Risk of COVID-19 Among Unvaccinated and Vaccinated Patients With Rheumatoid Arthritis: A General Population Study

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Objective. To determine whether patients with rheumatoid arthritis (RA) are at higher risks for SARS-CoV-2 infection and its severe outcomes before and after COVID-19 vaccination.

Methods. Using a UK primary care database, we conducted 2 cohort studies to compare the risks of SARS-CoV-2 infection, hospitalization, and death from COVID-19 between patients with RA and the general population according to their COVID-19 vaccination status. We used exposure score overlap weighting to balance baseline characteristics between 2 comparison cohorts.

Results. Among unvaccinated individuals, the weighted incidence rates of SARS-CoV-2 infection (9.21 versus 8.16 of 1,000 person-months), hospitalization (3.46 versus 2.14 of 1,000 person-months), and death (1.19 versus 0.62 of 1,000 person-months) were higher among patients with RA than the general population over 3 months of follow-up; the corresponding adjusted hazard ratios (HRs) were 1.10 (95% confidence interval [95% CI] 1.00–1.24), 1.62 (95% CI 1.34–1.96), and 1.88 (95% CI 1.37–2.60), respectively. Among vaccinated individuals, the weighted rates of breakthrough infection (4.17 versus 3.96 of 1,000 person-months; HR 1.10 [95% CI 1.00–1.20]) and hospitalization (0.42 versus 0.32 of 1,000 person-months; HR 1.29 [95% CI 0.96–1.75]) were higher among patients with RA than the general population over 9 months of follow-up; however, no apparent difference in the risk of these outcomes was observed over 3 and 6 months of follow-up between 2 comparison cohorts.

Conclusion. Patients with RA are still at higher risks of SARS-CoV-2 infection and COVID-19 hospitalization than the general population after receiving COVID-19 vaccines. These findings support booster COVID-19 vaccinations and adherence of other preventive strategies among patients with RA.

INTRODUCTION

The ongoing COVID-19 pandemic has affected millions of people worldwide and resulted in an unprecedented health and economic toll. As of March 2022, >464 million infection cases and >6.0 million deaths associated with COVID-19 have been reported globally (1). During the COVID-19 pandemic, a number of studies found that patients with immune-mediated inflammatory diseases had a higher susceptibility to SARS-CoV-2 infection and severe outcomes than the general population (2). Rheumatoid arthritis (RA) is a common immune-mediated inflammatory disease, and patients with RA often use immunosuppressive agents, such as steroids and disease-modifying antirheumatic drugs, that contribute to a higher risk for SARS-CoV-2 infection. Moreover, comorbidities caused by RA such as cardiovascular disease and interstitial lung disease have the potential to contribute a high risk of poor responses (3–5). Indeed, several studies have found that patients with RA are at higher risk of...
SIGNIFICANCE & INNOVATIONS

- This study shows that the risks of SARS-CoV-2 breakthrough infection or COVID-19 hospitalization is higher among patients with rheumatoid arthritis (RA) than the general population comparators over 9 months of follow-up.
- These results support the recent recommendations for booster vaccinations in people with autoimmune inflammatory rheumatic diseases, and other preventive strategies, such as wearing face masks and keeping social distancing, should be encouraged among patients with RA even after vaccination.

SARS-CoV-2 infection and severe outcomes of COVID-19 than individuals without RA (6–12).

Despite recent introduction of some effective therapies for treating SARS-CoV-2 infection, vaccination remains the most promising approach at present for controlling this pandemic because of its efficacy at reducing the risk of SARS-CoV-2 infection and severe outcomes in the general population (13). Although the immunogenicity and safety of anti-SARS-CoV-2 vaccines were demonstrated in patients with chronic inflammatory conditions and in those receiving immunosuppressive therapy, immune responses against SARS-CoV-2 after vaccination were blunted (14–16). Moreover, concerns have been raised that the protection provided by vaccines against severe COVID-19 decreases gradually over time (17). A recent systematic review and meta-regression analysis found that COVID-19 vaccine efficacy or effectiveness decreased somewhat by 6 months after vaccination, underscoring the importance of evaluating vaccine efficacy or effectiveness against severe outcomes beyond 6 months (18). However, to date, there is a paucity of data on the risk of SARS-CoV-2 infection and severe outcomes (leading to hospitalization or death) after COVID-19 vaccination in patients with RA, leaving knowledge gaps regarding the need for booster vaccinations and adherence to other risk mitigation strategies after vaccination especially beyond 6 months.

To determine whether patients with RA are at higher risks for SARS-CoV-2 infection and severe outcomes after COVID-19 vaccination, and to inform physicians, other health professionals, vaccine recipients, and RA guideline development, we conducted 2 cohort studies to quantify the risks of SARS-CoV-2 infection, COVID-19 hospitalization, and death among patients with RA compared with individuals without RA from the general population (hereafter referred to as the general population) according to their COVID-19 vaccination status.

