Prior Immunosuppressive Therapy and Severe Illness Among Patients Diagnosed with SARS-CoV-2: a Community-Based Study

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BACKGROUND: An estimated 10 million people in the USA are immunocompromised, a risk factor for severe COVID-19. Data informing whether immune-mediated medications lead to more severe infection are sparse.

OBJECTIVE: Determine whether outpatient immunosuppressive therapies that treat autoimmune inflammatory disease or prevent solid organ transplant rejection are associated with severe illness after diagnosis with SARS-CoV-2

DESIGN: Retrospective cohort study

PARTICIPANTS: Adults with a positive PCR nasal swab for SARS-CoV-2 from February 25 to September 9, 2020, cared for within a large integrated health care organization

MAIN MEASURES: Exposure was defined as an outpatient fill of prednisone, immunomodulator, small-molecule, or biologic therapy in the 105 days prior to a positive SARS-CoV-2 PCR test. The main outcome was either hospitalization, ICU admission, or death within 45 days after diagnosis of SARS-CoV-2. Multivariable logistic regression models were adjusted for age, race, gender, body mass index, comorbidities, and autoimmune disease.

KEY RESULTS: A total of 39,686 adults had a positive PCR test. In the primary analysis, prior prednisone use was associated with severe illness after diagnosis with SARS-CoV-2 (odds ratio (OR) 1.31; 95% confidence interval (CI) 1.08–1.60); however, immunomodulator (OR 0.88; 95% CI 0.57–1.34) and biologic/small-molecule therapy (OR 1.26; 95% CI 0.79–2.00) were not. Secondary analyses showed variable risk among therapies: Janus-kinase inhibitors had an increased odds of severe illness (OR 3.35; 95% CI 1.16–9.67), thiopurines/conventionaldisease-modifying antirheumatic drugs had a reduced odds (OR 0.53; 95% CI 0.32–0.88), and tumor necrosis factor inhibitors were not associated (OR 0.45; 95% CI 0.18–1.08).

CONCLUSIONS AND RELEVANCE: Outpatient use of prednisone is associated with severe illness after diagnosis of SARS-CoV-2. Immunomodulator and biologic/small-molecule therapy were not associated, but different risk subgroups were identified. Our findings can inform risk-benefit discussions in the clinic and risk-based recommendations for patients on these therapies.

INTRODUCTION

An estimated 10 million people in the USA have an altered immune system, a potential risk factor for severe and fatal infection from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Patients on immune-modifying therapies such as prednisone, immunomodulators, biologics, and targeted small-molecule therapy are concerned that these medications may unacceptably impair the immune system and allow SARS-CoV-2 to spread unchecked in the body.[2–4]

Despite these concerns, it is unclear whether these immune-modifying therapies, used to treat conditions such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, and systemic lupus erythematosus as well as prevent rejection from solid organ transplantation, in fact worsen the severity of SARS-CoV-2 if infection occurs.[5] Prior studies have studied highly selected populations from single-specialty international registries or from referral centers, raising questions of generalizability as well as complete capture of key medication exposure, confounders, and outcomes.[6–18]

To address this gap, we assessed the relationship between use of prednisone, immunomodulators, biologics, and targeted small-molecule therapy prior to the diagnosis of SARS-CoV-2 and subsequent hospitalization, ICU admission, or death, all within a single integrated regional health care system in Northern California. We also explored the association between COVID-19 outcomes and acute (< 7 days) vs chronic prednisone use, monotherapy vs combination therapy, specific medication subgroups (anti-TNF, thiopurine/DMARDS, JAK inhibitors), as well as underlying immune-mediated disease.

METHODS

Study Design and Setting

We conducted a retrospective cohort study among health plan members of Kaiser Permanente Northern California (KPNC),

a large integrated health care delivery system that provides care for nearly 4.4 million members throughout the urban, suburban, and semirural regions in Northern California. The membership is diverse and similar in socioeconomic characteristics to the region's census demographics, including the proportions with commercial insurance, Medicare, and Medicaid.[19]

The Research Determination Committee for the Kaiser Permanente Northern California region determined the project does not meet the regulatory definition of research involving human subject per 45 CFR 46.102(d).

