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Outcomes of COVID-19 in patients with rheumatoid arthritis: A multicenter research network study in the United States

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ARTICLE INFO

Objectives: To investigate outcomes of Coronavirus Disease-2019 (COVID-19) in patients with rheumatoid arthritis (RA) as compared to the general population. Additionally, outcomes were explored among RA patients stratified by sex, race, and medications use through sub-cohort analyses.

Methods: This comparative cohort study used a US multicenter research network (TriNetX) to extract data on all adult RA patients who were diagnosed with COVID-19, and adults without RA who were diagnosed with COVID-19 (comparative cohort) anytime from January 20, 2020 to April 11, 2021. COVID-19 outcomes were assessed within 30 days after its diagnosis. Baseline characteristics that included demographics and comorbidities were controlled in propensity score matching.

Results: A total of 9730 RA patients with COVID-19 and 656,979 non-RA with COVID-19 were identified. Before matching, the risk of all outcomes including mortality (RR: 2.11, 95%CI: 1.90 to 2.34), hospitalization (RR: 1.60, 1.55 to 1.66), intensive care unit-ICU admission (RR: 1.86, 1.71 to 2.05), mechanical ventilation (RR: 1.62, 1.44 to 1.82), severe COVID-19 (RR: 1.89, 1.74 to 2.06), acute kidney injury (RR: 2.13, 1.99 to 2.29), kidney replacement therapy/hemodialysis (RR: 1.40, 1.03 to 1.89), acute respiratory distress syndrome-ARDS (RR: 1.76, 1.53 to 2.02), ischemic stroke (RR: 2.62, 2.24 to 3.07), venous thromboembolism-VTE (RR: 2.30, 2.07 to 2.56), and sepsis (RR: 1.97, 1.81 to 2.13) was higher in RA compared to non-RA. After matching, the risks did not differ in both cohorts except for VTE (RR: 1.18, 1.01 to 1.38) and sepsis (RR: 1.27, 1.12 to 1.43), which were higher in the RA cohort. Male sex, black race, and glucocorticoid use increased the risk of adverse outcomes. The risk of hospitalization was higher in rituximab or interleukin 6 inhibitors (IL-6i) users compared to tumor necrosis factor inhibitors (TNFi) users, with no significant difference between Janus kinase inhibitors (JAKi) or abatacept users and TNFi users.

Conclusion: This large cohort study of RA-COVID-19 found that the risk of all outcomes was higher in the RA compared to the non-RA cohort before matching, with no difference in the majority of outcomes after matching, implying the risk being attributed to adjusted factors. However, the risk of VTE and sepsis was higher in RA cohort even after matching, indicating RA as an independent risk factor. Male sex, black race, and glucocorticoid use were associated with an increased risk of hospitalization compared to TNFi users.

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Keywords: Rheumatoid arthritis, COVID-19, SARS-CoV-2, Risk, Epidemiology

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has led to unexpected health threats with over 161 million confirmed cases and over 3 million deaths worldwide in a disaster of unprecedented magnitude in the last century [1]. During the pandemic, patients with rheumatic diseases share concerns about their potential heightened risk of acquiring COVID-19 infection as well as worse COVID-19 outcomes [2,3]. Several studies addressed the implications of COVID-19 for patients with rheumatic diseases, with conflicting reports substantiating varying risk of severe COVID-19 [4–6]. Faye et al. found...
no increased risk in adverse COVID-19 outcomes among 62 hospitalized patients from New York with autoimmune disease compared to age- and sex-matched controls [4]. In contrast, a population-based study from England, which included 10,926 COVID-19-related deaths using the OpenSAFELY platform, showed that a diagnosis of autoimmune diseases (rheumatoid arthritis-RA, lupus, or psoriasis) was associated with an increased risk of COVID-19-related mortality [5]. Interestingly, a Spanish study on hospitalized patients found worse COVID-19 outcomes in those with connective tissue disease but not inflammatory arthritis (456 rheumatic patients and matched non-rheumatic control) [6], suggesting varying risk in individual rheumatic diseases. Hence, a detailed exploration of outcomes in individual rheumatic diseases is urgently needed.

RA is the most common systemic autoimmune rheumatic disease, with a worldwide prevalence of 0.25% [7]. To our knowledge, there has been only one study to date that provided data specific to RA and COVID-19 [8]. Greater risk for COVID-19 hospitalization or death was reported in that study using the US Veterans Affairs COVID-19 shared database (n = 856 RA with COVID-19) [8]. While it provided initial insights, its population was composed mainly of older males, consistent with the demographic profile of the Veterans Affairs, which limits its generalizability to general RA patients [8]. Larger studies may potentially allow individual risk stratification and robust analysis of key variables influencing adverse outcomes in the general RA population.

Therefore, the aim of this study was to use a multicenter research network to investigate the risk of COVID-19 outcomes in RA compared to a matched general population without RA. It further explored the COVID-19 outcomes among RA subgroups (i.e. sex, race, and medications use). This RA-specific information would provide guidance to rheumatologists regarding the risk of adverse COVID-19 outcomes in RA patients, which in turn, may lead to better care for these patients.

Methods

Study design

This was a retrospective comparative cohort study. Its design was informed by the previous literature [9–11].

Data source

This study used the TriNetX database, a federated health research network aggregating longitudinal electronic health records of 69 million patients from 49 US health care organizations with real-time updates. The Western Institutional Review Board has granted TriNetX a waiver due to its status as a federated network. All data is de-identified with aggregated counts and statistical summaries provided for the variables of interest. Accessible data from the platform include demographics, diagnoses, medications, laboratory values, and procedures. All data, when appropriate, were queried based on either the International Classification of Diseases tenth revision (ICD-10), Current Procedural Terminology (CPT) codes, or Logical Observation Identifiers Names and Codes (LOINC).

