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Prevalence and Outcome of Asthma in Adult Patients Admitted to the Emergency Department for COVID-19: A Case-Control Study

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Abstract: (1) Background: Viral respiratory infections are common triggers for asthma exacerbation, often leading patients to the emergency department (ED). COVID-19, the disease caused by the SARS-CoV-2 virus, typically presents with respiratory symptoms, from minor symptoms, up to and including severe acute respiratory failure. Data on the association between asthma and COVID-19 are conflicting, and those from an ED setting are scarce. Our aims were to assess the prevalence and outcome of patients with asthma admitted to the ED for COVID-19. (2) Methods: We performed a case-control study, extracting data from a registry of adult patients with confirmed COVID-19 consecutively admitted to the ED of our hospital between March 2020 and January 2021. (3) Results: We identified 83 patients with asthma out of 935 individuals (prevalence 8.9%). There were no significant differences between cases and controls regarding both the proportion of hospital admissions and patients with critical COVID-19. (OR 1.37; 95% CI 0.52–3.56; and (OR 0.74; 95% CI 0.31–1.78 respectively). (4) Conclusions: In patients admitted to the ED for COVID-19, the prevalence of asthma was not higher than expected, and asthma was not associated with a worse outcome, in terms of the rate of hospitalization and critical COVID-19 disease.

Keywords: asthma; COVID-19; emergency department

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1. Introduction

Asthma is a common chronic respiratory disease usually characterized by chronic airway inflammation and a combination of variable respiratory symptoms and expiratory airflow limitation [1]. Asthma affects people of all ages and is associated with significant morbidity and mortality. Its prevalence varies according to different age groups and countries and is influenced by many other variables, including definition and setting. The overall prevalence in 2019 ranged from 5.4 to 9.8%, based on different definitions of asthma [2]. However, there is a significant variation (1–18%) between different countries [1,2]. Adult patients with asthma are frequently admitted to the Emergency Department (ED) for exacerbations or uncontrolled symptoms [3]. Different well-known triggers, including viral respiratory infections, can modify the airway hyper-responsiveness typical of asthma, leading to airway obstruction and rapid worsening of respiratory symptoms [4].

The pandemic associated with SARS-CoV-2 infection has affected hundreds of millions of people worldwide due to its high prevalence and rapid transmission [5]. Symptoms and disease severity are extremely variable. The clinical manifestations of SARS-CoV-2 infection may involve different organs or systems, i.e., gastrointestinal, cardiovascular, nervous, and

hematological, among others. However, the most common complication is an interstitial pneumonia that could be associated with different degrees of respiratory failure, up to and including acute respiratory distress syndrome [6]. Millions of deaths occurred worldwide due to severe clinical forms of COVID-19, mainly due to such respiratory complications. Several factors, some virus-related (such as viral load and variant) and some host-related (including age, gender, and comorbidities), play a role in determining the clinical picture of SARS-CoV-2 infection [7]. On the other hand, the availability of specific vaccines has radically changed the course of COVID-19. Full vaccination with booster doses has been associated with a significant improvement in clinical outcome, especially in high-risk patients, such as the elderly and frail [8,9].

Regarding comorbidities, initially asthma, like other chronic lung diseases, was considered a risk factor for severe COVID-19. Several studies on the relationship between asthma and COVID-19 have since been published. They were extremely heterogeneous in terms of sample size, population, design, and setting, providing conflicting results. Most of them concluded that asthma was not a risk factor for severe COVID-19, sometimes even suggesting a protective role [10–14]. However, other studies reported that asthma was associated with a worse outcome [15–17].

Furthermore, most of the available data on the relationship between asthma and COVID-19 comes from large national datasets or retrospective cohorts of patients hospitalized for COVID-19. However, both are associated with possible bias. In fact, the former allow the collection of data on large samples, but is often less precise and accurate, while the latter guarantee higher quality results, but regarding from the most seriously ill patients.

Our hypothesis is that the emergency department is the best environment to study the interaction between asthma and SARS-CoV-2 infection as, globally, it is the true watershed between primary healthcare and the hospital. Only two retrospective cohort studies of asthma and COVID-19 patients in the emergency room are currently available [18,19]. In addition to the prevalence of asthma, these studies assessed only one or two general outcomes, such as hospitalization and/or mortality rate. In a preliminary study by our group on COVID-19 patients consecutively enrolled in an Italian ED during the first pandemic wave, the prevalence of asthma was very low (2.5%), and the risk of hospitalization was significantly lower compared to that of non-asthmatics [14]. In a large sample study conducted in the United States, the prevalence of asthma was high (20.9%), and hospitalization and mortality rates were similar between asthmatics and non-asthmatics [15]. Interestingly, the authors also demonstrated that the T-helper 2 (Th2) asthma phenotype, characterized by higher absolute eosinophil count (AEC), was associated with decreased morbidity and mortality [19].

Given the lack of data on this topic from the emergency department setting, we decided to carry out a case-control study that would allow us to more accurately test whether asthma was a risk factor for a worse outcome in patients with COVID-19.

