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.

Respiratory Medicine 176 (2021) 106275

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Association of inhaled and systemic corticosteroid use with Coronavirus Disease 2019 (COVID-19) test positivity in patients with chronic pulmonary diseases

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ARTICLE INFO

Keywords:
COVID-19
Asthma
COPD
Corticosteroid
Pulmonary diseases

ABSTRACT

Background: The effects of chronic inhaled and systemic corticosteroids use on COVID-19 susceptibility and severity are unclear. Since many patients with chronic pulmonary diseases rely on corticosteroids to control disease, it is important to understand the risks of their use during the pandemic. We aim to study if the use of inhaled or systemic corticosteroids affects the likelihood of developing COVID-19 infection.

Methods: We used the National Jewish Health electronic medical record research database to identify a cohort of all subjects who were tested for suspected COVID-19 between March 11 - June 23, 2020. Testing results, medication use, and comorbidities were obtained from the medical record. Following a comparison of different propensity score weighting methods, overlap propensity score weighting was used to analyze the association between medication use and COVID-19 diagnosis.

Results: The cohort consisted of 928 patients, of which 12% tested positive. The majority (66%) of patients had a history of chronic pulmonary diseases. There was no significant association between inhaled corticosteroid use and testing positive for COVID-19. Interestingly, systemic corticosteroid use was associated with a lower odds ratio (0.95, 95% CI: 0.91–0.99) of testing positive for COVID-19. Similar results were noted when the analysis was restricted to those with any chronic pulmonary diseases, with asthma or with chronic obstructive pulmonary disease (COPD).

Conclusions: Our study supports the recommendation that patients with chronic pulmonary diseases, including asthma and COPD who require treatment with either inhaled or systemic corticosteroids, should continue their use during the COVID-19 pandemic.

1. Introduction

Coronavirus Disease 2019 (COVID-19) has become a pandemic and morbidity and mortality remain high worldwide. Patients with COVID-19 with pre-existing comorbidities, including chronic pulmonary diseases, have worse outcomes including greater hospitalizations, intensive care unit admission, and mortality [1,2]. Surprisingly, different from diabetes, the prevalence of chronic pulmonary diseases among patients with severe acute respiratory syndrome (SARS) and COVID-19 was lower compared to the general population [3]. One possibility for the low prevalence of chronic pulmonary diseases in COVID-19 patients is that therapies used to treat these diseases may be protective and/or decrease the susceptibility to infection with SARS-Coronavirus-2 (SARS-CoV-2), the virus that causes COVID-19. One of the most commonly prescribed medications used in chronic pulmonary diseases, especially asthma and chronic obstructive pulmonary disease (COPD), is corticosteroids, administered by inhalation and less often, systemically. A recent systematic review and meta-analysis of COVID-19 outcomes in

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, SARS-coronavirus 2; COPD, chronic obstructive pulmonary disease; NJH, National Jewish Health; ACE/ARBs, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers; ICD-10, International Classification of Disease-10; BMI, body mass index; ATO, overlap weights for estimating the average treatment effect among the overlap population; CI, confidence interval.

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https://doi.org/10.1016/j.rmed.2020.106275
Received 29 August 2020; Received in revised form 23 November 2020; Accepted 26 November 2020
Available online 28 November 2020

patients with chronic pulmonary diseases using inhaled corticosteroids concluded that there was insufficient evidence to support whether the use of inhaled corticosteroids resulted in adverse or beneficial outcomes for COVID-19 [4]. One explanation is that different inhaled corticosteroids (e.g. fluticasone v.s. budesonide) may have different effects on the risk of pneumonia [5] and thus by analogy potentially COVID-19. Despite recent evidence of beneficial effects of dexamethasone in treating COVID-19- associated acute lung injury [6,7], systemic corticosteroids, and other immunosuppressive drugs or biologics are known to dose-dependently increase the risk for a variety of other infections. Therefore, they are intuitively thought to also increase the risk of acquiring COVID-19. Currently, there is no sufficient evidence whether and/or how corticosteroids affect COVID-19 susceptibility. In our study, we sought to investigate the association between the use of inhaled or systemic corticosteroid and the likelihood of testing positive for COVID-19 in symptomatic individuals suspected of having acute viral respiratory disease, drawn from a cohort of subjects with a high prevalence of pre-existing chronic pulmonary diseases. The goal of this study is to provide insight into potential risks and/or benefits of the continuation of inhaled or systemic corticosteroids in patients with chronic pulmonary disease who may be vulnerable to COVID-19.

