Risk of COVID-19 in Rheumatoid Arthritis: A National Veterans Affairs Matched Cohort Study in At-Risk Individuals

Bryant R. England, MD, PhD; Punyasha Roul, MS; Yangyuna Yang, MBBS, PhD; Andre C. Kalil, MD, MPH; Kaleb Michaud, PhD; Geoffrey M. Thiele, PhD; Brian C. Sauer, PhD, MS; Joshua F. Baker, MD, MSCE; Ted R. Mikuls, MD, MSPH

Affiliations:
1. Medicine & Research Service, VA Nebraska-Western Iowa Health Care System, Omaha, NE
2. Division of Rheumatology & Immunology, University of Nebraska Medical Center, Omaha, NE
3. Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE
4. FORWARD, The National Databank for Rheumatic Diseases, Wichita, KS
5. Salt Lake City VA & University of Utah, Salt Lake City, UT
6. Corporal Michael J. Crescenz VA & University of Pennsylvania, Philadelphia, PA

Word count: 3,297
References: 34
Tables/Figures: 5 Tables, 1 Figure
Supplementary Materials: 1 Tables

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ART.41800

This article is protected by copyright. All rights reserved
Funding: Study funded by University of Nebraska Medical Center College of Medicine. BRE received support from the VA CSR&D (IK2 CX002203), Rheumatology Research Foundation, and the National Institute of General Medical Sciences (U54 GM115458) which funds the Great Plains IDeA-CTR Network. TRM is supported by the VA BLR&D (I01 BX004660), the Rheumatology Research Foundation, and the National Institute of General Medical Sciences (U54 GM115458). JFB is supported by the VA CSR&D (I01 CX001703).

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Disclosures: PR, YY, AK none. BRE has served as a consultant to Boehringer-Ingelheim. TRM received research funding from Bristol Myers Squib and Horizon and has served as a consultant to Pfizer, Sanofi, Gilead, and Horizon. GMT served as a speaker for unbranded information for Sanofi.

Running head: RA and COVID-19

Correspondence: Bryant R. England, MD, PhD; 986270 Nebraska Medical Center, Omaha, NE 68198-6270. Phone: 402-559-7288. Fax: 402-559-6788. Email: Bryant.england@unmc.edu
ABSTRACT (248 words)

Background: While rheumatoid arthritis (RA) and its treatments are associated with an increased infection risk, it remains unclear whether these factors impact the risk or severity of COVID-19.

Methods: We conducted a matched cohort study using national Veterans Affairs data. Among non-deceased individuals on January 1, 2020 who received VA care in 2019, we matched RA to non-RA patients (1:1) on age, sex, and VA site. COVID-19 and severe COVID-19 (hospitalization or death) were obtained from a national VA COVID-19 surveillance database through December 10, 2020. We used multivariable Cox models to compare the risk of COVID-19 and COVID-19 hospitalization or death after adjusting for demographics, comorbidities, health behaviors, and county level COVID-19 incidence rates.

Results: RA and non-RA patients (n=33,886 each) were male predominant (84.5%) and had a mean age of 67.8 years. During follow-up, there were 1,503 COVID-19 diagnoses, 388 severe COVID-19 cases, and 228 non-COVID-19 related deaths. After multivariable adjustment, RA was associated with a higher risk of COVID-19 (hazard ratio [HR] 1.25 [95% confidence interval 1.13, 1.39]) and COVID-19 hospitalization or death (HR 1.35 [1.10, 1.66]). DMARDs and prednisone, but not RA autoantibody seropositivity, as well as black race, Hispanic ethnicity, and several chronic conditions were associated with COVID-19 and COVID-19 hospitalization or death.

Conclusions: Patients with RA are at higher risk for COVID-19 and COVID-19 hospitalization or death than non-RA. With a COVID-19 risk that approaches other recognized chronic conditions, these findings suggest RA patients should be prioritized for COVID-19 prevention and management.

Keywords: rheumatoid arthritis, COVID-19, SARS-CoV-2, epidemiology
INTRODUCTION

Despite marked improvements in the long-term outcomes for patients with rheumatoid arthritis (RA) (1), infections frequently complicate the natural course of RA and are likely over-represented in this patient population through several mechanisms. The immune dysregulation inherent to RA itself, RA treatments such as disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids, and chronic conditions RA patients are predisposed to developing are all associated with an increased risk of infection and serious infections (2, 3). However, most of this research has focused on bacterial, and not viral, etiologies.

COVID-19 appears to yield a disproportionate impact among vulnerable populations, particularly among the elderly and those with chronic diseases (4, 5). With the rapid development of effective vaccines for COVID-19, individuals with select chronic conditions that predispose to a more severe COVID-19 disease course have been prioritized for vaccine administration (6). High-risk chronic conditions and behaviors specified in these recommendations include cancer, chronic kidney disease, cardiovascular disease, prior solid organ transplantation, obesity, sickle cell disease, smoking, type 2 diabetes mellitus, and pregnancy (6). RA and other rheumatic diseases that require immunosuppressive therapies for management have not been prioritized. While vaccine supply is increasing in the U.S., the need, timing, and prioritization of subsequent booster vaccination is unknown.

