Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study

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Summary

Background In the ongoing COVID-19 pandemic, the susceptibility of patients with rheumatic diseases to COVID-19 remains unclear. We aimed to investigate susceptibility to COVID-19 in patients with autoimmune rheumatic diseases during the ongoing COVID-19 pandemic.

Methods We did a multicentre retrospective study of patients with autoimmune rheumatic diseases in Hubei province, the epicentre of the COVID-19 outbreak in China. Patients with rheumatic diseases were contacted through an automated telephone-based survey to investigate their susceptibility to COVID-19. Data about COVID-19 exposure or diagnosis were collected. Families with a documented history of COVID-19 exposure, as defined by having at least one family member diagnosed with COVID-19, were followed up by medical professionals to obtain detailed information, including sex, age, smoking history, past medical history, use of medications, and information related to COVID-19.

Findings Between March 20 and March 30, 2020, 6228 patients with autoimmune rheumatic diseases were included in the study. The overall rate of COVID-19 in patients with an autoimmune rheumatic disease in our study population was 0·43% (27 of 6228 patients). We identified 42 families in which COVID-19 was diagnosed between Dec 20, 2019, and March 20, 2020, in either patients with a rheumatic disease or in a family member residing at the same physical address during the outbreak. Within these 42 families, COVID-19 was diagnosed in 27 (63%) of 43 patients with a rheumatic disease and in 28 (34%) of 83 of their family members with no rheumatic disease (adjusted odds ratio [OR] 2·68 [95% CI 1·14–6·27]; p=0·023). Patients with rheumatic disease who were taking hydroxychloroquine had a lower risk of COVID-19 infection than patients taking other disease-modifying anti-rheumatic drugs (OR 0·09 [95% CI 0·01–0·94]; p=0·044). Additionally, the risk of COVID-19 was increased with age (adjusted OR 1·04 [95% CI 1·01–1·06]; p=0·0081).

Interpretation Patients with autoimmune rheumatic disease might be more susceptible to COVID-19 infection than the general population.

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Introduction

The pathogen causing COVID-19 was identified as a novel coronavirus by sequencing of lower respiratory tract samples from affected patients. This novel coronavirus shares 79·6% sequence identity with severe acute respiratory syndrome coronavirus (SARS-CoV)[1] and has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its detection in December, 2019, the virus spread rapidly to more than 200 countries and territories around the world and was declared a pandemic on March 11, 2020. There is currently no specific treatment available for COVID-19.

Although comorbidities such as diabetes and cardiac disease have been identified as risk factors for severe COVID-19,[2] whether patients with autoimmune rheumatic disease have an increased vulnerability to this infection remains unknown. Autoimmune rheumatic diseases are characterised by irregular functioning of the immune system and immune-mediated inflammation in target tissues. Patients with autoimmune rheumatic diseases rely on immunosuppressive disease-modifying anti-rheumatic drugs (DMARDs) to control symptoms and disease progression, and are therefore immunocompromised and more susceptible to infections than the general population.[3] However, several DMARDs, including hydroxychloroquine and baricitinib, are being investigated for their antiviral effects in COVID-19 and might affect the susceptibility of patients with rheumatic diseases to SARS-CoV-2 infection.[4,5]

The immune system has an important role in the defence against viruses and virus-associated tissue damage. Most patients with SARS-CoV-2 infection will completely recover as a result of effective immune responses. Thevarajan and colleagues[6] noted that circulating concentrations of antibody-secreting cells and activated follicular helper T cells, two important immune cell populations

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Research in context

Evidence before this study

We searched PubMed, ScienceDirect, and Google Scholar on March 15, 2020, for studies reporting susceptibility to COVID-19 in patients with rheumatic disease, using the search terms "COVID-19 susceptibility" or "coronavirus disease susceptibility" or "novel coronavirus susceptibility" and "rheumatic disease" or "rheumatic condition". We identified no published research articles reporting on the susceptibility to COVID-19 in patients with rheumatic disease. We also searched for studies assessing the effects of anti-rheumatic medications on COVID-19 in patients with rheumatic disease, using the search terms "COVID-19" or "coronavirus disease" or "novel coronavirus" and "rheumatic disease" or "rheumatic condition" and "anti-rheumatic medication"; we did not identify any research articles assessing the potential effect of anti-rheumatic medications on COVID-19 in these patients.

