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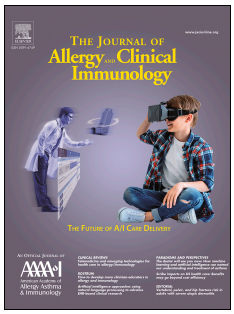

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Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19

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Abstract:

Background: The Centers for Disease Control and Prevention advises that patients with moderate-to-severe asthma belong to a high-risk group that is susceptible to severe COVID-19. However, the association between asthma and COVID-19 has not been well-established.

Objective: The primary objective was to determine the prevalence of asthma among COVID-19 patients in a major U.S. health system. We assessed the clinical characteristics and comorbidities in asthmatic and non-asthmatic COVID-19 patients. We also determined the risk of hospitalization associated with asthma and/or inhaled corticosteroid use.

Methods: Medical records of patients with COVID-19 were searched by a computer algorithm (March 1–April 15, 2020), and chart review was used to validate the diagnosis of asthma and medications prescribed for asthma. All patients were PCR-confirmed COVID-19. Demographics and clinical features were characterized. Regression models were used to assess the associations between asthma and corticosteroid use and the risk of COVID-19-related hospitalization.

Results: Of 1,526 patients identified with COVID-19, 220 (14%) were classified as having asthma. Asthma was not associated with an increased risk of hospitalization (RR of 0.96 [95%CI: 0.77-1.19]) after adjusting for age, sex, gender, and comorbidities. The

ongoing use of ICS did not increase the risk of hospitalization in a similar adjusted model (RR of 1.39 [95%CI: 0.90-2.15]).

Conclusions: Despite a substantial prevalence of asthma in our COVID-19 cohort, asthma was not associated with an increased risk of hospitalization. Similarly, the use of ICS with or without systemic corticosteroids was not associated with COVID-19-related hospitalization.

Abstract word count: 243

Clinical Implications:

The prevalence of asthma among patients with COVID-19 was 14.4% versus the national asthma prevalence of 8-9%. Asthma and inhaled corticosteroids were not associated with risk of hospitalization due to COVID-19.

Capsule Summary:

This retrospective study found an asthma prevalence of 14% in a general COVID-19 cohort. A diagnosis of asthma or the use of inhaled corticosteroids was not associated with an increased risk of COVID-19-related hospitalization.

Key words: COVID-19, SARS-CoV-2, asthma, risk factors, morbidity, severity, corticosteroid, long-acting beta-agonist, allergic rhinitis, rhinosinusitis

Abbreviations:

ACE2	Angiotensin-converting enzyme 2
AR	Allergic rhinitis
BMI	Body mass index
CAD	Coronary artery disease
CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
DM	Diabetes mellitus

101	EDW	Enterprise Data Warehouse
102	GERD	Gastroesophageal reflux disease
103	HTN	Hypertension
104	ICD	International Classification of Diseases
105	ICS	Inhaled corticosteroids
106	ICU	Intensive care unit
107	LABA	Long-acting beta-agonist
108	LDH	Lactate dehydrogenase
109	MMRW	Morbidity and Mortality Weekly Report
110	OSA	Obstructive sleep apnea
111	PCR	Polymerase chain reaction
112	RR	Relative risk
113	SARS-CoV 2	Severe acute respiratory syndrome coronavirus 2

Introduction:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) is a novel betacoronavirus that was first detected in December 2019. The coronavirus disease 2019 (COVID-19) has rapidly spread globally causing severe pneumonia along with additional complications including death in the most severely affected individuals. Community spread likely has occurred rapidly because the virus transmits easily, even in asymptomatic patients, and remains viable in respiratory droplets and fomites.[1] Three months after first emerging, fueled by community transmission, there were approximately 2.6 million cases reported globally – including 900,000 cases in the United States and 40,000 cases in Illinois according to the Centers for Disease Control and Prevention (CDC). The outcomes of COVID-19 are worsened by several comorbidities, including hypertension, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, and obesity.[2, 3] Whether asthma stands among these exacerbating factors requires further study.

Asthma is one of the most common chronic diseases in the U.S. (approximately 8-9% of the population) with acute exacerbations being a frequent cause of hospitalizations and/or emergency room visits.[4, 5] Respiratory viruses are well-known triggers of asthma exacerbations.[6-8] Coronaviruses are respiratory viruses and have been implicated in both upper respiratory infections and asthma exacerbations.[9] What is currently unclear is how the SARS-CoV-2 impacts patients with asthma. Data from published studies suggest that the prevalence of asthma in the COVID-19 population in China was <1%.[10,

[11] The reported prevalence of asthma in patients with COVID-19 in the U.S. varies from 7.4-17%.[2, 12-14]

Currently, the CDC classifies patients with underlying moderate-to-severe asthma as a high-risk group that is susceptible to severe COVID-19 illness. For patients with asthma, the symptoms of COVID-19, including cough, shortness of breath, and chest tightness, are difficult to distinguish from a severe asthma exacerbation. This symptom pattern overlap may make it more difficult for both patients and their treating physicians to diagnose and manage their disease. The degree of risk and associated clinical outcomes for people with asthma, however, is not clearly understood based on available data.

Published studies have concentrated on hospitalized COVID-19 patients which makes it difficult to determine if asthma is a risk factor for COVID-19 or increases COVID-19-related morbidity. The primary objective of the current study was to determine the prevalence of asthma and comorbidities associated with asthma in inpatients and outpatients with COVID-19. Secondly, we tested the risk of COVID-19-related hospitalization among those with asthma compared to those without asthma. Finally, we examined the association of corticosteroid use in patients with asthma and COVID-19.

Methods

Identification of patients with COVID-19

This retrospective study was conducted across 10 hospitals affiliated with Northwestern Medicine, one of the largest health systems in Chicago and surrounding Illinois suburbs. Study patients were identified by automated chart review utilizing Northwestern Medicine's Enterprise Data Warehouse (EDW), an electronic repository of inpatient and outpatient health records of more than 6.6 million distinct patients (from Illinois and surrounding states) seen within the health system. This study was approved by the Northwestern University Feinberg School of Medicine's Institutional Review Board.

Patients of all ages (including 2 patients <18 years old) were included in this study if they were evaluated between March 1, 2020 and April 15, 2020 within Northwestern Medicine and had received the International Classification of Disease, 10th Revision (ICD-10) diagnosis code for COVID-19 (U07.1). Presumed COVID-19 patients (U07.2) without laboratory Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) were not included in this study. Of the 1,837 patients identified with COVID-19, 295 were excluded as the presence of SARS-CoV-2 was not confirmed. Mortality in our study cohort was determined up to April 30, 2020.

Identification of asthma among patients with COVID-19

Data collected from RT-PCR-confirmed COVID-19 patients (N=1,542) were subsequently stratified based on the presence (N=236) or absence (N=1,306) of comorbid asthma as assessed by ICD-9 or ICD-10 codes (any 493.xx or J45.xx) (Figure

1). Manual chart review of all asthmatics was then performed to confirm a diagnosis of asthma. The criteria used to classify asthma included either a physician diagnosis of asthma or self-reported history of asthma. Patients with a diagnosis of childhood asthma (N=16) but no diagnosis of asthma as an adult were excluded.

