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ORIGINAL RESEARCH

COVID-19 outcomes in patients with rheumatoid arthritis with biologic or targeted synthetic DMARDs

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ABSTRACT

Objectives We aimed to investigate the role of rheumatoid arthritis (RA) with biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARD) exposure in COVID-19 outcomes.

Methods Our study retrieved data from the US Collaborative Network in TriNetX between 1 January 2018 and 31 December 2022. We investigated b/tsDMARD use for RA: interleukin 6 inhibitor (IL-6i), Janus-associated kinase inhibitors (JAKi) or tumour necrosis factor-alpha inhibitors (TNFi, reference group). The outcomes of COVID-19 were the incidence of infection and adverse outcomes (hospitalisation, critical care services, mechanical ventilation and mortality). The HR and 95% CI of the outcomes were calculated between propensity score-matched (PSM) patients with different b/tsDMARDs.

Results After PSM, 2676 JAKi vs 2676 TNFi users and 967 IL-6i vs 967 TNFi users were identified. As for COVID-19 incidence, JAKi users did not reach statistical significance (HR: 1.058, 95% CI: 0.895 to 1.250) than TNFi users. RA with JAKi users had a significant risk for hospitalisation (HR: 1.194, 95% CI: 1.003 to 1.423), mortality (HR: 1.440, 95% CI: 1.049 to 1.976) and composite adverse outcomes (HR: 1.242, 95% CI: 1.051 to 1.468) compared with TNFi users. Mortality risk tended to be significantly higher in the JAKi group without COVID-19 vaccination (HR: 1.511, 95% CI: 1.077 to 2.121). IL-6i users compared with TNFi users did not have the above findings.

Conclusions RA with JAKi users had a significant risk for hospitalisation, mortality or composite adverse outcomes, especially higher mortality among those without COVID-19 vaccination. COVID-19 vaccination should be encouraged in these target cohorts. When using JAKi for patients with RA, clinicians should be vigilant about these adverse outcomes to prevent their occurrence or detect them early for early intervention.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A previous international registry study of the COVID-19 Global Rheumatology Alliance (C19-GRA) analysed people with rheumatoid arthritis (RA) using biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) at the time of COVID-19 onset and investigated COVID-19 outcomes from 24 March 2020 to 12 April 2021. Compared with the use of tumour necrosis factor inhibitors (TNFi), people with RA using rituximab or Janus-associated kinase inhibitors (JAKi) were more likely to experience poor COVID-19 outcomes (hospitalisation, death, mechanical ventilation).

WHAT THIS STUDY ADDS

⇒ Our study retrieved data from the US Collaborative Network in TriNetX between 1 January 2018 and 31 December 2022. RA with JAKi users had a significant risk for hospitalisation (HR: 1.194, 95% CI: 1.003 to 1.423), mortality (HR: 1.440, 95% CI: 1.049 to 1.976) and composite adverse outcomes (HR: 1.242, 95% CI: 1.051 to 1.468) compared with TNFi users. In the C19-GRA study, JAKi users were likely to need mechanical ventilation, and this result was also found in our study from the sensitivity analysis by excluding subjects who were comorbid with other autoimmune diseases before the index date. Despite the differences between our study and the C19-GRA study from the period and different variants of concern, our study reached similar findings as those in the C19-GRA study that JAKi users compared with TNFi users cast a significant risk for poor outcomes of COVID-19. However, no vaccination effect was analysed in the C19-GRA study. Our findings added that mortality risk tended to be significantly higher in the JAKi group without COVID-19 vaccination (HR: 1.511, 95% CI: 1.077 to 2.121).

INTRODUCTION

COVID-19, caused by SARS-CoV-2, has had a great impact and challenge worldwide. The clinical spectrum of COVID-19 ranges from no symptoms to critical illness.[1] Age, race, underlying medical conditions and immunosuppressants are associated with a higher risk for severe COVID-19.[2]

SARS-CoV-2 infection may be associated with an exaggerated immune response driven by interleukin 6 (IL-6), tumour necrosis factor-alpha and cytokine storms, which have been identified as the key contributors to producing severe disease. Rheumatoid arthritis (RA) is characterised by the

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ RA with JAKi users had a significant risk for hospitalisation, mortality or composite adverse outcomes, especially higher mortality among those without COVID-19 vaccination. COVID-19 vaccination should be encouraged in these target cohorts. When using JAKi for patients with RA, clinicians should be vigilant about these adverse outcomes to prevent their occurrence or detect them early for early intervention.

hyperactivation of T cells, and proinflammatory cytokines act as contributing factors in developing synovial inflammation. Cytokine and immune activation patterns in patients with COVID-19 seem to resemble those in RA cases.[3] Some common treatment strategies, including cytokine inhibition, are against both COVID-19 and RA.[3 4]

The therapy for RA includes conventional synthetic, biologic or targeted synthetic disease-modifying antirheumatic drugs (csDMARDs and b/tsDMARDs) according to the disease severity. Over the past two decades, b/tsDMARDs have been effective in the treatment of RA. These drugs have played a significant role in improving clinical symptoms and enhancing patients' quality of life. bDMARDs, including tumour necrosis factor-alpha inhibitors (TNFi) and IL-6 inhibitors (IL-6i), and tsDMARDs, including Janus-associated kinase inhibitors (JAKi), are important for controlling RA disease activity and are widely used at present.[3]

Some evidence suggests that TNFi for rheumatic diseases may be associated with less severe COVID-19 outcomes.[5 6] The treatment with anti-IL-6 and baricitinib (a JAKi) for patients with COVID-19 has led to better outcomes in several studies.[7–10] Tofacitinib (a JAKi) was found to lower the risk of death or respiratory failure among patients hospitalised with COVID-19 pneumonia.[11] However, a recent study suggested that people with RA using JAKi at COVID-19 onset were more likely to have poor COVID-19 outcomes than people with RA using TNFi.[12]

We aimed to investigate the role of RA with b/tsDMARD exposure in COVID-19 outcomes, and we used the TriNetX database from a US Collaborative Network to analyse this association. The follow-up period in our study covered different variants of concern (VOCs) eras.

METHODS

Study design and data source

This is a retrospective cohort study. The data used in the present study were aggregated from TriNetX, the world's largest living ecosystem of real-world data and evidence for the life sciences and healthcare. It contains the deidentified electronic health records of more than 250 million persons from more than 120 global healthcare organisations (HCOs). It uses the harmonised framework for assessing data quality.[13] This framework recognises conformance, completeness and plausibility as three categories of quality metrics. We used the US Collaborative Network, the subnet of the TriNetX platform, to perform the related analysis. This network included 56 HCOs. Due to our study objective, we constrained the study period from 1 January 2018 to 31 December 2022 and built a cohort out of more than 54 million participants.

Study subjects

Study subjects included patients with RA (≥19 years old) enrolled in the TriNetX database. To clarify the effects of medications of interest in patients with RA, we excluded those with neoplasms. The study subjects were then divided into three cohorts based on their b/tsDMARD regimens. JAKi users were defined by drug regimens including tofacitinib, baricitinib, ruxolitinib, upadacitinib, fedratinib, abrocitinib or pacritinib (Anatomical Therapeutic Chemical (ATC code): L01EJ) greater than or equal to two instances. TNFi users were identified by prescriptions for infliximab, etanercept, adalimumab, certolizumab pegol or golimumab (ATC: L04AB) greater than or equal to two instances. IL-6i users were those prescribed greater than or equal to two instances of tocilizumab (ATC: L04AC07). To clarify the effect of the specific b/tsDMARD, we further excluded individuals who ever switched to another b/tsDMARD or combined use. In other words, the JAKi cohort only used the JAKi regimen and was never prescribed a TNFi or IL-6i. All groups excluded patients diagnosed with suspected COVID-19 (defined by the international classification of diseases 10th edition clinically modified, ICD-10-CM or laboratory results, details in online supplemental material L1) or deceased before the index date. The index date was the date of the prescription of the b/tsDMARD regimen for a patient meeting the inclusion criteria in the database.

