COVID-19 in rheumatoid arthritis: prevalence, hospital admission, and risk of all-cause mortality before and after the COVID-19 pandemic

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Abstract

Objective

COVID-19 infection can trigger a cytokine storm, treatable with immunomodulating therapies similar to those used in rheumatoid arthritis (RA). This study investigated COVID-19 prevalence, hospitalisation, emergency department (ED) visits, and the impact of RA treatment and baseline characteristics on mortality in RA patients.

Methods

RA patients from the Ontario Best Practices Research Initiative (OBRI) were linked to Ontario healthcare records held at the Institute for Clinical Evaluative Sciences (ICES). The study examined COVID-19 infection, ED visits, hospitalisation, and intensive care unit (ICU) admissions between January 1st 2020, and March 31st 2022, and the risk of all-cause mortality before and after the pandemic.

Results

Among 2,969 RA patients, 596 (20.1%) had COVID-19. Of those with COVID-19, 108 (18.1%) were hospitalised or visited ED. Females were more likely to be infected (81.9% vs. 76.5%; adj ORs:1.30; 95% CI: 1.01–1.66). COVID-19 patients were more likely to use biologics (52.5% vs. 46.1%; adj ORs:1.28; 95% CI: 1.04-1.57) or Janus Kinase inhibitors (JAKi) (13.4% vs. 9.5%; adj ORs:1.44; 95% CI: 1.08–1.93). Older age (>80 years) (adj HR: 10.9; 95% CI:6.49–18.2), smoking (adj HR: 1.85; 95% CI:1.41–2.42), and higher disease activity score (adj HR: 1.09; 95% CI:1.00–1.18) were associated with higher all-cause mortality both before and after the COVID-19 pandemic, with stronger associations in the latter. JAKi were negatively associated with increased death before the pandemic (adj HR: 0.55; 95% CI: 0.34–0.91).

Conclusion

COVID-19 was higher in females, younger patients, those with comorbidities, and those using advanced therapies. Compared to pre-pandemic, higher death rates during the pandemic were associated with older age, oral steroid use, smoking, and higher disease activity.

Key words

rheumatoid arthritis, COVID-19 pandemic, population health data source, clinical data, all-cause mortality, hospitalisation

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Introduction

As of April 13, 2024, COVID-19 infections had spread to 231 countries, with approximately a global total of 704.6 million cases and around 7.0 million deaths. In Canada, there have been 4,946,090 confirmed cases and 59,034 deaths (1). Risk factors such as increased age, male gender, hypertension, diabetes mellitus, morbid obesity, cardiovascular disease, chronic lung disease and malignancy portend increased risk of severe disease (2-4). Patients with rheumatoid arthritis (RA) have an elevated risk of serious non-COVID-19 infections, directly linked to RA disease activity as well as medications used for treatment (5-8). As with other infections, it is possible that RA may elevate the risk of COVID-19 infection and its severity, due to disease-related immunosuppressive effects and iatrogenic immunomodulation. However, to date, there is a paucity of supporting data. With the recognition that COVID-19 can lead to cytokine release syndrome and secondary ARDS, treatment has largely been shifted to immunomodulating therapies that are routinely used to treat RA given their possible ability to interfere with COVID-19 pathogenesis. For example, a meta-analysis of nine randomised controlled trials, including 11888 COVID-19 patients with 1485 death events, showed a 20% reduction in mortality with JAK inhibitor therapies (9). International rheumatology societies such as the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) as well as national rheumatology associations including the Canadian Rheumatology Association (CRA) and the Italian Society of Rheumatology advised against interruption of any DMARDs during the pandemic (10-13). Despite these recommendations from several societies, as rheumatologists, we lack evidence-based answers to patients' ongoing questions regarding *their* COVID-19 risk.

