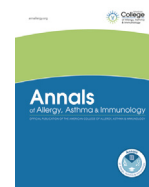




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The relationship between asthma, eosinophilia, and outcomes in coronavirus disease 2019 infection



Kam Sing Ho, MD^{*}; Daniel Howell, MD[†]; Linda Rogers, MD[‡];
Bharat Narasimhan, MD^{*}; Hannah Verma, BSc[‡]; David Steiger, MD^{||}

^{*} Department of Medicine, Mount Sinai Morningside & Mount Sinai West Hospitals, Icahn School of Medicine at Mount Sinai, New York, New York

[†] Department of Pulmonary & Critical Care, Mount Sinai Hospital, Icahn School of Medicine at Mount Sinai, New York, New York

[‡] Department of Political Science, Yale University, New Haven, Connecticut

^{||} Department of Pulmonary & Critical Care, Mount Sinai Beth Israel, Mount Sinai Morningside & Mount Sinai West Hospitals, Icahn School of Medicine at Mount Sinai, New York, New York

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ABSTRACT

Background: The impact of asthma diagnosis and asthma endotype on outcomes from coronavirus disease 2019 (COVID-19) infection remains unclear.

Objective: To describe the association between asthma diagnosis and endotype and clinical outcomes among patients diagnosed as having COVID-19 infection.

Methods: Retrospective multicenter cohort study of outpatients and inpatients presenting to 6 hospitals in the Mount Sinai Health System New York metropolitan region between March 7, 2020, and June 7, 2020, with COVID-19 infection, with and without a history of asthma. The primary outcome evaluated was in-hospital mortality. Secondary outcomes included hospitalization, intensive care unit admission, mechanical ventilation, and hospital length of stay. The outcomes were compared in patients with or without asthma using a multivariate Cox regression model. The outcomes stratified by blood eosinophilia count were also evaluated.

Results: Of 10,523 patients diagnosed as having COVID-19 infection, 4902 were hospitalized and 468 had a diagnosis of asthma (4.4%). When adjusted for COVID-19 disease severity, comorbidities, and concurrent therapies, patients with asthma had a lower mortality (adjusted odds ratio [OR], 0.64 (0.53–0.77); $P < .001$) and a lower rate of hospitalization and intensive care unit admission (OR, 0.43 (0.28–0.64); $P < .001$ and OR, 0.51 (0.41–0.64); $P < .001$, respectively). Those with blood eosinophils greater than or equal to 200 cells/ μL , both with and without asthma, had lower mortality.

Conclusion: Patients with asthma may be at a reduced risk of poor outcomes from COVID-19 infection. Eosinophilia, both in those with and without asthma, may be associated with reduced mortality risk.

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Introduction

Since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019, comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and tobacco use have been associated with increased severity of coronavirus disease

2019 (COVID-19) infection.^{1–3} Early data from China described a low prevalence of asthma in hospitalized patients, suggesting underlying asthma was not a risk factor for poor outcomes owing to COVID-19.^{4,5} Other cohort studies evaluating asthma as a risk factor for worse outcomes have revealed conflicting results, with some reports suggesting increased risk particularly for more severe asthma and others suggesting asthma may not be a risk factor for worse outcomes.^{6–11}

Our current understanding of the pathophysiology of asthma is focused on 2 primary immunologic pathways, or endotypes, that underlie the disease. These 2 endotypes include one characterized by airway eosinophilia and type 2 inflammation and the other without substantial eosinophilia or type 2 inflammation with either neutrophilic inflammation or pauci-inflammatory disease.^{12–15} Peripheral

Reprints: Kam Sing Ho, MD, Department of Medicine, Mount Sinai Morningside & Mount Sinai West Hospitals, Icahn School of Medicine at Mount Sinai, 1000 10th Ave, New York, NY 10019; E-mail: Kam.ho@mountsinai.org.

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blood eosinophil counts can be used to identify these endotypes and are increasingly used to inform asthma treatment.^{12,16} Eosinophils are potent proinflammatory cells¹⁷ and function as regulatory cells involved in protective immunity, including antiviral responses. Patients with eosinophilic asthma are at an increased risk of viral-induced asthma exacerbations and may have a reduced innate response against respiratory viruses.^{18,19} Eosinophils, however, may also promote protective responses against respiratory viruses.²⁰ It is unclear if eosinophilic inflammation in asthma is protective or increases the risk of poor COVID-19 infection outcomes.

