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**Title: Impact of Risk Factors on COVID-19 Outcomes in Unvaccinated People with Rheumatic Diseases**

**Subtitle: A Comparative Analysis of Pandemic Epochs Using the COVID-19 Global Rheumatology Alliance Registry**

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**Key words:** COVID-19, rheumatic diseases, outcomes, variants

**Running Head:** Risk Factors on COVID-19 Outcomes

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## ABSTRACT

**Background:** Approximately one-third of individuals worldwide have not received a COVID-19 vaccine. While studies have investigated risk factors linked to severe COVID-19 among unvaccinated people with rheumatic diseases(RD), we know less about whether these factors changed as the pandemic progressed. We aimed to identify risk factors associated with severe COVID-19 in unvaccinated individuals in different pandemic epochs corresponding to major variants of concern.

**Methods:** Patients with RD and COVID-19 were entered into the COVID-19 Global Rheumatology Alliance registry between March 2020 and June 2022. An ordinal logistic regression model (not hospitalized, hospitalized, and death) was used with date of COVID-19 diagnosis, age, sex, race and/or ethnicity, comorbidities, RD activity, medications, and the human development index(HDI) as covariates. The main analysis included all unvaccinated patients across COVID-19 pandemic epochs; sub-analyses stratified patients according to rheumatic disease types.

**Results:** Among 19,256 unvaccinated people with RD and COVID-19, those who were older, male, had more comorbidities, used glucocorticoids, had higher disease activity, or lived in lower HDI regions had worse outcomes across epochs. For those with rheumatoid arthritis, sulfasalazine and B-cell depleting therapy were associated with worse outcomes, and TNF-inhibitors were associated with improved outcomes. In those with connective tissue disease or vasculitis, B-cell depleting therapy was associated with worse outcomes.

**Conclusions:** Risk factors for severe COVID-19 outcomes were similar throughout pandemic epochs in unvaccinated people with RD. Ongoing efforts, including vaccination, are needed to

reduce COVID-19 severity in this population, particularly in those with medical and social vulnerabilities identified in this study.

**Significance & Innovation:**

1. Among unvaccinated people with rheumatic disease and COVID-19, B-cell depleting therapy was associated with worse outcomes for those with connective tissue disease/vasculitis or rheumatoid arthritis across the pandemic epochs.
2. Those from lower human development index regions (those with fewer resources and access to medical care) had worse outcomes across the COVID-19 pandemic epochs.
3. This is the final paper from the COVID-19 Global Rheumatology Alliance Registry that collected patient outcomes from those with rheumatic disease and COVID-19 to compare the differences between risk factors for more severe COVID-19 outcomes across the major pandemic epochs.



Despite widespread availability in many countries, approximately one-third of the global population has not received a COVID-19 vaccine. In the United States, one in five people remains unvaccinated.<sup>1</sup> Additionally, a small proportion of people with rheumatic diseases have a blunted or absent antibody response to vaccination.<sup>2</sup> While there has been substantial research identifying risk factors associated with poor outcomes in people with rheumatic disease during the initial waves of the COVID-19 pandemic,<sup>3</sup> it is not clear if these risk factors were similar through subsequent waves caused by different viral variants. Addressing this knowledge gap is important to direct global efforts to protect vulnerable individuals through directed vaccination campaigns and other measures.

COVID-19 variants of concern have acquired viral mutations that influence transmissibility and severity. The Alpha strain, which emerged in the United Kingdom in 2020, was more infectious than the initial SARS-CoV-2 variant first detected in China. The Delta and Omicron variants that followed in 2021 have had even higher transmissibility.<sup>4,5</sup> While evidence is still evolving, there is some indication that certain strains also caused more severe disease. For example, the Delta variant was associated with substantially higher risks of hospitalization and death than previous variants, though it remains unclear whether this resulted from increased virulence, few effective therapies, or overwhelmed health care systems.<sup>6</sup> Similarly, the Omicron variant seemed to cause severe disease less frequently, although vaccination, immunity from prior COVID-19, and advances in clinical care have likely contributed to improved outcomes.<sup>6</sup>

Among unvaccinated individuals during the early part of the pandemic, data from the COVID-19 Global Rheumatology Alliance as well as other sources, identified that many risk factors for severe COVID-19 outcomes in people with rheumatic diseases were similar to those in the general population; for example, older age, comorbidities like renal or lung disease, and male sex are associated with a higher risk of hospitalization and death from COVID-19.<sup>3,7</sup> Risk factors or severe outcomes specific to rheumatic diseases have also been identified, including higher disease activity and use of specific medications, such as glucocorticoids and B-cell depleting therapies.<sup>8,9</sup> Some medications that were of concern initially, such as TNF inhibitors, have not been associated with poor outcomes.<sup>10</sup> However, because most of these data were generated earlier in the pandemic, it is unknown whether these associations remained consistent across pandemic epochs, including more recent periods during which outcomes have improved significantly for the general population.

In this paper, we present a final comprehensive analysis of data collected in the COVID-19 Global Rheumatology Alliance registry for people with rheumatic diseases. Using data on almost 20,000 individuals, we aimed to identify risk factors associated with severe COVID-19 in unvaccinated individuals in different pandemic epochs corresponding to the major variants of concern between 2020 and 2022. We also examine immunosuppressive medications associated with more severe COVID-19 among subgroups of individuals with rheumatoid arthritis, spondyloarthritis, and connective tissue diseases or vasculitis.

## METHODS

*Data Source.* The COVID-19 Global Rheumatology Alliance physician-reported registry was launched on March 24<sup>th</sup>, 2020. Data were entered voluntarily by rheumatologists or under the

Accepted Article

supervision of rheumatologists; patients were eligible for inclusion if they had a pre-existing rheumatic disease and a COVID-19 diagnosis. Data were entered from 79 countries, either directly into the global or European data entry systems or transferred from national registries (Argentina, France, Germany, Italy, Portugal, and Sweden). Details of the registry have been described previously.<sup>7-9,11</sup> Briefly, C19-GRA data regarding individuals with rheumatic diseases diagnosed with COVID-19 were captured from rheumatology physicians via a data entry portal. This analysis was limited to cases entered by physicians for their patients from March 24<sup>th</sup>, 2020, to June 30<sup>th</sup>, 2022 (N=23,785). Since the registry collected anonymous data, the United Kingdom Health Research Authority and the University of California San Francisco Institutional Review Board considered it exempt from patient consent.

*COVID-19 outcome.* Both confirmed and presumptive cases of COVID-19 were reported. We used an ordinal severity outcome in the analyses, with mutually exclusive categories including: 1) not hospitalized and did not die, 2) hospitalized and did not die, or 3) death. These outcomes are analogous to outcome measures used in many trials evaluating COVID-19 therapeutics. Only the highest severity level of the outcome occurring during the patient's disease course was included, and all individuals were required to have a resolved clinical course, meaning that the ultimate outcome of their SARS-CoV-2 infection was recorded.

*COVID-19 epochs.* COVID-19 epochs were defined and stratified by dates roughly corresponding to presence of each COVID-19 variant in most countries: Epoch 1 (initial wave, COVID-19 diagnoses between January 1<sup>st</sup>, 2020, to October 31<sup>st</sup>, 2020); Epoch 2 (Alpha variant, COVID-19 diagnoses between November 1<sup>st</sup>, 2020, to May 31<sup>st</sup>, 2021); Epoch 3 (Delta variant, COVID-19 diagnoses between June 1<sup>st</sup>, 2021, to November 25<sup>th</sup>, 2021); Epoch 4 (Omicron variant, COVID-19 diagnoses between November 26<sup>th</sup>, 2021 – study end [June 30<sup>th</sup>, 2022]); **Figure 1.** We chose the variant start dates that aligned with the majority of countries within our registry using ourworldindata.org, although the timing of variant introductions likely varied across countries." For the start dates for variant exposure across specific countries, please visit ourworldindata.org.

*COVID-19 vaccination status.* Vaccination status was included in the registry starting in January 2021, which was approximately one month after FDA emergency use authorization for the first COVID-19 vaccine manufactured by Pfizer. Unvaccinated patients were defined as not having received any vaccinations for COVID-19 before COVID diagnosis. If the patient was missing vaccination status, but vaccines were not yet available at that time in their country, the patient was categorized as unvaccinated. Data for vaccine distributions by country were gathered from www.ourworldindata.org.<sup>12</sup>

*Covariates.* Patient information including age (years), sex (male or female), race and/or ethnicity, rheumatic disease diagnosis, rheumatic disease medication prior to COVID-19 diagnosis, rheumatic disease activity (by physician global assessment), and common comorbidities (hypertension and/or cardiovascular disease, diabetes mellitus, chronic renal insufficiency/end-stage renal disease (ESRD)), were collected by physician report. We

additionally adjusted for the Human Development Index (HDI),<sup>13</sup> and time since the start of Epoch 1(both described below).

