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Impact of Risk Factors on COVID-19 Outcomes in Unvaccinated People With Rheumatic Diseases: A Comparative Analysis of Pandemic Epochs Using the COVID-19 Global Rheumatology Alliance Registry

Jinoos Yazdany,[1] Anna Ware,[2] Zachary S. Wallace,[3] Suleman Bhana,[4] Rebecca Grainger,[5] Eric Hachulla,[6] Christophe Richez,[7] Patrice Cacoub,[8] Jonathan S. Hausmann,[9] Jean W. Liew,[10] Emily Sirotich,[11] Lindsay Jacobsohn,[1] Anja Strangfeld,[12] Elsa F. Mateus,[13] Kimme L. Hyrich,[14] Laure Gossec,[15] Loreto Carmona,[16] Saskia Lawson-Tovey,[17] Lianne Kearsley-Fleet,[18] Martin Schaefer,[19] Sandra Lucia Euzebio Ribeiro,[20] Samar Al-Emadi,[21] Rebecca Hasseli,[22] Ulf Müller-Ladner,[23] Christof Specker,[24] Hendrik Schulze-Koops,[25] Miguel Bernardes,[26] Vanessa Machado Fraga,[27] Ana Maria Rodrigues,[28] Jeffrey A. Sparks,[29] Lotta Ljung,[30] Daniela Di Giuseppe,[31] Liselotte Tidblad,[31] Leanna Wise,[32] Alí Duarte-García,[33] Manuel F. Ugarte-Gil,[34] Iris Jazmín Colunga-Pedraza,[35] Marco Ulises Martínez-Martínez,[36] Deshire Alpizar-Rodriguez,[37] Ricardo Machado Xavier,[38] Carolina A. Isnardi,[39] Mariana Pera,[40] Guillermo Pons-Estel,[41] Zara Izadi,[1] Milena A. Gianfrancesco,[1] Greta Carrara,[42] Carlo Alberto Scirè,[43] Anna Zanetti,[42] and Pedro M. Machado[44]

Objective. Approximately one third of individuals worldwide have not received a COVID-19 vaccine. Although studies have investigated risk factors linked to severe COVID-19 among unvaccinated people with rheumatic diseases (RDs), 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 RDs 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; subanalyses stratified patients according to RD types.

Results. Among 19,256 unvaccinated people with RDs 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 tumor necrosis factor inhibitors were associated with improved outcomes. In those with connective tissue disease or vasculitis, B-cell–depleting therapy was associated with worse outcomes.

Conclusion. Risk factors for severe COVID-19 outcomes were similar throughout pandemic epochs in unvaccinated people with RDs. 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.

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.[1] Additionally, a small proportion of people

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[1]Jinoos Yazdany, MD, MPH, Lindsay Jacobsohn, BA, Zara Izadi, MPharm, MAS, Milena A. Gianfrancesco, MPH, PhD: University of California, San Francisco; [2]Anna Ware, MPH: National Center for Collaborative Healthcare Innovation, Palo Alto Department of Veterans Affairs Healthcare System, Palo Alto, California; [3]Zachary S. Wallace, MD, MSc: Massachusetts General Hospital and Harvard Medical School, Boston; [4]Suleman Bhana, MD, FACR: Pfizer, New York City, New York; [5]Rebecca Grainger, MBChB, BMedSci, PhD: University of Otago

SIGNIFICANCE & INNOVATIONS

- 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.
- 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.
- This is the final report 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.

with rheumatic diseases have a blunted or absent antibody response to vaccination.[2] Although 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, it is not clear whether these risk factors were similar through subsequent waves caused by different viral variants.[3] 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.[4,5] Although the 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, although it remains unclear whether this resulted from increased virulence, few effective therapies, or overwhelmed health care systems.[6] 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.[6]

