



The impact of asthma on in-hospital outcomes of COVID-19 patients

Jeffrey F. Mather, Wassim Mosleh & Raymond G. McKay

To cite this article: Jeffrey F. Mather, Wassim Mosleh & Raymond G. McKay (2021): The impact of asthma on in-hospital outcomes of COVID-19 patients, Journal of Asthma, DOI: [10.1080/02770903.2021.1944187](https://doi.org/10.1080/02770903.2021.1944187)

To link to this article: <https://doi.org/10.1080/02770903.2021.1944187>



View supplementary material [↗](#)



Published online: 29 Jun 2021.



Submit your article to this journal [↗](#)



Article views: 44



View related articles [↗](#)



View Crossmark data [↗](#)



The impact of asthma on in-hospital outcomes of COVID-19 patients

Jeffrey F. Mather, MS^a , Wassim Mosleh, MD^b and Raymond G. McKay, MD^c

^aDivision of Research Administration, Hartford Hospital, Hartford, CT, USA; ^bDivision of Cardiology, University of Connecticut, Farmington, CT, USA; ^cDivision of Cardiology, Hartford Hospital, Hartford, CT, USA

ABSTRACT

Objective: The impact of asthma as a possible risk factor for adverse clinical outcomes in patients diagnosed with COVID-19 remains controversial. The purpose of this study was to examine the impact of asthma on adverse clinical outcomes in a COVID-19 hospitalized cohort.

Methods: Retrospective, propensity-matched observational study of consecutive COVID-19-positive patients between February 24, 2020, and November 3, 2020 at a single health care system.

Results: In the initial population of 1925 patients, 4.4% presented with asthma. Propensity score matching reduced the total sample to $n=1045$: 88 (8.4%) with asthma and $n=957$ without asthma. A total of 164 (15.7%) patients died during the hospitalization, including 7 (8.0%) in the asthma group and 157 (16.4%), $p=.037$, in the non-asthmatic cohort. There was no difference between these groups in need for mechanical ventilation, length of stay on a ventilator, or hospital length of stay.

Logistic regression analysis demonstrated that asthma was an independent predictor of lower mortality, while older age, BMI $> 30 \text{ kg/m}^2$, heart failure, chronic kidney disease, and admission National Early Warning Score (NEWS) were significantly associated with an increased risk of in-hospital death. There were no significant differences between asthmatic and non-asthmatic cohorts with respect to need for mechanical ventilation, length of mechanical ventilation, serum markers of severe COVID-19 disease, or overall length of hospital stay.

Conclusion: We conclude that asthma in hospitalized COVID-19 patients is associated with a lower risk of mortality and no increase in disease severity in hospitalized COVID-19 patients.

Abbreviations: COVID-19: coronavirus disease 2019; NEWS: National Early Warning Score; BMI: body mass index; ACE2: angiotensin-converting-enzyme-2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; EMR: electronic medical record; LOS: length of stay; VIF: variance inflation factor; NLR: neutrophil-lymphocyte ratio; OR: odds ratio; CI: confidence interval; CKD: chronic kidney disease; IC: inhaled corticosteroid; LABA: long-acting beta2-agonist; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; WBC: white blood cell count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

ARTICLE HISTORY

Received 10 March 2021

Revised 19 May 2021

Accepted 13 June 2021

KEYWORDS

Asthma; COVID-19; hospital mortality; risk factors

Introduction

The impact of asthma as a risk factor for severe COVID-19 illness remains controversial. While early case series from China reported a low prevalence of asthma and respiratory allergy in the COVID-19 population (1,2), more recent reviews have documented an asthma rate in hospitalized patients that is higher than the documented asthma prevalence in the general population (3,4). Similarly, recent publications have documented an increase in severe COVID-19 disease in patients with non-atopic asthma (5) and longer ventilation times in younger asthmatic patients (6), and other studies have documented decreased

expression of the ACE2 receptor in allergic asthma patients, suggesting a decreased susceptibility to viral infection and disease progression (7). Given the controversy over the effect of asthma on COVID-19 prognosis, this study examined the impact of asthma on clinical outcomes in a COVID-19 hospitalized cohort.

Methods

Setting and design

This retrospective, observational study was performed at Hartford Hospital, an 890-bed tertiary care medical center in Hartford, CT. The Hartford Hospital

CONTACT Jeffrey F. Mather  Jeff.Mather@hhchealth.org  Division of Research Administration, Hartford Hospital, 80 Seymour Street, Hartford, CT 06115, USA.