SUBJECTS AND METHODS

Data source. We used data from The Health Improvement Network (THIN) database (now called IQVIA Medical Research Database). THIN is an electronic medical record database used by general practitioners (GPs) in the UK. It consists of data on ~17 million persons in the UK and represents the UK population regarding patient demographic characteristics and the prevalence of medical conditions. During consultation with patients, health information is recorded on site by the GP using a computerized system. The computerized information includes socio-demographic characteristics, anthropometrics, lifestyle factors, and details from visits to GPs (i.e., prescriptions, diagnoses from specialist referrals, hospital admissions, and results of laboratory tests). The Read classification system is used to code specific diagnoses (19), whereas a dictionary based on the Multilex classification system is used to code drugs (20). This study was approved by the THIN Scientific Review Committee (20SRC003-A2) and received approval from the Medical Ethics Committee at Xiangya Hospital (2018091077), with waiver of informed consent.

Study design. We conducted 2 cohort studies to compare the risks of SARS-CoV-2 infection, COVID-19 hospitalization, and death between patients with RA and the general population according to their COVID-19 vaccination status. 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.25028)(5). This method has been previously validated in the UK General Practice Research Database, with a positive predictive value of ~80% for RA (21). Eligible participants consisted of those who were 18–90 years of age between December 8, 2020 (i.e., when the first COVID-19 vaccination was available to the public in the UK) and October 31, 2021, had no previously documented SARS-CoV-2 infection, and had at least 2 years of continuous enrollment with a general practice.

Cohort definition. For each eligible individual in the unvaccinated cohort, follow-up started on December 8, 2020 (i.e., index date) and ended on the day of first dose of vaccine received, developing the outcomes of interest (i.e., SARS-CoV-2 infection, COVID-19 hospitalization, or death), or the end of the study period (October 31, 2021), whichever occurred first. For each eligible individual in the vaccinated cohort, follow-up started on the day the first dose of vaccine was received (i.e., index date) and ended on the day of developing the outcomes of interest (i.e., SARS-CoV-2 infection, COVID-19 hospitalization, or death) or the end of the study period (October 31, 2021), whichever occurred first.

Assessment of outcomes. The primary outcome was a documented diagnosis of SARS-CoV-2 infection (22), and the secondary outcomes were hospitalization for COVID-19 and death from COVID-19. Confirmed SARS-CoV-2 infection
diagnosis was made based on Read codes (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25028) according to a previous study using UK general population–based data (22). Hospitalization for COVID-19 was defined as a hospitalization record in THIN within 30 days after documentation of SARS–CoV-2 infection, and death from COVID-19 was defined as a death within 30 days of SARS–CoV-2 infection (23–26).

### Table 1. Baseline characteristics of patients with rheumatoid arthritis (RA) and the general population without RA in the unvaccinated cohort