Few observational studies have evaluated whether rheumatic diseases and related immunosuppressive therapies are associated with COVID-19 outcomes. Findings from an international registry of rheumatic disease patients identified links between rheumatic disease severity, prednisone, and select immunosuppressive therapies with higher risk of mortality, specifically among those with RA (7). Subsequent analyses suggested that confounding by indication may explain the association between prednisone and COVID-19 outcomes (8). This study also confirmed observations made in the general population, such as associations between ethnic minorities and comorbidities with severe COVID-19 disease and death (7, 9). In another multicenter study utilizing electronic health records, patients with COVID-19 and systemic autoimmune rheumatic diseases had a higher risk of severe outcomes compared with matched comparators, though this appeared largely related to accompanying comorbidities (10). A separate multicenter healthcare system study similarly found associations of rheumatic diseases with mechanical ventilation in COVID-19 to be attenuated by comorbidities (11). In a report using a national sample of primary care patients from the UK, patients with diagnoses of RA, lupus, or psoriasis were found to
have a 19% higher risk of COVID-19 death (12). While these studies and others begin to shed light on the outcomes of those that are infected with COVID-19, the aforementioned studies are prone to selection bias related to patient enrollment and/or conditioning on a positive SARS-CoV-2 test. Moreover, these studies included heterogeneous populations, with a number of different rheumatic conditions and treatments that are likely to reduce the precision of estimates generated.

Recognizing these gaps in our understanding and the significant limitations of prior study designs, the objective of this study was to compare the risk of SARS-CoV-2 infection and the development of severe COVID-19 between patients with RA and matched comparator patients in an at-risk population. We hypothesized that patients with RA would have a higher risk of acquiring an infection and would be more likely to require hospitalization or die from COVID-19.

**PATIENTS & METHODS**

**Study Design**

We conducted a retrospective, matched cohort study within national Veterans Health Administration (VHA) data. We identified RA patients who were active in the VHA system as of January 1, 2020 by using administrative algorithms that required multiple RA diagnostic codes, a rheumatologist diagnosis of RA, and receipt of a DMARD or positive RA autoantibody test (rheumatoid factor [RF] or anti-cyclic citrullinated protein [anti-CCP] antibody). Such algorithms have >90% positive predictive value for RA (13). Patients with RA were age- and sex-matched (1:1) to a patient receiving care (outpatient or inpatient encounter) during the 2019 calendar year at the same VA medical center without RA diagnostic codes. Patients with other autoimmune conditions (rheumatic and non-rheumatic) or receiving immunosuppressants were not excluded from the non-RA group, to ensure the control group was fully reflective of the VA non-RA population. Both RA and non-RA patients were required to be alive as of January 1, 2020. Patients were subsequently followed from January 1, 2020 to the first of COVID-19, death, or end of study period (December 10, 2020). This study received IRB approval.

**COVID-19 identification**

COVID-19 and related outcomes were obtained through the Veterans Affairs (VA) COVID-19 shared data resource. This is a national VA COVID-19 surveillance database that captures COVID-19 testing, results, severity of disease, and patient outcomes for secondary research studies (14-16). In addition to capturing molecular SARS-CoV-2 tests/results and COVID-19 diagnoses within the VA,
natural language processing and medical record validation are performed to identify COVID-19 cases that were diagnosed outside the VA system (17). However, negative SARS-CoV-2 tests outside the VA are not captured in this resource. The primary definition of COVID-19 disease included positive tests within or outside the VA. We also assessed COVID-19 that required hospitalization or resulted in death within 30 days of infection. In sensitivity analyses, respiratory illnesses that may be from SARS-CoV-2 but lacked confirmation (per the VA COVID-19 shared data resource definition) were also classified as COVID-19 (17). Death data was collected from the VA COVID-19 shared data resource and vital status records maintained by the VA.

**Covariates**

Covariates were obtained from the VA Corporate Data Warehouse (CDW) and included race, ethnicity, body mass index (BMI), urban vs. rural residence, presence of a VA service connected condition (a condition directly related to military service that receives VA benefits), private insurance status, smoking status (current, former, and never), comorbidities, number of hospitalizations in the prior year, and county level COVID-19 rates as of November 16th, 2020. Demographics (e.g. race, ethnicity) were obtained from administrative VA data collected upon enrollment into the VA. BMI was calculated from the nearest visit preceding January 1, 2020 using vital signs data from VA encounters, as previously described (18, 19). Smoking status was assessed by selecting and coding health factors recorded in the VA electronic medical record (20). Comorbid conditions were assessed through the Elixhauser comorbidity index (excluding rheumatoid arthritis/collagen vascular diseases) and specific conditions within the Elixhauser comorbidity index that are recognized to portend higher COVID-19 risk: heart failure, chronic lung disease, diabetes, hypertension, cancer, chronic kidney disease, and liver disease (21). We required at least 1 diagnostic code from outpatient or inpatient encounters during 2019 for a condition to be considered present. International Classification of Diseases (ICD), 10th revision codes for the comorbidities were from the Healthcare Cost and Utilization Project Elixhauser Comorbidity Software (https://www.hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comorbidity_icd10.jsp). Cumulative county level COVID-19 rates since the start of the pandemic were obtained from the COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University (https://github.com/cssegisanddata/covid-19, accessed November 16th, 2020) (22).

