EPIDEMIOLOGICAL SCIENCE

Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'

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ABSTRACT

Objective To investigate differences in manifestations and outcomes of coronavirus disease 2019 (COVID-19) infection between those with and without rheumatic disease.

Methods We conducted a comparative cohort study of patients with rheumatic disease and COVID-19 (confirmed by severe acute respiratory syndrome coronavirus 2 PCR), compared in a 1:2 ratio with matched comparators on age, sex and date of COVID-19 diagnosis, between 1 March and 8 April 2020, at Partners HealthCare System in the greater Boston, Massachusetts area. We examined differences in demographics, clinical features and outcomes of COVID-19 infection. The main outcomes were hospitalisation, intensive care admission, mechanical ventilation and mortality.

Results We identified 52 rheumatic disease patients with COVID-19 (mean age, 63 years; 69% female) and matched these to 104 non-rheumatic disease comparators. The majority (39, 75%) of patients with rheumatic disease were on immunosuppressive medications. Patients with and without rheumatic disease had similar symptoms and laboratory findings. A similar proportion of patients with and without rheumatic disease were hospitalised (23 (44%) vs 42 (40%)), p=0.50) but those with rheumatic disease required intensive care admission and mechanical ventilation more often (11 (48%) vs 7 (18%), multivariable OR 3.11 (95% CI 1.07 to 9.05)). Mortality was similar between the two groups (3 (6%) vs 4 (4%), p=0.69).

Conclusions Patients with rheumatic disease and COVID-19 infection were more likely to require mechanical ventilation but had similar clinical features and hospitalisation rates as those without rheumatic disease. These findings have important implications for patients with rheumatic disease but require further validation.

Key messages

What is already known about this subject?
- Very little is known about the outcomes of patients with COVID-19 who have underlying rheumatic disease.

What does this study add?
- We found that patients with rheumatic disease required hospitalisation and died with similar frequencies when compared with patients without rheumatic disease.
- However, those with rheumatic disease had threefold higher odds of requiring intensive care/mechanical ventilation compared with those without rheumatic disease.

How might this impact on clinical practice or future developments?
- Patients with rheumatic disease may be at higher risk of severe COVID-19 respiratory complications compared with matched comparators.
- Further studies are needed to determine what factors contribute to the increased rates of intensive care and intubation among hospitalised rheumatic disease patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become an unprecedented global health crisis, with over 3 million confirmed cases and 200 000 deaths worldwide thus far.[1 2] Whether patients with rheumatic disease, many of whom are on immunosuppression, are at higher risk of COVID-19 and its complications is unknown. However, the scope and severity of the pandemic are highly concerning to patients and providers alike, especially in 'hot spots' of disease.[3]

Prior coronavirus outbreaks including severe acute respiratory syndrome in 2002 and Middle Eastern respiratory syndrome in 2012 did not show increased case fatality rates among patients on immunosuppression (eg, transplantation and chemotherapy) in contrast to rates observed in the context of other respiratory viral illnesses such as influenza.[4 5] However, given the smaller scale of these prior coronavirus outbreaks, epidemiological studies in other populations were limited. Previous reports of COVID-19 in patients with rheumatic disease have been limited to case reports and small

case series with no comparison groups; these have demonstrated mixed outcomes, though results are difficult to generalise given variable COVID-19 case definitions and small sample sizes.[6–9] Understanding COVID-19 outcomes in rheumatic disease is of particular interest since several classes of rheumatic disease medications (eg, interleukin-6 receptor inhibitors) are currently being studied as treatments for a cytokine storm-like complication responsible for much of the morbidity and mortality associated with COVID-19.[10–12]

In the USA, the greater Boston, Massachusetts, area is considered a 'hot spot' for COVID-19 infection. Massachusetts has had over 50 000 confirmed infections thus far.[13] Given the limited data on COVID-19 in patients with rheumatic disease, we performed a matched cohort study of patients in the Partners HealthCare System (PHS) to examine features and outcomes of COVID-19 infection in patients with rheumatic disease compared with those without rheumatic disease.

