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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.

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Association between Immunosuppressive Drugs and Coronavirus Disease 2019 Outcomes in Patients with Noninfectious Uveitis in a Large US Claims Database

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Purpose: To determine the dose-dependent risk of systemic corticosteroids (SCs) and the risk of other immunosuppressive therapies on coronavirus disease 2019 (COVID-19) infection, hospitalization, and death in patients with noninfectious uveitis (NIU).

Design: A retrospective cohort study from January 20, 2020, to December 31, 2020 (an era before widespread COVID-19 vaccination), using the Optum Labs Data Warehouse, a US national de-identified claims database.

Participants: Patients who had at least 1 NIU diagnosis from January 1, 2017.

Methods: Unadjusted and adjusted hazard ratios (HRs) were estimated for each variable and COVID-19 outcome using Cox proportional hazards models, with time-updated dichotomous indicators for outpatient immunosuppressive medication exposure. To assess the dose-dependent effect of SC exposure, the average daily dose of prednisone over the exposed interval was included in the adjusted models as a continuous variable, in addition to the dichotomous variable.

Main Outcome Measures: Incidence rates of COVID-19 infection, COVID-19–related hospitalization, and COVID-19–related in-hospital death.

Results: This study included 52 286 NIU patients of whom 12 000 (23.0%) were exposed to immunosuppressive medications during the risk period. In adjusted models, exposure to SCs was associated with increased risk of COVID-19 infection (HR, 2.66; 95% confidence interval [CI], 2.19–3.24; $P < 0.001$), hospitalization (HR, 3.26; 95% CI, 2.46–4.33; $P < 0.001$), and in-hospital death (HR, 1.99; 95% CI, 0.93–4.27; $P = 0.08$). Furthermore, incremental increases in the dosage of SCs were associated with a greater risk for these outcomes. Although tumor necrosis factor-α (TNF-α) inhibitors were associated with an increased risk of infection (HR, 1.48; 95% CI, 1.08–2.04; $P = 0.02$), other immunosuppressive treatments did not increase the risk of COVID-19 infection, hospitalization, or death.

Conclusions: This study from an era before widespread COVID-19 vaccination demonstrates that outpatient SC exposure is associated with greater risk of COVID-19 infection and severe outcomes in patients with NIU. Future studies should evaluate the impact of immunosuppression in vaccinated NIU patients. Limiting exposure to SCs and use of alternative therapies may be warranted. *Ophthalmology 2022;■:1–11 © 2022 by the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

Noninfectious uveitis (NIU) comprises a spectrum of intraocular inflammatory conditions that are most commonly treated with immunosuppressive therapy. Corticosteroids are frequently used for the management of NIU; however, patients often require the addition of other immunosuppressants including disease-modifying anti-rheumatic drugs (DMARDs) and biologics. Although these medications have the benefit of controlling inflammation, they have also been shown to predispose patients to infection.[1–3]

As a result, the use of corticosteroids and other immunosuppressants has received increased scrutiny during the coronavirus disease 2019 (COVID-19) pandemic, particularly for patients with preexisting medical comorbidities that increase the risk of severe COVID-19 outcomes. Thus far, studies investigating the association between these treatments and the development of COVID-19 have yielded mixed results.[4–16] In a study from our group examining COVID-19 risk in patients with NIU compared with the general population, we found systemic corticosteroid (SC) use was associated with a higher risk of COVID-19 infection, COVID-19–related hospitalization, and death.[17] However, the impact of the level of corticosteroid exposure was not assessed in that prior study.

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Although recommendations for the medical management of patients with NIU in the context of the COVID-19 pandemic have been published,[18–21] evidence-based recommendations are lacking. This is in large part due to a paucity of studies assessing the impact of immunosuppressive drug type, dose, and treatment duration on the risk of developing COVID-19 and severe sequelae. Therefore, the purpose of this study was to determine the dose-dependent risk of SCs and other immunosuppressive therapies on COVID-19–related outcomes in patients with NIU.

Methods

Data Source

This was a retrospective cohort study using Optum Labs Data Warehouse (OLDW; Optum Labs), a de-identified administrative claims and electronic health record database that includes enrollment information, medical claims, and outpatient pharmacy claims for commercial and Medicare Advantage enrollees of all ages.[22] Medical claims included diagnosis codes, that is, International Classification of Diseases 10th Revision (ICD-10), Current Procedural Terminology codes, dates of service, and provider specialty codes. Pharmacy information included National Drug Code, brand name, generic name, quantity, days' supply, drug strength, drug administration route, and the date the prescription was filled. The OLDW contains longitudinal records from 1994 to present day for approximately 200 million individuals across the United States. Approximately 26 million individuals were enrolled in the database in 2020, accounting for 8% of the US population and 12% of the US privately insured population.[23] Comparisons between the US Census and the OLDW demonstrate that distributions in age, sex, and race/ethnicity are comparable between the two. The OLDW is a national database with a higher proportion of enrollees in the south and central regions.

Study Population

Patients who had at least 1 healthcare visit in any setting with an ICD-10 code for NIU in any position from January 1, 2017, to December 31, 2020, were identified. All codes used to identify NIU are included in Appendix 1 (available at www.aaojournal.org). The start of the risk period (index date) was January 20, 2020 (the date of the first known COVID-19 case in the United States) for patients who had an NIU diagnosis before January 20, 2020. For patients whose first NIU diagnosis code appeared after January 20, 2020, the date of their first NIU diagnosis was considered the index date. Patients were required to have at least 365 days of continuous enrollment with both medical and pharmacy coverage before their index date to capture baseline comorbid conditions. Patients were excluded if they developed NIU after COVID-19 infection. Patients with an infectious uveitis ICD-10 code (Appendix 1, available at www.aaojournal.org) at any time during the NIU identification period were excluded from the study. Figure 1 provides cohort selection details.

