CLINICAL SCIENCE

Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry

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ABSTRACT

Objectives COVID-19 outcomes in people with rheumatic diseases remain poorly understood. The aim was to examine demographic and clinical factors associated with COVID-19 hospitalisation status in people with rheumatic disease.

Methods Case series of individuals with rheumatic disease and COVID-19 from the COVID-19 Global Rheumatology Alliance registry: 24 March 2020 to 20 April 2020. Multivariable logistic regression was used to estimate ORs and 95% CIs of hospitalisation. Age, sex, smoking status, rheumatic disease diagnosis, comorbidities and rheumatic disease medications taken immediately prior to infection were analysed.

Results A total of 600 cases from 40 countries were included. Nearly half of the cases were hospitalised (277, 46%) and 55 (9%) died. In multivariable-adjusted models, prednisone dose ≥10 mg/day was associated with higher odds of hospitalisation (OR 2.05, 95% CI 1.06 to 3.96). Use of conventional disease-modifying antirheumatic drug (DMARD) alone or in combination with biologics/Janus Kinase inhibitors was not associated with hospitalisation (OR 1.23, 95% CI 0.70 to 2.17 and OR 0.74, 95% CI 0.37 to 1.46, respectively). Non-steroidal anti-inflammatory drug (NSAID) use was not associated with hospitalisation status (OR 0.64, 95% CI 0.39 to 1.06). Tumour necrosis factor inhibitor (anti-TNF) use was associated with a reduced odds of hospitalisation (OR 0.40, 95% CI 0.19 to 0.81), while no association with antimalarial use (OR 0.94, 95% CI 0.57 to 1.57) was observed.

Conclusions We found that glucocorticoid exposure of ≥10 mg/day is associated with a higher odds of hospitalisation and anti-TNF with a decreased odds of hospitalisation in patients with rheumatic disease. Neither exposure to DMARDs nor NSAIDs were associated with increased odds of hospitalisation.

Key messages

What is already known about this subject?

- Data regarding outcomes for people with rheumatological disease and COVID-19 remain scarce and limited to small case series.
- Due to underlying immune system dysfunction and the common use of immunosuppressants, there is concern about poorer outcomes in this population and uncertainty about medication management during the pandemic.

What does this study add?

- Moderate to high dose glucocorticoids were associated with a higher risk of hospitalisation for COVID-19.
- Biologic therapies, NSAIDs and antimalarial drugs like hydroxychloroquine were not associated with a higher risk of hospitalisation for COVID-19.

How might this impact on clinical practice or future developments?

- This study demonstrates that most individuals with rheumatological diseases or on immunosuppressive therapies recover from COVID-19, which should provide some reassurance to patients.

INTRODUCTION

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is of particular concern for people with rheumatic disease or those who are immunosuppressed. Whether having a rheumatic disease or receiving immunosuppressive treatment is associated with severe infection and subsequent poor outcomes is unknown. In general, immunosuppression and the presence of comorbidities are associated with an increased risk of serious infection in people with

rheumatic diseases[1] therefore, people with rheumatic disease may be at higher risk for a more severe course with COVID-19, including hospitalisation, complications and death. Importantly, some medications used to treat rheumatic diseases, such as hydroxychloroquine and interleukin-6 (IL-6) inhibitors, are being studied for the prevention and/or treatment of COVID-19 and its complications including cytokine-storm.[2–4] At present, the implications of COVID-19 for people living with rheumatic diseases remain poorly understood.

To address this knowledge gap, a global network of rheumatologists, scientists and patients developed a physician-reported case registry of people with rheumatic diseases diagnosed with COVID-19.[5 6] This report aims to (1) describe the demographic and clinical characteristics of the first 600 patients submitted to the COVID-19 Global Rheumatology Alliance (C19-GRA) physician registry and (2) identify factors associated with hospitalisation for COVID-19 in this population.

