RESEARCH LETTER

Risk factors for SARS-CoV-2 infection in patients with rheumatic diseases

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Introduction Rheumatic diseases (RD) and their treatment may be associated with an increased risk of infection. A more severe course of SARS-CoV-2 infection has been reported in patients with comorbidities.[1-4] The factors influencing the course of SARS-CoV-2 infection include age, comorbidities, treatment, and the activity of the underlying disease.[2-5]

Treatment of RD includes the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, synthetic disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine and methotrexate, and biologic DMARDs such as tumor necrosis factor α (TNF-α) blockers, interleukin 6 (IL-6) blockers, and rituximab.[6,7] Some medications used to treat RD, such as chloroquine, hydroxychloroquine, tocilizumab, and corticosteroids have also been used in the treatment of COVID-19.[2,8-11]

This study aimed to assess the prevalence, course, and risk factors of SARS-CoV-2 infection in patients with RD.

Patients and methods The study was approved by the ethics committee of Pomeranian Medical University in Szczecin (KB-0012/76/2020; 22JUN2020), and all patients provided informed consent. We analyzed 210 White patients with diagnosed RD from northwestern Poland. A survey was conducted from December 15, 2020 to January 31, 2021. The interviews were carried out using a pre-prepared questionnaire by 2 students who accompanied rheumatologists in the outpatient clinic. We collected data on patients' age, sex, disease duration, disease activity, comorbidities, treatment, smoking status, history of SARS-CoV-2 infection, symptoms and treatment as well as information on the course of COVID-19 in family members.

Statistical analysis We performed a sample size estimation (minimal sample size, 208; 95% CI margin of error, 5%). Data distribution was evaluated using the Kolmogorov–Smirnov test. Data were presented as mean (SD) or median (interquartile range). Groups were compared using the *t* test and the Mann–Whitney test. The parameters were evaluated using the Pearson χ^2 test and logistic regression analysis. A *P* value of less than 0.05 was considered significant. All statistical data were analyzed using STATA 11, license number 30110532736 (StatSoft Inc, Tulsa, Oklahoma, United States).

Results Out of 450 patients scheduled for a visit in the outpatient clinic, 210 were included in the analysis. Demographic and clinical characteristics of patients with RD are summarized in TABLE 1. Patients were divided into 4 groups according to the type of RD. The rheumatoid arthritis (RA) group included seropositive and seronegative RA cases (n = 61 [29%]). In the spondyloarthritis (SpA) group, we included patients with ankylosing spondylitis, nonradiographic axial SpA, psoriatic arthritis, synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (n = 83 [39.5%]). The connective tissue disease (CTD) group comprised individuals with systemic lupus erythematosus, polymyositis, dermatomyositis, Sjögren syndrome, antiphospholipid syndrome, eosinophilic fasciitis, scleroderma, polyarteritis nodosa, and polymyalgia rheumatica (n = 60 [28.6%]). The last group (other RD) included gouty arthritis and juvenile idiopathic arthritis cases (n = 6 [2.9%]).

Symptoms of COVID-19 occurred in 53 patients (96.4%) with a positive result of a SARS-CoV-2 infection test. The reported symptoms included loss of smell in 37 individuals (67.2%), weakness in 37 (67.2%), loss of taste in 34 (61.8%), headache in 23 (41.8%), muscle pain in 21 (38.2%), cough in 20 (36.4%), fever in 16 (29.1%), joint pain in 17 (30.9%), and dyspnea in 16 patients (29.1%).