Race and/or ethnicity were reported by the physician entering the case, and multiple categories could be selected. Physicians recorded race and ethnicity with the data available to them, which typically includes data available in the electronic health record (EHR), patient-reported race and ethnicity, or data derived from inference. In this study, race and/or ethnicity was categorized as either White, African American, Latin American/Hispanic, Asian (East, South, or Southeast), other or mixed race, or missing/unknown for patients missing race or ethnicity data. All other race or ethnicity combinations patients were categorized as “other/mixed race.”

Rheumatic disease diagnosis was classified into three groups: (1) rheumatoid arthritis (RA), (2) spondyloarthritis (including patients with psoriatic arthritis, reactive arthritis, axial spondyloarthritis, other spondyloarthritis, or a combination of these), and (3) connective tissue diseases (CTD)/vasculitis (including systemic lupus erythematosus (SLE), vasculitis, systemic sclerosis, ANCA-associated vasculitis, mixed connective tissue disease, undifferentiated connective tissue disease/overlap, giant cell arteritis, idiopathic inflammatory myopathies (including polymyositis, dermatomyositis), other vasculitis, Kawasaki disease, Sjogren's, Behcet's disease, polymyalgia rheumatica).

Patients with multiple rheumatic diseases were adjudicated so that those with more than one diagnosis within the same disease category (e.g., SLE and vasculitis) stayed within that disease category (CTD/vasculitis), and those with multiple rheumatic diseases within two or more primary categories (e.g., RA and SLE) were adjudicated using a hierarchy: SLE > RA > psoriatic arthritis > vasculitis > axial spondyloarthritis/other spondyloarthritis > other. This method of adjudicating multiple rheumatic diseases has been used in previous studies.<sup>8</sup> Patients with gout (n= 498), osteoarthritis (n=166), or other rheumatic disease diagnosis not mentioned above (n=2,367) were excluded from this analysis (**Supplementary Table S1: Patient Flowchart**).

Medications used prior to COVID-19 diagnosis were analyzed using mutually exclusive medication categories for the main analysis including all patients. Overarching medication groups used in the main analysis were categorized as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) including antimalarials (hydroxychloroquine, chloroquine), azathioprine, chloroquine, cyclophosphamide, cyclosporine, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, mercaptopurine, mesalamine, methotrexate, minocycline hydrochloride, mycophenolate mofetil/mycophenolic acid penicillamine, primaquine, sulfasalazine, tacrolimus, and thalidomide; targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) or non-tumor necrosis factor inhibitors (TNFi) including tofacitinib, baricitinib, apremilast, upadacitinib, abatacept, belimumab, rituximab, IL-1 inhibitors [anakinra, canakinumab, rilonacept], IL-6 inhibitors [tocilizumab, sarilumab], IL-12/23 inhibitors [ustekinumab, guselkumab], IL-17 inhibitors [secukinumab, ixekizumab], and IL-23 inhibitors [guselkumab, risankizumab, tildrakizumab]; TNFi including adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; combination csDMARD and TNFi therapy; and lastly combination csDMARD and non-TNFi. Patients on medications that did not fall into one of

the above categories were excluded from the models (N=26). Glucocorticoids were also included in the model and were categorized by prednisolone-equivalent dosage (none, 1-5 mg/day, >5-10 mg/day, and >10 mg/day). Glucocorticoid dose was reported as the prescribed dose at the time of COVID-19 diagnosis.

The HDI (ourworldindata.org) was used to account for social determinants of health in the models given significant regional variability in both access to healthcare resources and socioeconomic status. Countries were assigned to the six WHO regions (www.who.int); the 'Americas' were further divided into north and south. The HDI is a summary composite score of a country's average achievements in three key dimensions of human development: health, knowledge, and standard of living. It is expressed as a continuous value between 0 and 1, with higher scores being associated with a country's higher human development.<sup>14</sup> Additionally, time since the start of Epoch 1 (January 1<sup>st</sup>, 2020) was also included as a continuous variable in all models to capture the variability over time in mitigation strategies and regulations enforcing personal protective equipment, hospital resource allocation, and quarantine procedures.

*Statistical Analysis.* We used ordinal logistic regression with COVID-19 severity as the dependent variable adjusting for covariates as described below.

Covariates with significant missingness (i.e., glucocorticoid dose and disease activity) were selected to be imputed. We assumed that missing data were "missing at random" and missing data were handled using multiple imputation, with twenty imputed data sets.

In the main analysis, we developed multivariable ordinal regression models with the covariates age, race and/or ethnicity, sex, rheumatic disease category as a categorical variable (RA, spondyloarthritis, CTD/vasculitis), overarching immunosuppressive medication as a categorical variable (none, csDMARD monotherapy [referent], TNFi monotherapy, non-TNFi or tsDMARD monotherapy, combination csDMARD and TNFi therapy, and combination csDMARD and non-TNFi therapy), common comorbidities, glucocorticoids as a categorical variable (none [referent], 1-5 mg, 5-10 mg, and >10 mg/day), time since the start of Epoch 1, and HDI. Separate models were developed for each COVID-19 epoch.

In stratified analyses, we developed a model for each rheumatic disease category using the same covariates listed above but using the specific medication combinations clinically indicated for that disease instead of the overarching medication groups. For example, within the spondyloarthritis stratum, we assessed methotrexate, TNFi, janus kinase inhibitor (JAKi), leflunomide, sulfasalazine, and IL-17-inhibitor monotherapies, and TNFi + Methotrexate combination therapy.

Medication combinations were included if there were  $\geq 40$  patients using that combination within the disease category; combinations were systematically chosen based on being the most commonly prescribed regimens for each disease category in the registry and to avoid any violation of positivity assumption in the model. Specific medication combinations meeting this threshold included methotrexate monotherapy, TNFi monotherapy, TNFi and methotrexate, JAKi monotherapy, leflunomide monotherapy, sulfasalazine monotherapy, IL-6 inhibitor

monotherapy, IL-17 inhibitor monotherapy, abatacept monotherapy, anti-CD20 monotherapy, azathioprine with or without hydroxychloroquine, and mycophenolate mofetil/mycophenolic acid with or without hydroxychloroquine.

*Sensitivity Analysis.* We conducted several sensitivity analyses to test the robustness of our findings; in these analyses individuals with missing outcome information were excluded, (N=492). First, we re-ran the main model including the covariates described above, stratified for each COVID-19 epoch without using multiple imputation. Second, since previous studies have found a significant interaction between glucocorticoid therapies and rheumatic disease activity, we also modeled the interaction between glucocorticoids and disease activity by adding an interaction term to our estimation. The results of this interaction were then reported in an additive sense using post-estimation equations for each COVID-19 epoch.<sup>15</sup>

Finally, although our primary focus was on unvaccinated patients, we also analyzed the impact of vaccination on COVID-19 outcomes. The main analysis was repeated including vaccinated individuals and vaccination dose status at time of COVID-19 diagnosis as a categorical variable (0 doses [referent], 1-2 doses, 3 or more doses, and missing). Due to large amounts of missingness in the patient's reported vaccination status, we analyzed all patients (vaccinated and unvaccinated) and a model excluding patients with missing vaccination status only in the epoch that had the least amount of missing data (i.e., Epoch 4).

Results were considered statistically significant using a two-sided  $p < 0.05$ . All analyses were conducted in Stata version 16.0 (StataCorp).

## RESULTS

As of June 30th, 2022, 23,785 patients were entered into the C-19 GRA registry. After applying our exclusion criteria (vaccinated patients [N=1,472], gout patients [N=498], osteoarthritis patients [N=166], other rheumatic disease categories [N=2,367], and other rheumatic medication users [N=26]), a total of 19,256 patients were included in the main analysis. This was stratified across the COVID-19 epoch periods: Epoch 1 (N=9,515); Epoch 2 (N=8,193); Epoch 3 (N=919); and Epoch 4 (N=629) (**Figure 1**).

### *Patient demographic and disease characteristics:*

Mean age remained consistent across the four COVID-19 epochs (mean [SD]: 54 [16.0], 54 [15.6], 51 [15.9], and 50 [16.1], respectively; **Table 1**). The majority of patients entered into the registry and included in this analysis were female ( $\geq 72.0\%$ ), non-Hispanic White ( $\geq 43.0\%$ ), and resided in Europe ( $\geq 30.1\%$ ), North America ( $\geq 18.6\%$ ), or South America ( $\geq 13.5\%$ ). The most common rheumatic diagnostic group was RA (N = 8,750 [45.4%]), followed by CTD/vasculitis (N=6,134 [31.8%]) and spondyloarthritis (N=4,479 [23.3%]) with roughly 15-20% of patients having moderate/severe disease activity across each epoch. Missing data was minimal (<5%) across variables, except for race and/or ethnicity as well as disease activity, particularly in Epoch 1 (**Table 1**).