Definition of covariates

The following covariate factors (within 1 year before the index date) were incorporated in the present study to reduce confounding effects.

Demographics

The demographics included age on the index date, sex, race encoded as white, black or African American, Asian and American Indian or Native Hawaiian, and socioeconomic status (SES) encoded as a proxy code (ICD 10 code Z55–Z65 Persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Lifestyles

Lifestyles play an important role in the progression of diseases. Thus, we incorporated those variables in the present study. The lifestyle variables were identified with the ICD-10 codes and matched in this study, including tobacco use (Z72.0, proxy smoking), nicotine dependence (F17, proxy smoking) and alcohol-related disorders (F10, proxy alcohol drinking).

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Comorbidities

All comorbidities with ICD-10 codes were dichotomous variables. The comorbidities matched in the present study included depressive episode (F32), essential hypertension (I10), ischaemic heart diseases (I20–I25), cerebrovascular diseases (I60–I69), diabetes mellitus (E8–E13), overweight and obesity (E66), hyperlipidaemia (E78.5), diseases of the liver (K70–K77), non-infective enteritis and colitis (K50–K52), sleep disorders (G47), psoriasis (L40), chronic kidney disease (N18), chronic lower respiratory diseases (J40–J47), systemic lupus erythematosus (M32), dermatopolymyositis (M33), Sjögren syndrome (M35.0), ankylosing spondylitis (AS, M45), Behçet's disease (M35.2), systemic sclerosis/scleroderma (M34) and atopic dermatitis (L20).

Procedures

To balance the health status or medical utilisation between groups, patients were matched on hospital inpatient services (defined by current procedural terminology, CPT code 1013659), preventive medicine services (CPT code 1013829), emergency department services (1013711) and office or other outpatient services (1013626) characteristics. COVID-19-related vaccination was also incorporated into the present study (details are presented in online supplemental material L2).

Medications

Subjects were divided into medication users or non-users based on the prescription information. In the present study, subjects were matched on non-steroidal anti-inflammatory drugs, systemic corticosteroid use and other DMARDs, such as abatacept, rituximab, sulfasalazine, minocycline, cyclophosphamide, methotrexate, leflunomide, azathioprine, penicillamine, hydroxychloroquine and cyclosporine (details are presented in online supplemental material L3).

Outcomes

The outcomes of interest included the following.

The incidence of COVID-19

COVID-19 was identified as a positive result in the SARS-CoV-2-related RNA test (TNX code:9088, Logical Observation Identifiers Names and Codes: 41458-1, 94746-5, 94511-3) or a related diagnosis defined by the ICD 10 code (U07.1, U07.2 COVID-19, J12.82 pneumonia due to COVID-19, U09 post COVID-19 condition or Z86.16 personal history of COVID-19).

Medical utilisation

Hospitalisation: CPT code 1013659, 1013699 or 1013729 or inpatient encounter.

Critical care services: CPT code 1013729.

Mechanical ventilation: ICD-10 procedure code 5A1935Z, 5A1945Z, 5A1955Z, 0BH17EZ, 0BH18EZ, 0BH13EZ, ICD-9-CM code 39.65 (extracorporeal membrane oxygenation) or CPT codes 31500, 1015098 and 1022227.

Mortality

Vital status was deceased.

Adverse outcomes

Combined with the outcomes of medical utilisation and mortality.

We used a 14-day washout period after the index date for measuring outcomes to prevent reverse causality. All outcomes that started 14 days after the first occurrence of the index event were included.

Statistical analyses

To reduce the effect of confounding factors, we then used the built-in capability of TriNetX to generate propensity scores and perform 1:1 matching by using greedy nearest neighbour matching with a calliper of 0.1 pooled SD of the two groups for age at index, sex, race, SES, lifestyle-related proxy variables, all comorbidities mentioned in the covariate definition section, procedures and medications. Comparisons between the two groups before and after matching were explored with a standardised mean difference (SMD). It is considered well-matched if the SMD is lower than 0.1. Based on the design of the TriNetX platform, propensity score matching will be reperformed for each analysis (JAKi vs TNFi and IL-6i vs TNFi).

Kaplan-Meier analysis was used to estimate the probability of the outcome of interest. The adjusted HRs (aHRs) and their associated 95% CIs, together with the test for proportionality, were calculated using R's Survival package V.3.2-3. Log-rank test results indicated whether the survival curves differed between groups and were performed within TriNetX. A p value<0.05 was considered statistically significant.

Subgroup analyses based on sex, age at index, race, COVID-19 vaccination status and corticosteroids for systemic use were performed to explore the difference between these groups. Four sensitivity analyses were also performed to illustrate the consistency of the results. First, competing risks will occur when subjects experience one or more severe outcomes that might compete with the outcome of interest. Therefore, referring to the solution proposed by Manja *et al*,[14] we include the competing event (death) in every endpoint. Second, we performed the same design in patients newly diagnosed with RA (never diagnosed with RA before 31 December 2017) to explore the possible influence of disease course. Third, we constrained the JAKi regimen into four RA-licensed JAKi, namely, tofacitinib, baricitinib, upadacitinib and filgotinib. Fourth, we excluded study subjects comorbid with other autoimmune diseases before the index date to reduce possible interference.

