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BRIEF REPORT

Increased Risk of COVID-19 in Patients With Rheumatoid Arthritis: A General Population-Based Cohort Study

Yilun Wang,[1] Kristin M. D'Silva,[2] April M. Jorge,[2] Xiaoxiao Li,[1] Houchen Lyv,[3] Jie Wei,[1] Chao Zeng,[1] Guanghua Lei,[1] and Yuqing Zhang[2]

Objective. Patients with rheumatoid arthritis (RA) are at an increased risk of acquiring infections owing to immunologic dysfunction and use of potent immunomodulatory medications; however, few data are available on their risk of COVID-19. We estimated the rate of COVID-19 among RA participants and compared it with that of the general population.

Methods. Using the Health Improvement Network, we identified RA patients before February 2020 and followed them to September 2020. We calculated the rate of COVID-19 among participants with RA and compared it with that of the general population using a Cox proportional hazards model, adjusting for potential confounders using overlap weighting of exposure score. We repeated the same analysis among participants with osteoarthritis, a nonautoimmune rheumatic disease, as a negative control exposure.

Results. We identified 225 cases of suspected and confirmed COVID-19 among 17,268 RA patients, and 14,234 cases among 1,616,600 participants in the general population (1.4 versus 0.9/1,000 person-months), with the adjusted hazard ratio (HR_{adj}) being 1.19 (95% confidence interval [95% CI] 1.04–1.36). Confirmed COVID-19 cases developed in 46 RA participants and in 2,249 in the general population (0.3 versus 0.1/1,000 person-months), with the HR_{adj} being 1.42 (95% CI 1.01–1.95). No statistically significant difference was observed for suspected and confirmed (HR 1.00 [95% CI 0.93–1.07]) or confirmed (HR 1.08 [95% CI 0.92–1.27]) COVID-19 rates between participants with osteoarthritis and the general population.

Conclusion. RA, but not osteoarthritis, was associated with an increased risk of COVID-19. Our findings provide timely evidence to support recommendations that booster vaccines and priority access to anti–SARS–CoV-2 monoclonal antibody treatments should be encouraged for RA patients.

INTRODUCTION

COVID-19 has become a global health crisis. By the end of 2020, >100 million cases have been diagnosed worldwide. To date, several studies have reported that patients with rheumatic diseases were at an increased risk of hospitalization (1) and had more severe sequalae after COVID-19 (2–4). However, the risk of developing COVID-19 may vary among the different rheumatic diseases (5), and most prior studies have evaluated heterogeneous rheumatic diseases in aggregate (1–4).

Rheumatoid arthritis (RA) is a common systemic autoimmune disorder, and patients with RA are at an increased risk of acquiring infections owing to immunologic dysfunction and use of potent immunomodulatory medications. To date, 3 studies have specifically compared the risk of COVID-19 between patients with RA and those without RA (6–8); the findings,

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[1]Yilun Wang, MD, PhD, Xiaoxiao Li, MS, Jie Wei, PhD, Chao Zeng, MD, PhD, Guanghua Lei, MD, PhD: Xiangya Hospital, Central South University, Changsha, China; [2]Kristin M. D'Silva, MD, April M. Jorge, MD, Yuqing Zhang, DSc: Massachusetts General Hospital, Harvard Medical School, Boston; [3]Houchen Lyv, MD, PhD: Xiangya Hospital, Central South University, Changsha, China, and General Hospital of Chinese PLA, Beijing, China.

Drs. Lei and Zhang contributed equally to this work.

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Address correspondence to Guanghua Lei, MD, PhD, Department of Orthopaedics, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan 410008, China. Email: lei_guanghua@csu.edu.cn.

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SIGNIFICANCE & INNOVATIONS

- This study shows that the risk of COVID-19 is higher among patients with rheumatoid arthritis (RA) than the general population.
- Patients with osteoarthritis, a nonautoimmune rheumatic disease, do not present a higher risk of COVID-19 than the general population.
- Our findings provide timely evidence to support recommendations that booster vaccines and priority access to anti–SARS–CoV-2 monoclonal antibody treatments should be encouraged for patients with RA.

however, were inconclusive. Two studies found that patients with RA had a higher risk of COVID-19 than individuals without RA (6,7), but another failed to confirm it (8).