Eligibility Criteria

The study population consisted of health plan members aged 18 years or more with laboratory evidence of a SARS-CoV-2 diagnosis, defined as a positive PCR nasal swab between February 25 and September 9, 2020.[20] The date of the positive SARS-CoV-2 PCR test served as the reference point for all exposure, outcome, and covariate measures.

Data Sources

Data for demographics, SARS-CoV-2 test results, medications, outcomes, and comorbidities were obtained from laboratory, pharmacy, medical visit, hospital, demographic, and membership electronic records.

Medication Exposure

The primary exposure was having any outpatient prescription fill for prednisone, immunomodulator, small-molecule, or biologic therapy in the 105 days prior to a positive SARS-CoV-2 PCR test. This window allowed the capture of prescriptions that may have been dispensed as 100-day supplies. We categorized non-steroid medications based on definitions and terms commonly understood across multiple autoimmune conditions.[21] All medications were assessed using flag variables, allowing patients to be on any number of combination therapies.

Immune-modifying therapies selected were those used to treat either inflammatory bowel disease (ulcerative colitis, Crohn's disease), rheumatoid arthritis, spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis), psoriasis, or systemic lupus erythematosus, or to prevent rejection from solid organ transplantation (Supplemental Table 1). The main oral steroid included was prednisone; there were few users of oral methylprednisolone, which we decided to remove for clear interpretation of prednisone results. Small-molecule therapies were grouped with biologic therapy to mitigate small cell size during multivariable analysis, similar to a prior study[7]. For therapies with counts less than 5, we presented and analyzed the data in larger aggregated groups or did not provide specific counts to protect personal health information (PHI).

Outcome Ascertainment

The primary outcome was severe illness after a SARS-CoV-2 diagnosis, defined as a composite outcome of hospitalization, ICU admission, or death in the 45 days after a positive test or until September 10, 2020, whichever occurred first. Each outcome was also analyzed individually. Although we selected an outcome window of 45 days to allow sufficient time to capture all potentially related deaths to COVID-19,[22] we repeated the analysis but restricted outcomes to 21 days, a common lag period between onset of disease and death.[23]

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of cohort members. Categorical variables were expressed as proportions. Multivariable logistic regression analysis assessed the relationship between category of immune-modifying therapy before a positive SARS-CoV-2 PCR test and subsequent severe illness. Each component outcome (hospitalization, ICU admission, death) was also analyzed in separate models.

Models were adjusted for factors associated with severe illness from SARS-CoV-2, including age, gender, race/ethnicity, body mass index (BMI), and Charlson comorbidity index, as well as cancer, chronic obstructive pulmonary disease, diabetes, and hypertension.[24–28] Models were also adjusted for underlying autoimmune disease as well as week of diagnosis, the latter to account for changing testing and treatment practices over time as well as the shortened length of follow-up for patients with a positive lab test near the end of the study period. For age, we selected the group aged 30–49 years as the reference group because it had the largest number of patients. BMI was categorized as underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30.0 kg/m^2).[29] Specific comorbidities (cancer, chronic obstructive pulmonary disease, diabetes, hypertension), as well as the Charlson comorbidity index, were assessed using a 1-year lookback period from date of SARS-CoV-2 testing. Specific immune conditions, including asthma (ICD10: J45); inflammatory bowel disease (K50–K51); solid organ transplantation of the kidney, heart, lung, or liver (Z94.0–Z94.4); psoriasis (L40 except L40.5); rheumatoid arthritis (M05–M06); spondyloarthropathy (L40.5, M45); and systemic lupus erythematosus (M32), were assessed using a 5-year lookback period to ensure full capture of disease. To address potential concerns about collinearity between health conditions and medications, we repeated the analysis, but without adjusting for underlying autoimmune disease.

