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COVID-19 Susceptibility in Bronchial Asthma

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What is already known about this topic? Bronchial asthma has not been adequately assessed in coronavirus disease 2019 (COVID-19). Respiratory allergy is associated with significant reductions in the expression of angiotensin-converting enzyme 2 receptor, which is the entry receptor for COVID-19.

What does this article add to our knowledge? We observed lower COVID-19 susceptibility in patients with preexisting asthma. Antileukotrienes, inhaled corticosteroid, and long-acting beta-agonist use does not have a significant impact on COVID-19 positivity proportions. Smoking is negatively associated with a likelihood of COVID-19 infection.

How does this study impact current management guidelines? The study supports the statement that during the COVID-19 pandemic physicians should continue to treat asthma according to the existing asthma guidelines and recommendations.

BACKGROUND: Bronchial asthma has not been adequately assessed in coronavirus disease 2019 (COVID-19). Respiratory allergy is associated with significant reductions in the expression of angiotensin-converting enzyme 2 receptor, which is the entry receptor for COVID-19.

OBJECTIVE: To observe COVID-19 susceptibility in patients with bronchial asthma, analyze the prevalence of asthma in a large cohort of consecutive outpatient subjects who were tested with the RT-PCR assay for COVID-19.

METHODS: This was a retrospective population-based cross-sectional study using data from a large nationwide health maintenance organization in Israel. All health maintenance organization enrollees who had been tested for COVID-19 from February to June 2020 were included. Differences in demographic and clinical characteristics between the subjects with negative and positive COVID-19 RT-PCR test results and between COVID-19 RT-PCR–positive subjects with and without asthma were analyzed.

RESULTS: A total of 37,469 subjects were tested for COVID-19 RT-PCR, and results for 2,266 (6.05%) of them were positive. A significantly higher proportion of smokers was observed in the COVID-19–negative group than in the COVID-19–positive group (4734 [13.45%] vs 103 [4.55%]; P < .001). Asthma was found in 153 (6.75%) subjects of the COVID-19–positive group and in 3388 (9.62%) subjects of the COVID-19–negative group (P < .001). No significant impact of antileukotrienes, inhaled corticosteroids, and long-acting beta-blockers use was revealed on COVID-19 positivity proportions. Multiple logistic regression analysis adjusted for sex, age, smoking, and comorbidity revealed a negative association of asthma with the likelihood of being positive for COVID-19 (odds ratio, 0.71; 95% CI, 0.58-0.87; P = .001).

CONCLUSIONS: We observed lower COVID-19 susceptibility in patients with preexisting asthma. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:684-92)

Key words: Asthma; COVID-19; Susceptibility; Smoking

INTRODUCTION

Certain demographic and clinical characteristics such as older age, male sex, preexisting hypertension, and chronic pulmonary or cardiovascular diseases may predispose coronavirus disease 2019 (COVID-19)-infected patients to more severe manifestations.1-3 Bronchial asthma (with an estimated 8.4% prevalence in the United States4 and 5.68% in Israel5) has not been adequately assessed in individuals having COVID-19. Previous epidemiological reports from China6 and Italy7 revealed that fever patients with COVID-19 had asthma. Asthma was reported in 9% of hospitalized patients with COVID-19 in New York8 and in 14% in the United Kingdom.9 However, all these prevalence data were derived from the COVID-19 inpatient population. Therefore, the prevalence of asthma may be different in outpatient patients with COVID-19.

Allergic and antiviral responses involve 2 different arms in the immune system, which are reciprocally operating, involving an extensive regulatory immunity network.16 It is possible, as in other viral infections,11 that a predominance of type 2 cytokines...
might lessen the accumulation of proinflammatory cytokines in the pathogenesis of COVID-19. In addition, respiratory allergy and controlled allergen exposures are associated with significant reductions in the expression of angiotensin-converting enzyme 2 (ACE2) receptor, which is the entry receptor for COVID-19.12 Type I interferons can upregulate the expression ACE2, and the deficient interferon responses in patients with asthma might reduce the COVID-19 invasion by limiting the expression of ACE2 on the target cells.13

We hypothesize that preexisting asthma might have an influence on COVID-19 susceptibility. For this reason, we have analyzed the prevalence of asthma in a large cohort of consecutive outpatient subjects who were tested with the RT-PCR assay for COVID-19.

METHODS

Data source

We conducted a retrospective population-based cross-sectional study using data from the Leumit Health Services (LHS) database, a large nationwide health maintenance organization in Israel, which provides services to an estimated 725,000 members. LHS has a comprehensive computerized database, continuously updated regarding subjects’ demographic characteristics, medical diagnoses, medical encounters, hospitalizations, and laboratory tests.