The primary aim of this study was to evaluate the outcomes of patients presenting to the Mount Sinai Health System with a diagnosis of asthma and COVID-19 infections. The secondary objective was to determine if peripheral blood eosinophil levels were associated with outcomes in hospitalized patients with COVID-19 infection, both with and without asthma. We hypothesized that asthma did not increase the risk of hospitalization or mortality with COVID-19 infection and that blood eosinophils greater than or equal to 200 cells/ μ L would be associated with improved outcomes compared with those with asthma and COVID-19 infection without blood eosinophils greater than or equal to 200 cells/ μ L.

Methods

Study Setting and Participants

This analysis included data from 6 large academic hospitals in the Mount Sinai Health System, which serve approximately 3.5 million patients in the New York metropolitan area.

Participants and Inclusion/Exclusion Criteria

We included all adults (≥ 18 years of age) presenting to 1 of 6 Mount Sinai Health System hospitals between March 7, 2020, and June 7, 2020, with reverse transcriptase polymerase chain reaction–confirmed SARS-CoV-2 infection by the nasopharyngeal or oropharyngeal swab. Only those patients with a definitive clinical outcome, having been discharged to the outpatient setting or having completed their hospital course (ie, discharged alive or died) at the time of analysis (July 7, 2020), were included for further study.

Data Source

We obtained deidentified data from the Mount Sinai Data Warehouse, an institutional database that contains all information related to health encounters at any 1 of the 6 Mount Sinai facilities. The institutional review board of Icahn School of Medicine at Mount Sinai approved the research project (IRB-20-03843).

Variables Assessed

We evaluated the following categories of variables: (1) patient-related variables: demographics (age, sex, self-reported race, and ethnicity), body mass index, physician-reported comorbidities, smoking status (active or former), and laboratory test results; (2) treatment-related variables: medications, need for intensive care unit (ICU) level of care, and need for invasive mechanical ventilation; and (3) outcome-related variables: discharged or died.

The severity of COVID-19 was defined by the World Health Organization COVID-19 guidance and was classified by the lowest obtained oxygen saturation during hospital course, from time of admission to time of discharge, into (1) mild pneumonia (oxygen saturation $> 93\%$ without supplemental oxygen), (2) severe pneumonia (hypoxia with oxygen saturation $< 93\%$ without supplemental oxygen), and (3) respiratory failure requiring mechanical ventilation.²¹ Charlson comorbidity index (CCI), a well-validated measure of comorbidity burden and predictor of mortality, was generated and summed to an index on a 0- to 3-point scale.²² We

evaluated maximum blood eosinophil count (cells/ μ L) during their COVID-19–related encounter, categorizing those with a maximum absolute eosinophil count greater than or equal to 200 cells/ μ L as having blood eosinophils greater than or equal to 200 cells/ μ L and those having absolute eosinophil count less than 200 cells/ μ L as having blood eosinophils less than 200 cells/ μ L.

Clinical Outcomes

Our primary outcome was in-hospital mortality. Additional secondary outcomes included hospital admissions, intubation, ICU admission, and hospital length of stay.

Statistical Analysis

All analyses were conducted with Stata version 15.1 (StataCorp, College Station, Texas) statistical software. Descriptive statistics include frequency analysis (percentages) for categorical variables and means plus and minus standard deviations or medians for continuous variables. Comparisons were determined using Student's *t* test for continuous variables and by χ^2 test or Fisher's exact test for categorical variables. All *P* values were 2-sided, with .05 as the threshold for statistical significance. Univariate logistic regression was performed to explore the association of clinical characteristics and laboratory parameters with the risk of death. Confounding variables were selected based on previous reports on the pathogenesis of COVID-19 and mortality.^{23–26} Currently, several reports have identified age, sex, and comorbid conditions as predictors of mortality. In addition, several serum laboratory markers (ie, C-reactive protein and D-dimer) have been identified to be associated with increased mortality; however, the precise mechanisms that determine outcomes in COVID-19 have not been fully elucidated. Thus, 2 multivariable models were built. Model 1 included the following: (1) patient demographics (age, biological sex, body mass index, race-ethnicity) and (2) clinical comorbidity (CCI [0–3], COPD, self-reported smoking [active and former]). Model 2 included the following additional confounders: (3) COVID-19 disease severity (mild pneumonia/severe pneumonia/mechanical ventilation); (4) laboratory indicators of dysregulated innate response (C-reactive protein [>150 mg/L], interleukin 6 [>80 pg/mL], ferritin [>2000 ng/L], D-dimer [>2.0 μ g/L]); and (5) concurrent therapies (corticosteroid and anticoagulation use).

