ORIGINAL ARTICLE

Prevalence of COVID-19 and seroprevalence to SARS-CoV-2 in a rheumatologic patient population from a tertiary referral clinic in Israel

Tali Eviatar [1,4] Ofir Elalouf,[1,4] Victoria Furer,[1,4] Yael Goldstein-Lahat,[1,4] Yael Paran,[2,4] Sara Pel,[1,4] Sharon Nevo,[1,4] Michael Zisapel,[1,4] Yifat Alcalay[3,4] and Ori Elkayam[1,4]

[1]Rheumatology Department, [2]Infectious Disease Unit, and [3]Immunology Laboratory, Tel Aviv Sourasky Medical Center, and [4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

Background: It is unclear if the prevalence of COVID-19 in rheumatologic patients is similar to that of the general population. There are no reports of seroprevalence of SARS-CoV-2 in these patients.

Aims: To investigate prevalence of COVID-19 cases and seroprevalence among rheumatologic patients and the risk factors for infection.

Methods: A cross-sectional study in a rheumatologic population. An online questionnaire was sent on 31 April 2020. Blood samples from 20% sample of patients were drawn for SARS-CoV-2 antibodies.

Patients were divided based on autoimmune (AI) diagnosis. Prevalence of COVID-19 by nasopharyngeal swab and by serology (seroprevalence) was compared to national data. Risk factors for infection of SARS-CoV-2 were assessed.

Results: The study group included 1204 patients, 74.5% had an AI diagnosis. The prevalence of COVID-19 was 0.16% in the rheumatologic patient population and 0.22% in the AI group, which was not different from prevalence in Israel on 4 May 2020 (0.18%, $P = 0.912$ and $P = 0.759$ respectively). Serologic tests were performed in 242 patients, of which five were found positive pointing to a seroprevalence of 2.07%. Exposure to a known COVID-19 patient was the only significant risk factor for being positive by swab or by serology. AI diagnosis, immunosuppression, corticosteroid, hydroxychloroquine did not influence the risk.

Conclusions: The prevalence of COVID-19 in a population of rheumatologic patients was similar to that of the general population. Mild/asymptomatic cases may be prevalent according to serologic tests. The major risk factor for infection is exposure to a known case of COVID-19, and immunosuppression did not play a role in the risk of infection.

Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), originated in Wuhan, China, in December 2019.[1] The virus swept across the world with more than 37 million confirmed cases and 1 million deaths as of 11 October 2020.[2] Patients with autoimmune inflammatory rheumatologic diseases (AIIRD) are more susceptible to infections, which is partly due to the immunosuppression used to treat their disease.[3,4] Risk factors

associated with a severe course of COVID-19 as well as with increased mortality include male sex, old age, hypertension, diabetes mellitus, ischaemic heart disease and malignancy. The severe symptoms associated with COVID-19 are related to overactivation or dysfunctional activation of the immune system, resulting in a cytokine storm syndrome.[5–8] Increased interleukin (IL)-6 levels predict a worse outcome.[9] These observations have led to reports and trials on rheumatologic medications, including hydroxychloroquine (HCQ), IL-6 and IL-1 inhibitors, as potential treatments for COVID-19.[10–15] These studies showed that

HCQ is not efficacious nor detrimental in the treatment or prevention of COVID-19,[13] and it produced conflicting results regarding tocilizumab treatment for COVID-19.[14,15] Trials are still being conducted to determine the place of these medications in the treatment of COVID-19 patients.

The first reports of COVID-19 in the setting of AIIRD came from Italy and Spain, which generally did not find an increased prevalence in AIIRD patients.[16–20] The main limitation of those reports was that they were based on patients' self-reporting, yielding a strong bias towards milder cases and no reports on mortality.[21] Another report from Spain found a higher prevalence of COVID-19 by polymerase chain reaction (PCR) analyses in patients with chronic inflammatory diseases.[22] Those authors reported that the use of targeted and biologic disease-modifying anti-rheumatic drugs (b/tsDMARDS) was associated with an increased prevalence of COVID-19. In the Italian COVID-19 registry,[23] b/tsDMARDS were not, and prednisone was associated with an increased risk of adverse outcomes. A case series from New York City[24] that included AIIRD and inflammatory bowel disease (IBD) patients found that hospitalised patients were more likely to be treated with prednisone, HCQ and conventional synthetic DMARDS (csDMARDS). Those conflicting reports raise the question of whether rheumatic diseases and anti-cytokine treatments represent a risk or a protective factor to SARS-CoV-2.

The evidence from serologic testing on seroprevalence to SARS-CoV-2 is preliminary.[25,26] Most patients infected with SARS-CoV-2 will apparently display antibodies to the virus within 14–20 days after infection, and the serologic response appears to be earlier and stronger in severe disease. Some patients do not develop immunogenicity, even at 1 month post-infection. Immunoglobulin (Ig) G appears early and together with IgM antibodies.[26] Recently reported seroprevalence rates to SARS-CoV-2 in different populations seem to be 11 times or more higher than reported cases.[27–29] We did not find any reports on asymptomatic patients and antibody response in AIIRD patients.