Participants

The RA with COVID-19 cohort included all patients who were 18 years of age or older, had a pre-existing diagnosis of RA, and were diagnosed with COVID-19 anytime from January 20, 2020 to April 11, 2021. Diagnosis of RA was based on ICD-10 codes (M05.x, M06.x). Diagnosis of COVID-19 was based on ICD-10 codes (U07.1, U07.2, J12.81, B34.2, B97.21, B97.29) and/or SARS-CoV-2 polymerase chain reaction (PCR) positivity. The comparative cohort was any adult without any history of documented RA who was diagnosed with COVID-19 anytime in the same time period (January 20, 2020, to April 11, 2021).

Outcomes

COVID-19 outcomes included mortality, hospitalization, intensive care unit ICU admission, mechanical ventilation, severe COVID-19 (composite of mechanical ventilation and mortality), acute kidney injury, kidney replacement therapy KRT/hemodialysis, acute respiratory distress syndrome ARDS, ischemic stroke, venous thromboembolism VTE, and sepsis. All examined outcomes were assessed within 30 days after COVID-19 diagnosis.

Other variables

Baseline characteristics included age, sex, race, body mass index BMI, comorbidities hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, alcohol-related disorders, and medications glucocorticoids, conventional disease-modifying antirheumatic drugs DMARDs, biologic/targeted synthetic DMARDs. Medications use was within the year preceding the COVID-19 diagnosis.

Statistical analysis

For comparison of COVID-19 outcomes between RA with COVID-19 and non-RA with COVID-19 cohort, 1:1 propensity score matching was used. This comparison was performed for the whole study period (COVID-19 diagnosis anytime between January 20, 2020, and April 11, 2021) and the first 90 days period of the pandemic (Jan 20 and April 19, 2020). Baseline characteristics that included demographics and comorbidities were controlled as covariates in propensity score matching. The greedy nearest-neighbor algorithm with a caliper of 0.1 pooled standard deviations was used for matching. Risk ratios were calculated both for unmatched and matched cohorts for each outcome. In addition, each outcome was compared among subgroups (i.e. sex, race, medications use) of RA with COVID-19 cohort. All subgroups comparisons were performed for the whole study period (Jan 20, 2020, to April 11, 2021). TriNetX obfuscates the event number if it is less than 11 due to privacy reasons, and any comparisons of these results could not be performed. This standard methodology was detailed elsewhere [9,12,13]. A two-sided p value less than 0.05 was considered statistically significant. All statistical analyses were performed on the TriNetX network. Statistical data presentation was according to recent review [14].

Results

Study population

Between January 20, 2020, and April 11, 2021, a total of 9,730 RA patients with COVID-19 and 656,979 non-RA with COVID-19 were identified. Baseline characteristics are summarized in Table 1. RA with COVID-19 cohort was older (mean age 61.1 vs. 47.6 years), and had a higher proportion of females (74.8% vs. 55.0%) and comorbidities (including hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) compared to non-RA with COVID-19 cohort. After propensity score matching, all baseline characteristics were well balanced between two cohorts (standardized difference < 0.1 for all).

COVID-19 outcomes in RA compared to non-RA cohort (COVID-19 diagnosis anytime between January 20, 2020, and April 11, 2021)

Before propensity score matching, the risk of all outcomes including mortality risk ratio RR with 95% CI 2.11 1.90 to 2.34, hospitalization (RR 1.60, 1.55 to 1.66), ICU admission (RR 1.86, 1.71 to 2.05),
mechanical ventilation (RR: 1.62, 1.44 to 1.82), severe COVID-19 (RR: 1.89, 1.74 to 2.06), acute kidney injury (2.13, 1.99 to 2.29), KRT/hemodialysis (RR: 1.40, 1.03 to 1.89), ARDS (RR: 1.76, 1.53 to 2.02), ischemic stroke (RR: 2.91, 2.24 to 3.70), VTE (RR: 2.30, 2.07 to 2.56), and sepsis (RR: 1.97, 1.81 to 2.13) was higher in RA compared to non-RA with COVID-19 compared to the whole study period (January 20, 2020, and April 11, 2021) in both RA and non-RA cohorts (Tables 2 and 3).

COVID-19 outcomes in RA compared to non-RA cohort during the first 90 days of the pandemic (COVID-19 diagnosis anytime between Jan 20 and April 19, 2020)

After propensity score matching, the risk of COVID-19 outcomes did not significantly differ in both cohorts except for VTE (1.18, 1.01 to 1.38) and sepsis (1.27, 1.12 to 1.43), which were higher in RA compared to non-RA cohort (Table 2).

COVID-19 outcomes by race within RA cohort

The risk of mortality (RR: 1.69, 1.20 to 2.37), hospitalization (RR: 1.38, 1.23 to 1.54), ICU admission (RR: 1.65, 1.26 to 2.16), mechanical ventilation (RR: 1.74, 1.22 to 2.48), severe COVID-19 (RR: 1.63, 1.24 to 2.13), acute kidney injury (RR: 1.82, 1.48 to 2.25), ARDS (RR: 2.32, 1.41 to 3.81), ischemic stroke (RR: 2.30, 1.37 to 3.87), VTE (RR: 1.86, 1.33 to 2.60), and sepsis (RR: 1.72, 1.33 to 2.21) was higher in black compared to the white race; however, the risk of KRT/hemodialysis (RR: 1.84, 0.85 to 3.98) was not statistically significantly different after propensity score matching (Table 5).