 Supplemental data for this article can be accessed at [publisher's website](#).

© 2021 Taylor & Francis Group, LLC

Institutional Review Board (Assurance number: FWA000000601) approved the study and certified its waiver of the requirement to obtain informed consent.

Study population

The study group was derived from an electronic database of consecutive patients screened for COVID-19 between February 2020 and November 2020 at Hartford Healthcare. All patients who tested positive for SARS-CoV-2 by nasopharyngeal polymerase chain reaction and who required inpatient admission were included in this study.

Asthma designation

Patients were classified, prior to hospitalization for COVID-19, as having mild or moderate asthma according to ICD-10-CM codes (see [appendix](#)) extracted from the EMR. Patients coded for chronic obstructive lung disease, emphysema, or chronic bronchitis were excluded. The list of the codes used to establish the asthmatic subgroup of patients appears in the [Appendix](#).

Primary and secondary outcomes

The primary outcome of the study was in-hospital death. Secondary outcomes included need for mechanical ventilation, length of mechanical ventilation, serum markers of severe COVID-19 disease, and length of hospital stay (LOS). Mortality data, ventilation status, all laboratory values, and LOS were extracted from the EMR.

Additional variables

Additional potentially predictive variables of in-hospital mortality were chosen based on the prior reports of risk factors for adverse acute outcomes in patients positive for COVID-19 (8). Analyzed covariates included baseline demographics, preexisting comorbidities, treatment with antiviral and antimalarial medications, and maximum NEWS (9). Demographic variables included age, gender, race, and BMI. Comorbidities included history of preexisting hypertension, diabetes mellitus, obesity (BMI > 30), coronary artery disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, and prior history of malignancy. Asthma medication was defined as documented use within a seven day window around COVID-19 testing. The following classes of medications were defined in this study: systemic corticosteroids, inhaled corticosteroids,

inhaled LABA, leukotriene modifiers, and long-acting bronchodilators. Inhospital treatment medications included use of hydroxychloroquine, azithromycin, remdesivir, and tocilizumab. Admission NEWS was determined for all patients based upon respiration rate, oxygen saturation, systolic blood pressure, and pulse rate at the time of initial hospitalization.

Additional sensitivity analysis

Two sensitivity analyses were performed. To determine whether there was any relationship between the level of patient acuity and the association of asthma with mortality, we performed an additional sensitivity analysis on two subsets of patients comparing results in patients with a NEWS ≤ 3 to patients with a NEWS > 3. An additional sensitivity analysis was also performed to determine the impact of any interaction between asthma and inhaled corticosteroids on the requirement for mechanical ventilation and on in-hospital mortality. To do so, we included a variable defined any combinations of asthma and inhaled corticosteroid use.

Statistical approach

Normally distributed continuous variables were compared with Student's *t*-test. If not normally distributed, Mann–Whitney *U*-test was used. Categorical variables were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Univariate analyses were performed in the matched dataset using mortality as the dependent variable, and logistic regression was performed by entering all predictors using *p* values of less than .15 cutoff. Multicollinearity was evaluated by the VIF. Overall model performance was measured using Nagelkerke's R^2 , a measure of explained variance, and the Hosmer–Lemeshow test. All effects were considered significant at *p* values of less than .05. The statistical analyses were performed with SPSS 21.0 (SPSS, Chicago, IL).

To control for the confounding effects introduced by factors related to both risk of in-hospital mortality and asthma presentation, a propensity score was developed to characterize the probability of having asthma. The propensity score was calculated from a logistic regression analysis by modeling asthma as the dependent variable and age, gender, and history of atrial fibrillation as the covariates. Patients with asthma were matched 1:15 with patients not treated with asthma using the nearest neighbor matching with a caliper of 0.2. The quality of the matching was determined by assessing whether variable or linear

combination of variables was significantly unbalanced after matching using the model imbalance chi-squared test (10) and the criterion of a standardized mean difference (11) less than 0.2. Propensity score matching was performed using Propensity Score Matching for SPSS, version 3.0.4 (SPSS, Chicago, IL).

Results

From February 20, 2020, to November 3, 2020, a total of 14130 patients tested positive for COVID-19. From this population, we selected 1925 patients who had an inpatient admission to Hartford Healthcare. The final selection resulted in a 1:15 propensity-matched cohort of 88 patients who were classified as asthmatics and 957 non-asthmatics.