All LHS members have similar health insurance and similar access to health care services. During each physician visit, a diagnosis is entered or updated according to the International Classification of Diseases, Ninth Revision (ICD-9). The validity of chronic diagnoses in the registry has been previously examined and confirmed as high.14,15

Study period and population. The study period was from February 1, 2020, to June 30, 2020 (the first COVID-19 patient was diagnosed in Israel in February 2020). The study included the Jewish and Arab population of Israel.

All LHS enrollees who had been tested for COVID-19 during the study period had been included. Testing was performed by physician referral, according to the Israeli Ministry of Health criteria for COVID-19 testing, which included direct exposure to a confirmed COVID-19 patient and/or presenting symptoms suggesting COVID-19 (cough, shortness of breath, or any other respiratory symptoms with fever). Nasopharyngeal swabs were taken and examined for COVID-19 by a real-time RT-PCR assay with internal positive and negative controls according to the guidelines of the World Health Organization. The Allplex 2019-nCoV Assay (Secgene, Inc, Seoul, Republic of Korea) was used until March 10, 2020, and since then the COBAS SARS-CoV-2 6800/8800 (Roche Pharmaceuticals, Basel, Switzerland). The study protocol was approved by the statutory clinical ethics committee in LHS and the Shamir Medical Center Institutional Review Board (Helsinki Committee) on human research.

Subjects

Data on demographic characteristics, laboratory results, and the ICD-9 codes were derived from our electronic medical records system. COVID-19 RT-PCR tests on nasopharyngeal swabs were performed by experienced personnel in a single centralized laboratory accordingly to international guidelines.16 All consecutive patients who tested for COVID-19 were included in the study. The electronic medical record of each subject was reviewed, and those patients with a diagnosis of asthma established by a physician and with prescribed asthma medications were recorded. The subjects were defined as having current asthma if they were identified by the presence of more than 1 ICD-9 code for asthma (493.00-493.92) and were prescribed any antiasthma medicine during the previous 12 months. Subjects with the ICD-9 codes for asthma (493.00-493.92), but without asthma medications and at least 1 asthma attack in the last 12 months were considered to be in remission or have an incorrect diagnosis of asthma. Asthma severity was assessed using the current Global Initiative for Asthma guideline, which offers recommendations for categorizing levels of asthma severity by medication requirements as mild (steps 1 and 2), moderate (steps 3-4), and severe (step 5).

Patients were excluded from the study group if they had a diagnosis of chronic obstructive pulmonary disease, emphysema, chronic bronchitis, cystic fibrosis, or interstitial lung disease. Active chronic diagnoses of comorbidities (allergic rhinitis, atopic dermatitis, diabetes, arterial hypertension, obesity, and systemic autoimmune diseases) from the 5 years before the COVID-19 RT-PCR testing were identified. Obesity was considered as a measurement of body mass index more than 30 m²/kg. Socioeconomic status (SES) data were taken from the Israeli Central Bureau of Statistics classification, which includes 20 subgroups, according to the home address. Classifications 1 to 9 were considered low-medium SES and 10 to 20 high SES.17 ICD-9 codes for exclusion criteria and comorbidities are presented in Table E1 in this article’s Online Repository at www.jaci-inpractice.org.

Statistical analyses

Differences in demographic and clinical characteristics between the subjects with negative and positive COVID-19 RT-PCR test results and between COVID-19 RT-PCR—positive subjects with and without asthma were analyzed using Student t test and Fisher exact χ² test for continuous and categorical variables, respectively, on the basis of normal distribution and variable characteristics. Categorical data are shown in counts and percentages. Data on continuous variables with normal distribution are presented as mean and 95% CI. The multiple regression analyses adjusted for sex, age, smoking, and comorbidities (allergic rhinitis, arterial hypertension, obesity, diabetes, systemic autoimmune diseases) were used to estimate the odds ratios (ORs) and 95% CI for the independent association between asthma and the COVID-19 RT-PCR test result. We furthermore performed sensitivity analysis while comparing the proportions of arterial hypertension, diabetes, and obesity between COVID-19—negative and COVID-19—positive groups by excluding the subjects younger than 40 years.

All statistical analyses were conducted using the Statistical Package STATA 12 software (StataCorp LP, College Station, Texas).