To our knowledge, no study has been conducted to describe the incidence of COVID-19 among patients with RA and compare it with that among the general population. To address this knowledge gap, we conducted 2 cohort studies to estimate the risk of COVID-19 among patients with RA and those with osteoarthritis (OA), a common nonautoimmune rheumatic disease, and compared it with that of the general population.

MATERIALS AND METHODS

Data source. The Health Improvement Network (THIN) is an electronic medical record database including general practitioner (GP) records in the UK and represents the UK population regarding demographic characteristics and medical conditions (THIN is a registered trademark of Cegedim in the UK and other countries). Reference made to the THIN database herein is intended to be descriptive of the data asset licensed by IQVIA. This study uses deidentified data provided by patients as a part of their routine primary care. It was approved by the THIN Scientific Review Committee (20SRC003_A1).

Study design and cohort definition. We conducted a cohort study to compare the risks of COVID-19 between patients with RA with the general population without RA. RA diagnosis was made using Read codes (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract) (9) that have been previously validated in the UK General Practice Research Database, with a positive predictive value of ~80%. Eligible participants included those between 18 and ~90 years of age and had at least 1 year of continuous enrollment with a general practice before January 29, 2020 (i.e., the index date when the first COVID-19 case was diagnosed in the UK). Participants were followed until the middle of September 2020. Individuals were excluded if they had missing information on body mass index, smoking status, alcohol use, or socioeconomic deprivation index score.

As there has been no purported association between OA and the risk of COVID-19, we further conducted a cohort study to compare the risks of COVID-19 between the patients with OA (i.e., a negative comparison group) and the general population without OA. OA diagnosis was made using Read codes according to previous studies using the THIN database (10). This approach has been preferred in validation studies, as opposed to other approaches, such as medical visits, referrals, or prescription records. Eligible participants included those age ≥40 years and who had at least 1 year of continuous enrollment with a general practice before the index date. Participants were also followed until the middle of September 2020. Exclusion criteria were in line with the RA cohort. This study received approval from the Medical Ethics Committee at Xiangya Hospital (2018091077), with waiver of informed consent.

Assessment of outcomes. The primary outcome was a composite of suspected and confirmed diagnoses of COVID-19 (suspected/confirmed COVID-19) based on Read codes recommended in national guidelines (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract) (11). The secondary outcome was a confirmed diagnosis of COVID-19 (11). According to National Health Service guidance and standard operating procedures for primary care and UK Faculty of Clinical Informatics guidelines, confirmed COVID-19 codes represent a positive reverse transcriptase polymerase chain reaction (RT-PCR) test result, while a suspected COVID-19 code represents a symptomatic presentation of COVID-19 and/or contact history with a confirmed patient. A recent study on suspected COVID-19 codes recorded in primary care suggested that clinical diagnosis of COVID-19 by physicians followed a similar trend to test positive cases confirmed by the UK National Testing Service.

Assessment of covariates. Sociodemographic, anthropometric, and lifestyle factors were assessed using the nearest available data prior to the index date; comorbidities were assessed before the index date; and medication use as well as health care utilization were assessed within 1 year prior to the index date (Table 1). These covariates were chosen, as they are potentially causal for RA, OA, and COVID-19.

Statistical analysis. Person-months of follow-up for each participant were calculated as the amount of time from the index date to the first of the following events: COVID-19, death, age 90 years, transferring out of the THIN GP practice, or the end of study follow-up on September 16, 2020. We calculated the incidence rates of suspected/confirmed and confirmed COVID-19, respectively. We estimated rate differences (RDs) between the

Table 1. Baseline characteristics of patients with rheumatoid arthritis (RA) and the general population without RA*

