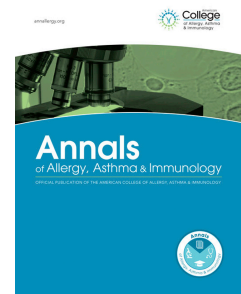


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The Relationship Between Asthma, Eosinophilia, and Outcomes in COVID-19 Infection

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Conflict of Interest

The authors (Kam Sing Ho, M.D., Daniel Howell, M.D., Linda Rogers, M.D., Bharat Narasimhan, Hannah Verma, BSc., David Steiger, M.D.) know of no conflict of interest associated with this publication, and there is no financial support for this work. This manuscript has been read and approved for submission by all the named authors who have contributed to this manuscript.

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Key words

Asthma, prevalence, COVID-19 infection, hospitalization, eosinophilia, T2 inflammation, ICU admission, mortality.

Abbreviations

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Coronavirus 2019 (COVID-19), chronic obstructive pulmonary disease (COPD), body mass index (BMI), Charlson comorbidity index (CCI), C-reactive protein (CRP), Interleukin-6 (IL-6)

Author Contribution

The authors (Kam Sing Ho, M.D., Daniel Howell, M.D., Linda Rogers, M.D., Bharat Narasimhan, Hannah Verma, BSc., David Steiger, M.D.) have made substantial contributions to conception and design, acquisition of data, analysis, and interpretation of data. Similarly, the authors (Kam Sing Ho, M.D., Daniel Howell, M.D., Linda Rogers, M.D., Bharat Narasimhan, Hannah Verma, BSc., David Steiger, M.D.) have drafted the article and reviewed it critically for important intellectual content. Finally, all authors (Kam Sing Ho, M.D., Daniel Howell, M.D., Linda Rogers, M.D., Bharat Narasimhan, Hannah Verma, BSc., David Steiger, M.D.) have given final approval of the version to be published; and have agreed to be accountable for all aspects of the work related to its accuracy or integrity.

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Background: The impact of asthma diagnosis and asthma endotype on outcomes from COVID-19 infection remains unclear.

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

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

Results : Of 10,523 patients diagnosed with COVID-19 infection, 4902 patients 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), $p<0.001$] and a lower rate of hospitalization and ICU admission [OR 0.43 (0.28-0.64) $p<0.001$ and OR 0.51 (0.41-0.64), $p<0.001$ respectively]. Those with blood eosinophils ≥ 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.

1 Introduction

2 Since the emergence of a novel coronavirus (SARS-CoV-2), in Wuhan, China, in
3 December 2019, comorbidities such as hypertension, diabetes mellitus, chronic
4 obstructive pulmonary disease (COPD), and tobacco use have been associated with
5 increased severity of COVID-19 infection [1-3]. Early data from China described a low
6 prevalence of asthma in hospitalized patients, suggesting that underlying asthma was
7 not a risk factor for poor outcomes due to COVID-19 [4-5]. Other cohort studies
8 assessing asthma as a risk factor for worse outcomes have shown conflicting results,
9 with some reports suggesting increased risk particularly for more severe asthma, and
10 others suggesting asthma may not be a risk factor for worse outcomes [6-11].

11 Our current understanding of asthma's pathophysiology is focused on two
12 primary immunological pathways, or endotypes, that underlie the disease. These two
13 endotypes include one characterized by airway eosinophilia and type 2 inflammation,
14 and the other without significant eosinophilia or type 2 inflammation with either
15 neutrophilic inflammation or pauci-inflammatory disease [12-15]. Peripheral blood
16 eosinophil counts can be used to identify these endotypes and are increasingly used to
17 inform asthma treatment [12,16]. Eosinophils are potent proinflammatory cells [17]
18 and function as regulatory cells involved in protective immunity, including antiviral
19 responses. Patients with eosinophilic asthma are at an increased risk of viral-induced
20 asthma exacerbations and may have a reduced innate response against respiratory
21 viruses [18-19]. Eosinophils, however, may also promote protective responses against
22 respiratory viruses [20]. It is unclear if eosinophilic inflammation in asthma is
23 protective or increases the risk of poor COVID-19 infection outcomes.