Patient characteristics

In the patient population prior to matching ($n=1928$), a total of 88 patients (4.6%) were classified as asthmatic. The mean age of the entire study group was 64.6 ± 18.1 years and included 993 males (51.5%). The rate of in-hospital mortality was 15.7%, and ventilation was required in 17.3% of patients.

Median (interquartile range) ventilation and hospital LOS were 5.7 (3.1–10.0) and 8.4 (2.8–15.3), respectively. When compared with the unmatched sample, the matched population was younger, had fewer males, and had a lower incidence of atrial fibrillation and heart failure, and a higher proportion of patients with obesity (Table 1).

After propensity score matching, asthmatic ($n=88$) and non-asthmatic patients ($n=957$) were well matched with the covariates, showing non-significant differences in age, gender, and incidence of atrial fibrillation. Compared to non-asthmatic patients, asthmatic patients had a higher mean BMI (37.8 ± 10.2 vs 31.6 ± 8.8 kg/m², $p < .001$), incidence of diabetes (34.1% vs 20.0%, $p = .002$), obesity (BMI >30 kg/m², 18.2% vs 5.9%, $p < .001$), and hypertension (51.1% vs 27.4%, $p < .001$). Asthmatic patients were more commonly treated with inhaled corticosteroids, inhaled LABA, leukotriene modifiers, and systemic corticosteroids prior to hospitalization (Table 1).

Hydroxychlorine, azithromycin, remdesivir, and tocilizumab treatment

A total of 210 (20.1%) of 1045 COVID-19 matched patients received hydroxychloroquine, 226 (21.6%) received azithromycin, 24 (2.3%) received remdesivir, and 125 (12.0%) received tocilizumab. There was no significant difference between the asthmatic and non-asthmatic cohorts with respect to treatment with any of these medications (Table 2).

Primary and secondary outcomes

A total of 164 (15.7%) patients died during the hospitalization, including 7 (8.0%) in the asthma group and 157 (16.4%), $p = .037$, in the non-asthmatic cohort. Using a multivariable logistic regression model to assess the independent risk factors associated with

Table 1. Baseline demographics, comorbidities, pre-hospital medications, and admission NEWS score.

Variables: <i>n</i> (%), median (IQR), mean ($\pm$ SD)	Unmatched	Matched		<i>p</i> value
	(<i>n</i> = 1925)	Asthmatic (<i>n</i> = 88)	Non-Asthmatic (<i>n</i> = 957)	
Demographics				
Age	64.6 $\pm$ 18.1	53.8 $\pm$ 16.2	56.2 $\pm$ 17.7	.23
Gender (male)	993 (51.5)	22 (25.0%)	330 (34.5%)	.072
Caucasian	1014 (52.6%)	32 (37.0%)	427 (45.9%)	.12
BMI	30.8 (8.4)	37.8 $\pm$ 10.2	31.6 $\pm$ 8.8	< .001
Comorbidities				
Atrial fibrillation	184 (9.5)	2 (2.3%)	30 (3.1%)	.65
COPD	40 (2.1%)	0 (0%)	18 (1.9%)	.39
CAD	175 (9.1)	11 (12.5%)	69 (7.2%)	.074
Malignancy	86 (4.5)	4 (4.5%)	40 (4.2%)	.87
Diabetes	424 (22.0)	30 (34.1%)	191 (20.0%)	.002
Heart Failure	163 (8.5)	7 (8.0%)	47 (4.9%)	.22
Hypertension	639 (33.1)	45 (51.1%)	262 (27.4%)	<.001
Obesity	96 (5.0)	16 (18.2%)	56 (5.9%)	<.001
Chronic Kidney Disease	389 (20.2)	17 (19.3%)	161 (16.8%)	.55
Out-Patient Medications				
Inhaled Corticosteroids	174 (9.0%)	22 (25.0%)	77 (8.0%)	<.001
Inhaled Long-Acting Beta2-Agonists	301 (15.6%)	36 (40.9%)	138 (14.4%)	<.001
Leukotriene Modifiers	61 (3.2%)	16 (18.2%)	21 (2.2%)	<.001
Long-Acting Bronchodilators	75 (3.9%)	3 (3.4%)	25 (4.6%)	.66
Systemic Corticosteroids	359 (18.6%)	33 (37.5%)	165 (17.2%)	<.001
Admission NEWS Score	3 (1–5)	3 (1–5)	3 (1–4)	.23

Abbreviations: BMI: body mass index, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease.