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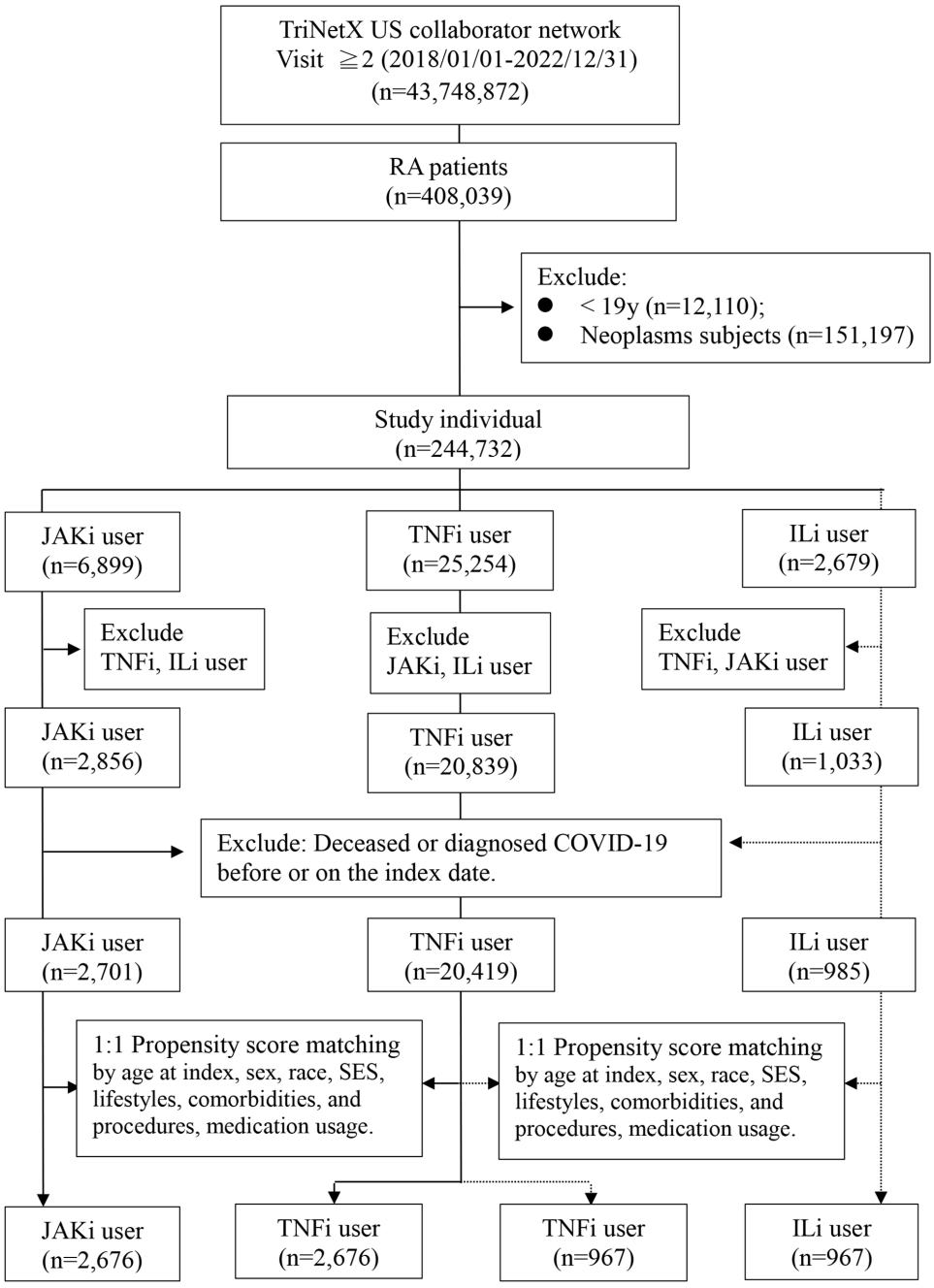

Figure 1 Flow chart of the selection. ILi, interleukin inhibitor; JAKi, Janus-associated kinase inhibitors; RA, rheumatoid arthritis; TNFi, tumour necrosis factor-alpha inhibitors.

RESULTS

Characteristics of the study subjects

Based on our study design, we identified a total of 2701 patients with RA treated with JAKi, 20 419 patients treated with TNFi and 985 patients treated with IL-6i during the study period. After propensity score matching, a total of 2676 JAKi users and the same number of TNFi users were identified. A total of 967 IL-6i users and the same number of TNFi users were also identified. The selection process is illustrated in figure 1.

The basic characteristics of the study subjects after matching are shown in table 1. Before matching (online supplemental table 1), the groups differed in demographics, comorbidities, medical utilisation and other DMARD usage. After matching, the difference between the groups was within the acceptable range (SMD<0.1).

Risk of COVID-19 incidence

Table 2 shows the HR (95% CI) with outcomes in the compared groups. Subjects treated with JAKi exhibited a slightly higher risk of COVID-19 than TNFi users, but the difference did not reach statistical significance (HR: 1.058, 95% CI: 0.895 to 1.250). Compared with TNFi users, IL-6i users showed similar results (HR: 1.028, 95% CI: 0.779 to 1.358). As shown in the Kaplan-Meier curves (figure 2A, B),

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Table 1 Baseline characteristics of study subjects (after propensity score matching)

Variables	After matching*					
	JAKi User (n=2676)	TNFi user (n=2676)	SMD[1]	IL-6i user (n=967)	TNFi user (n=967)	SMD[2]
Age at index						
Mean±SD	55.8±13.6	56.1±14.0	0.016	55.5±16.1	55.9±15.1	0.028
Sex						
Female	2184 (81.6)	2196 (82.1)	0.012	767 (79.3)	761 (78.7)	0.015
Male	492 (18.4)	480 (17.9)	0.012	199 (20.6)	205 (21.2)	0.015
Race, n (%)						
White	1963 (73.4)	1977 (73.9)	0.012	710 (73.4)	714 (73.8)	0.009
Black or African American	266 (09.9)	264 (09.9)	0.003	105 (10.9)	94 (09.7)	0.037
Asian	66 (02.5)	62 (02.3)	0.010	22 (02.3)	19 (02.0)	0.022
American Indian or Alaska Native	11 (00.4)	10 (00.4)	0.006	10 (01.0)	10 (01.0)	<0.001
Native Hawaiian or other Pacific Islander	10 (00.4)	10 (00.4)	<0.001	10 (01.0)	10 (01.0)	<0.001
Unknown race	368 (13.8)	365 (13.6)	0.003	123 (12.7)	135 (14.0)	0.037
Social economic status						
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	16 (00.6)	18 (00.7)	0.009	10 (01.0)	10 (01.0)	<0.001
Lifestyles						
Tobacco use (proxy smoking)	35 (01.3)	29 (01.1)	0.021	13 (01.3)	10 (01.0)	0.029
Nicotine dependence (proxy smoking)	131 (04.9)	110 (04.1)	0.038	32 (03.3)	32 (03.3)	<0.001
Alcohol-related disorders (proxy alcohol drinking)	14 (00.5)	10 (00.4)	0.022	10 (01.0)	10 (01.0)	<0.001
Comorbidities						
Depressive episode	163 (06.1)	131 (04.9)	0.053	72 (07.4)	64 (06.6)	0.032
Essential (primary) hypertension	471 (17.6)	439 (16.4)	0.032	200 (20.7)	169 (17.5)	0.082
Ischaemic heart diseases	99 (03.7)	97 (03.6)	0.004	43 (04.4)	40 (04.1)	0.015
Cerebrovascular diseases	40 (01.5)	38 (01.4)	0.006	26 (02.7)	29 (03.0)	0.019
Diabetes mellitus	194 (07.2)	189 (07.1)	0.007	83 (08.6)	65 (06.7)	0.070
Overweight and obesity	181 (06.8)	163 (06.1)	0.027	82 (08.5)	81 (08.4)	0.004
Hyperlipidaemia, unspecified	231 (08.6)	233 (08.7)	0.003	113 (11.7)	112 (11.6)	0.003
Diseases of liver	61 (02.3)	67 (02.5)	0.015	29 (03.0)	31 (03.2)	0.012
Non-infective enteritis and colitis	59 (02.2)	38 (01.4)	0.059	15 (01.6)	12 (01.2)	0.026
Sleep disorders	182 (06.8)	176 (06.6)	0.009	89 (09.2)	68 (07.0)	0.080
Psoriasis	84 (03.1)	74 (02.8)	0.022	10 (01.0)	10 (01.0)	<0.001
Chronic kidney disease	62 (02.3)	66 (02.5)	0.010	29 (03.0)	37 (03.8)	0.046
Chronic lower respiratory diseases	234 (08.7)	212 (07.9)	0.030	78 (08.1)	63 (06.5)	0.060
Systemic lupus erythematosus	69 (02.6)	69 (02.6)	<0.001	23 (02.4)	22 (02.3)	0.007
Dermatopolymyositis	25 (00.9)	19 (00.7)	0.025	10 (01.0)	10 (01.0)	<0.001
Sjögren syndrome	101 (03.8)	100 (03.7)	0.002	37 (03.8)	35 (03.6)	0.011
Ankylosing spondylitis	14 (00.5)	16 (00.6)	0.010	10 (01.0)	10 (01.0)	<0.001
Behçet's disease	10 (00.4)	10 (00.4)	<0.001	0 (00.0)	0 (00.0)	–
Systemic sclerosis/scleroderma	11 (00.4)	18 (00.7)	0.036	33 (03.4)	23 (02.4)	0.062
Atopic dermatitis	10 (00.4)	10 (00.4)	<0.001	10 (01.0)	10 (01.0)	<0.001
Medical utilisation						
Hospital inpatient services	75 (02.8)	63 (02.4)	0.028	47 (04.9)	46 (04.8)	0.005
Preventive medicine services	143 (05.3)	127 (04.7)	0.027	33 (03.4)	30 (03.1)	0.017
Emergency department services	221 (08.3)	200 (07.5)	0.029	105 (10.9)	91 (09.4)	0.048
Office or other outpatient services	1533 (57.3)	1504 (56.2)	0.022	606 (62.7)	605 (62.6)	0.002