METHODS

Details of the registry design have been described elsewhere.[5–7] Briefly, C19-GRA data regarding individuals with rheumatic diseases diagnosed with COVID-19 are captured from rheumatology physicians via two parallel international data entry portals for regulatory reasons: one limited to European countries (eular.org/eular_covid19_database.cfm; hosted by The University of Manchester, UK) and a second for all other sites (rheum-covid.org/provider-global/; hosted by the University of California, San Francisco, California, USA). Two patients sit on the C19-GRA steering committee and they contributed to the design of the registry, the questions being asked and the analysis of the results. The C19-GRA has a Patient Board, composed entirely of patients. These patients, and others, will be involved in disseminating the results of this analysis once published. No public were involved in the design or analysis of this project.

Physicians indicated whether the diagnosis of COVID-19 was based on PCR, antibody, metagenomic testing, CT scan, laboratory assay or a presumptive diagnosis based on symptoms only. Data elements for this analysis included physician city, state and country. Countries were assigned to the six WHO regions (www.who.int); the 'Americas' was further divided into north and south. Case information including age, sex, smoking status, rheumatic disease diagnosis, disease activity and comorbidities was collected. Medications prior to COVID-19 were categorised as: conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, tacrolimus); biologic DMARDs (bDMARDs; abatacept, belimumab, CD-20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, tumour necrosis factor inhibitors (anti-TNF)) and targeted synthetic DMARDs (tsDMARDs) namely Janus Kinase (JAK) inhibitors. Physicians reported the approximate number of days from symptom onset to symptom resolution or to death. The primary outcome of interest was hospitalisation for COVID-19. As of 20 April 2020, a total of 604 cases were entered in the registry; hospitalisation status was unknown for four cases and these were excluded from analysis.

Continuous variables are reported as median (IQR). Categorical variables are reported as number and percentage (%). In univariable analyses, differences in demographic and rheumatic disease-specific features according to hospitalisation status were compared using χ^2 tests for categorical variables and Mann-Whitney U tests for continuous variables. The independent associations between demographic and disease-specific features with the odds of COVID-19 hospitalisation were estimated using multivariable-adjusted logistic regression and reported as OR and 95% CIs; covariates included in the model were age group ($\leq$65 years vs >65 years), sex, rheumatic disease (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) or other spondyloarthritis, vasculitis and other), key comorbidities (hypertension, lung disease, diabetes, cardiovascular disease and chronic renal insufficiency/end-stage renal disease), smoking status (ever vs never), physician-reported disease activity (remission, minimal/low disease activity, moderate disease activity or severe/high disease activity; or as a binary variable: remission and minimal/low disease activity vs moderate and severe/high disease activity), DMARD type (no DMARD, csDMARD only, b/tsDMARD only, csDMARD and b/tsDMARD combination therapy), non-steroidal anti-inflammatory drugs (NSAID) use (yes vs no) and prednisone-equivalent glucocorticoid use (0 mg/day, 1–9 mg/day, $\geq$10 mg/day). Categories with cell sizes <10 by hospitalisation status were collapsed to ensure sufficient power in the adjusted model. For univariable and multivariable models, patients with more than one of the following diseases recorded were classified as follows: SLE>RA>PsA>vasculitis>axSpA/other spondyloarthritis>other. Cardiovascular disease and hypertension were collapsed as a single comorbidity in the regression model due to significant collinearity between the two variables. Due to concerns regarding the possibility of confounding by indication, disease activity and prednisone-equivalent glucocorticoid use were analysed by including only one of the variables in the multivariable analysis at a time, and by including both variables in the multivariable analysis at the same time. Unknown/missing data (14% smoking status, 12% NSAIDs, 1% glucocorticoids) were treated as a separate category in multivariable models. In exploratory analyses, the independent association between antimalarials and specific b/tsDMARD therapies with hospitalisation status was estimated using multivariable logistic regression.