Our objectives were, in adult patients hospitalized for COVID-19, to asses:

(1) the prevalence of asthma;
(2) whether asthma was associated with hospitalization and critical COVID-19; and
(3) whether AEC affected clinical outcomes.

2. Materials and Methods

We conducted this case-control study by extracting data from a consecutive registry of adult patients with evidence of SARS-CoV-2 infection admitted to the ED of our hospital between March 2020 and January 2021. The Agostino Gemelli University Hospital, one of the largest in Rome (Italy), is a tertiary center with > 80,000 visits to the ED every year. The registry was created by consulting the electronic health records of two different health information systems, the former specific for ED and the latter for hospitalized patients.

The inclusion criteria were: age $\geq$ 18 years, ED admission for symptoms compatible with COVID-19, and evidence of SARS-CoV-2 infection obtained by a molecular nasopharyngeal swab performed after hospital arrival.

We searched the registry for all individuals with asthma, who, as for all other comorbidities, were identified on the basis of the International Classification of Diseases, Tenth Revision (ICD-10) codes recorded in the medical records. For each COVID-19 asthma patient, we identified one COVID-19 non-asthma patient comparator, matched by age, sex, race, and enrollment period (within 14 days).We collected the following data from all individuals: demographic variables, smoking habits, body mass index (BMI), main comorbidities (diabetes mellitus, arterial hypertension, significant cardiopathies such as chronic heart failure and/or ischemic heart disease, and COPD), ongoing treatment with inhaled or oral corticosteroids (ICS or OCS), PaO_2 ratio/FiO_2 upon arrival, C-reactive protein (CRP), and AEC. As widely adopted, multimorbidity was defined as the presence in the same individual of $\geq$2 chronic diseases [20]. In addition, we registered the principal pharmacological treatments for COVID-19 administered to hospitalized patients.

Incomplete data and unavailability of the molecular swab report for SARS-CoV-2 made after arrival in our ED were exclusion criteria. The end-points explored were: hospitalization, intensive care unit (ICU) admission, pharmacological treatment for COVID-19, need for high-flow nasal cannula oxygenation (HFNCO), non-invasive ventilation (NIV), continuous positive airway pressure (CPAP), mechanical ventilation (MV), death, and length of stay (LOS). LOS was calculated since arrival at the ED until hospital discharge/demise. We classified as critical COVID-19 all individuals with any of the following: need for ventilatory support through CPAP and/or NIV and/or MV and/or ICU admission and/or death related to COVID-19. In addition, we consulted the electronic health records of our hospital to assess whether individuals included in the present study and discharged to home after the first contact had returned to the ED within 1 month of enrollment.

Primary outcomes were the proportion of patients requiring hospitalization and those with critical COVID-19. Need for HFNCO, in-hospital mortality, and LOS were also compared between the two groups. Finally, in patients with asthma, we assessed the relationship between AEC and the primary outcomes.

We reported the data as percentages for categorical variables and as mean (standard deviation) for continuous variables. We compared categorical variables by $\chi 2$ test or Fisher exact test, and continuous variables by independent t-test or Mann–Whitney U test. We used multivariate logistic regression analysis to assess whether asthma was independently associated with hospitalization and critical COVID-19. All variables showing p value ≤ 0.1 during univariate analysis were included in the multivariate model. We performed the statistical analysis using IBM SPSS 26 software (IBM Corp., Armonk, NY, USA); p-values < 0.05 were considered statistically significant.

The present study was approved by the Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli—IRCCS, Rome, Italy (approval number 0014840/22).

3. Results

Our registry initially included 1069 adult patients with symptomatic SARS-CoV-2 infection. However, 134 individuals were excluded due to a missing molecular swab report after ED admission (38) or incomplete data (96). Overall, 83 patients with asthma were identified (prevalence 8.9%). A total of 83 COVID-19 patients without asthma—matched to cases for age, sex, race, and enrollment period—served as the controls (Figure 1).

Table 1 shows the demographic data, clinical characteristics, home treatment with inhaled or systemic steroids, values of the most common markers of acute inflammation (C-reactive protein, CRP, mg/L), and oxygenation (PaO_2/FiO_2) in the asthma cases and the controls. Although not specifically matched, the number of individuals who received the first vaccination in the last two weeks before hospitalization was the same (6%). The low vaccinated rate observed in the present study was consistent with the enrollment period (until January 2021). A significantly higher prevalence of arterial hypertension and multimorbidity was observed in the control group (33.7% vs. 55.4% and 36.1% vs. 57.8%, respectively; $p = 0.005$ for both analyzes). As expected, home treatment with inhaled corticosteroids (ICS) was significantly more common in the asthma group (50.6% vs. 3.6%;

$p < 0.001$). No significant differences were observed between cases and controls regarding the other variables, including oxygenation parameters (PaO_2/FiO_2), inflammatory markers (CRP), and absolute number of circulating eosinophils.