p values denote comparison between groups using chi-squared test or Mann–Whitney U -test.

in-hospital mortality, asthma was associated with a decreased risk (OR 0.32, 95% CI 0.13–0.78, $p = .013$). Figure 1 shows the results of the analysis. In addition to asthma, variables that were significant in the model and show an association with an increased risk of death include the following: age (OR 1.05, 95% CI 1.03–1.07); cancer (OR 3.89, 95% CI 1.80–8.41); kidney disease (OR 2.03, 95% CI 1.25–3.29); use of long-acting beta agonists (OR 2.81, 95% CI 1.47–5.38); NLR (OR 1.04, 95% CI 1.02–1.05); and NEWS (OR 1.14, 95% CI 1.05–1.23).

Table 2. Treatment with hydroxychloroquine, azithromycin, remdesivir, and tocilizumab.

Agent	Group		<i>p</i> value
	Asthmatic (<i>n</i> = 88)	Non-Asthmatic (<i>n</i> = 957)	
Hydroxychloroquine	17 (19.3%)	193 (20.2%)	.85
Azithromycin	25 (28.4%)	201 (21.0%)	.11
Remdesivir	2 (2.3%)	22 (2.3%)	.99
Tocilizumab	12 (13.6%)	113 (11.8%)	.61

p values denote comparison between groups using chi-squared or Fisher's exact test, as required.

There were no significant differences between asthmatic and non-asthmatic cohorts in need for mechanical ventilation, length of mechanical ventilation, or overall LOS (Table 3). When assessing laboratory values, median levels of monocytes and procacitonin were significantly decreased in asthmatic patients, while ALT and albumin were significantly increased (Table 4).

Additional sensitivity analysis

The first sensitivity analysis demonstrated a relationship between the level of patient acuity and the effect of asthma on mortality. In the cohort with a mean NEWS of ≤ 3 , after adjusting for age, race, history of atrial fibrillation, cancer, diabetes, heart failure, hypertension, CKD, obesity, NLR, medications used, the asthma association was not significant (OR 0.43, 95% CI 0.13–1.45). In the cohort with a mean NEWS of >3 with similar adjustment, however, asthma was significant (OR 0.23, 95% CI 0.05–0.99, $p = .049$).

