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MAJOR ARTICLE

Pre-existing autoimmunity is associated with increased severity of COVID-19: A retrospective cohort study using data from the National COVID Cohort Collaborative (N3C)

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Background*:* Identifying individuals with a higher risk of developing severe COVID-19 outcomes will inform targeted or more intensive clinical monitoring and management. To date, there is mixed evidence regarding the impact of pre-existing autoimmune disease (AID) diagnosis and/or immunosuppressant (IS) exposure on developing severe COVID-19 outcomes.

Methods: A retrospective cohort of adults diagnosed with COVID-19 was created in the National COVID Cohort Collaborative enclave. Two outcomes, life-threatening disease, and hospitalization were evaluated by using logistic regression models with and without adjustment for demographics and comorbidities.

Results: Of the 2,453,799 adults diagnosed with COVID-19, 191,520 (7.81%) had a pre-existing AID diagnosis and 278,095 (11.33%) had a pre-existing IS exposure. Logistic regression models adjusted for demographics and comorbidities demonstrated that individuals with a pre-existing AID (OR = 1.13, 95% CI 1.09 - 1.17; *P*< 0.001), IS (OR= 1.27, 95% CI 1.24 - 1.30; *P*< 0.001), or both (OR = 1.35, 95% CI 1.29 - 1.40; *P*< 0.001) were more likely to have a life-threatening COVID-19 disease. These results were consistent when evaluating hospitalization. A sensitivity analysis evaluating specific IS revealed that TNF inhibitors were protective against life-

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threatening disease (OR = 0.80, 95% CI 0.66- 0.96; *P*=0.017) and hospitalization (OR = 0.80, 95% CI 0.73 - 0.89; *P*< 0.001).

Conclusions: Patients with pre-existing AID, exposure to IS, or both are more likely to have a life-threatening disease or hospitalization. These patients may thus require tailored monitoring and preventative measures to minimize negative consequences of COVID-19.

Keywords: retrospective analysis; COVID-19; Severe COVID-19; Autoimmunity; Immunosuppressants; TNF inhibitors; Autoimmune disease; N3C cohort

INTRODUCTION

The coronavirus disease of 2019 (COVID-19) pandemic has affected more than 664 million individuals and caused more than 6.7 million deaths worldwide, as of January 10th, 2023[1]. The public health burden and magnitude of the pandemic underlie the importance of identifying patients at elevated risk of developing severe disease to inform targeted clinical monitoring and management. CDC guidelines provide a list of medical conditions, including, but not limited to, cancer, chronic kidney/liver/lung diseases and diabetes, that increase the risk of worse outcomes from COVID-19[2]. With the notable exception of type I diabetes, autoimmune diseases (AID) are excluded from this list. This is counter-intuitive, since these are common diseases (24 million people suffer from AID in the United States alone[3]), are typically life-long and incurable and are often treated with immunosuppressive drugs (IS), which could theoretically modify immunological responses to the SARS-CoV-2 virus. Therefore, it is important to directly evaluate, on a population-scale, the impact of AID and IS on severity outcomes of COVID-19 to help inform healthcare guidelines and raise awareness for patients with AID so they can appropriately protect themselves from severe outcomes of COVID-19.

To date, there is mixed evidence regarding the association between AID and severity outcomes of COVID-19. For example, SARS-CoV-2-infected patients with rheumatic and musculoskeletal diseases were reported to have a higher risk of developing COVID-19 and of having hospitalization and severe COVID-19, including requiring ICU admission and mechanical ventilation[4]. Another recent study observed a higher risk of respiratory failure among patients with rheumatic disease with COVID-19[5–7]. In contrast, a retrospective study of patients with AID hospitalized with COVID-19 did not show increased risk of ICU admission, intubation, or death[8]. Another meta-analysis of observational and case-control studies, constrained to limited demographics (age, gender) and marked by considerable heterogeneity across studies, reported a high prevalence of COVID-19 in patients with AID, yet similar hospitalization and mortality rates of these patients compared to those without AID[9]. These studies are limited by relatively small sample size, limited number of AID evaluated, inadequate representative population sampling, and/or failure to adjust for key confounders and known risk factors. Thus, whether

AID are significant risk factors for worse outcomes from COVID-19 in larger cohorts that include a broad demographic and across the gamut of AID remains unknown.

An additional important confounder is whether IS also contribute to adverse outcomes from COVID-19. A recent study showed that solid-organ transplantation patients exposed to chronic immunosuppression and later diagnosed with COVID-19 have overall more severe disease[10]. Further, patients treated with IS for cancer and solid-organ transplantation may be at higher risk of severe COVID-19 outcomes, although patients with other AID may not be[11]. Another study concluded that individuals on long term IS have worse outcomes when hospitalized with COVID-19 compared to those not on these medications[12]. Immunosuppression may thus be as relevant to COVID-19 outcomes as the underlying diseases. A meta-analysis study demonstrated that exposure to glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), or the combination of biologic or targeted synthetic DMARDs (b/tsDMARDS) and csDMARDS was associated with severe COVID-19 while b/tsDMARDs monotherapy (e.g., anti-TNF monotherapy) was associated with less severe COVID-19[9]. These findings imply that some forms of IS for AID could be protective against COVID-19. Indeed, some clinical data suggest that prior treatment with TNF inhibitors may protect patients with psoriasis, at least compared with other forms of therapy[13]. Similarly, treatment with IL-1, IL-6, and JAK inhibitors are beneficial in patients with more severe COVID-19, and emerging data from the Accelerating COVID-19 Therapeutic Interventions and Vaccines study (ACTIV-1)[14] also suggest that anti-TNF therapy and abatacept may be beneficial in this context. Thus, a large-scale evaluation of IS in the context of AID to differentiate those that are protective from those that are harmful could help refine healthcare guidelines for patients using these medications.

