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

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ABSTRACT

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 adverse outcomes in RA with COVID-19. Rituximab or IL-6i users were associated with an increased risk of hospitalization compared to TNFi users.

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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 (January 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),

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 (74.82%)	7197 (73.967%)	0.0195
Race (%)						
White	W: 6,494 (66.74%)	W: 403,286 (61.39%)	W: 0.1118	W: 6494 (66.74%)	W: 6583 (67.66%)	W: 0.0195
Black	B: 1783 (18.33%)	B: 110,799 (16.87%)	B: 0.0383	B: 1783 (18.33%)	B: 1780 (18.29%)	B: 0.0008
Asian	A: 149 (1.53%)	A: 16,448 (2.50%)	A: 0.0692	A: 149 (1.53%)	A: 169 (1.74%)	A: 0.0162
BMI, kg/m^2	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 (25.20%)	0.8685	6308 (64.83%)	6411 (65.89%)	0.0222
Chronic lower lung disease	4190 (43.06%)	97,794 (14.88%)	0.6534	4190 (43.06%)	4183 (42.99%)	0.0015
Diabetes mellitus	3156 (32.44%)	81,575 (12.42%)	0.4944	3156 (32.44%)	3234 (33.24%)	0.0171
Ischemic heart disease	2725 (28.01%)	49,717 (7.57%)	0.5547	2725 (28.01%)	2666 (27.40%)	0.0135
Chronic kidney disease	1895 (19.48%)	34,535 (5.26%)	0.4424	1895 (19.48%)	1806 (18.56%)	0.0233
Heart failure	1786 (18.36%)	28,342 (4.31%)	0.4542	1786 (18.36%)	1667 (17.13%)	0.0320
Cerebrovascular disease	1642 (16.88%)	30,595 (4.66%)	0.4021	1642 (16.88%)	1554 (15.97%)	0.0244
Nicotine dependence	1611 (16.56%)	49050 (7.47%)	0.2824	1611 (16.56%)	1556 (15.99%)	0.0153
Alcohol-related disorders	470 (4.83%)	16,708 (2.54%)	0.1216	470 (4.83%)	388 (3.99%)	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.

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: 2.62, 2.24 to 3.07), VTE (RR: 2.30, 2.07 to 2.56), and sepsis (RR: 1.97, 1.81 to 2.13) was higher in RA with COVID-19 compared to non-RA with COVID-19 cohort. 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 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 RA compared to non-RA cohort (Table 3). However, the risk of COVID-19 outcomes was numerically 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 (Tables 2 and 3).

COVID-19 outcomes by sex within RA cohort

Male sex was associated with a higher risk of hospitalization (RR: 1.19, 1.08 to 1.30), ICU admission (RR: 1.38, 1.10 to 1.73), mechanical ventilation (RR: 2.02, 1.46 to 2.79), severe COVID-19 (RR: 1.33, 1.07 to 1.66), acute kidney injury (1.35, 1.13 to 1.61), VTE (RR: 1.38, 1.02 to 1.86), and sepsis (RR: 1.30, 1.06 to 1.61); whereas, the risk of mortality (RR: 1.10, 0.84 to 1.43), KRT/hemodialysis (RR: 1.62, 0.74 to 3.57), ARDS (RR: 1.44, 0.98 to 2.12), or ischemic stroke (RR: 1.35, 0.90 to 2.02) did not significantly differ between sexes after propensity score matching (Table 4).