Added value of this study

To the best of our knowledge, this is the first study based on a primary dataset of cases and close contacts to analyse the susceptibility of patients with autoimmune rheumatic disease to COVID-19. Patients with autoimmune rheumatic disease had a higher rate of COVID-19 than their family members living in the same household during the outbreak (63% *vs* 34%). This finding provides some insight into the risk of COVID-19 in patients with autoimmune rheumatic diseases.

Implications of all the available evidence

Our results indicate that patients with rheumatic disease might be more susceptible to COVID-19 than the general population. These findings can be valuable for strategic planning and management of patients with rheumatic disease during the ongoing COVID-19 pandemic.

responsible for antiviral immunity, were increased before symptomatic recovery of a patient with COVID-19 and concurrent with the clearance of SARS-CoV-2. Recent studies have also shown that antibodies against SARS-CoV-2 could be generated efficiently after recovery of COVID-19 and might provide protection against COVID-19 through convalescent plasma transfusion.[7,8] These results suggest that an antiviral immune response is crucial for viral clearance. However, hyperactivation of the immune response in COVID-19 might also cause tissue damage in the lungs and other organs.[2,9] Therefore, several immunomodulating drugs including corticosteroids, hydroxychloroquine, and anti-cytokine agents are being used for the treatment of severe cases of COVID-19.[5] In the ongoing COVID-19 pandemic, there is an urgent need for timely research to assess the susceptibility of patients with rheumatic disease to SARS-CoV-2 infection and the potential risks and benefits of using anti-rheumatic drugs in COVID-19 treatment.

Analyses of comorbidities in patients with COVID-19 suggest that diabetes, respiratory disease, and cardiovascular disease might be risk factors for COVID-19.[10] However, the susceptibility to COVID-19 among patients with low-prevalence disorders, such as rheumatic diseases, is difficult to assess in the general population. We aimed to investigate susceptibility to COVID-19 in patients with autoimmune rheumatic diseases in Hubei province, China.

Methods

Study design and participants

We did a multicentre retrospective observational study of patients with rheumatic disease in Hubei province, the epicentre of the COVID-19 outbreak in China. The study protocol was approved by the institutional review board of Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, and was registered with chictr.org, ChiCTR2000031504. We did a telephone-based survey of patients with rheumatic disease to investigate their susceptibility to COVID-19. Verbal consent was obtained from patients at the start of the survey. As this study was carried out during the height of the pandemic in China, the ethics committee approved that verbal consent be obtained at the start of the survey, and waived the need for written consent. The inclusion criteria were as follows: a confirmed diagnosis of rheumatic disease, including rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, polymyositis or dermatomyositis, IgG4-related disease, or undifferentiated connective tissue disease; and a disease duration of at least 3 months. The following patients were excluded from the study: patients who were diagnosed with rheumatic diseases that do not require an immunosuppressive therapy, such as gout, osteoarthritis, and ankylosing spondylitis (in China, most patients with ankylosing spondylitis are treated with non-steroidal anti-inflammatory drugs and a relatively small proportion [about 10% in this study] used immunosuppressive agents such as tumour necrosis factor [TNF] inhibitors); patients with invalid contact information or who did not answer the telephone after three consecutive calls at an interval of 1 per day; and patients who declined participation or discontinued before completion of the survey.