RESULTS

In the initial analysis, we assessed and compared various demographic and clinical characteristics in the subjects positive and negative for COVID-19. A total of 37,469 subjects were tested.
for COVID-19 by RT-PCR and 2,266 (6.05%) of them had a positive result. There was no significant difference between the 2 groups in sex. The body mass index was higher in the COVID-19-negative group (25.95 ± 7.25 kg/m²) than in the COVID-19-positive group (25.37 ± 6.63 kg/m²; \( P < .001 \)).

COVID-19-negative group was characterized by a higher prevalence of the subjects relating to children and adolescent age clusters (<5-19 years). A significantly higher proportion of smokers was observed in the COVID-19-negative group than in the COVID-19-positive group (4734 [13.45%] vs 103 [4.55%]; \( P < .001 \)) (Table I).

Prevalence of arterial hypertension (6835 [19.42%]) and diabetes (4165 [11.83%]) was higher in the COVID-19-negative group than in the COVID-19-positive group (276 [12.18%], \( P < .001 \), and 200 [8.83%], \( P < .001 \), respectively) (Table I).

| Characteristic                          | COVID-19–negative subjects (n = 35,203) | COVID-19–positive subjects (n = 2,266) | P       |
|----------------------------------------|----------------------------------------|----------------------------------------|---------|
| Sex: male, n (%)                       | 18,053 (51.28)                         | 1,200 (52.96)                          | .13     |
| Age (y), mean ± SD                     | 38.62 ± 23.43                          | 33.31 ± 20.77                          | <.001   |
| <5 y, n (%)                            | 1,820 (5.17)                           | 100 (4.41)                             | <.001   |
| 5-19 y, n (%)                          | 6,024 (17.11)                          | 602 (26.57)                            | <.001   |
| 20-39 y, n (%)                         | 12,386 (35.18)                         | 758 (33.45)                            | .09     |
| 40-59 y, n (%)                         | 7,875 (22.37)                          | 510 (22.51)                            | .88     |
| 60-79 y, n (%)                         | 4,461 (12.67)                          | 242 (10.68)                            | .006    |
| ≥80 y, n (%)                           | 2,637 (7.49)                           | 54 (2.38)                              | <.001   |
| Body mass index (kg/m²), mean ± SD    | 25.95 ± 7.25                           | 25.37 ± 6.63                           | <.001   |
| SES, n (%)                             |                                        |                                        |         |
| Low-medium                              | 22,886 (65.01)                         | 1,832 (80.85)                          | <.001   |
| High                                   | 9,063 (25.74)                          | 278 (12.27)                            | <.001   |
| Smoking status, n (%)                  |                                        |                                        |         |
| Current smoking                        | 4,734 (13.45)                          | 103 (4.55)                             | <.001   |
| Past smoker                            | 1,830 (5.20)                           | 69 (3.05)                              | <.001   |
| Never smoked                           | 24,079 (68.40)                         | 1,692 (74.67)                          | <.001   |
| Atopy                                  |                                        |                                        |         |
| Eosinophils (cells × 10⁹/L), mean ± SD | 0.23 ± 0.22                            | 0.23 ± 0.25                            | .37     |
| Eosinophils >0.5 cells × 10⁹/L, n (%)  | 2,319 (6.59)                           | 148 (6.53)                             | .92     |
| Allergic rhinitis, n (%)               | 4,566 (12.97)                          | 237 (10.46)                            | .83     |
| Atopic dermatitis, n (%)               | 1,266 (3.60)                           | 72 (3.18)                              | .29     |
| Asthma, n (%)                          | 3,388 (9.62)                           | 153 (6.75)                             | <.001   |
| Medications, n (%)                     |                                        |                                        |         |
| Antihistamines                         | 3,079 (8.75)                           | 134 (5.91)                             | <.001   |
| Nasal antihistamines                   | 227 (0.64)                             | 12 (0.53)                              | .50     |
| Antileukotrienes                       | 79 (0.22)                              | 2 (0.09)                               | .18     |
| Nasal corticosteroids                  | 1,497 (4.23)                           | 116 (5.1)                              | .06     |
| ICs                                    | 265 (0.75)                             | 19 (0.83)                              | .65     |
| Long-acting beta-agonists (LABAs)      | 40 (0.11)                              | 5 (0.22)                               | .15     |
| ICSs + LABAs                           | 811 (2.51)                             | 64 (2.82)                              | .34     |
| Systemic corticosteroids (Prednison)   | 3,154 (8.96)                           | 94 (4.15)                              | <.001   |
| Comorbidity, n (%)                     |                                        |                                        |         |
| Arterial hypertension                  | 6,835 (19.42)                          | 276 (12.18)                            | <.001   |
| Obesity                                | 6,794 (23.99)                          | 431 (24.59)                            | .57     |
| Diabetes                               | 4,165 (11.83)                          | 200 (8.83)                             | <.001   |
| Systemic autoimmune diseases           | 72 (0.20)                              | 5 (0.22)                               | .87     |