24 This study's primary aim was to assess the outcomes of patients presenting to
25 the Mount Sinai Health System with a diagnosis of asthma and COVID-19 infections. This
26 study's secondary objective was to determine if peripheral blood eosinophil levels were
27 associated with outcomes in hospitalized patients with COVID-19 infection, both with
28 and without asthma. We hypothesized that asthma did not increase the risk of
29 hospitalization or mortality with COVID-19 infection and that blood eosinophils ≥ 200

cells/uL would be associated with improved outcomes compared to patients with asthma and COVID-19 infection without blood eosinophils ≥ 200 cells/uL.

Methods

Study Setting and Participants

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

Participants & Inclusion / Exclusion Criteria

We included all adults (≥ 18 years of age) presenting to one of six Mount Sinai Health System hospitals between March 7th to June 7th, 2020, with reverse transcriptase polymerase-chain-reaction (RT-PCR) 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 (i.e., discharged alive or died) at the time of analysis (July 7th, 2020) were included for further study.

Data Source

We obtained de-identified data from the Mount Sinai Data Warehouse (MSDW), an institutional database that contains all information related to health encounters at any one of the six 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 assessed the following categories of variables: (1) Patient-related variables: demographics (age, gender, self-reported race, and ethnicity), body-mass-index, physician-reported comorbidities, smoking status (active or former); and laboratory tests (2) Treatment-related variables: medications; need for intensive care unit (ICU) level of care; the 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 (WHO) 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 0-3-point scale [22]. We assessed maximum blood eosinophil count (cells/ μL) during their COVID-19-related encounter, categorizing those with a maximum absolute eosinophil count (AEC) ≥ 200 cells/ μL as having blood eosinophils ≥ 200 cells/ μL , and those having and AEC <200 cells/ μL as having a low blood eosinophils < 200 cells/ μL .

Clinical Outcomes

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

Statistical Analysis

All analyses were conducted with Stata version 15.1 (StataCorp) statistical software. Descriptive statistics include frequency analysis (percentages) for categorical variables and means $\pm$ standard deviations (SD) or medians for continuous variables. Comparisons were determined using Student's t-test for continuous variables and by Chi-square test or Fisher exact test for categorical variables. All p-values were 2-sided, with 0.05 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, gender, and comorbid conditions as predictors of mortality. In addition, several serum lab markers (i.e. 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, two multivariable models were built. Model 1 included: (1) patient demographics (age,

biological gender, body mass index, race-ethnicity) and (2) clinical comorbidity (Charlson comorbidity index [0-3], chronic obstructive pulmonary disease, self-reported smoking [active and former]). Model 2 included 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 outcomes-related variables. Laboratory variables were complete, except for ferritin, IL-6, and procalcitonin (all missing variables were less than 3%). To test whether missing data could introduce bias into the study, we made the assumption 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 females was observed among the cohort with asthma when compared to the cohort without asthma (68.4% vs 44.7%, $p<0.001$). Similarly, a higher proportion of whites (17.8% vs 3.6%, $p<0.001$) and blacks (27.4% vs 20.3%, $p<0.001$) were noted in the group with asthma versus without asthma. Higher comorbidity burdens were noted in those with asthma when compared to those without asthma, as reflected by higher rates of CCI >3 (51.0% vs 41.3%, $p<0.001$), and included higher rates of COPD (11.5% vs 2.3%, $p<0.001$), hypertension, chronic kidney disease (CKD), diabetes, obstructive sleep apnea (OSA) ($p < 0.01$), obesity (BMI > 30) and cigarette smoking (37.2% vs 20.3%, $p<0.001$).