Data collection

Patient demographic information (including age, sex, telephone number), medical history, and data on current medication use were retrieved from the Smart System of Disease Management (SSDM). Information about COVID-19 exposure or diagnosis in patients and their families was collected by an automated telephone survey. The answers were converted into text in a spreadsheet by an automatic speech recognition programme (Azure, Microsoft). The following information was acquired

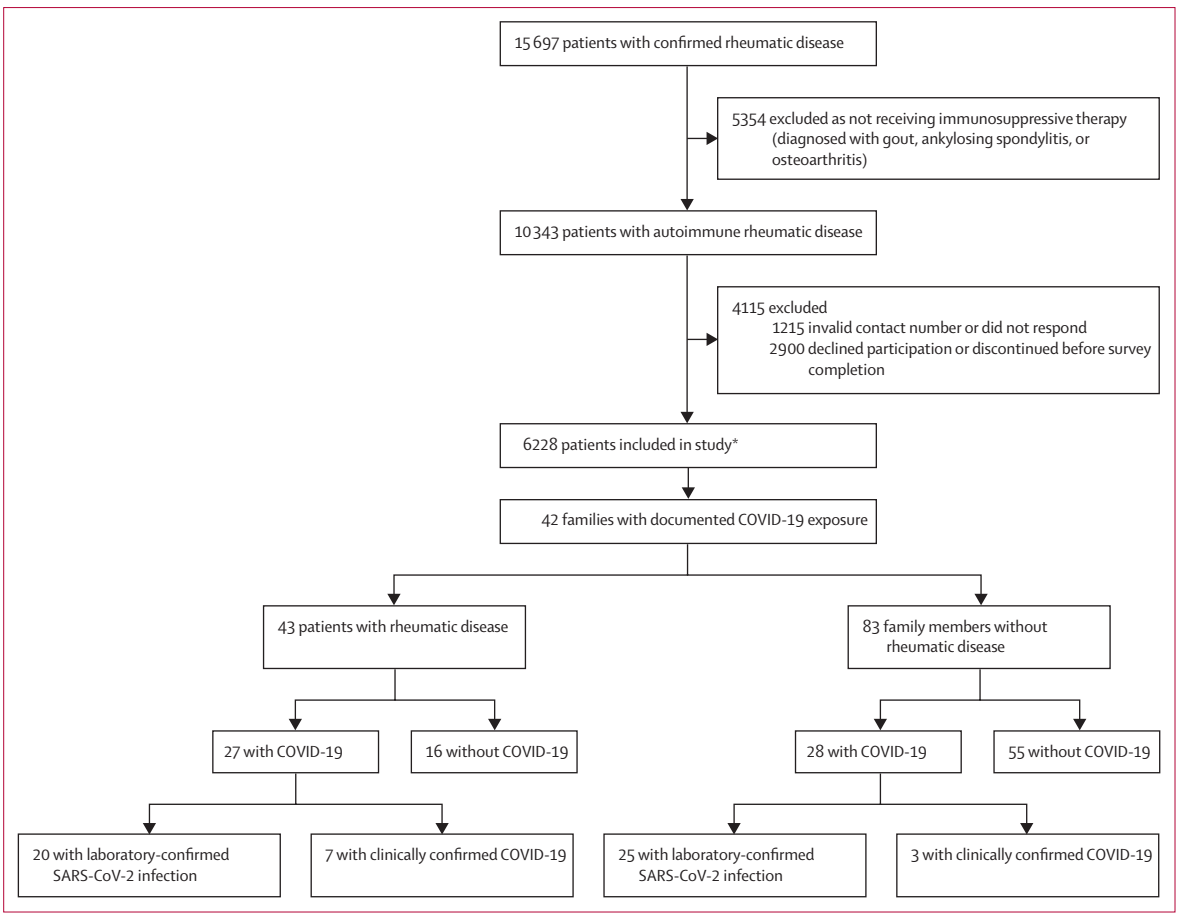

Figure: **Selection of patients**
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Information collected from 6228 patients and their family members residing at the same physical address during the COVID-19 outbreak to identify all families with at least one household member diagnosed with COVID-19 between Dec 20, 2019, and March 20, 2020.