| Characteristic                        | Before overlap weighting | After overlap weighting |
|---------------------------------------|--------------------------|-------------------------|
|                                       | RA (n = 15,901)          | General cohort (n = 1,558,423) | RA (n = 15,286) | General cohort (n = 15,286) |
|                                       | SMD                      | SMD                     |                          |
| Demographic characteristics           |                          |                         |                          |
| Age, years                            | 64.8 ± 13.7              | 47.9 ± 17.2             | 1.091                    | 64.5 ± 13.7 | 64.5 ± 15.6 | <0.001 |
| Socioeconomic Deprivation Index score, %†|                          |                         | 0.097                    |                         |            | <0.001 |
| Missing                               | 10.2                     | 12.8                    |                          | 10.2                    | 10.2                    |          |
| 1                                     | 15.8                     | 14.9                    |                          | 15.9                    | 15.9                    |          |
| 2                                     | 18.6                     | 17.5                    |                          | 18.6                    | 18.6                    |          |
| 3                                     | 20.4                     | 19.3                    |                          | 20.4                    | 20.4                    |          |
| 4                                     | 19.7                     | 18.9                    |                          | 19.6                    | 19.6                    |          |
| 5                                     | 15.3                     | 16.7                    |                          | 15.3                    | 15.3                    |          |
| Women, %                              | 70.8                     | 48.9                    | 0.459                    | 70.3                    | 70.3                    | <0.001 |
| BMI, kg/m²                             | 28.3 ± 6.4               | 27.5 ± 6.0              | 0.135                    | 28.3 ± 6.4 | 28.3 ± 6.4 | 0.002 |
| Region, %                             | 0.061                    |                         |                          |                         | <0.001 |
| England                               | 16.7                     | 18.7                    |                          | 16.8                    | 16.8                    |          |
| Northern Ireland                      | 13.0                     | 13.4                    |                          | 13.0                    | 13.0                    |          |
| Scotland                              | 39.5                     | 39.0                    |                          | 39.4                    | 39.4                    |          |
| Wales                                 | 30.8                     | 28.8                    |                          | 30.8                    | 30.8                    |          |
| No. of COVID-19 tests                 | 0.1 ± 0.3                | 0.1 ± 0.3               | 0.024                    | 0.1 ± 0.3 | 0.1 ± 0.3 | <0.001 |
| Influenza vaccination within previous year, % | 69.7                     | 25.4                    | 0.988                    | 68.9                    | 68.9                    | <0.001 |
| Lifestyle factors                     |                          |                         |                          |                          |                         |          |
| Drinking, %                           | 0.223                    |                         |                          |                         | <0.001 |
| None                                  | 27.0                     | 19.4                    |                          | 26.5                    | 26.5                    |          |
| Past                                  | 5.1                      | 2.9                     |                          | 5.0                     | 5.0                     |          |
| Current                               | 68.0                     | 77.7                    |                          | 68.5                    | 68.5                    |          |
| Smoking, %                            | 0.305                    |                         |                          |                         | <0.001 |
| None                                  | 48.3                     | 58.3                    |                          | 48.6                    | 48.6                    |          |
| Past                                  | 35.6                     | 21.9                    |                          | 35.2                    | 35.2                    |          |
| Current                               | 16.1                     | 19.8                    |                          | 16.2                    | 16.2                    |          |
| Charlson comorbidity index score       | 0.47 ± 1.00              | 0.20 ± 0.67             | 0.311                    | 0.46 ± 1.00 | 0.46 ± 0.98 | <0.001 |
| Comorbidity, %                        |                          |                         |                          |                          |                         |          |
| Hypertension                          | 42.7                     | 17.2                    | 0.579                    | 42.2                    | 42.2                    | <0.001 |
| Diabetes mellitus                     | 18.5                     | 8.9                     | 0.282                    | 18.4                    | 18.4                    | <0.001 |
| Hyperlipidemia                        | 12.9                     | 5.0                     | 0.28                      | 12.8                    | 12.8                    | <0.001 |
| Chronic kidney disease                | 11.5                     | 2.6                     | 0.354                    | 11.1                    | 11.1                    | <0.001 |
| Pneumonia or infection                | 11.5                     | 5.2                     | 0.229                    | 11.1                    | 11.1                    | <0.001 |
| Chronic obstructive pulmonary disease | 9.7                      | 2.4                     | 0.312                    | 9.4                     | 9.4                     | <0.001 |
| Cancer                                | 12.6                     | 5.7                     | 0.241                    | 12.5                    | 12.5                    | <0.001 |
| Venous thromboembolism                | 5.4                      | 1.5                     | 0.214                    | 5.2                     | 5.2                     | <0.001 |
| Atrial fibrillation                   | 6.3                      | 2.0                     | 0.221                    | 6.2                     | 6.2                     | <0.001 |
| Ischemic heart disease                | 11.1                     | 3.6                     | 0.289                    | 10.9                    | 10.9                    | <0.001 |
| Myocardial infarction                 | 5.3                      | 1.8                     | 0.189                    | 5.2                     | 5.2                     | <0.001 |
| Congestive heart failure              | 3.7                      | 1.0                     | 0.179                    | 3.6                     | 3.6                     | <0.001 |
| Stroke                                | 3.9                      | 1.5                     | 0.153                    | 3.9                     | 3.9                     | <0.001 |
| Health care utilization within previous year |                      |                         |                          |                          |                         |          |
| Hospitalizations‡                     | 0.5 ± 1.3                | 0.2 ± 0.8               | 0.264                    | 0.4 ± 1.2 | 0.4 ± 1.5 | <0.001 |
| General practice visits‡              | 5.3 ± 6.4                | 1.8 ± 3.3               | 0.695                    | 5.1 ± 5.8 | 5.1 ± 11.3 | <0.001 |
| Specialist referrals‡                 | 0.4 ± 0.9                | 0.2 ± 0.6               | 0.308                    | 0.4 ± 0.9 | 0.4 ± 1.1 | <0.001 |

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; SMD = standardized mean 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 year.
Assessment of covariates. The covariates included sociodemographic factors (age, sex, Townsend Deprivation Index), geographic location, body mass index (BMI), lifestyle factors (alcohol drinking and smoking status), previous COVID-19 test performed, influenza vaccination during the past 1 year before the index date, comorbidities at any time from Table 2.

Baseline characteristics of patients with rheumatoid arthritis (RA) and the general population without RA in the vaccinated cohort*

