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Authors

Miller, D Claire
Sun, Yuwei
Chen, Evan M
et al.

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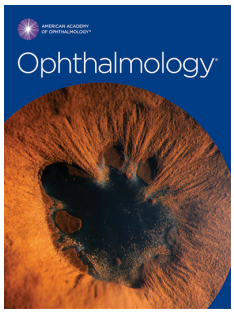

The association between non-infectious uveitis and COVID-19 outcomes: an analysis of United States claims-based data

D. Claire Miller, MS, Yuwei Sun, MS, Evan M. Chen, MD, Benjamin F. Arnold, PhD, Nisha R. Acharya, MD, MS

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Authors: D. Claire Miller, MS;[1] Yuwei Sun, MS;[1] Evan M. Chen, MD;[1,2] Benjamin F. Arnold, PhD;[1,2] Nisha R. Acharya, MD, MS[1,2,3,4]

Affiliations:

[1] F.I. Proctor Foundation, University of California, San Francisco, California

[2] Department of Ophthalmology, University of California, San Francisco, California

[3] Department of Epidemiology and Biostatistics, University of California, San Francisco, California

[4] OptumLabs Visiting Fellow, Eden Prairie, MN

Correspondence:

Nisha R. Acharya

490 Illinois Street, 2nd floor, San Francisco CA 94158

Email: nisha.acharya@ucsf.edu

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Address for reprints: 490 Illinois Street, 2nd floor, San Francisco, CA 94158

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Abstract

Purpose*:* To identify if non-infectious uveitis (NIU) is associated with a greater risk of coronavirus disease 2019 (COVID-19) infection, hospitalization, and death.

Design*:* A retrospective cohort study from January 20, 2020 to December 31, 2020 using a national claims-based database.

Participants: Enrollees who had continuous enrollment with both medical and pharmacy coverage for three years prior to January 20, 2020. Patients with an NIU diagnosis within three years of the start of the study were included in the NIU cohort. Those with infectious uveitis codes or new NIU diagnoses during the risk period were excluded.

Methods: Cox proportional hazards models were used to identify unadjusted hazard ratios as well as adjusted hazard ratios for all covariates for each outcome measure. Adjusted models accounted for patient demographics, health status, and immunosuppressive medication use during the risk period.

Main Outcome Measures: Rates of COVID-19 infection, COVID-19-related hospitalization, and COVID-19-related in-hospital death identified with International Classification of Disease 10th revision codes.

Results: This study included 5,806,227 patients of which 29,869 (0.5%) had a diagnosis of NIU. On unadjusted analysis, patients with NIU had a higher rate of COVID-19 infection (5.7% vs. 4.2%, p<0.001), COVID-19-related hospitalization (1.2% vs. 0.6%, p<0.001) and COVID-19-related death (0.3% vs. 0.1%, p<0.001). However, in adjusted models, NIU was not associated with a greater risk of COVID-19 infection (hazard ratio [HR] = 1.05; 95% confidence interval [CI]: 1.00 – 1.10; p = 0.04), hospitalization (HR = 0.98; 95% CI: 0.88 – 1.09; p = 0.67) or death (HR = 0.90, 95% CI: 0.72 – 1.13, p = 0.37). Use of systemic corticosteroids was significantly associated with higher risk of COVID-19 infection, hospitalization, and death.

Conclusions: Patients with NIU were significantly more likely to be infected with COVID-19 and experience severe disease outcomes. However, this association was due to the demographics, comorbidities, and medications of patients with NIU, rather than to NIU alone. Patients utilizing systemic corticosteroids were significantly more likely to be infected with COVID-19 and were at greater risk of hospitalization and in-hospital death. Additional investigation is necessary to identify the impact of corticosteroid exposure on COVID-19-related outcomes.

Introduction

Since the advent of the coronavirus disease 2019 (COVID-19), a major public health goal has been to protect individuals at highest risk of infection. In light of pre-existing literature indicating that select inflammatory diseases are associated with greater rates of infection,[1–3] there was concern that patients with inflammatory conditions may constitute a high-risk group for COVID-19. To date, studies have yielded mixed findings even among those examining the same disease. Reports from the initial phase of the pandemic found that patients with rheumatic disease had higher rates of COVID-19-related hospitalization and were more likely to require ventilation,[4–6] while more recent long-term studies have indicated no difference in outcomes after controlling for comorbidities.[7]

Non-infectious uveitis (NIU) comprises a spectrum of ocular inflammatory conditions that can manifest in isolation or in the context of other systemic inflammatory diseases. Thus, during the early phase of the pandemic, concerns arose that uveitis may similarly increase COVID-19 susceptibility or worsen the severity of infection due to underlying dysregulated immune function.[3,8–10] Uveitis patients also frequently require in-person care to assess disease status and modify treatment regimens, increasing the risk of exposure.

Currently, COVID-19-specific evidence-based uveitis management guidelines have not been established due to limited understanding of the relationship between ocular inflammatory conditions and COVID-19-related outcomes. Furthermore, existing studies on this topic have been limited in sample size and have mostly focused on uveitis management during the pandemic. Therefore, the purpose of this study was to determine if NIU confers a greater risk for COVID-19 infection, severe disease course or death.

Methods

Study Design

A retrospective cohort study was conducted using a de-identified healthcare claims database, OptumLabs® Data Warehouse (OLDW; OptumLabs®, Eden Prairie, MN).[11] OLDW contains de-identified, longitudinal health information on enrollees, representing a diverse mixture of ages, ethnicities and geographical regions across the United States. The claims data in OLDW includes medical and pharmacy claims, laboratory results, and enrollment records for Medicare Advantage and commercial insurance enrollees of all ages. OLDW does not contain data for patients who only have original Medicare (parts A and B), Medicaid, or who are Veterans Administration enrollees.