through a subsequent telephone call carried out by medical professionals: total number of family members residing at the same address during the outbreak, infection status of COVID-19, date of COVID-19 diagnosis, severity, laboratory tests of SARS-CoV-2 RNA, hospital admission status (admitted to hospital or self-quarantined after outpatient diagnosis), past medical history, and age and sex of infected individuals. The use of current anti-rheumatic medications was also confirmed with patients during the survey to ensure the records in the medical system were accurate. COVID-19 cases among patients with rheumatic disease and their household members were identified by self-reporting of inpatient diagnosis or outpatient diagnosis in local designated hospitals through telephone surveys. Families with at least one household member diagnosed with COVID-19 between Dec 20, 2019, and March 20, 2020, were identified and all members of the household were considered to have direct COVID-19 exposure history. All patients with rheumatic disease and their family members without rheumatic disease, residing at the same physical address during the outbreak, were considered close contacts and tested for SARS-CoV-2 RNA in designated local hospitals when there was a confirmed case in the family. Individuals who were diagnosed with COVID-19 either self-isolated or were admitted to hospital after the diagnosis. Diagnosis of COVID-19 was determined according to the Guidance for Coronavirus Disease 2019 (5th edition) released by the National Health Commission of China: either confirmed by a positive SARS-CoV-2 RNA test or by clinical diagnosis (close contact history plus COVID-19 symptoms plus typical high-resolution CT imaging features of COVID-19). All real-time PCR tests of SARS-CoV-2 RNA were done in designated local hospitals for COVID-19.

Statistical analysis

For patients and their family members, the incidence of COVID-19 was calculated as the total number of infected individuals divided by the number of individuals with COVID-19 exposure history. All statistical analyses were done with GraphPad Prism version 8.3.0 (GraphPad Software) or SPSS, version 25 (IBM SPSS Statistics).

See Online for appendix

	Patients (n=6228)
Sex	
Male	811 (13·0%)
Female	5417 (87·0%)
Age category	
<18 years	69 (1·1%)
18–29 years	772 (12·4%)
30–39 years	1312 (21·1%)
40–49 years	1337 (21·5%)
50–59 years	1578 (25·3%)
60–69 years	843 (13·5%)
≥70 years	232 (3·7%)
Missing	85 (1·4%)
Rheumatic disease	
Rheumatoid arthritis	2766 (44·4%)
Systemic lupus erythematosus	1964 (31·5%)
Sjögren's syndrome	652 (10·5%)
IgG4-related disease	64 (1·0%)
Undifferentiated connective tissue disease	208 (3·3%)
Other	574 (9·2%)
DMARDs*	
Corticosteroids	1193 (51·7%)
Hydroxychloroquine	616 (26·7%)
Leflunomide	967 (41·9%)
Thalidomide	54 (2·3%)
Methotrexate	565 (24·5%)
Mycophenolate mofetil	224 (9·7%)
Biological DMARDs	56 (2·4%)
Targeted synthetic DMARDs	36 (1·6%)
Tacrolimus	90 (3·9%)
Cyclophosphamide	17 (0·7%)
Cyclosporine A	93 (4·0%)
Missing	3919

Data are n or n (%). DMARDs=disease-modifying anti-rheumatic drugs. *Data on DMARD use are provided for 2309 patients, and percentages reported for this subpopulation. Some patients were taking two or more DMARDs.

Table 1: **Demographics of participating patients**

Descriptive and frequency statistics (mean, [SD] and percentages) were used to describe baseline demographic information and clinical information. Age, sex, smoking history, and comorbidities previously reported to be associated with COVID-19 mortality[2,10–12] were selected as covariates by clinical relevance. For the logistic regression models, missing data such as age and sex of family members were imputed with the fully conditional specification method with ten imputations for each missing data value. Binary logistic regression analyses were done with SPSS, version 25, to analyse the effect of rheumatic disease, demographic factors, or anti-rheumatic medications on COVID-19 infection in individuals with exposure history. Conditional logistic regression was used to adjust for multiple potential confounders including the cluster effect of family, when assessing the potential effect of rheumatic disease on COVID-19 infection. For this study, patients with rheumatic disease and their family members were clustered at the family level. Comparison of continuous variables between two groups was done with the student's *t* test. All tests were two-tailed and p values less than 0·05 were considered significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 20 and March 30, 2020, we identified 15 697 patients with a confirmed diagnosis of a rheumatic disease in Hubei province, China, from an SSDM medical record system. After exclusion of 5354 patients who were not receiving immunosuppressive therapy, 10 343 patients with autoimmune rheumatic diseases were contacted by telephone (figure). Among these 10 343 patients, 1215 had an invalid telephone number or did not answer the telephone, resulting in a pick-up rate of 88·3% (9128 of 10 343). 2900 patients who declined participation or discontinued the study before completion of the survey were also excluded. Therefore, we analysed data from 6228 patients with autoimmune rheumatic diseases. The characteristics of included and excluded patients are summarised in the appendix (p 1).

