OPTIMIZING USE OF IMMUNOSUPPRESSIVE THERAPIES AND THROMBOPROPHYLAXIS: ASSOCIATIONS WITH SEVERE DISEASE AND DEATH AMONG ADULTS HOSPITALIZED WITH COVID-19 IN THE UNITED STATES

by

Kathleen (Kayte) Michelle Andersen

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Abstract

Background. As of December 15, 2021, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 50 million infections and 800,000 deaths in the United States. Given the novelty of the virus, the identification of high risk groups and understanding of optimal treatment regimens remains a pressing global health priority. This dissertation sought to improve understanding of therapeutics among adults hospitalized with COVID-19.

Methods. First, we used electronic health record data from an academic medical system to assess whether adults with COVID-19 with chronic pharmacologic immunosuppression have worse short-term clinical outcomes than non-immunosuppressed adults. Second, we used a national electronic health record repository of COVID-19 patients in the United States to evaluate whether the risks associated with immunosuppression vary by medication class. Third, we used electronic health records to evaluate the comparative effectiveness of high-intensity versus standard thromboprophylaxis among adults hospitalized with COVID-19.

Results. Overall, there was no evidence of increased risk of invasive mechanical ventilation or in-hospital death among individuals taking chronic immunosuppressive medications, such as those to manage autoimmune disorders, treat cancer, or prevent solid organ transplant rejection. Further analyses of the nation-wide cohort continued to find no increased risk of invasive mechanical ventilation with long-term immunosuppression, and no increased risk of death with 302 of 303 drugs examined. Rituximab, a treatment for lymphoma and rheumatologic conditions, was associated with a significantly increased risk of death. Separately, our study of over 50,000 adults within the HCA CHARGE database did not find reductions in risk of clinical

worsening, severe disease or death with high-intensity thromboprophylaxis regimens after accounting for time-varying exposure definitions and relevant confounders.

Conclusions. While many important questions remain, this dissertation provides robust evidence suggesting the general safety of chronic immunosuppressive medicines, as well as the absence of benefit of high-intensity thromboprophylaxis, among U.S. adults hospitalized with COVID-19.

Primary Reader and Advisor: G. Caleb Alexander, MD MS

Professor, Department of Epidemiology

Johns Hopkins Bloomberg School of Public Health

Non-Voting Member and Co-Advisor: Jodi B. Segal, MD MPH

Professor, Medicine and the Departments of Health Policy and Management, and Epidemiology

Johns Hopkins University School of Medicine and Bloomberg School of Public Health

Thesis Reader: Derek K. Ng, PhD

Assistant Professor, Department of Epidemiology

Johns Hopkins Bloomberg School of Public Health

Thesis Reader: Brian T. Garibaldi, MD

Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine

Johns Hopkins University School of Medicine

Thesis Reader: Christopher G. Chute, MD DrPH

Professor, Medicine, Nursing, and the Department of Health Policy and Management

Johns Hopkins University School of Medicine and Bloomberg School of Public Health

Abbreviations

CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease of 2019
EUA	Emergency use authorization
HCA-CHARGE	COVID-19 Consortium of HCA Healthcare and Academia for Research GEneration
JH-CROWN	Johns Hopkins Coronavirus registry
N3C	National COVID Cohort Collaborative
NIH	National Institutes of Health
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
US FDA	United States Food and Drug Administration
WHO	World Health Organization

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At the beginning of my second year, I was invited to join a writing accountabili0ty group. Some Friday afternoons we wrote, some we instead had to cut words out, and some we closed the laptops and went for a drink (or two) instead. Neia Prata Menezes, Amrita Rao and Jean Olivier Twahirwa Rwema, ironically I am at a loss for words for how much the three of you mean to me.

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This dissertation is dedicated to all of the heroes of the pandemic, who bravely served the community as healthcare and other essential workers, as well as the volunteers in the vaccine trials who assumed personal risk for the greater good.

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Chapter 1: Introduction

SARS-COV-2 Infection and Coronavirus Disease of 2019

The first confirmed case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the United States (US) was identified in Snohomish County, Washington on January 20, 2020.[1] In the days and weeks that followed, widespread community transmission with shortages of personal protective equipment and limited access to testing led to a nationwide outbreak. Coronavirus disease of 2019 (COVID-19), the symptomatic manifestation of SARS-CoV-2 infection, is a disease that can range in severity from asymptomatic infections to critical illness. Commonly reported symptoms include fever, cough, fatigue, headache, and new loss of taste or smell.[2] For some, symptoms persist weeks or months after infection.[3]

Despite the US containing roughly 4% of the world population, as of December 15, 2021 the US had accrued 18% of the world's confirmed cases and 15% of the world's COVID-attributable deaths.[4] In 2020, COVID-19 was the third-leading cause of death in the US.[5]

Evolution of Optimal Treatment Strategies

Given the novelty of the virus and the dynamic nature of scientific discovery, treatment strategies have evolved during the pandemic. Early on, there was particular interest in chloroquine and hydroxychloroquine, anti-malarial drugs also used for the treatment of some rheumatologic conditions. Hydroxychloroquine was shown to have *in vitro* antiviral efficacy against SARS-CoV-2 in early March 2020.[6] Given that hydroxychloroquine was an already available drug, coupled with a dearth of other COVID-19 treatments at the time, there was a swift adoption noted nationwide.[7] The US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) on March 28, 2020. Evidence accrued of a lack of benefit,[8,9]

as well as demonstrable harm for some,[10–12] and the FDA rescinded the EUA less than three months later.[13]

Remdesivir is an ribonucleic acid (RNA) polymerase inhibitor, which interferes with RNA production to decrease viral load.[14] Initially developed in 2009, remdesivir has been investigated for use in several indications, including hepatitis C, respiratory syncytial virus and Ebola virus disease, but did not receive FDA approval for these uses. On May 1, 2020, three clinical trials formed the evidence base for an EUA for remdesivir use among hospitalized COVID-19 patients, showing reduced time to clinical improvement but no overall effect on odds of mortality.[15–17] On October 22, 2020, remdesivir became the first COVID-19 treatment to receive FDA approval. Evidence is emerging that remdesivir is optimally effective when used in patients with moderate disease, that is who are hospitalized and require supplemental oxygen but not through a high-flow device or invasive mechanical ventilation. [18]

Glucocorticoids such as dexamethasone have been a mainstay in the management of acute respiratory distress for decades.[19] It is therefore not surprising that dexamethasone, a long-acting glucocorticoid, was found to significantly reduce mortality among hospitalized adults with supplemental oxygen requirements.[20] Since the release of the RECOVERY trial results in mid-June 2020, the majority of hospitalized adults who received invasive mechanical ventilation in one analysis of 43 academic health system in the US received dexamethasone. However, there was potential underuse of dexamethasone, with 1 in 5 patients that received invasive mechanical ventilation not receiving dexamethasone despite treatment guidelines; use varied substantially by health center.[7]

Other products have undergone assessment for potential efficacy and effectiveness in COVID-19. In consideration of the risks and benefits associated with use, the National Institutes of

Health (NIH) treatment guidelines as of November 2021 recommended against azithromycin, canakinumab, colchicine, convalescent plasma for non-immunosuppressed adults, HIV protease inhibitors such as lopinavir with ritonavir, interferon alpha or beta, mesenchymal stem cell based therapy, nitazoxanide or nonspecific immunoglobulins as inpatient COVID-19 treatments.[18] As of December 2021, the NIH treatment guidelines stipulate “insufficient evidence to recommend either for or against use” of anakinra, convalescent plasma in immunosuppressed adults, fluvoxamine, granulocyte-macrophage colony-stimulating factor inhibitors, ivermectin, SARS-CoV-2 specific immunoglobulins, vitamin C, vitamin D or zinc as inpatient COVID-19 treatments.[18] Development continues for new drugs, vaccine and related biologic products for the prevention and management of COVID-19.

Groups at Higher Risk

SARS-CoV-2 is a unique virus in that a large proportion of infections are asymptomatic, meaning that people can spread the virus without knowing they have been infected. For those who become symptomatic, some will experience severe disease. The definition of severe disease varies by countries, but is defined by the US Centers for Disease Control and Prevention (CDC) as the need for hospitalization, intensive care, invasive mechanical ventilation, or death.[21] Among these higher risk groups, there was prioritization of early vaccine supply, as well as ongoing guidance to practice physical distancing and wear a mask.
High risk groups include older adults and people who belong to racial and ethnic groups that have experienced long-standing effects of systemic racism and other factors.

There are also many medical conditions which have been associated with increased risks of severe COVID-19. The evidence base is evolving, and as of December 15, 2021, the following were listed by the CDC as high risk groups: cancer, chronic kidney disease, chronic liver disease, chronic lung disease, dementia or other neurologic conditions, Type 1 and Type 2

diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state, mental health conditions, overweight and obesity, pregnancy, sickle cell disease or thalassemia, current or former smoking, solid organ or blood stem cell transplant, stroke or cerebrovascular disease, substance use disorder and tuberculosis. Whether the conditions themselves, or the medications associated with their management, increase risk remains unclear.

Immunosuppression Poses Unique Challenges

Immunosuppressive medications are drugs or biologics that interfere with a person's immune system. There are many indications for immunosuppressive medications, which can be broadly broken into antineoplastic therapies for cancer, rheumatologic therapies for autoimmune disorders, and antimetabolite therapies to prevent solid organ transplant rejection. In the case of rheumatologic and antimetabolite drugs, patients generally take these medications for the rest of their life to prevent irreversible joint or organ damage. However, these same medications may also leave them more susceptible to opportunistic bacterial and viral infections. Interestingly, no increase risk was noted with immunosuppressive medication use in prior coronavirus outbreaks.[22,23]

COVID-19 Appears to be a Microthrombotic Disease

Current treatment guidelines suggest anticoagulative therapy among adults hospitalized with COVID-19, both for venous thromboembolism prevention due to immobility and/or critical illness as well as emerging evidence of microvascular manifestations of disease.[24–27] One of the first studies to examine incidence early in the pandemic found that venous and arterial clots were common, with 16% of all persons hospitalized with COVID-19 in New York City in March and

April 2020 experiencing thromboemboli; mortality was twice as high among people with a thrombotic event.[28]

In response to a known risk, and with a rapidly evolving evidence base, the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis issued guidance in May 2020 for prescribers to consider high-intensity thromboprophylaxis, that is supra-prophylactic but subtherapeutic anticoagulation.[29] As of December 15, 2021, both the World Health Organization (WHO) and NIH treatment guidelines stated that there is insufficient evidence to recommend for or against the use of high-intensity doses.[30,31]

Specific Aims of This Dissertation

1. To examine whether persons using immunosuppressive medicines at the time of admission had worse short-term clinical outcomes than those who do not, using a registry of 2,121 consecutive adults admitted to the Johns Hopkins Medicine system with COVID-19 in March – August 2020.

2. To assess whether associations between immunosuppressive medications and COVID inpatient outcomes vary by medication class, using a national electronic health record repository of over 220,000 adults hospitalized with COVID-19 in the United States between March 2020 – June 2021.

3. To evaluate whether the need for therapeutic anticoagulation, as well as incidence of severe disease and death, differed among people who received either standard or high-intensity thromboprophylaxis, using electronic health records from a large private healthcare network capturing 5% of inpatient care in the United States between February 2020 – February 2021.

Chapter 2: Association Between Chronic Use of Immunosuppressive Drugs and Clinical Outcomes From COVID-19 Hospitalization: A Retrospective Cohort Study in a Large U.S. Health System

Kathleen M. Andersen, MSc 1,2; Hemalkumar B. Mehta, MS, PhD 1,2;
Natasha Palamuttam, BA 3; Daniel Ford, MD 4; Brian T. Garibaldi, MD MEHP 5;
Paul G. Auwaerter, MD 6; Jodi Segal, MD, MPH 1,2,4,7; G. Caleb Alexander, MD, MS 1,2,4

1. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205
2. Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205
3. Division of Health Sciences Informatics, Johns Hopkins University School of Medicine, Baltimore, MD 21287
4. Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD 21287
5. Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287
6. The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD 21287
7. Department of Health Policy & Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205

Brief 40-word summary
Among adults with confirmed or suspected COVID-19, chronic use of immunosuppressive drugs was neither associated with worse nor better clinical outcomes such as mechanical ventilation, in-hospital mortality, or length of stay.

Correspondence
G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168; Fax: 410 955 0863
Email: galexan9@jhmi.edu

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Key Points

Question. Is there an association between chronic use of immunosuppressive drugs and severity of COVID-19?

Findings. Among a cohort with confirmed or suspected COVID-19, after controlling for potentially confounding covariates, there were no statistically significant differences in the adjusted hazard of mechanical ventilation (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.46-1.35), in-hospital mortality (HR 0.66, 95% CI 0.28-1.55) or length of stay (HR 1.16, 95% CI 0.92-1.47) among individuals with chronic use of immunosuppressive drugs and their counterparts. Results were generally consistent in sensitivity analyses varying definitions of chronic immunosuppression and including non-invasive ventilation as a clinical outcome.

Meaning. Chronic use of immunosuppressive drugs was neither associated with worse nor better clinical outcomes among adults hospitalized with COVID-19 in one U.S. health system.

Abstract

Importance. It is unclear whether chronic use of immunosuppressive drugs worsens or improves the severity of coronavirus disease (COVID-19), with plausible mechanisms for both.

Objective. To test whether adults with COVID-19 using immunosuppressive medicines at hospital admission have worse short-term clinical outcomes than those who do not.

Design. Retrospective cohort study using electronic health record data, with adjustment for confounding with propensity score-derived stabilized inverse probability of treatment weights

Setting. Large academic health system, including five hospitals and approximately 2,500 total beds, primarily serving Maryland, Virginia and Washington, D.C.

Participants. 2,121 consecutive adults with acute in-patient hospital admission between March 4, 2020 and August 29, 2020 with confirmed or suspected COVID-19.

Exposure. Chronic immunosuppression, defined as prescriptions for immunosuppressive drugs that were current at the time of admission.

Main Outcome and Measures. (1) Mechanical ventilation; (2) in-hospital mortality; and (3) length of stay.

Results. There were 2,121 patients admitted in the health system with laboratory-confirmed (1,967, 93%) or suspected (154, 7%) COVID-19 during the study period, with a median age of 55 years (interquartile range 40-67). Of these, 108 (5%) were classified as using immunosuppressing medicines before COVID-19 infection, primarily due to the use of prednisone (>7.5 mg/day), tacrolimus or mycophenolate mofetil. Among the entire cohort, 311 (15%) received mechanical ventilation; the median (interquartile range) length of stay was 5.2 (2.5-10.6) days, and 1,927 (91%) survived to discharge. As of August 29, 2020, 39 persons

(2%) remained hospitalized. After adjustment, there were no statistically significant differences in the risk of mechanical ventilation (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.46-1.35), in-hospital mortality (HR 0.66, 95% CI 0.28-1.55) or length of stay (HR 1.16, 95% CI 0.92-1.47) among individuals with immunosuppression and their counterparts. Results were generally consistent in sensitivity analyses using other definitions of chronic immunosuppression and including non-invasive ventilation as a clinical outcome.

Conclusions and Relevance. Chronic use of immunosuppressive drugs was neither associated with worse nor better clinical outcomes among adults hospitalized with COVID-19 in one U.S. health system.

Introduction

As of September 11, 2020, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has caused more than 6.4 million infections and 193,000 deaths in the United States.1 The gravity of the pandemic has unleashed unprecedented scientific activity focused on better understanding the pathogenesis and epidemiology of coronavirus disease 2019 (COVID-19) as well as identifying treatments that may change its course.2

It is unclear how immunosuppression impacts outcomes among those with COVID-19. While some information suggests chronic immunosuppression may be a risk factor for more severe disease,3 early evidence from individuals with COVID-19 in China did not suggest such an association,4 nor did evidence from prior coronavirus outbreaks, including the Middle East respiratory syndrome (MERS)5 and severe acute respiratory syndrome (SARS).6 In addition, there is early evidence of the benefits of acute immunosuppression with dexamethasone among individuals with COVID-19 receiving oxygen or mechanical ventilation.7 European studies have examined the association between chronic immunosuppression and COVID-19 outcomes. In a cross-sectional analysis of Northern Italian patient treated with calcineurin inhibitors, the clinical course of COVID-19 was mild.8 Another study assessed COVID-19 outcomes within a multicenter prospective observational registry of patients with rheumatologic disease treated with biologic agents; disease course and mortality was similar to the general population.9 Most analyses of the relationship between chronic immunosuppression and COVID-19 have focused on disease-based definitions of specific clinical subpopulations, such as individuals with rheumatoid arthritis or organ transplantation, and have found nonsignificant effects (adjusted mortality odds ratio = 1.1, 95% confidence interval 0.8-1.6)10 or small hazardous effects (adjusted mortality hazard ratio = 1.19, 95% confidence interval 1.11-1.27).11

To better understand whether chronic immunosuppression worsens outcomes for hospitalized patients with COVID, we conducted a retrospective cohort study using electronic medical record data.

Methods

Data and subjects

We used the Johns Hopkins CROWN Registry, a cohort of COVID-19 patients derived using a computable phenotype based on International Classification of Diseases-10 (ICD-10) diagnostic codes and laboratory results.12 The Johns Hopkins CROWN registry collects data from a large academic health system, including five hospitals and approximately 2,500 beds, serving a large area in Maryland, Virginia and Washington, D.C. We included adults age 18 years or older hospitalized with suspected or confirmed COVID-19 between March 12, 2020 and August 29, 2020. We excluded patients who were ventilated upon admission (transferred patients or ventilated in the emergency department) and persons who had “do not resuscitate” or “do not intubate” advanced directives placed within 24 hours of admission. We followed persons from the date of their COVID-19 admission through discharge, death, or August 29, 2020, whichever came first.

Exposures

Based on prescription medicines used at the time of hospital admission, we defined two mutually exclusive exposure groups. We categorized patients as immunosuppressed if they had medications for immunosuppressive drugs current on the date of COVID-19 hospitalization. These were defined as WHO Anatomical Therapeutic Chemical (ATC) Class L04 “Selective Immunosuppressants”, Class L01 “Antineoplastic agents”, or prednisone >7.5mg or equivalent. Everyone else was defined as immunocompetent for the primary analysis.

Outcomes

Our primary outcome was use of mechanical ventilation, defined as the time from hospital admission to the first use of mechanical ventilation. Secondary outcomes included in-hospital mortality and hospital length of stay.

Covariates

We identified potential confounders through a review of the peer-reviewed literature11,13,14 and expert consultation. We considered calendar week, hospital, sociodemographics (age, sex, zip code, self-reported race and ethnicity), clinical features (substance use disorder, alcohol use, smoking history, body mass index [BMI], admission from a nursing home), days between positive SARS-CoV-2 PCR test and hospital admission, vital signs within 24 hours of admission (body temperature, pulse, respiratory rate, SaO2/FiO2 ratio), and laboratory measures ± 2 days of admission (elevated C-reactive protein, creatinine, troponin, albumin, high or low white blood cell count). We generated the Rx-Risk score15 and calculated the summary Elixhauser Comorbidity Index for each person, using all lookback data available in the electronic medical record.16 We also controlled for specific autoimmune or inflammatory conditions, namely chronic obstructive pulmonary disease, rheumatic diseases, renal disease, cancer and HIV. We created indicator variables for missing binary covariates and dropped patients who were missing a continuous covariate.

Statistical Analyses

We used means and standard deviations for continuous variables or frequency and percentages for count variables to characterize the study cohort. The primary analysis used an inverse probability of treatment weighting (IPTW) approach to control for confounding.17 To derive propensity scores, we constructed a logistic regression model to predict immunosuppression status by including all patient demographics and clinical characteristics listed in the “Covariates”

section above. We calculated stabilized inverse probability treatment weights18 and trimmed at 1st and 99th percentile to avoid exertion of outliers. We calculated standardized mean differences (SMD) in the original weighted samples to assess covariate balance. We used Fine and Gray's competing risk model for mechanical ventilation and length of stay, where death was considered as a competing risk.19 Multivariable Cox proportional hazards regression models were used for in-hospital mortality. Any variables unbalanced after weighting (SMD>10%) were additionally controlled for in regression analyses.20

In secondary analyses, we used propensity score matching or propensity score-adjusted regression. For propensity score matching, we used a 1:1 greedy matching algorithm and a caliper of 0.5 pooled standard deviations of the estimated propensity score.

Sensitivity Analyses

First, to examine whether the absence of data predating hospitalization created misclassification bias, we restricted our analysis to persons with at least one health system encounter prior to COVID-19 admission. Second, to examine whether our results would vary when considering broader groups of immunosuppression diagnoses, we repeated our analyses including the Agency for Healthcare Research and Quality's Immunocompromised State Diagnosis Codes.21 To do so, we used all available lookback time up to and including the date of COVID-19 admission. Third, we made our definition more strict by considering prednisone >10mg as immunosuppressed. Finally, to examine whether our results would vary based on a less conservative definition of respiratory failure, we included high-flow nasal cannulae or non-invasive positive pressure ventilation. In each sensitivity analysis, we recalculated propensity scores and updated the set of unbalanced covariates for doubly robust adjustment.

Analyses were conducted using SAS software, Version 9.4 of the SAS System for Windows. The Johns Hopkins Medicine Institutional Review Board reviewed this study (#IRB00248349), waived the requirement for informed consent, and deemed the work to be exempt research.

Results

There were 2,492 adults admitted between March 4, 2020 and August 29, 2020 with confirmed or suspected COVID-19. We excluded 71 due to ventilation at hospital admission and 300 had advanced directives at admission. The median age was 55 years (interquartile range 40-67). Of the remaining 2,121 individuals, 108 (5%) used immunosuppressing medications and 2,013 (95%) did not (Table 1). The medications most often used were prednisone >7.5mg, tacrolimus and mycophenolate mofetil.

Characteristics At Admission

Among immunocompromised patients, the mean age was 55.0±14.8 years, 49% were male, 45% Black and 18% Hispanic (Table 2). Prior to IPTW, immunocompromised persons more likely to be non-Hispanic, have past tobacco use, and used significantly more medicines. Individuals with chronic immunosuppression also had higher mean Elixhauser Comorbidity Index scores (10.2±12.7) compared with their counterparts (4.0±8.6). Weighting reduced the differences between groups although differences remained, most notably for comorbidity burden and Rx-Risk score.

Association Between Chronic Immunosuppression and Clinical Outcomes

There was no significant difference in the proportion of persons discharged alive (88% among immunocompromised versus 91% among immunocompetent, p=0.28). (Table 3) The distribution of COVID19 admissions by calendar week did not differ between the two groups (Figure 1). The median length of hospital stay was not different (6.9 versus 5.1 days, p=0.09).

The proportion undergoing mechanical ventilation was similar (16% versus 15%, p=0.75). Median time to ventilation was slightly longer (3.0 versus 2.6 days, p=0.02). For in-hospital death, neither the proportion (7% versus 7%, p=0.73) nor the median time to death (27.2 versus 13.3 days, p=0.25) differed by immune system status.

In the unadjusted regression analyses, there was no difference in the hazard of each of the outcomes (Table 4). Similarly, after IPTW, there were no statistically significant differences in the likelihood of mechanical ventilation (HR 0.79, 95%CI 0.46-1.35), in-hospital mortality (HR 0.66, 95%CI 0.28-1.55) or length of stay (HR 1.16, 95%CI 0.92-1.47) among individuals with chronic immunosuppression and their counterparts. Results were generally similar using propensity score matching and propensity score adjustment.

Sensitivity Analyses

Restriction to the subset of persons with at least one encounter prior to the date of their COVID-19 admission yielded substantively similar findings as the main analysis (Table 5). Analyses that considered immunosuppression diagnoses, with or without medications, identified 232 individuals (11%) with immunosuppression; most had end stage renal disease (n=56) or HIV (n=32). With the inclusion of these patients, we found a significantly shorter length of stay with immunosuppression, but no difference in use of mechanical ventilation or death (Table 6). In analyses to restrict the exposure definition to individuals on prednisone >10mg per day, we again found no significant difference in risk of mechanical ventilation or death, although immunosuppressed persons were discharged sooner (HR 0.72, 95%CI 0.60-0.85). Finally, with expansion of the outcome definition to include non-invasive ventilation, there remained no significant difference between groups (HR 1.15, 95%CI 0.76-1.74) (Table 7).

Discussion

The COVID-19 pandemic continues to cause widespread morbidity and mortality. We examined one important subpopulation, individuals with chronic use of immunosuppressive medications. After adjustment for potentially confounding covariates, there were no statistically significant differences in the risk of mechanical ventilation, in-hospital mortality or length of stay among those with immunosuppression and their counterparts. Our results were consistent in sensitivity analyses varying both exposure and outcome definitions. These findings are important because of the magnitude of continuing morbidity and mortality attributable to the pandemic, as well as the frequent use of immunosuppressive medications for the management of a range of chronic conditions.

While our study adds to case series and investigations of specific subpopulations of individuals with immunosuppression[10,11,22-24] suggesting similar clinical COVID-19 outcomes among individuals with immunosuppression and their counterparts, our study was not designed to characterize the pharmacodynamics of these medications and how they may interact with COVID. The immunosuppressive agents we considered have varied mechanisms of action targeting cellular and humoral immune responses. It is possible that chronic immunosuppression might decrease the severity of the hyperinflammatory response that can complicate SARS-CoV-2 infection, and thus protect against the severity of any cytokine storm. In addition, individuals on chronic immunosuppressive medications, once hospitalized with COVID-19 infection, may be managed in ways that mitigate potential harms that would otherwise accrue, such as through the use of stress-dose steroids among those on chronic prednisone. On the other hand, chronic immunosuppression might also plausibly increase morbidity and mortality caused by earlier disease stages that are predominated by harms from viral replication, as well as predispose individuals to greater risks from secondary infection.

Our analyses have limitations. First, our relatively small sample sizes of individuals with these conditions precluded analyses among distinct clinical subpopulations such as those with solid organ transplant or HIV/AIDS. Second, exposure misclassification, which was based on medications used at the time of hospital admission, is possible. Third, we characterized a limited set of short-term outcomes; further work is needed to examine the association between chronic immunosuppression and longer-term morbidity and mortality. Fourth, our analysis took place during a period with dynamic clinical treatment protocols (e.g., proning, criteria for intensive care unit transfer), although we are not aware that these were differentially applied to individuals based on their use of chronic immunosuppressive medications. Finally, our approach has limitations inherent to observational research, including the potential for unmeasured confounding.

These limitations notwithstanding, our analysis also has many strengths. We examined the real-world experience of a large and diverse cohort of individuals hospitalized with COVID-19 within a health system that included five hospitals serving a large geographic region. Our data came from a comprehensive patient registry that included sequentially identified persons with confirmed or suspected COVID-19. Data elements of the electronic medical record included medical history, laboratory data, vital signs, medication administration record, ventilatory support and respiratory mechanics. In addition, we used a variety of methods to maximize causal inference, such as excluding persons who had advanced directives such that they were not at risk of the primary outcome, stabilized inverse probability of treatment weighting with doubly robust adjustment, and accounting for the competing risk of death where death was not the primary outcome. We also included several sensitivity analyses to examine how varying assumptions would modify our substantive findings and interpretation, and updated the propensity score calculations for each sensitivity analyses.

Our findings raise several important questions for future research. More work is needed to understand how the use of chronic immunosuppressive drugs may affect the safety and efficacy of dexamethasone, given its ability to reduce short-term mortality among hospitalized individuals receiving respiratory support.7 Also, it is unclear whether pre-existing duration of chronic immunosuppressive use may affect the associations of interest. In addition, it is unknown whether specific patient characteristics, such as age or other independent risk factors for more severe disease,25,26 may modify the relationship between chronic immunosuppression and COVID-19 outcomes. Finally, as we note above, more research is needed to understand whether and how provider behavior and in-hospital treatment may contribute to the lack of independent harm that we observe from use of chronic immunosuppressive therapies.

Conclusion

In this analysis of a large, diverse cohort of adults hospitalized with COVID-19 in the United States, we did not find differences in risk of mechanical ventilation, in-hospital mortality or length of stay among individuals with and without chronic use of immunosuppressive medications. Our results contribute to a growing body of evidence that should provide reassurance to clinicians and patients using chronic immunosuppressive medicines.27,28

Notes

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Disclosures

Ms Andersen, Dr. Mehta, Ms Palamuttam, Dr. Ford, Dr. Garibaldi, and Dr. Segal do not have potential conflicts of interest. Dr. Auwaerter is a shareholder of Johnson & Johnson. Dr. Alexander previously served as Chair of the FDA Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; and is a consultant and holds equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

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Table 1. Medications and Diagnoses Among 270 Persons With an Immunocompromised State Prior to COVID-19.