COVID-19 outcomes by glucocorticoid use within RA cohort

The risk of mortality (RR: 1.80, 1.42 to 2.28), hospitalization (RR: 1.40, 1.29 to 1.52), ICU admission (RR: 1.56, 1.27 to 1.92), mechanical ventilation (RR: 1.75, 1.32 to 2.31), severe COVID-19 (RR: 1.81, 1.48 to 2.21), acute kidney injury (RR: 1.22, 1.05 to 1.42), VTE (RR: 1.88, 1.47 to 2.41), and sepsis (RR: 1.40, 1.16 to 1.68) was higher in glucocorticoid users compared to non-users; however, the risk of KRT/hemodialysis (RR: 1.39, 0.68 to 2.82), ARDS (RR: 1.35, 0.98 to 1.85), or ischemic stroke (RR: 1.00, 0.71 to 1.41) was not statistically significantly different after propensity score matching (Table 6).

COVID-19 outcomes by DMARD class within RA cohort

The risk did not significantly differ in biologic/targeted synthetic DMARDs users compared to only conventional DMARDs users for any of the outcomes after propensity score matching (Table 7).

Table 1
Baseline characteristics of cohorts before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2021).

| Characteristics          | Before Propensity Matching | After Propensity Matching |
|--------------------------|----------------------------|---------------------------|
|                          | RA with COVID-19 (n = 9,730) | non-RA with COVID-19 (n = 656,979) | Standardized Difference | RA with COVID-19 (n = 9,730) | non-RA with COVID-19 (n = 9,730) | Standardized Difference |
| Age, years               | 61.1 ± 15.3                 | 47.6 ± 18.7               | 0.7926                      | 61.1 ± 15.3                 | 61.4 ± 15.4               | 0.0163                      |
| Female sex (%)           | 7280 (74.82%)               | 361,619 (55.04%)         | 0.4237                      | 7280                        | 7197                      | 0.0195                      |
| Race (%)                 | W: 6,494                   | W: 403,266 (61.39%)      | W: 0.1118                   | W: 6,494                    | W: 6,583                  | W: 0.0195                   |
| Black (%)                | B: 1,783                   | B: 1,10,799 (18.33%)     | B: 0.0692                   | B: 1,783                     | B: 1,780                  | B: 0.0008                   |
| Asian (%)                | A: 1,49                     | A: 1,6,448 (16.56%)      | A: 1.33 (2.50%)             | A: 149                      | A: 169                    | A: 0.0162                   |
| BMI, kg/m²               | 31.5 ± 7.77                 | 30.5 ± 7.47               | 0.1318                      | 31.5 ± 7.77                  | 31.5 ± 7.65               | 0.0018                      |

Comorbidities (%)

| Hypertension             | 6308 (64.83%)               | 165,531                   | 0.8685                      | 6308                        | 6411                      | 0.0222                      |
| Chronic lower lung disease | 4190 (43.06%)             | 97,794 (14.88%)          | 0.6534                      | 4190                        | 4183                      | 0.0015                      |
| Diabetes mellitus        | 3156 (32.44%)              | 81,575 (12.42%)          | 0.4944                      | 3156                        | 3234                      | 0.0171                      |
| Ischemic heart disease   | 2725 (28.01%)              | 45,717 (7.57%)           | 0.5547                      | 2725                        | 2666                      | 0.0135                      |
| Chronic kidney disease   | 1895 (19.48%)              | 34,535 (5.26%)           | 0.4424                      | 1895                        | 1806                      | 0.0233                      |
| Heart failure            | 1786 (17.13%)              | 28,342 (4.66%)           | 0.4542                      | 1786                        | 1676                      | 0.0320                      |
| Cerebrovascular disease  | 1642 (16.88%)              | 30,595 (5.34%)           | 0.4021                      | 1642                        | 1554                      | 0.0244                      |
| Nicotine dependence      | 1611 (15.97%)              | 49050 (7.47%)            | 0.2824                      | 1611                        | 1556                      | 0.0153                      |
| Alcohol-related disorders| 470 (4.83%)                | 16,708 (2.54%)           | 0.1216                      | 470                         | 388                       | 0.0411                      |

Data are mean ± standard deviation or frequency (percentage). Age, sex, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching.
Table 2
COVID-19 outcomes in cohorts before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2020).

| Outcome                  | Before Propensity Matching | After Propensity Matching | Risk Ratio [95% CI] | Pvalue |
|--------------------------|----------------------------|---------------------------|---------------------|--------|
| RA with COVID-19         | RA with COVID-19 (n = 9,730) | RA with COVID-19 (n = 9,730) |                     |        |
| RA without COVID-19      | RA without COVID-19 (n = 656,799) | RA without COVID-19 (n = 656,799) |                     |        |
| Mortality                | 357 (3.67%)                 | 11,440 (1.74%)            | 2.11 (-0.0001)      | 0.2593 |
| Hospitalization          | 2334 (23.99%)               | 98,253 (14.96%)           | 1.60 (-0.0001)      | 0.1010 |
| ICU admission            | 466 (4.79%)                 | 16,782 (2.55%)            | 1.86 (-0.0001)      | 0.1597 |
| Mechanical ventilation   | 287 (8.11%)                 | 11,961 (3.80%)            | 1.62 (-0.0001)      | 0.3886 |
| Severe COVID-19          | 510 (5.24%)                 | 18,207 (2.77%)            | 1.89 (-0.0001)      | 0.1787 |
| Acute kidney injury      | 789 (8.11%)                 | 24,959 (3.80%)            | 2.13 (-0.0001)      | 0.1421 |
| KRT/Hemodialysis         | 42 (0.44%)                  | 2,066 (0.32%)             | 1.40 (0.0314)       | 0.2559 |
| ARDS                     | 203 (2.09%)                 | 7,808 (1.19%)             | 1.76 (-0.0001)      | 0.2797 |
| Ischemic Stroke          | 159 (1.63%)                 | 4,097 (0.62%)             | 2.62 (-0.0001)      | 0.2949 |
| VTE                      | 338 (3.47%)                 | 9,904 (1.51%)             | 2.30 (-0.0001)      | 0.0344 |
| Sepsis                   | 563 (5.79%)                 | 19,316 (2.94%)            | 1.97 (-0.0001)      | 0.0001 |

Age, sex, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. ICU Intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism.