To assess the robustness of the results, sensitivity analyses were performed. First, we repeated the above analyses after excluding patients with a 'presumptive diagnosis', meaning that the patient's physician thought he/she had symptoms consistent with the disease, but there was no evidence of the patient having: a) a confirmatory COVID test; b) documentation of chest imaging showing bilateral infiltrates in keeping with COVID-19 pneumonia or c) close contact with a known COVID-19-positive patient. Second, we limited the analyses to patients whose COVID-19 outcome was known (resolved/died) or for whom at least $\geq$14 days from symptom onset (or diagnosis date if symptom onset was unknown) had elapsed, as it is unlikely that a patient would be hospitalised >2 weeks after onset. Third, we excluded cases with missing/unknown values within the covariate set included in the multivariable analyses. Data were considered statistically significant at $p<0.05$. Cell counts <5 are represented by 'n<5' in tables to protect patient anonymity. All analyses were conducted in Stata V.16.0 (StataCorp).

Data quality was assessed by two data quality teams (one at the University of Manchester, UK and the University of California, San Francisco) who also confirmed there were no duplicate entries. Due to the deidentified and non-interventional nature of the study, it was determined by the institutional review board that patient consent was not required. C19-GRA physician registry was determined 'not human subjects research' by the UK Health Research Authority and the University of Manchester, as

Table 1 Demographic and clinical characteristics of patients with rheumatic disease with COVID-19 (n=600)

	N (%)
Region	
Region of the Americas: North	340 (57)
Region of the Americas: South	16 (3)
European region	218 (36)
African region	<5 (<1)
Eastern Mediterranean region	11 (2)
South-East Asian region	<5 (<1)
Western Pacific region	13 (2)
Female	423 (71)
Age (years)	
18–29	32 (5)
30–49	169 (28)
50–65	229 (38)
>65	170 (28)
Median (IQR)	56 (45–67)
Most common rheumatic disease diagnoses*	
Rheumatoid arthritis	230 (38)
Systemic lupus erythematosus	85 (14)
Psoriatic arthritis	74 (12)
Axial spondyloarthritis or other spondyloarthritis	48 (8)
Vasculitis	44 (7)
Sjögren's syndrome	28 (5)
Other inflammatory arthritis	21 (4)
Inflammatory myopathy	20 (3)
Gout	19 (3)
Systemic sclerosis	16 (3)
Polymyalgia rheumatica	12 (2)
Sarcoidosis	10 (2)
Other	28 (5)
Most common comorbidities	
Hypertension	199 (33)
Lung disease†	127 (21)
Diabetes	69 (12)
Cardiovascular disease	63 (11)
Chronic renal insufficiency/end-stage renal disease	40 (7)
Disease activity (n=575)	
Remission	173 (30)
Minimal or low disease activity	286 (50)
Moderate disease activity	102 (18)
Severe or high disease activity	14 (2)
Smoking status (n=518)	
Ever	129 (25)
Never	389 (75)
Medication prior to COVID-19 diagnosis‡	
No DMARD	97 (16)
csDMARD only, including antimalarial therapy	272 (45)
csDMARD only, excluding antimalarial therapy	220 (37)
Antimalarial, with or without other DMARD	130 (22)
Antimalarial only	52 (9)
b/tsDMARDs only	107 (18)
csDMARD+b/tsDMARD combination therapy	124 (21)
NSAIDs (n=531)	111 (21)
Prednisone-equivalent glucocorticoids (n=592)	
None	403 (68)
1–9 mg/day	125 (21)
≥10 mg/day	64 (11)
Hospitalised	277 (46)
Deceased	55 (9)
Reported days from onset to resolution or death (n=275), median (IQR)	13 (8–17)

N (column %) for categorical variables unless otherwise noted.
Percentages may not sum to 100 due to rounding.
*Cases could have more than one disease diagnosis. 'Other' rheumatic disease category included (each n<10): undifferentiated connective tissue disease; ocular inflammation; autoinflammatory syndrome; mixed connective tissue disease; antiphospholipid antibody syndrome; calcium pyrophosphate deposition disease; systemic juvenile idiopathic arthritis; juvenile idiopathic arthritis, not systemic; IgG4-related disease.
†Chronic obstructive pulmonary disease, asthma, interstitial lung disease or other not specified.
‡csDMARD medications included: antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, tacrolimus; b/tsDMARD included: abatacept, belimumab, CD-20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, anti-TNF and Janus Kinase inhibitors.
b/tsDMARD, biologic or targeted synthetic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

well as under United States Federal Guidelines assessed by the University of California, San Francisco and patient consent was not required. We did not systematically capture how cases were identified before being entered into the registry and therefore we cannot detail this. However, we are aware of a number of large institutions that are systematically collecting all cases in their health system/district and entering them into the registry.