The mean age of patients was 45·9 (SD 14·4) years and there were more female than male patients (5417 [87·0%] of 6228 *vs* 811 [13·0%] of 6228). The disease distribution and details of anti-rheumatic medications in these patients are summarised in table 1.

42 families reported having at least one household member diagnosed with COVID-19 between Dec 20, 2019, and March 20, 2020; in total, 43 patients with autoimmune rheumatic disease and 83 of their relatives reported exposure to COVID-19. 27 (0·43%) of 6228 patients with autoimmune rheumatic disease reported that they were diagnosed with COVID-19. 20 patients and 25 family members had laboratory-confirmed COVID-19 (SARS-CoV-2 RNA positive), whereas seven patients and three family members had clinically confirmed COVID-19 (SARS-CoV-2 RNA negative, but had close contact history plus COVID-19 symptoms plus typical high-resolution CT imaging features of COVID-19; figure). In 16 families, only patients with autoimmune rheumatic disease had COVID-19; in 11 families, both patients with autoimmune rheumatic disease and family members without a rheumatic disease had COVID-19; and in 15 families, only family members without autoimmune rheumatic disease had COVID-19 (appendix p 6). In five families, patients with rheumatic disease developed symptoms first; in three families, household members without rheumatic disease developed symptoms first; and in three families,

household members developed symptoms around the same time.

To further compare infection rates in patients with rheumatic disease versus those without, we analysed infection rates in the 42 families with confirmed COVID-19 exposure history. No significant difference in age was observed between patients with rheumatic disease and those without (mean age 49·2 [SD 11·6] years *vs* 48·4 [19·1] years, p=0·82; table 2). 27 (63%) of 43 patients with rheumatic disease and 28 (34%) of 83 family members without rheumatic disease developed COVID-19 (odds ratio [OR] 3·32 [95% CI 1·54–7·14], p=0·0023; table 3). The OR was 2·68 (95% CI 1·14–6·27; p=0·023) after adjustment for age and sex as confounding factors (table 3). Similar results were observed when only laboratory-confirmed cases were analysed (appendix pp 2–3). The risk of COVID-19 was increased with age after adjustment for sex and rheumatic disease (OR 1·04 [95% CI 1·01–1·06]; p=0·0081). We did not observe a significant effect of sex on the risk of COVID-19 after adjustment (OR 0·60 [95% CI 0·26–1·35]; p=0·22; table 3).

To analyse whether anti-rheumatic drugs are associated with susceptibility to COVID-19 in patients with rheumatic disease, we compared the characteristics of patients with COVID-19 to those without COVID-19 (table 4). The mean age of patients with COVID-19 was 50·9 (SD 10·4) years and that of non-COVID-19 patients was 46·3 (13·4) years (p=0·22). 16 (37%) of the 43 patients with rheumatic disease and a history of exposure to COVID-19 were on hydroxychloroquine medication. There were no significant differences in age, sex, comorbidities, and prescriptions for other immunosuppressive drugs between patients taking hydroxychloroquine and those who did not take hydroxychloroquine (appendix p 4). However, patients with SLE tended to be prescribed hydroxychloroquine more often than patients with other rheumatic diseases. Therefore, SLE was included as a confounder when assessing the potential effects of anti-rheumatic medications on COVID-19. Nine (56%) of 16 patients without COVID-19 and with autoimmune rheumatic disease were taking hydroxychloroquine, whereas seven (26%) of 27 patients with rheumatic disease and COVID-19 were on hydroxychloroquine treatment. After adjustment for age, sex, smoking, infection in family members, comorbidities, and SLE, patients with rheumatic disease taking hydroxychloroquine had a lower risk of COVID-19 than those who were taking other DMARDs (OR 0·09 [95% CI 0·01–0·94], p=0·044). By contrast, the rate of corticosteroid use in patients with COVID-19 was similar to that in those without COVID-19 (OR 1·06 [95% CI 0·21–5·40], p=0·72). All patients were taking low-dose to medium-dose corticosteroids, ranging from 5 mg per day to 15 mg per day (converted to dose of prednisone, appendix p 5). We observed no significant differences in age, sex, smoking history, comorbidities, and the use of other DMARDs.