Covariates

Baseline covariates included age in 2020, sex, race/ethnicity, homeownership, region, insurance type, smoking status, and presence of comorbidities in the 1 year before the index date based on ICD-10 codes. Comorbidities were chosen on the basis of the risk factors for severe COVID-19 illness reported by the Centers for Disease Control and Prevention as of February 2021 (Appendix 2, available at www.aaojournal.org).[24] Use of systemic immunosuppressive medication in outpatient settings was identified during the risk period and categorized into the following groups: SCs, DMARDs, tumor necrosis factor-α (TNF-α) inhibitors, interleukin-6 (IL-6) inhibitors, other biologic immunosuppressive therapies, and other nonbiologic immunosuppressive drugs that do not fit into the previous categories. Prescription fills for immunosuppressive medications were identified by text search of drug names in pharmacy claims. Generic names of medications and routes used to search for prescriptions and their categorizations are listed in Appendix 3 (available at www.aaojournal.org). Hydroxychloroquine was not included in the analysis to avoid introducing confounding by indication. Local treatment for NIU during the risk period, including topical corticosteroid treatments (ophthalmic drops or ointments) and corticosteroid injections or implants (intraocular implants, intraocular or periocular injections), were included to fully capture treatments for uveitis. Inclusion of these medications also served as a surrogate for uveitis activity and severity (Appendix 4, available at www.aaojournal.org). Medications administered in inpatient settings were not available from OLDW.

Assessment of Immunosuppressive Medication Exposure Episodes

Time-varying dichotomous exposure to each category of immunosuppressive medication was characterized on the basis of dispensing information available in outpatient pharmacy claims. Patients were considered exposed to an immunosuppressive medication from the day the prescription was dispensed until the days' supply had elapsed. The duration of medication use was based on the "days' supply" variable provided within the pharmacy claim, which was recorded by the pharmacist as an estimate of the number of days that a prescription was expected to last if the prescription instructions were followed. Supplemental Methods 1 (available at www.aaojournal.org) describes how gaps and overlaps between subsequent prescription fills were handled.[25,26]

As our main exposure of interest, average daily dosage (mg) of a prescription fill for SC was calculated using the formula $drug\ strength \times \frac{quantity}{days'\ supply}$. For example, if a prednisone prescription fill had a 7-day supply, quantity drug unit of 21 pills, and drug strength of 10 mg per each unit, the average daily dose of this prednisone fill would be 10 mg * 21/7 days = 30 mg/day. The tapering regimen of SC was not available from pharmacy claims. To standardize doses, all SC doses were converted into prednisone equivalents (Appendix 5, available at www.aaojournal.org).[27]

Outcomes

Outcomes of interest included COVID-19 infection, COVID-19 hospitalization, and COVID-19 in-hospital death, which were assessed from January 20, 2020, to December 31, 2020 (an era prior to widespread COVID-19 vaccination). Methods for outcome identification have been previously described by our group (Appendix 6, available at www.aaojournal.org).[17] Coronavirus disease 2019 infection and hospitalization dates were taken as the first date at which the outcome criteria were met. Patients could be censored at disenrollment from the medical plan, death unrelated to COVID-19, or the end of the risk period (December 31, 2020).

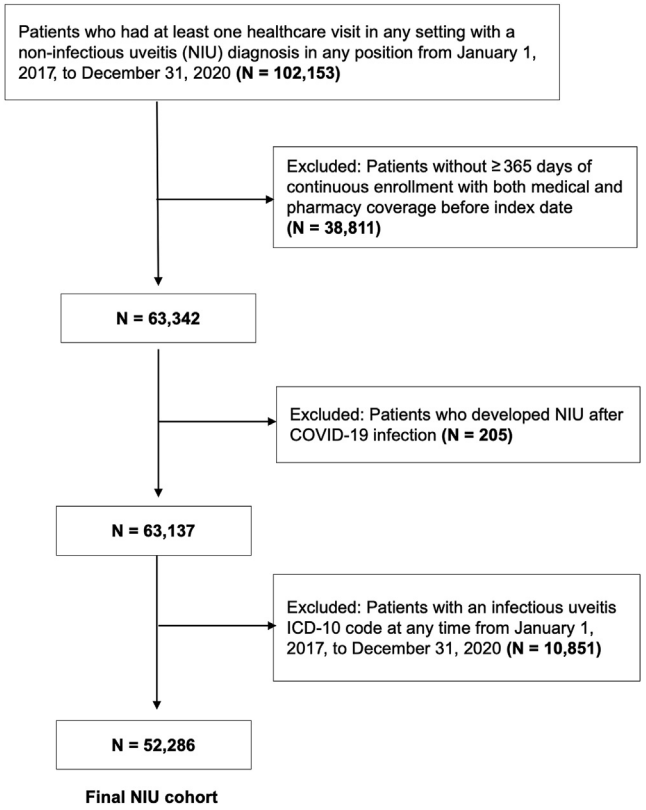

Figure 1. Cohort flow diagram. COVID-19 = coronavirus disease 2019; ICD-10 = International Classification of Diseases 10th Revision.

Statistical Analysis

Primary Analysis. Incidence rates of COVID-19 outcomes (infection, hospitalization, in-hospital death) during unexposed and exposed person-time were calculated for each systemic immunosuppressive medication category. Unadjusted and adjusted hazard ratios (HRs) were estimated for each variable and COVID-19 outcome using Cox proportional hazards models, with time-updated covariates for immunosuppressive medication exposure. The exposure status for each immunosuppressive medication category was included as a dichotomous variable in the Cox models. The adjusted models were adjusted for baseline demographics, comorbidities, and NIU local treatment. To assess the effect of the level of SC exposure among those who were exposed, the average daily dose (mg) of prednisone over the time interval was included in the adjusted models as a continuous variable, in addition to the dichotomous variable.[28] The 95% confidence intervals (CIs) for the model were estimated using robust standard errors. The HRs were reported per 10 mg unit change in the average daily dose of prednisone.