METHODS

Study population

PHS is a large healthcare system that includes tertiary care hospitals (Massachusetts General Hospital and Brigham and Women's Hospital), community hospitals and primary and specialty outpatient centres in the greater Boston, Massachusetts area. We identified patients seen at PHS who were ≥18 years of age and had a positive test result for SARS-CoV-2 by PCR clinical assay between 30 January 2020 and 8 April 2020, using the PHS centralised data warehouse, Research Patient Data Registry (RPDR).[14] Due to national test shortages, PHS prioritised testing for symptomatic patients who were inpatients or in the emergency room.

Rheumatic disease case identification

From this group of COVID-19 positive patients, we identified those with rheumatic disease by searching the list of all diagnoses associated with all encounters in PHS using terms from a comprehensive list of rheumatic disease (online supplementary table 1). Rheumatic disease diagnoses were determined to be present if the reviewing rheumatologist (study authors, KMD or NS-B) agreed with the treating physician's assessment as documented in the electronic health record (EHR); there were no instances of disagreement. Patients with remote polymyalgia rheumatica (last prednisone use ≥5 years prior), crystalline arthropathy, fibromyalgia or osteoarthritis were excluded, as they are not typically considered systemic autoimmune rheumatic diseases,[15] which were the focus of this study.

Non-rheumatic disease comparator identification

Each patient with a rheumatic disease was matched to a comparator patient without a rheumatic disease from the same COVID-19-positive PHS population in a 1:2 ratio at the index date of initial positive COVID-19 test, based on age (±5 years), sex and date of SARS-CoV-2 test that had a positive result (±3 days). For comparators with multiple test dates, the earliest test date yielding a positive result was used. Potential comparators were excluded if they were on chronic immunosuppressive medications (including glucocorticoids and conventional synthetic, targeted synthetic and biological disease-modifying antirheumatic drugs (DMARDs)) for other indications.

Data collection

Clinical variables of interest were systematically extracted from the EHR by manual review if not available as structured data in RPDR. For all patients, we extracted data on demographics, rheumatic disease characteristics, comorbidities, symptoms at the time of COVID-19 infection diagnosis, COVID-19 pharmacological treatment and COVID-19 clinical outcomes (including hospitalisation, intensive care admission, mechanical ventilation and death). If symptoms or comorbidities were not noted in the EHR, they were considered absent. All patients requiring intensive care were intubated and mechanically ventilated, and these were collapsed into a single group (intensive care admission/mechanical ventilation) for analyses. When evaluating the use of COVID-19 treatments, hydroxychloroquine and interleukin-6 receptor inhibitors were only considered as COVID-19 treatments if they were given for the purpose of COVID-19 treatment; hydroxychloroquine continued at a baseline home dose was not counted. For length of hospitalisation and mechanical ventilation, the first and last day were included in the total count. Details collected about rheumatic disease included diagnosis, years since initial diagnosis, disease activity at the time of COVID diagnosis and most recent immunomodulatory or immunosuppressive medication. Laboratory results, such as complete blood cell counts, creatinine, liver function tests and inflammatory markers, were collected as close to the time of SARS-CoV-2 diagnosis or initial hospital admission as possible. For patients with repeated laboratory measurements during the clinical course of their infection, the highest/peak (ie, D-dimer, C reactive protein (CRP), erythrocyte sedimentation rate (ESR) and ferritin) measurements of key results of interest were also extracted. Clinical documentation and communications, including telephone notes and electronic patient messages, were reviewed to evaluate whether the patient's rheumatologist was aware of the COVID-19 infection diagnosis and whether any instructions were given to the patient regarding management of their rheumatic disease medications in the context of infection.

