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Immunosuppressive Medications and COVID-19 Outcomes in Patients with Noninfectious Uveitis in the Era of COVID-19 Vaccinations

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Purpose: To determine the risk of coronavirus disease 2019 (COVID-19) infection, hospitalization, and death in the era of COVID-19 vaccination among patients with noninfectious uveitis (NIU) taking immunosuppressive therapies.

Design: Retrospective cohort study from July 1, 2021, to June 30, 2022, using data from the Optum Labs Data Warehouse (OLDW) de-identified claims database.

Participants: Patients with a diagnosis of NIU from January 1, 2017, and who had $\geq$ 1 year of continuous enrollment in the OLDW.

Methods: Incidence rates (IRs) were calculated for each COVID-19 outcome. 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 systemic corticosteroid (SC) exposure, the average daily dose of prednisone over the exposed interval was included in the adjusted models.

Main Outcome Measures: Hazard ratios and IRs for COVID-19 infection, hospitalization, and death.

Results: This study included 62 209 patients with NIU. A total of 12 895 (20.7%) were exposed to SCs during the risk period. Incidence rates were increased when exposed to SCs versus unexposed for all COVID-19 outcomes. Incidence rates were also increased for all COVID-19 outcomes when exposed to SCs without COVID-19 vaccination versus exposed to SCs with $\geq$ 1 vaccination. In adjusted models, SCs were associated with increased risk of COVID-19 infection (HR, 3.57; 95% confidence interval [CI], 3.24−3.93; $P < 0.0001$), hospitalization (HR, 2.75; 95% CI, 2.07−3.65; $P < 0.0001$), and death (HR, 2.49; 95% CI 1.29−4.82; $P = 0.007$). Incremental increases in SC dose were associated with a greater risk for all outcomes. Disease-modifying antirheumatic drugs were associated with a decreased risk of infection (HR, 0.84; 95% CI, 0.74−0.96; $P = 0.01$), and tumor necrosis factor-α inhibitors were associated with an increased risk of infection (HR, 1.18; 95% CI, 1.01−1.39; $P = 0.04$).

Conclusions: Systemic corticosteroid exposure continues to be associated with greater risk of COVID-19 infection, hospitalization, and death among patients with NIU in an era of widespread COVID-19 vaccination. Unvaccinated individuals who are exposed to immunosuppressive treatments have a greater risk of severe outcomes. Coronavirus disease 2019 vaccination should be strongly encouraged in these patients.

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Supplemental material available at www.aaojournal.org.

Noninfectious uveitis (NIU) comprises a spectrum of ocular inflammatory conditions characterized by intraocular inflammation and may be associated with other autoimmune diseases or can be limited to the eye. If untreated, severe cases can result in irreversible damage and loss of vision. Treatment of uveitis commonly consists of corticosteroids or other immunosuppressive medications such as disease-modifying anti-rheumatic drugs (DMARDs) and biologics. Additionally, uveitis can be chronic or recurrent and therefore may require long-term use of immunosuppressants. Although these therapies are used to control inflammation, they may also increase the risk of infection.[1−3] Use of corticosteroids specifically can reduce neutrophil recruitment and delay viral clearance.[1,3−6] Due to this increased

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risk of infection, there has been heightened concern for those who are immunocompromised since the beginning of the COVID-19 pandemic. Currently, the Centers for Disease Control cites immunocompromised status as a risk factor for severe COVID-19 outcomes.[7]

To date, there is limited information on COVID-19 outcomes in patients with uveitis. In a study conducted by our group, we found that NIU itself was not an independent risk factor for COVID-19 outcomes, but rather, the increased risk in this patient population could be explained by factors such as demographics and comorbidities.[8] In another study, we explored the association between immunosuppressive medications and COVID-19 infection, hospitalization, and death among patients with NIU and found that exposure to systemic corticosteroids (SCs) was associated with increased risk.[9] However, these studies were conducted in an era prior to the availability of COVID-19 vaccinations and may not be generalizable to those who are vaccinated.

After emergency use authorization was granted by the United States (US) Food and Drug Administration on December 11, 2020, the first COVID-19 vaccination was delivered on December 14, 2020.[10] It is known that vaccination provides protection against COVID-19 infection and severe outcomes, but the impact of immunosuppression in patients who are vaccinated remains unclear. Therefore, the aim of this study was to determine if SCs and other immunosuppressive medications are associated with an increased risk of severe COVID-19 outcomes in patients with NIU in the era of COVID-19 vaccinations.

Methods

Data Source

This retrospective cohort study utilized data from Optum Labs Data Warehouse (OLDW; Optum Labs) which is a national database consisting of deidentified health care claims.[11] The OLDW contains longitudinal electronic health record and administrative claims information for commercial and Medicare Advantage enrollees since 1993. Administrative medical claims include International Classification of Diseases 10th Revision (ICD-10) diagnosis codes, Current Procedural Terminology codes, and pharmacy information. Enrollees in the OLDW represent a mixture of ages and geographical regions across the US, and all ages. The OLDW demographics are comparable with the US census with a larger proportion of enrollees in the south and central regions of the US.

Study Population and Time Period

To be eligible for this study, individuals were required to be continuously enrolled in both medical and pharmacy coverage in the 365 days prior to index date (baseline period) to allow for assessment of clinical characteristics. Individuals with an ICD-10 code for NIU from January 1, 2017, to June 30, 2022, were identified. The ICD-10 codes used to capture NIU diagnoses are included in Appendix 1 (available at https://www.ophthalmologyscience.org).

The study period was defined as July 1, 2021, which is when the Delta variant became the dominant circulating COVID-19 variant, to June 30, 2022. The index date (start of follow-up period for outcomes) was July 1, 2021. If the first NIU diagnosis was after this date, then the date of NIU diagnosis was considered the index date. Individuals were excluded if their NIU developed after COVID-19 infection. Individuals with any infectious uveitis diagnoses during the study period were also excluded (Appendix 1, available at https://www.ophthalmologyscience.org) (Fig 1).

COVID-19 vaccines were identified by the presence of a Current Procedural Terminology or Health care Common Procedure Coding System code in the medical claims, or an 11-digit National Drug Code or drug name text search in the pharmacy claims (Appendix 2, available at https://www.ophthalmologyscience.org).

