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Authors

Sechrist, Samantha

Tang, Emily

Arnold, Benjamin

et al.

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BMJ Open Association between immunosuppressive medications and COVID-19 hospitalisation and death: a retrospective cohort study

Samantha J Sechrist,^{1,2} Emily Tang ,¹ Benjamin F Arnold ,^{1,3} Nisha R Acharya ^{1,4,5}

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¹Francis I Proctor Foundation for Research in Ophthalmology, San Francisco, California, USA

²University of California San Francisco School of Medicine, San Francisco, California, USA

³Ophthalmology, University of California San Francisco, San Francisco, California, USA

⁴Department of Ophthalmology, University of California San Francisco, San Francisco, California, USA

⁵Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

Correspondence to

Dr Nisha R Acharya;
nisha.acharya@ucsf.edu

ABSTRACT

Importance Immunocompromised status is a risk factor for severe SARS-CoV-2 infection. Little is known about how systemic corticosteroid dose and concurrent use of immunosuppressants are associated with COVID-19 outcomes.

Objective To assess the association between corticosteroid dose/duration and concurrent immunosuppressant use on COVID-19 hospitalisation and death in the era of COVID-19 vaccinations.

Design This is a retrospective cohort study using a deidentified insurance claims database from 1 July 2020 to 30 June 30, 2022, with the risk period starting on 1 July 2021. Impact of corticosteroid exposures and concurrent use of other immunosuppressants was assessed with attributable risk analysis and Cox regression that included COVID-19 vaccination status and time-updated dichotomous immunosuppressive medication exposures.

Participants There were 10 109 596 eligible patients enrolled during the risk period, each with at least 365 days of continuous enrolment prior to 1 July 2021.

Exposures Systemic corticosteroids, disease-modifying antirheumatic drugs (DMARDs), tumour necrosis factor-alpha inhibitors (TNFis) and other immunosuppressive drug categories.

Main outcomes Incidence rate ratios and hazard ratios for COVID-19 hospitalisation and death.

Results Corticosteroids were prescribed to 1 379 049 (13.6%) of 10 109 596 individuals. After adjustment, corticosteroids were associated with an increased risk of COVID-19 hospitalisation (HR: 5.40; 95% CI 5.27 to 5.53; $p < 0.0001$) and death (HR: 5.90; 95% CI 5.59 to 6.22; $p < 0.0001$). Among individuals exposed to corticosteroids without a record of COVID-19 vaccination, risks for COVID-19 hospitalisation and death were increased by 3- and 14.5-fold. The population attributable risk of corticosteroid use for COVID-19 hospitalisations was 13.9% (95% CI 13.5 to 14.3%). There was a significantly increased risk of COVID-19 hospitalisation associated with the use of corticosteroids plus DMARDs (HR: 1.55; 95% CI 1.42 to 1.70; $p < 0.0001$) or plus TNFis (HR: 1.60; 95% CI 1.15 to 2.22; $p = 0.005$).

Conclusions Corticosteroids are associated with greater risk of COVID-19 hospitalisation and death, especially among unvaccinated individuals. Concurrent use of

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Large sample size.
- ⇒ Diverse population from the USA.
- ⇒ Linked medical and pharmacy claims data.
- ⇒ May not be generalisable to people without health insurance.
- ⇒ COVID-19 vaccinations may be undercaptured.

DMARDs and TNFis with corticosteroids confers greater risk.

INTRODUCTION

The Centres for Disease Control (CDC) cites immunocompromised status as a risk factor for severe SARS-CoV-2 infection. Due to impaired immune defences from both underlying disease and immunosuppressive treatments, these patients are at higher risk of infection and severe COVID-19 outcomes.¹ Although immunosuppressive medications reduce inflammation from underlying disease, they also increase the risk of infection.²⁻⁴

Previous studies investigating associations between immunosuppressive therapies and COVID-19 outcomes mostly focused on immunocompromised patients.⁵⁻¹⁶ Furthermore, many of these studies were conducted prior to COVID-19 vaccination availability and Omicron and Delta variant predominance. Patients who are taking corticosteroids and other immunosuppressive therapies for chronic immune-mediated conditions are immunocompromised because of their treatments and may face higher risks of infections and potentially worse COVID-19 outcomes. Rituximab, an anti-CD20 monoclonal antibody, has been associated with increased odds of COVID-19-related death compared with methotrexate monotherapy in patients with rheumatic diseases likely due to B-cell

depletion and compromised immunity against viruses, including less development of SARS-CoV-2 antibodies. As COVID-19 variants evolve, understanding the role of immunosuppressants on outcomes remains critical, yet there is limited information about their effect on the general population. Although studies have shown an association between corticosteroids and worse COVID-19 outcomes, information on specific doses and durations of systemic corticosteroid (SC) use and concurrent use of multiple immunosuppressants is scarce. To address these gaps, the aims of this study were to assess the association between SC exposure, including dose and duration, non-corticosteroid immunosuppressants and concurrent immunosuppressant use on COVID-19 hospitalisation and death in the era of widespread COVID-19 vaccination and Delta and Omicron predominance.