Wellington and Te Whatu Ora, Health New Zealand Capital, Coast and Hutt Valley, Wellington, New Zealand; [6]Eric Hachulla, MD: Service de Médecine Interne et Immunologie Clinique, Centre Hospitalier Universitaire (CHU) de Lille, pour la Filière des maladies Auto-Immunes et Autoinflammatoires Rares, Lille, France; [7]Christophe Richez, MD, PhD: Service de Rhumatologie, Centre de référence des maladies autoimmunes systémiques rares de l'Est et du Sud-Ouest de France, CHU de Bordeaux, pour la Société Française de Rhumatologie, Bordeaux, France; [8]Patrice Cacoub, MD: AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Société Nationale Française de Médecine Interne, Paris, France; [9]Jonathan S. Hausmann, MD: Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts; [10]Jean W. Liew, MD, MS: Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts; [11]Emily Sirotich, PhD: Yale School of Medicine, New Haven, Connecticut; [12]Anja Strangfeld, MD, PhD: German Rheumatism Research Center and Charité University Hospital, Berlin, Germany; [13]Elsa F. Mateus, PhD: Portuguese League Against Rheumatic Diseases, Lisbon, Portugal, and European Alliance of Associations for Rheumatology, Kilchberg, Switzerland; [14]Kimme L. Hyrich, MD, PhD: Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester Academic Health Science Centre and NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [15]Laure Gossec, MD, PhD: Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique and AP-HP, Pitié-Salpêtrière hospital, Paris, France; [16]Loreto Carmona, MD, PhD: Instituto de Salud Musculoesquelética, Madrid, Spain; [17]Saskia Lawson-Tovey, BA: Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, University of Manchester, and NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [18]Lianne Kearsley-Fleet, PhD: Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; [19]Martin Schaefer, PhD: German Rheumatism Research Center, Berlin, Germany; [20]Sandra Lucia Euzebio Ribeiro, MD: Federal University of Amazonas, Manaus, Brazil; [21]Samar Al-Emadi, MBBS: Hamad General Hospital, Doha, Qatar; [22]Rebecca Hasseli, MD: University Hospital Munster, Munster, Germany, and Justus Liebig University Giessen, Kerckhoff, Germany; [23]Ulf Müller-Ladner, MD: Justus Liebig University Giessen, Kerckhoff, Germany; [24]Christof Specker, MD: Kliniken Essen-Mitte, Essen, Germany; [25]Hendrik Schulze-Koops, MD: University of Munich, Munich, Germany; [26]Miguel Bernardes, MD, PhD: University of Porto and Centro Hospitalar e Universitário de São João, Porto, Portugal; [27]Vanessa Machado Fraga, MD: Hospital Garcia de Orta, Almada, Portugal; [28]Ana Maria Rodrigues, MD, PhD: Sociedade Portuguesa de Reumatologia and Comprehensive Health Research Centre, Nova Medical School, Universidade Nova de Lisboa, Lisbon, Portugal; [29]Jeffrey A. Sparks, MD, MMSc: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [30]Lotta Ljung, MD, PhD: Karolinska Institutet and Academic Specialist Centre, Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden; [31]Daniela Di Giuseppe, PhD, Liselotte Tidblad, MD: Karolinska Institutet, Stockholm, Sweden; [32]Leanna Wise, MD, MPH: Keck School of Medicine, University of Southern California, Los Angeles; [33]Alí Duarte-García, MD, MSc: Mayo Clinic, Rochester, Minnesota; [34]Manuel F. Ugarte-Gil, MD, MSc: Grupo Peruano de Estudio de Enfermedades Autoinmunes Sistémica, Universidad Científica del Sur and Hospital Nacional Guillermo Almenara Irigoyen - EsSalud, Lima, Peru; [35]Iris Jazmín Colunga-Pedraza, MD, PhD: Hospital Universitario José Eleuterio González, Monterrey, Mexico; [36]Marco Ulises Martínez-Martínez, MD, MSc, PhD: Hospital General de Subzona No. 9, Instituto Mexicano del Seguro Social, San Luis, Potosí, Mexico; [37]Deshire Alpizar-Rodriguez, MD, PhD: Colegio Mexicano de Reumatología, Mexico City, Mexico; [38]Ricardo Machado Xavier, MD, PhD: Universidade Federal do Rio Grande do Sul, Serviço de Reumatologia, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [39]Carolina A. Isnardi, MD: Argentine Society of Rheumatology, Buenos Aires, Argentina; [40]Mariana Pera, MD: Hospital Angel C. Padilla, San Miguel de Tucuman, Tucuman, Argentina; [41]Guillermo Pons-Estel, MD, MSc, PhD: Universidad Nacional de Rosario, Rosario, Argentina, and College of Physicians of the Province of Santa Fe 2nd, Santa Fe, Argentina; [42]Greta Carrara, MSc, Anna Zanetti, PhD: Italian Society for Rheumatology, Milan, Italy; [43]Carlo Alberto Scirè, MD, PhD: Italian Society for Rheumatology and School of Medicine, University of Milano-Bicocca, Milan, Italy; [44]Pedro M. Machado, MD, PhD: University College London, NIHR University College London Hospitals Biomedical Research Centre, University College London Hospitals NHS Foundation Trust, and Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK.

Authors Yazdany and Ware contributed equally to this work.

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Address correspondence via email to Jinoos Yazdany, MD, MPH, at jinoos.yazdany@ucsf.edu

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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 such as renal or lung disease, and male sex are associated with a higher risk of hospitalization and death from COVID-19.[3,7] 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[8,9] Some medications that were of concern initially, such as tumor necrosis factor inhibitors (TNFis), have not been associated with poor outcomes.[10] 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 study, 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 (COVID-19 GRA) physician-reported registry was launched on March 24, 2020. Data were entered voluntarily by rheumatologists or under the supervision of rheumatologists; patients were eligible for inclusion if they had a preexisting 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.[7–9,11] Briefly, COVID-19 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, 2020, to June 30, 2022 (n = 23,785). Because 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 the 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, 2020, and October 31, 2020), Epoch 2 (alpha variant, COVID-19 diagnoses between November 1, 2020, and May 31, 2021), Epoch 3 (delta variant, COVID-19 diagnoses between June 1, 2021, and November 25, 2021), and Epoch 4 (omicron variant, COVID-19 diagnoses between November 26, 2021, and study end [June 30, 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.