Medications current at admission (n=170 drugs among 108 persons)	
Prednisone > 7.5mg	75 (44%)
Tacrolimus	32 (19%)
Mycophenolate mofetil	15 (9%)
Azathioprine	4 (2%)
Methotrexate sodium	4 (2%)
Carboplatin	4 (2%)
Cyclosporine	4 (2%)
Paclitaxel	3 (2%)
Rituximab	3 (2%)
Bortezomib	2 (1%)
Cyclophosphamide	2 (1%)
Daratumumab	2 (1%)
Oxaliplatin	2 (1%)
Pembrolizumab	2 (1%)
Bevacizumab	1 (< 1%)
Carfilzomib	1 (< 1%)
Cisplatin	1 (< 1%)
Doxorubicin	1 (< 1%)
Fluorouracil	1 (< 1%)
Gemcitabine	1 (< 1%)
Ibrutinib	1 (< 1%)
Imatinib	1 (< 1%)
Irinotecan	1 (< 1%)
Leflunomide	1 (< 1%)
Lenalidomide	1 (< 1%)
Methylprednisolone	1 (< 1%)
Pemetrexed	1 (< 1%)
1 (< 1%)Secukinumab	1 (< 1%)
Sirolimus	1 (< 1%)
Vincristine	1 (< 1%)
ICD-10 Diagnosis Code (n=204 persons)	
N18.6 “End stage renal disease”	56 (28%)
B20. “Human Immunodeficiency Virus [HIV] disease”	32 (16%)
D89.9 “Disorder involving the immune mechanism, unspecified”	23 (11%)
N18.5 “Chronic kidney disease, stage 5”	19 (9%)
D61.818 “Other pancytopenia”	13 (6%)
D70.9 “Neutropenia, unspecified”	11 (5%)
D72.819 “Decreased white blood cell count, unspecified”	9 (4%)
D72.810 “Lymphocytopenia”	6 (3%)
M35.9 “Systemic involvement of connective tissue, unspecified”	4 (2%)
D61.810 “Antineoplastic chemotherapy induced pancytopenia”	3 (1%)
E43 “Unspecified severe protein-calorie malnutrition”	3 (1%)
Z94.4 “Liver transplant status”	3 (1%)
D70.1 “Agranulocytosis secondary to cancer chemotherapy”	2 (1%)
D70.2 “Other drug-induced agranulocytosis”	2 (1%)
D70.8 “Other neutropenia”	2 (1%)

Z94.2 “Lung transplant status”	2 (1%)
Z94.81 “Bone marrow transplant status”	2 (1%)
D75.81 “Myelofibrosis”	1 (< 1%)
D80.1 “Nonfamilial hypogammaglobulinemia”	1 (< 1%)
D80.3 “Selective deficiency of immunoglobulin G [IgG] subclasses”	1 (< 1%)
D80.4 “Selective deficiency of immunoglobulin M [IgM]”	1 (< 1%)
D83.9 “Common variable immunodeficiency”	1 (< 1%)
D89.813 “Graft-versus-host disease, unspecified”	1 (< 1%)
D89.89 “Other specified disorders involving the immune mechanism, not elsewhere classified”	1 (< 1%)
T86.49 “Other complications of liver transplant”	1 (< 1%)
Z48.298 “Encounter for aftercare following other organ transplant”	1 (< 1%)
Z94.0 “Kidney transplant status”	1 (< 1%)
Z94.84 “Stem cells transplant status”	1 (< 1%)
Z99.2 “Dependence on renal dialysis”	1 (< 1%)

Note: 42 persons had both a medication and a diagnosis, and are double represented in this table.

Table 2. Characteristics of Individuals on Date of Hospitalization With Confirmed or Suspected COVID-19, by Immune System Status Prior to COVID-19.

	Original sample (n=2,121)			After inverse probability of treatment weighting		
	Immunocompromised (n=108)	Immunocompetent (n=2,013)	Absolute standardized mean difference	Immunocompromised	Immunocompetent	Absolute standardized mean difference
Age	55.0 (14.8)	54.3 (17.6)	0.0420	55.0 (13.7)	54.9 (17.3)	0.0056
Male sex	53 (49%)	1,062 (53%)	0.0737	39 (47%)	1,049 (54%)	0.1342
Race						
White	34 (32%)	479 (24%)	0.1725	24 (29%)	479 (24%)	0.0885
Black	49 (45%)	751 (37%)	0.1643	33 (40%)	741 (38%)	0.0469
Neither white nor Black	25 (23%)	783 (39%)	0.3455	26 (31%)	733 (38%)	0.1306
Ethnicity						
Hispanic	19 (18%)	646 (32%)	0.3404	22 (27%)	606 (31%)	0.0889
Non-Hispanic	87 (80%)	1,359 (68%)	0.3009	60 (72%)	1,339 (69%)	0.0863
Refused or unknown	2 (2%)	8 (< 1%)	0.1383	1 (1%)	8 (< 1%)	0.0145
Drug abuse	7 (6%)	53 (3%)	0.1853	4 (5%)	56 (3%)	0.1058
Current alcohol use						
Yes	34 (32%)	524 (26%)	0.1206	20 (24%)	522 (27%)	0.0727
No	53 (49%)	929 (46%)	0.0586	39 (47%)	892 (46%)	0.0333
Missing or not asked	21 (19%)	560 (28%)	0.1981	24 (29%)	539 (27%)	0.0330
Smoking history						
Current smoker	15 (14%)	194 (9%)	0.1323	7 (9%)	195 (10%)	0.0465
Former smoker	25 (23%)	296 (15%)	0.2168	18 (21%)	300 (15%)	0.1650
Non-smoker	51 (47%)	1,101 (55%)	0.1499	42 (50%)	1,052 (54%)	0.0773
Missing or not asked	17 (16%)	422 (21%)	0.1352	16 (20%)	406 (21%)	0.0295
Body mass index						
Not overweight or obese	21 (20%)	337 (17%)	0.0703	12 (14%)	333 (17%)	0.0714
Overweight	26 (24%)	435 (22%)	0.0587	19 (23%)	420 (21%)	0.0213
Obese	25 (23%)	645 (32%)	0.2000	22 (26%)	619 (32%)	0.1178
Missing	36 (33%)	596 (29%)	0.0803	31 (37%)	581 (30%)	0.1502
Admission from skilled nursing facility	3 (3%)	114 (6%)	0.1439	4 (5%)	111 (6%)	0.0256

Days between positive COVID test and hospital admission	0.4 (2.2)	0.3 (1.7)	0.0561	0.7 (1.7)	0.3 (1.8)	0.2121
Vital signs within 24 hours of admission						
Temperature in ^{o}C	36.9 (0.5)	37.1 (0.6)	0.3946	37.0 (0.5)	37.1 (0.6)	0.2087
Pulse	85 (12)	85 (14)	0.0556	85 (12)	85 (14)	0.0038
Respiratory rate >22/min	41 (38%)	913 (45%)	0.1504	38 (46%)	901 (46%)	0.0029
SaO_2/FiO_2 ratio	409 (113)	391 (113)	0.1540	380 (110)	391 (113)	0.1009
Laboratory measures ± 2 days of admission						
↑ C-reactive protein	75 (87%)	1,485 (92%)	0.0961	59 (87%)	1,446 (92%)	0.0676
↑ Creatinine	36 (34%)	458 (23%)	0.2372	17 (21%)	463 (24%)	0.0724
↑ Troponin	17 (20%)	296 (18%)	0.0289	13 (19%)	293 (18%)	0.0270
↑ White blood cells	20 (19%)	393 (20%)	0.0256	17 (21%)	372 (28%)	0.0494
↓ Albumin	53 (52%)	1,027 (52%)	0.0389	43 (54%)	988 (52%)	0.0134
↓ White blood cells	40 (38%)	606 (30%)	0.1472	27 (33%)	606 (31%)	0.0323
Rx-Risk score	13 (11)	6 (8)	0.7835	9 (7)	6 (9)	0.4221
Elixhauser comorbidity score	10.2 (12.7)	4.0 (8.6)	0.5737	5.6 (8.6)	4.4 (9.0)	0.1348
Chronic obstructive pulmonary disease	11 (10%)	92 (4%)	0.2392	6 (7%)	89 (5%)	0.1125
Rheumatic disease	7 (7%)	33 (2%)	0.2472	2 (2%)	37 (2%)	0.0398
Renal disease	27 (25%)	200 (10%)	0.4048	10 (13%)	211 (11%)	0.0567
Cancer	19 (18%)	133 (7%)	0.3417	9 (10%)	141 (7%)	0.1096
HIV	4 (4%)	29 (2%)	0.1472	1 (1%)	29 (1%)	0.0364

Continuous variables are represented as mean (standard deviation), and categorical variables as counts (%). Fifty seven individuals had unavailable vital signs and were exclude from IPTW sample (46 body temperature, 32 pulse, 44 SaO2/FiO2 ratio)

Lab results were missing for persons who did not have test ordered ± 2 days of admission: 415 C-reactive protein, 26 creatinine, 411 troponin, 11 white blood cell count, 6 albumin. In IPTW sample, indicator variables were used for missing labs as data were assumed to be missing at random given clinical utility. Lab values in table represent individuals with abnormal values above or below referent standard, and the denominator for the proportions exclude persons missing the test.

Table 3. Unadjusted Clinical Outcomes by Immune System Status Prior to COVID-19 (N=1,668 individuals).

	Immune system status prior to COVID-19		P-value
	Immunosuppressed (n=108)	Immunocompetent (n=2,013)	
Discharged alive	95 (88%)	1,832 (91%)	0.2848
Remains hospitalized as of August 29, 2020	6 (6%)	33 (2%)	0.0032
Mechanical ventilation	17 (16%)	294 (15%)	0.7452
< 2 days after admission	6 (35%)	161 (55%)	
2-7 days	7 (41%)	113 (38%)	
> 7 days	4 (24%)	20 (7%)	
Median time to mechanical ventilation	3.0 (1.3-6.8)	2.6 (0.4-3.7)	0.0159
In-hospital death	7 (7%)	148 (7%)	0.7348
< 2 days after admission	0	10 (7%)	
2-7 days	1 (14%)	23 (16%)	
> 7 days	6 (86%)	115 (78%)	
Median time to death	27.2 (7.9-56.7)	13.3 (8.1-22.7)	0.2453
Length of stay, median days (IQR)	6.9 (2.8-13.2)	5.1 (2.5-10.5)	0.0853
Among those discharged	6.1 (2.2-10.1)	4.8 (2.3-9.1)	0.2136
Among those still admitted as of August 29, 2020	13.2 (10.3-18.8)	18.3 (9.2-24.2)	0.7407
Among those who died	27.2 (7.9-56.7)	13.3 (8.1-22.6)	0.2453

For counts, the p-value was calculated using a Chi-squared test. For median times, the p-value was calculated using the Wilcoxon rank sum test for difference in medians.

Table 4. Association Between Chronic Immunosuppression and Clinical Outcomes in COVID-19.

	Hazard ratio (95% Confidence Interval)		
	Mechanical Ventilation[1]	In-Hospital Death	Length of Stay[1]
Unadjusted regression analysis	0.97 (0.61-1.55)	0.61 (0.30-1.25)	0.87 (0.71-1.05)
Primary analysis			
Inverse probability treatment weights	0.79 (0.46-1.35)	0.66 (0.28-1.55)	1.16 (0.92-1.47)
Secondary analyses			
Propensity score matching[2]	0.91 (0.50-1.67)	1.50 (0.41-5.45)	0.89 (0.67-1.17)
Propensity score adjustment	1.10 (0.66-1.84)	0.59 (0.28-1.22)	0.990 (0.80-1.22)

[1] The models for risk of ventilation and length of stay incorporated the competing risk of death using Fine & Gray's methodology.

[2] Matches were made using 1:1 greedy matching, and 108 pairs were identified.

Table 5. Sensitivity Analysis Restricting Cohort to Individuals With Prior Health System Encounters.

	Hazard ratio (95% Confidence Interval)		
	Mechanical Ventilation[1]	In-Hospital Death	Length of Stay[1]
Unadjusted regression analysis	0.35 (0.12-1.05)	0.67 (0.26-1.76)	0.84 (0.63-1.12)
Primary analysis			
Inverse probability treatment weights	0.68 (0.09-5.30)	0.96 (0.08-12.32)	0.92 (0.62-1.37)
Secondary analyses			
Propensity score matching[2,3]	2.00 (0.33-11.97)	---	0.92 (0.62-1.37)
Propensity score adjustment	0.52 (0.18-1.52)	0.50 (0.18-1.35)	0.91 (0.66-1.26)

In this sensitivity analysis, 50 persons (8%) were immunocompromised and 608 (92%) immunocompetent.

[1] The models for risk of ventilation and length of stay incorporated the competing risk of death using Fine & Gray's methodology.

[2] Matches were made using 1:1 greedy matching, and 50 pairs were identified.

[3]For the propensity-score matched hazard of death, convergence was not attained in 25 iterations. The validity of model fit is questionable, and therefore not presented.

Table 6. Sensitivity Analysis Including Diagnoses to Define Chronic Immunosuppression.

	Hazard ratio (95% Confidence Interval)		
	Mechanical Ventilation[1]	In-Hospital Death	Length of Stay[1]
Unadjusted regression analysis	0.994 (0.73-1.35)	1.08 (0.72-1.63)	0.75 (0.66-0.86)
Primary analysis			
Inverse probability treatment weights	0.70 (0.50-1.001)	1.16 (0.78-1.72)	0.81 (0.67-0.98)
Secondary analyses			
Propensity score matching[2]	0.86 (0.58-1.26)	1.29 (0.64-2.60)	0.87 (0.72-1.04)
Propensity score adjustment	1.11 (0.75-1.64)	0.91 (0.53-1.58)	1.11 (0.75-1.64)

[1] The models for risk of ventilation and length of stay incorporated the competing risk of death using Fine & Gray's methodology.

Table 7. Sensitivity Analysis Including Non-Invasive Ventilation in Definition of Primary Outcome.

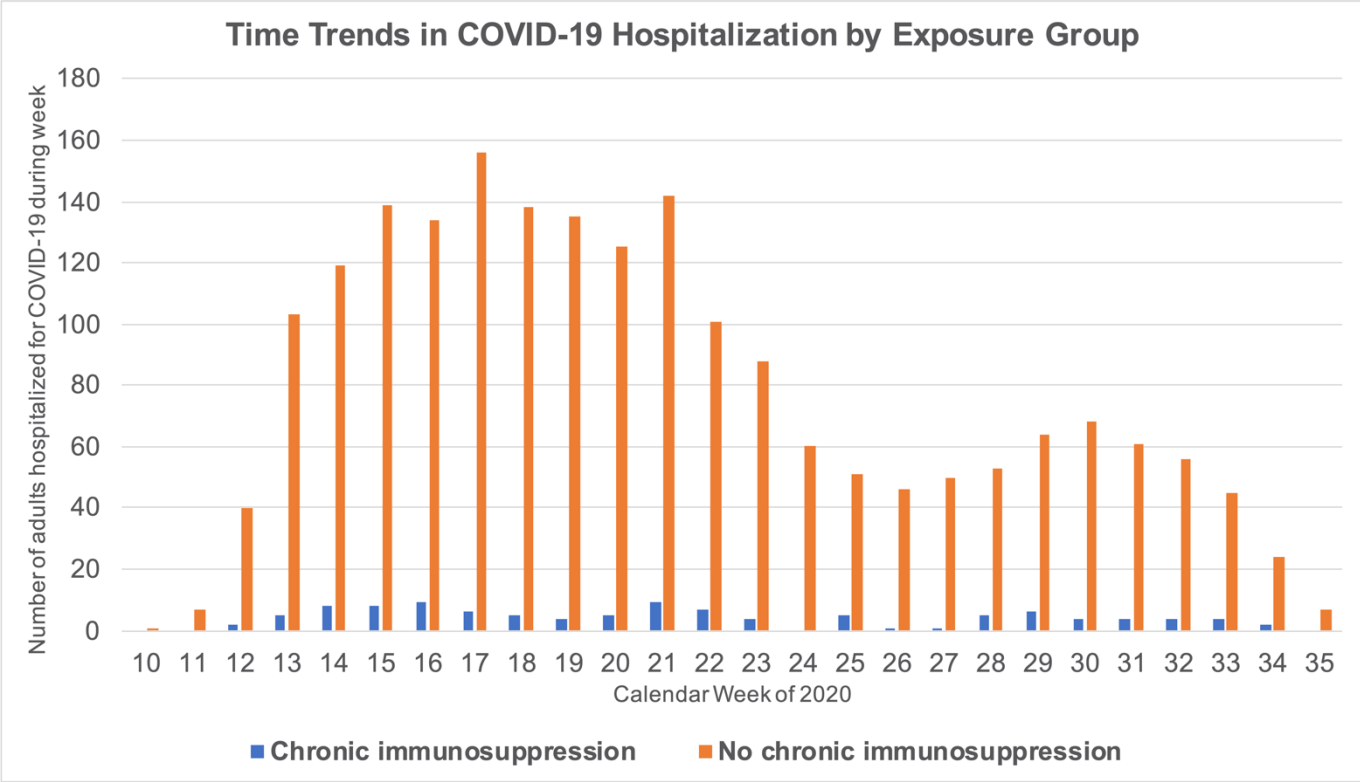
	Hazard ratio (95% Confidence Interval)
Unadjusted regression analysis	1.17 (0.85-1.61)
Primary analysis	
Inverse probability treatment weights	1.15 (0.76-1.74)
Secondary analyses	
Propensity score matching[2]	1.25 (0.65-2.42)
Propensity score adjustment	1.35 (0.94-1.95)

*In this sensitivity analysis, 479 (23%) experienced ventilation: 98 (5%) non-invasive positive pressure ventilation, 390 high-flow nasal cannula (19%), and 311 (15%) from mechanical ventilation. For persons who experienced multiple forms of ventilation, the first occurrence was used as the time of the outcome.

[1] The models for risk of ventilation incorporated the competing risk of death using Fine & Gray's methodology.

[2] Matches were made using 1:1 greedy matching, and 108 pairs were identified.

Figure 1. Distribution of Calendar Week of COVID19 Admission, by Immune System Status.



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Chapter 3: Long-term Use of Immunosuppressive Medicines and In-Hospital COVID-19 Outcomes: A Retrospective Cohort Study Using Data From the National COVID Cohort Collaborative

Kathleen M. Andersen, MSc[1,2]; Benjamin A. Bates, MD[3]; Emaan S. Rashidi, MHS[1,2]; Amy L. Olex, MS[4]; Roslyn B. Mannon, MD[5]; Rena C. Patel, MD[6]; Jasvinder Singh, MD[7,8]; Jing Sun, MD[1]; Paul G. Auwaerter, MD[9]; Derek K. Ng, PhD[1]; Jodi B. Segal, MD[1,2,10]; Brian T. Garibaldi, MD[11]; Hemalkumar B. Mehta, PhD[1,2]; G. Caleb Alexander, MD[1,2,10]; for the National COVID Cohort Collaborative (N3C) Consortium

1. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
2. Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
3. Rutgers Center for Pharmacoepidemiology and Treatment Science, New Brunswick, NJ
4. Wright Center for Clinical and Translational Research, Virginia Commonwealth University, Richmond, VA
5. Division of Nephrology, University of Nebraska Medical Center, Omaha, NE
6. Departments of Medicine and Global Health, University of Washington, Seattle WA
7. Medicine Service, VA Medical Center, Birmingham, AL
8. Department of Medicine at School of Medicine, and Division of Epidemiology at School of Public Health, University of Alabama at Birmingham, Birmingham, AL
9. The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD
10. Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD
11. Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Brief 40-word summary

Among a racially diverse group of male and female adults hospitalized with COVID, there was no statistically significant increased risk of mechanical ventilation or in-hospital mortality among adults with chronic use of most immunosuppressive drugs, with the exception of rituximab.

Correspondence

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street W6035, Baltimore, MD 21205
Phone: 410 955 8168
Email: galexan9@jhmi.edu

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Research in Context

Evidence before this study. There is mixed evidence regarding the impact of immunosuppression and immunosuppressive medicines on COVID-19 outcomes. It is further unclear whether associations vary by medication class.

Added value of this study. This retrospective cohort study evaluated the risk of severe COVID-19 for 15 pharmacologic classes, using electronic health information from 42 health systems in the United States. In this cohort, with the exception of rituximab, there was no increased risk in ventilation or death for the rheumatologic, antineoplastic or antimetabolite therapies examined. Our sample size was large enough to consider separately a variety of drug classes with distinct molecular mechanisms of action including the targeting of B-cell versus T-cell mediated immunity.

Implications of all available evidence. Our results add to a growing body of evidence suggesting the overall safety of several products against the backdrop of continued COVID-related morbidity and mortality. These findings are important because of how commonly these products are used, and ongoing questions regarding the degree to which they increase the risks of poor outcomes among individuals who are hospitalized with COVID-19.

Abstract

Background. Many individuals take chronic medicines that alter their immune system, yet it is unclear whether they have worse outcomes when hospitalized with COVID.

Methods. We conducted a retrospective cohort study using the National COVID Cohort Collaborative (N3C), the largest longitudinal electronic health record repository of COVID-19 inpatient care in the U.S between January 1, 2020 and June 11, 2021 within 42 health systems. We compared adults with immunosuppressive medications used prior to admission to adults without chronic immunosuppression. We considered immunosuppression overall, as well as whether such associations vary by 17 classes and 3 broad indications for immunosuppressive medicines. We used Fine and Gray's proportional subdistribution hazards models to estimate the hazard ratio (HR) for the risk of invasive mechanical ventilation, with the competing risk of death. We used Cox proportional hazards models to estimate HR and CI for in-hospital death. Models were adjusted using doubly robust propensity score methodology.

Findings. Of 222,575 hospitalized individuals, 16,494 (7%) were chronically immunosuppressed with medications for diverse conditions, including rheumatologic disease (33%), solid organ transplant (28%), or cancer (22%). None of the 17 medication classes examined were associated with an increased risk of invasive mechanical ventilation. While there was no statistically significant association between most drugs and in-hospital death, there were increases noted with rituximab for rheumatologic disease (HR 1.72, CI 1.10-2.69) and for cancer (HR 2.57, CI 1.86-3.56). While not statistically significant, the effect size suggests an elevated risk of death for people with anthracycline prescriptions (HR 1.51, CI 0.990-2.31). Results were consistent across

subgroup analyses to separately consider racial and ethnicity identities, as well as sensitivity analyses that varied exposure, covariate, and outcome definitions.

Interpretation. Among this cohort, with the exception of rituximab, there was no increased risk in ventilation or death for the rheumatologic, antineoplastic or antimetabolite therapies examined.

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Introduction

As of October 1, 2021, the SARS-CoV-2 virus has infected over 43 million people in the United States, and caused more than 698,000 deaths.(1) Although increasing vaccination uptake and other public health measures have reduced the burden of the pandemic, substantial morbidity and mortality continue to accrue in the unvaccinated.

There is mixed evidence regarding the impact of immunosuppression and immunosuppressive medicines on COVID-19 outcomes. Certainly, immunosuppression raises the incidence and severity of many infectious diseases; case reports from China and Europe, as well as guidelines from the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) indicate that conditions requiring pharmacologic immunosuppression, such as solid organ transplant (2) and cancer, are risk factors for SARS-CoV-2 infection. However, previous studies have found that individuals with autoimmune diseases, such as rheumatoid arthritis or inflammatory bowel disease, have a greater incidence of COVID-19, but not resultant invasive ventilation or death. (3–5) Case series of solid organ transplant patients with SARS-CoV-2 infection have compared risk of severe COVID to that of the general population, finding higher hospitalization and case fatality rates in initial months of the pandemic. (6–8) Despite the insights from these early studies, there remain unanswered questions, such as whether time trends in COVID-19 management could explain these apparent increased risks.

As with many other clinical contexts, for any given immunosuppressive condition there are many potential drug combinations that might be used. Several single center evaluations, including our own, (9) suggest no increased risk of severe COVID-19 among those taking chronic immunosuppressive medicines, (10–12) and the theoretical possibility that such medicines may dampen the cytokine storm associated with severe COVID-19 has not been substantiated in the literature. Much of the prior chronic immunosuppressive medication literature has used small samples of patients, precluding the evaluation of specific medicine classes.

To address these research gaps, we performed a retrospective cohort study using the National COVID Cohort Collaborative (N3C), the largest U.S. electronic health record repository, which captures COVID-19 care delivered between January 2020 and June 2021. In addition to evaluating overall risk, we also evaluated whether therapeutic class of immunosuppressive medications alters the risk of invasive mechanical ventilation or death.

Methods

Study setting and population

The N3C is a national electronic health record repository supported by the National Institutes of Health's National Center for Advancing Translational Science. (13,14) It contains detailed inpatient and outpatient records, as well as drug exposure information, for a racially, ethnically and geographically diverse group of individuals. Data are reviewed for completeness and accuracy by a data quality team, and the data are harmonized using the Observational Medical Outcomes Partnership Common Data Model. As of June 17, 2021, the N3C had records for over 2,130,000 COVID-positive persons, the majority of which were for outpatient encounters. We used individual patient data within a limited data set to conduct our analyses. The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol #IRB00249128 or individual site agreements with the NIH.

Inclusion and exclusion criteria

We defined COVID-positive individuals as those with confirmed SARS-CoV-2 infection (at least one positive SARS-CoV-2 test result, >99% of which was by RT-PCR) or suspected CoV-2 infection. Suspected infections required at least one strong positive diagnosis code, or two weak positive codes, as outlined in the GitHub repository. (15) We defined a COVID-related hospitalization as the first inpatient visit up to 21 days after the date of confirmed or suspected SARS-CoV-2. To account for delays in test reporting while minimizing the possibility of

nosocomial infections, (16) we also included hospitalized individuals designated as COVID-positive up to 5 days after admission. We limited our analyses to individuals with complete hospitalization episodes, documented by either discharge or death.

We sequentially excluded individuals with missing age or sex information, under 18 years of age, those transferred to the N3C data partner already on a ventilator, and individuals with implausible information, such as a COVID-19 diagnosis in 2018 or a date of death predating their date of admission. In addition, we excluded six clinical sites from our analysis that did not meet N3C standards of data quality, leaving 42 sites for analysis. (14)

Exposures

We defined two mutually exclusive exposure groups: immunosuppressed or non-immunosuppressed persons up to and including at the time of admission. Persons were considered immunosuppressed if they had exposure to at least one of the following: rheumatologic drugs (interleukin inhibitors, janus kinase inhibitors, tumor necrosis factor alpha inhibitors, all other drugs in the WHO Anatomical Therapeutic Chemical (ATC) L04 “Selective Immunosuppressants”), antimetabolite drugs (azathioprine, calcineurin inhibitors, mycophenolic acid [formulated either as mycophenolate sodium or mycophenolate mofetil]), cancer therapies (anthracyclines, checkpoint inhibitors, cyclophosphamide, protein kinase inhibitors, all other in the WHO ATC class L01 “Antineoplastic agents”), rituximab, targeted cancer therapies, and oral glucocorticoids (dexamethasone, prednisone, prednisolone or methylprednisolone) (Table 8). We classified people as having chronic immunosuppression at the time of admission if they had one or more of these medications. We used the electronic health record fields of prescription record start and stop dates, and required immunosuppression to be started at least 14 days prior to their date of admission, and either continued during admission or actively stopped on or after the date of admission. We excluded 57 people whose only immunosuppressant was a glucocorticoid prescribed on or after the date of COVID-19 diagnosis but prior to admission. For oral

glucocorticoids, we further required a diagnosis that was consistent with long-term use of steroids, as defined in Figure 2. People without any of the immunosuppressive drugs active on the date of admission were considered non-immunosuppressed.

Outcomes

Our primary outcome was the time from admission to invasive mechanical ventilation, using the standard N3C definition which employs concept codes for condition occurrence, procedure or observation codes. Our secondary outcome was time from admission to in-hospital death. To reduce their influence in the models, we winsorized the upper 1% of times to event. (17) For people whose first ventilation code could not precisely define the date of ventilation, such as "Respiratory support, 24-96 hours" or "Respiratory support, greater than 96 hours", we used the shortest date of the interval range as the time to event.

Covariates

We selected covariates *a priori* for use in a propensity score model based on the availability of data and information from the peer-reviewed literature, (18,19) government and international agency recommendations, and our own clinical, biostatistical and epidemiologic expertise. We used the following covariates: the week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities (Table 9).

Statistical Analyses

We characterized our study cohort using means with standard deviations for continuous variables and frequency with percentages for count variables. We then constructed propensity scores, (20) using a logistic regression model including each of the covariates described above to predict the probability of being on immunosuppressive medications at the time of admission. For the

propensity score estimation, we created missing data indicators for each variable, as this effectively creates a match on both observed but also missing data patterns.

We used propensity score matching, given substantial areas of non-overlap for the exposed and unexposed groups, with a 4:1 nearest neighbor matching algorithm without replacement and a caliper of 0.2 pooled standard deviations of the estimated propensity score. (21) We evaluated the absolute value of the standardized mean difference (SMD) in the unmatched and the propensity score matched sample, using the R 'cobalt' package, to assess covariate balance in a sample-size independent manner. We implemented doubly robust adjustment, where covariates that remained unbalanced (SMD > 10%) after matching were included in the regression models described below. (22)

We assessed for elevated risk of outcomes comparing immunosuppressed individuals and non-immunosuppressed individuals with all 17 immunosuppressive drug classes combined. We used cluster-robust standard errors that accounted for the matched nature of the data to calculate unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI). We used Fine and Gray's proportional subdistribution hazards models to estimate the risk of mechanical ventilation, accounting for the competing risk of death. (23) We used Cox proportional hazards models to estimate the risk of death. (24) We calculated the E-value to quantify the amount of independent unmeasured confounding that would have to be present in order to qualitatively change the interpretation of results. (25)

Evaluation of Potential Effect Measure Modification

We generated new propensity scores and repeated the propensity score matching process in each subgroup and sensitivity analysis, as well as the set of doubly robust adjustment variables. We stratified models by race and ethnicity groups, which were generally reported by the patient or family member at the time of hospital registration in the local EHR. (26) We grouped race and ethnicity as does the U.S. Census and evaluated whether or not the associations of interest

differed by patient race and ethnicity. We also disaggregated data for males and females, in accordance with SAGER guidelines for reporting of sex information; gender identity was not available.

Sensitivity Analyses

First, to assess whether the absence of glucocorticoid dose information could create exposure misclassification, we excluded persons who had a record of glucocorticoid use without any dose information. Second, we restricted the cohort to persons with at least one prior health system encounter prior to COVID, to assess whether the lack of lookback data may have affected covariate ascertainment. Third, we included people who were hospitalized at least 2 days, as persons discharged the same or next day may be clinically distinct from those with longer stays. Fourth, we added vital signs and lab values at the time of admission to the model. Given that these variables may be strongly associated with the outcome, we did not include them in our primary analyses but instead considered in sensitivity analyses. Lastly, for the people whose ventilation procedure code indicated a date range rather than single date, we varied the choice of date to consider the latest day in the period.