**Medications and RA autoantibody status**
We assessed recent treatments based on dispensings or infusions of DMARDs and prednisone in the 180 days prior to or including January 1, 2020. The exception being rituximab, which we assessed during an infusion period up to 365 days prior to January 1, 2020. Medications included were conventional synthetic DMARDs (csDMARDs; methotrexate, hydroxychloroquine, sulfasalazine, leflunomide), and biologic or targeted-synthetic DMARDs (b/tsDMARDs; TNF inhibitors [etanercept, adalimumab, certolizumab, golimumab, infliximab], abatacept, IL-6 inhibitors [tocilizumab and sarilumab], rituximab, janus kinase inhibitors [JAKi; tofacitinib, baricitinib, upadacitinib]). Prior work has shown that few RA patients in the VA obtain DMARDs from non-VA sources (23). RA autoantibody seropositivity was determined from RF and anti-CCP antibody laboratory data within the VA CDW.

Statistical analysis

Descriptive statistics were used to compare characteristics of RA and non-RA patients. We used multivariable Cox regression models to assess COVID-19 risk in RA vs. non-RA patients, censoring for non-COVID-19 death or end of study period. Models were clustered by the matched pair and included the aforementioned covariates. Similar models and covariates were used to compare the risk of COVID-19 hospitalization or death between RA and non-RA. Sensitivity analyses were performed including respiratory illnesses that may be related to SARS-CoV-2 but lacked testing confirmation as evidence of COVID-19 and modeling individual comorbidities rather than the Elixhauser comorbidity score. Secondary analyses were stratified by RA autoantibody status (seropositive, seronegative, and unknown), recent DMARDs (none, csDMARDs, b/tsDMARDs), prednisone (yes, no), and combined DMARDs and prednisone. We used multiple imputation with 10 imputations to address missing covariate data. Each imputed covariate (race, ethnicity, smoking status, BMI, urban/rural residence, and insurance status) was missing in <7% of patients.

Recognizing improvement in COVID-19 outcomes later in the pandemic among both patients with and without rheumatic diseases (24, 25), we assessed time-dependent differences in COVID-19 risk through proportional hazards testing. Schoenfeld residuals and interactions between RA status and log(time) were not significant (all p>0.3). Similarly, log-log survival and Schoenfeld residual plots did not suggest violation of the proportional hazards assumption (data not shown). All analyses were completed using Stata MP version 15.1 (StataCorp, College Station, TX).

Funding

This article is protected by copyright. All rights reserved
RESULTS

We identified 33,886 patients with RA and matched them to 33,886 patients without RA. Patients with RA were more likely to be current smokers, have a higher BMI, greater comorbidity burden by the Elixhauser score, and had more hospitalizations in the prior year (Table 1). The majority of patients with RA were seropositive for RF or anti-CCP (60.5%). DMARDs were dispensed within the prior 180 days (i.e. recent treatment) for 73% of the patients with RA, with 34.2% receiving a b/tsDMARD. The frequency of individual DMARDs is provided in Supplemental Table 1.

COVID-19 incidence rates

Over 62,894 patient-years of follow-up and using the primary COVID-19 definition of confirmed SARS-CoV-2, there were 1,503 diagnoses of COVID-19. Of these, 388 cases resulted in hospitalization (n=345 hospitalizations) or death (n=84 deaths). During the same period of observation, there were 288 non-COVID related deaths. Using a more sensitive case-definition that included both possible and confirmed COVID-19 respiratory illnesses, there were 2,037 COVID-19 diagnoses and 468 cases that resulted in hospitalization or death. Crude incidence rates of SARS-CoV-2 infection and COVID-19 hospitalization or death were higher in RA compared with matched non-RA (Table 2).

Risk of COVID-19 in RA

In unadjusted (matched on age, sex, and VA site) and adjusted models that further accounted for demographics, comorbidities, healthcare utilization and access, and county level COVID-19 incidence rates, RA was associated with a significantly higher risk of COVID-19. RA was associated with a 25% (Table 3; adjusted hazard ratio [aHR] 1.25 [95% CI 1.13, 1.39]) higher risk of COVID-19 and a 35% (aHR 1.35 [95% CI 1.10, 1.66]) higher risk of COVID-19 hospitalization or death. Results were consistent in sensitivity analyses that included possible COVID-19 cases (Table 3).

In addition to RA status, other factors that were significantly associated with higher risk of COVID-19 were black race, Hispanic ethnicity, higher Elixhauser comorbidity scores, lack of insurance, presence of a service-connected condition, underweight or obese BMI, greater number of hospitalizations in the prior year, and higher county level COVID-19 rates (Table 4). Fewer factors
were significantly associated with COVID-19 hospitalization or death, these being higher Elixhauser comorbidity scores, lack of insurance, greater number of hospitalizations in the prior year, and higher county level COVID-19 rates. In sensitivity analyses that incorporated individual comorbidities rather than the Elixhauser score, RA was associated with a higher risk of COVID-19 and COVID-19 hospitalization or death to a similar degree as heart failure (aHR 1.30 all COVID-19; aHR 1.70 COVID-19 hospitalization or death), chronic lung disease (aHR 1.28 all COVID-19; aHR 1.32 COVID-19 hospitalization or death), diabetes (aHR 1.29 all COVID-19; aHR 1.85 COVID-19 hospitalization or death), liver disease (aHR 1.35 all COVID-19; aHR 1.52 COVID-19 hospitalization or death), and chronic kidney disease (aHR 1.14 all COVID-19; aHR 1.76 COVID-19 hospitalization or death) (Table 5).