2. Material and methods

2.1. Study design

This is a retrospective cohort analysis of a prospective, observational study of all patients tested for COVID-19 at National Jewish Health (NJH). Data were extracted and validated by the clinical informatics team from electronic health records (Allscripts Analytics) using NJH data SCOUT software.

2.2. Study population

The cohort included all adult patients (≥18 years old) tested for COVID-19 at NJH from March 11 to June 23, 2020. As a respiratory hospital, the majority of patients have underlying pulmonary diseases. The exclusion criteria are shown in the Supplement. Initial indications for testing included any symptoms of fever, cough (new or worsening), shortness of breath (new or worsening), or direct personal contact with known COVID-19 suspects or actual cases. After March 24, 2020, sore throat and persistent nausea or vomiting, diarrhea, or abdominal pain were added to the testing indications.

2.3. Laboratory testing

All the laboratory specimens were collected by nasopharyngeal swab by trained medical staff. Before March 20, 2020, specimens were sent to ARUP or Quest laboratory. After March 20, testing was performed by the NJH Advanced Diagnostics (ADx) laboratory using a reverse transcription-polymerase chain reaction SARS-CoV-2 assay that was Clinical Laboratory Improvement Amendments (CLIA) validated.

2.4. Study outcome, medication, and medical history assessment

The study outcome was a positive laboratory test for COVID-19. We extracted medication data for each patient based on the history in the electronic health record. We defined the medication used as any active prescription that began between March 1, 2019 (preceding 12–15 months) and remained active at the time of COVID-19 testing. Details are shown in the Supplement. We reported the following classes of medication in this study: 1) systemic corticosteroids including oral and injected; 2) inhaled corticosteroids including stand-alone corticosteroids or in combination with other drugs (e.g. long-acting beta-agonist); 3) immunosuppressants other than corticosteroids including methotrexate, mycophenolate mofetil, azathioprine, leflunomide, cyclosporine, tacrolimus, mycophenolic acid, sirolimus, and everolimus; 4) hydroxychloroquine; 5) biologics and JAK inhibitors including anti- IL-5, -IL-6, -IL-12/23, -IL-17, -IgE, -CD20, and -TNF-α inhibitors; 6) angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACE/ARBs).

Medical history was extracted for each patient based on presence in the electronic health record. Diagnoses were based on the International Classification of Disease-10 (ICD-10) codes. We characterized patients as having or not having a history of the following: myocardial infarction, congestive heart failure, rheumatic disease, diabetes, and renal disease based on ICD-10 codes. These diagnoses were included as outlined in the Charlson comorbidity index, a well-validated tool used widely in healthcare-related research [8,9]. For chronic pulmonary disease, we included interstitial lung disease, cystic fibrosis, and sarcoidosis to chronic pulmonary disease defined by the Charlson comorbidity index. We also added hypertension as a comorbidity of interest. A full disease group definition with ICD-10 codes are shown in e-Table 1.

Table 1
Characteristics of patients in the study.