The literature presents conflicting evidence regarding the impact of RA on both the risk of contracting COVID-19 and the severity of the disease. An Italian study that was conducted at the early stages of COVID-19 included 232 patients with common rheumatic musculoskeletal disease (RMD) (14). The investigators found that RA is the most common RMD affected by COVID-19, with very high rates of hospitalisation (69.8%) and death (19%); however, they did not identify a significant link between immunomodulatory treatments and an increased risk of poor outcomes. A contemporaneous French study of 200 consecutive patients with RMDs, half of whom were receiving bDMARDs (15). The study reported a low PCR-confirmed COVID-19 positivity rate of 4%, with no observed impact of bDMARD use on clinical outcomes. In contrast, a larger database study of 69,549 RA patients showed that 22,956 were diagnosed with COVID-19 between January 2020 and September 2021, with rituximab use linked to higher hospitalisation, ICU admission, and invasive ventilation rates (16). In another nationwide population-based study from Denmark, which spanned the first three years of the pandemic, researchers found similar COVID-19 infection rates among patients with various RMDs and the general population. However, the risk of hospitalisation and severe COVID-19 was approximately doubled in the RMD group, although the study did not analyse the impact of specific treatments (17). These discrepancies highlight how variations in study design, patient populations, treatment exposures, and the timing within the pandemic can substantially influence findings and interpretationsWe aimed to identify the prevalence of COVID-19 infection, severe COVID-19 infection requiring hospitalisation, intensive care unit (ICU) admission, intubation and the impact of patient and disease related features as well as certain treatments on all-cause mortality in the RA population before and after the COVID-19 pandemic.

Methods

We conducted a cross-sectional analysis to identify RA patients diagnosed with COVID-19 and investigate its association with patient characteristics. We also looked at the association between patient characteristics, using enrolment data from the Ontario Best Practices Research Initiative (OBRI), and the risk of

all-cause mortality before and after the COVID-19 pandemic (COVID-19 pandemic in Canada: March 17th 2020) using a retrospective cohort study design. All sites had received ethics approval to enroll patients, and all participants signed informed consent, which was both informed and written. The consent did not include minors, requiring participants to be 18 years of age or older. The ethics approval reference number is REB 07-0729 AE, granted by the University Health Network.

Study population

Adult patients (≥18 years) with RA enrolled in the OBRI between Jan 1st 2008 and April 25th 2021 were linked to the Institute for Clinical Evaluative Sciences (ICES) healthcare administrative data. We identified RA patients who were diagnosed with COVID-19 between Jan 1st 2020, and Mar 31st 2022. COVID-19 was defined by a positive COVID test from the Ontario Laboratory Information System (OLIS) or the Ontario Health Insurance Plan (OHIP) (080 code). Hospitalisation or emergency department (ED) visits were defined by the presence of an International Classification of Diseases, ICD-10 [U071] code in the Discharge Abstract Database (DAD) or National Ambulatory Care Reporting System (NACRS). Only the first episode of COVID-19 was considered as a study outcome in patients with multiple episodes during the study period.

Of the 3,066 patients enrolled in the OBRI and linked to ICES, 2 were excluded due to duplicate records, 89 lacked valid OHIP coverage (*e.g.* non-residents), and 6 were ineligible at enrolment (either under 18 at enrolment or under 16 at RA diagnosis). This resulted in a final cohort of 2,969 patients for analysis. For all-cause mortality analysis, each RA patient was followed from their enrolment in the OBRI up to death, loss to follow-up or end of the study period (Mar 31st 2025), whichever occurred first.

Data sources

OBRI is a multicentre RA registry established in 2008. To date, the OBRI has collected longitudinal data from both rheumatologists and patients across Ontario, for over 3,800 patients which corresponds to approximately 4% of the RA population in Ontario. Patients are recruited from both academic and community centres and, therefore, represent a range of the patient population. The advantage of this database is that it allows us to study a sample of the RA population across Ontario with detailed clinical data that are not available in the ICES database.

At OBRI enrolment and each subsequent visit, rheumatologists complete case report forms capturing key benchmark clinical covariates (Disease Activity Score-28 (DAS-28), Clinical Disease Activity Index (CDAI), tender/swollen joints, comorbid conditions) and current/past RA medication history. The patients are concurrently followed at regular 6-month intervals by trained telephone interviewers who conduct 20-minute interviews on a variety of patient-reported outcomes (PROs) including patient quality of life (European Quality of Life (EQ5D-5L), work productivity, sleep quality, fatigue), functional status (Health Assessment Questionnaire (HAQ), Rheumatoid Arthritis Disease Activity Index [RADAI]), demographics (health insurance coverage, household annual income, rural residential status), and current medications.