To definitively establish whether individuals with AID or those treated with IS experience worse severity outcomes from COVID-19, we leveraged data from the N3C enclave, which harmonizes and holds electronic health records (EHRs) from 75 health systems with 15,231,849 million individuals' data throughout the US, of which 5,858,748 have had COVID-19[15,16]. N3C represents the largest retrospective US cohort of SARS-CoV-2 patients. We hypothesized that patients with a prior diagnosis of an AID and/or exposure to IS are more likely to have worse COVID-19 outcomes (manifesting life-threatening disease or hospitalization). To address this hypothesis, we leveraged logistic regression models and conducted sensitivity analyses to ensure results were robust to vaccination status and antiviral treatment, to different race and gender groups, and to identify whether TNF inhibitors were protective against worse disease outcomes.

METHODS

Cohort definition

The N3C enclave[17] release version V90 from Limited DataSets data (N=15,231,849 patients), including individuals entered at or before August 25th 2022 was used. We selected a subset of

2,453,799 patients that had a laboratory confirmed positive COVID-19 diagnosis based on a positive SARS-CoV-2 polymerase chain reaction (PCR) or antigen (Ag) test between January 1st 2020 and June 30th 2022 inclusive (**Figure 1**). We excluded patients with age missing or <=18, missing gender, with <1 encounter visit before or <1 encounter visit after COVID-19 diagnosis date, and patients from sites with data that did not meet quality check criteria.

Comorbidities, drug exposures, and other clinical information of patients diagnosed with COVID-19 are reported in N3C as far back as January 1st 2018[12,18]. Binarized comorbidities (**Supplementary Table 1**) were considered pre-existing if their diagnosis date preceded that of COVID-19 .

Severity outcomes

COVID-19 severity outcomes in N3C are based on the Clinical Progression Scale established by WHO[15,19]. Unaffected (WHO severity 0) patients were removed. Severity of remaining patients was classified as mild (WHO severity 1-3), mild_ED (WHO severity 3), moderate (WHO severity 4-6, hospitalized patients without invasive ventilation), severe (WHO severity 7-9, hospitalized patients with invasive ventilation or extracorporeal membrane oxygenation), mortality or hospice (WHO severity 10). We further categorized binary severity outcomes as follows: 1) life-threatening disease (Deceased/Severe vs. Moderate/Mild_ED/Mild); 2) hospitalization (Dead/Severe/Moderate vs. Mild/Mild_ED).

Definition of pre-existing AID and IS exposure

A curated list of 106 AID based on two previously published lists[20,21] was used to identify COVID-19 patients with or without AID within N3C (**Supplementary Table 2 for variable coding details and Supplementary Figure 1A**). For defining IS exposure, previously published fifteen drug classes representing 303 different drugs[12] (**Supplementary Figure 1B**) were considered. Of note, the computable phenotypes used in this manuscript differ from what has been previously published from this database as it was developed by the authors rather than the Immunosuppressed/Compromised Clinical Domain team.

A sub-analysis of AID patients with and without prior exposure to TNF inhibitors included those exposed to Etanercept, Infliximab, Afelimomab, Adalimumab, certolizumab pegol, Golimumab, or Opinercept.

Definition of vaccination status and anti-viral usage

We defined a sub-cohort of patients diagnosed with COVID-19 between December 23rd, 2021, and June 30th 2022 to enable adjusting models for vaccination status and exposure to antivirals. This time frame was selected because oral antiviral therapy became available through the FDA Emergency Use Authorization mechanism in late December 2021. Only sites with vaccination rates reasonably matching CDC records for that site's geographic region were included. Patients

were considered vaccinated if they had at least one vaccination administered prior to COVID-19 diagnosis date. Patients exposed to antivirals were treated with at least one dose of any oral antiviral (Paxlovid (Nirmatrelvir/ritonavir), LAGEVRIO (molnupiravir)) or one monoclonal antibody (bebtelovimab) for COVID-19 between the first COVID-19 diagnosis date and up to 10 days before/thereafter.

Statistical analysis

Statistical modeling (**Supplementary Figure 2**) was conducted within the N3C enclave using SQL, Python(3.6.7), statsmodels (version 0.12.2), Patsy (version 0.5.2), and scipy(1.6.2). Statistical significance was defined for p-values < 0.05 and 95% confidence intervals around the estimated odd ratios are reported. The baseline characteristic table 1 was created by using the tableone python package[22].

RESULTS

Cohort description

We defined a large cohort within the N3C data enclave[17] to evaluate the impact of prior AID diagnosis and exposure to IS on COVID-19 severity outcomes (**Figure 1** and **Supplementary Figure 1A**). Of 15,231,849 individuals, 2,453,799 patients were diagnosed with COVID-19, as indicated by a positive RT-PCR or antigen test between Jan 1st, 2020 and June 30th 2022 inclusive. Among these 2,453,799 patients, 220,353 (9%) were hospitalized and 54,932 (2.2%) had life-threatening disease (**Table 1**). Patients were further categorized as those with a pre-existing (prior to COVID-19 diagnosis) AID (N=191,520 patients), exposure to IS (N=278,095 patients), or both (N=56,813) (**Figure 1; Supplementary Figure 1A & Figure 1B**).