Identification of clinical characteristics and comorbidities

Automated chart review was performed to identify clinical characteristics including age, gender, race/ethnicity, smoking status, and obesity (body mass index (BMI) ≥30). ICD-9 and ICD-10 codes were used to identify clinical comorbidities including hypertension (HTN), diabetes mellitus (DM), obstructive sleep apnea (OSA), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), allergic rhinitis (AR), rhinosinusitis and immunodeficiency. Immunodeficiency was defined as the presence of common variable immunodeficiency, antibody deficiency, or IgA deficiency. (Supplemental Table 1).

Assessment of asthma medications

For each patient with asthma, a manual chart review was performed to document a prescription of inhaled corticosteroids (ICS), combination inhaled corticosteroids plus long-acting beta-agonists (ICS/LABA), and/or systemic corticosteroids at the time of the diagnosis of COVID-19 or hospitalization.

Identification of laboratory values

When available, laboratory measurements including white blood cell counts, absolute eosinophil counts, absolute lymphocyte counts, platelet counts as well as ferritin, lactate dehydrogenase (LDH), D-dimer, creatinine, and C-reactive protein (CRP) levels were evaluated in each study patient at the time of COVID-19 diagnosis. If more than one lab value was available, the first value obtained up to 4 weeks after the diagnosis of COVID-19 was used for this study.

Statistical analysis

Demographic data and clinical characteristics were computed for all included participants and compared using Chi-square tests. Differences in laboratory values were compared using non-parametric Mann-Whitney tests or Kruskal-Wallis, where appropriate. Poisson regression models were used to calculate the relative risk (RR) of hospital admission (inpatient with or without intensive care unit (ICU) versus outpatient). For the analysis samples with all COVID-19 patients (N=1,526), the association between asthma and COVID-19 hospitalization was determined. Model covariables included: (1) age, gender, and race/ethnicity (Model 1), and (2) age, gender, race/ethnicity, smoking status, and comorbidities (Model 2). Comorbidities included obesity, HTN, DM, OSA, CAD and COPD, AR, rhinosinusitis, and immunodeficiency. Similar models were used for the analysis sample of only COVID-19 patients with asthma (N=220) in which the association between ICS use and hospitalization was tested. There were only a small number of patients (N=15) among 220 asthmatics receiving systemic corticosteroids. In a sensitivity analysis, we repeated the analysis after excluding these 15 patients to examine if systemic corticosteroids may have any

impact on the association of using ICS with the risk of hospitalization. Data were displayed and statistics were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA).

Results

Prevalence of asthma among patients with COVID-19

An automated electronic review of patient medical records identified 1,837 patients with an ICD-10 diagnosis code of COVID-19 in our system between March 1, 2020 and April 15, 2020. Of these, 1,542 (84%) had confirmed disease by RT-PCR and were included in subsequent analyses (Table 1). The majority of patients with COVID-19 (N=1,306) did not have asthma. Of the 236 patients with comorbid COVID-19 and asthma by ICD code, 16 patients did not have a diagnosis of adult asthma on further chart review. Our final analysis thus included 1,526 patients with COVID-19, of which 220 (14.4%) had asthma (Figure 1).

Demographics and clinical characteristics of COVID-19 patients with and without asthma

We assessed and compared various demographic and clinical characteristics in COVID-19 patients with and without comorbid asthma (Table 1). The majority (55.3%) of COVID-19 patients were between 40-69 years of age regardless of asthma status. Slightly more than half (53%) of all COVID-19 patients were female with a significant female predominance in the asthma cohort (70.9%). The primary race/ethnicities of the total COVID-19 cohort were non-Hispanic White (42.1%), non-Hispanic African American (23.5%), and Hispanic or Latino (21.2%). Within those with asthma, the percentage of patients identifying as non-Hispanic African American was 35.5% which was significantly higher compared to 21.4% in the non-asthma cohort. Although Hispanics comprised a significant proportion of the asthma cohort (12.7%), their

representation was even higher in the non-asthma group (22.7%). Hospitalization rate and mortality did not significantly differ between COVID-19 patients with asthma or without asthma.

Comparison of clinical comorbidities of COVID-19 patients with and without asthma

Next, we determined the prevalence of various comorbidities in COVID-19 patients based on their asthma status (Figure 2). Rates of obesity, HTN, OSA, CAD, COPD, and GERD were significantly increased in the cohort of COVID-19 patients with asthma compared to COVID-19 patients without asthma (Figure 2A). COVID-19 patients with asthma also had a higher prevalence of allergic rhinitis, rhinosinusitis and immunodeficiencies (Figure 2B).

Assessment of laboratory data at the time of COVID-19 diagnosis by asthma status

Results of various laboratory tests were collected for all hospitalized patients at the time of their COVID-19 diagnosis. If more than one lab value was available, we used the first value for up to 4 weeks after the diagnosis (Figure 3). Complete blood counts showed a white blood cell count and eosinophil count within normal limits which did not differ significantly between patients with and without asthma (Figure 3A-B). Platelet counts were significantly lower in the non-asthma subgroup versus asthma ($P = 0.006$) (Figure 3C). Ferritin, LDH, and CRP, which have been described as markers of COVID-19 severity,[15] were all significantly lower in COVID-19 patients with asthma compared to

COVID-19 patients without asthma (*P* < 0.0001, 0.048, 0.0004*, respectively)*. D-dimer was also lower in asthmatics compared to non-asthmatics although this was not statistically significant (P = 0.052). Absolute lymphocyte counts (x1000/µL) (median [Q1-Q3]) were lower in the ICU asthmatic patients with COVID-19 (0.8 [0.7-1.2]) compared to both non-ICU hospitalized (1.2 [0.8-1.6]) and outpatient asthmatics (1.2 [1.0-1.7]) (*P* = 0.03).

Relative risks for COVID-19-associated hospitalization due to asthma

We used two different models to evaluate if asthma was associated with an increased risk of hospitalization for COVID-19. After adjusting for baseline age, gender, and race/ethnicity (Model 1), asthmatics did not have a higher risk of COVID-19-related hospitalization compared to non-asthmatics (RR 1.01; 95%CI: 0.83-1.24) (Table 2, Model 1). When further adjusted for multiple risk factors including smoking, obesity, CAD, DM, HTN, OSA, COPD, AR, rhinosinusitis, and immunodeficiency (Model 2), there was still no difference in the relative risk of hospitalization between the asthma and non-asthma cohorts (RR 0.96; 95% CI: 0.77-1.19) (Table 2, Model 2).