The aims of the present study were to investigate the prevalence of COVID-19 cases and SARS-CoV-2 seroprevalence among rheumatology clinic patients and to assess risk factors for infection rate among the AIIRD patients.

Methods

We conducted a cross-sectional study in a population of patients from the Rheumatology Clinic at the Tel Aviv Sourasky Medical Centre (TASMC), a tertiary referral medical institution. The study was conducted in May 2020, 1.5 months after the national lockdown on 15 March 2020. At that time, it was also mandatory to wear a face mask in public and in the workplace, gathering beyond the nuclear family was prohibited and social distancing was highly encouraged. The present analysis was approved by the institutional ethical committee (no. 0257-20-TLV), and patients gave informed consent.

Online questionnaire

An online questionnaire (Appendix S1) was sent on 31 April 2020 to all patients attending the Department of Rheumatology at TASMC between 1 March 2019 and 26 April 2020. Responses received by 4 May 2020 were used for analysis. Inclusion criteria were as follows: age ≥ 18 years consent to complete missing data from information in their electronic case files, and having an AIIRD (rheumatoid arthritis (RA), spondyloarthritis (SpA, including ankylosing spondylitis, peripheral SpA, reactive arthritis and IBD-associated SpA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), systemic sclerosis (SSc), idiopathic inflammatory myositis (IIM), sarcoidosis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), giant cell arthritis (GCA), polymyalgia rheumatica (PMR), Behçet disease, antiphospholipid syndrome (APS), non-inflammatory rheumatic disease (osteoarthritis, OA), gout, calcium pyrophosphate deposition disease and fibromyalgia). Exclusion criteria were age under 18 years, inability to give consent and unwillingness to participate.

In cases where the patient did not know his diagnosis, the information was completed from the electronic case file.

Each patient was asked about exposure to a known COVID-19 patient and comorbidities that are known to be risk factors for COVID-19 and its complications. Those comorbidities included obesity, smoking history, hypertension, diabetes mellitus, chronic obstructive pulmonary disease or asthma, cardiovascular disease (ischaemic heart disease and cerebrovascular disease), malignancy, chronic kidney disease and hypercoagulability. The principal investigator (TE) confirmed that treatments reported by the patients were appropriate for their diagnoses. We also validated the accuracy of the reported diagnosis in a representative sample of 212 patients, and recorded matching or non-matching of diagnoses. We compared the demographic and diagnostic characteristics of the patients who answered the questionnaire to all the patients who attended the clinic between 1 March 2019 and 29 April 2020.

Serology testing

Serologic testing was performed in a sample of the responders that constituted 20% of the responders (on a 'first come, first served' basis). SARS-CoV-2 IgG and IgA

serology testing was carried out with the EUROIMMUN (Medizinische Labordiagnostika AG) anti-SARS-CoV-2 ELISA IgG and IgA test. This is a semi-quantitative test in which results <0.8 are considered negative, those between ≥0.8 to 1.1 borderline, and ≥1.1 positive. According to the manufacturer's insert, the test specificity is 98.5% and it is not affected by the presence of rheumatoid factors. The test sensitivity is greater if carried out more than 10 days after the onset of symptoms, and 80% when only IgG antibodies are tested compared to 100% when IgG is combined with IgA antibodies.[30,31]

Definitions

Responders to the questionnaire were divided based on a diagnosis of an AIIRD. The autoimmune disease group (AI group) that consisted of patients with RA, SpA, PsA, AS, SLE, SS, SSc, IIM, sarcoidosis, AAV, GCA or PMR, Behçet disease, APS and undefined arthritis, other vasculitides, and so on. Non-autoimmune disease group (non-AI group) consisted of patients with a diagnosis of OA, crystal-induced arthritis and fibromyalgia. A patient with an AIIRD diagnosis and secondary OA or fibromyalgia was allocated to the AI group.

COVID-19/SARS-CoV-2 status

1 Positive swab group: patients that reported in the questionnaire being diagnosed with SARS-CoV-2 by RT-PCR nasopharyngeal swab.
2 Positive serology group: patients who were positive according to serologic testing who had positive IgG or IgA.
3 Borderline serology group: patients that had borderline serologic results.

Calculation of estimated prevalence

The prevalence of COVID-19 was estimated under the assumption that seropositive rate was the same among the responders to the questionnaire and the non-responders. Prevalence was assessed for the AI group, and the study group as a whole. This estimation was compared to the official reported national prevalence on 4 May 2020.[32] In order to check for a potential sampling bias, three essential demographic and clinical covariates (age, sex and diagnosis) were compared between all of the questionnaire responders and those among them who were entered into the study.