To be eligible for inclusion in the study, enrollees were required to be continuously enrolled with both medical and pharmacy coverage for three years (1095 days) prior to and on January 20, 2020. This date was chosen as the index date and start of the risk period for all patients because this was the date of the first known COVID-19 case in the US. Non-infectious uveitis (NIU) patients were identified by an International Classification of Disease 10th revision (ICD-10) code appearing at any time during the lookback period of continuous enrollment from January 20, 2017 through January 20, 2020. The NIU diagnosis could have been incident or prevalent during this lookback period. All codes utilized to identify NIU are included in eBox 1. Patients without any of these codes in the three-year lookback period were considered to not have a prior history of NIU. Individuals with an infectious uveitis ICD-10 code (eBox 1) at any time during the three-year lookback period were excluded from the study. Individuals who were newly diagnosed with NIU (no NIU ICD-10 codes in the lookback period but an NIU ICD-10 code during the risk period) were also excluded from the study.

COVID-19-related outcomes were assessed from January 20, 2020 through December 31, 2020. Outcomes of interest included COVID-19 infection, COVID-19 hospitalization, and COVID-19-related in-hospital death. COVID-19 infection was identified using ICD-10 codes B97.29 (other coronavirus as the cause of diseases classified elsewhere; used before 4/1/2020) or U07.1 (COVID-19 infection; used on and after 4/1/2020) in any type of encounter,[12] or a

positive polymerase chain reaction (PCR) lab test during the study period. COVID-19 hospitalization was identified by ICD-10 codes B97.29 or U07.1 in any position associated with an inpatient encounter during the study period. In-hospital mortality during the study period was determined based on discharge status codes. The mortality data also included additional levels of de-identification such that a death could not be attributed to a specific claim or cause; however, deaths in patients with medical claims including ICD-10 codes B97.29 or U07.1 that appeared within 30 days prior to the death date were classified as COVID-19 deaths.

Baseline covariates considered as potential confounders included sex (female, male, unknown), age in 2020, years of continuous enrollment, race/ethnicity (Asian, black, Hispanic, white, other/multiple races/unknown), homeownership (probable homeowner, probable renter, unknown), region (Midwest, Northeast, South, West, other/unknown), smoking status (never smoker, current/former smoker, unknown), and presence or absence of comorbidities in the one year prior to the index date based on ICD-10 codes. Comorbidities were chosen based on the risk factors for severe COVID-19 illness reported by the Centers for Disease Control and Prevention (CDC) as of February 2021 (eBox 2).[13] Use of systemic immunosuppressive medication was identified during the risk period and categorized into the following groups: systemic corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs), tumor necrosis factor alpha (TNF-α) inhibitors, interleukin-6 (IL-6) inhibitors, other biologic immunosuppressive therapies, and other non-biologic immunosuppressive drugs that do not fit into previous categories. Hydroxychloroquine was not included in the analysis to avoid introducing confounding by indication. Medication use was determined by text search of drug names in pharmacy claims, with one or more fills during the risk period considered active use of that medication. Generic names of medications and routes used to search for prescriptions and their categorizations are listed in eBox 3.

Statistical Analysis

Baseline covariates, characteristics of NIU patients, and immunosuppressive medication use during the risk period were summarized using descriptive statistics. Unadjusted hazard ratios (HR) were estimated for each variable and COVID-19 outcome (infection, hospitalization, in-hospital death) using Cox proportional hazards models. Adjusted hazard ratios for each outcome were also estimated using Cox proportional hazards models to compare patients with NIU to those without NIU. Each adjusted model was adjusted for baseline demographics, comorbidities, and immunosuppressive medication use during the risk period. As a sensitivity analysis, immunosuppressive medications were excluded from models to identify if they might mediate, and thus potentially mask, the effect of NIU on COVID-19 outcomes. A subgroup adjusted analysis was performed by age group (under 50 vs. 50 years of age and over) for each COVID-19 outcome to understand if the effect of NIU may differ in younger individuals versus older individuals. These models were similarly adjusted for demographics, comorbidities, and immunosuppressive medications.

COVID-19 infection and hospitalization dates were recorded as the first date in which the previously outlined outcome criteria were met. For example, if a patient tested positive for COVID-19 more than once, the date of the first positive test was recorded as the event date. Likewise, if a patient was hospitalized more than once with COVID-19, the date of the first hospitalization was recorded as the event date. In each model, patients could be censored at disenrollment from the medical plan, death unrelated to COVID-19, or the end of the risk period (12/31/2020). A patient was considered to have experienced the event if their event date occurred before any of the other censoring events. Time to event or censoring was calculated as days from January 20, 2020. Proportional hazards assumptions were checked using plots of survival curves vs. time and Schoenfeld residual tests and plots.

Statistical analyses were performed in R (Version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). P-values less than 0.005 were considered statistically significant to be conservative. This study was approved by the

Institutional Review Board of the University of California, San Francisco and was conducted in adherence with the tenets of the Declaration of Helsinki.

Results

Characteristics of Study Population

A total of 5 806 227 patients were included in the analysis, and 29 869 of those had NIU (0.5%). Table 1 summarizes the baseline characteristics of the cohort by NIU status. The mean age of patients in the overall cohort in the year 2020 was 50.3 years (standard deviation [SD] = 23.5), and the mean age of patients with NIU was 65.2 years (SD = 17.4). Females comprised a larger proportion of patients with NIU compared to those without NIU (60.7% vs. 51.4%). Patients with NIU were also more likely to be Black, probable homeowners, and current or former smokers. Approximately 20% of patients with NIU had another autoimmune disease, and almost all other comorbidities were more prevalent in the NIU group at baseline (Table 1).