At study enrolment, patients can consent to link their data to Ontario's Provincial Repository of health data, held at ICES. These RA cases were linked directly (deterministic linkage), using their unique Ontario Health Insurance Plan (OHIP) number, to ICES healthcare records.

ICES is an independent, not-for-profit research institute whose legal status under Ontario's health information privacy law allows them to collect and analyse administrative health-related data without requiring patient consent. Records of publicly funded health care for all residents with OHIP coverage are captured in the ICES databases. The following ICES databases were used: Discharge Abstract Database (DAD), Same Day Surgery (SDS), National Ambulatory Care Reporting System (NACRS) for emergency department visits, Ontario Laboratory Information System (OLIS) for lab results, OHIP for physician billings (diagnostic and fee codes), and the Registered Persons Database (RPDB), a population registry of vital statistics (Supplementary Table S1). DAD was also used to identify patients who admitted into ICU or went under ventilation (Suppl. Table S2).

Statistical analysis

Descriptive statistics, specifically mean and standard deviation (SD) for continuous variables and counts and proportions for categorical variables, were generated for all baseline characteristics, including sociodemographics and medication use. Comparisons between RA patients with and without COVID-19 were conducted using the independent-samples t-test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Multivariable logistic regression models were also used to assess the association between covariates and the risk of COVID-19 infection and related hospitalisation. We set the COVID-19 pandemic date as baseline for our cross-sectional study. This study included disease activity, comorbidities, and PROs data collected within two years prior to and three months following baseline. For treatment records, patients were assumed to be on treatment if there were no stop records during this time window. We employed multivariable Cox regression models to investigate the association between clinical disease activity, PROs, comorbidity, and RA medications with all-cause mortality, both overall and specifically before and during the COVID-19 pandemic. For all-cause mortality analysis, baseline was defined as the OBRI enrolment date. Patients' characteristics were measured within ± 60 days of enrolment.

A p-value of <0.05 was considered statistically significant. In accordance with ICES data privacy policies, cell sizes ≤5 individuals were not reported (NR). Statistical Analysis Software (SAS v. 9.4) was used for all analyses.

Results

Baseline characteristics

Among 2,969 patients with RA, we identified 596 patients diagnosed with COV-

Table I. Characteristics of RA patients and their association with risk of COVID-19 infection.

	Variable value n=2,669	RA with COVID-19 n=596	RA without COVID-19 n=2,373	Multivariable regression odds ratio (95% CI) n=2,551 (COVID-19 n=526)
Sex at enrolment	Female - n (%)	488 (81.9%)	1816 (76.5%)	**1.30 (1.01-1.66)**
Age group at enrolment, years	Missing data-n (%)	<6	<6	-
	<30 - n (%)	24 (4.0%)	54 (2.3%)	**2.01 (1.14-3.54)**
	30-40 - n (%)	45 (7.6%)	122 (5.2%)	**1.55 (1.02-2.35)**
	40-50 - n (%)	110 (18.5%)	345 (14.6%)	1.29 (0.96-1.74)
	50-60 - n (%)	157 (26.3%)	681 (28.7%)	Ref
	60-70 - n (%)	167 (28.0%)	702 (29.6%)	1.04 (0.81-1.35)
	70-80 - n (%)	79 (13.3%)	384 (16.2%)	0.94 (0.68-1.29)
	>80 - n (%)	14 (2.4%)	81 (3.4%)	0.97 (0.52-1.83)
Education at enrolment	Missing data-n (%)	70 (11.7%)	340 (14.3%)	-
	Post-secondary	311 (59.1%)	1130 (55.6%)	1.06 (0.86-1.29)
Disease duration at enrolment, years	Mean (SD)	8.0 (9.1)	7.9 (9.6)	1.00 (0.99-1.01)
	Missing data - n (%)	<6	<6	-
Positive RF at enrolment	Missing data - n (%)	<6	8 (0.34%)	-
	Yes - n (%)	554 (93.0%)	2219 (93.8%)	0.89 (0.61-1.31)
Biologic agent use	n (%)	313 (52.5%)	1093 (46.1%)	**1.28 (1.04-1.57)**
JAKi use	n (%)	80 (13.4%)	225 (9.5%)	**1.44 (1.08-1.93)**
csDMARD use	n (%)	570 (95.6%)	2267 (95.5%)	1.15 (0.72-1.83)
Oral steroid use	n (%)	192 (32.2%)	742 (31.3%)	1.01 (0.81-1.24)

RA: rheumatoid arthritis; RF: rheumatoid factor; JAKi: Janus kinase inhibitors; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

ID-19 infection (20.1%), either through a positive test (n=331; 11.2%) or from a record in OHIP (n=371;12.5%).

