Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Original Article

Eosinophilia Is Associated with Improved COVID-19 Outcomes in Inhaled Corticosteroid-Treated Patients

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What is already known about this topic? Low eosinophil counts during acute severe acute respiratory syndrome coronavirus 2 infection are associated with worse outcomes.

What does this article add to our knowledge? Baseline preexisting immune profile might affect COVID-19-related outcomes; the association between eosinophilia and disease outcomes varies by inhaled corticosteroid therapy.

How does this study impact current management guidelines? If confirmed by future randomized trials, eosinophilia can be used as a biomarker to guide therapy with inhaled corticosteroids in COVID-19.

BACKGROUND: In addition to their proinflammatory effect, eosinophils have antiviral properties. Similarly, inhaled corticosteroids (ICS) were found to suppress coronavirus replication *in vitro* and were associated with improved outcomes in coronavirus disease 2019 (COVID-19). However, the interplay between the two and its effect on COVID-19 needs further evaluation.

OBJECTIVE: To determine the associations among preexisting blood absolute eosinophil counts, ICS, and COVID-19–related outcomes.

METHODS: We analyzed data from the Cleveland Clinic COVID-19 Research Registry (April 1, 2020 to March 31, 2021). Of the 82,096 individuals who tested positive, 46,397 had blood differential cell counts obtained before severe acute respiratory syndrome coronavirus 2 testing dates. Our end points included the need for hospitalization, admission to the intensive care unit (ICU), and in-hospital mortality. The effect of eosinophilia on outcomes was estimated after propensity weighting and adjustment.

RESULTS: Of the 46,397 patients included in the final analyses, 19,506 had preexisting eosinophilia (>0.15 × 10^3 cells/μL), 5,011 received ICS, 9,096 (19.6%) were hospitalized, 2,129 required ICU admission (4.6%) and 1,402 died during index hospitalization (3.0%). Adjusted analysis associated eosinophilia with lower odds for hospitalization (odds ratio [OR] [95% confidence interval (CI)]: 0.86 [0.79-0.93]), ICU admission (OR [95% CI]: 0.79 [0.69-0.90]), and mortality (OR [95% CI]: 0.80 [0.68-0.95]) among ICS-treated patients but not untreated ones. The correlation between absolute eosinophil count and the estimated probability of hospitalization, ICU admission, and death was nonlinear (*U*-shaped) among patients not treated with ICS, and negative in treated patients.

CONCLUSIONS: The association between eosinophilia and improved COVID-19 outcomes depends on ICS. Future randomized controlled trials are needed to determine the role of ICS and its interaction with eosinophilia in COVID-19 therapy. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:742-50)

Key words: *Severe acute respiratory syndrome coronavirus 2; COVID-19; Inhaled corticosteroids; Asthma; Chronic obstructive pulmonary disease; Eosinophilia*

INTRODUCTION

In March 2020, the coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic and has since caused more than 4.5 million deaths worldwide.[1] Older age, male sex, Black race, tobacco use, and multiple comorbidities are associated with increased COVID-19 severity.[2] Although the cause of sex- and age-based differences in COVID-19 severity

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Abbreviations used
ACE2- Angiotensin converting enzyme 2
AEC- Absolute eosinophil count
BMI- Body mass index
CBC- Complete blood count
CCCRR- Cleveland Clinic COVID-19 Research Registry
COPD- Chronic obstructive pulmonary disease
COVID-19- Coronavirus disease 2019
ICS- Inhaled corticosteroids
ICU- Intensive care unit
RCT- Randomized controlled trial
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2
T2- Type 2

remains unknown, it suggests that an individual's baseline preexisting immune profile may determine the host immune response to SARS-CoV2 infection to influence outcomes.

Entry of SARS-CoV-2 into respiratory epithelial cells relies on two essential host proteins: angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2.[3] Expression of these critical host genes differs in patients with type 2 (T2) inflammation, which is characterized by the presence of eosinophilia and elevated FeNO.[4,5] When considering SARS-CoV-2 infection, higher blood eosinophil counts were previously associated with better outcomes in patients with and without asthma.[6-8] However, most of these epidemiologic studies relied on eosinophil counts obtained during the acute SARS-CoV-2 infection[6,7,9] or were limited to small sample sizes.[8]

Severe COVID-19 is associated with a number of distinct immunologic signatures.[10] SARS-CoV-2 infection reconfigures leukocyte phenotype in a severity-specific fashion, in which severe COVID-19 is associated with lymphopenia and T-cell exhaustion,[11,12] neutrophil activation,[13,14] and hematopoietic alterations resulting in immature and dysfunctional neutrophils.[12,15] Severe disease is associated with depletion of CD16 monocytes, dendritic cells, and natural killer cells, and changes in the transcriptional phenotype of these cells as well.[10] In contrast to patients with severe COVID-19, those with mild disease exhibit notably reduced proinflammatory plasma cytokines. These findings suggest that the immune response of those with mild disease efficiently eliminates viral infection, thus evading the hyperinflammatory state associated with severe disease.[16,17]

Although the effect of SARS-CoV-2 on the immune system has been well-studied, little is known about the effect of the baseline immune profile on COVID-19 outcomes or the interaction between high eosinophil counts and inhaled corticosteroids (ICS). Previous reports suggested that corticosteroid therapy, both inhaled and intranasal, might have a beneficial role in COVID-19 related to alterations in viral host interactions or anti-inflammatory effects.[18-23] A recent phase II open-label randomized controlled trial (RCT) of 146 individuals demonstrated that early administration of inhaled budesonide reduced the risk for progression to severe COVID-19 and overall COVID-19—related health care use.[18] However, the effect of ICS on COVID-19—related outcomes in asthma patients is controversial and may be confounded by asthma severity and T2 inflammation.[24-28] In this study, we evaluated preexisting complete blood cell counts with differential in a large, general population, prospectively collected COVID-19 registry to test the hypothesis that peripheral blood eosinophil counts influence risk for severe COVID-19 through interactions that are modulated by concurrent ICS therapy.

METHODS

Subjects

The Cleveland Clinic COVID-19 Research Registry (CCCRR) database[23,29-33] was used to study 82,096 individuals who had a positive SARS-CoV-2 test between April 1, 2020 and March 31, 2021. We excluded 5,596 children aged 18 years and younger, 290 pregnant women, 87 patients with missing hospitalization data, and 91 patients with a body mass index (BMI) less than 15 or greater than 80 kg/m^2 (see Appendix E1 and Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Baseline complete blood count differential cell subtypes

Of the 76,032 individuals who met inclusion criteria, 46,397 had a complete blood count (CBC) with differential measured at least 2 weeks before the date of the SARS-CoV-2 test (defined as preexisting or baseline). Of those, 5,011 were prescribed ICS therapy and 41,386 did not have an ICS prescription in electronic health records.

Peri-testing differential cell subtypes

Of the 76,032 individuals who met inclusion, 12,944 had a CBC with differential measured within 48 hours of the SARS-CoV-2 test date. Of those, 9,650 had both a baseline (preexisting) and a peri-testing CBC with differential measurements available for analysis. Unless specified as peri-testing, all differential cell counts results in this article refer to baseline (preexisting) measurements.

Study outcomes and groups definition

The primary outcome was COVID-19—related hospitalizations. We also studied two secondary outcomes: the rate of COVID-19—related admissions to the intensive care unit (ICU) and mortality during index hospitalization. To study the effect of high eosinophil counts and ICS use on COVID-19—related outcomes, we performed two separate sensitivity analyses involving 3,066 patients with chronic obstructive pulmonary disease (COPD) or emphysema, and 6,739 asthmatic patients with available baseline absolute eosinophil count (AEC) measurements. Patients with asthma or COPD were identified using International Classification of Diseases, 10th Revision codes, and such diagnoses were verified by trained medical personnel using standardized protocols.[32] These sensitivity analyses were done based on evidence that eosinophils are potentially protective against severe COVID-19.[8,9] We chose a baseline AEC cutoff of 0.15×10^3 cells/μL to define eosinophilia because this threshold was previously found to drive treatment choices in asthma and COPD[34-38] and was associated with better COVID-19 outcomes in asthma.[8] We define eosinopenia ($<0.1 \times 10^3$ cell/μL) based on previous reports associating this threshold with severe COVID-19.[39] Analyses were stratified by ICS therapy to evaluate whether such therapy is associated with improved COVID-19 outcomes as previously reported.[18] We did not consider new prescriptions for ICS ordered after the date of the SARS-CoV-2 test result.

The effect of COVID-19 on immune cell profile reconfiguration was assessed by evaluating the association between COVID-19 outcomes and peri-testing of CBC differential cell subtypes in 12,944 patients. We also examined the association between outcomes and changes from baseline in these cell subtypes in 9,650 patients.

Statistical methods

In this retrospective analysis of a prospectively collected COVID-19 registry, we present data as counts with percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. Two group comparisons of continuous nonnormally distributed variables were performed using Wilcoxon rank sum test and normally distributed continuous variables were compared using *t* test. Categorical variables were compared using χ^2 test.

To account for observed covariate differences between patients with and without eosinophilia (ie, AEC $> 0.15 \times 10^3/\mu L$), we used inverse weighting on the propensity score. The propensity score for each patient is the predicted probability of eosinophilia from a nonparsimonious logistic regression model using covariates known a priori to be associated with severe COVID-19.[2,40] Such covariates include the month of testing, demographics, BMI (log transformed), smoking status, pack-years smoking history, comorbidities, time between the AEC test date and SARS-CoV-2 test date (log transformed), and relevant medication prescriptions including immunosuppressive therapy (see Figure E2 and Appendix E2 in this article's Online Repository at www.jaci-inpractice.org). All covariates had variance inflation factor of less than 2, which suggests the absence of multicollinearity. Adjusted odds ratios (ORs) were then calculated to estimate the effect of eosinophilia on outcomes by weighting each patient with the inverse propensity score and controlling for the propensity as a covariate in the model. Similar propensity-weighted approaches were applied in all sensitivity analyses. To assess the nonlinearity of the association between blood eosinophil counts and the probability of poor COVID-19 outcomes (ie, hospitalization, ICU admission, or hospital mortality), we compared logistic regression models fitted with a restricted cubic spline function for the AEC (log10-transformed) with three knots with models assuming a linear association using the likelihood ratio test. Adjustment for the month of testing was included to avoid the chronological bias introduced by changes in SARS-CoV-2 testing policies, therapies and management protocols, and improvements in mortality.[41,42]

All covariates included in the regression models were missing fewer than 3% of subjects. We carried out multiple imputation (five imputations) for missing variables using the Multivariate Imputation by Chained Equations package and pooled separate results using Rubin's rules to obtain the final results.[43] Multivariate Imputation by Chained Equations replaces each missing value with a plausible value drawn from a distribution specifically designed for each missing data point. We also repeated all analyses using the original complete non-imputed data (ie, excluding individuals with missing data). Based on the CCCRR registry sample size, a power analysis, completed subsequent to the initiation of this study, comparing two proportions between two groups of unequal sample size (eosinophil count <0.15 [$\times 10^3/\mu L$] vs >0.15 [$\times 10^3/\mu L$]), demonstrated that we had greater than 90% power to detect significant differences in hospitalization rates between patients with high versus low eosinophil counts at a significance level of $\alpha = 0.05$ irrespective of the effect size (small, medium, or large). All *P* values were two-tailed, performed at a significance level of .05. All statistical analyses were conducted with R software (version 4.0.5, R Project for Statistical Computing, Vienna, Austria).