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 2
COVID-19 outcomes in cohorts 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 (n = 9,730)	non-RA with COVID-19 (n = 656,979)	Risk Ratio [95% CI]	P value	RA with COVID-19 (n = 9,730)	non-RA with COVID-19 (n = 9,730)	Risk Ratio [95% CI]	P value
Mortality	357 (3.67%)	11,440 (1.74%)	**2.11 (1.90, 2.34)**	< 0.0001	357 (3.67%)	328 (3.37%)	1.09 (0.94, 1.26)	0.2593
Hospitalization	2334 (23.99%)	98,253 (14.96%)	**1.60 (1.55, 1.66)**	< 0.0001	2334 (23.99%)	2237 (22.99%)	1.04 (0.99, 1.10)	0.1010
ICU admission	466 (4.79%)	16,782 (2.55%)	**1.86 (1.71, 2.05)**	< 0.0001	466 (4.79%)	425 (4.37%)	1.10 (0.96, 1.25)	0.1597
Mechanical ventilation	287 (2.95%)	11,961 (1.82%)	**1.62 (1.44, 1.82)**	< 0.0001	287 (2.95%)	267 (2.74%)	1.08 (0.91, 1.27)	0.3886
Severe COVID-19†	510 (5.24%)	18,207 (2.77%)	**1.89 (1.74, 2.06)**	< 0.0001	510 (5.24%)	469 (4.82%)	1.09 (0.96, 1.23)	0.1787
Acute kidney injury	789 (8.11%)	24,959 (3.80%)	**2.13 (1.99, 2.29)**	< 0.0001	789 (8.11%)	734 (7.54%)	1.08 (0.98, 1.18)	0.1421
KRT/Hemodialysis	42 (0.44%)	2,066 (0.32%)	**1.40 (1.03, 1.89)**	0.0314	42 (0.44%)	53 (0.56%)	0.79 (0.53, 1.19)	0.2559
ARDS	203 (2.09%)	7,808 (1.19%)	**1.76 (1.53, 2.02)**	< 0.0001	203 (2.09%)	182 (1.87%)	1.12 (0.92, 1.36)	0.2797
Ischemic Stroke	159 (1.63%)	4,097 (0.62%)	**2.62 (2.24, 3.07)**	< 0.0001	159 (1.63%)	141 (1.449%)	1.13 (0.9, 1.41)	0.2949
VTE	338 (3.47%)	9,904 (1.51%)	**2.30 (2.07, 2.56)**	< 0.0001	338 (3.47%)	286 (2.94%)	**1.18 (1.01, 1.38)**	0.0344
Sepsis	563 (5.79%)	19,316 (2.94%)	**1.97 (1.81, 2.13)**	< 0.0001	563 (5.79%)	445 (4.57%)	**1.27 (1.12, 1.43)**	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.
† Composite of mechanical ventilation and mortality.