Compared to RA patients without COVID-19, those with COVID-19 had similar disease duration (8.0 *vs*. 7.9 years) and prevalence of positive rheumatoid factor (93.0% *vs*. 93.8%). However, differences were observed in terms of sex, age, and treatment. Females were significantly more likely to have COVID-19 infection (81.9% *vs*. 76.5%). There was a difference in the ages of patients with and without COVID-19 infection: Among patients with COVID-19, 4.03% were under 30 years old, 7.6% were 30–40 years old, and 18.5% were 40–50 years old. In comparison, 2.28% of patients without COVID-19 were under 30 years old, 5.2% were 30–40 years old, and 14.6% were 40–50 years old. These associations remained statistically significant after applying multivariable logistic regression models [Female: adjORs=1.30; 95%CI: 1.01–1.66); age under 30 years adjORs=2.01; 95%CI: 1.14–3.54); age 30–40 years: adjORs=1.55; 95%CI: 1.02–2.35)] (Table I).

Patients with COVID-19 infection were statistically more likely to use biologic agents (52.5% *vs*. 46.1%) and JAKi (13.4% *vs*. 9.5%). The association between using biologic agents (adjORs=1.28; 95%CI: 1.04–1.57) and JAK inhibitors (adjORs=1.44; 95%CI: 1.08–1.93) remained significant after adjusting for other covariates (Table I).

Table II. Hospitalisation and ED visit in patients with COVID-19 infection.

	COVID-19 infection n=596
Any ED visit or hospitalisation, n (%)	**108 (8.1%)**
ED visits, n (%)	**36** (6.0%)
Hospitalisation, n (%)	**33** (5.5%)
Both ED visits and hospitalisation, n (%)	39 (6.5%)
ICU admission (with or without ventilation), n (%)	24 (4.0%)

ED: emergency department; ICU: intensive care unit.

Hospitalisation and ED visits

Out of 596 patients with COVID-19 infection, 108 (18.1%) had a record of ED visit (n=36; 6.04%) or hospitalisation (n=33; 5.53%), or both (n=39; 6.54%). Twenty-four patients were admitted to ICU with or without ventilation (4.03%) (Table II). Except for disease duration (adjORs=1.02; 95%CI: 1.00-1.24), there were no significant associations between patients' characteristics and medication profiles and increased risk of COVID-19 infection-related hospitalisation after applying the multivariable logistic regression analysis (Suppl. Table S3).

All-cause mortality in RA patients

Table III shows baseline characteristics of RA patients with and without death events during follow-up. During the mean 115-month follow-up period, 531

Table III. Baseline characteristics of RA patients with and without death event (± 60 days of OBRI enrolment).