No missing variables were observed for patient-related, therapy-related, and outcome-related variables. Laboratory variables were complete, except for ferritin, interleukin 6, and procalcitonin (all missing variables were $<3\%$). To test whether missing data could introduce bias into the study, we assumed that data were not missing at random and applied the multivariate imputation method. Overall, 20 imputed data sets were constructed using information from all covariates used in the regression model. Results with and without missing information were not meaningfully different. Thus, results without imputation are reported.

Results

Baseline Characteristics of the Total Study Population

Overall, the study population comprised 10,523 patients, of whom 4.47% ($n = 468$) were found to have a diagnosis of asthma. The mean age of the population was 58.4 years and was similar between those with and without asthma (Table 1). A higher proportion of female individuals was observed among the cohort with asthma when compared with the cohort without asthma (68.4% vs 44.7%; $P < .001$). Similarly, a higher proportion of White patients (17.8% vs 3.6%; $P < .001$) and Black patients (27.4% vs 20.3%; $P < .001$) were noted in the group with asthma vs without asthma. Higher comorbidity burdens were noted in those with asthma when compared

Table 1
Characteristics of All Patients With Coronavirus Disease 2019 With or Without Asthma (Outpatient and Inpatient)

Characteristics	Overall (N = 10,523)	Asthma (N = 468)	No asthma (N = 10,055)	P value
Age, y ^a	58.35 ± 18.81	59.38 ± 17.75	58.31 ± 18.86	.20
Age ≥ 65 y	4294 (40.81)	196 (41.88)	4098 (40.76)	.63
Female sex	4816 (45.77)	320 (68.38)	4496 (44.71)	<.001
Race-ethnicity ^b				
White	2162 (20.55)	76 (16.24)	2086 (20.74)	.013
Black	1917 (18.22)	117 (25.00)	1800 (17.90)	<.001
Hispanic	4629 (43.99)	225 (48.07)	4404 (43.80)	.12
Asian	564 (5.36)	9 (1.92)	555 (5.52)	<.001
Others	1251 (11.89)	41 (8.76)	1210 (12.03)	.03
Coexisting conditions ^c				
Hypertension	2662 (25.30)	245 (52.35)	2417 (24.04)	<.001
Diabetes	1679 (15.96)	151 (32.26)	1528 (15.20)	<.001
CKD	916 (8.70)	76 (16.24)	840 (8.35)	<.001
COPD	286 (2.72)	54 (11.54)	232 (2.31)	<.001
OSA	196 (1.86)	44 (9.40)	152 (1.51)	<.001
Smokers	2212 (21.02)	174 (37.18)	2038 (20.27)	<.001
Obese (BMI ≥ 30)	756 (7.18)	131 (27.99)	625 (6.22)	<.001
Charlson comorbidity index				
0	2949 (28.02)	107 (22.86)	2842 (28.26)	<.001
1	1414 (13.44)	52 (11.11)	1362 (13.55)	
2	1769 (16.81)	70 (14.96)	1699 (16.90)	
≥3	4391 (41.73)	239 (51.07)	4152 (41.29)	

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

^aMean ± SD.

^bPatient-reported race-ethnicity.

^cPhysician-reported comorbidities.

with those without asthma, as reflected by higher rates of CCI greater than 3 (51.0% vs 41.3%; $P < .001$), and included higher rates of COPD (11.5% vs 2.3%; $P < .001$), hypertension, chronic kidney disease, diabetes, obstructive sleep apnea ($P < .01$), obesity (body mass index > 30), and cigarette smoking (37.2% vs 20.3%; $P < .001$).

Baseline Characteristics of Hospitalized Patients

From the initial study population of 10,523, 46.5% (N = 4902) formed the hospitalized study population, (Table 2). Among the hospitalized patients, 4.7% (N = 233) had asthma listed in their electronic medical records as a diagnosis. Those with asthma were more likely to be of female sex (70.8% vs 42.8%; $P < .001$), obese (30.0% vs 7.0%, $P < .001$), and of minority race-ethnicity compared with those without asthma. Comorbidities, including hypertension, diabetes, chronic kidney disease, COPD, obstructive sleep apnea, and smoking, were significantly higher among those with asthma. Disease severity, inflammatory biomarkers, and rates of blood eosinophils greater than or equal to 200 cells/ μL and less than 200 cells/ μL were similar between both groups. Those with asthma were more likely to receive corticosteroids and systemic anticoagulation treatment during hospitalizations.