RESULTS

The demographic and clinical characteristics of the first 600 cases in the C19-GRA physician registry are shown in table 1. The majority of cases in the registry were from North America and Europe, female and in the 50–65 age range, the countries that the cases were reported from are shown in online supplementary table 1. The most common rheumatic disease was RA (230, 38%), followed by SLE (85, 14%) and PsA (74, 12%). The most common comorbidities were hypertension (199, 33%), lung disease (127, 21%), diabetes (69, 12%), cardiovascular disease (63, 11%) and chronic renal insufficiency/end-stage renal disease (40, 7%). Most cases were never smokers (389, 75%) and either in remission or had minimal/low disease activity (459, 80%). Five patients were pregnant (1%). Nearly half of the cases reported to the registry were hospitalised (277, 46%), and 9% (55) were deceased. COVID-19 diagnoses were predominately made through PCR testing (437, 73%), followed by laboratory assay of unknown type (58, 10%), CT scan (42, 7%) or other (31, 5%) (individuals could be tested using more than one method). Fifty-two (9%) cases had a presumptive diagnosis only (online supplementary table 2). The median number of days from COVID-19 symptom onset to resolution or death was 13 (IQR: 8–17). Demographic and clinical characteristics stratified by sex are presented in online supplementary table 3.

Demographic and clinical characteristics stratified by hospitalisation status are shown in table 2. Differences by age group in hospitalisation status were observed: most hospitalised patients were over age 65 (43%), compared with 16% of non-hospitalised cases ($p<0.01$). In unadjusted analyses, differences in hospitalisation status by disease revealed a higher percentage of people who were hospitalised had SLE and vasculitis (17% and 9%, respectively) versus those who were not hospitalised (11% and 5%, respectively), while a lower proportion of patients who were hospitalised had PsA and axSpA or other spondyloarthritis (8% and 6%, respectively) compared with those who were

Table 2 Demographic and clinical factors of patients with rheumatic disease diagnosed with COVID-19 by hospitalisation status

	Not hospitalised n=323	Hospitalised n=277	P value
Female	238 (74%)	185 (67%)	0.10
Age group (years)			<0.01
<30	25 (8%)	7 (3%)	
30–49	113 (35%)	56 (20%)	
50–65	134 (41%)	95 (34%)	
>65	51 (16%)	119 (43%)	
Median (IQR), years	52 (42–60)	62 (51–71)	<0.01
Most common rheumatic disease diagnoses†			<0.01
Rheumatoid arthritis	121 (37%)	104 (38%)	
Systemic lupus erythematosus	37 (11%)	48 (17%)	
Psoriatic arthritis	52 (16%)	22 (8%)	
Axial spondyloarthritis or other spondyloarthritis	32 (10%)	16 (6%)	
Vasculitis	15 (5%)	24 (9%)	
Other	66 (20%)	63 (23%)	
Most common comorbidities			
Hypertension	75 (23%)	124 (45%)	<0.01
Lung disease*	44 (14%)	83 (30%)	<0.01
Diabetes	21 (7%)	48 (17%)	<0.01
Cardiovascular disease	23 (7%)	40 (14%)	<0.01
Chronic renal insufficiency/end-stage renal disease	7 (2%)	33 (12%)	<0.01
Disease activity (n=575)			0.49
Remission	88 (28)	85 (32)	
Minimal or low disease activity	157 (50)	129 (49)	
Moderate disease activity	60 (19)	42 (16)	
Severe or high disease activity	6 (2)	8 (3)	
Ever smoker (n=518)	61 (21%)	68 (30%)	0.03
Rheumatic disease medication prior to COVID-19 diagnosis‡			<0.01
No DMARD	45 (14%)	52 (19%)	
csDMARD only	123 (38%)	149 (54%)	
b/tsDMARDs only	76 (24%)	31 (11%)	
csDMARD+b/tsDMARD combination therapy	79 (24%)	45 (16%)	
Any antimalarial therapy	64 (20%)	66 (24%)	0.23
Antimalarial only	27 (8%)	25 (9%)	0.77
NSAIDs (n=531)	72 (25%)	39 (16%)	0.02
Prednisone-equivalent glucocorticoids (n=592)			<0.01
None	241 (75%)	162 (60%)	
1–9 mg/day	58 (18%)	67 (25%)	
≥10 mg/day	21 (7%)	43 (16%)	
Reported days from onset to resolution or death (n=275), median (IQR)	14 (7–16)	12 (8–17)	0.72