Overall, 676 927 patients (11.7%) were prescribed at least one of the six immunosuppressive drug categories during the risk period up to COVID-19 infection or censoring. Table 2 summarizes the immunosuppressive medications taken during the risk period up to infection date or censoring by NIU status. Systemic corticosteroids were the most prescribed immunosuppressive treatments during this period, with 18.0% of NIU patients and 10.7% of patients without NIU taking these drugs. NIU patients were also prescribed the other five drug categories more frequently than patients without NIU (Table 2).

Factors associated with COVID-19 infection

There were 1 708 cases of COVID-19 infection in patients with NIU compared to 258 388 in patients without NIU, corresponding to cumulative incidence of 5.7% and 4.5%, respectively. The unadjusted hazard ratio for COVID-19 infection comparing patients with NIU to patients without NIU was 1.25 (95% CI: 1.19 – 1.31; $p<0.001$) (Table 3). Age, Black race,

Hispanic ethnicity, current or former smoking, and all other comorbidities were also associated with increased hazard of infection in the unadjusted analyses (Table 3). By medication category, use of corticosteroids, DMARDs, TNF-α inhibitors, other biologics, and other immunosuppressive drugs conferred a higher unadjusted hazard of COVID-19 infection.

However, after adjusting for demographic, comorbid, and treatment covariates, NIU was not significantly associated with COVID-19 infection (HR = 1.05; 95% CI: 1.00 – 1.10; p = 0.04) (Table 4). Systemic corticosteroid use remained significantly associated with COVID-19 infection after adjustment (HR = 1.19; 95% CI: 1.18 – 1.20; p<0.001). TNF-α inhibitors were also significantly associated with COVID-19 infection after adjustment, while DMARDs and other immunosuppressive drugs were associated with decreased hazard of infection in the full model. In the sensitivity analysis removing medication data to assess mediation, the estimated hazard of infection was similar to that in the full model (Table 4).

Factors associated with COVID-19-related hospitalization

There were 363 NIU patients hospitalized with COVID-19 during the risk period, compared to 35 958 patients without NIU, corresponding to cumulative incidence of 1.2% and 0.6%, respectively. In the unadjusted analysis, the hazard ratio of COVID-19 hospitalization comparing patients with NIU to those without NIU was 1.91 (95% CI: 1.72 – 2.12; p<0.001) (Figure 1 and Supplemental Table 5). Many factors associated with greater risk of COVID-19 infection including most comorbidities, age, Black race or Hispanic ethnicity, current or former smoking and use of any immunosuppressive medication, were also associated with increased hazard of hospitalization in the unadjusted analyses. In addition, male gender was also associated with COVID-19 hospitalization (Figure 1 and Supplemental Table 5).

In the adjusted analysis, NIU was not significantly associated with an increased hazard of COVID-19 hospitalization (HR = 0.98; 95% CI: 0.88 – 1.09; p = 0.67) (Figure 1 and

Supplemental Table 6). Other comorbidities, including autoimmune disease, cardiovascular disease, and diabetes, as well as age, male gender, and Black or Hispanic race/ethnicity remained significantly associated with increased hazard of hospitalization after adjustment (Supplemental Table 6). Patients taking systemic corticosteroids had a 57.1% increase in their hazard of hospitalization after adjustment (95% CI: 53.1% - 61.1%; p<0.001), and those taking DMARDs had a 14.7% increase (95% CI: 6.6%, 23.5%, p = p<0.001). The estimated hazard ratio for NIU did not change substantially when the immunosuppressive medications were removed from the model (Supplemental Table 6).

Factors associated with COVID-19-related in-hospital death

Among patients with NIU, 75 had a COVID-19 related death in an inpatient facility compared to 7 518 in the group without NIU, corresponding to cumulative incidence of 0.3% and 0.1%, respectively. The unadjusted hazard ratio for in-hospital COVID-19 death among patients with NIU compared to those without NIU was 1.88 (95% CI: 1.50 – 2.37; p<0.001) (Figure 2 and Supplemental Table 7). In other unadjusted analyses, age, male gender, Black race, Hispanic ethnicity, current or former smoking and nearly all comorbid conditions also increased the hazard of in-hospital death (Supplemental Table 7). Systemic corticosteroids, DMARDs, and other immunosuppressive drugs were all associated with in-hospital death in the unadjusted analyses (Figure 2 and Supplemental Table 7).

After adjusting for all other covariates, NIU was no longer associated with in-hospital COVID-19 death (HR = 0.90, 95% CI: 0.72 – 1.13, p = 0.37) (Figure 2 and Supplemental Table 8). Age, male gender, Black race, and Hispanic ethnicity remained significantly associated with increased hazard of in-hospital death after adjustment (Supplemental Table 8). Most comorbidities, including autoimmune disease, cardiovascular disease, hypertension, and chronic kidney disease also remained significant predictors of death. Use of systemic corticosteroids was associated with a 75.9% increase in hazard of death (95% CI: 66.7% -

85.6%; p<0.001) after adjusting for demographics and comorbidities, but no other immunosuppressive drugs had significant effects on the hazard of COVID-19 death after adjustment (Figure 2 and Supplemental Table 8). In the sensitivity analysis, the estimated hazard of in-hospital death for NIU patients was similar when the immunosuppressive drug categories were removed. However, for other conditions that often require immunosuppressive treatments, including autoimmune diseases, cancer, and solid organ transplantation, the estimated hazards of in-hospital death increased substantially when the medications were removed from the model (Supplemental Table 8).

Subgroup analysis by age

There were 2 641 914 patients under age 50, 5 488 of whom had NIU (0.2%). There were 3 164 310 patients age 50 and older, 24 381 of whom had NIU (0.8%). In the subgroup of patients under age 50, rates of COVID-19 infection and hospitalization were slightly higher in patients with NIU compared to patients without NIU. There were no COVID-19 in-hospital deaths in patients with NIU in the subgroup under age 50. After adjusting for demographics, comorbidities, and immunosuppressive medication use, NIU was not associated with COVID-19 infection, hospitalization, or in-hospital death in the under age 50 subgroup or the age 50 and over subgroup (Supplemental Table 9).