| Characteristic                           | Before overlap weighting | After overlap weighting |
|-----------------------------------------|--------------------------|-------------------------|
|                                         | RA (n = 14,330)          | General cohort (n = 1,208,659) | SMD      | RA (n = 13,760) | General cohort (n = 13,760) | SMD      |
| Demographic characteristics             |                          |                         |          |                  |                          |          |
| Age, years                              | 65.3 ± 13.4              | 50.1 ± 17.2             | 0.986    | 65.1 ± 13.4      | 65.1 ± 15.1              | <0.001   |
| Socioeconomic Deprivation Index score, %|                          |                         | 0.059    |                  |                          |          |
| Missing                                 | 10.1                     | 11.8                    |          | 10.1             | 10.1                    |          |
| 1                                       | 15.8                     | 15.5                    |          | 15.9             | 15.9                    |          |
| 2                                       | 18.8                     | 18.9                    |          | 18.9             | 18.9                    |          |
| 3                                       | 20.6                     | 19.8                    |          | 20.5             | 20.5                    |          |
| 4                                       | 19.5                     | 18.6                    |          | 19.5             | 19.5                    |          |
| 5                                       | 15.2                     | 15.5                    |          | 15.2             | 15.2                    |          |
| Women, %                                | 71.0                     | 50.7                    | 0.427    | 70.5             | 70.5                    | <0.001   |
| BMI, kg/m²                               | 28.4 ± 6.4               | 27.8 ± 6.1              | 0.099    | 28.4 ± 6.4       | 28.4 ± 6.5              | 0.006    |
| Region, %                               | 0.24                     |                         |          |                  |                          | <0.001   |
| England                                 | 13.8                     | 14.2                    |          | 13.9             | 13.9                    |          |
| Northern Ireland                        | 13.2                     | 13.9                    |          | 13.3             | 13.3                    |          |
| Scotland                                | 42.0                     | 41.3                    |          | 41.9             | 41.9                    |          |
| Wales                                   | 30.9                     | 30.6                    |          | 30.9             | 30.9                    |          |
| Type of first dose vaccination, %       |                          |                         | 0.282    |                  |                          | <0.001   |
| AstraZeneca                             | 67.2                     | 54.1                    |          | 67.2             | 67.8                    |          |
| Pfizer                                  | 31.8                     | 43.3                    |          | 31.8             | 31.3                    |          |
| Moderna or Janssen                      | 1.0                      | 2.6                     |          | 1.0              | 0.9                     |          |
| Type of second dose vaccination, %      |                          |                         | 0.307    |                  |                          | 0.064    |
| No second dose                          | 5.1                      | 7.3                     |          | 5.1              | 4.4                     |          |
| AstraZeneca                             | 64.4                     | 51.2                    |          | 64.4             | 65.2                    |          |
| Pfizer                                  | 30.3                     | 39.5                    |          | 30.3             | 30.0                    |          |
| Moderna or Janssen                      | 0.2                      | 2.0                     |          | 0.2              | 0.4                     |          |
| No. of COVID-19 tests                   | 0.1 ± 0.3                | 0.2 ± 0.4               | 0.090    | 0.1 ± 0.3        | 0.1 ± 0.3               | <0.001   |
| Influenza vaccination within previous year, % | 74.4                   | 33.8                    | 0.892    | 73.8             | 73.8                    | <0.001   |
| Lifestyle factors                       |                          |                         |          |                  |                          |          |
| Drinking, %                             | 26.4                     | 18.1                    | 0.240    |                  |                          | <0.001   |
| Past                                    | 5.1                      | 3.0                     |          | 5.0              | 5.0                     |          |
| Current                                 | 68.5                     | 78.9                    |          | 69.0             | 69.0                    |          |
| Smoking, %                              | 48.4                     | 59.3                    | 0.288    |                  |                          | <0.001   |
| Past                                    | 36.0                     | 23.0                    |          | 35.6             | 35.6                    |          |
| Current                                 | 15.6                     | 17.7                    |          | 15.7             | 15.7                    |          |
| Charlson comorbidity index score         | 0.46 ± 0.99              | 0.23 ± 0.71             | 0.271    | 0.46 ± 0.99      | 0.46 ± 0.96             | <0.001   |
| Comorbidity, %                          |                          |                         |          |                  |                          |          |
| Hypertension                            | 43.3                     | 20.0                    | 0.519    | 42.8             | 42.8                    | <0.001   |
| Diabetes mellitus                       | 18.5                     | 10.1                    | 0.242    | 18.4             | 18.4                    | <0.001   |
| Hyperlipidemia                          | 13.1                     | 5.8                     | 0.253    | 12.9             | 12.9                    | <0.001   |
| Chronic kidney disease                  | 11.6                     | 3.0                     | 0.335    | 11.2             | 11.2                    | <0.001   |
| Pneumonia or infection                  | 11.6                     | 5.6                     | 0.214    | 11.2             | 11.2                    | <0.001   |
| Chronic obstructive pulmonary disease   | 9.8                      | 2.8                     | 0.293    | 9.5              | 9.5                     | <0.001   |
| Cancer                                  | 13.0                     | 6.6                     | 0.214    | 12.9             | 12.9                    | <0.001   |
| Venous thromboembolism                  | 5.2                      | 1.7                     | 0.195    | 5.0              | 5.0                     | <0.001   |
| Atrial fibrillation                     | 6.4                      | 2.3                     | 0.202    | 6.3              | 6.3                     | <0.001   |
| Ischemic heart disease                  | 11.0                     | 4.3                     | 0.256    | 10.8             | 10.8                    | <0.001   |
| Myocardial infarction                   | 5.2                      | 2.1                     | 0.166    | 5.1              | 5.1                     | <0.001   |
| Congestive heart failure                | 3.7                      | 1.2                     | 0.161    | 3.6              | 3.6                     | <0.001   |
| Stroke                                  | 4.0                      | 1.7                     | 0.199    | 3.9              | 3.9                     | <0.001   |
| Health care utilization within previous year |                      |                         |          |                  |                          |          |
| Hospitalizations†                       | 0.4 ± 1.2                | 0.2 ± 0.7               | 0.229    | 0.4 ± 1.7        | 0.4 ± 1.3               | <0.001   |
| General practice visits‡                | 4.9 ± 6.3                | 1.7 ± 3.3               | 0.644    | 4.7 ± 5.6        | 4.7 ± 10.8              | <0.001   |
| Specialist referrals‡                   | 0.4 ± 0.9                | 0.2 ± 0.6               | 0.268    | 0.4 ± 0.9        | 0.4 ± 1.0               | <0.001   |