Exploratory Analyses

Exploratory analyses were performed to address additional data gaps, guided by clinical relevance, prior literature, and groupings with enough outcomes for meaningful analysis.[7,9,10,13] These analyses assessed the relationship between severe SARS-CoV-2 and acute (< 7 days) vs longer (≥ 7 days) steroid use, as well as combinations of medication classes and more granular groupings of therapies including TNF inhibitors, JAK inhibitors, and thiopurines/conventionaldisease–modifying

antirheumatic drugs (DMARDs) (methotrexate, hydroxychloroquine, leflunomide). The remaining therapies were categorized as to whether they had an indication outside of autoimmune disease (typically transplant or cancer) or not (see Table 3 for a list). We did not assess outcomes based on steroid dose (1–9 mg vs. 10 mg or more)[7] as tapers were often written as free text elements that often fluctuated, and thus not accurately reflected in the electronic pharmacy record. Exploratory analyses were adjusted for the same factors as the primary analysis.

RESULTS

Demographic Characteristics

We identified 39,686 adults with a positive PCR nasal swab for SARS-CoV-2. A total of 2.4% (n = 958) had received a prior prescription for oral prednisone, 0.8% (n = 327) for an immunomodulator, 0.4% (n = 152) for a biologic, and 0.1% (n = 47) for a small-molecule therapy (Table 1). These proportions were similar to the background population (data not shown). A total of 5069 had an underlying diagnosis of asthma, 1199 had an immune-mediated condition listed in Table 1, and 90 had undergone prior solid organ transplantation. A total of 10.0% (n = 3977) had at least one outcome of interest. Most patients on an immunomodulator were prescribed either thiopurine, hydroxychloroquine, methotrexate, or leflunomide. Nearly half of the patients dispensed a small molecule were on a JAK inhibitor. Most patients on a biologic were on a TNF inhibitor, with less than 15% on rituximab. Additional characteristics of those with and without any severe COVID-19 outcome are shown in Table 1.

Medication Use and Severe Illness After SARS-CoV-2 Diagnosis

After adjustment for covariates, outpatient prednisone use was associated with severe illness after diagnosis with SARS-CoV-2 (odds ratio (OR) 1.31; 95% confidence interval (CI) 1.08–1.60), including hospitalization (OR 1.32; 95% CI 1.08–1.60), ICU admission (OR 1.84; CI 1.38–2.46), and death (OR

Table 1 Characteristics of 39,686 Members Testing Positive for SARS-CoV-2 and a 45-Day Composite Outcome of any Hospitalization, ICU Admission, or Death