The prevalence of obesity and systemic autoimmune diseases was similar in both groups. Although the utilization of systemic antihistamines in the COVID-19–negative group was higher, multiple logistic regression model adjusted for sex, age, smoking, and comorbidity did not reveal the significant impact of use of antihistamines, inhaled corticosteroids (ICs), long-acting beta-agonists, and antileukotrienes on COVID-19 positivity proportions (Table II). A total of 153 (6.75%) cases with an active diagnosis of asthma were found among the COVID-19–infected patients. In the COVID-19–negative subjects, more cases (3388 [9.62%]) of asthma had been observed (\( P < .001 \)) (Table I). Multiple logistic regression analyses adjusted for sex, age, smoking, and comorbidity revealed that a diagnosis of asthma was negatively associated with the likelihood of being positive for COVID-19 (OR, 0.71; 95% CI, 0.58-0.87; \( P = .001 \)) (Table II).
In the COVID-19—negative group, we observed higher proportions of smokers (4734 [13.45%] vs 103 [4.55%]; \( P < .001 \)), allergic rhinitis (4566 [12.97%] vs 237 [10.46%]; \( P < .001 \)), and arterial hypertension (6835 [19.42%] vs 276 [12.18%]; \( P < .001 \)) than in the COVID-19—positive group (Table I). Multiple logistic regression analysis adjusted for sex, age, SES, smoking, and comorbidity showed that smoking and arterial hypertension were negatively associated with a likelihood of COVID-19 positivity (\( OR, 0.28; 95\% \) CI, 0.23-0.35; \( P < .001 \)), whereas obesity and low-medium SES were associated with an increased likelihood of being positive for COVID-19 (OR, 1.14; 95\% CI, 1.02-1.29; \( P = .026 \)) and (OR, 2.39; 95\% CI, 2.07-2.77; \( P < .001 \), respectively) (Table II).

No significant impact of use of antileukotrienes, ICS, and long-acting beta-agonists was revealed on COVID-19 positivity proportions.

Demographic and clinical characteristics in the COVID-19—positive patients with and without comorbid asthma are presented in Table III. No significant differences were observed between the 2 groups in sex, body mass index, and smoking. The proportions of subjects aged 5 to 19 years (543 [25.69%]) and 20 to 39 years (726 [34.36%]) years were higher in COVID-19—positive patients with asthma than in those without asthma (59 [38.56%], \( P < .001 \), and 32 [20.91%], \( P < .001 \), respectively). COVID-19—positive patients with asthma were characterized by higher proportions of allergic rhinitis than COVID-19—positive without asthma (192 [9.08%] vs 45 [29.41%]; \( P < .001 \)). For other comorbid conditions (atopic dermatitis, arterial hypertension, obesity, and systemic autoimmune diseases), no statistically significant differences were observed between the 2 groups.

COVID-19—positive subjects with asthma were characterized by higher levels of blood eosinophils (0.31 ± 0.28 cells \( \times 10^9/L \)), higher proportions of eosinophils (19 [12.42%]; \( P < .001 \)), and higher blood levels of IgE (224.61 ± 372.23 kIU/L) than the COVID-19—positive subjects without asthma (0.21 ± 0.22 cells \( \times 10^9/L \), \( P < .001 \); and 90.54 ± 131.21 kIU/L, \( P < .001 \), respectively) (Table III).

Hospitalization rates did not significantly differ between COVID-19 patients with and without asthma (Table III).

Medications prescribed during the previous 12 months, by therapeutic category in the patients with asthma with negative and positive COVID-19 RT-PCR results, are presented in Table IV. No significant differences were observed between the 2 groups in asthma severity and prescriptions of the antiasthmatic drugs.