Using Model 1, we assessed the individual risk of age, gender, or race/ethnicity on COVID-19 related hospitalization. In this analysis, younger age (<40 years) was associated with a lower relative risk of hospitalization (RR 0.34; 95% CI: 0.27-0.42). Patients of Hispanic or Latino ethnicity (RR 1.44; 95% CI: 1.21-1.72) or non-Hispanic African American (1.23; 95% CI: 1.03-1.46) race had significantly higher risks of COVID-19 related hospitalization compared to non-Hispanic White patients

(Supplemental Table 2). These demographic risks for hospitalization were present irrespective of asthma status. Even when adjusting for comorbidities using Model 2, Hispanics continued to be at increased risk of hospitalization due to COVID-19 (RR 1.35; 95%CI: 1.12-1.63; Supplemental Table 2). However, in this model, non-Hispanic African Americans no longer had a significantly elevated relative risk of hospitalization compared to non-Hispanic White patients (Supplemental Table 2). Age (≥70 years), male gender, and comorbid diagnoses of diabetes (RR 1.16; 95% CI: 1.00-1.36), and OSA (RR 1.23; 95% CI: 1.01-1.49) also elevated the relative risk of COVID-19 hospitalization regardless of asthma status (Supplemental Table 2, Model 2). Rhinosinusitis was associated with a significantly lower risk of hospitalization compared to the absence of rhinosinusitis (RR 0.78; 95% CI: 0.61-0.99) (Supplemental Table 2, Model 2). Patients with allergic rhinitis also showed a trend towards lower hospitalization although not statistically significant (RR 0.83; 95% CI: 0.64-1.07). These associations with rhinosinusitis and allergic rhinitis were observed in COVID-19 patients with or without asthma.

Relative risk for COVID-19-associated hospitalization due to corticosteroid use

We also explored the relationship between inhaled corticosteroids and the risk of hospitalization in COVID-19 patients with asthma using two different statistical models. Over half (52%, N=114) of COVID-19 patients with asthma were not prescribed either ICS or ICS/LABA at the time of diagnosis (Supplemental Table 3). Whereas, among those with asthma, 11.8% and 36.4% had documentation of ICS (N=26) or ICS/LABA (N=80) respectively at the time of COVID-19 diagnosis. The breakdown of inhaler use

among COVID-19 patients by the level of medical care is shown in Figure 4. Although, the percentage of COVID-19 patients with asthma stratified by ICS use and level of medical care was not statistically different (P=0.10), the proportion of patients not using ICS or ICS/LABA was highest (57.1%) in the outpatient group, and lowest (31.6%) in the ICU group. The proportion of patients using ICS/LABA was lowest in the outpatient group (28.6%), and highest in the ICU group (57.9%).

In general, among COVID-19 patients with asthma, the risk for hospitalization was not significantly different between those with documentation of ICS or ICS/LABA prescriptions in their medical records and those who were not prescribed maintenance inhalers (Model 1: RR 1.22; 95%CI 0.84-1.76; Model 2: RR 1.39; 95% CI: 0.90-2.15) (Table 3). The individual baseline risk factors used to adjust for relative risk assessing ICS use and COVID-19-related hospital admission are listed in Supplemental Table 4.

Fifteen patients with asthma were receiving systemic corticosteroids at the time of COVID-19 diagnosis. Out of those 15, 13 patients had been prescribed a short course of prednisone for an asthma exacerbation in the 2 weeks before their COVID-19 diagnosis. Systemic corticosteroid use prior to COVID-19 diagnosis was not different between the outpatient and inpatient managed subgroups. We repeated the regression model to determine the impact of ICS on COVID-19 hospitalization risk after removing the 15 patients prescribed systemic corticosteroids. The findings were nearly identical, and the use of ICS did not increase or decrease the risk of COVID-19 hospitalization in patients with asthma and COVID-19 (RR 1.47; 95% CI: 0.93-2.32). Only one patient

344 was receiving an asthma-related biologic (omalizumab). This patient required an ICU
345 stay and was intubated for COVID-19 but was successfully discharged after 16 days of
346 hospitalization.
347

Discussion

To the best of our knowledge, this is the first comprehensive cohort study of patients with COVID-19 and comorbid asthma. In this study, asthma was present in 14.4% of COVID-19 patients which included both hospitalized and non-hospitalized patients. Compared to the general U.S. and metropolitan Chicago population which is estimated to have an asthma prevalence of 8-9% and 9.5%, respectively, asthma is enriched in our COVID-19 population.[4, 5, 16] Among only hospitalized patients with COVID-19 in this cohort, the prevalence of asthma was 13.5%, which supports recent published U.S. data observing asthma prevalence between 7.4%-17% in COVID-19 hospitalized patients.[2, 12, 13, 17] This is in stark contrast to the low prevalence of asthma (<1%) noted in China.[10, 11] Geographic differences in the frequency of asthma or methods of ascertainment may be contributing to these heterogenous findings.

Importantly, despite the high prevalence of asthma in our study, we observed no significant difference in risk of hospitalization or mortality due to COVID-19 in asthmatic compared to non-asthmatic patients. The overall mortality rate (4.7%) in our COVID-19 population aligned closely with the national mortality rate of 6.0% during this time period as published on the Johns Hopkins Coronavirus Resource Center (May 6, 2020). In this cohort, the mortality rate (3.6%) in the COVID-19 population with asthma at the time of this study was not different than the mortality rate in the COVID-19 population without asthma (4.9%).

Well-established comorbidities that are associated with COVID-19 were present in this cohort of asthma (Figure 2). Interestingly, patients with asthma and COVID-19, compared to COVID-19 patients without asthma, had an increased prevalence of multiple comorbidities. Previous studies have shown that obesity, OSA, and GERD are associated with asthma.[18-20] In the general COVID-19 cohort, DM and OSA were associated with a higher risk of hospitalization; however, this was no longer true when evaluating the asthma subgroup alone. Further investigation is needed to determine why these comorbidities, despite being more prevalent in asthmatics, do not appear to worsen COVID-19-related outcomes.

Dramatic racial disparities have been reported during the COVID-19 pandemic and this was true in our study. Non-Hispanic African Americans made up almost one-quarter of our overall COVID-19 cohort despite the 6.1% prevalence of African Americans in our healthcare system. Moreover, African Americans were disproportionately higher in the asthma group (36%) compared to the non-asthma group (21%). Of the COVID-19 patients with asthma in this study, 12.7% were Hispanic or Latino. This data is in contrast to the national findings. According to the CDC, African Americans and Hispanics comprise 9.6% and 6.0% of the adult asthma population, respectively.[5] After controlling for age, sex, and race, African Americans had a higher risk of COVID-19-related hospitalization in the general COVID-19 cohort. Depending on the model used, the risk of COVID-19-related hospitalization was even higher in an adjusted analysis for the Hispanic or Latino population (35-44%).