Continued

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Table 1 Continued

Variables	After matching*					
	JAKi User (n=2676)	TNFi user (n=2676)	SMD[1]	IL-6i user (n=967)	TNFi user (n=967)	SMD[2]
COVID-19 vaccination						
BNT†	45 (01.7)	51 (01.9)	0.017	19 (02.0)	22 (02.3)	0.022
Moderna‡	10 (00.4)	10 (00.4)	<0.001	10 (01.0)	10 (01.0)	<0.001
Janssen§	0 (00.0)	0 (00.0)	–	0 (00.0)	0 (00.0)	–
Medication						
NSAIDs	813 (30.4)	788 (29.4)	0.020	244 (25.2)	217 (22.4)	0.066
Corticosteroids for systemic use	1291 (48.2)	1308 (48.9)	0.013	514 (53.2)	515 (53.3)	0.002
Other DMARDs						
Abatacept	131 (04.9)	125 (04.7)	0.011	66 (06.8)	62 (06.4)	0.017
Rituximab	30 (01.1)	21 (00.8)	0.035	11 (01.1)	12 (01.2)	0.010
Sulfasalazine	175 (06.5)	172 (06.4)	0.005	37 (03.8)	32 (03.3)	0.028
Minocycline	11 (00.4)	12 (00.4)	0.006	10 (01.0)	0 (00.0)	**0.145**
Cyclophosphamide	0 (00.0)	10 (00.4)	0.087	0 (00.0)	0 (00.0)	–
Methotrexate	698 (26.1)	675 (25.2)	0.020	205 (21.2)	203 (21.0)	0.005
Leflunomide	252 (09.4)	253 (09.5)	0.001	72 (07.4)	69 (07.1)	0.012
Azathioprine	31 (01.2)	29 (01.1)	0.007	18 (01.9)	20 (02.1)	0.015
Penicillamine	0 (00.0)	0 (00.0)	–	0 (00.0)	0 (00.0)	–
Hydroxychloroquine	473 (17.7)	433 (16.2)	0.040	137 (14.2)	135 (14.0)	0.006
Cyclosporine	31 (01.2)	26 (01.0)	0.018	14 (01.4)	15 (01.6)	0.009

Note: If the patient number is less than or equal to 10, the results show the count as 10.
Bold value represents a standardised difference greater than 0.1.

*Propensity score matching was performed on age at index, sex, race, socioeconomic status, lifestyles, comorbidities, medical utilisation, COVID-19 vaccination and medication usage.
†Value presented here only includes SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 30 µg/0.3 mL dosage, diluent reconstituted, for intramuscular use (UMLS:CPT:91300).
‡Value presented here only includes SARS-CoV-2 (COVID-19) vaccine, mRNA-LNP, spike protein, preservative free, 100 µg/0.5 mL dosage, for intramuscular use (UMLS:CPT:91301).
§Value presented here only includes SARS-CoV-2 (COVID-19) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5×10^{10} viral particles/0.5 mL dosage, for intramuscular use (UMLS:CPT:91303).
BNT, Pfizer–BioNTech; DMARDs, disease-modifying antirheumatic drugs; IL-6i, interleukin 6 inhibitor; JAKi, Janus-associated kinase inhibitors; LNP, Lipid Nanoparticle; NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardised mean difference; TNFi, tumour necrosis factor-alpha inhibitors.

there were no significantly different risks of COVID-19 incidence found between these compared cohorts (log-rank test, p=0.508 in JAKi vs TNFi, and p=0.843 in IL-6i vs TNFi).

Medical utilisation

Compared with the TNFi cohort, the JAKi cohort exhibited a significantly higher risk of hospitalisation (HR: 1.194, 95% CI: 1.003 to 1.423). There was no significant difference between JAKi users and TNFi users in critical care services or mechanical ventilation utilisation (table 2, online supplemental figures 1A, 2A and 3A). There was no significant difference between IL-6i users and TNFi users in medical utilisation (online supplemental materials 1B, 2B and 3B).

Mortality

Compared with the TNFi cohort, the JAKi cohort also revealed a significantly higher mortality risk (HR: 1.440, 95% CI: 1.049 to 1.976, log-rank test, p=0.023) (table 2, online supplemental figure 4A). There was no significant difference in mortality risk between IL-6i users and TNFi users (HR: 0.835, 95% CI: 0.517 to 1.348, online supplemental figure 4B).

Adverse outcomes

The JAKi cohort displayed a notably higher risk of composite adverse outcomes (HR: 1.242, 95% CI: 1.051 to 1.468) than the TNFi cohort (table 2). There was no significant difference between IL-6i users and TNFi users in adverse outcome incidence (HR: 1.209, 95% CI: 0.924 to 1.581). As shown in the Kaplan-Meier curves (figure 3A), the JAKi cohort exhibited a higher risk of adverse outcome incidence (log-rank test, p=0.010), whereas IL-6i users did not show this tendency (figure 3B).

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Table 2 The risk of outcomes

Outcomes	Patients with outcome JAKi (n=2676)	TNFi (n=2676)	HR (95% CI)*	Patients with outcome IL-6i (n=967)	TNFi (n=967)	HR (95% CI)*
Disease incidence						
COVID-19	264	290	1.058 (0.895 to 1.250)	98	101	1.028 (0.779 to 1.358)
Medical utilisation						
Hospitalisation	261	244	**1.194 (1.003 to 1.423)**	103	89	1.296 (0.976 to 1.721)
Critical care services	69	63	1.237 (0.878 to 1.742)	20	24	0.862 (0.476 to 1.560)
Mechanical ventilation	36	30	1.373 (0.844 to 2.232)	11	10	1.154 (0.490 to 2.718)
Mortality						
Deceased	87	69	**1.440 (1.049 to 1.976)**	30	38	0.835 (0.517 to 1.348)
Adverse outcomes†	292	264	**1.242 (1.051 to 1.468)**	111	103	1.209 (0.924 to 1.581)

Note: If the patient number is less than or equal to 10, the results show the count as 10.
Bold font indicates statistical significance.
*Patients in each cohort after propensity score matching performed on age at index, sex, race, socioeconomic status, lifestyles, comorbidities, medical utilisation, COVID-19 vaccination and medication usage.
†Including hospitalisation, critical care services, mechanical ventilation, or deceased.
IL-6i, interleukin 6 inhibitors; JAKi, Janus-associated kinase inhibitors; TNFi, tumour necrosis factor alpha inhibitors.

