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Short communication

Asthma in a large COVID-19 cohort: Prevalence, features, and determinants of COVID-19 disease severity

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ABSTRACT

Background: Asthma prevalence among COVID-19 patients seems to be surprisingly low. However the clinical profile of COVID-19 asthmatic patients and potential determinants of higher susceptibility/worse outcome have been scarcely investigated. We aimed to describe the prevalence and features of asthmatic patients hospitalized for COVID-19 and to explore the association between their clinical asthma profile and COVID-19 severity.
Methods: Medical records of patients admitted to COVID-Units of six Italian cities major hospitals were reviewed. Demographic and clinical data were analyzed and compared according to the COVID-19 outcome (death/need for ventilation vs discharge at home without requiring invasive procedures).
Results: Within the COVID-Units population (n = 2000) asthma prevalence was 2.1%. Among the asthmatics the mean age was 61.1 years and 60% were females. Around half of patients were atopic, blood eosinophilia was normal in most of patients. An asthma exacerbation in the 6 months before the Covid-Unit admittance was reported by 18% of patients. 24% suffered from GINA step 4–5 asthma, and 5% were under biologic treatment. 31% of patients were not on regular treatment and a negligible use of oral steroid was recorded. Within the worse outcome group, a prevalence of males was detected (64 vs 29%, p = 0.026); they suffered from more severe asthma (43 vs 14%, p = 0.040) and were more frequently current or former smokers (62 vs 25%, p = 0.038).
Conclusions: Our report, the first including a large COVID-19 hospitalized Italian population, confirms the low prevalence of asthma. On the other side patients with GINA 4/5 asthma, and those not adequately treated, should be considered at higher risk.

1. Introduction

Asthmatic patients usually present an increased susceptibility to respiratory viral infections [1]. Nevertheless according to the available evidence asthma prevalence among COVID-19 patients is surprisingly low [2–5]. A lower expression of ACE 2 receptors described in T2-high asthma as well as the effects of inhaled corticosteroids, may account for this finding [6,7], although the protective role of inhalation therapy is under debate [8]. On the other side, asthmatic patients admitted to intensive care for COVID-19 seemed to experience a more severe disease

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[9]. However the clinical profile of asthmatics hospitalized for COVID 19 have been scarcely investigated [4,5,10], and the relationship between asthma and SARS-Cov-2 remains controversial [2,3,6].

Our retrospective study aimed to describe the prevalence and features of asthmatic patients hospitalized for COVID-19 and to explore the association between their clinical asthma profile and COVID-19 severity.

2. Materials and methods

Electronic medical records of patients admitted to COVID-Units of six cities major hospitals in the North and Center of Italy during the Italian pandemic peak (1st March - 30th April 2020) were reviewed. COVID-19 patients were identified on the basis of ICD-10 coding in discharge diagnosis. Asthmatics were identified through a specific exemption code, which is released by specialists in the case asthma diagnosis is confirmed by clinical and functional (positive methacholine challenge test OR positive bronchodilator reversibility test) assessment. Demographic and clinical data of patients, as listed in Table 1, were analyzed and compared in two subpopulations stratified according to the COVID-19 outcome. Death, admittance to intensive care unit or need for ventilation were identified as markers of more severe COVID-related illness (worse outcome subgroup) whilst patients discharged at home without requiring invasive procedures were grouped as better outcome. The study was approved by the Institutional Review Boards (2649CESC).

2.1. Statistical analysis

A preliminary Shapiro-Wilk test was performed. Data are reported as percentages for categorical variables and as mean (standard deviation) or median [interquartile range] for continuous variables. Categorical variables were compared by the $\chi 2$ test or the Fisher exact test, while continuous variables were assessed by the independent *t*-test or the non-parametric Mann-Whitney *U* test. A univariate regression analysis was used to identify predictors of a worse outcome (the dependent variables). All analyses were performed using IBM SPSS, version 17.0 (IBM Corp., Armonk, NY, USA) and p-values of <0.05 was considered statistically significant.