N (column %) for categorical variables unless otherwise noted.
Percentages may not sum to 100 due to rounding.
P value calculated using χ^2 tests for categorical variables and Mann-Whitney U tests for continuous variables.
*Chronic obstructive pulmonary disease, asthma, interstitial lung disease or other not specified.
†Patients with more than one disease within these five diagnoses were classified as follows: systemic lupus erythematosus>rheumatoid arthritis>psoriatic arthritis>vasculitis>axial/other spondyloarthritis>other. Other rheumatic disease category included (each n<10): undifferentiated connective tissue disease; ocular inflammation; autoinflammatory syndrome; mixed connective tissue disease; antiphospholipid antibody syndrome; calcium pyrophosphate deposition disease; systemic juvenile idiopathic arthritis; juvenile idiopathic arthritis, not systemic; IgG4-related disease.
‡csDMARD medications included: antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclophosphamide, ciclosporin, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, tacrolimus; b/tsDMARD included: abatacept, belimumab, CD-20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, anti-TNF and Janus Kinase inhibitors.
b/tsDMARD, biologic or targeted synthetic DMARDs; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; IL, interleukin; NSAID, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

not (16% and 10%, respectively). There were more comorbidities among hospitalised cases, including hypertension (45% vs 23%), lung disease (30% vs 14%), diabetes (17% vs 7%), cardiovascular disease (14% vs 7%) and chronic renal insufficiency/end-stage renal disease (12% vs 2%) (all p<0.01). There was no association between disease activity and hospitalisation status (p=0.49). NSAID use was reported less frequently among hospitalised patients than non-hospitalised patients (16% vs 25%, p=0.02), while there was a higher proportion of patients receiving high doses of glucocorticoids among those who were hospitalised than not hospitalised (16% vs 7% for doses ≥10 mg/day, p=0.01). We found no significant difference in hospitalisation status by sex, antimalarial therapy (either monotherapy or in combination with other DMARDs) or reported days from symptom onset to symptom resolution or death.

In a multivariable model, age over 65 years (OR=2.56, 95% CI 1.62 to 4.04), hypertension/cardiovascular disease (OR=1.86, 95% CI 1.23 to 2.81), lung disease (OR=2.48, 95% CI 1.55 to 3.98), diabetes (OR=2.61, 95% CI 1.39 to 4.88) and chronic renal insufficiency/end-stage renal disease (OR=3.02, 95% CI 1.21 to 7.54) were associated with higher odds of hospitalisation (all p<0.05) (table 3). Treatment with b/tsDMARD monotherapy just prior to COVID-19 diagnosis was significantly associated with a lower odds of hospitalisation compared with no DMARD therapy (OR=0.46, 95% CI 0.22 to 0.93; p=0.03). Glucocorticoid therapy at prednisone-equivalent doses ≥10 mg/day, however, was associated with a higher odds of hospitalisation compared with no glucocorticoid therapy (OR=2.05, 95% CI 1.06 to 3.96; p=0.03). Neither adding disease activity to the model with glucocorticoids nor replacing glucocorticoids by disease activity changed the direction, strength or significance of the relationship between the various variables and hospitalisation status in a meaningful way (data not shown).

