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Letter to the Editor:

Risk factors for hospitalization, intensive care, and mortality among patients with asthma and COVID-19

To the Editor:

Respiratory viral illnesses are a well-established trigger of asthma exacerbations in children and adults and risk factor for poor outcomes and high health care utilization. Early studies from China identified chronic pulmonary disease as a risk factor for novel coronavirus disease 2019 (COVID-19) severity and death. US-based studies report that approximately 7% to 9% of hospitalized patients with COVID-19 had chronic lung disease, with asthma more prevalent than chronic obstructive pulmonary disease (COPD) (9% vs 5.4%, respectively). Recent analyses of COVID-19 cohorts suggest that chronic respiratory disease may unexpectedly be less of a risk factor for COVID-19 infection and severity than nonrespiratory diseases. However, most studies to date do not distinguish asthma from COPD within chronic respiratory disease, limiting identification of asthma-specific risk factors.

This case series used data (March 3, 2020, to June 8, 2020) from the Massachusetts-based Mass General Brigham (MGB, formerly Partners HealthCare) health system’s electronic health record. Inclusion criteria were (1) COVID-19 positive based on nasopharyngeal or sputum severe acute respiratory syndrome coronavirus 2 RT-PCR test administered between March 3, 2020, and May 20, 2020; (2) age 18 years or more at COVID-19 diagnosis; (3) previously diagnosed asthma, assessed as active asthma diagnosis on problem list or 2 or more separate encounters with International Classification of Diseases, Ninth Revision and or International Classification of Diseases, Tenth Revision codes (detailed in Table E1 in this article’s Online Repository at www.jacionline.org) as a primary or secondary diagnosis; and (4) MGB primary care provider. Data on demographic characteristics, socioeconomic markers, baseline body mass index, insurance, smoking status, baseline outpatient-prescribed asthma medications, comorbidities including allergic and respiratory diseases, and clinical course of COVID-19 care were extracted. Patients’ encounter history was followed for 14 days from COVID-19 diagnosis for hospitalization and intensive care unit (ICU) admission, or by June 8, 2020, for mortality.

We examined associations of demographic and clinical characteristics with hospitalization and ICU admission among those hospitalized for COVID-19, and mortality. Groups were compared using the Mann-Whitney-Wilcoxon test for continuous characteristics with hospitalization and ICU admission among those hospitalized for COVID-19, and mortality. Groups were compared using the Mann-Whitney-Wilcoxon test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Unadjusted P value less than or equal to .1 was used as a cutoff for choosing variables to enter into subsequent risk factor analysis. We performed univariable and multivariable analysis using age-stratified logistic regression. Statistical significance was accepted at a 2-sided P value of less than or equal to .05. A Bonferroni-corrected P value of less than .0016 was used to adjust for multiple testing. Statistical analyses were performed in R software, version 3.5.3 (R Foundation for Statistical Computing).

A total of 1827 patients met inclusion criteria (Table I). The median age was 54 years (interquartile range, 37-66 years), and 1232 (67.4%) were female. More than two-thirds of patients were triaged to outpatient care; 565 patients (30.9%) were hospitalized, and of those, less than half (n = 236 [41.8%]) were admitted to the ICU. Almost all hospitalized patients were admitted to inpatient (99.3%) or ICU (97.9%) services within 14 days of COVID-19 diagnosis. The mortality rate among patients with asthma was 5.4% (n = 98) across all patients (outpatient and hospitalized), 15.6% for hospitalized patients, and 23.3% for ICU patients, with 70 (71.4%) patients dying within 14 days of COVID-19 diagnosis (see Table E2 in this article’s Online Repository at www.jacionline.org). Twenty-three (4.1%) hospitalized patients remained hospitalized at the time of study censoring. Mortality rate for all adult MGB COVID-19–positive patients during this same time period was 4.5% overall, 15.7% for hospitalized, and 23.5% for ICU patients.

Compared with the outpatient group, hospitalized patients had higher baseline use of inhaled-corticosteroid (ICS)-long-acting-beta-agonist combination and anticholinergic controller medications. Controller medication use did not differ in the hospitalized general inpatient versus ICU groups. More patients in the outpatient group had only a short-acting beta-agonist (SABA) prescribed in the previous year compared with hospitalized patients (P < .001), whereas a higher percentage of hospitalized patients had been prescribed combined SABA-anticholinergic reliever medications (P < .001) (Table I); 54.7% of patients prescribed SABA-anticholinergic relievers were also prescribed a controller medication. Only baseline SABA medications differed between general inpatient and ICU patients (P = .024). Patients receiving biologics for asthma therapy did not differ across groups (see Table E3 in this article’s Online Repository at www.jacionline.org).