Discussion

Patients with NIU had higher unadjusted hazards of COVID-19 infection, hospitalization, and in-hospital death. However, after adjusting for demographics and comorbidities, there was no significant difference in the risk of COVID-19 infection, hospitalization, or in-hospital death between patients with and without NIU. These results indicate that the higher rates of COVID-19 infection and severe disease in uveitis patients may be explained by the characteristics of patients with NIU, rather than a history of NIU alone. Indeed, age, gender, race/ethnicity, and

comorbidities such as autoimmune disease, cardiovascular disease, diabetes, and chronic kidney disease were all strongly associated with COVID-19 hospitalization and in-hospital death in this analysis. These characteristics are known risk factors for severe COVID-19 outcomes.[14,15]

The removal of immunosuppressive medications from regression models in the sensitivity analysis did not impact the estimates of hazards of the three COVID-19 outcomes for patients with NIU, suggesting that the use of immunosuppressive medications among patients with NIU did not mediate the association between NIU and COVID-19 outcomes. However, for patients with autoimmune disease, cancer, or solid organ transplants, immunosuppressive medications may act as partial mediators in the relationship between the disease and COVID-19 in-hospital death.

In our analysis of a national-level claims database, the cumulative incidence of COVID-19 among patients with NIU was 5.7%, which is in the range of reported incidence among previous international studies with more limited cohorts. In a report of 59 patients with uveitis in Saudi Arabia, 15.3% tested positive for COVID-19, but none developed any symptoms during follow-up or required hospitalization.[16] In Spain, Fanlo et al. surveyed patients with uveitis associated with a systemic autoimmune disease in April and May of 2020. Of 28 patients with uveitis, half reported symptoms of possible COVID-19 infection, but only two were tested and just one tested positive.[17] A study in Italy monitored 125 children with juvenile idiopathic arthritis-associated uveitis during the initial lockdown in March 2020, and there were no known cases of infection.[18] As in all estimates of COVID-19 incidence, our analysis likely underestimates the true incidence of COVID-19 infection among patients with NIU due to lack of diagnostic testing. Additionally, patients with NIU enrolled in commercial and Medicare Advantage plans may have different rates of COVID-19 infection than a population with different insurance coverage or lack of insurance coverage.

Independent of uveitis or other autoimmune disease, this study found that use of systemic corticosteroids during the risk period was associated with significantly higher hazard of infection, hospitalization, and death with COVID-19. Use of DMARDs during the risk period was associated with significantly lower hazard of infection, but higher hazard of hospitalization after adjustment. While TNF-α inhibitors and other non-biologic treatments were associated with higher hazard of infection, no other immunosuppressive treatment categories had a significant impact on the hazard of hospitalization or death. Other studies have identified systemic corticosteroids as a risk factor for COVID-19 hospitalization and death both in the general population[19] and among cohorts with existing autoimmune disease,[20,21] though conflicting studies have found no effect of corticosteroids or other immunosuppressive treatments on the risk of severe COVID-19.[22,23] Among studies that looked at TNF-α inhibitors or DMARDs specifically, several found no impact on COVID-19 hospitalization or severe outcomes,[19,20] while others found a protective effect of TNF-α inhibitors against hospitalization for COVID-19.[21,22]

Some studies investigating autoimmune disease and immunosuppressive therapy as risk factors for COVID-19 infection and severe outcomes included patients with uveitis, but the number of patients with uveitis was too small to draw conclusions about uveitis as a risk factor itself.[22,24,25] Our study provides the first estimates of the hazard of COVID-19 infection, hospitalization, and death in patients with NIU, as well as estimates of the cumulative incidence of these outcomes in NIU patients during 2020. In addition, this study provides novel information on whether patients with NIU carry a higher risk of severe COVID-19 outcomes compared to the general population. Our large sample size allowed observation of rare events such as hospitalization and death, and allowed for adjustment of many potential confounders, giving clearer insight into the effects of uveitis independent of other COVID-19 risk factors.

The results of this study have several implications for patients with NIU as well as for those receiving systemic corticosteroid therapy. Immunosuppressed patients, including those with NIU,

may not be as protected by COVID-19 vaccination given their immune status,[26] so mitigating their risk of infection remains an important issue. We found that patients on systemic corticosteroid therapy experience COVID-19 hospitalization and death at higher rates than the general population, raising concerns about the use of systemic corticosteroid therapy to treat active inflammation during the pandemic. It is unknown if the association we observed is dose or duration dependent, and further research is necessary to elucidate the impact of systemic corticosteroid use on COVID-19 infection susceptibility and adverse outcomes. Given our findings, future uveitis treatment guidelines may want to encourage physicians caring for patients with NIU, particularly those on systemic corticosteroids, to provide counseling about possible increased risk and to encourage infection mitigation efforts. Local corticosteroid therapies may be considered as an alternative, although this carries some risks of ocular adverse events.