Impact of Asthma on Clinical Outcomes

Univariate analysis revealed a lower all-cause mortality, the primary study end point, among those with asthma (unadjusted odds ratio [OR], 0.59; 95% confidence interval [CI], 0.49–0.71; $P < .001$) as outlined in Table 3. This lower risk persisted after adjusting for confounders, including patient demographics and comorbid conditions (model 1: adjusted OR, 0.28; 95% CI, 0.19–0.41; $P < .001$). When inflammatory markers and associated therapies (corticosteroids and anticoagulation) were also accounted for as confounders, the risk of mortality was less pronounced than that of the initial model 1 (model 2: adjusted OR, 0.64; 95% CI, 0.53–0.77; $P < .001$). More specifically, patients with asthma have higher rates of corticosteroid and anticoagulation use and lower overall inflammatory markers. When model 2 was adopted to adjust for these confounders, or imbalances, the diagnosis of asthma was

associated with a less prominent reduction in mortality from COVID-19 (model 2, OR, 0.64), relative to model 1 (OR, 0.28).

Regarding secondary end points, the crude rates of hospitalization among patients with or without asthma were 49.8% (n = 233/468) and 46.4% (n = 4669/10,055), respectively. We observed a lower risk of hospitalization in those with asthma (unadjusted OR, 0.82; 95% CI, 0.77–0.87; $P < .001$), which remained after adjusting for the confounders, including patient demographics and comorbid conditions (model 1: adjusted OR, 0.93; 95% CI, 0.86–0.99; $P < .001$). When inflammatory markers were also accounted for as confounders, the risk of hospitalization was lower than that of the initial model 1 (model 2: adjusted OR, 0.43; 95% CI, 0.28–0.64; $P < .001$). In essence, patients with asthma have higher rates of corticosteroids and anticoagulation use and lower overall inflammatory markers. When imbalance in corticosteroid and anticoagulation use and the differences in inflammatory markers was adjusted between the 2 cohorts, we observed a more prominent reduction in hospitalization risk among patients with asthma with COVID-19 (model 2, OR, 0.43) relative to model 1 (OR, 0.93).

Similarly, a lower risk of the need for ICU admission was observed (model 1: adjusted OR, 0.98; 95% CI, 0.97–0.98; $P < .001$). After further adjusting for the use of corticosteroids and anticoagulation and inflammatory markers, we observed a more prominent reduced risk of ICU admissions (model 2: adjusted OR, 0.51; 95% CI, 0.41–0.64; $P < .001$). However, we observed no significant association between the impact of asthma and the need for intubation (model 1: adjusted OR, 0.92; 95% CI, 0.86–1.00; $P = .05$; model 2: adjusted OR, 0.56; 95% CI, 0.17–1.86; $P = .35$), which was similar in those with and without asthma.

Impact of Blood Eosinophil Greater Than or Equal to 200 Cells/ μL on Clinical Outcomes

Maximal absolute eosinophil count at any time during hospitalization exceeding 200 cells/ μL was associated with a significantly lower risk of mortality among patients with asthma (Table 4, model 1: adjusted OR, 0.16; 95% CI, 0.09–0.28; $P < .001$), when compared with those without asthma (model 1: adjusted OR, 0.26; 95% CI, 0.23–0.29; $P < .001$).

Table 2
Characteristics of Hospitalized Patients With Coronavirus Disease 2019 With or Without Asthma Who Completed Their Hospital Course (Discharged or Died)