	With rheumatic disease (n=43)	Without rheumatic disease (n=83)	p value
Age, years	49·2 (11·6)	48·4 (19·1)	0·82
Sex			
Male	10 (23%)	34/55 (62%)	0·00014
Female	33 (77%)	21/55 (38%)	..
Data missing	0	28	..
COVID-19	27 (63%)	28 (34%)	0·0018*

Data are mean (SD), n (%), or n/N (%). Data shown for patients with rheumatic disease and their family members residing at the same physical address during the outbreak (Dec 20, 2019, to March 20, 2020). *p=0·012 after adjustment for age and family member infection status.

Table 2: **Characteristics of individuals with COVID-19 exposure history**

	OR (95% CI)	p value	Adjusted OR (95% CI)*	Adjusted p value*
Rheumatic disease	3·32 (1·54–7·14)	0·0023	2·68 (1·14–6·27)	0·023
Age (years)	1·03 (1·01–1·06)	0·019	1·04 (1·01–1·06)	0·0081
Sex (male *vs* female)	0·40 (0·20–0·83)	0·013	0·60 (0·26–1·35)	0·22

OR=odds ratio. The OR is expressed as the estimated increase in the odds of infection per year increase in age. *OR and p values in multivariable logistic model.

Table 3: **Results from logistic regression analyses of patients with rheumatic disease and history of exposure to COVID-19**

Discussion

The risk of COVID-19 in patients with rheumatic disease remains unclear.[4] Although patients with rheumatic disease on certain medications are immunocompromised and vulnerable to infection, several anti-rheumatic medications have been proposed to have an antiviral effect. Nevertheless, data about the epidemiological characteristics of COVID-19 in patients with rheumatic disease are scarce. Our study provides some insight into COVID-19 susceptibility in patients with autoimmune rheumatic diseases.

Patients with autoimmune rheumatic diseases rely on DMARDs to control autoimmune processes and disease progression. Because of their dysregulated immune function and the immunosuppressive effect of DMARDs, patients on these medications have increased vulnerability to infections. Autoimmune rheumatic diseases are frequently complicated by primary immunodeficiency.[13] Therefore, an autoimmune disease itself can result in immunosuppression and increased risk of infection. Additionally, the use of DMARDs is associated with increased risk of infection.[14] A recent analysis of clinical features of COVID-19 in 21 patients with rheumatic diseases showed that patients with rheumatic diseases might be at an increased risk of developing respiratory failure if they develop COVID-19.[15] Some DMARDs such as hydroxychloroquine and baricitinib have been proposed to have antiviral effects in patients with SARS-CoV-2 infection. Biological DMARDs, such as interleukin (IL)-6 and IL-1 inhibitors, have also been suggested for treatment of COVID-19 in a subset of patients with hyperinflam-

	Rheumatic disease with COVID-19 (n=27)	Rheumatic disease without COVID-19 (n=16)	p value
Age, years	50·9 (10·4)	46·3 (13·4)	0·22
Sex			
Male	6 (22%)	4 (25%)	0·84
Female	21 (78%)	12 (75%)	0·84
Smoking history	3 (11%)	2 (13%)	0·89
DMARDs			
Corticosteroids	15 (56%)	8 (50%)	0·72
Hydroxychloroquine	7 (26%)	9 (56%)	0·047*
Leflunomide	8 (30%)	8 (50%)	0·18
Thalidomide	2 (7%)	0	0·27
Methotrexate	5 (19%)	3 (19%)	0·96
Mycophenolate mofetil	1 (4%)	1 (6%)	0·70
Biological DMARDs	1 (4%)	0	0·44
Rheumatic disease category†			
Rheumatoid arthritis	16 (59%)	7 (44%)	0·32
Systemic lupus erythematosus	8 (30%)	4 (25%)	0·75
Sjögren's syndrome	2 (7%)	0	0·27
Undifferentiated connective tissue disease	1 (4%)	1 (6%)	0·70
Other rheumatic disease	4 (15%)	4 (25%)	0·74
Comorbidities			
Cardiovascular	7 (26%)	3 (19%)	0·59
Diabetes	3 (11%)	0	0·17
Pulmonary disease	3 (11%)	0	0·17
Other	1 (4%)	1 (6%)	0·70