METHODS

Study design and setting

This is a retrospective cohort study that used Optum Labs Data Warehouse (OLDW; Optum Labs, Eden Prairie, Minnesota), a deidentified administrative claims and electronic health record database consisting of demographic information, medical claims and outpatient pharmacy claims of commercial and Medicare Advantage enrollees of all ages since 1994 in the USA.¹⁷ Medical claims comprised of diagnosis codes, that is, International Classification of Disease 10th revision (ICD-10), Current Procedural Terminology codes, dates of service and provider specialty codes. Pharmacy information included the National Drug Code, brand name, generic name, quantity, days' supply, drug strength, drug administration route and the prescription fill date.

Patient and public involvement

None.

Study population

Patients enrolled in OLDW between 1 July 2021 and 30 June 2022 were included. Each patient had at least 365 days of continuous enrolment with medical and pharmacy coverage before 1 July 2021, to capture baseline comorbidities. Medical and pharmacy coverage refers to health insurance benefits that provide access to health-care services such as physician visits, hospital care, medical treatments (medical coverage), as well as prescription medications or vaccinations (pharmacy coverage). The risk period started on 1 July 2021, which is the date designated by the US CDC as the start of the Delta variant dominant period. Cohort selection details are shown in online supplemental eAppendix 1.

Covariates

Baseline covariates included age in 2021, sex, race/ethnicity, geographic region and comorbidities. Comorbidities were captured based on ICD-10 codes (online supplemental eAppendix 2). Outpatient

immunosuppressant use during the risk period was categorised into the following groups: SCs, disease-modifying antirheumatic drugs (DMARDs), tumour necrosis factor-alpha inhibitors (TNFis), interleukin-6 (IL-6) inhibitors, anti-CD20 monoclonal antibodies, other biologic immunosuppressive therapies and other non-biologic immunosuppressive drugs that did not fit into the previous categories. Prescription fills for immunosuppressants and COVID-19 treatments were identified by text search of drug names in pharmacy claims (online supplemental eAppendices 3 and 4). Records of previous COVID-19 infection and vaccination were also included (online supplemental eAppendices 5 and 6).

Assessment of immunosuppressant exposure episodes

Time-varying dichotomous exposure was calculated for each immunosuppressant category based on outpatient pharmacy claims using methods previously described by our group (online supplemental methods 1, eAppendices 7 and 8).^{13 18}

Outcomes

Outcomes of interest included COVID-19 hospitalisation and COVID-19 in-hospital death, which were identified during the risk period (1 July 2021–30 June 2022) as described previously (online supplemental eAppendix 5).¹⁹ The first COVID-19 hospitalisation date was taken if there were multiple hospitalisations. Patients were censored if disenrolled from the medical plan, experienced death unrelated to COVID-19 or reached the end of the risk period.

Statistical analysis

Baseline covariates, clinical characteristics and immunosuppressant exposure during the risk period up to COVID-19 hospitalisation or censoring were summarised using descriptive statistics. Incidence rates (IRs) of COVID-19 outcomes (hospitalisation, in-hospital death) were calculated based on immunosuppressant categories (exposed vs non-exposed to a medication in that category) and COVID-19 vaccination status. Time-varying Cox regression using robust standard errors was applied to estimate associations of COVID-19 outcomes with time-updated covariates for each immunosuppressant exposure, baseline demographics (age, sex, region, race/ethnicity) and comorbidities, which were included as binary variables. Exposure to immunosuppressants dispensed was considered 'ever exposed' to that medication and included as a dichotomous variable in the models. The average daily prednisone dose (mg) during periods of SC exposure was included as a continuous covariate and reported per 10 mg unit change, in addition to the dichotomous SC exposure variable.

A risk-stratification-based method was performed as a secondary analysis to better understand the association between SC dose and duration and risk of COVID-19 outcomes (online supplemental methods 2).

Table 1 Baseline characteristics of general population cohort by systemic corticosteroid exposure status* (n=10 109 596)