Data extraction and management was performed using Spark SQL and Python, and analyses used Spark R, in the N3C Enclave.

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Results

Cohort Description on the Date of COVID Admission

We identified 222,575 people who met the inclusion criteria (Figure 2). The average length of stay was 8.5 days (standard deviation 13.9). Trends in hospital admissions coincided with national trends in infection waves, with peaks in March-April 2020, July 2020, and November-December 2020 (Figure 3). Immunosuppressed adults were older, more often female and less likely to be Hispanic or Latinx than non-immunosuppressed persons (Table 10). Among the hospitalized adults, 7% had active medication records for immunosuppressive medications at the time of admission (Table 11), including medications commonly used for a rheumatologic condition (33%), antimetabolite drugs (28%) or for cancer treatment (22%). Comorbidities were more prevalent in the immunosuppressed population (Table 12). Vital signs on the first day of admission were similar (Table 13); abnormal creatinine and troponin concentrations, and abnormal white blood cell counts were more prevalent in the immunosuppressed group.

We included 12,841 immunosuppressed and 29,386 non-immunosuppressed persons in the propensity score-matched analyses. In this cohort, some but not all standardized mean differences indicated remaining imbalance between groups (Figure 4). Figure 5 shows overlap of the propensity scores between groups before and after propensity score matching.

Risk of Severe COVID

Overall, 17,470 (7%) people received invasive mechanical ventilation (Figure 6) and 21,801 (10%) people died (Figure 7). Invasive mechanical ventilation was an indicator of poor prognosis, as 47% of people who required ventilation later died in-hospital. In unadjusted analyses, individuals who were immunosuppressed were at greater risk of invasive mechanical ventilation (9% vs 6%, HR 1.36, CI 1.29-1.43) and in-hospital death (14% vs 9%, HR 1.05, CI 1.01-1.10) (Table 14). However, in the propensity score matched cohort, immunosuppression was associated with a reduced risk of invasive ventilation (HR 0.89, CI 0.83-0.96) while there was no overall association

between chronic immunosuppression and the risk of in-hospital death (HR 0.97, CI 0.91-1.02). These analyses had an E-value of 1.50 for invasive mechanical ventilation and 1.21 for death (Table 15). The direction of the results when people were grouped by treatment indications (rheumatologic, antimetabolite or cancer therapies) were similar to overall results (Figures 8 and 9). There was a significant reduction in risk of invasive mechanical ventilation (hazard ratios range from 0.69-0.79), and no significant effects on in-hospital death.

Results from sensitivity analyses varying the exposure definition for glucocorticoids, ascertaining covariates from prior health system experience**,** applying a minimum length of stay of two days, and adding laboratory and vital sign measures from the day of admission yielded substantively similar findings to the main analyses (Table 16). For the people with a range of dates rather than a single date of invasive mechanical ventilation placement, using the longest date in the range, rather than the shortest, did not change the interpretation of results.

Outcomes Based on Specific Therapeutic Classes

For invasive mechanical ventilation, each of the drug classes was associated with reduced or null effects; no drug class was associated with an increase in invasive mechanical ventilation (Figure 8). For in-hospital death, we found a significant reduction with JAK inhibitors (HR 0.42, CI 0.24-0.73) (Figure 9). Rituximab in rheumatologic conditions (HR 1.72, CI 1.10-2.69) and as a cancer therapy (HR 2.57, CI 1.86-3.56) was associated with an increased risk of in-hospital death. All other drugs evaluated did not have statistically significant associations with in-hospital death. While not statistically significant, the effect size suggests an elevated risk of death for people with anthracycline prescriptions (HR 1.51, CI 0.990-2.31).

Outcomes for Racial and Ethnic Groups

We evaluated potential effect measure modification by racial and ethnic identity. Immunosuppressive drug use was protective against mechanical ventilation for Non-Hispanic

Black and Non-Hispanic white persons, as well as for people with unknown racial and ethnic identity. However, among Asian, Hispanic, and persons of another race immunosuppression had no effect (Table 17). Consistent with the overall effect estimate, the risk of death for immunosuppressed persons in each racial and ethnic group was not significantly different between exposure groups.

Outcomes by Sex

In analyses stratified by sex as recorded in the electronic health record, results were again generally consistent. No drug class was associated with an increased risk of invasive mechanical ventilation. Most of the classes had statistically protective effects in males (Figure 10) and null effects in females (Figure 11). For in-hospital death, rituximab was associated with an increased risk of death in females with cancer (Figure 12), but not females with a rheumatologic condition or males for either indication (Figure 13), The risk of death with checkpoint inhibitors was increased for males, but not females.

Discussion

While cases, hospitalizations and deaths are decreasing in the United States in mid-2021, the SARS-CoV-2 pandemic is ongoing worldwide and important questions remain. In this analysis of over 220,000 adults hospitalized with COVID, there was no discernible increased risk of invasive mechanical ventilation or death with most of the therapies we examined. These findings are important because of how commonly these products are used, and ongoing questions regarding the degree to which they increase the risks of poor outcomes among individuals who are hospitalized with COVID-19.

Our findings regarding immunosuppressive therapies extend the results of our earlier work and that of others examining the association between use of these medication classes and COVID-19 outcomes. Where our findings diverge from other publications may be attributed to differences

in study design, in that we defined immunosuppression by medications rather than diagnoses, we restricted analyses to hospitalized COVID patients, and we had the statistical power and methods to powerfully address confounding and effect modification. By using a larger and more diverse cohort, our results add to a growing body of evidence suggesting the overall safety of several products against the backdrop of continued COVID-related morbidity and mortality. Our sample size also allowed for us to examine specific subclasses of therapies that vary considerably in their mechanisms of action, and we found similar safety of these varied classes with respect to the outcomes examined among this cohort.

While our main analyses, and for the subgroups of rheumatologic and antimetabolite drugs, found that immunosuppression reduced the risk of invasive mechanical ventilation, we did not find this with rituximab. Rituximab, a chimeric monoclonal antibody, binds to the cell surface protein CD20 and induces B cell apoptosis. This mechanism of action powerfully interferes with antibody response to infection, and can lead to prolonged viral replication. It is therefore not surprising that we found null effects for ventilation and an increased risk of death, given the impaired antiviral humoral response.

Conversely, we found a decreased risk of death with chronic JAK inhibitor use. Baricitinib and tofacitinib have each shown to be efficacious in clinical trials as COVID therapies among persons not using them prior to SARS-CoV-2 infection. (27,28) An international registry of rheumatoid arthritis patients with COVID reported increased odds of death for people on JAK inhibitors, as compared to TNF inhibitors. Their results may differ from ours given their population was not restricted to hospitalized patients. (29)

Our results generate important scientific and clinical questions for further exploration. For example, studies are needed to assess whether chronic immunosuppressive use, especially with products such as glucocorticoids, may attenuate the mortality benefit attributable to dexamethasone for COVID patients requiring supplemental oxygen. (30) Also, our study was not

designed to inform questions regarding whether chronic immunosuppressive medicines, present at hospital admission, should be continued during hospitalization for COVID, and if so, under what treatment protocols. Of course, such protocols, as well as current clinical practice, may vary for different subpopulations of individuals, such as those with rheumatologic disease as compared to those with a history of solid organ transplant. It is also unclear whether the associations we describe could be in part due to differential treatment across our study groups once hospitalized. Immunosuppressed patients may have been hospitalized at earlier stages in disease, and treated more aggressively because of the perception of higher risk, both of which could account for the decreased risk of ventilation and lack of an increase in mortality. Of note, there were no significant differences in the proportion of people who received remdesivir, in-hospital dexamethasone, or pre-admission monoclonal antibodies for SARS-CoV-2 management. Future studies could account for the time-varying nature of in-patient treatment, as well as treatment indicators such as laboratory measures of inflammation or ability to mount an inflammatory response.

Our analyses have several limitations. First, the N3C does not contain information on advanced directives, which may lead to misclassification of risk of ventilation and death. Second, the N3C does not contain information on supplemental oxygen. Given the RECOVERY trial found dexamethasone reduced the risk of death in people with oxygen requirements, (30) but increased the risk of death if they did not require supplemental oxygen, it is possible that the null effect we report is an average of increased and decreased risk by an unmeasured confounder. Third, we used WHO ATC classes for a standardized definition for immunosuppressive medications, which does not include therapies that some may consider to be immunosuppressive such as hydroxychloroquine, medications for HIV care, or multiple sclerosis, or other immunocompromising conditions. Instead, in this analysis, these people were considered to be not immunosuppressed. Fourth, persons who stopped their immunosuppressive medication in the short term before admission, such as at the time of COVID-19 diagnosis due to concern of

immunosuppression leading to worse outcomes, and did not report current immunosuppression at the time of admission would be misclassified as non-immunosuppressed in this analysis. Fifth, care delivered in the N3C may not represent settings outside of academic medical centers or in hospitals outside of the United States. Finally, our analysis was strongly dependent on valid risk adjustment, but we recognize that the Charlson-Deyo instrument may not fully capture the risks associated with underlying comorbidities and indication for immunosuppressive therapy. Residual and unmeasured confounding due to indication, particularly among the subset of cancer patients, may be a source of bias.

The limitations notwithstanding, our analyses also have several strengths. We used a national, diverse cohort of over 220,000 adults in the United States hospitalized with COVID-19. In addition, we used doubly robust propensity score methods, and considered the competing risk of death for analyses examining ventilation. Finally, our sample size was large enough to consider separately a variety of drug classes with distinct molecular mechanisms of action including the targeting of B-cell versus T-cell mediated immunity.

Conclusion

In this cohort, with the exception of rituximab, there was no increased risk in ventilation or death for the rheumatologic, antineoplastic or antimetabolite therapies examined.

Notes

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave (**covid.cd2h.org/enclave**) and supported by NCATS U24 TR002306. This research was possible because of the patients whose information is included within the data from participating organizations (**covid.cd2h.org.dtas)** and the organizations and scientists (**covid.cd2h.org/duas**) who have contributed to the on-going development of this community resource: https://doi.org/10.1093/jamia/ocaa196.

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Data Sharing Statement. The code for this work can be found at https://github.com/National-COVID-Cohort-Collaborative/CS-ISC. The N3C Data Enclave (covid.cd2h.org/enclave) houses fully reproducible, transparent, and broadly available limited and de-identified datasets (HIPAA definitions: https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html). Data is accessible by investigators at institutions that have signed a Data Use Agreement with NIH who have taken human subjects and security training and attest to the N3C User Code of Conduct. Investigators wishing to access the limited dataset must also supply an institutional IRB protocol. All requests for data access are reviewed by the NIH Data Access Committee. A full description of the N3C Enclave governance has been published; information about how to apply for access is available on the NCATS website: https://ncats.nih.gov/n3c/about/applying-for-access. Reviewers and health authorities will be given access permission and guidance to aid reproducibility and outcomes assessment.

Table 8. Immunosuppressive Drugs Considered in Exposure Definition

Interleukin inhibitors	daciluzumab, basiliximab, anakinra, rilonacept, ustekinumab, tocilizumab, canakinumab, briakinumab, secukinumab, siltuximab, brodalumab, ixekizumab, sarilumab, sirukumab, guselkumab, tildrakizumab, risankizumab
Janus kinase inhibitors	tofacitinib, baricitinib, upadacitinib
Tumor necrosis factor alpha inhibitors	etanercept, infliximab, afelimomab, adalimumab, certolizumab pegol, golimumab, opinercept
Other selective immunosuppressa-nts	muromonab-cd3, antilymphocyte immunoglobulin (horse), antithmyocyte immunoglobulin (rabbit), sirolimus, leflunomide, alefacept, everolimus, gusperimus, efalizumab, abetimus, natalizumab, abatacept, eculizumab, belimumab, fingolimod, belatacept, teriflunomide, apremilast, vedolizumab, alemtuzumab, begelomab, ocrelizumab, ozanimod, emapalumab, cladribine, imlifidase, siponimod50eclometh, ravulizumab, thalidomide, lenalidomide, pirfenidone, pomalidomide, dimethyl fumarate, darvadstrocel Defined using products cataloged in the WHO Anatomical Therapeutic Chemistry Class L04 “Selective Immunosuppressants” that were not interleukin inhibitors, janus kinase inhibitors, tumor necrosis factor alpha inhibitors or monoclonal antibodies.
Azathioprine	azathioprine
Calcineurin inhibitors	ciclosporin, cyclosporine, tacrolimus, voclosporin
Mycophenolic acid	mycophenolic acid, mycophenolate sodium, mycophenolate mofetil
Anthracyclines	doxorubicin, daunorubicin, epirubicin, aclarubicin, zorubicin, idarubicin, mitoxantrone, pirarubicin, valrubicin, amrubicin, pixantrone
Checkpoint inhibitors	ipilimumab, nivolumab, pembrolizumab, avelumab, atezolizumab, cemiplimab, durvalumab
Cyclophosphamide	cyclophosphamide
Protein kinase inhibitors	imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, lapatinib, nilotinib, temsirolimus, everolimus, pazopanib, vandetanib, afatinib, bosutinib, vemurafenib, crizotinib, axitinib, ruxolitinib, ridaforolimus, regorafenib, masitinib, dabrafenib, ponatinib, trametinib, cabozantinib, ibrutinib, ceritinib, lenvatinib, nintedanib, cediranib, palbociclib, tivozanib, osimertinib, alectinib, rociletinib, cobimetinib, midostaurin, olmutinib, binimetinib, ribociclib, brigatinib, lorlatinib, neratinib, encorafenib, dacomitinib, icotinib, abemaciclib, acalabrutinib, quizartinib, larotrectinib,

	gilteritinib, entrectinib, fedratinib, toceranib
Other cancer therapies	chlorambucil, melphalan, chlormethine, ifosfamide, trofosfamide, prednimustine, bendamustine, busulfan, treosulfan, mannosulfan, thiotepa, triaziquone, carboquone, carmustine, lomustine, semustine, streptozocin, fotemustine, nimustine, ranimustine, uramustine, etoglucid, itobronitol, pipobroman, temozolomide, dacarbazine, methotrexate, raltitrexed, pemetrexed, pralatrexate, mercaptopurine, tioguanine, cladribine, fludarabine, clofarabine, nelarabine, rabacfosadine, cytarabine, fluorouracil, tegafur, carmofur, gemcitabine, capecitabine, azacitidine, decitabine, floxuridine, fluorouracil, tegafur, trifluridine, vinblastine, vincristine, vindesine, vinorelbine, vinflunine, vintafolide, etoposide, teniposide, demecolcine, paclitaxel, docetaxel, paclitaxel poliglumex, cabazitaxel, trabectedin, dactinomycin, bleomycin, plicamycin, mitomycin, ixabepilone, cisplatin, carboplatin, oxaliplatin, satraplatin, polyplatillen, procarbazine, porfimer sodium, methyl aminolevulinate, aminolevulinic acid, temoporfin, efaproxiral, padeliporfin, amsacrine, asparaginase, altretamine, hydroxycarbamide, lonidamine, pentostatin, masoprocol, estramustine, mitoguazone, topotecan, tiazofurine, irinotecan, alitretinoin, mitotane, pegaspargase, bexarotene, arsenic trioxide, denileukin diftitox, bortezomib, anagrelide, oblimersen, sitimagene ceradenovec, vorinostat, romidepsin, omacetaxine mepesuccinate, eribulin, panobinostat, vismodegib, aflibercept, carfilzomib, olaparib, idelalisib, sonidegib, belinostat, ixazomib, talimogene laherparepvec, venetoclax, vosaroxin, niraparib, rucaparib, etirinotecan pegol, plitidepsin, epacadostat, enasidenib, talazoparib, copanlisib, ivosidenib, glasdegib, entinostat, alpelisib, selinexor, tagraxofusp, belotecan, tigilanol tiglate, cytarabine Defined using WHO Anatomical Therapeutic Chemistry Class L01 products that were not anthracyclines, checkpoint inhibitors, cyclophosphamide, or protein kinase inhibitors.
Rituximab	rituximab
Targeted cancer therapies	edrecolomab, trastuzumab, gemtuzumab ozogamicin, cetuximab, bevacizumab, panitumumab, catumaxomab, ofatumumab, brentuximab vedotin, pertuzumab, trastuzumab emtansine, obinutuzumab, dinutuximab beta, blinatumomab, ramucirumab, necitumumab, elotuzumab, daratumumab, mogamulizumab, inotuzumab ozogamicin, olaratumab, bermekimab Defined using monoclonal antibody products in WHO Anatomical Therapeutic Chemistry Class L04 products that were not interleukin, tumor necrosis factor alpha or janus kinase inhibitors.
Oral glucocorticoids	dexamethasone, prednisone, prednisolone, methylprednisolone

Table 9. Definitions for Variables Included in Propensity Score.

Week of admission	
Contributing data site	
Age at admission	
Sex	As recorded in local electronic health record
Race and ethnicity	Often, self-reported. Operationalized using Census Track designations of Asian, Hispanic or Latinx, non-Hispanic Black, non-Hispanic white, Another race or missing.
Smoking history	Current or former smoker
Body mass index	We used WHO cutpoints to categorize the body mass index (BMI) as underweight, normal weight, overweight, obese or missing. We took the measure closest to the date of, and considered improbable values, which we defined as < 15 kg/m^2 or >70 kg/m^2, as missing data.
Days between COVID-19 diagnosis and hospital admission	
Cardiovascular disease	ICD-10 codes I25.x
Chronic hypertension	ICD-10 codes I10.x
Medications current at the time of admission used to treat risk factors for severe COVID-19 outcomes	
Congestive heart failure	potassium canrenoate, canrenone, eplerenone, metoprolol, sacubitril with valsartan, spironolactone or digoxin
Diabetes	One variable for each of Biguanides (WHO ATC A10BA): phenformin, metformin, buformin Alpha glucosidase inhibitors (WHO ATC A10BF): acarbose, miglitol, voglibose Sulfonylureas (WHO ATC A10BB and A10BC): glibenclamide, chlorpropamide, tolbutamide, glibornuride, tolazamide, carbutamide, glipizide, gliquidone, gliclazide, metahexamide, glisoxepide, glimepiride, acetohexamide, glymidine Thiazolidinediones (WHO ATC A10BG): troglitazone, rosiglitazone, pioglitazone Dipeptidyl peptidase-4 inhibitors (WHO ATC A10BH): sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, gemigliptin, evogliptin

	Glucagon-like peptide-1 agonists (WHO ATC A10BJ): exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide Sodium-glucose transport protein-2 inhibitors (WHO ATC A10BK): dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipraglifozin, sotagliflozin Other oral antidiabetic drugs (WHO ATC A10BX): guar gum, repaglinide, nateglinide, pramlintide, benfluorex, mitiglinide Insulin
Dementia	(WHO ATC N06D) donepezil, galantamine, rivastigmine or memantine
Pulmonary disorders	One variable for each of Short acting beta agonists (WHO ATC R03CC): salbutamol, terbutaline, fenoterol, hexoprenaline, isoetarine, pirbuterol, procaterol, tretoquinol, carbuterol, tulobuterol, bambuterol, clenbuterol Long acting beta agonists (WHO ATC R03AC): bambuterol, clenbuterol, formoterol, indacaterol, olodaterol, salmeterol Inhaled corticosteroids (WHO ATC R03BA): beclometasone, budesonide, flunisolide, betamethasone valerate, fluticasone, triamcinolone acetonide, mometasone, ciclesonide, fluticasone furoate Leukotriene modifiers (WHO ATC R03DC): zafirlukast, pranlukast, montelukast Other drugs for pulmonary disorders (WHO ATC R03): hexoprenaline, tretoquinol, clenbuterol, ipratropium bromide, oxitropium bromide, stramoni, tiotropium bromide, aclidinium bromide, glycopyrronium bromide, umeclidinium bromide, revefenacin, cromoglicic acid, nedocromil, fenspiride, isoprenaline, methoxyphenamine, orciprenaline, fenoterol, hexoprenaline, tretoquinol, reproterol, diprophylline, choline theophyllinate, proxyphylline, theophylline, aminophylline, etamiphylline, theobromine, bamifylline, acefylline piperazine, bufylline, doxofylline, mepyramine theophyllinacetate
Obesity	Orlistat, lorcaserin, phentermine, bupropion with naltrexone, liraglutide
Renal disease	(WHO ATC B03XA, A11CC and V03AE) Erythropoietin, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, ergocalciferol, dihydrotachysterol, alfacalcidol, calcitriol, sevelamer, lanthanum carbonate, or sucroferric oxyhydroxide
Comorbidities present at	Defined using the conditions included in the Charlson

admission	Comorbidity Index, using all-available lookback data in the N3C Enclave, which can be as far as January 1, 2018. We used the standard N3C definitions for all conditions, except for HIV where we used the Immunosuppressed Domain Team's definition. Cancer: code set 535274723 Congestive heart failure: 359043664 Dementia: 78746470 Diabetes: 719585646 Diabetes with complications: 403438288 HIV infection: 382527336 Liver disease, mild: 494981955 Liver disease, severe: 248333963 Metastatic cancer: 378462283 Myocardial infarction: 259495957 Paralysis: 489555336 Peptic ulcer disease: 510748896 Pulmonary disorder: 514953976 Peripheral vascular disease: 376881697 Renal disease: 220495690 Rheumatic disease: 765004404 Stroke: 652711186
History of solid organ transplant	Kidney (N3C Enclave code set ID 913892613), liver (204996696), heart (976928531) or lung (335991647). Other less common organ transplants, such as pancreas, were explored but sample size limitations precluded further use.

Drugs were defined using WHO Anatomical Therapeutic Chemical (WHO ATC) class, and diagnoses were defined using ICD-10 codes.

Table 10. Characteristics of Individuals on Date of Hospitalization With Confirmed or Suspected COVID-19, by Immune System Status Prior to COVID-19.

	Immunosuppressed N = 16,494	Not immunosuppressed N = 206,081
Age in years	61 (16)	59 (19)
Male sex	7,263 (44%)	104,006 (51%)
Race and Ethnicity		
Asian	335 (2%)	6,612 (3%)
Hispanic or Latinx	1,672 (10%)	30,759 (15%)
Non-Hispanic Black	3,820 (23%)	38,461 (19%)
Non-Hispanic white	7,989 (48%)	92,629 (45%)
Another race	113 (1%)	1,030 (< 1%)
Missing or unknown	2,565 (16%)	36,590 (18%)
Current or former smoker	4,814 (29%)	36,544 (18%)
Body mass index		
Underweight	329 (2%)	1,850 (1%)
Not overweight or obese	2,893 (18%)	18,899 (9%)
Overweight	3,299 (20%)	26,494 (13%)
Obese	5,789 (35%)	40,757 (20%)
Missing	4,184 (25%)	118,081 (57%)
Days between COVID-19 diagnosis and hospital admission	1.6 (4.0)	1.3 (3.7)
Solid organ transplant recipient	3,423 (21%)	2,338 (1%)
Cardiovascular disease	5,922 (36%)	34,116 (17%)
Chronic hypertension	12,397 (75%)	94,658 (46%)

Continuous variables are represented as mean (standard deviation), and categorical variables as counts (%).

Table 11. Frequency of Immunosuppressive Drug Classes in Cohort.

	Number of people with drug class current at the time of admission
Rheumatologic drugs	5,366 (33%)
Glucocorticoid with rheumatologic condition	4,281 (26%)
Interleukin inhibitors	377 (2%)
Janus kinase inhibitors	85 (1%)
Rituximab with rheumatologic condition	132 (1%)
Tumor necrosis factor alpha inhibitors	343 (2%)
Other selective immunosuppressants	994 (6%)
Antimetabolite drugs	4,288 (26%)
Azathioprine	436 (3%)
Calcineurin inhibitors	3,403 (21%)
Mycophenolic acid	2,788 (17%)
Glucocorticoids with solid organ transplant	2,598 (16%)
Cancer therapies	3,569 (22%)
Anthracyclines	328 (2%)
Checkpoint inhibitors	159 (1%)
Cyclophosphamide	280 (2%)
Protein kinase inhibitors	582 (4%)
Rituximab with cancer	186 (1%)
Targeted cancer therapies	343 (2%)
Other cancer therapies	2,633 (16%)
Rituximab without rheumatologic or cancer diagnosis	84 (< 1%)
Glucocorticoid for chronic pulmonary disease	6,828 (42%)

People can be on more than one immunosuppressive drug at a time. Drug categories are defined in Table 9.

Table 12. Prevalence of 17 Comorbidities Among Adults Hospitalized With COVID-19.

	Immunosuppressed N = 16,494	Non-immunosuppressed N = 206,081	SMD
Acute myocardial infarction	2,382 (14%)	9,030 (4%)	0.35
Congestive heart failure	4,915 (30%)	20,510 (10%)	0.51
Peripheral vascular disease	3,783 (23%)	15,852 (8%)	0.43
Cerebral vascular accident	3,226 (20%)	15,695 (8%)	0.35
Dementia	827 (5%)	8,426 (4%)	0.04
Pulmonary disease	8,646 (52%)	28,114 (14%)	0.91
Connective tissue disorder	2,827 (17%)	5,975 (3%)	0.49
Peptic ulcer disease	785 (5%)	2,370 (1%)	0.21
Liver disease	3,059 (19%)	10,229 (5%)	0.43
Diabetes	7,728 (47%)	42,928 (21%)	0.57
Diabetes complications	4,569 (28%)	19,305 (9%)	0.49
Paralysis	580 (4%)	2,636 (1%)	0.15
Renal disease	6,397 (39%)	23,375 (11%)	0.67
Cancer	4,465 (27%)	14,168 (7%)	0.56
Metastatic cancer	1,363 (8%)	2,392 (1%)	0.34
Severe liver disease	743 (5%)	2,014 (1%)	0.22
HIV	210 (1%)	1,162 (1%)	0.07

SMD: standardized mean difference, represented as the absolute value.

Table 13. Laboratory Measures and Vital Signs on Day of Admission, Before and After Propensity Score Matching.

	Before Propensity Score Matching			After Propensity Score Matching		
	Immunosuppressed	Non-immunosuppressed	SMD	Immunosuppressed	Non-immunosuppressed	SMD
Fever	537 (8%)	5,672 (10%)	0.04	424 (9%)	1,040 (9%)	0.01
Low mean arterial pressure	22 (1%)	157 (< 1%)	0.02	Fewer than 20 (1%)	35 (< 1%)	0.01
High mean arterial pressure	1,065 (25%)	11,017 (29%)	0.08	814 (25%)	1,962 (26%)	0.01
Low oxygen saturation	968 (14%)	8,932 (16%)	0.05	749 (14%)	2,077 (16%)	0.06
Rapid pulse	1,290 (25%)	10,310 (25%)	0.00	1,039 (26%)	2,230 (23%)	0.05
Rapid breathing	1,610 (26%)	14,851 (27%)	0.02	1,279 (26%)	3,283 (27%)	0.03
↓ Albumin	2,930 (37%)	35,951 (42%)	0.10	2,280 (37%)	5,608 (39%)	0.05
↑ ALT	2,122 (26%)	32,840 (39%)	0.29	1,721 (27%)	4,614 (31%)	0.09
↑ AST	3,868 (39%)	50,172 (52%)	0.26	3,065 (40%)	7,589 (45%)	0.11
↑ C-reactive protein	2,837 (90%)	30,691 (92%)	0.10	2,243 (90%)	5,341 (91%)	0.05
↑ Creatinine	3,620 (37%)	26,528 (25%)	0.26	2,514 (33%)	5,698 (32%)	0.02
↑ Troponin	2,756 (71%)	22,921 (62%)	0.20	2,109 (69%)	5,006 (68%)	0.04
↑ White blood cells	1,563 (16%)	10,242 (10%)	0.20	1,148 (15%)	1,904 (11%)	0.13
↓ White blood cells	1,479 (15%)	19,763 (19%)	0.09	1,203 (16%)	3,115 (18%)	0.04

ALT: alanine aminotransferase; AST: aspartate aminotransferase; SMD: standardized mean difference, represented as the absolute value. Vital signs and lab values in the table represent individuals with abnormal values above or below referent standard, and the denominator for the proportions exclude persons missing a result. We defined abnormal vital signs within 24 hours of admission (body temperature >38^{0}C, mean arterial pressure < 60mmHg or >100mmHg, oxygen saturation from pulse oximetry < 93%, pulse >99 beats per minute, respiratory rate >22 breaths per minute) and abnormal lab results within 24 hours of admission (albumin < 3.5 g/dL, alanine aminotransferase (ALT) > 35 u/L, C-reactive protein > 8 mg/L, creatinine > 1.3 mg/dL, detectable troponin, white blood cell count < 4 cells per 10^3/uL or > 11 cells per 10^3/uL).[25]

Table 14. Association Between Chronic Immunosuppression and Clinical Outcomes in COVID-19, in Propensity Score Matched Cohort.

	Invasive Mechanical Ventilation[1]	In-Hospital Death
Immunosuppressed (n = 16,494)	1,520 (9%)	2,334 (14%)
Non-immunosuppressed (n = 206,081)	13,220 (6%)	19,467 (9%)
Hazard Ratio (95% Confidence Interval) comparing Immunosuppressed to Non-immunosuppressed adults		
Unadjusted regression in entire cohort	**1.36 (1.29-1.43)**	**1.05 (1.01-1.10)**
Unadjusted regression in matched cohort	**0.88 (0.82-0.94)**	1.01 (0.96-1.07)
Propensity score matching with doubly robust adjustment	**0.89 (0.83-0.96)**	0.97 (0.91-1.02)
E-value	1.50	1.21
Propensity score matching with doubly robust adjustment, among males	**0.86 (0.78-0.95)**	0.97 (0.90-1.05)
Propensity score matching with doubly robust adjustment, among females	**0.89 (0.81-0.994)**	0.95 (0.88-1.04)

Table 15. E-Values for Strength of Association Between Immunosuppressive Medication Classes and Clinical Outcomes in COVID.