Covariates

Cox proportional hazard ratio (HR) models were adjusted for age at index date, sex, race/ethnicity, region, smoking status, presence of comorbidities in the year preceding the index date, dominant variant (Delta or Omicron), prior history of COVID-19 infection, record of $\geq$ 1 COVID-19 vaccination, and COVID-19 treatment (pre-exposure prophylaxis with Evusheld, COVID-19 outpatient treatments, and COVID-19 inpatient treatments). Treatment with topical and local corticosteroids, including ophthalmic drops or ointments and corticosteroid intraocular/periocular injections or intraocular implants were included as a covariate to serve as a surrogate for active NIU and disease severity (Appendix 3, available at https://www.ophthalmologyscience.org). Prior history of COVID-19 infection was assessed from the baseline period up to 30 days prior to hospitalization or death outcomes. To ensure that the COVID-19 infection outcome would correspond to a new infection during the risk period, a prior history of COVID-19 infection was assessed from the baseline period up to 90 days prior to the COVID-19 infection date during the study risk period. COVID-19 treatments are described in Appendix 4 and 5 (available at https://www.ophthalmologyscience.org). Comorbidities included those identified as risk factors for severe COVID-19 infection according to the Center for Disease Control and Prevention as of December 5, 2022 (Appendix 6, available at https://www.ophthalmologyscience.org).

In the risk period, use of outpatient systemic immunosuppressive medication was identified and categorized as SCs, DMARDs, tumor necrosis factor-α (TNF-α) inhibitors, interleukin-6 (IL-6) inhibitors, other biologic immunosuppressive therapies, and other nonbiologic immunosuppressive therapies that do not fit into the previous categories. Immunosuppressive medication prescription fills were identified by text search of medication names in pharmacy claims (Appendix 7, available at https://www.ophthalmologyscience.org).

Time-varying dichotomous exposure to immunosuppressive medication was based on dispensing information in outpatient pharmacy claims. Exposure to an immunosuppressive medication was defined as the day the prescription was dispensed until the days' supply lapsed. The medication duration was defined by the "days supply" variable from the pharmacy claim, which indicates the number of days a prescription should last if the instructions of the prescription were followed as intended. A description of methods for handling gaps and overlaps between prescription fills is provided in Supplemental Methods 1 (available at https://www.ophthalmologyscience.org). The SC prescriptions were converted into prednisone equivalents for standardization (Appendix 8, available at https://www.ophthalmologyscience.org), and the average daily dose (mg) of a SC prescription was calculated as follows.

$$average\ daily\ dose = drug\ strength \times \frac{quantity}{days'\ supply}$$

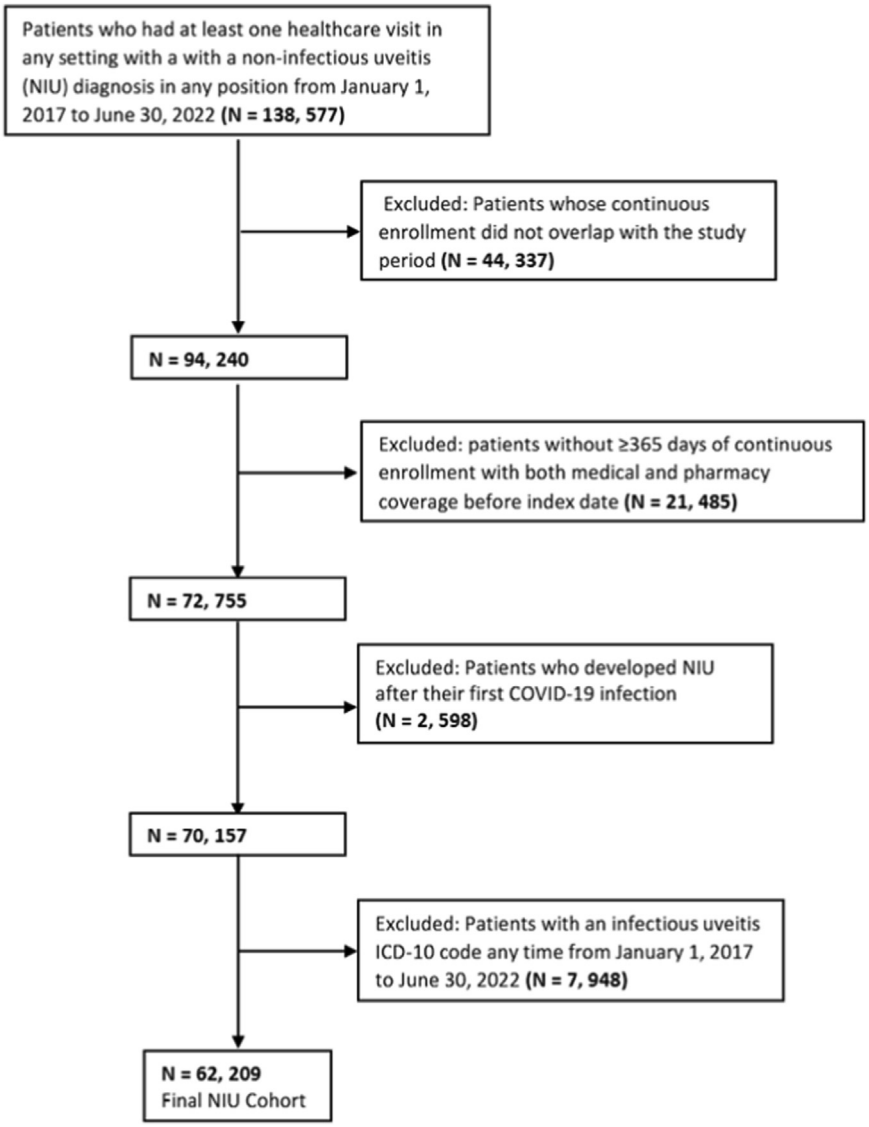

Figure 1. Cohort selection flow diagram. COVID-19 = coronavirus disease 2019; ICD-10 = International Classification of Diseases 10th Revision.

Outcomes

Outcomes were infection, hospitalization, and death due to COVID-19. These outcomes were assessed in an era of widespread COVID-19 vaccination during Delta and Omicron predominance (July 1, 2021, to June 30, 2022). Outcomes were identified using methods described in the Appendix 9 (available at https://www.ophthalmologyscience.org). Dates for infection, hospitalization, and death were based on the first date that met outcome criteria.