Characteristic	Any outcome N = 3977 N (%)	No outcome N = 35,709 N (%)	All patients N = 39,686 N (%)
Female	1833 (46.1)	18,835 (52.8)	20,668 (52.1)
Age (years)			
18–29	245 (6.2)	9545 (26.7)	9790 (24.7)
30–49	998 (25.1)	15,747 (44.1)	16,745 (42.2)
50–65	1260 (31.7)	7874 (22.1)	9134 (23.0)
> 65	1474 (37.1)	2543 (7.1)	4017 (10.1)
Race/ethnicity			
Asian	574 (14.4)	3970 (11.1)	4544 (11.5)
Black	406 (10.2)	2408 (6.7)	2814 (7.1)
Hispanic	1778 (44.7)	17,679 (49.5)	19,457 (49.0)
White	898 (22.6)	7462 (20.9)	8360 (21.1)
Other/unknown	321 (8.1)	4190 (11.7)	4511 (11.4)
Body mass index			
Underweight	73 (1.8)	233 (0.7)	306 (0.8)
Healthy weight	649 (16.3)	6133 (17.2)	6782 (17.1)
Overweight	1021 (25.7)	10,478 (29.3)	11,499 (29.0)
Obese	2052 (51.6)	14,869 (41.6)	16,921 (42.6)
Charlson comorbidity score			
0	1691 (42.5)	27,220 (76.2)	28,911 (72.9)
1	699 (17.6)	5103 (14.3)	5802 (14.6)
≥ 2	1587 (39.9)	3386 (9.5)	4973 (12.5)
Specific comborbidities			
Cancer	164 (4.1)	406 (1.1)	570 (1.4)
Chronic obstructive pulmonary disease	549 (13.8)	2068 (5.8)	2617 (6.6)
Diabetes	1158 (29.1)	2055 (5.8)	3213 (8.1)
Hypertension	1265 (31.8)	1535 (4.3)	2800 (7.1)
Specific immune conditions			
Asthma	745 (18.7)	4324 (12.1)	5069 (12.8)
Inflammatory bowel disease	44 (1.1)	172 (0.5)	216 (0.5)
Organ transplantation	39 (1.0)	51 (0.1)	90 (0.2)
Psoriasis	98 (2.5)	453 (1.3)	551 (1.4)
Rheumatoid arthritis	72 (1.8)	244 (0.7)	316 (0.8)
Spondyloarthropathy	6 (0.2)	63 (0.2)	69 (0.2)
Systemic lupus erythematosis	12 (0.3)	35 (0.1)	47 (0.1)
Therapies (not mutually exclusive)			
Prednisone	197 (5.0)	761 (2.1)	958 (2.4)
Conventional immunomodulator	83 (2.1)	244 (0.7)	327 (0.8)
Biologic	28 (0.7)	124 (0.4)	152 (0.4)
Small molecule	9 (0.2)	38 (0.1)	47 (0.1)
None	3723 (93.6)	34,683 (97.1)	38,406 (96.8)

1.70; CI 1.17–2.47) (Table 2). Immunomodulator (OR 0.88; CI 0.57–1.34) and biologic/small-molecule therapy (OR 1.26; CI 0.79–2.00) were not associated.

Sensitivity Analyses

To address concerns about collinearity between health conditions and medications, we repeated the analysis, this time not adjusting for underlying autoimmune disease, but still adjusting for other covariates. For any outcome, the odds ratio for steroids was 1.38 (95% CI 1.13–1.67), immunomodulators 1.05 (95% CI 0.77–1.44), and biologic/small-molecule therapies 1.09 (95% CI 0.71–1.68).

Restricting outcomes to 21 days after diagnosis did not meaningfully change the overall combined outcome for prednisone (OR 1.34, 95% CI 1.10–1.63), immunomodulator (OR 0.94, 95% CI 0.61–1.44), or small molecule/biologic (OR 1.29, 95% CI 0.81–2.05), nor the individual outcomes, except that prednisone was no longer statistically significantly associated with death (OR 1.39, 95% CI 0.88–2.18).

Exploratory Analyses

After adjustment for covariates, use of acute prednisone (< 7 days) was associated with ICU admission, but not other outcomes (Table 3). Chronic use (≥ 7 days) had a comparable point estimate for death as in the main

analysis but was no longer statistically significant (OR 1.59; 95% CI 0.86–2.95). It remained significant for any outcome, inpatient admission, and ICU admission.

Neither monotherapy with immunomodulators (OR 0.76; 95% CI 0.46–1.27) nor with biologics/small molecules (OR 0.82; 95% CI 0.43–1.55) increased the odds of severe illness with SARS-CoV-2, whereas prednisone monotherapy did increase the odds (OR 1.25; 95% CI 1.01–1.54). Patients on multiple therapies had increased odds of severe illness, but only the combination of a biologic/small molecule with prednisone was statistically significant (OR 3.57; 95% CI 1.17–10.85) (Table 3).