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			
	RA with COVID-19 (n = 920)	non-RA with COVID-19 (n = 44,658)	Risk Ratio [95% CI]	P value	RA with COVID-19 (n = 920)	non-RA with COVID-19 (n = 920)	Risk Ratio [95% CI]	P value
Mortality	76 (8.3%)	2,107 (4.7%)	**1.75 (1.41, 2.18)**	< 0.0001	76 (8.30%)	64 (7.0%)	1.19 (0.86, 1.63)	0.2914
Hospitalization	340 (37.0%)	10,759 (24.1%)	**1.53 (1.41, 1.67)**	< 0.0001	340 (37.0%)	309 (33.6%)	1.10 (0.97, 1.25)	0.1304
ICU admission	89 9.7%	2605 5.8%	**1.66 (1.36, 2.03)**	< 0.0001	89 (9.7%)	77 (8.4%)	1.16 (0.86, 1.55)	0.3288
Mechanical ventilation	59 (6.4%)	2545 (5.7%)	1.13 (0.88, 1.44)	0.3556	59 (6.4%)	61 (6.6%)	0.97 (0.68, 1.37)	0.8502
Severe COVID-19†	100 (10.9%)	3,758 (8.4%)	**1.29 (1.07, 1.56)**	0.0081	100 (10.9%)	106 (11.5%)	0.94 (0.73, 1.22)	0.6573
Acute kidney injury	138 (15.0%)	3747 (8.4%)	**1.79 (1.53, 2.09)**	< 0.0001	138 (15.0%)	129 (14.0%)	1.07 (0.86, 1.34)	0.5514
KRT/Hemodialysis	< 11¶	302 (0.7%)	NA	NA	< 11¶	< 11¶	NA	NA
ARDS	37 (4.0%)	2045 (4.6%)	0.88 (0.64, 1.21)	0.4227	37 (4.0%)	45 (4.9%)	0.82 (0.54, 1.26)	0.3661
Ischemic Stroke	21 (2.3%)	428 (1%)	**2.38 (1.54, 3.67)**	< 0.0001	21 (2.3%)	12 (1.3%)	1.75 (0.87, 3.54)	0.1139
VTE	40 (4.3%)	1028 (2.3%)	**1.89 (1.39, 2.57)**	< 0.0001	40 (4.3%)	28 (3.0%)	1.43 (0.89, 2.30)	0.1381
Sepsis	114 (12.4%)	3760 (8.4%)	**1.47 (1.24, 1.75)**	< 0.0001	114 (12.4%)	88 (9.6%)	1.3 (1.00, 1.68)	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 = 7,280)	Risk Ratio [95% CI]	P value	Male RA with COVID-19 (n = 2,429)	Female RA with COVID-19 (n = 2,429)	Risk Ratio [95% CI]	P value
Mortality	113 (4.62%)	244 (3.35%)	**1.38 (1.11, 1.71)**	0.0040	110 (4.53%)	100 (4.12%)	1.10 (0.84, 1.43)	0.4805
Hospitalization	736 (30.07%)	1598 (21.95%)	**1.37 (1.27, 1.48)**	< 0.0001	725 (29.85%)	611 (25.15%)	**1.19 (1.08, 1.30)**	0.0002
ICU admission	164 (6.70%)	302 (4.15%)	**1.62 (1.34, 1.94)**	< 0.0001	164 (6.75%)	119 (4.90%)	**1.38 (1.10, 1.73)**	0.0058
Mechanical ventilation	109 (4.45%)	178 (2.45%)	**1.82 (1.44, 2.30)**	< 0.0001	107 (4.41%)	53 (2.18%)	**2.02 (1.46, 2.79)**	< 0.0001
Severe COVID-19†	173 (7.07%)	337 (4.63%)	**1.53 (1.28, 1.82)**	< 0.0001	169 (6.96%)	127 (5.23%)	**1.33 (1.07, 1.66)**	0.0118
Acute kidney injury	269 (10.99%)	520 (7.14%)	**1.54 (1.34, 1.77)**	< 0.0001	266 (10.95%)	197 (8.11%)	**1.35 (1.13, 1.61)**	0.0007
KRT/ Hemodialysis	16 (0.68%)	26 (0.37%)	**1.86 (1.00, 3.47)**	0.0463	16 (0.68%)	10 (0.42%)	1.62 (0.74, 3.57)	0.2245
ARDS	63 (2.57%)	140 (1.92%)	1.34 (0.10, 1.80)	0.0515	62 (2.55%)	43 (1.77%)	1.44 (0.98, 2.12)	0.0609
Ischemic Stroke	54 (2.21%)	105 (1.44%)	**1.53 (1.11, 2.12)**	0.0100	54 (2.22%)	40 (1.65%)	1.35 (0.90, 2.02)	0.1448
VTE	100 (4.09%)	238 (3.27%)	1.25 (0.99, 1.57)	0.0566	98 (4.04%)	71 (2.92%)	**1.38 (1.02, 1.86)**	0.0345
Sepsis	188 (7.68%)	375 (5.15%)	**1.49 (1.26, 1.77)**	< 0.0001	185 (7.62%)	142 (5.85%)	**1.30 (1.06, 1.61)**	0.0138

Age, race, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebro-vascular 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.