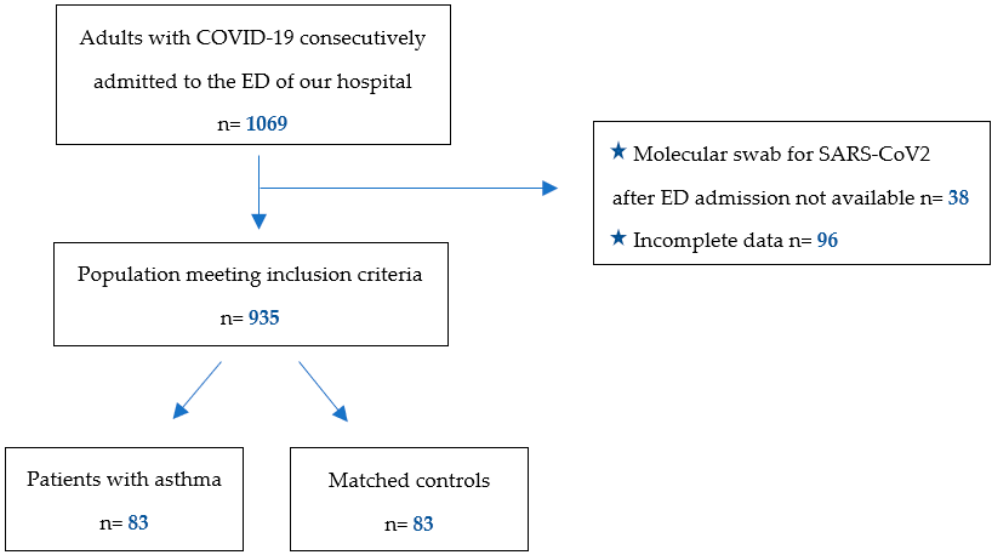

Figure 1. Flowchart of the study population. ED: emergency department.

Table 1. Characteristics of cases and controls admitted to our ED for symptomatic COVID-19. Abbreviations: SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; OCS, oral corticosteroids; AEC, absolute eosinophil count.

Variables	Asthma (N = 83)	Controls (N = 83)	*p* Value
Age (mean ± SD, years)	54.6 ± 14.6	54.6 ± 14.5	ns
Sex, males (%)	42 (50.6%)	42 (50.6%)	ns
Race:			
Caucasian (%)	74 (50.6%)	74 (50.6%)	ns
Others (%)	9 (10.8%)	9 (10.8%)	ns
Pandemic wave:			
First (%)	24 (28.9%)	24 (28.9%)	ns
Second (%)	59 (71.1%)	59 (71.1%)	ns
Vaccinated (first dose) (%)	5 (6%)	5 (6%)	ns
BMI > 24.9 (%)	33 (39.8%)	38 (45.8%)	ns
Current smokers (%)	13 (15.7%)	20 (24.1%)	ns
Diabetes (%)	12 (14.5%)	16 (19.3%)	ns
Hypertension (%)	28 (33.7%)	46 (55.4%)	0.005
Cardiopathy (%)	6 (7.2%)	9 (10.8%)	ns
COPD (%)	7 (8.4%)	4 (4.8%)	ns
Multimorbidity (%)	30 (36.1%)	48 (57.8%)	0.005
ICS (%)	42 (50.6%)	3 (3.6%)	<0.001
OCS (%)	6 (7.2%)	2 (2.4%)	ns
PaO_2/FiO_2 (mean ± SD, mmHg)	298.5 ± 109.1	298.2 ± 103.3	ns
CRP (mean ± SD, mg/L)	64.2 ± 73.7	68.6 ± 74.9	ns
AEC (mean ± SD, cells/μL)	42.0 ± 78.4	41.2 ± 51.3	ns
AEC ≥ 150 cells/μL (%)	4 (4.8%)	6 (7.2%)	ns

Slightly more patients with asthma were admitted to the hospital than the controls (70/83, 84.3% vs. 66/83, 79.5%), with no statistical differences ($p = 0.52$; OR 1.37; 95% CI 0.52–3.56; Table 2). The characteristics of the hospitalized cases and the controls were

similar to those reported in Table 1, with significant differences in arterial hypertension, multimorbidity, and home ICS treatment with ICS.

Table 2. Clinical outcomes in COVID-19 patients, with and without asthma, and the most common pharmacologic treatments for COVID-19 administered to the hospitalized patients. The *p*-value describes the level of statistical significance in the univariate analysis. Abbreviations: ICU, intensive care unit; LOS, length of stay.