	Never exposed† (n=8 730 547)	Ever exposed† (n=1 379 049)	All (n=10 109 596)
Age			
Mean (SD)	45.9 (23.5)	54.3 (20.7)	47.1 (23.3)
Median (Q1, Q3)	47.0(27.0, 67.0)	58.0(41.0, 70.0)	49.0(29.0, 67.0)
Sex			
Female	4 383 754 (50.2)	798 134 (57.9)	5 181 888 (51.3)
Male	4 345 127 (49.8)	580 774 (42.1)	4 925 901 (48.7)
Unknown	1666 (0.0)	141 (0.0)	1807 (0.0)
Race/ethnicity			
White	5 341 439 (61.2)	955 571 (69.3)	6 297 010 (62.3)
Asian	420 151 (4.8)	33 571 (2.4)	453 722 (4.5)
Black	814 700 (9.3)	145 078 (10.5)	959 778 (9.5)
Hispanic	974 510 (11.2)	130 337 (9.5)	1 104 847 (10.9)
Unknown/missing	1 179 747 (13.5)	114 492 (8.3)	1 294 239 (12.8)
Region			
South	3 538 880 (40.5)	723 435 (52.5)	4 262 215 (42.2)
Midwest	2 353 195 (27.0)	358 920 (26.0)	2 712 115 (26.8)
Northeast	1 029 139 (11.8)	143 594 (10.4)	1 172 733 (11.6)
West	1 559 402 (17.9)	152 264 (11.0)	1 711 666 (16.9)
Other/unknown	249 931 (2.9)	936 (0.1)	250 867 (2.5)
Charlson Comorbidity Index			
Mean (SD)	1.07 (1.33)	1.46 (1.36)	1.12 (1.34)
Median (Q1, Q3)	0(0, 2.00)	1.00(0, 3.00)	0(0, 2.00)
Asthma	351 975 (4.0)	157 189 (11.4)	509 164 (5.0)
Another autoimmune disease	422 443 (4.8)	174 541 (12.7)	596 984 (5.9)
Cancer	364 298 (4.2)	108 703 (7.9)	473 001 (4.7)
Cerebrovascular disease	316 892 (3.6)	87 661 (6.4)	404 553 (4.0)
Chronic kidney disease	537 689 (6.2)	144 283 (10.5)	681 972 (6.7)
Chronic liver disease	158 334 (1.8)	49 959 (3.6)	208 293 (2.1)
Chronic lung disease	388 453 (4.4)	186 581 (13.5)	575 034 (5.7)
Diabetes (any type)	1 107 062 (12.7)	247 442 (17.9)	1 354 504 (13.4)
Disabilities	271 983 (3.1)	47 453 (3.4)	319 436 (3.2)
Heart disease	707 919 (8.1)	209 509 (15.2)	917 428 (9.1)
HIV/AIDS	19 895 (0.2)	3563 (0.3)	23 458 (0.2)
Primary immunodeficiency	11 894 (0.1)	6778 (0.5)	18 672 (0.2)
Mental health disorder	429 149 (4.9)	112 825 (8.2)	541 974 (5.4)
Neurologic disease	143 514 (1.6)	21 512 (1.6)	165 026 (1.6)
Obesity	1 173 666 (13.4)	313 131 (22.7)	1 486 797 (14.7)
Pregnancy (risk period)	129 298 (1.5)	15 251 (1.1)	144 549 (1.4)
Solid organ transplantation	16 927 (0.2)	11 887 (0.9)	28 814 (0.3)
Number of comorbidities category			
0	5 221 105 (59.8)	518 624 (37.6)	5 739 729 (56.8)
1	1 847 801 (21.2)	357 485 (25.9)	2 205 286 (21.8)
2–3	1 302 572 (14.9)	358 131 (26.0)	1 660 703 (16.4)
4+	359 069 (4.1)	144 809 (10.5)	503 878 (5.0)

Continued

Table 1 Continued

	Never exposed† (n=8 730 547)	Ever exposed† (n=1 379 049)	All (n=10 109 596)
Smoking status (baseline or risk period)			
Never	1 280 469 (14.7)	272 796 (19.8)	1 553 265 (15.4)
Current/former	1 217 425 (13.9)	375 686 (27.2)	1 593 111 (15.8)
Unknown	6 232 653 (71.4)	730 567 (53.0)	6 963 220 (68.9)
COVID-19 infection (baseline or risk period)	1 158 862 (13.3)	350 187 (25.4)	1 509 049 (14.9)
Had ≥1 COVID-19 vaccination records (24 December 2020 up to end date)	3 896 643 (44.6)	619 133 (44.9)	4 515 776 (44.7)
Received any outpatient COVID-19 treatments (risk period)	89 856 (1.0)	45 315 (3.3)	135 171 (1.3)
Received tixagevimab/cilgavimab, preventative COVID-19 treatment (risk period)	1975 (0.0)	2282 (0.2)	4257 (0.0)
Received any inpatient COVID-19 treatments (risk period)	118 (0.0)	20 230 (1.4)	20 348 (0.2)

*Systemic corticosteroid (SC) exposure during the risk period up to COVID-19 hospitalisation or censoring is reported in this table. Patients with at least one prescription dispensing during risk period were considered 'ever exposed'.
†Numbers are reported as No. (%) unless otherwise specified.

We also determined the attributable risk proportion (ARP) and the population ARP (PARP) of corticosteroid exposure on COVID-19 hospitalisations.

To examine the effect of concurrent usage of immunosuppressants on COVID-19 hospitalisation, we evaluated the following combinations of drug exposures compared with DMARDs only: (1) DMARDs+SCs, (2) DMARDs+TNF-alpha inhibitors (TNFis) and (3) DMARDs+TNFis+SCs. We also assessed combinations compared with TNFis only: (1) TNFis+SCs, (2) TNFis+DMARDs and (3) TNFis+DMARDs+SCs. Categories were defined as ≥1 day of exposure; individuals who had no exposures or different exposure categories were excluded. Cox models were run separately, adjusting for baseline demographics and comorbidities.

Statistical analyses were performed in R (V.4.2.1, R Foundation for Statistical Computing, Vienna, Austria. <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.

RESULTS

Characteristics of the study population

There were 10 109 596 patients included in the cohort. More female patients were exposed to SCs than male patients (57.9% vs 42.1%). Patients who were exposed to SCs were older (mean: 54.3 years, SD: 20.7 years) and generally had a higher prevalence of comorbidities compared with those who were not exposed (mean: 45.9 years, SD: 23.5 years) (table 1, online supplemental table S1).