Number of patients 2,969	Variable value	RA without death n=2,438	RA with death n=531	*p*-value
Sex	Female - n (%)	1,938 (79.5%)	366 (68.9%)	**<0.0001**
Age group, years	Missing data - n (%)	<6	<6	
	<30 - n (%)	72-75	<6	**<0.0001**
	30-40 - n (%)	159-163	<6	
	40-50 - n (%)	437 (18.0%)	18 (3.4%)	
	50-60 - n (%)	769 (31.6%)	69 (13.0%)	
	60-70 - n (%)	690 (28.4%)	179 (33.7%)	
	70-80 - n (%)	264 (10.9%)	199 (37.5%)	
	>80 - n (%)	33 (1.4%)	62 (11.7%)	
Education	Missing data-n (%)	297 (12.2%)	113 (21.0%)	
	Post-secondary	1,259 (58.8%)	182 (43.5%)	**<0.0001**
Marital status	Married - n (%)	1,518 (62.3%)	263 (49.5%)	**<0.0001**
Health insurance coverage	Missing data - n (%)	289 (11.9%)	66 (12.4%)	
	Private & public - n (%)	1,491 (69.4%)	256 (55.1%)	**<0.0001**
Smoking status	Missing data - n (%)	286 (11.7%)	66 (12.4%)	
	Past/current - n (%)	1,119 (52.0%)	314 (67.5%)	**<0.0001**
Disease activity profile				
Disease duration, years	Mean (SD)	7.4 (9.1)	9.91 (11.0)	**<0.0001**
	Missing data - n (%)	<6	<6	
Positive RF	Missing data - n (%)	7 (0.3%)	<6	
	Yes - n (%)	2282 (93.9%)	491 (92.6%)	0.2930
ESR	Mean (SD)	22.1 (20.6)	29.8 (22.8)	**<0.0001**
	Missing data (%)	365 (15.0%)	64 (12.1%)	
CRP (mg/L)	Mean (SD)	11.9 (23.4)	16.2 (30.1)	**0.0013**
	Missing data (%)	533 (21.8%)	107 (20.1%)	
CDAI (0-76)	Mean (SD)	20.1 (13.5)	21.8 (14.0)	**0.0124**
	Missing data (%)	293 (12.0%)	59 (11.1%)	
Patient-reported outcomes profile				
HAQ-DI (0-3)	Mean (SD)	1.09 (0.74)	1.42 (0.76)	**<0.0001**
	Missing data (%)	280 (11.4%)	66 (12.4%)	
Fatigue (0-10)	Mean (SD)	4.76 (3.09)	5.16 (3.19)	**0.0106**
	Missing data (%)	284 (11.6%)	67 (12.6%)	
HAQ-pain (0-3)	Mean (SD)	1.38 (0.85)	1.53 (0.87)	**0.0006**
	Missing data (%)	281 (11.5%)	66 (12.4%)	
Medication profile				
Biologic agent use	n (%)	1,168 (47.9%)	238 (44.8%)	0.1967
Biologic+csDMARDs	n (%)	1,076 (44.1%)	216 (40.7%)	0.1454
JAKi use	n (%)	274 (11.2%)	31 (10.2%)	**0.0002**
JAKi+csDMARDs	n (%)	264 (10.8%)	29 (5.46%)	**0.0002**
csDMARD use	n (%)	2,332 (97.6%)	505 (97.9%)	0.6898
Oral steroids use	n (%)	709 (29.1%)	221 (41.6%)	**<0.0001**
Comorbidity profile				
Number of main comorbidities	Mean (SD)	1.17 (1.29)	2.00 (1.60)	**<0.0001**
	Missing data (%)	288 (11.8%)	65 (12.2%)	
Cardiovascular disease	Missing data (%)	362 (14.8%)	100 (18.8%)	
	n (%)	154 (7.4%)	103 (23.9%)	**<0.0001**
Hypertension	Missing data (%)	396 (16.2%)	109 (20.5%)	
	n (%)	578 (28.3%)	233 (55.2%)	**<0.0001**
Diabetes Mellitus	Missing data (%)	487 (20.0%)	177 (33.3%)	
	n (%)	134 (6.9%)	66 (18.6%)	**<0.0001**
Lung diseases	Missing data (%)	492 (20.1%)	177 (33.3%)	
	n (%)	149 (7.7%)	80 (22.6%)	**<0.0001**
Cancer disease	Missing data (%)	362 (14.8%)	100 (18.8%)	
	n (%)	154 (7.4%)	103 (23.9%)	**<0.0001**
Depression disease	Missing data (%)	472 (19.4%)	182 (34.2%)	
	n (%)	265 (13.5%)	72(20.6%)	**0.0005**

RA: rheumatoid arthritis; RF: rheumatoid factor; CDAI: Clinical Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index; JAKi: Janus kinase inhibitors; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

(17.9%) out of 2,969 RA patients died. Compared to the group without death, the proportion of females (68.9% *vs*. 79.5%), individuals aged 30–40 years (0.56% vs. 6.70%), 40–50 years (3.4% *vs*. 18.0%), and 50–60 years (13.0% *vs*. 31.6%) was lower in the death group. Similarly, the percentage of individuals with post-secondary education (43.5% *vs*. 58.8%), married individuals (49.5% *vs*. 62.3%), and those with private health insurance (55.1% *vs*. 69.4%) was significantly lower among patients who experienced death compared to those who did not.