	Asthma	Controls	*p* Value
Hospitalization (%)	70 (84.3%)	66 (79.5%)	ns
Critical COVID-19 (%)	21/70 (27.7%)	23/66 (34.8%)	ns
ICU admission (%)	17/70 (24.3%)	21/66 (31.8%)	ns
High flow nasal cannula (%)	10/70 (14.3%)	13/66 (19.7%)	ns
Non-invasive ventilation (%)	8/70 (11.4%)	11/66 (16.7%)	ns
Mechanical ventilation (%)	8/70 (11.4%)	15/66 (22.7%)	ns
In-hospital mortality (%)	8/70 (11.4%)	6/66 (9.1%)	ns
LOS (mean ± SD, days)	13.1 ± 7.8	14.6 ± 9.7	ns
In-hospital treatments:			
Corticosteroids (%)	45/70 (64.3%)	41/66 (62.1%)	ns
Anticoagulants (%)	48/70 (68.6%)	53/66 (80.3%)	ns
Antivirals (%)	15/70 (21.4%)	19/66 (28.8%)	ns
Immunomodulators (%)	8/70 (11.4%)	5/66 (7.6%)	ns

There were also no significant differences in the rate of critical COVID-19 (cases 21/70, 27.7% vs. controls 23/66, 34.8%; $p = 0.50$; OR 0.74; 95% CI 0.31–1.78). The proportion of individuals requiring HFNCO, in-hospital mortality, and mean LOS were similar in the cases and controls (Table 2). Pharmacological treatment for COVID-19, which could influence the outcomes, was administered in a similar proportion of cases and controls (Table 2).

Even in the multivariate analysis, there was no significant association between asthma and hospitalization (OR 1.93; 95% CI 0.83–4.53; $p = 0.52$) or critical COVID-19 (OR 0.74; 95% CI 0.31–1.78; $p = 0.50$).

Interestingly, even with the limitation of the small sample size, a higher eosinophil count was associated with a better outcome in the group of asthma patients. Indeed, AEC was significantly lower in asthmatics classified as critical COVID-19 patients (23.5 ± 26.4 vs. 49.2 ± 89.9 cells/μL; $p < 0.05$; Figure 2). Furthermore, AEC was lower in the hospitalized patients than in the patients discharged from the ED (40.3 ± 79.4 vs. 51.5 ± 74.9 cells/μL), without reaching a statistical significance. Furthermore, the AEC was lower in the hospitalized patients than in the patients discharged from the ED (40.3 ± 79.4 vs. 51.5 ± 74.9 cells/μL), but without reaching statistical significance.

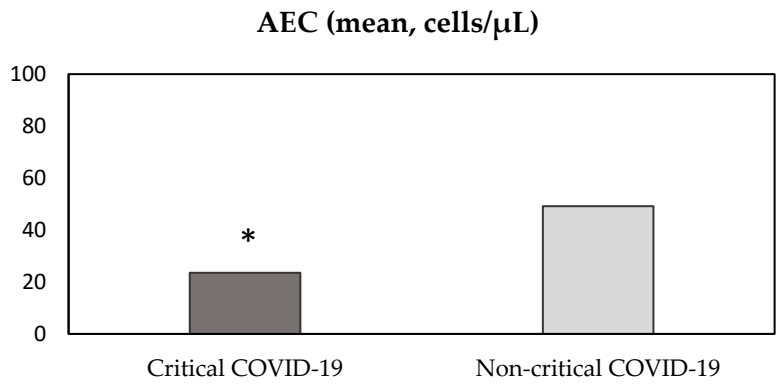

Figure 2. Mean absolute eosinophil count (AEC) in patients with asthma admitted to the ED at our institution, classified as critical or non-critical COVID-19. * = $p < 0.05$.

Finally, regarding the small group of patients discharged from the ED after enrollment, a total of 2 out of 13 patients with asthma (15.4%), and 1 out of 17 controls (5.8%) returned to the ED within 1 month (p = ns). All required medical attention for worsening symptoms related to COVID-19 and were hospitalized. None of them were classified as critical COVID-19 patients.