RESULTS

Demographics and clinical characteristics

Of the 46,397 patients included in the final analysis, 9,096 were hospitalized (19.6%), 2,129 required ICU admission (4.6%), and 1,402 died during hospitalization (3.0%). In addition, 6,739 carried the diagnosis of asthma and 3,066 were diagnosed with COPD or emphysema. Baseline eosinophilia ($>0.15 \times 10^3$ cells/μL) was present in 19,506, and ICS were used in 5,011 individuals.

Patient demographics and clinical characteristics varied considerably between individuals with and without eosinophilia. Median age of patients with eosinophilia was 56.3 years (IQR, 42.1-69.3 years) and 10,609 were female (54.4%). Median age of patients with low eosinophil levels was 50.6 years (IQR, 35.8-64.4 years) and 16,623 were female (61.8%) (Table I). Clinical characteristics of patients with asthma and COPD are detailed in Tables E1 and E2 (in this article's Online Repository at www.jaci-inpractice.org).

Baseline eosinophilia is associated with improved COVID-19–related outcomes

In parallel with the higher rate of comorbidities and medication use, patients with eosinophilia had higher rates of hospitalization (21.2% vs 18.4%; $P < .001$), ICU admission (5% vs 4.3%; $P < .001$), and in-hospital mortality (3.4% vs 2.7%; $P < .001$) than those without preexisting eosinophilia in unadjusted comparisons (Table I). However, analyses adjusted using inverse probability weighting for demographics, BMI, smoking history, medications, comorbidities, the month of testing, and the time between the AEC test date and the SARS-CoV-2 test date (Figure E2) demonstrated that patients with eosinophilia (n = 19,506) were at a significantly lower odds for hospitalization (adjusted OR [95% confidence interval (CI)]: 0.96 [0.93-0.99]) and ICU admission (adjusted OR [95% CI]: 0.92 [0.87-0.98]) compared with patients without eosinophilia (n = 26,891). Preexisting eosinophilia was not associated with improved in-hospital mortality (adjusted OR [95% CI]: 0.94 [0.88-1.03], $P = .19$).

Association between COVID-19–related outcomes and baseline AEC is nonlinear and varies according to ICS use

Logistic regression fitted with a restricted cubic spline function for the AEC (log10-transformed) with three knots optimally described the nonlinear relationship between AEC and outcome measures (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Using a likelihood ratio test, nonlinear models were found to be different from models assuming a linear association ($P < .001$).

Interaction plots of the predicted probabilities of COVID-19–related hospitalization, ICU admission, and in-hospital mortality as a function of AEC, stratified by ICS use, demonstrate that the relationship between AECs and COVD-19–related outcomes is modified by ICS therapy (all interaction $P < .001$) (Figure 1). The predicted probability for COVID-19–related outcomes was higher among individuals with elevated AEC not treated with ICS, but not among ICS-treated patients. Interaction plots between other types of white blood cells and ICS did not show a significant interaction except for neutrophils (*P* for interaction = .002) (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). A significant interaction also existed between ICS and the eosinophil-to-lymphocyte ratio (*P* for interaction $< .001$), but not with the neutrophil-to-lymphocyte ratio (*P* for interaction = .23) or the lymphocyte-to monocyte ratio (*P* for interaction = .58) (see Figure E4 in this article's Online Repository at www.jaci-inpractice.org).

TABLE I. Clinical characteristics and outcomes by eosinophilia (>0.15 × 10^3 /μL) for all patients in registry stratified by ICS

Variable	All patients		*P*	No ICS		*P*	ICS		*P*
Eosinophil count	<0.15 [×10^3/μL]	>0.15 [×10^3/μL]		<0.15 [×10^3/μL]	>0.15 [×10^3/μL]		<0.15 [×10^3/μL]	>0.15 [×10^3/μL]	
n	26,891	19,506		24,428	16,958		2,463	2,548	
Demographics									
Age, y	50.6 [35.6-64.4]	56.3 [42.1-69.3]	<.001	49.7 [34.8-63.6]	55.5 [41.2-68.6]	<.001	59.3 [47.2-70.8]	61.3 [48.9-72.5]	.002
Female sex	16,623 (61.8)	10,609 (54.4)		14,976 (61.3)	9,024 (53.2)	<.001	1,647 (66.9)	1,586 (62.2)	.002
Body mass index, kg/m^2	29.1 [25.0-34.3]	30.5 [26.3-35.9]	<.001	28.9 [24.9-34.0]	30.3 [26.2-35.6]	<.001	30.8 [25.9-37.2]	31.6 [26.9-37.8]	<.001
Race*			<.001			<.001			<.001
Black	6,075 (22.6)	3,549 (18.2)		5,465 (22.4)	3,030 (17.9)		610 (24.8)	520 (20.4)	
White	18,364 (68.3)	14,117 (72.4)		16,713 (68.4)	12,285 (72.4)		1,651 (67.0)	1,832 (71.9)	
Others	2,452 (9.1)	1,838 (9.4)		2,250 (9.2)	1,643 (9.7)		202 (8.2)	196 (7.7)	
Hispanic ethnicity	961 (3.6)	697 (3.6)	.989	873 (3.6)	622 (3.7)	.466	86 (3.5)	92 (3.6)	.09
Smoking history			<.001			<.001			.998
Current	1,902 (7.1)	1,595 (8.2)		1,705 (7.0)	1,393 (8.3)		197 (8.0)	203 (8.0)	
Past	6,629 (24.7)	5,543 (28.5)		5,658 (23.2)	4,536 (26.9)		971 (39.5)	1,007 (39.5)	
Pack-years smoking	11.0 [4.0-25.0]	14.0 [5.0-30.0]	<.001	10.0 [3.5-22.0]	12.0 [5.0-28.0]	<.001	20.0 [6.4-40.0]	20.0 [7.5-40.0]	.564
Eosinophil count (×10^3/μL)†	0.08 [0.04-0.11]	0.24 [0.20-0.33]	<.001	0.08 [0.05-0.11]	0.23 [0.19-0.32]	<.001	0.08 [0.03-0.11]	0.27 [0.20-0.38]	<.001
Comorbidities									
Chronic obstructive pulmonary disease or emphysema	1,524 (5.7)	1,542 (7.9)	<.001	673 (2.8)	680 (4.0)	<.001	851 (34.6)	862 (33.8)	.611
Asthma	3,559 (13.3)	3,180 (16.3)	<.001	2,145 (8.8)	1,695 (10.0)	<.001	1,414 (57.5)	1,485 (58.3)	.574
Diabetes	4,060 (15.1)	4,178 (21.4)	<.001	3,383 (13.8)	3,449 (20.3)	<.001	677 (27.5)	730 (28.6)	.376
Hypertension	9,284 (34.5)	8,582 (44.0)	<.001	7,916 (32.4)	7,101 (41.9)	<.001	1,368 (55.5)	1,482 (58.2)	.065
Coronary artery disease	2,083 (7.7)	2,286 (11.7)	<.001	1,642 (6.7)	1,803 (10.6)	<.001	441 (17.9)	483 (19.0)	.356
Heart failure	1,699 (6.3)	1,661 (8.5)	<.001	1,267 (5.2)	1,225 (7.2)	<.001	432 (17.5)	436 (17.1)	.717
Cancer history	3,051 (11.3)	2,487 (12.8)	<.001	2,599 (10.6)	2,034 (12.0)	<.001	452 (18.4)	454 (17.8)	.65
Connective tissue disease	751 (2.8)	571 (2.9)	.405	568 (2.3)	415 (2.4)	.442	183 (7.4)	156 (6.1)	.074
Immunosuppressive disease	2,417 (9.0)	1,850 (9.5)	.07	1,939 (7.9)	1,465 (8.6)	.011	478 (19.4)	385 (15.1)	<.001
Medications									
Nonsteroidal anti-inflammatory drugs	4,098 (15.2)	3,098 (15.9)	.06	3,684 (15.1)	2,644 (15.6)	.16	414 (16.8)	454 (17.8)	.365
Angiotensin converting enzyme inhibitors	2,436 (9.1)	2,314 (11.9)	<.001	2,174 (8.9)	2,003 (11.8)	<.001	262 (10.6)	311 (12.2)	.089
Angiotensin receptor blockers	1,719 (6.4)	1,685 (8.6)	<.001	1,416 (5.8)	1,358 (8.0)	<.001	303 (12.3)	327 (12.8)	.6
Intranasal corticosteroids	6,637 (24.7)	5,339 (27.4)	<.001	5,437 (22.3)	4,122 (24.3)	<.001	1,200 (48.7)	1,218 (47.8)	.534
Intensive care unit	2,463 (9.2)	2,547 (13.1)	<.001	0	0	NA	2,463 (100.0)	2,548 (100.0)	NA
Immunosuppressive therapy‡	264 (1.0)	190 (1.0)	.973	173 (0.7)	123 (0.7)	.886	91 (3.7)	67 (2.6)	.038
Outcomes									
Hospitalization	4,952 (18.4)	4,144 (21.2)	<.001	4,099 (16.8)	3,352 (19.8)	<.001	853 (34.6)	792 (31.1)	.008
Admission to intensive care unit	1,153 (4.3)	976 (5.0)	<.001	895 (3.7)	769 (4.5)	<.001	258 (10.5)	207 (8.1)	.005
Hospital mortality	734 (2.7)	668 (3.4)	<.001	576 (2.4)	535 (3.2)	<.001	158 (6.4)	133 (5.2)	.08

ICS, inhaled corticosteroids; *NA*, not available.

Data are presented as n (%) for categorical variables and median [interquartile range] for continuous variables.

*"Other" race category includes American Indians or Alaska Natives, Asian individuals, Native Hawaiian or Other Pacific Islanders, and individuals with multiple racial backgrounds.

†Defined by a baseline blood absolute eosinophil count > 0.15 (x103 cells/ μL) obtained at least 2 weeks before severe acute respiratory syndrome coronavirus 2 test date.

‡Includes chronic systemic corticosteroid therapy.