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; SMD = standardized mean 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 year.
enrollment to the index date (Charlson comorbidity index, as well as individual conditions of hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, pneumonia or infection, chronic obstructive pulmonary disease, cancer, venous thromboembolism, atrial fibrillation, ischemic heart disease, myocardial infarction, congestive heart failure, and stroke), and health care utilization (hospitalizations, general practice visits, and specialist referrals) during the past 1 year before the index date. Among the vaccinated cohort, we also collected information on the type of the first dose of vaccine that participants received.

Statistical analysis. For both cohorts, we used exposure score (analogous to propensity score) overlap weighting to balance baseline characteristics between the comparison groups. Specifically, 2 sets of exposure scores for RA were calculated. First, the exposure score for RA was generated using a logistic regression model that included the covariates of age, sex, BMI, Socioeconomic Deprivation Index score, region, lifestyle factors, number of previous COVID-19 tests, and health care utilization (i.e., exposure score for partial adjustment). Second, additional covariates, i.e., comorbidities (including Charlson comorbidity index score and individual comorbidities), were added to the logistic regression model to generate the exposure score for RA (i.e., exposure score for full adjustment). Patients 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 (27,28). We assessed the distribution of the baseline characteristics before and after overlap weights using the standardized mean differences for the comparison groups (29).

Among the unvaccinated cohort, we calculated the incidence rate for the primary and secondary outcomes among patients with RA and the general population using overlap weighting of the exposure score to control for confounders. We performed a Cox proportional hazards model to examine the relation of RA to the risk of SARS-CoV-2 infection, hospitalization, and death, accounting for the competing risk of death (30) using overlap weighting of the exposure score. Because >80% of unvaccinated subjects received a first dose of the vaccine within 3 months after the vaccination program began, we restricted our analyses to 3 months of follow-up time in the unvaccinated cohort to minimize potential selection bias (30). We tested the proportional hazards assumption by plotting the cumulative incidence curve of each outcome. If the proportional hazards assumption was violated, we conducted a weighted Cox regression to obtain a weighted hazard ratio (HR) (31). We took the same approach to compare the risk of COVID-19 breakthrough infection, hospitalization, and death from COVID-19 among the vaccinated cohort. However, the follow-up time was extended to 9 months. In addition, we conducted a subgroup analysis to compare the risks of breakthrough infection and severe outcomes during the different periods (i.e., SARS-CoV-2 alpha variant predominance period from January 1, 2021 to May 16, 2021, as well as SARS-CoV-2 delta variant predominance period from May 17, 2021 to October 31, 2021) between vaccinated patients with RA and the vaccinated general population (32).

All P values were 2-sided, and P values less than 0.05 were considered significant. All statistical analyses were performed with SAS, version 9.4. The data that support the findings of this study are available within the article and its supplementary information files or from the corresponding author upon reasonable request.

Table 3. Association between rheumatoid arthritis (RA) and the risk of SARS-CoV-2 infection, COVID-19 hospitalization, and death in the unvaccinated cohort over 3 months

| Outcomes                      | RA (n = 15,901) | General cohort (n = 1,558,423) |
|-------------------------------|----------------|-------------------------------|
| SARS-CoV-2 infection          |                |                               |
| Events, no.                   | 327            | 33,889                        |
| Mean follow-up, months        | 2.23           | 2.60                          |
| Weighted IR, per 1,000 person-months† | 9.21           | 8.16                          |
| Weighted HR (95% CI)‡         | 1.11 (1.00–1.24) | 1.00 (Ref.)                  |
| Weighted IR, per 1,000 person-months‡ | 9.20           | 8.31                          |
| Weighted HR (95% CI)‡         | 1.10 (1.00–1.20) | 1.00 (Ref.)                  |
| COVID-19 hospitalization      |                |                               |
| Events, no.                   | 128            | 3,299                         |
| Mean follow-up, months        | 2.25           | 2.64                          |
| Weighted IR, per 1,000 person-months‡ | 3.46           | 2.14                          |
| Weighted HR (95% CI)‡         | 1.62 (1.34–1.96) | 1.00 (Ref.)                  |
| Weighted IR, per 1,000 person-months‡ | 3.46           | 2.08                          |
| Weighted HR (95% CI)‡         | 1.67 (1.38–2.02) | 1.00 (Ref.)                  |
| COVID-19 death                |                |                               |
| Events, no.                   | 44             | 561                           |
| Mean follow-up, months        | 2.26           | 2.64                          |
| Weighted IR, per 1,000 person-months‡ | 1.19           | 0.62                          |
| Weighted HR (95% CI)‡         | 1.88 (1.37–2.60) | 1.00 (Ref.)                  |
| Weighted IR, per 1,000 person-months‡ | 1.18           | 0.64                          |
| Weighted HR (95% CI)‡         | 1.80 (1.30–2.48) | 1.00 (Ref.)                  |