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]	P value	Black RA with COVID-19 (n = 1,780)	White RA with COVID-19 (n = 1,780)	Risk Ratio [95% CI]	P value
Mortality	86 (4.82%)	204 (3.14%)	**1.54 (1.20, 1.97)**	0.0006	86 (4.83%)	51 (2.87%)	**1.69 (1.20, 2.37)**	0.0023
Hospitalization	540 (30.29%)	1419 (21.85%)	**1.39 (1.27, 1.51)**	< 0.0001	538 (30.23%)	390 (21.91%)	**1.38 (1.23, 1.54)**	< 0.0001
ICU admission	132 (7.40%)	282 (4.34%)	**1.71 (1.40, 2.08)**	< 0.0001	132 (7.42%)	80 (4.49%)	**1.65 (1.26, 2.16)**	0.0002
Mechanical ventilation	80 (4.49%)	162 (2.50%)	**1.80 (1.38, 2.34)**	< 0.0001	80 (4.49%)	46 (2.58%)	**1.74 (1.22, 2.48)**	0.0020
Severe COVID-19†	130 (7.29%)	298 (4.59%)	**1.59 (1.30, 1.94)**	< 0.0001	130 (7.30%)	80 (4.49%)	**1.63 (1.24, 2.13)**	0.0004
Acute kidney injury	228 (12.79%)	410 (6.31%)	**2.03 (1.74, 2.36)**	< 0.0001	228 (12.81%)	125 (7.02%)	**1.82 (1.48, 2.25)**	< 0.0001
KRT/Hemodialysis	18 (1.07%)	18 (0.28%)	**3.79 (1.98, 7.26)**	< 0.0001	18 (1.07%)	10 (0.58%)	1.84 (0.85, 3.98)	0.1140
ARDS	51 (2.86%)	109 (1.68%)	**1.70 (1.23, 2.37)**	0.0013	51 (2.87%)	22 (1.24%)	**2.32 (1.41, 3.81)**	0.0006
Ischemic Stroke	46 (2.58%)	82 (1.26%)	**2.04 (1.43, 2.92)**	< 0.0001	46 (2.58%)	20 (1.12%)	**2.30 (1.37, 3.87)**	0.0012
VTE	95 (5.33%)	189 (2.91%)	**1.83 (1.44, 2.33)**	< 0.0001	95 (5.34%)	51 (2.87%)	**1.86 (1.33, 2.60)**	0.0002
Sepsis	152 (8.53%)	302 (4.65%)	**1.83 (1.52, 2.21)**	< 0.0001	151 (8.48%)	88 (4.94%)	**1.72 (1.33, 2.21)**	<0.0001

Age, sex, body mass index, and comorbidities (hypertension, chronic lower lung disease, diabetes mellitus, ischemic heart disease, chronic kidney disease, heart failure, cerebro-vascular 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).