Subgroup analyses

Sex

We further examined the risk of outcomes in subgroups stratified by sex (online supplemental table 2). In females, the JAKi cohort exhibited a significantly higher risk of critical care services and adverse outcomes than the TNFi cohort (aHRs: 1.826 and 1.204, respectively).

Age

We also explored the risk of outcomes in subgroups stratified by age group (19–64 years, ≥65 years). In the age group of 19–64 years, IL-6i users had significantly higher risks of hospitalisation and combination adverse outcomes than TNFi users (aHR: 1.495, 95% CI: 1.031 to 2.166, aHR: 1.490, 95% CI: 1.040 to 2.136, respectively, online supplemental table 3).

Race

We also investigated the risk of outcomes among the white and black/African American populations (online supplemental table 4). Among white patients, the JAKi cohort exhibited a significantly higher risk of mortality than the TNFi cohort (aHR: 1.477, 95% CI: 1.035 to 2.107).

COVID-19 vaccination

Vaccination against COVID-19 (details are provided in online supplemental material L2) may be an important factor that interferes with the occurrence of COVID-19. Thus, we also explored the risk of outcomes in subgroups stratified by vaccination status (table 3). In the patients with COVID-19 vaccination, there was no significant difference between JAKi and TNFi users or IL-6i and TNFi users in COVID-19 incidence, medical utilisation, mortality or composite adverse outcomes. In those subjects without vaccination, JAKi users had higher risks of mortality (aHR: 1.511, 95% CI: 1.077 to 2.121) than the TNFi cohort.

Corticosteroid usage

To explore the influence of disease severity, we then stratified the study subjects by corticosteroid usage (online supplemental table 5). There were no significant differences in the risk of developing COVID-19, medical utilisation or mortality risk between JAKi users and TNFi users or between IL-6i users and TNFi users.

We summarised the results of the above subgroup analysis and visualised them in forest plots (figures 4 and 5).

Sensitivity analysis

After accounting for competing risks, the JAKi cohort was still significantly associated with increased risks of hospitalisation, critical care service utilisation, mortality and adverse outcomes (aHRs: 1.242, 1.297, 1.440 and 1.242, respectively, online supplemental table 6) in comparison to the TNFi cohort.

We used the same study design applied to patients with newly diagnosed RA (online supplemental table 7). Subjects treated with JAKi exhibited a higher risk of critical care service utilisation than TNFi users (aHR: 1.650, 95% CI: 1.012 to 2.689).

When the JAKi regimen was constrained to four RA-licensed JAKi (tofacitinib, baricitinib, upadacitinib and filgotinib), the results were similar to those of the original study. The JAKi cohort revealed higher risks of critical care service utilisation and mortality (aHRs: 1.425 and 1.447, respectively, online supplemental table 8) than TNFi users.

After excluding subjects who were comorbid with other autoimmune diseases before the index date, the JAKi cohort exhibited increased risks of COVID-19 incidence, critical care services, mechanical ventilation utilisation and mortality (aHRs: 1.254, 1.935, 2.487 and 1.495, respectively, online supplemental table 9) in comparison to the TNFi cohort

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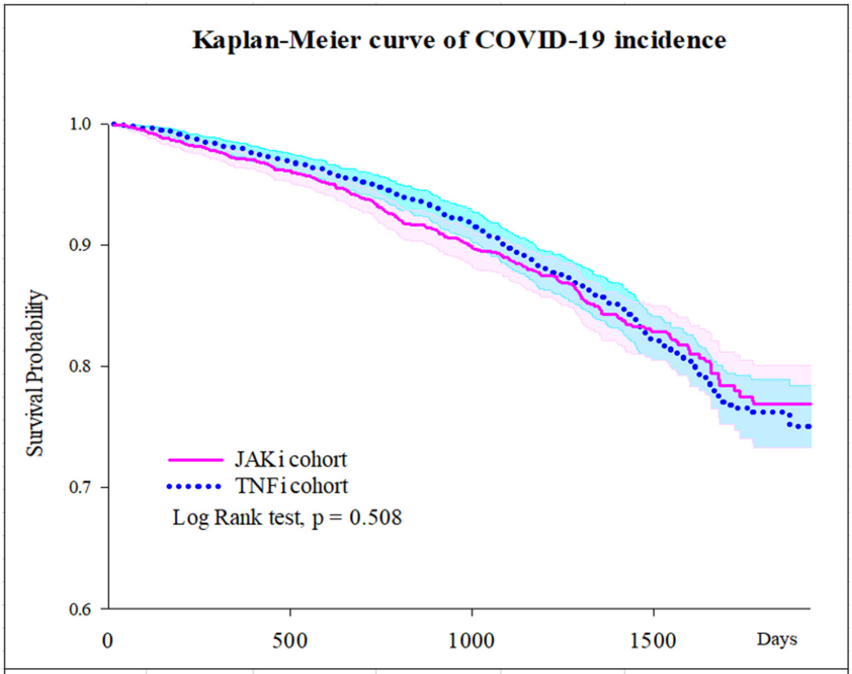
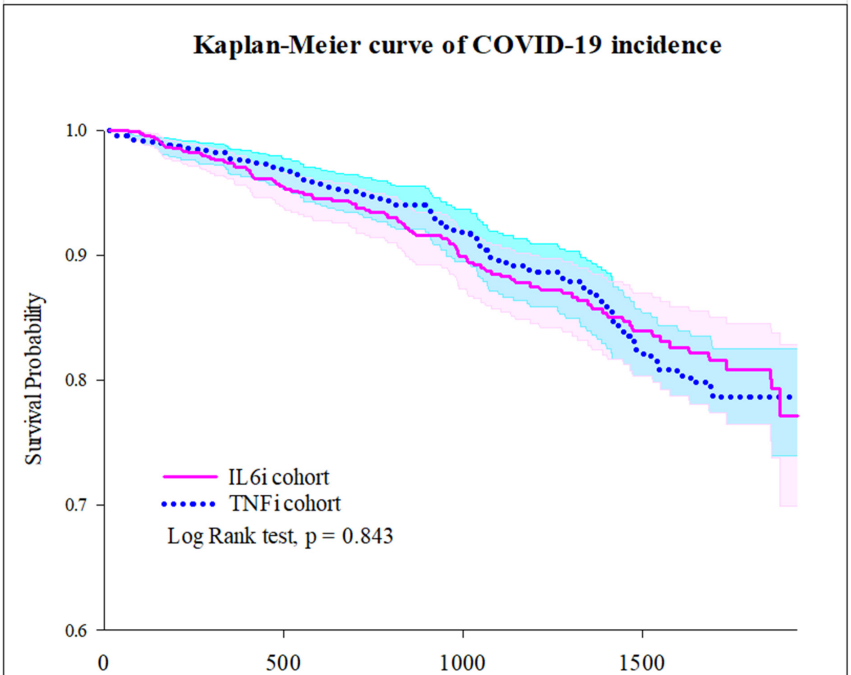
A JAKi vs. TNFi



Days after index date	14	380	746	1112	1478
Number at risk					
JAKi cohort	2,672	2,600	2,529	2,471	2,428
TNFi cohort	2,675	2,624	2,565	2,489	2,422

B IL6i vs. TNFi



Days after index date	14	380	746	1112	1478
Number at risk					
IL6i cohort	966	940	915	890	862
TNFi cohort	967	946	926	898	881

Figure 2 Kaplan-Meier curves of COVID-19 incidence. (A) JAKi versus TNFi. (B) IL-6i versus TNFi. IL-6i, interleukin 6 inhibitor; JAKi, Janus-associated kinase inhibitors; TNFi, tumour necrosis factor-alpha inhibitors.