**Risk of COVID-19 by RA autoantibody status and medications**

In secondary analyses, we compared the risk of COVID-19 and COVID-19 hospitalization or death between RA and non-RA based on RA autoantibody status and medications. Patients with seronegative and seropositive RA had a similar higher risk of COVID-19 and COVID-19 hospitalization or death, independent of potential confounders (Figure 1A and 1B). Compared to non-RA patients, a higher risk of COVID-19 and COVID-19 hospitalization or death was observed among RA patients treated with csDMARDs, b/tsDMARDs, and prednisone (Figure 1A and 1B). RA patients treated with b/tsDMARDs and prednisone were at the highest risk of COVID-19 (aHR 1.66 [95%CI 1.36, 2.03]) and COVID-19 hospitalization or death (aHR 2.12 [95% CI 1.48, 3.03]) relative to non-RA patients.

**DISCUSSION**

In this large, at-risk cohort of matched RA and non-RA patients nationally in the VA, we found that patients with RA were at a significantly higher risk of SARS-CoV-2 infection and COVID-19 hospitalization or death. Those treated with DMARDs and prednisone were at the highest risk of COVID-19 and more severe disease. This was independent of potential confounders including demographics, comorbidities, health care utilization and access, and county level COVID-19 rates. Strikingly the heightened risk of COVID-19 related to RA was consistent with the risk posed by other chronic conditions that receive priority vaccination status. Thus, the immediate implication of our
findings is the suggestion similar consideration for vaccine prioritization should be given to patients with RA receiving immunosuppressive therapies.

After adjusting for potential confounders, we estimated that RA was associated with 25% increased risk of COVID-19 and 35% increased risk of COVID-19 hospitalization or death. These are among the first data to link RA with a higher risk of COVID-19. Moreover, our results linking RA with a higher risk of viral infection is an important contribution to our understanding of how RA may affect the risk of developing other viral infections, since prior literature has focused on bacterial infections (3). Our findings of a higher risk of a more severe COVID-19 disease course in RA are consistent with results from a UK at-risk study of RA, psoriasis, and lupus patients that found a 19% higher risk of COVID-19 death (12) as well as a study of COVID-19 patients that observed a 14% higher risk of hospitalization in those with a rheumatic disease (10). Our findings are also in line with prior estimates for the risk of serious infection (bacterial or non-bacterial) in RA relative to non-RA patients, a 50% increased risk in the FORWARD registry (26).

In our study, RA patients receiving csDMARDs, b/tsDMARDs, and prednisone had a higher risk of COVID-19 and higher risk of severe COVID-19 disease course. While we are not aware of prior literature linking these therapies to COVID-19 risk in RA, others have similarly found that select immunosuppressive therapies, specifically rituximab and prednisone, were associated with a more severe disease course among patients, including RA, with COVID-19 (7, 10, 27). The highest risk RA sub-group in our study was those who were receiving both b/tsDMARDs and prednisone. These individuals had a >2-fold higher risk of COVID-19 hospitalization or death compared to non-RA patients. Similar risks have been identified in RA patients with b/tsDMARDs and prednisone for non-COVID-19 severe infections (28, 29). While there has been hope that some therapies might suppress the hyperinflammatory features of COVID-19 and improve outcomes, findings in this study highlight that the timing of immunosuppressive therapies (preceding or at the time of exposure, early infection, or severe infection stages) may be crucial for measuring their potential impact on disease outcomes. Use of immunosuppressive medications may predispose to COVID-19 infection or a more severe disease course early, but during the hyper-inflammatory phase of severe COVID-19 (30), select immunosuppressive therapies may become beneficial. Our findings, and those of others, also raise concerns that patients with other medical conditions receiving these immunosuppressive therapies may be at higher risk of COVID-19 and severe COVID-19 disease. Importantly, confounding by indication is recognized to complicate such observational studies of therapies and COVID-19 and causal conclusions cannot be drawn (8). Further study is warranted.
Our findings have clear relevance to health policy surrounding COVID-19 prevention and management. Risk stratification for vaccination, for example, has primarily been established by age, occupational risks, and the presence of several chronic conditions. RA or the use of immunosuppressive therapies outside the setting of prior organ transplant are not considered chronic conditions that receive priority vaccination status (6). Our results suggest that RA patients receiving DMARDs and/or prednisone should be considered for priority status of prevention efforts including initial and booster vaccination. The 35% increased risk of COVID-19 hospitalization or death related to RA falls within the range we estimated for other conditions that receive priority status (aHR ranging from 1.18 to 1.85). With <1.0% of the population having RA (31), the inclusion of RA as a priority group is unlikely to drastically impact vaccine or treatment supplies for other individuals, while protecting a vulnerable population. Moreover, since treatment with DMARDs and/or prednisone were linked to more severe COVID-19 in both ours (RA only) and others studies (included other rheumatic diseases (7, 10)), prioritization may be warranted for any medical conditions requiring chronic immunosuppressive medications.