3. Results

Overall 42 asthmatic patients were identified, representing 2.1% of the whole COVID-Units population (n = 2000). Table 1 summarizes demographic and clinical characteristics of the study population. Atopy characterized around half of the asthmatic patients, and blood eosinophilia was reported to be within the reference range (<0.45 10^9/L) in 91.6% of patients. The occurrence of asthma exacerbation in the 6 months before the Covid Unit admittance was reported by 18% of patients,. Only 5% were treated with biologics for severe asthma.

By reviewing the prescribed asthma treatment, 24% of patients were classified as severe asthmatics according to GINA recommendations; nevertheless 31% of patients at the admission were not on regular treatment. In patients with worse outcome a prevalence of males was detected; they suffered from more severe asthma (GINA level 4 and 5) and were more frequently current or former smokers. Higher C-reactive protein level and longer hospital stay were associated with worse outcome (Table 2).

According to the univariate regression analysis (Table 3) GINA step 4–5 asthma is significantly associated with the probability of a worse outcome.

4. Discussion

To our knowledge our work provides the first focus on asthma in a large Italian population of COVID-19 hospitalized patients. The overall prevalence is similar to previous studies [2–5] and, interestingly, is much lower than asthma prevalence in the general Italian population (6%) [11].

The unexpected low proportion of asthmatics among the COVID-19 hospitalized patients is still under debate. Of note, up to now asthma has not been specifically and extensively investigated as potential risk factor and few studies clearly report its frequency among the baseline clinical features of COVID-19 patients. Further focused research may clarify the issue.

In our study population, the higher number of females (60%) is consistent with the general trends of asthma distribution [12]. On the opposite, US reports described a higher prevalence of asthmatics within COVID-19 population when compared to our findings and to asthma prevalence in the US general population [10]. Of note, the US study

Table 1
General characteristics of asthmatic patients hospitalized due to COVID-19.

Variables	Total cohort (N = 42)	Asthmatics with a better outcome (N = 28)	Asthmatics with a worse outcome (N = 14) (death: 4, intensive care unit: 4, need for ventilation: 6)	p-value
Age, years	61.1 ± 14.7	58.9 ± 15.8	65.7 ± 11.5	0.16
Age, ≤ 50 years, n (%)	8 (19)	7 (25)	1 (7)	0.23
Sex, male/female, n (%)	17 (40)/ 25 (60)	8 (29)/20 (71)	9 (64)/5 (36)	**0.03**
Smoking habit, n (%) Current or former smokers Non-smokers	15 (37) 26 (63)	7 (25) 21 (75)	8 (62) 5 (38)	**0.04**
Pack/year	31.9 ± 23.6	24 ± 20.2	41.9 ± 26.4	0.29
Pre-existing medical illness				
Arterial hypertension, n (%)	18 (43)	10 (36)	8 (57)	0.19
Chronic heart disease, n (%)	8 (19)	3 (11)	5 (36)	0.09
Diabetes mellitus, n (%)	3 (7)	2 (7)	1 (7)	>0.99
Nasal polyps, n (%)	8 (19)	6 (21)	2 (14)	0.58
Atopy, n (%)	20 (48)	12 (43)	8 (57)	0.38
Obesity[a], n (%)	15 (37)	9 (32)	6 (50)	0.31
GINA step 4–5, n (%)Δ	10 (24)	4 (14)	6 (43)	**0.04**
Patients with an exacerbation during previous 6-months, % Δ	7 (18)	4 (15)	3 (25)	0.65
Domiciliary therapy[b]				
As-needed therapy, n (%)	13 (31)	8 (29)	5 (36)	0.73
ICS/LABA, n (%)	25 (59)	19 (68)	6 (43)	0.12
ICS/LABA/LAMA, n (%)	4 (9)	1 (4)	3 (21)	0.10
Biological therapy, n (%)	2 (5)	1 (4)	1 (7)	>0.99
OCS, n (%)	4 (10)	3 (11)	1 (7)	>0.99
ACE inhibitors, n (%)	15 (36)	8 (29)	7 (50)	0.17
PPIs, n (%)	4 (9)	2 (7)	2 (14)	0.59
Diuretics, n (%)	2 (5)	0 (0)	2 (14)	0.11