Statistical analysis

Categorical variables were presented as number (percentage), and continuous variables are reported as mean ±SD or median ±IQR, as appropriate. Continuous variables were compared using a two-sample t-test for continuous normally distributed variables or Mann-Whitney U test for continuous non-normally distributed variables. Categorical variables were compared using χ^2 tests. Multivariable logistic regression was used to estimate ORs and 95% CIs when comparing outcomes among patients with rheumatic disease to those without rheumatic disease. The level of significance was set as a two-tailed $p<0.05$, and statistical analyses were completed using SAS statistical software (V.9.4).

RESULTS

Study population

As of 8 April 2020, there were 2154 patients with a positive test result for SARS-CoV-2 in PHS. Of these, 52 (2.2%) had a rheumatic disease, including rheumatoid arthritis (19, 37%), systemic lupus erythematosus (10, 19%), polymyalgia rheumatica (7, 13%), spondyloarthritis (7, 13%), myositis (3, 6%), vasculitis (3, 6%) and sarcoidosis (1, 2%) (table 1). Patients with rheumatic disease and those without rheumatic disease were well matched; the mean age was 63 years and 69% were women in each group. The distribution of race and ethnicity was similar across both groups ($p=0.2$ and $p=0.2$, respectively) with a notable proportion of black/African-American (11 (21%) and 18 (17%)) and Hispanic/Latinx (10 (19%) and 30 (29%)) patients among those with and without rheumatic disease, respectively. The median number of comorbidities was similar in those with rheumatic

Table 1 Clinical characteristics of patients with systemic rheumatic disease with COVID-19 infection (n=52) and age, sex and diagnosis date matched comparators (n=104) at the time of COVID-19 infection diagnosis

Characteristic	Rheumatic disease (n=52)	No rheumatic disease (n=104)	P value
Age (mean, SD, years)	62.5±15.1	63.1±14.9	0.81
Female	36 (69)	72 (69)	1.00
Race			0.20
White	30 (58)	47 (45)	
Black or African-American	11 (21)	18 (17)	
Asian	1 (2)	7 (7)	
Other*	10 (19)	32 (31)	
Hispanic or Latinx ethnicity	10 (19)	30 (29)	0.19
Body mass index (mean, SD, kg/m^2)	29.8±q6.5	29.6±6.8	0.88
Smoking status			0.05
Never	29 (56)	70 (67)	
Former	20 (38)	20 (19)	
Current	2 (4)	6 (6)	
Unknown	1 (2)	8 (8)	
Comorbidities (median (IQR))	1 (0–2)	1 (0–2)	0.30
Hypertension	34 (65)	50 (50)	0.06
Diabetes	13 (25)	29 (29)	0.63
Coronary artery disease	12 (23)	10 (10)	**0.03**
Heart failure	4 (8)	11 (11)	0.53
Pulmonary disease†	21 (40)	28 (28)	0.11
Interstitial lung disease	3 (6)	0	**0.01**
Asthma	14 (27)	17 (16)	0.11
Chronic obstructive pulmonary disease	2 (4)	7 (7)	0.47
Obstructive sleep apnoea	7 (13)	4 (4)	**0.03**
Rheumatological diagnosis‡			
Rheumatoid arthritis	19 (37)		
Systemic lupus erythematosus	10 (19)		
Polymyalgia rheumatica	7 (13)		
Seronegative spondyloarthritis	7 (13)		
Myositis	3 (6)		
Giant cell arteritis	1 (2)		
Sarcoidosis	1 (2)		
Small vessel vasculitis	2 (4)		
Juvenile idiopathic arthritis	1 (2)		
Kikuchi's disease	1 (2)		
Rheumatic disease duration (mean, SD, years)	13.0±9.8		
Rheumatic disease status			
Remission	19 (37)		
Active disease	33 (63)		
Hydroxychloroquine	9 (17)		
Hydroxychloroquine monotherapy	5 (10)		
Any immunosuppressive medication§	39 (75)		
Biological DMARDs	16 (31)		
TNF inhibitor	7 (13)		
IL-6 receptor inhibitor	1 (2)		
Belimumab	2 (4)		
Rituximab	3 (6)		
IL-12/IL-23 inhibitor	2 (4)		
Abatacept	1 (2)		
Targeted synthetic DMARDs	3 (6)		
Tofacitinib	3 (6)		
Conventional synthetic DMARDs	16 (31)		
Methotrexate	9 (17)		
Leflunomide	4 (8)		
Mycophenolate mofetil	3 (6)		
Oral glucocorticoid	19 (37)		
Prednisone-equivalent daily dose (median, IQR, mg)	5 (5–10)		