Baseline Characteristics of Hospitalized Patients

From the initial study population of 10,523, 46.5% (N=4902) formed the hospitalized study population. Among 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 female (70.8% vs. 42.8%, $p<0.001$), obese (30.0 % vs. 7.0 %, $p<0.001$), and of minority race-ethnicity compared to those without asthma. Comorbidities, including hypertension, diabetes, CKD, COPD, OSA, and smoking were significantly higher among those with asthma. Disease severity, inflammatory biomarkers, and rates of blood eosinophils ≥ 200 cells/uL and < 200 cells/uL 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 endpoint, among those with asthma (unadjusted OR 0.59; 95% CI 0.49-0.71; $p<0.001$) 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; $p<0.001$). When inflammatory markers and associated therapies (corticosteroids and anticoagulation) were also accounted for as confounders, the risk of mortality was less pronounced than the initial model 1 (Model 2: adjusted OR 0.64; 95% CI 0.53-0.77; $p<0.001$). More specifically, patients with asthma have higher rates of corticosteroids 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 endpoints, the crude rates of hospitalization among patients with or without asthma were 49.8% (n=233/468) and 46.4% (n=4669/10055), respectively. We observed a lower risk of hospitalization in those with asthma (unadjusted OR 0.82; 95% CI 0.77-0.87; $p<0.001$), 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; $p<0.001$). When inflammatory markers were also accounted for as confounders, the risk of hospitalization was lower than the initial

model 1 (Model 2: adjusted OR 0.43; 95% CI 0.28-0.64; $p<0.001$). In essence, patients with asthma have higher rates of corticosteroids and anticoagulation use and lower overall inflammatory markers. When the imbalance in the use of corticosteroids and anticoagulation use and the differences in inflammatory markers were adjusted between the two 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; $p<0.001$). 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; $p<0.001$). On the other hand, 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; $p=0.05$; Model 2: adjusted OR 0.56; 95% CI 0.17-1.86; $p=0.35$) was similar in those with and without asthma.

Impact of Blood Eosinophil ≥ 200 cells/ μ L on Clinical Outcomes

Maximal absolute eosinophil count at any time during hospitalization exceeding 200 cells/ μ L was associated with a significantly lower risk of mortality among patients with asthma (Model 1: adjusted OR 0.16; 95% CI 0.09-0.28; $p<0.001$), when compared to those without asthma (Model 1: adjusted OR 0.26; 95% CI 0.23-0.29; $p<0.001$).

After further adjusting for the use of corticosteroids and anticoagulation, and inflammatory markers, this association was even more prominent (Model 2: adjusted OR 0.09, 95% CI 0.02-0.36, $p<0.001$), when compared to those without asthma (Model 2: adjusted OR 0.30, 95% CI 0.24-0.38, $p<0.001$).

Discussion

In this study of 10,523 patients diagnosed with 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/uL 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 hospitalized patients, which is the same prevalence reported by Beurnier et al in their cohort of 768 hospitalized patients, with a significantly reduced mortality among the asthma subgroup when compared to a control group without asthma [27]. In reviewing these results, Farne and Singanayagam suggested that asthma might be protective against poor outcomes in COVID-19 [28]. 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 has 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 two 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 to 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]. 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 COVID-19 patients with asthma had not only a lower rate of hospitalization but also a lower ICU admission rate and a lower mortality rate compared to COVID-19 patients without asthma. Mortality in those with asthma was 72% and 36 % lower when compared to those without asthma in model 1 and model 2 respectively. The large difference between these two models may be explained by the significant difference in steroid and anticoagulation use, two therapies with data showing 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 two 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 over 25,000 people who died from COVID-19 had at least one comorbid condition, and while 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 prior year, has been associated with a slightly increased hazard ratio of mortality (HR 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 to 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 that impact 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 assessing the independent impact of asthma diagnosis on outcomes due to COVID-19 and may account for differences in our results compared to other series where adjustment for other comorbid 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 however may misclassify asthma phenotype when used in isolation [39-41]. There is no defined threshold for elevated blood eosinophils

and levels as low as 150 cells/ μ L have been used. Our lab 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 [42]. TMPRSS2 is essential for viral entry and viral spread in the host cells. ACE2 expression facilitates viral replication in airway epithelium and susceptibility to infection [43]. 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. While 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 demonstrate that increased type 2 inflammation reduces ACE2 airway epithelial expression [44-47]. 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 a reduced cytotoxic immune response that can be harmful to the host [45].