	E-value	
	Invasive Mechanical Ventilation	In-Hospital Death
Rheumatologic drugs	2.26	1.11
Glucocorticoid with rheumatologic condition	1.63	1.25
Interleukin inhibitors	2.30	2.00
Janus kinase inhibitors	2.78	4.19
Rituximab with rheumatologic condition	2.37	2.83
Tumor necrosis factor alpha inhibitors	2.04	1.16
Other selective immunosuppressants	2.08	1.46
Antimetabolite drugs	1.85	1.25
Azathioprine	2.50	2.12
Calcineurin inhibitors	2.40	1.32
Mycophenolic acid	1.67	1.39
Glucocorticoids with solid organ transplant	2.66	1.29
Cancer therapies	2.08	1.16
Anthracyclines	3.18	1.69
Checkpoint inhibitors	2.08	2.39
Cyclophosphamide	2.08	1.97
Protein kinase inhibitors	2.17	1.60
Rituximab with cancer	2.00	1.31
Targeted cancer therapies	2.30	1.46
Other cancer therapies	1.50	4.58

The e-value is calculated as HR + sqrt(HR x (HR – 1)), where HR = hazard ratio. In cases where the hazard ratio was less than 1, the inverse of the hazard ratio is used to calculate the e-value.

Table 16. Results from Sensitivity Analyses.

	Invasive Mechanical Ventilation[1]	In-Hospital Death
Restricting glucocorticoid definition to persons with dose information available	**0.79 (0.69-0.89)**	1.06 (0.95-1.17)
Restricting Cohort to Persons With At Least 1 Prior Encounter With Health System Prior to COVID-19 Hospitalization	0.93 (0.86-1.000)	0.97 (0.91-1.03)
Restricting Cohort to Persons With Minimum 2 Days Length of Stay	**0.89 (0.83-0.96)**	0.97 (0.91-1.03)
Adding Laboratory Measures and Vitals Signs from Day of Admission	0.96 (0.89-1.03)	0.96 (0.90-1.01)
Varying Ventilation Onset Definition to latest date in range*	**0.86 (0.80-0.92)**	**--**

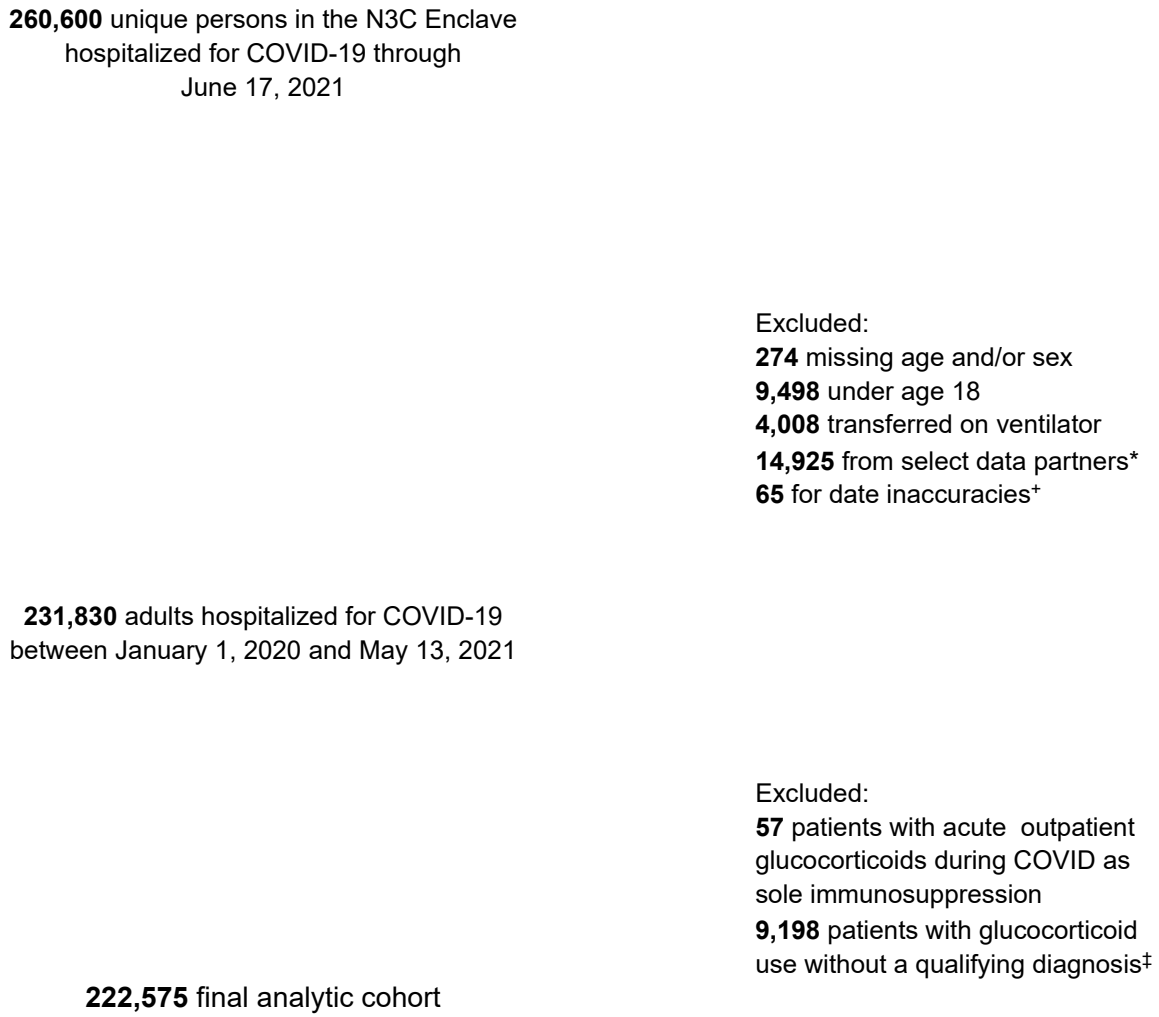
* For 4% of the cohort, their first code indicating invasive ventilation indicated ventilation placement in the range of 24-96 hours prior. For these people, in this sensitivity analysis, we used 96 hours. For 7% of the cohort, the first code indicating invasive ventilation had been placed “greater than 96 hours”. For these people, in this sensitivity analysis, we used the date of admission as the earliest possible date at risk.

Table 17. Association Between Chronic Immunosuppression and Clinical Outcomes in COVID, for Race and Ethnicity Groups.

	Hazard Ratio (95% Confidence Interval) Comparing Immunosuppressed to Non-Immunosuppressed Persons	
	Invasive Mechanical Ventilation	In-Hospital Death
Asian	0.72 (0.42-1.24)	0.65 (0.36-1.20)
Hispanic or Latinx	0.95 (0.77-1.18)	1.10 (0.90-1.34)
Non-Hispanic Black	**0.82 (0.70-0.95)**	0.88 (0.76-1.02)
Non-Hispanic white	0.90 (0.82-1.000)	0.97 (0.90-1.04)
Another race*	1.29 (0.45-3.73)	1.28 (0.56-2.91)
Missing or unknown race	**0.68 (0.55-0.84)**	1.02 (0.86-1.21)

*We created the category of “Another race” due to sample size limitations. The category includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other.

Figure 2. Analytic Cohort Derivation.

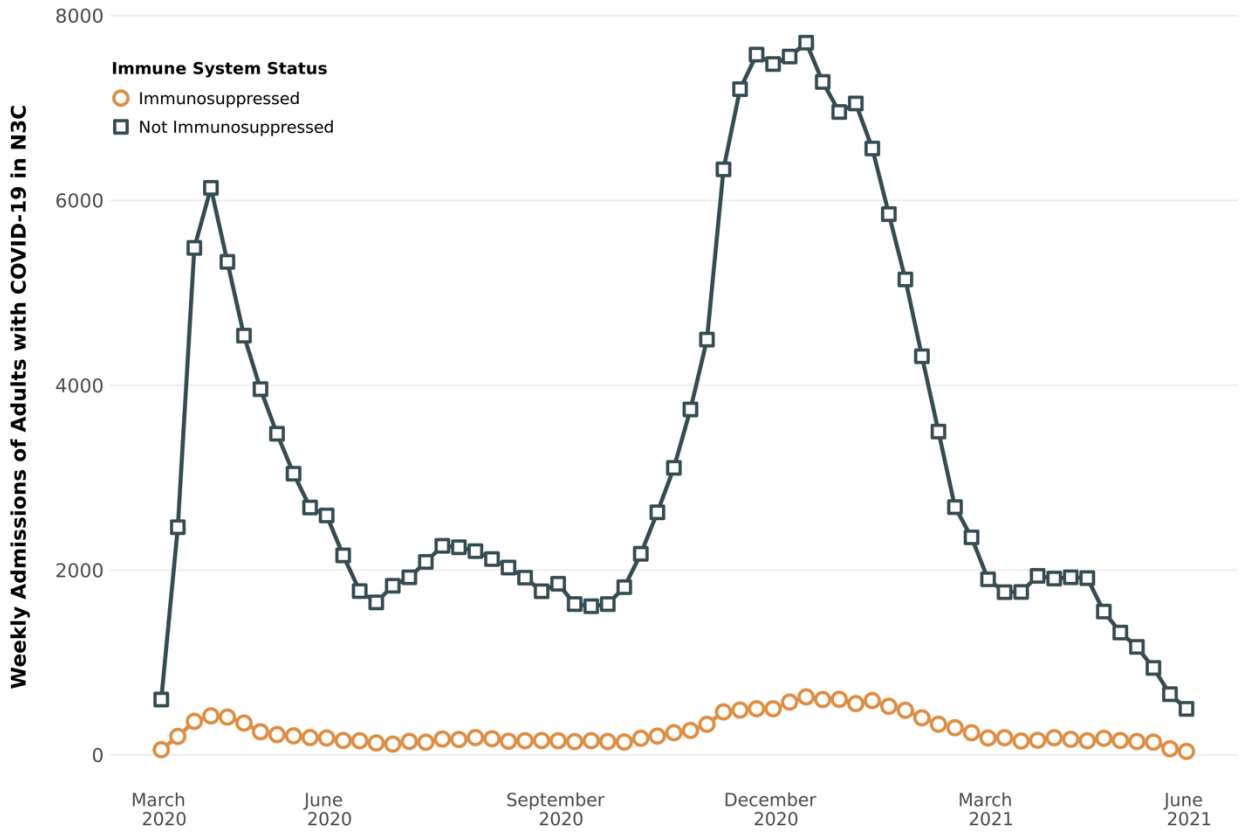


N3C: National COVID Cohort Collaborative.
* In accordance with N3C data quality procedures, we excluded six data partner sites: one with overall data quality concerns, one that shifted dates by up to 90 days before sending data to the N3C, three sites with over 100 hospitalized COVID-positive adults yet zero recorded deaths, and one site with over 100 COVID-positive adults yet zero recorded as receiving invasive mechanical ventilation.

+ Date inaccuracies included persons with a date of COVID diagnosis before January 1, 2020, a date of death before January 1, 2020, or a date of death that preceded date of admission.

‡ Diagnoses that would suggest chronic glucocorticoid use were psoriasis, ulcerative colitis, rheumatoid arthritis, chronic obstructive pulmonary disease, asthma, systemic lupus erythematosus, vasculitis, ankylosing spondylitis, axial spondyloarthropathy, psoriatic arthritis, or a history of solid organ transplantation.

Figure 3. Weekly Volume of Admissions in the N3C, March 18, 2020 through June 2, 2021.



As per N3C data policies, data are suppressed for weeks before March 18, 2020 and after June 2, 2021, as at least one group had 20 or fewer people.

Figure 4. Covariate Balance Before and After Propensity Score Matching.

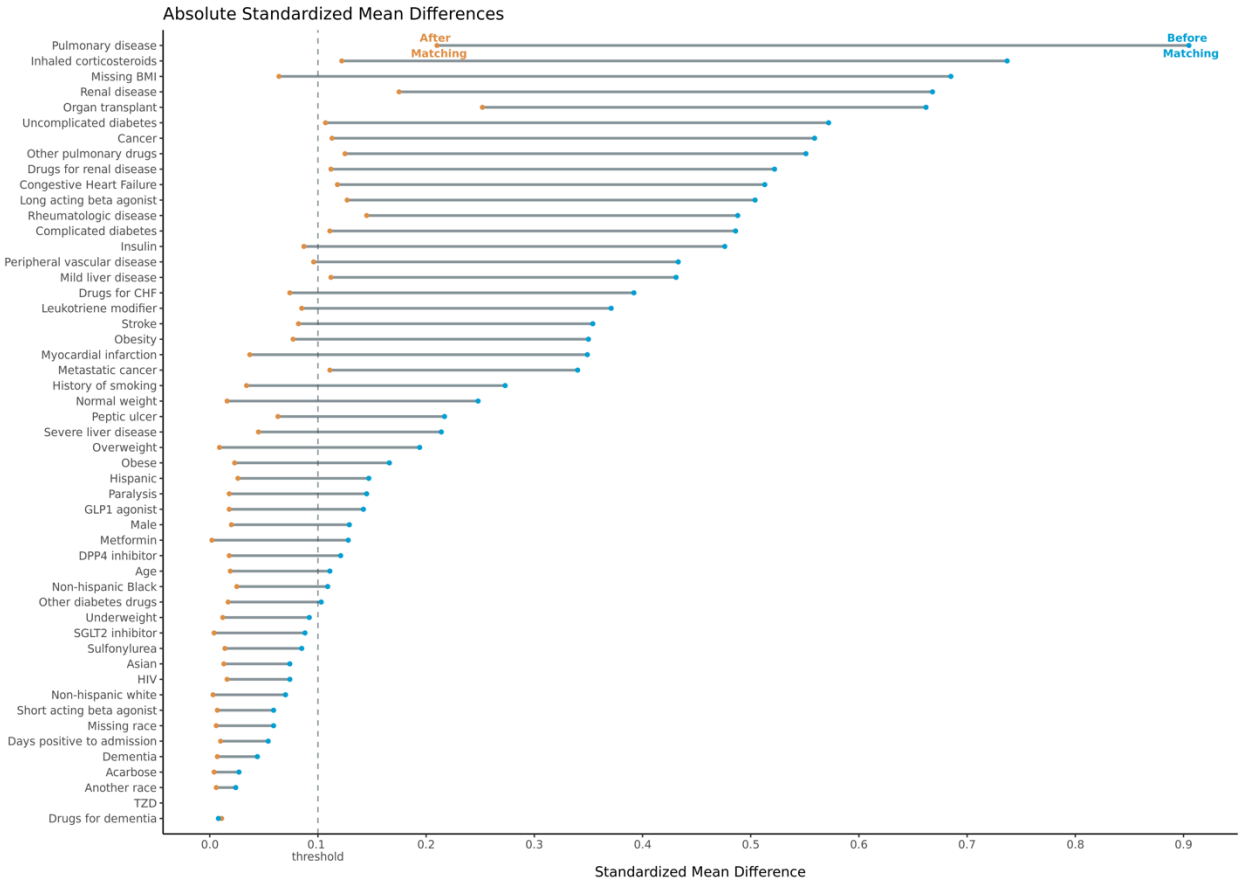


Figure 5. Propensity Score Distribution Before and After Matching.

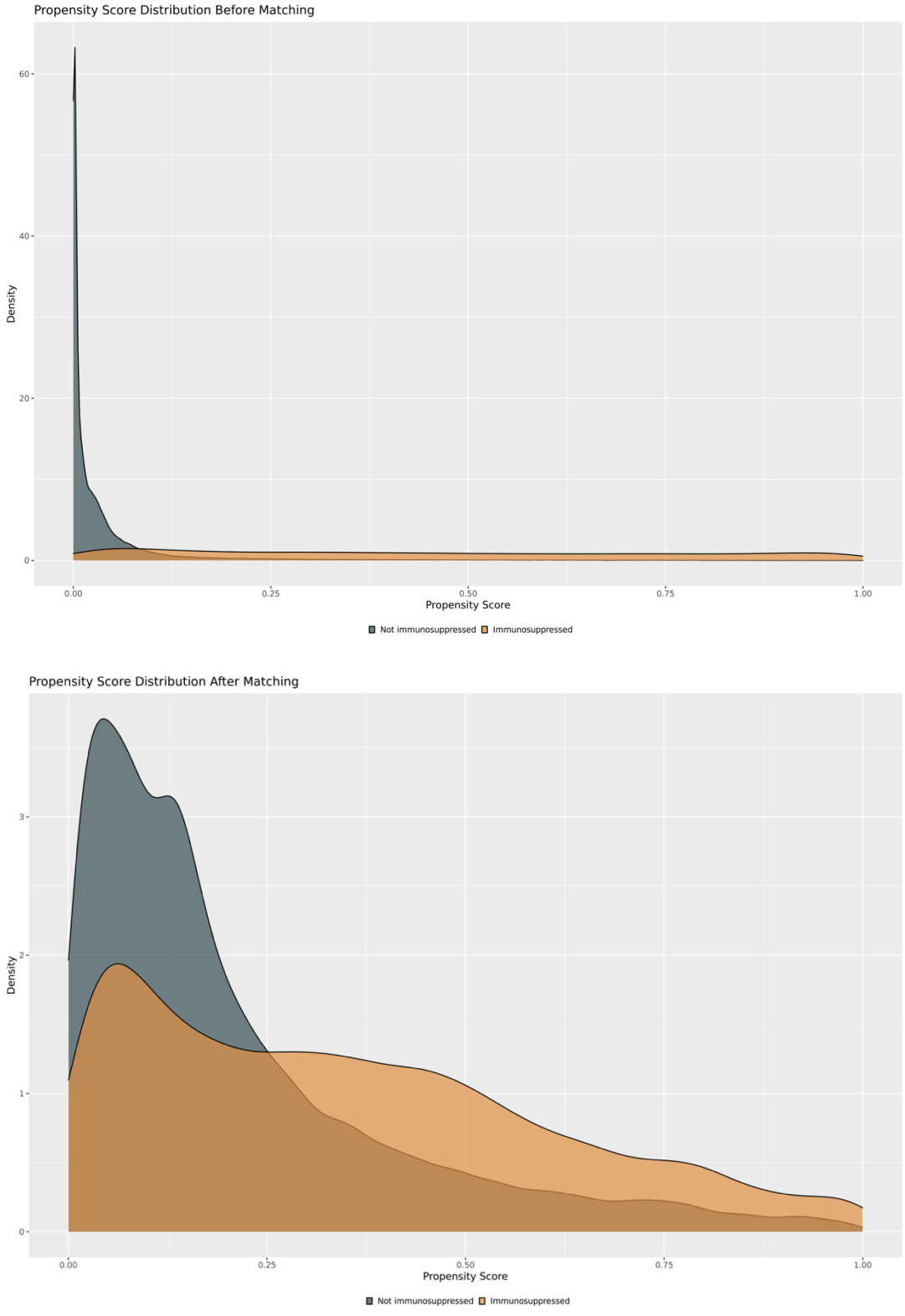
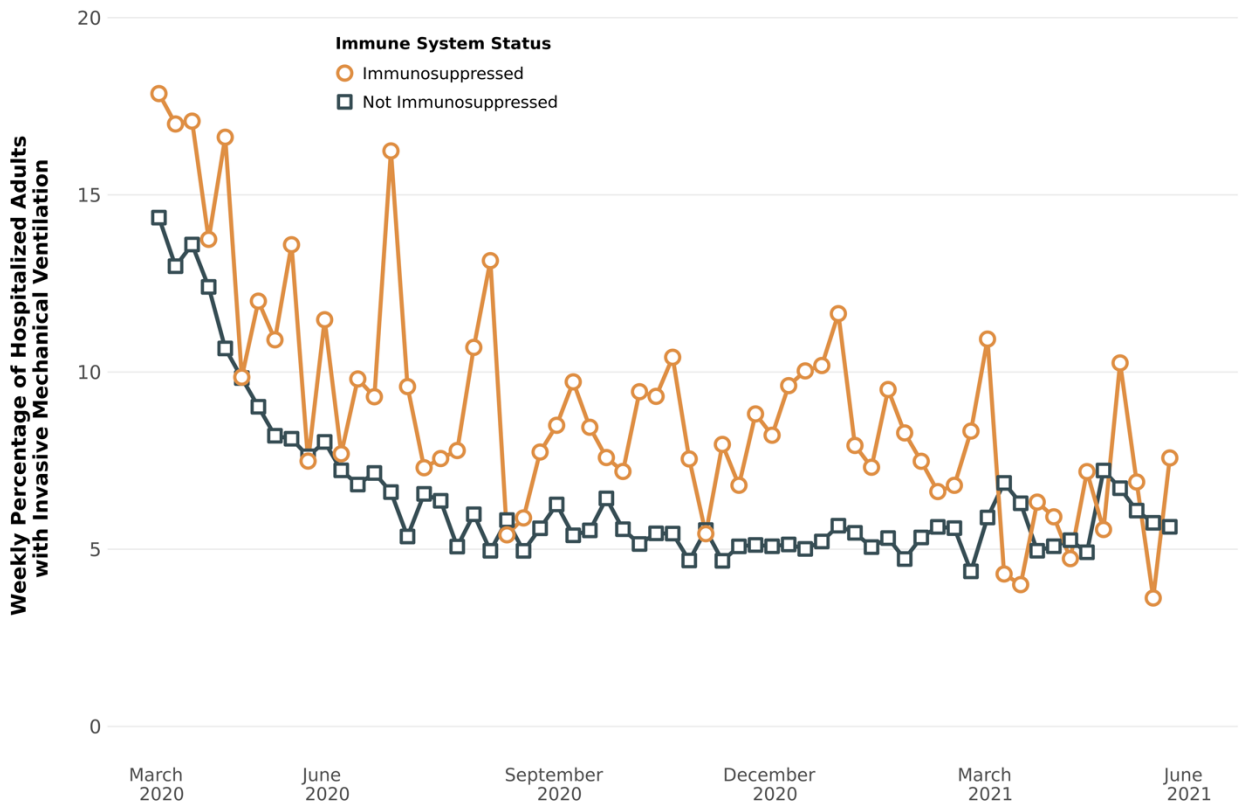
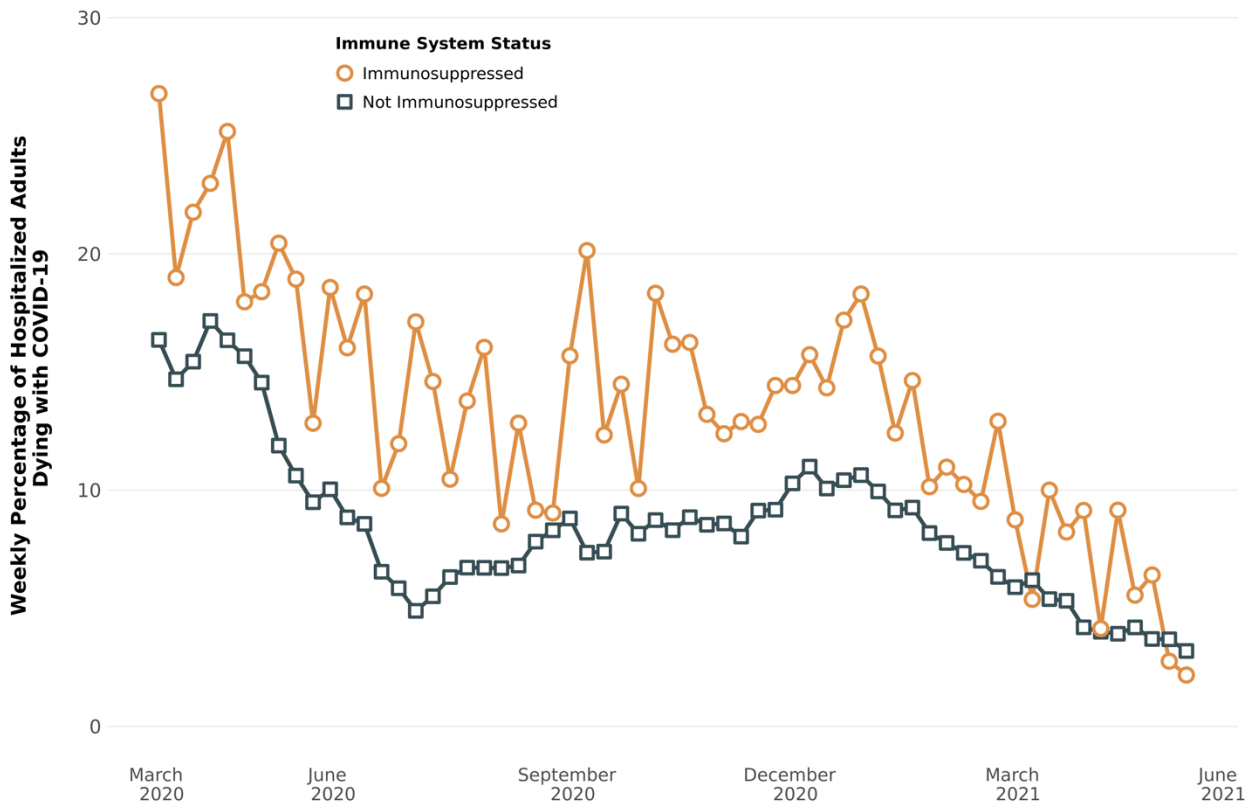


Figure 6. Weekly Percentage of Hospitalized Adults With Invasive Mechanical Ventilation, by Immune System Status.



This graph does not present data before March 18, 2020 and after June 2, 2021, where the small number of people at risk may not accurately reflect patterns.

Figure 7. Weekly Percentage of Hospitalized Adults Dying With COVID-19, by Immune System Status.



This graph does not present data before March 18, 2020 and after June 2, 2021, where the small number of people at risk may not accurately reflect patterns.

Figure 8. Association Between Chronic Immunosuppression and Invasive Mechanical Ventilation, by Medication Classes.

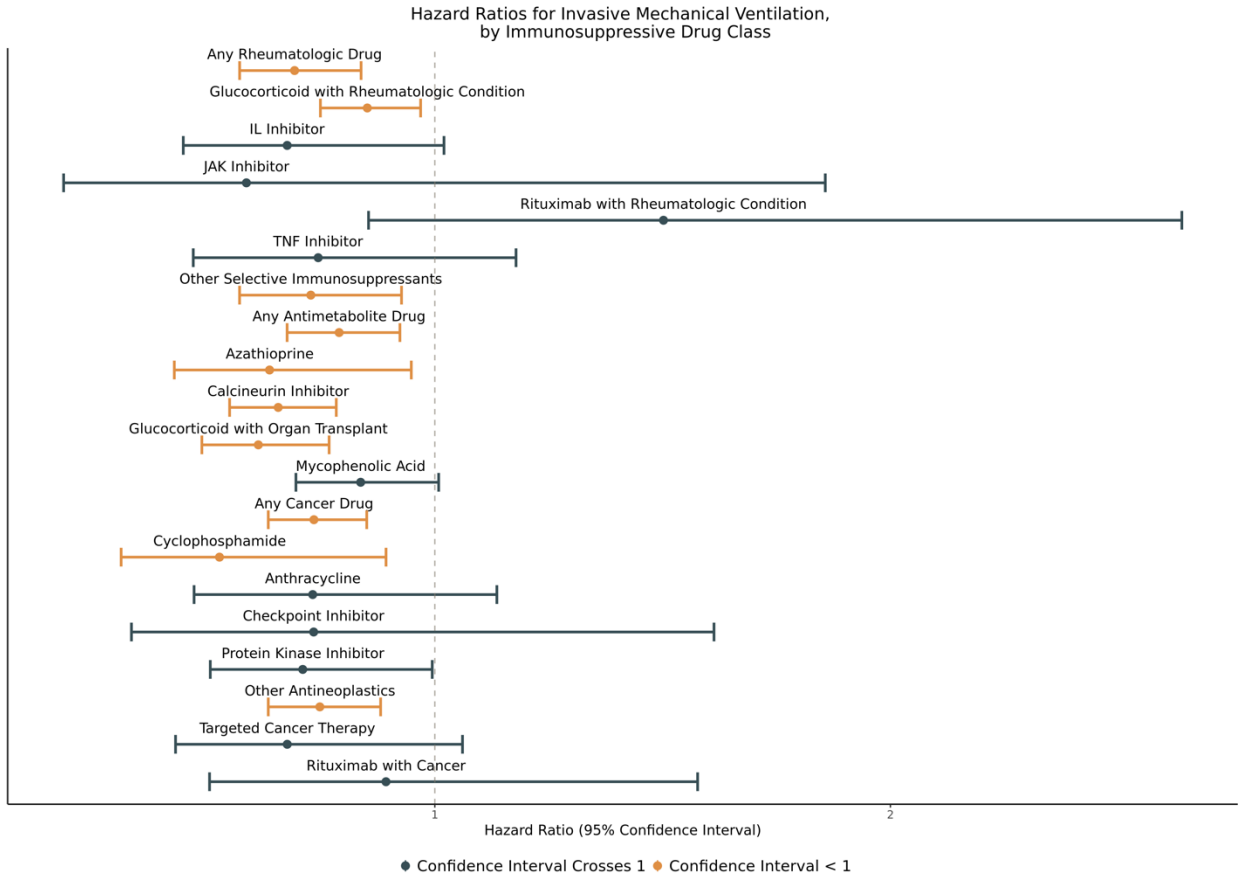


Figure 9. Association Between Chronic Immunosuppression and In-Hospital Death, by Medication Classes.