Data are represented by mean ±SD or number (percentage) unless otherwise indicated. There were no known pregnancies in either cohort.
*Other race includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and not reported.
†Pulmonary disease included interstitial lung disease, asthma, chronic obstructive pulmonary disease or obstructive sleep apnoea.
‡Of the seven patients with spondyloarthropathy, four had psoriatic arthritis, two had ankylosing spondylitis and one had reactive arthritis. Of the two patients with small vessel vasculitis, one had granulomatosis with polyangiitis and one had cutaneous leukocytoclastic vasculitis.
§Hydroxychloroquine was not included as an immunosuppressive medication. Glucocorticoids, biological DMARDs, conventional synthetic DMARDs and targeted synthetic DMARDs were included. TNF inhibitor use included three patients on etanercept, two on infliximab and two on adalimumab.
DMARD, disease-modifying antirheumatic drug; IL, interleukin; TNF, tumour necrosis factor.

disease compared with those without rheumatic disease (1 (0, 2) vs 1 (0, 2), p=0.3). Coronary artery disease (12 (23%) vs 10 (10%), p=0.03), interstitial lung disease (3 (6%) vs 0, p=0.01) and obstructive sleep apnoea (7 (13%) vs 4 (4%), p=0.03) were more common in patients with rheumatic disease. Follow-up time was similar between rheumatic disease patients and comparators (29.1 (±6.8) days vs 29.0 (±6.4) days, respectively, p=0.92).

Among patients with rheumatic disease, 19 (37%) were in remission, while 33 (63%) had active disease at the time of COVID-19 diagnosis. Patients with rheumatic disease were on a variety of immunomodulatory medications: 9 (17%) were on hydroxychloroquine and 39 (75%) were on any immunosuppressive medication (including glucocorticoids and conventional synthetic, targeted synthetic and biological DMARDs, as outlined in table 1). Nineteen (37%) patients were on oral glucocorticoids with a median prednisone-equivalent dose of 5 mg/day.

Manifestations of COVID-19 infection

Symptoms attributed to COVID-19 infection were similar in those with rheumatic disease compared with those without rheumatic disease (table 2), with the most common ones including cough (35 (67%) vs 76 (74%)), fever (34 (65%) vs 66 (64%)), shortness of breath (21 (40%) vs 49 (48%)) and myalgia (26 (50%) vs 40 (39%)). Baseline laboratory values were similar in both groups except that those with rheumatic disease had higher white blood cell counts (6.1 K/µL (5.1–8.5) vs 5.6 K/µL (4.3–7.2), p=0.03). Absolute lymphocyte count at the time of presentation was similar in both groups (0.9 K/µL vs 0.9 K/µL, p=0.39). Though ferritin concentrations were similar at presentation, those with rheumatic disease had a lower peak ferritin than those without rheumatic disease (739 µg/L (379–1402) vs 1196 µg/L (433–2347), p=0.04). Peak levels of ESR, CRP and D-dimer were similar in both groups.