There are several limitations to this study. First, there is limited granularity inherent to healthcare claims data which could contribute to misclassification of NIU patients vs. non-NIU patients and COVID-19 outcomes, particularly infection if testing was incompletely reported in the claims database. However, the cumulative incidence of infection, hospitalization, and death up to 12/31/2020 reported by both the CDC and Johns Hopkins University are very similar to the rates reported in this study.[27,28] Second, we could not obtain data on deaths occurring outside of a healthcare facility, so it is possible that not all deaths related to COVID-19 (or other causes) were captured. Knowledge of COVID-19 pathophysiology and treatment significantly improved over the study's risk period. It is possible that over the course of the study, trends in COVID-19 management differentially impacted outcomes among NIU and non-NIU patients. Additionally, OLDW does not include individuals who are enrolled in basic Medicare plans, Medicaid, or who are uninsured, so the cohort analyzed in this study may represent a more economically advantaged population in the United States. We made efforts to adjust for socioeconomic factors in the analysis; however, we did not have access to socioeconomic variables other than homeownership and race/ethnicity in the database. Other measures of socioeconomic status

like education and occupation, which could impact risk for COVID-19, were not available in the database. Lastly, the inclusion of Medicare Advantage enrollees as well as the strict 3 year continuous enrollment requirement used for this study may skew the study population to be older than the overall US population. However, the age distribution of the NIU group is comparable to that reported in other US claims-based studies on NIU incidence and prevalence.[29] While the older age of the cohort could increase crude rates of COVID-19 cases and severe illness, this should not greatly impact the ascertainment of risk factors in the adjusted analyses, which adjusted for age and known comorbidity risk factors for COVID-19. We also conducted a subgroup analysis of patients under age 50 vs. age 50 and over to understand if a younger group of NIU patients may have higher risk of severe COVID-19 outcomes, and found similar results in the younger and older groups. Overall, the sheer size of the population included in OLDW, as well as the diversity in geography, ethnicity, and age make this a much more generalizable sample than other alternatives.

In the US and abroad, many patients remain unvaccinated and susceptible to COVID-19, and there remains potential for resurgence of the virus. In this study, patients with NIU experienced COVID-19 infection, hospitalization, and death at significantly greater rates than patients without NIU. Increased risk is likely due to the demographic characteristics and medical conditions of patients with NIU, rather than NIU itself. Furthermore, patients treated with systemic corticosteroid therapy may be at increased risk of infection and severe COVID-19 outcomes. Future studies are needed to evaluate the impact of the level of corticosteroid exposure on COVID-19 risk.

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Table 1. Baseline characteristics of cohort by uveitis status (N=5,806,227)

Characteristic	No NIU N=5,776,358 (99.5%)	NIU N=29,869 (0.5%)	All N=5,806,227 (100.0%)
Age (years)			
Mean (SD)	50.2 (23.5)	65.2 (17.4)	50.3 (23.5)
Median [Q1, Q3]	53.0 [32.0, 71.0]	70.0 [56.0, 77.0]	53.0 [32.0, 71.0]
Continuous enrollment (years)			
Mean (SD)	6.6 (3.8)	6.5 (3.7)	6.6 (3.8)
Median [Q1, Q3]	5.1 [4.0, 8.1]	5.1 [4.1, 8.1]	5.1 [4.0, 8.1]
Gender			
Female	2,968,650 (51.4%)	18,128 (60.7%)	2,986,778 (51.4%)
Male	2,804,701 (48.6%)	11,705 (39.2%)	2,816,406 (48.5%)
Unknown	3,007 (0.1%)	36 (0.1%)	3,043 (0.1%)
Race			
Asian	298,833 (5.2%)	1,228 (4.1%)	300,061 (5.2%)
Black	581,630 (10.1%)	5,667 (19.0%)	587,297 (10.1%)
Hispanic	673,319 (11.7%)	2,927 (9.8%)	676,246 (11.6%)
White	3,719,784 (64.4%)	17,912 (60.0%)	3,737,696 (64.4%)
Other/Unknown	502,792 (8.7%)	2,135 (7.1%)	504,927 (8.7%)
Region			
Midwest	1,528,179 (26.5%)	7,053 (23.6%)	1,535,232 (26.4%)
Northeast	635,989 (11.0%)	4,387 (14.7%)	640,376 (11.0%)
South	2,488,756 (43.1%)	14,750 (49.4%)	2,503,506 (43.1%)
West	944,533 (16.4%)	3,620 (12.1%)	948,153 (16.3%)
Other/Unknown	178,901 (3.1%)	59 (0.2%)	178,960 (3.1%)
Homeownership			
Probable homeowner	3,959,324 (68.5%)	22,037 (73.8%)	3,981,361 (68.6%)
Probable renter	440,749 (7.6%)	2,119 (7.1%)	442,868 (7.6%)
Unknown	1,376,285 (23.8%)	5,713 (19.1%)	1,381,998 (23.8%)
Smoking status (baseline or risk period)			
Never	844,880 (14.6%)	6,183 (20.7%)	851,063 (14.7%)
Current or former	931,095 (16.1%)	7,382 (24.7%)	938,477 (16.2%)
Unknown	4,000,383 (69.3%)	16,304 (54.6%)	4,016,687 (69.2%)
Asthma	324,875 (5.6%)	2,745 (9.2%)	327,620 (5.6%)
Autoimmune disease	419,741 (7.3%)	6,013 (20.1%)	425,754 (7.3%)
Cancer	311,186 (5.4%)	3,131 (10.5%)	314,317 (5.4%)
Cardiovascular disease	605,002 (10.5%)	6,003 (20.1%)	611,005 (10.5%)
Cerebrovascular disease	272,104 (4.7%)	3,102 (10.4%)	275,206 (4.7%)
Chronic kidney disease	440,518 (7.6%)	4,893 (16.4%)	445,411 (7.7%)
Chronic lung disease	437,757 (7.6%)	4,315 (14.4%)	442,072 (7.6%)
Diabetes (any type)	841,908 (14.6%)	8,652 (29.0%)	850,560 (14.6%)
Hemoglobin disease	8,476 (0.1%)	121 (0.4%)	8,597 (0.1%)

HIV/AIDS	11,916 (0.2%)	107 (0.4%)	12,023 (0.2%)
Hypertension	1,998,776 (34.6%)	18,145 (60.7%)	2,016,921 (34.7%)
Liver disease	11,030 (0.2%)	102 (0.3%)	11,132 (0.2%)
Neurologic disease	230,073 (4.0%)	2,100 (7.0%)	232,173 (4.0%)
Obesity	623,910 (10.8%)	4,970 (16.6%)	628,880 (10.8%)
Solid organ transplantation	15,753 (0.3%)	355 (1.2%)	16,108 (0.3%)
Pregnancy (risk period)	62,129 (1.1%)	180 (0.6%)	62,309 (1.1%)

<11 patients were missing age. NIU=non-infectious uveitis; HIV=human immunodeficiency virus; AIDS=acquired immunodeficiency syndrome.