393 The assessment of laboratory values demonstrates that patients with asthma had
394 significantly lower levels of ferritin, CRP, and LDH, compared to non-asthma patients.
395 These are markers of disease severity in COVID-19. This is the first report to our
396 knowledge to describe a potential decreased inflammatory burden in COVID-19 patients
397 with comorbid asthma, despite these patients having higher levels of other comorbid
398 diseases compared to non-asthmatics. These findings suggest that underlying immune
399 modulation either due to asthma or asthma treatment may have a mitigating effect on
400 COVID-19, but more studies are needed to understand this.
401
402 Interestingly, asthma did not increase the risk of hospitalization after adjusting for
403 covariates. This is notable as it has been anticipated that underlying chronic lung
404 disease such as asthma, which are typically triggered by a viral illness, would place
405 these patients at increased risk of severe exacerbations.[21] The role of ICS in asthma
406 patients and COVID-19 is not established and has brought concern to many patients.[22,
407 23] Almost half (48%) of the patients with asthma were using ICS before COVID-19 in our
408 study. After controlling for baseline risk factors, the use of ICS did not increase the risk
409 of COVID-19-related hospitalization. In this study, only fifteen patients were prescribed
410 systemic corticosteroids before diagnosis, so this limits our ability to make any
411 conclusion specifically regarding oral corticosteroid use in COVID-19. However, it is
412 reassuring that in the model assessing the risk of ICS, oral corticosteroids did not
413 change the risk of hospitalization.
414

It has been postulated that type 2 immune modulation decreases expression of ACE2, the known receptor for COVID-19 cellular entry.[24-26] Jackson et al. published early data which suggests that patients with allergic asthma have decreased ACE2 expression in nasal and bronchial epithelial cells.[27] Peters et al. observed that ICS use was associated with the reduction of expression of both ACE2 and TMPRSS2 (a host serine protease critical to spike protein priming for cell entry) in asthmatics from the Severe Asthma Research Program (SARP) cohort.[28] A separate, preliminary, *in vitro* study with ciclesonide showing viral suppression of SARS-CoV-2 begets the question of whether certain ICS commonly used by asthma patients could provide clinical protection.[29] These experimental studies in non-COVID-19 patients suggest a potential protective role for ICS. Although our real-world data on ICS use in COVID-19 patients does not show a lower risk of hospitalization, it is reassuring since we did not see an increase in hospitalization in patients who were receiving an ICS. Interestingly, we found patients with rhinosinusitis and allergic rhinitis, which are predominantly type 2 inflammatory diseases, have reduced risk of COVID-19-related hospitalization. Assessing if intranasal corticosteroids are protective in COVID-19 patients, especially in those with allergic rhinitis and rhinosinusitis, needs further investigation.

There are several limitations to our study. Data were obtained retrospectively so we are limited to drawing associations rather than causal inferences. Our study population and some of the variables used for analyses were based on ICD codes which may have mis-captured data. To minimize this, we performed chart reviews for the asthma cohort to confirm the diagnosis of both asthma and COVID-19, prescribed medications, and

the level of care required for COVID-19. Also, because of the study design, we cannot assume adherence with the prescribed medications. An additional limitation of our study is that we did not assess the contribution of asthma severity or control to COVID-19-related hospitalization as we were limited by our study design. Although we cannot make inferences based on asthma severity, COVID-19-associated level of care (ICU vs. non-ICU) was not significantly different between patients prescribed ICS or ICS/LABA and those not on ICS or ICS/LABA. Our findings are based on data collected between March 1- April 15 (with the exception of mortality assessed until April 30, 2020) and might change as additional data is collected after the study period. While it may be possible that patients with asthma were more likely to be tested as asthma is a chronic lung disease, our asthma prevalence data was similar to the prevalence reported by the Morbidity and Mortality Weekly Report from the CDC during this study period.[13] Lastly, widespread COVID-19 testing was not available during our data collection period so selected patients may represent a bias towards more severe COVID-19 disease.

In summary, we found that asthma prevalence was 14% in our cohort of COVID-19 patients. Despite a high prevalence of comorbid diseases that are associated with COVID-19 severity, it is reassuring that neither asthma nor the use of ICS was associated with an increased risk of COVID-19 hospitalization. With this in mind, physicians need to be vigilant of older patients, those with comorbidities (especially DM and OSA based on this study), African Americans, and Hispanics who present with COVID-19 symptoms since they are at increased risk of hospitalization. This is true in the general population as well as in asthmatics, according to this study. Further

investigation is necessary to understand the possible protective role of type 2 inflammation in asthma and COVID-19.

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544
545

Figure Legends:

Figure 1. Algorithm for identifying patients with COVID-19 and patients with asthma. COVID-19 patients were identified using the ICD-10 diagnosis code and COVID-19 polymerase chain reaction (PCR). Patients with asthma were identified by ICD diagnosis code and confirmed by chart review.

Figure 2. **Prevalence of comorbid diseases in COVID-19 patients stratified by asthma status.** (A) Comorbid diseases associated with metabolic syndrome, heart disease, and chronic lung diseases, and (B) allergic diseases were evaluated. Immunodeficiency includes patients with a diagnosis of immunodeficiency, antibody deficiency, or IgA deficiency. Obesity was determined based on reported BMI (≥ 30). For two patients who were younger than 20 years old, the weight-for-age percentile was used instead of BMI. Bars represent mean ± SEM. Statistical comparisons were performed using Chi-square tests. ***P* ≤ 0.01, ****P* ≤ 0.001, *****P* ≤ 0.0001. 180 patients had missing BMI values. Hypertension (HTN), obstructive sleep apnea (OSA), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and gastroesophageal reflux disease (GERD).

Figure 3. Laboratory values at the time of COVID-19 diagnosis in hospitalized patients with a concurrent diagnosis of asthma compared to non-asthma. (A) White blood cells, (B) absolute eosinophils, (C) platelets, (D) ferritin, (E) lactate dehydrogenase (LDH), (F) D-Dimer, (G) Creatinine, and (H) C-reactive protein (CRP) lab values are plotted using a box and whisker plot. The box extends from the 25th to

569 75th percentiles. The line within the box denotes median and a "+" is shown at the mean.
570 Whiskers represent min and max values. "Y" (Yes) denotes the group with asthma, and
571 "N" (No) denotes the non-asthma group. Statistical analysis was performed with non-
572 parametric Mann-Whitney two-tailed tests. *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, ****$P \leq$
573 0.0001.
574
575 **Figure 4. Percentage of COVID-19 patients with asthma using inhaled or oral**
576 **corticosteroids by the level of care.** Percentage of COVID-19 patients with asthma
577 (1) not taking ICS, (2) using ICS alone or (3) using ICS/LABA at the time of COVID-19
578 diagnosis. Oral steroids were used by 15 out of 220 asthma patients: outpatient (N=7),
579 inpatient – no ICU (N=8) and inpatient – ICU (N=0). Bars represent mean ± SEM.
580 Statistics were performed using Chi-square test ($P = 0.10$).

Table 1. Demographics and clinical characteristics of patients with COVID-19 confirmed by RT-PCR and stratified by asthma status.