Data are mean (SD) or n (%). DMARDs=disease-modifying anti-rheumatic drugs. *p=0·044 after adjusting for age, sex, smoking, systemic lupus erythematosus, infection in other family members, and comorbidities (odds ratio 0·09 [95% CI 0·01–0·94]). †Some patients had more than one diagnosis.

Table 4: **Characteristics of patients with rheumatic disease and history of COVID-19 exposure**

mation.[16] A study from Italy reported four cases of confirmed COVID-19 and four highly suggestive cases of COVID-19 in which all eight patients were taking biological or targeted synthetic DMARDs for rheumatoid arthritis or spondyloarthritis.[17] None of these patients developed severe respiratory complications and the authors suggested that these treatments might suppress the aberrant inflammatory and cytokine response that is responsible for severe respiratory complications in COVID-19.[17] Anakinra, a biological DMARD that blocks IL-1 signalling, has also shown beneficial effects in reducing COVID-19 mortality and invasive mechanical ventilation rates in patients with hyperinflammation, although clinical trials are required to confirm efficacy.[18,19] In an analysis of data from the COVID-19 Global Rheumatology Alliance physician-reported registry, the use of TNF inhibitors in patients with rheumatic diseases was associated with reduced risk of hospital admission for COVID-19.[20] Therefore, the overall effect of DMARDs on COVID-19 infection might be complex. In this study, we evaluated the overall susceptibility to COVID-19 in patients with rheumatic disease and the potential effects of some DMARDs on COVID-19. We identified 27 patients with COVID-19 from 6228 patients with autoimmune rheumatic diseases; the overall COVID-19 infection rate of 0·43% in patients with autoimmune rheumatic diseases in Hubei province was higher than the calculated overall infection rate of 0·12% in Hubei province as of March 20, 2020 (67 800 COVID-19 cases out of Hubei's population of 58 500 000).[21] We identified another 16 families in which household members without rheumatic diseases had COVID-19. Together, there were 42 families (43 patients with rheumatic diseases and 83 family or household members without) in which at least one household member had COVID-19. To assess the susceptibility to COVID-19 in patients with rheumatic diseases, we compared infection rates in patients with autoimmune rheumatic disease with infection rates in household members without rheumatic disease. Consistent with our previous analysis, further analysis of families with COVID-19 exposure history indicated that the rate of infection was higher in patients with rheumatic diseases than in their family members. These results indicate that patients with rheumatic disease might be more vulnerable to COVID-19 than the general population. A large proportion (potentially as high as 86·2%) of COVID-19 cases worldwide have been reported to be asymptomatic and might not have been identified without extensive contact tracing and testing,[22] and the incubation periods for most COVID-19 cases in China were less than 14 days.[23] Although all family members within the same household as a confirmed case were tested for SARS-CoV-2 RNA in this study, the identification of the first case in the family might have largely depended on the manifestation of COVID-19 symptoms, especially during the early stages of the outbreak. Therefore, the overall infection rate calculated in this study might be an underestimate considering the number of unidentifiable asymptomatic cases. Future population-wide epidemiological studies with serology tests are needed to address this issue. We also found that the risk of SARS-CoV-2 infection increases with age, which is consistent with recent publications.[24] Based on these findings, patients with rheumatic diseases should take all necessary precautions to protect themselves from COVID-19 and reduce the risk of SARS-CoV-2 infection.