* 95% CI = 95% confidence interval; HR = hazard ratio; IR = incidence rate; Ref. = reference.
† Values were time-stratified, overlap-weighted estimates of the propensity score; weighted Cox regression using the coxphw method was applied if the proportional hazards assumption was violated. Results were obtained from the fully adjusted model.
‡ Values were time-stratified, overlap-weighted estimates of the propensity score; weighted Cox regression using the coxphw method was applied if the proportional hazards assumption was violated. Results were obtained from the partially adjusted model.
RESULTS

The flow chart depicting participant selection is shown in Supplementary Figure 1, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25028. We identified 15,901 patients with RA and 1,558,423 individuals from the general population among the unvaccinated cohort; we also identified 14,330 patients with RA and 1,208,659 individuals from the general population among the vaccinated cohort. As shown in Table 1 and Table 2, before exposure score overlap weighting, patients with RA tended to be older, were more likely to be female, had more hospitalizations and GP visits, and had a lower percentage of influenza vaccination. After exposure score overlap weighting, the baseline characteristics were well balanced between the comparison groups, with all standardized differences <0.1 (Table 1 and Table 2).

Unvaccinated cohort. In the unvaccinated cohort, the risk of SARS-CoV-2 infection (fully weighted incidence rate 9.21 versus 8.16 of 1,000 person-months), COVID-19 hospitalization (fully weighted incidence rate 3.46 versus 2.14 of 1,000 person-months), and COVID-19 death (fully weighted incidence rate 1.19 versus 0.62 of 1,000 person-months) were higher among patients with RA than among the general population over 3 months (Table 3 and Figure 1). The corresponding fully adjusted HRs were 1.11 (95% confidence interval [95% CI] 1.00–1.24), 1.62 (95% CI 1.34–1.96), and 1.88 (95% CI 1.37–2.60), respectively. RA was also associated with an increased risk of SARS-CoV-2 infection, COVID-19 hospitalization, and death after using the exposure score for partial adjustment (Table 3).

Vaccinated cohort. Among the vaccinated cohort, there were no apparent differences in the risk of breakthrough infection, COVID-19 hospitalization, and death over 3 months. The fully weighted incidence rates for each outcome were 1.39, 0.22, and 0.00 of 1,000 person-months among the patients with RA, and 1.68, 0.23, and 0.04 of 1,000 person-months among the...
Table 4. Association between rheumatoid arthritis (RA) and the risk of breakthrough infection, COVID-19 hospitalization, and death in the vaccinated cohort