Variable	RA (n = 17,268)	Non-RA (n = 1,616,600)	Stand. diff. before overlap weighting	Stand. diff. after overlap weighting
Demographic characteristic				
Age, mean ± SD years	64.9 ± 13.5	53.3 ± 16.8	0.762	<0.001
Socioeconomic deprivation index score, mean ± SD†	2.8 ± 1.3	2.8 ± 1.3	0.026	<0.001
Women	71.2	54.0	0.362	<0.001
BMI, mean ± SD kg/m^2	28.3 ± 6.4	27.7 ± 6.0	0.098	<0.001
Region			0.079	0.007
England	27.7	31.2		
Northern Ireland	10.9	10.7		
Scotland	33.8	32.3		
Wales	27.6	25.8		
Lifestyle factors				
Drinking			0.221	<0.001
None	26.8	19.0		
Past	5.0	3.1		
Current	68.2	77.9		
Smoking			0.223	<0.001
None	48.6	56.5		
Past	35.8	25.5		
Current	15.6	18.0		
Comorbidity				
Hypertension	44.3	25.4	0.404	<0.001
Diabetes mellitus	19.2	12.5	0.187	<0.001
Chronic kidney disease	12.6	4.6	0.286	<0.001
Pneumonia or infection	11.3	5.9	0.196	<0.001
Chronic obstructive pulmonary disease	10.0	3.6	0.257	<0.001
Influenza	5.1	3.2	0.097	<0.001
Cancer	12.5	7.8	0.156	<0.001
Venous thromboembolism	5.5	2.2	0.173	<0.001
Atrial fibrillation	6.4	3.2	0.150	<0.001
Ischemic heart disease	11.6	5.7	0.212	<0.001
Congestive heart failure	3.8	1.6	0.136	<0.001
Stroke	3.9	2.1	0.107	<0.001
Medication‡				
Antihypertensive	50.2	29.2	0.440	<0.001
Antidiabetic medicine	10.3	7.0	0.117	<0.001
Statin	37.2	20.2	0.383	<0.001
Loop diuretics	9.7	3.3	0.262	<0.001
Thiazide diuretics	6.4	3.7	0.124	<0.001
Health care utilization, mean ± SD				
Hospitalizations‡	0.6 ± 1.5	0.3 ± 0.9	0.247	<0.001
General practice visits‡	7.1 ± 7.1	3.4 ± 4.5	0.624	<0.001
Specialist referrals‡	0.7 ± 1.2	0.4 ± 0.9	0.274	<0.001

* Values are the percentage unless indicated otherwise. BMI = body mass index; stand. diff. = standard difference.
† The socioeconomic deprivation index score was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).
‡ Frequency during the past 1 year.

RA group and the comparison group. We performed a Cox proportional hazards model to examine the relation of RA to the risk of suspected/confirmed (or confirmed) COVID-19. We used the Fine and Gray approach to account for the competing risk of death. Specifically, if a person was diagnosed with COVID-19 after the index date, the outcome variable was defined as "Yes" (code 1), and the follow-up time was calculated from the index date to the date of COVID-19 diagnosis. If a person lost follow-up before she/he was diagnosed with COVID-19, the outcome variable was defined as "No" (code 0), and the follow-up time was calculated from the index date to the date of lost follow-up. If a person died before she/he developed COVID-19, the outcome variable was defined as "No" but coded as 2 (a competing risk), and the follow-up time was calculated from the index date to the date of death. We tested the proportional hazards assumption by using the Kolmogorov-type supremum test. We used exposure score, analogous to propensity score, overlap weighting to balance baseline characteristics between the compared groups. Specifically, the exposure score for RA was calculated using the logistic regression model with the

covariates described previously. Individuals with RA were weighted by the probability of not having RA (i.e., 1-exposure score), and individuals without RA were weighted by the probability of having RA (i.e., exposure score). Overlap weights were bounded and smoothly reduced the influence of individuals at the tails of the exposure score distribution without making any exclusions. We repeated the same analysis among patients with OA as a negative control exposure.

We further performed 4 sensitivity analyses to assess the robustness of our findings. First, considering the potential role of disease-modifying antirheumatic drug (DMARD) use in COVID-19, we compared RA with and RA without DMARD use to the risk of COVID-19, respectively. Second, because individuals with missing values were not included in our analyses, we performed imputation analyses to account for missing data. Specifically, missing values of the variables listed previously were imputed by a sequential regression method based on a set of covariates as predictors. Third, we compared the risk of COVID-19 between patients with RA and the general population as well as patients with OA and the general population after late April 2020, when COVID-19 testing was available to the general population in the UK (12). Finally, we conducted a cohort study to compare the risk of COVID-19 between patients with RA and patients with OA.