Secondary Analysis. To gain more insight into the association between the level of corticosteroid exposure and COVID-19 hospitalization outcome, a risk-stratification–based method was developed in addition to the main analysis. Patients with NIU were classified into groups on the basis of predefined corticosteroid exposure levels determined by duration and average daily dose in exposed episodes (Supplemental Methods 2, available at www.aaojournal.org). A duration of less than 30 days was considered short-term.[29] A time-fixed Cox proportional hazards model with corticosteroid exposure level was used, adjusting for baseline demographics, comorbidities, NIU local treatment, and the other 5 immunosuppressive medication categories. Risk of exposure to $\leq$ 5 mg/day prednisone was also assessed.

Subgroup Analysis. An adjusted subgroup analysis was performed by age group ($<$ 50 vs. $\geq$ 50 years) for each COVID-19 outcome to understand whether the effect of immunosuppression differed in younger individuals versus older individuals. We also performed 3 subgroup analyses on NIU patients without asthma, without other autoimmune diseases, and without chronic lung diseases. The analyses were performed only for the hospitalization outcome because of the small event number for the death outcome. These analyses applied the same models described in the primary analysis and were similarly adjusted for demographics, comorbidities, and immunosuppressive medications.

Statistical analyses were performed in R (Version 4.0.2, R Foundation for Statistical Computing, https://www.R-project.org/). *P* values less than 0.05 were considered statistically significant. 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. Only de-identified data were available for this study. Informed consent was waived by the Institutional Review Board.

Results

Characteristics of the Study Population

In our study, 38 811 patients were excluded because of $<$ 365 days of continuous enrollment with medical and pharmacy coverage before the index date. The mean age of patients in the overall cohort was 62.8 years (standard deviation, 17.8) compared with 55.1 (standard deviation, 18.7) in the excluded patients. The percent of female patients was comparable between the included and excluded patients (60.2% vs. 57.5%).

Among 52 286 patients with NIU in the study cohort, 9516 patients (18.2%) were exposed to SCs during the risk period. The age distribution was similar in patients who received SC and those who did not. The SC users were more likely to be female and were twice as likely as SC nonusers to have another autoimmune disease (34.0% vs. 16.9%, Table 1 and Table S1, available at www.aaojournal.org). With regard to anatomic classification of uveitis, 39 530 patients (75.6%) had anterior uveitis, 11 948 patients (22.9%) had posterior/panuveitis, 687 patients (1.3%) had intermediate uveitis, and 121 patients (0.2%) had unknown or sarcoid-related uveitis in which the anatomic subtype was not specified.

Immunosuppressive Medication Use

Overall, 12 000 patients (23.0%) with NIU were prescribed a medication in at least 1 of the 6 immunosuppressive drug categories during the risk period up to COVID-19 hospitalization or censoring (Table 2). Systemic corticosteroids (18.2%) were the most prescribed immunosuppressive treatments during this period, followed by DMARDs (4.7%). Among the overall cohort, 15 093 patients (28.9%) were treated with local corticosteroids (ophthalmic steroid drops or steroid injections/implants)

Table 1. Baseline Characteristics of NIU Cohort by Systemic Corticosteroid Exposure Status * (N = 52 286)

Characteristic	Never Exposed N = 42 770 (81.8%)	Ever Exposed N = 9516 (18.2%)	All N = 52 286 (100.0%)
Age at 2020 (yrs)			
Mean (SD)	62.6 (18.2)	63.9 (15.8)	62.8 (17.8)
Median [Q1, Q3]	68.0 [51.0, 76.0]	68.0 [54.0, 75.0]	68.0 [52.0, 76.0]
Gender†			
Female	25 172 (58.9%)	6331 (66.5%)	31 503 (60.3%)
Male	<17 557 (<41.0%)	>3174 (>33.4%)	20 731 (39.6%)
Unknown	>41 (>0.1%)	<11 (<0.1%)	52 (0.1%)
Race			
Asian	1716 (4.0%)	228 (2.4%)	1944 (3.7%)
Black	6980 (16.3%)	1803 (18.9%)	8783 (16.8%)
Hispanic	4013 (9.4%)	784 (8.2%)	4797 (9.2%)
White	23 687 (55.4%)	5303 (55.7%)	28 990 (55.4%)
Unknown/missing	6374 (14.9%)	1398 (14.7%)	7772 (14.9%)
Region†			
Midwest	10 136 (23.7%)	2149 (22.6%)	12 285 (23.5%)
Northeast	6565 (15.3%)	1100 (11.6%)	7665 (14.7%)
South	20 370 (47.6%)	5393 (56.7%)	25 763 (49.3%)
West	<5595 (<13.1%)	>863 (>9.1%)	6458 (12.4%)
Other/unknown	>104 (>0.2%)	<11 (<0.1%)	115 (0.2%)
Insurance type			
Commercial	18 758 (43.9%)	3623 (38.1%)	22 381 (42.8%)
Medicare Advantage	24 012 (56.1%)	5893 (61.9%)	29 905 (57.2%)
Home ownership			
Probable homeowner	28 254 (66.1%)	6191 (65.1%)	34 445 (65.9%)
Probable renter	2891 (6.8%)	703 (7.4%)	3594 (6.9%)
Unknown/missing	11 625 (27.2%)	2622 (27.6%)	14 247 (27.2%)
Smoking status (baseline or risk period)			
Never	3419 (8.0%)	820 (8.6%)	4239 (8.1%)
Current or former	9563 (22.4%)	3121 (32.8%)	12 684 (24.3%)
Unknown	29 788 (69.6%)	5575 (58.6%)	35 363 (67.6%)
Asthma	3065 (7.2%)	1633 (17.2%)	4698 (9.0%)
Autoimmune disease	7218 (16.9%)	3237 (34.0%)	10 455 (20.0%)
Cancer	3917 (9.2%)	1136 (11.9%)	5053 (9.7%)
Cardiovascular disease	7493 (17.5%)	2206 (23.2%)	9699 (18.5%)
Cerebrovascular disease	3977 (9.3%)	1063 (11.2%)	5040 (9.6%)
Chronic kidney disease	6077 (14.2%)	1704 (17.9%)	7781 (14.9%)
Chronic lung disease	4848 (11.3%)	2271 (23.9%)	7119 (13.6%)
Diabetes (any type)	11 751 (27.5%)	2731 (28.7%)	14 482 (27.7%)
Hemoglobin disease	169 (0.4%)	45 (0.5%)	214 (0.4%)
HIV/AIDS	170 (0.4%)	30 (0.3%)	200 (0.4%)
Hypertension	23 992 (56.1%)	6143 (64.6%)	30 135 (57.6%)
Liver disease	135 (0.3%)	30 (0.3%)	165 (0.3%)
Neurologic disease	2698 (6.3%)	681 (7.2%)	3379 (6.5%)
Obesity	6734 (15.7%)	2012 (21.1%)	8746 (16.7%)
Solid organ transplantation	391 (0.9%)	164 (1.7%)	555 (1.1%)
Pregnancy (risk period)	336 (0.8%)	59 (0.6%)	395 (0.8%)

