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Omicron variant infection in inflammatory rheumatological conditions – outcomes from a COVID-19 naive population in Aotearoa New Zealand

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Summary

Background Due to geographic isolation and border controls Aotearoa New Zealand (AoNZ) attained high levels of population coronavirus disease-19 (COVID-19) vaccination before widespread transmission of COVID-19. We describe outcomes of SARS-CoV-2 infection (Omicron variant) in people with inflammatory rheumatic diseases in this unique setting.

Methods This observational study included people with inflammatory rheumatic disease and SARS-CoV-2 infection in AoNZ between 1 February and 30 April 2022. Data were collected via the Global Rheumatology Alliance Registry including demographic and rheumatic disease characteristics, and COVID-19 vaccination status and outcomes. Multivariable logistic regression was used to explore associations of demographic and clinical factors with COVID-19 hospitalisation and death.

Findings Of the 1599 cases included, 96% were from three hospitals that systematically identified people with inflammatory rheumatic disease and COVID-19. At time of COVID-19, 1513 cases (94.6%) had received at least two COVID-19 vaccinations. Hospitalisation occurred for 104 (6.5%) cases and 10 (0.6%) patients died. Lower frequency of hospitalisation was seen in cases who had received at least two vaccinations (5.9%), compared to the unvaccinated (20.6%) or those with a single vaccine dose (10.7%). In multivariable adjusted models, people with gout or connective tissue diseases (CTD) had increased risk of the combined outcome of hospitalisation/death, compared to people with inflammatory arthritis. Glucocorticoid and rituximab use were associated with increased rates of hospitalisation/death. All patients who died had three or more co-morbidities or were over 60 years old.

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Interpretation In this cohort with inflammatory rheumatic diseases and high vaccination rates, severe outcomes from SARS-CoV-2 Omicron variant were relatively infrequent. The outcome of Omicron variant infection among vaccinated but SARS-CoV-2 infection-naive people with inflammatory rheumatic disease without other known risk factors were favourable.

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Keywords: COVID-19; SARS-CoV-2; Outcomes; Rheumatic disease

Research in context

Evidence before this study

As the SARS-CoV-2 virus evolves there is a need for ongoing reporting of data on outcomes for people with rheumatic diseases. Studies from early in the pandemic found people with inflammatory rheumatic diseases had higher risk of poor outcomes from COVID-19, particularly people using >10 mg/day of prednisone or B-cell depleting therapy. Infections with current SARS CoV-2 variants, such as Omicron, have severe disease less frequently, with lower proportions of patients requiring hospitalisation/ventilation and lower mortality. Additionally, availability of therapies with supporting evidence for benefit in treating SARS COVID-19 and effective vaccination programs have further reduced the severity of COVID-19 in the general population. The outcomes of COVID-19 for people with rheumatic diseases with limited exposure to previous SARS-CoV-2 variants have not been extensively reported, and in particular in a highly vaccinated cohort. We wished to identify research reporting outcomes of SARS-CoV-2 Omicron-variant infection in people with inflammatory rheumatic disease, particularly where vaccination rates are reported. We searched PubMed and medRxiv for research articles published between January 2020 and 31 January 2023 using the following terms: (COVID-19 OR SARS-CoV-2) AND (Omicron or B.1.1.529) AND (Rheumatic) and identified 38 studies. Of these, four were relevant to our study. The populations in these studies all had relatively high vaccination rates, however none of the groups had limited exposure to prior COVID-19 waves, or clearly reported repeat or naive infections.

Added value of this study

In this study we reported a well described cohort of patients with SARS-CoV-2 Omicron variant infection, not exposed to earlier COVID-19 waves. As a result of national electronic documents and regional patient databases we were able to identify vaccination number, date, patient demographics, details on rheumatic disease treatment, COVID-19 therapies and outcomes with low rates of missing data. Overall, hospitalisation and death rates were low in our study cohort at 6.5% and 0.6% respectively. We identified lower rates of poor outcomes in those who had been vaccinated and higher co-morbidity burden in those who died. We found that amongst different rheumatic categories people with Connective tissue diseases or Gout had higher risk of poor outcomes than people with inflammatory arthritis. Like previous studies we report that rituximab and prednisone >10 mg/day are risk factors for hospitalisation/death, but additionally have identified that prednisone use <10 mg/day also appears to be a significant risk factor.

Implications of all the available evidence

Our findings show that in patients with inflammatory rheumatic diseases, the overall rate of hospitalisation and death from Omicron infection is low. Important risk factors for poor outcome remain with rituximab use, prednisone at doses both above and below 10 mg and co-morbidity burden all being significant. We have also shown the benefit of vaccination with reduced rates of hospitalisation in those who had completed their primary vaccinations. We believe our findings will help clinicians and patients by providing data on outcomes from the Omicron phase of COVID-19, of particular relevance to people with rheumatic disease who have avoided SARS-CoV-2 infection to date, for example by shielding. Our research provides data to inform and assist decisions around medication use, vaccination and risk with current SARS-Cov-2 variants for people with inflammatory rheumatic conditions.