The top 3 most abundant AID are rheumatoid arthritis (N=27,664), psoriasis (N=25,749), and Type I diabetes mellitus (N=24,443) (**Figure 2A**). The top three most frequent IS drugs that patients were exposed to were glucocorticoids, other antineoplastic agents, and calcineurin inhibitors. (**Figure 2B**). Most patients with COVID-19 have a single pre-existing AID diagnosis (159,770) and exposure to a single IS (n=237,238 patients, representing 85.31% of patients with IS exposure) (**Figure 2C**). Lastly, we note that the most frequent conditions and IS drugs showed a larger proportion of patients with life-threatening conditions or hospitalization (**Supplementary Figure 3**).

Association between prior exposure to AID, IS, or both (AID-IS) with COVID-19 severity outcomes.

Two binary (presence/absence) clinically relevant COVID-19 severity outcomes were defined: life-threatening disease and hospitalization (**see Methods**). We tested whether a pre-existing diagnosis of AID, exposure to IS, or both were associated with these outcomes using univariate

and multivariate models adjusted for demographics (**Supplementary Table 3**). In our final analyses (**Table 2**), the model was adjusted for demographics and pre-existing comorbidities and show that patients were almost 21% more likely to be hospitalized if they had pre-existing AID (OR = 1.21, 95% CI 1.19 - 1.24, $P < 0.001$), 19% more likely if they had prior exposure to IS (OR = 1.19, 95% CI 1.17 - 1.21, $P < 0.001$), or 31% more likely if they had both (OR = 1.31, 95% CI 1.28 - 1.34, $P < 0.001$). Similarly, when adjusting for demographics and comorbidities, patients were 13% more likely to develop life-threatening COVID-19 if they had pre-existing AID (OR = 1.13, 95% CI 1.10 - 1.17, $P < 0.001$), 27% more likely if they had prior exposure to IS (OR = 1.27, 95% CI 1.24 - 1.30, $P < 0.001$), or 35% more likely if they had both (OR = 1.35, 95% CI 1.29 - 1.40, $P < 0.001$) (**Table 2**). Similar results were obtained when stratifying by race and gender for both COVID-19 outcomes (**Supplementary Table 4 & Table 5**).

Association between AID, IS, or both with COVID-19 severity outcomes in a cohort subset adjusting for COVID-19 vaccination and antiviral exposure

The FDA has authorized antiviral medications and monoclonal antibodies to treat mild to moderate COVID-19 in outpatients diagnosed with COVID-19 who were prone to have severe disease manifestations. We specifically considered two small molecule antivirals (Paxlovid(Nirmatrelvir/ritonavir), Lagevrio(molnupiravir), and one monoclonal antibody Bebtelovimab) that was granted emergency use authorization by the FDA on or after December 2021 (the beginning of the Omicron epoch). Although bebtelovimab has since lost activity against the most recent dominant Omicron variants in the United States (BQ.1,BQ.1.1, and XBB), it was active against prior common US Omicron variants during the period of this study. Of the 248,743 patients diagnosed with COVID-19 between December 23rd, 2021 to June 30th 2022, 134,812 (54.2%) were vaccinated and 3,974 (1.6%) exposed to antivirals (see **Methods, Supplementary Figure 1C**). As expected, when adjusting for demographics and comorbidities, we found that usage of antivirals was protective (life-threatening disease (OR = 0.31, 95% CI 0.21-0.45; $P < 0.001$) and hospitalization (OR = 0.30, 95% CI 0.25-0.36; $P < 0.001$) (**Supplementary Table 6**). Most importantly, independent of exposure to antivirals and vaccination status, patients with pre-existing AID (OR = 1.34, 95% CI 1.25 - 1.43, $P < 0.001$), IS exposure (OR = 1.61, 95% CI 1.51 - 1.72, $P < 0.001$), or both (OR = 1.90, 95% CI 1.73 - 2.10, $P < 0.001$) were more likely to be hospitalized. Similarly, patients with pre-existing AID (OR = 1.18, 95% CI 1.02 - 1.36, $P < 0.001$), prior IS exposure (OR = 1.60, 95% CI 1.42 - 1.81, $P < 0.001$), or both (OR= 1.94, 95% CI 1.63 - 2.30, $P < 0.001$) are more likely to have life-threatening disease, independent of exposure to antivirals and vaccination (**Supplementary Table 6**). We confirmed that associations of AID and/or IS exposure and worse COVID-19 outcomes were consistent in a sub-cohort comprising patients identified prior to vaccination roll-out **(Supplementary Table 7 and 8)**

Association between TNF inhibitors and other IS with COVID-19 severity outcomes in AID patients

In view of prior data suggesting that TNF inhibitors may be protective against COVID-19[13], we investigated the association of exposure to TNF inhibitors prior to COVID-19 diagnosis with COVID-19 severity outcomes in patients with a prior AID diagnosis. Of the 191,520 patients with a pre-existing AID diagnosis, 4,789 were exposed to TNF inhibitors at least 14 days prior to COVID-19 diagnosis. When adjusting for demographics and comorbidities, we found that exposure to TNF inhibitors protected against severe COVID-19 outcomes (OR of life-threatening disease 0.80, 95% CI 0.66-0.96, $P = 0.017$), and hospitalization (OR = 0.80, 95% CI 0.73-0.89, $P < 0.001$) (**Table 3**). While other IS were individually evaluated, only TNF inhibitors showed this protective effect.