Statistical Analysis

Primary Analysis. Coronavirus disease 2019 outcome incidence rates (IRs) were calculated during unexposed and exposed person-time for each systemic immunosuppressive medication category and the dominant COVID-19 variant (Delta vs. Omicron). For each variable and COVID-19 outcome, unadjusted and adjusted HRs were estimated using Cox proportional hazards models, with time-updated exposure status for each immunosuppressive medication as a dichotomous variable. Models were adjusted for baseline demographics, comorbidities, average daily dose of SCs, NIU local treatment, COVID-19 treatment (prophylactic treatment with Evusheld and outpatient COVID-19 treatments were included for all outcomes, and inpatient COVID-19 treatments were included for the COVID-19 death outcome), history of prior COVID-19 infection, and vaccination status ($\geq$ 1 record). In addition to the dichotomous variable, the average daily dose (mg) of prednisone over the time interval was included in the adjusted models as a continuous variable to evaluate the effect of the level of SC exposure among those who were exposed.

Secondary Analysis. A secondary analysis was performed to study the association between SC exposure dose and COVID-19 hospitalization using a risk-stratification-based method. Patients with NIU were categorized into groups based on SC exposure level by duration and the average daily dose in which short-term was defined as $<$ 30 days (Supplemental Methods 2, available at https://www.ophthalmologyscience.org). A time-fixed Cox proportional hazards model with SC exposure level was used, which adjusted

for baseline demographics, comorbidities, NIU local treatment, and the other 5 immunosuppressive medication categories. We also assessed the risk of exposure to ≤ 5 mg/day prednisone equivalent corticosteroid doses.

Subgroup Analyses. We conducted an adjusted subgroup analysis using the same model as the primary analysis to assess for any differences in the effect of immunosuppression on COVID-19 hospitalization in younger versus older individuals (< 50 vs. ≥ 50 years old) and in patients with and without underlying autoimmune disease(s). We also calculated the IRs of COVID-19 outcomes among individuals exposed to SCs who had ≥ 1 record of COVID-19 vaccination versus those who did not have any record of COVID-19 vaccination.

Statistical analyses were performed in R (version 4.2.1, R Foundation for Statistical Computing, https://www.R-project.org). P values < 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 deidentified data were available for this study. Informed consent was waived by the institutional review board.

Results

Characteristics of the Study Population

A total of 62 209 patients with NIU were included in the study cohort. Of these, 12 895 patients (20.7%) were exposed to SCs during the risk period. The distribution of age and comorbidities was comparable between the patients who received SCs versus those who did not, aside from a higher percentage of having autoimmune diseases in the exposed group (14.8% vs. 29.2%) (Table 1). The prevalence of each specific autoimmune condition among those with history of another autoimmune disease is reported in Table S2 (available at https://www.ophthalmologyscience.org). There was also a higher percentage of women in the exposed group (57.9% vs. 65.6%). Record of ≥ 1 COVID-19 vaccination was 43.5%, or 27 049 individuals, and was similar between the exposed and unexposed group (42.6% vs. 43.7%). Within the overall study cohort, 46 497 (74.7%) had uveitis anatomically classified as anterior uveitis, 14 695 (23.6%) had posterior/panuveitis, 891 (1.4%) had intermediate uveitis, and 127 (0.20%) had unknown or sarcoid-related uveitis that did not have a specified anatomical subtype.

There were 65 822 patients excluded from the study due to having < 365 days of continuous enrollment with medical and pharmacy coverage prior to the index date or having continuous enrollment that did not overlap with the study period. The mean age was 62.6 years (standard deviation, 17.9) for those in the study cohort compared with 57.3 years (standard deviation, 18.97) for those who were excluded. The percentage of female patients in the study cohort was comparable to those who were excluded from the study (59.5% vs. 58.2%).

Immunosuppressive Medication Use

A total of 15 625 (25.1%) patients with NIU were prescribed ≥ 1 immunosuppressant from the 6 drug categories during the risk period (Table 3). Of the 6 immunosuppressant categories, the most prescribed treatment during this period was SCs (20.7%), followed by DMARDs (4.6%). In the overall cohort, 17 666 patients (28.4%) received topical ophthalmic steroid drops or local steroid injections/implants, during the risk period; 31.3% of patients were ever exposed to SCs, and 27.6% of those never exposed were treated with topical or local corticosteroids.

Twenty-eight thousand six hundred twenty-two SC prescriptions were filled by 12 895 SC users. The average prescription duration was 22 days, and median duration was 10 days (interquartile range; 6–30 days). The median prednisone equivalent average daily dose per prescription was 17.5 mg/day (interquartile range, 10–31 mg/day), and 21.6% of SC prescriptions had an average daily dose of ≥ 40 mg/day. Nineteen thousand six hundred ninety-six of the 28 622 (68.8%) SC prescriptions were prednisone. Among those who used SCs, 57.7% had 1 prescription fill, 19.2% had 2 prescription fills, and 23.1% had 3 or more prescription fills. Use of SCs by dosage and length of exposure is reported in Table S4 (available at https://www.ophthalmologyscience.org).

Exposures Associated with COVID-19 Infection

For the entire study cohort, there were 6292 cases of COVID-19 infections within 47 795 person-years (PY), corresponding to an overall IR of 131.6 per 1000 PY. Among those exposed to SCs, the IR of COVID-19 infection was 588.1 cases per 1000 PY compared with 118.3 cases per 1000 PY among those not exposed to SCs, corresponding to an IR ratio of 4.97 (Table 5). The IR was slightly higher in the exposed person-time for DMARDs, TNF-α inhibitors, IL-6 inhibitors, other biologics, and other immunosuppressive medications (Table 5).

The unadjusted HR for COVID-19 infection comparing SC exposed and unexposed person-time was 5.004 (95% confidence interval [CI], 4.62–5.42; $P < 0.0001$). Systemic corticosteroid exposure was also significantly associated with COVID-19 infection in the adjusted model with an HR of 3.57 (95% CI, 3.24–3.93; $P < 0.0001$). For those exposed to SCs, an increase of 10 mg of systemic prednisone (or equivalent) average daily dose was associated with a 16% increased risk of COVID-19 infection (HR, 1.16; 95% CI, 1.14–1.18; $P < 0.0001$). The remaining immunosuppressive medication categories were not significantly associated with increased hazard of COVID-19 infection after adjustment, except for the TNF-α inhibitors (HR, 1.18; 95% CI, 1.01–1.39; $P = 0.04$). Disease-modifying antirheumatic drugs were significantly associated with a decreased hazard of COVID-19 infection (HR, 0.84; 95% CI, 0.74–0.96; $P = 0.01$) (Table 6).