Immunosuppressant use

There were 1 474 862 (14.6%) patients who had at least one immunosuppressant exposure during the risk period. There were 1 379 049 (13.6%) individuals prescribed SCs and 96 201 (0.95%) received DMARDs. <0.5% of the cohort received a medication from each of the other immunosuppressive categories (table 2).

The average SC prescription duration was 15 days, and the median was 6 days (IQR: 5–16 days). The median prednisone equivalent average daily dose per prescription was 253.4 mg/day (IQR: 44.6–1250 mg/day) for intravenous steroids and 17.95 mg/day (IQR: 15–40 mg/day) for oral steroids. SCs were further classified by dosage and length of exposure (online supplemental table S2).

Exposures associated with COVID-19 hospitalisation and death

There were 77 647 COVID-19 hospitalisations within 8 786 685 person-years (PY) in the study cohort (overall IR of 8.8 per 1000 PY). The IR ratio (IRR) of hospitalizations among those exposed versus unexposed to SCs was 12.29. For all other immunosuppressant categories, IRs remained higher in the exposed person-time (table 3).

There were 13 783 COVID-19 deaths within 8 817 480 PY (IR: 1.6 per 1000 PY). The IRR of COVID-19 death among those exposed versus unexposed to SCs was 16.54. IRs remained higher in the exposed person-time for DMARDs and anti-CD20 monoclonal antibodies. There were zero deaths in those exposed to IL-6 inhibitors (table 3).

The HR compares the likelihood of an event (eg, COVID-19 death) occurring at any given time in the treatment group versus the control group (eg, SC exposed vs SC unexposed). The unadjusted HR for COVID-19 hospitalisation and death comparing SC exposed and unexposed person-time was 12.11 (95% CI 11.85–12.38; p<0.0001)

Table 2 Immunosuppressive drug prescriptions during the risk period* (n=10 109 596)

Drug class/generic name	Number (%) of cohort with ≥1 prescription fill†
Overall	1 474 862 (14.6)
Systemic corticosteroids	1 379 049 (13.6)
Prednisone	814 085 (8.1)
Methylprednisolone	539 234 (5.3)
Dexamethasone	120 773 (1.2)
Budesonide	11 604 (0.1)
Hydrocortisone	8037 (0.08)
Prednisolone	49 410 (0.5)
Disease-modifying antirheumatic drugs	96 201 (0.95)
Methotrexate	53 658 (0.5)
Mycophenolic acid (mycophenolate mofetil, enteric-coated mycophenolate sodium)	17 129 (0.2)
Tacrolimus	12 566 (0.1)
Leflunomide	12 381 (0.1)
Azathioprine	11 631 (0.1)
Cyclosporine	2150 (0.02)
Tumour necrosis factor-alpha inhibitors	31 147 (0.3)
Interleukin-6 inhibitors	1611 (0.02)
Anti-CD20 monoclonal antibodies	843 (0.008)
Ofatumumab	556 (0.005)
Rituximab	150 (0.001)
Ocrelizumab	>128 (0.001)
Obinutuzumab	<11 (0.0)
Other biologics	34 553 (0.3)
Dupilumab	10 482 (0.1)
Ustekinumab	5806 (0.06)
Secukinumab	4467 (0.04)
Risankizumab	3533 (0.04)
Guselkumab	3211 (0.03)
Abatacept	2161 (0.02)
Omalizumab	1993 (0.02)
Interferon beta-1a	1462 (0.01)
Ixekizumab	1140 (0.01)
Belimumab	751 (0.007)
Interferon beta-1b	214 (0.002)
Vedolizumab	161 (0.002)
Anakinra	159 (0.002)
Tildrakizumab	65 (0.001)
Natalizumab	41 (0.0)
Brodalumab	40 (0.0)
Eculizumab	31 (0.0)
Rilonacept	28 (0.0)

Continued

Table 2 Continued

Drug class/generic name	Number (%) of cohort with ≥1 prescription fill†
Canakinumab‡	>11 (0.0)
Alemtuzumab‡	<11 (0.0)
Other immunosuppressive drugs	35 727 (0.4)
Sulfasalazine	13 214 (0.1)
Apremilast	6258 (0.06)
Tofacitinib citrate	4003 (0.04)
Upadacitinib	2334 (0.02)
Mercaptopurine	2060 (0.02)
Glatiramer acetate	1981 (0.02)
Dimethyl fumarate	1893 (0.02)
Teriflunomide	1518 (0.02)
Ruxolitinib phosphate	1068 (0.01)
Fingolimod hydrochloride	979 (0.01)
Cyclophosphamide	479 (0.005)
Diroximel farate	257 (0.003)
Baricitinib	218 (0.002)
Cladribine	210 (0.002)
Ozanimod hydrochloride	177 (0.002)
Siponimod	166 (0.002)
Monomethyl fumarate	65 (0.001)

*Frequencies and percentages reflect the proportion of patients who filled one or more prescriptions during risk period up to COVID-19 hospitalisation outcome date (results differ slightly for death outcome).
 †Numbers are reported as No. (%) unless otherwise specified.
 ‡In order to protect patient privacy, medications with small cell numbers (<11 patients) were masked.