DISCUSSION

Using N3C, we identified 2,453,799 patients diagnosed with PCR or antigen testing-confirmed COVID-19, of whom 191,520 had a prior diagnosis of AID, 278,095 had a prior IS exposure, and 56,813 had both. Our cohort comprises data from the beginning of the pandemic to June 30th 2022, which includes epochs spanning the ancestral strain as well as five major variants (Alpha, Beta, Gamma, Delta, and Omicron). This cohort thus appropriately represents a broad population of patients diagnosed with COVID-19 and AID in the US over time.

We found that COVID-19 patients with a prior diagnosis of AID, exposure to IS, or both are more likely to have life-threatening disease or be hospitalized. These results were robust to adjustments for demographics and comorbidities. Further, a sensitivity analysis in a subset of our cohort confirmed that AID and/or IS are risk factors of worse COVID-19, independent of exposure to antiviral treatments and/or had at least one COVID-19 vaccination dose. We note that our observed protective effect of vaccination against worse outcomes may be underestimated given our inclusion criteria of a single vaccination dose. Nonetheless, our results help clarify the ambiguity in previous studies in answering the difficult question of whether prior AID diagnosis or exposure to IS are risk factors for worse COVID-19 disease outcomes.

Race and gender are known to be associated with COVID-19 severity. For example, Asian American individuals have a higher risk of COVID-19 positivity and ICU admission than White individuals[23,24], and socioeconomic disparity and clinical care quality are associated with COVID-19 mortality and incidence in racial and ethnic minority groups[24]. Further, severity and mortality of COVID-19 are higher in males than in females[25,26]. Our results confirmed that effects of AID, IS, or both on COVID-19 severity outcomes were significant across the different race and gender groups.

Finally, we clarified whether some specific IS showed contrary effects. Indeed, a recent study suggested TNF inhibitor monotherapy was associated with a lower risk of adverse COVID-19 outcomes compared to other commonly prescribed immunotherapy among patients with AID[27]. Here, we confirm that patients with a prior AID diagnosis and exposed to TNF inhibitors prior to infection are less likely to be hospitalized or have life-threatening COVID-19. We also confirm that this protective effect is unique to TNF inhibitors .

There are limitations to this study worth noting. First, the medical history of COVID-19 patients is limited to January 1, 2018 or later, with some patients having limited interaction with participating health care systems prior to their index diagnosis, making it difficult to fully assess pre-existing conditions and comorbidities and to precisely determine the diagnosis date of AID. To mitigate these risks, patients with at least one encounter visit before diagnosis were included to increase the robustness of past medical history documentation. Second, N3C data are aggregated from many health care systems, covering four common data models that vary in granularity. Harmonization of these disparate data thus requires assumptions and inferences to be made that could incur systematic biases. Similarly, the ability to accurately determine race within N3C is diminished by variations in how race is reported in different healthcare systems[28]. Nonetheless, we highlight the meticulous efforts from the N3C collaborative in evaluating and improving the quality of phenotypes generated within[29,] N3C. Third, missingness is a known issue with vaccination data, as patients may receive vaccine doses at pop-up clinics, drugstores, or at their place of employment, which may not be recorded in the patient's records. To counteract this missingness, we only included sites whose rate of vaccination in N3C data was within range of the CDC vaccination rate for that site's geographic region[30]. Finally, we recognize limitations related to the retrospective design of this study, inability to handle all possible confounders, including biases in standard of care across hospitals and physician behavior, and the possibility that follow-up data among patients could be incomplete (e.g. patients seeking care in institutions not affiliated with N3C). Despite these limitations, this study is an important step toward increasing our understanding, at a population level, of whether prior exposure to AID, IS, or both pose an additional risk to patients in developing worse COVID-19 disease outcomes.

CONCLUSIONS

To the best of our knowledge, this study represents the largest, most comprehensive systematic analysis of the effects of AID, IS, or both on COVID-19 severity outcomes. Our study suggests that patients with a prior AID diagnosis, prior exposure to IS or both have a higher risk of life-threatening COVID-19 disease or hospitalization. These associations were consistent in different race and gender subsets. Importantly, this study provides a more definitive answer to previous discrepant findings on whether patients with AID and/or IS are at higher risk for worse COVID-

19 related outcomes, providing clinicians with helpful data that may help guide their treatment and monitoring plans.

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Source code: See https://github.com/arjunyadaw/N3C-Autoimmune-Disease-model.git.

Author Contributions: Concept and design: ASY, BA, DS, EAM

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: ASY and EAM

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FIGURE LEGENDS:

Figure 1: Workflow to define the AID cohort within N3C. A total of 15,231,849 patients were identified in the N3C enclave release version V90. Of these, 2,453,799 were COVID-19 positive between 2020-01-01 to 2022-06-30, as confirmed by a RT-PCR or Antigen test, and had non-missing values for '"age"' and "gender". Patients were grouped based on whether they were diagnosed with an AID or exposed to IS prior to COVID-19. See Methods for further details on inclusion/exclusion criteria.