Statistical analysis

Continuous variables were described as mean, median, standard deviation, minimum, and maximum and were compared with the Mann–Whitney test in the absence of normality. Categorical binary variables were compared for proportion differences with the Fisher exact test, and risk difference (RD, also known as attributable risk) was computed for risk factors of interest. A two-sided *P*-value <0.05 was considered statistically significant. All analyses were performed with R-studio Version 1.3.959.

Results

A total of 7081 patients was eligible for study entry. The questionnaire was sent to 6557 patients, of which 1202 agreed to participate. One patient was excluded because of unknown diagnosis (Fig. 1).

The median age of the responders was 56 years (interquartile range (IQR) 43–67), and 74.4% (893 patients) were females (Table 1). The entire clinic population (responders and non-responders) had 69.8% females, and the median age was 58 years.

The AI group included 895 patients (74.5%). The clinical characteristics of the AI and non-AI groups are presented in Table 1. There were 183 patients with RA (15.2%), 151 (12.6%) with PsA, 140 (11.7%) with SLE, 109 (9.1%) with SpA/AS, 86 (7.2%) with connective tissue diseases (CTD, including SS, IIM, SSc, MCTD, and undifferentiated CTD), 36 (3%) with large-vessel vasculitis and PMR, 12 (1%) with AAV, 163 (13.6%) with primary fibromyalgia and 67 (5.6%) with OA. A sample of 212 patients (17.7% of responders) was evaluated for the validation of diagnoses of which 186 (88%) matched.

The entire clinic population had more crystal-induced arthritis and OA patients and fewer SLE and PsA patients (data not shown) in comparison with the study group.

Four hundred and forty-seven (37.2%) patients had no comorbidity known to be a risk factor for COVID-19 morbidity or mortality (excluding age and sex). Seven hundred and fifty-one (62.5% of the study population, 81.1% of the AI group and 8.2% of the non-AI group) patients were medically immunosuppressed, and 158 (13.1% of the study population) patients were taking corticosteroids. Details of the medications given in each group are presented in Table 1.

Twenty-six (2.2%) patients were exposed to a known case of COVID-19: one of them was positive for COVID-19 by swab (Patient 1 in Table 2) and two were positive for SARS-CoV-2 by serology (Patients 1 and 6 in Table 2). Seventeen (63%) were cases of distant exposure (e.g. a client in a barber shop, a student, a daughter's friend, a shopper in the same grocery store). Four
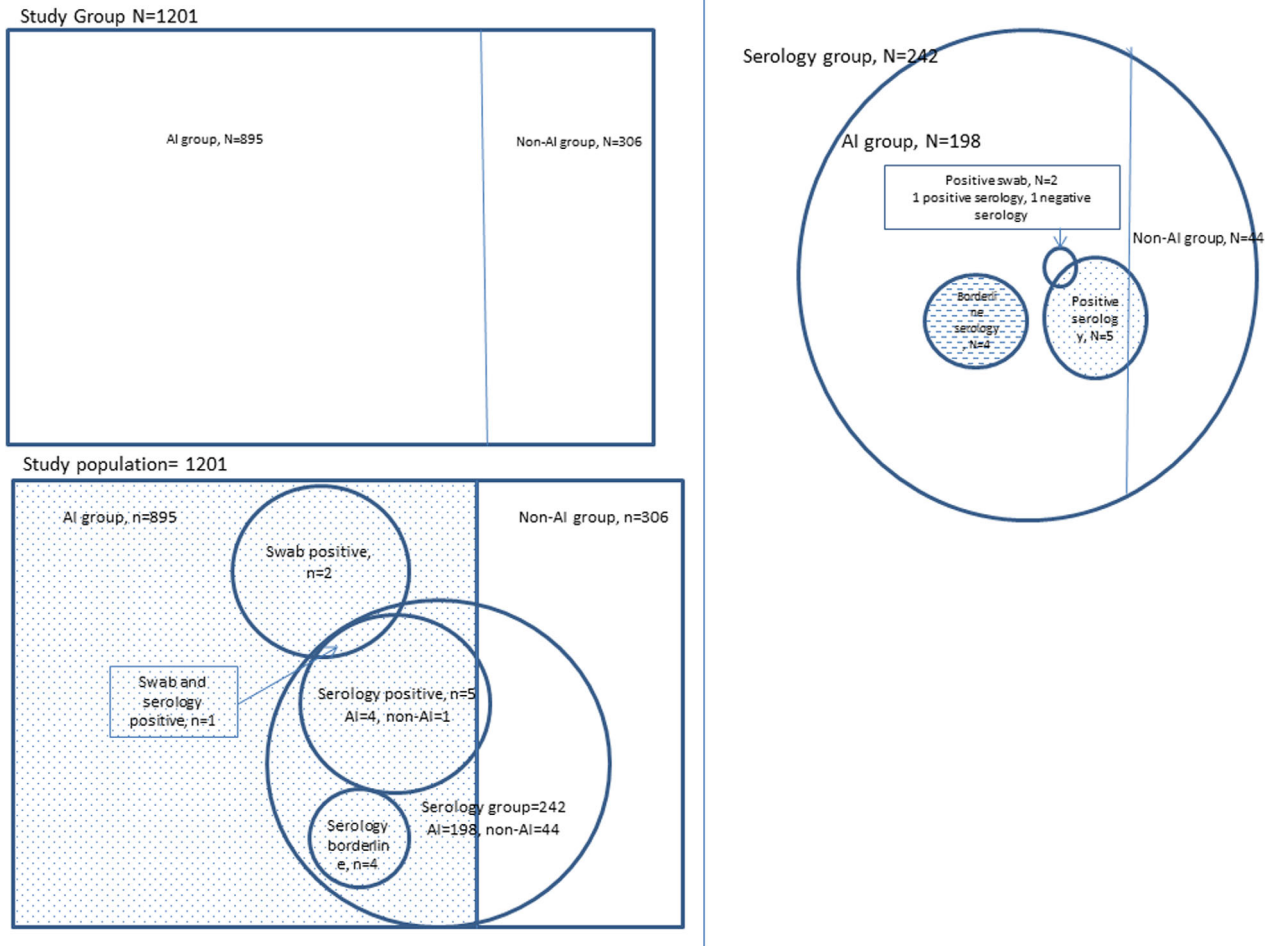
Figure 1 Graphic representation of the study group. Positive COVID-19 swab and SARS-CoV-2 serology patient are detailed in their assigned group. AI, autoimmune.