Characteristics*	Total (n = 928)	Tested Positive (n = 113, 12%)	Tested Negative (n = 815, 88%)	P-Value
Age (years) ± SD	53 ± 16	50 ± 16	53 ± 16	0.04
Male	310 (33)	53 (47)	257 (32)	0.002
Body mass index (Kg/m^2)†	29 ± 8	28 ± 6	29 ± 8	0.05
Smoking status†				0.13
Current, %	7	2	7	0.11
Past, %	38	35	39	0.59
Never, %	55	63	54	0.15
Pack-years†	10 ± 19	9 ± 20	10 ± 19	0.48
Hypertension	198 (21)	18 (16)	180 (22)	0.14
Diabetes	80 (9)	11 (10)	69 (8)	0.60
Chronic pulmonary diseases	612 (66)	57 (50)	555 (68)	<0.001
Asthma or COPD	524 (56)	49 (43)	475 (58)	0.003
Asthma‡	423 (45)	41 (36)	381 (47)	0.04
COPD‡	185 (20)	16 (14)	169 (21)	0.10
Interstitial lung diseases‡	59 (6)	4 (4)	55 (7)	0.22
Cystic fibrosis‡	25 (3)	1 (1)	24 (3)	0.35
Sarcoidosis‡	21 (2)	5 (4)	16 (2)	0.16
Myocardial infarction	8 (1)	1 (1)	7 (1)	1
Congestive heart failure	20 (2)	2 (2)	18 (2)	1
Renal diseases	16 (2)	1 (1)	15 (2)	0.7
Rheumatic diseases	74 (8)	9 (8)	65 (8)	1
ACEI/ARB	94 (10)	8 (7)	86 (11)	0.32
Inhaled corticosteroids	348 (38)	39 (35)	309 (38)	0.53
Systemic corticosteroids	214 (23)	13 (12)	201 (25)	0.001
Immunosuppressants	35 (4)	3 (3)	32 (4)	0.79
Hydroxychloroquine	19 (2)	2 (2)	17 (2)	1
Biologics/JAK inhibitors	68 (7)	6 (5)	62 (8)	0.45

Definition of abbreviations: SD: standard deviation; COPD: chronic obstructive pulmonary disease; ACEI: angiotensin conversion enzyme inhibitor; ARB: angiotensin II receptor blocker.
Bold when P-value < 0.05.
*All characteristics except age are reported as number and percentage.
†Calculated based on 708 patients (63, 8% positive, and 645, 92% negative) with complete information on BMI, smoking status, and pack-years.
‡Patients may have several concurrent pulmonary diseases, e.g. patients may have both asthma and interstitial lung diseases.

2.5. Other covariates to be considered

We extracted information on race, body mass index (BMI), smoking status, and pack-years through the medical records. We did not include race in our analysis as this variable was unknown for 35% of patients due to a combination of declining reporting, self-reported as unknown, and/or more than two races. BMI, smoking status, and pack-year history were extracted from the most recent visit after March 1, 2019 (preceding 12–15 months to the time of testing). Smoking status was missing in 24% of our study cohort.

2.6. Statistical analysis

To address confounding by indication, given that patients who are prescribed medications are more likely to have underlying comorbidities associated with COVID-19 susceptibility, the propensity score method was used for this observational study. The propensity score was interpreted as the likelihood of receiving the medication of interest. The propensity score was estimated from a multivariate logistic regression model using age, gender, comorbidities, and other medication classes mentioned (except for the medication of interest). Race (35% unknown), BMI (24% missing), smoking status (24% missing), and pack-years (24% missing) were not included in our main model due to missing values. Using the method developed by Li and Thomas's group [10] and the R package *PSweight* for the analysis, we first compared different propensity score weighting methods then chose the method with the best performance for the analysis (Supplement). Each patient's weight was the likelihood of that patient being assigned to the opposite medication group. The propensity score weighting method was then applied to test the association between the medication of interest and testing positive for COVID-19. We also performed subgroup analysis by stratifying subjects: 1) with chronic pulmonary diseases, 2) without chronic pulmonary diseases, and 3) with asthma or COPD (with or without other concurrent pulmonary diseases), respectively. We also performed conventional logistic regression analysis adjusted for all the variables above to test for association between the medication of interest and testing positive for COVID-19.