Clinical management and outcomes of COVID-19 infection

Table 3 includes details of the outcomes associated with COVID-19 infections and treatments administered. Of the patients receiving immunosuppressive medications at baseline (n=39), medications were held in 12 (23%) and continued in 6

Table 2 Manifestations of COVID-19 infection in patients with systemic rheumatic disease with COVID-19 (n=52) and age, sex and diagnosis date matched comparators (n=104)

Characteristic	Rheumatic disease (n=52)	No rheumatic disease (n=104)	P value
Symptoms at initial presentation			
Cough	35 (67)	76 (74)	0.40
Fever	34 (65)	66 (64)	0.87
Myalgia	26 (50)	40 (39)	0.18
Malaise	22 (42)	35 (34)	0.31
Shortness of breath	21 (40)	49 (48)	0.40
Sore throat	19 (37)	32 (31)	0.49
Diarrhoea	18 (35)	26 (25)	0.22
Headache	15 (29)	22 (22)	0.50
Rhinorrhoea	14 (27)	27 (26)	0.92
Chest pain	6 (12)	15 (15)	0.60
Anosmia	4 (8)	16 (16)	0.17
Abdominal pain	3 (6)	9 (9)	0.51
Confusion	1 (2)	7 (7)	0.27
Laboratory values*†			
White blood cell count, K/µL (n=30/82)	6.1 (5.1 to 8.5)	5.6 (4.3 to 7.2)	**0.03**
Absolute lymphocyte count, K/µL (n=30/81)	0.9 (0.7 to 1.5)	0.9 (0.6 to 1.3)	0.39
Haemoglobin, g/dL (n=31/83)	12.8 (11.5 to 13.6)	13.4 (12.1 to 14.2)	0.23
Platelets, K/µL (n=31/82)	206 (172 to 249)	187 (153 to 229)	0.34
D-dimer, ng/mL (n=22/64)	955 (550 to 2041)	1059 (643 to 1650)	0.57
Ferritin, µg/L (n=22/62)	513 (256 to 952)	419 (201 to 1063)	0.54
AST, U/L (n=26/73)	42 (28 to 59)	33 (28 to 68)	0.58
ALT, U/L (n=26/73)	25 (17 to 46)	27 (18 to 48)	0.18
Creatinine, mg/dL (n=33/79)	1.0 (0.8 to 1.4)	1.0 (0.8 to 1.1)	0.33
ESR, mm/hour (n=20/51)	49 (36 to 62)	47 (27 to 84)	0.75
CRP, mg/L (n=23/60)	95.6 (51.9 to 178.4)	60.4 (48.8 to 110.5)	0.11
Peak ferritin, µg/L (n=22/57)	739 (379 to 1402)	1196 (433 to 2347)	**0.04**
Peak ESR, mm/hour (n=20/49)	69 (36 to 121)	85 (54 to 124)	0.47
Peak CRP, mg/L (n=26/67)	176 (52 to 262)	143 (61 to 212)	0.40
Peak D-dimer, ng/mL (n=22/61)	1251 (550 to 4000)	1446 (884 to 2972)	0.83

Data are represented by median (IQR) or number (percentage).
Bold signifies P<0.05.
*Laboratory values represent those closest to diagnosis or hospital admission, unless otherwise indicated. White cell count and absolute lymphocyte count from one patient excluded due to outlier from underlying comorbidity. Reference ranges: white cell count: 4.5–11.0 K/uL; absolute lymphocyte count: 1.0–4.8 K/uL; haemoglobin: 13.5–17.5 g/dL; platelets: 150–400 K/µL; D-dimer: <500 ng/mL; ferritin: 20–300 µg/L; AST: 9–32 U/L (women), 10–40 U/L (men); ALT: 7–33 U/L (women), 10–55 U/L (men); creatinine: <1.1 mg/dL; ESR: <13 mm/hour; CRP: <8 mg/L.
†For each lab value, N for cases/comparators is given in parentheses since not all patients had all tests performed.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; K/µL, thousands per microlitre; Ref, reference range.

(12%) patients; this status was unknown in 34 (65%). Documentation that the rheumatologist was notified about the patient's condition and/or medication management was only present in five (10%) patients.

A similar proportion of patients with and without rheumatic disease were hospitalised because of COVID-19 (23 (44%) vs 42 (40%), OR 1.26 (95% CI 0.64 to 2.48), p=0.5). These results were unchanged after adjusting for age, BMI, smoking status and number of comorbidities (adjusted OR 1.22 (95% CI 0.56 to 2.63), p=0.6) (table 4).