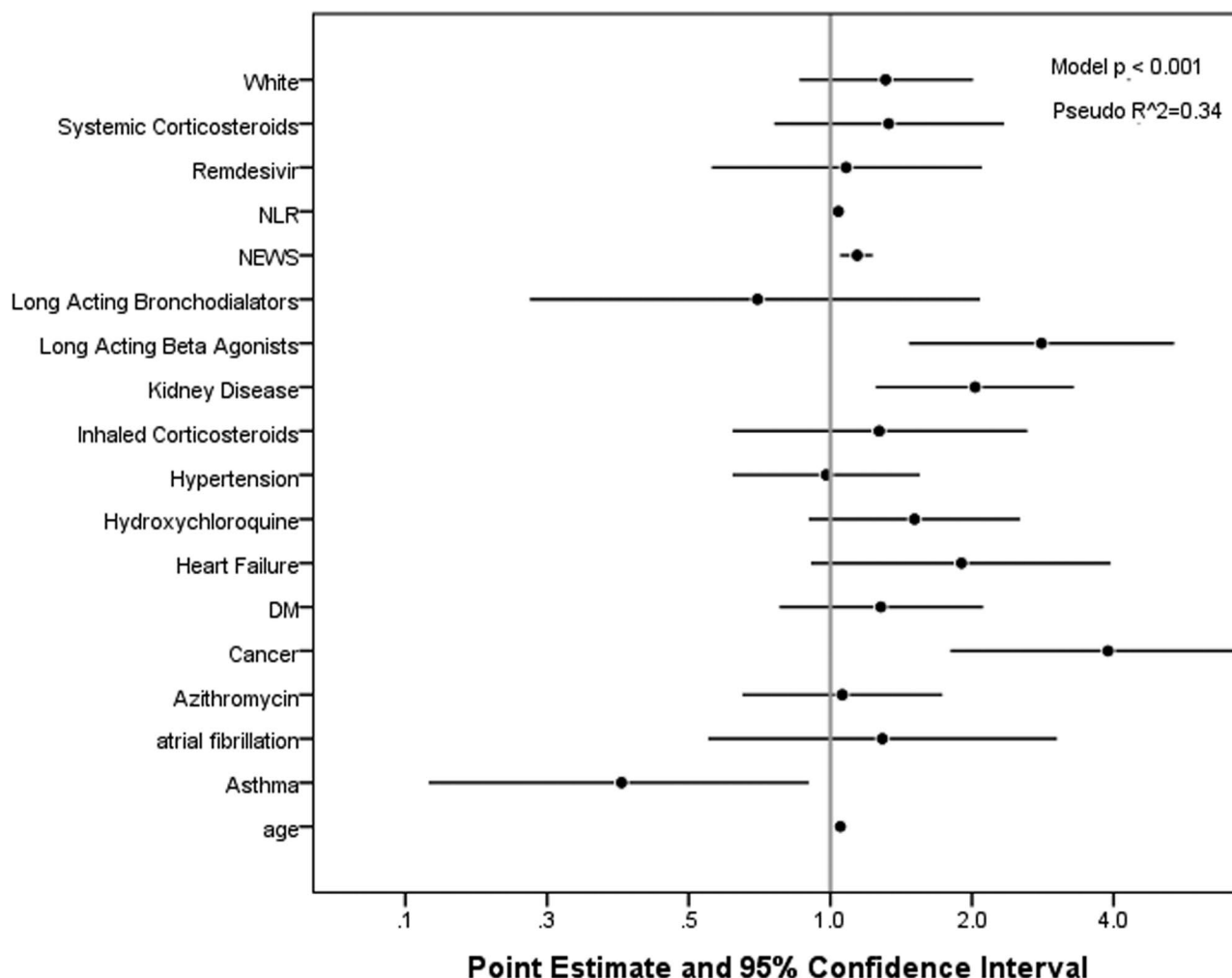


Figure 1. Odd's ratio (95% CI) for in-hospital mortality.

The second sensitivity analysis was performed to analyze any interaction between asthma and inhaled corticosteroids. When included in the logistic regression model with adjustment as described above using mortality as the outcome and using a cohort of no asthma and no IC as the comparison group, asthma/no IC showed a borderline significant association (OR 0.23, 95% CI 0.05–1.01, $p=.051$), no asthma/IC use and asthma/IC were both not significant (OR 1.2, 95% CI 0.54–2.5; OR 0.46, 95% CI 0.18–2.2, respectively).

When using requirement for ventilation as the outcome, no combination of asthma and IC showed a significant association.

Discussion

The US Centers for Disease Control and Prevention (CDC) lists asthma as a risk factor for severe COVID-19 illness (8). In contrast, the main finding of our single-center, retrospective study is that asthma

is associated with a reduced risk for in-hospital mortality for SARS-CoV-2 infection. Our study also documented no increase in the risk for severe COVID-19 disease in an asthmatic cohort, and non-significant differences between asthmatics and non-asthmatics in the need for mechanical ventilation, length of mechanical ventilation, or overall LOS. Our findings are in agreement with a similar, but larger, matched cohort study where asthma was associated with a similar risk of intubation and hospitalization, but a lower risk of mortality (12).

There are several possible explanations for our observation. Expression of the ACE2 receptor, the principal entry receptor for SARS-CoV-2 infection, may be reduced in the setting of respiratory allergy and controlled allergen exposure (7). Notably, ACE2 expression was the lowest in those with both high levels of allergic sensitization and asthma, suggesting that atopic asthmatics may have decreased susceptibility to viral infection and disease progression. In contrast, non-atopic asthma was not associated with the reduced ACE2 expression. Others have postulated that the Th2-asthma phenotype, characterized by peripheral blood eosinophilia (≥ 150 cells/ μ L), may also play a role in COVID-19 morbidity and mortality. The Th2-asthma type display decreased ACE2 expression, while asthma patients with low eosinophil counts present with increased ACE2 expression (7). In hospitalized COVID-19 patients, the Th2-phenotype has been associated with the decreased mortality (13).

The therapies used by asthmatic patients could reduce the risk of SARS-CoV-2 infection or prevent the development of severe disease (14). *In vitro* models

Table 3. In-hospital outcomes of asthmatic and non-asthmatic cohorts.

Outcome	Group		<i>p</i> value
	Asthmatic (n = 88)	Non-Asthmatic (n = 957)	
Death	7 (8.0%)	157 (16.4%)	.037
Mechanical ventilation	16 (18.2%)	165 (17.2%)	.82
Length of mechanical ventilation (median days [IQR])	10.0 (5.0–16.2)	8.3 (2.7–15.3)	.67
Hospital length of stay (median days [IQR])	5.5 (3.5–9.5)	5.7 (3.1–10.0)	.48

p values denote comparison between groups using chi-squared test or Mann–Whitney *U*-test.