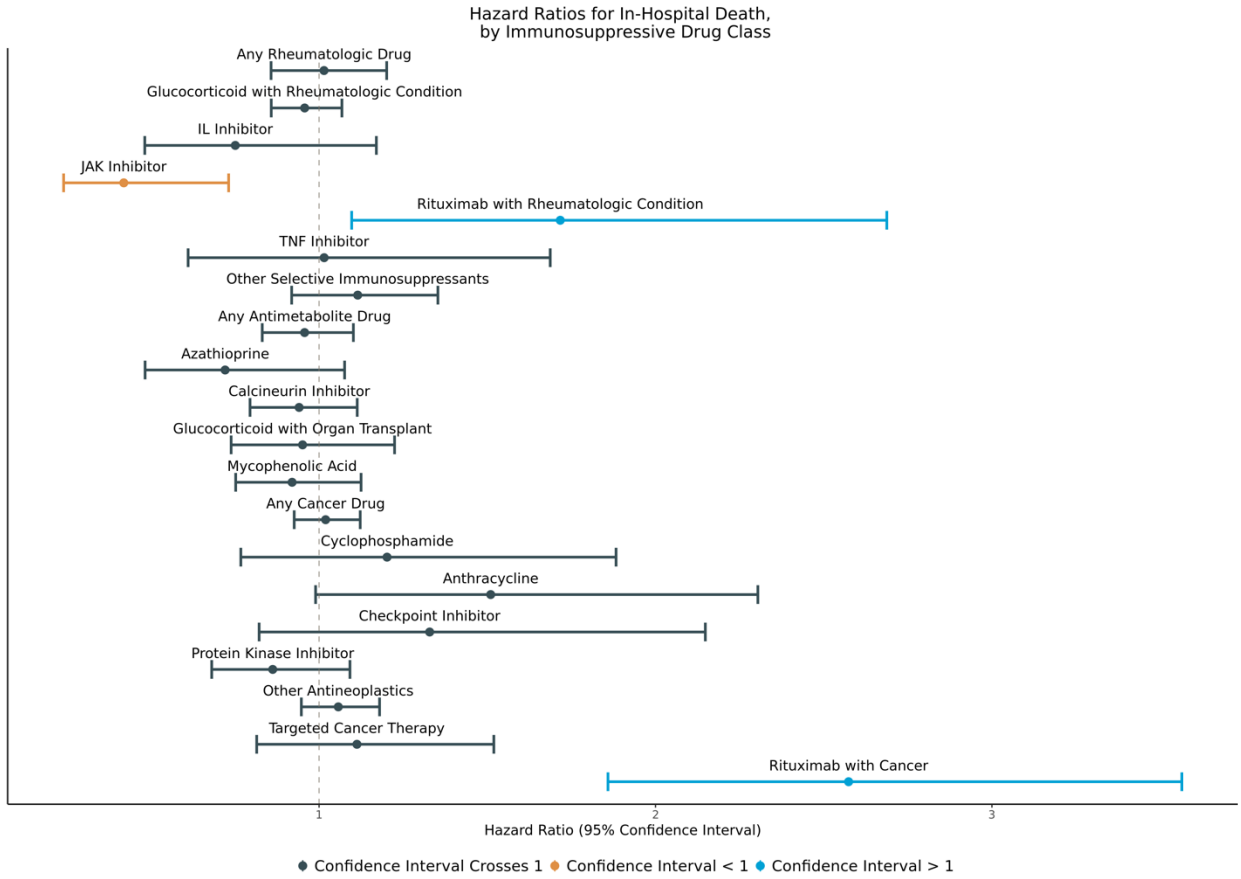
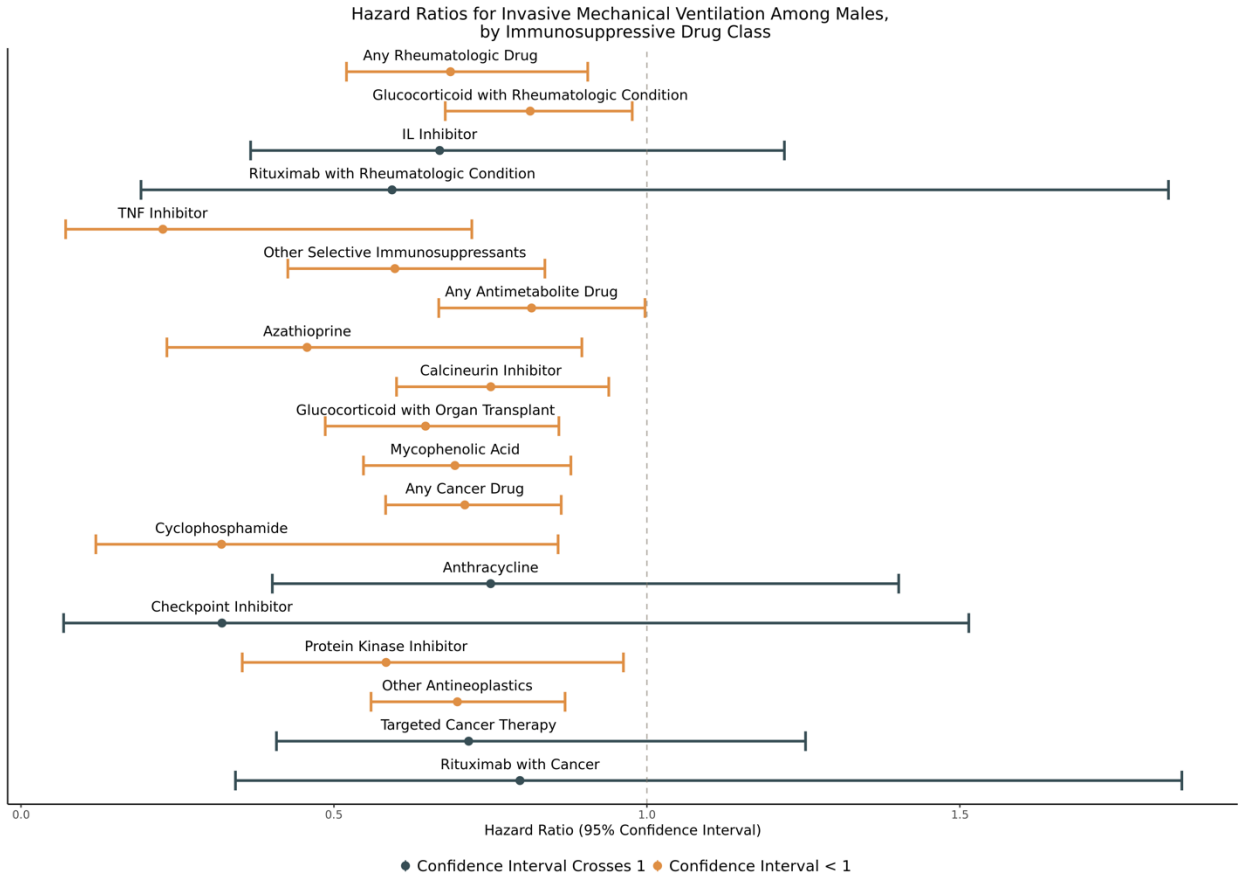


Figure 10. Association Between Chronic Immunosuppression and Invasive Mechanical Ventilation Among Males, by Medication Classes.



The hazard ratio calculated for janus kinase (JAK) inhibitors was 4.90 (95% confidence interval 0.44-54.97), and is not represented on this plot.

Figure 11. Association Between Chronic Immunosuppression and Invasive Mechanical Ventilation Among Females, by Medication Classes.

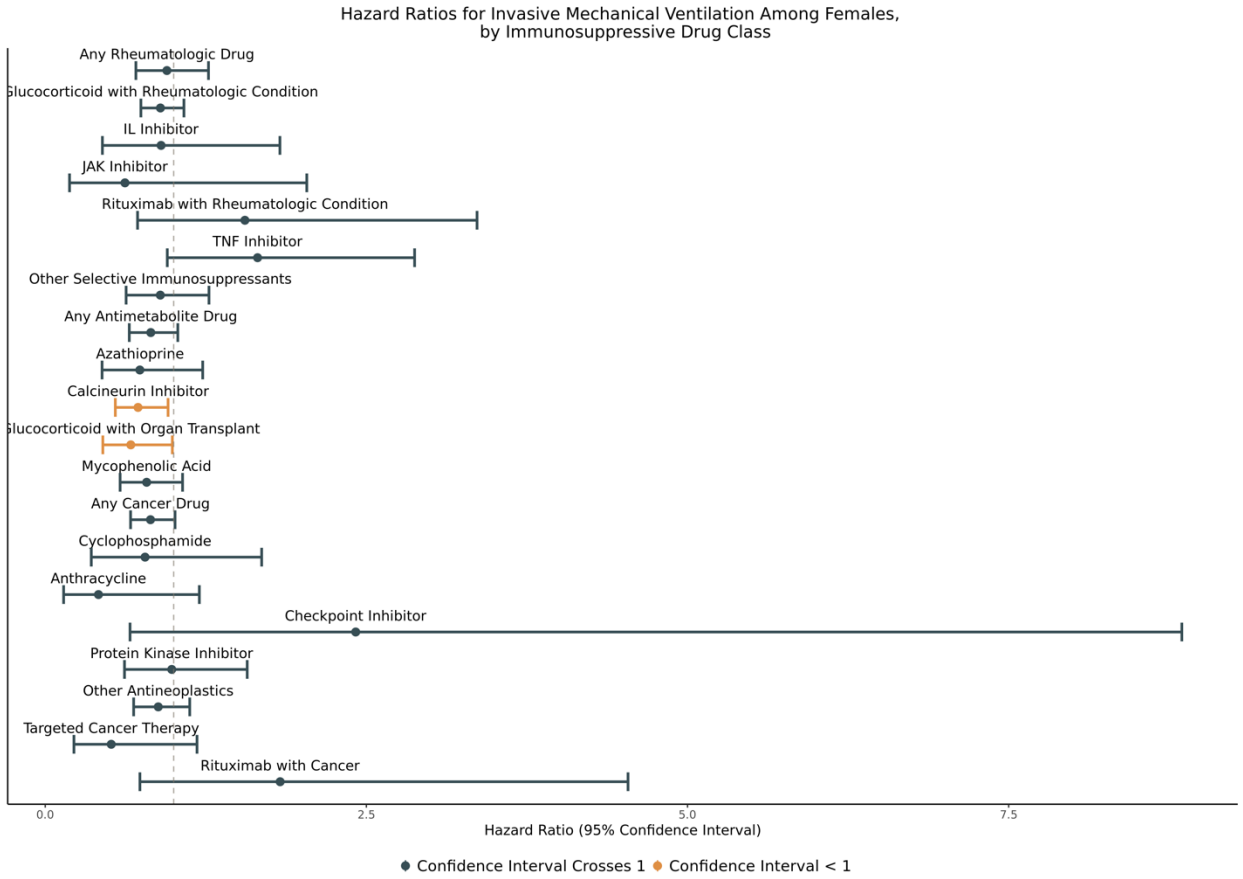
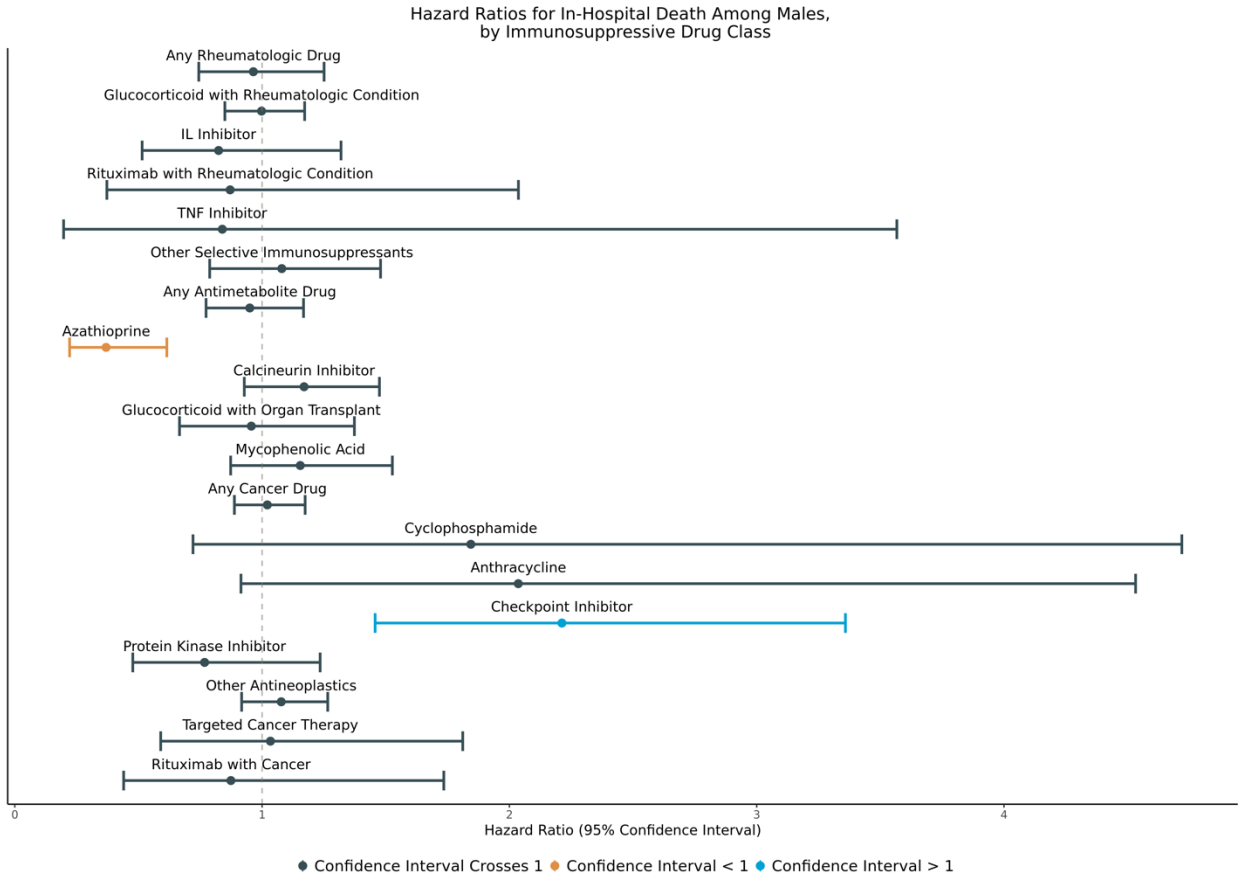
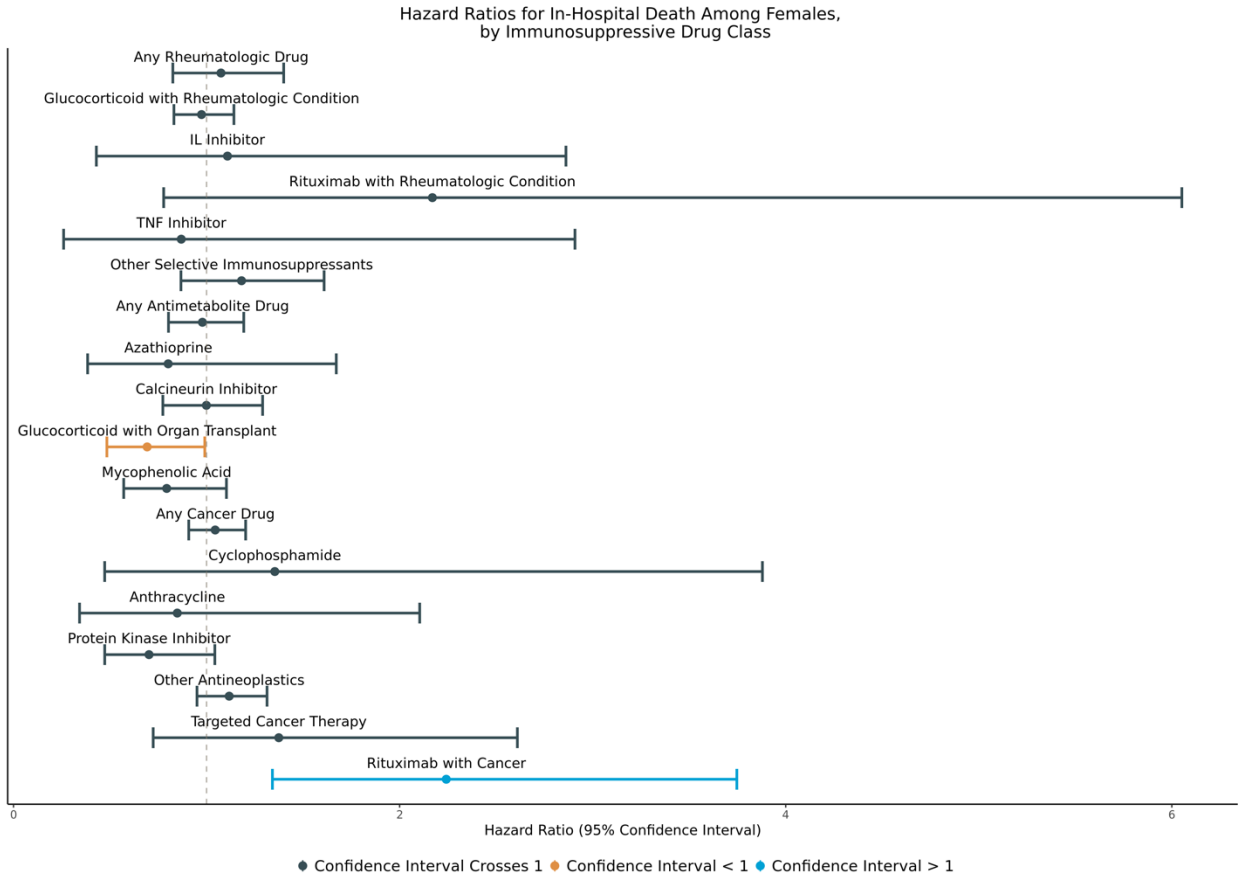


Figure 12. Association Between Chronic Immunosuppression and In-Hospital Death Among Males, by Medication Classes.



There were no males with janus kinase (JAK) inhibitors who required invasive mechanical ventilation in the propensity score matched cohort.

Figure 13. Association Between Chronic Immunosuppression and In-Hospital Death Among Females, by Medication Classes.



The hazard ratio calculated for checkpoint inhibitors was 2.89 (95% confidence interval 0.71-11.76), and is not represented on this plot.

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Chapter 4: High-Intensity Versus Standard Thromboprophylaxis Among Adults Hospitalized With COVID-19: A Retrospective Cohort Study

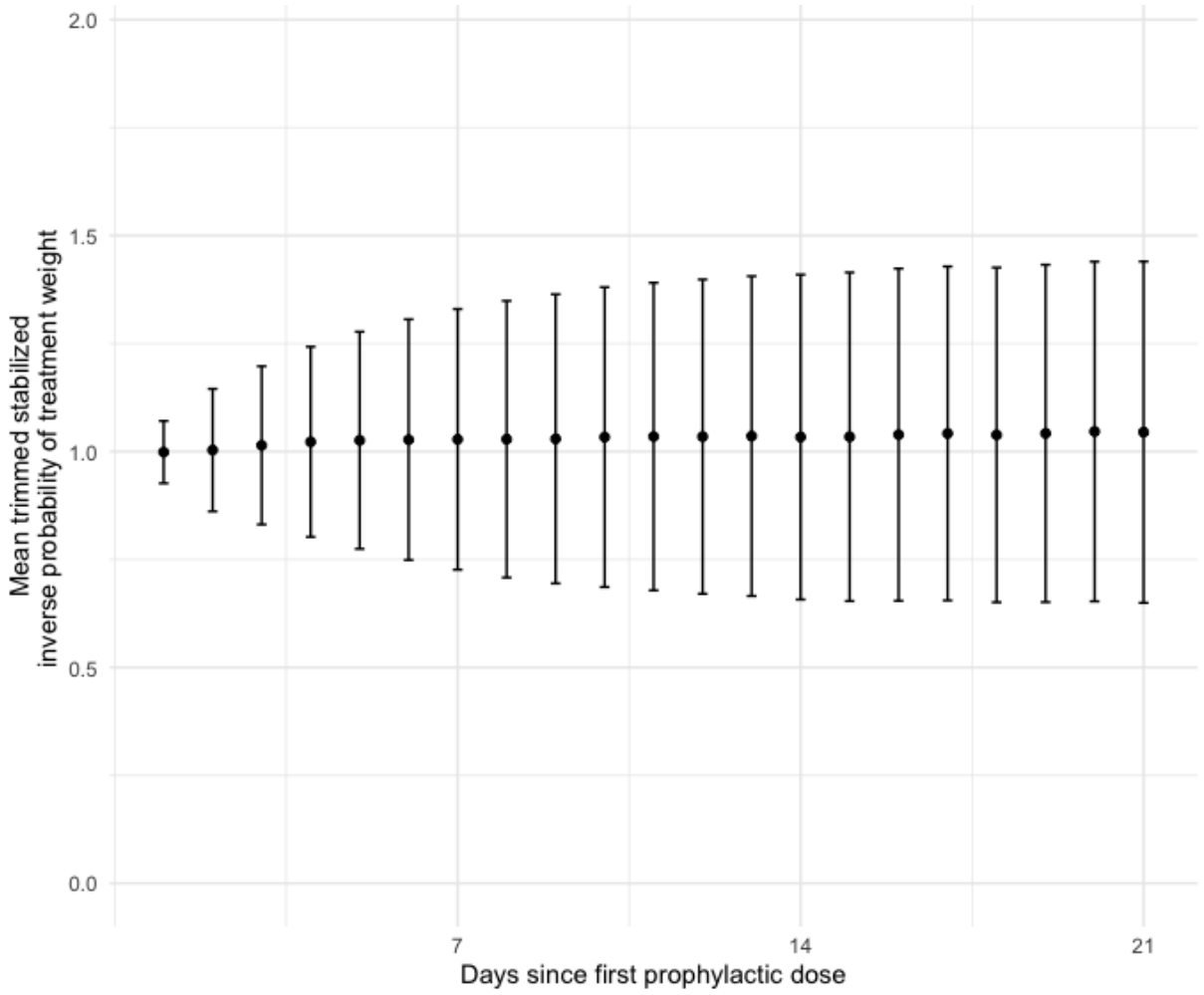
Prologue

In my third aim, I sought to examine whether higher doses of thromboprophylaxis was associated with a reduction in the risk of severe disease or in-hospital death among adults hospitalized with COVID-19. However, analyses of thromboprophylaxis intensity posed particular challenges of both time-varying exposure as well as potential time-varying confounding. Specifically, a clinician may increase or decrease a person's anticoagulation intensity on any given day in consideration of their current vital signs and laboratory measures. These same vital signs and laboratory measures are important prognostic indicators for the outcomes of interest of severe disease and death. Marginal structural models, with a discrete rather than continuous time axis, can properly account for time-varying exposures and time-varying confounding by using inverse probability of treatment weights that are recalculated at the beginning of each person-period using both time-fixed but also updated time-varying covariates. Under the assumptions of exchangeability, positivity, consistency and correct propensity score model specification, the hazard ratios with 95% confidence intervals from marginal structural models can be interpreted as the causal effect of the exposure on the risk of the outcome.

While we had initially planned to pursue marginal structural models to evaluate the comparative effectiveness of high-intensity versus standard prophylaxis, we instead present results from time-dependent Cox models. Our first intractable concern was treatment weight model specification. If the model is properly specified, the mean of the stabilized inverse probability of treatment weights will be 1.0, indicating approximation of randomization in the sample. After dozens of iterations of covariate combinations, and even with weight truncations as broad as the

10th and 90th percentile, we were unable to achieve a mean stabilized weight below 1.04. Further, even in the best iteration of model fit as measured by mean score, we found the variance of the stabilized weight monotonically increased, and dramatically, over time as illustrated in the figure below.

Figure 14: Means and Standard Deviations of Trimmed Stabilized Inverse Probability of Treatment Weights by Follow-Up Day



Paradoxically, the inverse probability of treatment weight model fit worsened, rather than improved, by including lagged measures of time-varying covariates. There was also a large amount of missingness of the single-most important time-varying covariate, with >50% of persons not having a D-Dimer measure at baseline.

In addition to the challenges with time-varying confounding, we also were concerned that the discrete data setup was the wrong choice for this research question. Marginal structural models use discrete time, where there is one row per person per defined time bin; we tried both 12 and 24-hour blocks. This creates a much longer data structure, which can create computational limitations, but also increases the probability of any given time period having zero events, which can in turn mean the model fails to converge. We could not find a discrete data structure finite enough to accurately model the therapeutic anticoagulation events, which happened most often within hours or days of first dose, that would also allow for deaths, some of which happen 30 days or more after the first dose.

Taken together, we decided our concerns about the validity of applying the marginal structural model framework to this data to answer this research question were larger than our ability to appropriately address concerns about time-varying confounding, and instead pursued time-fixed adjusted models with a variety of sensitivity analyses to examine potential sources of bias.

HIGH-INTENSITY VERSUS STANDARD PROPHYLAXIS ANTICOAGULATION AMONG ADULTS HOSPITALIZED WITH COVID-19: A RETROSPECTIVE COHORT STUDY

Kathleen M. Andersen, MSc[1,2]; Corey S. Joseph, MPH[1,2]; Hemalkumar B. Mehta, PhD[1,2]; Michael B. Streiff, MD[3]; Joshua F. Betz, MS[4]; Robert C. Bollinger Jr, MD MPH[5,6]; Arielle M. Fisher, PhD[7]; Amita Gupta, MD MHS[5,8]; Charles F. LeMaistre, MD[7]; Matthew L. Robinson, MD[5]; Yanxun Xu, PhD[9]; Derek K. Ng, PhD[1]; G. Caleb Alexander, MD MS[1,2,10]; Brian T. Garibaldi, MD MEHP[11] on behalf of the COVID-19 Consortium of HCA Healthcare and Academia for Research GEneration (CHARGE)

1. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
2. Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
3. Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD
4. Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
5. Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, MD
6. Center for Clinical Global Health Education, Johns Hopkins University School of Medicine, Baltimore, MD
7. Sarah Cannon, Genospace, HCA Healthcare Research Institute, Nashville, TN
8. Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore MD
9. Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD
10. Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
11. Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

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Brief 40-word summary

In this retrospective cohort of 51,193 adults hospitalized in the United States with COVID-19, we did not find reductions in the risk of clinical worsening, severe disease or death with high-intensity thromboprophylaxis as compared to standard doses.

Correspondence

Brian T. Garibaldi, MD, MEHP
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University School of Medicine
1830 East Monument Street
Baltimore, MD 21205
Phone: 443-804-8286
Email: bgariba1@jhmi.edu

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Key Points

Question. While evidence suggests that COVID-19 is associated with increased risk of thromboembolism, does high-intensity thromboprophylaxis offer benefits beyond standard doses?

Findings. In this retrospective cohort study of adults hospitalized with COVID-19, we evaluated the comparative effectiveness of high-intensity versus standard doses of thromboprophylaxis. We did not find reductions in the risk of clinical worsening, severe disease or death with the high-intensity dosing regimens, after accounting for time-varying exposures and relevant confounders.

Meaning. Our findings do not support the routine use of high-intensity thromboprophylaxis doses among adults hospitalized with COVID-19.

Abstract

Importance. Current clinical guidelines recommend thromboprophylaxis for adults hospitalized with COVID-19, yet it is unknown whether higher doses of thromboprophylaxis offer benefits beyond standard doses. Our objective was to compare the real-world effectiveness of standard versus high-intensity thromboprophylaxis in preventing the need for escalation to therapeutic anticoagulation, severe disease or death.

Design and setting. Retrospective cohort study using the HCA Healthcare COVID-19 Registry, a compilation of electronic health records of COVID-19 patients treated in facilities affiliated with a geographically diverse health system accounting for approximately 5% of all healthcare encounters in the United States. We studied adults hospitalized with COVID-19 between February 23, 2020 and February 11, 2021.

Participants. 51,193 adults hospitalized with confirmed SARS-CoV-2 infection.

Exposure. Standard dose (enoxaparin 30 or 40 mg per day, fondaparinux 2.5 mg, low dose apixaban or rivaroxaban, or heparin 5000 units twice or thrice per day) versus high-intensity (enoxaparin 30 or 40 mg twice daily, or up to 1.2 mg per kilogram of body weight daily, heparin 7500 units thrice per day, heparin 10,000 units twice or thrice per day, or dabigatran 220 mg daily) thromboprophylaxis.

Main Outcome and Measures. We separately examined the risk of escalation to therapeutic anticoagulation, severe disease (first occurrence of high-flow nasal cannula, non-invasive positive pressure ventilation or invasive mechanical ventilation), and death. To summarize risk, we present hazard ratios (HR) with 95% confidence intervals (CI) using adjusted time-dependent Cox proportional hazards regression models.

Results. Persons whose first thromboprophylaxis dose was high intensity were younger, more often obese and had greater oxygen support requirements. High-intensity rather than standard-dose thromboprophylaxis was associated with increased risk of therapeutic anticoagulation (HR 3.24, CI 3.08 to 3.41), severe disease (HR 1.22, CI 1.16 to 1.27) and death (HR 1.37, CI 1.21 to

1.55). Increased risks associated with high-intensity thromboprophylaxis persisted in subgroup and sensitivity analyses varying populations and definitions of exposures, outcomes and covariates.

Conclusions and Relevance. Our findings do not support the routine use of high-intensity thromboprophylaxis to prevent clinical worsening, severe disease or death among adults hospitalized with COVID-19 in the United States.