Further analyses were conducted to examine the independent association of antimalarials and specific b/tsDMARDs with hospitalisation. A total of 22% of cases were taking antimalarials before hospitalisation. The largest subgroup of b/tsDMARD therapies was anti-TNF medications (52%). We found no significant association between antimalarial therapy and hospitalisation (OR=0.94, 95% CI 0.57 to 1.57; p=0.82) after adjusting for sex, age over 65 years, rheumatic disease, smoking status, comorbidities, other csDMARD monotherapy, b/tsDMARD monotherapy, csDMARD-b/tsDMARD combination therapy (excluding antimalarials), NSAID use and glucocorticoid dose. A significant inverse association between any anti-TNF therapy and hospitalisation was found (OR=0.40, 95% CI 0.19 to 0.81; p=0.01), after controlling for sex, age over 65 years, rheumatic disease, smoking, comorbidities, csDMARD monotherapy, other b/tsDMARD monotherapy, csDMARD-b/tsDMARD combination therapy (excluding anti-TNF), NSAID use and glucocorticoid dose. Small numbers of non-anti-TNF b/tsDMARDs precluded analysing the association of these individual agents with hospitalisation (online supplementary table 4).

Our findings remained largely unchanged in sensitivity analyses excluding those with a presumptive diagnosis (n=52; online supplementary table 5), those with unknown outcomes (n=214; online supplementary table 6) and those with missing/unknown values (n=142; online supplementary table 7).

DISCUSSION

This manuscript describes the largest collection of COVID-19 cases among patients with rheumatic diseases, with 600 cases from 40 countries. We identified factors associated with higher odds of COVID-19 hospitalisation, including older age, presence of comorbidities and higher doses of prednisone (≥10 mg/day). We did not see an association between prior NSAID use or antimalarials and hospitalisation for COVID-19. We did find b/tsDMARD monotherapy to be associated with a lower odds of hospitalisation, an effect that was largely driven by anti-TNF

Table 3 Unadjusted and adjusted logistic regression models examining the association between demographic and clinical characteristics and COVID-19 hospitalisation status

	No. hospitalised/ No. cases (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P value*
Female	185/423 (44)	0.72 (0.51 to 1.02)	0.83 (0.54 to 1.28)	0.39
Age >65 years	119/170 (70)	4.02 (2.74 to 5.89)	2.56 (1.62 to 4.04)	<0.01
Rheumatic disease diagnosis†				
Rheumatoid arthritis	104/225 (46)	*Ref*	*Ref*	--
Systemic lupus erythematosus	48/85 (56)	1.51 (0.91 to 2.49)	1.80 (0.99 to 3.29)	0.06
Psoriatic arthritis	22/74 (30)	0.49 (0.28 to 0.86)	0.94 (0.48 to 1.83)	0.85
Axial spondyloarthritis or other spondyloarthritis	16/48 (33)	0.58 (0.30 to 1.12)	1.11 (0.50 to 2.42)	0.80
Vasculitis	24/39 (62)	1.86 (0.93 to 3.73)	1.56 (0.66 to 3.68)	0.31
Other	63/129 (49)	1.11 (0.72 to 1.71)	0.94 (0.55 to 1.62)	0.82
Comorbidities (present vs not)				
Hypertension or cardiovascular disease	136/218 (62)	2.83 (1.01 to 4.00)	1.86 (1.23 to 2.81)	<0.01
Lung disease‡	83/127 (65)	2.71 (1.80 to 4.08)	2.48 (1.55 to 3.98)	<0.01
Diabetes	48/69 (70)	3.01 (1.76 to 5.18)	2.61 (1.39 to 4.88)	<0.01
Chronic renal insufficiency/end-stage renal disease	33/40 (83)	6.11 (2.66 to 14.04)	3.02 (1.21 to 7.54)	0.02
Ever smoker (vs never smoker)	68/129 (53)	1.41 (1.13 to 1.77)	1.18 (0.90 to 1.53)	0.23
Rheumatic disease medication prior to COVID-19 diagnosis§				
No DMARD	52/97 (54)	*Ref*	*Ref*	--
csDMARD only	249/272 (55)	1.05 (0.66 to 1.67)	1.23 (0.70 to 2.17)	0.48
b/tsDMARDs only	31/107 (29)	0.35 (0.20 to 0.63)	0.46 (0.22 to 0.93)	0.03
csDMARD+b/tsDMARD combination therapy	45/124 (36)	0.49 (0.29 to 0.85)	0.74 (0.37 to 1.46)	0.38
NSAIDs	39/111 (35)	0.55 (0.35 to 0.84)	0.64 (0.39 to 1.06)	0.08
Prednisone-equivalent glucocorticoids				
None	162/403 (40)	*Ref*	*Ref*	--
1–9 mg/day	67/125 (54)	1.72 (1.15 to 2.57)	1.03 (0.64 to 1.66)	0.91
≥10 mg/day	43/64 (67)	3.05 (1.74 to 5.32)	2.05 (1.06 to 3.96)	0.03