In contrast, patients who were current or past smokers (67.5% *vs*. 52.0%), had longer disease duration (mean 9.91 *vs*. 7.4 years), higher ESR (mean 29.8 *vs*. 22.1), CRP (mean 30.1 *vs*. 23.4), and CDAI (mean 21.8 *vs*. 20.1) had an increased mortality. Similar results were observed for PROs. The mean of HAQ-DI, fatigue, and HAQ-pain at baseline were higher in patients who experienced death event (Table III).

As expected, the mean comorbidity score and the proportion of individual comorbidities were higher in the group that experienced death event. For example, the death event was 3.2 times higher in patients with cardiovascular disease (23.9% *vs*. 7.4%) and 2.7 times higher in patients with diabetes mellitus (18.6% *vs*. 6.9%). Patients who were on JAKi in combination with csDMARDs were less likely to have a death event (5.46% *vs*. 10.8%). Conversely, patients who used oral steroids were more likely to die (41.6% *vs*. 29.1%).

Table IV shows the association between clinical disease activity, PROs, comorbidity, RA medications and death event, overall and by the COVID-19 pandemic (before and after 17 March 2020), using a multivariable Cox regression analysis. Overall, the death event was increased in patients older than 60 years compared to patients aged 50-60 years. Similarly, past or current smoking (adj HRs: 1.95; 95% CI: 1.51–2.52), longer disease duration (adj HRs: 1.01; 95% CI: 1.00–1.03), higher DAS28-ESR (adj HRs: 1.10; 95% CI: 1.01–1.19), higher comorbidity number (adj HRs: 1.17; 95% CI: 1.08–1.26), and use of oral steroids (adj HR: 1.32; 95% CI:

Table IV. The association between sociodemographic, clinical, and treatment profile and death, multivariable Cox regression analysis overall and by COVID-19 pandemic.

		COVID-19 pandemic March 17th 2020		
		Before n=1,583 (death event=284)	**After** n=319 (death event=26)	**Total** n=1,902 (death event=310)
		HRs (95% CI)	HRs (95% CI)	
Sex	Female - n (%)	**0.54 (0.41-0.72)**	1.20 (0.38-3.82)	**0.56 (0.43-0.73)**
Age group, years	<30 - n (%)	n/a	n/a	n/a
	30-40 - n (%)	0.36 (0.09-1.51)	n/a	0.36 (0.09-1.51)
	40-50 - n (%)	0.39 (0.19-0.80)	n/a	**0.40 (0.20 -0.82)**
	50-60 - n (%)	Ref	Ref	Ref
	60-70 - n (%)	**2.12 (1.46-3.08)**	**11.7 (1.32-103)**	**2.25 (1.57-3.24)**
	70-80 - n (%)	**5.84 (4.01-8.51)**	**38.0 (3.91-368)**	**6.13 (4.25-8.85)**
	>80 - n (%)	**10.9 (6.49-18.2)**	**1031 (63.9-16649)**	**13.2 (8.06-21.7)**
Education	Post-secondary	0.93 (0.73-1.18)	**0.38 (0.15-1.00)**	0.87 (0.69-1.10)
Marital status	Married	0.82 (0.63-1.06)	1.58 (0.55-4.54)	0.86 (0.67-1.10)
Health insurance coverage	Private & public - n (%)	1.00 (0.78-1.29)	0.93 (0.35-2.47)	1.01 (0.79-1.28)
Smoking status	Past/current - n (%)	**1.85 (1.41-2.42)**	**4.99 (1.72-14.5)**	**1.95 (1.51-2.52)**
Disease activity profile				
Disease duration, years		**1.02 (1.00-1.03)**	1.00 (0.95-1.05)	**1.01 (1.00-1.03)**
DAS28-ESR		**1.09 (1.00-1.18)**	**1.46 (1.06-2.01)**	**1.10 (1.01-1.19)**
Patient-reported outcomes profile				
HAQ-DI (0-3)		1.25 (0.99-1.18)	0.78 (0.31-2.00)	1.23 (0.98-1.54)
Fatigue (0-10)		1.25 (0.99-1.58)	1.19 (0.97-1.45)	0.99 (0.95-1.04)
HAQ-pain (0-3)		1.00 (0.83-1.21)	0.54 (0.23-1.28)	0.98 (0.82-1.18)
Biologic agent use		1.28 (0.98-1.66)	0.84 (0.27-2.57)	-
JAKi use		**0.55 (0.34-0.91)**	0.33 (0.07-1.51)	**0.53 (0.33-0.84)**
csDMARD use		0.61 (0.26-1.41)	n/a	0.71 (0.31-1.63)
Oral steroid use		1.23 (0.95-1.59)	**6.38 (2.23—18.2)**	**1.32 (1.03--1.67)**
Number of main comorbidities		**1.16 (1.07-1.26)**	1.02 (0.78-1.34)	**1.17 (1.08-1.26)**