Use of thiopurines/traditional DMARDs prior to diagnosis of SARS-CoV-2 had a reduced odds of severe illness (OR 0.53; 95% CI 0.32–0.88), JAK inhibitors had an increased odds (OR 3.35, 95% CI 1.16–9.67), and anti-TNF therapy was not associated (OR 0.45, 95% CI 0.18–1.08) (Table 3). Among the remaining therapies, prior use of biologic/small-molecule therapies used exclusively in autoimmune diseases (see list in Table 3) did not have an increased odds of severe illness (OR 0.83; 95% CI 0.37–1.89). In contrast, biologics and immunomodulators with an indication beyond autoimmune disease (i.e., typically cancer or transplant) had an increased odds (OR 3.84, 95% CI 2.01–7.35).

Table 2 Adjusted Associations of 45-Day Severe Outcomes of Patients Testing Positive for SARS-CoV-2. $N = 39,686$

	Any outcome OR (95% CI) N = 3977	Hospitalization OR (95% CI) N = 3819	ICU admission OR (95% CI) N = 991	Death OR (95% CI) N = 600
Medication class (vs none)				
Prednisone	1.31 (1.08–1.60)	1.32 (1.08–1.60)	1.84 (1.38–2.46)	1.70 (1.17–2.47)
Conventional immunomodulator	0.88 (0.57–1.34)	0.99 (0.65–1.51)	0.95 (0.49–1.85)	1.71 (0.85–3.47)
Small molecule or biologic	1.26 (0.79–2.00)	1.27 (0.80–2.01)	1.32 (0.64–2.69)	1.51 (0.66–3.48)
Immune condition (vs none)				
Asthma	1.08 (0.98–1.20)	1.11 (1.00–1.23)	1.10 (0.92–1.32)	0.85 (0.67–1.07)
Inflammatory bowel disease	1.22 (0.82–1.81)	1.15 (0.77–1.72)	0.83 (0.41–1.69)	0.76 (0.35–1.68)
Organ transplantation	1.84 (1.00–3.40)	1.86 (1.01–3.40)	1.58 (0.67–3.71)	0.69 (0.24–1.95)
Psoriasis	1.15 (0.89–1.49)	1.17 (0.90–1.51)	1.63 (1.10–2.39)	0.92 (0.53–1.58)
Spondyloarthopathy	0.37 (0.14–0.97)	0.38 (0.15–0.99)	0.19 (0.02–1.51)	0.37 (0.04–3.08)
Rheumatoid arthritis	0.95 (0.66–1.36)	0.93 (0.65–1.34)	0.97 (0.55–1.69)	0.67 (0.36–1.24)
Systemic lupus erythematosis	1.22 (0.53–2.83)	1.31 (0.57–2.99)	1.11 (0.32–3.80)	1.00 (0.25–4.00)
Charlson comorbidity score	1.15 (1.13–1.18)	1.12 (1.09–1.14)	1.07 (1.04–1.11)	1.18 (1.14–1.23)
Hypertension	3.19 (2.88–3.53)	3.28 (2.95–3.63)	3.31 (2.80–3.91)	2.24 (1.83–2.73)
Female (vs. male)	0.68 (0.63–0.73)	0.67 (0.63–0.73)	0.46 (0.40–0.53)	0.63 (0.53–0.75)
Age, years				
18–29	0.48 (0.42–0.56)	0.48 (0.42–0.56)	0.41 (0.29–0.58)	0.31 (0.11–0.89)
30–49	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
50–65	2.00 (1.83–2.20)	2.02 (1.84–2.22)	2.55 (2.13–3.06)	7.03 (4.52–10.94)
> 65	4.87 (4.35–5.45)	4.52 (4.03–5.06)	4.66 (3.77–5.75)	32.91 (21.30–50.84)
Race/ethnicity				
Asian	1.74 (1.53–1.98)	1.82 (1.60–2.07)	2.07 (1.63–2.63)	0.82 (0.61–1.10)
Black	1.55 (1.34–1.80)	1.60 (1.41–1.86)	1.84 (1.41–2.39)	1.03 (0.76–1.40)
Hispanic	1.43 (1.29–1.58)	1.49 (1.35–1.64)	2.02 (1.68–2.44)	0.89 (0.71–1.11)
White	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Other/unknown	1.18 (1.01–1.37)	1.18 (1.01–1.38)	1.55 (1.16–2.06)	0.99 (0.70–1.39)
Body mass index[*]				
Underweight	2.20 (1.57–3.10)	1.47 (1.02–2.12)	1.31 (0.71–2.45)	3.13 (2.00–4.92)
Normal weight	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Overweight	0.97 (0.86–1.09)	1.03 (0.92–1.17)	1.06 (0.86–1.32)	0.55 (0.43–0.70)
Obese	1.60 (1.43–1.79)	1.72 (1.53–1.92)	1.66 (1.35–2.04)	0.81 (0.65–1.02)