Table 3
COVID-19 outcomes in cohorts before and after propensity matching during the first 90 days of the pandemic (COVID-19 diagnosis anytime between Jan 20 and April 19, 2020).

| Outcome                  | Before Propensity Matching | After Propensity Matching | Risk Ratio [95% CI] | Pvalue |
|--------------------------|----------------------------|---------------------------|---------------------|--------|
| RA with COVID-19         | RA with COVID-19 (n = 920) | RA with COVID-19 (n = 920) |                     |        |
| RA without COVID-19      | RA without COVID-19 (n = 6,658) | RA without COVID-19 (n = 6,658) |                     |        |
| Mortality                | 76 (8.3%)                  | 2,107 (4.7%)              | 1.75 (-0.0001)      | 0.3661 |
| Hospitalization          | 340 (37.0%)                | 10,759 (24.1%)            | 1.53 (-0.0001)      | 0.1304 |
| ICU admission            | 89 (9.7%)                  | 2,950 (5.8%)              | 1.66 (-0.0001)      | 0.3288 |
| Mechanical ventilation   | 59 (6.4%)                  | 2,545 (5.7%)              | 1.13 (0.3556)       | 0.0852 |
| Severe COVID-19          | 100 (10.9%)                | 3,758 (8.4%)              | 1.29 (0.0081)       | 0.6573 |
| Acute kidney injury      | 138 (15.0%)                | 3,747 (8.4%)              | 1.79 (-0.0001)      | 0.5514 |
| KRT/Hemodialysis         | < 11†                      | 302 (0.7%)                | NA                  | NA     |
| ARDS                     | 37 (4.0%)                  | 2045 (4.6%)               | 0.88 (0.4227)       | 0.3661 |
| Ischemic Stroke          | 21 (2.3%)                  | 428 (1.0%)                | 2.38 (-0.0001)      | 0.3878 |
| VTE                      | 40 (4.3%)                  | 1028 (2.3%)               | 1.89 (-0.0001)      | 0.3811 |
| Sepsis                   | 114 (12.4%)                | 3760 (8.4%)               | 1.47 (-0.0001)      | 0.0525 |

Age, sex, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. ICU Intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism, NA Not applicable.

TriNetX obfuscates the number if it is less than 11 due to privacy reasons.

† Composite of mechanical ventilation and mortality.
Table 4
COVID-19 outcomes in subgroup (male vs. female) in RA with COVID-19 cohort before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2021).

| Outcome                     | Before Propensity Matching | After Propensity Matching |
|-----------------------------|----------------------------|---------------------------|
|                             | Male RA with COVID-19 (n = 2,448) | Female RA with COVID-19 (n = 2,780) | Risk Ratio [95% CI] | Pvalue | Male RA with COVID-19 (n = 2,429) | Female RA with COVID-19 (n = 2,429) | Risk Ratio [95% CI] | Pvalue |
| Mortality                   | 113 (4.62%)                  | 244 (3.35%)               | 1.38            | 0.0040 | 110 (4.33%)                 | 100 (4.12%)               | 1.10            | 0.4805 |
| Hospitalization             | 736 (30.07%)                 | 1598 (21.95%)             | 1.37            | < 0.0001 | 725 (28.85%)               | 611 (25.35%)              | 1.15            | 0.0002 |
| ICU admission               | 164 (6.70%)                  | 302 (4.15%)               | 1.62            | < 0.0001 | 164 (6.75%)                | 119 (4.90%)               | 1.38            | 0.0058 |
| Mechanical ventilation     | 109 (4.45%)                  | 178 (4.45%)               | 1.82            | < 0.0001 | 107 (4.14%)                | 53 (2.18%)                | 2.02            | < 0.0001 |
| Severe COVID-19             | 173 (7.07%)                  | 317 (4.63%)               | 1.53            | < 0.0001 | 169 (6.96%)                | 127 (5.23%)               | 1.33            | 0.0118 |
| Acute kidney injury         | 269 (10.99%)                 | 520 (7.14%)               | 1.54            | < 0.0001 | 266 (10.95%)               | 197 (8.11%)               | 1.35            | 0.0007 |
| KRT/Hemodialysis            | 116 (0.68%)                  | 26 (0.37%)                | 1.86            | 0.0463 | 16 (0.68%)                 | 10 (0.42%)                | 1.62            | 0.2245 |
| ARDS                        | 63 (2.57%)                   | 140 (1.92%)               | 1.34            | 0.0515 | 62 (2.55%)                 | 43 (1.77%)                | 1.44            | 0.0069 |
| Ischemic Stroke             | 54 (2.21%)                   | 105 (1.44%)               | 1.53            | 0.0100 | 54 (2.22%)                 | 40 (1.65%)                | 1.35            | 0.1448 |
| VTE                         | 100 (4.09%)                  | 238 (3.27%)               | 1.25            | 0.0566 | 96 (4.04%)                 | 71 (2.92%)                | 1.28            | 0.0345 |
| Sepsis                      | 188 (7.68%)                  | 375 (5.15%)               | 1.49            | < 0.0001 | 185 (7.62%)               | 142 (5.85%)               | 1.30            | 0.0118 |

Age, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. ICU Intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism.