P values less than 0.05 (2-tailed) were considered significant for all tests. All statistical analyses were performed with SAS software, version 9.4, and RStudio, version 1.1,456 (R Foundation). Full references for the statistical analysis are shown in Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract.

RESULTS

The flow chart depicting the participant selection process is shown in Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/

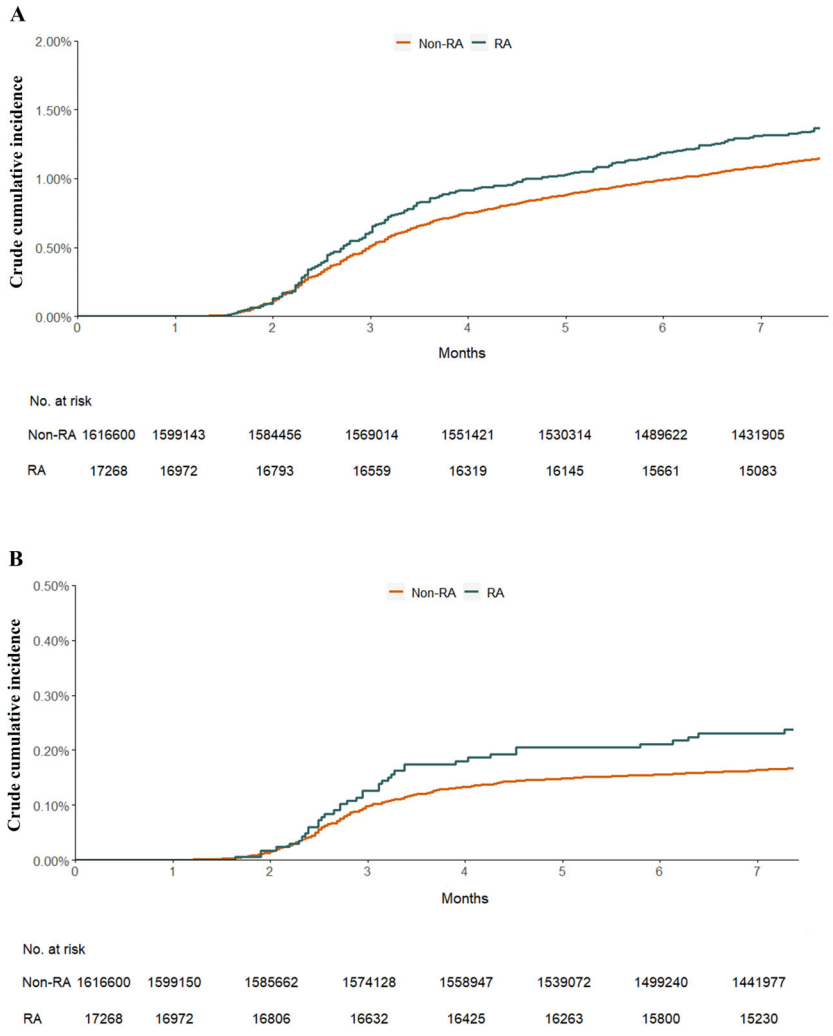

Figure 1. Crude cumulative incidence of suspected and confirmed COVID-19 (**A**) and confirmed COVID-19 (**B**) in 17,268 patients with rheumatoid arthritis (RA) as compared with 1,616,600 individuals without RA.

Table 2. Association between rheumatoid arthritis (RA) and the risk of COVID-19*

	RA (n = 17,268)	Non-RA (n = 1,616,600)
Suspected and confirmed COVID-19		
Event, no.	225	14,234
Mean follow-up, months	7.3	7.3
Incidence rate, per 1,000 person-months	1.4	0.9
Overlap weighted RD (95% CI), per 1,000 person-months	0.3 (0.1–0.5)	0.0 (ref.)
Crude HR (95% CI)	1.49 (1.31–1.69)	1.00 (ref.)
Overlap weighted HR (95% CI)	1.19 (1.04–1.36)	1.00 (ref.)
Overlap weighted HR (95% CI)†	1.20 (1.03–1.44)	1.00 (ref.)
Missing data imputation HR (95% CI)	1.19 (1.04–1.37)	1.00 (ref.)
Confirmed COVID-19		
Event, no.	46	2,249
Mean follow-up, months	7.3	7.4
Incidence rate, per 1,000 person-months	0.3	0.1
Overlap weighted RD (95% CI), per 1,000 person-months	0.1 (0.0–0.2)	0.0 (ref.)
Crude HR (95% CI)	1.93 (1.44–2.58)	1.00 (ref.)
Overlap weighted HR (95% CI)	1.42 (1.01–1.95)	1.00 (ref.)
Overlap weighted HR (95% CI)†	1.53 (1.08–2.28)	1.00 (ref.)
Missing data imputation HR (95% CI)	1.34 (1.07–1.63)	1.00 (ref.)