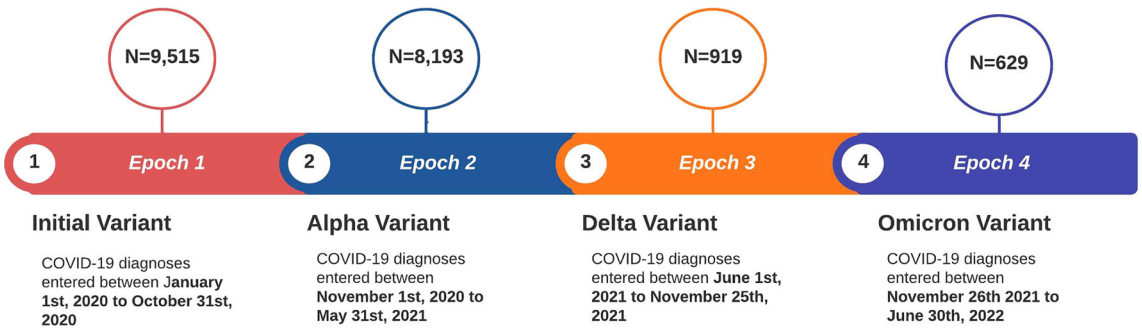

Figure 1. Pandemic epochs included in this study and corresponding number of patients represented in each epoch.

COVID-19 vaccination status. Vaccination status was included in the registry starting in January 2021, which was approximately 1 month after Food and Drug Administration 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 https://ourworldindata.org/.[12]

Covariates. Patient information including age (years), sex (male or female), race and/or ethnicity, rheumatic disease diagnosis, rheumatic disease medication before 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) and time since the start of Epoch 1 (both described in the following section).[13]

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 include data available in the electronic health record, patient-reported race and ethnicity, or data derived from inference. In this study, race and/or ethnicity was categorized as 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 (CTDs)/vasculitis (including systemic lupus erythematosus [SLE], vasculitis, systemic sclerosis, antineutrophilic cytoplasmic antibody–associated vasculitis, mixed CTD, undifferentiated CTD/overlap, giant cell arteritis, idiopathic inflammatory myopathies [including polymyositis, and dermatomyositis], other vasculitis, Kawasaki disease, Sjögren's syndrome, Behcet's disease, and polymyalgia rheumatica).

Patients with multiple rheumatic diseases were adjudicated so that those with more than one diagnosis within the same disease category (eg, SLE and vasculitis) stayed within that disease category (CTDs/vasculitis) and those with multiple rheumatic diseases within two or more primary categories (eg, 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 (8). 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).

Medications used before COVID-19 diagnosis were analyzed using mutually exclusive medication categories for the main analysis including all patients. Overarching medications groups used in the main analysis were categorized as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including antimalarials (hydroxychloroquine and 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 (ts) DMARDs or non-TNFis, including tofacitinib, baricitinib, apremilast, upadacitinib, abatacept, belimumab, rituximab, interleukin-1 (IL-1) inhibitors (anakinra, canakinumab, and rilonacept), IL-6 inhibitors (tocilizumab and sarilumab), IL-12/23 inhibitors (ustekinumab and guselkumab), IL-17 inhibitors (secukinumab and ixekizumab), and IL-23 inhibitors (guselkumab, risankizumab, and tildrakizumab); TNFis, including adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; combination csDMARD and TNFi therapy; and lastly, combination csDMARD and non-TNFis. 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, 6–10 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 health care resources and socioeconomic status. Countries were assigned to the six World Health Organization regions (https://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.[14] Additionally, time since the start of Epoch 1 (January 1, 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 in the following. Covariates with significant missingness (ie, 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 20 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, and CTDs/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/day, 6–10 mg/day, 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 with 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 ≥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 + 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 reran the main model including the covariates described above, stratified for each COVID-19 epoch without using multiple imputation. Second, because 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 postestimation equations for each COVID-19 epoch.[15]

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). Because of 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 (ie, 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 30, 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 (≥72.0%), were non-Hispanic White (≥43.0%), and resided in Europe (≥30.1%), North America (≥18.6%), or South America (≥13.5%). The most common rheumatic diagnostic group was RA (n = 8,750 [45.4%]), followed by CTDs/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 were 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) versus 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 CTDs/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 being 35.1% among those with RA, 10.2% among those with spondyloarthritis, and 46.0% among those with CTDs/vasculitis (Supplementary Table S2).