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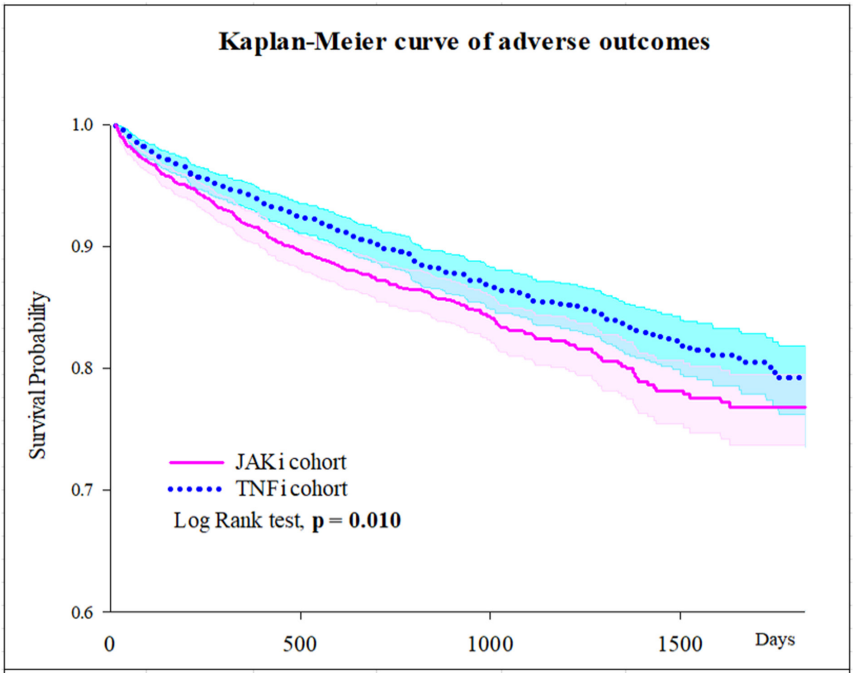
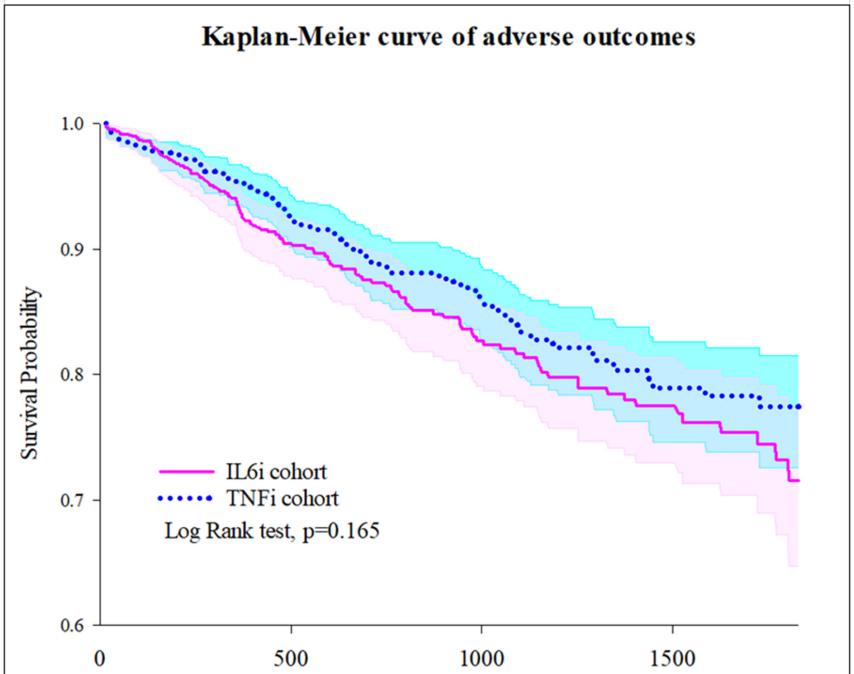
A JAKi vs. TNFi



Days after index date	14	380	746	1112	1478
Number at risk					
JAKi cohort	2,044	1,886	1,818	1,781	1,756
TNFi cohort	2,050	1,937	1,872	1,827	1,802

B IL6i vs. TNFi



Days after index date	14	380	746	1112	1478
Number at risk					
IL6i cohort	710	660	635	614	599
TNFi cohort	735	702	666	646	618

Figure 3 Kaplan-Meier curves of adverse outcome incidence. (A) JAKi versus TNFi. (B) IL-6i versus TNFi. IL-6i, interleukin 6 inhibitor; JAKi, Janus-associated kinase inhibitors; TNFi, tumour necrosis factor-alpha inhibitors.

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Table 3 The risk of outcomes stratified by COVID-19 vaccination status

Outcomes	With vaccination*					
	Patients with outcome		HR (95% CI)††	Patients with outcome		HR (95% CI)††
	JAKi	TNFi		IL-6i	TNFi	
Total, N	444	444		161	161	
Disease incidence						
COVID-19	64	79	1.005 (0.722 to 1.400)	28	38	0.738 (0.452 to 1.204)
Medical utilisation						
Hospitalisation	53	51	1.260 (0.856 to 1.855)	25	18	1.322 (0.721 to 2.425)
Critical care services	15	13	1.368 (0.649 to 2.800)	10	10	0.505 (0.126 to 2.020)
Mechanical ventilation	10	10	1.152 (0.287 to 4.622)	10	10	1.561 (0.261 to 9.350)
Mortality						
Deceased	10	10	2.128 (0.752 to 6.023)	10	10	2.498 (0.484 to 12.88)
Adverse outcomes‡‡	55	53	1.272 (0.870 to 1.860)	26	18	1.377 (0.754 to 2.512)
	Without vaccination§§					
Total, N	2224	2224		802	802	
Disease incidence						
COVID-19	201	210	1.113 (0.917 to 1.352)	71	78	1.015 (0.736 to 1.400)
Medical utilisation						
Hospitalisation	206	210	1.082 (0.892 to 1.312)	77	72	1.154 (0.837 to 1.592)
Critical care services	54	51	1.174 (0.800 to 1.722)	17	20	0.909 (0.476 to 1.735)
Mechanical ventilation	32	25	1.429 (0.846 to 2.414)	10	10	1.062 (0.398 to 2.829)
Mortality						
Deceased	78	59	**1.511 (1.077 to 2.121)**	25	32	0.854 (0.506 to 1.441)
Adverse outcomes‡‡	235	232	1.127 (0.940 to 1.352)	84	84	1.083 (0.800 to 1.466)

Note: If the patient number is less than or equal to 10, the results show the count as 10.
Bold font indicates statistical significance.
*Subjects who were ever vaccinated with COVID-19-related vaccines documented in their health record.
†Patients in each cohort were matched for age at index, sex, race, socioeconomic status, lifestyles, comorbidities, medical utilisation, COVID-19 vaccination status and medication usage.
‡Including hospitalisation, critical care services, mechanical ventilation or deceased.
§Subjects who were never vaccinated with COVID-19-related vaccines documented in their health record.
IL-6i, interleukin 6 inhibitors; JAKi, Janus-associated kinase inhibitors; TNFi, tumour necrosis factor alpha inhibitors.