More cases with severe outcomes occurred in the first epoch (26.6% hospitalized and 7.1% deceased in Epoch 1) vs. the last epoch (6.4% hospitalized and 1.8% deceased in Epoch 4; **Table 1**).

Among all patients, the most common medication regimen was methotrexate monotherapy (15.8%; **Supplementary Table S2**). Regarding rheumatic diagnosis groups, the most common medication regimens were methotrexate monotherapy for those with RA (23.4%), TNFi monotherapy (36.6%) for those with spondyloarthritis; and mycophenolate mofetil/mycophenolic acid with or without hydroxychloroquine (10.2%) for those with CTD/vasculitis (**Supplementary Table S2**). Among those prescribed glucocorticoids, the most common dose range across all groups was 1-5 mg/day (19.1%); with the proportion using any dose of glucocorticoids was 35.1% among those with RA, 10.2% among those with spondyloarthritis, and 46.0% among those with CTD/vasculitis (**Supplementary Table S2**).

*Main analysis:*

**Table 2** presents associations between COVID-19 outcome status and covariates across the 4 epochs using the imputed data sets.

We found a consistent relationship between HDI and COVID-19 outcome status across the first three epochs, with lower HDI being associated with more severe COVID-19 related outcomes (OR [95% CI]: 0.97 [0.96, 0.98]; 0.97 [0.96, 0.98]; 0.94 [0.91, 0.96], for Epoch 1, 2, and 3, respectively). Older age was also consistently associated with more severe COVID-19 outcomes.

In Epochs 1 and 2, all common comorbidities (hypertension and/or cardiovascular disease, diabetes mellitus, chronic renal insufficiency/ESRD, morbid obesity, and lung disease) were significantly associated with severe COVID-19 outcomes. The comorbidities that remained significant by Epoch 3 were chronic renal insufficiency/ESRD (OR [95% CI]: 8.16 [4.40, 15.10],  $p < 0.01$ ) and lung disease (2.83 [1.65, 4.86],  $p < 0.01$ ; **Table 2**). Findings were similar in Epoch 4, although did not reach statistical significance, likely due to a smaller sample size.

Among the rheumatic disease categories, compared to RA as the referent, spondyloarthritis was associated with less risk of severe COVID-19 outcomes (0.77 [0.64, 0.93],  $p = 0.01$ ) and CTD/Vasculitis with more risk of severe COVID-19 related outcomes (1.61 [1.40, 1.87],  $p < 0.01$ ) in the first two epochs. These results remained consistent in later epochs but were not statistically significant. Additionally, patients with moderate/high rheumatic disease activity had more severe COVID-19 outcomes across most epochs (**Table 2**).

Among medication combinations, we found that TNFi (either TNFi monotherapy or combination csDMARD and TNFi) were associated with a lower frequency of severe COVID-19 outcomes (statistically significant in Epochs 1 and 2) while combinations of csDMARD and Non-TNFi/tsDMARDs were associated with more frequent severe outcomes compared to csDMARD monotherapy (**Table 2**). Additionally, we found that the higher the dose of glucocorticoids, the greater the association with more severe COVID-19 related outcomes (1-5mg: 1.55 [1.02, 2.35],  $p = 0.01$  vs. >10mg: 3.10 [1.67, 5.74],  $p < 0.01$ ; Epoch 3, **Table 2**).

### *Stratified Analyses by Disease Category*

For sub-analysis among each rheumatic diagnostic group stratified across the 4 COVID-19 epochs, we analyzed data for 8,750 individuals with RA (Epoch 1 [N=4,167]; Epoch 2 [N=3,921]; Epoch 3 [N=421]; and Epoch 4 [N=241]; **Table 3**), 4,479 individuals with spondyloarthritis (Epoch 1 [N=2,172]; Epoch 2 [N=2,018]; Epoch 3 [N=156]; and Epoch 4 [N=133]; **Table 4**), and 20,452 individuals with CTD/Vasculitis (Epoch 1 [N=3,235]; Epoch 2 [N=2,297]; Epoch 3 [N=346]; and Epoch 4 [N=256]; **Table 5**). Analyses were underpowered in Epoch 4 and were therefore not conducted.

Like the main analysis with all patients, results stratified across each rheumatic diagnosis group showed similar findings for age, gender, HDI, common comorbidities, disease activity, and glucocorticoid use in relation to the outcome of interest. Additionally, consistent with findings from the main analyses, patients taking TNFi monotherapy prior to their COVID-19 diagnosis had less severe COVID-19 outcomes for each rheumatic diagnostic group (**Table 3-5**).

Among those with RA, anti-CD20 drugs had the strongest association with severe COVID-19 outcomes (highest in Epoch 3: OR 3.51 [1.34, 11.1],  $p=0.03$ ; **Table 3**). IL-6 inhibitors were consistently associated with less severe COVID-19, although this only reached statistical significance in Epoch 2 (0.18 [0.05, 0.62],  $p=0.01$ ), likely because of small sample sizes; **Table 3**. We saw similar findings among those with CTD/vasculitis: anti-CD20 drugs were associated with more severe COVID-19 outcomes and IL-6 inhibitors were associated with less severe outcomes (**Table 5**). No spondyloarthritis-specific drugs were associated with worse outcomes (**Table 4**).

#### *Sensitivity analyses:*

Findings were largely consistent when examining the main analysis among a non-imputed complete-case dataset (**Supplementary Table S3**). Using post-estimation equations to analyze the interaction between glucocorticoid therapies and rheumatic disease activity, we found that higher disease activity (e.g. moderate/severe disease activity vs. low disease activity/remission) and higher glucocorticoid dose categories were associated with severe COVID-19 outcomes (**Supplementary Table S4**); in other words, we found that higher doses of glucocorticoids were associated with more severe COVID-19, particularly in patients with moderate/severe disease activity. Finally, for the models including COVID vaccination status, reported vaccinations were the highest in COVID Epoch 4, as expected. Data missingness was significant, with around 20% missing vaccination status for each Epoch (**Supplementary Table S5**). For this reason, we opted to include vaccination status in our models among all patients (with missingness as a category), as well as excluding those missing vaccination status for Epoch 4 only. Results were consistent between the two analyses, with the direction of the effect of vaccination being protective, particularly for those with  $\geq 3$  vaccines (**Supplementary Table S6**).

## **DISCUSSION**

In this study, we performed an analysis of the accumulated data entered by rheumatologists around the world into the COVID-19 Global Rheumatology Alliance registry. We focused this

investigation on individuals who are unvaccinated, a still substantial minority of this population globally, and examined risk factors for severe COVID-19 outcomes across pandemic epochs. Like previous studies, we found that older age, male sex, and comorbidities were associated with more severe outcomes in all epochs, and that high disease activity, particularly in those using glucocorticoids, was associated with hospitalizations and deaths. We also demonstrate the significant impact of social determinants of health, as measured by the human development index, on COVID-19 outcomes across pandemic epochs. Our findings corroborate previous studies showing that those using TNFi have favorable outcomes and that individuals with RA using B-cell depleting drugs, sulfasalazine, and combinations of csDMARDs and non-TNFi biologics (except for IL-6 inhibitors) have worse COVID-19 outcomes; B-cell depleting therapies were also associated with more severe outcomes among those with CTD and vasculitis. In hospitalized patients with COVID-19, higher levels of TNF have been linked to a greater severity of the illness and an increased risk of mortality.<sup>16</sup> Therefore, neutralization of TNF, a major cytokine in the excess inflammatory phase of COVID-19, could play a role in the treatment of COVID-19, and trials are ongoing. A recent large randomized, placebo-controlled clinical trial led by the National Institutes of Health showed that treating adults hospitalized with COVID-19 with infliximab (a chimeric monoclonal antibody that binds to and inhibits TNF) did not significantly shorten time to recovery but was associated with improved 14-day clinical status and substantial reduction in 28-day mortality compared with standard of care.<sup>17</sup> Importantly, our results were consistent across pandemic epochs corresponding to different variants of concern, suggesting that specific medical and social vulnerabilities were associated with a higher risk for severe outcomes of COVID-19 regardless of viral strain.