Table 6
COVID-19 outcomes in subgroup (glucocorticoids use vs. no 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 glucocorticoids use (n = 4016)	RA with COVID-19 without glucocorticoids use (n = 5714)	Risk Ratio	P value	RA with COVID-19 with glucocorticoids use (n = 3808)	RA with COVID-19 without glucocorticoids use (n = 3808)	Risk Ratio	P value
Mortality	199 (4.96%)	162 (2.84%)	**1.75 (1.43, 2.14)**	< 0.0001	185 (4.86%)	103 (2.71%)	**1.80 (1.42, 2.28)**	< 0.0001
Hospitalization	116 (28.91%)	1120 (19.60%)	**1.48 (1.37, 1.58)**	< 0.0001	1080 (28.36%)	773 (20.30%)	**1.40 (1.29, 1.52)**	< 0.0001
ICU admission	249 (6.20%)	205 (3.59%)	**1.73 (1.44, 2.07)**	< 0.0001	218 (5.73%)	140 (3.68%)	**1.56 (1.27, 1.92)**	< 0.0001
Mechanical ventilation	149 (3.71%)	124 (2.17%)	**1.71 (1.35, 2.16)**	< 0.0001	131 (3.44%)	75 (1.97%)	**1.75 (1.32, 2.31)**	< 0.0001
Severe COVID-19†	275 (6.85%)	226 (3.96%)	**1.73 (1.46, 2.06)**	< 0.0001	251 (6.59%)	139 (3.65%)	**1.81 (1.48, 2.21)**	< 0.0001
Acute kidney injury	378 (9.41%)	388 (6.79%)	**1.39 (1.21, 1.59)**	< 0.0001	336 (8.82%)	276 (7.25%)	**1.22 (1.05, 1.42)**	0.0114
KRT/Hemodialysis	21 (0.54%)	20 (0.36%)	1.51 (0.82, 2.78)	0.1841	18 (0.49%)	13 (0.35%)	1.39 (0.68, 2.82)	0.3670
ARDS	98 (2.44%)	95 (1.66%)	**1.468 (1.11, 1.94)**	0.0068	89 (2.34%)	66 (1.73%)	1.35 (0.98, 1.85)	0.0620
Ischemic Stroke	71 (1.77%)	88 (1.54%)	1.148 (0.84,1.57)	0.3828	63 (1.65%)	63 (1.65%)	1.00 (0.71, 1.41)	1.0000
VTE	194 (4.83%)	138 (2.42%)	**2.00 (1.61, 2.48)**	< 0.0001	175 (4.60%)	93 (2.44%)	**1.88 (1.47, 2.41)**	< 0.0001
Sepsis	287 (7.15%)	261 (4.57%)	**1.57 (1.33, 1.84)**	< 0.0001	258 (6.78%)	185 (4.86%)	**1.40 (1.16, 1.68)**	0.0004

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.
† Composite of mechanical ventilation and mortality.

Discussion

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 VTE and sepsis during COVID-19 infection. Among RA patients with COVID-19, sub-cohort analyses showed that male sex, black race, and glucocorticoid use had an increased risk of adverse outcomes compared to the female sex, white race, and non-use, respectively. 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.

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

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	0.81	0.2136	46	43	1.07	0.7464
	3.42%	4.22%	(0.58, 1.13)		(3.44%)	3.216%	(0.71, 1.61)	
Hospitalization	289	678	0.89	0.0651	289	289	1.00	1.0000
	21.47%	24.05%	(0.79, 1.01)		(21.62%)	21.616%	(0.87, 1.16)	
ICU admission	68	144	0.99	0.9385	68	62	1.10	0.5895
	5.05%	5.11%	(0.75, 1.31)		(5.09%)	4.637%	(0.78, 1.53)	
Mechanical ventilation	46	87	1.11	0.5695	46	38	1.21	0.3751
	3.42%	3.09%	(0.78, 1.57)		(3.44%)	2.842%	(0.79, 1.85)	
Severe COVID-19§	68	169	0.84	0.2192	68	65	1.05	0.7896
	5.05%	6.00%	(0.64, 1.11)		(5.09%)	4.862%	(0.75, 1.46)	
Acute kidney injury	93	207	0.94	0.6127	93	80	1.16	0.3068
	6.91%	7.34%	(0.74, 1.19)		(6.96%)	5.984%	(0.87, 1.55)	
KRT/Hemodialysis	10	10	2.08	0.0935	10	10	1.00	0.9973
	0.75%	0.36%	(0.87, 4.98)		(0.76%)	0.755%	(0.42, 2.40)	
ARDS	40	56	**1.50**	0.0475	40	32	1.25	0.3392
	2.97%	1.99%	**(1.00, 2.23)**		(2.99%)	2.393%	(0.79, 1.98)	
Ischemic Stroke	16	37	0.91	0.7388	16	13	1.23	0.5754
	1.19%	1.31%	(0.51, 1.62)		(1.20%)	0.972%	(0.59, 2.55)	
VTE	53	107	1.04	0.8236	53	52	1.02	0.9207
	3.94%	3.80%	(0.75, 1.43)		(3.96%)	(3.89%)	(0.70, 1.48)	
Sepsis	79	164	1.01	0.9470	78	65	1.20	0.2638
	5.87%	5.82%	(0.78, 1.31)		5.834%	4.862%	(0.87, 1.65)	

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.