DISCUSSION

Our study found that compared with RA of TNFi users as a reference comparator, JAKi users were not at increased risk for COVID-19 incidence, critical care services or mechanical ventilation. However, JAKi users had a significant risk for hospitalisation (aHR: 1.194, 95% CI: 1.003 to 1.423), mortality (aHR: 1.440, 95% CI: 1.049 to 1.976) and adverse outcomes (aHR: 1.242, 95% CI: 1.051 to 1.468). From subgroup analysis, JAKi users without COVID-19 vaccination had a significantly higher risk for mortality (1.511, 1.077–2.121). The JAKi group stratified by race revealed that white people had a significantly higher risk for mortality than black/African Americans (1.477, 1.035–2.107). The female JAKi users tended to have a significantly higher risk for critical care services (1.826, 1.156–2.884) and adverse outcomes (1.204, 1.001–1.447).

Taking these stratified subgroup analyses together, it was noteworthy that JAKi users who were white or were not COVID-19 vaccinated had significant risks for mortality. A significantly higher mortality could also be found from these three sensitivity analyses from the competing risk of death, RA-licensed JAKi, and excluding subjects who were comorbid with other autoimmune diseases before the index date. The significant critical care services were identified from these four sensitivity analyses. A significant risk in mechanical ventilation (2.487, 1.322–4.679) was found from the sensitivity analysis by excluding subjects who were comorbid with other autoimmune diseases before the index date.

We found that compared with the RA of TNFi users, IL-6i users were not at increased risk for COVID-19,

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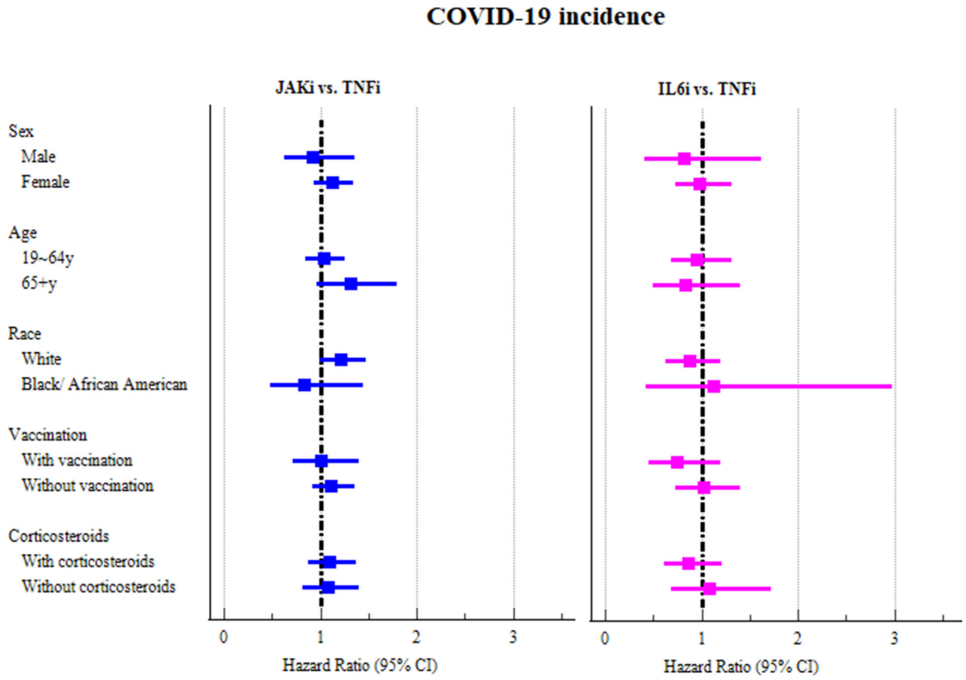

Figure 4 Forest plots of COVID-19 incidence. IL-6i, interleukin 6 inhibitor; JAKi, Janus-associated kinase inhibitors; TNFi, tumour necrosis factor-alpha inhibitors.

medical utilisation, mortality or adverse outcomes. In the subgroup analysis, the IL-6i group aged 16–64 years old had a significantly higher risk for hospitalisation (1.495, 1.031–2.166) and adverse outcomes (1.490, 1.040–2.136).

The previous international registry study of the COVID-19 Global Rheumatology Alliance (C19-GRA) suggested that patients with RA using rituximab or JAKi at COVID-19 onset were more likely to experience poor COVID-19 outcomes (hospitalisation, death, mechanical ventilation) than TNFi users.[12] Regarding hospitalisation and death, we had similar findings. In the C19-GRA study, JAKi users were likely to need mechanical ventilation (OR: 2.03, 95% CI: 1.56 to 2.62), and this result was also found in our study from the sensitivity analysis by excluding subjects who were comorbid with other

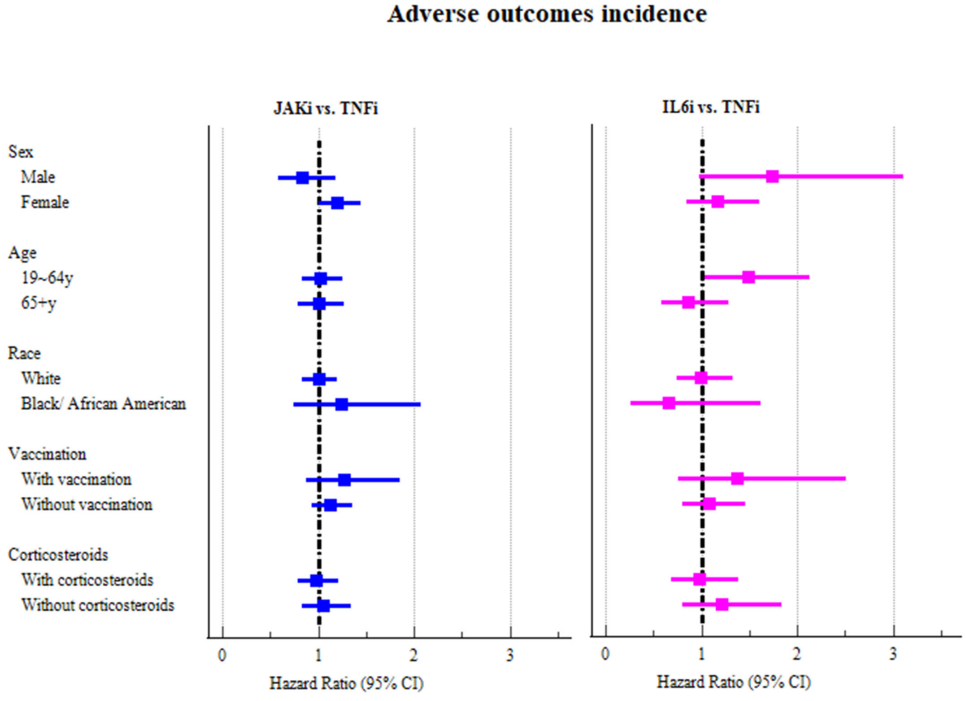

Figure 5 Forest plots of adverse outcomes. IL-6i, interleukin 6 inhibitor; JAKi, Janus-associated kinase inhibitors; TNFi, tumour necrosis factor-alpha inhibitors.