Besides inhaled and systemic corticosteroids, we performed the ancillary analyses of immunosuppressants, hydroxychloroquine, and biologics/JAK inhibitors since the power to detect true associations were low due to the small number of patients using those medications. We also used ancillary analysis of models that included BMI, smoking status, and pack-years as covariates due to similar concerns of lack of power to detect true associations.

To assess the sensitivity of our results to the diagnostic test used, we re-analyzed data using the same protocol but restricting it to patients in whom COVID-19 testing was performed exclusively in the NJH ADx laboratory. All analyses, including data cleaning, were performed in R (R Foundation for Statistical Computing, Vienna, Austria).

2.7. Study approval

The Institutional Review Board (IRB) committee at NJH through BRANY (Biomedical Research Alliance of New York) has rendered a decision for exemption of IRB approval.

3. Results

The results are reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline [11]. The study population consisted of 928 patients tested for COVID-19. The mean age was 53 and 310 (33%) were male (Table 1). 708 of the 928 patients had information on BMI, smoking status, and pack-years. The mean BMI was 29, 7% were current smokers and 38% were past smokers with mean pack-years of 10 (Table 1). Most patients, 612 (66%) had chronic pulmonary diseases, of whom 524 (56% of the whole cohort) had asthma or COPD. Some may have had other concurrent pulmonary diseases, for example, both asthma and cystic fibrosis (Table 1). A positive COVID-19 result was observed in 113 tested patients (12%), a group that had a lower prevalence of chronic pulmonary diseases (P-value <0.001), a higher prevalence of being male (P-value = 0.002), and less systemic corticosteroid use (P-value = 0.001) compared to the group that tested negative. The full details of the patients' characteristics are shown in Table 1.

Among all patients, 348 (38%) used inhaled corticosteroids, and 214 (23%) used systemic corticosteroids. The results of propensity score weighting methods comparisons showed that overlap weighting (ATO) had the best performance (Supplement and e-Figure). The patient characteristics after the overlap propensity score weighting are shown in Table 2. Therefore, we used the overlap weighting method for the remainder of our analyses.

There was no significant association between inhaled corticosteroids use and testing positive for COVID-19 in either overlap propensity score-weighted analysis or conventional logistic regression analysis using all or subgroups of patients (The 95% CI of the odds ratio across one). For the analysis of systemic corticosteroid use, we observed an odds ratio of 0.95 (95% CI: 0.91–0.99) using overlap propensity score weighting and 0.50 (95% CI: 0.26–0.94) using conventional logistic regression adjusted for all covariates in all patients. In the subgroup analysis of systemic corticosteroid use, we observed an odds ratio of 0.95 (95% CI: 0.91–0.99) using overlap propensity score weighting and 0.39 (95% CI: 0.18–0.84) using conventional logistic regression in subgroups of patients with chronic pulmonary disease. An odds ratio of 0.93 (95% CI: 0.89–0.97) using overlap propensity score weighting and 0.33 (95% CI: 0.14–0.78) using conventional logistic regression were observed in subgroups of patients with asthma and/or COPD. However, these findings were not observed in patients without chronic pulmonary diseases (Table 3).

In the conventional logistic regression model including all patients (Table 4), we observed a higher likelihood of testing positive for COVID-19 in males, with an odds ratio of 1.95 (95% CI:1.29–2.95) and lower likelihood in patients with chronic pulmonary diseases, with an odds ratio of 0.53 (95% CI:0.34–0.89).

There were no significant associations between ACE/ARBs, immunosuppressants, hydroxychloroquine, or biologics/JAK inhibitors use and testing positive for COVID-19 in either overlap propensity score-weighted analysis or conventional logistic regression analysis using all

Table 2
Overlap propensity score-weighted characteristics among corticosteroid usage groups (n = 928).