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TABLE 1 Demographic and clinical characteristics of the study group

Parameter		Study group (n = 210)		RA patients (n = 61)		SpA patients (n = 83)		CTD patients (n = 60)		Other RD patients (n = 6)	
		SARS-CoV-2 (+)	SARS-CoV-2 (–)	SARS-CoV-2 (+)	SARS-CoV-2 (–)	SARS-CoV-2 (+)	SARS-CoV-2 (–)	SARS-CoV-2 (+)	SARS-CoV-2 (–)	SARS-CoV-2 (+)	SARS-CoV-2 (–)
Patients		55 (26.2)	155 (73.8)	20 (32.8)	41 (67.2)	14 (16.9)	69 (83.1)	20 (33.3)	40 (66.7)	1 (16.7)	5 (83.3)
Sex, n	Female	45	99	18	34	9	31	17	32	1	2
	Male	10	56	2	7	5	38	3	8	0	3
Age, y, median (IQR)		54 (39–64)	56.5 (43–65)	54 (39–60.5)	61 (49–67)	49.5 (34–66)	50.5 (42–63)	50.5 (43–65.5)	61 (47–67.5)	21 (21–21)	22 (20–33)
Disease duration, y, median (IQR)		7 (2–12)	7 (3–16)	8.5 (4.5–14)	5.5 (3–16)	6.5 (10–50)	10 (5–17)	3 (1.3–9.5)	5 (3–11)	5 (5–5)	6 (5–18)
VAS, mm, median (IQR)		30 (20–40)	20 (10–50)	30 (10–30)	30 (10–60)	30 (10–50)	20 (10–60)	40 (30–60)	20 (10–40)	30 (30–30)	15 (10–30)
BASDAI, median (IQR)		3 (1–5)	2 (1–5)	0	0	3 (1–5)	2 (10–60)	0	0	0	0
SLEDAI, mean (SD)		6.1 (4.2)	5.8 (5.27)	0	0	0	0	6.11 (4.2)	5.8 (5.3)	0	0
DAS28, mean (SD)		2.9 (1.1)	3.27 (1.38)	2.7 (0.9)	3.3 (1.4)	3.7 (1.2)	3.3 (1.5)	0	0	0	0
COVID-19 disease duration, d, median (IQR)		11 (9–14)	0	12 (10–14)	0	12.5 (9–14)	0	10 (7.5–15)	0	10 (10–10)	0
Cigarette smoking		6 (10.9)	16 (10.3)	2 (10)	8 (19.5)	0	9 (13)	2 (10)	3 (7.5)	1 (100)	0
BMI >25 kg/m^2		27 (49.1)	79 (51)	8 (40)	23 (56.1)	8 (57.1)	23 (33.3)	10 (50)	9 (22.5)	1 (100)	2 (40)
Treatment of RD											
NSAIDs		7 (12.7)	47 (30.3)	1 (5)	13 (31.7)	5 (35.7)	33 (47.8)	0	1 (2.5)	1 (100)	0
CS		28 (50.9)	73 (47.1)	8 (40)	23 (56.1)	3 (21.4)	20 (29)	16 (80)	25 (62.5)	1 (100)	5 (100)
MTX		30 (54.5)	85 (37.4)	20 (100)	36 (87.8)	4 (28.6)	38 (55.1)	5 (25)	9 (22.5)	1 (100)	2 (40)
Biologic DMARDs		15 (27.3)	54(34.8)	7 (35)	19 (46.3)	7 (50)	32 (46.4)	1 (5)	3 (7.5)	0	0
TNF-α blockers		11 (20)	37 (23.9)	3 (15)	5 (12.2)	7 (50)	30 (43.5)	1 (5)	2 (5)	0	0
TCZ		3 (5.5)	7 (4.5)	3 (15)	7 (17.1)	0	0	0	0	0	0
RTX		0	3 (1.9)	0	0	0	0	0	0	0	0
CQ		10 (18.2)	11 (7.1)	4 (20)	3 (7.3)	1 (7.1)	0	5 (25)	8 (20)	0	0
HCQ		7 (12.7)	15 (9.7)	0	1 (2.4)	0	0	7 (35)	14 (35)	0	0
SSZ		7 (12.7)	44 (28.4)	3 (15.0)	13 (31.7)	4 (28.6)	31 (44.9)	0	0	0	0
AZA		5 (9.1)	6 (3.9)	0	0	0	1 (1.4)	5 (25)	4 (10)	0	1 (20)
LEF		2 (3.6)	2 (1.3)	1 (5)	2 (4.9)	1 (7.1)	0	0	0	0	0
Comorbidities											
CHD		4 (7.3)	15 (9.7)	2 (10)	4 (9.8)	0	4 (5.8)	2 (10)	7 (17.5)	0	0
Hypertension		19 (34.5)	51 (32.9)	8 (40)	13 (31.7)	5 (35.7)	17 (24.6)	5 (25)	18 (45)	1 (100)	3 (60)
COPD		2 (3.6)	3 (1.9)	0	0	1 (7.1)	0	0	2 (5)	0	1 (20)
Diabetes mellitus		1 (1.8)	10 (6.5)	0	4 (9.8)	1 (7.1)	3 (4.3)	0	2 (5)	0	1 (20)
Dyslipidemias		9 (16.4)	18 (11.6)	3 (15)	5 (12.2)	2 (14.3)	3(4.3)	3 (15)	8 (20)	1 (100)	2 (40)
Kidney failure		1 (1.8)	2 (1.3)	0	0	0	0	1 (5.3)	2 (5)	0	0
Hypothyroidism		14 (25.5)	20 (12.9)	7 (35)	5 (12.2)	0	6 (8.7)	7 (35)	9 (22.5)	0	0