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; NIU = noninfectious uveitis; SD = standard deviation.
*Systemic corticosteroid (SC) exposure during the risk period up to COVID-19 hospitalization or censoring is reported in this table. Patients with at least 1 prescription dispensing during risk period were considered "ever exposed." Counts and proportions were similar with COVID-19 infection and COVID-19 in-hospital death.
†OptumLabs requires cell counts of less than 11 to be reported as less than 11, rather than reporting true values, to protect patient privacy. To prevent back-calculation, the value in a corresponding cell of the same subgroup is lowered and reported with a greater-than sign to ensure that the total case count within the subgroup stays the same. Each affected subgroup's count and proportion were reported with greater-than and less-than signs.

during the risk period, with a slightly higher treatment rate (32.6%) among SC users.

Systemic Corticosteroid Use

A total of 22 948 SC prescriptions were filled by 9516 SC users, with an average duration of 24 days and median duration of 14 days (interquartile range, 6–30 days). The median prednisone equivalent average daily dose per prescription was 17.5 mg/day (interquartile range, 10–30.8 mg/day), with 21.5% having an average daily dose of $\geq$ 40 mg/day. Table S2 (available at www.aaojournal.org) details SC use in the study cohort by dosage and length of exposure. The most prescribed SC was prednisone, which accounted for 72.4% of SC prescriptions

Table 2. Immunosuppressive Drug Prescriptions during the Risk Period * (N = 52 286)

Drug Class/Generic Name	Number (%) of NIU Cohort with at Least 1 Prescription Fill
Overall	12 000 (23.0%)
SCs	9516 (18.2%)
Prednisone	6573 (12.6%)
Methylprednisolone	3315 (6.3%)
Dexamethasone	680 (1.3%)
Budesonide	126 (0.2%)
Hydrocortisone	88 (0.2%)
Prednisolone	28 (0.05%)
DMARDs	2450 (4.7%)
TNF-α inhibitors	1382 (2.6%)
IL-6 inhibitors	44 (0.08%)
Other biologics	356 (0.7%)
Other immunosuppressive drugs	658 (1.3%)

DMARD = disease-modifying anti-rheumatic drugs; IL-6 = interleukin 6; NIU = noninfectious uveitis; SC = systemic corticosteroid; TNF-α = tumor necrosis factor alpha.
*Frequencies and percentages reflect the proportion of patients who filled 1 or more prescriptions during risk period up to COVID-19 hospitalization outcome date (results differ slightly for infection and death outcomes).

during the risk period. Among SC users, 56.7% had 1 prescription fill, 17.7% had 2 prescription fills, and 25.6% had 3 or more prescription fills.

Exposures Associated with COVID-19 Infection

The incidence rate of COVID-19 infection was 114.8 cases per 1000 person-years in patients exposed to SC compared with 39.9 cases per 1000 person-years in the SC unexposed group, corresponding to an incidence rate ratio of 2.88 (Table 3). The incidence rate was slightly higher in the exposed person-time for DMARDs, TNF-α inhibitors, other biologics, and other immunosuppressive drugs (Table 3). The unadjusted HR for COVID-19 infection comparing SC exposed and unexposed person-time was 2.92 (95% CI, 2.45−3.48; $P < 0.001$) (Table 4).

Exposure to SC remained significantly associated with COVID-19 infection in the adjusted model (HR, 2.66; 95% CI, 2.19−3.24; $P < 0.001$). Among those who were exposed, a 10 mg increase in systemic prednisone (or equivalent) average daily dose was associated with a 3% increased risk of COVID-19 infection (HR, 1.03; 95% CI, 1.01−1.06; $P = 0.007$). The TNF-α inhibitors were significantly associated with increased hazard of COVID-19 infection after adjustment (HR, 1.48; 95% CI, 1.08−2.04; $P = 0.02$), whereas the rest of the immunosuppressive drugs were not significantly associated after adjustment.

Exposures Associated with COVID-19−Related Hospitalization

The incidence rate of COVID-19−related hospitalization was 56.7 cases per 1000 person-years in patients exposed to SC compared with 13.5 cases per 1000 person-years in the SC unexposed group, corresponding to an incidence rate ratio of 4.20 (Table 3). The unadjusted HR for COVID-19−related hospitalization comparing SC-exposed and SC-unexposed person-time was 4.26 (95% CI, 3.31−5.48; $P < 0.001$) (Table 4).