Characteristics	Inhaled corticosteroid*		Systemic corticosteroid*	
	Yes	No	Yes	No
Subject counts, n	348	580	214	714
Age (years)	53	53	54	54
Male	34	34	30	30
Hypertension	22	22	24	24
Diabetes	9	9	9	9
Chronic pulmonary diseases	78	78	86	86
Myocardial infarction	1	1	1	1
Congestive heart failure	2	2	2	2
Renal diseases	1	1	2	2
Rheumatic diseases	7	7	10	10
ACEI/ARB	11	11	10	10
Inhaled corticosteroids	N/A	N/A	48	48
Systemic corticosteroids	26	26	N/A	N/A
Immunosuppressants	3	3	5	5
Hydroxychloroquine	2	2	3	3
Biologics/JAK inhibitors	7	7	11	11

Definition of abbreviations: ACEI: angiotensin conversion enzyme inhibitor; ARB: angiotensin II receptor blocker; N/A: not applicable.
*Reported as overlap propensity score-weighted mean or percentage for each group.

Table 3
Association between corticosteroid use and testing positive for COVID-19 in different subgroups.

Study population	Inhaled corticosteroid		Systemic corticosteroid	
	Overlap propensity score-weighted	Logistic regression†	Overlap propensity score-weighted	Logistic regression†
All patients (n = 928)	1.02 (0.97–1.06)*	1.19 (0.75–1.88)	0.95 (0.91–0.99)	0.50 (0.26–0.94)
With chronic pulmonary diseases (n = 612)	1.03 (0.98–1.08)	1.49 (0.84–2.64)	0.95 (0.91–0.99)	0.39 (0.18–0.84)
Without chronic pulmonary diseases (n = 316)	1.02 (0.96–1.09)	0.71 (0.29–1.69)	1.06 (0.88–1.33)	0.97 (0.29–3.25)
With asthma or COPD (n = 524)	1.05 (0.99–1.11)	1.81 (0.96–3.42)	0.93 (0.89–0.97)	0.33 (0.14–0.78)

Definition of abbreviations: COPD: chronic obstructive pulmonary disease.
*Reported as odds ratio and 95% confidence interval; bold when odds ratio is significant.
†Adjusted for all other covariates.

Table 4
Conventional logistic regression in all patients (n = 928).

Variables	Odds ratio	95% CI	P-Value
Age	0.99	0.98–1.00	0.21
Male	1.95	1.29–2.95	0.002
Hypertension	0.87	0.45–1.65	0.66
Diabetes	1.68	0.79–3.57	0.18
Chronic pulmonary diseases	0.53	0.34–0.84	0.006
Myocardial infarction	1.27	0.13–12.0	0.84
Congestive heart failure	0.72	0.15–3.43	0.68
Renal diseases	0.70	0.09–5.82	0.74
Rheumatic diseases	1.39	0.62–3.15	0.42
ACEI/ARB	0.70	0.30–1.66	0.42
Inhaled corticosteroids	1.19	0.75–1.88	0.45
Systemic corticosteroids	0.50	0.26–0.94	0.03
Immunosuppressants	0.98	0.27–3.52	0.97
Hydroxychloroquine	1.09	0.22–5.44	0.92
Biologics/JAK inhibitors	0.96	0.38–2.42	0.94

Definition of abbreviations: CI: confidence interval; ACEI: angiotensin conversion enzyme inhibitor; ARB: angiotensin II receptor blocker.
Bold when the odds ratio is significant.

or subgroups of patients.