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: AZA, azathioprine; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CQ, chloroquine; CS, corticosteroids; CTD, connective tissue disease; DAS28, Disease Activity Score-28; DMARDs, disease-modifying antirheumatic drugs; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RTX, rituximab; SLEDAI, systemic lupus erythematosus disease activity index; SpA, spondyloarthritis; SSZ, sulfasalazine; TCZ, tocilizumab; TNF-α, tumor necrosis factor α; VAS, visual analog scale for pain

Two patients (3.6%) were symptomless, whereas 9 (16.4%) required hospitalization. COVID-19 treatment was applied in 37 patients (67.3%), with paracetamol and azithromycin being the most frequently administered drugs (21 [38.2%] and 17 [30.9%] patients, respectively).

The course of COVID-19 was mild in 78.2% of patients and severe in 16.4%, with 3 deaths. The patients who died were a 73-year-old woman with psoriatic arthritis, hypertension, and diabetes mellitus treated with adalimumab, leflunomide, and corticosteroids; a 73-year-old woman with RA treated with methotrexate and corticosteroids; and a 66-year-old man with ankylosing spondylitis, kidney failure, hypertension, and chronic obstructive pulmonary disease treated with corticosteroids. In 54.5% of patients, symptoms of COVID-19 completely resolved, whereas symptoms such as weakness (29.1%) and reduced exercise tolerance (20%) were the ones that most frequently remained. Compared with their family members, the course of COVID-19 was milder in 48.8% of patients and similar in 17.2%.

A comparison of patients with RD who were SARS-CoV-2–positive according to particular symptoms showed that the median age in this group was higher in individuals with symptoms such as fever (P <0.001), dyspnea (P <0.001), cough (P = 0.009), and weakness (P = 0.003). Loss of smell was associated with a lower median age of patients with RD (P = 0.02). The median score in visual analog scale for pain was higher only in patients with weakness (P = 0.009). On the contrary, patients who experienced loss of smell (P = 0.007) and taste (P = 0.007) had a lower median score. The Bath Ankylosing Spondylitis Disease Activity Index did not influence any symptoms (all P >0.05). Myalgia (P = 0.01) and arthralgia (P = 0.01) occured more often in patients with a higher mean Disease Activity Score-28 (Supplementary material, *Table S1*).

The most common comorbidities among patients infected with SARS-CoV-2 were obesity (49.1%), hypertension (34.5%), and hypothyroidism (25.5%) (**TABLE 1**).

