic COVID-19 admitted patients in our study (5.03%) is similar to previous ones conducted in our geographical zone.[12,13] These data are in line with 6.4% of asthmatic patients admitted for COVID-19 in European studies, with an intermediate prevalence between 2.2% in Asia and 10.2% in North America.[14]

Allergic asthma phenotype was determined in 38% of admitted patients, consistent with the prevalence rates of 26–39% reported among asthmatics adults over 50 years.[15,16]

The mean spirometric values prior to admission were within normal limits, without significant differences between severe and non-severe outcomes, although the sample analyzed was small.

According to multivariate regression analysis, concomitant AF, elevated LDH level, lower SpO_2 saturation, and previous treatment with moderate or high dose inhaled corticosteroids at admission were independent risk factors for severe outcomes, in line with reported published research.[17–20,27] Other major risk factors for a poor prognosis of COVID-19 (age, obesity, hypertension, diabetes, cancer, etc.) were not detected in our study.

Regarding eosinophils, the mean absolute eosinophil count (AEC) in our COVID-19 asthmatic patients was low (50.4 ± 110.3). Eosinopenia is a common finding in COVID-19 disease[1] probably related to worse outcomes in asthmatic patients,[21,22] nonetheless, in our cohort of patients with asthma we did not find significant differences in absolute eosinophil count on admission in terms of outcomes, as in previous reports.[27]

The strengths of our work lie in the enrolled patients being representative of the real-life asthmatic patients hospitalized with COVID-19 as well as in the large set of clinical and biochemical data collected. Nonetheless, it presents some limitations. Data were collected from a single hospital with a retrospective design. Comparative group control and outpatients with asthma were not included in the analysis. Previous spirometry and some laboratory data (IL-6, ferritin) were only disposable in a limited number of patients. Finally, a larger cohort study is needed to verify our conclusions.

Conclusion

Our results suggest that admitted adult patients with asthma did not have a higher risk of severe COVID-19. 5% of asthmatic patients had a result of death vs 14.8% of the global admitted population (p<0.001). The prevalence of asthma in COVID-19 hospitalized patients was consistent with asthma prevalence in the general population. Asthmatic patients with more requirements in their treatments (moderate or high doses of ICS) and coexistence of AF, had a higher risk of

the severe outcome. SpO2 ≤ 94% and LDH>300 on admission were other independent factors for a poor prognosis in asthmatics patients hospitalized with COVID-19.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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