Among patients with rheumatic disease, those hospitalised were older (67 (±15) vs 59 (±14) years, p=0.05), had more comorbidities (2 (1.0–2.0) vs 1 (0.0–1.0), p=0.03) and more frequently had diabetes (9 (39%) vs 4 (14%)), p=0.04). A greater proportion of hospitalised patients were black/African-American than among the group not hospitalised (30% vs 14%), though the differences in the overall race distribution between hospitalised and non-hospitalised patients were not statistically significant (online supplementary table 2). Type of rheumatic disease, disease severity and baseline rheumatological medications (including hydroxychloroquine or any immunosuppressive medication) were similar between hospitalised and non-hospitalised patients with rheumatic disease.

Baseline demographics, BMI, smoking status and comorbidities were similar among hospitalised patients with rheumatic disease and comparators (online supplementary table 3). Among hospitalised patients, those with and without rheumatic disease had similar proportions requiring supplemental oxygen (74% vs 67%, p=0.55); however, there were significantly more patients with rheumatic disease who required intensive care admission/mechanical ventilation (48% vs 18%, p=0.01). Compared with those without rheumatic disease, those with a rheumatic disease had over a threefold higher odds of requiring mechanical ventilation (OR 3.22 (95% CI 1.16 to 8.92), p=0.02), and this persisted after adjusting for age, BMI, smoking and comorbidities (adjusted OR 3.11 (95% CI 1.07 to 9.05), p=0.04). When specifically adjusting for age, hypertension, coronary artery disease and lung disease, odds of mechanical ventilation remained higher in

Table 3 Clinical outcomes of patients with systemic rheumatic disease with COVID-19 infection (n=52) and age, sex and diagnosis date matched comparators (n=104)

Characteristic	Rheumatic disease (n=52)	No rheumatic disease (n=104)	P value
Hospitalisation	23 (44)	42 (40)	0.50
Length of stay (days)	8 (4–21)	9 (4–16)	0.83
Oxygen required*	17 (74)	26 (67)	0.55
Intensive care admission/ mechanical ventilation*†	11 (48)	7 (18)	**0.01**
Days of mechanical ventilation	15 (4–24)	12 (5–28)	0.53
Pharmacological treatment‡	23 (44)	36 (35)	0.24
Hydroxychloroquine§	16 (31)	19 (19)	0.10
Azithromycin	18 (35)	26 (26)	0.25
Interleukin-6 receptor inhibitor	1 (2)	0	0.16
Remdesivir	2 (4)	0	0.05
Management of immunosuppressive medications during infection¶			
Medications held	12 (23)		
Medications continued	6 (12)		
Unknown	34 (65)		
Rheumatologist notified	5 (10)		
Deceased	3 (6)	4 (4)	0.69

Data are represented by median (IQR) or number (percentage).
*Denominator used for calculation is the number of hospitalised patients.
†No patients required extracorporeal membrane oxygenation. All patients with intensive care admission were also mechanically ventilated.
‡One patient among the cases and eight patients among the comparators were enrolled in randomised placebo-controlled trials, which included study drugs of tocilizumab, sarliumab and remdesivir, and the patients' randomisation arms are unknown.
§Hydroxychloroquine given for the purpose of COVID-19 treatment or beyond baseline dose if patient was already receiving this as a medication for rheumatic disease.
¶Hydroxychloroquine was not included as an immunosuppressive medication. Glucocorticoids, biological DMARDs, conventional synthetic DMARDs and targeted synthetic DMARDs were included.
DMARDs, disease-modifying antirheumatic drugs.