All models also adjust for week of SARS-CoV-2-positive lab test
*Also adjusts for missing/unknown status

Table 3 Exploratory Analyses of Specific Medication Exposures and Any Severe COVID-19 Outcome

	Number of outcomes/number of cases	Adjusted OR (95% CI) N = 3977
Original analysis (Table2)		
No immune-mediated medication	3723/38,406	Ref
Prednisone	197/958	1.31 (1.08–1.60)
Immunomodulator	83/327	0.88 (0.57–1.34)
Small-molecule/biologic therapy	36/193	1.26 (0.79–2.00)
Short-term vs longer prednisone[*]		
No immune-mediated medication	3723/38,406	Ref
Short-term prednisone (< 7 days)	62/432	1.08 (0.80–1.48)
Longer prednisone (≥ 7 days)	123/491	1.49 (1.15–1.93)
Immunomodulator	83/327	0.85 (0.56–1.31)
Small-molecule/biologic therapy	36/193	1.25 (0.78–1.98)
Monotherapy vs combination therapy		
No immune-mediated medication	3723/38,406	Ref
Monotherapy		
Prednisone	149/821	1.25 (1.01–1.54)
Immunomodulator	34/167	0.76 (0.46–1.27)
Small molecule/biologic	16/115	0.82 (0.43–1.55)
Combination therapy		
Prednisone + immunomodulator	35/99	1.12 (0.56–2.25)
Prednisone + small molecule/biologic	6/17	3.57 (1.17–10.85)
Immunomodulator + small molecule/biologic	7/40	1.17 (0.45–3.04)
All three	7/21	2.99 (0.94–9.49)
Selected medication groupings		
No immune-mediated medication	3723/38,406	Ref
Prednisone	197/958	1.27 (1.04–1.55)
Thiopurines/traditional DMARDs[†]	34/220	0.53 (0.32–0.88)
Anti-TNF	7/94	0.45 (0.18–1.08)
JAK-I	7/23	3.35 (1.16–9.67)
Other therapies used only in immune-mediated inflammatory disease[††]	9/66	0.83 (0.37–1.89)
Other therapies used also in other diseases (i.e., transplant, cancer)[§]	60/129	3.84 (2.01–7.35)

All models adjust for patient age, sex, race/ethnicity, body mass index, immune-mediated disease (asthma, inflammatory bowel disease, organ transplantation, psoriasis, rheumatoid arthritis, spondyloarthropathy, lupus), hypertension, Charlson comorbidity score, and week of SARS-CoV-2-positive lab test. Therapies with at least 1 patient are listed
[*]35 patients missing length of prednisone
[†]Azathioprine, 6-mercaptopurine, methotrexate, hydroxychloroquine, leflunomide
[††]Apremilast, tocilizumab, ustekinumab, guselkumab, secukinumab, vedolizumab, belimumab, abatacept
[§]Cyclosporine, tacrolimus, everolimus, cyclophosphamide, mycophenolate, rituximab

Immune-Mediated Disease

Organ transplantation was associated with a borderline increased odds of severe illness with SARS-CoV-2 (OR 1.84, 95% CI 1.00–3.40) while spondyloarthropathy had a reduced odds (OR 0.37, 95% CI 0.14–0.97) (Table 2). Transplantation increased the odds of hospitalization, as did asthma (borderline) while spondyloarthropathy had reduced odds. Psoriasis was associated with increased odds of ICU admission. None of the other immune conditions listed in Table 2 were associated with increased odds of ICU admission or mortality.