In our cohort, higher blood eosinophils ≥ 200 cells/ μ L conferred a mortality benefit on both those with asthma and those without asthma. Those with asthma and blood eosinophils >200 cells/ μ L had a 91% and 84% lower mortality in model 1 and 2 respectively than those with eosinophils <200 cell/ μ L. Eosinophils possess antiviral properties that include the production of RNA'ses 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 versus respiratory syncytial virus and Influenza viruses [20,48]. Conversely, low blood eosinophils have been demonstrated to predict mortality in critically ill patients [49] and is associated with an increased risk of mortality in patients admitted with an acute exacerbation of COPD [50]. Acute inflammation secondary to infectious and non-infectious stimuli can suppress eosinophils [51]. Supporting the possible relationship between asthma endotype, eosinophils, and outcomes, a higher Th1 profile was observed in those who died of COVID-19 [5]. Additionally, in a small French cohort study, blood eosinophils

>500 cells/ μ L developed in one third of their subjects and was associated with reduced ICU mortality [52].

Furthermore, in a large population cohort study, non-allergic asthma was associated with a 48% increase in the risk of severe COVID-19 infection, which was not observed in those with allergic asthma [53]. In another large Korean cohort study, non-allergic 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 [54]. 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 to those without allergic rhinitis (ref). 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 impacted by the therapeutic use of corticosteroids in critically ill COVID 19 patients. Eosinophils were largely absent in autopsy studies from patients who died of COVID 19 [55-56].

There are several limitations to our study. Electronic medical record (EMR) diagnosis of asthma is prone to both under and overdiagnosis of asthma; indeed, up to one-third of EMR diagnosis of asthma has been estimated to be inaccurate [57-59]. 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 analyse the blood eosinophils as a categorical variable due to the manner of lab reporting which reports values to the nearest hundred. Secondly, the higher rate of COPD and smokers in our asthma group raises suspicion for misdiagnosis of COPD as asthma. Since COPD is amongst 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. Thirdly, 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, impacting outcome and eosinophil grouping. Lastly, this is a retrospective study that is potentially vulnerable to uncontrolled confounders that we did not

305 identify. While we find a reduced risk of poor outcome overall associated with an
306 asthma diagnosis, we did not account for asthma severity, which has previously been
307 associated with a worse outcome [54].

308

309 Discussion

310 To conclude, patients with asthma as a group may be at a reduced risk of poor
311 outcomes from COVID-19 infection. Blood eosinophils ≥ 200 cells/uL, both in those with
312 and without asthma, may impact mortality risk. Future studies are required to clarify
313 the risk associated with various asthma endotypes, and differences in asthma severity
314 in COVID-19. Further work is required to determine the impact of the underlying
315 immune predisposition of individuals on outcomes from COVID-19 infection.

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**Table 1. Characteristics of all COVID-19 patients with or without Asthma.
(Outpatient & Inpatient)**

Characteristics	Overall (N=10,523)	Asthma (N=468)	No Asthma (N=10,055)	P- value
Age — yr☆	58.35 ± 18.81	59.38 ± 17.75	58.31 ± 18.86	0.20
Age ≥ 65 yr	4294 (40.81)	196 (41.88)	4098 (40.76)	0.63
Female gender	4816 (45.77)	320 (68.38)	4496 (44.71)	<0.001
Race-ethnicity†				
White	2162 (20.55)	76 (16.24)	2086 (20.74)	0.013
Black	1917 (18.22)	117 (25.00)	1800 (17.90)	<0.001
Hispanic	4629 (43.99)	225 (48.07)	4404 (43.80)	0.12
Asian	564 (5.36)	9 (1.92)	555 (5.52)	<0.001
Others	1251 (11.89)	41 (8.76)	1210 (12.03)	0.03
Coexisting Conditions				
Hypertension	2662 (25.30)	245 (52.35)	2417 (24.04)	<0.001
Diabetes	1679 (15.96)	151 (32.26)	1528 (15.20)	<0.001
CKD	916 (8.70)	76 (16.24)	840 (8.35)	<0.001
COPD	286 (2.72)	54 (11.54)	232 (2.31)	<0.001
OSA	196 (1.86)	44 (9.40)	152 (1.51)	<0.001
Smokers	2212 (21.02)	174 (37.18)	2038 (20.27)	<0.001
Obese (BMI ≥ 30)	756 (7.18)	131 (27.99)	625 (6.22)	<0.001
Charlson Comorbidity Index				
0	2949 (28.02)	107 (22.86)	2842 (28.26)	<0.001
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)	