Table 4 Associations between presence versus absence of rheumatic disease and COVID-19 outcomes

Outcomes (OR, 95% CI)	Rheumatic disease (n=52)	No rheumatic disease (n=104)	P value
Hospitalisation			
Unadjusted	1.26 (0.64 to 2.48)	1.0 (ref)	0.50
Adjusted model 1	1.27 (0.61 to 2.64)	1.0 (ref)	0.52
Adjusted model 2	1.22 (0.56 to 2.63)	1.0 (ref)	0.61
Adjusted model 3	1.10 (0.51 to 2.38)	1.0 (ref)	0.81
Mechanical ventilation/intensive care admission*			
Unadjusted	3.22 (1.16 to 8.92)	1.0 (ref)	**0.02**
Adjusted model 1	3.26 (1.17 to 9.09)	1.0 (ref)	**0.02**
Adjusted model 2	3.11 (1.07 to 9.05)	1.0 (ref)	**0.04**
Adjusted model 3	2.92 (1.002 to 8.490)	1.0 (ref)	**0.049**
Death			
Unadjusted	1.53 (0.33 to 7.11)	1.0 (ref)	0.59
Adjusted model 1†	1.58 (0.31 to 8.03)	1.0 (ref)	0.58

Model 1 adjusted for age and body mass index (BMI). Model 2 adjusted for age, BMI, smoking and number of comorbidities. Model 3 adjusted for age, hypertension, coronary artery disease and presence of lung disease.
*All patients who required intensive care required mechanical ventilation.
†Model 2 and model 3 were not performed for mortality outcome due to low event rate.

rheumatic disease patients compared with matched comparators (OR 2.92, 95% CI 1.002 to 8.490). Mechanical ventilation was required across a number of different rheumatic diseases. There was no significant difference in mortality in those with rheumatic disease compared with those without rheumatic disease (three deaths (6%) vs 4 deaths (4%); OR 1.53 (95% CI 0.33 to 7.11), p=0.6). As of 26 April 2020, seven (13%) patients with rheumatic disease and four (4%) patients without rheumatic disease remained hospitalised, despite having a similar hospital length of stay between rheumatic disease patients and comparators (11.6 (±9.4) days vs 11.4 (±8.6) days, respectively, p=0.93).

DISCUSSION

In this matched cohort study of patients with COVID-19 infection, we found that patients with rheumatic disease had similar symptoms and odds of hospitalisation and mortality but threefold higher odds of intensive care admission/mechanical ventilation compared with patients without rheumatic disease. Our estimates regarding intensive care admission/mechanical ventilation and mortality are likely conservative since more patients with rheumatic disease remain hospitalised at the time of submission compared with comparators. Our findings are important benchmarks in the care of patients with rheumatic disease as the COVID-19 pandemic continues to unfold and highlight the need for close monitoring when patients with rheumatic disease are diagnosed with COVID-19.

To our knowledge, this is the first study to evaluate the outcomes of COVID-19 infection in patients with rheumatic disease compared with those without rheumatic disease. A recent study reporting outcomes in a group of patients with rheumatic disease in New York City found that only one patient (7%) needed mechanical ventilation but included only patients with inflammatory arthritis or inflammatory bowel disease, a younger population than ours, and a mix of patients with definite and suspected COVID-19 infections.[7] Our findings regarding high rates of respiratory complications are similar to those described in a cohort of lupus patients (65% required supplemental oxygen and 29% required mechanical ventilation), though that study did not include a comparator population.[9] The hospitalisation rate in patients with rheumatic disease in our study is similar to that reported in the Global Rheumatology Alliance (GRA) Physician-Reported Registry[16] (44% vs 46%), and the mortality rate in patients without rheumatic disease was similar to that reported in MA[13] (4% in our cohort vs 5% in MA during the same time period), supporting the external validity of our findings. However, the GRA reported higher rates of fever, cough and shortness of breath than our cohort, which may be due to differences in how symptoms were recorded and extracted across the world.[17] We also found a surprising proportion of patients who were black/African-American or Hispanic/Latinx (21 (40%) of rheumatic disease patients and 48 (46%) without rheumatic disease), which differs from the typical demographics at PHS but are congruent with widely reported observations regarding racial and ethnic disparities in the risk of COVID-19 infection and its complications.[18 19]