Introduction

Over 250 million infections and more than 5 million deaths have accrued worldwide from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as of November 8, 2021.[1] Coronavirus disease of 2019 (COVID-19), the syndrome caused by SARS-CoV-2, is associated with an increased rate of thromboembolic events,[2–5] despite the routine use of thromboprophylaxis among hospitalized patients.[6–9] In response to rapidly evolving evidence, the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) issued guidance in May 2020 for prescribers to consider high-intensity thromboprophylaxis, which provides a level of anticoagulation greater than standard prophylactic doses, yet less than therapeutic levels used to manage deep venous thrombosis or pulmonary embolism.[10] As of November 2021, both the World Health Organization and National Institutes of Health treatment guidelines state that there is insufficient evidence to recommend for or against the use of high-intensity thromboprophylaxis.[11,12]

Several investigations compared therapeutic (full dose) anticoagulation to standard thromboprophylaxis doses in hospitalized adult populations and settings. For example, there is evidence that therapeutic anticoagulation offers a benefit over standard thromboprophylaxis in noncritically ill patients hospitalized with COVID-19[13] but is not effective if started after onset of critical illness.[14,15] Whether these findings extend to comparisons of standard and high-intensity thromboprophylaxis is unclear.[12,16–19] A recent clinical trial of 562 patients in the intensive care unit (ICU) did not find significant differences in thrombosis, risk of extracorporeal membrane oxygenation (ECMO) or death between standard and high-dose thromboprophylaxis; importantly, no differences in safety outcomes were noted.[20] Of note, this trial implemented differential dosing for persons with high body mass index (BMI), which limits the generalizability to centers that do not use weight-based thromboprophylaxis dosing. The role of standard versus high-intensity thromboprophylaxis in non-ICU patients is unknown.

In addition to uncertainty as to optimal prophylactic doses, important questions remain regarding the effects of changes in intensity throughout the course of an inpatient stay. To date, studies have examined smaller datasets, and have not considered the time-varying exposures that might bias intention-to-treat analyses.[7,21–25] We compared the real-world effectiveness of standard versus high-intensity thromboprophylaxis in preventing the need for escalation to therapeutic anticoagulation, severe disease or death among adults hospitalized with COVID-19 in the United States from February 2020 through February 2021.

Methods

Study setting and population

Our analyses included individuals that received care at a facility affiliated with HCA Healthcare, a large health system with over 2,000 sites of care including 186 hospitals across 20 states. We defined a COVID hospitalization as an adult with a positive SARS-CoV-2 test result and a clinical diagnosis of COVID-19. The COVID-19 Consortium of HCA Healthcare and Academia for Research GEneration (CHARGE) is a group of 11 academic centers that have partnered with HCA Healthcare and the federal Agency for Health Research and Quality (AHRQ) to learn from the clinical experience of HCA Healthcare. The dataset has been previously described[26] and includes detailed information on demographics, clinical encounters, prescription drugs, vital signs and laboratory measures.

Inclusion and exclusion criteria

We used the CHARGE standard definition of a continuous COVID-19 clinical care episode (Table 18) and selected a person's first inpatient encounter for this analysis. We excluded people who were pregnant, had severe renal impairment, or who had a pulmonary embolism,

cerebral infarction, or deep vein thrombosis at the time of admission, given the differential indications for anticoagulation in these populations. We also excluded people admitted to centers with no ICU beds, such as an inpatient psychiatric hospital or rehabilitation center, where the indication for admission is unlikely to be acute COVID-19. We required a positive SARS-CoV-2 test result no more than 21 days before their admission; to exclude nosocomial infections, positive tests could be no later than 5 days into their admission. Finally, we excluded persons who did not receive any anticoagulation at any point in their stay, whose first anticoagulation strategy was therapeutic dosing, and persons who were using anticoagulation prior to admission.

Exposures

We used HCA's treatment protocols to define our exposure groups. We defined standard thromboprophylaxis doses as enoxaparin 30 or 40 mg once daily, fondaparinux 2.5 mg once daily, heparin 5000 units twice or thrice daily, apixaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily or 10 mg once daily (Table 19). We defined high-intensity thromboprophylaxis as enoxaparin 30 mg or 40 mg twice daily, or any enoxaparin dose greater than 40mg which was up to 1.0mg/kg/day plus 20% rounding factor, heparin 7500 units three times daily, heparin 10,000 units two or three times daily, or dabigatran 220 mg once daily.

Unlike previous work where we could reasonably employ time-fixed exposure definitions,[27] anticoagulation necessitates a time-varying exposure definition to allow for changes in intensity throughout the hospitalization. We defined follow-up time as beginning at the precise date and time of thromboprophylaxis administration. We considered people to be continuously exposed until 24 hours after the last administration, reflecting the relatively short-acting nature of thromboprophylaxis, unless treatment intensity changed before then.

Outcomes

First, based on clinical guidelines as well as expert opinion, we defined therapeutic anticoagulation as enoxaparin greater than 1.2 mg/kg/day, intravenous heparin, therapeutic doses of direct-acting oral anticoagulants as per their United States Food and Drug Administration (FDA) label, or any dose of warfarin. While the effectiveness of thromboprophylaxis would be most clearly demonstrated with an absolute or relative reduction in risk of thrombotic events, we were not able to answer this question using these data. The CHARGE dataset does not contain timestamps for recorded diagnosis codes, and given the time-varying nature of anticoagulation exposures during a hospitalization, we were unable to analyze the incidence of clots as a function of any given exposure strategy. We therefore considered the date and time of first therapeutic anticoagulation dose as a surrogate measure for clinical worsening or a suspected deep venous thrombosis or pulmonary embolism.

Second, we defined severe disease as the first occurrence of high-flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV), or invasive mechanical ventilation (IMV). Third, we examined the risk of death, and included persons who were discharged to hospice.

Covariates

We adjusted for demographics, smoking status, overweight or obesity as defined by BMI, and select medications current at the time of admission (Table 20). We used the 2022 Elixhauser Comorbidity Index to summarize comorbidity burden.[28] We included laboratory measures and vital signs at the time of admission to be relevant baseline confounders, but not post-initiation as we considered these to be mediators rather than confounders of the causal effect (Figure 15).

Statistical Analyses

We calculated absolute standardized mean differences (SMD) to compare people given the first strategy of anticoagulation they received, with >0.10 interpreted as a meaningful difference. We used time-dependent Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the risk of each outcome of interest, while controlling for patient characteristics.

Subgroup Analyses

While HCA COVID-19 inpatient treatment protocols did not modify dosing for patients with increased body weight, it is possible that some facilities or prescribers made dosing adjustments which could affect our exposure definition. In subgroup analyses, high-intensity doses in persons with Class III obesity (BMI >40 kg/m^2) were instead considered standard thromboprophylaxis, as persons with larger bodies may require higher doses to achieve similar anticoagulation effects.[29]

In order to evaluate whether effectiveness differed by baseline severity of disease, we also stratified analyses by oxygen support at the time of first dose, comparing people with no or low-flow oxygen requirements to those with advanced levels of respiratory support (HFNC, NIPPV, or IMV).

Sensitivity Analyses

First, we removed laboratory measures and vital signs from the time of admission from our set of adjusted covariates, given that these prognostic factors may be strongly associated with the outcomes of interest. Second, we implemented inverse probability of treatment weights in a marginal structural model framework to evaluate if laboratory measures and vital signs exerted time-varying confounding.[30] Third, we calculated e-values, which are a form of quantitative bias

assessment to estimate the strength of association that an independent unmeasured confounder would need to exert in order to change the interpretation of our findings.[31] Fourth, we excluded persons who died within 48 hours of admission, in order to emulate the exclusion criteria for short life expectancy from several previous anticoagulation-related clinical trials.[13,14,20]

Analyses were conducted using SAS software, version 9.4, of the SAS System for Windows, and data visualizations were produced using R Version 4.0.2.

This research was deemed minimal risk with a waiver of consent by both Johns Hopkins Medicine (IRB00286926) as well as an external institutional review board (WIRB-Copernicus Group [WCG]).

Results

Characteristics at anticoagulation initiation

We identified 51,193 adults hospitalized with confirmed SARS-CoV-2 infection who met inclusion and exclusion criteria (Figure 16) and received thromboprophylaxis (Figure 17). The median time from admission to first dose was 7 hours. Persons whose first prophylaxis dose was high intensity were younger and more often obese (Table 21). At the time of first dose, persons with HFNC, NIPPV or IMV were more likely to receive high-intensity rather than standard doses. No differences in pre-admission medications for common chronic comorbidities were noted. High-intensity thromboprophylaxis was more often chosen for people with elevated alanine aminotransferase and low albumin as well as abnormal vital signs (Table 22).

Risk of outcomes from adjusted regression models

Overall, 14% of persons changed from thromboprophylaxis to therapeutic anticoagulation, 18% progressed to severe disease and 11% died within 10 days of their last prophylactic dose (Table 23). Adults who were receiving high-intensity doses, as compared to standard doses, were more than three times as likely to switch to therapeutic anticoagulation (HR 3.24, CI 3.08-3.41). High-intensity doses were also associated with an increased risk of severe disease (HR 1.22, CI 1.16-1.27). We used a range of timepoints to define the relevant time window for the prophylaxis-associated risk of death, from 24 hours up to 10 days after the last dose, and found an increased risk of death for each (HR range from 1.37-1.41).

Subgroup analyses

In analyses where we applied dose adjustment for persons with Class III obesity, hazard ratios were slightly attenuated but risks remained elevated (Table 24). In stratified analyses, we evaluated whether baseline disease severity modified the effect of high-intensity thromboprophylaxis (Table 25). In persons with no or low flow oxygen at the time of their first-ever prophylactic dose, the risk of therapeutic anticoagulation (HR 3.56, CI 3.30-3.77) and death within 10 days (HR 1.47, CI 1.38-1.57) for patients receiving high-intensity prophylaxis was larger than in the overall analyses. Conversely, in persons with severe disease (high oxygen requirements), the risk of therapeutic anticoagulation (HR 2.26, CI 2.04-2.51) and death (HR 1.18, CI 1.087-1.30) was attenuated.

Sensitivity analyses

Results from sensitivity analyses were consistent with main analyses. For example, in the main analysis, an unmeasured confounder would have to be associated with therapeutic anticoagulation by a risk ratio of more than 5.61-fold in order for the result to no longer be a statistically significant increased risk (Table 26). We found statistically significant increases in the risk of therapeutic anticoagulation (HR range from 2.97-3.54), severe disease (HR range

from 1.22-1.60) and death (HR range from 1.33-1.70) with high-intensity prophylaxis (Tables 27-29).

Discussion

COVID-19 has been associated with an increased risk of venous and arterial thromboembolism which may suggest high-intensity thromboprophylaxis as a treatment consideration, particularly in severe cases. Nevertheless, current treatment guidelines have not recommended routine use of high-intensity thromboprophylaxis. In this retrospective comparative effectiveness study, our findings do not support the use of high-intensity thromboprophylaxis to prevent clinical worsening, severe disease or death among adults hospitalized with COVID-19 in the United States. These results persisted in a variety of subgroup and sensitivity analyses. Further, the large e-values suggest that an unmeasured confounder would have to have a large magnitude of effect in order to change our findings to null or protective effects; importantly, this hypothetical variable would need to exert influence independently of each of the confounders already included in the adjustment set. While the effect estimates we derived indicate statistically significant increases in risk associated with high-dose prophylaxis, we are unable to discern whether this is a true causal effect or due to residual confounding. Therefore, we conclude that our results are not consistent with reduced risk, rather than clear evidence of increased risk. These findings are important, given that thromboprophylaxis plays a significant role in the inpatient management of COVID-19, and reflect one of several examples of evolving standards of care throughout the pandemic.[32]

Our findings add to a growing body of evidence that has failed to show benefits of high-intensity thromboprophylaxis among adults hospitalized with COVID-19. A small clinical trial showed no difference in risk of thrombosis, ECMO or death between standard and high-intensity doses with weight-based adjustments.[20] In our subgroup analyses where we applied weight-based

adjustments, we again found increases in risk of therapeutic anticoagulation as a proxy for thrombosis, severe disease and death. There are several potential explanations for the divergence of our findings from the earlier clinical trial. First, the definitions of the outcomes differed. For example, our definition of severe disease used oxygen support devices more commonly used in the United States such as HFNC and IMV. Second, our observational analysis may suffer from residual confounding by indication, whereby patients with a worse prognosis were preferentially given high-intensity doses and the variables affecting those choices were not captured in our models. Third, the trial had 562 participants and our study had over 50,000 persons, and perhaps the increased statistical precision allowed for elucidation of effect.

One limitation of this work is the inability to quantify the incidence of thromboembolic events and treatment-associated major bleeds. We attempted to derive an algorithm consisting of discharge diagnosis codes and imaging procedure codes consistent with the presence of a thrombotic event and time stamps for the initiation of therapeutic anticoagulation. However, most patients had multiple imaging studies, and fewer than 1% of persons were identified with this strategy, whereas the literature suggests as many as 14% of hospitalized COVID-19 patients develop venous thromboembolism during their stay.[5,33–35] Another limitation was the lack of model fit with the marginal structural model framework, precluding its use as the main analysis. The mean of the stabilized weights indicated remaining residual confounding, and there was a large amount of missingness of the single-most important time-varying covariate, with >50% of persons not having a D-Dimer measure at baseline.

Our conclusions are drawn from 186 hospitals in 20 states, and address facilities both with and without weight-based anticoagulation protocols. We examined the real-world experience, in consideration of time-varying treatment intensity changes, of over 50,000 hospitalized adults to

directly address a knowledge gap identified by the National Institutes of Health COVID-19 treatment guidelines.[12] An additional strength of this work is that nearly half of our cohort identified as a race other than white, and a third identified as Hispanic or Latinx, both of which are high risk groups given the disproportionate burden of disease incidence and severity due to systemic racism and other factors.[36] The data period of February 2020 - February 2021 captures a relatively homogenous period in which there was not widespread vaccination nor the delta variant, each of which have important implications for disease presentation and severity.

Important questions remain unanswered. We could not answer questions about thromboembolic events, nor major bleeds, given data limitations. We did not consider groups whose anticoagulation protocols substantially differ from the general adult population. More work is needed to understand optimal thromboprophylaxis among people with chronic outpatient anticoagulation use, as well as among people who are pregnant or have severe renal impairment.

CONCLUSION

This study of over 50,000 adults contributes to a growing body of evidence that does not support the use of higher than routine thromboprophylaxis doses in hospitalized COVID-19 patients.

Notes

Ethics statement. This research was deemed minimal risk with a waiver of consent by both Johns Hopkins Medicine (IRB00286926) as well as an external institutional review board (WIRB-Copernicus Group [WCG]).

Data availability statement. Data were made available by HCA Healthcare, and study-specific limited data sets were accessible for research via a secure platform hosted within a private

virtual network. Requests to access the data can be addressed to Genospace. Authors of this manuscript are willing to share statistical programming code upon request.

Transparency statement. The manuscript's guarantors (KMA, CSJ, GCA and BTG) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Role of the funding source. HCA Healthcare prioritized and provided resources for this research and was involved in the decision to submit for publication. Data collection, analysis, interpretation of the data and the writing of this report were performed independently by the authors. All authors had full access to all of the data in the study, including statistical reports and tables, and take responsibility for the integrity of the data and the accuracy of the data analysis. The views expressed in this publication represent those of the authors and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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Drug Administration Pulmonary and Asthma Drug Advisory Committee, has received speaking fees and served on an advisory panel for Gilead Sciences, Inc., consulting fees from Janssen Research and Development, LLC, and speaker fees from Atea Pharmaceuticals, Inc. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

Table 18. COVID-19 Clinical Care Episode Definition.

An encounter was considered to be a COVID clinical care episode if it met any of the following definitions:

1. COVID-19 ICD-10 code at rank 1
2. COVID-19 ICD-10 code at any rank, and a strong positive non-COVID ICD-10 code at any rank
3. COVID-19 ICD-10 code at any rank, and a weak positive non-COVID ICD-10 code at rank 1
4. Persons without a COVID-19 ICD-10 code who had an admission within 14 after a positive SARS-CoV-2 test result and a strong positive non-COVID ICD-10 code at any rank

COVID-19 ICD-10 codes	
U07.1	2019 novel coronavirus disease (COVID-19)
B97.29	Other coronavirus as the cause of diseases classified elsewhere
Strong positive non-COVID ICD-10 code	
A41.89	Other specified sepsis
A41.9	Sepsis, unspecified organism
J12.81	Pneumonia due to SARS-associated coronavirus
J12.89	Other viral pneumonia
J12.82	Pneumonia due to coronavirus disease
J12.9	Viral pneumonia, unspecified
J18.8	Other pneumonia, unspecified organism
J18.9	Pneumonia, unspecified organism
J96.20	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia
J96.21	Acute and chronic respiratory failure with hypoxia
J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
J96.01	Acute respiratory failure with hypoxia
J96.02	Acute respiratory failure with hypercapnia
J96.90	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia
J96.91	Respiratory failure, unspecified with hypoxia
J80	Acute respiratory distress syndrome

J98.8	Other specified respiratory disorders
J22	Unspecified acute lower respiratory infection
J20.8	Acute bronchitis due to other specified organism
J40	Bronchitis, not specified as acute or chronic
J16.8	Pneumonia due to other specified infectious organisms
Weak positive non-COVID ICD-10 codes	
E86.0	Dehydration
E86.1	Hypovolemia
E87.1	Hypo-osmolality and hyponatremia
E86.9	Volume depletion, unspecified
J06.9	Acute upper respiratory infection, unspecified
D72.810	Lymphocytopenia
R41.82	Altered mental status, unspecified
E87.2	Acidosis
R05	Cough
J95.851	Ventilator associated pneumonia

Table 19. Exposure Definition.

	Standard prophylaxis	High-intensity prophylaxis	Therapeutic anticoagulation
Enoxaparin	30 mg QD 40 mg QD	30 mg BID 40 mg BID >40mg up to 0.6 mg/kg BID or 1.2 mg/kg QD	0.61-1.5 mg/kg BID 1.21-3.0 mg/kg QD
Fondaparinux	2.5 mg SC QD		5-10 mg SC QD
Heparin	5000U SC BID 5000U SC TID	7500U SC TID 10000U SC BID 10000U SC TID	IV route
Oral anticoagulants	Apixaban 2.5 mg BID Rivaroxaban 5 mg BID Rivaroxaban 10 mg QD	Dabigatran 220 mg QD	Apixaban 5 mg BID Dabigatran 150 mg BID Rivaroxaban 20 mg QD Warfarin, any strength

QD: daily; BID: twice a day; TID: three times a day.

IV: intravenous; SC: subcutaneous; U: Units.

Weight-based enoxaparin could include one loading dose (example: one 40mg dose followed by 90mg for a 87kg person). There were no persons in this cohort with dalteparin administered during their admission.

Table 20. Covariate Definitions for Adjusted Models.

	Parameterization in Model
Age at admission	Indicator variables for each of 18-29, 30-39, 40-49, 50-64, 65-74, 75+ years
Sex	Male or female
Body mass index	Neither overweight nor obese (body mass index [BMI] 18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) or obese (≥ 30 kg/m^2), using the mean of any available body weight measures during admission
Calendar month of admission	
Self-identified race and ethnicity group	Mutually exclusive variables for Asian, Black, white, multiracial, another race (without further detail available), or missing race information. Separately, persons were considered to be Hispanic/Latinx, or neither Hispanic nor Latinx.
Current or former smoker	
2021 Elixhauser Comorbidity Index score	
Antidiabetic medications current at the time of admission	Any of acarbose, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, insulin, metformin, sodium-glucose transport protein 2 inhibitors, sulfonylureas, thiazolidinediones, or other diabetes drugs
Antihypertensive medications current at the time of admission	Any of diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, or calcium channel blockers.
Antiplatelet medications current at the time of admission	Any of clopidogrel, ticlopidine, acetylsalicylic acid, dipyridamole, carbasalate calcium, epoprostenol, indobufen, iolprost, abciximab, aloxiprin, eptifibatide, tirofiban, triflusal, beraprost, treprostinil, prasugrel, cilostazol, ticagrelor, cangrelor, vorapaxar, or selexipag. As defined by World Health Organization Anatomical Therapeutic Chemical Classification Group B01AC.
Aspirin current at the time of admission	

Immunosuppressive medications current at the time of admission	303 drugs, as defined by WHO Anatomical Therapeutic Chemical Classification Group L01 (Antineoplastic agents) and L04 (Selective Immunosuppressants)
Inhaled corticosteroids current at the time of admission	Any of beclomethasone, budesonide, flunisolide, betamethasone valerate, fluticasone, triamcinolone acetonide, mometasone, ciclesonide, fluticasone furoate.
Statin current at the time of admission	Any of simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin.
Systemic glucocorticoids current at the time of admission	Any of betamethasone, dexamethasone, fluocortolone, methylprednisolone, paramethasone, prednisolone, prednisone, triamcinolone, hydrocortisone or cortisone.
Abnormal laboratory measures at baseline	One indicator variable for each of the following, as measured within 24 hours of admission: Absolute lymphocyte count < 1 x 10^3 cells /uL Alanine aminotransferase > 35 units/L Albumin < 3.5 g/dL Hemoglobin < 13.5 g/dL if male, <12 if female Platelet count < 150 x 10^3 cells /uL White blood cell count < 4 x 10^3 cells /uL White blood cell count >11 x 10^3 cells /uL
Abnormal vital signs at baseline	One indicator variable for each of the following, if the value was abnormal at any measurement within 24 hours of admission: Pulse > 90 beats per minute Respiratory rate > 22 breaths per minute Body temperature > 38°C Mean arterial pressure > 100 mmHg SpO_2:FiO_2 ratio < 200 units

Table 21. Characteristics at the Time of First Inpatient Prophylactic Anticoagulation Dose.

	Standard Prophylaxis n = 36,969 (72%)	High-Intensity Prophylaxis n = 14,224 (28%)	Absolute standardized mean difference
Age	62.4 (16.8)	59.9 (16.3)	0.15
Male	19,391 (52%)	7,575 (53%)	0.02
Self-Identified Race			
Asian	1,326 (4%)	382 (3%)	0.05
Black	6,249 (17%)	2,230 (16%)	0.03
White	21,120 (57%)	8,084 (57%)	0.01
Multiracial	334 (1%)	114 (1%)	0.01
Another race	6,990 (19%)	3,020 (21%)	0.06
Missing	793 (2%)	330 (2%)	0.01
Hispanic or Latinx ethnicity	11,449 (31%)	4,936 (35%)	0.08
Current or former smoker	6,545 (18%)	2,486 (17%)	0.01
Body mass index			
Not overweight or obese	6,642 (18%)	1,802 (13%)	0.15
Overweight	9,848 (27%)	3,303 (23%)	0.08
Obese	14,578 (39%)	7,641 (54%)	0.29
Missing	5,900 (16%)	1,478 (10%)	0.17
Highest level of oxygen support prior to anticoagulation initiation			
None	18,577 (50%)	6,345 (45%)	0.11
Low flow	14,846 (40%)	5,854 (41%)	0.02
High flow or non-invasive ventilation	2,962 (8%)	1,712 (12%)	0.13
Invasive mechanical ventilation	584 (2%)	311 (2%)	0.04
Medications current at the time of admission			
Antidiabetics	4,621 (13%)	1,924 (14%)	0.03
Antihypertensives	9,197 (25%)	3,606 (25%)	0.01
Antiplatelets	1,805 (5%)	617 (4%)	0.03
Aspirin	5,302 (14%)	1,876 (13%)	0.03
Immunosuppression	1,666 (5%)	603 (4%)	0.01
Inhaled corticosteroids	1,587 (4%)	680 (5%)	0.02
Statins	7,266 (20%)	2,688 (19%)	0.02
Systemic glucocorticoids	1,803 (5%)	674 (5%)	0.01

Continuous variables are represented as mean (standard deviation), and categorical variables as count (percentage). There were 2 people for whom oxygen liters per minute value were outside plausible ranges and their oxygen support status could not be determined. For detailed definitions, see Table 20.

Table 22. Laboratory Measures and Vital Signs at Admission.

	Standard Prophylaxis n = 36,969 (72%)	High-Intensity Prophylaxis n = 14,224 (28%)	Absolute standardized mean difference
Absolute lymphocyte count < 1 x 10^3 cells /uL	17,020 (46%)	6,903 (49%)	0.05
Missing	8,689 (24%)	3,405 (24%)	0.01
Alanine aminotransferase > 35 units/L	14,527 (39%)	6,512 (46%)	0.13
Missing	8,220 (22%)	2,572 (18%)	0.10
Albumin < 3.5 g/dL	23,544 (64%)	10,180 (72%)	0.17
Missing	4,472 (12%)	1,183 (8%)	0.13
Hemoglobin < 13.5 g/dL if male, <12 if female	15,905 (43%)	5,848 (41%)	0.04
Missing	2,093 (6%)	541 (4%)	0.09
Platelet count < 150 x 10^3 cells /uL	7,187 (19%)	2,347 (17%)	0.08
Missing	2,107 (6%)	537 (4%)	0.09
White blood cell count < 4 x 10^3 cells /uL	6,174 (17%)	2,797 (20%)	0.08
White blood cell count > 11 x 10^3 cells /uL	6,378 (17%)	2,240 (16%)	0.04
Missing	2,532 (7%)	687 (5%)	0.09
Pulse > 90 beats per minute	24,905 (67%)	10,296 (72%)	0.11
Missing	15 (< 1%)	1 (< 1%)	0.02
Respiratory rate > 22 breaths per minute	14,692 (40%)	7,353 (52%)	0.24
Missing	19 (< 1%)	3 (< 1%)	0.02
Body temperature > 38℃	11,540 (31%)	4,361 (31%)	0.01
Missing	42 (< 1%)	11 (< 1%)	0.01
Mean arterial pressure < 60 mmHg	24,302 (66%)	9,804 (69%)	0.07
Missing	17 (< 1%)	3 (< 1%)	0.01
SpO_2:FiO_2 ratio < 200 units	6,028 (16%)	3,787 (27%)	0.25
Missing	3,728 (10%)	1,055 (7%)	0.09

We were not able to consider C-reactive protein (44% of people did not have a measurement available within 24 hours of admission), D-dimer (54%) or Troponin I (74%).

Table 23. Risk of Specific Severe Outcomes With Time-Dependent Cox Proportional Hazards Models.

	Events	Person-Days of Follow-Up	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Therapeutic anticoagulation				
High-intensity	4,558	77,948	**3.49 (3.31-3.67)**	**3.24 (3.08-3.41)**
Standard	2,745	191,929	reference	reference
Severe disease				
High-intensity	3,361	9,187	**1.59 (1.52-1.66)**	**1.22 (1.16-1.27)**
Standard	5,648	107,771	reference	reference
Death within 24 hours of last prophylaxis dose				
High-intensity	509	113,826	**1.49 (1.32-1.67)**	**1.37 (1.21-1.55)**
Standard	660	220,934	reference	reference
Death within 3 days of last prophylaxis dose				
High-intensity	1,378	158,549	**1.50 (1.40-1.61)**	**1.41 (1.31-1.52)**
Standard	1,748	303,173	reference	reference
Death within 7 days of last prophylaxis dose				
High-intensity	2,110	245,300	**1.51 (1.42-1.60)**	**1.37 (1.29-1.46)**
Standard	2,662	464,037	reference	reference
Death within 10 days of last prophylaxis dose				
High-intensity	2,634	308,421	**1.56 (1.48-1.64)**	**1.39 (1.32-1.47)**
Standard	3,211	582,580	reference	reference

HR: hazard ratio; 95% CI: 95% confidence interval. For a detailed list of covariates in the adjusted models, see Table 20.

Table 24. Risk of Specific Severe Outcomes, With Dose Adjustments for Persons With Body Mass Index > 40 kg/m^2.

	Adjusted Hazard Ratio (95% Confidence Interval) Comparing High-Intensity to Standard Prophylaxis
Therapeutic anticoagulation	**3.17 (3.02-3.33)**
Severe disease	**1.14 (1.09-1.19)**
Death within 24 hours of last prophylactic dose	**1.39 (1.22-1.56)**
Death within 3 days of last prophylactic dose	**1.35 (1.26-1.46)**
Death within 7 days of last prophylactic dose	**1.34 (1.26-1.43)**
Death within 10 days of last prophylactic dose	**1.36 (1.29-1.43)**

There were 4,159 persons with a body mass index > 40 kg/m^2 with a total of 4,659 person-periods which were reclassified from high-intensity prophylaxis to standard prophylaxis in this analysis.

Table 25. Risk of Specific Severe Outcomes, Stratified by Oxygen Requirements at Time of First Dose.

	Adjusted Hazard Ratios (95% Confidence Interval) Comparing High-Intensity to Standard Prophylaxis	
	No or low-flow oxygen	Severe disease at time of first dose
Therapeutic anticoagulation	**3.56 (3.37-3.77)**	**2.26 (2.04-2.51)**
Severe disease	**1.21 (1.15-1.27)**	--
Death within 24 hours of last prophylactic dose	**1.47 (1.26-1.71)**	1.13 (0.92-1.39)
Death within 3 days of last prophylactic dose	**1.47 (1.34-1.61)**	**1.22 (1.07-1.39)**
Death within 7 days of last prophylactic dose	**1.45 (1.35-1.56)**	**1.16 (1.05-1.29)**
Death within 10 days of last prophylactic dose	**1.47 (1.38-1.57)**	**1.18 (1.07-1.30)**

Table 26. Sensitivity Analyses to Quantify E-Values for Strength of Association Between Prophylaxis Intensity and Clinical Outcomes With COVID.