† Either biologic/targeted synthetic DMARDs monotherapy, or combination with cDMARDs. b/ts DMARDs included adalimumab, etanercept, infliximab, golimumab, certolizumab, tocilizumab, sarilumab, rituximab, upadacitinib, tofacitinib, baricitinib, abatacept.

‡ Only conventional DMARDs use (without combination with b/ts DMARDs). cDMARDs included methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine.

§ Composite of mechanical ventilation and mortality.

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 relative to the SARS-CoV-2 infection course, and the difference in individual drugs in these classes (e.g. a varying targeting/affinity for different Janus kinases among individual JAKi) [32]. As we are moving towards rapid and effective vaccination against COVID-19, RA patients on glucocorticoids or rituximab and with comorbidities may be prioritized for vaccine administration.

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

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 with Rituximab (n = 202)	RA with COVID-19 with TNFi† (n = 937)	Risk ratio (95% CI)	P value	RA with COVID-19 with Rituximab (n = 198)	RA with COVID-19 with TNFi† (n = 198)	Risk ratio (95% CI)	P value
Mortality	< 11¶	21 (2.2%)	NA	NA	< 11¶	< 11¶	NA	NA
Hospitalization	65 (32.2%)	150 (16.0%)	**2.01 (1.57, 2.58)**	< 0.0001	64 (32.3%)	36 (18.2%)	**1.78 (1.24, 2.54)**	0.0012
ICU admission	18 (8.9%)	30 (3.2%)	**2.78 (1.58, 4.89)**	0.0002	18 (9.1%)	< 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	20 (9.9%)	50 (5.3%)	**1.86 (1.13, 3.05)**	0.0143	19 (9.6%)	15 (7.6%)	1.27 (0.66, 2.42)	0.4731
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	17 (8.4%)	21 (2.2%)	**3.76 (2.02, 6.99)**	< 0.0001	17 (8.6%)	< 11¶	NA	NA
Sepsis	18 (8.9%)	34 (3.6%)	**2.46 (1.42, 4.26)**	0.0011	17 (8.6%)	11 ¶ (5.6%)	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.
† Tumor necrosis factor inhibitors inhibitors included adalimumab, etanercept, infliximab, golimumab, certolizumab,.
§ Composite of mechanical ventilation and mortality.

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 with IL-6i† (n = 166)	RA with COVID-19 with TNFi‡ (n = 937)	Risk ratio (95% CI)	P value	RA with COVID-19 with IL-6i† (n = 160)	RA with COVID-19 with TNFi‡ (n = 160)	Risk ratio (95% CI)	P value
Mortality	15 (9.0%)	21 (2.2%)	**4.03 (2.12, 7.66)**	< 0.0001	15 (9.4%)	< 11¶	NA	NA
Hospitalization	50 (30.1%)	150 (16.0%)	**1.88 (1.43, 2.48)**	< 0.0001	45 (28.1%)	30 (18.8%)	**1.50 (1.00, 2.25)**	0.0477
ICU admission	17 (10.2%)	30 (3.2%)	**3.2 (1.81, 5.67)**	< 0.0001	15 (9.4%)	< 11¶	NA	NA
Mechanical ventilation	18 (10.8%)	19 (2.0%)	**5.35 (2.87, 9.97)**	< 0.0001	< 11¶	< 11¶	NA	NA
Severe COVID-19§	23 (13.9%)	31 (3.3%)	**4.19 (2.51, 7.00)**	< 0.0001	22 (13.8%)	< 11¶	NA	NA
Acute kidney injury	23 (13.9%)	50 (5.3%)	**2.6 (1.63, 4.14)**	< 0.0001	20 (12.5%)	< 11¶	NA	NA
KRT/Hemodialysis	< 11¶	< 11¶	NA	NA	< 11¶	< 11¶	NA	NA
ARDS	19 (11.4%)	12 (1.3%)	**8.94 (4.42, 18.06)**	< 0.0001	17 (10.6%)	< 11¶	NA	NA
Ischemic Stroke	< 11¶	< 11¶	NA	NA	< 11¶	< 11¶	NA	NA
VTE	15 (9.0%)	21 (2.2%)	**4.03 (2.12, 7.66)**	< 0.0001	14 (8.8%)	< 11¶	NA	NA
Sepsis	23 (13.9%)	34 (3.6%)	**3.82 (2.31, 6.31)**	< 0.0001	18 (11.3%)	< 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.
† Interleukin 6 inhibitors included tocilizumab, and sarilumab.
‡ Tumor necrosis factor inhibitors included adalimumab, etanercept, infliximab, golimumab, certolizumab,.
§ Composite of mechanical ventilation and mortality.