(14.8%) exposures were to a close friend. Only two (7.7%) exposures were to a first- or second-degree family member, and three sources of exposure were unknown (those three patients had been notified of the exposure through electronic surveillance).

COVID-19 prevalence according to nasopharyngeal swab results

The prevalence of COVID-19 in the questionnaire population was 2/1201, (0.16%) and 2/895 (0.22%) in the AI group. The nationwide prevalence of COVID-19 by nasopharyngeal swab results in the general population on 4 May 2020 was 16 246/8 884 000: 0.18%,[32] which was not statistically different from the prevalence in the questionnaire population, or the AI group ($P = 0.912$ and $P = 0.759$, respectively). Both patients who were positive to SARS-CoV-2 by swab were in their 20s, and

neither was immunosuppressed. Both recovered without complications (Table 2).

SARS-CoV-2 seroprevalence

Serologic testing for IgG and IgA SARS-CoV-2 antibodies was performed for 242 patients. Those patients were more likely to be from the AI group and were more medically immunosuppressed (Table A1 in the Appendix). The positive serology prevalence among them was 2.07% (5/242), and the positive and borderline prevalence was 3.72% (9/242). In the positive serology group, the age range was 25–54 years, with a mean of 42.8 years, 60% of them were female. Two patients who were known to be positive by swab testing underwent serological testing, and one (Patient 1 in Table 2) was found to be positive by serology. The other patient (Patient 2) was found to be seronegative, reported having fever and headache when

Table 1 Demographic and clinical characteristics of the questionnaire responders

	Total, N = 1201	AI group, N = 895	Non-AI group, N = 306	P-value
Age, median (IQR) (years)	56.00 (43.00, 67.00)	55.00 (42.00, 67.00)	60.00 (48.00, 69.00)	0.001
Female (%)	893 (74.4)	662 (73.9)	231 (75.5)	0.755
Comorbidities				
Hypertension (%)	296 (24.6)	202 (22.6)	94 (30.7)	0.006
Diabetes mellitus (%)	147 (12.2)	98 (10.9)	49 (16.0)	0.028
CVD (%)	103 (8.6)	68 (7.6)	35 (11.4)	0.049
COPD/asthma (%)	137 (11.4)	98 (10.9)	39 (12.7)	0.443
Active cancer	19 (1.6)	8 (0.9)	11 (3.6)	0.003
Past cancer	93 (7.7)	58 (6.5)	35 (11.4)	0.007
Hypercoagulability	24 (2.0)	18 (2.0)	6 (2.0)	1
CKD	7 (0.6)	5 (0.6)	2 (0.7)	1
Number of comorbidities (%)				
0	447 (37.2)	362 (40.4)	85 (27.8)	<0.001
1	439 (36.6)	328 (36.6)	111 (36.3)	
2	198 (16.5)	135 (15.1)	63 (20.6)	
≥3	117 (9.7)	70 (7.8)	47 (15.4)	
Number of comorbidities (as ordinal)	1.00 (0.00, 2.00)	1.00 (0.00, 1.00)	1.00 (0.00, 2.00)	<0.001
Rheumatic disease treatments				
Corticosteroids	157 (13.1)	151 (16.9)	6 (2.0)	<0.001
Hydroxychloroquine	225 (18.7)	222 (24.8)	3 (1.0)	<0.001
cDMARDS	414 (34.5)	396 (44.2)	18 (5.9)	<0.001
bDMARDS	331 (27.6)	327(36.5)	4 (1.3)	<0.001
tsDMARDS	31 (2.6)	31 (3.5)	0 (0.0)	0.002
Anti-IL-6	29 (2.4)	28 (3.1)	1 (0.3)	0.011
Rituximab	46(3.8)	46 (5.1)	0 (0.0)	<0.001
Cyclophosphamide	3 (0.2)	3 (0.3)	0 (0.0)	0.727
Other immunosuppressive	53 (4.4)	51 (5.7)	2 (0.7)	<0.001
Total immunosuppressed (%)	751 (62.5)	726 (81.1)	25 (8.2)	<0.001