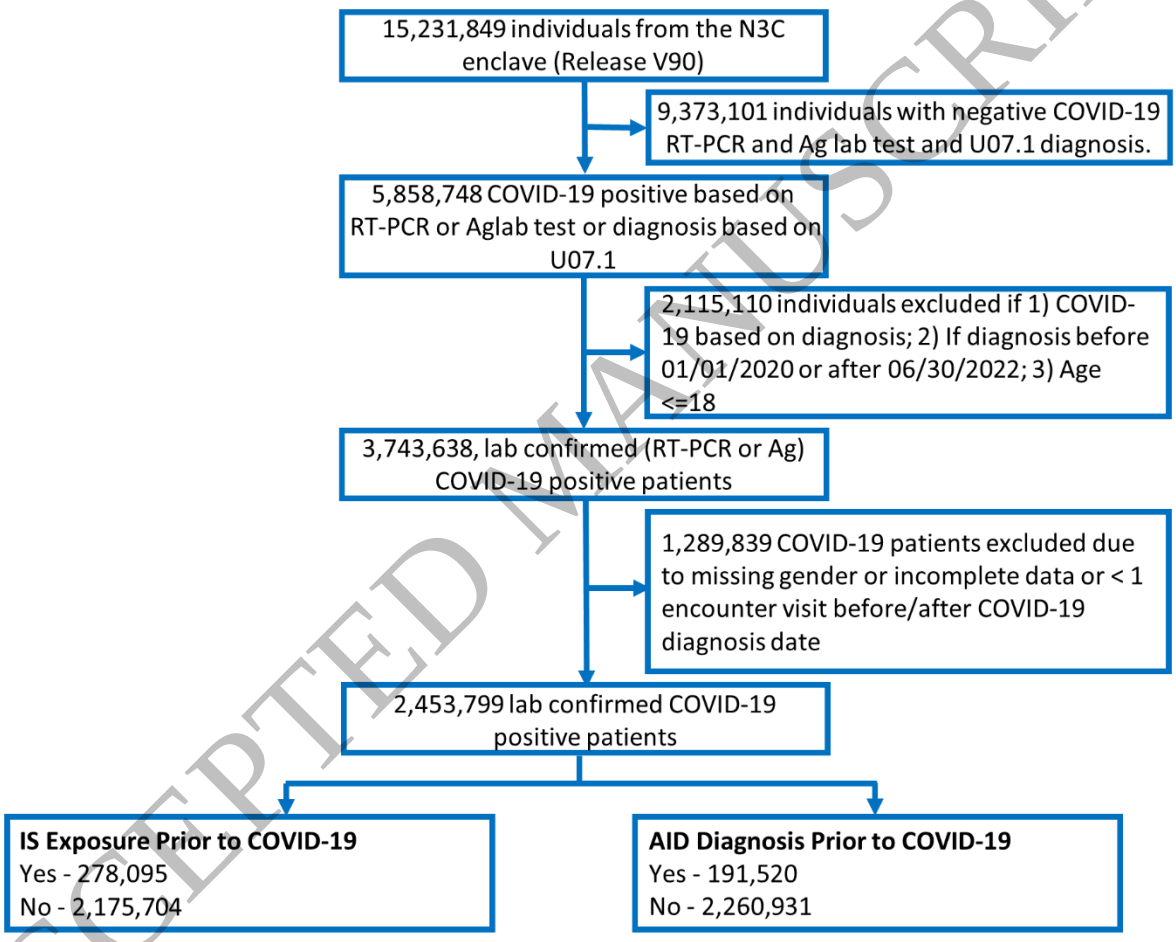
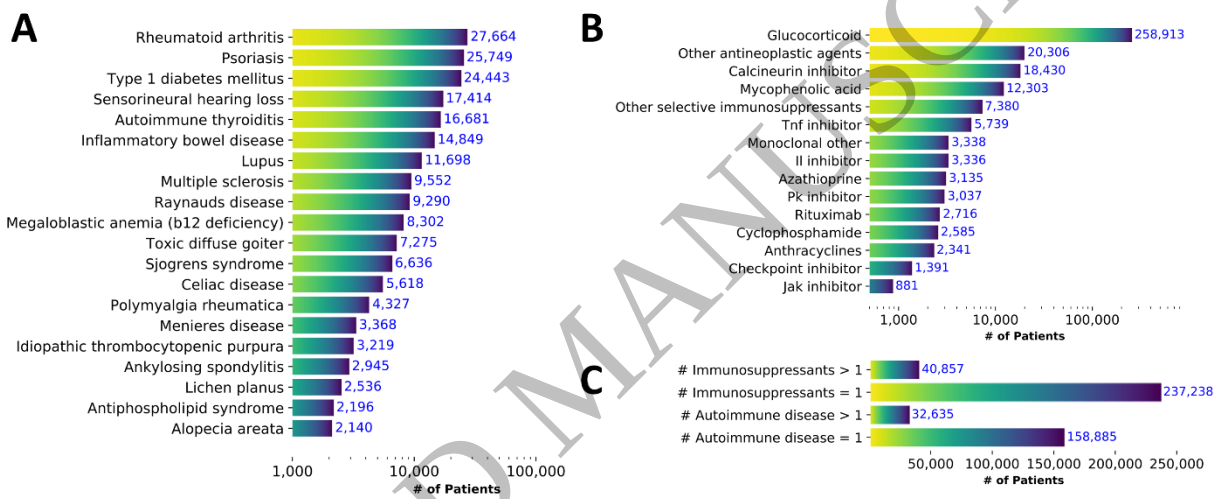