	Lower bound of the 95% CI	Point estimate	Upper bound of the 95% CI
Therapeutic anticoagulation	5.61	5.93	6.28
Severe disease	1.59	1.74	1.86
Death within 24 hours of last prophylactic dose	1.71	2.08	2.47
Death within 3 days of last prophylactic dose	1.95	2.17	2.41
Death within 7 days of last prophylactic dose	1.90	2.08	2.28
Death within 10 days of last prophylactic dose	1.97	2.13	2.30

CI: confidence interval. The e-value is calculated as HR + sqrt(HR x (HR – 1)), where HR = hazard ratio.

Table 27. Sensitivity Analyses to Remove Laboratory Measures and Vital Signs From Adjustment Set.

	Adjusted Hazard Ratio (95% Confidence Interval) Comparing High-Intensity to Standard Prophylaxis
Therapeutic anticoagulation	**3.54 (3.37-3.72)**
Severe disease	**1.48 (1.42-1.55)**
Death within 24 hours of last prophylactic dose	**1.65 (1.46-1.86)**
Death within 3 days of last prophylactic dose	**1.69 (1.57-1.81)**
Death within 7 days of last prophylactic dose	**1.65 (1.55-1.75)**
Death within 10 days of last prophylactic dose	**1.70 (1.58-1.76)**

Table 28. Sensitivity Analyses Using Marginal Structural Models

	Adjusted Hazard Ratio (95% Confidence Interval) Comparing High-Intensity to Standard Prophylaxis
Therapeutic anticoagulation	**2.98 (2.82-3.15)**
Severe disease	**1.58 (1.51-1.64)**
Death within 24 hours of last prophylactic dose, up to a maximum of 21 days after first dose	**1.11 (0.84-1.48)**

We used discrete time periods of 24-hours, starting with the first administration of prophylactic anticoagulation, and defined the exposure level as the current intensity at the beginning of each person-period. We used a maximum of 21 days of follow-up, which was informed by the distribution of event times in order to minimize days with zero events.

We used inverse probability of treatment weights, which incorporated age group, overweight or obesity, sex, month of admission, race and ethnicity, smoking history, Elixhauser Comorbidity Index score, and indicators for antidiabetic, antihypertensive, antiplatelet, aspirin, immunosuppressive medications, inhaled corticosteroids, statins and systemic glucocorticoids current at the time of admission in the numerator and D-dimer results from the prior 24-hours in the denominator. We used stabilized weights, and truncated the 5th and 95th percentile of the weights. The mean of the weights across all time points was 1.04 (standard deviation 0.35).

With weighted pooled logistic regression models and robust variance estimates, we estimated hazard ratios with 95% confidence intervals.

Table 29. Sensitivity Analyses to Exclude Persons Who Died Within 48 Hours of Admission.

	Adjusted Hazard Ratio (95% Confidence Interval) Comparing High-Intensity to Standard Prophylaxis
Therapeutic anticoagulation	**3.24 (3.09-3.41)**
Severe disease	**1.22 (1.16-1.27)**
Death within 24 hours of last prophylactic dose	**1.49 (1.30-1.72)**
Death within 3 days of last prophylactic dose	**1.45 (1.35-1.57)**
Death within 7 days of last prophylactic dose	**1.40 (1.32-1.49)**
Death within 10 days of last prophylactic dose	**1.42 (1.34-1.50)**

In this analysis, 84 persons from the main analysis were excluded. Among them, 10 (12%) received high-intensity prophylaxis and 74 (88%) standard prophylaxis.

Figure 15. Directed Acyclic Graphs of Assumptions Regarding the Association Between Prophylaxis Intensity, Risk Factors, and Severe COVID.

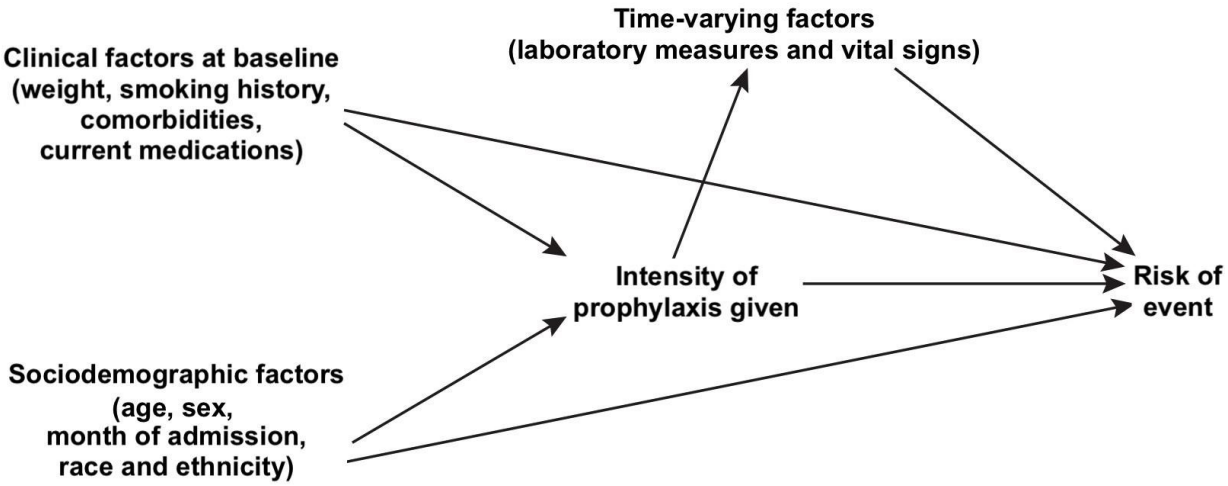
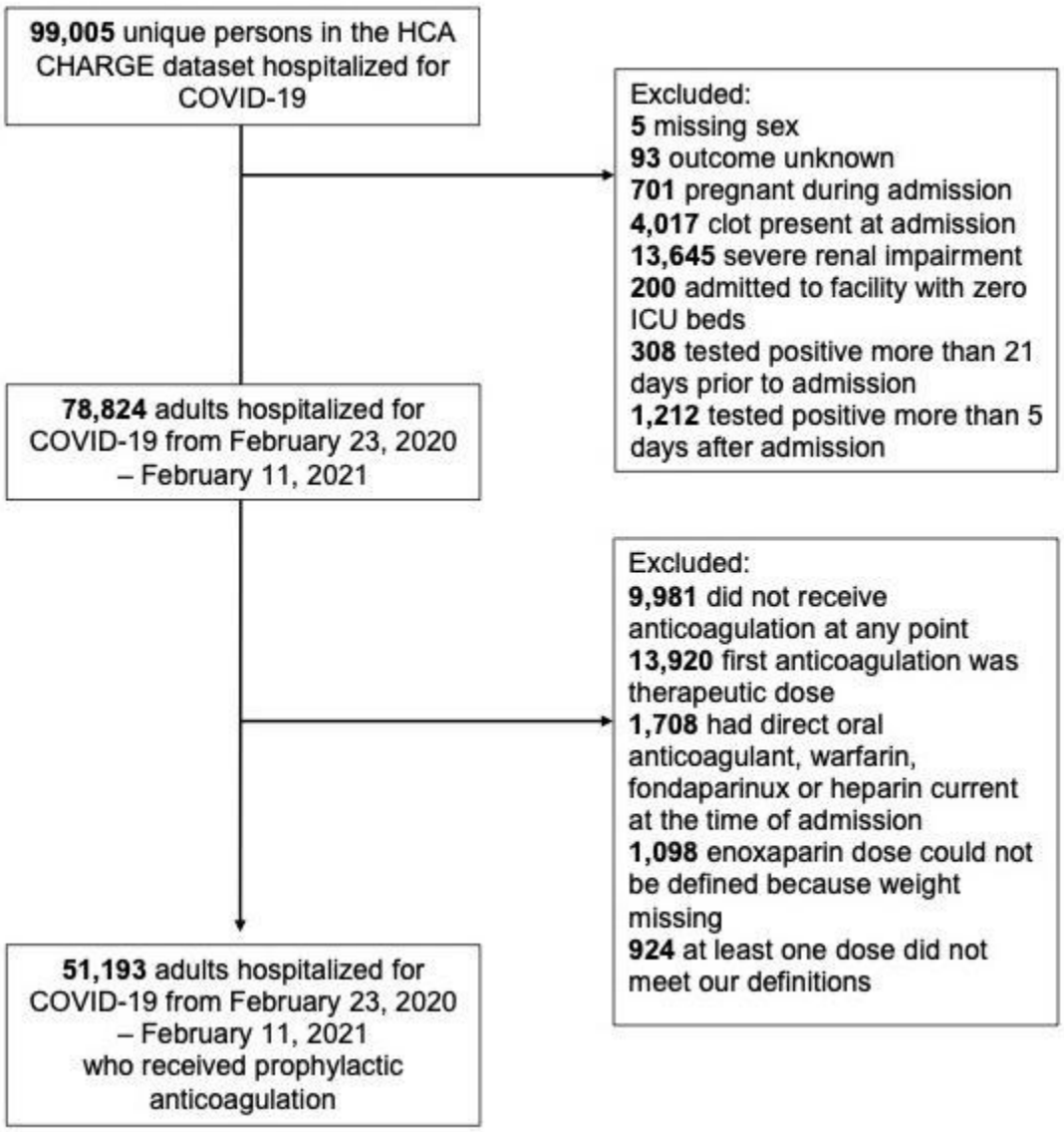
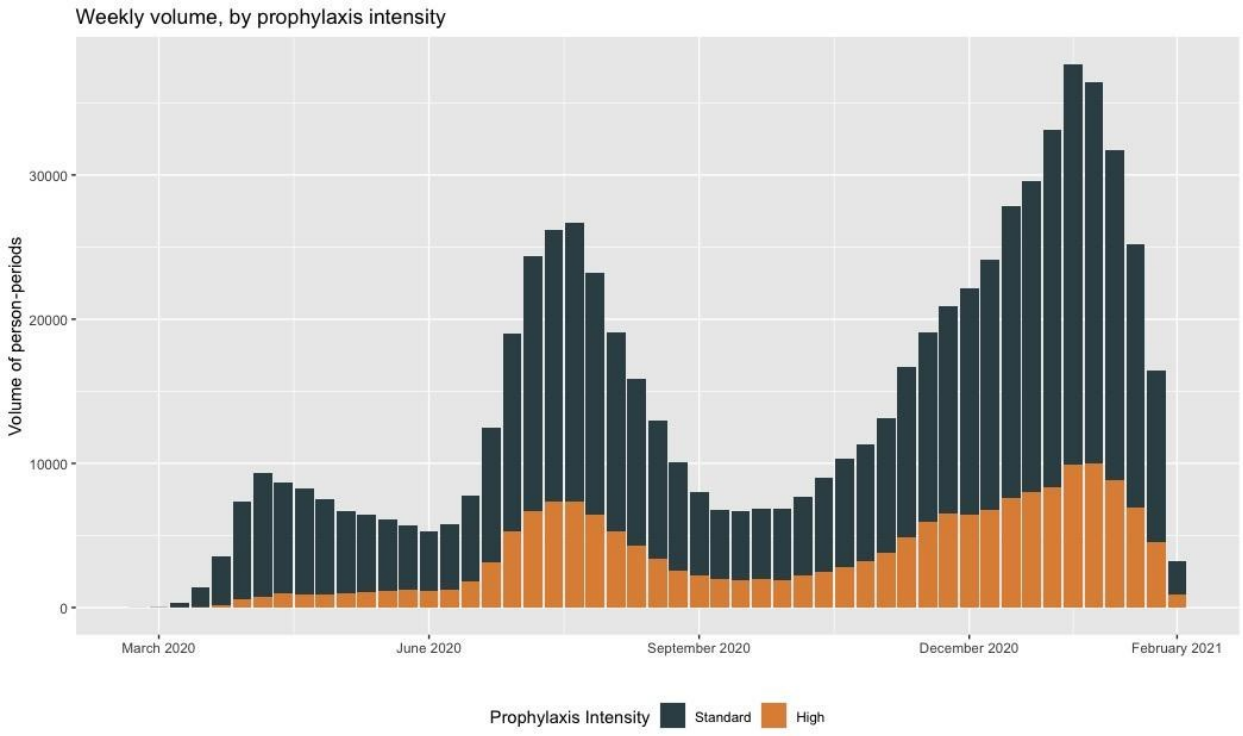


Figure 16. Analytic Cohort Derivation.



Severe renal impairment was defined as an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2, using the CKD-EPI equation, measured within 24 hours of admission.

Figure 17. Temporal Trends of Doses Administered to Hospitalized Adults, by Prophylactic Intensity.



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Chapter 5: Conclusions

Synthesis of Primary Findings

While many important questions remain, this dissertation provides robust evidence suggesting the general safety of chronic immunosuppressive medicines, as well as the absence of benefit of high-intensity thromboprophylaxis, among U.S. adults hospitalized with COVID-19. In Aims I and II, we found reassuring results for most people on immunosuppressive medications. With the exception of rituximab, we did not find increased risks of mechanical ventilation or death for persons using a wide range of medications, such as those for cancer therapy, autoimmune disorders, or to prevent solid organ transplant rejection. In contrast to Aim I, which was performed among a much smaller cohort within one healthcare institution, Aim II leveraged a national repository of electronic health record data and was able to examine specific classes of immunosuppressive products. Taken together, for persons prescribed immunosuppressive medications other than rituximab, there is no indication that they should be concerned that their medication increases the risk for severe COVID-19. Given rituximab's mechanism of action is to powerfully interfere with antiviral humoral response, our finding of increased risk of death for both cancer and rheumatologic patients with this drug is plausible.

Aim III does not support the routine use of high-intensity prophylaxis doses to prevent clinical worsening, severe disease or death among adults hospitalized with COVID-19 in the United States. Our results persisted in a variety of subgroup and sensitivity analyses, and are robust against independent unmeasured confounding. While the effect estimates indicate statistically significant increases in the risk of outcomes of interest, we are unable to discern whether this is a true causal effect or residual confounding; thus, we interpret our results as not consistent with reduced risk, rather than clear evidence of increased risk. These findings are important, given that prophylactic anticoagulation is a mainstay of inpatient COVID-19 care.

Remaining Questions

For persons with chronic immunosuppressive medication use, important questions remain. First, it is unclear whether these persons have reduced responses to dexamethasone. It is possible that their immune and adrenal systems have adapted to immunosuppressive medications, in particular people with chronic glucocorticoid use, and they may not experience the same mortality benefit of new users. Additionally, questions remain whether immunosuppressive medications, particularly those given daily such as tacrolimus and mycophenolate, should be continued or discontinued upon COVID-19 admission.

For anticoagulation, the comparative effectiveness of the dosing schedules would have been most clearly demonstrated by comparing the incidence of thromboembolic events, as thromboprophylaxis is intended to prevent the formation of a clot leading deep vein thrombosis or pulmonary embolism. While all products require a balancing of risks and benefits, in the case of anticoagulation this balance is especially stark, given the potential catastrophic consequences of preventable thromboembolism, on the one hand, and iatrogenic hemmorrhage, on the other. Unfortunately, the dataset did not contain timestamps for diagnosis codes that would have allowed for us to time to event analyses. We attempted to derive an algorithm with an exit diagnosis code for a clot, with an imaging study consistent with suspected clot and timestamped initiation of therapeutic anticoagulation. However, we found multiple imaging studies for most patients, and we found fewer than 1% of persons were identified with this strategy, whereas the literature suggests as high as 14% of hospitalized COVID-19 patients develop venous thromboembolism during their stay.[6,32–34] We also did not consider several important groups of people, such as those with chronic outpatient anticoagulation use, as well as among people who are pregnant or have severe renal impairment, given their anticoagulation protocols would have been substantially different from the general adult population.

Clinical and Public Health Impact

The combined results of Aims I and II support the continuation of long-term immunosuppressive medications among cancer, rheumatologic and solid organ transplant patients in the United States. While there was some concern at the outset of the pandemic that patients, with or without prescriber guidance, were discontinuing immunosuppressive medications due to fears of acquiring COVID-19 or experiencing worse outcomes, our results do not support the routine discontinuation of medications such as those to prevent joint damage due to rheumatoid arthritis or the rejection of a solid organ transplant.

In addition to replicating the overall findings of Aim I in a larger and more robust population and analysis, Aim II also identified an important high risk subgroup. While rituximab should not necessarily be stopped out of COVID-related concerns, it is important that patients and prescribers be aware of its association with in-hospital death among COVID-19 patients. Clinical and public health professionals should prioritize anti-SARS-CoV-2 monoclonal antibody therapies, such as bamlanivimab plus etesevimab, casirivimab plus imdevimab or sotrovimab, for rituximab users if infected, regardless of severity of symptoms at onset. Furthermore, given that rituximab severely impacts the response to neoantigen immunizations,[35] our results reinforce the need for high levels of vaccination in the overall community, sometimes referred to as “herd immunity”, in order to provide protection to the most medically vulnerable members of society.

In Aim III, we directly addressed a research gap identified by the National Institutes of Health COVID-19 treatment guidelines. Prophylactic anticoagulation is currently recommended for all adults hospitalized with COVID-19 but the optimal dose remains unknown, and our findings do not support the routine use of high doses of thromboprophylaxis.

Taken together, these aims demonstrate the power of interdisciplinary collaboration, and rapid response to a global emergency. This work and that of many others has shown the importance of rigorous observational methods to address important and time sensitive questions that are relevant to the lives of hundreds of millions of individuals impacted by the COVID-19 pandemic.

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10. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(9):1036-1041. doi:10.1001/jamacardio.2020.1834

11. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. *Heart Rhythm*. 2020;17(9):1472-1479. doi:10.1016/j.hrthm.2020.05.008

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14. VEKLURY (remdesivir) FDA Label. Accessed September 20, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf

15. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764

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20. Dexamethasone in Hospitalized Patients with Covid-19 | NEJM. Accessed June 2, 2021. https://www.nejm.org/doi/full/10.1056/NEJMoa2021436

21. CDC. COVID-19 and Your Health. Centers for Disease Control and Prevention. Published February 11, 2020. Accessed March 18, 2021. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/immunocompromised.html

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26. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. *Chest*. 2020;158(3):1143-1163. doi:10.1016/j.chest.2020.05.559

27. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis*. 2020;50(1):72-81. doi:10.1007/s11239-020-02138-z

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34. Poissy J, Goutay J, Caplan M, et al. Pulmonary Embolism in Patients With COVID-19. *Circulation*. 2020;142(2):184-186. doi:10.1161/CIRCULATIONAHA.120.047430

35. Bingham CO, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum*. 2010;62(1):64-74. doi:10.1002/art.25034

Vita

Andersen, Kathleen (Kayte) Michelle kande108@jhmi.edu
ORCID iD 0000-0003-2670-800X Citizen of United States and Canada

PROFILE

PhD candidate studying pharmacoepidemiologic methodology and biostatistical techniques to answer questions of population-level drug safety, effectiveness and utilization. Specific expertise in designing studies, and analyses of administrative claims and electronic health record data, to answer questions pertaining to central nervous system, rheumatologic, cardiovascular and infectious disease pharmacotherapy, as well as of biologic products and medical devices. Track record of producing valuable scientific products with each of American, Canadian and British population-based data sources. Extensive experience leading and engaging with scientific teams to advance scientifically compelling questions. Skillful science communicator, with ability to answer questions in both technical and lay terms.

EDUCATION

Doctor of Philosophy, Epidemiology **September 2018 – December 2021**
Johns Hopkins Bloomberg School of Public Health, Baltimore, United States
Co-advisors: G. Caleb Alexander, MD MS and Jodi Segal, MD MPH
Certificate in Pharmacoepidemiology and Drug Safety awarded December 2019

Dissertation: Optimizing Use of Immunosuppressive Therapeutics and Thromboprophylaxis: Associations with Severe Disease & Death Among Adults Hospitalized with COVID-19 in the U.S.
Prior to COVID-19, I had developed a full protocol and plans for "Real-world Evaluation of the Use and Comparative Effectiveness of PCSK9 Inhibitors"

Member, Department of Epidemiology's Inclusion, Diversity, Equity, Anti-Racism, and Science Group and the Johns Hopkins Precision Medicine Center of Excellence for COVID-19
Scholar, Johns Hopkins Center for Drug Safety & Effectiveness.

Master of Science **2016 – 2018**
McGill University, Montreal, Canada
Thesis: "Pharmacologic management of major neurocognitive disorders in the United Kingdom: a population-based drug utilization study". Rated by external reviewer as top 10% of theses.

Bachelor of Science, Pharmacology & Therapeutics **2011 – 2014**
McGill University, Montreal, Canada

SELECT SKILLS

Mastery in data management, manipulation and analyses of large, complex datasets in SAS.
Experienced in programming with SQL, Stata and R.

English	Read, Write, Speak, Understand, Peer Review
French	Read, Write, Speak, Understand

PROFESSIONAL EXPERIENCE

Consultant (Seasonal contract) **December 2020 and January 2021**

Valeo Pharmaceuticals, Pointe-Claire, Quebec

- Writing clinical summaries of published literature for adjacent products.

Research Assistant (Part-time) **September 2018 – November 2021**

Johns Hopkins Center for Drug Safety and Effectiveness, Baltimore, Maryland

- Key point of contact for Johns Hopkins faculty working with MarketScan and IQVIA LRX data. Provides training materials, reviews data user agreements, funding and external data requirements.
- Facilitating cohort derivation, data linkage, statistical analyses and manuscript preparation.
- Formal tutoring of statistical programming software for masters and doctoral students.

Johns Hopkins Department of International Health, Baltimore, Maryland

- Translating research protocols, materials and questionnaires from French to English.

Research Assistant (Part-time) **2016 – 2018**

2017-2018: Jewish Eldercare Centre site coordinator (Université de Sherbrooke). Clinician and family member recruitment to complete survey weeks after an Alzheimer's-related death in long-term care.

2016-2017: Developed database for 2,339 Canadian long-term care facilities. Assisted literature review and interviews to assess clinical information needs & gaps (Centre Hospitalier de Université de Montréal).

Clinical Research Coordinator (Full-time) **2014 – 2016**

Inflammatory Arthritis Center of Excellence, Hospital for Special Surgery, New York, New York

Consortium of Early Arthritis Trials (PI: V Bykerk)

- Recruitment and follow-ups visits for early rheumatoid arthritis patients.
- Developed training protocols and materials for major protocol revision.
- Translated site, patient, and provider surveys from English to French.
- Assisted with a fellow's research project at all stages, from study design to dissemination.
- Created study database on REDCap, with scoring algorithms, complex branched logic & logic checks.

Pharmacy Technician (Part-time) **2014**

Pharmacie Melas-Desjardins, Kirkland, Quebec (closed September 2018)

- Dispensed prescriptions under pharmacist supervision, maintained drug inventory, placed orders and restocked pharmacy shelves.

Research Assistant (Part-time) **2009 – 2014**

McGill University Health Centre, Montreal, Quebec

PROFESSIONAL ACTIVITIES

Society for Epidemiologic Research (SER) 2020 – present

International Society for Pharmacoepidemiology (ISPE) 2017 – present

Abstract reviewer for African Regional Interest Group Meeting 2021, Mid-Year Conference 2021, Mid-Year 2020 Meeting, 2020 Full Conference and ISPE COVID-19 session.

Outcomes Measurement in Rheumatology (OMERACT) 2017 – 2018

Fellow for the Drug Safety Working Group. Assisted with protocol development and implementation of a mixed methods study of patient-reported outcome measures of safety in rheumatology clinical trials. Presented the protocol and results in Terrigal, New South Wales, Australia in May 2018.

AWARDS

Doctoral Training Grant **2018 – 2021**

National Heart, Lung and Blood Institute (NHLBI) Pharmacoepidemiology T32 HL 139426 Training Program, with full tuition support, doctoral student stipend and travel award.

Outstanding Academic and Community Service **2020 – 2021**

Dorothy and Arthur Samet Award from the Johns Hopkins Bloomberg School of Public Health.

Masters Training Award **2016 – 2018**

Maimonides Medical Research Foundation, Montreal, QC. Full tuition support and student stipend.

Travel Award **2018**

Canadian Institute of Health Research's Institute of Aging Community Travel Award ($1000).

PUBLICATIONS

Journal Articles

1. Garibaldi BT, Wang K, Robinson ML, Betz J, Alexander GC, **Andersen KM,** Joseph CS, Mehta HB, Korwek K, Sands KE, Fisher AM, Bollinger R, Xu Y. Real World Effectiveness of Remdesivir in Individuals Hospitalized with COVID-19: A Retrospective, Multicenter Comparative Effectiveness Study. *Clinical Infectious Diseases. (Accepted December 10, 2021).*

2. Ellenbogen MI, **Andersen KM,** Marine JE, Wang NY, Segal JB. Changing patterns of Use of Implantable Cardiac Monitors from 2011 to 2018 for a Large Commercially-Insured US Population. *Medicine (Accepted December 1, 2021).*

3. **Andersen KM,** Bates B, Rashidi ES, Olex AL, Mannon RB, Patel RC, Singh J, Auwaerter PG, Ng DK, Segal JB, Garibaldi BT, Mehta HB, Alexander GC. Long-Term Use of Immunosuppressive Medicines and In-Hospital COVID-19 Outcomes: A Retrospective Cohort Study Using Data from the National COVID Cohort Collaborative (N3C). *The Lancet Rheumatology*. doi: 10.1016/S2665-9913(21)00325-8.

4. Gurley E, Redd A, Peetluk L, Jarrett B, Hanrahan C, Schwartz S, Rao A, Jaffe A, Peer A, Jones C, Lutz C, McKee C, Patel E, Rosen J, Garrison-Desany H, Mckay H, Muschelli J, **Andersen KM,** Link M, Wada N, Baral P, Young R, Boon D, Grabowski MK. Curating and translating the evidence about SARS-CoV-2 and COVID-19 for frontline public health and clinical care: The Novel Coronavirus Research Compendium (NCRC). *Public Health Practice*. Link to preprint.

5. Sun J, Patel RC, Zheng Q, Madhira V, Olex AL, Islam J, French E, Chiang TPY, Akselrod H, Moffitt R, Alexander GC, **Andersen KM,** Brown TT, Chute C, Crandall K, Franceschini N, Mannon RB, Kirk GD. COVID-19 Disease Severity Among People with HIV Infection or Solid Organ Transplant in the United States. *Annals of Internal Medicine* (*Submitted July 30, 2021).* Link to preprint.

6. Molino AR, **Andersen KM,** James BD, Fox MP, Murray EJ, Jarrett BA. The Expert Next Door: A Commentary on Interactions with Friends and Family During the SARS-CoV-2 Pandemic. (2021). *American Journal of Epidemiology).* doi: 10.1093/aje/kwab245.