The sensitivity analysis of patients 40 years or older is presented in Table V. We revealed the statistically significant differences in arterial hypertension between COVID-19—positive and COVID-19—negative subjects (265 [32.88%] vs 6506 [43.54%]; \( P < .001 \)). Obesity proportions were higher in

### TABLE II. Features associated with COVID-19—positive diagnosis

| Feature                                      | Multiple logistic regression model adjusted for sex and age, OR (95% CI) | \( P \)  | Multiple logistic regression model adjusted for sex, age, SES, smoking and comorbidity,* OR (95% CI) | \( P \)  |
|----------------------------------------------|------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------------------|-------|
| **Sex: male**                                | 1.13 (1.04-1.23)                                                       | <.001 | 1.26 (1.13-1.40)                                                                           | <.001 |
| **Age (y)**                                  | 0.98 (1.04-1.23)                                                       | .026  | 0.99 (0.98-1.00)                                                                           | .042  |
| **Low-medium SES**                          | 2.04 (1.95-2.87)                                                       | <.001 | 2.51 (2.15-2.94)                                                                           | <.001 |
| **Asthma**                                   | 0.67 (0.56-0.79)                                                       | <.001 | 0.73 (0.61-0.90)                                                                           | .003  |
| **Smoking status**                           |                                                                       |       |                                                                                               |       |
| Current smoking                              | 0.31 (0.25-0.38)                                                       | <.001 | 0.32 (0.23-0.39)                                                                           | <.001 |
| Past smoker                                  | 0.54 (0.42-0.69)                                                       | <.001 | 0.57 (0.45-0.62)                                                                           | <.001 |
| Never smoked                                 | 1.12 (1.01-1.23)                                                       | .026  | 1.11 (1.00-1.21)                                                                           | .043  |
| **Atopy**                                    |                                                                       |       |                                                                                               |       |
| Eosinophils \( >0.5 \) \( \times 10^9/L \)  | 0.89 (0.69-1.08)                                                       | .20   | 0.94 (0.71-1.14)                                                                           | .38   |
| Eosinophils \( >0.5 \) \( \times 10^9/L \)  | 0.87 (0.74-1.04)                                                       | .08   | 0.92 (0.75-1.15)                                                                           | .50   |
| Allergic rhinitis, n (%)                     | 0.83 (0.72-0.95)                                                       | .008  | 0.88 (0.75-1.04)                                                                           | .14   |
| Atopic dermatitis                            | 1.02 (0.79-1.29)                                                       | .89   | 1.15 (0.87-1.51)                                                                           | .29   |
| **Medications**                              |                                                                       |       |                                                                                               |       |
| Antihistamines                               | 0.71 (0.59-0.85)                                                       | <.001 | 0.95 (0.85-1.06)                                                                           | .39   |
| Nasal antihistamines                         | 0.90 (0.50-1.61)                                                       | .73   | 1.34 (0.74-2.43)                                                                           | .33   |
| Antileukotrienes                             | 0.35 (0.18-0.64)                                                       | .15   | 0.52 (0.07-3.88)                                                                           | .53   |
| Nasal corticosteroids                        | 0.82 (0.69-0.99)                                                       | .06   | 0.94 (0.75-1.29)                                                                           | .08   |
| ICSs                                         | 0.63 (0.34-1.15)                                                       | .13   | 0.85 (0.36-1.98)                                                                           | .71   |
| Long-acting beta-agonists (LABAs)            | 0.52 (0.07-3.82)                                                       | .52   | 1.23 (0.16-9.47)                                                                           | .84   |
| ICSs + LABAs                                 | 0.59 (0.38-0.93)                                                       | .023  | 1.22 (0.75-1.97)                                                                           | .42   |
| Systemic corticosteroids                     | 0.49 (0.39-0.61)                                                       | <.001 | 0.64 (0.51-0.89)                                                                           | <.001 |
| **Comorbidity**                              |                                                                       |       |                                                                                               |       |
| Arterial hypertension                        | 0.78 (0.67-0.92)                                                       | .003  | 0.79 (0.66-0.95)                                                                           | .013  |
| Diabetes                                     | 1.02 (0.86-1.21)                                                       | .81   | 1.09 (0.87-1.34)                                                                           | .87   |
| Obesity                                      | 1.02 (0.91-1.13)                                                       | .74   | 1.14 (1.02-1.29)                                                                           | .026  |
| Systemic autoimmune diseases                 | 1.32 (0.53-3.27)                                                       | .55   | 1.95 (0.77-4.92)                                                                           | .16   |

*Comorbidity: Allergic rhinitis, arterial hypertension, obesity, diabetes, systemic autoimmune diseases.

*OR (95% CI): Odds ratio (95% confidence interval).

\( \text{OR}, 1.14; 95\% \) CI, 1.02-1.29; \( P = .026 \) and (OR, 2.39; 95\% CI, 2.07-2.77; \( P < .001 \), respectively) (Table II).
COVID-19—positive (4421 [29.58%]) than in COVID-19—negative subjects (274 [33.99%]; \( P = .002 \)). No significant differences were observed between the groups in the prevalence of diabetes.