Data are shown as percentages or as medians [interquartile range]. Percentages are calculated for non-missing data.
Abbreviations ICS indicate inhaled corticosteroids; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroids; ACE, angiotensin converting enzyme; PPIs, proton pump inhibitors.
Δ Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Available from: www.ginasthma.org.
[a] Obesity was defined according to the BMI ≥30 kg h^2.
[b] Evaluated as therapy at admission.

Table 2
Clinical and laboratory characteristics at hospital admittance.

Variables	Total cohort (N = 42)	Asthmatics with a better outcome (N = 28)	Asthmatics with a worse outcome (N = 14)	p-value
Time from onset to hospitalization, days	6 [5]	6 [5]	6 [3]	0.95
Length of hospital stay, days	13.5 [12]	7.5 [12]	17 [12]	**0.002**
Symptoms at admission, n (%)				
Fever	35 (83)	22 (79)	13 (93)	0.39
Cough	30 (71)	20 (71)	10 (71)	>0.99
Dyspnea	25 (59)	14 (50)	11 (79)	0.07
Asthenia	12 (29)	8 (29)	4 (29)	>0.99
Myalgia	3 (7)	2 (7)	1 (7)	>0.99
Anosmia/ageusia	6 (14)	2 (7)	4 (29)	0.15
Headache/confusion	2 (5)	2 (7)	0 (0)	0.54
Nausea/vomiting/ diarrhoea	7 (17)	4 (14)	3 (21)	0.67
Bilateral interstitial involvement, n (%)	19 (56)	9 (43)	10 (77)	0.05
$PaCO_2$, mmHg	34.5 ± 8.3	33.1 ± 5.1	38.2 ± 13.7	0.25
PaO_2/FiO_2	231.9 [224.5]	302.3 [186.3]	107.6 [75.01]	**0.004**
Lactate level, mmol/L	1.06 ± 0.30	0.97 ± 0.23	1.22 ± 0.38	0.15
Leucocytes, cells/μL	5440 [3040]	5240 [2830]	5700 [5060]	0.42
Neutrophil to lymphocyte ratio	4.61 [4.73]	3.88 [2.36]	6.47 [6.69]	0.14
Eosinophils, cells/μL	10 [62.6]	10 [40]	0 [80]	0.41
Haemoglobin, grams/dL	13.1 ± 2.4	13.1 ± 2.3	13.1 ± 2.9	>0.99
Platelets, $1 \cdot 10^3$ cells/μL	211.7 ± 75.7	211.2 ± 73.1	212.7 ± 83.6	0.95
C-reactive protein, mg/L	37.5 [100]	17.6 [59]	88.9 [127]	**0.03**
Procalcitonin, ng/mL	0.13 [0.23]	0.13 [0.16]	0.08 [0.39]	0.97
D-dimer, ng/mL	544.5 [1000]	595.5 [1082]	537 [2974]	0.64
Fibrinogen, mg/dL	465.1 ± 178.5	462.6 ± 168.4	472.2 ± 226.5	0.92
LDH, U/L	312.6 ± 104.4	296.5 ± 93.8	350.3 ± 126.8	0.30
Therapy during hospitalization, n (%)				
Lopinavir/Ritonavir	33 (79)	21 (75)	12 (86)	0.69
Remdesivir	1 (2)	1 (4)	0 (0)	>0.99
Hydroxychloroquine	39 (93)	25 (89)	14 (100)	0.54
Tocilizumab	13 (31)	5 (18)	8 (57)	**0.01**
Steroids	14 (33)	9 (32)	5 (36)	>0.99
Azithromycin	10 (24)	3 (11)	7 (50)	**0.008**
LMWH	24 (57)	13 (46)	11 (79)	**0.047**

Data are shown as number (percentages) or as medians [interquartile range]. Percentages are calculated for non-missing data.; *Abbreviations:* $PaCO_2$ indicate partial pressure of arterial carbon dioxide; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen; LDH, lactic acid dehydrogenase, LMWH, low-molecular-weight heparin.

included non-hospitalized patients, who might have experienced mild or no symptoms. Furthermore, US population includes a not-negligible component of Afro Americans; in those racial minorities, both higher prevalence of asthma and more severe COVID-19 have been described, mainly due to socio-economic and environmental conditions acting as specific risk factors [13].