4. Discussion

Our case-control study found a prevalence of asthma of 8.9% in ED patients with COVID-19, similar to that reported in the general adult population and in most studies of patients hospitalized for COVID-19. Furthermore, in our study, asthma was not a risk factor for hospitalization or critical COVID-19. The prevalence of asthma worldwide in 2019 ranged from 5.4 to 9.8%, based on different definitions of asthma [2]. As shown by a census carried out by Italian general practitioners, the national prevalence was 9.1%, similar to the 8.8% observed in the Lazio region [21]. As showed by several studies published in the last two years, the prevalence of asthma in adults with COVID-19 was extremely variable. It ranged from 0.32% to 25.8%, with a pooled prevalence between 8.08% and 9.38%, based on studies included in a recent meta-analysis [22–24]. Based on the available limited data from Italy, the prevalence of asthma in adults with COVID-19 was lower than expected. Two retrospective cohort studies on patients hospitalized for COVID-19 in Northern Italy showed a prevalence of asthma of 2.1% and 3.8%, respectively [12,25]. In a brief report by our group on a retrospective cohort of 734 newly diagnosed COVID-19 patients admitted to the ED of our hospital, asthma prevalence was 2.5% [18]. To the best of our knowledge, in addition to the results produced by our group, only one other study has been published regarding the relationship between asthma and COVID-19 in the emergency department setting. It was a large retrospective cohort (4558 individuals) enrolled in United States (New York City, Bronx), reporting a high prevalence (20.9%) of asthma [19]. The extreme variability in asthma prevalence observed in these studies of COVID-19 patients is difficult to explain. It could depend on several factors, including geographical and racial differences, pandemic wave, setting, sample size, and other study-related methodological factors. The same variables may have also influenced the conflicting results of the studies assessing whether asthma was a risk factor for a worse COVID-19 outcome [10–17]. This is demonstrated by several meta-analysis published in recent months, choosing to include or not very heterogeneous studies, which sometimes presented asthma as a protective or neutral factor [22–24,26] and sometimes, as a risk factor for worse outcome [27–29]. However, especially when looking at more recent and higher quality studies, asthma does not appear as a risk factor for a worse outcome of COVID-19. As previously mentioned, most of the published studies enrolled hospitalized patients, thus creating a bias related to the loss of information regarding what happens before hospitalization. The emergency department can be a good middle ground between what has happened outside the hospital, concerning which it is very difficult to obtain sufficiently detailed information (see the large insurance or government datasets), and what happens inside the hospital wards. As mentioned, our study is the only one, along with that of Ferastraoaru et al., which enrolled patients admitted to the ED [19]. The proportion of asthmatics hospitalized for COVID-19 (78.8%) was extremely similar to that observed in our case-control study (84.3%). The outcomes explored were different, but mortality was similar in patients with asthma, without other significant comorbidities, and controls without asthma and with a comparable comorbidity burden. On the other hand, our findings that asthma is not a risk factor for critical COVID-19 were consistent with more recent prospective and retrospective studies on hospitalized patients [10–14]. Some pathophysiology recalls could help explain why a chronic respiratory disease associated with morbidity and mortality, especially during exacerbation triggered by infectious agents, does not represent a risk factor for SARS-CoV-2 infection and for severe COVID-19. Two key steps affect the entry of SARS-CoV-2 into human cells: the angiotensin converting the enzyme 2 receptor (ACE-2), binding the spike protein of the virus and the transmembrane serine protease 2 (TMPRSS-

2), which triggers the same protein [30]. It has been demonstrated that asthma patients do not overexpress the ACE-2 gene in the lungs compared to the expression of healthy individuals [31,32]. This may be related to the IL-13 release from eosinophilic cells [33]. As mentioned above, eosinophilia is the marker of a particular subgroup of asthmatics, the Th2 phenotype [1]. Furthermore, chronic ICS intake, the mainstay of asthma therapy, is associated with decreased expression of ACE-2 and TMPRSS-2 mRNA [32]. Finally, at least in the eosinophilic asthma phenotype, the imbalance of the inflammatory response towards the overexpression of Th2 cytokines may counteract the Th1 response induced by COVID-19. This could reduce the risk of complications of SARS-CoV-2 infection related to the storm of Th1 pro-inflammatory cytokines, including IL-6, among others [34]. As evidence of this, Ferastraoaru showed that the Th2 phenotype played a potentially protective role against a worse outcome in patients with asthma and COVID-19 [19]. Interestingly, our study also showed a possible association between eosinophils and outcome in patients with asthma and COVID-19. The mean absolute eosinophil count was significantly higher in asthmatics with a better clinical course of COVID-19, confirming the protective role of these cells.

Our study has some limitations. In our opinion, one of the main limitations is that it was monocentric, retrospective, and enrolled a limited number of patients with asthma. We attempted to characterize the asthmatic pattern using AEC detected upon arrival in the ED. However, this value could be strongly affected by chronic use of corticosteroids and/or by the SARS-CoV-2 infection itself [35,36]. In addition, the study refers to a different period from the current one, which has profoundly changed due to full mass vaccination and the appearance of new variants, specifically Omicron. To date, based on our study and last year's evidence, we can conclude that asthma by itself is not a risk factor for SARS-CoV-2 infection and for a worse outcome of COVID-19. This may be due, at least in part, to eosinophils, which are particularly elevated in a subset of asthmatic patients. Eosinophils are able to decrease the pulmonary expression of ACE-2 and the storm of pro-inflammatory Th1 cytokines, including IL-6, which are both pathogenetic factors associated with the more severe clinical course of COVID-19.

Further, large prospective studies are warranted to confirm these results and to explore whether different asthma phenotypes or characteristics may influence the outcomes of patients with asthma and COVID-19 infection.