Figure 2: Description of Cohort Exposures. Top 20 most abundant AID (A) and immunosuppressant exposures (B) prior to COVID-19 diagnosis of lab confirmed COVID-19 patients. “L04 other” include “Selective immunosuppressants” that were not IL inhibitors, JK inhibitors, TNF alpha inhibitors or monoclonal antibodies. “L01 other” includes “Other cancer therapies” not anthracyclines, checkpoint inhibitors, cyclophosphamide, or protein kinase inhibitors. “other antineoplastic agents” includes mAbs, Cancer Drugs L01 Other Cancer Therapies defined using WHO Anatomical Therapeutic Chemistry Class L01 products that were not anthracyclines, checkpoint inhibitors, cyclophosphamide, or protein kinase inhibitors. (C) Number of patients with single/multiple AIDs and patients single/multiple immunosuppressants exposure



Pre-existing autoimmunity is a risk factor for more severe COVID-19

Yadaw et al., 2023 | *Clinical Infectious Diseases*

National COVID Cohort Collaborative

Goal: Directly evaluate impact of autoimmunity and immunosuppressive drugs on COVID-19 severity to help inform healthcare guidelines and raise awareness for patients at risk

Retrospective Cohort

2,453,799 adults with COVID-19
- **191,151** had preexisting autoimmune disease (AID)
- **278,095** had prior exposure to immunosuppressants (IS)
- **54,932** had both preexisting AID and IS

Model adjusted for demographics, comorbidities (1/1/2020 - 6/30/2022)	Life-threatening condition	Hospitalized condition
AID only	1.13 (1.09 - 1.17)	1.21 (1.19 - 1.24)
IS only	1.27 (1.24 - 1.30)	1.19 (1.17 - 1.21)
AID + IS	1.35 (1.29 -1.40)	1.31 (1.28 - 1.34)
Model adjusted for vaccine status/antivirals (12/23/2021- 6/30/2022)		
AID only	1.18 (1.02 - 1.36)	1.34 (1.25 - 1.43)
IS only	1.60 (1.42 - 1.81)	1.61 (1.51 - 1.72)
AID + IS	1.94 (1.63 - 2.30)	1.90 (1.73 - 2.10)
Vaccination	0.72 (0.70 - 0.75)	0.69 (0.68 - 0.70)
Antivirals	0.31 (0.21 - 0.45)	0.30 (0.25 - 0.36)
TNF inhibitors are protective for AID patients		
TNF inhibitor	0.80 (0.66 - 0.96)	0.80 (0.73 - 0.89)

Outcomes

Adults with pre-existing AID, IS exposure, or both are more likely to have worse disease outcomes.

Results are consistent when taking vaccination status and antiviral treatments into account.

COVID-19 vaccination, antiviral treatments, and TNF inhibitor therapy were protective.

Conclusion: Patients with pre-existing AID, exposure to IS, or both are more likely to be hospitalized or have life-threatening disease after COVID-19 infection. These patients may thus require closer monitoring and preventative measures to minimize negative consequences of COVID-19.

Graphical Abstract

Table 1: Characteristics of COVID-19 positive patients with and without autoimmune diseases (AID)/Immunosuppressants (IS) usage. Distribution of all covariables differ between patients with/without AID and with/without IS (all two-tailed Student's t-test for continuous variables and Chi-square test for categorical variables p-values <0.001).

	Overall N3C sample (n = 2,453,799)	**Patients without AID prior COVID-19 (n = 2,262,279)**	**Patients with AID prior to COVID-19 (n = 191,520)**	**Patients without IS prior COVID-19 (n = 2,175,704)**	**Patients with IS prior to COVID-19 (n = 278,095)**
COVID-19 severity					
Life threatening, n(%)	54932 (2.2)	46335 (2.0)	8597 (4.5)	41212 (1.9)	13720 (4.9)
Hospitalized, n(%)	220353 (9.0)	189519 (8.4)	30834 (16.1)	174587 (8.0)	45766 (16.5)
Demographic					
Age (years), mean (SD)	47.4 (18.0)	46.9 (18.0)	53.8 (17.2)	46.8 (18.0)	52.3 (17.4)
BMI (kg/m^2), mean (SD)	32.3 (8.4)	32.2 (8.3)	32.9 (8.6)	31.8 (8.2)	33.9 (9.0)
Gender, n(%)					
Female	1454673 (59.3)	1323247 (58.5)	131426 (68.6)	1281335 (58.9)	173338 (62.3)
Male	999126 (40.7)	939032 (41.5)	60094 (31.4)	894369 (41.1)	104757 (37.7)
Race, n(%)					
Black or African American	342511 (14.0)	316416 (14.0)	26095 (13.6)	295376 (13.6)	47135 (16.9)
White	1790481 (73.0)	1644325 (72.7)	146156 (76.3)	1590559 (73.1)	199922 (71.9)
Asian	61597 (2.5)	57870 (2.6)	3727 (1.9)	56531 (2.6)	5066 (1.8)
Missing/Unknown/Other	255270 (10.4)	239977 (10.6)	15293 (8.0)	229739 (10.6)	25531 (9.2)