Characteristics	Overall (N = 4902)	Asthma (N = 233)	No asthma (N= 4669)	P value
Age, y ^a	64.99 ± 16.92	64.36 ± 15.88	65.02 ± 16.97	.53
Age ≥ 65 y	2723 (55.55)	124 (53.22)	2599 (55.67)	.49
Female sex	2164 (44.14)	165 (70.82)	1999 (42.81)	<.001
Race ^b				
White	1055 (21.52)	37 (15.88)	1018 (21.80)	.006
Black	1032 (21.05)	65 (27.90)	967 (20.71)	.06
Hispanic	1961 (40.00)	105 (45.06)	1856 (39.75)	.17
Asian	246 (5.02)	2 (0.86)	244 (5.22)	<.001
Others	608 (12.40)	24 (10.30)	584 (12.51)	.32
Coexisting conditions				
Hypertension	1585 (32.33)	141 (60.52)	1444 (30.93)	<.001
Diabetes	1029 (20.99)	86 (36.91)	943 (20.20)	<.001
CKD	571 (11.65)	54 (23.18)	517 (11.07)	<.001
COPD	192 (3.92)	36 (15.45)	156 (3.34)	<.001
OSA	104 (2.12)	21 (9.01)	83 (1.78)	<.001
Smokers	1285 (26.21)	99 (42.49)	1186 (25.40)	<.001
Obese (BMI ≥ 30)	400 (8.16)	70 (30.04)	330 (7.07)	<.001
COVID-19 disease severity ^c				
Mild	762 (15.54)	36 (15.45)	726 (15.55)	.51
Moderate	3445 (70.28)	170 (72.96)	3275 (70.14)	
Severe (intubated)	695 (14.18)	27 (11.59)	668 (14.31)	
Charlson comorbidity index				
0	715 (14.59)	27 (11.59)	688 (14.74)	.08
1	564 (11.51)	29 (12.45)	535 (11.46)	
2	908 (18.52)	32 (13.73)	876 (18.76)	
≥3	2715 (55.39)	145 (62.23)	2570 (55.04)	
Hospital length of stay				
Median (d) ^d	6.99 (5.51-12.79)	7.87 (4.08-13.89)	6.95 (3.44-12.76)	.72
Serum eosinophils				
Maximum over hospital course				
Eosinophils < 200	3192 (65.12)	140 (60.09)	3052 (65.37)	.10
Eosinophils ≥ 200	1597 (32.58)	89 (38.20)	1508 (32.30)	.06
Maximal inflammatory markers				
CRP > 150 (mg/L)	2215 (15.19)	112 (48.07)	2103 (45.04)	.38
D-dimer > 2.0 (μg/L)	912 (20.11)	39 (18.40)	873 (20.19)	.60
Ferritin > 2000 (ng/L)	1312 (26.76)	49 (21.03)	1263 (27.05)	.05
Interleukin 6 > 80 (pg/mL)	1279 (26.09)	60 (25.75)	1219 (26.11)	.94
Medications ^d				
Hydroxychloroquine	3304 (67.30)	153 (65.95)	3151 (67.37)	.67
Azithromycin	3158 (64.33)	144 (62.07)	3014 (64.44)	.48
Tocilizumab	243 (4.95)	14 (6.03)	229 (4.90)	.44
Remdesivir	144 (2.93)	5 (2.16)	139 (2.97)	.69
Corticosteroids	1354 (27.62)	95 (40.77)	1259 (26.97)	<.001
Methylprednisolone	1098 (22.37)	70 (30.17)	1028 (22.02)	.01
Prednisone	446 (9.09)	52 (22.41)	394 (8.42)	<.001
Dexamethasone	155 (3.16)	11 (4.74)	144 (3.08)	.17
Hydrocortisone	18 (0.37)	1 (0.43)	17 (0.36)	.58
Anticoagulation	4413 (90.02)	219 (93.99)	4194 (89.83)	.04
Heparin	2816 (57.36)	140 (60.34)	2676 (57.22)	.38
Enoxaparin	2368 (48.24)	123 (53.02)	2245 (48.00)	.14
Apixaban	1140 (23.22)	60 (25.86)	1080 (23.09)	.34
Rivaroxaban	126 (2.57)	7 (3.02)	119 (2.54)	.39
Clinical outcomes				
ICU admission	1050 (21.39)	45 (19.40)	1005 (21.52)	.51
Discharged	3575 (72.93)	181 (77.68)	3394 (72.69)	.10
Death	1408 (28.72)	54 (23.18)	1354 (29.00)	.06

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ICU, intensive care unit; OSA, obstructive sleep apnea.

^aMean ± SD.

^bPatient-reported ethnicity.

^cCOVID-19 disease severity - mild pneumonia (lowest SpO₂ during hospitalization >94%, severe pneumonia (lowest SpO₂ during hospitalization <94%), mechanical ventilation.

^dPhysician-reported comorbidities.

After further adjusting for the use of corticosteroids and anti-coagulation and inflammatory markers, this association was even more prominent (model 2: adjusted OR, 0.09; 95% CI, 0.02-0.36, $P < .001$) when compared with those without asthma (model 2: adjusted OR, 0.30; 95% CI, 0.24-0.38, $P < .001$).