7. **Andersen KM,** Schieir O, Valois MF, Bartlett SJ, Bessette L, Boire G, Haraoui B, Hazlewood G, Hitchon C, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk VP. A Bridge Too Far? Real-world Practice Patterns of Early Glucocorticoid Use in the Canadian Early Arthritis Cohort. *ACR Open Rheumatology.* doi: 10.1002/acr2.11334

8. Mehta HB, An H, **Andersen KM,** Mansour O, Madhira V, Rashidi ES, Bates B, Setoguchi S, Joseph C, Kocis PT, Moffit R, Bennett TD, Chute CG, Garibaldi BT, Alexander GC, for the National COVID Cohort Collaborative (N3C). Use of Hydroxychloroquine, Remdesivir, and Dexamethasone Among Adults Hospitalized with COVID-19 in the United States: Results from the National COVID Cohort Collaborative (N3C). *Annals of Internal Medicine.* doi: 10.7326/M21-0857

9. **Andersen KM,** Mehta HB, Palamuttam N, Ford D, Garibaldi BT, Auwaerter PG, Segal JB, Alexander GC. (2021). Association Between Chronic Immunosuppression and Clinical Outcomes from COVID-19 Hospitalization: a Retrospective Cohort Study Within a Large U.S. Health System. *Clinical Infectious Diseases.* doi: 10.1093/cid/ciaa1488

10. Bartlett SJ, Gutierrez AK, **Andersen KM,** Bykerk VP, Curtis JR, Haque UJ, Orbai AM, Jones MR, Bingham III CO. (2020). Identifying Minimal and Meaningful Change in PROMIS® for Rheumatoid Arthritis: Use of Multiple Methods and Perspectives. *Arthritis Care and Research*. doi: 10.1002/acr.24501

11. Ngo M-D, Zummer M, **Andersen KM,** Richard N. (2020). First Biologic Drug Persistence in Patients With Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: A Real-World Canadian Physicians' Experience. *Journal of Clinical Rheumatology.* doi: 10.1097/RHU.0000000000001693

12. Li X, **Andersen KM,** Chang HY, Curtis JR, Alexander GC. (2019). Comparative Risk of Serious Infections Among Real-World Users of Biologics for Psoriasis or Psoriatic Arthritis. *Annals of the Rheumatic Diseases.* doi: 10.1136/annrheumdis-2019-216102

13. **Andersen KM,** Kelly A, Lyddiatt A, Bingham CO III, Bykerk VP, Batterman A, Westreich J, Jones MK, Cross M, Brooks P, March L, Shea B, Tugwell P, Simon LS, Christensen RC, Bartlett SJ. (2019). Patient Perspective on DMARD Safety Concerns in Rheumatology Trials: Results from Inflammatory Arthritis Patient Focus Groups and OMERACT Attendees Discussion. *Journal of Rheumatology, 46(8):1053-1058.* doi: 10.3899/jrheum.181185

14. **Andersen KM,** Cheah JTL, March L, Bartlett SJ, Beaton D, Bingham CO III, Brooks PM, Christensen R, Conaghan PG, D'Agostino MA, de Wit M, Dueck A, Goodman SM, Grosskleg S, Hill CL, Howell M, Mackie SL, Richards B, Shea B, Singh JA, Strand V, Tugwell P, Wells GA, Simon LS. (2019). Improving Benefit-Harm Assessment of Therapies from the Patient Perspectives: OMERACT Pre-Meeting Towards Consensus on Core Sets for Randomized Controlled Trials. *Journal of Rheumatology, 46(9):1168-1172.* doi: 10.3899/jrheum.181123

15. Klokker L, Berthelsen D, Woodworth T, **Andersen KM,** Furst D, Devoe DJA, Williamson PR, Suarez-Almazor M, Strand V, Leong A, Goel N, Boers M, Brooks P, March L, Sloan V, Tugwell P, Simon LS, Christensen R. (2019). Identifying Possible Outcome Domains from Existing Outcome Measures to Inform an OMERACT Core Domain Set for Safety in Rheumatology Trials. *Journal of Rheumatology, 46(9):1173-1178.* doi: 10.3899/jrheum.190196

16. Reid RE, Roumeliotis G, Carver TE, **Andersen KM,** Reid TGR, Christou NV, Andersen RE. Effect of Employment Status on Physical Activity and Sedentary Behavior Long-Term Post-Bariatric Surgery. (2018). *Obesity Surgery,* 28(3): 869-873. doi: 10.1007/s11695-017-3079-6

17. Orange D, Agius P, DiCarlo E, Szymonifka J, McNamara M, Mirza S, **Andersen KM,** Cummings RW, Figgie M, Lingampalli N, Jiang C, Frank M, Geiger H, Robine N, Pernis A, Ivashkiv L, Darnell R, William R, Gravallese EM, Bykerk VP, Goodman SM, Donlin L. (2018). Identification of Three Rheumatoid Arthritis Disease Subtypes by Machine Learning Integration of Synovial Histologic Features and RNA Sequencing Data. *Arthritis & Rheumatology, 70(5):690-701. doi:* 10.1002/art.40428

18. Goodman SM, DiCarlo E, Bykerk VP, Reidy C, Cummings RW, Donlin LT, Orange D, Hoang A, McNamara M, Mirza S, **Andersen KM,** Bartlett SJ, Szymonifkaj J, Figgie MP. (2018). Flares in Patients with Rheumatoid Arthritis After Total Hip and Total Knee Arthroplasty: Rates, Characteristics and Risk Factors. *Journal of Rheumatology, 45(5), 604-611. doi: 10.3899/jrheum.170366*

19. Schulman E, Bartlett S, Schieir O, Zheng M, **Andersen KM,** Colmegna I, Hitchon C, Boire G, Jamal S, Thorne C, Tin D, Keystone E, Haraoui B, Pope J, Goodman SM, Bykerk VP and CATCH investigators. (2017). Overweight and Obesity Reduce the Likelihood of Achieving Sustained Remission in Early Rheumatoid Arthritis: Results from the Canadian Early Arthritis Cohort Study. *Arthritis Care and Research,* 70(8):1185-1191. *doi: 10.1002/acr.23457*

20. Reid RE, Carver TE, Reid T, Picard-Turcotte MA, **Andersen KM,** Christou N, Andersen RE. (2017). Effects of Neighborhood Walkability on Physical Activity and Sedentary Behavior Long-Term Post-Bariatric Surgery. *Obesity Surgery*, 27(6), 1589-94. doi: 10.1007/s11695-016-2494-4
21. Reid RE, Carver TE, **Andersen KM,** Court O, Andersen RE. (2015). Physical Activity and Sedentary Behavior in Bariatric Patients Long-Term Post-Surgery. *Obesity Surgery*, 25(6), 1073-7. doi:10.1007/s11695-015-1624-8
22. Shahrbanian S, Auais M, Duquette P, **Andersen KM,** Mayo NE. (2013). Does Pain in Individuals with Multiple Sclerosis Affect Employment? A systematic review and meta-analysis. *Pain Research and Management*, doi: 10.1155/2013/829464.

Protocols

1. **Andersen KM,** Kroger E, Filion KB, Wilchesky M, Champoux N, Reyneir P, Ernst P, Platt R, Grad R, Suissa S. Alzheimer's treatment and the risk of serious adverse events. Clinical Practice Research Datalink (CPRD). https://cprd.com/protocol/alzheimers-treatment-and-risk-serious-adverse-events
2. **Andersen KM,** Bartlett SJ, Shea BJ, Leong AL, Klokker L, Berthelsen D, Woodworth T, Devoe D, Williamson P, Terwee CV, Suarez-Alzamor ME, Strand V, Goel N, Boers M, Furst DE, Tugwell P, Brooks PM, Simon LS, Christensen R. Developing a core outcome set for safety in Rheumatology Trials Using a Mixed-Methods Approach: Protocol for an OMERACT multicenter study. Registered with the Core Outcome Measures in Effectiveness Trials (COMET): www.comet-initiative.org/studies/details/1120.
3. Berthelsen DB, **Andersen KM,** Lyddiatt A, Ioannidis JPA, Tugwell P, Furst DE, Devoe D, Williamson P, Terwee CB, Suarez-Almazor ME, Strand V, Woodworth T, Leong AL, Goel N, Conaghan PG, Boers M, Shea BJ, Bartlett SJ, Brooks PM, Simon LS, Christensen R. Identifying candidate harm domains from rheumatology drug trials to inform the OMERACT Safety Working Group: protocol for an overview of systematic reviews surveying randomized trials. Registered with the PROSPERO international register of systematic reviews (CRD42018108393): http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018108393

MEDIA AND PRESS COVERAGE

1. Study: Immune-suppressing meds may not increase severe COVID-19 risk (November 2021).
2. JHU examines if COVID patients on immunosuppressive medications face higher risk of death (November 2021).
3. Outcomes for Hospitalized COVID-19 Patients Taking Immunosuppressive Medications Similar to Non-Immunosuppressed Patients (November 2021).
4. Public Health on Call (Podcast): Episode 271 – COVID-19 and Immunosuppressant Drugs (March 2021).
5. New Study Finds Many Immunosuppressive Drugs Don't Increase Risk of Dying from COVID-19 (March 2021).
6. Immunosuppressive Medicines Do Not Worsen COVID-19 Outcomes (February 2021).
7. 'No need' to suspend immunosuppressive drugs due to COVID-19: No impact on risk outcomes (February 2021).
8. Johns Hopkins Students Answer the Buzziest COVID-19 Vaccine Questions (February 2021). This content was cross posted to Twitter and Instagram.
9. Study suggests immunosuppressive drugs do not contribute to severity of COVID-19 (January 2021).
10. COVID-19 Outcomes for Patients on Immunosuppressive Drugs on Par with Non-Immunosuppressed Patients (January 2021).
11. Johns Hopkins Students React to Social Media Comments about COVID-19, Vaccines, and more (November 2020). This content was cross posted to Twitter and Instagram.

ACADEMIC SERVICE

Social Media and Website Chair, Epidemiology Student Organization 2019 – 2021
Instagram (@ESO_at_JHSPH), Twitter (@ESO_at_JHSPH).

Johns Hopkins Chapter of the International Society for Pharmacoepidemiology (SISPE) 2018 – 2021
Student Council President 2019-2021. Executive member 2018-2019.

Journal Club and Research In Progress Coordinator 2019 – 2020
General Epidemiology & Methodology, Department of Epidemiology.

Family Medicine Graduate Student Society 2017 – 2018
Vice President of Communications. Wrote successful applications for "Best Medium-Sized Student Association" and "Best Academic Event Award".

Activities During COVID Pandemic

I was the Social Media Strategist for the Johns Hopkins School of Public Health Novel Coronavirus Research Compendium (@JHSPH_NCRC). I wrote tweet threads referencing expert summary statements, to drive traffic to website, from April - August, 2020. On a personal note, I managed inventory and supplies, and led distribution for 7,000+ cloth face masks with the Beaconsfield Quilting Guild in Beaconsfield, Quebec, Canada.

TEACHING EXPERIENCE

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Practical Skills in Clinical Epidemiology and Investigation — September- October 2021

Developed content and delivered 45-minute lecture on data management using real world data sources. Shared grading responsibilities with course faculty.

Epidemiologic Inference in Public Health II — September – December 2020

Worked closely with course faculty to transition this course to an online format in the 4 weeks prior to the course offering. Involved in content development, lecture recording, creating questions for and piloting online exams, holding weekly office hours and responding to posts on discussion forum.

Epidemiologic Inference in Public Health I — June and July 2020

Developed a new lab exercise regarding ethical and science communication challenges pertaining to the COVID-19 pandemic, which was implemented in introductory Epidemiology courses at the Johns Hopkins Bloomberg School of Public Health.

Pharmacoepidemiology: Drug Utilization — January – March 2020

With course faculty, I substantially revamped this course. We added a module on the opioid epidemic, added new styles of assessment and I developed content for each of 4 LiveTalks.

Epidemiologic Inference in Public Health — January – March 2020

Pharmacoepidemiology Methods — November and December 2019

Epidemiology Methods 1 — September and October 2019

Teaching Epidemiologic Methods and Concepts at the Graduate Level — Summer 2019

Tutor, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

Tutored two students in Epidemiology Methods 2, two students in Epidemiology Methods 3, and one student in all Epidemiology Methods course material for departmental comprehensive exam.

Formal Mentoring

2019-2021: Mentor to 4 pharmacoepidemiology doctoral students, as well as key point of contact for admitted students to the program.

2017-2018: Tannenbaum Fellow for the Faculty of Medicine at McGill University. Mentor for six medical residents in family medicine for research protocol development and research plan execution, one of whom won for the best research project among 130 family medicine residents across McGill University.

PRESENTATIONS

Seminars

1. Potential pearls and pitfalls of using the United States Department of Veterans Affairs Data (October 2021). *Johns Hopkins Pharmacoepidemiology Journal Club.*
2. Selection bias in estimating observed versus expected COVID cases (October 2021). *Johns Hopkins General Epidemiology & Methodology Journal Club.*
3. An introduction to pharmacoepidemiology for general epidemiologists (February 2021). *Johns Hopkins General Epidemiology & Methodology Journal Club.*
4. An introduction to best practices for pharmacoepidemiologic evaluations in the COVID-19 era (September 2020). *Johns Hopkins Pharmacoepidemiology Journal Club.* Baltimore, United States.
5. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i): using real-world evidence to evaluate cardiovascular outcomes (April 2020). *Johns Hopkins Department of Clinical Pharmacology Grand Rounds.* Baltimore, United States.
6. An introduction to critical evaluation of general epidemiologic methodology (September 2019). *Johns Hopkins General Epidemiology & Methodology Journal Club.* Baltimore, United States.
7. Pharmaceutical marketing as a driving factor in the United States opioid epidemic (April 2019). *Johns Hopkins Social Epidemiology Journal Club.* Baltimore, United States.
8. Using pharmacoepidemiologic methods to study drug-drug interactions (April 2019). *Johns Hopkins Clinical Pharmacology Grand Rounds.* Baltimore, United States.
9. Discussion of the case-crossover design (November 2018). *Johns Hopkins General Epidemiology & Methodology Journal Club.* Baltimore, United States.

Oral Presentations

1. **Andersen KM,** Rashidi ES, An H, Mehta HB, Ng DK, Garibaldi BT, Segal JB, Alexander GC (August 2021). Utilizing the National COVID Cohort Collaborative (N3C) to evaluate risk of serious outcomes with COVID-19 among chronically immunosuppressed persons. *International Conference on Pharmacoepidemiology and Therapeutic Risk Management.*
2. Mehta HB, An H, **Andersen KM,** Mansour O, Madhira V, Rashidi ES, Bates B, Setoguchi S, Joseph C, Kocis PT, Moffit R, Bennett TD, Chute CG, Garibaldi BT, Alexander GC, for the National COVID Cohort Collaborative (N3C) (August 2021). Use of Hydroxychloroquine, Remdesivir, and Dexamethasone Among Adults Hospitalized with COVID-19 in the United States: Results from the National COVID Cohort Collaborative (N3C). *International Conference on Pharmacoepidemiology and Therapeutic Risk Management.*
3. **Andersen KM,** Mehta HB, Palamuttam N, Ford D, Garibaldi BT, Auwaerter PG, Segal JB, Alexander GC (May 2021). Cardiopulmonary outcomes among immunocompromised persons during COVID-19 hospitalization: a retrospective cohort study. *National Heart, Lung and Blood Institute Cardiovascular, Epidemiology, Biostatistics, and Prevention Trainee Session.*

4. **Andersen KM,** Rashidi ES, Garibaldi BT, Alexander GC, Segal JB, Mehta HB (April 2021). Performance of Elixhauser and Charlson comorbidity indices to predict mortality among adults hospitalized with COVID-19 in the United States. *International Society for Pharmacoepidemiology Mid-Year Meeting.*

5. **Andersen KM,** Mehta HB, Palamuttam N, Ford D, Garibaldi BT, Auwaerter PG, Segal JB, Alexander GC (November 2020). Clinical Outcomes During COVID-19 Hospitalization: A Retrospective Cohort Study Comparing Immunocompromised to Immunocompetent Persons. *International Conference on Pharmacoepidemiology All-Access COVID-19 Sessions.*

6. **Andersen KM.** (March 2020). The opportunity cost of sticker shock: the real-world use, safety and effectiveness of the PCSK9 inhibitors (3 Minute Thesis). *American Heart Association EPI | Lifestyle Scientific Session.* Phoenix, Arizona.

7. Li X, **Andersen KM,** Chang HY, Curtis JR, Alexander GC (August 2019). Risk of serious infections among new users of interleukin-17 or interleukin-12/23, compared to tumor necrosis (TNF)-alpha inhibitors, for the treatment of psoriasis and psoriatic arthritis: a retrospective cohort study. *International Conference on Pharmacoepidemiology and Therapeutic Risk Management.* Philadelphia, United States.

8. Ngo MD, Zummer M, **Andersen KM,** Richard N (May 2019). Comparaison de la persistance du premier médicament biologique chez les patients atteints de spondylarthrite ankylosante et de spondylarthrite axiale non radiographique: données du registre SPARCC. *Laurentian Conference of Rheumatology.* Estérel, Canada.

   Won award for the best presentation at the conference.

9. **Andersen KM,** Filion KB, Kroger E, Champoux N, Reynier P, Wilchesky M (July 2018). Treatment initiation characteristics of anti-dementia drug therapies in the United Kingdom: a 20-year retrospective population-based inception cohort. *Alzheimer's Association International Conference.* Chicago, United States.

10. **Andersen KM,** Filion KB, Kroger E, Champoux N, Reynier P, and Wilchesky M (May 2018). Prescribing patterns for Major Neurocognitive Disorder among primary care physicians in the United Kingdom: a population-based inception cohort. *Family Medicine Graduate Research Symposium.* Montreal, Canada.

11. **Andersen KM,** Bartlett SJ, Shea BJ, Tugwell P, Brooks PM, Simon LS, Christensen R. (May 2018). Developing a core outcome set for safety in rheumatology trials using a mixed-methods approach: protocol for an OMERACT multicenter study. *Outcomes Measurement in Rheumatology 2018,* Terrigal, New South Wales, Australia.

12. Marrone E, Hebert P, Heckman G, Karanofsky M, Hirdes J, Morinville A, Nugus P, **Andersen KM**, Wilchesky M (May 2018).: Presenting a Mixed Methods Study Evaluating the Clinical Information Needs of Canadian Long-Term Care Family Physicians. *Family Medicine Graduate Research Symposium, Montreal, Canada.*

13. **Andersen KM,** Filion KB, Kroger E, Champoux N, Wilchesky M. (May 2017). Alzheimer's treatment and the risk of serious events in a large population-based clinical database. *Family Medicine Graduate Research Symposium,* Montreal, Canada.

Poster Presentations

1. **Andersen KM,** Mehta HB, Palamuttam N, Ford D, Garibaldi BT, Auwaerter PG, Segal JB, Alexander GC (March 2021). Leveraging the Johns Hopkins COVID-19 Precision Medicine Center of Excellence to evaluate clinical outcomes among immunocompromised persons. *Transformative Technology in Engineering and Medicine.*
2. Olex AL, Madhira V, French E, Mannon R, Patel R, Levitt E, Islam JY, Franceschini N, Sun J, Wang L, O'Neil S, Bhattacharyya S, Indra A, **Andersen KM,** N3C Consortium. (November 2020). Assessing the Impact of COVID-19 on Immunocompromised Persons. *Fall Clinical and Translational Science Awards Program.*
3. **Andersen KM,** Ng DK, Blaha MJ, Segal JB, Alexander GC (September 2020). Longitudinal Changes Among Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitor (PCSK9i) Users in the United States. *International Conference on Pharmacoepidemiology & Therapeutic Risk Management.*
4. **Andersen KM,** Ng DK, Blaha MJ, Alexander GC, Segal JB (September 2020). Selection Bias Associated with Lab Records in Administrative Claims from the United States. *International Conference on Pharmacoepidemiology & Therapeutic Risk Management.*
5. Akenroye A, **Andersen KM,** Keet C, Segal JB, Alexander GC (September 2020). Seasonal Differences in Omalizumab Utilization Among Persons with Allergic Asthma in the United States. *International Conference on Pharmacoepidemiology & Therapeutic Risk Management.*
6. **Andersen KM,** Schieir O, Valois MF, Bartlett SJ, Bessette L, Boire G, Hazlewood G, Hitchon C, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk VP (February 2020). Does Concomitant Use of Multiple Steroid Routes in Early RA Facilitate Oral Steroid Discontinuation? Results from a Real-World Canadian Cohort. *Canadian Rheumatology Association.* Vancouver, Canada.
7. Ngo MD, Zummer M, **Andersen KM,** Richard N (February 2020). First Biologic Drug Persistence in Patients with Ankylosing Spondylitis Compared to Non-radiographic Axial Spondyloarthritis: A Canadian Assessment. *Canadian Rheumatology Association.* Vancouver, Canada.
8. **Andersen KM,** Schieir O, Valois MF, Bartlett SJ, Bessette L, Boire G, Hazlewood G, Hitchon C, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk VP (November 2019). Duration of Oral Corticosteroid Therapy Does Not Change With the Addition of a Parenteral Injection: Results from a Real-World Canadian Early RA Cohort. *American College of Rheumatology.* Atlanta, United States.
9. Basodan D, **Andersen KM,** Li X, Curtis JR, Alexander GC (November 2019). Utilization of Biologic Treatments in Oligoarticular and Polyarticular Juvenile Idiopathic Arthritis. *American College of Rheumatology.* Atlanta, United States.

10. Xi L, **Andersen KM,** Chang HY, Alexander GC, Curtis JR (November 2019). Comparative Risk of Serious Infections among Real-World Users of Biologics for Psoriasis or Psoriatic Arthritis: A Retrospective Cohort Study. *American College of Rheumatology.* Atlanta, United States.

11. **Andersen KM,** Basodan D, Li X, Alexander GC (August 2019). Trends in biologic utilization for the management of juvenile idiopathic arthritis (JIA) in the United States, 1997-2018. *International Conference on Pharmacoepidemiology and Therapeutic Risk Management.* Philadelphia, United States.

12. Li X, **Andersen KM,** Chang HY, Curtis JR, Alexander GC. Comparative risk of serious infections with interleukin-17, interleukin-12/23 and tumor necrosis factor-alpha inhibitors: a retrospective cohort study (April 2019). *Johns Hopkins Department of Epidemiology Master's Student Poster Session.* Baltimore, United States.

13. **Andersen KM,** Kelly A, Lyddiatt A, Bingham C.O. III, Bykerk V, March L, Shea B, Tugwell P, Brooks P, Simon LS, Christensen R, Bartlett SJ on behalf of OM Safety Working Group (February 2019). Inflammatory arthritis DMARD adverse effects are pervasive and can greatly impact QoL, work and social roles: initial results from the OMERACT Safety Working Group. *Canadian Rheumatology Association Annual Meeting.* Montreal, Canada.

14. **Andersen KM,** Kelly A, Lyddiatt A, Bingham C.O. III, Bykerk V, Cross M, Batterman A, Westreich J, Jones MK, March L, Shea B, Tugwell P, Brooks P, Simon LS, Christensen R, Bartlett SJ on behalf of OM Safety Working Group (October 2018). DMARD adverse effects among inflammatory arthritis patients are pervasive and can greatly impact quality of life and social roles: initial focus group results from the OMERACT Safety Working Group. *American College of Rheumatology Annual Meeting.* Chicago, United States.

15. Dunn M, Tissera H, **Andersen KM,** Doucet A, Fournier R (May 2018). Can an online patient information tool improve physician satisfaction and efficiency of medical visits? – A quantitative study. *Saint Mary's Hospital Resident Research Day, Montreal, Canada.*

16. Hecht E, Gao Y, **Andersen KM** (May 2018)**.** A systematic review of palliative care decisions in primary care. *Saint Mary's Hospital Resident Research Day, Montreal, Canada.*

17. Varlan I, Vezina N, Sprole D, **Andersen KM** (May 2018)**.** Laceration technique familiarity among family medicine residents. *Saint Mary's Hospital Resident Research Day, Montreal, Canada.*

18. Marrone E, Hebert P, Heckman G, Karanofsky M, Hirdes J, Morinville A, Nugus P, **Andersen KM**, Wilchesky M (April 2018). Designing a Pan-Canadian Survey to Evaluate the Clinical Information Needs of Geriatric Long-Term Care Physicians and Nurses. *2018 McGill Interprofessional Health Research Symposium*, Montreal, Canada.

19. Marrone E, Hebert P, Heckman G, Karanofsky M, Hirdes J, Morinville A, Nugus P, **Andersen KM**, Wilchesky M (April 2018). Clinical Information Needs in Geriatric Long-Term Care: Protocol of a Canadian National Assessment Study. *Canadian Geriatrics Society,* Montreal, Canada.

20. **Andersen KM,** Filion KB, Kroger E, Champoux N, Reynier P, and Wilchesky M (March 2018). Are new users of cholinesterase inhibitors and memantine different in terms of their characteristics? *Epidemiology, Biostatistics, and Occupational Health Departmental Research Day 2018,* Montreal, Canada.

21. Schieir O, Valois M-F, Bartlett SJ, **Andersen KM,** Hitchon CA, Pope JE, Boire G, Haraoui B, Tin D, Thorne C, Keystone EC, Bykerk VP. (February 2018). Time trends over a decade show earlier intensified medication strategies and improved outcomes in Canadians with early inflammatory arthritis. *Canadian Rheumatology Association Annual Meeting,* Vancouver, Canada.

22. **Andersen KM,** Filion KB, Kroger E, Champoux N, Wilchesky M. (November 2017). Primary care management of Alzheimer's disease and related disorders in the United Kingdom: a population-based retrospective cohort study of treatment initiation and tolerability patterns. *North American Primary Care Research Group Annual Meeting,* Montreal, Canada.

23. Bayard MF, Schieir O, Szymonikfa J, McNamara M, **Andersen KM,** Bykerk VP, Bartlett SJ. (June 2017). Exploring the Impact of Stiffness on Physical Function: An Analysis from an Early Arthritis Cohort. *European League Against Rheumatism,* Madrid, Spain.

24. Orange D, Agius P, Mirza S, McNamara M, Cummings R, Szymonika J, **Andersen KM,** Darnell R, Ivashkiv L, Figgie M, Pernis A, Gravallese EM, DiCarlo EF, Bykerk V, Goodman S, Donlin L. (June 2017). Identifying Rheumatoid Arthritis Subtypes Using Synovial Tissues Expression Profiling. *European League Against Rheumatism*, Madrid, Spain.

25. Reid RER, Carver TE, Reid TGR, Jirasek K, **Andersen KM,** Christou NV, Andersen RE FACSM. (June 2017). Effect of Employment Status on Physical Activity and Sedentary Behavior Long-Term Post-Bariatric Surgery. *American College of Sports Medicine*, Denver, United States.

26. Reid RER, Carver TE, **Andersen KM,** Christou NV, Delisle-Houde P, Insogna JA, Andersen RE. (March 2017). Differences in Physical Activity, Sedentary Time, and Weight Regain Across Follow-Up Periods after RYGB. *Congrès de L'Assocation Québécoise des Sciences de l'Activité Physique,* Sherbrooke, Canada.

27. Bartlett S, Schieir O, **Andersen KM,** Boire G, Haraoui B, Hitchon C, Keystone E, Pope J, Thorne C, Tin D, Bykerk V, CATCH Canadian Early Arthritis Cohort Investigators. (February 2017). Sex, Smoking and Excess Weight: Effects on DAS28 Trajectories in the First 2 Years in RA. *Canadian Rheumatology Association,* Ottawa, Canada.

28. **Andersen KM,** Cetin-Sahin D, Perretti M, Wilchesky M. (October 2016). Reducing antipsychotic use in Canadian long-term care facilities: Are medication reviews and interdisciplinary team involvement 2 keys to success?. *Canadian Association on Gerontology*, Montreal, Canada.

29. Bartlett SJ, Schieir O, **Andersen KM,** Boire G, Haraoui B, Hitchon C, Keystone EC, Pope JE, Thorne JC, Tin D, Bykerk BP and Canadian Early Arthritis Cohort (CATCH) Investigators. (October 2016). Smoking and Excess Weight Attenuate Rate of Improvement over First 3 Years in Early RA. *American College of Rheumatology,* Washington D.C., United States.

30. Orange D, Goodman SM, Agius P, Cummings R, **Andersen KM,** Darnell R, Ivashkiv L, Pernis AB, DiCarlo EF, Bykerk VP and Donlin LT. (October 2016). RA Flare after Total Hip and Total Knee Arthroplasty: Preliminary Outcomes at 1 Year. *American College of Rheumatology*, Washington D.C., United States.

31. **Andersen KM,** Schieir O, Lin D, Bartlett SJ, Boire G, Haraoui B, Hitchon C, Jamal S, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk VP. (June 2016). Is Early Steroid Use Associated with Remission at 6 months in Early RA? Results from the Canadian Early RA Cohort (CATCH). *European League Against Rheumatism,* London, England.

32. **Andersen KM,** Lin D, Bartlett SJ, Boire G, Haraoui B, Hitchon C, Jamal S, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk VP. (February 2016). Can oral and parenteral steroid in the first three months modify disease course in early RA? Results from the Canadian Early RA Cohort (CATCH). *Canadian Rheumatology Association Annual Meeting,* Lake Louise, Canada.

33. Bartlett SJ, Bingham CO, Schieir O, **Andersen KM,** Lin D, Boire G, Haraoui B, Hitchon C, Jamal S, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk VP. (February 2016). Self-management of RA flares varies by severity and duration: results from CATCH. *Canadian Rheumatology Association Annual Meeting*, Lake Louise, Canada.

34. **Andersen KM,** Lin D, Bartlett SJ, Boire G, Haraoui B, Hitchon C, Jamal S, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk VP. (October 2015). Characteristics and outcomes associated with early corticosteroid use in a large multicenter Canadian RA cohort. *American College of Rheumatology Annual Meeting*, San Francisco, United States.

35. Bartlett SJ, Bingham CO, Lin D, **Andersen KM,** Boire G, Hitchon C, Haraoui B, Keystone EC, Tin D, Thorne JC, Pope JE, Bykerk VP, CATCH Investigators, OMERACT Flare Group. (October 2015). Working harder to stay in control: Patient reports of flare in early RA are associated with higher disease activity and more intensive self-management. *American College of Rheumatology Annual Meeting,* San Francisco, United States.

36. Goodman SM, Friedlander R, Figgie C, Hoang A, **Andersen KM,** Pernis AB, Rozo CT, DiCarlo EF, Figgie MP, Donlin LT, Bykerk V. (October 2015). Flares occur frequently in RA patients undergoing arthroplasty. *American College of Rheumatology Annual Meeting,* San Francisco, United States.

37. Goodman SM, Friedlander R, Figgie C, Pernis AB, T. RC, Gravallese EM, DiCarlo EF, Donlin LT, Figgie MP, Khianey R, Hoang A, **Andersen KM,** Chowdhury L, Bykerk VP. (October 2015). Histologic scoring of arthroplasty synovial samples may predict RA flare. *American College of Rheumatology Annual Meeting*, San Francisco, United States.

38. Schulman E, **Andersen KM,** Zhang M, Goodman SM, Lin D, Boire G, Haraoui B, Hitchon C, Jamal S, Keystone EC, Pope JE, Tin D, Thorne JC, Bykerk V. (October 2015). High body mass index negatively impacts time to achieving sustained remission in early rheumatoid arthritis: Results from a multicenter early arthritis cohort study. *American College of Rheumatology Annual Meeting*, San Francisco, United States.

39. Goodman SM, Ma Y, Zhang W, Schulman E, Bartlett S, **Andersen KM,** Hitchon C, Boire G, Jamal S, Thorne C, Tin D, Keystone E, Haraoui B, Pope JE, Bykerk VP on behalf of the CATCH Investigators. (June 2015). Body Mass Index is an Independent Risk Factor for Not Achieving Sustained Remission in Early Rheumatoid Arthritis: Results from the CATCH Observational Study. *European League Against Rheumatism*, Rome, Italy.

40. Goodman SM, Ma Y, Zhang W, Schulman E, Bartlett S, **Andersen KM,** Hitchon C, Boire G, Jamal S, Thorne C, Tin D, Keystone E, Haraoui B, Pope JE, Bykerk VP and CATCH Investigators. (October 2014). High BMI Negatively Affects Patients' Ability to Achieve Sustained Remission in Early RA in a Multicenter Canadian Cohort. *American College of Rhuematology Annual Meeting, Boston, United States.*

41. **Andersen KM,** Carver TE, Reid R, Andersen RE. (June 2014). Self-Reported vs. Objectively Measured Physical Activity and Sedentary Behavior in Former Bariatric Surgery Patients. *American College of Sports Medicine Annual Meeting*, Orlando, United States.

42. Feder J, Carver TE, **Andersen KM,** Lemke H, Andersen RE. (June 2014). The Effects of Physical Activity Levels On Bone Mineral Density After Bariatric Surgery. *American College of Sports Medicine Annual Meeting*, Orlando, United States.