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autoimmune diseases before the index date (aHR: 2.487, 95% CI: 1.322 to 4.679).

We further analysed the differences between this C19-GRA study and ours and found first that the study's cohorts selected patients with RA on b/tsDMARDs at the onset of COVID-19 and did not define the index date of the treatments in contrast to our index date of at least 14 days from enrolment to further strengthen the exposure effects of b/tsDMARDs. Second, their study period from 24 March 2020 to 12 April 2021 was different from ours, which was from 1 January 2018 to 31 December 2022. The cohorts in these two studies experienced different eras of VOCs. Their study might cover chiefly wild-type, alpha, beta and gamma VOCs. Our study was further extended to cover the delta and omicron VOC eras.[15] The virulence of the virus, the implementation of the vaccine and more effective treatments differed. Vaccination propagation only began in 2021. No vaccination effect was analysed in the C19-GRA study. Despite the differences in the study background mentioned above, our study reached similar findings as those in the C19-GRA study that JAKi users had a significant risk for poor outcomes of COVID-19 compared with TNFi users.

Despite a low vaccination rate of approximately 16.7% in our study subjects, we found that JAKi users without COVID-19 vaccination had a significantly higher risk for mortality. A study from a Danish nationwide matched-cohort study from January to October 2021 suggested that the overall risk of COVID-19 hospitalisation was increased in patients with RA compared with the general population regardless of vaccination, but the absolute risk of hospitalisation was remarkably lower among all individuals who were vaccinated.[16] Our findings further highlight the importance of COVID-19 vaccination in people with RA,[17] especially those receiving JAKi.

Some evidence suggests that TNFi for rheumatic diseases, including RA and AS, may be associated with less severe COVID-19 outcomes.[5 6] The treatment with IL-6i and baricitinib led to better outcomes for patients with COVID-19 in several studies.[7–10] The impact of b/tsDMARDs on COVID-19 outcomes arouses particular concern, since some of these drugs, such as tocilizumab and baricitinib, have been studied and advised treatments for COVID-19.[18] Tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo among patients hospitalised with COVID-19 pneumonia.[11] However, it is noteworthy that the Food and Drug Administration required warnings about the increased risk of serious heart-related events, cancer, blood clots and death for JAKi (tofacitinib, baricitinib and upadacitinib) when used to treat chronic inflammatory conditions.[19] The clinical trial from the Oral Rheumatoid Arthritis Trial Surveillance showed a higher risk of major adverse cardiovascular events and cancers with tofacitinib than with TNFi in RA during a median follow-up of 4 years.[20] We did not know whether the drug-associated side effects of JAKi might contribute to the higher COVID-19 hospitalisation and mortality from the C19-GRA study and our findings in RA cases.

Our study showed that JAKi patients who used steroids did not have a significant risk for all COVID-19 outcomes. However, in a South Korean study[21] involving 8297 patients with autoimmune inflammatory rheumatic diseases, the risk of COVID-19-related death was greater than that in a matched cohort without rheumatic disease (OR: 1.69, 95% CI: 1.01 to 2.84). The treatment with high-dose steroids (≥10 mg per day) had an increased risk of a positive SARS-CoV-2 test (1.47, 1.05–2.03), severe outcomes (1.76, 1.06–2.96) and death (3.34, 1.23–8.90). Notably, the above study did not examine the use of JAKinhibitors.

Steroids are known to have benefits when initiated for moderate-to-severe COVID-19, but are also associated with worse outcomes among those on baseline steroids at the time of infection.[5 22 23] Continuation of steroids at the lowest possible dose is suggested, and sudden withdrawal is not recommended.[3] The American College of Rheumatology (ACR) further endorsed the use of low-dose glucocorticoids when clinically indicated and acknowledged that higher doses when a patient faces a severely threatening disease may be necessary, including SARS-CoV-2 exposure.[24] The ACR also recommends, regardless of COVID-19 severity, temporarily stopping csDMARDs or b/tsDMARDs (except for IL-6i) in patients with COVID-19 7–14 days after symptom resolution or 10–17 days after a positive SARS-CoV-2 test.[24] However, patients might encounter possible disease flare-ups during or after COVID-19 infection. In addition to the temporary cessation of DMARDs, prompt antiviral drugs and specific monoclonal antibody treatment should be initiated in the early stage of COVID-19 infection among patients with RA receiving JAKi or rituximab.

Our study has several strengths. First, the TriNetX database in this study, which is a global health-collaborative clinical research platform, currently contains the largest global COVID-19 dataset. Multiple studies have used TriNetX to study the associated risk and outcomes of COVID-19.[25–28] It provides an accurate account of the burden of specific diagnoses on healthcare systems due to information from real-time electronic medical records (EMRs). Both insured and uninsured patients are included. Moreover, the study population was racially diverse and included black or African American, Asian, American Indian or Alaska Native, Native Hawaiian and other populations. Second, we used laboratory-based diagnosis in addition to ICD codes, which offered a more accurate definition for recruiting patients with COVID-19. Third, we performed integrative subgroup and sensitivity analyses. Fourth, vaccination was considered and included in the subgroup analysis. Fifth, we analysed not only old diagnosed RA cases but also newly diagnosed RA cases.

Our study also has certain limitations. First, over 80% of the participants in our study were American and only 2% were Asian; thus, the generalisability of

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our conclusions to Asians or Europeans is limited. Second, we used validated outcome definitions and propensity score matching to avoid bias, but misclassification bias and residual confounding could not be completely avoided because of weaknesses inherent to an EMR study. Third, we did not include COVID-19 medication for analysis. Evolutionary effective treatments might affect COVID-19 outcomes. Fourth, under the *TriNetX* interface, we can use only 2 by 2 comparison analysis, and analysis of 3 groups was not feasible. Fifth, we cannot provide the dose, adherence and duration of medication in this database. Selection bias and treatment effect may be affected by regimen adhesion, dosage, duration and other factors. Sixth, due to the number of limited cases (approximately 2000), further analysis of the time sequence of VOCs will be difficult to conduct. Further study will be performed in the future. Seventh, TriNetX data come from hospital-based EMRs instead of population-based data. Therefore, vaccination can be speculated to be under-reported. However, please note that our covariates were defined within 1 year before the index date. For example, if the index date of subject A was 1 May 2020, even if the subject received the vaccination after the index date, we did not present the vaccination record by our definition of covariates.

In summary, RA with JAKi users had a significant risk for hospitalisation, mortality or composite adverse outcomes, especially higher mortality among those without COVID-19 vaccination. COVID-19 vaccination should be encouraged in these target cohorts. When using JAKi for patients with RA, clinicians should be vigilant about these adverse outcomes to prevent their occurrence or detect them early for early intervention.

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Competing interests The authors declare no competing interests.

Patient consent for publication Not applicable.

Ethics approval The TriNetX platform is compliant with the Health Insurance Portability & Accountability Act and General Data Protection Regulation. The Western Institutional Review Board granted TriNetX a waiver because it only aggregates counts and statistical summaries of deidentified information. As an HCO member of TriNetX, Chung Shan Medical University Hospital can access to deidentified data in the TriNetX network. In addition, the use of TriNetX for the present study was approved under the authority of the Institutional Review Board of Chung Shan Medical University Hospital (CSMUH No: CS2-21176).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as an online supplemental information.

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