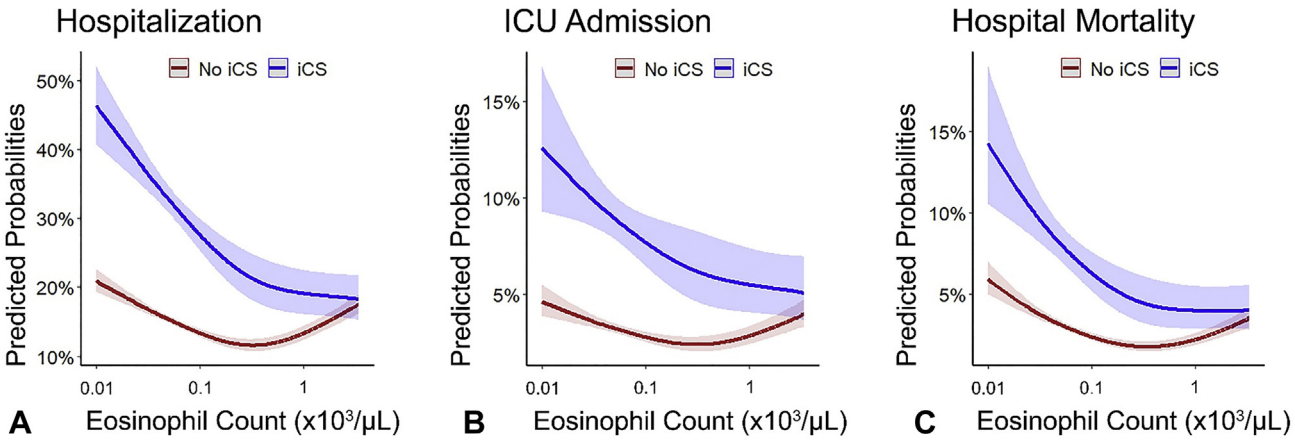

FIGURE 1. Predicted probabilities of coronavirus disease 2019–related (**A**) hospitalization, (**B**) admission to the intensive care unit (ICU), and (**C**) hospital mortality as a function of baseline peripheral blood absolute eosinophil count (AEC), stratified by inhaled corticosteroids (ICS) use. These interaction plots show that the association between coronavirus disease 2019–related outcomes and AEC depends on the use of ICS (all *P* values for interaction < .001). The probabilities were calculated by fitting a logistic regression using a restricted cubic spline function for the AEC (log10-transformed). The 95% confidence intervals are indicated by the shaded area around the fitted line.

Baseline eosinophilia is associated with improved COVID-19–related outcomes only in ICS-treated patients

Compared with patients without eosinophilia, propensity-weighted models showed that patients with eosinophilia had lower odds for hospitalization (adjusted OR [95% CI]: 0.86 [0.79-0.93]), ICU admission (adjusted OR [95% CI]: 0.79 [0.69-0.90]), and in-hospital mortality (adjusted OR [95% CI]: 0.80 [0.68-0.95]) among ICS-treated, but not untreated patients (Table II). Stratified analysis showed similar protective effects in patients with COPD or emphysema or with asthma (Table II).

Among patients with COPD who were treated with ICS, eosinophilia was associated with lower odds for hospitalization (adjusted OR [95% CI]: 0.80 [0.70-0.91]), ICU admission (adjusted OR [95% CI]: 0.78 [0.65-0.93]), and mortality (adjusted OR [95% CI]: 0.80 [0.70-0.91]). Similarly, patients with asthma and eosinophilia had lower odds for COVID-19–related hospitalization (adjusted OR [95% CI]: 0.78 [0.69-0.87]) and ICU admission (adjusted OR [95% CI]: 0.72 [0.59-0.87]). Eosinophilia was not associated with lower in-hospital mortality (adjusted OR [95% CI]: 0.84 [0.66-1.09]; $P = .12$) among asthmatic patients treated with ICS. Eosinophilia was not associated with better COVID-19–related outcomes among patients with asthma or patients with COPD not treated with ICS (Table II).

Results from analyses using the original non-imputed data (ie, complete cases) were consistent with findings from the main analyses using imputed data (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

In contrast to eosinophilia, eosinopenia ($<0.1 \times 10^3$ cells/μL) was associated with worse COVID-19 outcomes irrespective of ICS use (see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

Median [IQR] time between the AEC test date and the SARS-CoV-2 test date was 530 days (234-1,274 days). To minimize bias introduced by the time between the AEC and SARS-CoV-2 test dates, we included the time variable as a covariate in all of our models. Furthermore, we performed two additional stratified analyses for those who had AEC measurements obtained within 1 year (n = 15,084) and 2 years (n = 24,095) from the SARS-CoV-2 test date, and found similar results among these patients (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

Fractional exhaled nitric oxide

Fractional exhaled nitric oxide measurements were available for 1,294 patients with asthma and correlated poorly with the AEC ($r = 0.173$; $P < .001$). After adjusting for AEC and the month of testing, FeNO measurements above 35 parts per billion were associated with lower hospitalization odds in 835 patients with asthma treated with ICS (adjusted OR [95% CI: 0.45 [0.28;-0.70]), but not in 468 asthmatic patients not receiving ICS therapy (adjusted OR [95% CI: 0.79 [0.32-1.77]). This beneficial association in the high-FeNO group treated with ICS was also significant after additional adjustments to demographics and comorbidities (see Table E7 in this article's Online Repository at www.jaci-inpractice.org).

Increased peri-testing blood AECs are associated with improved COVID-19–related outcomes

Peri-testing AECs were obtained in 12,944 patients within 48 hours of having a positive SARS-CoV-2 test. Of those, 1,280 had a peri-testing AEC above 0.15×10^3 cells/μL (9.9%), 1,665 were receiving ICS (12.9%), 8,369 were hospitalized (64.7%), 2,023 were admitted to the ICU (25.6%), and 1,312 died during hospitalization (10.1%). Propensity-weighted analyses showed that eosinophilia was associated with lower odds for hospitalization (adjusted OR [95% CI]: 0.83 [0.78-0.87]), ICU admission (adjusted OR [95% CI]: 0.59 [0.54-0.63]), and in-hospital mortality (adjusted OR [95% CI]: 0.58 [0.0.53-0.64]).

COVID-19–related reduction of peri-testing AEC from baseline is associated with worse outcomes

Of the 9,650 patients with both baseline and peri-testing AEC measurements available, 1,536 were receiving ICS therapy, 6,436

TABLE II. Clinical outcome results of patients with preexisting eosinophilia* compared with patients without eosinophilia, stratified by ICS therapy and airway disease category

	All patients		Chronic obstructive pulmonary disease		Asthma	
	No ICS	ICS	No ICS	ICS	No ICS	ICS
Outcome	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
n	41,320	5,009	1,352	1,714	3,840	2,899
Unadjusted						
Hospitalization	1.22 (1.16-1.29)	0.85 (0.76-0.96)	1.01 (0.82-1.25)	0.75 (0.62-0.90)	1.02 (0.86-1.20)	0.78 (0.66-0.91)
ICU admission	1.25 (1.13-1.38)	0.76 (0.62-0.92)	0.95 (0.69-1.30)	0.74 (0.57-0.95)	1.01 (0.70-1.45)	0.70 (0.53-0.93)
Hospital mortality	1.35 (1.20-1.52)	0.80 (0.63-1.02)	0.86 (0.61-1.22)	0.78 (0.58-1.04)	1.07 (0.67-1.71)	0.87 (0.61-1.25)
Adjusted for age, sex, ethnicity, race, and month of testing						
Hospitalization	0.99 (0.96-1.03)	0.82 (0.75-0.89)	0.96 (0.83-1.12)	0.77 (0.67-0.88)	0.87 (0.77-0.98)	0.73 (0.64-0.81)
ICU admission	1.00 (0.93-1.07)	0.73 (0.63-0.83)	0.92 (0.74-1.15)	0.75 (0.63-0.90)	0.85 (0.66-1.10)	0.66 (0.54-0.80)
Hospital mortality	0.95 (0.87-1.04)	0.74 (0.62-0.87)	0.78 (0.61-1.00)	0.76 (0.62-0.94)	0.78 (0.56-1.10)	0.75 (0.58-0.97)
Adjusted for age, sex, race, ethnicity, smoking history, pack-years smoking, medications, comorbidities, time between absolute eosinophil count test date and severe acute respiratory syndrome coronavirus 2 test date, and month of testing†						
Hospitalization	0.98 (0.94-1.01)	0.86 (0.79-0.93)	0.99 (0.85-1.15)	0.80 (0.70-0.91)	0.89 (0.79-1.00)	0.78 (0.69-0.87)
ICU admission	0.97 (0.90-1.04)	0.79 (0.69-0.90)	0.86 (0.68-1.07)	0.78 (0.65-0.93)	0.84 (0.65-1.09)	0.72 (0.59-0.87)
Hospital mortality	0.99 (0.91-1.08)	0.80 (0.68-0.95)	0.83 (0.65-1.05)	0.80 (0.70-0.91)	0.86 (0.62-1.20)	0.84 (0.66-1.09)

CI, confidence interval; *ICS*, inhaled corticosteroids; *ICU*, intensive care unit; *OR*, odds ratio.

*Baseline preexisting eosinophilia were defined by a blood absolute eosinophil count of greater than 0.15×10^3 cells/μL, obtained at least 2 weeks before the severe acute respiratory syndrome coronavirus 2 test date.

†The effect of a high blood absolute eosinophil count greater than 0.15×10^3 cells/μL on hospital outcomes is estimated by weighting each patient with the inverse propensity score and controlling for the propensity score as a covariate in the model. Medications included nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, ICS, intranasal corticosteroids, and immunosuppressive therapy (including systemic corticosteroids). Comorbidities include asthma, chronic obstructive pulmonary disease or emphysema, diabetes, hypertension, coronary artery disease, heart failure and cancer (historical or current), immunosuppressive diseases, and connective tissue diseases.

were hospitalized, 1,551 were admitted to the ICU, and 1,035 died during hospitalization. Median drop from baseline in the AEC during SARS-CoV-2 infection was 0.09 × 10^3 cells/μL (IQR, 0.02-0.18).

After weighting on the inverse propensity score and adjustment, patients with more than a 0.09 × 10^3 cells/μL decrease in AEC from baseline had higher odds of being hospitalized (adjusted OR [95% CI]: 1.21 [1.14-1.28])), being admitted to the ICU (adjusted OR [95% CI]: 1.21 [1.12-1.30]), or dying during hospitalization (adjusted OR [95% CI]: 1.21 [1.12-1.30]) compared with those with a less significant drop in AEC.