The higher odds of intensive care admission/mechanical ventilation among hospitalised patients with rheumatic disease is concerning, but the factors underlying this association are unclear. Compared with those without rheumatic disease, patients with rheumatic disease more often had coronary artery

disease and pulmonary disease, but our findings persisted after adjusting for comorbidities. However, there may be residual confounding due to unmeasured differences in severity of comorbidities or conditions not measured. Differences in exposures to immunosuppressive medications, which were commonly used in patients with rheumatic disease, are another potential explanation. Additional studies are needed with larger sample sizes to understand whether certain immunosuppressive medications predispose patients with rheumatic disease to respiratory failure. It is possible that these results may also be applicable to other patient populations who are immunosuppressed, but dedicated confirmatory studies are required. Future studies can also examine COVID-19 outcomes in other rheumatic diseases such as gout.

The potential efficacy of hydroxychloroquine for the prevention and treatment of COVID-19 infections has received widespread attention and led to significant controversy.[20] In our study, a minority of patients with rheumatic disease were on hydroxychloroquine at the time of diagnosis, which limits our ability to draw conclusions regarding the impact of this medication on infection outcomes. However, it is apparent from our data that patients treated with hydroxychloroquine for rheumatic disease developed COVID-19 infection and are still at risk for poor outcomes.

The impact on outcomes of continuing or holding immunosuppression in the context of COVID-19 is unknown, though current recommendations by the American College of Rheumatology suggest holding all immunosuppressive medications, with the potential exception of interleukin-6 receptor inhibitors.[21] We were only able to confirm that immunosuppressive medications were held in a minority (12, 23%) of cases in the setting of infection; therefore, the impact of holding versus continuing immunosuppression on COVID-19 outcomes is unclear. In the majority (34, 65%) of cases, there was no documentation of communication between providers managing COVID-19 and the patient's rheumatologist. Our findings regarding COVID-19 outcomes and rheumatic disease highlight the need for close communication among providers managing COVID-19 and rheumatologists for patients with rheumatic disease.

A particular strength of our study is that it is the first to compare outcomes among patients with rheumatic disease to a comparator group and identify rheumatic disease patients from a population of patients with a diagnosis of COVID-19 based on positive COVID-19 PCR testing in a large healthcare system rather than from a single clinic or disease cohort.[6–9] However, our study has certain limitations. First, the generalisability of our findings may be limited because our cohort was assembled from PHS, which includes two tertiary care facilities. However, PHS also includes primary care clinics and community hospitals. Second, while it is possible that some patients may have been hospitalised outside of our system after being tested within our system, thorough follow-up notes were available in 94% of patients, and thus it is likely that outside hospitalisations would have been detected. Third, we only included patients who were COVID-19 positive by PCR, thus excluding patients who may have been asymptomatic, had milder disease or may not have qualified for testing given the ongoing testing shortages in the USA. To minimise any differences in indications for testing, we matched patients according to the approximate date their tests were performed. Fourth, our sample size limited the power of some analyses, such as outcomes in specific rheumatic conditions. Additionally, there was no statistical difference in mortality, but there were numerically more deaths in the rheumatic disease group (6%) than the non-rheumatic disease comparator group (4%). This difference may have large public health significance if confirmed in larger sample sizes, so our study does not eliminate a true effect of rheumatic disease on COVID-19 infection outcomes. However, this is a rapidly evolving pandemic with significant implications for patients with rheumatic disease, and we judged the importance of sharing data to inform clinical care to be paramount.

In conclusion, we found that patients with rheumatic disease had similar rates of hospitalisation though higher rates of intensive care admission and mechanical ventilation compared with those without rheumatic disease. These results are concerning and underscore the need for close monitoring of patients with rheumatic disease during the pandemic. Additional studies are needed to confirm and identify factors responsible for the observed differences.

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