Introduction

Aotearoa New Zealand (AoNZ) has been in a unique position throughout the coronavirus disease-19 (COVID-19) pandemic due to its geographical isolation and public health response. From March 2020, the AoNZ government adopted a COVID-19 elimination strategy, which largely prevented significant community spread in 2020 and 2021.[1] A comprehensive vaccination programme using the Pfizer mRNA vaccine started with border workers and healthcare workers in February 2021 and was extended to people with inflammatory rheumatic disease after July 2021.[2] From October 2021,

a third primary vaccination was offered to people using immunomodulatory and immunosuppressive medications and further booster vaccines were offered after November 2021. By February 2022, 91.5% people aged over 18 years of age had completed the primary vaccination series, and 73% had received booster doses.[2] After late January 2022 community transmission of the Omicron (B.1.1.529) variant of COVID-19 started to occur in AoNZ.[3]

Data from the initial waves of the COVID-19 pandemic show that people with inflammatory rheumatic disease have increased risk of SARS-CoV-2 infection and of severe outcomes.[4] Factors associated with increased risk of severe outcomes included those found in the general population, such as increased age and comorbidities, and disease specific factors such as high disease activity, use of glucocorticoids, and other medications, including sulfasalazine and rituximab.[4–6] Recent data have shown that the rate of poor outcomes due to COVID-19 for people with rheumatic disease were highest during early COVID-19 waves, with the proportion of hospitalisation and death decreasing after widespread access to effective treatments for COVID-19 became available, vaccination rates increased, and new variants such as Omicron emerged.[7,8] An analysis from the United States reported lower hospitalisation rates and reduced mortality by 70% for the Omicron variant wave (December 2021–January 2022) compared to the initial COVID-19 outbreak (March–June 2020).[7] A Dutch prospective study also reports lower rates of hospitalisation for people with immune-mediated inflammatory disease and COVID-19 during the Omicron wave.[9] These study populations had variable rates of COVID-19 vaccination and SARS-CoV-2 re-infections. The outcomes from COVID-19 in populations not exposed to early COVID-19 variants and in populations with high levels of effective vaccination remains unclear.

This study reports outcomes of SARS-CoV-2 Omicron variant in early 2022 in people with inflammatory rheumatic conditions in AoNZ. This population had high rates of SARS-CoV-2 vaccination and virtually no exposure to earlier variants, with a rolling total of just over 12,000 confirmed cases in AoNZ by December 2021, prior to widespread community transmission of the Omicron variant.[10] The AoNZ health system allocates every New Zealander a national health identifier (NHI) at birth, against which all medical data is recorded including vaccination and the required centralised reporting of SARS-CoV-2 infections. This enabled identification of all people attending hospital rheumatology clinics who also had a SARS-CoV-2 infection reported during this period. The combination of this unique population with national medical data infrastructure allowed us to study the outcomes of SARS-CoV-2 Omicron-variant in people with rheumatic diseases in AoNZ.

Methods

Study design and participants

This retrospective observational study included people with inflammatory rheumatic disease in six government funded secondary care services (hospitals) in AoNZ. In 2022, New Zealanders were able to collect COVID-19 rapid antigen test (RAT) for self-testing free of charge and were required to test if experiencing symptoms of COVID-19. Positive RATs were self-reported to the AoNZ Ministry of Health via an app or website which linked the positive RAT to the person's NHI. COVID-19 testing with polymerase chain reaction (PCR) occurred with presentation to primary care (RAT were also utilised in primary care) or if presenting to hospital, and these results were also reported to the AoNZ Ministry of Health and linked to the patient's NHI.

People were included if they were aged 18 years or over, and had an inflammatory rheumatic disease including inflammatory joint disease, gout, connective tissue disease, vasculitis or other (e.g., sarcoidosis). People attending rheumatology clinics with non-inflammatory conditions such as osteoarthritis, fibromyalgia, or regional soft-tissue conditions were excluded.

At four hospitals, data analysts provided the NHIs of people who had attended an outpatient rheumatology clinic in the previous 24 months and had COVID-19 recorded between 1 February 2022 and 30 April 2022. In addition, ad hoc case ascertainment could be made when people with rheumatic disease who had not attended the hospital clinics, presented to the hospital with recorded COVID-19 in the data collection period. At the two other centres cases were only identified in an ad-hoc manner by clinic staff.

Ethical approval for the study was obtained from University of Otago (HD20/028) with locality approval also obtained at each hospital site. Patient consent was deemed not required for this anonymous reporting of data.

Procedures

Data were identified from the hospital electronic medical record (clinical letters, admission and discharge documents, laboratory records) and entered directly into the COVID-19 Global Rheumatology Alliance (C19-GRA) physician-reported registry global entry system (University of California, San Francisco) by a rheumatologist or under supervision of a rheumatologist. This data collection process has been previously described in detail.[5,11] NHI number also includes record of death which is updated on a monthly basis ensuring full capture of deaths, as data collection was at minimum 1 month after study time period.

Case characteristics included age, sex at birth, ethnicity, comorbidities, and smoking status. Rheumatic inflammatory disease diagnosis, physician determined disease activity at last clinic visit, and disease

modifying anti-rheumatic drugs (DMARDs) and glucocorticoid dose were recorded. Rheumatic conditions were separated into three categories "Inflammatory arthritis" (Rheumatoid arthritis, idiopathic arthritis, spondyloarthritis, psoriatic arthritis, and other inflammatory arthritis); "Gout"; "Connective tissue disease and other" (systemic lupus erythematosus (SLE), mixed CTD, undifferentiated CTD, systemic sclerosis, Sjogren's syndrome, ANCA-associated vasculitis, other vasculitis, polymyalgia rheumatica, anti-phospholipid syndrome and inflammatory myopathy). The dates and formulation of COVID-19 vaccination were recorded. Features of SARS-CoV-2 infection including date, treatments, COVID-19 outcomes including death, hospitalisation, level of care required, and other serious events were collected through admission and discharge documents, as well as death records for those not hospitalised.