**DISCUSSION**

This study evaluated the possible association between the diagnosis of asthma and the likelihood of having a positive test result for COVID-19 in a large population cohort. Both pediatric and adult cases with asthma were included. In a multivariate logistic regression model, the preexisting diagnosis of asthma had a statistically significant negative association with the likelihood of COVID-19 infection.

At present, it is still unknown whether an asthma phenotype contributes to the definite protection of patients from COVID-19. Our literature review did not reveal publications with similar findings. Asthma has a high prevalence in the general population and has not been adequately documented in subjects positive for COVID-19. The China Centers for Disease Control reported that only 2.4% of 44,672 patients with COVID-19 had chronic respiratory diseases, including asthma. A study from Italy had also shown a relatively low prevalence of asthma among patients with COVID-19.

The observed reduction in health care utilization by patients with chronic asthma may be explained by the changes in risk factors brought on by COVID-19, such as air quality, the indoor environment, physical activity, weight control, medication management, and health care delivery. An online survey conducted by the World Allergy Organization Pediatric Asthma Committee has also revealed that children with asthma do not appear to be disproportionately affected by COVID-19.

The largest epidemiologic study of COVID-19 in China, which included 44,672 confirmed cases of COVID-19, did not identify asthma as a risk factor of COVID-19 severity. Other smaller epidemiological studies from several regions of Europe, Russia, the Middle East, and South America reported lower proportions of asthma among patients with COVID-19.

In our study, we did not find any difference in hospitalization rates between patients with COVID-19 with and without concomitant asthma. A recent study showed that asthma as comorbidity may not increase the mortality of COVID-19 in hospitalized patients. But reliable data on the influence of comorbid asthma on the possibility of hospitalization and the duration of hospitalization of COVID-19 patients are still too limited.

**TABLE III.** Demographic and clinical characteristics of COVID-19—positive patients with and without asthma

| Characteristic | COVID-19—positive subjects without asthma (n = 2113) | COVID-19—positive subjects with asthma (n = 153) | P     |
|---------------|---------------------------------------------------|---------------------------------|-------|
| Sex: male, n (%) | 1115 (52.73) | 85 (55.56) | .51   |
| Age (y)       | 33.44 ± 17.81 | 31.41± 19.25 | .16   |
| <5 y, n (%)   | 91 (4.31) | 9 (5.88) | .36   |
| 5-19 y, n (%) | 543 (25.69) | 59 (38.56) | <.001 |
| 20-39 y, n (%) | 726 (34.36) | 32 (20.91) | <.001 |
| 40-59 y, n (%) | 478 (23.56) | 32 (20.91) | .65   |
| ≥60-79 y, n (%) | 224 (10.6)  | 18 (11.76) | .65   |
| ≥80 y, n (%)  | 51 (2.41)  | 3 (1.96)  | .72   |
| Body mass index (kg/m²) | 25.41 ± 6.36 | 25.02 ± 5.24 | .46   |
| Smoking status, n (%) | | | |
| Current smoking | 85 (4.02) | 8 (5.23) | .47   |
| Past smoker    | 129 (6.11) | 11 (7.19) | .59   |
| Never smoked   | 1352 (63.98) | 94 (61.44) | .53   |
| Eosinophils (cells × 10⁹/L), mean ± SD | 0.21 ± 0.22 | 0.31 ± 0.28 | <.001 |
| Eosinophils >0.5 cells × 10⁹/L, n (%) | 126 (5.99) | 19 (12.42) | .002  |
| Allergic rhinitis, n (%) | 192 (9.08) | 45 (29.41) | <.001 |
| Atopic dermatitis, n (%) | 73 (3.46) | 9 (5.89) | .12   |
| IgE (kIU/L), mean ± SD | 90.54 ± 131.21 | 224.61 ± 372.23 | <.001 |
| Comorbidity, n (%) | | | |
| Arterial hypertension | 260 (12.31) | 16 (10.45) | .49   |
| Obesity        | 396 (18.74) | 35 (22.87) | .21   |
| Diabetes       | 238 (11.26) | 23 (15.03) | .16   |
| Systemic autoimmune diseases | 4 (0.19) | 1 (0.65) | .24   |
| Hospitalization, n (%) | 173 (8.19) | 17 (11.11) | .21   |