| Outcomes                   | RA (n = 14,330) | General cohort (n = 1,208,659) | Outcomes                  | RA (n = 14,330) | General cohort (n = 1,208,659) |
|----------------------------|-----------------|--------------------------------|---------------------------|-----------------|--------------------------------|
| **Three-month follow-up**  |                 |                                |                           |                 |                                |
| Breakthrough infection     |                 |                                |                           |                 |                                |
| Events, no.                | 57              | 13,609                         | Mean follow-up, months    | 5.72            | 5.49                           |
| Mean follow-up, months     | 2.89            | 2.90                           | Weighted IR, per 1,000    | 0.03            | 0.03                           |
| Weighted IR, per 1,000     | 1.39            | 1.68                           | person-months†             | 1.03 (0.79–1.34)| 1.00 (Ref.)                     |
| Weighted HR (95% CI)†‡     |                 |                                | Weighted HR (95% CI)†‡     |                 |                                |
| COVID-19 hospitalization    |                 |                                |                           |                 |                                |
| Events, no.                | 9               | 478                            | Weighted HR, per 1,000    | 0.96 (0.49–1.89)| 1.00 (Ref.)                     |
| Mean follow-up, months     | 2.90            | 2.92                           | person-months†             | 0.22            | 0.23                           |
| Weighted HR (95% CI)†‡     |                 |                                | Weighted HR, per 1,000    | 0.22 (0.49–1.89)| 1.00 (Ref.)                     |
| Weighted HR, per 1,000     | 1.38            | 1.68                           | person-months‡             | 0.95            | 1.00 (Ref.)                     |
| Weighted HR (95% CI)‡     |                 |                                | Weighted HR (95% CI)‡     |                 |                                |
| COVID-19 death             |                 |                                |                           |                 |                                |
| Events, no.                | 0               | 39                             | Weighted HR, per 1,000    | 0                | 0.05                           |
| Mean follow-up, months     | 2.90            | 2.92                           | person-months‡             | 0                | 0.05                           |
| Weighted HR (95% CI)‡     |                 |                                | Weighted HR (95% CI)‡     |                 |                                |
| Six-month follow-up        |                 |                                |                           |                 |                                |
| Breakthrough infection     |                 |                                |                           |                 |                                |
| Events, no.                | 177             | 32,321                         | Weighted HR, per 1,000    | 1.07 (0.92–1.24)| 1.00 (Ref.)                     |
| Mean follow-up, months     | 5.69            | 5.44                           | person-months†             | 2.19            | 2.33                           |
| Weighted IR, per 1,000     | 0.20            | 0.21                           | Weighted HR (95% CI)†‡     |                 |                                |
| Weighted IR, per 1,000     | 0.20            | 0.21                           | COVID-19 hospitalization  | 0.93 (0.95–1.01)| 1.00 (Ref.)                     |
| Events, no.                | 17              | 1,015                          | Weighted HR, per 1,000    | 0.93 (0.57–1.52)| 1.00 (Ref.)                     |
| Mean follow-up, months     | 5.72            | 5.49                           | person-months‡             | 0.20            | 0.21                           |
| Weighted IR, per 1,000     | 0.20            | 0.21                           | Weighted HR (95% CI)‡     |                 |                                |
| Weighted HR, per 1,000     | 1.07 (0.92–1.24)|                                | Weighted HR (95% CI)‡     |                 |                                |
| COVID-19 death             |                 |                                |                           |                 |                                |
| Events, no.                | 3               | 60                             | Weighted HR, per 1,000    | 0.95 (0.58–1.55)| 1.00 (Ref.)                     |
| Mean follow-up, months     | 2.90            | 2.92                           | person-months‡             | 0                | 0.05                           |
| Weighted IR, per 1,000     | 1.38            | 1.68                           | Weighted HR (95% CI)‡     |                 |                                |
| Weighted HR, per 1,000     | 1.01 (0.78–1.32)|                                | Weighted HR (95% CI)‡     |                 |                                |

* 95% CI = 95% confidence interval; HR = hazard ratio; IR = incidence rate; Ref. = reference.
† Values were time-stratified, overlap-weighted estimates of the propensity score; weighted Cox regression using the coxphw method was applied if the proportional hazards assumption was violated. Results were obtained from the fully adjusted model.
‡ Values were time-stratified, overlap-weighted estimates of the propensity score; weighted Cox regression using the coxphw method was applied if the proportional hazards assumption was violated. Results were obtained from the partially adjusted model.

For the general population, respectively (Table 4 and Figure 2). The corresponding fully adjusted HRs were 1.03 (95% CI 0.79–1.34) and 0.96 (95% CI 0.49–1.89) for breakthrough infection and COVID-19 hospitalization, respectively. No increased risk of breakthrough infection (2.19 versus 2.33 of 1,000 person-months; HR 1.07 [95% CI 0.92–1.24]), COVID-19 hospitalization (0.20 versus 0.21 of 1,000 person-months; HR 0.93 [95% CI 0.57–1.52]), and death (0.03 versus 0.03 of 1,000 person-months; HR 0.93 [95% CI 0.31–2.82]) was observed when the analyses were restricted to the 6-month follow-up period. After using the exposure score for partial adjustment, RA was not associated with an increased risk of SARS-CoV-2 infection and COVID-19.
hospitalization over 3 months of follow-up (Table 4). Similarly, no increased risks of breakthrough infection, COVID-19 hospitalization, and death were observed over 6 months of follow-up (Table 4).

Over 9 months of follow-up, the fully weighted incidence rates of breakthrough infection, COVID-19 hospitalization, and death were 4.17, 0.42, and 0.05 of 1,000 person-months among the individuals with RA; the corresponding rates among the general population were 3.96, 0.32, and 0.04 of 1,000 person-months, respectively. The fully adjusted HRs were 1.10 (95% CI 1.00–1.20) for breakthrough infection, 1.29 (95% CI 0.96–1.75) for hospitalization, and 1.41 (95% CI 0.65–3.05) for death.

Figure 2. Cumulative incidence of breakthrough infection (A), COVID-19 hospitalization (B), and COVID-19 death (C) among patients with rheumatoid arthritis (RA) (broken red line) as compared with the general population (solid blue line) in the vaccinated cohort during the total follow-up period. The area shaded in red shows the 95% confidence interval (95% CI) for patients with RA, and the area shaded in blue shows the 95% CI for the general population.
(Table 4 and Figure 2). Using the exposure score for partial adjustment did not change the results materially (Table 4).