Characteristic — N (%)	**All Patients** 1526 (100)	**Non-asthma** 1306 (86)	**Asthma** 220 (14.4)	***P* value***
Age				**0.05**
<40	414 (27.1)	351 (26.9)	63 (28.6)	
40-69	844 (55.3)	713 (54.6)	131 (59.6)	
≥70	268 (17.6)	242 (18.5)	26 (11.8)	
Gender				**<0.0001**
Female	808 (53)	652 (49.9)	156 (70.9)	
Race/Ethnicity				**<0.0001**
Non-Hispanic African American	358 (23.5)	280 (21.4)	78 (35.5)	
Non-Hispanic White	643 (42.1)	548 (42)	95 (43.2)	
Hispanic or Latino	324 (21.2)	296 (22.7)	28 (12.7)	
Non-Hispanic Asian	70 (4.6)	63 (4.8)	7 (3.2)	
Other	201 (13.2)	182 (13.9)	19 (8.6)	
Smoking Status				**<0.0001**
Current Smoker	53 (3.5)	43 (3.3)	10 (4.5)	
Former Smoker	336 (22)	285 (21.8)	51 (23.2)	
Never Smoker	897 (58.8)	748 (57.3)	149 (67.7)	
Unknown	240 (15.7)	230 (17.6)	10 (4.6)	
Hospitalization	853 (55.9)	738 (56.5)	115 (52.3)	0.242
Mortality[†]	72 (4.7)	64 (4.9)	8 (3.6)	0.413

**P* value indicated is for the comparison between asthma and non-asthma groups using Chi-square test.
[†]Mortality data in this cohort was determined up to April 30, 2020.

Table 2. Adjusted relative risk (95% CI) for COVID-19-related hospital admission from March 1-April 15, 2020 by asthma status.

Baseline Risk Factor Profile	**Asthma vs. Non-Asthma**	***P* value**
Model 1	RR (95% CI)	
Adjusted for age, gender, race/ethnicity	1.01 (0.83-1.24)	0.90
Model 2		
Adjusted for age, gender, race/ethnicity, smoking, obesity, CAD, diabetes, HTN, OSA, COPD, allergic rhinitis, rhinosinusitis, immunodeficiency	0.96 (0.77-1.19)	0.71

CAD- coronary artery disease, HTN- hypertension, OSA- obstructive sleep apnea, COPD- chronic obstructive pulmonary disease

Table 3. Asthma-specific adjusted relative risk (95% CI) for COVID-19-related hospital admission by inhaled corticosteroid use.

Asthma-specific Baseline Risk Factor Profile	**ICS +/- LABA vs. No ICS +/- LABA**	***P* value**
Model 1	RR (95% CI)	
Adjusted for age, gender, race/ethnicity	1.22 (0.84-1.76)	0.30
Model 2		
Adjusted for age, gender, race/ethnicity, smoking, obesity, CAD, diabetes, HTN, OSA, COPD, allergic rhinitis, rhinosinusitis, immunodeficiency	1.39 (0.90-2.15)	0.13

CAD- coronary artery disease; HTN- hypertension, OSA- obstructive sleep apnea, COPD- chronic obstructive pulmonary disease

Figure 1.

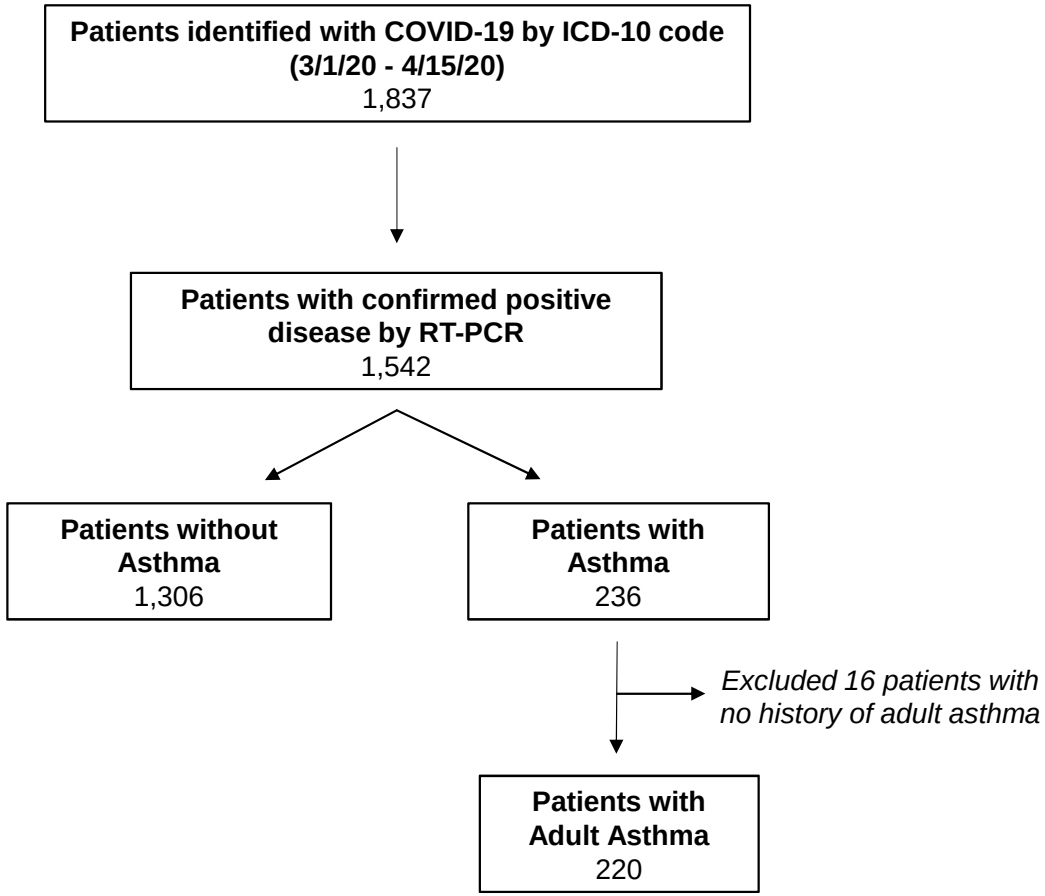

Patients identified with COVID-19 by ICD-10 code (3/1/20 - 4/15/20)
1,837
Patients with confirmed positive disease by RT-PCR
1,542
Patients without Asthma
1,306
Patients with Asthma
236
Excluded 16 patients with no history of adult asthma
Patients with Adult Asthma
220

Figure 2.