When stratifying the patients according to COVID-19 severity, atopy was equally distributed. This observation seems in contrast with the hypothetical "protective" role of atopic status [6]. Of note in our study atopy was defined on the basis of clinical history only, that may hamper the accuracy of the information. However, when looking at the clinical profile of our patients, including the low eosinophil count, the proportion of smokers, the low prevalence of nasal polyposis, the negligible use of biologics for asthma, a prevalent T2 low phenotype can be hypothesized. The proportion of current/former smokers in our population could suggest a potential differential diagnosis with COPD; however the exemption code for asthma, as detailed in Material and Methods paragraph, allowed us to specifically identify asthmatic patients.

Table 3
Univariate regression analysis on predictors of COVID-19 disease worse outcome.

Variables	Univariate analysis		
	OR	95% CI	p value
Sex			
Male	1	–	
Female	0.22	0.06 to 0.87	**0.03**
Smoking habit			
Current or former	1	–	
Non-smoker	0.21	0.05 to 0.85	**0.03**
GINA step 4-5	4.50	1.007 to 20.10	**0.049**
PaO_2/FiO_2, +1	0.979	0.960 to 0.998	**0.03**
C-reactive protein, +1 mg/L	1.012	1.000 to 1.023	**0.04**

Regarding eosinophils, no significant differences in terms of baseline peripheral eosinophilia were detected in our sub-populations, which seems in contrast with the finding from other authors [2]. Of note they reported an association between worse COVID-19 outcome and low levels of eosinophils during the illness course, whilst our observation refers to baseline values. However, further studies are needed to address and clarify the issue.

31% of patients at the admission were not on regular treatment but they only used rescue medications. It has been hypothesized that inhaled steroids could somehow modulate the susceptibility to Covid-19 infection [6]. Our observation did not seem to confirm the same hypothesis, in fact the lack of a regular inhaled treatment was equally distributed among patients with better and worse outcome. However the small sample size does not allow generalizing our results, and the protective role of inhalation therapy is still under debate [8]. Of note, the proportion of GINA 4 and 5 stage patients was significantly higher in the worse outcome subgroup. It suggests that severe asthma might act as a risk factor for worse COVID-19 disease, as supported by the results of the univariate regression analysis (Table 3), especially when not adequately treated. However the hypothesis needs to be confirmed by larger studies.

When comparing the two subpopulations stratified by COVID-19 outcome, smoking habit more frequently characterized the worse outcome patients, which is quite expected, as smoke acts as independent risk factor in many conditions. However it can be hypothesized that smoke may amplify the relevance of asthma in determining a higher susceptibility. The more significant increase of C-reactive protein and the longer duration of hospitalization in our patients with poorer outcome reflect what has been previously described in COVID-19 populations, although they seem to be non-specific markers associated with severe COVID infection independently of the presence or severity of asthma [2,3]. In contrast with previous reports [2,3] no difference in D-Dimer was observed between the groups in our study. Of note, differently from the mentioned reports, our values refer to baseline assessment and not the illness course.

5. Conclusion

A major limitation of our study is the lack of direct comparison with a COVID-19 non-asthmatic population. Also, due to its retrospective design, some baseline patients' characteristics potentially impacting on the disease outcomes, including asthma subtype baseline blood eosinophil count, IgE level, previous thromboembolic events, information on influenza vaccination, are missing.