and 15.77 (95% CI 15.04 to 16.53; $p<0.0001$), respectively, and remained significant in the adjusted models (table 4). In the adjusted analyses, there was a 3.7% increased risk of COVID-19 hospitalisation (HR: 1.037; 95% CI 1.035 to 1.038; $p<0.0001$) and a 2.4% increased risk of death (HR: 1.024; 95% CI 1.022 to 1.026; $p<0.0001$) with every 10 mg average daily dose increase in prednisone equivalent SC use (table 4). Anti-CD20 monoclonal antibodies (HR: 3.47; 95% CI 1.97 to 6.11; $p<0.0001$) and other non-biologic immunosuppressive medications (HR: 1.21; 95% CI 1.0 to 1.34; $p=0.0001$) were significantly associated with an increased risk for hospitalisation, and DMARDs (HR: 0.91; 95% CI 0.86 to 0.96; $p=0.0003$) and TNF-alpha inhibitors (HR: 0.86; 95% CI 0.75 to 0.99; $p=0.04$) were significantly associated with decreased risk for hospitalisation. IL-6 inhibitors and other biologic therapies were not significantly associated with hospitalisation. Other non-biologic immunosuppressive medications (HR: 1.33; 95% CI 1.06 to 1.66; $p=0.01$) were significantly associated with an increased risk for death (table 4).

Table 3 Incidence of COVID-19 outcomes (hospitalisation 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 hospitalisation							
Overall: 77 647 cases within 8786685.0 person-years, corresponding to an incidence rate of 8.8 per 1000 person-years							
Systemic corticosteroids	8986	92 549.6	97.1	68 661	8694135.4	7.9	12.29
DMARDs	2127	61 621.2	34.5	75 520	8725063.8	8.7	3.97
TNF- α inhibitors*	202	19 714.4	10.2	77 445	8766970.5	8.8	1.16
IL-6 inhibitors	13	866.6	15.0	77 634	8785818.4	8.8	1.70
Anti-CD20 monoclonal antibodies	12	357.4	33.6	77 635	8786327.6	8.8	3.82
Other biologic therapies	194	19 095.8	10.2	77 453	8767589.2	8.8	1.16
Other immunosuppressive drugs	408	20 922.0	19.5	77 239	8765763.0	8.8	2.22
COVID-19 death							
Overall: 13 783 cases within 8817480.0 person-years, corresponding to an incidence rate of 1.6 per 1000 person-years							
Systemic corticosteroids	2027	94 361.6	21.5	11 756	8723118.3	1.3	16.54
DMARDs	430	62 362.3	6.9	13 353	8755117.7	1.5	4.60
TNF- α inhibitors	31	19 787.2	1.567	13 752	8797692.8	1.563	1.003
IL-6 inhibitors	0	872.9	0.0	13 783	8816607.1	1.6	0.00
Anti-CD20 monoclonal antibodies*	/	/	2.8	/	/	1.6	1.75
Other biologic therapies	31	19 174.2	1.62	13 752	8798305.8	1.56	1.04
Other immunosuppressive drugs	79	21 076.3	3.7	13 704	8796403.7	1.6	2.31

*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. Anti-CD20, anti-CD20 monoclonal antibodies; DMARD, disease-modifying antirheumatic drugs; IL-6, interleukin 6; TNF- α , tumour necrosis factor alpha.

COVID-19 outpatient treatment was associated with a higher risk of COVID-19 hospitalisation (HR: 3.29; 95% CI 3.16 to 3.43; $p < 0.0001$). Tixagevimab/cilgavimab (Evusheld), a preventative COVID-19 treatment, was associated with a 98% reduced risk of hospitalisation (HR: 0.02; 95% CI 0.01 to 0.04; $p < 0.0001$). There was a 72.4% and 64.6% reduced risk with previous COVID-19 infection (HR: 0.276; 95% CI 0.268 to 0.284; $p < 0.0001$) and with at least one COVID-19 vaccination (HR: 0.354; 95% CI 0.347 to 0.360; $p < 0.0001$), respectively (online supplemental table S3). There were zero deaths in those who had exposure to tixagevimab/cilgavimab. COVID-19 inpatient treatment was associated with a higher risk of COVID-19 death (HR: 19.46; 95% CI 17.83 to 21.23; $p < 0.0001$). There was a 72% and 92% reduced risk of death with previous COVID-19 infection (HR: 0.28; 95% CI 0.27 to 0.30; $p < 0.0001$) and with at least one COVID-19 vaccination (HR: 0.08; 95% CI 0.07 to 0.09; $p < 0.0001$) (online supplemental table S4). Among those exposed to SCs, the IRR of those without a record of COVID-19 vaccination was 3.1- and 14.5-fold higher for hospitalisation and death, respectively.

In the risk-stratification secondary adjusted analysis, the estimates suggested an increased risk of hospitalisation and death for most exposure levels of corticosteroids (figure 1).

Attributable risk proportion of corticosteroid exposure on COVID-19 hospitalisations

In the ARP analysis, 54.2% (95% CI 53.5 to 54.9%) of the COVID-19 hospitalisations could be directly attributed to corticosteroid use in those who took SCs. The PARP was 13.9% (95% CI 13.5 to 14.3%).