Table 4. Laboratory findings in all patients and in the subpopulations with and without asthma.

	Laboratory values, median (IQR)				<i>p</i> value [†]
	Reference range	All patients (n = 1045)	Asthmatic (n = 88)	Non-asthmatic (n = 957)	
Hematologic					
WBC, $\times 10^9/L^{\ddagger}$	3.5–9.5	9.9 (7.0–14.8)	9.9 (7.4–14.9)	9.9 (7.0–14.8)	.60
Lymphocytes, $\times 10^9/L^{\S}$	1.50–4.50	0.8 (0.50–1.3)	0.7 (0.5–1.1)	0.8 (0.5–1.3)	.09
NLR, $\times 10^9/L^{\ddagger}$	0.78–3.53	6.6 (3.8–12.4)	8.1 (3.8–15.3)	6.6 (3.8–12.1)	.32
Monocytes, $\times 10^9/L^{\S}$	0.2–1.50	0.33 (0.20–0.53)	0.27 (0.18–0.44)	0.34 (0.20–0.55)	.001
Platelets, $\times 10^9/L^{\S}$	150–400	185 (138–236)	193 (151–237)	184 (137–236)	.31
Eosinophils, $\times 10^9/L^{\ddagger}$	0–0.7	0.08 (0.01–0.19)	0.06 (0.01–0.20)	0.08 (0.01–0.19)	.43
Biochemical					
AST, U/L [§]	10–40	29 (20–49)	30 (24–44)	29 (20–50)	.29
ALT, U/L [§]	10–40	22 (14–36)	27 (17–43)	22 (14–36)	.02
BUN, mg/dL [§]	7–20	11 (7–17)	10 (7–14)	11 (7–17)	.26
Albumin, g/dL [§]	3.5–5.5	3.1 (2.6–3.5)	3.3 (2.9–3.7)	3.1 (2.6–3.5)	.01
Infection Related indices					
CRP, mg/dL [†]	0.0–0.3	9.2 (4.1–17.0)	7.0 (3.9–14.7)	9.5 (4.2–17.2)	.38
ESR, mm/h [†]	0–15	61.0 (35.5–83.0)	66.5 (40.2–105.3)	60 (34.5–81.0)	.11
Serum ferritin, ng/mL [†]	11–336	611 (277–964)	554 (262–894)	624 (280–973)	.11
Procalcitonin, ng/mL [†]	0.10–0.49	0.17 (0.09–0.56)	0.11 (0.08–0.28)	0.18 (0.09–0.58)	.01

Abbreviations: WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

[†]Mann–Whitney *U*-test.

[‡]Maximum value used.

[§]Minimum value used.

have shown that inhaled corticosteroids, alone or in combination with bronchodilators, suppress coronavirus replication and cytokine production (15). Inhaled corticosteroids also downregulate the SARS-CoV-2 ACE2 receptor in patients with chronic obstructive pulmonary disease (16). In addition, an Interim Position Statement from the PRINCIPLE trial documents a self-reported recovery time shorter in COVID19-positive patients treated with inhaled budesonide compared with usual care (17); however, there was no significant difference in hospitalization or mortality. We did not observe an effect of inhaled corticosteroids on either intubation or in-hospital mortality, suggesting that inhaled corticosteroids did not contribute to the reduction in mortality in asthmatic patients.

Our finding of an association between LABA and increased in-hospital mortality agrees with previous findings where asthma-related deaths and non-fatal serious adverse events were significantly increased in a systematic review comparing the pooled results of formoterol or salmeterol monotherapy versus placebo (18). In addition, LABA monotherapy may mask airway inflammation and thereby increase the risk of fatal and near-fatal respiratory events (19).

Ongoing randomized studies are needed to examine this possibility (ClinicalTrials.gov Identifier: NCT04331054), as well as the effect of other anti-asthma medications including inhaled anti-cholinergic, leukotriene modifiers, cromolyn sodium, theophylline, and oral corticosteroids.

Another possibility is that altered mast cell function in asthmatics may ameliorate the most serious consequences of SARS-CoV-2 infection. The potential role of dysfunctional mast cell activation in severe COVID-19 pathology (20–22), the observed differences in mast cell biology in asthmatics (23,24), and the concept of a protective effect of asthma on SARS-CoV-2 mortality raise the possibility that asthma can induce protection against virus-induced immunopathology. Partial support for this concept is provided by prior studies documenting an asthma-mediated protection for severe illness during the 2009 influenza pandemic (24) and by prior animal studies showing that asthma was associated with a reduced incidence of cytokine storm following an influenza viral challenge (25).