Ethinicity, n(%)					
Hispanic or Latino	269354 (11.0)	252829 (11.2)	16525 (8.6)	244580 (11.2)	24774 (8.9)
Not hispanic or Latino	1966475 (80.1)	1805569 (79.8)	160906 (84.0)	1739697 (80.0)	226778 (81.5)
Missing/Unknown	217970 (8.9)	203881 (9.0)	14089 (7.4)	191427 (8.8)	26543 (9.5)
Smoking status, n(%)					
Non-smoker	2173346 (88.6)	2014857 (89.1)	158489 (82.8)	1959001 (90.0)	214345 (77.1)
Current or former smoker	280453 (11.4)	247422 (10.9)	33031 (17.2)	216703 (10.0)	63750 (22.9)
Comorbidities					
Cardiovascular disease, n(%)	296990 (12.1)	237822 (10.5)	54154 (28.3)	216891 (10.0)	80099 (28.8)
Dementia, n(%)	32023 (1.3)	26950 (1.2)	5073 (2.6)	25810 (1.2)	6213 (2.2)
Chronic pulmonary disease, n(%)	333222 (13.6)	281063 (12.4)	52159 (27.2)	242727 (11.2)	90495 (32.5)
Liver mild, n(%)	113751 (4.6)	91069 (4.0)	22682 (11.8)	79800 (3.7)	33951 (12.2)
Liversevere, n(%)	13463 (0.5)	9817 (0.4)	3646 (1.9)	8378 (0.4)	5085 (1.8)
Type 2 diabetes, n(%)	308690 (12.6)	255620 (11.3)	53070 (27.7)	242472 (11.1)	66218 (23.8)
Kidney, n(%)	138958 (5.7)	108921 (4.8)	30037 (15.7)	97804 (4.5)	41154 (14.8)
Cancer, n(%)	137706 (5.6)	115144 (5.1)	22562 (11.8)	95543 (4.4)	42163 (15.2)
MetS, n(%)	22737 (0.9)	19051 (0.8)	3686 (1.9)	12304 (0.6)	10433 (3.8)
HIV, n(%)	10959 (0.4)	9882 (0.4)	1077 (0.6)	8625 (0.4)	2334 (0.8)

Abbreviations: AID, autoimmune disease; IS, Immunosuppressants; BMI, body mass index ; MetS, Metastatic cancer; HIV, Human Immunodeficiency virus; Cardiovascular disease (Myocardial infarction or Congestive heart

failure or Peripheral vascular disease or Stroke); Life-threatening (Death, ECMO or mechanical ventilation) vs (Moderate or Mild_ED or Mild); Hospitalized: (Death, ECMO or mechanical ventilation or Moderate) vs (Mild_ED or Mild).

Table 2: Multivariate logistic regression model of severity outcomes adjusted for demographics and comorbidities (January 1, 2020, to June 30, 2022, n = 2,453,799)

	Life-threatening condition (Yes: 54,932, No: 2,398,867) OR (95% CI)	***P* value**	**Hospitalized condition (Yes: 220,353, No: 2,233,446) OR (95% CI)**	***P* value**
AID/Immunosuppressants (IS) status				
AID only	1.13 (1.09 - 1.17)	<0.001	1.21 (1.19 - 1.24)	<0.001
IS only	1.27 (1.24 - 1.30)	<0.001	1.19 (1.17 - 1.21)	<0.001
AID + IS only	1.35 (1.29 -1.40)	<0.001	1.31 (1.28 - 1.34)	<0.001
Demographics				
Age	2.84 (2.81 - 2.88)	<0.001	1.94 (1.93 - 1.95)	<0.001
BMI	1.08 (1.07 - 1.09)	<0.001	1.10 (1.09 - 1.11)	<0.001
Gender				
Female	1 [Reference]		1 [Reference]	
Male	1.51 (1.48 - 1.53)	<0.001	1.29 (1.28 - 1.30)	<0.001
Race				
White	1 [Reference]		1 [Reference]	
Others/unknown	1.20 (1.16 - 1.25)	<0.001	1.18 (1.16 - 1.20)	<0.001
Black or African American	1.37 (1.33 - 1.40)	<0.001	1.77 (1.75 - 1.80)	<0.001
Race asian	1.32 (1.24 - 1.40)	<0.001	1.35 (1.31 - 1.40)	<0.001
Ethnicity				
Not Hispanic or Latino	1 [Reference]		1 [Reference]	
Hispanic or Latino	1.18 (1.13 - 1.22)	<0.001	1.39 (1.36 - 1.41)	<0.001

Smoking status				
Nonsmoker	1 [Reference]		1 [Reference]	
Current or Former	1.37 (1.34 - 1.40)	<0.001	1.61 (1.59 - 1.63)	<0.001
Comorbidities				
Cardiovascular disease	1.69 (1.66 - 1.73)	<0.001	1.67 (1.65 - 1.69)	<0.001
Dementia	2.22 (2.16 - 2.30)	<0.001	1.99 (1.94 - 2.04)	<0.001
Chronic pulmonary disease	1.23 (1.21 - 1.26)	<0.001	1.29 (1.27 - 1.30)	<0.001
Liver mild	1.34 (1.30 - 1.38)	<0.001	1.25 (1.22 - 1.27)	<0.001
Liver severe	3.05 (2.89 - 3.23)	<0.001	2.33 (2.23 - 2.42)	<0.001
Kidney disease	1.77 (1.73 - 1.81)	<0.001	1.88 (1.86 - 1.91)	<0.001
Cancer	1.45 (1.41 - 1.49)	<0.001	1.24 (1.22 - 1.26)	<0.001
Metastatic cancer	3.31 (3.17 - 3.46)	<0.001	2.19 (2.12 – 2.26)	<0.001
Type 2 Diabetes Mellitus	1.32 (1.29 - 1.35)	<0.001	1.46 (1.44 - 1.48)	<0.001
HIV	1.24 (1.12 - 1.38)	<0.001	1.26 (1.19 - 1.33)	<0.001

Demographic factors include age, BMI, gender, race, ethnicity, smoking status.
Comorbidities include cardiovascular disease (MI + CHF + PVD + stroke), dementia, pulmonary disease, liver disease (mild and severe), Type 2 diabetes, kidney disease, cancer (metastatic and non-metastatic), and HIV infection.