Table 5
COVID-19 outcomes in race subgroup (black vs. white) in RA with COVID-19 cohort before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2021).

| Outcome                     | Before Propensity Matching | After Propensity Matching |
|-----------------------------|----------------------------|---------------------------|
|                             | Black RA with COVID-19 (n = 1,783) | White RA with COVID-19 (n = 6,494) | Risk Ratio [95% CI] | Pvalue | Black RA with COVID-19 (n = 1,780) | White RA with COVID-19 (n = 1,780) | Risk Ratio [95% CI] | Pvalue |
| Mortality                   | 86 (4.82%)                  | 204 (3.14%)               | 1.54            | 0.0006 | 86 (4.83%)                  | 51 (2.87%)                | 1.69            | 0.0023 |
| Hospitalization             | 540 (30.29%)                | 1419 (21.85%)             | 1.39            | < 0.0001 | 538 (30.23%)               | 390 (21.91%)              | 1.38            | < 0.0001 |
| ICU admission               | 132 (7.40%)                 | 282 (4.34%)               | 1.71            | < 0.0001 | 132 (7.42%)                | 80 (4.49%)                | 1.65            | 0.0002 |
| Mechanical ventilation     | 80 (4.49%)                  | 162 (2.50%)               | 1.80            | < 0.0001 | 80 (4.49%)                 | 46 (2.58%)                | 1.74            | 0.0020 |
| Severe COVID-19             | 130 (7.29%)                 | 298 (4.59%)               | 1.59            | < 0.0001 | 130 (7.30%)                | 80 (4.49%)                | 1.63            | 0.0004 |
| Acute kidney injury         | 128 (7.79%)                 | 410 (6.31%)               | 2.03            | < 0.0001 | 228 (12.81%)               | 125 (7.02%)               | 1.82            | < 0.0001 |
| KRT/Hemodialysis            | 18 (1.07%)                  | 18 (0.28%)                | 3.79            | < 0.0001 | 18 (1.07%)                 | 10 (0.58%)                | 1.84            | 0.0114 |
| ARDS                        | 51 (2.86%)                  | 109 (1.68%)               | 1.70            | 0.0013 | 51 (2.87%)                 | 22 (1.24%)                | 2.32            | 0.0006 |
| Ischemic Stroke             | 46 (2.58%)                  | 82 (1.26%)                | 2.04            | < 0.0001 | 46 (2.58%)                | 20 (1.12%)                | 2.30            | 0.0012 |
| VTE                         | 95 (5.33%)                  | 189 (2.91%)               | 1.83            | < 0.0001 | 95 (5.34%)                 | 51 (2.87%)                | 1.86            | 0.0002 |
| Sepsis                      | 152 (8.53%)                 | 302 (4.65%)               | 1.83            | < 0.0001 | 151 (8.48%)               | 88 (4.94%)                | 1.72            | < 0.0001 |

Age, sex, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. ICU Intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism.

Composite of mechanical ventilation and mortality.

COVID-19 outcomes by biologic/targeted synthetic DMARD class within RA cohort

The risk of hospitalization was higher in rituximab (RR: 1.78, 1.24 to 2.54) or interleukin 6 inhibitors (IL-6i) (RR: 1.50, 1.00 to 2.25) users compared to tumor necrosis factor inhibitors (TNFi) users; whereas, the risk of hospitalization did not significantly differ in Janus kinase inhibitors (JAKi) (RR: 1.27, 0.95 to 1.71) or abatacept (RR: 0.84, 0.55 to 1.29) users compared to TNFi users, after propensity score matching (Tables 8–11).
In this large study of RA-COVID-19, we found that the risk of all COVID-19 outcomes was higher in RA compared to the non-RA cohort before matching. However, the risk of the majority of outcomes (i.e., mortality, hospitalization, ICU admission, mechanical ventilation, severe COVID-19, acute kidney injury, KRT/hemodialysis, ARDS, and ischemic stroke) did not significantly differ in both cohorts after matching, implying that the risk for these adverse outcomes could be mainly attributed to adjusted factors (i.e., age and comorbidities). An increased risk of VTE and sepsis in the RA cohort persisted after matching, indicating RA being an independent risk factor for these adverse outcomes compared to the female sex, white race, and non-use of glucocorticoids.

The risk of all COVID-19 outcomes was higher in RA compared to the non-RA cohort before matching; however, the risk was not significantly persisted for the majority of outcomes. This finding implies that the risk for worse COVID-19 outcomes in RA compared to the non-RA cohort could be primarily related to older age and a higher proportion of comorbidities among the RA cohort. Previous studies have shown an increased risk of adverse COVID-19 outcomes with older age or certain comorbidities including cardiovascular disease, diabetes mellitus, chronic lower lung disease, and chronic kidney disease among the general population[5,15–17] or patients with rheumatic diseases[6,18–21]. Present findings underscore the importance of addressing comorbidities in patients with RA to reduce the burden of COVID-19.

Prior to this study, there has been only one study providing data specific to RA and COVID-19 [8]. In that study using the US Veterans Affairs COVID-19 shared database, England et al. found that RA was associated with a higher risk of hospitalization or mortality (n = 856 RA with COVID-19) after adjustment for demographics, comorbidities, healthcare utilization and access, and county level COVID-19 incidence rates [8]. Conversely, the present study, which included 9730 patients with RA and COVID-19, showed that the risk of the majority of outcomes (i.e., mortality, hospitalization, ICU admission, mechanical ventilation, severe COVID-19, acute kidney injury, KRT/hemodialysis, ARDS, and ischemic stroke) was not significantly different after matching. This contrasting finding may be explained by the differences in study populations (previous study composed mainly of older males, consistent with the demographic profile of the Veterans Affairs [8]; whereas the present study composed mainly of females consistent with the general epidemiology of RA). Our study extends the previous study with a wider representation of general population, and a larger number of patients with RA and COVID-19.