Increased risk for hospitalization versus outpatient care was significantly associated (Table II) with older age (unadjusted odds ratio [OR], 1.46; 95% CI, 1.38-1.55; P < .001, for every increase of 10 years), male sex (adjusted OR [aOR], 1.75; 95% CI, 1.36-2.24; P < .001), black (aOR, 1.65; 95% CI, 1.19-2.27; P = .002) and Asian (aOR, 3.19; 95% CI, 1.56-6.54; P = .0015) race, diabetes mellitus (aOR, 1.33; 95% CI, 1.0-1.75; P < .05), comorbid COPD (aOR, 1.92; 95% CI, 1.35-2.72; P < .001), cardiovascular disease (aOR, 1.52; 95% CI, 1.16-2.0; P = .002), or an active outpatient prescription for combined SABA-anticholinergic medication (aOR, 1.74; 95% CI, 1.09-2.8; P < .05). Sixty-two percent of hospitalized SABA-anticholinergic users also had COPD. Patients with only SABA prescriptions were less likely to be hospitalized (aOR, .59; 95% CI, 0.43-0.8; P < .001). Male sex, Asian race, COPD, and SABA-only remained significant after correcting for multiple comparisons (bolded aORs in Table II).

Although obesity, chronic kidney disease, and marital status were significantly associated with increased risk of ICU admission compared with general inpatient hospitalization, they were not robust to Bonferroni correction. Similarly, cardiovascular disease (aOR, 2.21; 95% CI, 1.21-4.04; P < .01) and male sex were the only variables that predicted higher odds of mortality but did not meet the significance threshold for multiple testing.

Several hospitalization risk factors for patients with asthma and COVID-19 reflect those identified in general populations of patients with COVID-19, including male sex, race, older age, and nonrespiratory comorbidities. Notably, male sex was a risk factor for hospitalization. However, asthma and COPD may paradoxically be less of a risk factor for COVID-19 infection and severity than nonrespiratory diseases, although further research is needed to confirm this finding.
TABLE I. Demographic and clinical characteristics of patients with a history of asthma and COVID-19, by care setting and mortality