Table 2. Immunosuppressive drug prescriptions during the risk period up to COVID-19 infection outcome by uveitis status (N=5,806,227)

Immunosuppressive drug category	**No NIU (N=5,776,358)**	**NIU (N=29,869)**	**All (N=5,806,227)**
Systemic corticosteroids	617,953 (10.7%)	5,369 (18.0%)	623,322 (10.7%)
DMARDs	51,208 (0.9%)	1,347 (4.5%)	52,555 (0.9%)
TNF-a inhibitors	15,891 (0.3%)	758 (2.5%)	16,649 (0.3%)
IL-6 inhibitors	734 (0.01%)	26 (0.1%)	760 (0.01%)
Other biologic therapies	13,488 (0.2%)	192 (0.6%)	13,680 (0.2%)
Other immunosuppressive drugs	20,346 (0.4%)	360 (1.2%)	20,706 (0.4%)

Frequencies and percentages reflect the proportion of patients who filled one or more prescriptions during risk period up to COVID-19 infection outcome date (results differ slightly for hospitalization and death outcomes). NIU=non-infectious uveitis; DMARDs=disease-modifying anti-rheumatic drugs; TNF-alpha=tumor necrosis factor alpha; IL-6=interleukin 6.

Table 3. Unadjusted analyses of associations with COVID-19 infection (N=5,806,227)

	No COVID-19 Infection N = 5,546,131	COVID-19 Infection N = 260,096	Unadjusted analysis	
Variable	**N (%) or Mean (SD)**	**N (%) or Mean (SD)**	**Hazard Ratio (95% CI)**	**p-value**
Non-infectious uveitis	28,161 (0.5)	1,708 (0.7)	1.25 (1.19, 1.31)	<0.001
Age (years)	50.1 (23.5)	53.8 (22.2)	1.006 (1.005, 1.006)	<0.001
Continuous enrollment (years)	6.5 (3.8)	6.6 (3.8)	1.001 (1.000, 1.002)	0.30
Gender				
Female	2,848,089 (51.4)	138,689 (53.3)	Reference	
Male	2,695,085 (48.6)	121,321 (46.6)	0.94 (0.93, 0.94)	<0.001
Unknown	2,957 (0.05)	86 (0.03)	0.56 (0.45, 0.69)	<0.001
Race/ethnicity				
White	3,578,712 (64.5)	158,984 (61.1)	Reference	
Asian	292,676 (5.3)	7,385 (2.8)	0.60 (0.59, 0.62)	<0.001
Black	557,820 (10.1)	29,477 (11.3)	1.20 (1.18, 1.21)	<0.001
Hispanic	636,600 (11.5)	39,646 (15.2)	1.45 (1.43, 1.46)	<0.001
Other/Unknown	480,323 (8.7)	24,604 (9.5)	1.11 (1.10, 1.13)	<0.001
Region				
South	2,384,178 (43.0)	119,328 (45.9)	Reference	
Midwest	1,465,322 (26.4)	69,910 (26.9)	0.94 (0.94, 0.95)	<0.001
Northeast	603,354 (10.9)	37,022 (14.2)	1.22 (1.20, 1.23)	<0.001
West	914,564 (16.5)	33,589 (12.9)	0.77 (0.76, 0.78)	<0.001
Other/Unknown	178,713 (3.2)	247 (0.1)	0.03 (0.03, 0.04)	<0.001
Homeownership				
Probable homeowner	3,806,910 (68.6)	174,451 (67.1)	Reference	
Probable renter	421,650 (7.6)	21,218 (8.2)	1.15 (1.13, 1.17)	<0.001
Unknown	1,317,571 (23.8)	64,427 (24.8)	1.11 (1.10, 1.12)	<0.001
Smoking status				
Never smoker	805,248 (14.5)	45,815 (17.6)	Reference	
Current/former smoker	887,685 (16.0)	50,792 (19.5)	1.02 (1.01, 1.04)	<0.001
Unknown	3,853,198 (69.5)	163,489 (62.9)	0.79 (0.78, 0.79)	<0.001
Asthma	308,506 (5.6)	19,114 (7.4)	1.33 (1.31, 1.35)	<0.001
Autoimmune disease	400,567 (7.2)	25,187 (9.7)	1.34 (1.32, 1.36)	<0.001
Cancer	297,991 (5.4)	16,326 (6.3)	1.16 (1.14, 1.18)	<0.001
Cardiovascular disease	568,500 (10.3)	42,505 (16.3)	1.67 (1.65, 1.69)	<0.001
Cerebrovascular	255,328 (4.6)	19,878 (7.6)	1.69 (1.66, 1.71)	<0.001
Chronic kidney disease	413,847 (7.5)	31,564 (12.1)	1.67 (1.65, 1.69)	<0.001
Chronic lung disease	413,014 (7.5)	29,058 (11.2)	1.54 (1.53, 1.56)	<0.001
Diabetes	793,551 (14.3)	57,009 (21.9)	1.62 (1.61, 1.64)	<0.001
Hemoglobin disorder	8,087 (0.2)	510 (0.2)	1.32 (1.21, 1.44)	<0.001
HIV/AIDS	11,157 (0.2)	866 (0.3)	1.67 (1.56, 1.79)	<0.001
Hypertension	1,902,370 (34.3)	114,551 (44.0)	1.43 (1.42, 1.44)	<0.001
Liver disease	10,363 (0.2)	769 (0.3)	1.72 (1.60, 1.85)	<0.001
Neurologic disease	207,005 (3.7)	25,168 (9.7)	2.84 (2.81, 2.88)	<0.001