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*

Characteristics	Epoch 1[a] (N = 9,515)	Epoch 2[b] (N = 8,193)	Epoch 3[c] (N = 919)	Epoch 4[d] (N = 629)
Age				
Age (year), mean ± SD	54 ± 16.0	54 ± 15.6	51 ± 15.9	50 ± 16.1
Sex, n (%)				
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)
Human development index, mean ± SD[e]	0.87 ± 0.1	0.89 ± 0.1	0.86 ± 0.1	0.88 ± 0.1
Race or ethnicity, n (%)				
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)
Regions, n (%)				
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)
Comorbidity count, n (%)				
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)
Common comorbidities, n (%)				
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^2	1,607 (16.9)	1,446 (17.7)	150 (16.3)	111 (17.7)
Lung disease[f]	1,378 (14.5)	891 (10.9)	87 (9.5)	64 (10.2)
Primary rheumatic disease category, n (%)				
Rheumatoid arthritis[g]	4,167 (43.8)	3,921 (47.9)	421 (45.9)	241 (38.1)
Spondyloarthritis[h]	2,172 (22.8)	2,018 (24.6)	156 (17.0)	133 (21.1)
Connective tissue disease/vasculitis[i]	3,235 (34.0)	2,297 (28.0)	346 (37.6)	256 (40.7)
Rheumatic disease activity, n (%)				
Remission/minimal	5,808 (61.0)	6,367 (77.7)	701 (76.2)	498 (79.2)
Moderate to 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)
Rheumatic disease medications, n (%)[j]				
None	1,539 (16.2)	1,265 (15.4)	132 (14.4)	80 (12.7)
csDMARD monotherapy[k]	4,328 (45.5)	3,571 (43.6)	447 (48.6)	288 (45.8)
TNFi monotherapy[l]	1,198 (12.6)	1,117 (13.6)	102 (11.1)	94 (14.9)
Non-TNFi biologics or tsDMARD monotherapy[m]	807 (805)	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)
Common medication regimens, n (%)				
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)
JAKi monotherapy	186 (2.0)	261 (3.2)	26 (2.8)	10 (1.6)
JAKi + 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)

(Continued)

Table 1. (*Cont'd*)

Characteristics	Epoch 1[a] (N = 9,515)	Epoch 2[b] (N = 8,193)	Epoch 3[c] (N = 919)	Epoch 4[d] (N = 629)
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)
Categories of glucocorticoid dose in prednisone daily equivalents, n (%)				
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)
COVID-19–related outcomes, n (%)				
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)

* BMI = body mass index; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ESRD = end-stage renal disease; IL = interleukin; JAKi = janus kinase inhibitor; TNFi = tumor necrosis factor inhibitor; tsDMARD = targeted synthetic DMARD.
a Initial wave: COVID-19 diagnoses between January 1, 2020, and October 31, 2020.
b Alpha variant: COVID-19 diagnoses between November 1, 2020, and May 31, 2021.
c Delta variant: COVID-19 diagnoses between June 1, 2021, and November 25, 2021.
d Omicron variant: COVID-19 diagnoses between November 26, 2021, and study end (June 30, 2022).
e 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.
f Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma.
g Rheumatoid arthritis designated as primary rheumatic diagnosis.
h Spondyloarthritis includes psoriatic arthritis, reactive arthritis, ankylosing spondylitis, or other spondyloarthritis.
i Connective tissue diseases/vasculitis include systemic lupus erythematosus, vasculitis, systemic sclerosis, antineutrophilic cytoplasmic antibody–associated vasculitis, mixed connective tissue disease, undifferentiated connective tissue disease/overlap, giant cell arteritis, inflammatory myopathies (including polymyositis, dermatomyositis), other vasculitis, Kawasaki disease, Sjögren's syndrome, Behcet's disease, and polymyalgia rheumatica.
j Rheumatic disease medication categories are not mutually exclusive.
k csDMARDs included auranofin, aurothioglucose, azathioprine, chloroquine hydrochloride, chloroquine phosphate, cyclophosphamide, cyclosporine, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, mercaptopurine, mesalamine, methotrexate, minocycline hydrochloride, n-acetylpenicillamine, penicillamine, primaquine, sulfasalazine, tacrolimus, and thalidomide.
l TNFis included adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.
m Non-TNFi biologics included abatacept, belimumab, rituximab, IL-1 inhibitors (anakinra, canakinumab, and rilonacept), IL-6 inhibitors (tocilizumab and sarilumab), IL-12/23 inhibitors (ustekinumab and guselkumab), IL-17 inhibitors (secukinumab and ixekizumab), and IL-23 inhibitors (guselkumab, risankizumab, and tildrakizumab); tsDMARDs included tofacitinib, baricitinib, apremilast, and upadacitinib.

Main analysis. Table 2 presents associations between COVID-19 outcome status and covariates across the four 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 (odds ratio [OR] and 95% confidence interval [95% CI] 0.97 [0.96–0.98], 0.97 [0.96–0.98], and 0.94 [0.91–0.96] for Epochs 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 but did not reach statistical significance, likely due to a smaller sample size.

Among the rheumatic disease categories, compared with RA as the referent, spondyloarthritis was associated with less risk of severe COVID-19 outcomes (OR [95% CI] 0.77 [0.64–0.93], $P = 0.01$) and CTDs/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 TNFis (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), whereas combinations of csDMARD and non-TNFi/tsDMARDs were associated with more frequent severe outcomes compared with 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 (1–5 mg: OR [95% CI] 1.55 [1.02–2.35], $P = 0.01$ vs >10 mg: 3.10 [1.67–5.74], $P < 0.01$; Epoch 3, Table 2).