One of the novel findings of this study is the consistent association between the HDI, a composite statistic developed by the United Nations that includes life expectancy, education, and per capita income, and COVID-19 outcomes.<sup>14</sup> In our study, a lower HDI was associated with higher risk for more severe COVID-19 outcomes among people with rheumatic diseases. Beyond clinical characteristics and immunosuppressive characteristics, our findings indicate that the social determinants of health captured in the HDI significantly contributed to more severe outcomes across pandemic epochs. Although limited global data using the HDI is available, one study demonstrated a strong relationship between a lower regional HDI and case fatality from COVID-19 in Brazil,<sup>18</sup> and another study reported a significant association with low HDI and the number of COVID-19 infections among BRICS countries.<sup>19</sup> An ecological study using country-wide statistics found that HDI correlated with both COVID-19 cases and deaths.<sup>20</sup> Previous studies from the COVID-19 Global Rheumatology Alliance also identify race, ethnicity, and societal pandemic policies and resources as important predictors of outcomes.<sup>21-23</sup> This literature is important insofar as it suggests that efforts to improve COVID-19 outcomes and reduce health disparities among people with rheumatic diseases require focus on both medical and social vulnerabilities.

The COVID-19 GRA registry was among the first to report the higher risk for severe COVID-19 outcomes among people using B-cell depleting agents. In our initial study, we found that those using rituximab had 4 times the odds of death compared to those using methotrexate alone<sup>8</sup> and compared to TNFi users among RA patients.<sup>9</sup> These findings have since been replicated in



numerous epidemiological investigations in both unvaccinated and vaccinated individuals;<sup>24-27</sup> diminished or absent antibody responses to vaccines likely underlie heightened risk among those who are vaccinated. A recent population-wide serologic study in the United Kingdom confirmed that a substantial number of individuals using B-cell depleting agents have not formed anti-spike antibodies, even after three or more COVID-19 vaccines.<sup>2</sup> Our findings add to this literature by demonstrating a strong association with severe COVID-19 outcomes in people using B-cell depleting therapies across pandemic epochs. Given the strength and consistency of findings to date regarding B-cell depleting drugs, clinicians who care for individuals receiving anti-CD20 drugs such as rituximab must continue to promote measures to protect these patients. This might include aggressively employing vaccines and available antiviral drugs and advocating for development of other preventive therapies that provide long term protection. In addition, clinicians considering use of B-cell depleting therapies for rheumatic disease should carefully appraise other possible effective therapies that may not be associated with severe outcomes.

In addition to those using B-cell depleting drugs, individuals who have high or moderate rheumatic disease activity (as measured by a provider global assessment) also had more severe COVID-19 outcomes across pandemic epochs. Interestingly, disease activity appears to have an additive interaction with glucocorticoid dose; in other words, increasing odds of severe outcomes were seen with higher glucocorticoid doses in those with high or moderate disease activity.<sup>15</sup> These findings imply that control of underlying rheumatic disease activity and minimization of the use of glucocorticoids will continue to be important strategies for preventing severe COVID-19 in this population.

This study has both strengths and limitations. A key strength is the robust worldwide collaboration and data collection effort, which has allowed us to achieve a large sample size and improve generalizability. Diverse patient populations were included given participation of rheumatologists from both academic, community and public health hospitals around the world. In addition, since data was entered by rheumatologists, clinical detail about rheumatic conditions, disease activity, and medication use was likely more reliable than that obtained with other observational data sources, such as administrative claims. These strengths have permitted rapid and accurate generation of data that has been corroborated by multiple other data sources. Limitations include that the registry represents data entered voluntarily by rheumatologists. While some collaborators entered all patients with COVID-19 cared for in their centers or regions, others entered data in a more ad hoc manner, which likely led to an overrepresentation of severe cases in the registry. Physicians were asked to enter each patient only once into the registry, as such, we were unable to assess the impact of multiple episodes of COVID-19 given that the GRA registry was cross-sectional. In regards to COVID-19 vaccination status, some physicians used their country or state's vaccine registry to input a patient's vaccination status while others collected this information from patient interviews or the medical record during clinical care. Therefore, a small degree of misclassification of vaccination status is possible. There were relatively fewer cases entered at later epochs of the pandemic, even though community case numbers had increased, which could induce some bias in reporting. Similar to other studies,<sup>28</sup> we found that the proportion of patients experiencing

severe outcomes decreased over time, but this should be interpreted cautiously given the lack of a population-based denominator. The registry did not include a comparator group, either one without rheumatic disease or one without COVID-19. Although a physician global assessment of disease activity was included, more specific measures of disease activity used in some diseases were not available. Finally, we estimated pandemic epochs based on publicly available data on variants of concern, but there is likely some degree of misclassification given the unavailability of specific sequencing data on individual patients and variable timing of viral strains in different regions.

In conclusion, the results of this study suggest that the risk factors for severe COVID-19 among unvaccinated individuals with rheumatic disease remained largely consistent across pandemic epochs, corresponding to the major variants of concern. Both risk factors identified in the general population, such as age, male sex, and comorbidities, and those specific to rheumatic diseases, such as higher disease activity and using specific medications (i.e., glucocorticoids and B-cell depleting therapies) were found to be associated with severe outcomes. Ongoing efforts, such as vaccination and anti-viral treatment, are needed to reduce COVID-19 severity in people with rheumatic diseases, particularly in those with the medical and social vulnerabilities identified in this study.

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**Table 1:** Baseline characteristics of unvaccinated individuals in the COVID-19 Global Rheumatology Alliance registry by COVID-19 epochs corresponding to major variants of concern, N (%)

Characteristics	Epoch 1 <sup>1</sup> (N=9,515)	Epoch 2 <sup>2</sup> (N=8,193)	Epoch 3 <sup>3</sup> (N=919)	Epoch 4 <sup>4</sup> (N=629)
<b>Age</b>				
Age (year), mean (SD)	54 (16.0)	54 (15.6)	51 (15.9)	50 (16.1)
<b>Sex, n (%)</b>				
Female	6,931 (72.8)	5,898 (72.0)	721 (78.5)	483 (76.8)
Male	2,577 (27.1)	2,291 (28.0)	198 (21.6)	146 (23.2)
Missing	7 (0.1)	4 (0.1)	0 (0.0)	0 (0.0)
<b>Human Development Index, mean (SD)<sup>5</sup></b>	0.87 (0.1)	0.89 (0.1)	0.86 (0.1)	0.88 (0.1)
<b>Race or Ethnicity, n (%)</b>				
Non-Hispanic White	4,091 (43.0)	5,440 (66.4)	525 (57.2)	406 (64.6)
Black	318 (3.3)	157 (1.9)	30 (3.3)	20 (3.2)
Latin American/Hispanic	2,306 (24.2)	1,117 (13.6)	211 (22.9)	80 (12.7)
Asian	490 (5.1)	397 (4.8)	80 (8.7)	38 (6.0)
Other/Mixed	304 (3.2)	134 (1.6)	29 (3.2)	62 (9.9)
Missing/Unknown	2,006 (21.1)	948 (11.6)	44 (4.8)	23 (3.7)
<b>Regions, n (%)</b>				
Europe	4,686 (49.3)	5,127 (62.6)	277 (30.1)	296 (47.1)
North America	2,267 (23.8)	1,527 (18.6)	269 (29.3)	167 (26.6)
South America	1,887 (19.8)	1,103 (13.5)	264 (28.7)	65 (10.3)
Eastern Mediterranean	335 (3.5)	137 (1.7)	17 (1.9)	45 (7.2)
Western Pacific Region	215 (2.3)	178 (2.2)	74 (8.0)	19 (3.0)
South-East Asia	66 (0.7)	80 (1.0)	0 (0.0)	0 (0.0)
African	53 (0.6)	39 (0.5)	14 (1.5)	2 (0.3)
<b>Comorbidity count, n (%)</b>				
No comorbidities	5,114 (53.8)	4,719 (57.6)	554 (60.3)	402 (63.9)
One comorbidity	2,610 (27.4)	2,142 (26.1)	248 (27.0)	150 (23.9)