Table 10

COVID-19 outcomes in subgroup (Janus kinase 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 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 (4.3%)	< 11¶	NA	NA
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 (4.0%)	< 11¶	NA	NA
Severe COVID-19§	23 (6.4%)	31 (3.3%)	1.94 (1.15, 3.28)	0.0121	21 (6.0%)	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¶	NA	NA
Ischemic Stroke	< 11¶	< 11¶	NA	NA	< 11¶	< 11¶	NA	NA
VTE	17 (4.7%)	21 (2.2%)	**2.12 (1.13, 3.97)**	0.0168	17 (4.8%)	< 11¶	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.
† Janus kinase inhibitors included upadacitinib, tofacitinib, and baricitinib.
‡ Tumor necrosis factor inhibitors included adalimumab, etanercept, infliximab, golimumab, certolizumab,.
§ Composite of mechanical ventilation and mortality.

Table 11

COVID-19 outcomes in subgroup (abatacept 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 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* = 189)	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 (3.2%)	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.
TriNetX obfuscates the number if it is less than 11 due to privacy reasons.
† Tumor necrosis factor inhibitors included adalimumab, etanercept, infliximab, golimumab, certolizumab,.
§ 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 outcomes 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). 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.

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References

[1] https://covid19.who.int/. Accessed on May 10, 2021.
[2] Kardeş S, Kuzu AS, Raiker R, et al. Public interest in rheumatic diseases and rheumatologist in the United States during the COVID-19 pandemic: evidence from Google trends. Rheumatol Int 2021;41:329–34.
[3] Kardeş S, Kuzu AS, Pakhchanian H, et al. Population-level interest in anti-rheumatic drugs in the COVID-19 era: insights from Google trends. Clin Rheumatol 2021;40:2047–55.
[4] Faye AS, Lee KE, Laszkowska M, et al. Risk of adverse outcomes in hospitalized patients with autoimmune disease and COVID-19: a matched cohort study from New York city. J Rheumatol 2020. doi: 10.3899/jrheum.200989.
[5] Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.
[6] Pablos JL, Galindo M, Carmona L, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis 2020;79:1544–9.
[7] Safiri S, Kolahi AA, Hoy D, et al. Global, regional and national burden of rheumatoid arthritis 1990−2017: a systematic analysis of the global burden of disease study 2017. Ann Rheum Dis 2019;78:1463–71.
[8] England BR, Roul P, Yang Y, et al. Risk of COVID-19 in rheumatoid arthritis: a national veterans affairs matched cohort study in at-risk individuals. Arthritis Rheumatol 2021. doi: 10.1002/art.41800.
[9] Singh S, Bilal M, Pakhchanian H, et al. Impact of obesity on outcomes of patients with coronavirus disease 2019 in the United States: a multicenter electronic health records network study. Gastroenterology 2020;159:2221–5 e6.
[10] D'Silva KM, Jorge A, Cohen A, et al. COVID-19 outcomes in patients with systemic autoimmune rheumatic diseases compared to the general population: a US multicenter, comparative cohort study. Arthritis Rheumatol 2020. doi: 10.1002/art.41619.
[11] Jorge A, D'Silva KM, Cohen A, et al. Temporal trends in severe COVID-19 outcomes in patients with rheumatic disease: a cohort study. Lancet Rheumatol 2021;3:e131–7.