AI, autoimmune; anti-IL-6, anti-interleukin-6; bDMARDS, biologic DMARDS; cDMARDS, conventional disease modifying anti rheumatic drugs; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IQR, interquartile range; tsDMARDS, targeted synthetic DMARDS.

questioned by telephone. Patient 2's first swab had been positive, but the next two swabs taken about 2 weeks later were negative. Among the positive serology cases, two cases (Patients 3 and 6) presented a symptom complex suspicious for COVID-19, but did not have fever. Patient 6 reported being exposed to several work colleagues that were positive by swab. Two cases had no or very mild symptoms and no known exposure. Another four cases were borderline by serology,; all of them female, with a mean age of 54 years (range of 36–71). Two of the borderline serology patients had suspicious symptoms, one of them with fever (Table 2).

Risk factors for being COVID-19-positive and SARS-CoV-2-seropositive

We examined various variables as risk factors for being positive to COVID-19 by swab testing. Only exposure to a known COVID-19 patient emerged as a significant risk factor (2% among the negative patients, 50% among the positive swab patients, yielding an RD of 48 $P = 0.04$). The

risk of being swab positive was not influenced by being in the AI group or being under immunosuppression, corticosteroid or HCQ treatment. The risk factors for being seropositive for SARS-CoV-2 antibodies were exposure to a known COVID-19 patient (4% in the negative serology patients and 40% in the positive serology patients, yielding an RD of 36%, $P = 0.02$), and being of younger age (median $\pm$ IQR, 51 ± 18 years and 58 ± 22 years for the positive and negative serology patients, respectively; $P = 0.05$).

Discussion

We investigated the prevalence of COVID-19 cases and SARS-CoV-2 seroprevalence in rheumatologic patients treated in a tertiary medical centre in Tel Aviv, Israel. We also assessed risk factors for infection in the AIIRD patients among them. The prevalence of COVID-19 was 0.16% in total, and 0.22% for the AI group, similarly to the reported prevalence in the general population nationwide.

Table 2 Clinical characteristic of SARS-CoV-2/COVID-19 positive patients

No.	Diagnosis	Treatment	Comorbidities	Exposure	Serology IgG/IgA	Swab	Symptoms	Course, hospitalisation and mortality
Positive by swab and serology								
1	Behcet syndrome	Colchicine	None	Close friend	Pos/Pos	Pos	Cough, rhinorrhoea, dyspnoea, anosmia, headache	Hospitalised in hotel, recovered after a month
Positive by swab								
2	PsA	IA steroid injection	None	None	Neg/NA	Pos (once, then neg)	Fever, headache	Ambulatory isolation, recovered by 2 weeks
Positive by serology								
3	Fibromyalgia	Medicinal cannabis	None	None	Pos/Neg	Neg (14.06.20)	Cough, rhinorrhoea, dyspnoea, fatigue, diarrhoea	Antibiotic tx.
4	SLE	HCQ, prednisone 5 mg/day	Active smoker	None	Pos/NA	NA	None	Asymptomatic
5	Reactive arthritis HLA B-27+	Adalimumab	None	None	Border/Pos	Neg (13.06.20)	Rhinorrhoea	Recovered without tx.
6	JIA	Tocilizumab	HTN, DM	Work colleagues	Pos/Pos	Neg (11.6.20)	Sore throat, headache, anosmia, rhinorrhoea	Ambulatory isolation
Borderline by serology								
7	SLE, SSc	HCQ, RTX-7/2019	APLA positive	None	Border/NA	NA	None	Asymptomatic
8	RA	Baricitinib, NSAIDS	None	None	Border/Neg	Neg (15.06.20)	None	Asymptomatic
9	Suspected CTD, Pso, microscopic colitis, family hx. of SLE	Budesonide 6 mg, MMF?	None	None	Border/Neg	Neg (14.06.20)	Cough, diarrhoea	Antibiotic tx. at home (roxithromycin)
10	FMF, RA, fibromyalgia, family hx. of SLE, SSc	HCQ, leflunomide, colchicine	Past smoker	None	Border/NA	NA	Fever, cough, dyspnoea, fatigue, myalgia	Diagnosed with pneumonia

APLA, antiphospholipid antibodies; Border, borderline; CTD, connective tissue disease; DM, diabetes mellitus; HCQ, hydroxychloroquine; HTN, hypertension; hx. history; Fem, female; FMF, familial Mediterranean fever; IA, intra-articular; Ig, immunoglobulin; MMF, mycophenolate mofetil; Neg, negative; NA, not available; No., number; Pos, positive; PsA, psoriatic arthritis; Pso, psoriasis; RA, rheumatoid arthritis; RTX, rituximab; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; tx., treatment.