Two or more comorbidities	1,791 (18.8)	1,332 (16.3)	117 (12.7)	77 (12.2)
<b>Common comorbidities, n (%)</b>				
Hypertension and/or Cardiovascular Disease	3,300 (34.7)	2,759 (33.6)	290 (31.5)	169 (26.9)
Diabetes mellitus	1,130 (11.9)	844 (10.3)	71 (7.8)	44 (7.0)
Chronic Renal Insufficiency/ESRD	509 (5.3)	374 (4.6)	41 (4.5)	22 (3.5)
Morbid Obesity, BMI 40+ kg/m <sup>2</sup>	1,607 (16.9)	1,446 (17.7)	150 (16.3)	111 (17.7)
Lung Disease <sup>6</sup>	1,378 (14.5)	891 (10.9)	87 (9.5)	64 (10.2)
<b>Primary Rheumatic Disease Category, n (%)</b>				
Rheumatoid Arthritis <sup>7</sup>	4,167 (43.8)	3,921 (47.9)	421 (45.9)	241 (38.1)
Spondyloarthritis <sup>8</sup>	2,172 (22.8)	2,018 (24.6)	156 (17.0)	133 (21.1)
Connective Tissue Disease /Vasculitis <sup>9</sup>	3,235 (34.0)	2,297 (28.0)	346 (37.6)	256 (40.7)
<b>Rheumatic Disease Activity, n (%)</b>				
Remission/Minimal	5,808 (61.0)	6,367 (77.7)	701 (76.2)	498 (79.2)
Moderate-Severe	1,526 (16.0)	1,264 (15.4)	185 (20.1)	104 (16.5)
Missing/Unknown	2,181 (22.9)	562 (6.9)	33 (3.6)	27 (4.3)
<b>Rheumatic Disease Medications, n (%)<sup>10</sup></b>				
None	1,539 (16.2)	1,265 (15.4)	132 (14.4)	80 (12.7)
csDMARDs monotherapy <sup>11</sup>	4,328 (45.5)	3,571 (43.6)	447 (48.6)	288 (45.8)
TNFi monotherapy <sup>12</sup>	1,198 (12.6)	1,117 (13.6)	102 (11.1)	94 (14.9)
Non-TNFi biologics or tsDMARD monotherapy <sup>13</sup>	807 (8.05)	869 (10.6)	85 (9.3)	48 (7.6)
combination csDMARD and TNFi	868 (9.1)	805 (9.8)	75 (8.2)	63 (10.0)
combination csDMARD and Non-TNFi/tsDMARD	775 (8.2)	566 (6.9)	78 (8.5)	56 (8.9)
<b>Common Medication Regimens, n (%)</b>				
Methotrexate monotherapy	1,490 (15.6)	1,379 (16.8)	109 (11.9)	73 (11.6)
TNFi monotherapy	1,174 (12.3)	1,086 (13.2)	101 (11.0)	94 (15.0)
Methotrexate + TNFi	584 (6.1)	598 (7.3)	47 (5.1)	43 (6.8)
JAK inhibitor monotherapy	186 (2.0)	261 (3.2)	26 (2.8)	10 (1.6)

JAK inhibitor + Methotrexate	104 (1.1)	106 (1.3)	15 (1.6)	4 (0.6)
Leflunomide monotherapy	198 (2.1)	198 (2.4)	24 (2.6)	17 (2.7)
Sulfasalazine monotherapy	170 (1.8)	154 (1.9)	14 (1.5)	13 (2.1)
Azathioprine +/- hydroxychloroquine	288 (3.0)	205 (2.5)	34 (3.7)	21 (3.3)
mycophenolate mofetil/mycophenolic acid +/- hydroxychloroquine	327 (3.4)	247 (3.0)	40 (4.4)	25 (4.0)
IL6-inhibitor monotherapy	127 (1.3)	185 (2.3)	10 (1.1)	11 (1.8)
IL17-inhibitor monotherapy	167 (1.8)	153 (1.9)	9 (1.0)	6 (1.0)
Abatacept monotherapy	166 (1.7)	137 (1.7)	19 (2.1)	7 (1.1)
Anti-CD20 monotherapy	455 (4.8)	302 (3.7)	51 (5.5)	38 (6.0)
<b>Categories of glucocorticoid dose in prednisone daily equivalents, n (%)</b>				
No use of glucocorticoids	6,253 (65.6)	5,627 (68.7)	603 (65.4)	464 (73.8)
1-5 mg/day	1,703 (17.9)	1,675 (20.4)	197 (21.5)	97 (15.4)
6-10 mg/day	290 (3.1)	256 (3.1)	26 (2.8)	15 (2.4)
>10 mg/day	883 (9.3)	530 (6.5)	82 (8.9)	52 (8.3)
Missing dose	396 (4.2)	105 (1.3)	11 (1.2)	1 (0.2)
<b>COVID-19 related outcomes, n (%)</b>				
Not hospitalized nor deceased	6,025 (63.3)	6,262 (76.4)	692 (75.3)	566 (90.0)
Hospitalized but not deceased	2,526 (26.6)	1,430 (17.4)	171 (18.6)	40 (6.4)
Deceased	680 (7.1)	321 (3.9)	40 (4.4)	11 (1.8)
Missing	284 (3.0)	180 (2.2)	16 (1.7)	12 (1.9)
<p><sup>1</sup>Epoch 1 (initial wave, COVID-19 diagnoses between January 1<sup>st</sup>, 2020, to October 31<sup>st</sup>, 2020)</p> <p><sup>2</sup>Epoch 2 (Alpha variant, COVID-19 diagnoses between November 1<sup>st</sup>, 2020, to May 31<sup>st</sup>, 2021)</p> <p><sup>3</sup>Epoch 3 (Delta variant, COVID-19 diagnoses between June 1<sup>st</sup>, 2021, to November 25<sup>th</sup>, 2021)</p> <p><sup>4</sup>Epoch 4 (Omicron variant, COVID-19 diagnoses between November 26<sup>th</sup>, 2021 – study end [June 30<sup>th</sup>, 2022])</p> <p><sup>5</sup>The human development index is a summary composite score of a country's average achievements in three key dimensions of human development: health, knowledge, and standard of living. It is expressed as a value between 0 and 1, with higher scores being associated with a country's higher human development.</p> <p><sup>6</sup>Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma</p> <p><sup>7</sup>Rheumatoid Arthritis designated as primary rheumatic diagnosis</p> <p><sup>8</sup>Spondyloarthritis includes psoriatic arthritis, reactive arthritis, ankylosing spondylitis, or other spondyloarthritis</p> <p><sup>9</sup>Connective Tissue Diseases/Vasculitis includes SLE, vasculitis, systemic sclerosis, ANCA-associated vasculitis, Mixed connective tissue disease, Undifferentiated connective tissue disease/overlap, Giant cell arteritis, Inflammatory myopathies (including polymyositis, dermatomyositis), other vasculitis, Kawasaki disease, Sjogren's, Bechcet's disease, and Polymyalgia rheumatica.</p> <p><sup>10</sup>Rheumatic disease medication categories are not mutually exclusive.</p>				



<sup>11</sup>csDMARDs included auranofin, aurothioglucose, azathioprine, chloroquine hydrochloride, chloroquine phosphate, cyclophosphamide, cyclosporine, gold sodium thiomalate, hydroxychloroquine sulphate, leflunomide, mercaptopurine, mesalamine, methotrexate, minocycline hydrochloride, n-acetylpencillamine, penicillamine, primaquine, sulfasalazine, tacrolimus, and thalidomide.

<sup>12</sup>TNF-inhibitors included adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.

<sup>13</sup>Non-TNF inhibitor biologics included abatacept, belimumab, rituximab, IL1 inhibitors [anakinra, canakinumab, rilonacept], IL-6 inhibitors [tocilizumab, sarilumab], IL-12/23 inhibitors [ustekinumab, guselkumab], IL-17 inhibitors [secukinumab, ixekizumab], and IL-23 inhibitors [guselkumab, risankizumab, tildrakizumab]; Targeted synthetic DMARDs included tofacitinib, baricitinib, apremilast, and upadacitinib.

csDMARD: conventional synthetic disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitor; tsDMARD: targeted synthetic disease-modifying antirheumatic drug

**Table 2:** Imputed odds of being one step higher in the ordinal severity outcome (not hospitalized, hospitalized, or death) stratified by COVID-19 epochs across all unvaccinated patients.