In the adjusted analysis, SC exposure tripled the hazard of hospitalization (HR, 3.26; 95% CI, 2.46−4.33; $P < 0.001$), and a 10-mg increase in the average daily dose of prednisone was associated with a 4% increased risk of COVID-19−related hospitalization (HR, 1.04; 95% CI, 1.01−1.08; $P = 0.01$). Use of all other immunosuppressive drugs was not significantly associated with hospitalization (Table 4).

After covariate adjustment, the point estimates suggested an increased risk for all the exposure levels of corticosteroids in the secondary analysis (Fig 2), although the CIs for short-term ≤ 10 mg/day, short-term > 10 mg/day, and ≤ 20 mg/day crossed 1. In our NIU cohort, 72 (0.14%) patients were exposed to short-term ≤ 5 mg/day prednisone, and less than 11 of them were hospitalized with COVID-19. The adjusted HR was 2.65 (95% CI, 0.66−10.64; $P = 0.17$). A total of 321 patients (0.61%) were exposed to long-term ≤ 5 mg/day prednisone, with an adjusted HR for COVID-19 hospitalization of 1.98 (95% CI, 1.01−3.87; $P = 0.05$).

Exposures Associated with COVID-19−Related In-Hospital Death

The incidence rate of COVID-19−related death in an inpatient facility was 7.3 cases per 1000 person-years in the SC exposed group compared with 2.7 cases per 1000 person-years in the SC unexposed group, corresponding to an incidence rate ratio of 2.70 (Table 3). The unadjusted HR for in-hospital COVID-19 death comparing SC exposed and unexposed person-time was 2.78 (95% CI, 1.41−5.50; $P = 0.003$) (Table 4). Disease-modifying anti-rheumatic drugs were not associated with in-hospital death, and we were not able to estimate the HR for other immunosuppressive medications because of zero deaths in the exposed group. After adjusting for all other covariates, SC exposure was associated with 2-fold increased risk of death; however, it was not statistically significant (HR, 1.99; 95% CI, 0.93−4.27; $P = 0.08$), probably because of relatively few death events and lower power.

Sociodemographic Factors Associated with COVID-19−Related Outcomes

In both unadjusted and adjusted analyses, increasing age and Black and Hispanic race/ethnicity were associated with an increased risk of infection, hospitalization, and in-hospital death due to COVID-19. In addition, comorbidities such as cardiovascular disease, chronic kidney disease, neurologic disease, and diabetes, among others, were associated with each COVID-19−related outcome in multivariable analyses. Specific associations between these factors and study outcomes are included in Tables S3 to S5 (available at www.aaojournal.org).

Table 3. Incidence of COVID-19 Outcomes (Infection, Hospitalization, and In-Hospital Death) per 1000 Person-Years by Immunosuppressive Medication Exposure

	Exposed			Unexposed			
	Number of Cases	*Number of Person-Years*	*Incidence Rate*	*Number of Cases*	*Number of Person-Years*	*Incidence Rate*	**Incidence Rate Ratio**
COVID-19 infection							
Overall: 1742 cases within 41 427 person-years, corresponding to an incidence rate of 42 per 1000 person-years							
SCs	138	1202	114.8	1604	40 225	39.9	2.88
DMARDs	64	1358	47.1	1678	40 069	41.9	1.12
TNF-α inhibitors	42	838	50.1	1700	40 590	41.9	1.20
IL-6 inhibitors	0	21	0.0	1742	41 406	42.1	0.00
Other biologic therapies*	/	/	47.4	/	/	42.0	1.13
Other immunosuppressive drugs	16	329	48.6	1726	41 098	42.0	1.16
COVID-19 hospitalization							
Overall: 618 cases within 41 875 person-years, corresponding to an incidence rate of 15 per 1000 person-years							
SC	69	1217	56.7	549	40 658	13.5	4.20
DMARDs	28	1373	20.4	590	40 502	14.6	1.40
TNF-α inhibitors*	/	/	8.3	/	/	14.9	0.56
IL-6 inhibitors	0	22	0.0	618	41 853	14.8	0.00
Other biologic therapies*	/	/	5.2	/	/	14.8	0.35
Other immunosuppressive drugs*	/	/	12.0	/	/	14.8	0.81
COVID-19 in-hospital death							
Overall: 118 cases within 42 018 person-years, corresponding to an incidence rate of 3 per 1000 person-years							
SC*	/	/	7.3	/	/	2.7	2.70
DMARDs*	/	/	2.9	/	/	2.8	1.04
TNF-α inhibitors	0	849	0.0	118	41 169	2.9	0.00
IL-6 inhibitors	0	22	0.0	118	41 996	2.8	0.00
Other biologic therapies	0	193	0.0	118	41 824	2.8	0.00
Other immunosuppressive drugs	0	334	0.0	118	41 684	2.8	0.00

COVID-19 = Coronavirus Disease 2019; DMARD = disease-modifying anti-rheumatic drugs; IL-6 = interleukin 6; SC = systemic corticosteroid; TNF-α = tumor necrosis factor alpha.
*To protect patient privacy, OptumLabs does not allow to report the true value of a count if it is less than 11. Only incidence rate was reported because the number of cases in the category is less than 11. The corresponding person-years are also not reported to prevent back-calculation.

Subgroup Analyses by Age and Certain Comorbidities

There were 11 520 (22% of the entire NIU cohort) patients aged less than 50 years, 1743 (15.1%) of whom were exposed to SC. There were 40 762 patients aged 50 years and older, 7773 (19.1%) of whom were exposed to SC. In the adjusted analysis, risk of SC exposure on COVID-19 infection and hospitalization was comparable between the older and younger age groups (Table S6, available at www.aaojournal.org). There were no COVID-19 in-hospital deaths in patients exposed to SC in the subgroup aged less than 50 years. The association between SC exposure and COVID-19 hospitalization remained in the subgroups without asthma, without other autoimmune diseases, and without chronic lung diseases (Table S7, available at www.aaojournal.org).