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[a] (N = 9,515)	Epoch 2[b] (N = 8,193)	Epoch 3[c] (N = 919)	Epoch 4[d] (N = 629)
Age	**1.04 (1.04–1.05)**	**1.05 (1.04–1.05)**	**1.03 (1.02–1.04)**	**1.04 (1.01–1.07)**
Sex				
Female	REF	REF	REF	REF
Male	**1.57 (1.40–1.77)**	**1.50 (1.30–1.71)**	1.32 (0.82–2.12)	1.39 (0.64–3.04)
Human development index[e]	**0.97 (0.96–0.98)**	**0.97 (0.96–0.98)**	**0.94 (0.91–0.96)**	0.97 (0.93–1.01)
Common comorbidities				
Hypertension and/or cardiovascular disease	**1.21 (1.07–1.36)**	**1.39 (1.21–1.60)**	1.22 (0.81–1.85)	1.45 (0.69–3.05)
Diabetes mellitus	**1.54 (1.32–1.79)**	**1.58 (1.33–1.89)**	1.62 (0.88–2.96)	1.74 (0.63–4.81)
Chronic renal insufficiency/ESRD	**2.26 (1.82–2.74)**	**2.24 (1.75–2.87)**	**8.16 (4.40–15.1)**	2.48 (0.85–7.25)
Morbid obesity, BMI 40+ kg/m^2	**1.30 (1.13–1.49)**	**1.19 (1.01–1.39)**	1.36 (0.85–2.18)	0.82 (0.33–2.02)
Lung disease[f]	**1.80 (1.58–2.07)**	**2.24 (1.91–2.64)**	**2.83 (1.65–4.86)**	2.18 (0.90–5.29)
Rheumatic disease category				
Rheumatoid arthritis[g]	REF	REF	REF	REF
Spondyloarthritis[h]	**0.81 (0.70–0.95)**	**0.77 (0.64–0.93)**	1.09 (0.60–1.94)	0.53 (0.12–2.43)
Connective tissue disease/vasculitis[i]	**1.14 (1.01–1.29)**	**1.61 (1.40–1.87)**	1.18 (0.74–1.76)	1.85 (0.87–3.94)
Rheumatic medications[j]				
None	**1.18 (1.02–1.37)**	0.96 (0.81–1.14)	0.88 (0.51–1.52)	1.27 (0.52–3.12)
csDMARD monotherapy[k]	REF	REF	REF	REF
TNFi monotherapy[l]	**0.51 (0.41–0.64)**	**0.67 (0.44–0.73)**	0.79 (0.34–1.80)	0.93 (0.26–3.38)
Non-TNFi biologics or tsDMARD[m]	1.06 (0.87–1.30)	1.11 (0.90–1.36)	**2.10 (1.21–3.63)**	0.90 (0.26–3.15)
Combination csDMARD and TNFi	**0.69 (0.56–0.85)**	**0.72 (0.56–0.92)**	1.21 (0.60–2.44)	0.32 (0.4–2.72)
Combination csDMARD and non-TNFi/tsDMARD	**1.35 (1.11–1.63)**	**1.53 (1.22–1.92)**	1.72 (0.91–3.27)	1.88 (0.71–5.00)
Glucocorticoid dose				
None	REF	REF	REF	REF
1–5 mg/day	**1.54 (1.36–1.78)**	**1.20 (1.03–1.38)**	**1.55 (1.02–2.35)**	1.70 (0.76–3.81)
6–10 mg/day	**1.87 (1.42–2.46)**	**1.70 (1.23–2.35)**	**2.32 (1.00–5.36)**	3.30 (0.92–5.43)
>10 mg/day	**3.01 (2.53–3.63)**	**2.62 (2.10–3.29)**	**3.10 (1.67–5.74)**	1.94 (0.70–5.30)
Rheumatic disease activity				
Remission/minimal	REF	REF	REF	REF
Moderate to severe	**1.41 (1.22–1.61)**	**1.63 (1.29–2.05)**	1.18 (0.59–2.37)	**2.15 (1.01–4.81)**

* Values are the odds ratio (95% confidence interval). Significant values are presented in bold text.
BMI = body mass index; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ESRD = end-stage renal disease; IL = interleukin; JAKi = janus kinase inhibitor; REF = reference; TNFi = tumor necrosis factor inhibitor; tsDMARD: targeted synthetic DMARD.
a Initial wave: COVID-19 diagnoses between January 1, 2020, and October 31, 2020.
b Alpha variant: COVID-19 diagnoses between November 1, 2020, and May 31, 2021.
c Delta variant: COVID-19 diagnoses between June 1, 2021, and November 25, 2021.
d Omicron variant: COVID-19 diagnoses between November 26, 2021, and study end (June 30, 2022).
e 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.
f Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma.
g Rheumatoid arthritis as designated as primary rheumatic diagnosis.
h Spondyloarthritis includes psoriatic arthritis, reactive arthritis, ankylosing spondylitis, and other spondyloarthritis.
i Connective tissue diseases/vasculitis includes systemic lupus erythematosus, vasculitis, systemic sclerosis, antineutrophilic cytoplasmic antibody–associated vasculitis, mixed connective tissue disease, undifferentiated connective tissue disease/overlap, giant cell arteritis, inflammatory myopathies (including polymyositis and dermatomyositis), other vasculitis, Kawasaki disease, Sjögren's syndrome, Behcet's disease, and polymyalgia rheumatica.
j Rheumatic medication categories are not mutually exclusive.
k csDMARDs included auranofin, aurothioglucose, azathioprine, chloroquine hydrochloride, chloroquine phosphate, cyclophosphamide, cyclosporine, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, mercaptopurine, mesalamine, methotrexate, minocycline hydrochloride, n-acetylpenicillamine, penicillamine, primaquine, sulfasalazine, tacrolimus, and thalidomide.
l TNFis included adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.
m Non-TNFi biologics included abatacept, belimumab, rituximab, IL-1 inhibitors (anakinra, canakinumab, and rilonacept), IL-6 inhibitors (tocilizumab and sarilumab), IL-12/23 inhibitors (ustekinumab and guselkumab), IL-17 inhibitors (secukinumab and ixekizumab), and IL-23 inhibitors (guselkumab, risankizumab, and tildrakizumab). tsDMARDs included tofacitinib, baricitinib, apremilast, and upadacitinib.