To further explore the effects of different corticosteroid formulations on susceptibility COVID-19, we have compared the prevalence of testing positive for COVID-19 among patients using different types of corticosteroids. For systemic corticosteroids, 191 of the 214 patients (89%) who received systemic corticosteroids used prednisone while 18 patients (8%) used methylprednisolone and the remaining 5 patients (3%) used other systemic corticosteroids. The prevalence of testing positive for COVID-19 in patients using prednisone was 5.7% compared to 5.6% of patients using methylprednisolone (Chi-square P-value = 0.97), suggesting no significant difference in the prevalence on the two different main systemic corticosteroid formulations use. For inhaled corticosteroids, we exclude 10 patients out of 348 patients who used more than one inhaled corticosteroid formulations. Among the remaining 338 patients, 156 patients (46%) who received inhaled corticosteroids used fluticasone while 138 patients (41%) used budesonide, and 44 patients (13%) used other inhaled corticosteroids (24 patients used beclomethasone, 16 patients used mometasone, and 4 patients used ciclesonide). The prevalence of testing positive for COVID-19 in patients using fluticasone was 12.2% compared to 8.7% of patients using budesonide (Chi-square P-value = 0.33), suggesting no significant difference in the prevalence on the two different main inhaled corticosteroid formulations use. For commonly used biologics in asthma such as anti-IL5 and anti-IgE, we observed a COVID-19 prevalence of 8.3% in patients using anti-IL5 (2 out of 24) and in patients using anti-IgE 11.1% (2 out of 18) (Chi-square P-value = 0.76), suggesting no difference in the prevalence on the two different biologics use. We performed analyses restricted to 708 patients (76% of the overall cohort) with recorded data on BMI, smoking status, and pack-years. When including these variables in the model, there was no significant association between any medication use and testing positive for COVID-19 in the overlap propensity score-weighted analysis. Conventional logistic regression analysis indicated that testing positive for COVID-19 was higher in males (OR 1.76; 95% CI:1.01–3.08, e-Table 2), borderline higher in patients using inhaled corticosteroids (OR 1.76; 95% CI:1.00–3.07, e-Table 2), borderline lower in those with chronic pulmonary diseases treated with systemic corticosteroids (OR 0.46; 95% CI: 0.21–1.00; e-Table 3), and significantly lower in asthma or COPD patients (OR 0.38; 95% CI: 0.16–0.91; e-Table 4). Full results were shown in the Supplement.

We performed a sensitivity analysis by re-analyzing data following the same protocol, restricted to patients whose COVID-19 testing was performed only at the NJH laboratory, which generated similar results (data not shown).

4. Discussion

Since corticosteroids are often used as the primary treatment for many patients with underlying chronic diseases, we used the rigorous method of overlap propensity score weighting to account for confounding by indications. In summary, being treated with systemic corticosteroids was associated with a decrease in the likelihood of testing positive for COVID-19, especially in patients with chronic pulmonary disease or airway diseases (asthma or COPD). However, using inhaled corticosteroids was not associated with a change in the likelihood of testing positive for COVID-19 in our study. We also observed a lower likelihood of testing positive for COVID-19 in patients with chronic pulmonary disease and a higher likelihood in males adjusting for other covariates.

The prevalence of positive COVID-19 tests in our study cohort (residents from Colorado) during the study period was 12.1%, which is similar to the 10.7% prevalence of COVID-19 in the state of Colorado as of June 23, 2020 (https://covid19.colorado.gov/; P-value = 0.14). While we do not know if the indications for the COVID-19 testing were similar between our cohort and other Colorado residents, these rates suggest that we did not have over or under testing at NJH.

Reports of the effect of inhaled corticosteroids on COVID-19 susceptibility are limited to date [4]. Inhaled corticosteroids have been associated with a higher risk for respiratory tract infections [12,13] and a higher prevalence of pneumonia in patients with asthma or COPD [14,15]. Interestingly, a recent study of asthma patients showed that inhaled corticosteroids may reduce *ACE2* and *TMPRSS2* gene expression in sputum cells which might suggest a protective effect on COVID-19 susceptibility since these molecules play important roles in SARS-CoV-2 infectivity [16]. However, there was no direct analysis of gene expression data and COVID-19 susceptibility as the study population was enrolled before the COVID-19 pandemic. Several *in vitro* studies [17,18] have shown that the inhaled corticosteroid ciclesonide may have antiviral effects on coronavirus, which spurred several ongoing clinical trials (www.clinicaltrials.gov). Our results did not identify either a beneficial or an adverse effect of inhaled corticosteroid on COVID-19 susceptibility, after controlling for other comorbidities and medication use, in either the entire cohort, those with chronic pulmonary diseases, or those with airway diseases. Although our findings may be limited due to power, they suggest that the continuation of inhaled corticosteroids for their original indication may not increase the risk of SARS-CoV-2 infection during the COVID-19 pandemic.