DISCUSSION

The main finding of our study was that the association between preexisting eosinophil counts and COVID-19–related outcomes depends on ICS therapy. Our results associating low blood eosinophil counts with poor COVID-19 outcomes support previous reports associating eosinophils with better outcomes in respiratory viral infections.[44] In addition to their role in allergy, asthma, and parasitic infections, eosinophils have antiviral properties mediated by Toll-like receptor signaling pathways.[44-49] For example, ovalbumin sensitization was associated with an 80% reduction in the viral content of the lungs of guinea pigs infected with parainfluenza, which was reversed by anti-IL-5 antibodies.[50]

Our study demonstrated that higher eosinophil counts were protective against poor COVID-19 outcomes in patients treated with ICS, but not in those without a prescription. These findings support previous data suggesting a beneficial role for ICS.[18] Although the mechanism remains largely unknown, recently published data suggest that corticosteroids may have direct and indirect effects on COVID-19 infection.[19-22,51] Dexamethasone binds directly to the ACE2 receptor and consequently inhibits the cellular entrance of SARS-CoV-2 after receptor binding to the spike protein.[22] Corticosteroids might also have direct antiviral properties by targeting the viral replication–transcription complex.[21] For example, ciclesonide and mometasone, two ICS used in human asthma, were found to suppress coronavirus replication *in vitro*.[21] In addition to their direct effects, corticosteroids were presumed to modulate SARS-CoV-2 infection through genomic mechanisms. In fact, ICS use was associated with lower expression of ACE2 and transmembrane serine protease 2 in sputum cells in a subset of asthmatics enrolled in the National Institutes of Health–National Heart, Lung, and Blood Institute Severe Asthma Research Program[19,51] and in airway epithelial cells obtained by bronchoscopy from individuals with COPD.[20]

Furthermore, ICS may indirectly modulate pulmonary inflammation by suppressing the immune response driven by T-helper cells.[52] During SARS-CoV-2 infection, viral replication causes epithelial cells pyroptosis and the release of damage-associated molecular patterns, which results in proinflammatory cytokines and chemokines release by neighboring cells and alveolar macrophages. This causes monocyte, macrophage, and T-cell migration to the lungs. There, these cells are activated and promote further inflammation.[53] In most patients, recruited virus-specific T cells eradicate the infection in the lung without causing significant damage. However, in patients with severe COVID-19, a defective immune response triggers the overproduction of proinflammatory cytokines (ie, cytokine storm) that mediates widespread lung damage, multiorgan failure, and sometimes death.[53] Although ICS are beneficial in obstructive airways diseases by inhibiting T-cell migration and activation within the airways, it is not known whether this mechanism underlies the beneficial effect of ICS in COVID-19.

The contribution of eosinophils to lung pathology during COVID-19 is not well-understood. Eosinophil-associated lung damage was previously reported in respiratory syncytial virus and severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) vaccination studies.[54] In contrast, autopsy specimens from patients with COVID-19 did not show significant eosinophil infiltration into the pulmonary tissue.[55] Our data demonstrate a nonlinear (U-shaped) association between baseline AEC and COVID-19 outcomes in the absence of ICS therapy, which suggests that eosinophilia may contribute to disease severity. In contrast, eosinophilia is not associated with worse outcomes among ICS-treated patients. These findings suggest that ICS somehow modulate disease severity for those with high but not low eosinophil counts. Eosinophils are an important aspect of the innate immune system owing to their antiviral properties, which could explain why patients with low eosinophil counts have poor outcomes.[45-48] Furthermore, we recently demonstrated worse outcomes in COVID-19 patients with severe asthma.[56] These findings suggest that the risk for severe COVID-19 is highest among individuals with eosinopenia who are treated with ICS. Further studies are needed to corroborate our findings and assess the effect of eosinophilia on the hyperinflammatory state seen in severe COVID-19.

Our data also revealed better outcomes in patients with elevated FeNO and support previous reports describing NO as a potent antiviral molecule.[57,58] Once activated, Toll-like receptor pathways can promote inducible nitric oxide synthase, which mediates NO production.[57] *In vitro* experiments showed that SARS-CoV-1 viral replication was inhibited by NO.[58] However, it remains unknown whether the replication of SARS-CoV-2, a single-stranded RNA virus that shares most of the genome of SARS-CoV-1, is also inhibited by NO.[58]

As a biomarker of T2 inflammation, FeNO is commonly used to determine the likelihood of corticosteroid responsiveness, monitor airway inflammation, and uncover nonadherence to ICS.[59] High FeNO was also associated with refractory airway T2 inflammation in a large subgroup of patients with asthma enrolled in the Severe Asthma Research Program.[60] Although FeNO measurements above 35 parts per billion were associated with better outcomes among ICS users, it remains unclear whether this reflects refractory airway T2 inflammation or poor adherence to ICS therapy in this cross-sectional study. There is also likely a component of indication bias (confounding by indication) to this finding. In CCCRR, 835 patients receiving ICS (28.8%) had FeNO measurements available, compared with 459 not receiving ICS (12.0%).

Finally, we replicate previously published data associating eosinophil count, lymphocyte counts, the eosinophil-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio measurements obtained during acute viral infection with COVID-19 outcomes.[6,8,10,12,53] To our knowledge, we are the first to associate baseline immune cell profiles with the response to SARS-CoV-2 infection progressing to hospitalization, ICU care, and death, and the impact of changes between baseline and peri-COVID-19 immune profiles on these severe outcomes. Although this will help us better identify patients at risk for severe COVID-19, further studies are needed to determine whether baseline differential cell types can be used as biomarkers

to guide therapy. We are also the first to show an interaction between eosinophilia and ICS determining risk from severe COVID-19 outcomes. Accordingly, future RCTs studying the therapeutic benefit of ICS in COVID-19 should account for the presence (or absence) of eosinophilia.

Our study had several limitations. Like other registry-based observational studies, it could be subject to bias, particularly as it relates to the use of ICS in individuals with more severe forms of asthma and COPD, a subgroup more likely to elicit early diagnostic testing and care. Owing to its cross-sectional design, we cannot assess the influence of longitudinal changes in baseline (preexisting) blood eosinophil counts. Our analyses of the CCCRR are also limited by the lack of information regarding the dose or type of ICS used by patients, and adherence to therapy. This is an important limitation because it remains unclear whether the association between ICS and COVID-19 outcome is dose-dependent or medication (vs class) specific. Because we limited our analysis to patients cared for at the Cleveland Clinic, our analyses did not account for patients admitted to other hospitals and those who died after being discharged to long-term acute care facilities. Socioeconomic factors are strong determinants of COVID-19 outcomes, especially in underrepresented minority groups, and it is possible that ICS-treated patients also reflect a subgroup of asthma and COPD patients with improved health care access. Regardless, we believe our study has many strengths, including a large sample size, strict and predefined methods for data collection, and a thorough analysis of data that considers nonlinear relationships and adjusts for patient demographics, medications, comorbidities, the month of SARS-CoV-2 testing, and the time between the AEC and SARS-CoV-2 test dates.

Our study demonstrates that the baseline immune profile might determine the risk for COVID-19—related hospitalization, ICU admission, and in-hospital mortality. It also shows that the association between eosinophilia and COVID-19 outcomes depends on ICS therapy. Our study highlights the need to risk-stratify patients with COVID-19 better, identify new biomarkers, and plan future RCTs to study the effect of ICS.

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ONLINE REPOSITORY

Appendix E1: Description of the Registry

The Cleveland Clinic COVID-19 Research Registry. The Cleveland Clinic COVID-19 Research Registry was previously described by us and others.[E1-E5] The registry was started by the Cleveland Clinic on March 8, 2020 and includes all patients tested for coronavirus disease 2019 (COVID-19) within its health care system by trained medical personnel using standardized protocols.[E4] Testing was performed by means of the Centers for Disease Control and Prevention's reverse transcription polymerase chain reaction severe acute respiratory syndrome coronavirus 2 assay, which uses MagNA Pure (Roche, Branchbug, NJ, USA) extraction and ABI 7500 DX PCR (Thermo Fisher Scientific, Waltham, MA, USA) instruments.[E4] The registry's clinical characterization and data collection are consistent with clinical features previously published on COVID-19.[E6-E10] Uniform clinical templates were implemented in electronic health records (Epic, Epic Systems Corporation, Verona, WI, USA) across the Cleveland Clinic Health System to standardize patient care and facilitate data extraction.[E1,E4,E5] Patients with a positive COVID-19 test were monitored by the COVID-19 home monitoring program, which consisted of telephone outreach by a registered nurse and self-monitoring through an app for patient entry of COVID-19 symptoms. Patients were asked for the presence of COVID-19–related symptoms, such as fever, cough, dyspnea, weakness, vomiting, diarrhea, or loss of appetite. Frequent comorbidities (eg, asthma, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, coronary artery disease, heart failure, and immunosuppressive diseases), and certain medications (nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and immunosuppressive therapy) were documented in the database. The immunosuppressive diseases definition was adapted from the Agency of Healthcare Research and Quality definition of immunocompromised state diagnosis.[E11] Outcomes related to hospitalizations and admission to the intensive care unit were extracted. Data from the electronic health records were verified manually by a trained research team using predefined processes published previously.[E5]

Institutional review board approval. This study and the Cleveland Clinic COVID-19 Research Registry were approved by the Cleveland Clinic Institutional Review Board (Institutional Review Board Nos. 20-283 and 20-391).

Appendix E2: Systemic Medications Used to Define Immunosuppressive Therapy

Abatacept	Dexamethasone	Pediapred
Actemra	Dexone	Predicort
Adalimumab	Dexpak	Prednisolone
Afinitor	Enbrel	Prednisone
A-Hydrocort	Entocort EC	Prelone
A-Methapred	Entyvio	Prograf
Anakinra	Envarsus XR	Rapamune
Arava	Etanercept	Rayos
Aristocort	Everolimus	Remicade
Aristospan	Flo-Pred	Risankizumab-rzaa
AsmalPred	Florinef	Rituxan
Astagraf XL	Fludrocortisone	Rituximab
Azasan	Golimumab	Sandimmune
Azathioprine	Guselkumab	SangCya
Basiliximab	Humira	Secukinumab
Beclomethasone	Hydrocortisone	Skyrizi
Belimumab	Hydrocortone	Siliq
Benlysta	Imuran	Simponi
Betamethasone	Infliximab	Simulect
Brodalumab	Ixekizumab	Sirolimus
Bubbli-Pred	Kenaject	Stelara
Budesonide	Kenalog	Sterapred
Celestone	Kineret	Tacrolimus
CellCept	Leflunomide	Taltz
Certolizumab	Medrol	Tocilizumab
Cimzia	Meprolone	Tofacitinib
Cortef	Methotrexate	Tremfya
Cortisone	Methylpred	Triamcinolone
Cosentyx	Methylprednisolone	Triesence
CPC-Cort-D	Meticorten	Tysabri
Cyclosprine	Millipred	Ustekinumab
Daclizumab	Mycophenolate	Vedolizumab
Decadron	Myfortic	Veripred
Deflazacort	Natalizumab	Xeljanz
Deltasone	Neoral	Zema
Depo-Medrol	Orapred	Zinbryta
Dexacen	Orencia	Zortress