Adjusted ORs from models including all variables shown.
*P value for multivariable logistic regression model (see 'Methods' section for details).
†Patients with more than one disease within these five diagnoses were classified as follows: systemic lupus erythematosus>rheumatoid arthritis>psoriatic arthritis>vasculitis>axial/other spondyloarthritis>other. Other rheumatic disease category included (each n<10): undifferentiated connective tissue disease; ocular inflammation; autoinflammatory syndrome; mixed connective tissue disease; antiphospholipid antibody syndrome; calcium pyrophosphate deposition disease; systemic juvenile idiopathic arthritis; juvenile idiopathic arthritis, not systemic; IgG4-related disease.
‡Chronic obstructive pulmonary disease, asthma, interstitial lung disease or other not specified.
§csDMARD medications included: antimalarials (hydroxychloroquine, chloroquine), azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, tacrolimus; b/tsDMARD included: abatacept, belimumab, CD-20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, anti-TNF and Janus Kinase inhibitors.
b/tsDMARD, biologic or targeted synthetic DMARDs; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

therapies. Over half of the reported cases did not require hospitalisation, including many patients receiving b/tsDMARDs. The rate of hospitalisation was higher than in cohorts of general patients with COVID-19 but this likely reflects the mechanism by which we collected the case information and should not be interpreted as the true rate of hospitalisation among patients with rheumatic disease infected with SARS-CoV-2.

Prior to this report, there had been several small case series of COVID-19 in patients with rheumatic disease reported from Europe.[8–11] With few exceptions,[12 13] prior large descriptive studies of patients with COVID-19 from China, Europe and the USA have not included rheumatic disease in their baseline comorbidities.[14–19] These studies have not allowed for further inference on the characteristics of patients with rheumatic disease and their associations with COVID-19 severity.

In accordance with previous studies of COVID-19 in different populations, we found that patients with comorbidities such as hypertension, cardiovascular disease and diabetes had higher odds of hospitalisation.[18–20] We also found that glucocorticoid use at a prednisone-equivalent dose ≥10 mg/day was associated with an increased odds of hospitalisation, which is in agreement with prior studies showing an increased risk of infection with higher dose of glucocorticoids.[21]

We did not find a significant association between antimalarial use and hospitalisation in adjusted analyses. The use of hydroxychloroquine for the treatment of COVID-19, which was based on in vitro studies, has had mixed results.[2 22] Studies from one group suggested a benefit on the surrogate outcome of viral clearance among hospitalised patients, but these studies either had inadequate or no comparator groups.[23 24] Two randomised controlled trials of hydroxychloroquine had conflicting findings.[25 26] A phase IIb randomised controlled trial comparing two doses of chloroquine among patients hospitalised with COVID-19 with historical controls from Wuhan detected a negative safety signal—QTc prolongation—but no clinical benefit.[27] Finally, two observational studies using propensity score matching to account for confounding by indication have found no significant benefit with either hydroxychloroquine alone or combined with azithromycin on clinical outcomes including mortality[28 29]; however,

these studies were limited by design issues and a high risk of bias due to unmeasured confounding.