* The number (rate) of deaths (i.e., competing event) in the RA cohort and the non-RA cohort was 291 (2.3/1,000 person-months) and 9,754 (0.8/1,000 person-months), respectively. 95% CI = 95% confidence interval; HR = hazard ratio; RD = rate difference; ref. = reference.
† Considering April 30, 2020, as the index date.

acr.24831/abstract. In total, we assembled 17,268 participants with RA and 1,616,600 participants without RA. As shown in Table 1, participants with RA were older on average and more likely to be women. However, the baseline characteristics were well balanced between the compared groups after exposure score overlap weighting (all standard differences <0.1).

The risk of suspected/confirmed COVID-19 was higher among the RA group than among the comparison group (Figure 1). As shown in Table 2, 225 cases of suspected/confirmed COVID-19 occurred in the RA group (1.4/1,000 person-months), and 14,234 cases occurred in the non-RA group (0.9/1,000 person-months). The overlap weighted RD of suspected/confirmed COVID-19 between the 2 groups was 0.3/1,000 person-months (95% confidence interval [95% CI 0.1–0.5]), and the adjusted hazard ratio (HR_{adj}) was 1.19 (95% CI 1.04–1.36). Of suspected/confirmed COVID-19 cases, 46 in the RA group (0.3/1,000 person-months) and 2,249 (0.1/1,000 person-months) in the comparison group were diagnosed with confirmed COVID-19. The HR of confirmed COVID-19 for patients with RA versus the general population was 1.42 (95% CI 1.01–1.95).

We assembled 161,065 participants with OA and 779,300 participants without OA from the general population (see Supplementary Figure 2 and Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract). No apparent association was observed between OA and risk of COVID-19 (see Supplementary Figure 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract). The HRs of suspected/confirmed and confirmed COVID-19 for OA were 1.00 (95% CI 0.93–1.07) and 1.08 (95% CI 0.92–1.27), respectively (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract).

Similar results were observed from the sensitivity analyses when we stratified participants with RA according to DMARD use (see Supplementary Tables 4 and 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract), performed imputation analyses to account for missing data (Table 2), analyzed the data obtained after April 30, 2020 (Table 2), and compared the risk of COVID-19 between participants with RA and those with OA (see Supplementary Tables 6 and 7, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24831/abstract).

DISCUSSION

Using a population-based representative sample from the UK, we found that the rate of COVID-19 was higher among patients with RA, but not OA, than that among the general population. There are limited data regarding the risk of COVID-19 among patients with rheumatic diseases, and few studies that have assessed the risk of COVID-19 infection and its sequalae. A meta-analysis of 6 case–control studies reported that the odds of COVID-19 among patients with rheumatic diseases were 60% higher than that among those without rheumatic diseases (odds ratio [OR] 1.60 [95% CI 1.13–2.25]) (1). Several observational studies also compared the sequalae (e.g., hospitalization, intensive care unit admission, and death) after COVID-19 among

patients with rheumatic diseases (2,3). However, these studies may be susceptible to potential collider bias by conditioning upon having a confirmed COVID-19 diagnosis, leading to biased conclusions (12). To date, 3 studies have specifically compared the risk of COVID-19 between patients with RA to those without RA (6–8). A retrospective study conducted in 7 hospitals in Spain reported that patients with RA had a similar prevalence of hospital PCR-confirmed COVID-19 as those without rheumatic diseases (crude OR 0.98 [95% CI 0.76–1.26]) (8). However, 1 age-, sex-, and Veterans Affairs site–matched cohort study using American Veterans Affairs data showed that veterans with RA were at a higher incidence of PCR-confirmed COVID-19 than non-RA veterans (HR 1.25 [95% CI 1.13–1.39]) after adjusting for demographic information, comorbidities, health behaviors, and county level COVID-19 incidence rates (7). Another cohort study conducted in Denmark found that the risk of COVID-19 hospitalization among patients with RA was much higher than that among the general population (HR 1.72 [95% CI 1.29–2.30]) after adjusting for sex and comorbidities, with age as underlying time scale (6). Likewise, our study findings are in line with those reported in the US and Denmark suggesting that the risk of incident COVID-19 is higher among patients with RA than in the general population, independent of major potential confounders (i.e., sociodemographic characteristics, anthropometrics, lifestyle factors, comorbidities, medication use, and health care utilization).