Consistent with other studies in the general population and in patients with rheumatic diseases, we found that race and ethnicity were major determinants of SARS-CoV-2 infection and severe COVID-19 (9, 32). Black patients had a 22% higher risk of SARS-CoV-2 infection and a 25% higher risk of COVID-19 hospitalization or death. Similarly, patients with Hispanic ethnicity had a 48% higher risk of SARS-CoV-2 infection and a 25% increased risk of COVID-19 hospitalization or death, though the latter did not reach statistical significance. Importantly, the associations between race and ethnicity with COVID-19 were independent of other demographics, comorbidity burden and individual chronic conditions, health care utilization and insurance, and county level COVID-19 rates which may mediate or confound such associations. Our findings, therefore, suggest additional factors such as differences in the severity of comorbid chronic conditions, community or occupational risks, time to receiving care, access during surges, or immune responses to SARS-CoV-2 may contribute to the racial and ethnic disparities of COVID-19 (32), which requires further study.

There are limitations to this study. There may be misclassification of RA status with the use of administrative algorithms. This is most likely to occur in RA patients who were not receiving DMARDs. Misclassification of non-RA patients as RA should only bias findings towards the null, resulting in an underestimation of the risk of COVID-19 in RA. Our study was designed to compare the risk of COVID-19 between RA and non-RA, rather than comparing the risk between specific medications or medication doses. To generate valid data for such comparisons and avoid
misinformation that has plagued the pandemic (33), alternative study designs would be required. DMARD and prednisone doses were not available for these analyses. Misclassification of COVID-19 may also have occurred, and the sensitivity for capturing non-VA COVID-19 cases through the VA standardized process has not been established. Our study population was composed primarily of older males (although >10,000 females were included), consistent with the demographics of the VA, but findings may not be generalizable to other populations. While male sex has been associated with more severe COVID-19 (34), it is not expected that the impact of RA and RA-therapies on COVID-19 risk would be differential between men and women. Finally, because of the observational nature of our study, unmeasured confounding may be present.

In conclusion, we observed RA patients to have a 25% increased risk of COVID-19 and 35% increased risk of COVID-19 hospitalization or death independent of several potential confounders. RA patients recently receiving DMARDs and prednisone were at the highest risk of COVID-19 and more severe COVID-19, risks that rivaled those accompanying other chronic conditions. Consideration should be given to establishing RA, and potentially other conditions that require treatment with similar immunosuppressive medications, as a chronic condition that receives prioritization for COVID-19 prevention and management strategies.
ACKNOWLEDGEMENTS

This study was supported using data from the VA COVID-19 Shared Data Resource. This work was also supported using resources and facilities of the Department of Veterans Affairs Informatics and Computing Infrastructure, VA HSR RES 13-457.
REFERENCES