Most studies to date have evaluated the effectiveness of corticosteroids as treatment for COVID-19, with the most recent (RECOVERY) showing that dexamethasone reduced mortality by up to 30% in those with severe disease (ventilated patients) [6,7]. Another study in patients with inflammatory bowel diseases found that preexistent use of systemic corticosteroids for inflammatory bowel diseases was associated with severe COVID-19 infection [19]. However, those studies were not designed to explore the association between systemic corticosteroid and COVID-19 susceptibility. There are, to our knowledge, no studies that have reported this association. A recent editorial cautioned that patients who are taking corticosteroids may have increased susceptibility to COVID-19, although our study suggests the contrary [20]. Guidelines from the American College of Rheumatology, based on expert opinion, recommend using the lowest effective dose of corticosteroids to control the underlying rheumatic disease [21]. Our study offers evidence that individuals on systemic corticosteroid treatment may have reduced COVID-19 susceptibility, especially those with airway diseases. Systemic corticosteroids might play an important role in preventing SARS-CoV-2 cellular uptake or they may render infected individuals asymptomatic since we only tested individuals presenting with symptoms suggestive of respiratory viral illness.

Our study showed that male gender is associated with a higher likelihood of testing positive for COVID-19. A previous study in six European countries indicated that sex differences in COVID-19 susceptibility varied with age, with a higher risk of males being noted in those above 50-years old [22]. This association may also be related to gender-specific (e.g. occupational) exposure risks. Emerging evidence supports that male gender is also associated with higher COVID-19 mortality, with a 1.7 times higher average case fatality rate in males than in females, based on sex-disaggregated data from 37 countries [23].

Our study revealed that patients with chronic pulmonary diseases have a lower prevalence of COVID-19 test positivity. This finding is consistent with observations in a recent editorial [3], implicating the possibility of underdiagnosed (missed) chronic pulmonary disease diagnoses in their population. However, this is unlikely in our cohort, where the prevalence of chronic pulmonary diseases was high (66%) with the population drawn from a health care center dedicated to respiratory conditions. Another explanation proposed in the above editorial was that medications used by patients with chronic pulmonary diseases may reduce COVID-19 susceptibility; this is in fact supported by our study. Interestingly, in our study, the protective effect of corticosteroids on COVID-19 susceptibility in patients with chronic pulmonary diseases remained significant even after adjusting for medication use and other comorbidities. This suggests that individuals with chronic pulmonary diseases may exhibit immunological differences that are protective against SARS-CoV-2 infection. Another potential explanation that seems more likely is that individuals with chronic pulmonary disease are more likely to practice preventive measures such as social distancing or face mask usage more effectively than those without chronic pulmonary disease. Besides, the difference in the prevalence may be related to the disproportionately higher numbers of COPD/asthma patients in our study cohort. Given this limitation and the fact that this outcome was not the primary focus of the study design, further investigations are needed to determine the interaction between underlying comorbidities and COVID-19 risk.