Discussion

In this study of 10,523 patients diagnosed as having COVID-19, including 5123 patients managed as outpatients and 4902

patients requiring hospitalization, asthma diagnosis was associated with lower mortality rate, lower hospitalization rate, and lower ICU admission rate than those without asthma when adjusting for comorbidities and concurrent therapies. Moreover, we identified better outcomes associated with absolute eosinophil counts greater than or equal to 200 cells/ μL in those with and without asthma.

We observed that 468 total study patients had a diagnosis of asthma (4.4%), and asthma was present in 4.8% of the hospitalized patients, which is the same prevalence reported by Beurnier et al²⁷

Table 3
Relationship Between Asthma Diagnosis and Hospitalization Outcomes

Composite end points	Analysis model	Odds ratio (95% confidence interval)	P value
Asthma			
Mortality ^a (N = 54)	Univariate	0.59 (0.49-0.71)	<.001
	Multivariable—model 1 ^b	0.28 (0.19-0.41)	<.001
	Multivariable—model 2 ^c	0.64 (0.53-0.77)	<.001
Hospitalization ^d (N = 233)	Univariate	0.82 (0.77-0.87)	<.001
	Multivariable—model 1 ^b	0.93 (0.86-0.99)	<.001
	Multivariable—model 2 ^c	0.43 (0.28-0.64)	<.001
ICU admission ^a (N = 45)	Univariate	0.89 (0.64-1.26)	.53
	Multivariable—model 1 ^b	0.98 (0.97-0.98)	<.001
	Multivariable—model 2 ^c	0.51 (0.41-0.64)	<.001
Intubation ^a (N = 28)	Univariate	0.54 (0.45-0.67)	<.001
	Multivariable—model 1 ^b	0.92 (0.86-1.00)	.05
	Multivariable—model 2 ^c	0.56 (0.17-1.86)	.35

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

^aAnalysis based on hospitalized patients.

^bMultivariable model 1—adjusted simultaneously for age, sex, BMI, race, Charlson comorbidity index, COPD, and smoking (current and former).

^cMultivariable model 2—adjusted simultaneously for age, sex, BMI, race, COVID-19 disease severity, Charlson comorbidity index, COPD, C-reactive protein (>150 mg/L), interleukin-6 (>80 μg/L), ferritin (>2000 ng/L), D-dimer (>2.0 μg/L), use of anticoagulation, use of corticosteroids, and smoking (current and former).

^dAnalysis based on all patients (hospitalized and nonhospitalized patients).

in their cohort of 768 hospitalized patients, with a significantly reduced mortality among the asthma subgroup when compared with a control group without asthma. In reviewing these results, Farne and Singanayagam²⁸ suggested that asthma might be protective against poor outcomes in COVID-19. The 4.4% overall prevalence of asthma in our cohort is much lower than the New York State 10.1% prevalence of asthma.²⁹ There have been conflicting data regarding asthma diagnosis as a risk factor for more severe courses from COVID-19 infection. A lower risk for hospitalization for those with asthma and COVID-19 has been noted in previous case series. Asthma was not identified as a risk factor for COVID-19 infection hospitalization in 2 studies in Chicago.^{30,31} Halpin described the prevalence of both asthma and COPD as being lower in patients with SARS-CoV-2 infection compared with the overall population prevalence of these diseases, and low rates of asthma were reported in case series of patients hospitalized for COVID-19 in Italy and China.^{5,27,33–35,58} However, rates that were similar to or exceeding the population prevalence have been reported by others, with rates as high as 25.8% reported in some series.^{2,6,7,30,31}

In our study, we found that patients with COVID-19 with asthma had not only a lower rate of hospitalization but also a lower ICU admission rate and a lower mortality rate than those with COVID-19 without asthma. Mortality in those with asthma was 72% and 36% lower than those without asthma in model 1 and model 2, respectively. The large difference between these 2 models may be explained by the significant difference in steroid and anticoagulation use, 2 therapies with data revealing improved clinical outcomes when used in COVID-19. Those with asthma received more of these therapies, and they were not controlled for in model

1. Similarly, asthma was underrepresented in a case series of 1591 hospitalized patients from Lombardy and was not a predictor of mortality in Wuhan.^{8,27} In a study of 1150 patients admitted to 2 New York city hospitals, 8% of critically ill patients were reported to have asthma, but asthma was not a predictor of mortality.³⁶ Overall, in New York State, 89.9% of more than 25,000 people who died from COVID-19 had at least 1 comorbid condition, and although COPD was among the top 10 comorbidities associated with mortality, asthma was not listed in the top 10 comorbidities.³⁷