Covariates	Epoch 1 <sup>1</sup> (N=9,515)	Epoch 2 <sup>2</sup> (N=8,193)	Epoch 3 <sup>3</sup> (N=919)	Epoch 4 <sup>4</sup> (N=629)
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
<b>Age</b>	<b>1.04 (1.04, 1.05)</b>	<b>1.05 (1.04, 1.05)</b>	<b>1.03 (1.02, 1.04)</b>	<b>1.04 (1.01, 1.07)</b>
<b>Sex</b>				
Female	REF	REF	REF	REF
Male	<b>1.57 (1.40, 1.77)</b>	<b>1.50 (1.30, 1.71)</b>	1.32 (0.82, 2.12)	1.39 (0.64, 3.04)
<b>Human Development Index<sup>5</sup></b>	<b>0.97 (0.96, 0.98)</b>	<b>0.97 (0.96, 0.98)</b>	<b>0.94 (0.91, 0.96)</b>	0.97 (0.93, 1.01)
<b>Common comorbidities</b>				
Hypertension and/or Cardiovascular Disease	<b>1.21 (1.07, 1.36)</b>	<b>1.39 (1.21, 1.60)</b>	1.22 (0.81, 1.85)	1.45 (0.69, 3.05)
Diabetes mellitus	<b>1.54 (1.32, 1.79)</b>	<b>1.58 (1.33, 1.89)</b>	1.62 (0.88, 2.96)	1.74 (0.63, 4.81)
Chronic Renal Insufficiency/ESRD	<b>2.26 (1.82, 2.74)</b>	<b>2.24 (1.75, 2.87)</b>	<b>8.16 (4.40, 15.1)</b>	2.48 (0.85, 7.25)
Morbid Obesity, BMI 40+ kg/m <sup>2</sup>	<b>1.30 (1.13, 1.49)</b>	<b>1.19 (1.01, 1.39)</b>	1.36 (0.85, 2.18)	0.82 (0.33, 2.02)
Lung Disease <sup>6</sup>	<b>1.80 (1.58, 2.07)</b>	<b>2.24 (1.91, 2.64)</b>	<b>2.83 (1.65, 4.86)</b>	2.18 (0.90, 5.29)
<b>Rheumatic Disease Category</b>				
Rheumatoid Arthritis <sup>7</sup>	REF	REF	REF	REF
Spondyloarthritis <sup>8</sup>	<b>0.81 (0.70, 0.95)</b>	<b>0.77 (0.64, 0.93)</b>	1.09 (0.60, 1.94)	0.53 (0.12, 2.43)
Connective Tissue Disease /Vasculitis <sup>9</sup>	<b>1.14 (1.01, 1.29)</b>	<b>1.61 (1.40, 1.87)</b>	1.18 (0.74, 1.76)	1.85 (0.87, 3.94)
<b>Rheumatic Medications<sup>10</sup></b>				
None	<b>1.18 (1.02, 1.37)</b>	0.96 (0.81, 1.14)	0.88 (0.51, 1.52)	1.27 (0.52, 3.12)
csDMARDs monotherapy <sup>11</sup>	REF	REF	REF	REF
TNFi monotherapy <sup>12</sup>	<b>0.51 (0.41, 0.64)</b>	<b>0.67 (0.44, 0.73)</b>	0.79 (0.34, 1.80)	0.93 (0.26, 3.38)
Non-TNFi biologics or tsDMARD <sup>13</sup>	1.06 (0.87, 1.30)	1.11 (0.90, 1.36)	<b>2.10 (1.21, 3.63)</b>	0.90 (0.26, 3.15)

combination csDMARD and TNFi	<b>0.69 (0.56, 0.85)</b>	<b>0.72 (0.56, 0.92)</b>	1.21 (0.60, 2.44)	0.32 (0.4, 2.72)
combination csDMARD and Non-TNFi/tsDMARD	<b>1.35 (1.11, 1.63)</b>	<b>1.53 (1.22, 1.92)</b>	1.72 (0.91, 3.27)	1.88 (0.71, 5.00)
<b>Glucocorticoid dose</b>				
None	REF	REF	REF	REF
1-5 mg/day	<b>1.54 (1.36, 1.78)</b>	<b>1.20 (1.03, 1.38)</b>	<b>1.55 (1.02, 2.35)</b>	1.70 (0.76, 3.81)
6-10 mg/day	<b>1.87 (1.42, 2.46)</b>	<b>1.70 (1.23, 2.35)</b>	<b>2.32 (1.00, 5.36)</b>	3.30 (0.92, 5.43)
>10 mg/day	<b>3.01 (2.53, 3.63)</b>	<b>2.62 (2.10, 3.29)</b>	<b>3.10 (1.67, 5.74)</b>	1.94 (0.70, 5.30)
<b>Rheumatic Disease Activity</b>				
Remission/Minimal	REF	REF	REF	REF
Moderate-Severe	<b>1.41 (1.22, 1.61)</b>	<b>1.63 (1.29, 2.05)</b>	1.18 (0.59, 2.37)	<b>2.15 (1.01, 4.81)</b>

\*Significant values with p<0.05 are bolded

<sup>1</sup>Epoch 1 (initial wave, COVID-19 diagnoses between January 1<sup>st</sup>, 2020, to October 31<sup>st</sup>, 2020)

<sup>2</sup>Epoch 2 (Alpha variant, COVID-19 diagnoses between November 1<sup>st</sup>, 2020, to May 31<sup>st</sup>, 2021)

<sup>3</sup>Epoch 3 (Delta variant, COVID-19 diagnoses between June 1<sup>st</sup>, 2021, to November 25<sup>th</sup>, 2021)

<sup>4</sup>Epoch 4 (Omicron variant, COVID-19 diagnoses between November 26<sup>th</sup>, 2021 – study end [June 30<sup>th</sup>, 2022])

<sup>5</sup>The human development index is a summary composite score of a country's average achievements in three key dimensions of human development: health, knowledge, and standard of living. It is expressed as a value between 0 and 1, with higher scores being associated with a country's higher human development.

<sup>6</sup>Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma

<sup>7</sup>Rheumatoid Arthritis as designated as primary rheumatic diagnosis

<sup>8</sup>Spondyloarthritis includes psoriatic arthritis, reactive arthritis, ankylosing spondylitis, other spondyloarthritis

<sup>9</sup>Connective Tissue Diseases/Vasculitis includes SLE, vasculitis, systemic sclerosis, ANCA-associated vasculitis, Mixed connective tissue disease, Undifferentiated connective tissue disease/overlap, Giant cell arteritis, Inflammatory myopathies (including polymyositis, dermatomyositis), other vasculitis, Kawasaki disease, Sjogren's, Bechcet's disease, and Polymyalgia rheumatica.

<sup>10</sup>Rheumatic medication categories are not mutually exclusive.

<sup>11</sup>csDMARDs included auranofin, aurothioglucose, azathioprine, chloroquine hydrochloride, chloroquine phosphate, cyclophosphamide, cyclosporine, gold sodium thiomalate, hydroxychloroquine sulphate, leflunomide, mercaptopurine, mesalamine, methotrexate, minocycline hydrochloride, n-acetylpenicillamine, penicillamine, primaquine, sulfasalazine, tacrolimus, and thalidomide.

<sup>12</sup>TNF-inhibitors included adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.

<sup>13</sup>Non-TNF inhibitor biologics included abatacept, belimumab, rituximab, IL1 inhibitors [anakinra, canakinumab, riloncept], IL-6 inhibitors [tocilizumab, sarilumab], IL-12/23 inhibitors [ustekinumab, guselkumab], IL-17 inhibitors [secukinumab, ixekizumab], and IL-23 inhibitors [guselkumab, risankizumab, tildrakizumab]. Targeted synthetic DMARDs included tofacitinib, baricitinib, apremilast, and upadacitinib.

csDMARD: conventional synthetic disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitor; tsDMARD: targeted synthetic disease-modifying antirheumatic drug; IL: Interleukin; JAKi: Janus kinases inhibitor

**Table 3.** Imputed odds of more severe COVID-19 using the ordinal outcome stratified by COVID-19 epochs for unvaccinated patients with Rheumatoid Arthritis using specific medication categories

Covariates	Epoch 1 <sup>1</sup> (N = 4,167)	Epoch 2 <sup>2</sup> (N = 3,921)	Epoch 3 <sup>3</sup> (N = 421)	Epoch 4 <sup>4</sup> (N = 241)
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
Age	<b>1.05 (1.04, 1.06)</b>	<b>1.06 (1.05, 1.06)</b>	<b>1.05 (1.02, 1.07)</b>	1.03 (0.98, 1.00)
Sex				
Female	Ref	Ref	Ref	Ref
Male	<b>1.41 (1.17, 1.72)</b>	<b>1.51 (1.21, 1.80)</b>	1.53 (0.80, 3.16)	2.85 (0.71, 11.71)
Human Development Index <sup>5</sup>	<b>0.97 (0.95, 0.98)</b>	<b>0.97 (0.96, 0.98)</b>	<b>0.95 (0.92, 0.99)</b>	1.06 (0.92, 1.21)
Common comorbidities, n (%)				
Hypertension and/or CVD	<b>1.20 (1.01, 1.42)</b>	<b>1.34 (1.10, 1.64)</b>	1.24 (0.66, 2.36)	1.00 (0.26, 4.43)
Diabetes mellitus	<b>1.46 (1.16, 1.83)</b>	<b>1.56 (1.21, 1.97)</b>	1.44 (0.77, 3.66)	2.14 (0.31, 14.60)
Chronic Renal Insufficiency/ESRD	<b>1.97 (1.59, 2.79)</b>	<b>1.91 (1.29, 2.74)</b>	<b>14.15 (4.2, 50.2)</b>	4.67 (0.55, 76.6)
Morbid Obesity, BMI 40+ kg/m <sup>2</sup>	<b>1.39 (1.12, 1.72)</b>	<b>1.24 (1.00, 1.66)</b>	0.80 (0.38, 1.71)	1.09 (0.23, 5.22)
Lung Disease <sup>6</sup>	<b>2.03 (1.76, 2.47)</b>	<b>2.24 (1.62, 2.85)</b>	<b>5.24 (2.04, 13.5)</b>	2.61 (0.60, 11.28)
Specific RA Medication regimens <sup>7</sup>				
Methotrexate monotherapy	<b>0.82 (0.70, 0.99)</b>	0.91 (0.72, 1.14)	1.12 (0.56, 2.62)	0.63 (0.12, 3.23)
TNFi monotherapy	<b>0.49 (0.33, 0.71)</b>	<b>0.53 (0.36, 0.80)</b>	0.57 (0.16, 2.00)	0.72 (0.03, 2.49)
TNFi + Methotrexate	<b>0.59 (0.42, 0.81)</b>	0.74 (0.51, 1.06)	1.45 (0.72, 4.11)	NA
JAKi monotherapy	0.76 (0.45, 1.00)	<b>1.64 (1.19, 2.24)</b>	1.81 (0.71, 5.63)	NA
Leflunomide monotherapy	<b>0.64 (0.42, 0.98)</b>	1.00 (0.65, 1.53)	0.18 (0.02, 1.72)	3.31 (0.36, 37.65)
Sulfasalazine monotherapy	<b>1.90 (1.14, 3.19)</b>	<b>2.00 (1.03, 3.87)</b>	<b>9.70 (1.07, 51.6)</b>	NA
IL-6-inhibitor monotherapy	0.62 (0.32, 1.20)	<b>0.46 (0.25, 0.84)</b>	0.75 (0.08, 9.22)	NA
Abatacept monotherapy	0.86 (0.51, 1.46)	0.65 (0.39, 1.09)	1.08 (0.34, 4.34)	1.30 (0.11, 14.77)
CD20 monotherapy	<b>3.11 (2.23, 4.74)</b>	<b>2.44 (1.79, 4.21)</b>	<b>3.51 (1.34, 11.1)</b>	3.96 (0.58, 27.19)
Rheumatic Disease Activity				