Subgroup analyses of concurrent immunosuppressant exposures and COVID-19 hospitalisation risk

Compared with those who were only exposed to DMARDs, those who had overlapping exposures with SCs had a 55% greater hazard of COVID-19 hospitalisation (HR: 1.55; 95% CI 1.42 to 1.70; $p < 0.0001$). There was a reduced hazard in those exposed to TNFis and DMARDs (HR: 0.88; 95% CI 0.64 to 1.21; $p = 0.43$) and an increased hazard in those exposed to TNFis, DMARDs and SCs (HR: 1.19; 95% CI 0.89 to 1.59; $p = 0.24$).

Compared with those who were only exposed to TNFis, those who were exposed to SCs and TNFis had a 60% greater hazard of COVID-19 hospitalisation (HR: 1.60; 95% CI 1.15 to 2.22; $p = 0.005$). Those who were exposed to TNFis, DMARDs and SCs had a 58% greater hazard of COVID-19 hospitalisation (HR: 1.58; 95% CI 1.09 to 2.29; $p = 0.02$). Exposure to DMARDs and TNFis was not significantly associated with higher risk (online supplemental table S5).

Table 4 Unadjusted and adjusted hazard ratios showing associations between immunosuppressive medication exposure and COVID-19 outcomes (hospitalisation and death) in the cohort

Immunosuppressive medication	Unadjusted HR (95% CI)	P value*	Adjusted HR (95% CI)	P value*
COVID-19 hospitalisation				
Systemic corticosteroids (SC) (any exposure)	12.11 (11.85, 12.38)	<0.0001	5.40 (5.27, 5.53)	<0.0001
SC average daily dose (per 10 mg)	2.52 (2.50, 2.53)	<0.0001	1.037 (1.035, 1.038)	<0.0001
DMARDs	4.006 (3.84, 4.18)	<0.0001	0.91 (0.86, 0.96)	0.0003
TNF- α inhibitors	1.17 (1.02, 1.34)	0.029	0.86 (0.75, 0.99)	0.038
IL-6 inhibitors	1.72 (0.998, 2.96)	0.051	0.62 (0.36, 1.07)	0.088
Anti-CD20 monoclonal antibodies	3.99 (2.27, 7.01)	<0.0001	3.47 (1.97, 6.11)	<0.0001
Other biologic therapies	1.18 (1.025, 1.36)	0.021	0.94 (0.82, 1.09)	0.43
Other immunosuppressive drugs	2.23 (2.02, 2.45)	<0.0001	1.21 (1.10, 1.34)	0.0001
COVID-19 death				
SC (any exposure)	15.77 (15.04, 16.53)	<0.0001	5.90 (5.59, 6.22)	<0.0001
SC average daily dose (per 10 mg)	2.71 (2.67, 2.76)	<0.0001	1.024 (1.022, 1.026)	<0.0001
DMARDs	4.56 (4.14, 5.02)	<0.0001	0.90 (0.80, 1.01)	0.075
TNF- α inhibitors	1.01 (0.71, 1.44)	0.96	0.84 (0.59, 1.20)	0.33
IL-6 inhibitors†	/	/	/	/
Anti-CD20 monoclonal antibodies	1.90 (0.27, 13.49)	0.52	2.08 (0.29, 14.77)	0.46
Other biologic therapies	1.07 (0.75, 1.52)	0.71	1.04 (0.73, 1.48)	0.83
Other immunosuppressive drugs	2.43 (1.95, 3.03)	<0.0001	1.33 (1.06, 1.66)	0.013

*P values calculated from Cox proportional hazards models.

†We were not able to estimate HR and corresponding p value due to zero outcome event in the exposed group.

Anti-CD20, anti-CD20 monoclonal antibodies; DMARD, disease-modifying antirheumatic drug; IL-6, interleukin 6; SC, systemic corticosteroid; TNF- α , tumour necrosis factor- α .

DISCUSSION

In this large retrospective cohort study of the general population using a US claims database, exposure to SCs was associated with an increased risk of COVID-19 hospitalisation and death in an era of COVID-19 vaccination. Among those exposed to SCs, there was a 5.4- and 5.9-fold increase in the risk of hospitalisation and death, respectively.

Studies addressing the associations between SCs and COVID-19 outcomes have yielded mixed results, and many of these studies were conducted prior to the availability of COVID-19 vaccinations and during the time period of earlier COVID variants.^{5–12} In the current era of COVID-19 vaccination, a study by Risk *et al* found an increased risk of COVID-19 hospitalisation among individuals taking DMARDs and glucocorticoids.²⁰ Our finding that over 50% of COVID-19 hospitalisations in those exposed to SCs were attributable to that exposure highlights the clinical significance of this risk factor.

For hospitalisation, both DMARDs and TNF-alpha inhibitors were significantly associated with a decreased risk in the adjusted model. The HRs were also in the protective direction for death but were not significant. It is unclear how conventional DMARDs may be protective against COVID-19 hospitalisation and death, though it has been postulated that DMARDs may be protective against COVID-19 infection via downregulation

of angiotensin-converting enzyme 2,²¹ which the virus uses for entry into epithelial cells.²² Other studies have found that TNF-alpha inhibitors may be associated with a decreased risk of COVID-19 hospitalisation, intensive care unit (ICU) admission and death.^{6 14 16 23} Mechanistically, TNF-alpha is increased in early and late stages of COVID-19 infection, so inhibiting this cytokine may help decrease the effects of a cytokine storm.²⁴ We found that anti-CD20 monoclonal antibodies, including rituximab, obinutuzumab and ofatumumab, were associated with increased risk, in line with prior studies.^{5 12 16 25–27} B- and T-cells protect against SARS-CoV-2 by playing a key role in viral clearance as well as protection against reinfection by eliciting a memory response.²⁸ Anti-CD20 therapies result in selective depletion of B-cells and to some degree T-cells,²⁹ so it is biologically plausible that taking these therapies increases risk. Furthermore, it may take 6–12 months after treatment to recover from this depletion.³⁰