Outcomes

The primary outcome was hospitalisation with or from COVID-19 or COVID-19 related death. Using multivariable regression analysis, we assess which factors (patient demographics, clinical characteristics, medications) were associated with it.

Statistical analysis

Complete case analyses were performed. No cases were excluded due to missing data with unavailable data on smoking and glucocorticoid dosing categorised as "unknown". Continuous variables are reported as medians and interquartile ranges (IQRs). Categorical variables are reported as numbers and percentages. Univariable analysis was completed to evaluate differences in demographic and rheumatic disease according to hospitalisation/death status and were compared using either $\chi 2$ or Fisher's exact depending on cell frequencies.

The independent associations between patient factors and COVID-19 hospitalisation/death were estimated using univariable and multivariable logistic regression to report odds ratios (ORs) and 95% confidence intervals. We constructed adjusted multivariable logistic models, including all variables with significant effect estimates in univariable logistic regression analyses. Covariates included were age (continuous), sex (male vs female), rheumatic disease (inflammatory arthritis vs gout, connective tissue diseases (CTD)), common comorbidities vs without that comorbidity, smoking status (never vs ever vs unknown), vaccination status (full, partial, none), glucocorticoid use (none vs > 0 and < 10 mg, ≥10 mg day, unknown), DMARD use (csDMARD vs bDMARD ± csDMARD), rituximab use. Those with multiple rheumatic conditions were adjudicated so that each primary rheumatic diagnosis category was mutually exclusive (i.e., individuals who were coded as having both SLE and Sjogren's disease were adjudicated as having SLE). Interactions between covariates were not assessed in the multivariable analyses due to small sample size.

Data were considered statistically significant with a two-sided p value of less than 0.05. All analyses were conducted in Stata version 16.0 (StataCorp). Due to the method of data collection, we had little to no missingness within the dataset.

Role of the funding source

This study did not have an external sponsor.

Results

A total of 1599 people were included. The median age was 49 years and the majority of patients were female (n = 1085, 67.9%) (Table 1). New Zealand European and Pacific peoples made up the largest proportion of the study demographic with 42% (n = 671) and 27.3% (n = 436) respectively, 15.8% (n = 253) were Asian and 11.6% (n = 186) Māori, a further 2.9% (n = 46) "Other" and 7 had missing data. Most had a diagnosis of an inflammatory arthritis (n = 1128, 70.5%), with a CTD in 304 patients (19%) and gout in 167 (10%). Over half (n = 905, 56.6%) of cases had no comorbidities. In the cases with comorbidities the commonest were obesity (36.8%), cardiovascular disease and/or hypertension (28.1%), and diabetes (13.1%). The most common treatment was conventional synthetic DMARD (csDMARD) monotherapy (n = 866, 54.2%), followed by biologic therapy alone or in combination with csDMARD (n = 272, 17.1%). Glucocorticoid therapy was used in 238 patients (14.9%) with 11.1% on prednisone-equivalent <10 mg/day and 3.8% on >/ = 10 mg/day. Rituximab had been used in 31 patients (1.9%). The Pfizer mRNA vaccine was used in 1547 (96.8%) of patients. At the time of SARS-CoV-2 infection 379 people had received two vaccine doses, 1015 three doses and 119 four doses. Overall, 1513 cases (94.6%) had received at least two COVID-19 vaccinations at least 14 days prior to the onset of COVID-19. Only 58 patients (3.6%) were unvaccinated and 28 (1.8%) had 1 vaccine dose.

Three hospitals in Te Ika-a-Māui (the North Island) contributed 1537/1599 (96%) of the cohort. Proportions of patients admitted were; Middlemore Hospital 50/664 (7.5%), Auckland City Hospital 32/388 (8.2%), and Wellington/Hutt Hospitals 18/517 (3.5%) (Supplemental Table S1).

There were 104 people with COVID-19 hospitalisation (6.5%). The mean age of people hospitalised was higher (57 years ([IQR 44, 71] vs 49 years [IQR 38, 60]). The rate of hospitalisation by ethnic group was 4.9% for New Zealand European, 4.7% for Asian, 9% for Māori and 9.4% for Pacific peoples. The proportion of people using prednisone equivalent doses of >/ = 10 mg/day who were hospitalised was 16/60 (26.7%); among rituximab users, 6/31 (19.4%) were hospitalised. More