However our data provide a first asthma prevalence report in a large Italian population of COVID-19 hospitalized patients, confirming that the proportion of asthmatics is very small and suggesting that asthma itself cannot be considered an independent risk factor for COVID 19. On the other side patients with asthma receiving GINA 4/5 therapy, and those not adequately treated, should be considered at higher risk of worse COVID-19 outcome.

Disclosure of potential conflict of interest

All the authors declare no conflicts of interest. The work has been partially supported by the Cariverona Foundation, ENACT Project.

Author statement

MC, AV, GS, AM: Conceptualization; MC, AV, AM, EV, DB, FC-B, FC, GG, FM, LP, OR: Data curation; EC: Formal analysis; Funding acquisition: not applicable; MC, AV, AM, EV, DB, FC-B, FC, GG, FM, LP, OR: Investigation; FA, DG, CM, OO, GP, AV, EC: Methodology; MA, GS, EC: Project administration; GS, CM, AV, OO, DG: Resources; EC: Software; FA, DG, GP, AV, OO, GS: Supervision; GS, FA, DG, CM, OO, GP, AV, EC Validation; All authors: Visualization; MC, EC: Writing - original draft; All authors: review & editing.

References

[1] M. Caminati, D.L. Pham, D. Bagnasco, G.W. Canonica, Type 2 immunity in asthma, World Allergy Organ. J 11 (1) (2018 Jun 26) 13.
[2] J.J. Zhang, X. Dong, Y.Y. Cao, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy 75 (2020) 1730–1741.
[3] X. Li, S. Xu, M. Yu, K. Wang, Y. Tao, Y. Zhou, et al., Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan, J. Allergy Clin. Immunol. 146 (2020) 110–114.
[4] M. Caminati, C. Lombardi, C. Micheletto, E. Roca, B. Bigni, F. Furci, et al., Asthmatic patients in COVID-19 outbreak: few cases despite many cases, J. Allergy Clin. Immunol. (20) (2020 Jun 22). S0091-6749, 30825-3.
[5] S. Avdeev, S. Moiseev, M. Brovko, A. Yavorovskiy, K. Umbetova, L. Akulkina, N. Tsareva, et al., Low prevalence of bronchial asthma and chronic obstructive lung disease among intensive care unit patients with COVID-19, Allergy 75 (2020) 2703–2704.
[6] D.J. Jackson, W.W. Busse, L.B. Bacharier, M. Kattan, G.T. O'Connor, R.A. Wood, et al., Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2, J. Allergy Clin. Immunol. 146 (2020) 203–220.
[7] M.C. Peters, S. Sajuthi, P. Deford, S. Christenson, C.L. Rios, M.T. Montgomery, et al., COVID-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids, Am. J. Respir. Crit. Care Med. 1 (202) (2020) 83–90.
[8] A. Schultze, A.J. Walker, B. MacKenna, C.E. Morton, K. Bhaskaran, J.P. Brown, et al., Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform, Lancet Respir. Med. 8 (2020) 1106–1120.
[9] M. Mahdavinia, K.J. Foster, E. Jauregui, D. Moore, D. Adnan, A.B. Andy-Nweye, et al., Asthma prolongs intubation in COVID-19, J. Allergy Clin. Immunol. Pract. 8 (2020) 2388–2391.
[10] K.D. Chhiba, G.B. Patel, T.H.T. Vu, M.M. Chen, A. Guo, E. Kudlaty, et al., Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19, J. Allergy Clin. Immunol. 146 (2020) 307–314.
[11] R. de Marco, V. Cappa, S. Accordini, M. Rava, L. Antonicelli, O. Bortolami, et al., Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010, Eur. Respir. J. 39 (4) (2012 Apr) 883–892.
[12] H. Fuseini, D.C. Newcomb, Mechanisms driving gender differences in asthma, Curr. Allergy Asthma Rep. 17 (3) (2017 Mar) 19.
[13] E.B. Brandt, A.F. Beck, T.B. Mersha, Air pollution, racial disparities, and COVID-19 mortality, J. Allergy Clin. Immunol. 146 (2020) 61–63.