We did not find a significant association between smoking and COVID-19 susceptibility in our subset of patients who had documented smoking history. This result may be due to the limited power of the smaller sample size (76% of the original cohort). Two recent studies [24,25] of human airway epithelium have shown that ACE2 expression is induced by active smoking and therefore may increase the susceptibility of smokers to SARS-CoV-2. In turn, a recent systemic meta-analysis indicated that current smokers had reduced the risk of SARS-CoV-2 infection, but increased risk of COVID-19 severity. However, the studies included in the meta-analysis only met “fair quality” criteria [26], suggestings that additional research is needed to help define the role of cigarette smoking on COVID-19 susceptibility and outcomes.

No association between ACE/ARBs and COVID-19 susceptibility was found in our study which is consistent with a recent large cohort study (18,472 patients) [27]. We also did not find an association between immunosuppressants (besides corticosteroid), hydroxychloroquine, or biologics/JAK2 inhibitors and COVID-19 susceptibility. Although this may be due to the smaller numbers, the results are consistent with a recent review article [28] in which morbidity and mortality rates in immunosuppressed patients did not differ from the general population. Current best practice guidelines worldwide recommend the continuation of immunosuppression treatment in patients requiring it for control of the underlying disease [28]. However, all current studies on this topic, including ours, are small, indicating that larger cohort studies of patients with diverse chronic diseases are needed.

There are certain limitations to our study. First, confounding factors are the main source of bias for any observational study. To minimize this bias, we used the overlap propensity score-weighted analysis. However, like all propensity score methods, overlap weighting cannot adjust for unmeasured variables and therefore, bias may still exist. As an example, if patients with chronic lung disease on corticosteroids were more like to self-isolate than other patient populations this might confound our studies as it could not be addressed. We think that this is unlikely as we made these recommendations to all of our patients. Second, our study population may not be generalizable to the general population as we have a well-defined population of patients with chronic pulmonary diseases, and potentially even those with more severe disease. Also, our study focuses on the outpatient setting and did not have information on hospitalization to address the severity of the infection. This limitation may explain why we did not find diabetes as a risk factor for COVID-19 susceptibility. However, our findings may be applied to patients with chronic pulmonary diseases Third, we do not have sufficient information about the dosage or duration of medication use and cannot assess how those might have affected the likelihood of testing positive for COVID-19 Fourth, the mean age of our study population is relatively young (53 years old) which may not be representative of the total population. This may be an important confounder and limitation to our study results since age is an independent factor of COVID severity and mortality [29]. Finally, similar to other electronic medical research, non-differential misclassification of binary variables may reduce the power of detecting a true association. Further studies including a larger population mixed with a variety of comorbidities and a detailed medical history and medication history assessment are needed.

5. Conclusions

To the best of our knowledge, this is the first report of the association between inhaled or systemic corticosteroid, diagnosis of chronic pulmonary diseases including airway diseases, and risk of testing positive for COVID-19. Our finding that systemic corticosteroids decreased COVID-19 susceptibility should be interpreted with caution due to the above-mentioned limitations. However, our study supports the recommendation that patients with chronic pulmonary diseases who have indications for either inhaled or systemic corticosteroid therapy should continue using them during the ongoing COVID-19 pandemic. Discontinuation of those medications for concern regarding COVID-19 risk may be unnecessary and detrimental, as corticosteroids may be essential to control asthma, COPD, and other chronic pulmonary diseases such as sarcoidosis, and autoimmune lung diseases.

Author contributions

S.L. had full access to all data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. S.L., T.E.F, I.P., and L.A.M. wrote the manuscript. S.L. developed the analysis plan and T.E.F. supervised S.L. with the data analysis. S.L. and L.A.M. designed the study. T.E.F, I.P., and L.A.M. supervised the

research.

Primary funding source

This work was supported by National Jewish Health, United States [Wollowick Chair for COPD Research (to IP)]; [Department of Medicine and Division of Environmental and Occupational Health Sciences] (to SL and LM).

Prior presentations

None.

Declaration of competing interest

All authors report no conflicts of interest related to this work.

Acknowledgments

The authors would like to thank Joy Zimmer for help with the data query and Briana Barkes for help with the institutional review board application.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106275.

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