We also did not detect a significant association between NSAID use and hospitalisation in adjusted analyses. Although no prior data in patients with COVID-19 have supported a deleterious effect of NSAIDs on clinical outcomes, early reports cautioned against the use of NSAIDs suggesting harm when used during the clinical course of COVID-19.[30] These observations, while anecdotal, may also relate to confounding by indication, since NSAIDs are also often sold over-the-counter and may not be documented in hospital records with the same accuracy as prescription medications, leading to a reporting bias.

We found a lower odds of hospitalisation with b/tsDMARDs monotherapy in our primary multivariable analysis, which was driven largely by anti-TNF therapies. The number of cases taking other biologic drugs or JAK inhibitors was small, and may have been insufficient to demonstrate other underlying effects if present. Although we caution against causal inference regarding drug effects given significant potential for residual confounding in our study, we also note that there is biological plausibility for the potential benefit of biologic medications in treating COVID-19, as evidenced by those with more severe disease having higher levels of cytokines, including IL-6 and TNF.[31 32] The use of IL-6 inhibitors is being investigated for COVID-19, particularly in cases complicated by aberrant inflammatory responses or 'cytokine storm'. This is based on two initial case series of fewer than 20 patients.[33 34] Anti-TNFs have also been suggested as a potential therapy in COVID-19, but this has been based solely on preclinical data.[35] Randomised, placebo-controlled trials are needed to clarify potential benefits or harms of biologic therapies in treating COVID-19.

Strengths of our study include the first large analysis of patients with rheumatic diseases and COVID-19. All case data were entered by rheumatology healthcare providers. The C19-GRA physician registry includes cases from 40 countries suggesting that our findings are more generalisable than single-centre or regional studies. The registry collects information on specific rheumatic disease diagnoses, which to date have not been captured in large, published case series of COVID-19.[15]

Despite these strengths, there are important limitations to these registry data. The C19-GRA registry is voluntary and does not capture all cases of COVID-19 in patients with rheumatic disease. This approach to data collection places limitations on causal conclusions and temporal relationships and therefore we can only make limited inferences based on our results. There is selection bias due to several factors, including geographic location, hospitalisation status and disease severity, with the more severe cases most likely to be captured. Therefore, the data cannot be used to comment on the incidence of COVID-19 in this patient population or its severity. Since the registry's inclusion criteria are restricted to those with rheumatic disease and COVID-19, this precludes the ability to make comparisons with those who do not have rheumatic disease, or those with rheumatic disease who do not have COVID-19. Although physicians may be contacted for follow-up information for unresolved cases, this is a cross-sectional analysis and there is the possibility that some patients may not have progressed to their maximum level of care prior to enrolment. In our dataset, 35% of cases were unresolved or had an unknown resolution status, although exclusion of these cases in sensitivity analyses did not change our conclusions. Furthermore, while we have collected information on medication use prior to COVID-19 diagnosis, we do not have specific data on the duration of treatment, medication dose, or additional historical treatments.

At the time of this report, the C19-GRA databases remain open for further case reports. With additional cases, we will be able to examine more detailed outcomes associated with specific rheumatic diseases and COVID-19 treatments, as well as the outcomes of COVID-19 in people with rheumatic diseases.

This series of cases demonstrates that the majority of patients with rheumatic diseases captured in our registry recover from COVID-19. In some cases, exposure to specific medication classes is associated with lower odds of hospitalisation; however, these findings should be interpreted with caution because of a high risk of bias. Results support the guidance issued by the American College of Rheumatology and the European League Against Rheumatism, which suggest continuing rheumatic medications in the absence of COVID-19 infection or SARS-CoV-2 exposure.[36 37]

In this series of people with rheumatic disease and COVID-19, use of DMARDs did not increase the odds of hospitalisation. As in the general population, people with rheumatic diseases who are older and/or have comorbidities have a higher odds of COVID-19-related hospitalisation. Anti-TNF treatment was associated with reduced odds of hospitalisation while prednisone use ≥10 mg/day was associated with a higher odds of hospitalisation. There was no difference in antimalarials, such as hydroxychloroquine, or NSAID use between those who were or were not hospitalised.

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