The findings in this report should be interpreted with caution since they are derived from a single-center, retrospective, observational study. We relied on physician-diagnosed asthma without confirmation as we were: (1) unable to obtain spirometry data to document reversible airflow obstruction or (2) obtain confirmation by a pulmonologist (26). Due to the risk of reducing the number of the asthma cohort, we

were unable to match patients on all covariates; however, the unmatched comorbidities were more prevalent in the asthma patients and thus would be expected to increase the rate of mortality, which we did not see. We examined COVID-19 outcomes only in mild or moderate asthma, with no subgroup analysis of the various atopic and non-atopic asthma phenotypes. Nevertheless, we found that asthma is associated with a lower mortality in COVID-19-hospitalized patients and no evidence of more severe disease compared to non-asthmatic cohorts.

Conclusions

The potential identification of asthma as a protective factor for severe COVID-19 disease adds to ongoing efforts to develop new treatments and infection prevention strategies for the SARS-CoV-2 pandemic. Additional studies are needed to corroborate our observations and, if confirmed, to determine the mechanism of asthma's protective effect.

Acknowledgements

We are grateful to Rick Seip for his help in the editing of this manuscript. We are indebted to all individuals who participated in our study. This **study was performed** at Hartford Hospital, 80 Seymour Street, Hartford CT 06115, USA.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article.

ORCID

Jeffrey F. Mather  <http://orcid.org/0000-0002-4824-2928>

References

1. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020;146(1):110–118. doi:10.1016/j.jaci.2020.04.006.
2. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, et al. China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020 May 14;55(5):2000547. doi:10.1183/13993003.00547-2020.
3. Chhiba KD, Patel GB, Vu THT, Chen MM, Guo A, Kudlaty E, Mai Q, Yeh C, Muhammad LN, Harris KE,