It is interesting to note that the risk of VTE and sepsis was significantly higher in RA compared to the non-RA cohort even after matching, indicating RA as an independent risk factor for these two outcomes. A meta-analysis showed an increased risk of VTE in RA compared to non-RA patients [22]. Additionally, evidence from a previous study investigating the risk of serious infections, including bacterial, viral, and fungal pathogens, shows that patients with RA are at an increased risk of sepsis compared to patients with non-inflammatory rheumatic and musculoskeletal diseases [23]. Proposed mechanisms underlying the thrombotic tendency in RA are endothelial injury, hypercoagulability, and plasma hyperviscosity induced by systemic inflammation [24]. These three mechanisms have been postulated as pathogenesis of thrombosis in COVID-19 as well [25]. Furthermore, RA patients may be at higher risk of sepsis due to the dysregulated host immune response resulting in a cytokine storm. Future research aimed at elucidating the mechanisms behind the VTE and sepsis in patients with RA and COVID-19 is required. Nevertheless, the increased baseline risks for VTE and sepsis in RA may...
predispose to develop VTE and sepsis in RA patients with COVID-19. Our finding highlights paying particular attention to VTE and sepsis in these patients.

In a previous study using the TriNetX database, Jorge et al. compared the outcomes of COVID-19 between the first 90 days (Jan 20 and April 19, 2020) and the subsequent 90 days (April 20 and July 19, 2020) periods in patients with rheumatic diseases [11]. They showed that the risks of severe COVID-19 outcomes were higher in the first 90 days compared to the second 90 days of the pandemic in patients with rheumatic diseases implying an improvement over time [11]. Considering these results, we investigated the risk of adverse COVID-19 outcomes in RA compared to non-RA during the first 90 days (Jan 20 and April 19, 2020) of the pandemic when there were some uncertainties regarding the management of COVID-19, and found that the risk of COVID-19 outcomes did not significantly differ in RA compared to non-RA cohort in this early period after matching. However, the risk of COVID-19 outcomes seems to be numerically (we did not compare statistically) higher in this first period compared to the whole study period (January 20, 2020, and April 11, 2021) in both RA and non-RA cohorts.

In sub-cohort analyses of RA patients with COVID-19, male sex and black race (compared to white race) were associated with adverse outcomes. These findings are in agreement with multiple studies in general population [5,15–17,26–28] or patients with rheumatic diseases [6,18,29]. This sex bias is thought to be driven by differences in innate and adaptive immune responses, and in the interplay of sex hormones and immune effectors between males and females [26,30]. This racial bias may be related to socioeconomic status and access to medical care [27,29].

In accordance with previous studies in rheumatic diseases [18–20] and RA [8], the present study found that glucocorticoids use was associated with adverse outcomes. However, higher disease activity might be the main driving factor for worse outcomes in glucocorticoids users [31]. We found that rituximab or IL-6i users were associated with an increased risk of hospitalization compared to TNFi users, with no significant difference in the risk of hospitalization between JAKi or abatacept users and TNFi users. This finding was partly (i.e. rituximab and abatacept) consistent with the recent Global Rheumatology Alliance study by Sparks et al., which showed a higher risk for worse outcomes in rituximab or JAKi users and no difference in IL-6i or abatacept users when compared to TNFi users [32]. The contrasting finding in IL-6i or JAKi users may be explained by the residual confounding such as disease activity and concomitant glucocorticoids or conventional DMARDs use, the timing of drug usage related to the SARS-CoV-2 infection course, and the difference in disease-modifying antirheumatic drugs, ICU intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism.

Limitations

The present study has some limitations. First, the accuracy of electronic health records could not be verified. In other words, there might be some errors in recorded ICD/CPT codes or in the assignment of these codes. Second, even though many covariates were adjusted in propensity score matching, residual confounding may be present, including socioeconomic status, geographical locations, health care access, and different health care settings. This information is not provided by the database due to privacy policy. Third, several important

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**Table 7**

COVID-19 outcomes in subgroup (b/tsDMARDs vs. only conventional DMARDs use) in RA with COVID-19 cohort before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2021).

| Outcome | Before Propensity Matching | After Propensity Matching |
|---------|----------------------------|---------------------------|
| RA with COVID-19 with b/tsDMARDs (n = 1,346) | RA with COVID-19 with cDMARDs (n = 2,819) | Risk ratio (95% CI) | P-value | RA with COVID-19 with b/tsDMARDs (n = 1,337) | RA with COVID-19 with cDMARDs (n = 1,337) | Risk ratio (95% CI) | P-value |
| Mortality | 46 | 119 | 0.38 | 0.2136 | 46 | 43 | 1.07 | 0.7464 |
| Hospitalization | 3.42% | 4.22% | 0.81 | (0.58, 1.13) | 0.0651 | 289 | 289 | 1.00 | 1.0000 |
| ICU admission | 21.47% | 24.05% | 0.89 | (0.79, 1.01) | 1.19 | 1.20 | 1.19 | (0.58, 1.13) |
| Mechanical ventilation | 46 | 87 | 0.52 | (0.75, 1.31) | 0.11 | 0.09 | (0.50, 0.89) |
| Severe COVID-19 | 3.42% | 3.09% | 1.11 | (0.78, 1.57) | 0.5695 | 46 | 3.8 | (0.78, 1.85) |
| Acute kidney injury | 5.05% | 6.00% | 0.84 | (0.64, 1.11) | 0.2192 | 68 | 65 | 1.05 | 0.7896 |
| KRT/Hemodialysis | 6.91% | 7.34% | 0.20 | (0.74, 1.19) | 0.0935 | 10 | 10 | 0.90 | 0.9973 |
| ARDS | 0.75% | 0.36% | 2.08 | (0.87, 4.98) | 0.0975 | 40 | 32 | 1.25 | 0.3392 |
| Ischemic Stroke | 2.97% | 1.99% | 1.50 | (1.00, 2.23) | 0.0475 | 40 | 32 | 1.25 | 0.3392 |
| VTE | 1.19% | 1.31% | 0.91 | (0.51, 1.62) | 0.7388 | 1.23 | 1.23 | 1.23 | 0.5754 |
| Sepsis | 3.94% | 3.80% | 1.01 | (0.75, 1.43) | 0.0423 | 53 | 52 | 1.02 | 0.9207 |
| | 5.87% | 5.82% | 1.00 | (0.78, 1.31) | 0.0470 | 74 | 65 | 1.20 | 0.2638 |

Age, sex, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. DMARDs disease-modifying antirheumatic drugs, ICU Intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism.