However, severe asthma, as defined by oral corticosteroid use in the previous year, has been associated with a slightly increased hazard ratio of mortality (hazard ratio, 1.13 [1.01-1.26]) in a large study of National Health Service records in England.¹⁰ It has previously been reported that there were no significant differences in mortality in those with asthma who had a hospital encounter for COVID-19 when compared with those without asthma in our health system.¹¹ Although our study period spanned a longer time frame during which treatment algorithms evolved to include more frequent use of corticosteroids and anticoagulation, our finding of lower risk of mortality in patients with asthma persisted when we adjusted for these treatment variables. In our cohort, we also identified a higher prevalence of many comorbid health conditions in those with asthma, including obesity, diabetes, and hypertension which affect outcomes such as hospitalization and mortality in those with asthma, as reported by others.³¹ Therefore, adjustment for these other health conditions remains key to evaluating the independent impact of asthma diagnosis on outcomes owing to COVID-19 and may account for differences in our results compared with other series in which adjustment for other comorbid

Table 4
Impact of Eosinophils on Mortality Among Hospitalized Coronavirus Disease 2019 Patients With or Without Asthma

Composite end point—mortality	Predictors	Analysis model	Odds ratio (95% confidence interval)	P value
Maximal eosinophil count during hospitalization				
Asthma	≥200 cells/μL (N = 77)	Univariate	1.70 (0.87-3.30)	.12
		Multivariable—model 1 ^a	0.16 (0.09-0.28)	<.001
		Multivariable—model 2 ^b	0.09 (0.02-0.36)	<.001
No asthma	≥200 cells/μL (N = 1407)	Univariate	1.87 (1.64-2.13)	<.001
		Multivariable—model 1 ^a	0.26 (0.23-0.29)	<.001
		Multivariable—model 2 ^b	0.31 (0.25-0.39)	<.001

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

^aMultivariable model 1—adjusted simultaneously for age, sex, BMI, race, Charlson comorbidity index, COPD, and smoking (current and former).

^bMultivariable model 2—adjusted simultaneously for age, sex, BMI, race, COVID-19 disease severity, Charlson comorbidity index, COPD, C-reactive protein (>150 mg/L), interleukin-6 (>80 μg/L), ferritin (>2000 ng/L), D-dimer (>2.0 μg/L), use of anticoagulation, use of corticosteroids, and smoking (current and former).

conditions conferring risk was in some cases more limited. Similarly, disparities in the prevalence of asthma according to race, ethnicity, and socioeconomic status are also well described, and these factors have also been clearly linked to outcomes from COVID-19 infection.³⁸ This highlights one of the strengths of our analysis, which adjusted for a broad range of covariates, including demographic factors, inflammatory markers, COVID-19 disease severity, comorbid conditions, and concomitant therapies.

Asthma diagnosis was associated with lower mortality in those specifically with an eosinophilic endotype. Eosinophilic asthma accounts for approximately 50% of all asthma cases and is related to type 2 inflammatory response.^{12,15,17} Elevated blood eosinophils have a high positive predictive value for type 2 inflammation when used in combination with other biomarkers but may misclassify asthma phenotype when used in isolation.^{39–40,16} There is no defined threshold for elevated blood eosinophils, and levels as low as 150 cells/ μ L have been used. Our laboratory measures to the nearest 100 cells/ μ L, and so we chose 200 cells/ μ L to define eosinophilic asthma. Recent studies may help us understand the relationship between eosinophilic asthma, type 2 inflammation, and outcomes in COVID-19. The SARS-CoV-2 virus enters the host cell by binding to the angiotensin 2 (ACE2) receptor, and the protease TMPRSS2 cleaves the viral spike protein allowing the SARS-CoV-2 to bind efficiently to ACE2.⁴¹ TMPRSS2 is essential for viral entry and spread in the host cells. ACE2 expression facilitates viral replication in airway epithelium and susceptibility to infection.⁴² Several studies have compared the expression of ACE2 and TMPRSS2 in the airway epithelium in patients with asthma with those who do not have asthma. Although there are inconsistent results regarding whether those with asthma have reduced ACE2 expression or increased TMPRSS2 expression in airway epithelium, there has been relatively consistent evidence to reveal that increased type 2 inflammation reduces ACE2 airway epithelial expression.^{43–46} This suggests a putative mechanism by which type 2 inflammation may be responsible for a less severe outcome from COVID-19 infection. A decrease in airway epithelial levels of ACE2 may offset the effect from increased expression of TMPRSS2 and lead to reduced viral entry and cytotoxic immune response that can be harmful to the host.⁴⁴