Spain reported a group of children with allergic asthma 14 years or younger with COVID-19. All patients presented mild symptoms, even though COVID-19 provoked asthma exacerbation. Another study from Children’s Hospital of Philadelphia reported reduced admissions and systemic steroid prescriptions in children with allergic asthma during the COVID-19 pandemic. The observed reduction in health care utilization by patients with chronic asthma may be explained by the changes in risk factors brought on by COVID-19, such as air quality, the indoor environment, physical activity, weight control, medication management, and health care delivery. An online survey conducted by the World Allergy Organization Pediatric Asthma Committee has also revealed that children with asthma do not appear to be disproportionately affected by COVID-19.
The information about smoking status was collected from the LHS database, where this information is mandatory in every subject. The value of smoking status is labeled "Smoking Status," and the possible choices in the electronic health record are "a smoker," which implies an active smoker or "never smoker." Prior smokers can be identified by the elimination of "smoker" status by a primary care practitioner. Imputation using Most Frequent statistical strategy to impute missing values was implemented to handle missing data, which were equal across the asthma and nonasthma groups. Consistent with the previous report, we observed an independent negative association between current smoking and the likelihood of COVID-19 infection. The nicotinic acetylcholine receptor plays a significant role in the pathophysiology of COVID-19, and there is certain evidence supporting the hypothesis that the COVID-19 virus is a nicotinic agent. Because of the possible protective effect of smoking, it has been suggested that pharmaceutical nicotine would be considered a potential treatment option in COVID-19. Notably, in previous severe acute respiratory syndrome outbreaks, patients with asthma appeared to be less susceptible to the coronavirus infection, which also uses ACE2 as an entry receptor. Reported entry receptors for most other coronaviruses do not include ACE2 and they exacerbate asthma on infection.

Most of our patients with asthma had mild asthma. We did not observe a link between preexisting asthma severity and COVID-19 positivity. Likewise, we did not reveal a significant impact of ICS and long-acting beta-agonist use on COVID-19 positivity proportions. Previous studies have shown that ICSs reduce proinflammatory and increase anti-inflammatory cytokine levels in patients with asthma. Recent basic research discovered that 2 host molecules ACE2 and transmembrane protease serine 2 play critical roles in the initiation of COVID-19 infection. The use of ICSs in subjects with asthma was dose-dependently associated with reduced ACE2 and transmembrane protease serine 2 mRNA expression. During viral attachment to host cells, the spike protein of COVID-19 binds to ACE2 as a receptor, while viral entry is assisted by priming of the spike protein by the transmembrane protease serine 2. It was reasonably speculated that by reducing airway inflammation, the

| Asthma severity and medications | COVID-19–negative subjects with asthma (n = 3388) | COVID-19–positive subjects with asthma (n = 153) | P |
|--------------------------------|-----------------------------------------------|-----------------------------------------------|---|
| Asthma severity, n (%)          |                                               |                                               |   |
| Mild asthma                     | 2441 (72.05)                                  | 113 (68.62)                                   | .53 |
| Moderate asthma                 | 629 (18.57)                                   | 23 (20.26)                                   | .27 |
| Severe asthma                   | 318 (9.39)                                    | 17 (11.11)                                   | .31 |
| Medications, n (%)              |                                               |                                               |   |
| Adrenergic bronchodilators      |                                               |                                               |   |
| Salbutamol                      | 1156 (34.12)                                  | 54 (35.29)                                   | .76 |
| Salmeterol                      | 11 (0.32)                                     | 1 (0.65)                                     | .49 |
| Formoterol                      | 19 (0.56)                                     | 1 (0.65)                                     | .88 |
| Anticholinergic bronchodilators |                                               |                                               |   |
| Ipratropium bromide             | 63 (1.86)                                     | 3 (1.92)                                     | .92 |
| Tiotropium                      | 3 (0.08)                                      | 0                                             | .61 |
| Leukotriene modifiers           |                                               |                                               |   |
| Montelukast                     | 94 (2.77)                                     | 5 (3.27)                                     | .71 |
| ICSs                            |                                               |                                               |   |
| Budesonide                      | 74 (2.18)                                     | 4 (2.61)                                     | .72 |
| Fluticasone                     | 157 (4.63)                                    | 9 (5.88)                                     | .47 |
| Mometasone                      | 219 (6.46)                                    | 12 (7.83)                                    | .49 |
| Beclomethasone                  | 183 (5.41)                                    | 9 (5.88)                                     | .53 |
| ICS/LABA combinations           |                                               |                                               |   |
| Fluticasone/salmeterol          | 31 (0.91)                                     | 1 (0.65)                                     | .74 |
| Fluticasone/vilanterol          | 276 (8.15)                                    | 14 (9.15)                                    | .49 |
| Budesonide/formoterol           | 398 (11.74)                                   | 25 (16.33)                                   | .09 |
| Beclomethasone/formoterol       | 75 (2.21)                                     | 7 (4.57)                                     | .06 |
| Systemic corticosteroids        |                                               |                                               |   |
| Prednisone                      | 182 (5.37)                                    | 11 (7.19)                                    | .33 |
| Biologicals                     |                                               |                                               |   |
| Anti–IL-5 (mepolizumab)         | 6 (0.17)                                      | 0                                             | .47 |
| Anti–IL-5R (benralizumab)       | 1 (0.03)                                      | 0                                             | .77 |
| Anti–IL-4R (dupilumab)          | 3 (0.09)                                      | 0                                             | .61 |
| LABA, Long-acting beta-agonists.
ICSs could exert some protective effects on patients with asthma in the early steps of COVID-19 infection. Although asthma was associated with a decreased risk for COVID-19 infection, our study does not support a role for ICSs in this protective effect.