To the best of our knowledge, this is the first study to report seroprevalence in a large rheumatologic population, which was 2.07%.

The prevalence of positive COVID-19 by swab testing in rheumatologic patients from Italy was very close to ours (0.21–0.38%), and similar to the regional prevalence of those studies.[17–19] In these studies, there were no reports of death (studies relied on patients' reports). In contrast, COVID-19 registries are biased toward more severe cases.[21,23,33] The Italian registry CONTROL-19[23]

reported a high mortality rate of 19% in their rheumato-logic population. The COVID-19 Global Rheumatology Alliance (C19-GRA)[33] reported 9% mortality in multina-tional cases. The US values reported by D'Silva *et al.* had comparable mortality rates of 6% and 4% for their rheu-matic and non-rheumatic patients, respectively.[34] Ye *et al.* from Wuhan reported similar mortality rates of rheumatic and non-rheumatic patients, but they were relatively high at 9.54% and 9.52% respectively.[35]

When conducting our survey, we knew of two patients from our clinic who died due to COVID-19, and another patient who was hospitalised and did not answer the questionnaire. If these patients were included in the analysis, an extrapolated case fatality rate of 13.5% was calculated (for details of the statistical analysis, please refer to the Appendix S2).

The major risk factor for infection with COVID-19 as well as for being SARS-CoV-2 antibody positive in our study was exposure to a known positive SARS-CoV-2 swab-tested patient, while an AI diagnosis or immuno-suppressive treatment did not seem to play a role, and HCQ treatment did not have a protective role. The posi-tive serology patients were younger, which may imply that younger patients take fewer precautions with regard to social distancing. This may also imply that the infec-tion is milder or the disease is asymptomatic in younger populations.[36–38]

The July 2020 publication of C19-GRA[33] that described the first 600 COVID-19/AIRD patients found that the risk factors for hospitalisation were older age, comorbidities and prednisone ≥10 mg/day. csDMARDS and HCQ did not affect hospitalisation. Ts and bDMARDS were associ-ated with a decreased risk of hospitalisation. Similar results were reported in the CONTROL-19 registry and in the SECURE-IBD registry for IBD patients.[21,23,39,40] A comparative cohort study from Chicago found that rheu-matologic and non-rheumatologic patients were hos-pitalised and died due to COVID-19 at the same rate, although rheumatologic patients were more likely to need mechanical ventilation and ICU stay.[34] The Chinese experience was similar, with similar mortality rate for rheumatologic patients, but more respiratory failure.[35]

The serology analyses included four cases of positive serology and four cases of borderline serology among patients who had not been tested before by nasopha-ryngeal swab. The positive serology prevalence was 2.07%, and the combined positive and borderline prev-alence was 3.72%. These results may imply that SARS-CoV-2 infection rate is 5–10 times more prevalent in this population than the prevalence produced by swab findings. Recent publications on general populations in different countries reported similar results. For

example, the seroprevalence was 2.5% in a hospital setting in Hubei.[26] It was 7.9% in a representative sam-ple from Geneva,[41] which is 11.6 times more than the prevalence of positive COVID-19 by swab. In Denmark, the seroprevalence among blood donors was 1.9%, which is 16 times higher than confirmed cases.[42] In Los Angeles, the seroprevalence rate was 4.65%, which is 43 times higher than reported cases.[28] In Lombardy, Italy, which is considered to be a 'red zone', seropreva-lence in blood donors reached 23%.[43] The results of the Centers for Disease Control and Prevention's sero-prevalence survey were that seroprevalence is 11 times higher than reported cases in most states in the United States.[29]

Our serology results indicate that most patients with rheumatic disease have mild, ambulatory or asymptom-atic disease.

Our study has several limitations. First, the primary diagnosis of COVID-19 by nasopharyngeal swab was based on patients' reports, although they were later confirmed in the electronic files. The electronic question-naire may have missed more cases of diagnosed COVID-19 cases – probably of older patients and may be of patients hospitalised or severely ill, and also all cases of mortality. Seroprevalence testing on a 'first come, first serve' basis has a potential for selection bias. In contrast, our study included a large population of rheumatologic patients.

The issue of seroprevalence in rheumatologic patients, and especially in biologic treated, including anti-CD-20-treated patients deserves further research. This will come to increase our understanding of the immunologic response in these patients, and antibody formation role in the clinical picture of different severities, up to the cytokine storm of severe COVID-19.