With regard to COVID-19 vaccination, the adjusted HR for COVID-19 infection with ≥ 1 COVID-19 vaccination was 0.48 (95% CI, 0.46–0.51; $P < 0.0001$) (Table S7, available at https://www.ophthalmologyscience.org). COVID-19 infection prophylactic treatment with Evusheld was significantly associated with a decreased hazard of COVID-19 infection in adjusted analyses (HR, 0.25; 95% CI, 0.11–0.61; $P = 0.002$) (Table S7, available at https://www.ophthalmologyscience.org).

Table 1. Baseline Characteristics of NIU Cohort by Systemic Corticosteroid Exposure Status* (N = 62 209)

	Never Exposed (n = 49 314)	Ever Exposed (n = 12 895)	All (N = 62 209)
Age			
Mean (SD)	62.5 (18.3)	63.3 (16.0)	62.6 (17.9)
Median [Q1, Q3]	68.0 [52.0, 76.0]	67.0 [54.0, 75.0]	68.0 [52.0, 75.0]
Sex†			
Female	28 568 (57.9%)	8458 (65.6%)	37 026 (59.5%)
Male	> 20 723 (> 42.0%)	> 4417 (> 34.3%)	> 25 151 (> 40.4%)
Race/ethnicity			
White	30 383 (61.6%)	8233 (63.8%)	38 616 (62.1%)
Asian	2271 (4.6%)	323 (2.5%)	2594 (4.2%)
Black	8702 (17.6%)	2479 (19.2%)	11 181 (18.0%)
Hispanic	5053 (10.2%)	1224 (9.5%)	6277 (10.1%)
Unknown/missing	2905 (5.9%)	636 (4.9%)	3541 (5.7%)
Region			
South	22 486 (45.6%)	7107 (55.1%)	29 592 (47.6%)
Midwest	11 867 (24.1%)	2943 (22.8%)	14 810 (23.8%)
Northeast	7898 (16.0%)	1540 (11.9%)	9439 (15.2%)
West	106 (0.2%)	17 (0.1%)	123 (0.2%)
Other/unknown	6957 (14.1%)	1287 (10.0%)	8244 (13.3%)
Charlson Comorbidity Index			
Mean (SD)	3.10 (2.52)	3.56 (2.69)	3.19 (2.56)
Median [Q1, Q3]	3.00 [1.00, 5.00]	3.00 [2.00, 5.00]	3.00 [1.00, 5.00]
Asthma	3345 (6.8%)	1935 (15.0%)	5280 (8.5%)
Another autoimmune disease	7307 (14.8%)	3763 (29.2%)	11 070 (17.8%)
Cancer	4519 (9.2%)	1554 (12.1%)	6073 (9.8%)
Cerebrovascular disease	4463 (9.1%)	1466 (11.4%)	5929 (9.5%)
Chronic kidney disease	7507 (15.2%)	2294 (17.8%)	9801 (15.8%)
Chronic liver disease	1718 (3.5%)	638 (4.9%)	2356 (3.8%)
Chronic lung disease	5078 (10.3%)	2515 (19.5%)	7593 (12.2%)
Diabetes (any type)	13 576 (27.5%)	3605 (28.0%)	17 181 (27.6%)
Disabilities	1236 (2.5%)	400 (3.1%)	1636 (2.6%)
Heart disease	8844 (17.9%)	2887 (22.4%)	11 731 (18.9%)
HIV/AIDS	207 (0.4%)	63 (0.5%)	270 (0.4%)
Primary immunodeficiency	169 (0.3%)	122 (0.9%)	291 (0.5%)
Mental health disorder	3558 (7.2%)	1315 (10.2%)	4873 (7.8%)
Neurologic disease	1516 (3.1%)	273 (2.1%)	1789 (2.9%)
Obesity	11 281 (22.9%)	3864 (30.0%)	15 145 (24.3%)
Pregnancy (risk period)	392 (0.8%)	78 (0.6%)	470 (0.8%)
Solid organ transplantation	440 (0.9%)	226 (1.8%)	666 (1.1%)
Number of comorbidities			
Mean (SD)	1.52 (1.58)	2.09 (1.76)	1.64 (1.63)
Median [Q1, Q3]	1.00 [0, 2.00]	2.00 [1.00, 3.00]	1.00 [0, 3.00]
Number of comorbidities category			
0	16 106 (32.7%)	2546 (19.7%)	18 652 (30.0%)
1	12 951 (26.3%)	3140 (24.4%)	16 091 (25.9%)
2–3	14 407 (29.2%)	4600 (35.7%)	19 007 (30.6%)
4+	5850 (11.9%)	2609 (20.2%)	8459 (13.6%)
Smoking status (baseline or risk period)			
Never	9930 (20.1%)	2844 (22.1%)	12 774 (20.5%)
Current/Former	10 590 (21.5%)	4159 (32.2%)	14 749 (23.7%)
Unknown	28 794 (58.4%)	5892 (45.7%)	34 686 (55.8%)
COVID-19 infection (baseline or risk period)	5776 (11.7%)	2837 (22.0%)	8613 (13.8%)
Had ≥ 1 COVID-19 vaccination records (12/24/2020 up to end date)	21 559 (43.7%)	5490 (42.6%)	27 049 (43.5%)
Received any outpatient COVID-19 treatments (risk period)	827 (1.7%)	505 (3.9%)	1332 (2.1%)
Received Evusheld, preventative COVID-19 treatment (risk period)	31 (0.1%)	53 (0.4%)	84 (0.1%)
Received any inpatient COVID-19 treatments (risk period)	0 (0.0%)	209 (1.6%)	209 (0.3%)
Ophthalmic steroid drops and/or steroid injections/implants (risk period)	13 626 (27.6%)	4040 (31.3%)	17 666 (28.4%)

AIDS = acquired immunodeficiency syndrome; COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; NIU = noninfectious uveitis; Q1 = first quartile (25th percentile); Q3 = third quartile (75th percentile); Q2 = median (50th percentile). 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 ≥ 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.
†In order to protect patient privacy, those whose sex was unknown have not been reported in this table due to small cell numbers.