急速に発症したCOVID-19の患者では、素早く対策を講じることが重要である。
failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching.

Intensive care unit, ICU

TriNetX obfuscates the number if it is less than 11 due to privacy reasons.

Table 8
COVID-19 outcomes in subgroup (rituximab vs. tumor necrosis factor inhibitors) in RA with COVID-19 cohort before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2021).

| Outcome                          | Before Propensity Matching | After Propensity Matching |
|----------------------------------|----------------------------|----------------------------|
| RA with COVID-19                 | RA with COVID-19            | Risk ratio (95% CI)        | P value | RA with COVID-19 | RA with COVID-19 | Risk ratio (95% CI) | P value |
| Mortality                        | 21                         | NA                         | NA       | 21               | NA                         | NA       | 11 |
| Hospitalization                  | 65                         | 2.01                       | < 0.0001 | 64               | 1.78                       | 0.0012  |
| ICU admission                    | 18                         | 2.78                       | 0.0002   | 18               | 1.24, 2.54                 |
| Mechanical ventilation           | 19                         | NA                         | NA       | 19               | NA                         | NA       | 11 |
| Severe COVID-19                  | 18                         | NA                         | NA       | 18               | NA                         | NA       | 11 |
| Sepsis                           | 20                         | 1.86                       | 0.0143   | 19               | 1.27                       | 0.4731  |
| KRT/Hemodialysis                 | 12                         | NA                         | NA       | 12               | NA                         | NA       | 11 |
| ARDS                             | 18                         | NA                         | NA       | 18               | NA                         | NA       | 11 |
| Ischemic Stroke                  | 21                         | NA                         | NA       | 21               | NA                         | NA       | 11 |
| VTE                              | 18                         | NA                         | NA       | 18               | NA                         | NA       | 11 |
| Sepsis                           | 23                         | NA                         | NA       | 23               | NA                         | NA       | 11 |

Table 9
COVID-19 outcomes in subgroup (interleukin 6 inhibitors vs. tumor necrosis factor inhibitors) in RA with COVID-19 cohort before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2021).

| Outcome                          | Before Propensity Matching | After Propensity Matching |
|----------------------------------|----------------------------|----------------------------|
| RA with COVID-19                 | RA with COVID-19            | Risk ratio (95% CI)        | P value | RA with COVID-19 | RA with COVID-19 | Risk ratio (95% CI) | P value |
| Mortality                        | 21                         | 4.03                       | < 0.0001 | 15               | NA                         | NA       |
| Hospitalization                  | 50                         | 1.88                       | < 0.0001 | 15               | NA                         | NA       |
| ICU admission                    | 17                         | 3.2                        | < 0.0001 | 17               | NA                         | NA       |
| Mechanical ventilation           | 18                         | 5.35                       | < 0.0001 | 17               | NA                         | NA       |
| Severe COVID-19                  | 23                         | 4.19                       | < 0.0001 | 22               | NA                         | NA       |
| Sepsis                           | 23                         | 2.6                        | < 0.0001 | 20               | NA                         | NA       |
| KRT/Hemodialysis                 | 19                         | NA                         | NA       | 19               | NA                         | NA       |
| ARDS                             | 12                         | 8.94                       | < 0.0001 | 12               | NA                         | NA       |
| Ischemic Stroke                  | 18                         | NA                         | NA       | 18               | NA                         | NA       |
| VTE                              | 18                         | 4.03                       | < 0.0001 | 18               | NA                         | NA       |
| Sepsis                           | 23                         | 3.82                       | < 0.0001 | 23               | NA                         | NA       |
ease-modifying antirheumatic drugs, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. Age, sex, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching.

Tumor necrosis factor inhibitors included adalimumab, etanercept, infliximab, golimumab, certolizumab, ixikizumab, and sarilumab. RA with COVID-19 cohort before and after propensity matching (COVID-19 diagnosis anytime between January 20, 2020 and April 11, 2021).

### Table 10

| Outcome | Before Propensity Matching | After Propensity Matching |
|---------|-----------------------------|---------------------------|
|         | RA with COVID-19 with JAKi (n = 358) | RA with COVID-19 with TNFi (n = 937) | Risk ratio (95% CI) | P value | RA with COVID-19 with JAKi (n = 352) | RA with COVID-19 with TNFi (n = 352) | Risk ratio (95% CI) | P value |
| Mortality | 16 (4.5%) | 21 (2.2%) | 1.99 (1.05, 3.78) | 0.0314 | 15 (< 11 | NA | NA |< 11 |
| Hospitalization | 82 (22.9%) | 150 (16.0%) | 1.43 (1.13, 1.82) | 0.0038 | 80 (22.7%) | 63 (17.9%) | 1.27 (0.95, 1.71) | 0.1113 |
| ICU admission | 17 (4.7%) | 30 (3.2%) | 1.48 (0.83, 2.66) | 0.1831 | 17 (4.8%) | 12 (3.4%) | 1.42 (0.69, 2.92) | 0.3430 |
| Mechanical ventilation | 15 (4.2%) | 19 (2.0%) | 2.07 (1.06, 4.02) | 0.0295 | 14 (< 11 | NA | NA | < 11 |
| Severe COVID-19 | 23 (6.4%) | 31 (3.3%) | 1.94 (1.15, 3.28) | 0.0121 | 21 (4.0%) | 13 (3.7%) | 1.62 (0.82, 3.17) | 0.1596 |
| Acute kidney injury | 27 (7.5%) | 50 (5.3%) | 1.41 (0.9, 2.22) | 0.1333 | 25 (7.1%) | 19 (5.4%) | 1.32 (0.74, 2.35) | 0.3502 |
| KRT/Hemodialysis | < 11 | < 11 | NA | NA | < 11 | < 11 | NA | NA |
| ARDS | 11 (3.1%) | 12 (1.3%) | 2.4 (1.07, 5.39) | 0.0290 | 11 (3.1%) | 11 (2.0%) | NA | NA |
| Ischemic Stroke | < 11 | < 11 | NA | NA | < 11 | < 11 | NA | NA |
| VTE | 17 (4.7%) | 21 (2.2%) | 1.13 (1.33, 0.97) | 0.0168 | 17 (4.8%) | 16 (4.8%) | NA | NA |
| Sepsis | 24 (6.7%) | 34 (3.6%) | 1.85 (1.11, 3.07) | 0.0167 | 23 (6.5%) | 14 (4.0%) | 1.64 (0.86, 3.14) | 0.1285 |