Table 3: Logistic Regression of severity outcomes in AID patients only with each IS exposure evaluated individually.

	Life-threatening condition (Yes: 8,597, No: 182,923) OR (95% CI)	***P* value**	**Hospitalized condition (Yes: 30,834, No: 160,686) OR (95% CI)**	***P* value**
Demographics				
Age	2.09 (2.02- 2.16)	<0.001	1.55 (1.53 - 1.58)	<0.001
BMI	1.04 (1.03 - 1.06)	<0.001	1.06 (1.05 - 1.07)	<0.001

Gender				
Female	1 [Reference]		1 [Reference]	
Male	1.36 (1.30- 1.42)	<0.001	1.29 (1.26 - 1.33)	<0.001
Race				
White	1 [Reference]		1 [Reference]	
Others/unknown	1.13 (1.02- 1.25)	0.02	1.15 (1.09 - 1.22)	<0.001
Black or African American	1.25 (1.17- 1.34)	<0.001	1.63 (1.57 - 1.68)	<0.001
Race asian	1.26 (1.06- 1.50)	0.01	1.13 (1.03 - 1.25)	0.01
Ethnicity				
Not Hispanic or Latino	1 [Reference]		1 [Reference]	
Hispanic or Latino	1.13 (1.03- 1.25)	0.01	1.28 (1.22 - 1.35)	<0.001
Smoking status				
Nonsmoker	1 [Reference]		1 [Reference]	
Current or Former	1.20 (1.13- 1.27)	<0.001	1.39 (1.35 - 1.44)	<0.001
Comorbidities				
Cardiovascular disease	1.88 (1.78- 1.98)	<0.001	1.67 (1.62 - 1.72)	
Dementia	2.20 (2.04- 2.38)	<0.001	2.09 (1.97 - 2.23)	<0.001
Chronic pulmonary disease	1.24 (1.18- 1.31)	<0.001	1.23 (1.20 - 1.27)	<0.001
Liver mild	1.19 (1.11- 1.27)	<0.001	1.13 (1.09 - 1.18)	<0.001
Liver severe	2.39(2.15 - 2.66)	<0.001	1.93 (1.78 - 2.09)	<0.001
Kidney disease	1.94 (1.85- 2.05)	<0.001	1.89 (1.83 - 1.95)	<0.001
Cancer	1.32 (1.25- 1.40)	<0.001	1.16 (1.12 - 1.21)	<0.001
Metastatic cancer	2.36 (2.12- 2.62)	<0.001	1.67 (1.54 - 1.81)	<0.001
Type 2 Diabetes Mellitus	1.35 (1.29- 1.42)	<0.001	1.50 (1.46 - 1.55)	<0.001
HIV	1.00 (0.77 - 1.30)	0.99	1.05 (0.90 - 1.22)	0.56

Immunosuppressants				
TNF inhibitor	0.80 (0.66 - 0.96)	0.02	0.80 (0.73 - 0.89)	<0.001
Calcineurin inhibitor	0.95(0.84 - 1.08)	0.46	0.99 (0.91 - 1.07)	0.70
IL inhibitor	1.03 (0.84 - 1.27)	0.76	1.08 (0.96 - 1.21)	0.221
Other selective IS	1.04 (0.91 - 1.20)	0.55	1.15 (1.06 - 1.25)	<0.001
Cyclophosphamide	1.05 (0.77 - 1.44)	0.74	0.90 (0.72 - 1.12)	0.35
Glucocorticoid	1.12 (1.06- 1.18)	<0.001	1.04 (1.01 - 1.08)	0.01
Azathioprine	1.13 (0.93- 1.38)	0.22	1.17 (1.04 - 1.31)	0.01
Other antineoplastic agents	1.24 (1.12- 1.37)	<0.001	1.04 (0.98 - 1.11)	0.22
JAK inhibitor	1.28 (0.91- 1.79)	0.16	1.37 (1.14 - 1.66)	0.001
Monoclonal other	1.33 (1.07- 1.65)	0.01	1.09 (0.92 - 1.29)	0.30
Mycophenolic acid	1.44 (1.25- 1.65)	<0.001	1.60 (1.47 - 1.74)	<0.001
Anthracyclines	1.54 (1.10- 2.14)	0.01	1.53 (1.19 - 1.98)	0.001
Rituximab	1.62 (1.35- 1.95)	<0.001	1.73 (1.53 - 1.96)	<0.001
PK inhibitor	1.63 (1.32- 2.01)	<0.001	1.76 (1.50 - 2.08)	<0.001
Checkpoint inhibitor	1.70 (1.28- 2.26)	<0.001	1.29 (0.99 - 1.67)	0.06

Demographic factors include age, BMI, gender, race, ethnicity, smoking status.
Comorbidities include cardiovascular disease (MI + CHF + PVD + stroke), dementia, pulmonary disease, liver disease (mild and severe), Type 2 diabetes, kidney disease, cancer (metastatic and non-metastatic), and HIV infection.
Immunosuppressants: Anthracyclines, Checkpoint inhibitor, Cyclophosphamide, PK inhibitor, Monoclonal other, Rituximab, Other antineoplastic agents, Azathioprine, Calcineurin inhibitor, IL inhibitor, JAK inhibitor, Mycophenolic acid, TNF inhibitor, Other selective immunosuppressants, Glucocorticoid.