TABLE E1. Clinical characteristics and outcomes by eosinophilia (>0.15 $\times 10^3/\mu L$) for patients with asthma in registry stratified by ICS use

Variable	All patients with asthma		*P*	No ICS		*P*	ICS		*P*
Eosinophil count	<0.15 [$\times 10^3/\mu L$]	>0.15 [$\times 10^3/\mu L$]		<0.15 [$\times 10^3/\mu L$]	>0.15 [$\times 10^3/\mu L$]		<0.15 [$\times 10^3/\mu L$]	>0.15 [$\times 10^3/\mu L$]	
n	3,559	3,180		2,145	1,695		1,414	1,485	
Demographics									
Age, y	48.9 [34.1-62.6]	52.9 [39.0-66.2]	<.001	42.8 [30.1-58.2]	48.3 [34.2-62.3]	<.001	55.8 [44.4-67.2]	58.0 [45.4-69.7]	.004
Female sex	2,610 (73.3)	2,142 (67.4)	<.001	1,565 (73)	1,138 (67.1)	<.001	1,045 (73.9)	1,004 (67.6)	<.001
Body mass index, kg/m^2	31.2 [26.2-37.5]	32.3 [27.3-38.4]	<.001	30.6 [25.8-36.9]	32.1 [27.1-38.0]	<.001	31.9 [26.9-38.4]	32.6 [27.4-39.0]	.036
Race			<.001			<.001			.012
Black	1,081 (30.4)	781 (24.6)		676 (31.5)	420 (24.8)		405 (28.6)	361 (24.3)	
White	2,089 (58.7)	2,082 (65.5)		1,208 (56.3)	1,079 (63.7)		881 (62.3)	1,003 (67.5)	
Others*	389 (10.9)	317 (10.0)		261 (12.2)	196 (11.6)		128 (9.1)	121 (8.1)	
Hispanic ethnicity	117 (3.3)	92 (2.9)	.347	68 (3.2)	59 (3.5)	.663	51 (3.6)	33 (2.2)	.043
Smoking history			.345			.13			.5
Current	320 (9.0)	284 (8.9)		208 (9.7)	181 (10.7)		112 (7.9)	103 (6.9)	
Past	1,052 (29.6)	992 (31.2)		542 (25.3)	465 (27.4)		510 (36.1)	527 (35.5)	
Pack-year smoking	10.0 [3.6-25.0]	11.4 [4.0-27.0]	.379	7.5 [2.0-20.0]	10.0 [4.0-22.5]	.004	15.0 [5.0-30.0]	14.0 [4.7-30.0]	.153
Eosinophil count ($\times 10^3/\mu L$)†	0.08 [0.04-0.12]	0.26 [0.20-0.36]	<.001	0.09 [0.05-0.12]	0.24 [0.20-0.34]	<.001	0.08 [0.03-0.11]	0.27 [0.20-0.38]	<.001
Comorbidities									
Diabetes	810 (22.8)	835 (26.3)	.001	401 (18.7)	390 (23.0)	.001	409 (28.9)	445 (30.0)	.566
Hypertension	1,631 (45.8)	1,676 (52.7)	<.001	815 (38.0)	775 (45.7)	<.001	816 (57.7)	901 (60.7)	.113
Coronary artery disease	420 (11.8)	430 (13.5)	.037	180 (8.4)	166 (9.8)	.147	240 (17.0)	264 (17.8)	.601
Heart failure	384 (10.8)	379 (11.9)	.155	150 (7.0)	146 (8.6)	.071	234 (16.5)	233 (15.7)	.563
Cancer history	457 (12.8)	463 (14.6)	.044	212 (9.9)	209 (12.3)	.018	245 (17.3)	254 (17.1)	.913
Connective tissue disease	241 (6.8)	186 (5.8)	.133	112 (5.2)	85 (5.0)	.83	129 (9.1)	101 (6.8)	.025
Immunosuppressive disease	510 (14.3)	399 (12.5)	.035	231 (10.8)	171 (10.1)	.528	279 (19.7)	228 (15.4)	.002
Medications									
Nonsteroidal anti-inflammatory drugs	795 (22.3)	659 (20.7)	.114	521 (24.3)	373 (22.0)	.104	274 (19.4)	286 (19.3)	.973
Angiotensin converting enzyme inhibitors	297 (8.3)	334 (10.5)	.003	155 (7.2)	158 (9.3)	.022	142 (10.0)	176 (11.9)	.134
Angiotensin receptor blockers	317 (8.9)	343 (10.8)	.011	134 (6.2)	147 (8.7)	.005	183 (12.9)	196 (13.2)	.881
Intranasal corticosteroids	1,528 (42.9)	1,328 (41.8)	.343	746 (34.8)	559 (33.0)	.257	782 (55.3)	769 (51.8)	.063
ICS	1,414 (39.7)	1,485 (46.7)	<.001	0	0	NA	1,414 (100.0)	1,485 (100.0)	NA
Immunosuppressive therapy‡	102 (2.9)	66 (2.1)	.046	38 (1.8)	26 (1.5)	.657	64 (4.5)	40 (2.7)	.011
Outcomes									
Hospitalization	850 (23.9)	717 (22.5)	.205	385 (17.9)	308 (18.2)	.892	465 (32.9)	409 (27.5)	.002
Admission to intensive care unit	193 (5.4)	149 (4.7)	.186	69 (3.2)	55 (3.2)	1	124 (8.8)	94 (6.3)	.016
Hospital mortality	103 (2.9)	92 (2.9)	1	39 (1.8)	33 (1.9)	.863	64 (4.5)	59 (4.0)	.268

ICS, inhaled corticosteroids; *NA*, not available.

Data are presented as n (%) for categorical variables and median [interquartile range] for continuous variables.

*"Other" race category includes American Indians or Alaska Natives, Asian individuals, Native Hawaiian or Other Pacific Islanders, and individuals with multiple racial backgrounds.

†Defined by a baseline blood absolute eosinophil count of greater than 0.15 ($\times 10^3$ cells/ μL) obtained at least 2 weeks before severe acute respiratory syndrome coronavirus 2 test date.

‡Includes chronic systemic corticosteroid therapy.

TABLE E2. Clinical characteristics and outcomes by eosinophilia (>0.15 $\times 10^3/\mu L$) for patients with chronic obstructive pulmonary disease in registry stratified by ICS use

Variable	All patients with COPD		*P*	No ICS		*P*	ICS		*P*
Eosinophil count	<0.15 [$\times 10^3/\mu L$]	>0.15 [$\times 10^3/\mu L$]		<0.15 [$\times 10^3/\mu L$]	>0.15 [$\times 10^3/\mu L$]		<0.15 [$\times 10^3/\mu L$]	>0.15 [$\times 10^3/\mu L$]	
n	1,524	1,542		673	680		851	862	
Demographics									
Age, y	68.8 [60.6-78.3]	71.1 [61.7-78.9]	.013	69.2 [60.6-78.4]	71.8 [62.1-79.6]	.007	68.7 [60.6-78.2]	70.1 [61.2-77.7]	.342
Female sex	883 (57.9)	827 (53.6)	.018	356 (52.9)	330 (48.5)	.121	527 (61.9)	497 (57.7)	.08
Body mass index, kg/m^2	29.2 [24.5-35.1]	30.1 [25.5-36.0]	.001	28.8 [23.9-34.0]	29.6 [25.4-35.6]	.001	29.9 [25.0-36.0]	30.2 [25.6-36.4]	.184
Race*			.046			.541			.067
Black	435 (28.5)	381 (24.7)		182 (27.0)	167 (24.6)		253 (29.7)	214 (24.8)	
White	994 (65.2)	1,051 (68.2)		453 (67.3)	470 (69.1)		541 (63.6)	581 (67.4)	
Others	95 (6.2)	110 (7.1)		38 (5.6)	43 (6.3)		57 (6.7)	67 (7.8)	
Hispanic ethnicity	36 (2.4)	38 (2.5)	.947	11 (1.6)	16 (2.4)	.453	26 (3.1)	23 (2.7)	.74
Smoking history			.251			.042			.911
Current	206 (13.5)	240 (15.6)		97 (14.5)	132 (19.6)		109 (12.8)	108 (12.5)	
Past	881 (57.9)	861 (56.1)		374 (55.7)	353 (52.5)		507 (59.6)	508 (59.0)	
Pack-years smoking	30.0 [14.3-47.0]	30.0 [14.0-48.5]	.72	27.0 [11.1-45.0]	30.0 [15.0-45.0]	.166	30.0 [15.0-50.0]	30.0 [12.5-50.0]	.505
Eosinophil count ($\times 10^3/\mu L$)†	0.08 [0.03-0.11]	0.27 [0.20-0.38]	<.001	0.08 [0.03-0.11]	0.25 [0.20-0.37]	<.001	0.08 [0.03-0.11]	0.27 [0.21-0.40]	<.001
Comorbidities									
Diabetes	630 (41.3)	673 (43.6)	.209	263 (39.1)	296 (43.5)	.108	367 (43.1)	377 (43.7)	.837
Hypertension	1,212 (79.5)	1,273 (82.6)	.036	511 (75.9)	569 (83.7)	<.001	701 (82.4)	704 (81.7)	.752
Coronary artery disease	541 (35.5)	579 (37.5)	.254	240 (35.7)	269 (39.6)	.155	301 (35.4)	310 (36.0)	.837
Heart failure	534 (35.0)	525 (34.0)	.589	207 (30.8)	211 (31.0)	.961	327 (38.4)	314 (36.4)	.421
Cancer history	443 (29.1)	416 (27.0)	.212	192 (28.5)	175 (25.7)	.274	251 (29.5)	241 (28.0)	.516
Connective tissue disease	117 (7.7)	122 (7.9)	.861	38 (5.6)	47 (6.9)	.397	79 (9.3)	75 (8.7)	.736
Immunosuppressive disease	460 (30.2)	424 (27.5)	.109	199 (29.6)	194 (28.5)	.718	261 (30.7)	230 (26.7)	.076
Medications									
Nonsteroidal anti-inflammatory drugs	296 (19.4)	323 (20.9)	.314	138 (20.5)	148 (21.8)	.617	158 (18.6)	175 (20.3)	.397
Angiotensin converting enzyme inhibitors	241 (15.8)	268 (17.4)	.264	108 (16.0)	129 (19.0)	.179	133 (15.6)	139 (16.1)	.83
Angiotensin receptor blockers	238 (15.6)	196 (12.7)	.024	96 (14.3)	78 (11.5)	.146	142 (16.7)	118 (13.7)	.097
Intranasal corticosteroids	549 (36.0)	581 (37.7)	.362	178 (26.4)	177 (26.0)	.91	371 (43.6)	404 (46.9)	.19
ICS	851 (55.8)	862 (55.9)	1	0	0	NA	851 (100.0)	862 (100.0)	NA
Immunosuppressive therapy‡	65 (4.3)	50 (3.2)	.163	19 (2.8)	12 (1.8)	.263	46 (5.4)	38 (4.4)	.399
Outcomes									
Hospitalization	823 (54.0)	772 (50.1)	.032	328 (48.7)	333 (49.0)	.975	495 (58.2)	439 (50.9)	.003
Admission to intensive care unit	257 (16.9)	219 (14.2)	.047	91 (13.5)	88 (12.9)	.814	166 (19.5)	131 (15.2)	.022
Hospital mortality	188 (12.3)	159 (10.3)	.087	78 (11.6)	70 (10.3)	.499	110 (12.9)	89 (10.3)	.109

ICS, inhaled corticosteroids; *NA*, not available.