Table 3. Immunosuppressive Drug Prescription During the Risk Period* (N = 62 209)

Drug Class/Generic Name	Number (%) of NIU Cohort with ≥ 1 Prescription Fill
Overall	15 625 (25.1%)
SCs	12 895 (20.7%)
Prednisone	8431 (13.6%)
Methylprednisolone	4837 (7.8%)
Dexamethasone	1000 (1.6%)
Budesonide	177 (0.3%)
Hydrocortisone	103 (0.2%)
Prednisolone	60 (0.09%)
DMARDs	2851 (4.6%)
Methotrexate	1790 (2.9%)
Mycophenolatic acid	490 (0.8%)
Azathioprine	353 (0.6%)
Leflunomide	288 (0.5%)
Tacrolimus	144 (0.2%)
Cyclosporine	51 (0.08%)
TNF-α inhibitors	1583 (2.5%)
IL-6 inhibitors	39 (0.1%)
Other biologics	557 (0.9%)
Secukinumab	135 (0.2%)
Ustekinumab	100 (0.2%)
Dupilumab	88 (0.1%)
Guselkumab	56 (0.09%)
Abatacept	45 (0.07%)
Ixekizumab	33 (0.05%)
Interferon beta-1A	26 (0.04%)
Omalizumab	25 (0.04%)
Risankizumab	22 (0.04%)
Belimumab	17 (0.03%)
Ofatumumab	12 (0.02%)
Others† (anti-CD20 mAbs, Vedolizumab, Anakinra, Eculizumab, Natalizumab, Alemtuzumab, Brodalumab, Canakinumab, Rilonacept)	17 (0.03%)
Other immunosuppressive drugs	697 (1.1%)
Sulfasalazine	343 (0.6%)
Apremilast	78 (0.1%)
Tofacitinib citrate	72 (0.2%)
Upadacitinib	50 (0.08%)
Dimethyl fumarate	34 (0.06%)
Glatiramer acetate	33 (0.05%)
Mercaptopurine	26 (0.04%)
Teriflunomide	19 (0.03%)
Ruxolitinib phosphate	15 (0.02%)
Diroximel fumarate	12 (0.02%)
Others† (Cyclophosphamide, Fingolimod HCl, Ozanimod HCl, Siponimod, Baricitinib, Cladribine)	30 (0.05%)

DMARDs = disease-modifying antirheumatic drugs; IL-6 = interleukin 6; mAbs = monoclonal antibodies; 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 coronavirus 2019 (COVID-19) hospitalization outcome date (results differ slightly for infection and death outcomes).
†In order to protect patient privacy, medications were grouped as Others due to small cell numbers.

Exposures Associated with COVID-19–Related Hospitalization

There were 771 cases of COVID-19 hospitalizations within 50 039.9 PY, corresponding to an overall IR of 15.4 per 1000 PY for the overall cohort. Among those exposed to SCs, the IR of COVID-19 hospitalization was 68.3 cases per 1000 PY compared with 13.8 cases per 1000 PY among those not exposed to SCs, corresponding to an IR ratio of 4.95 (Table 5). The IR was slightly increased in the exposed person-time for DMARDs and other biologics (Table 5).

The unadjusted HR for COVID-19 hospitalization comparing SC exposed and unexposed person-time was 4.89 (95% CI, 3.96–6.04; $P < 0.0001$). In adjusted models, SC exposure was also significantly associated with COVID-19 hospitalization with an HR of 2.75 (95% CI, 2.07–3.65; $P < 0.0001$). For those exposed to SCs, an increase of 10 mg of systemic prednisone (or equivalent) average daily dose was associated with a 17% increased risk of COVID-19 hospitalization (HR, 1.17; 95% CI, 1.09–1.26; $P < 0.0001$) (Table 6). In order to achieve robust estimates, the TNF-α inhibitors, other biologics, and other immunosuppressives categories could not be included in the adjusted model due to sparse numbers in the outcome.[12] We were not able to estimate an HR for IL-6 inhibitors due to zero outcome events in the exposed group. Disease-modifying anti-rheumatic drugs were not significantly associated with an increased hazard of COVID-19 hospitalization after adjustment.

The adjusted HR for COVID-19 hospitalization with ≥ 1 COVID-19 vaccination was 0.13 (95% CI, 0.10–0.17; $P < 0.0001$) (Table S8, available at https://www.ophthalmologyscience.org). COVID-19 outpatient treatment was significantly associated with an increased hazard of COVID-19 hospitalization in adjusted analyses (HR, 5.35; 95% CI 3.89–7.35; $P < 0.0001$).

In the risk-stratification secondary analysis, after covariate adjustment, the point estimates suggested an increased risk of hospitalization for most exposure levels of corticosteroids, although the CIs for many categories crossed 1 (Fig 2).

Exposures Associated with COVID-19–Related Death

There were 132 cases of COVID-19 deaths within 50 331.4 PY, corresponding to an IR of 2.6 per 1000 PY in the overall cohort. Among those exposed to SCs, the IR of COVID-19 death was 12.8 cases per 1000 PY compared with 2.3 cases per 1000 PY among those not exposed to SCs, corresponding to an IR ratio of 5.57 (Table 5). The IR was increased in the exposed person-time for DMARDs, TNF-α inhibitors, and other biologics (Table 5).

The unadjusted HR for COVID-19 death comparing SC exposed and unexposed person-time was 5.48 (95% CI, 3.37–8.91; $P < 0.0001$). In adjusted models, SC exposure was also significantly associated with COVID-19 death with an HR of 2.49 (95% CI, 1.29–4.82; $P = 0.007$). For those

Table 5. Incidence of COVID-19 Outcomes (Infection, Hospitalization, and 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: 6292 cases within 47 795.0 person years, corresponding to an incidence rate of 131.6 per 1000 person-years							
SC	797	1356.1	588.1	5495	46 438.9	118.3	4.97
DMARDs	278	1569.1	177.2	6014	46 225.9	130.1	1.36
TNF-α inhibitors	168	918.5	182.9	6124	46 876.5	130.6	1.40
IL-6 inhibitors*	/	/	176.4	/	/	131.6	1.34
Other biologic therapies	52	280.6	185.3	6240	47 514.4	131.3	1.41
Other immunosuppressive drugs	53	367.0	144.4	6239	47 428.0	131.5	1.20
COVID-19 hospitalization							
Overall: 771 cases within 50 039.9 person years, corresponding to an incidence rate of 15.4 per 1000 person-years							
SC	99	1449.7	68.3	672	48 590.1	13.8	4.95
DMARDs	44	1666.3	26.4	727	48 373.6	15.0	1.76
TNF-α inhibitors*	/	/	5.1	/	/	15.6	0.33
IL-6 inhibitors	0	23.8	0.0	771	50 039.9	15.4	0.00
Other biologic therapies*	/	/	26.7	/	/	15.3	1.75
Other immunosuppressive drugs*	/	/	15.4	/	/	15.4	1.00
COVID-19 death							
Overall: 132 cases within 50 331.4 person years, corresponding to an incidence rate of 2.6 per 1000 person-years							
SC	19	1483.2	12.8	113	48 844.3	2.3	5.57
DMARDs*	/	/	4.8	/	/	2.5	1.92
TNF-α inhibitors*	/	/	3.0	/	/	2.6	1.15
IL-6 inhibitors	0	23.8	0.0	132	50 307.6	2.6	0.00
Other biologic therapies*	/	/	3.3	/	/	2.6	1.27
Other immunosuppressive drugs*	/	/	2.5	/	/	2.6	0.96