	All Participants (N = 1599)	Not hospitalised (N = 1495)	Hospitalised (N = 104)
	N (%)	N (%)	N (%)
Gender			
Female	1086 (67.9)	1007 (67.4)	79 (76.0)
Male	513 (32.1)	488 (32.6)	25 (24.0)
Age (years)			
18–29	170 (10.6)	157 (10.5)	13 (12.5)
30–49	644 (40.3)	622 (41.6)	22 (21.2)
50–65	522 (32.7)	489 (32.7)	33 (31.7)
>65	263 (16.5)	227 (15.2)	36 (34.6)
Median (IQR)	49 (38,61)	49 (3:60)	57 (44,71)
Ethnicity			
NZ European	671 (42.0)	638 (42.7)	33 (31.7)
Asian	253 (15.8)	241 (16.1)	12 (11.5)
Māori	186 (11.6)	169 (11.3)	17 (16.4)
Pacific peoples	436 (27.3)	395 (26.4)	41 (39.4)
Other	46 (2.9)	45 (3.0)	1 (1.0)
Missing	7 (0.4)	7 (0.5)	–
Most common rheumatic disease diagnoses[e]			
Inflammatory arthritis[b]	1128 (70.5)	1081 (72.3)	47 (45.2)
Gout	167 (10.4)	152 (10.2)	15 (14.4)
Connective Tissue Disease and Other[c]	304 (19.0)	262 (17.5)	42 (40.4)
No comorbidities	905 (56.6)	884 (59.1)	21 (20.2)
Most common comorbidities[a]			
Cancer	45 (2.8)	34 (2.3)	11 (10.6)
Cerebrovascular disease	46 (2.9)	36 (2.4)	10 (9.6)
COPD and/or asthma	173 (10.8)	153 (10.2)	20 (19.2)
CVD and/or Hypertension	449 (28.1)	391 (26.2)	58 (55.8)
Diabetes	210 (13.1)	177 (11.8)	33 (31.7)
Interstitial lung disease	4 (0.3)	4 (0.3)	0 (0.0)
Neurological and/or neuromuscular disease	1 (0.1)	1 (0.1)	0 (0.0)
Obesity	590 (36.8)	530 (35.5)	60 (57.7)
Renal disease	106 (6.6)	89 (6.0)	17 (16.4)
Number of comorbidities (Median, IQR)	0 (0,1)	0 (0:1)	1 (1:2)
Smoking Status			
Never	603 (37.7)	555 (37.1)	48 (46.2)
Ever	266 (16.6)	235 (15.7)	31 (29.8)
Unknown	730 (45.7)	705 (47.2)	25 (24.0)
Medication prior to COVID-19 diagnosis			
Glucocorticoids			
No glucocorticoids	1327 (83.0)	1267 (84.8)	60 (57.7)
Glucocorticoid-equivalent 1 mg to <10 mg	178 (11.1)	152 (10.2)	26 (25.0)
Glucocorticoid-equivalent >/ = 10 mg	60 (3.8)	44 (2.9)	16 (15.4)
Glucocorticoid-Equivalent Dose Unknown	34 (2.1)	32 (2.1)	2 (1.9)
csDMARD monotherapy	866 (54.2)	805 (53.9)	61 (58.7)
b/tsDMARD (monotherapy or in combination with csDMARD)	273 (17.1)	260 (17.4)	13 (12.5)
Rituximab (alone or in combination)	31 (1.9)	25 (1.7)	6 (5.8)
Vaccination at time of COVID-19 diagnosis			
None	58 (3.6)	46 (3.1)	12 (11.5)
1st vaccine dosage	28 (1.8)	25 (1.7)	3 (2.9)
2nd vaccine dosage	379 (23.7)	348 (23.3)	31 (29.8)
3rd vaccine dosage	1015 (63.5)	960 (64.2)	55 (52.9)
4th vaccine dosage	119 (7.4)	116 (7.8)	3 (2.9)
COVID-19 treatment[d]			
No treatment except supportive care	1490 (93.2)	1444 (96.6)	46 (44.2)
Remdesivir	25 (1.6)	1 (0.1)	24 (23.1)

(Table 1 continues on next page)

	All Participants (N = 1599)	Not hospitalised (N = 1495)	Hospitalised (N = 104)
	N (%)	N (%)	N (%)
(Continued from previous page)			
IL-6 inhibitors (e.g., tocilizumab, sarilumab, siltuximab)	4 (0.3)	0 (0.0)	4 (3.9)
JAK inhibitors (e.g., tofacitinib, baricitinib, upadacitinib, ruxolitinib)	2 (0.1)	0 (0.0)	2 (1.9)
Glucocorticoids	58 (3.6)	20 (1.3)	38 (36.5)
IVIG	1 (0.1)	0 (0.0)	1 (1.0)
Plasma from recovered patients	3 (0.2)	0 (0.0)	3 (2.9)
Azithromycin	1 (0.1)	0 (0.0)	1 (1.0)
Colchicine	1 (0.1)	0 (0.0)	1 (1.0)
Deceased	10 (0.6)	3 (0.2)	7 (6.7)

[a]These comorbidities were identified from electronic medical records as documented by hospital medical staff. In AoNZ noting obesity refers to a BMI = /> 30kg/m^2. [b]Inflammatory arthritis included the following: rheumatoid arthritis, idiopathic arthritis (both juvenile and systemic), spondyloarthritis (including axial spondyloarthritis, ankylosing spondylitis, reactive spondyloarthritis, and other spondyloarthritis), psoriatic arthritis, and other inflammatory arthritis. [c]Connective tissue disease and Other included the following: systemic lupus erythematosus, connective tissue disease (both mixed and undifferentiated), ANCA-associated vasculitis (e.g., GPA, EGPA), other vasculitis (including Kawasaki disease), Sjogren's syndrome, systemic sclerosis, Bechet's syndrome, giant cell arteritis, polymyalgia rheumatica, anti-phospholipid antibody syndrome, and inflammatory myopathy (e.g., dermatomyositis, polymyositis). [d]People may have received multiple treatments for COVID-19. [e]Those with multiple rheumatic conditions were adjudicated so that each primary rheumatic diagnosis category is mutually exclusive.

Table 1: **Demographic and clinical characteristics of people with rheumatic disease diagnosed with COVID-19, presented by all participants and by hospitalisation status.**

details on interventions among those hospitalised are included in Supplemental Table S2.

Of those hospitalised, 12/104 (11.5%) were unvaccinated and 3 people (3%) had received a single vaccine dose. A higher proportion of people who were unvaccinated were hospitalised 12/58 (20.6%) compared to single dose 3/28 (10.7%) and those with 2 or more vaccinations 89/1513 (5.9%). Of the 104 patients hospitalised with SARS-CoV-2 infection, 46 (44%) had supportive measures only. Of the hospitalised patients, 58 (56%) received specific treatment; this included glucocorticoids (n = 38), remdesivir (n = 24), IL-6 inhibitors (n = 4) or JAK inhibitors (n = 2). There were 20 non-hospitalised cases who had glucocorticoids dispensed at the time of SARS-CoV-2 infection, which could indicate treatment for COVID-19 or for a concomitant condition.