Data are presented as n (%) for categorical variables and median [interquartile range] for continuous variables.

*"Other" race category includes American Indians or Alaska Natives, Asian individuals, Native Hawaiian or Other Pacific Islanders, and individuals with multiple racial backgrounds.

†Defined by a baseline blood absolute eosinophil count > 0.15 (x103 cells/ μL) obtained at least 2 weeks before severe acute respiratory syndrome coronavirus 2 test date.

‡Includes chronic systemic corticosteroid therapy.

TABLE E3. Multivariable logistic regression* fitted with restricted cubic spline function for absolute eosinophil count (log10-transformed) with three knots describing nonlinear relationship between eosinophil count and outcomes measures such as hospitalization, admission to intensive care unit, and in-hospital mortality

Outcome	Estimate	SE	z Value	*P*
Hospitalization				
X	−0.646	0.066	−9.841	<2e-16
X′	0.514	0.070	7.311	2.6e-13
Intensive care unit admission				
X	−0.500	0.110	−4.524	6.1e-06
X′	0.383	0.118	3.255	0.001
Died				
X	−0.784	0.130	−6.035	1.6e-09
X′	0.599	0.142	4.222	2.4e-5

Medications in the model include nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, inhaled corticosteroids, intranasal corticosteroids, and immunosuppressive therapy that includes systemic corticosteroids). Comorbidities in the model include diabetes, hypertension, coronary artery disease, heart failure and cancer (historical or current), immunosuppressive diseases, and connective tissue diseases.

*Adjusted for demographics, body mass index, smoking, medications, comorbidities, and the month of testing.

TABLE E4. Association between eosinophilia* and coronavirus disease 2019–related outcomes using complete cases (ie, excluding patients with missing data and without imputation)

	All patients		Chronic obstructive pulmonary disease		Asthma	
	No ICS	ICS	No ICS	ICS	No ICS	ICS
Outcome	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
n	39,888	4,973	1,336	1,701	3,802	2,883
Unadjusted						
Hospitalization	1.23 (1.17-1.29)	0.85 (0.75-0.95)	1.01 (0.82-1.25)	0.75 (0.62-0.90)	1.01 (0.86-1.19)	0.77 (0.66-0.91)
ICU admission	1.26 (1.14-1.39)	0.75 (0.62-0.91)	0.95 (0.69-1.30)	0.74 (0.57-0.95)	1.01 (0.70-1.45)	0.70 (0.53-0.93)
Hospital mortality	1.35 (1.20-1.52)	0.80 (0.63-1.02)	0.86 (0.61-1.22)	0.78 (0.58-1.04)	1.07 (0.67-1.71)	0.87 (0.61-1.25)
Adjusted for age, sex, ethnicity, race, and month of testing.						
Hospitalization	0.97 (0.93-1.03)	0.81 (0.73-0.91)	0.96 (0.78-1.20)	0.77 (0.63-0.93)	0.84 (0.70-1.00)	0.72 (0.62-0.85)
ICU admission	0.97 (0.89-1.06)	0.72 (0.60-0.88)	0.93 (0.68-1.26)	0.74 (0.58-0.96)	0.84 (0.58-1.22)	0.65 (0.49-0.85)
Hospital mortality	0.92 (0.83-1.03)	0.74 (0.59-0.93)	0.80 (0.57-1.11)	0.76 (0.58-1.01)	0.78 (0.49-1.25)	0.76 (0.53-1.09)
Adjusted for age, sex, race, ethnicity, smoking history, pack-years smoking, medications, comorbidities, time between absolute eosinophil count test date and severe acute respiratory syndrome coronavirus 2 test date, and month of testing†						
Hospitalization	0.96 (0.91-1.02)	0.84 (0.74-0.94)	0.98 (0.79-1.22)	0.78 (0.64-0.95)	0.84 (0.71-1.00)	0.76 (0.65-0.89)
ICU admission	0.96 (0.87-1.06)	0.77 (0.64-0.94)	0.89 (0.65-1.21)	0.77 (0.60-0.99)	0.86 (0.59-1.24)	0.71 (0.54-0.94)
Hospital mortality	0.98 (0.87-1.11)	0.79 (0.63-1.00)	0.85 (0.61-1.18)	0.78 (0.59-1.04)	0.81 (0.50-1.31)	0.83 (0.57-1.20)

CI, confidence interval; *ICS*, inhaled corticosteroids; *ICU*, intensive care unit; *OR*, odds ratio.

*Baseline preexisting eosinophilia were defined by a blood absolute eosinophil count of greater than 0.15×10^3 cells/μL, obtained at least 2 weeks before the severe acute respiratory syndrome coronavirus 2 test date.

†The effect of a high blood absolute eosinophil count greater than 0.15×10^3 cells/μL on hospital outcomes is estimated by weighting each patient with the inverse propensity score and controlling for the propensity score as a covariate in the model. Medications included nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, ICS, intranasal corticosteroids, and immunosuppressive therapy (including systemic corticosteroids). Comorbidities include asthma, chronic obstructive pulmonary disease or emphysema, diabetes, hypertension, coronary artery disease, heart failure and cancer (historical or current), immunosuppressive diseases, and connective tissue diseases.

TABLE E5. Coronavirus disease 2019–related outcomes results of patients with different blood AEC categories compared with patients with eosinopenia defined by AEC less than 0.1 $\times$ 10^3 cell/μL[E12]

		Hospitalization	Intensive care unit admission	Hospital mortality
All patients	**n**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
AEC ($\times 10^3$ cell/μL)				
<0.1*	15,512	1	1	1
0.1-0.2	18,250	0.74 (0.70-0.79)	0.83 (0.73-0.92)	0.66 (0.58-0.77)
0.2-0.3	6,933	0.79 (0.73-0.86)	0.89 (0.77-1.02)	0.77 (0.65-0.91)
>0.3	5,702	0.88 (0.81-0.96)	0.91 (0.79-1.05)	0.84 (0.71-0.99)
No inhaled corticosteroids				
<0.1*	14,088	1	1	1
0.1-0.2	16,468	0.75 (0.71-0.81)	0.84 (0.74-0.95)	0.68 (0.58-0.79)
0.2-0.3	6,082	0.82 (0.75-0.89)	0.96 (0.82-1.12)	0.80 (0.66-0.97)
>0.3	4,748	0.94 (0.86-1.03)	0.95 (0.81-1.12)	0.95 (0.79-1.16)
Inhaled corticosteroids				
<0.1*	1,424	1	1	1
0.1-0.2	1,782	0.68 (0.58-0.81)	0.74 (0.58-0.95)	0.61 (0.44-0.83)
0.2-0.3	851	0.65 (0.53-0.79)	0.63 (0.46-0.86)	0.67 (0.46-0.96)
>0.3	954	0.64 (0.53-0.79)	0.75 (0.56-1.01)	0.52 (35-76)

AEC, absolute eosinophil count; *CI*, confidence interval; *OR*, odds ratio.
The analysis was adjusted for demographics, baseline AEC, month of testing, smoking status, pack-years smoking, medications, and comorbidities.
*Patients with preexisting AEC measurements were stratified into four categories. Those with an AEC greater than 0.3, 0.2 to 03, and 0.1 to 0.2 were compared with patients with eosinopenia (defined by an AEC less than 0.1 $\times$ 10^3 cell/μL).

TABLE E6. Hospitalization risk comparing patients with an AEC greater than 0.15 $\times$ 10^3/μL versus those with an AEC less than 0.15 $\times$ 10^3/μL

		All patients		Chronic obstructive pulmonary disease		Asthma	
Time between AEC test date and SARS-CoV-2 test date	**n**	**No ICS**	**ICS**	**No ICS**	**ICS**	**No ICS**	**ICS**
<2 y*	24,095	0.97 (0.90-1.03)	0.85 (0.75-0.97)	1.05 (0.82-1.33)	0.79 (0.64-0.98)	0.89 (0.73-1.10)	0.78 (0.65-0.93)
<1 y†	15,058	0.93 (0.86-1.00)	0.81 (0.70-0.95)	1.17 (0.89-1.54)	0.77 (0.61-0.98)	0.93 (0.73-1.18)	0.76 (0.62-0.94)

AEC, absolute eosinophil count; *ICS*, inhaled corticosteroids; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.
The analysis was stratified by the time between the AEC test date and the severe acute respiratory syndrome coronavirus 2 test date inhaled corticosteroids therapy and airway disease category.
Effect of a high blood absolute eosinophil count greater than 0.15 $\times$ 10^3 cells/μL on hospital outcomes is estimated by weighting each patient with the inverse propensity score and controlling for the propensity score as a covariate in the model. Medications include nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, ICS, intranasal corticosteroids, and immunosuppressive therapy (that includes systemic corticosteroids). Comorbidities include asthma, chronic obstructive pulmonary disease/emphysema, diabetes, hypertension, coronary artery disease, heart failure and cancer (historical or current), immunosuppressive disease, and connective tissue disease.
*Patients for whom AEC measurements were obtained within 2 years (median [interquartile range]: 291 [126-457] days) of the SARS-CoV-2 test date.
†Patients for whom AEC measurements were obtained within 1 year (median [interquartile range]: 173 [55-275] days) of the SARS-CoV-2 test date.

TABLE E7. Association between high fractional of exhaled nitric oxide measurements (FeNO >35 parts per billion) and hospitalization risk stratified by ICS use

Adjustment	ICS (odds ratio [95% confidence interval])	No ICS (odds ratio [95% confidence interval])
n	835	459
Adjusted for baseline absolute eosinophil count and month of testing	0.45 (0.28-0.70)	0.79 (0.32-1.77)
Adjusted for demographics,* baseline absolute eosinophil count, and month of testing	0.70 (0.53-0.92)	0.86 (0.61-1.22)
Adjusted for demographics, baseline absolute eosinophil count,* month of testing, smoking status, pack-years smoking, medications, and comorbidities†	0.72 (0.55-0.95)	0.85 (0.60-1.20)

ICS, inhaled corticosteroids.

*Demographics include age, sex, ethnicity. and race.