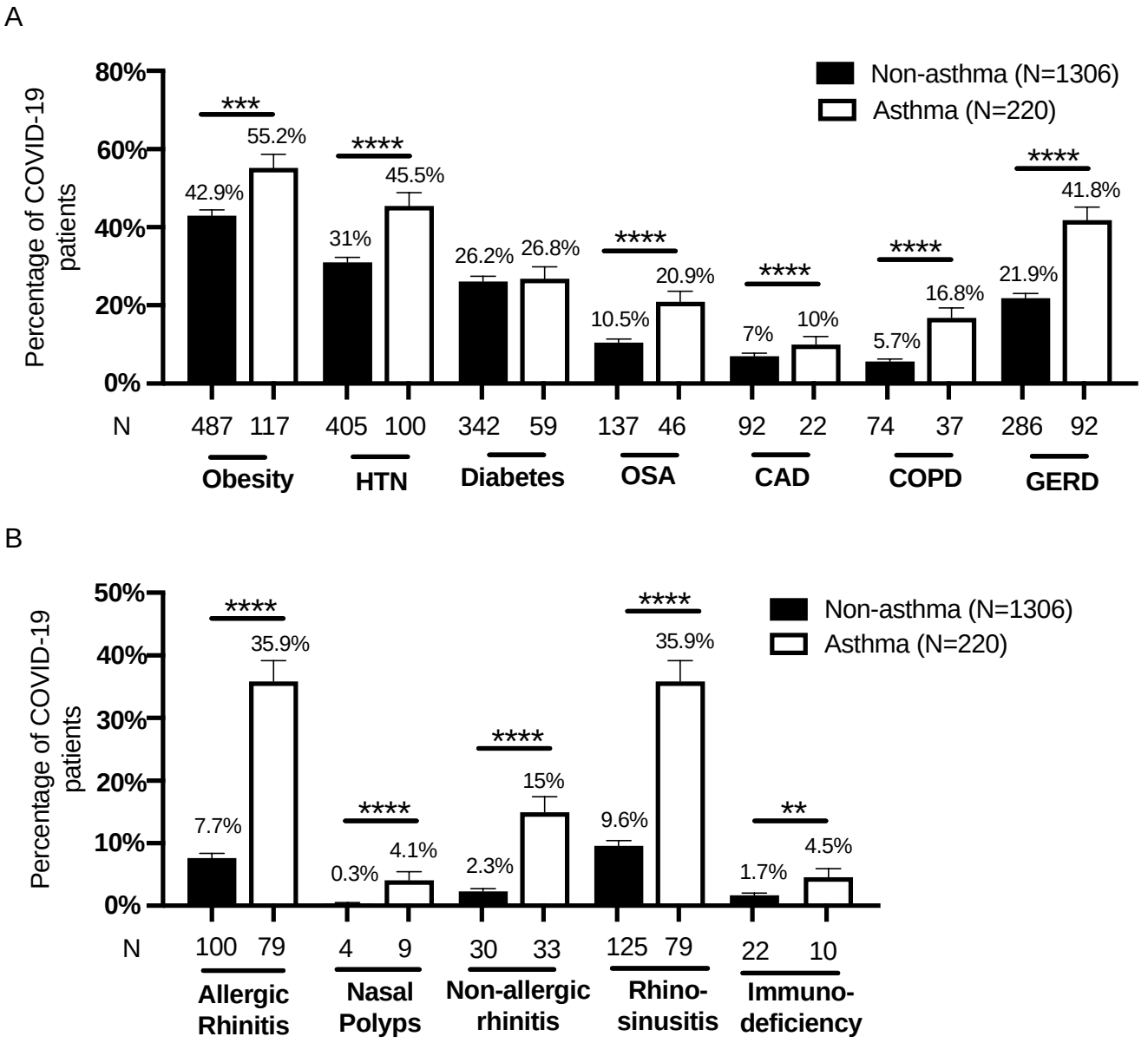

A
Percentage of COVID-19 patients
80%
60%
40%
20%
0%
Non-asthma (N=1306)
Asthma (N=220)
***
****
42.9%
55.2%
31%
45.5%
26.2%
26.8%
10.5%
20.9%
7%
10%
5.7%
16.8%
21.9%
41.8%
N
487 117
405 100
342 59
137 46
92 22
74 37
286 92
Obesity
HTN
Diabetes
OSA
CAD
COPD
GERD
B
Percentage of COVID-19 patients
50%
40%
30%
20%
10%
0%
Non-asthma (N=1306)
Asthma (N=220)
****
**
7.7%
35.9%
0.3%
4.1%
2.3%
15%
9.6%
35.9%
1.7%
4.5%
N
100 79
4 9
30 33
125 79
22 10
Allergic Rhinitis
Nasal Polyps
Non-allergic rhinitis
Rhino-sinusitis
Immuno-deficiency