In unadjusted and adjusted logistic regression models, age and sex did not show any statistically significant association with the combined outcomes of hospitalisation and/or death (Table 2, Supplemental Table S3). Regarding ethnicity, using the adjusted regression model only Pacific peoples had a significant association with hospitalisation or death (OR 1.98 (95% CI 1.10, 3.68) p = 0.03) compared to the NZ European group. Māori had an increased adjusted OR of 1.78, but this did not reach statistical significance (95% CI 0.81, 3.89; p = 0.15). With inflammatory arthritis as the referent, both the diagnoses of gout (OR 2.3 (95% confidence interval (CI) 1.02, 4.77) p = 0.04) and connective tissue diseases (OR 2.78 (95% CI 1.61, 4.80) p = < 0.00) were associated with the combined outcome. Several comorbidities were associated with an increased odds of hospitalisation and/or death including cancer (adjusted OR 5.98 (95% CI 2.53, 14.2) p = 0.00), CVD and/or hypertension (adjusted OR 2.62 (95% CI 1.37, 5.03) p = 0.01) and diabetes (adjusted OR 2.18 (95% CI 1.27, 3.69) p = 0.01). The other comorbidities did not have an association with increased odds of severe outcomes.

Treatment with glucocorticoids with prednisone-equivalent >/ = 10 mg/day was associated with an increased odds of severe COVID-19 outcomes (adjusted OR 5.63 (95% CI 2.40, 13.19) p = < 0.00) with less strong associations with use of lower doses of glucocorticoids (prednisone-equivalent glucocorticoid <10 mg (OR 3.01 (95% CI 1.76, 5.13) p = < 0.00). Rituximab use was also associated with an increased likelihood of poor outcomes (OR 4.61 (95% CI 1.65, 12.85) p = < 0.01). Both csDMARD therapy and biologic or targeted DMARD therapy did not show any statistically significant association with hospitalisation and/or death.

There were 10 deaths with COVID-19 (10/1599, 0.6%) (Table 3). Most people who died were over 50 years of age (8/10), with five being over 70 years old. The two youngest patients who died had considerable comorbidity burden (3+) including end stage renal disease. One patient who died was unvaccinated with all the other patients who died having received at least two vaccine doses. COVID-19 treatment in patients who died included anti-IL-6 therapy with glucocorticoids (n = 1), and glucocorticoids either alone or in combination with other treatment (n = 5) for COVID-19, with the other patients having supportive treatment only.

Discussion

In this cohort of people with rheumatic disease who were highly vaccinated and COVID-naive, the outcomes of SARS-CoV-2 Omicron (B.1.1.529) variant infection were favourable with relatively low percentages of hospitalisation (6.5%), and mortality (0.6%). People with rheumatic disease who were vaccinated had lower rates of hospital admission and death than those who were not vaccinated. In our cohort a diagnosis of gout or

	Unadjusted OR (95% CI; N = 1599)	Multivariate Adjusted model[a]	
		Adjusted OR (95% CI; N = 1599[a]	Adjusted p-value[a]
Female	1.43 (0.91, 2.43)	1.78 (0.94, 3.39)	0.08
Age (years)	1.03 (1.02, 1.04)	1.01 (0.99, 1.03)	0.27
Most common rheumatic disease diagnoses[b]			
Inflammatory arthritis	Ref	Ref	Ref
Gout	2.13 (1.16, 3.88)	2.20 (1.02, 4.77)	0.04
Connective tissue disease and Other	3.46 (2.24, 5.32)	2.78 (1.61, 4.80)	<0.00
Ethnicity			
NZ European	Ref	Ref	Ref
Asian	0.93 (0.46, 1.90)	1.04 (0.48, 2.23)	0.92
Māori	2.01 (1.19, 3.38)	1.78 (0.81, 3.89)	0.15
Pacific peoples	2.00 (1.22, 2.27)	1.98 (1.10, 3.68)	0.03
Other/Missing	0.36 (0.05, 2.77)	0.51 (0.06, 4.13)	0.53
No comorbidities	0.17 (0.10, 0.27)	—	—
Most common comorbidities (Ref–without specified comorbidity)			
Cancer	5.58 (2.79, 11.16)	5.98 (2.53, 14.20)	<0.00
Cerebrovascular disease	4.17 (2.01, 8.65)	1.92 (0.87, 4.30)	0.11
COPD and/or asthma	3.00 (1.40, 3.78)	1.52 (0.83, 2.80)	0.18
CVD and/or hypertension	3.77 (2.53, 5.63)	2.62 (1.37, 5.03)	0.01
Diabetes	3.31 (2.14, 5.14)	2.18 (1.27, 3.69)	0.01
Obesity	2.62 (1.76, 3.91)	0.96 (0.51, 1.80)	0.90
Renal disease	2.98 (1.70, 5.22)	1.13 (0.52, 2.45)	0.77
Number of comorbidities	2.12 (1.80, 2.50)	—	—
Smoking Status			
Never	Ref	Ref	Ref
Ever	1.63 (1.02, 2.62)	1.41 (0.84, 2.36)	0.14
Unknown	0.43 (0.26, 0.70)	0.45 (0.27, 0.69)	0.01
Medication prior to COVID-19 diagnosis			
Glucocorticoids			
No glucocorticoids	Ref	Ref	Ref
Glucocorticoid-equivalent >0 mg and <10 mg	4.11 (2.56, 6.61)	3.01 (1.76, 5.13)	<0.00
Glucocorticoid-equivalent >/ = 10 mg or more	7.68 (4.10, 14.39)	5.63 (2.40, 13.19)	<0.00
csDMARD monotherapy	1.18 (0.80, 1.75)	—	—
b/tsDMARD (monotherapy or in combination with csDMARD)	0.72 (0.40, 1.27)	—	—
rituximab	4.28 (1.80, 10.18)	4.61 (1.65, 12.85)	0.01