Other Prognostic Factors

A higher Charlson score, hypertension, male sex, age > 50, non-white race, and extremes of BMI (underweight and obese) were all associated with severe illness after diagnosis with SARS-CoV-2 (Table 2).

DISCUSSION

In this study, we addressed whether the use of corticosteroids and other immune-weakening medicines prior to a diagnosis of SARS-CoV-2 increased the risk of subsequent hospitalization, ICU admission, and death. The present study builds on the emerging but limited data on this topic derived primarily from international registries, referral center studies, and administrative claims data.[6–17] We found outpatient use of prednisone was associated individually and in aggregate with hospitalization, ICU admission, and death, indicating a strong effect across the spectrum of severity. In contrast, immunomodulator and biologic/small-molecule therapy were not associated.

The association between steroid use prior to the SARS-CoV-2 diagnosis and subsequent hospitalization, ICU admission, and death observed in our study is similar to what has been observed in single-specialty rheumatology, IBD, and psoriasis studies.[6–10,12,15] This finding is also consistent with the known effects of steroids, which worsen viremia, prolong the viral shedding time, and increase the severity of infection by diminishing the immune system's antiviral defenses.[30] While we were unable to provide a more granular dose-dependent exposure with outcomes, the consistency in results for prednisone (except for death), when use was assessed as ≥ 7 days and outcomes were restricted to 21 days, supports a biologic association between chronic outpatient prednisone

and worse outcomes after SARS-CoV-2 diagnosis, although residual confounding cannot be completely excluded.

In contrast, immunomodulators and biologic/small-molecule therapies prior to SARS-CoV-2 diagnosis were not associated with severe illness in the primary analysis, consistent with results from other retrospective studies.[6–8,10,16,18] These therapies can also affect the immune system, and thus, the contrast with prednisone is notable. The difference in point estimates for these therapies when used as monotherapy compared to combination therapy supports current recommendations that chronic use of immunomodulator, biologic, and small-molecule therapy does not appear to meaningfully increase the risk of severe outcomes after diagnosis of SARS-CoV-2. Our results are consistent with recommendations that patients should not change or discontinue therapy for fear of worse outcomes.[31–33] Of course, appropriate measures should be taken to avoid infection and mitigate severe infection.

Our exploratory analyses are consistent with other single-specialty studies reporting anti-TNF therapy does not increase the odds of severe illness with SARS-CoV-2.[6,8,10] TNF is significantly elevated in severe COVID-19, and its inhibition could provide benefit in reducing cytokine storm, a systemic inflammatory response to SARS-CoV-2 believed to contribute to its morbidity and mortality.[7] Our observed reduced odds of severe illness with thiopurines/DMARDs is similar to the few other available studies, which have shown no increased risk with methotrexate or hydroxychloroquine,[9,10] except for a referral study showing borderline association with hydroxychloroquine (OR 4.79; 95% CI 1.00–22.86).[10] Data are sparse for other therapies. Two registry and one referral study have individually reported no association with severe COVID-19 for CTLA4-Ig,[9] anti-IL6,[9] anti-IL17,[9,10] anti-IL12/23,[13] and anti-integrin therapy,[13] with sparse data for other anti-cytokine therapies. We caution that ongoing accrual of data is needed to better assess the risk of severe outcomes with individual therapies.