Results from subgroup analysis showed no increased risk of breakthrough infection, COVID-19 hospitalization, or COVID-19 death in patients with RA compared with the general population during the alpha-variant period (see Supplementary Table 2, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25028). During the delta-variant period, the adjusted HRs of breakthrough infection, COVID-19 hospitalization, and COVID-19 death were 1.12 (95% CI 1.01–1.23), 1.43 (95% CI 1.01–2.00), and 2.05 (95% CI 0.89–4.70) for patients with RA compared with the general population, respectively (see Supplementary Table 3, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25028).

DISCUSSION

Using data collected from THIN in the UK, we showed that the risks of SARS-CoV-2 infection and its severe outcomes (i.e., COVID-19 hospitalization or death) are higher among individuals with RA than the general population before COVID-19 vaccination. Although COVID-19 vaccination greatly reduced the risk of breakthrough infection, COVID-19 hospitalization, and death, the risk of breakthrough infection and COVID-19 hospitalization is still higher among individuals with RA than the general population over 9 months of follow-up.

Several studies have found that patients with RA are at higher risk of SARS-CoV-2 infection and severe outcomes than individuals without RA (6–12). In a study of 33,886 people with RA in the US Veterans Affairs system, the risk of COVID-19 diagnosis and the risk of hospitalization or death was higher for patients with RA than for 33,886 individuals without RA (8). Using data from the UK Biobank with nearly half a million people, RA was found to be a risk factor for COVID-19 diagnosis and associated death (12). We also found that among the nonvaccinated population, individuals with RA are indeed more susceptible to SARS-CoV-2 infection, COVID-19 hospitalization, and death than the general population. These findings provide additional evidence to support EULAR recommendations that patients with rheumatic and musculoskeletal diseases should be strongly advised to comply with all infection prevention and control measures prescribed by public health authorities before SARS-CoV-2 vaccination (17).

Although studies have shown that vaccination for SARS-CoV-2 was immunogenic in the majority of patients with autoimmune inflammatory rheumatic diseases, such immune responses among these patients were often blunted when compared to responses of individuals without these conditions (14–16). A retrospective cohort study analyzed data from the National COVID Cohort Collaborative (NSC) and found that patients with RA had a noticeably higher rate of breakthrough infection than those without immune dysfunction (33). Patients included in that study were recruited from academic medical centers only; thus, the findings may not be generalizable to the general population. In addition, that study did not examine the association between RA and the risk of severe outcomes of COVID-19 sequelae. Using data from a general population-based study, we provided the real-world evidence that both the rates of SARS-CoV-2 infection and COVID-19 hospitalization were higher in individuals with RA than in the general population over 9 months of follow-up after COVID-19 vaccination, providing crucial information for updating COVID-19 vaccine policy.

Our study has several strengths. Our findings are likely generalizable to other populations with similar characteristics because the results were derived from a sample of the general population. Moreover, major potential confounders were well balanced after exposure overlap weighting. The study also has several limitations. First, we cannot rule out the residual confounders given the nature of an observational study. Second, because the number of COVID-19 deaths among vaccinated patients with RA was relatively small, our study may not have an adequate power to detect a small increased risk of COVID-19 death. Third, owing to the lack of information of biologic disease-modifying antirheumatic drugs, we were unable to examine whether the use of these medications by patients with RA may modify their risk of breakthrough infection and COVID-19 severity (34). Fourth, while the effects of current COVID-19 vaccines against the omicron variant, the current dominant strain in the UK, were not examined in the current study, previous studies have reported that a booster dose of the currently available COVID-19 vaccines reduced the risk and severity of breakthrough infection due to the omicron variant (35–39). Thus, until variant-specific vaccines are in use, individuals should consider receiving a booster dose of the currently available COVID-19 vaccines to reduce the risk of COVID-19 infection and disease severity.

Future studies are needed to examine how variant-specific vaccines impact COVID-19 outcomes for contemporary viral variants among patients with RA. Fifth, in the current study, we adopted definitions of hospitalization for COVID-19 and death from COVID-19 occurring within 30 days after documentation of SARS-CoV-2 infection that previous studies have used (24–26). Although there is a possibility that unrelated hospital admission or death could occur within 30 days after documentation of SARS-CoV-2 infection, we believe that such misclassification, if it occurred, is probably small and nondifferential. As a result, it would bias the effect estimates toward the null. Finally, patients with RA who are receiving immunomodulatory treatments may be more likely to be admitted to the hospital than the general population due to medical complexity and immunosuppressed state. However, the risks of breakthrough infection and COVID-19 death were also higher among patients with RA than the general population, suggesting that such bias is unlikely to completely explain away the higher risk of COVID-19 infection among patients with RA than among the general population.

In conclusion, patients with RA are still at higher risk of SARS-CoV-2 infection and COVID-19 hospitalization than the
general population after receiving COVID-19 vaccines. These findings support the need for COVID-19 booster vaccinations and adherence to other preventive strategies among 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.

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