In our cohort, higher blood eosinophils greater than or equal to 200 cells/ μ L conferred a mortality benefit on both those with asthma and those without asthma. Those with asthma and blood eosinophils greater than 200 cells/ μ L had a 91% and 84% lower mortality in model 1 and model 2, respectively, than those with eosinophils less than 200 cells/ μ L. Eosinophils possess antiviral properties that include the production of RNAs and reactive nitrogen species, and eosinophils can serve as antigen-presenting cells to enhance adaptive immunity. There is in vitro and in vivo evidence of eosinophil activity vs respiratory syncytial and influenza viruses.^{20,47} Conversely, low blood eosinophils have been found to predict mortality in critically ill patients⁴⁸ and are associated with an increased risk of mortality in patients admitted with an acute exacerbation of COPD.⁴⁹ Acute inflammation secondary to infectious and noninfectious stimuli can suppress eosinophils.⁵⁰ Supporting the possible relationship between asthma endotype, eosinophils, and outcomes, a higher T_H1 profile was observed in those who died of COVID-19.⁵ In addition, in a small French cohort study, blood eosinophils greater than 500 cells/ μ L developed in one-third of their subjects and was associated with reduced ICU mortality.⁵¹

Furthermore, in a large population cohort study, nonallergic asthma was associated with a 48% increase in the risk of severe COVID-19 infection, which was not observed in those with allergic asthma.⁵² In another large Korean cohort study, nonallergic asthma was associated with increased susceptibility to COVID-19 infection, increased odds of severe outcome from COVID-19, and increased length of stay for COVID-19 hospitalization.⁵³ However, in this

study, those with allergic rhinitis, a disease mediated by type 2 inflammation, were more likely to have a positive COVID-19 test compared with those without allergic rhinitis.⁵³ Low eosinophil counts have been associated with more severe disease in COVID-19 pneumonia.⁴ Low eosinophil counts were observed in 81.2% of 85 patients dying from COVID-19 pneumonia who underwent autopsy,⁵ but these findings may have been affected by the therapeutic use of corticosteroids in critically ill patients with COVID-19. Eosinophils were largely absent in autopsy studies from patients who died of COVID-19.^{54,55}

There are several limitations to our study. Electronic medical record (EMR) diagnosis of asthma is susceptible to both underdiagnosis and overdiagnosis of asthma; indeed, up to one-third of EMR diagnosis of asthma has been estimated to be inaccurate.^{32,56,57} However, as described in Table 1, many of the other publications relating to COVID-19 and asthma have relied on EMR diagnosis. Furthermore, we were unable to analyze the blood eosinophils as a categorical variable owing to the manner of laboratory reporting which reports values to the nearest hundred. Second, the higher rate of COPD and smokers in our asthma group raises suspicion for misdiagnosis of COPD as asthma. Because COPD is among the most common comorbidities in patients with fatal COVID-19 disease, we account for this bias by adjusting for smoking and COPD in our multivariate analysis. Third, we cannot exclude that some patients discharged after diagnosis for outpatient treatment of COVID-19 could potentially have been readmitted to non-Mount Sinai system hospitals. We do not have data on atopic status of patients or other measures of type 2 inflammation as previously discussed. We also cannot rule out that patients, especially those with asthma, were treated with oral corticosteroids before hospital admission, affecting outcome and eosinophil grouping. Lastly, this is a retrospective study that is potentially vulnerable to uncontrolled confounders that we did not identify. Although we find a reduced risk of poor outcome overall associated with an asthma diagnosis, we did not account for asthma severity, which has previously been associated with a worse outcome.⁵³

Conclusion

Patients with asthma as a group may be at a reduced risk of poor outcomes from COVID-19 infection. Blood eosinophils greater than or equal to 200 cells/ μ L, both in those with and without asthma, may affect mortality risk. Future studies are required to clarify the risk associated with various asthma endotypes and differences in asthma severity in COVID-19. Further work is required to determine the impact of the underlying immune predisposition of individuals on outcomes from COVID-19 infection.

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