Conclusion

We showed that the prevalence of COVID-19 in a repre-sentative population of rheumatologic patients is similar to that of the general population. Mild or asymptomatic cases may be prevalent according to serologic tests. The major risk factor for infection was exposure to a known case of COVID-19, while immunosuppression by itself did not appear to play a role in the risk of infection.

Acknowledgement

References

1 Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727–33.

2 World Health Organization (WHO). Coronavirus disease (COVID-19) global epidemiological situation. Geneva: WHO; 2020 [cited 2020 Oct 17]. Available from URL: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20201012-weekly-epi-update-9.pdf

3 Furer V, Rondaan C, Heijstek M, van Assen S, Bijl M, Agmon-Levin N et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients wit. *RMD Open* 2019; **5**: e001041.

4 Rondaan C, Furer V, Heijstek MW, Agmon-Levin N, Bijl M, Breedveld FC et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. *RMD Open* 2019; **5**: e001035.

5 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033–4.

6 McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in Covid-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmunity Reviews*. 2020; **19**(6): 102537.

7 Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G. COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation*. 2020; **27**: 1451–1454.

8 Ye Q, Wang B. Mao J. the pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J Infect* 2020; **80**: 607–13.

9 Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*. 2020; **46**: 846–848.

10 Wu R, Wang L, Kuo HCD, Shannar A, Peter R, Chou PJ et al. An update on current therapeutic drugs treating COVID-19. *Curr Pharmacol Rep* 2020; **6**: 56–70.

11 Chakraborty C, Sharma AR, Bhattacharya M, Sharma G, Lee SS, Agoramoorthy G. COVID-19: Consider IL-6 receptor antagonist for the therapy of cytokine storm syndrome in SARS-CoV-2 infected patients. *Journal of Medical Virology*. 2020; **92**: 2260–2262.

12 Antwi-Amoabeng D, Kanji Z, Ford B, Beutler BD, Riddle MS, Siddiqui F. Clinical outcomes in COVID-19 patients treated with tocilizumab: An individual patient data systematic review. *Journal of Medical Virology*. 2020; **92**: 2516–2522.

13 Putman M, Chock YPE, Tam H, Kim AHJ, Sattui SE, Berenbaum F, Danila MI, Korsten P, Sanchez-Alvarez C, Sparks JA, Coates LC, Palmerlee C, Peirce A, Jayatilleke A, Johnson SR, Kilian A, Liew J, Prokop LJ, Murad MH, Grainger R, Wallace ZS, Duarte-García A. Antirheumatic Disease Therapies for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. *Arthritis & Rheumatology*. 2021; **73**: 36–47.

14 Ramiro S, Mostard RLM, Magro-Checa C, van Dongen CMP, Dormans T, Buijs J et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. *Ann Rheum Dis* 2020; **79**: 1143–51.

15 F. Hoffmann-La Roche Ltd. Media & Investor Release: Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. 2020.

16 Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis Engl* 2020; **0**: 4–5.

17 Emmi G, Bettiol A, Mattioli I, Silvestri E, Di Scala G, Urban ML, Vaglio A, Prisco D. SARS-CoV-2 infection among patients with systemic autoimmune diseases. *Autoimmunity Reviews*. 2020; **19**: 102575.

18 Zen M, Fuzzi E, Astorri D, Saccon F, Padoan R, Ienna L, Cozzi G, Depascale R, Zanatta E, Gasparotto M, Benvenuti F, Bindoli S, Gatto M, Felicetti M, Ortolan A, Campaniello D, Larosa M, Lorenzin M, Ramonda R, Sfriso P, Schiavon F, Iaccarino L, Doria A. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A cross-sectional study on 916 patients. *Journal of Autoimmunity*. 2020; **112**: 102502.

19 Quartuccio L, Valent F, Pasut E, Tascini C, De Vita S. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: A population-based study in the first two months of COVID-19 outbreak in Italy. *Joint Bone Spine*. 2020; **87**: 439–443.

20 Jovani V, Calabuig I, Peral-Garrido ML, Tovar-Sugrañes E, López-González M-C, Bernabeu P, Martínez A, Esteve-Vives J, León-Ramírez JM, Moreno-Perez O, Boix V, Gil J, Merino E, Vela P, Andrés M. Incidence of severe COVID-19 in a Spanish cohort of 1037 patients with rheumatic diseases treated with biologics and JAK-inhibitors. *Annals of the Rheumatic Diseases*. 2020; annrheumdis–2020.

21 Gianfrancesco M, Yazdany J, Robinson PC. Epidemiology and outcomes of novel coronavirus 2019 in patients with immune-mediated inflammatory diseases. *Curr Opin Rheumatol* 2020; **32**: 434–40.