| Demographic | Hospitalized (n = 1827) | Hospitalized (n = yes, 565) | ICU (n = 565) | P value | ICU (yes) (n = 236) | P value | Mortality (n = 1827) | P value |
|-------------|-------------------------|----------------------------|---------------|---------|----------------------|---------|----------------------|---------|
| Age (y), median (IQR) | 54 (37-66) | 50 (33-61) | 63 (50-75) | <.001 | 62 (49-75) | 65 (51-75-75) | .28 | 53 (36-65) | 76 (68-85) | <.001 |
| Race | 1827 | 1262 | 565 | <.001 | 13 of 565 (2.3) | 8 of 236 (3.4) | .71 | 251 of 197 (12.7) | 19 (9) | <.001 |
| | 1827 | 1262 | 565 | <.001 | 35 of 565 (6.2) | 17 of 236 (7.2) | .26 | 260 of 197 (13.5) | 0 | 98 of 0 (0) |
| | 1827 | 1262 | 565 | <.001 | 37 of 565 (6.7) | 26 of 236 (11) | .24 | 242 of 197 (12.4) | 1 | 98 of 0 (1) |
| | 1827 | 1262 | 565 | <.001 | 57 of 565 (10.1) | 47 of 236 (19.9) | .36 | 369 of 197 (21.3) | 0 | 8 of 0 (8.2) |
| | 1827 | 1262 | 565 | <.001 | 67 of 565 (20.4) | 53 of 236 (22.5) | .29 | 292 of 197 (16.9) | 0 | 98 of 0 (19.4) |
| | 1827 | 1262 | 565 | <.001 | 59 of 565 (10.1) | 48 of 236 (20.3) | .19 | 178 of 197 (10.3) | 0 | 30 of 0 (30.6) |
| | 1827 | 1262 | 565 | <.001 | 61 of 565 (18.5) | 37 of 236 (15.7) | .17 | 137 of 197 (7.9) | 0 | 39 of 0 (39.8) |
| Sex | 1827 | 1262 | 565 | <.001 | 199 of 565 (35.7) | 141 of 236 (59.7) | .93 | 1177 of 197 (66.1) | 55 | 98 of 0 (51.6) |
| Race | 1827 | 1262 | 565 | <.001 | 53 of 236 (22.6) | 38 of 236 (16.1) | .42 | 43 of 197 (22.4) | 0 | 10 of 0 (10.2) |
| Education level | 1827 | 1262 | 565 | <.001 | 15 of 236 (6.4) | 7 of 236 (3.0) | .03 | 169 of 197 (8.7) | 0 | 39 of 0 (39.8) |
| Ethnicity, Hispanic | 1827 | 1262 | 565 | <.001 | 15 of 236 (6.4) | 7 of 236 (3.0) | .03 | 169 of 197 (8.7) | 0 | 39 of 0 (39.8) |
| | 1827 | 1262 | 565 | <.001 | 24 of 236 (10.0) | 12 of 236 (5.1) | .05 | 147 of 197 (7.5) | 0 | 39 of 0 (39.8) |
| | 1827 | 1262 | 565 | <.001 | 38 of 236 (16.4) | 19 of 236 (8.1) | .07 | 127 of 197 (6.7) | 0 | 39 of 0 (39.8) |
| | 1827 | 1262 | 565 | <.001 | 59 of 236 (25.2) | 38 (16.1) | .42 | 43 of 197 (22.4) | 0 | 10 of 0 (10.2) |
| | 1827 | 1262 | 565 | <.001 | 83 of 236 (35.2) | 53 of 236 (22.5) | .29 | 272 of 197 (13.1) | 0 | 15 of 0 (15.3) |

(Continued)
*Data reflect patients diagnosed with COVID-19 between March 3, 2020, and May 20, 2020. Of 78,870 patients tested for COVID-19 in this period, 60.2% (n = 47,468) were female. Characteristics (except death) as of date of COVID-19 diagnosis.

†All P values are unadjusted.
‡Self-reported.
§As recorded by ICD code or problem list in the electronic health record. Diabetes mellitus includes type 1 and type 2. Chronic rhinosinusitis includes with and without nasal polyps.
¶With an FDA-approved indication for asthma.
\#Mortality data collected until June 8, 2020.
factor despite female predominance in COVID-19 testing and in positive diagnosis among patients with asthma.

In distinguishing asthma within chronic respiratory disease categorization, we found that a comorbid diagnosis of COPD was a strong risk factor for hospitalization, and the only comorbidity that remained statistically significant after correction for multiple comparisons. Mild asthma managed with SABA alone was more common in patients triaged to outpatient care, and these patients were less likely to be hospitalized. In contrast, we found no differences in risk for hospitalization or ICU-level care with ICS or combined ICS-long-acting beta-agonist use. Asthma-specific variables did not predict ICU care or mortality, and the differences between risk for inpatient hospitalization and ICU admission are a compelling area for future investigation.

MGB health system serves the largest volume of hospitalized patients with COVID-19 in New England. However, despite having an MGB primary care provider, some patients may have sought COVID-19 care out of our hospital system. Asthma prevalence in MGB COVID-19–positive patients (13.1%) is slightly higher than the asthma prevalence in a large New York City cohort (9%).

Electronic health record prescription data are not linked to pharmacy fill data; future research could use administrative claims data to strengthen associations with baseline asthma medication use. Finally, a small number of patients remained hospitalized at the time of censoring, which may have led to underreporting of subsequent ICU admissions or deaths. Available data support that mortality was similar for patients with COVID-19 with or without asthma in the MGB outpatient and inpatient settings.

Our findings highlight the importance of distinguishing asthma from chronic pulmonary diseases in COVID-19 research to establish an evidence base for risk evaluation and suggest that individuals with asthma-COPD overlap may be especially at risk. Further research examining the course of hospitalized patients is necessary to elucidate predictors of disease progression and clinical outcomes.

We gratefully acknowledge Jian Ying’s, PhD, valuable advice with the statistical analyses.

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https://doi.org/10.1016/j.jaci.2020.07.018