☆Mean ± Standard deviation

† Patient-reported race-ethnicity

★Physician-reported comorbidities

Table 2. Characteristics of Hospitalized COVID-19 Patients 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 — yr☆	64.99 ± 16.92	64.36 ± 15.88	65.02 ± 16.97	0.53
Age ≥ 65 yr	2723 (55.55)	124 (53.22)	2599 (55.67)	0.49
Female gender	2164 (44.14)	165 (70.82)	1999 (42.81)	<0.001
Race†				
White	1055 (21.52)	37 (15.88)	1018 (21.80)	0.006
Black	1032 (21.05)	65 (27.90)	967 (20.71)	0.06
Hispanic	1961 (40.00)	105 (45.06)	1856 (39.75)	0.17
Asian	246 (5.02)	2 (0.86)	244 (5.22)	<0.001
Others	608 (12.40)	24 (10.30)	584 (12.51)	0.32
Coexisting Conditions				
Hypertension	1585 (32.33)	141 (60.52)	1444 (30.93)	<0.001
Diabetes	1029 (20.99)	86 (36.91)	943 (20.20)	<0.001
CKD	571 (11.65)	54 (23.18)	517 (11.07)	<0.001
COPD	192 (3.92)	36 (15.45)	156 (3.34)	<0.001
OSA	104 (2.12)	21 (9.01)	83 (1.78)	<0.001
Smokers	1285 (26.21)	99 (42.49)	1186 (25.40)	<0.001
Obese (BMI ≥ 30)	400 (8.16)	70 (30.04)	330 (7.07)	<0.001
COVID-19 Disease Severity+				
Mild	762 (15.54)	36 (15.45)	726 (15.55)	0.51
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)	0.08
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 (days)★	6.99 (5.51-12.79)	7.87 (4.08-13.89)	6.95 (3.44-12.76)	0.72
Serum Eosinophils				
Maximum over hospital course				
Eosinophils < 200	3192 (65.12)	140 (60.09)	3052 (65.37)	0.10
Eosinophils ≥ 200	1597 (32.58)	89 (38.20)	1508 (32.30)	0.06
Maximal Inflammatory markers				
CRP > 150 (mg/L)	2215 (15.19)	112 (48.07)	2103 (45.04)	0.38
D-dimer > 2.0 (µg/L)	912 (20.11)	39 (18.40)	873 (20.19)	0.60
Ferritin > 2000 (ng/L)	1312 (26.76)	49 (21.03)	1263 (27.05)	0.05
Interleukin-6 > 80 (pg/mL)	1279 (26.09)	60 (25.75)	1219 (26.11)	0.94
Medications★				
Hydroxychloroquine	3304 (67.30)	153 (65.95)	3151 (67.37)	0.67
Azithromycin	3158 (64.33)	144 (62.07)	3014 (64.44)	0.48
Tocilizumab	243 (4.95)	14 (6.03)	229 (4.90)	0.44
Remdesivir	144 (2.93)	5 (2.16)	139 (2.97)	0.69
Corticosteroids	1354 (27.62)	95 (40.77)	1259 (26.97)	<0.001