1. Sparks JA. Rheumatoid Arthritis. Ann Intern Med. 2019;170(1):ITC1-ITC16.
2. Jani M, Barton A, Hyrich K. Prediction of infection risk in rheumatoid arthritis patients treated with biologics: are we any closer to risk stratification? Curr Opin Rheumatol. 2019;31(3):285-92.
3. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford). 2013;52(1):53-61.
4. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
6. Dooling K. The Advisory committee on immunization practices’ updated interim recommendation for allocation of COVID-19 vaccine—United States, December 2020. MMWR Morbidity and mortality weekly report. 2021;69.
7. Strangfeld A, Schafer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2021.
8. Schafer M, Strangfeld A, Hyrich KL, Carmona L, Gianfrancesco M, Lawson-Tovey S, et al. Response to: 'Correspondence on 'Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician reported registry" by Mulhearn et al. Ann Rheum Dis. 2021.
9. Gianfrancesco MA, Leykina LA, Izadi Z, Taylor T, Sparks JA, Harrison C, et al. Association of Race and Ethnicity With COVID-19 Outcomes in Rheumatic Disease: Data From the COVID-19 Global Rheumatology Alliance Physician Registry. Arthritis Rheumatol. 2020.
10. D'Silva KM, Jorge A, Cohen A, McCormick N, Zhang Y, Wallace ZS, et al. COVID-19 Outcomes in Patients with Systemic Autoimmune Rheumatic Diseases (SARDs) Compared to the General Population: A US Multi-Center Comparative Cohort Study. Arthritis Rheumatol. 2020.
11. Serling-Boyd N, D'Silva KM, Hsu TY, Wallwork R, Fu X, Gravallese EM, et al. Coronavirus disease 2019 outcomes among patients with rheumatic diseases 6 months into the pandemic. Ann Rheum Dis. 2020.
12. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
13. Chung CP, Rohan P, Krishnaswami S, McPheeters ML. A systematic review of validated methods for identifying patients with rheumatoid arthritis using administrative or claims data. Vaccine. 2013;31 Suppl 10:K41-61.
14. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and Death After Initial Hospital Discharge Among Patients With COVID-19 in a Large Multihospital System. JAMA. 2021;325(3):304-6.
15. Bowe B, Cai M, Xie Y, Gibson AK, Maddukuri G, Al-Aly Z. Acute Kidney Injury in a National Cohort of Hospitalized US Veterans with COVID-19. Clin J Am Soc Nephrol. 2020;16(1):14-25.
16. Luo J, Jeyapalina S, Stoddard GJ, Kwok AC, Agarwal JP. Coronavirus disease 2019 in veterans receiving care at veterans health administration facilities. Ann Epidemiol. 2021;55:10-4.
17. Updates to the VA COVID-19 Shared Data Resource and its Use for Research. Available from: https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/video_archive.cfm?SessionID=3834.
18. Baker JF, Billig E, Michaud K, Ibrahim S, Caplan L, Cannon GW, et al. Weight Loss, the Obesity Paradox, and the Risk of Death in Rheumatoid Arthritis. Arthritis Rheumatol. 2015;67(7):1711-7.
19. England BR, Baker JF, Sayles H, Michaud K, Caplan L, Davis LA, et al. Body Mass Index, Weight Loss, and Cause-Specific Mortality in Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2018;70(1):11-8.
20. McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, et al. Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. Nicotine Tob Res. 2011;13(12):1233-9.
21. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998;36(1):8-27.
22. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-4.
23. Schwab P, Sayles H, Bergman D, Cannon GW, Michaud K, Mikuls TR, et al. Utilization of Care Outside the Veterans Affairs Health Care System by US Veterans With Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2017;69(6):776-82.
24. Dennis JM, McGovern AP, Vollmer SJ, Mateen BA. Improving Survival of Critical Care Patients With Coronavirus Disease 2019 in England: A National Cohort Study, March to June 2020. Crit Care Med. 2021;49(2):209-14.
25. Jorge A, D'Silva KM, Cohen A, Wallace ZS, McCormick N, Zhang Y, et al. Temporal trends in severe COVID-19 outcomes in patients with rheumatic disease: a cohort study. Lancet Rheumatol. 2021;3(2):e131-e7.
26. Mehta B, Pedro S, Ozen G, Kalil A, Wolfe F, Mikuls T, et al. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open. 2019;5(1):e000935.
27. Ungaro RC, Agrawal M, Park S, Hirten R, Colombel JF, Twyman K, et al. Autoimmune and Chronic Inflammatory Disease Patients with COVID-19. ACR Open Rheumatol. 2021;3(2):111-5.
28. Singh JA, Cameron C, Noorbaloocchi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet. 2015;386(9990):258-65.
29. George MD, Baker JF, Winthrop K, Hsu JY, Wu Q, Chen L, et al. Risk for Serious Infection With Low-Dose Glucocorticoids in Patients With Rheumatoid Arthritis: A Cohort Study. Ann Intern Med. 2020;173(11):870-8.
30. Cao X. COVID-19: immunopathology and its implications for therapy. Nature reviews immunology. 2020;20(5):269-70.
31. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-22.
32. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. N Engl J Med. 2020;382(26):2534-43.
33. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-Garcia A, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. Ann Intern Med. 2020;172(12):819-21.
34. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020;11(1):6317.
FIGURE LEGENDS

Figure 1. Risk of COVID-19 and COVID-19 hospitalization or death in RA subgroups. Values are hazard ratios and 95% confidence intervals after matching on age and sex and adjusting for race, ethnicity, smoking status, body mass index, Elixhauser comorbidity score, insurance status, urban/rural residence, number of hospitalizations in prior year, service-connected condition and county level COVID-19 rates.
Table 1. Baseline characteristics of RA and non-RA patients

|                             | RA (n = 33,886) | Non-RA (n = 33,886) | P value |
|-----------------------------|-----------------|---------------------|---------|
| Age, years                  | 67.8 (11.1)     | 67.8 (11.1)         | n/a     |
| Male sex, %                 | 84.5            | 84.5                | n/a     |
| Race, %                     |                 |                     | 0.01    |
| White                       | 74.4            | 73.7                |         |
| Black                       | 17.3            | 17.2                |         |
| Other                       | 3.3             | 2.9                 |         |
| Unknown                     | 5.1             | 6.2                 |         |
| Ethnicity, %                |                 |                     | <0.001  |
| Non-Hispanic                | 90.7            | 91.0                |         |
| Hispanic                    | 6.1             | 5.0                 |         |
| Unknown                     | 3.2             | 3.9                 |         |
| Smoking status, %           |                 |                     | <0.001  |
| Current                     | 50.0            | 40.8                |         |
| Former                      | 31.8            | 31.3                |         |
| Never                       | 15.7            | 21.4                |         |
| Unknown                     | 2.5             | 6.6                 |         |
| BMI categories, %           |                 |                     | <0.001  |
| <18.5 kg/m²                 | 0.7             | 0.6                 |         |
| 18.5-25 kg/m²               | 8.4             | 9.0                 |         |
| 25-30 kg/m²                 | 28.8            | 30.8                |         |
| 30-35 kg/m²                 | 31.1            | 31.1                |         |
| >35 kg/m²                   | 31.0            | 27.9                |         |
| Unknown                     | 0.1             | 0.7                 |         |
| Elixhauser comorbidity score| 3.0 (2.2)       | 2.5 (2.0)           | <0.001  |
| Urban-rural residence, %    |                 |                     | 0.33    |
| Urban                       | 63.5            | 64.0                |         |
| Rural                       | 34.9            | 34.4                |         |
| Highly rural                | 1.5             | 1.5                 |         |
| Unknown                     | 0.1             | 0.1                 |         |
| RF or anti-CCP antibody     |                 |                     | <0.001  |
|                      | Value | p-value |
|----------------------|-------|---------|
| Seropositive         | 60.5  |         |
| Seronegative         | 25.7  |         |
| Unknown              | 13.9  |         |
| DMARDs in prior 180 days*, % |       | <0.001  |
| None                 | 27.4  | 98.9    |
| csDMARDs             | 37.6  | 0.5     |
| b/tsDMARDs           | 34.2  | 0.5     |
| Prednisone in prior 180 days, % | 24.7  | 3.6     | <0.001  |
| Number of hospitalizations in prior year | 0.2 (0.8) | 0.1 (0.6) | <0.001  |
| Insurance beneficiary, % | 80.9  | 78.7    | <0.001  |
| Service-connected condition, % | 62.6  | 58.7    | <0.001  |