[12] Raiker R, Pakhchanian H, Hussain A, Deng M. Outcomes of COVID-19 in patients with skin cancer. Br J Dermatol 2021. doi: 10.1111/bjd.20386.
[13] Pakhchanian H, Raiker R, Mukherjee A, et al. Outcomes of COVID-19 in CKD patients: a multicenter electronic medical record cohort study. Clin J Am Soc Nephrol 2021. doi: 10.2215/CJN.13820820.
[14] Misra DP, Zimba O, Gasparyan AY. Statistical data presentation: a primer for rheumatology researchers. Rheumatol Int 2021;41:43–55.
[15] Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:759–65.
[16] Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York city: prospective cohort study. BMJ 2020;369:m1966.
[17] Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: a federated electronic medical record analysis. PLoS Med 2020;17:e1003321.
[18] Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66.
[19] Esatoglu SN, Tascilar K, Babaoğlu H, et al. COVID-19 among patients with inflammatory rheumatic diseases. Front Immunol 2021;12:651715.
[20] Haberman RH, Castillo R, Chen A, et al. COVID-19 in patients with inflammatory arthritis: a prospective study on the effects of comorbidities and disease-modifying antirheumatic drugs on clinical outcomes. Arthritis Rheumatol 2020;72:1981–9.
[21] Ahmed S, Gasparyan AY, Zimba O. Comorbidities in rheumatic diseases need special consideration during the COVID-19 pandemic. Rheumatol Int 2021;41:243–56.
[22] Ungprasert P, Srivali N, Spanuchart I, Thongprayoon C, Knight EL. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol 2014;33:297–304.
[23] Mehta B, Pedro S, Ozen G, et al. Serious infection risk in rheumatoid arthritis compared with non-inflammatory rheumatic and musculoskeletal diseases: a US national cohort study. RMD Open 2019;5:e000935.
[24] Ketfi C, Boutigny A, Mohamedi N, et al. Risk of venous thromboembolism in rheumatoid arthritis. Jt Bone Spine 2021;88:105122.
[25] Ahmed S, Zimba O, Gasparyan AY. Thrombosis in coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. Clin Rheumatol 2020;39:2529–43.
[26] Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun 2020;11:6317.
[27] Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. N Engl J Med 2020;382:2534–43.
[28] Escobar GJ, Adams AS, Liu VX, et al. Racial disparities in COVID-19 testing and outcomes: retrospective cohort study in an integrated health system. Ann Intern Med 2021. doi: 10.7326/M20-6979.
[29] Gianfrancesco MA, Leykina LA, Izadi Z, et al. Association of race and ethnicity with COVID-19 outcomes in rheumatic disease: data from the COVID-19 global rheumatology alliance physician registry. Arthritis Rheumatol 2021;73:374–80.
[30] Raza HA, Sen P, Bhatti OA, Gupta L. Sex hormones, autoimmunity and gender disparity in COVID-19. Rheumatol Int 2021. doi: 10.1007/s00296-021-04873-9.
[31] Schäfer M, Strangfeld A, Hyrich KL, et al. Response to: 'correspondence on 'factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 global rheumatology alliance physician reported registry'' by Mulhearn et al. Ann Rheum Dis 2021. doi: 10.1136/annrheumdis-2021-220134.
[32] Sparks JA, Wallace ZS, Seet AM, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: results from the COVID-19 global rheumatology alliance physician registry. Ann Rheum Dis 2021. doi: 10.1136/annrheumdis-2021-220418.