Remission/Minimal	Ref	Ref	Ref	Ref
Moderate-Severe	1.13 (0.93, 1.38)	<b>1.31 (1.01, 1.60)</b>	1.19 (0.51, 2.55)	2.36 (0.32, 17.38)
<b>Glucocorticoid dose</b>				
None	Ref	Ref	Ref	Ref
1-5 mg/day	<b>1.57 (1.31, 1.88)</b>	1.11 (0.92, 1.35)	<b>2.33 (1.20, 4.53)</b>	0.72 (0.11, 4.77)
6-10 mg/day	<b>1.86 (1.22, 2.85)</b>	1.02 (0.60, 1.72)	3.03 (0.78, 11.79)	4.04 (0.33, 49.02)
>10 mg/day	<b>2.37 (1.80, 3.10)</b>	<b>2.33 (1.63, 3.30)</b>	2.32 (0.76, 6.95)	NA
<p>*Significant values with p&lt;0.05 are bolded</p> <p><sup>1</sup>Epoch 1 (initial wave, COVID-19 diagnoses between January 1<sup>st</sup>, 2020, to October 31<sup>st</sup>, 2020)</p> <p><sup>2</sup>Epoch 2 (Alpha variant, COVID-19 diagnoses between November 1<sup>st</sup>, 2020, to May 31<sup>st</sup>, 2021)</p> <p><sup>3</sup>Epoch 3 (Delta variant, COVID-19 diagnoses between June 1<sup>st</sup>, 2021, to November 25<sup>th</sup>, 2021)</p> <p><sup>4</sup>Epoch 4 (Omicron variant, COVID-19 diagnoses between November 26<sup>th</sup>, 2021 – study end [June 30<sup>th</sup>, 2022])</p> <p><sup>5</sup>The human development index is a summary composite score of a country's average achievements in three key dimensions of human development: health, knowledge, and standard of living. It is expressed as a value between 0 and 1, with higher scores being associated with a country's higher human development.</p> <p><sup>6</sup>Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma</p> <p>CVD: cardiovascular disease; ESRD: end stage renal disease; TNFi: tumor necrosis factor inhibitor; IL: Interleukin; JAKi: Janus kinases inhibitor</p> <p><sup>7</sup>Specific medication regimens were each compared to all other patients within this rheumatic diagnostic group who were not prescribed this regimen.</p>				

**Table 4.** Imputed odds of more severe COVID-19 using the ordinal outcome stratified by COVID-19 epochs for unvaccinated patients with Spondyloarthritis using specific disease categories

Covariates	Epoch 1 <sup>1</sup> (N = 2,172)	Epoch 2 <sup>2</sup> (N = 2,018)	Epoch 3 <sup>3</sup> (N = 156)	Epoch 4 <sup>4,**</sup> (N = 133)
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
<b>Age</b>	<b>1.04 (1.03, 1.06)</b>	<b>1.06 (1.04, 1.07)</b>	<b>1.06 (1.00, 1.13)</b>	NA
<b>Sex</b>				
Female	Ref	Ref	Ref	Ref
Male	<b>1.63 (1.23, 2.16)</b>	1.2 (0.86, 1.67)	1.01 (0.36, 2.80)	NA
<b>Human Development Index<sup>5</sup></b>	<b>0.96 (0.94, 0.98)</b>	<b>0.96 (0.93, 0.98)</b>	<b>0.89 (0.82, 0.98)</b>	NA
<b>Common comorbidities</b>				
Hypertension and/or CVD	0.85 (0.61, 1.17)	1.12 (0.72, 1.63)	1.00 (0.36, 3.43)	NA
Diabetes mellitus	<b>1.82 (1.41, 2.64)</b>	<b>1.56 (1.00, 2.42)</b>	0.98 (0.18, 5.49)	NA
Chronic Renal Insufficiency/ESRD	<b>2.62 (1.29, 5.32)</b>	<b>2.07 (1.00, 4.29)</b>	1.31 (0.05, 31.72)	NA
Morbid Obesity, BMI 40+ kg/m <sup>2</sup>	1.34 (0.98, 1.89)	1.40 (0.95, 2.07)	1.54 (0.43, 5.55)	NA
Lung Disease <sup>6</sup>	<b>2.22 (1.26, 3.28)</b>	<b>2.01 (1.23, 3.28)</b>	1.50 (0.17, 13.54)	NA
<b>Specific Rheumatic Medications<sup>7</sup></b>				
Methotrexate monotherapy	1.03 (0.69, 1.54)	0.96 (0.58, 1.62)	4.32 (0.95, 19.58)	NA
TNFi monotherapy	<b>0.58 (0.33, 0.70)</b>	0.77 (0.49, 1.19)	2.18 (0.61, 7.87)	NA
TNFi + Methotrexate	0.63 (0.37, 1.08)	0.93 (0.54, 1.61)	4.37 (0.72, 26.68)	NA
JAKi monotherapy	0.71 (0.23, 2.21)	0.96 (0.13, 6.95)	NA	NA
Leflunomide monotherapy	1.55 (0.63, 3.79)	0.88 (0.23, 3.31)	NA	NA
Sulfasalazine monotherapy	0.98 (0.49, 1.95)	1.81 (0.94, 3.48)	NA	NA
IL-17-inhibitor monotherapy	0.73 (0.43, 1.24)	0.51 (0.25, 1.06)	NA	NA
<b>Rheumatic Disease Activity</b>				
Remission/Minimal	Ref	Ref	Ref	Ref
Moderate-Severe	1.32 (0.86, 1.75)	<b>1.84 (1.21, 2.79)</b>	1.33 (0.22, 6.10)	NA
<b>Glucocorticoid dose</b>				

None	Ref	Ref	Ref	Ref
1-5 mg/day	<b>1.68 (1.00, 2.82)</b>	1.55 (0.97, 2.47)	1.29 (0.32, 5.20)	NA
6-10 mg/day	2.25 (0.79, 6.43)	<b>5.25 (1.72, 16.01)</b>	0.98 (0.20, 110.83)	NA
>10 mg/day	0.93 (0.44, 1.97)	<b>5.55 (2.46, 12.55)</b>	NA	NA