Figure 3

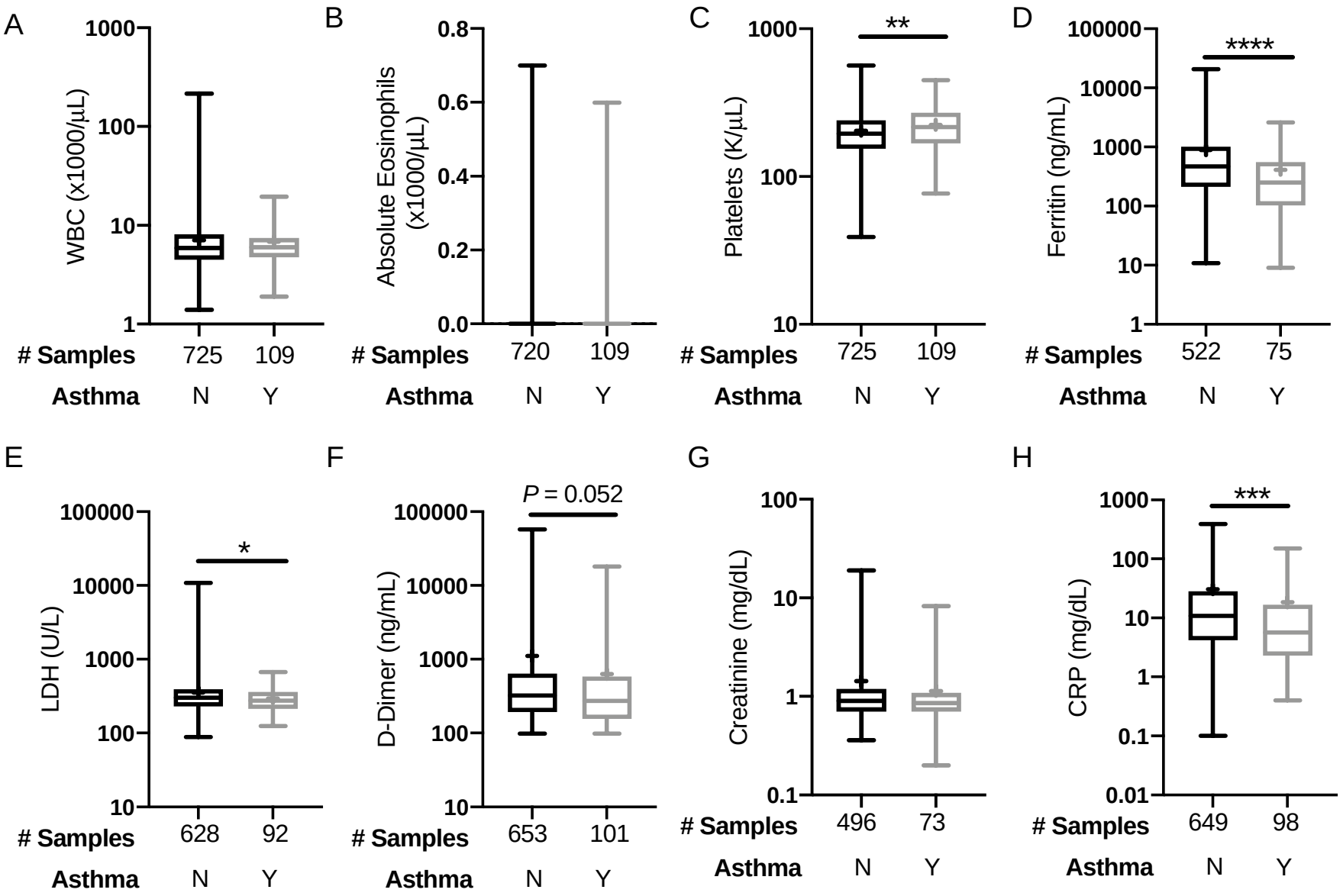
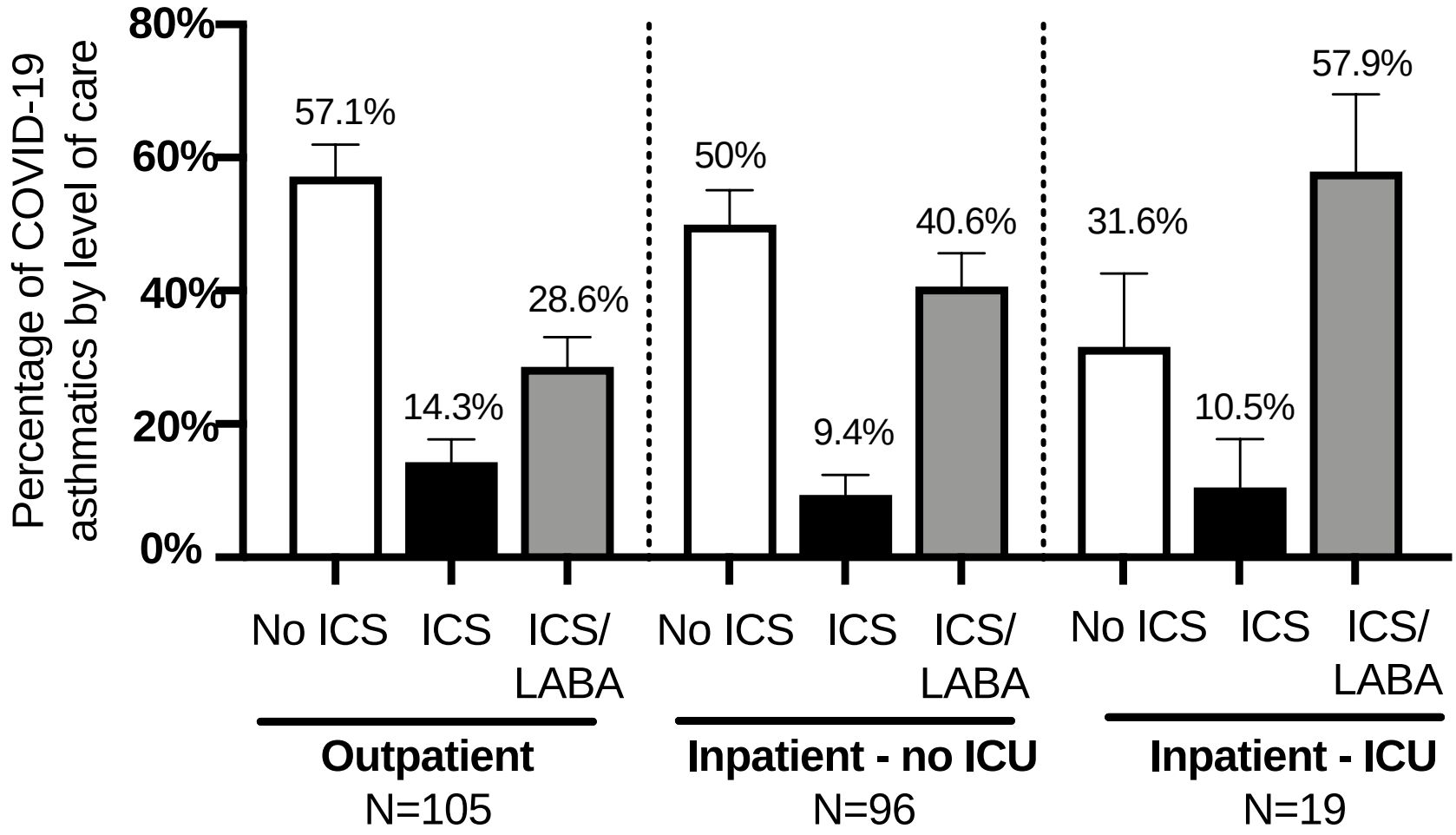

A
WBC (x1000/µL)
1000
100
10
1
Samples 725 109
Asthma N Y
B
Absolute Eosinophils (x1000/µL)
0.8
0.6
0.4
0.2
0.0
Samples 720 109
Asthma N Y
C
**
Platelets (K/µL)
1000
100
10
Samples 725 109
Asthma N Y
D
****
Ferritin (ng/mL)
100000
10000
1000
100
10
1
Samples 522 75
Asthma N Y
E
*
LDH (U/L)
100000
10000
1000
100
10
Samples 628 92
Asthma N Y
F
P = 0.052
D-Dimer (ng/mL)
100000
10000
1000
100
10
Samples 653 101
Asthma N Y
G
Creatinine (mg/dL)
100
10
1
0.1
Samples 496 73
Asthma N Y
H
***
CRP (mg/dL)
1000
100
10
1
0.1
0.01
Samples 649 98
Asthma N Y

Figure 4.


Percentage of COVID-19 asthmatics by level of care
80%
60%
40%
20%
0%
57.1%
14.3%
28.6%
50%
9.4%
40.6%
31.6%
10.5%
57.9%
No ICS
ICS
ICS/ LABA
No ICS
ICS
ICS/ LABA
No ICS
ICS
ICS/ LABA
Outpatient
N=105
Inpatient - no ICU
N=96
Inpatient - ICU
N=19

Supplemental Table 1: ICD.9 and ICD.10 Classification Codes.