Stratified analyses by disease category. For subanalyses among each rheumatic diagnostic group stratified across the four 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 CTDs/vasculitis (Epoch 1 [n = 3,235], Epoch

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[a] (N = 4,167)	Epoch 2[b] (N = 3,921)	Epoch 3[c] (N = 421)	Epoch 4[d] (N = 241)
Age	**1.05 (1.04–1.06)**	**1.06 (1.05–1.06)**	**1.05 (1.02–1.07)**	1.03 (0.98–1.00)
Sex				
Female	REF	REF	REF	REF
Male	**1.41 (1.17–1.72)**	**1.51 (1.21–1.80)**	1.53 (0.80–3.16)	2.85 (0.71–11.71)
Human development index[e]	**0.97 (0.95–0.98)**	**0.97 (0.96–0.98)**	**0.95 (0.92–0.99)**	1.06 (0.92–1.21)
Common comorbidities, n (%)				
Hypertension and/or CVD	**1.20 (1.01–1.42)**	**1.34 (1.10–1.64)**	1.24 (0.66–2.36)	1.00 (0.26–4.43)
Diabetes mellitus	**1.46 (1.16–1.83)**	**1.56 (1.21–1.97)**	1.44 (0.77–3.66)	2.14 (0.31–14.60)
Chronic renal insufficiency/ESRD	**1.97 (1.59–2.79)**	**1.91 (1.29–2.74)**	**14.15 (4.2–50.2)**	4.67 (0.55–76.6)
Morbid obesity, BMI 40+ kg/m^2	**1.39 (1.12–1.72)**	**1.24 (1.00–1.66)**	0.80 (0.38–1.71)	1.09 (0.23–5.22)
Lung disease[f]	**2.03 (1.76–2.47)**	**2.24 (1.62–2.85)**	**5.24 (2.04–13.5)**	2.61 (0.60–11.28)
Specific RA medication regimens[g]				
Methotrexate monotherapy	**0.82 (0.70–0.99)**	0.91 (0.72–1.14)	1.12 (0.56–2.62)	0.63 (0.12–3.23)
TNFi monotherapy	**0.49 (0.33–0.71)**	**0.53 (0.36–0.80)**	0.57 (0.16–2.00)	0.72 (0.03–2.49)
TNFi + methotrexate	**0.59 (0.42–0.81)**	0.74 (0.51–1.06)	1.45 (0.72–4.11)	NA
JAKi monotherapy	0.76 (0.45–1.00)	**1.64 (1.19–2.24)**	1.81 (0.71–5.63)	NA
Leflunomide monotherapy	**0.64 (0.42–0.98)**	1.00 (0.65–1.53)	0.18 (0.02–1.72)	3.31 (0.36–37.65)
Sulfasalazine monotherapy	**1.90 (1.14–3.19)**	**2.00 (1.03–3.87)**	**9.70 (1.07–51.6)**	NA
IL-6 inhibitor monotherapy	0.62 (0.32–1.20)	**0.46 (0.25–0.84)**	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	**3.11 (2.23–4.74)**	**2.44 (1.79–4.21)**	**3.51 (1.34–11.1)**	3.96 (0.58–27.19)
Rheumatic disease activity				
Remission/minimal	REF	REF	REF	REF
Moderate to severe	1.13 (0.93–1.38)	**1.31 (1.01–1.60)**	1.19 (0.51–2.55)	2.36 (0.32–17.38)
Glucocorticoid dose				
None	REF	REF	REF	REF
1–5 mg/day	**1.57 (1.31–1.88)**	1.11 (0.92–1.35)	**2.33 (1.20–4.53)**	0.72 (0.11–4.77)
6–10 mg/day	**1.86 (1.22–2.85)**	1.02 (0.60–1.72)	3.03 (0.78–11.79)	4.04 (0.33–49.02)
>10 mg/day	**2.37 (1.80–3.10)**	**2.33 (1.63–3.30)**	2.32 (0.76–6.95)	NA

* Values are odds ratio (95% confidence interval). Significant values ($P < 0.05$) are presented in bold text.
BMI = body mass index; CVD = cardiovascular disease; ESRD = end-stage renal disease; IL = interleukin; JAKi = janus kinase inhibitor; NA = not applicable; RA = rheumatoid arthritis; REF = reference; TNFi = tumor necrosis factor inhibitor.
a Initial wave: COVID-19 diagnoses between January 1, 2020, and October 31, 2020.
b Alpha variant: COVID-19 diagnoses between November 1, 2020, and May 31, 2021.
c Delta variant: COVID-19 diagnoses between June 1, 2021, and November 25, 2021.
d Omicron variant: COVID-19 diagnoses between November 26, 2021, and study end (June 30, 2022).
e 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.
f Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma.
g Specific medication regimens were each compared with all other patients within this rheumatic diagnostic group who were not prescribed this regimen.