Discussion

Among patients with NIU, exposure to SC was associated with an approximately 3-fold increased risk of COVID-19 infection and hospitalization. Use of SC was associated with in-hospital death but was not statistically significant. Although TNF-α inhibitors were associated with an increased risk of infection, they were not associated with an increased risk of hospitalization or death, and other immunosuppressive treatments did not significantly increase the risk of COVID-19–related outcomes.

Our results point to a dose-dependent risk of SC exposure for COVID-19 outcomes and a possible duration effect. In the main analysis, incremental increases in the daily dosage of SCs were significantly associated with a greater risk for COVID-19 infection and hospitalization. In the risk-stratification analysis based on SC dose and duration levels, the point estimates suggested an increased risk for all the exposure levels of corticosteroids, but the overlapping CIs make it difficult to reach definitive conclusions on differential risks by dose and duration, likely due to small sample size and low event rate in some subgroups. In examining long-term exposure compared with short-term exposure of the same dose level of corticosteroid, the HR point estimates for long-term exposure were larger than those for short-term exposure, suggesting a possible duration effect. However, the results were not conclusive because the CIs overlapped. The results for $\leq$ 5 mg/day prednisone exposure showed that long-term exposure to low-dose SCs still imposed a risk of worse COVID-19 outcomes, but we do not have the precision in our estimates to definitively conclude this.

In the setting of the COVID-19 pandemic, significant public health and research efforts have focused on examining

Table 4. Unadjusted and Adjusted Hazard Ratios Showing Associations between Immunosuppressive Medication Exposure and COVID-19 Outcomes (Infection, Hospitalization, and In-Hospital Death) in NIU Patients

Outcome	Unadjusted HR (95% CI)	*P* Value*	Adjusted HR (95% CI)	*P* Value
COVID-19 infection				
SC (any exposure)	2.92 (2.45–3.48)	<0.001	2.66 (2.19–3.24)	<0.001
SC average daily dose (per 10 mg)	1.54 (1.47–1.63)	<0.001	1.03 (1.01–1.06)	0.007
DMARDs	1.11 (0.87–1.43)	0.41	0.84 (0.64–1.09)	0.19
TNF-α inhibitors	1.18 (0.87–1.61)	0.28	1.48 (1.08–2.04)	0.02
IL-6 inhibitors†	/	/	/	/
Other biologics	1.11 (0.58–2.13)	0.76	1.07 (0.55–2.07)	0.85
Other immunosuppressive drugs	1.15 (0.71–1.88)	0.57	1.10 (0.67–1.81)	0.71
COVID-19 hospitalization				
SC (any exposure)	4.26 (3.31–5.48)	<0.001	3.26 (2.46–4.33)	<0.001
SC average daily dose (per 10 mg)	1.63 (1.62–1.79)	<0.001	1.04 (1.01–1.08)	0.01
DMARDs	1.38 (0.94–2.02)	0.10	1.04 (0.68–1.57)	0.87
TNF-α inhibitors	0.55 (0.26–1.16)	0.12	1.18 (0.55–2.52)	0.68
IL-6 inhibitors†	/	/	/	/
Other biologics	0.34 (0.05–2.40)	0.28	0.43 (0.06–3.08)	0.40
Other immunosuppressive drugs	0.82 (0.31–2.18)	0.68	0.98 (0.36–2.64)	0.96
COVID-19 in-hospital death				
SC (any exposure)	2.78 (1.41–5.50)	0.003	1.99 (0.93–4.27)	0.08
SC average daily dose (per 10 mg)	1.48 (1.22–1.79)	<0.001	1.06 (0.98–1.16)	0.12
DMARDs	1.03 (0.38–2.78)	0.96	1.12 (0.38–3.33)	0.84
TNF-α inhibitors†	/	/	/	/
IL-6 inhibitors†	/	/	/	/
Other biologics†	/	/	/	/
Other immunosuppressive drugs†	/	/	/	/

CI = confidence interval; COVID-19 = coronavirus disease 2019; DMARD = disease-modifying anti-rheumatic drug; HR = hazard ratio; IL-6 = interleukin 6; NIU = noninfectious uveitis; SC = systemic corticosteroid; TNF-α = tumor necrosis factor-α.
**P* values calculated from Cox proportional hazard models.
†We were not able to estimate the HR and corresponding *P* value because of zero outcome event in the exposed group.