Obesity	588,969 (10.6)	39,911 (15.3)	1.48 (1.47, 1.50)	<0.001
Solid organ transplant	15,075 (0.3)	1,033 (0.4)	1.44 (1.35, 1.53)	<0.001
Pregnancy	58,723 (1.1)	3,586 (1.4)	1.30 (1.26, 1.34)	<0.001
Systemic corticosteroids	585,400 (10.6)	37,922 (14.6)	1.34 (1.33, 1.36)	<0.001
DMARDs	49,539 (0.9)	3,016 (1.2)	1.22 (1.18, 1.27)	<0.001
TNF-alpha inhibitors	15,731 (0.3)	918 (0.4)	1.20 (1.13, 1.28)	<0.001
IL-6 inhibitors	718 (0.01)	42 (0.02)	1.18 (0.87, 1.60)	0.28
Other biologics	12,896 (0.2)	784 (0.3)	1.24 (1.16, 1.33)	<0.001
Other immunosuppressive drugs	19,496 (0.4)	1,210 (0.5)	1.25 (1.18, 1.33)	<0.001

P-values calculated from Cox proportional hazards models. Reference groups for comorbidities and medications are the group of patients without the given disease or without a prescription for the given medication. HIV=human immunodeficiency virus; AIDS=acquired immunodeficiency syndrome; DMARDs=disease-modifying anti-rheumatic drugs; TNF-alpha=tumor necrosis factor alpha; IL-6=interleukin 6.

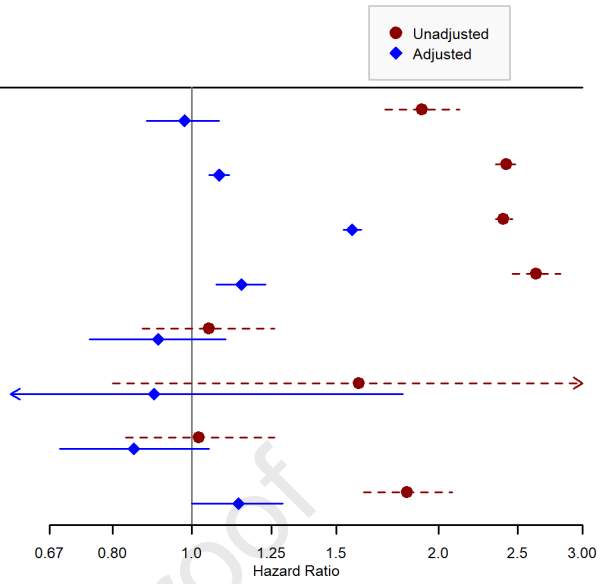
Table 4. Fully adjusted and reduced (no immunosuppressives) model results showing associations between demographic and clinical characteristics and COVID-19 infection

	Fully Adjusted Model Immunosuppressives included		**Reduced Model** Immunosuppressives removed	
Variable	**Adjusted HR (95% CI)**	**p-value**	**Adjusted HR (95% CI)**	**p-value**
Non-infectious uveitis	1.05 (1.00, 1.10)	0.04	1.06 (1.01, 1.12)	0.03
Age (years)	0.998 (0.998, 0.999)	<0.001	0.998 (0.998, 0.999)	<0.001
Continuous enrollment (years)	1.004 (1.003, 1.005)	<0.001	1.004 (1.003, 1.005)	<0.001
Male vs. Female	0.98 (0.98, 0.99)	<0.001	0.98 (0.97, 0.99)	<0.001
Unknown vs. Female	0.55 (0.44, 0.68)	<0.001	0.55 (0.44, 0.68)	<0.001
Asian vs. White	0.70 (0.68, 0.71)	<0.001	0.69 (0.68, 0.71)	<0.001
Black vs. White	1.12 (1.11, 1.14)	<0.001	1.12 (1.11, 1.13)	<0.001
Hispanic vs. White	1.57 (1.55, 1.59)	<0.001	1.57 (1.55, 1.58)	<0.001
Other/Unknown vs. White	1.10 (1.08, 1.11)	<0.001	1.10 (1.08, 1.11)	<0.001
Midwest vs. South	1.05 (1.04, 1.06)	<0.001	1.05 (1.04, 1.06)	<0.001
Northeast vs. South	1.28 (1.27, 1.30)	<0.001	1.27 (1.26, 1.29)	<0.001
West vs. South	0.87 (0.86, 0.88)	<0.001	0.86 (0.85, 0.87)	<0.001
Other/Unknown vs. South	0.03 (0.03, 0.04)	<0.001	0.03 (0.03, 0.04)	<0.001
Probable renter vs. Probable homeowner	1.12 (1.11, 1.14)	<0.001	1.12 (1.11, 1.14)	<0.001
Unknown vs. Probable homeowner	1.24 (1.23, 1.25)	<0.001	1.24 (1.23, 1.25)	<0.001
Current/former smoker vs. Never smoker	0.91 (0.90, 0.93)	<0.001	0.92 (0.91, 0.93)	<0.001
Unknown smoking status vs. Never smoker	0.88 (0.88, 0.89)	<0.001	0.88 (0.87, 0.89)	<0.001
Asthma	1.10 (1.09, 1.12)	<0.001	1.13 (1.11, 1.15)	<0.001
Autoimmune disease	1.05 (1.03, 1.06)	<0.001	1.06 (1.04, 1.07)	<0.001
Cancer	0.95 (0.93, 0.96)	<0.001	0.95 (0.94, 0.97)	<0.001
Cardiovascular disease	1.20 (1.19, 1.22)	<0.001	1.20 (1.19, 1.22)	<0.001
Cerebrovascular	1.05 (1.03, 1.06)	<0.001	1.05 (1.03, 1.06)	<0.001
Chronic kidney disease	1.14 (1.13, 1.16)	<0.001	1.14 (1.13, 1.16)	<0.001
Chronic lung disease	1.12 (1.11, 1.14)	<0.001	1.14 (1.13, 1.16)	<0.001
Diabetes	1.24 (1.23, 1.25)	<0.001	1.24 (1.22, 1.25)	<0.001
Hemoglobin disorder	1.10 (1.01, 1.20)	0.03	1.10 (1.01, 1.20)	0.03
HIV/AIDS	1.41 (1.32, 1.51)	<0.001	1.41 (1.32, 1.51)	<0.001
Hypertension	1.04 (1.03, 1.05)	<0.001	1.05 (1.03, 1.06)	<0.001
Liver disease	1.16 (1.08, 1.25)	<0.001	1.16 (1.08, 1.24)	<0.001
Neurologic disease	2.33 (2.29, 2.36)	<0.001	2.31 (2.28, 2.34)	<0.001
Obesity	1.21 (1.20, 1.22)	<0.001	1.22 (1.20, 1.23)	<0.001