†The effect of a high FeNO (>35 parts per billion) on hospitalization risk is estimated by weighting each patient with the inverse propensity score and controlling for the propensity score as a covariate in the model. Medications include immunosuppressive therapy (that includes systemic corticosteroids), angiotensin converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, and intranasal corticosteroids. Comorbidities include body mass index, smoking history (both current and remote), diabetes, hypertension, coronary artery disease, heart failure, cancer history, immunosuppressive disease, and connective tissue disease.

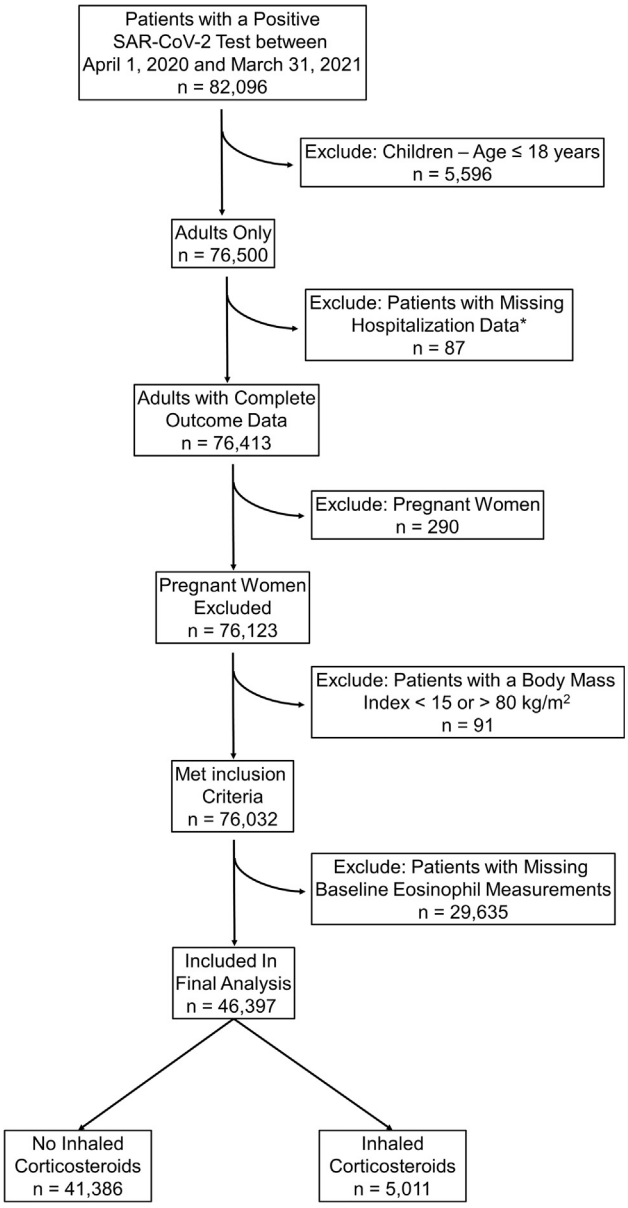


FIGURE E1. Flowchart of patients in final analysis. *SAR-CoV-2*, severe acute respiratory syndrome coronavirus 2.

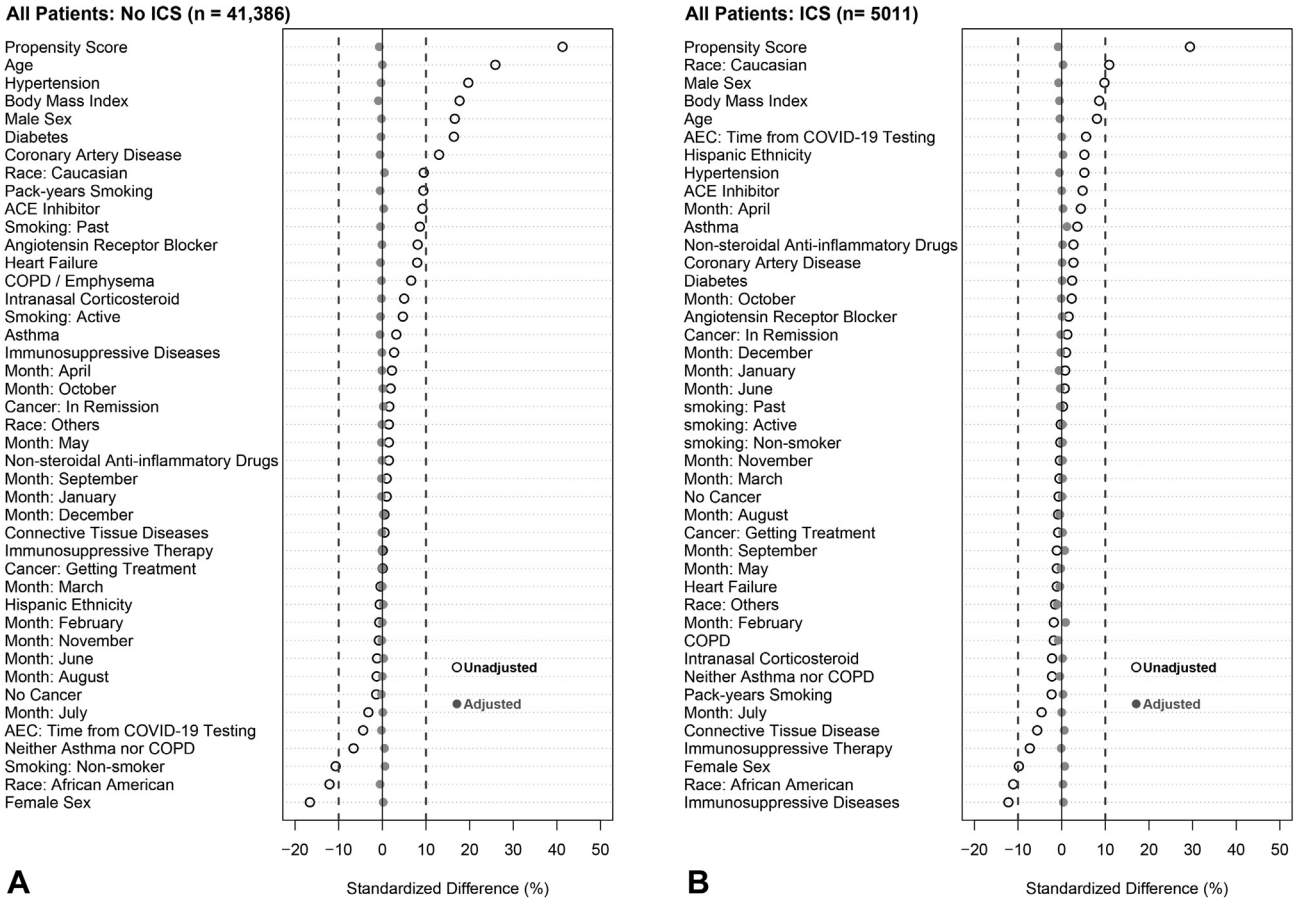
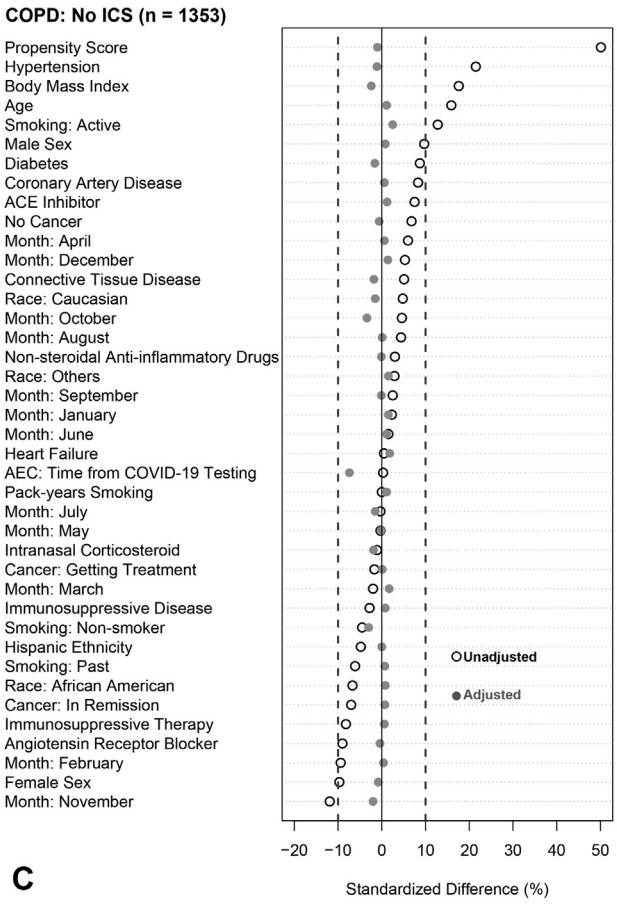


FIGURE E2. Standardized mean differences before and after weighting on inverse propensity score and controlling for propensity score as a covariate in the model. Analysis was stratified into six groups: (**A**) all patients not receiving inhaled corticosteroids (ICS), (**B**) all patients receiving ICS, (**C**) patients with chronic obstructive pulmonary disease (COPD) not receiving ICS, (**D**) patients with COPD who were receiving ICS, (**E**) patients with asthma who were not receiving ICS, and (**F**) patients with asthma who were receiving ICS. An absolute standardized difference of 0% indicates no residual bias; values $<10\%$ indicate inconsequential bias. Open black circles show standardized mean differences for each covariate before weighting. Solid gray circles show differences after weighting. *ACE*, angiotensin-converting enzyme; *AEC*, absolute eosinophil count; *COVID-19*, coronavirus disease 2019.