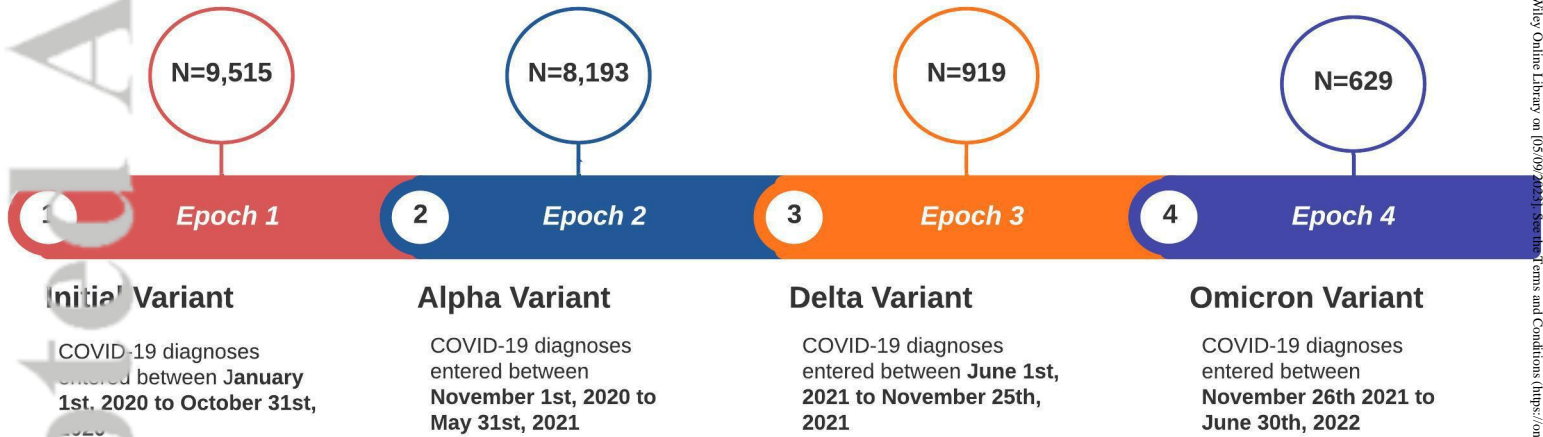
\*Significant values with p<0.05 are bolded  
\*\*Convergence not achieved in last COVID-19 epoch due to lack of power  
<sup>1</sup>Epoch 1 (initial wave, COVID-19 diagnoses between January 1<sup>st</sup>, 2020, to October 31<sup>st</sup>, 2020)  
<sup>2</sup>Epoch 2 (Alpha variant, COVID-19 diagnoses between November 1<sup>st</sup>, 2020, to May 31<sup>st</sup>, 2021)  
<sup>3</sup>Epoch 3 (Delta variant, COVID-19 diagnoses between June 1<sup>st</sup>, 2021, to November 25<sup>th</sup>, 2021)  
<sup>4</sup>Epoch 4 (Omicron variant, COVID-19 diagnoses between November 26<sup>th</sup>, 2021 – study end [June 30<sup>th</sup>, 2022])  
<sup>5</sup>The human development index is a summary composite score of a country's average achievements in three key dimensions of human development: health, knowledge, and standard of living. It is expressed as a value between 0 and 1, with higher scores being associated with a country's higher human development.  
<sup>6</sup>Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma  
CVD: cardiovascular disease; ESRD: end stage renal disease; TNFi: tumor necrosis factor inhibitor; IL: Interleukin; JAKi: Janus kinases inhibitor  
<sup>7</sup>Specific medication regimens were each compared to all other patients within this rheumatic diagnostic group who were not prescribed this regimen.

**Table 5.** Imputed odds of more severe COVID-19 using the ordinal outcome stratified by COVID-19 epochs for unvaccinated patients with Connective Tissue Disease/Vasculitis (N=6,136) using specific disease categories.

Covariates	Epoch 1 <sup>1</sup> (N =3,235)	Epoch 2 <sup>2</sup> (N = 2,297)	Epoch 3 <sup>3</sup> (N = 346)	Epoch 4 <sup>4</sup> (N = 256)
	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*	OR (95% CI)*
<b>Age</b>	<b>1.04 (1.03, 1.04)</b>	<b>1.04 (1.03, 1.05)</b>	1.01 (0.99, 1.03)	<b>1.05 (1.01, 1.09)</b>
<b>Sex,</b>				
Female	Ref	Ref	Ref	Ref
Male	<b>1.67 (1.36, 2.16)</b>	<b>1.64 (1.27, 2.19)</b>	1.52 (0.59, 3.89)	0.99 (0.33, 2.97)
<b>Human Development Index<sup>5</sup></b>	<b>0.98 (0.95, 0.97)</b>	<b>0.97 (0.95, 0.99)</b>	<b>0.92 (0.88, 0.96)</b>	<b>0.94 (0.89, 0.99)</b>
<b>Common comorbidities</b>				
Hypertension and/or Cardiovascular Disease	<b>1.42 (1.15, 1.77)</b>	<b>1.62 (1.25, 2.10)</b>	1.12 (0.52, 2.38)	1.34 (0.4, 3.18)
Diabetes mellitus	<b>1.63 (1.09, 2.06)</b>	<b>1.75 (1.37, 2.80)</b>	1.51 (0.53, 5.16)	2.09 (0.51, 9.32)
Chronic Renal Insufficiency/ESRD	<b>2.06 (1.44, 2.71)</b>	<b>2.25 (1.48, 3.37)</b>	<b>12.16 (5.57, 24.6)</b>	2.92 (0.7, 15.00)
Morbid Obesity, BMI 40+ kg/m <sup>2</sup>	<b>1.33 (1.03, 1.73)</b>	1.08 (0.78, 1.47)	<b>2.43 (1.01, 5.87)</b>	0.66 (0.12, 2.32)
Lung Disease <sup>6</sup>	<b>1.40 (1.11, 1.76)</b>	<b>2.26 (1.73, 2.95)</b>	2.00 (0.98, 4.89)	1.87 (0.49, 6.13)
<b>Specific Rheumatic Medications<sup>7</sup></b>				
Methotrexate monotherapy	0.81 (0.52, 1.14)	0.80 (0.56, 1.26)	0.72 (0.16, 3.48)	0.54 (0.04, 5.91)
TNFi monotherapy	<b>0.27 (0.11, 0.63)</b>	<b>0.21 (0.05, 0.80)</b>	NA	2.91 (0.26, 13.58)
Azathioprine +/- hydroxychloroquine	1.05 (0.77, 1.42)	0.88 (0.62, 1.25)	0.68 (0.17, 2.08)	1.77 (0.55, 6.61)
mycophenolate mofetil/mycophenolic acid +/- hydroxychloroquine	0.89 (0.61, 1.20)	1.17 (0.85, 1.67)	0.55 (0.20, 1.50)	0.68 (0.16, 3.54)
IL-6-inhibitor monotherapy	0.41 (0.13, 1.24)	<b>0.18 (0.05, 0.62)</b>	NA	NA
CD20 (y/n)	<b>1.90 (1.32, 2.80)</b>	<b>3.25 (2.17, 5.10)</b>	<b>4.95 (2.14, 13.67)</b>	1.38 (0.28, 6.28)
<b>Rheumatic Disease Activity</b>				
Remission/Minimal	Ref	Ref	Ref	Ref
Moderate-Severe	<b>1.90 (1.62, 2.43)</b>	<b>1.87 (1.39, 2.53)</b>	1.74 (0.99, 3.51)	<b>3.46 (1.16, 9.97)</b>



Glucocorticoid dose				
None	Ref	Ref	Ref	Ref
1-5 mg/day	<b>1.67 (1.34, 2.07)</b>	1.27 (0.98, 1.62)	1.26 (0.62, 2.60)	2.24 (0.67, 7.67)
6-10 mg/day	<b>1.75 (1.18, 2.60)</b>	<b>2.35 (1.50, 3.69)</b>	4.43 (1.76, 11.16)	2.70 (0.44, 16.49)
>10 mg/day	<b>3.58 (2.79, 4.72)</b>	<b>2.30 (1.65, 3.21)</b>	2.67 (1.16, 6.53)	3.17 (0.76, 13.32)
<p>*Significant values with p&lt;0.05 are bolded</p> <p><sup>1</sup>Epoch 1 (initial wave, COVID-19 diagnoses between January 1<sup>st</sup>, 2020, to October 31<sup>st</sup>, 2020)</p> <p><sup>2</sup>Epoch 2 (Alpha variant, COVID-19 diagnoses between November 1<sup>st</sup>, 2020, to May 31<sup>st</sup>, 2021)</p> <p><sup>3</sup>Epoch 3 (Delta variant, COVID-19 diagnoses between June 1<sup>st</sup>, 2021, to November 25<sup>th</sup>, 2021)</p> <p><sup>4</sup>Epoch 4 (Omicron variant, COVID-19 diagnoses between November 26<sup>th</sup>, 2021 – study end [June 30<sup>th</sup>, 2022])</p> <p><sup>5</sup>The human development index is a summary composite score of a country's average achievements in three key dimensions of human development: health, knowledge, and standard of living. It is expressed as a value between 0 and 1, with higher scores being associated with a country's higher human development.</p> <p><sup>6</sup>Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma</p> <p>CVD: cardiovascular disease; ESRD: end stage renal disease; TNFi: tumor necrosis factor inhibitor; IL: Interleukin; JAKi: Janus kinases inhibitor</p> <p><sup>7</sup>Specific medication regimens were each compared to all other patients within this rheumatic diagnostic group who were not prescribed this regimen.</p>				



covid timeline.jpeg