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Informed Consent Statement: The ethics committee of our hospital waived written informed consent due to the retrospective nature of the study, assessing only clinical data without exposing patients to any potential risk.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Nista, Enrico Celestino; Nuzzo, Eugenia; Oggiano, Marco; Ojetti, Veronica; Pagano, Francesco Cosimo; Paiano, Gianfranco; Pais, Cristina; Paolillo, Federico; Pallavicini, Federico; Palombo, Andrea; Papa, Alfredo; Papanice, Domenico; Papparella, Luigi Giovanni; Paratore, Mattia; Parrinello, Giuseppe; Pasciuto, Giuliana; Pasculli, Pierpaolo; Pecorini, Giovanni; Perniola, Simone; Pero, Erika; Petricca, Luca; Petrucci, Martina; Picarelli, Chiara; Piccioni, Andrea; Piccolo, Annalisa; Piervincenzi, Edoardo; Pignataro, Giulia; Pignataro, Raffaele; Pintaudi, Gabriele; Pisapia, Luca; Pizzoferrato, Marco; Pizzolante, Fabrizio; Pola, Roberto; Policola, Caterina; Pompili, Maurizio; Pontecorvi, Flavia; Pontecorvi, Valerio; Ponziani, Francesca; Popolla, Valentina; Porceddu, Enrica; Porfidia, Angelo; Porro, Lucia Maria; Potenza, Annalisa; Pozzana, Francesca; Privitera, Giuseppe; Pugliese, Daniela; Pulcini, Gabriele; Racco, Simona; Raffaelli, Francesca; Ramunno, Vittoria; Rapaccini, Gian Ludovico; Richeldi, Luca; Rinninella, Emanuele; Rocchi, Sara; Romanò, Bruno; Romano, Stefano; Rosa, Federico; Rossi, Laura; Rossi, Raimondo; Rossini, Enrica; Rota, Elisabetta; Rovedi, Fabiana; Rubino, Carlotta; Rumi, Gabriele; Russo, Andrea; Sabia, Luca; Salerno, Andrea; Salini, Sara; Salvatore, Lucia; Samori, Dehara; Sandroni, Claudio; Sanguinetti, Maurizio; Santarelli, Luca; Santini, Paolo; Santolamazza, Danilo; Santoliquido, Angelo; Santopaolo, Francesco; Santoro, Michele Cosimo; Sardeo, Francesco; Sarnari, Caterina; Saviano, Angela; Saviano, Luisa; Scaldaferri, Franco; Scarascia, Roberta; Schepis, Tommaso; Schiavello, Francesca; Scoppettuolo, Giancarlo; Sedda, Davide; Sessa, Flaminio; Sestito,

Luisa; Settanni, Carlo; Siciliano, Matteo; Siciliano, Valentina; Sicuranza, Rossella; Simeoni, Benedetta; Simonetti, Jacopo; Smargiassi, Andrea; Soave, Paolo Maurizio; Sonnino, Chiara; Staiti, Domenico; Stella, Claudia; Stella, Leonardo; Stival, Eleonora; Taddei, Eleonora; Talerico, Rossella; Tamburello, Elio; Tamburrini, Enrica; Tanzarella, Eloisa Sofia; Tarascio, Elena; Tarli, Claudia; Tersali, Alessandra; Tilli, Pietro; Timpano, Jacopo; Torelli, Enrico; Torrini, Flavia; Tosato, Matteo; Tosoni, Alberto; Tricoli, Luca; Tritto, Marcello; Tumbarello, Mario; Tummolo, Anita Maria; Vallecoccia, Maria Sole; Valletta, Federico; Varone, Francesco; Vassalli, Francesco; Ventura, Giulio; Verardi, Lucrezia; Vetrone, Lorenzo; Vetrugno, Giuseppe; Visconti, Elena; Visconti, Felicia; Viviani, Andrea; Zaccaria, Raffaella; Zaccone, Carmelina; Zelano, Lorenzo; Zileri Dal Verme, Lorenzo; and Zuccalà, Giuseppe.