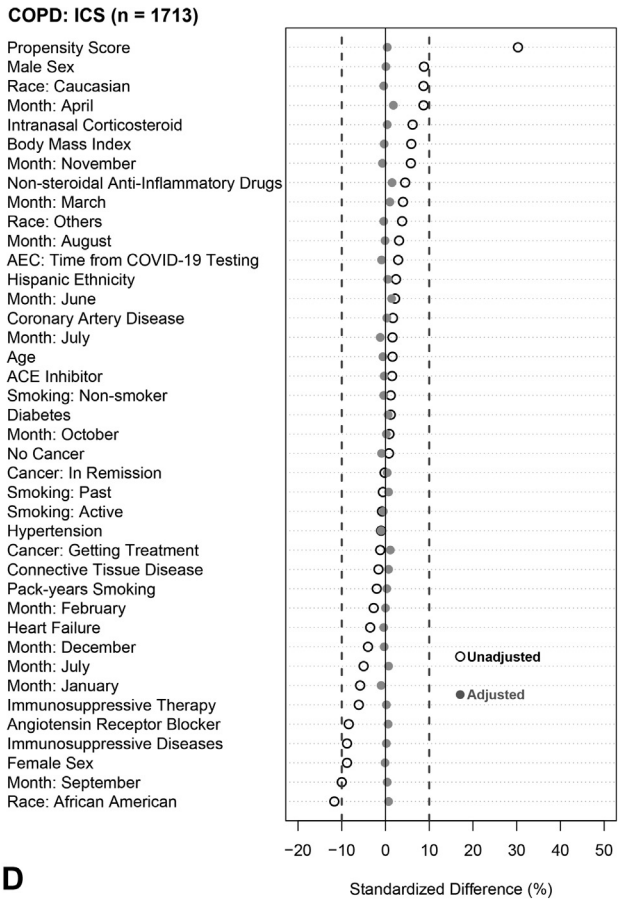
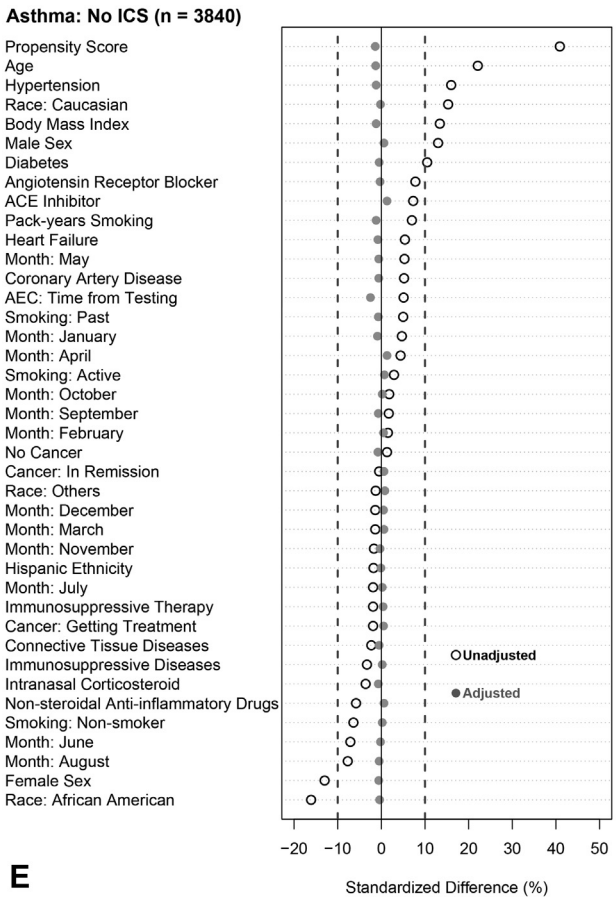


FIGURE E2. Continued



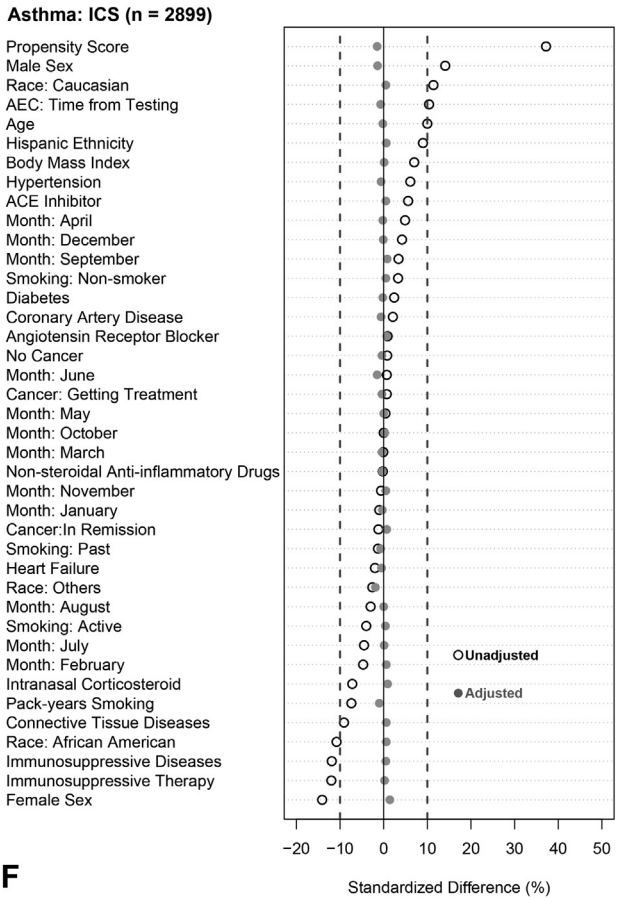


FIGURE E2. Continued

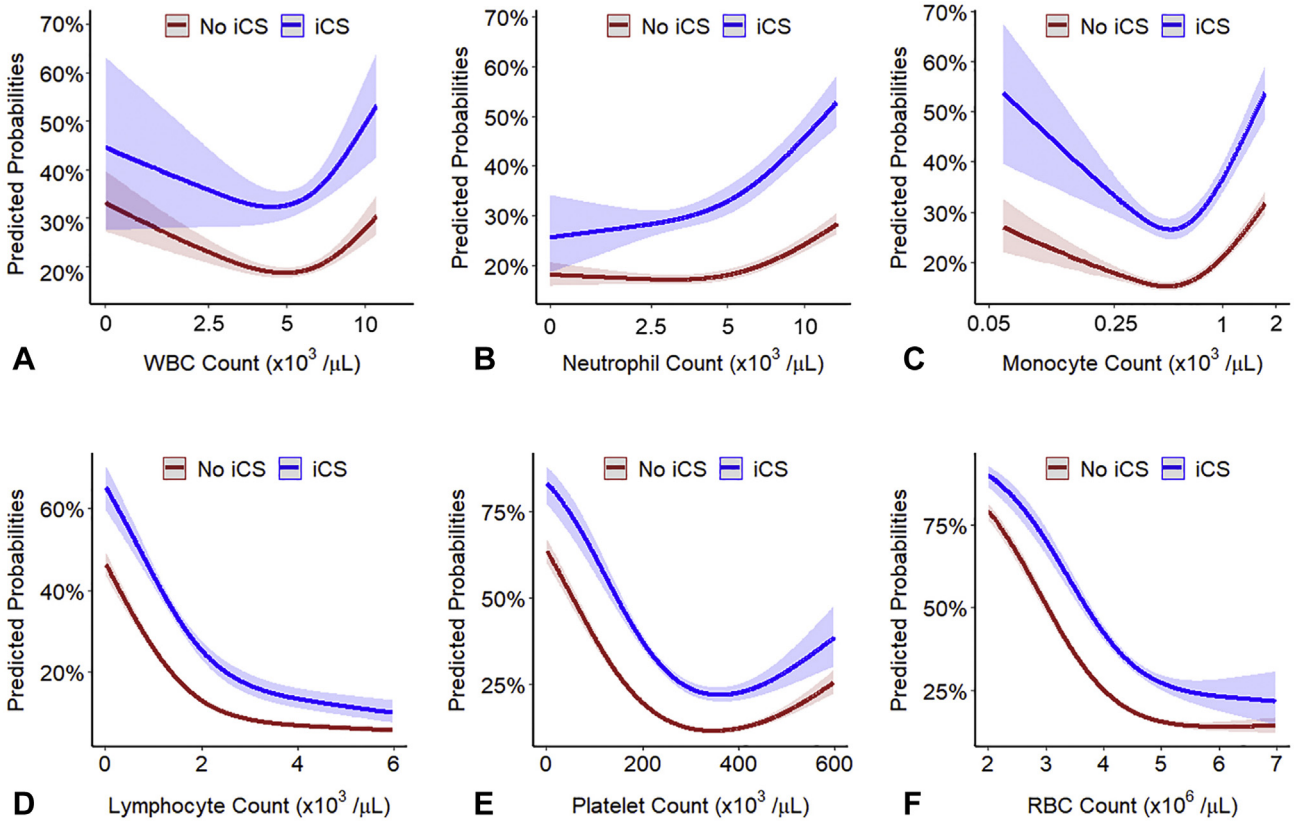


FIGURE E3. Predicted probabilities of coronavirus disease 2019 (COVID-19)-related hospitalization as a function of (**A**) baseline white blood cell count (WBC), (**B**) absolute neutrophil count (ANC), (**C**) absolute monocyte count (AMC), (**D**) absolute lymphocyte count, (**E**) platelet count, and (**F**) red blood cell (RBC) count in peripheral blood stratified by inhaled corticosteroid (iCS) use. The probabilities were calculated by fitting a logistic regression using a restricted cubic spline function for each of the parameters. Log10 transformation was applied to nonnormally distributed variables (WBC, ANC, and AMC). The 95% confidence intervals are indicated by the shaded areas around the fitted lines.

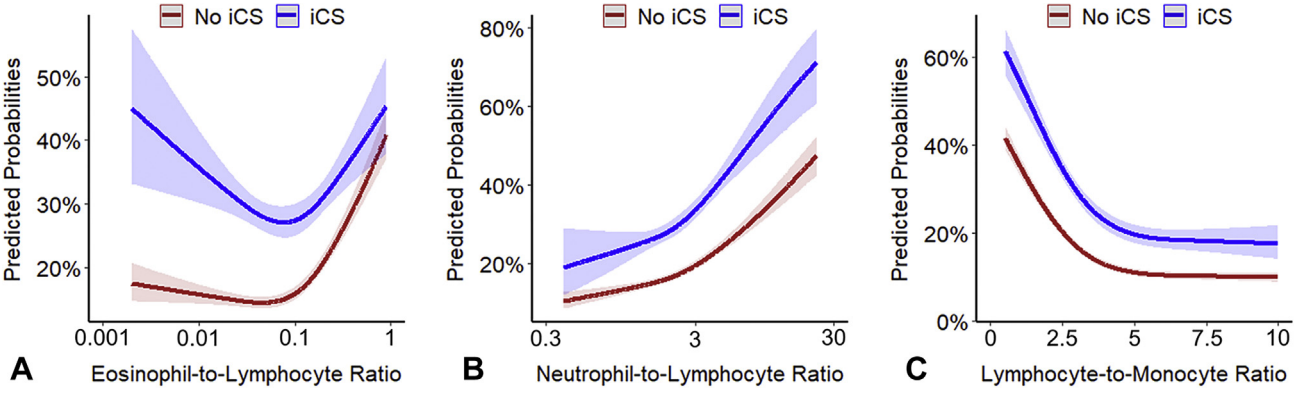


FIGURE E4. Predicted probabilities of coronavirus disease 2019 (COVID-19)-related hospitalization as a function of the (**A**) baseline eosinophil-to-lymphocyte ratio (ELR), (**B**) neutrophil-to-lymphocyte ratio (NLR), and (**C**) lymphocyte-to-monocyte ratio (LMR) in peripheral blood stratified by inhaled corticosteroid (iCS) use. The probabilities were calculated by fitting a logistic regression using a restricted cubic spline function for each of the parameters. Log10 transformation was applied to nonnormally distributed variables (ELR and NLR). The 95% confidence intervals are indicated by the shaded areas around the fitted lines.

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