DAS28-ESR: Disease Activity Score 28-Erythrocyte Sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; JAKi: Janus kinase inhibitors; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

1.03–1.67) were significantly associated with increased death event. Conversely, female patients (adj HRs: 0.56; 95% CI: 0.43–0.73), post-secondary educated patients (adj HRs: 0.38; 95% CI: 0.15–1.00), and those on JAKi (adj HRs: 0.53; 95% CI: 0.33–0.84) were significantly associated with lower number of death (Table IV).

When we split the cohort into before and after the COVID-19 pandemic, similar findings were found for the association of co-variates mentioned above and death event during the COVID-19 pandemic (Table IV). Although the number of patients who enrolled in the OBRI after COVID-19 pandemic was small, the death event was also increased in patients older than 60 years, current or past smokers (adj HRs: 4.99; 95% CI: 1.72–14.5), those with higher DAS28-ESR (adj HRs: 1.46; 95% CI: 1.06–2.01), and those who used oral steroids (adj HRs: 6.38; 95% CI: 2.23–18.2) (Table IV). Having post-secondary education was also significantly associated with a lower number of deaths during the COVID-19 pandemic (adj HRs: 0.38; 95% CI: 0.15–1.00).

Discussion

In this study, we examined the prevalence of COVID-19 infection and evaluated the impact of rheumatoid arthritis (RA) treatment and baseline characteristics on mortality among RA patients, using OBRI clinical data linked to provincial administrative healthcare records. We found that 20% of adult RA patients were infected by COVID-19 between Jan 1st 2020, and Mar 31st 2022, and 18% of infected patients were hospitalised or had visited the emergency department. There was a significant positive association between the likelihood of having COVID-19 infection and being female, under 40 years old, using biologic agents or JAKi's.

According to a recent meta-analysis, the pooled prevalence of COVID-19 in RA was reported as 11% (95% CI 6–17%), based on 36 studies from all over the world (18). This pooled prevalence is less than our result of 20%, although many studies included in the meta-analysis found similar results as ours, and there was high heterogeneity across the

studies. The differences are likely to be due to the country where the study was conducted and how severe the pandemic was in that region, the study design, how COVID-19 infection is defined, and the timing of the study. Therefore, to understand whether RA increases the risk of COVID-19, a comparison with the whole population in the same region and period is required. Although this was not our intention, and not included in our study design, the prevalence of COVID-19 in the same region (Ontario) was separately reported for similar dates (Jan 1st 2020 to Dec 31st 2021), using the same ICES database: The general population in Ontario was found to have a prevalence of 11.5% for COVID-19, when using a positive test as the description for COVID-19 infection (19). In our study, the prevalence of the positive test was also 11.2%, suggesting similar risk in RA and a non-RA population in Ontario. Another study also found a similar positive COVID-19 test proportion in patients with immune-mediated inflammatory disease (IMID) *versus* the general population in Ontario (20).

The same meta-analysis found a pooled prevalence of 29% for hospitalisation, which was lower for our patients (18%) (18). Interestingly, the factors that led to increased risk of infection, including treatment with biologics, were not associated with the risk of hospitalisation. Other studies also did not identify a significant link between immunomodulatory treatments and an increased risk of COVID-19 severity, including hospitalisation, ICU admission, and mechanical ventilation (14, 21).

The same observation continued for the mortality, with no association between treatment with biologics and death. One potential explanation for our paradoxical observation (increased risk of infection, but not hospitalisation or mortality) may be due to the effect of biologic medications on RA patients' independence. These medications allow patients to better maintain their social lives and work activities, thereby increasing their risk of exposure to infections, including COVID-19, without affecting the severity of the disease.