Methylprednisolone	1098 (22.37)	70 (30.17)	1028 (22.02)	0.01
Prednisone	446 (9.09)	52 (22.41)	394 (8.42)	<0.001
Dexamethasone	155 (3.16)	11 (4.74)	144 (3.08)	0.17
Hydrocortisone	18 (0.37)	1 (0.43)	17 (0.36)	0.58
Anticoagulation	4413 (90.02)	219 (93.99)	4194 (89.83)	0.04
Heparin	2816 (57.36)	140 (60.34)	2676 (57.22)	0.38
Enoxaparin	2368 (48.24)	123 (53.02)	2245 (48.00)	0.14
Apixaban	1140 (23.22)	60 (25.86)	1080 (23.09)	0.34
Rivaroxaban	126 (2.57)	7 (3.02)	119 (2.54)	0.39
Clinical Outcomes				
ICU admission	1050 (21.39)	45 (19.40)	1005 (21.52)	0.51
Discharged	3575 (72.93)	181 (77.68)	3394 (72.69)	0.10
Death	1408 (28.72)	54 (23.18)	1354 (29.00)	0.06

☆Mean ± Standard deviation

† Patient-reported ethnicity

★Physician-reported comorbidities

Table 3. Relationship between asthma diagnosis and hospitalization outcomes

Composite Endpoints	Analysis Model	Odds Ratio (95% Confidence Interval)	P-value
Asthma			
Mortality☆ (N=54)	Univariate Multivariable - Model 1 † Multivariable - Model 2 †	0.59 (0.49-0.71) 0.28 (0.19-0.41) 0.64 (0.53-0.77)	<0.001 <0.001 <0.001
Hospitalization★ (N=233)	Univariate Multivariable - Model 1 † Multivariable - Model 2 †	0.82 (0.77-0.87) 0.93 (0.86-0.99) 0.43 (0.28-0.64)	<0.001 <0.001 <0.001
ICU Admission☆ (N=45)	Univariate Multivariable - Model 1 † Multivariable - Model 2 †	0.89 (0.64-1.26) 0.98 (0.97-0.98) 0.51 (0.41-0.64)	0.53 <0.001 <0.001
Intubation☆ (N=28)	Univariate Multivariable - Model 1 † Multivariable - Model 2 †	0.54 (0.45-0.67) 0.92(0.86-1.00) 0.56 (0.17-1.86)	<0.001 0.05 0.35

† Multivariable Model 1 — adjusted simultaneously for age, gender, BMI, Race, Charlson comorbidity index, chronic obstructive pulmonary disease (COPD), and smoking (current and former)

†Multivariable Model 2 — adjusted simultaneously for age, gender, BMI, Race, Covid-19 Disease Severity, Charlson comorbidity index, chronic obstructive pulmonary disease (COPD), C-reactive protein (>150), Interleukin-6 (>80), Ferritin (>2000), D-dimer (>2.0 µg/L), use of anticoagulation, use of corticosteroids, and smoking (current and former)

★Analysis based on all patients (hospitalized and non-hospitalized patients)

☆Analysis based on hospitalized patients

Table 4. Impact of Eosinophils on Mortality Among Hospitalized COVID-19 Patients with or without Asthma.

Composite Endpoint - Mortality	Predictors	Analysis Model	Odds Ratio (95% Confidence Interval)	P-value
Maximal Eosinophil count during hospitalization				
Asthma	≥200 cells/μL (N=77)	Univariate Multivariable - Model 1 † Multivariable - Model 2 ‡	1.70 (0.87-3.30) 0.16 (0.09-0.28) 0.09 (0.02-0.36)	0.12 <0.001 <0.001
No asthma	≥200 cells/μL (N=1407)	Univariate Multivariable - Model 1 † Multivariable - Model 2 ‡	1.87 (1.64-2.13) 0.26 (0.23-0.29) 0.31 (0.25-0.39)	<0.001 <0.001 <0.001

† Multivariable Model 1 — adjusted simultaneously for age, gender, BMI, Race, Charlson comorbidity index, chronic obstructive pulmonary disease (COPD), and smoking (current and former)

‡ Multivariable Model 2 — adjusted simultaneously for age, gender, BMI, Race, Covid-19 Disease Severity, Charlson comorbidity index, chronic obstructive pulmonary disease (COPD), C-reactive protein (>150), Interleukin-6 (>80), Ferritin (>2000), D-dimer (>2.0 μg/L), use of anticoagulation, use of corticosteroids, and smoking (current and former)