This study also provides insight into the risks of concurrent immunosuppressant use and COVID-19 hospitalisation, which has been lacking in previous studies. Our results point towards an increased risk, specifically when SCs are added to DMARDs and TNF-alpha inhibitors. The harmful effect of outpatient SC use on COVID-19 outcomes is a consistent finding in all our analyses. Combination therapy with DMARDs and TNFis was in the protective direction for COVID-19 hospitalisation. This suggests

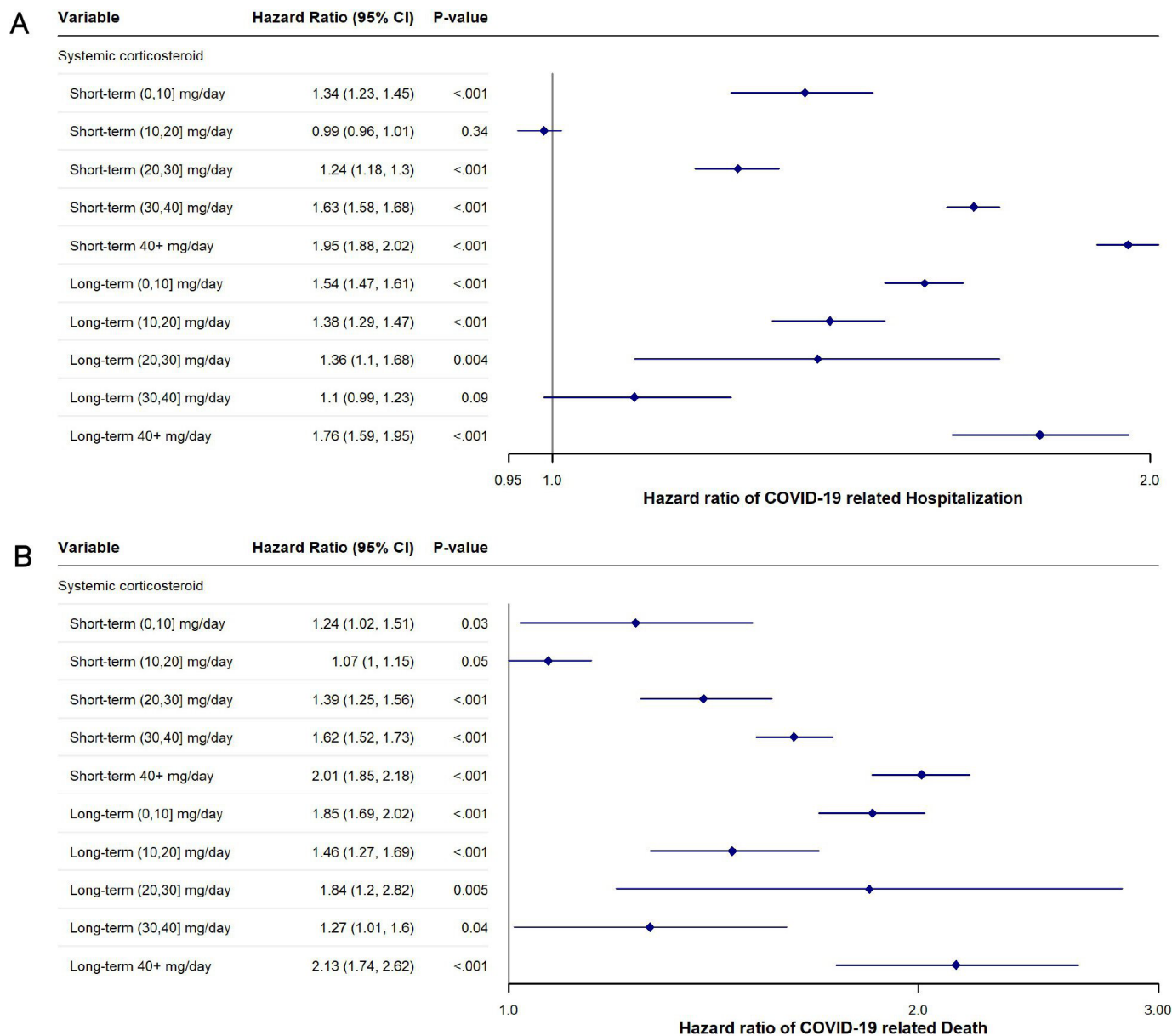


Figure 1 (A) Adjusted hazard ratios of coronavirus disease 2019 hospitalisation associated with systemic corticosteroid dose and duration. (B) Adjusted hazard ratios of coronavirus disease 2019 death associated with systemic corticosteroid dose and duration. A duration of <30 days was considered short term and ≥ 30 days was considered long term. All systemic corticosteroid (SC) doses were converted into prednisone equivalents and broken down by 10 mg increments.

that outpatient use of TNFis may have a protective effect, whether used alone or in combination with DMARDs. A single-centre study by Veenstra *et al*, including 213 individuals on immunosuppressants, found that those taking multiple immunosuppressive medications (DMARD plus a biologic or multiple DMARDs) were associated with increased odds of COVID-19 positivity and hospitalisation.¹⁴ However, that study was not able to attribute this increased association to any particular medication or medication category; therefore, it is unclear why this association was observed. In contrast, our study included SCs in a multidrug analysis and found that the addition of SCs accounted for the increased association with COVID-19 hospitalisation in all combinations, indicating the safety of DMARDs and TNFis when used together or alone.