ICD code	Code diagnosis
U07.1	COVID-19
V15.82, Z87.891	Former smoker (N=336)
305.1, F17.200	Current smoker (N=53)
Any 493.x, any J45.x	Asthma (N=220)
496, 491.xx, 492.xx, any J44.x	Chronic Obstructive Pulmonary Disease (N=111)
494.0, 494.1, any J47.x	Bronchiectasis (N=19)
530.81, 530.11, K21.0, K21.9	Gastro-esophageal Reflux Disease (N=378)
461.9, 473.8, 473.9, J01.90, J32.9	Rhinosinusitis (N=204)
471.xx, J33.9	Nasal polyposis (N=13)
Any 477.x, any J30.x	Allergic rhinitis (N=179)
327.23, G47.33	Obstructive Sleep Apnea (N=183)
472, J31.0	Non-allergic rhinitis (N=63)
297.06, D83.9, 279.xx, D80.6, D80.3	Common Variable Immunodeficiency, Antibody deficiency, IgA deficiency (N=32)
250, E11.9	Diabetes Mellitus (N=401)
414.01, 125.10	Coronary Artery Disease (N=114)
401.9, R03.0	Hypertension (N=505)

Supplemental Table 2. Individual baseline risk factors and associated adjusted relative risk (95% CI) for COVID-19-related hospital admission.

	Hospital Admission					
Individual Baseline Risk Factors	**Model 1**			**Model 2**		
	RR	**95% CI**		**RR**	**95% CI**	
Asthma vs. Non-Asthma	1.01	0.83	1.24	0.96	0.77	1.19
Age						
<40	**0.34**	0.27	0.42	**0.50**	0.38	0.64
40-69	**0.66**	0.56	0.78	**0.76**	0.64	0.91
≥70	1 (ref)			1 (ref)		
Gender						
Female	**0.82**	0.71	0.94	**0.86**	0.75	0.99
Race/Ethnicity						
Non-Hispanic African American	**1.23**	1.03	1.46	1.11	0.93	1.32
Non-Hispanic White	1 (ref)			1 (ref)		
Hispanic or Latino	**1.44**	1.21	1.72	**1.35**	1.12	1.63
Non-Hispanic Asian	0.93	0.63	1.35	0.96	0.65	1.42
Other	0.94	0.71	1.26	1.07	0.80	1.43
Smoking Status						
Current Smoker				1.10	0.75	1.61
Former Smoker				1.06	0.89	1.25
Never Smoker				1 (ref)		
Other/Unknown				**1.35**	1.08	1.70
Concurrent Diagnoses						
Obesity (BMI≥30)*				1.10	0.95	1.27
Hypertension				1.14	0.97	1.33
Diabetes mellitus				**1.16**	1.00	1.36
Obstructive sleep apnea				**1.23**	1.01	1.49
Coronary artery disease				1.02	0.80	1.29
COPD				1.18	0.93	1.50
Allergic rhinitis				0.83	0.64	1.07
Rhinosinusitis				**0.78**	0.61	0.99
Immunodeficiency				1.14	0.75	1.75

*****BMI data was not available for 180 study patients.

Supplemental Table 3. Descriptive analysis of COVID patients with asthma stratified by inhaled corticosteroid use.

Characteristic — N (%)	**No maintenance inhalers** 114 (51.8)	**ICS or ICS/LABA** 106 (48.2)	**Total** 220 (100)	**Chi-Square *P* value**
Age				0.162
<40	37 (58.7)	26 (41.3)	**63**	
40-69	61 (46.6)	70 (53.4)	**131**	
≥70	16 (61.5)	10 (38.5)	**26**	
Gender				0.961
Male	33 (51.6)	31 (48.4)	**64**	
Female	81 (51.9)	75 (48.1)	**156**	
Race/Ethnicity				0.873
Non-Hispanic African American	44 (56.4)	34 (43.6)	**78**	
Non-Hispanic White	46 (48.4)	49 (51.6)	**95**	
Hispanic or Latino	14 (14.0)	14 (50.0)	**28**	
Non-Hispanic Asian	4 (57.1)	3 (42.9)	**7**	
Other	6 (50.0)	6 (50.0)	**12**	
Smoking Status				0.787
Current Smoker	4 (40.0)	6 (60.0)	**10**	
Former Smoker	28 (54.9)	23 (45.1)	**51**	
Never Smoker	76 (51.0)	73 (49.0)	**149**	
Unknown	5 (83.3)	1 (16.7)	**6**	
Concurrent Diagnoses				
Obesity (BMI≥30)	65 (55.6)	52 (44.4)	**117**	0.301
Hypertension	50 (50.0)	50 (50.0)	**100**	0.622
Diabetes mellitus	34 (57.6)	25 (42.4)	**59**	0.297
Obstructive sleep apnea	20 (43.5)	26 (56.5)	**46**	0.203
Coronary artery disease	13 (59.1)	9 (40.9)	**22**	0.472
COPD	13 (35.1)	24 (64.9)	**37**	**0.026**
Allergic rhinitis	25 (31.6)	54 (68.4)	**79**	**<0.0001**
Rhinosinusitis	30 (38.0)	49 (62.0)	**79**	**0.002**
Nasal polyps	2 (22.2)	7 (77.8)	**9**	0.07
GERD	44 (47.8)	48 (52.2)	**92**	0.315
Oral Steroid Use			**15**	
Biologics			**1***	

*omalizumab

COPD- chronic obstructive pulmonary disease; GERD- gastroesophageal reflux disease

Supplemental Table 4. Individual baseline risk factors and associated asthma-specific adjusted relative risk (95% CI) for COVID-19-related hospital admission.

	Hospital Admission					
Individual Baseline Risk Factors	**Model 1**			**Model 2**		
	RR	**95% CI**		**RR**	**95% CI**	
ICS vs. non-ICS	1.22	0.84	1.76	1.39	0.9	2.15
Age						
<40	**0.31**	0.17	0.59	**0.43**	0.20	0.91
40-69	**0.59**	0.36	0.95	0.66	0.38	1.15
≥70	1 (ref)			1 (ref)		
Gender						
Female	0.99	0.66	1.49	1.10	0.71	1.70
Race/Ethnicity						
Non-Hispanic African American	1.24	0.82	1.88	1.20	0.76	1.91
Non-Hispanic White	1 (ref)			1 (ref)		
Hispanic or Latino	1.42	0.80	2.51	1.28	0.69	2.36
Non-Hispanic Asian	0.89	0.27	2.88	1.11	0.33	3.82
Other	1.12	0.44	2.85	1.19	0.45	3.15
Smoking Status						
Current Smoker				1.50	0.57	4.00
Former Smoker				1.31	0.82	2.10
Never Smoker				1 (ref)		
Other/Unknown				1.83	0.63	5.30
Concurrent Diagnoses						
Obesity (BMI≥30)*				1.23	0.80	1.89
Hypertension				1.25	0.79	2.00
Diabetes mellitus				1.29	0.82	2.03
Obstructive sleep apnea				0.96	0.59	1.57
Coronary artery disease				1.37	0.76	2.46
COPD				1.07	0.63	1.80
Allergic rhinitis				0.92	0.56	1.49
Rhinosinusitis				0.83	0.52	1.33
Immunodeficiency				0.39	0.12	1.30

*****BMI data was not available for 180 study patients.