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 before their COVID-19 diagnosis had less severe COVID-19 outcomes for each rheumatic diagnostic group (Tables 3–5).

Among those with RA, anti-CD20 drugs had the strongest association with severe COVID-19 outcomes (highest in Epoch 3: OR [95% CI] 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 (OR [95% CI] 0.18 [0.05–0.62], $P = 0.01$), likely because of small sample sizes (Table 3). We saw similar findings among those with CTDs/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 nonimputed complete-case data set (Supplementary Table S3). Using postestimation equations to analyze the interaction between glucocorticoid therapies and rheumatic disease activity, we found that

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[a] (N = 2,172)	Epoch 2[b] (N = 2,018)	Epoch 3[c] (N = 156)	Epoch 4[d,e] (N = 133)
Age	**1.04 (1.03–1.06)**	**1.06 (1.04–1.07)**	**1.06 (1.00–1.13)**	NA
Sex				
Female	REF	REF	REF	REF
Male	**1.63 (1.23–2.16)**	1.2 (0.86–1.67)	1.01 (0.36–2.80)	NA
Human development index[f]	**0.96 (0.94–0.98)**	**0.96 (0.93–0.98)**	**0.89 (0.82–0.98)**	NA
Common comorbidities				
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	**1.82 (1.41–2.64)**	**1.56 (1.00–2.42)**	0.98 (0.18–5.49)	NA
Chronic renal insufficiency/ESRD	**2.62 (1.29–5.32)**	**2.07 (1.00–4.29)**	1.31 (0.05–31.72)	NA
Morbid obesity, BMI 40+ kg/m^2	1.34 (0.98–1.89)	1.40 (0.95–2.07)	1.54 (0.43–5.55)	NA
Lung disease[g]	**2.22 (1.26–3.28)**	**2.01 (1.23–3.28)**	1.50 (0.17–13.54)	NA
Specific rheumatic medications[h]				
Methotrexate monotherapy	1.03 (0.69–1.54)	0.96 (0.58–1.62)	4.32 (0.95–19.58)	NA
TNFi monotherapy	**0.58 (0.33–0.70)**	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
Rheumatic disease activity				
Remission/minimal	REF	REF	REF	REF
Moderate to severe	1.32 (0.86–1.75)	**1.84 (1.21–2.79)**	1.33 (0.22–6.10)	NA
Glucocorticoid dose				
None	REF	REF	REF	REF
1–5 mg/day	**1.68 (1.00–2.82)**	1.55 (0.97–2.47)	1.29 (0.32–5.20)	NA
6–10 mg/day	2.25 (0.79–6.43)	**5.25 (1.72–16.01)**	0.98 (0.20–110.83)	NA
>10 mg/day	0.93 (0.44–1.97)	**5.55 (2.46–12.55)**	NA	NA

* Values are odds ratio (95% confidence interval). Significant values ($P < 0.05$) are presented in bold text.
BMI = body mass index; CVD = cardiovascular disease; ESRD = end-stage renal disease; IL = interleukin; JAKi = janus kinase inhibitor; NA = not applicable; REF = reference; TNFi = tumor necrosis factor inhibitor.
a Initial wave: COVID-19 diagnoses between January 1, 2020, and October 31, 2020.
b Alpha variant: COVID-19 diagnoses between November 1, 2020, and May 31, 2021.
c Delta variant: COVID-19 diagnoses between June 1, 2021, and November 25, 2021.
d Omicron variant: COVID-19 diagnoses between November 26, 2021, and study end (June 30, 2022).
e Convergence not achieved in last COVID-19 epoch because of lack of power.
f 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.
g Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma.
h Specific medication regimens were each compared with all other patients within this rheumatic diagnostic group who were not prescribed this regimen.

higher disease activity (eg, 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 ≥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 HDI, on COVID-19 outcomes across pandemic epochs. Our findings corroborate previous studies showing that those using TNFis have favorable outcomes