Chloroquine and hydroxychloroquine were originally used as oral antimalarial medicines and are now widely used to treat rheumatic disease because of their mild immunosuppressive effects. Recent studies have shown that chloroquine and hydroxychloroquine could suppress SARS-CoV-2 replication in vitro at a concentration that is clinically achievable.[25,26] Current investigations into the role of hydroxychloroquine in COVID-19 are inconclusive. Although some reports suggest an improvement in symptoms[27,28] after the use of chloroquine or hydroxychloroquine, other studies have reported no benefits,[29–31] or even hazardous or toxic effects.[32] Therefore, further

randomised controlled trials are required to assess the efficacy and safety of hydroxychloroquine in patients with COVID-19. In contrast to trials done to assess the therapeutic effect of hydroxychloroquine in the general population,[27–32] only a small number of reports have evaluated the preventive effects of chronically administered hydroxychloroquine on COVID-19 in patients with rheumatic diseases, with inconclusive outcomes.[33] In the present study, we retrospectively analysed the association between the use of hydroxychloroquine and COVID-19 in patients with rheumatic disease. We found that the rate of symptomatic COVID-19 was lower in patients taking hydroxychloroquine than in patients taking other DMARDs. Notably, however, the benefits of hydroxychloroquine were observed in comparison with other immunosuppressive medications in patients with rheumatic diseases and so these findings are not generalisable to patients who do not require immunosuppression. As reported in this study, patients with rheumatic diseases were at increased risk of developing COVID-19, which might be partially caused by immunosuppressants. Therefore, the overall effects of hydroxychloroquine in the general population require further investigation. Due to the hyperactive status of immune activation in severe cases of viral infection, corticosteroids have been used in many patients with coronavirus infections, including severe acute respiratory syndrome, Middle East respiratory syndrome (MERS), and COVID-19, to control immune-mediated damage of lung tissue.[2,9,34] However, the use of corticosteroids in such cases is controversial because of their rapid immunosuppressive effects, which might affect the antiviral activity of the immune system. Arabi and colleagues[34] retrospectively analysed 309 critically ill patients with MERS and concluded that corticosteroid therapy did not improve 90-day mortality, but instead delayed the clearance of viral RNA. In our study, we did not observe a significant effect of corticosteroids on COVID-19.

This study has some limitations. First, because of the small number of patients with rheumatic disease who were not on medication, we were not able to identify whether the vulnerability to COVID-19 was associated with rheumatic disease or anti-rheumatic medications. Second, the number of patients with exposure to hydroxychloroquine was small and the lower COVID-19 incidence observed in comparison with patients taking other immunosuppressive medications should be interpreted with caution. Third, since this is a retrospective observational study, potential biases are inevitable. For example, some patients with rheumatic disease and COVID-19 might have been unable to answer the telephone: some of them might have already died of COVID-19 or their health conditions might have limited their ability to participate in the study. Additionally, a higher proportion of patients included in the study were on DMARD treatment than those who were excluded (59% *vs* 43%) and a lower proportion of patients included in the study had rheumatoid arthritis (44% *vs* 52%; appendix p 1). Future randomised controlled trials might provide better insight into these differences. The fourth limitation was in relation to SARS-CoV-2 RNA tests. Many factors such as specimen collection and the limit of detection for SARS-CoV-2 RNA PCR tests can cause false-negative results, and thus might potentially affect overall infection rates. Last, the sample size of patients with rheumatic disease and with COVID-19 was relatively small. We did not apply propensity score weighting approaches because of the small sample size. Future investigations in larger studies are needed to gather more evidence. In summary, our data suggest that patients with rheumatic disease might be more susceptible to COVID-19 than the general population.

Contributors

JZ and Lingli Dong conceived the idea and designed the study. GS, HY, AH, QH, LS, AZ, TZ, SS, HL, XH, WZ, BW, XC, AC, CY, and Li Dong collected data. JZ and XR analysed the data and wrote the manuscript. JZ, ZB, and Lingli Dong edited the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Access to de-identified data or related documents can be requested through submission of a proposal with a valuable research question, necessary data protection plan, and ethical approvals. A contract will be signed. Data requests should be addressed to the corresponding author.

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