Values mean (SD) unless otherwise indicated

*Rituximab assessed in prior 365 days

Abbreviations: b, biologic; BMI, body mass index; cs, conventional-synthetic; DMARDs, disease-modifying anti-rheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; ts, targeted-synthetic
Table 2. Incidence rates of COVID-19 and severe COVID-19 in RA and non-RA.

| Diagnosis                        | Events | Person-years follow-up | Incidence rate per 1,000 PY (95% CI) |
|----------------------------------|--------|------------------------|-------------------------------------|
| **All COVID-19**                 |        |                        |                                     |
| Non-RA                           | 647    | 31,552                 | 20.5 (19.0, 22.1)                   |
| RA                               | 856    | 31,342                 | 27.3 (25.5, 29.2)                   |
| **COVID-19 hospitalization or death** |        |                        |                                     |
| Non-RA                           | 153    | 31,552                 | 4.8 (4.1, 5.7)                      |
| RA                               | 235    | 31,342                 | 7.5 (6.6, 8.5)                      |
| **Sensitivity Analyses***        |        |                        |                                     |
| **All COVID-19**                 |        |                        |                                     |
| Non-RA                           | 863    | 31,465                 | 27.4 (25.7, 29.3)                   |
| RA                               | 1174   | 31,217                 | 37.6 (35.5, 39.8)                   |
| **COVID-19 hospitalization or death** |        |                        |                                     |
| Non-RA                           | 181    | 31,465                 | 5.8 (5.0, 6.7)                      |
| RA                               | 287    | 31,217                 | 9.2 (8.2, 10.3)                     |

*Sensitivity analyses additionally included respiratory illnesses suspected to be COVID-19 disease

Abbreviations: CI, confidence interval; PY, person-years; RA, rheumatoid arthritis
Table 3. Risk of COVID-19 and severe COVID-19 in RA and non-RA.

|                          | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* |
|--------------------------|------------------------|-----------------------|
| **All COVID-19**         |                        |                       |
| Non-RA                   | 1 (Ref)                | 1 (Ref)               |
| RA                       | 1.34 (1.21, 1.48)      | 1.25 (1.13, 1.39)     |
| **COVID-19 hospitalization or death** |                        |                       |
| Non-RA                   | 1 (Ref)                | 1 (Ref)               |
| RA                       | 1.55 (1.26, 1.90)      | 1.35 (1.10, 1.66)     |

*Sensitivity analysis*

| **All COVID-19**         |                        |                       |
| Non-RA                   | 1 (Ref)                | 1 (Ref)               |
| RA                       | 1.38 (1.26, 1.50)      | 1.29 (1.18, 1.41)     |
| **COVID-19 hospitalization or death** |                        |                       |
| Non-RA                   | 1 (Ref)                | 1 (Ref)               |
| RA                       | 1.60 (1.33, 1.93)      | 1.39 (1.15, 1.68)     |

RA and non-RA matched on age, sex, and VA site.

*Adjusted for race, ethnicity, smoking status, Elixhauser comorbidity score, insurance status, urban/rural residence, number of hospitalizations in prior year, service-connected condition, county level COVID-19 incidence rates.