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References

1. Reddel, H.K.; Bacharier, L.B.; Bateman, E.D.; Brightling, C.E.; Brusselle, G.G.; Buhl, R.; Cruz, A.A.; Duijts, L.; Drazen, J.M.; FitzGerald, J.M.; et al. Global Initiative for Asthma Strategy 2021: Executive summary and rationale for key changes. *Eur. Respir. J.* **2022**, *59*, 2102730. [CrossRef] [PubMed]
2. Song, P.; Adeloye, D.; Salim, H.; Dos Santos, J.P.; Campbell, H.; Sheikh, A.; Rudan, I. Global, regional, and national prevalence of asthma in 2019: A systematic analysis and modelling study. *J. Glob. Health* **2022**, *12*, 04052. [CrossRef] [PubMed]
3. Pugliese, F.R.; Guglielmelli, E.; Angelini, D.; Cicchini, C.; Castaldo, E.; Di Girolamo, F.; Fedeli, A.; Ronzoni, D.; Rumi, F.; Franceschi, F. Pharmacoeconomic management of patient with severe asthma in the Emergency Department: Retrospective multicentric and cost of illness study. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 11729–11739. [CrossRef] [PubMed]
4. Busse, W.W.; Lemanske, R.F., Jr.; Gern, J.E. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* **2010**, *376*, 826–834. [CrossRef]
5. Mehraeen, E.; Salehi, M.A.; Behnezhad, F.; Moghaddam, H.R.; SeyedAlinaghi, S. Transmission Modes of COVID-19: A Systematic Review. *Infect. Disord. Drug Targets* **2021**, *21*, e170721187995. [CrossRef]
6. Long, B.; Carius, B.M.; Chavez, S.; Liang, S.Y.; Brady, W.J.; Koyfman, A.; Gottlieb, M. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. *Am. J. Emerg. Med.* **2022**, *54*, 46–57. [CrossRef]
7. Dadras, O.; Afsahi, A.M.; Pashaei, Z.; Mojdeganlou, H.; Karimi, A.; Habibi, P.; Barzegary, A.; Fakhfouri, A.; Mirzapour, P.; Janfaza, N.; et al. The relationship between COVID-19 viral load and disease severity: A systematic review. *Immun. Inflamm. Dis.* **2022**, *10*, e580. [CrossRef]
8. Mehraeen, E.; Dadras, O.; Afsahi, A.M.; Karimi, A.; Pour, M.M.; Mirzapour, P.; Barzegary, A.; Behnezhad, F.; Habibi, P.; Salehi, M.A.; et al. Vaccines for COVID-19: A Systematic Review of Feasibility and Effectiveness. *Infect. Disord. Drug Targets* **2022**, *22*, e230921196758. [CrossRef]
9. Grewal, R.; Kitchen, S.A.; Nguyen, L.; Buchan, S.A.; Wilson, S.E.; Costa, A.P.; Kwong, J.C. Effectiveness of a fourth dose of covid-19 mRNA vaccine against the omicron variant among long term care residents in Ontario, Canada: Test negative design study. *BMJ* **2022**, *378*, e071502. [CrossRef]
10. Cao, L.; Lee, S.; Krings, J.G.; Rauseo, A.M.; Reynolds, D.; Presti, R.; Goss, C.; Mudd, P.A.; O'Halloran, J.A.; Wang, L. Asthma in patients with suspected and diagnosed coronavirus disease 2019. *Ann. Allergy Asthma. Immunol.* **2021**, *126*, 535–541.e532. [CrossRef]
11. Robinson, L.B.; Wang, L.; Fu, X.; Wallace, Z.S.; Long, A.A.; Zhang, Y.; Camargo, C.A., Jr.; Blumenthal, K.G. COVID-19 severity in asthma patients: A multi-center matched cohort study. *J. Asthma* **2022**, *59*, 442–450. [CrossRef] [PubMed]
12. Nicola, S.; Borrelli, R.; Ridolfi, I.; Bernardi, V.; Borrelli, P.; Guida, G.; Antonelli, A.; Albera, C.; Marengo, S.; Briozzo, A.; et al. COPD, but Not Asthma, Is Associated with Worse Outcomes in COVID-19: Real-Life Data from Four Main Centers in Northwest Italy. *J. Pers. Med.* **2022**, *12*, 1184. [CrossRef] [PubMed]
13. Calmes, D.; Graff, S.; Maes, N.; Frix, A.N.; Thys, M.; Bonhomme, O.; Berg, J.; Debruche, M.; Gester, F.; Henket, M.; et al. Asthma and COPD Are Not Risk Factors for ICU Stay and Death in Case of SARS-CoV2 Infection. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 160–169. [CrossRef] [PubMed]
14. Basin, S.; Valentin, S.; Maurac, A.; Poussel, M.; Pequignot, B.; Brindel, A.; Poupet, G.; Robert, C.; Baumann, C.; Luc, A.; et al. Progression to a severe form of COVID-19 among patients with chronic respiratory diseases. *Respir. Med. Res.* **2022**, *81*, 100880. [CrossRef] [PubMed]
15. Ludwig, A.; Brehm, C.E.; Fung, C.; Jia, S.; Troost, J.P.; Leuenberger, L.; Kaakati, R.; Tarantine, C.; Christoph, E.; Sjoding, M.W.; et al. Asthma and coronavirus disease 2019-related outcomes in hospitalized patients: A single-center experience. *Ann. Allergy Asthma Immunol.* **2022**, *129*, 79–87.e76. [CrossRef]
16. Chhiba, K.D.; Patel, G.B.; Vu, T.H.T.; Chen, M.M.; Guo, A.; Kudlaty, E.; Mai, Q.; Yeh, C.; Muhammad, L.N.; Harris, K.E.; et al. Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. *J. Allergy Clin. Immunol.* **2020**, *146*, 307–314.e304. [CrossRef]
17. Shi, T.; Pan, J.; Vasileiou, E.; Robertson, C.; Sheikh, A. Risk of serious COVID-19 outcomes among adults with asthma in Scotland: A national incident cohort study. *Lancet Respir. Med.* **2022**, *10*, 347–354. [CrossRef]