[a]Multivariable model; including age, gender and all other variables with significant effect estimates in the univariable logistic regression analyses (age, common rheumatic diseases, common comorbidities, smoking status, glucocorticoid dose, and rituximab use). [b]Those with multiple rheumatic conditions were adjudicated so that each primary rheumatic diagnosis category is mutually exclusive.

Table 2: **Unadjusted and adjusted logistic regression models examining the association between demographic and clinical characteristics and the outcome of COVID-19 hospitalisation and/or death (N = 107).**

connective tissue disease was associated with an increased risk of admission to hospital and/or death compared to inflammatory arthritis. Similar to other research, we found an increased risk of poor COVID-19 outcomes in people treated with glucocorticoids in a dose-dependent manner and in people treated with rituximab.[5,12,13] There was no increased risk of poor outcomes associated with treatment with csDMARDs and other biologic therapy.

Our data are unique in that our population had not been exposed to previous SARS-CoV-2 variants and had high rates of recent vaccination at the time of Omicron infection. These data are highly relevant to many people with rheumatic disease who have been limiting social interactions (shielding) for more than 2 years now, and are generally reassuring.

Overall the proportion of hospitalisation and death at 6.5% and 0.6% are much lower than comparable rheumatic disease patient cohorts from earlier epochs of the COVID-19 pandemic in other countries.[4] These are consistent with more recent studies showing reduced rates of severe infection with the Omicron variant, even in our population with almost no previous virus-induced immunity to SARS-CoV-2.[7,14] During the time period of this study, the estimated rate of death from COVID-19 in the entire AoNZ population was 0.11%.[15] The death rate in our cohort cannot be directly compared to the population death rate for a number of reasons

Age and sex	Comorbidities	Rheumatic Diagnosis	Medication at time of COVID-19 vaccination	COVID-19 vaccination status	Hospitalisation	Treatment for COVID-19
21–30, F	Chronic renal insufficiency/end stage renal disease, hypertension, CVD	Systemic lupus erythematosus	Azathioprine, antimalarials	2 doses	Hospitalised	No treatment except supportive care
31–40, F	Chronic renal insufficiency/end stage renal disease, COPD/asthma, morbid obesity (BMI ≥40)	Systemic juvenile idiopathic arthritis	Antimalarials	2 doses	Hospitalised	Glucocorticoids
51–60, F	Chronic renal insufficiency/end stage renal disease, hypertension	Systemic lupus erythematosus	Tacrolimus, mycophenolate mofetil/mycophenolic acid	3 doses	Hospitalised	Remdesivir, glucocorticoids, and plasma from recovered patients
51–60, M	Hypertension, COPD/asthma, obesity (BMI ≥30)	Rheumatoid arthritis	Leflunomide, antimalarials, CD-20 inhibitors	2 doses	Not hospitalised	No treatment except supportive care
61–70, F	Hypertension	Rheumatoid arthritis	Methotrexate, antimalarials	0 doses	Hospitalised	No treatment except supportive care
71–80, F	Hypertension, cancer	Rheumatoid arthritis	None	3 doses	Not hospitalised	No treatment except supportive care
71–80, M	Hypertension, cerebrovascular disease, cancer	Gout	Thalidomide/lenalidomide	3 doses	Hospitalised	Glucocorticoids
71–80, M	COPD/asthma, cancer	Rheumatoid arthritis	Antimalarials	2 doses	Hospitalised	Glucocorticoids
81–90, M	Hypertension, CVD, COPD/asthma, chronic neurological or neuromuscular disease	Rheumatoid arthritis	None	3 doses	Not hospitalised	No treatment except supportive care
81–90, M	None	Other inflammatory arthritis	Methotrexate, leflunomide	3 doses	Hospitalised	IL-6 inhibitor and glucocorticoids

Table 3: **Patient characteristics among those who died following COVID-19 diagnosis (N = 10).**

including; differences in age and sex for our adult cohort with rheumatic disease and the wider population, the contribution of cases largely from 3 hospitals in AoNZ, and changes in mortality definitions for COVID-19 related deaths.[15] Importantly, during the study period there was not access to nirmatrelvir/ritonavir or prophylactic monoclonal antibody therapy in AoNZ, which may have improved these outcomes.[16] It is important to highlight that of the 10 deceased patients in our cohort, 50% had three or more comorbidities including end stage renal disease, cardiovascular disease and advanced age. These risk factors are consistent with known risk factors in the wider population and may have contributed to poor outcomes independent of the rheumatic diseases. In the 10 patients who died, five received supportive care only and were not hospitalised. During the study period people who were hospitalised in AoNZ could be treated with either anti-IL-6 or JAK inhibitors. Although the registry data collection did not enable detailed data collection on this patient group, it seems possible that these patients had contraindications to treatment with advanced therapies, which may have included secondary bacterial infection or their co-morbidities.