- et al. Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. *J Allergy Clin Immunol* 2020 Aug;146(2):307–314.e4. doi:10.1016/j.jaci.2020.06.010.
4. Butler MW, O'Reilly A, Dunican EM, Mallon P, Feeney ER, Keane MP, McCarthy C. Prevalence of comorbid asthma in COVID-19 patients. *J Allergy Clin Immunol* 2020 Aug;146(2):334–335. doi:10.1016/j.jaci.2020.04.061.
5. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA, Jr., Liang L. Association of asthma and its genetic predisposition with the risk of severe COVID-19. *J Allergy Clin Immunol* 2020 Aug;146(2):327–329.e4. doi:10.1016/j.jaci.2020.06.001.
6. Mahdavinia M, Foster KJ, Jauregui E, Moore D, Adnan D, Andy-Nweye AB, Khan S, Bishehsari F. Asthma prolongs intubation in COVID-19. *J Allergy Clin Immunol Pract* 2020 Jul-Aug;8(7):2388–2391. doi:10.1016/j.jaip.2020.05.006.
7. Jackson DJ, Busse WW, Bacharier LB, Kattan M, O'Connor GT, Wood RA, Visness CM, Durham SR, Larson D, Esnault S, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol* 2020 Jul;146(1):203–206.e3. doi:10.1016/j.jaci.2020.04.009.
8. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19). People who are at higher risk for severe illness. Available from: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html.
9. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* 2013 Apr;84(4):465–470. doi: 10.1016/j.resuscitation.2012.12.016. [23295778]
10. Hansen BB, Bowers J. Covariate balance in simple, stratified and clustered comparative studies. *Stat Sci* 2008; 23:219–236. doi:10.1214/08-STS254.
11. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46(3):399–424. doi:10.1080/00273171.2011.568786.
12. Robinson LB, Wang L, Fu X, Wallace ZS, Long AA, Zhang Y, Camargo CA, Jr, Blumenthal KG. COVID-19 severity in asthma patients: a multi-center matched cohort study. *J Asthma* 2021 Mar 2;1–14. doi:10.1080/02770903.2020.1857396.
13. Ferastraoaru D, Hudes G, Jerschow E, Jariwala S, Karagic M, de Vos G, Rosenstreich D, Ramesh M. Eosinophilia in asthma patients is protective against severe COVID-19 illness. *J Allergy Clin Immunol Pract* 2021 Jan 22;9(3):1152–1162.e3. doi:10.1016/j.jaip.2020.12.045.
14. Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? *Lancet Respir Med* 2020 May;8(5):436–438. doi:10.1016/S2213-2600(20)30167-3.
15. Halpin DMG, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. *Eur Respir J* 2020 May 7;55(5):2001009. Cited in: PMID: 32341100; PMCID: PMC7236828. doi:10.1183/13993003.01009-2020.
16. Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, Woodruff PG, Mauger DT, Erzurum SC, Johansson MW, et al. COVID-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids. *Am J Respir Crit Care Med* 2020 Jul 1;202(1):83–90. doi:10.1164/rccm.202003-0821OC.
17. Interim Position Statement: Inhaled budesonide for adults (50 years and over) with COVID-19. NHS England and NHS Improvement; 13 April 2021. Available from: <https://www.england.nhs.uk/coronavirus/publication/interim-position-statement-inhaled-budesonide-for-adults-50-years-and-over-with-covid-19/> [last accessed 10 May 2021].
18. Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2014 Feb 6;2014(2):CD010314. doi:10.1002/14651858.CD010314.pub2.
19. Johnson M. Molecular mechanisms of beta(2)-adrenergic receptor function, response, and regulation. *J Allergy Clin Immunol* 2006 Jan;117(1):18–24; quiz 25. doi:10.1016/j.jaci.2005.11.012.
20. Malone RW, Tisdall P, Smith Liu FP, Huang Y, White Km XP, Miorin L, Olmo EMD, Alon A, Delaforge E, et al. COVID-19: famotidine, histamine, mast cells, and mechanisms. *Res Sq [Preprint]*. 2020 Jun 22. doi:10.21203/rs.3.rs-30934/v2.
21. Kritas SK, Ronconi G, Caraffa A, Gallenga CE, Ross R, Conti P. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. *J Biol Regul Homeost Agents* 2020 January-February;34(1):9–14. doi:10.23812/20-Editorial-Kritas.
22. Kilinc E, Baranoglu Y. Mast cell stabilizers as a supportive therapy can contribute to alleviate fatal inflammatory responses and severity of pulmonary complications in COVID-19 infection. *Anadolu Klin Tip Bilim Derg* 2020;25(Suppl 1):111–118.
23. Bradding P, Walls AF, Holgate ST. The role of the mast cell in the pathophysiology of asthma. *J Allergy Clin Immunol* 2006 Jun;117(6):1277–1284. doi:10.1016/j.jaci.2006.02.039.
24. Méndez-Enríquez E, Hallgren J. Mast cells and their progenitors in allergic asthma. *Front Immunol* 2019 May 29;10:821. doi:10.3389/fimmu.2019.00821.
25. Fajt ML, Wenzel SE. Mast cells, their subtypes, and relation to asthma phenotypes. *Ann Am Thorac Soc* 2013 Dec; 10 Suppl(10 Suppl):S158–S64. doi:10.1513/AnnalsATS.201303-064AW.
26. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemiere C, Field SK, McIvor RA, Hernandez p, Mayers I, Canadian Respiratory Research Network, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA*. 2017;317(3):269–279. doi:10.1001/jama.2016.19627.

APPENDIX: ICD-10-CM Codes Used To Identify Asthmatic Patients

Mild intermittent asthma without complication	J45.20
Mild intermittent asthma	J45.20
Intermittent asthma without complication	J45.20
Intermittent asthma	J45.20
Mild intermittent asthma with acute exacerbation	J45.21
Mild intermittent asthma with exacerbation	J45.21
Mild persistent asthma	J45.30
Mild persistent asthma without complication	J45.30
Mild persistent asthma with acute exacerbation	J45.31
Moderate persistent asthma without complication	J45.40
Moderate persistent asthma with acute exacerbation	J45.41
Asthma exacerbation	J45.901
Acute asthma exacerbation	J45.901
Asthma with acute exacerbation	J45.901
Acute exacerbation of extrinsic asthma	J45.901
Asthma flare	J45.901
Asthma	J45.909
Uncomplicated asthma	J45.909
RAD (reactive airway disease)	J45.909
Moderate asthma	J45.909
Mild asthma without complication	J45.909
Oral steroid-dependent asthma	J45.909
Asthma without acute exacerbation	J45.909
Bronchial asthma	J45.909
Childhood asthma	J45.909
Cough variant asthma	J45.991