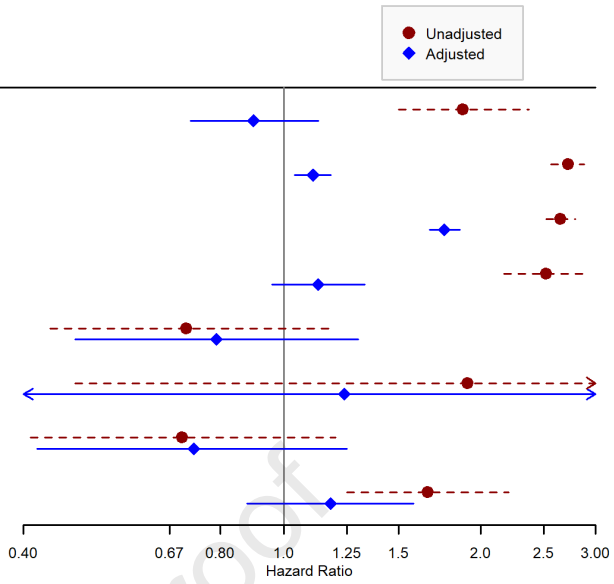
Solid organ transplant	1.11 (1.04, 1.18)	0.001	1.11 (1.04, 1.18)	<0.001
Pregnancy	1.36 (1.31, 1.40)	<0.001	1.36 (1.31, 1.40)	<0.001
Systemic corticosteroids	1.19 (1.18, 1.20)	<0.001		
DMARDs	0.91 (0.88, 0.95)	<0.001		
TNF-alpha inhibitors	1.11 (1.04, 1.19)	0.002		
IL-6 inhibitors	0.96 (0.71, 1.30)	0.79		
Other biologics	1.00 (0.93, 1.07)	0.94		
Other immunosuppressive drugs	0.87 (0.83, 0.93)	<0.001		

P-values calculated from Cox proportional hazards models. Reference groups for comorbidities and medications are the group of patients without the given disease or without a prescription for the given medication. HIV=human immunodeficiency virus; AIDS=acquired immunodeficiency syndrome; DMARDs=disease-modifying anti-rheumatic drugs; TNF-alpha=tumor necrosis factor alpha; IL-6=interleukin 6.

Variable	Hazard Ratio (95% CI)	P-value
Non-infectious uveitis	1.91 (1.72, 2.12)	<0.001
	0.98 (0.88, 1.09)	0.67
Autoimmune disease	2.42 (2.35, 2.48)	<0.001
	1.08 (1.05, 1.11)	<0.001
Systemic corticosteroids	2.41 (2.35, 2.46)	<0.001
	1.57 (1.53, 1.61)	<0.001
DMARDs	2.63 (2.47, 2.82)	<0.001
	1.15 (1.07, 1.24)	<0.001
TNF-alpha inhibitors	1.05 (0.87, 1.26)	0.64
	0.91 (0.75, 1.10)	0.33
IL-6 inhibitors	1.60 (0.80, 3.20)	0.18
	0.90 (0.45, 1.81)	0.77
Other biologics	1.02 (0.83, 1.26)	0.84
	0.85 (0.69, 1.05)	0.13
Other non-biologic immunosuppressives	1.84 (1.62, 2.08)	<0.001
	1.14 (1.00, 1.29)	0.04



Variable	Hazard Ratio (95% CI)	P-value
Non-infectious uveitis	1.88 (1.50, 2.37)	<0.001
	0.90 (0.72, 1.13)	0.37
Autoimmune disease	2.72 (2.57, 2.88)	<0.001
	1.11 (1.04, 1.18)	0.002
Systemic corticosteroids	2.65 (2.52, 2.79)	<0.001
	1.76 (1.67, 1.86)	<0.001
DMARDs	2.52 (2.17, 2.92)	<0.001
	1.13 (0.96, 1.33)	0.14
TNF-alpha inhibitors	0.71 (0.44, 1.17)	0.18
	0.79 (0.48, 1.30)	0.35
IL-6 inhibitors	1.91 (0.48, 7.65)	0.36
	1.24 (0.31, 4.98)	0.76
Other biologics	0.70 (0.41, 1.20)	0.20
	0.73 (0.42, 1.26)	0.25
Other non-biologic immunosuppressives	1.66 (1.25, 2.21)	<0.001
	1.18 (0.88, 1.58)	0.26



Précis

Non-infectious uveitis is not a risk factor for COVID-19 infection, hospitalization, and death; however, patients taking systemic corticosteroids may have increased risk of severe outcomes from COVID-19.