A recent meta-analysis using data from earlier periods of the pandemic has shown an overall increased risk of SARS-CoV-2 infection and death in people with rheumatic diseases.[4] People with inflammatory joint disease have been shown to have higher risk of both SARS-CoV-2 infection and higher likelihood for poor outcomes than the general population.[12,17,18] In this study using inflammatory joint disease as a comparison group for gout and CTDs we found that CTDs and gout were associated with higher risk of severe COVID-19 outcomes. These data are consistent with other studies showing an overall increased risk of hospitalisation/death with these conditions.[18–22] This suggests clinicians need to pay particular attention to COVID-19 risk mitigation strategies such as vaccination and use of anti-viral treatments in patients with gout and CTD, both generally smaller patient populations in specialist rheumatology clinics. Nevertheless, the overall risks of poor outcomes of COVID-19 in this highly vaccinated group of people with inflammatory rheumatic diseases supports the premise that vaccination is a useful strategy in all people with rheumatic disease.

Earlier studies examining outcomes of COVID-19 in people with rheumatic disease did not identify a diagnosis of gout as associated with adverse outcomes,[17] however more recent data from the Global Rheumatology Alliance, and the UK Biobank have clearly shown gout as a risk factor for hospitalisation, and, particularly in women, death.[19,22,23] These discrepancies may be due to poor case ascertainment in earlier studies. In our cohort we report a relatively large number of people with gout (n = 167), 10% of the cohort, and a diagnosis of gout was associated with a two-fold increased risk of poor outcomes of COVID-19. The high proportion of people with gout in our study probably reflects the high prevalence of gout in AoNZ, particularly in Māori (Indigenous New Zealanders) and in Pacific peoples at 8.5% and 14.8% respectively.[24] Both Māori and Pacific peoples are known to be at increased risk of poor outcomes of COVID-19. This is consistent with our data,

with nearly double the risk of hospitalisation or death in our cohort of Pacific peoples (OR 1.98, p = 0.03) compared to New Zealand European.[25] With the Māori population, there is a suggestion of increased risk of poor outcomes (OR 1.78), however these results did not reach statistical significance (p = 0.15). We note lower numbers of patients in this group (186 for Māori vs 436 for Pacific peoples, 671 NZ European), and with a larger cohort we may have had more precision for our estimates. Our data collection method did not provide data to allow adjustment for socioeconomic deprivation, which may be a relevant confounder given the association of gout with individual deprivation, but also the relationship of deprivation with worse COVID-19 outcomes.[26,27]

Previous research has identified the use of rituximab or glucocorticoids, most notable with doses of >10 mg/day prednisone equivalent, as risk factors for worse outcomes in COVID-19.[5,9,28] Our relatively large study of a well characterised population also reports a similar association of increased odds of hospitalisation or death from COVID-19 in people using either rituximab or glucocorticoids. However, in our cohort we also report an increased risk of poor COVID-19 outcomes with glucocorticoids doses of prednisone-equivalent of <10 mg/day. This difference may be due to the larger cohort or our systematic identification of cases. It could also be confounded due to comorbidities precluding treatment with other agents or the relatively limited range of biological DMARDs available and funded in AoNZ.

Our study has a number of strengths. Our geographic isolation and border control provides a globally unique population in which to specifically address the Omicron-variant COVID-19 outcomes for people with inflammatory rheumatic disease who are vaccinated and naive to previous SARS-CoV-2 variants. Our systematic case ascertainment in three hospitals with large rheumatic disease clinics and centralised linking with national-level COVID-19 testing data means we were able to achieve high case ascertainment. We feel the study cohort was reasonably large in the context of our overall population of about 5 million. The timing of data collection, after the study period, means late hospitalisation or death were not missed, and we had very little missing data in general. Additionally, since all national health data are linked, it is very unlikely any instances of hospitalisation or death will have been missed. Furthermore, study data were collected from a national electronic health record giving a highly accurate report of vaccination status and death. Data were reviewed and entered by rheumatologists, fellows, or under their direct supervision.

We must also acknowledge some potential limitations to our study. Firstly, we did not have a control population group which limits some of the conclusions that can be drawn from these data, and is an issue highlighted in other GRA registry studies. Instead, these analyses provide information on risk factors for more severe outcomes among a population with COVID-19 and rheumatic diseases. Additionally, this study was restricted to patients with diagnosed rheumatic disease and COVID-19 and are not generalizable to the AoNZ general public. The absence of comparators limits our ability to assess whether risk of severe COVID-19 outcomes is higher among people living with rheumatic disease who were diagnosed with COVID-19 as compared to those populations. Secondly, while data could have been submitted from a number of regions, 98% of cases were from Te Ika-a-Māui (the North Island), and importantly the Tāmaki Makaurau (Auckland) region accounted for nearly two-thirds of cases. This patient group may not be representative of people with rheumatic diseases throughout AoNZ and worldwide, which may limit generalisability of these results. We also acknowledge that we have not analysed the 98% of cases from three hospitals separately. Any bias introduced from the small number of cases contributed from outside these sites would be negligible, due to the standardised nature of healthcare in AoNZ and national level guidelines regarding COVID-19 management. Third, the majority of cases were identified through matching rheumatology service databases to NHIs with positive SARS-CoV-2 PCR results, or, for the vast majority, positive RAT. In the time period of this study most people self-tested with a RAT at home and self-reported a positive result online or via an app. RAT were available for free from many sites, such as pharmacies, in urban and rural settings. This method of self-RAT reporting may introduce selection bias of people who have greater resources to access RAT and online reporting tools. However, under-reporting by people who tested positive for SARS-CoV-2 and were not hospitalised would lead to an over-representation of more severe cases (hospitalised or engaged with community health services). As such, under-reporting might mean our rates of severe outcomes are actually higher than true rates, a further reassurance when interpreting these data. An estimate of the rate of reporting of self-administered RAT positive tests from population modelling during our sample period was 0.62 (personal communication, Dr Leighton Watson, University of Canterbury). A further limitation of our data set is that we were unable to report cause of death for cases who died outside of hospital as primary care records are not included in hospital electronic records and our ethical approval for this study was limited to records review only. We also categorised people into three groups based on rheumatological diagnosis, both "inflammatory arthritis" and "connective tissue disease and other" groups consist of a range of conditions which limits specific applicability of these results to patients on an individual basis. Finally, due to sample size and a small