While it is reassuring that these treatments do not increase the risk of severe infection or mortality, COVID-19 has numerous long-term effects that can significantly impact patients' lives, including long COVID, which should not be underestimated.

Understanding the impact of JAKi's on RA during the COVID-19 infection is complicated due to several intervening factors: 1. Higher disease activity is associated with increased risk of COVID-19 and its severity. Therefore, by reducing inflammation, JAKi's would likely reduce the risk; 2). Increased risk of thrombosis is a major concern with the JAKi's, which is also a shared concern with COVID-19 infections. JAKi's might further increase the risk of thrombosis during the infection; 3. JAKi's are effective in reducing the severe lung involvement in COVID19, therefore commonly implemented in COVID treatments globally. It is possible that RA patients who were on JAKi's did not develop severe COVID-19 pneumonia, even if they had the infection. Due to all these factors that are likely to play a role at the same time, the impact of JAKi's on RA outcomes during the COVID-19 pandemic has controversial results. The data from the TriNetX database showed that RA patients using JAKi had a significant risk for hospitalisation (HR: 1.19, 95% CI: 1.00–1.42), mortality (HR: 1.44, 95% CI: 1.05–1.98) and composite adverse outcomes (HR: 1.24, 95% CI: 1.05–1.47) compared with TNFi users (22). The data from the COVID-19 Global Rheumatology Alliance physician-reported registry did not find any association (23). In our study, we found an opposite association: the death event was lower for patients who were on JAKi's. In addition to the potential reasons listed above, it is difficult to control for inevitable selection bias within and across registries, in which patients who have higher risk are less likely to initiate a JAKi therapy after the publication of the ORAL surveillance trial results (24). Therefore, there may be major differences between patient profiles across registries with respect to specific therapies, despite similarities on a group level. Our observation supported better outcomes with JAKi's; however, it is impossible to conclude causality due to the study design.

One striking observation is that private health insurance is significantly linked to reduced mortality (55.1% having private insurance among non-survivors *vs*. 69.4% in survivors). The health care system is free of charge in Ontario, and all patients have equal access to physicians and hospitals. However, access to medications is not included in the public health care coverage and is likely more accessible to patients with private insurance. This is not only important for access to RA medications but also for the treatment of all the other comorbidities patients face. Our data also found that, understandably, having multiple comorbidities was a risk factor for increased mortality. We wonder whether having private insurance or not resulted in the comorbidities being inadequately treated due to limited access to drugs. Our data do not allow further characterisation of the problems or causes but certainly raises a concern on equity in patient care and deserves further research.

Increasingly, it is recognised that comorbidities or multimorbidity negatively impact RA patients' outcomes and survival. A holistic approach for our patients is essential, and the only way to optimise patient care.

There are some limitations in our study. Misclassification of some RA patients may have affected the association between RA diagnosis and study outcomes. There is also a potential risk of unmeasured and residual confounders in this observational study. We assume that the impact of misclassification would be small as we used the Ontario Rheumatoid Arthritis database (ORAD) to validate RA patients enrolled in the OBRI. The ORAD has been created using a validated algorithm (25). In the cross-sectional analysis, we could not adjust for disease activity, comorbidities, and PROs as covariates due to a high proportion of missing data for these variables. Including these variables with missing data in the analysis may have reduced the statistical power. Therefore, the interpretation of these results, particularly the findings related to sex and age in COVID-19 infection, in comparison to previous studies, remains open to discussion.

A strength of this study is that we incorporated data from both administrative databases and our clinical registry to account for the influence of clinical characteristics and medication profiles on COVID-19 infection and all-cause mortality.

In conclusion, using Ontario population-based health administrative databases, we found that 20% of adult RA patients were infected by COVID-19 and 18% of these infected patients were hospitalised or visited the emergency department. Compared to pre-COVID-19 pandemic, increased risk of all-cause mortality was stronger in patients who used oral steroid therapies, were smokers, and had higher disease activity during COVID-19 pandemic period, but not biologic therapies or JAKi's. The impact of comorbidities on mortality and finding that patients with private insurance had increased survival is another indication that patients should be approached as a whole, and not just for their RA.

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