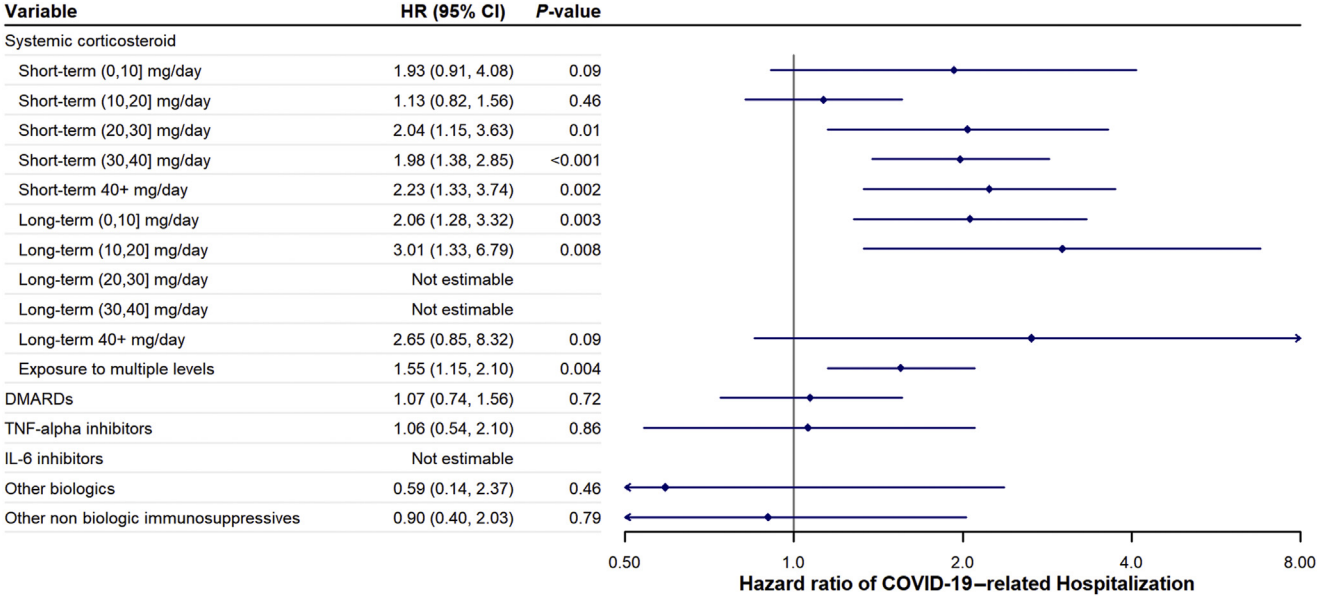

Figure 2. Adjusted hazard ratios (HRs) of coronavirus disease 2019 (COVID-19) hospitalization associated with immunosuppressive medications. Appendix 3 (available at www.aaojournal.org) shows the specific medications included in each category. A duration of less than 30 days was considered short-term. All systemic corticosteroid (SC) doses were converted into prednisone equivalents. The HRs for SC exposure long-term (20, 30 mg/day), long-term (30, 40 mg/day), and IL-6 inhibitors were not estimable because of the zero number of outcome event in the exposed group. CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IL-6 = interleukin 6; TNF-α = tumor necrosis factor-α.

the relationship between corticosteroids and COVID-19 outcomes, and mixed results have been published in the literature. A Danish nationwide cohort study found a 60% increased risk of COVID-19 hospitalization associated with SC exposure.[7] An Israeli study[6] consisting of adult asthmatic patients found no association between SCs and COVID-19 infection, whereas the same study reported that having ≥ 3 steroid prescriptions in the previous year before testing positive for COVID-19 was associated with an increased risk of 90-day all-cause mortality. Another 4 studies also identified an increased risk of hospitalization or death associated with corticosteroids in COVID-19 patients.[5,11,12,16] In contrast to those studies that reported an increased risk of severe COVID-19 outcomes associated with SC exposure, there are studies that have not found an association.[8,9] Andersen et al[8,9] found no harmful effect of SC exposure for in-hospital death among adults hospitalized with COVID-19. However, it is unclear whether the associations could be in part due to differential treatment across study groups once hospitalized. Our study was not designed to inform the impact of corticosteroids once diagnosed or hospitalized with COVID-19. We were not able to account for inpatient COVID-19 treatments such as remdesivir and dexamethasone because of incomplete inpatient medication data available in OLDW. Likewise, it is unclear whether differential treatment received in hospital settings would affect the association between outpatient corticosteroid and mortality. More research is needed to understand whether and how in-hospital COVID-19 treatment may affect the risk of mortality.

Mechanistically, prolonged corticosteroid use has been demonstrated to increase the risk of contracting and developing more severe infectious disease by reducing neutrophil recruitment and delaying viral clearance.[1,3,30–33] This process, which has been observed in similar respiratory infections such as influenza, Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome, and other viral diseases, may explain the greater likelihood of infection and hospitalization found in our study.[34–36] Another factor that may contribute to the significantly greater risk of infection may be that patients who are on SCs more frequently required face-to-face medical care, possibly increasing exposure to COVID-19. We note that in a prior study conducted by our research group, uveitis itself was not associated with COVID-19 infection or severity after adjustment for demographics, comorbidities, and medications.[17] Furthermore, several studies have found that after controlling for comorbidities and medication use, immunosuppression specifically, and not the presence of autoimmune disease, is associated with COVID-19 infection risk and adverse outcomes.[14,37–39] Our subgroup analyses show that the association between SC exposure and COVID-19 outcomes hold in patients without other autoimmune diseases or chronic lung conditions. These findings suggest that SC use, rather than the underlying disease, most strongly impacts COVID-19 risk.

Although TNF-α inhibitor use was associated with a higher rate of infection, we did not observe an increased risk of COVID-19–related infection, hospitalization, or mortality with other categories of immunosuppressives, including DMARDs, IL-6 inhibitors, and other biologic or non-biologic therapies. It was also reassuring that TNF-α inhibitors and other immunosuppressive therapies were not associated with an increased risk of hospitalization or death. Our findings are corroborated by other epidemiological studies and are scientifically plausible given current knowledge of COVID-19 pathophysiology.[12,40–43] Tumor necrosis factor-α and other cytokines play an important role in viral host cell entry and contribute to the aberrant inflammatory response that causes organ damage.[44–46] In contrast to broader immunosuppressants that suppress host antiviral immunity such as SCs, it is plausible that cytokine-targeted medications may reduce the likelihood of infection and adverse outcomes.[37,47,48] It is currently unclear if long-term use of these immunosuppressives results in a similar protective effect as treatment during the acute phase of infection; however, some studies have indicated that long-standing treatment with TNF-α and IL-6 inhibitors before COVID-19 infection may have a protective effect on COVID-19 disease severity.[12,14,47]