number of outcome events, we were limited in the complexity of the multivariable models that we could construct. Thus, there were potential confounders that we elected to not include for adjustment in our models, and we were unable to assess for potential interactions.

Conclusion

Our data report reassuring findings for people with rheumatic disease with infection with SARS-CoV-2 Omicron variant where hospitalisation or death were relatively infrequent in our highly vaccinated cohort. Many people with poor outcomes had a significant comorbidity burden, similar to what has been shown in the wider population. Consistent with research in other populations with rheumatic diseases, rituximab and prednisone use were identified as being significant risk factors for poor COVID-19 outcomes. Additionally, gout, a rheumatic disease which has been underrepresented during the pandemic was also significantly associated with worse outcomes. These data may be helpful for clinicians and patients in discussions around vaccination and COVID-19 overall risk, and influence ongoing treatments plans such as reducing steroid exposure.

Contributors

JB conception, formal analysis, investigation, writing original draft, writing review and editing. AM data curation, formal analysis, methodology, formal analysis, methodology, software, writing review and editing. ND conception, methodology, investigation, writing review and editing. MS conception, investigation, writing review and editing. RNK investigation, writing review and editing. AC investigation, writing review and editing. VQ investigation, writing review and editing. SB conception, methodology, writing review and editing. MGM conception, writing review and editing. JSH conception, writing review and editing. JWL conception, methodology, writing review and editing. PMM conception, methodology, writing review and editing. PS conception, writing review and editing. ES conception, writing review and editing. ZSW conception, methodology, writing review and editing. PCR conception, methodology, funding acquisition, writing review and editing. JY conception, methodology, funding acquisition, project administration, resources, writing review and editing. RG conception, methodology, investigation, project administration, resources, supervision, writing original draft, writing review and editing

Data sharing statement

Researchers interested in performing additional analyses from the registry are invited to submit proposals through the COVID-19 Global Rheumatology Alliance https://rheum-covid.org/. For approved projects, we will be able to provide summary tables and data analyses as requested. We do not currently have approval from an Institutional Review Board to make the raw data available to other researchers.

Declaration of interests

JB has no conflicts of interest to declare. AM has no conflicts of interest to declare. ND reports personal fees from AstraZeneca, Dyve Biosciences, Horizon, Selecta, Arthrosi, JW Pharmaceutical Corporation, PK Med, LG Chem, JPI, PTC Therapeutics, Protalix, Unlocked Labs, Hikma outside the submitted work. MS reports speaking fees from Novartis. RNK has no conflicts of interest to declare. AC has no conflicts of interest to declare. VQ has no conflicts of interest to declare. SB reports consulting fees from AbbVie, Horizon, Novartis, and Pfizer. SB is an employee of Pfizer, Inc. MGM has no conflicts of interest to declare. JH has research grants from the Rheumatology Research Foundation and the Childhood Arthritis and Rheumatology Research Foundation. JH reports speaking fees from Novartis, Fresenius Kabi, Pfizer, and Biogen. JL has a research grant from Pfizer. PMM has received consulting/speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartisg, Orphazyme, Pfizer, Roche and UCB, all unrelated to this manuscript, and is supported by the National Institute for Health Research (NIHR), University College London Hospitals (UCLH), Biomedical Research Centre (BRC). PS reports an honorarium from the COVID-19 Global Rheumatology Alliance. ES reports grants from the COVID-19 Global Rheumatology Alliance, Canada's drug and health technology agency, the Canadian Institute for Health Research, and McMaster University. ES reports honoraria from the Canadian Rheumatology Association and the Canadian Arthritis Patient's Alliance. PR was unable to report his conflicts of interest as he is deceased. ZW reports research grants from BMS, Sanofi, the National Institute of Health and the Rheumatology Research Foundation. ZW reports royalties from the IgG4 symptom severity score and consulting fees from Sanofi, Horizon, MedPace, Viela Bio, Zenas, and Shionogi. ZW reports participation on data monitoring boards for Sanofi, Horizon, Novartis, Visterra/Otsuka, and Shinogi. JY is supported by NIH/NIAMS K24 AR07534 and AHRQ R01HS028024. She has received research grants from Gilead, Aurinia, BMS Foundation and Astra Zeneca and performed consultation for Astra Zeneca, Pfizer, and Aurinia. RG reports personal and/or speaking fees from AbbVie, Janssen, Novartis, Pfizer, Cornerstones and travel assistance from Pfizer (all < $10,000). The views expressed here are those of the authors and participating members of the COVID-19 Global Rheumatology Alliance and do not necessarily represent the views of the American College of Rheumatology (ACR), the European Alliance of Associations for Rheumatology (EULAR), the (UK) National Health Service (NHS), the National Institute for Health Research (NIHR), or the (UK) Department of Health, or any other organisation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100843.

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