Age, sex, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. DMARDs disease-modifying antirheumatic drugs, ICU Intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism, NA Not applicable.

TriNetX obfuscates the number if it is less than 11 due to privacy reasons.

1. Janus kinase inhibitors included upadacitinib, tofacitinib, and baricitinib.
2. Tumor necrosis factor inhibitors included adalimumab, etanercept, infliximab, golimumab, certolizumab,
3. Composite of mechanical ventilation and mortality.

### Table 11

| Outcome | Before Propensity Matching | After Propensity Matching |
|---------|-----------------------------|---------------------------|
|         | RA with COVID-19 with Abatacept (n = 191) | RA with COVID-19 with TNFi (n = 937) | Risk ratio (95% CI) | P value | RA with COVID-19 with Abatacept (n = 189) | RA with COVID-19 with TNFi (n = 352) | Risk ratio (95% CI) | P value |
| Mortality | < 11 | 21 (2.2%) | NA | NA | < 11 | < 11 | NA | NA |
| Hospitalization | 32 (16.8%) | 150 (16.0%) | 1.05 (0.74, 1.48) | 0.7985 | 32 (16.9%) | 38 (20.1%) | 0.84 (0.55, 1.29) | 0.4269 |
| ICU admission | < 11 | 30 (2.2%) | NA | NA | < 11 | < 11 | NA | NA |
| Mechanical ventilation | < 11 | 19 (2.0%) | NA | NA | < 11 | < 11 | NA | NA |
| Severe COVID-19 | < 11 | 31 (3.3%) | NA | NA | < 11 | < 11 | NA | NA |
| Acute kidney injury | < 11 | 50 (5.3%) | NA | NA | < 11 | 14 (7.4%) | NA | NA |
| KRT/Hemodialysis | < 11 | < 11 | NA | NA | < 11 | < 11 | NA | NA |
| ARDS | < 11 | 12 (1.3%) | NA | NA | < 11 | < 11 | NA | NA |
| Ischemic Stroke | < 11 | < 11 | NA | NA | < 11 | < 11 | NA | NA |
| VTE | < 11 | 21 (2.2%) | NA | NA | < 11 | < 11 | NA | NA |
| Sepsis | < 11 | 34 (3.6%) | NA | NA | < 11 | < 11 | NA | NA |

Age, sex, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebrovascular disease, nicotine dependence, and alcohol-related disorders) were included as covariates in propensity score matching. DMARDs disease-modifying antirheumatic drugs, ICU Intensive care unit, KRT Kidney replacement therapy, ARDS Acute respiratory distress syndrome, VTE Venous thromboembolism, NA Not applicable.

TriNetX obfuscates the number if it is less than 11 due to privacy reasons.

1. Janus kinase inhibitors included upadacitinib, tofacitinib, and baricitinib.
2. Tumor necrosis factor inhibitors included adalimumab, etanercept, infliximab, golimumab, certolizumab,
3. Composite of mechanical ventilation and mortality.
data were not available; for example, disease activity measures. Fourth, the database provides no information on adherence of patients to their prescribed medications; therefore sub-cohort analyses of medications should be interpreted with caution. Lastly, although it represents a large sample size of the American population as a whole because the database includes electronic health records of multiple health care organizations across the US, the present results may not be generalized to other populations.

Conclusion
This large cohort study of RA-COVID-19 found that the risk of all COVID-19 outcomes was higher in RA compared to the non-RA cohort before matching. However, the risk of the majority of COVID-19 outcomes was higher in RA compared to the non-RA cohort even after matching, implying that the risk for these adverse outcomes could be mainly attributed to adjusted factors (i.e., age and comorbidities). The risk of VTE and sepsis was higher in the RA cohort even after matching, indicating RA as an independent risk factor for these two outcomes. Among RA patients with COVID-19, sub-cohort analyses showed that male sex, black race, and glucocorticoid use were associated with adverse outcomes. Rituximab or IL-6i users were associated with an increased risk of hospitalization compared to TNFi users.

Author contributions
Conceptualization: RR, CD, HP, and SK. Formal analysis: RR, CD, and HP. Funding acquisition: None. Writing – original draft: SK. Writing – review & editing: RR, CD, HP, SA, CK, LG, SK.

Declaration of Competing Interest
SA has received honorarium as speaker for Pfizer (unrelated to the current study), and has no other potential conflicts of interest. SK has received congress travel, accommodation, and participation fee support (12th Anatolian Rheumatology Days) from Abbvie. All other authors declare no competing interests.

Credit authorship contribution statement
Sakir Ahmed: Writing – original draft.

Role of the funding source
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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