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

exposed to SCs, an increase of 10 mg of systemic prednisone (or equivalent) average daily dose was associated with a 20% increased risk of COVID-19 death (HR, 1.20; 95% CI, 1.03−1.40; $P = 0.02$) (Table 6). In order to achieve robust estimates, the DMARDs, TNF-α inhibitors, other biologics, and other immunosuppressives categories could not be included in the adjusted model due to sparse numbers in the outcome.[12] We were not able to estimate an HR for IL-6 inhibitors due to zero outcome events in the exposed group.

The adjusted HR for COVID-19 death with ≥ 1 COVID-19 vaccination was 0.20 (95% CI, 0.11−0.35; $P < 0.0001$) (Table S9, available at https://www.ophthalmologyscience.org). COVID-19 inpatient treatment was significantly associated with an increased hazard of COVID-19 death in adjusted analyses (HR, 15.73; 95% CI, 7.06−35.04; $P < 0.0001$).

Sociodemographic Factors Associated with COVID-19 Outcomes

In adjusted analyses, Hispanic ethnicity was associated with an increased risk of infection (HR, 1.19; 95% CI 1.10−1.29; $P < 0.0001$). For COVID-19 hospitalization, increasing age (HR, 1.01; 95% CI, 1.004−1.02; $P = 0.002$) and male sex (HR, 1.21; 95% CI 1.04−1.40; $P = 0.01$) were significantly associated with increased risk. For COVID-19 death, increasing age (HR, 1.02; 95% CI, 1.01−1.04; $P = 0.005$), male sex (HR, 1.65; 95% CI, 1.15−2.36; $P = 0.007$), and Black race/ethnicity (HR, 1.53; 95% CI, 1.02−2.31; $P = 0.04$) were also significantly associated with increased risk. Specific associations between these factors and study outcomes are included in Tables S7−S9 (available at https://www.ophthalmologyscience.org).

Subgroup Analyses of COVID-19 Hospitalization by Age

There were 13 670 patients (22.0% of NIU cohort) < 50 years of age. A total of 2441 (17.9%) were exposed to SCs. There were 48 539 patients (78.0% of entire NIU cohort) > 50 years of age, of whom 10 454 (21.5%) were exposed to SCs. The adjusted HR for COVID-19 hospitalization among those aged ≤ 49 years old was 5.63 (95% CI, 1.97−16.04; $P = 0.001$) and was 2.67 (95% CI, 1.98−3.60; $P < 0.0001$) among those aged ≥ 50 years old (Table S10, available at https://www.ophthalmologyscience.org).

Subgroup Analyses of COVID-19 Hospitalization by Underlying Autoimmune Disease

There were 11 070 patients (17.8% of NIU cohort) who had an underlying autoimmune disease; 3763 (34.0%) were

Table 6. Unadjusted and Adjusted Hazard Ratios Showing Associations between Immunosuppressive Medication Exposure and COVID-19 Outcomes (Infection, Hospitalization, and Death) in NIU Patients

Immunosuppressive Medication	Unadjusted HR (95% CI)	P Value*	Adjusted HR (95% CI)	P Value*
COVID-19 infection‡				
SC (any exposure)	5.004 (4.62, 5.42)	< 0.0001	3.57 (3.24, 3.93)	< 0.0001
SC average daily dose (per 10 mg)	2.06 (2.004, 2.12)	< 0.0001	1.16 (1.14, 1.18)	< 0.0001
DMARDs	1.36 (1.21, 1.53)	< 0.0001	0.84 (0.74, 0.96)	0.01
TNF-α inhibitors	1.39 (1.20, 1.62)	< 0.0001	1.18 (1.01, 1.39)	0.04
Other biologics	1.41 (1.07, 1.85)	0.02	1.004 (0.76, 1.32)	0.98
Other immunosuppressive drugs	1.095 (0.83, 1.44)	0.52	0.94 (0.71, 1.23)	0.64
COVID-19 hospitalization‡				
SC (any exposure)	4.89 (3.96, 6.04)	< 0.0001	2.75 (2.07, 3.65)	< 0.0001
SC average daily dose (per 10 mg)	1.88 (1.74, 2.02)	< 0.0001	1.17 (1.09, 1.26)	< 0.0001
DMARDs	1.76 (1.30, 2.39)	0.0003	1.30 (0.92, 1.83)	0.14
IL-6 inhibitors†	/	/	/	/
COVID-19 death‡				
SC	5.48 (3.37, 8.91)	< 0.0001	2.49 (1.29, 4.82)	0.007
SC average daily dose (per 10 mg)	2.004 (1.74, 2.32)	< 0.0001	1.20 (1.03, 1.40)	0.02
IL-6 inhibitors†	/	/	/	/

CI = confidence interval; COVID-19 = coronavirus disease 2019; DMARDs = disease-modifying antirheumatic 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 hazards models.
†We were not able to estimate hazard ratio and corresponding P-value due to zero outcome event in the exposed group.
‡To achieve robust estimates, immunosuppressive drug categories we are only included in the Cox proportional hazards models for each outcome if the number of patients exposed was zero or >11.

exposed to SCs. There were 51 139 patients (82.2% of the entire NIU cohort) who did not have an underlying autoimmune disease, and 9132 (17.9%) were exposed to SCs. The adjusted HR for COVID-19 hospitalization among those with an underlying autoimmune disease was 2.81 (95% CI, 1.83−4.32; $P < 0.0001$) and was 2.79 (95% CI, 1.91−4.06; $P < 0.0001$) among those without (Tables S11 and S12, available at https://www.ophthalmologyscience.org).