Previous studies on the effect of dose and duration of SCs on COVID-19 outcomes have been scarce and have yielded mixed results. Some studies have found that prednisone doses ≥ 7.5 and ≥ 10 mg/day were associated with an increased risk of hospitalisation, while other studies found that risk was only increased when doses were ≥ 20 mg/day.^{5 6 15 31 32} Our results point towards a dose-dependent increased risk of SCs and worse COVID-19 outcomes. In our primary analyses, there was a 3.7% increased risk of COVID-19 hospitalisation and a 2.4% increased risk of COVID-19 death for every 10 mg prednisone equivalent increase in the average daily dose of SCs. In the risk-stratification analysis on SC dose and duration, we found a non-linear increased risk of both hospitalisation and death regardless of dose and duration. This

non-linearity may be attributed to tapering protocols, which are common in SC management, complicating the dose-response relationship. Furthermore, the relationship between corticosteroid doses and outcomes may not be directly proportional. These complex dynamics may explain why intermediate doses show higher HRs than expected and support the need for caution with any dose of SC.

Although overall coverage of COVID-19 vaccination was 45%, it was still associated with a reduced risk of hospitalisation and death. The lower-than-expected coverage can be partly attributed to the initial mass vaccination campaigns in the USA in 2021, which provided vaccinations that were covered by the US government. These vaccinations were not always linked to an insurance claim, and thus would not be captured in this database. Additionally, among individuals exposed to SCs who did not have a record of COVID-19 vaccination, the risk for COVID-19 hospitalisation and death was increased by 3-fold and nearly 15-fold, respectively, suggesting that COVID-19 vaccination was protective among those who were exposed to SCs. COVID-19 vaccination helps prevent severe disease among those who are immunosuppressed, even though the antibody response to vaccination in these individuals is lower than in those who are immunocompetent.^{33 34} It is crucial for physicians to continue advising immunosuppressed patients to be up-to-date with their COVID-19 vaccinations.

Our study also adjusted for receipt of pre-exposure prophylaxis with tixagevimab/cilgavimab as well as outpatient and inpatient COVID-19 treatments as they may affect hospitalisation and death, although it is no longer authorised by the US Food and Drug Administration as of 26 January 2023. Receipt of tixagevimab/cilgavimab was significantly associated with a decreased risk of COVID-19 hospitalisation. Notably, none of the individuals who had a COVID-19-related death had taken tixagevimab/cilgavimab. Receipt of outpatient and inpatient COVID-19 treatments was associated with an increased risk of both outcomes, likely indicating that these treatments were given to individuals with more severe infection, who were already at greater risk for worse outcomes. Furthermore, delays in initiating therapy or reduced effectiveness of conventional treatments such as monoclonal antibodies or antiviral medications in immunocompromised patients may have contributed to these results.

Strengths and limitations

This study includes a large, diverse population in the USA with over 10 million individuals. This sample size allowed for adjustment for many potential confounders, to assess many different immunosuppressive therapies, and to assess the risk of concurrent therapy exposure. Additionally, classifying exposure to the immunosuppressant categories as time-updated variables avoids immortal-time bias and provides more accurate effect size estimates.^{13 35 36}

There are several limitations to this study. This study only includes data from individuals who have commercial

insurance or Medicare Advantage; therefore, those with basic Medicare, Medicaid, or who are uninsured could not be assessed. As the study includes those with Medicare Advantage, our study population may skew towards an older population. Identification of COVID-19 outcomes relied on the use of ICD-10 codes; therefore, outcomes could be potentially misclassified. Additionally, it is not possible to assess patients' medication adherence since pharmacy claims only reflect prescription fills. Some immunosuppressive therapies have longer-lasting effects after stopping, but it was not feasible to account for this in our study. Finally, COVID-19 vaccination records are incompletely captured in claims databases,³⁷ so the protective effects of vaccination may be underestimated.

Conclusions

This study demonstrates that outpatient SC exposure is associated with greater risk of COVID-19 hospitalisation and death in an era of widespread COVID-19 vaccination. Among those taking combinations of DMARDs and TNFis, risk increased when SCs were added. Thus, it may be important for physicians to minimise the use of SCs when possible. Our results also indicate that unvaccinated individuals exposed to immunosuppressants have a greater risk of severe outcomes. COVID-19 vaccination should be strongly encouraged in patients taking immunosuppressive therapies.

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ORCID iDs

Emily Tang <http://orcid.org/0000-0003-4097-0186>

Benjamin F Arnold <http://orcid.org/0000-0001-6105-7295>

Nisha R Acharya <http://orcid.org/0000-0002-9762-9475>

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