In univariable analysis, treatment with corticosteroids at a dose exceeding 10 mg/day (P = 0.04) or hydroxychloroquine (P = 0.02) as well as hypothyroidism (P = 0.03) were associated with higher odds of developing COVID-19. On the oher hand, disease duration longer than 15 years (P = 0.008), SpA (P = 0.01), and treatment with corticosteroids at a dose up to 10 mg/day (P = 0.03), sulfasalazine (P = 0.02), or NSAIDs (P = 0.01) were associated with a lower risk of COVID-19. No association between other comorbidities, body mass index, cigarette smoking, or disease activity with the risk of COVID-19 was observed (Supplementary material, *Table S2*).

Discussion We evaluated the prevalence, course, and risk factors of SARS-CoV-2 infection in RD patients during the so-called second wave of the COVID-19 pandemic. The novelty of our study is the analysis of both healthy and SARS-CoV-2–infected patients with RD. The predominance of female sex in the study group results from the fact that the assessed RDs are more prevalent among women.

The results of an analysis of a German registry of RD patients who had COVID-19 from March 30, 2020 to November 1, 2020 showed that individuals with SpA had a reduced risk of hospitalization due to COVID-19, whereas the risk was increased in patients with other RDs.[12] In our study, SpA patients were almost twice as likely to contract COVID-19 than patients with RA or CTDs, but they had a reduced risk of COVID-19 compared with patients in the other RD group. However, we did not observe an increased risk of COVID-19 in patients with RA and CTDs compared with those with other RDs.

In our cohort, SARS-CoV-2 infection was observed most frequently in middle-aged RD patients. This is in line with the results of other studies in which older age was associated with a higher risk of death in RD patients with COVID-19.[5-7]

We observed that disease duration exceeding 15 years was associated with a lower risk of COVID-19. Other investigators reported that a high activity of RD increased the risk of a severe course of SARS-CoV-2 infection and death.[5,7] In our study, the disease activity was low in the majority of patients, and no differences were observed between COVID-19–positive and COVID-19–negative patients. A longer disease duration was linked to longer treatment with DMARDs, which may have had an influence on the cytokine activity in patients exposed to SARS-CoV-2. This may have contributed to a lower risk of developing symptomatic COVID-19.

We observed that the use of corticosteroids at a dose exceeding 10 mg/day increased the risk of SARS-CoV-2 infection. Other authors reported the same association—higher doses of corticosteroids affected the rate of SARS-CoV-2 infection in RD patients.[5-7,10] Our analysis showed a decreased risk of infection in patients treated with sulfasalazine; however, the use of chloroquine increased this risk. Other studies in RD patients proved the opposite.[7,9] Moreover, in vitro studies showed that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 infection.[8,10]

Studies comparing patients with COVID-19 and SARS-CoV-2–negative individuals indicated no influence of treatment with biological DMARDs on an increased risk of infection in RD patients.[5-7] Our study confirmed no such association.

Cytokine storm with increased serum IL-6 concentration is believed to play a role in the pathogenesis of SARS-CoV-2 infection.[13] Previous studies proved that the use of IL-6 blockers in RD patients decreased the risk of infection and its severe course.[5,6] Nevertheless, we did not find any association between the use of IL-6 blockers and a lower risk of SARS-CoV-2 infection. We believe that this discrepancy is due to the fact that

the mean age and disease activity of our patients were lower than in other studies.

Previous researches indicated that comorbidities such as hypertension, metabolic disorders as well as cigarette smoking were the main risk factors predisposing to SARS-CoV-2 infection and severe course of COVID-19.[4-6] Our study did not point to such conclusions. However, we noticed that hypothyroidism increased the risk of SARS--CoV-2 infection twice. We did not find any literature data on the effect of hypothyroidism on the risk of COVID-19.

In conclusion, SpA diagnosis was associated with a lower risk of SARS-CoV-2 infection compared with other RDs. The risk of SARS-CoV-2 infection in RD patients was higher in those with longer disease duration and treated with high doses of corticosteroids or hydroxychloroquine, and lower in those treated with sulfasalazine or NSAIDs. The disease activity did not influence the risk of SARS-CoV-2 infection in patients with RD. Hypothyroidism was the only reported comorbidity that increased the risk.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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