Abbreviations: CI, confidence interval; HR, hazard ratio; RA, rheumatoid arthritis
| Table 4. Fully adjusted models evaluating risk of COVID-19 and COVID-19 hospitalization or death in RA and non-RA patients |
|---------------------------------------------------------------|
| All COVID-19 | aHR (95% CI) | COVID-19 hospitalization or death | aHR (95% CI) |
| RA (vs. non-RA) | 1.25 (1.13, 1.39)* | 1.35 (1.10, 1.66)* |
| Race | | | |
| White | 1 (Ref) | 1 (Ref) |
| Black | 1.22 (1.07, 1.39)* | 1.25 (0.97, 1.60) |
| Other | 1.29 (0.99, 1.68) | 1.23 (0.71, 2.11) |
| Ethnicity | | | |
| Hispanic | 1.48 (1.23, 1.78)* | 1.25 (0.85, 1.86) |
| Smoking status | | | |
| Current | 0.78 (0.68, 0.90) | 1.09 (0.80, 1.50) |
| Former | 0.90 (0.78, 1.04) | 1.31 (0.94, 1.82) |
| Never | 1 (Ref) | 1 (Ref) |
| Elixhauser comorbidity score per 1 unit | 1.12 (1.09, 1.15)* | 1.24 (1.20, 1.30)* |
| Insurance (no vs. yes) | 1.40 (1.24, 1.58)* | 1.88 (1.49, 2.37)* |
| Service-connected condition | 1.22 (1.10, 1.37)* | 1.08 (0.87, 1.34) |
| BMI category | | | |
| <18.5 kg/m² | 1.78 (1.01, 3.15)* | 1.30 (0.38, 4.47) |
| 18.5-25 kg/m² | 1 (Ref) | 1 (Ref) |
| 25-30 kg/m² | 1.21 (0.96, 1.54) | 1.29 (0.79, 2.11) |
| 30-35 kg/m² | 1.36 (1.08, 1.72)* | 1.42 (0.88, 2.31) |
| >35 kg/m² | 1.51 (1.19, 1.90)* | 1.59 (0.98, 2.57) |
| Urban/rural status | | | |
| Urban | 1 (Ref) | 1 (Ref) |
| Rural | 0.90 (0.80, 1.01) | 0.98 (0.78, 1.22) |
| Highly rural | 1.06 (0.70, 1.61) | 0.79 (0.29, 2.14) |
| Number of hospitalizations in prior year | 1.11 (1.05, 1.16)* | 1.13 (1.06, 1.21)* |
| County incidence rate per 100,000 | 1.00 (1.00, 1.00)* | 1.00 (1.00, 1.00)* |
RA and non-RA matched on age, sex, and VA site
*P<0.05

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval;
RA, rheumatoid arthritis
Table 5. Sensitivity analysis of fully adjusted models evaluating risk of COVID-19 and COVID-19 hospitalization or death in RA and non-RA patients with individual chronic conditions

|                      | All COVID-19 aHR (95% CI) | COVID-19 hospitalization or death aHR (95% CI) |
|----------------------|---------------------------|---------------------------------------------|
| RA (vs. non-RA)      | 1.27 (1.14, 1.41)*        | 1.39 (1.13, 1.71)*                           |
| Race                 |                           |                                             |
| White                | 1 (Ref)                   | 1 (Ref)                                     |
| Black                | 1.25 (1.09, 1.42)*        | 1.24 (0.97, 1.59)                           |
| Other                | 1.26 (0.97, 1.65)         | 1.18 (0.67, 2.08)                           |
| Ethnicity            |                           |                                             |
| Hispanic             | 1.50 (1.24, 1.80)*        | 1.30 (0.88, 1.92)                           |
| Smoking status       |                           |                                             |
| Current              | 0.78 (0.68, 0.90)         | 1.15 (0.84, 1.57)                           |
| Former               | 0.90 (0.78, 1.04)         | 1.30 (0.93, 1.80)                           |
| Never                | 1 (Ref)                   | 1 (Ref)                                     |
| Heart failure        | 1.30 (1.09, 1.15)*        | 1.70 (1.25, 2.32)*                           |
| Chronic lung disease | 1.28 (1.13, 1.44)*        | 1.32 (1.04, 1.67)*                           |
| Diabetes mellitus    | 1.29 (1.16, 1.45)*        | 1.85 (1.47, 2.33)*                           |
| Hypertension         | 0.96 (0.86, 1.08)         | 1.18 (0.91, 1.52)                           |
| Liver disease        | 1.35 (1.11, 1.63)*        | 1.52 (1.09, 2.12)*                           |
| Cancer               | 1.16 (0.98, 1.37)         | 1.35 (1.00, 1.82)*                           |
| Renal disease        | 1.14 (0.97, 1.34)         | 1.76 (1.34, 2.32)*                           |
| Insurance (no vs. yes)| 1.40 (1.24, 1.59)*        | 2.01 (1.59, 2.56)*                           |
| Service-connected condition | 1.24 (1.11, 1.38)* | 1.12 (0.90, 1.38)                           |
| BMI category         |                           |                                             |
| <18.5 kg/m²          | 1.85 (1.04, 3.27)*        | 1.32 (0.39, 4.52)                           |
| 18.5-25 kg/m²        | 1 (Ref)                   | 1 (Ref)                                     |
| 25-30 kg/m²          | 1.21 (0.96, 1.54)         | 1.22 (0.74, 2.00)                           |
| 30-35 kg/m²          | 1.38 (1.10, 1.74)*        | 1.32 (0.81, 2.15)                           |
| >35 kg/m²            | 1.57 (1.24, 1.98)*        | 1.49 (0.91, 2.45)                           |
### Urban/rural status

| Status                  | RA | Non-RA |
|-------------------------|----|--------|
| Urban                   | 1  | 1 (Ref) |
| Rural                   | 0.89 (0.80, 1.00) | 0.95 (0.76, 1.18) |
| Highly urban            | 1.04 (0.68, 1.58) | 0.72 (0.26, 2.00) |

| Number of hospitalizations in prior year | RA | Non-RA |
|-----------------------------------------|----|--------|
| 1.17 (1.12, 1.22)*                      |    | 1.23 (1.16, 1.30)* |

| County incidence rate per 100,000       | RA | Non-RA |
|-----------------------------------------|----|--------|
| 1.00 (1.00, 1.00)*                      |    | 1.00 (1.00, 1.00)* |

RA and non-RA matched on age, sex, and VA site

*P<0.05

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval;
RA, rheumatoid arthritis