22 Pablos JL, Abasolo L, Alvaro-Gracia JM, Blanco FJ, Blanco R, Castrejón I, Fernandez-Fernandez D, Fernandez-Gutierrez B, Galindo-Izquierdo M, Gonzalez-Gay MA, Manrique-Arija S, Mena Vázquez N, Mera Varela A, Retuerto M, Seijas-Lopez A. Prevalence of hospital PCR-confirmed COVID-19 cases in patients with chronic inflammatory and autoimmune rheumatic diseases. *Annals of the Rheumatic Diseases*. 2020; **79**: 1170–1173.

23 Scirè CA, Carrara G, Zanetti A, Landolfi G, Chighizola C, Alunno A, et al. COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). *Clin Exp Rheumatol Italy* 2020; **38**: 748–53.

24 Haberman R, Axelrad J, Chen A, Castillo R, Yan D, Izmirly P, Neimann A, Adhikari S, Hudesman D, Scher JU. Covid-19 in immune-mediated inflammatory diseases — case series from New York. *New England Journal of Medicine*. 2020; **383**: 85–88.

25 Kellam P, Barclay W. The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection. *J Gen Virol* 2020; **101**: 791–7.

26 Xu X, Sun J, Nie S, Li H, Kong Y, Liang M, *et al.* Seroprevalence of immunoglobulin M and G antibodies against SARS-CoV-2 in China. *Nat Med United States* 2020; **26**: 1193–5.

27 Wampler Muskardin TL. IV anakinra for macrophage activation syndrome may hold lessons for treatment of cytokine storm in the setting of COVID19. *ACR Open Rheumatol* 2020; **2**: 283–5.

28 Sood N, Simon P, Ebner P, Eichner D, Reynolds J, Bendavid E *et al.* Seroprevalence of SARS-CoV-2-specific antibodies among adults in Los Angeles County, California, on April 10–11, 2020. *JAMA* 2020; **323**: 2425–7.

29 Centers for Disease Control and Prevention (CDC). Commercial Laboratory Seroprevalence Surveys. Coronavirus. COVID-19. Atlanta, GA: CDC; 2020 [cited 2020 Jul 4]. Available from URL: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/commercial-lab-surveys.html

30 EUROIMMUN. Anti-SARS-CoV-2 ELISA (IgG). Instructions for use. Manufacturer insert. Lübeck, Germany: EUROIMMUN, Medizinische Labordiagnostik AG; 2020.

31 EUROIMMUN. Anti-SARS-CoV-2 ELISA (IgA). Instructions for use. Lübeck, Germany: EUROIMMUN, Medizinische Labordiagnostik AG; 2020.

32 State of Israel, Ministry of Health. Coronavirus. 2020 [cited 2020 Jul 2]. Available from URL: https://govextra.gov.il/ministry-of-health/corona/corona-virus/

33 Gianfrancesco M, Hyrich KL, Adely SA, Carmona L, Danila MI, Gossec L *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2020; **79**: 859–66.

34 D'Silva K M, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravallese E M, Choi H K, Sparks J A, Wallace Z S. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. *Annals of the Rheumatic Diseases*. 2020; **79**(9): 1156–1162.

35 Ye C, Cai S, Shen G, Guan H, Zhou L, Hu Y, Tu W, Chen Y, Yu Y, Wu X, Chen Y, Zhong J, Dong L. Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. *Annals of the Rheumatic Diseases*. 2020; **79**: 1007–1013.

36 Kim G-U, Kim M-J, Ra SH, Lee J, Bae S, Jung J *et al.* Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. *Clin Microbiol Infect* 2020; **26**: 948.e1–3.

37 Huang L, Zhang X, Zhang X, Wei Z, Zhang L, Xu J *et al.* Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16–23 years outside Wuhan and characteristics of young patients with COVID-19: a prospective contact-tracing study. *J Infect* 2020; **80**: e1–13.

38 Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection. *Annals of Internal Medicine*. 2020; **173**: 362–367.

39 Brenner EJ, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD *et al.* Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020; **159**: 481–491.e3.

40 Brenner EJ, Colombel J-F, Ungaro R, Kappelman MD. SECURE-IBD Database. Current Summary Data. 2020 [cited 2020 Sep 22]. Available from URL: https://covidibd.org/current-data/

41 Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H *et al.* Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet* 2020; **6736**: 1–7.

42 Erikstrup C, Hother CE, Pedersen OBV, Mølbak K, Skov RL, Holm DK *et al.* Estimation of SARS-CoV-2 infection fatality rate by real-time antibody screening of blood donors. *Clin Infect Dis* 2020: ciaa849.

43 Percivalle E, Cambiè G, Cassaniti I, Nepita EV, Maserati R, Ferrari A *et al.* Prevalence of SARS-CoV-2 specific neutralising antibodies in blood donors from the Lodi Red Zone in Lombardy, Italy, as at 06 April 2020. *Euro Surveill* 2020; **25**: 2001031.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix S1: Questionnaire.
Appendix S2: Case fatality rate statistical analysis.
Table S1: Comparison between questionnaire patients who had a SARS-CoV-2 serologic test to those who did not have a test.