We did find prior use of therapies with a strong use outside of autoimmune disease (typically transplant or cancer) also increased the odds of severe illness. A registry study reported similar findings for mycophenolate mofetil (OR 7.67; 95% CI 1.73–28.04) as well as B cell–depleting rituximab (OR 4.34; 95% CI 1.77–10.63),[9] which are used in autoimmune disease but also transplant and cancer, respectively. Data for other therapies were not reported.[9] The reasons for this observation may be several, including more profound immunosuppression compared to other therapies, indication bias, or unmeasured confounders, such as frailty in patients on these therapies.[34]

It is notable our retrospective study showed outpatient exposure to prednisone and JAK inhibitors prior to SARS-CoV-2 diagnosis had an increased odds of severe SARS-COV-2 outcomes whereas randomized trials of intravenous corticosteroids or tofacitinib (JAK inhibitor) used in hospitalized patients already infected with SARS-CoV-2 and requiring respiratory support reduced mortality[35,36] (presumably from mitigating the cytokine storm).[37] A trend toward increased risk

of severe COVID-19 with JAK-inhibitor therapy prior to SARS-CoV-2 diagnosis has been observed in a retrospective French registry and a New York referral center study, but not on univariate analysis in an IBD registry study.[9,10,14] All three studies reported low patient numbers and concerns for confounding. Thus, while it may be that the aggravating, beneficial, or neutral effect of outpatient immunosuppressive therapy on COVID-19 outcomes may depend on timing and the balance of antiviral containment and anti-inflammatory response,[9,30] this hypothesis should be considered speculative in the absence of more definitive data.

Although not the primary aim of study, this study confirmed the relationship between older age, male gender, hypertension, preexisting comorbidities, non-white race, and obesity with severe illness with SARS-CoV-2.[24–27,38] It also provided novel data in that most immune-mediated inflammatory diseases in our study did not increase the odds for ICU admission or mortality, after adjusting for immunosuppressive medication type, specific comorbidities, and demographic risk factors. We found organ transplantation increased the odds of hospitalization and asthma had a borderline association, whereas psoriasis increased the odds of ICU admission, the latter perhaps due to its strong association with significant comorbid conditions.[39]

There are several study limitations. We grouped therapies into clinically meaningfully and commonly used categories, but acknowledge that these treatments have different mechanisms of action, different effects on the immune system, and potentially different effects on outcomes depending on when used in the natural history of SARS-CoV-2 infection.[40] Ongoing studies are necessary to accrue sufficient data to provide risk estimates for individual therapies. It is also possible that outcomes occurring outside of the health setting and not captured in membership files may have been missed, although this is uncommon. Finally, disease severity is not well captured in administrative data. While prednisone could be a marker of more severe immune-mediated disease or other condition requiring hospitalization within 45 days, we feel it should not be associated with short-term ICU admission and death if a confounder, particularly after adjustment for age, disease, and comorbidity. Thus, while we propose a true biologic association between prednisone and SARS-CoV-2 infection leading to the observed outcomes, residual confounding cannot be excluded completely.

A key strength of the study is the setting, conducted within a single, large, integrated, community-based health care system. This permitted inclusion of a racially and medically diverse population of patients with detailed collection of medication, outcome, and key prognostic factors. This increased the generalizability of the findings as well as permitted overcoming potential issues with prior studies, including small sample size, limited inclusion of key variables for multivariable analysis, convenience sampling of physician-reported cases, and finally pooling of data from many different countries, each with their own health system, practices, and resources.

In summary, in a large, diverse, community-based population, outpatient use of prednisone was associated with severe illness after diagnosis of SARS-CoV-2. Immunomodulator and biologic/small-molecule therapies were not associated. We propose our findings can help risk-benefit discussions in the clinic and support recommendations that patients should not stop or reduce immunomodulator, biologic, or small-molecule therapy due to concerns of an elevated risk of severe illness from SARS-CoV-2.[2–4,31–33] For those therapies where we showed an increased odds, providers can discuss with patients the limitations of the current data and review evolving medical society recommendations regarding medication management,[31–33] as well as reinforce strategies to mitigate risk of severe SARS-CoV-2 infection, which currently involves vaccination, particularly in vulnerable groups.

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Declarations:

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