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[a] (N = 3,235)	Epoch 2[b] (N = 2,297)	Epoch 3[c] (N = 346)	Epoch 4[d] (N = 256)
Age	**1.04 (1.03–1.04)**	**1.04 (1.03–1.05)**	1.01 (0.99–1.03)	**1.05 (1.01–1.09)**
Sex				
Female	REF	REF	REF	REF
Male	**1.67 (1.36–2.16)**	**1.64 (1.27–2.19)**	1.52 (0.59–3.89)	0.99 (0.33–2.97)
Human development index[e]	**0.98 (0.95–0.97)**	**0.97 (0.95–0.99)**	**0.92 (0.88–0.96)**	**0.94 (0.89–0.99)**
Common comorbidities				
Hypertension and/or CVD	**1.42 (1.15–1.77)**	**1.62 (1.25–2.10)**	1.12 (0.52–2.38)	1.34 (0.4–3.18)
Diabetes mellitus	**1.63 (1.09–2.06)**	**1.75 (1.37–2.80)**	1.51 (0.53–5.16)	2.09 (0.51–9.32)
Chronic renal insufficiency/ESRD	**2.06 (1.44–2.71)**	**2.25 (1.48–3.37)**	**12.16 (5.57–24.6)**	2.92 (0.7–15.00)
Morbid obesity, BMI 40+ kg/m^2	**1.33 (1.03–1.73)**	1.08 (0.78–1.47)	**2.43 (1.01–5.87)**	0.66 (0.12–2.32)
Lung disease[f]	**1.40 (1.11–1.76)**	**2.26 (1.73–2.95)**	2.00 (0.98–4.89)	1.87 (0.49–6.13)
Specific rheumatic medications[g]				
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	**0.27 (0.11–0.63)**	**0.21 (0.05–0.80)**	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)	**0.18 (0.05–0.62)**	NA	NA
CD20 (y/n)	**1.90 (1.32–2.80)**	**3.25 (2.17–5.10)**	**4.95 (2.14–13.67)**	1.38 (0.28–6.28)
Rheumatic disease activity				
Remission/minimal	REF	REF	REF	REF
Moderate to severe	**1.90 (1.62–2.43)**	**1.87 (1.39–2.53)**	1.74 (0.99–3.51)	**3.46 (1.16–9.97)**
Glucocorticoid dose				
None	REF	REF	REF	REF
1–5 mg/day	**1.67 (1.34–2.07)**	1.27 (0.98–1.62)	1.26 (0.62–2.60)	2.24 (0.67–7.67)
6–10 mg/day	**1.75 (1.18–2.60)**	**2.35 (1.50–3.69)**	4.43 (1.76–11.16)	2.70 (0.44–16.49)
>10 mg/day	**3.58 (2.79–4.72)**	**2.30 (1.65–3.21)**	2.67 (1.16–6.53)	3.17 (0.76–13.32)

* Values are odds ratio (95% confidence interval). Significant values ($P < 0.05$) are presented in bold text.
BMI = body mass index; CVD = cardiovascular disease; ESRD = end-stage renal disease; IL = interleukin; REF = reference; TNFi = tumor necrosis factor inhibitor.
a Initial wave: COVID-19 diagnoses between January 1, 2020, and October 31, 2020.
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d Omicron variant: COVID-19 diagnoses between November 26, 2021, and study end (June 30, 2022).
e 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.
f Lung disease includes chronic obstructive pulmonary disease, interstitial lung disease, and asthma.
g Specific medication regimens were each compared with all other patients within this rheumatic diagnostic group who were not prescribed this regimen.

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 CTDs 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.[16] 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.[17] 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.[14] 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 are available, one study demonstrated a strong relationship

between a lower regional HDI and case fatality from COVID-19 in Brazil, and another study reported a significant association with low HDI and the number of COVID-19 infections among Brazil, Russia, India, China, and South Africa countries.[18,19] An ecological study using countrywide statistics found that the HDI correlated with both COVID-19 cases and deaths.[20] Previous studies from the COVID-19 Global Rheumatology Alliance also identify race, ethnicity, and societal pandemic policies and resources as important predictors of outcomes.[21–23] 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 four times the odds of death compared with those using methotrexate alone and compared with TNFi users among RA patients.[8,9] These findings have since been replicated in numerous epidemiological investigations in both unvaccinated and vaccinated individuals; diminished or absent antibody responses to vaccines likely underlie heightened risk among those who are vaccinated.[24–27] 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 antispike antibodies, even after three or more COVID-19 vaccines.[2] 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.[15] 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 academic, community, and public health hospitals around the world. In addition, because data were entered by rheumatologists, clinical details about rheumatic conditions, disease activity, and medication use were likely more reliable than those obtained with other observational data sources, such as administrative claims. These strengths have permitted rapid and accurate generation of data that have been corroborated by multiple other data sources. Limitations include that the registry represents data entered voluntarily by rheumatologists. Although 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 regard to COVID-19 vaccination status, some physicians used their country or state's vaccine registry to input a patient's vaccination status, whereas 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, 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.[28] 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 (ie, glucocorticoids and B-cell–depleting therapies) were found to be associated with severe outcomes. Ongoing efforts, such as vaccination and antiviral 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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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Yazdany and Ms. Ware had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Yazdany, Ware, Wallace, Grainger, Liew, Hyrich, Lawson-Tovey, Kearsley-Fleet, Schaefer, Sparks, Izadi, Gianfrancesco, Machado.

Acquisition of data. Ware, Bhana, Hachulla, Richez, Cacoub, Hausmann, Sirotich, Jacobsohn, Strangfeld, Mateus, Gossec, Carmona, Ribeiro, Al-Emadi, Hasseli, Müller-Ladner, Specker, Schulze-Koopps, Bernardes, Machado Fraga, Rodrigues, Giuseppe, Tidblad, Wise, Duarte-García, Ugarte-Gil, Colunga-Pedraza, Martínez-Martínez, Alpizar-Rodriguez, Xavier, Isnardi, Pera, Pons-Estel, Carrara, Scirè, Zanetti.

Analysis and interpretation of data. Yazdany, Ware, Grainger, Liew, Hyrich, Kearsley-Fleet, Sparks, Izadi, Gianfrancesco, Machado.

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