Our study revealed a negative association between blood eosinophil levels and COVID-19 susceptibility. Type 2 inflammation is characterized by blood eosinophilia, whereas eosinopenia is a biomarker of severe COVID-19. Single-stranded RNA viruses can activate eosinophils through eosinophil-derived neurotoxin and TLR-7/MyD88-dependent mechanisms, triggering the antiviral immunity of eosinophils.

An additional finding of our study is the higher prevalence of arterial hypertension and diabetes in COVID-19-negative subjects. Many previously published studies showed that arterial hypertension is more prevalent among patients with COVID-19, and hypertension is considered as one of the most important risk factors for COVID-19 infection. In the stratified analysis of demographic and clinical characteristics in patients 40 years or older, we observed the analogous differences in the proportions of arterial hypertension between COVID-19—positive and COVID-19—negative subjects, as in a whole study sample. Remarkably, in the stratified analysis of the patients 40 years or older, no impact of comorbid diabetes on COVID-19 susceptibility was observed. Diabetes and prediabetic state are recognized as risk factors for COVID-19 susceptibility and COVID-19 severity. It is possible that preexisting hypertension and diabetes have an influence on public behavior and protective health measures taken by the hypertensive and diabetic patients, decreasing contacts with COVID-19—infected subjects.

Obesity proportions were found to be higher in our COVID-19—positive subjects in the sensitivity analysis, which is consistent with published data. Obesity is a risk factor for COVID-19 hospital admission and higher mortality from COVID-19 in countries with high obesity proportions. It is hypothesized that a high concentration of ACE2 in visceral adipose tissue potentially predisposes to COVID-19 infection and modulates the course of COVID-19.

Future studies are needed to better define how chronic comorbidity might modify compliance with public health measures to limit the effects of the COVID-19 pandemic.

One of the main strengths of our study is that it provides data from a large cohort of outpatients from a nationwide database. Most previous retrospective studies of COVID-19 comorbidities are hospital-based and thus often have the limitations of studies with a hospital-based setting. Our study has several potential limitations, mainly due to the retrospective, diagnostic code—based nature. Second, because asthma is a heterogeneous...
disease, we have no information about asthma phenotypes, specifically about whether asthma was allergic or not. There are racial differences within the population studied, but because race is not a feature in our data set, this is an additional limitation of the study. Lastly, because patients with chronic obstructive pulmonary disease were excluded, the burden of asthma-chronic obstructive pulmonary disease overlap in patients with COVID-19 was not evaluated.

CONCLUSIONS

We observed lower COVID-19 severity in patients with preexisting asthma. Our observation deserves further replication in larger samples and with patients from other institutions.

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### TABLE E1. ICD-9 codes for exclusion diagnoses and comorbidities

| Exclusion criteria diagnoses                                      | 490-496               |
|------------------------------------------------------------------|-----------------------|
| Chronic obstructive pulmonary disease                            | 490-496               |
| Emphysema                                                        | 492.8, V81.3          |
| Chronic bronchitis                                               | 491.0-491.9          |
| Comorbidities                                                    |                       |
| Allergic rhinitis                                                | 477.0-477.9          |
| Diabetes                                                         | 250.00-250.93         |
| Arterial hypertension                                            | 401-405              |
| Atopic dermatitis                                                | 691.0-681.8          |
| Systemic autoimmune diseases                                    |                       |
| Rheumatoid arthritis                                            | 714.0-714.9          |
| Systemic lupus erythematosus                                    | 710.0                |
| Sjögren syndrome                                                | 710.2                |
| Polymyositis                                                     | 710.4                |
| Dermatomyositis                                                  | 710.3                |
| Undifferentiated connective tissue disease                       | 710.9                |