The findings of this study suggest that patients with uveitis on SCs, particularly those with higher doses or sustained use, may be at greater risk of COVID-19 infection and severe outcomes. Ophthalmologists currently providing care for these patients should think about methods to reduce their patients' risk of exposure or severe disease by promoting mask wearing and vaccination. Clinicians can also consider clinical interventions to reduce COVID-19 exposure risk for patients on SCs, such as dedicated time slots for immunosuppressed patients or telehealth follow-up for patients with stable disease. We note that the exact pathophysiologic relationship between immunosuppressive medications and COVID-19 remains unclear, and further research is needed to assess causality. However, the results of this study raise the question of whether local corticosteroid therapy or other nonsteroid systemic therapy should be used preferentially to limit exposure to SCs. This study is from a time period before widespread COVID-19 vaccination, and the results may not be generalizable to vaccinated individuals. People taking immunosuppressive drugs may not be as protected by COVID vaccination, so it will be important for future studies to evaluate the impact of immunosuppression in vaccinated NIU patients.

Strengths and Limitations

This study provides novel information on the dose-dependent risk of SC exposure on COVID-19 infection, hospitalization, and death in patients with NIU. We examined a large and diverse cohort of individuals with NIU within a healthcare insurance database that included comprehensive information on enrollees' medical history and medication use. The large sample size allowed for adjustments of many potential confounders, giving clearer insight into the effects of immunosuppression in a rare disease subgroup. Characterizing exposure in a time-varying manner avoided immortal-time bias and allowed for more accurate estimates of effect size compared with only adjusting for baseline exposures.[49,50]

This study has several limitations. First, despite the mixture of ages and geographic regions in OLDW, the

study does not include individuals with basic Medicare plans, Medicaid, or no insurance, so our results may not be completely generalizable to other healthcare settings. Our study population was skewed toward an older population given the inclusion of Medicare patients, requirement of $\geq$ 365 days of continuous enrollment before the index date, and the fact that prevalence of uveitis increases with age.[51] To assess if the risk of immunosuppression differs between younger and older age groups, we conducted a subgroup analysis of patients aged less than 50 years versus more than 50 years and found similar results. Second, the observed exposure period may not fully represent the true exposed period. The half-life of SC is relatively short; whereas for other drugs, it could take weeks to months for them to take effect, and the effect could linger after stopping. Because of this variability, it is not feasible to make a reasonable assumption for every drug. Third, it is possible that we did not capture all aspects of uveitis disease status that may contribute to worse COVID-19 outcomes. However, in addition to the systemic immunosuppressive therapies, we accounted for local uveitis treatment as a surrogate for uveitis disease severity, and this was not associated with increased risk of COVID-19 outcomes (Tables S3–S5, available at www.aaojournal.org). The fact that we observed such a striking association between SC exposure and COVID-19 outcomes but not with other immunosuppressive medications indicates that SC exposure, rather than the underlying NIU disease severity, is more likely to be the main driver of COVID-19 outcomes. The aim of this study was to estimate associations between immunosuppressive medication exposure and COVID-19 outcomes and not to estimate a causal effect. Fourth, potential confounders were only captured at baseline, although they might change over time. Fifth, misclassification of COVID-19 infection outcome is possible. We used both COVID-19 diagnosis code and polymerase chain reaction test to identify COVID-19 infection. Although the accuracy of COVID-19 diagnosis codes in capturing inpatient discharges in administrative data has been validated by Kadri et al,[52] there are no published studies evaluating the accuracy for nonhospitalized infection. It is also possible that people exposed to SC were more likely to access health care than those unexposed to SC. This could lead to selection bias and lead time bias because the SC users may be more likely to be tested and to be diagnosed earlier than those unexposed, resulting in an overestimation of the risk of SC exposure on COVID-19 infection outcome. Of note, 14.9% SC users and 10.9% SC nonusers had at least 1 COVID-19 laboratory test in the study period. Among those with at least 1 COVID-19 laboratory test, SC exposed and unexposed had a similar average number of tests (1.4 test per individual). Insurance information is usually asked in mass COVID-19 testing sites, but it is not mandatory to report insurance. Additionally, laboratory tests in OLDW are only available from laboratory vendors that contract with the insurer; thus, we likely underestimated the true number of positive COVID-19 tests. This bias should not influence hospitalization and death outcomes because these outcomes are more dependent on severity of illness rather than access to the healthcare system. Last, we were not able to analyze some specific drug classes separately because of limited sample size in these subgroups.

Conclusions

There are no definitive guidelines for the use of corticosteroid therapy during the COVID-19 pandemic, in part because of a lack of research to support recommendations. Uveitis comprises many heterogeneous inflammatory ocular conditions, which makes the implementation of guidelines particularly difficult. This study from an era before widespread COVID-19 vaccination indicates that SC exposure is associated with greater risk of COVID-19 infection and severe illness including hospitalization and death in NIU patients. These findings point to the need to consider limiting exposure to SCs in patients with NIU during the COVID-19 pandemic, and future studies should evaluate the impact of immunosuppression in vaccinated NIU patients.

Footnotes and Disclosures

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Author Contributions:

Conception and design: Sun, Miller, Acharya

Data collection: Sun, Miller, Acharya

Analysis and interpretation: Sun, Miller, Akpandak, Chen, Arnold, Acharya

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Overall responsibility: Sun, Miller, Akpandak, Chen, Arnold, Acharya

Abbreviations and Acronyms:
CI = confidence interval; **COVID-19** = coronavirus disease 2019; **DMARD** = disease-modifying anti-rheumatic drug; **HR** = hazard ratio; **ICD-10** = International Classification of Diseases 10th Revision; **IL-6** = interleukin 6; **NIU** = noninfectious uveitis; **OLDW** = Optum Labs Data Warehouse; **SC** = systemic corticosteroid; **TNF-α** = tumor necrosis factor-α.

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