Subgroup Analyses by COVID-19 Vaccination among Those Exposed to SCs

Among those exposed to SCs without a record of COVID-19 vaccination, the IR of COVID-19 infection was 757.2 per 1000 PY compared with 358.4 per 1000 PY in those exposed to SCs with ≥ 1 record of COVID-19 vaccination, corresponding to an IR ratio of 2.11. Among those exposed to SCs without a record of COVID-19 vaccination, the IR of COVID-19 hospitalization was 104.9 per 1000 PY, compared with 19.4 per 1000 PY in those exposed to SCs without a record of COVID-19 vaccination, corresponding to an IR ratio of 5.41. Among those exposed to SCs without a record of COVID-19 vaccination, the IR of COVID-19 death was 17.6 per 1000 PY, compared with 6.3 per 1000 PY in those exposed to SCs with ≥ 1 record of COVID-19 vaccination, corresponding to an IR ratio of 2.79.

Discussion

In this large US-based retrospective cohort study of patients with NIU, exposure to SCs was associated with an increased risk of COVID-19 infection, hospitalization, and death in an era of COVID-19 vaccination. There was approximately a 3.6-fold increase in risk of infection, 2.8-fold increase in risk of hospitalization, and 2.5-fold increase in risk of death among those exposed to SCs.

We observed a dose-dependent increased risk of SCs and COVID-19 outcomes. In our primary analyses, there was a 16% increased risk of COVID-19 infection and 17% increased risk of COVID-19 hospitalization for every 10 mg increase in the average daily dose of SCs. In our secondary risk-stratification analysis on SC dose and duration, we found that there is an increased risk at a low dose (0−10 mg/day) with both short-term and long-term use. Therefore, there may be an increased risk of COVID-19 hospitalization at low doses regardless of duration. The results for the >40 mg/day long-term use group had a wide CI, likely due to small cell numbers in this group. Due to small numbers, we were not able to assess smaller dose categories such as 0 to 5 mg/day. Other studies assessing steroid doses and COVID-19 outcomes in those with autoimmune conditions have found that steroid doses ≥ 7.5 mg/day and ≥ 10 mg/day were associated with a higher risk of hospitalization, which is consistent with our findings.[13−16]

Previous studies in the prevaccine era have been mixed with regard to the effect of corticosteroids and COVID-19 outcomes.[15−22] In a study by Risk et al[23] performed in the postvaccine era, DMARDs and glucocorticoids were associated with an increased risk of COVID-19 hospitalization compared with not taking any immunosuppressive medications. That study assessed immunosuppression as a baseline exposure, whereas in our study, we assessed SC exposure as a time-updated variable after index date; therefore, our definition of immunosuppression indicates active SC exposure. Despite this difference, the hazards for

Variable	Hazard Ratio (95% CI)	P-value
Systemic corticosteroid		
Short-term (0,10] mg/day	2.16 (1.22, 3.85)	0.009
Short-term (10,20] mg/day	0.92 (0.69, 1.23)	0.56
Short-term (20,30] mg/day	1.19 (0.67, 2.12)	0.55
Short-term (30,40] mg/day	1.59 (1.13, 2.24)	0.007
Short-term 40+ mg/day	1.92 (1.18, 3.12)	0.009
Long-term (0,10] mg/day	1.99 (1.33, 2.97)	<0.001
Long-term (10,20] mg/day	1.91 (0.85, 4.29)	0.12
Long-term (20,30] mg/day	3.24 (1.04, 10.14)	0.04
Long-term (30,40] mg/day	1.38 (0.44, 4.32)	0.58
Long-term 40+ mg/day	0.86 (0.12, 6.16)	0.88
Multiple dose categories and duration	1.27 (0.96, 1.67)	0.09
DMARDs	1.32 (0.96, 1.81)	0.09

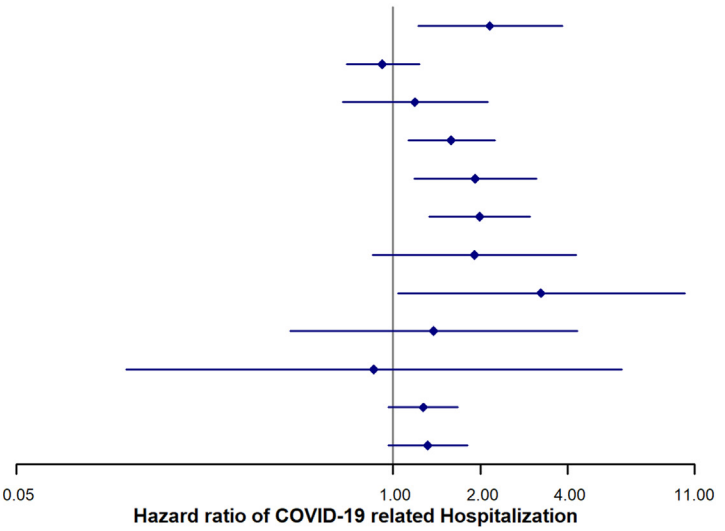

Figure 2. Adjusted HRs of coronavirus disease 2019 (COVID-19) hospitalization associated with immunosuppressive medications. A duration of < 30 days was considered short-term and ≥ 30 days was considered long-term. All systemic corticosteroid doses were converted into prednisone equivalents and broken down by 10 mg increments. CI = confidence interval; DMARDs = disease-modifying antirheumatic drugs; HR = hazard ratios.

glucocorticoids and COVID-19 hospitalization were similarly around a 3-fold increased risk. Our results for DMARDs and COVID-19 hospitalization were also in the harmful direction; however, our result for this category was not statistically significant, so a definitive conclusion about exposure to DMARDs and risk of COVID-19 hospitalization cannot be made.

We saw a protective effect of DMARDs with COVID-19 infection in the adjusted model. Mechanistically, DMARDs may be protective against COVID-19 infection by down-regulating angiotensin-converting enzyme 2,[24] which is used by severe acute respiratory syndrome coronavirus 2 to enter epithelial cells.[25] However, the association between DMARDs and COVID-19 outcomes requires further study.