Several mechanisms may explain the positive association between RA and risk of COVID-19. Studies have demonstrated that premature aging of the immune system in RA contributes to weakened protection against infectious organisms (13). Glucocorticoids are commonly used in the treatment of RA, and there is evidence that glucocorticoid use increases the risk of serious infections in a dose-dependent manner (14). Additionally, other chronic immunosuppressive medications commonly used to treat RA, including biologics and non-biologic DMARDs, may also increase susceptibility to respiratory infections (15), making patients with RA more susceptible to COVID-19.

Our study has several strengths. First, our results were derived from a general population sample from the UK; thus, the study findings are likely generalizable. Second, the risk of developing COVID-19 may vary among the different rheumatic diseases (5). Our study provided the timely evidence that patients with RA, a common autoimmune inflammatory rheumatic disease, but not OA, are at an increased risk of COVID-19. These findings not only could help professional organizations in updating their guidelines around COVID-19 for patients with RA, but they could also shed light on our understanding of the roles of systemic autoimmunity and inflammation in acquiring COVID-19. Third, major potential confounders were addressed and were well balanced after using overlap weights of exposure score. In addition, the sensitivity analyses did not change the results materially, suggesting that the observed associations are robust.

Several limitations of the study deserve comment. First, the sensitivity for capturing COVID-19 cases through the utilized approaches has not been assessed in THIN, and our estimate of COVID-19 incidence could be underestimated. Second, it is possible that patients with RA seek medical care more often and are therefore more likely to have COVID-19 tests than the general population during the COVID-19 pandemic period, which may lead to the higher observed risk of COVID-19 among patients with RA. Since data on the number of COVID-19 tests is unavailable in THIN, we cannot directly assess whether surveillance bias may affect our study findings. Nevertheless, when we compared the risk of COVID-19 infection between 2 comparison cohorts after late April 2020, when COVID-19 testing was available to the general population in the UK (12), RA, but not OA, was still associated with an increased risk of COVID-19. In addition, when we compared the risk of COVID-19 between participants with RA and those with OA, the results were consistent with those between RA and the general population. These findings suggest that a higher risk of COVID-19 among participants with RA than in the general population or participants with OA may not be completely explained by surveillance bias. Third, as we cannot determine the source of the case (i.e., ambulatory encounters or hospitalizations), the testing patterns, and the disease severity of COVID-19 in THIN, future studies are needed to assess the association between RA and the severity of COVID-19. Fourth, it is of great interest to examine whether severity of RA may affect susceptibility to the risk of COVID-19 infection; however, this information was unavailable in THIN. Future studies are required to test this hypothesis. Finally, while the HR generated from imputation analyses (suspected/confirmed COVID-19 HR 1.19; confirmed COVID-19 HR 1.34) was smaller than that from completed data analysis (suspected/confirmed COVID-19 HR 1.19; confirmed COVID-19 HR 1.42), the difference in these effect estimates appears small. Nevertheless, as in any observational study, we cannot rule out the potential selection bias due to missingness, and future studies are needed to verify our findings.

In conclusion, RA, but not OA, was associated with an increased risk of COVID-19. Our findings provide timely evidence to support recommendations that booster vaccines and priority access to anti–SARS–CoV-2 monoclonal antibody treatments should be encouraged for patients with RA.

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 submitted for publication. Dr. Lei 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. Lei, Zhang.

Acquisition of data. Wang, D'Silva, Jorge, Li, Lyv, Wei, Zeng, Lei, Zhang.

Analysis and interpretation of data. Wang, D'Silva, Jorge, Li, Lyv, Wei, Zeng, Lei, Zhang.

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