18. Gabrielli, M.; Pignataro, G.; Candelli, M.; Sacco Fernandez, M.; Bizzarri, M.; Esperide, A.; Franceschi, F.; Gemelli Against, C. Asthma in patients admitted to emergency department for COVID-19: Prevalence and risk of hospitalization. *Intern. Emerg. Med.* **2022**, *17*, 917–920. [CrossRef]
19. Ferastraoaru, D.; Hudes, G.; Jerschow, E.; Jariwala, S.; Karagic, M.; de Vos, G.; Rosenstreich, D.; Ramesh, M. Eosinophilia in Asthma Patients Is Protective Against Severe COVID-19 Illness. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 1152–1162.e1153. [CrossRef]
20. Johnston, M.C.; Crilly, M.; Black, C.; Prescott, G.J.; Mercer, S.W. Defining and measuring multimorbidity: A systematic review of systematic reviews. *Eur. J. Public Health* **2019**, *29*, 182–189. [CrossRef]
21. Cricelli, C.; Brignoli, O.; Medea, G.; Parretti, D.; Lombardo, F.; Lora Aprile, P.; Lapi, F.; Cricelli, I. Rapporto Osservasalute 2020–Impatto epidemiologico delle cronicità in Medicina Generale. 2021, pp. 137–163. Available online: https://osservatoriosullasalute.it/wp-content/uploads/2022/10/ro-2021-cronicita.pdf (accessed on 1 November 2022).
22. Otunla, A.; Rees, K.; Dennison, P.; Hobbs, R.; Suklan, J.; Schofield, E.; Gunnell, J.; Mighiu, A.; Hartmann-Boyce, J. Risks of infection, hospital and ICU admission, and death from COVID-19 in people with asthma: Systematic review and meta-analyses. *BMJ Evid. Based Med.* **2022**, *27*, 263–273. [CrossRef] [PubMed]
23. Sunjaya, A.P.; Allida, S.M.; Di Tanna, G.L.; Jenkins, C. Asthma and risk of infection, hospitalization, ICU admission and mortality from COVID-19: Systematic review and meta-analysis. *J. Asthma* **2022**, *59*, 866–879. [CrossRef] [PubMed]
24. Sunjaya, A.P.; Allida, S.M.; Di Tanna, G.L.; Jenkins, C.R. Asthma and COVID-19 risk: A systematic review and meta-analysis. *Eur. Respir. J.* **2022**, *59*, 2101209. [CrossRef] [PubMed]
25. Caminati, M.; Vultaggio, A.; Matucci, A.; Senna, G.; Almerigogna, F.; Bagnasco, D.; Chieco-Bianchi, F.; Cosini, F.; Girelli, D.; Guarnieri, G.; et al. Asthma in a large COVID-19 cohort: Prevalence, features, and determinants of COVID-19 disease severity. *Respir. Med.* **2021**, *176*, 106261. [CrossRef] [PubMed]
26. Hou, H.; Xu, J.; Li, Y.; Wang, Y.; Yang, H. The Association of Asthma With COVID-19 Mortality: An Updated Meta-Analysis Based on Adjusted Effect Estimates. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 3944–3968.e3945. [CrossRef]
27. Han, X.; Xu, J.; Hou, H.; Yang, H.; Wang, Y. Significant association of pre-existing asthma with an increased risk for ICU admission among COVID-19 patients: Evidence based on a meta-analysis. *J. Infect.* **2022**, *84*, 418–467. [CrossRef]
28. Mattey-Mora, P.P.; Begle, C.A.; Owusu, C.K.; Chen, C.; Parker, M.A. Hospitalised versus outpatient COVID-19 patients' background characteristics and comorbidities: A systematic review and meta-analysis. *Rev. Med. Virol.* **2022**, *32*, e2306. [CrossRef]
29. Shi, L.; Xu, J.; Xiao, W.; Wang, Y.; Jin, Y.; Chen, S.; Duan, G.; Yang, H. Asthma in patients with coronavirus disease 2019: A systematic review and meta-analysis. *Ann. Allergy Asthma Immunol.* **2021**, *126*, 524–534. [CrossRef]
30. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271–280.e278. [CrossRef]
31. Maes, T.; Bracke, K.; Brusselle, G.G. COVID-19, Asthma, and Inhaled Corticosteroids: Another Beneficial Effect of Inhaled Corticosteroids? *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 8–10. [CrossRef]
32. Peters, M.C.; Sajuthi, S.; Deford, P.; Christenson, S.; Rios, C.L.; Montgomery, M.T.; Woodruff, P.G.; Mauger, D.T.; Erzurum, S.C.; Johansson, M.W.; et al. COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 83–90. [CrossRef]
33. Bonser, L.R.; Eckalbar, W.L.; Rodriguez, L.; Shen, J.; Koh, K.D.; Ghias, K.; Zlock, L.T.; Christenson, S.; Woodruff, P.G.; Finkbeiner, W.E.; et al. The Type 2 Asthma Mediator IL-13 Inhibits Severe Acute Respiratory Syndrome Coronavirus 2 Infection of Bronchial Epithelium. *Am. J. Respir. Cell Mol. Biol.* **2022**, *66*, 391–401. [CrossRef]
34. Liu, S.; Zhi, Y.; Ying, S. COVID-19 and Asthma: Reflection During the Pandemic. *Clin. Rev. Allergy Immunol.* **2020**, *59*, 78–88. [CrossRef]
35. Lindsley, A.W.; Schwartz, J.T.; Rothenberg, M.E. Eosinophil responses during COVID-19 infections and coronavirus vaccination. *J. Allergy Clin. Immunol.* **2020**, *146*, 1–7. [CrossRef]
36. Evans, P.M.; O'Connor, B.J.; Fuller, R.W.; Barnes, P.J.; Chung, K.F. Effect of inhaled corticosteroids on peripheral blood eosinophil counts and density profiles in asthma. *J. Allergy Clin. Immunol.* **1993**, *91*, 643–650. [CrossRef]