Tumor necrosis factor alpha inhibitors were associated with an increased risk of infection in our study, but due to sparse outcome data, this medication category could not be assessed in adjusted models for hospitalization or death in order to avoid sparse data bias.[12] Similarly, other biologics and other immunosuppressive drug categories could not be included in the hospitalization model, and IL-6 inhibitors could not be assessed in the infection model. Only an HR for SCs could be assessed for the death model. Mechanistically, it is known that anti-TNF-α medications can promote viral infections as TNF plays an essential role in antiviral defenses.[26–28] Therefore, it is plausible that anti-TNFs increase risk of COVID-19 infection. The literature also notes that anti-TNFs, and other cytokine inhibitors such as anti-IL-6 agents, may be beneficial against active COVID-19 disease by attenuating the cytokine storm that is damaging to organs and leads to more severe outcomes.[29] However, it is unclear whether this protection during the acute phase of infection would similarly be seen with long-term use of these immunosuppressives.

In comparison to our prior study performed in an unvaccinated NIU population, we observed an increased IR of COVID-19 infection in the current study. The IRs of COVID-19 hospitalization and death were similar to our previous study in the unvaccinated era. The observed increase in infection may be due to the known increase in cases with the Delta and Omicron variants. In the general population, concurrent increases in the incidence of hospitalization with Delta and Omicron have been seen because of the increase in cases and not because of increased disease severity, as these variants are known to be less virulent. As our study population is an insured population, these individuals may overall be healthier than the general population, which may be why we have not seen a corresponding increase in hospitalization compared with our prevaccine era study.

To assess whether there are any differences in risk with regard to age, we analyzed the risk of exposure to immunosuppressive medication for those who were ≤ 49 years old and those who were ≥ 50 years old. We found that risk of COVID-19 hospitalization remains elevated in both age groups when exposed to SCs, indicating that SCs are associated with an increased risk for hospitalization regardless of age. Due to wide CIs, there is less precision in the HRs for SC exposure and hospitalization for these age groups, but the signal remains in the direction of increased risk. We also analyzed the risk of exposure to immunosuppressive medications in patients with and without underlying autoimmune diseases. The risk of COVID-19 hospitalization from exposure to SCs was comparable in each of these subgroups and to our main analysis.

Our prevaccine era study did not account for COVID-19 treatments, so it was unclear whether outpatient or in-hospital treatments such as remdesivir or dexamethasone would impact the association between outpatient

immunosuppressive medication use and COVID-19 outcomes.[9] In the current study, we were able to include pre-exposure prophylaxis treatment with Evusheld, outpatient COVID-19 treatments, and inpatient COVID-19 treatments in our Cox models. We found that Evusheld was significantly associated with decreased risk of COVID-19 infection, indicating a protective effect. On the other hand, outpatient and inpatient COVID-19 treatment were associated with increased risk of COVID-19 outcomes. However, the patients who received treatment for COVID-19 may have been sicker and therefore at increased risk for worse outcomes.

In the current study, record of ≥ 1 COVID-19 vaccination was associated with decreased risk of COVID-19 infection, hospitalization, and death in both adjusted and unadjusted models. Additionally, among those who were exposed to SCs and did not have a record of COVID-19 vaccination, the risk for COVID-19 infection, hospitalization, and death were increased by 2-fold, 5-fold, and nearly 3-fold, respectively. This indicates that COVID-19 vaccination was protective in patients with uveitis against all outcomes and was even protective specifically among those who were exposed to SCs. This points toward the need to strongly encourage vaccination in patients with uveitis who are on immunosuppressive therapies. Although the antibody response to vaccination may be lower in immunosuppressed individuals, receipt of COVID-19 vaccination still helps to prevents severe disease.[30,31] It is important for physicians to continue to counsel their patients on being fully up to date with their COVID-19 vaccinations.

Strengths and Limitations

One of the strengths of this study is the large sample size. With a large sample size, we were able to adjust for many potential confounders and therefore, more distinctly provide information on the effects of immunosuppressive medications in patients with NIU. Additionally, this large NIU cohort represents a diverse range of individuals across the US. By assessing exposure to the immunosuppressive medication categories as time-updated variables, we are able to avoid immortal-time bias and thus get more accurate estimates of effect size than if we adjusted as time-fixed variables.[9,32,33]

There are several limitations to this study, including those inherent to insurance claims datasets. As this study only includes data from individuals who have commercial insurance or Medicare Advantage, those with basic Medicare, Medicaid, or who are uninsured are not included in this study. Additionally, because the study includes those with Medicare Advantage, our study population may be more representative of an older population. As identification of COVID-19 outcomes relied on the use of ICD-10 codes, there is potential for misclassification of outcomes due to potential incomplete claims data and duration of medication usage, as well as factors that are unobservable in claims data such as patient nonadherence to medications. It is also a known issue in insurance claims data that COVID-19 vaccination is incompletely captured.[34] Therefore, it is unknown whether those who are classified as unvaccinated in the study are truly unvaccinated. However, because we found a protective effect for those who had ≥ 1 record of COVID-19 vaccination, the underreporting of COVID-19 vaccination in claims data points toward the potential that this protective association is likely even stronger. Another limitation of this study is that we were not able to analyze some immunosuppressive categories in the Cox models and were not able to analyze certain drug classes separately due to limited sample sizes and outcome data in these groups.

Conclusions

This study demonstrates that outpatient SC exposure continues to be associated with greater risk of COVID-19 infection, hospitalization, and death in patients with NIU in an era of widespread COVID-19 vaccination. Our results also indicate that those who are exposed to immunosuppressive medications who are not vaccinated have a greater risk of severe outcomes. Given these results, limiting exposure to SCs and use of alternative therapies may be prudent in patients with NIU, and the potential risk discussed in patient-physician counseling. COVID-19 vaccination should be strongly encouraged in patients taking immunosuppressive therapies.

Footnotes and Disclosures

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Author Contributions:

Conception and design: Sechrist, Tang, Sun, Arnold, Acharya

Analysis and interpretation: Sechrist, Tang, Sun, Arnold, Acharya

Data collection: Sechrist, Tang, Sun, Acharya; Obtained funding: Acharya; Overall responsibility: Sechrist, Tang, Acharya

Abbreviations and Acronyms:
CI = confidence interval; **COVID-19** = coronavirus disease 2019; **DMARDs** = disease-modifying anti-rheumatic drugs; **HR** = hazard ratio; **ICD-10** = International Classification of Diseases 10th Revision; **IL-6** = interleukin-6; **IR** = incidence rate; **NIU** = noninfectious uveitis; **OLDW** = Optum Labs Data Warehouse; **PY** = person-years; **SC** = systemic corticosteroid; **TNF-α** = tumor necrosis factor alpha; **US** = United States.

Keywords:
Corticosteroids, COVID-19 hospitalization, COVID-19 vaccination, Noninfectious uveitis, Immunosuppressive medications.

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