Arch Rheumatol 2023;38(1):44-55
doi: 10.46497/ArchRheumatol.2023.9289

ORIGINAL ARTICLE

Clinical course and prognostic factors of COVID-19 infection in patients with chronic inflammatory-rheumatic disease: A retrospective, case-control study

Kemal Nas[1], Ertuğrul Güçlü[2], Yaşar Keskin[3], Gamze Dilek[1], Mehtap Kalçık Unan[1], Nurselin Can[2], İbrahim Tekeoğlu[1], Ayhan Kamanlı[1]

[1]*Department of Physical Medicine and Rehabilitation, Division of Rheumatology and Immunology, Sakarya University School of Medicine, Sakarya, Türkiye*
[2]*Department of Infectious Diseases and Clinical Microbiology, Sakarya University Faculty of Medicine, Sakarya, Türkiye*
[3]*Department of Physical Medicine and Rehabilitation, Bezmialem Vakıf University Faculty of Medicine, Istanbul, Türkiye*

ABSTRACT

Objectives: This study aims to investigate the prognosis of novel coronavirus disease-2019 (COVID-19) infection in patients with the chronic inflammatory-rheumatic disease and evaluate the effects of immunosuppressive drugs on the prognosis, clinical characteristics, laboratory findings and hospitalization periods of the rheumatic patients with COVID-19 infection.

Patients and methods: Between April 2020 and March 2021, a total of 101 patients (30 males, 71 females; mean age: 48±14.4 years; range, 46 to 48 years) with the rheumatic diseases diagnosed with COVID-19 infection were included. A total of 102 age- and sex-matched patients (35 males, 67 females; mean age: 44±14.4 years; range, 28 to 44 years) who were diagnosed with COVID-19 infection and had no history of rheumatic disease in the same period were included as the control group. Data including demographic characteristics of the patients, presence of any symptoms of COVID-19 disease, laboratory data at the time of diagnosis, and treatments administered were collected.

Results: The rate of hospitalization was higher in 38 (37%) patients without rheumatic diseases than in 31 (31%) patients with rheumatic diseases (p=0.324). The rate of lung infiltration on radiographic examination was higher in patients without rheumatic diseases (40% *vs.* 49%) (p=0.177). COVID-19 infection symptoms such as anosmia 45 (45%), ageusia 51 (50%), shortness of breath 45(45%), nausea 29 (29%), vomiting 16 (16%), diarrhea 25 (25%) and myalgia-arthralgia 81 (80%) were higher in patients with rheumatic diseases. In terms of laboratory values, lymphocyte count (p=0.031) was statistically higher in patients without rheumatic diseases. Hydroxychloroquine (35%), oseltamivir 10 (10%), antibiotics 27 (26%), acetylsalicylic acid 52 (51%), and supplementary oxygen 25 (25%) treatments which used to cure COVID 19 infection were administered more in patients without rheumatic diseases. The number of treatments administered was higher in patients without rheumatic diseases (p<0.001).

Conclusion: Patients with the chronic inflammatory-rheumatic disease have more symptoms due to COVID-19 infection, but the disease course is not poor and hospitalization rates are lower.

Keywords: Autoimmune systemic rheumatic diseases, COVID-19, disease course, prognostic factors.

The clinical spectrum of novel coronavirus disease-2019 (COVID-19) is quite wide and ranges from asymptomatic to life-threatening or fatal disease. Several risk factors have been associated with a poor prognosis including advanced age, sex, and comorbidities such as diabetes, hypertension, lung, and cardiovascular diseases.[1-3]

Received: October 14, 2021 ***Accepted:*** February 07, 2022 ***Published online:*** September 20, 2022

Correspondence: Kemal Nas, MD. Sakarya Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Romatoloji ve İmmünoloji Bilim Dalı, 54050 Korucuk, Sakarya, Türkiye. E-mail: kemalnas@yahoo.com

Citation:
Nas K, Güçlü E, Keskin Y, Dilek G, Kalçık Unan M, et al. Clinical course and prognostic factors of COVID-19 infection in patients with chronic inflammatory-rheumatic disease: A retrospective, case-control study. Arch Rheumatol 2023;38(1):44-55.

The COVID-19 pandemic caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is particularly worrying for patients with rheumatic diseases or those who are immunocompromised. In general, immunosuppression and presence of comorbidities are associated with an increased risk of significant infections in patients with rheumatic diseases.[4] Therefore, these individuals may be at a higher risk for a severe clinical course that can lead to hospitalization, complications, and death during COVID-19 disease.[4]

Immuno-mediated diseases and immunosuppressive treatments increase susceptibility to viral and bacterial infections and, therefore, it is predicted that understanding the effects of COVID-19 infection on the patients is an urgent need.[5-7]

Vabret et al.[8] reported that it would be particularly interesting to examine how severe COVID-19 disease-associated with a hyperinflammatory process affects COVID-19 expression in patients with a pre-existing inflammatory disease or using immunosuppressive agents. Some medicines such as hydroxychloroquine and interleukin-6 (IL-6) inhibitors, which are used in the treatment of rheumatic diseases, are being investigated for the prevention and treatment of COVID-19 disease and/or management of complications including cytokine storm that may develop due to the disease.[9-11]

In a series of patients with rheumatic diseases and COVID-19 infection, it was reported that the use of disease-modifying antirheumatic drugs (DMARDs) did not increase the possibility of hospitalization. As in the general population, the study showed higher COVID-19-related hospitalization rates in patients with an older age and/or patients that have rheumatic diseases with comorbidities.[4] In another study, patients with rheumatic diseases and COVID-19 infection had a higher rate of mechanical ventilation, but had similar clinical characteristics and hospitalization rates to COVID-19 patients without the rheumatic disease. They reported that important inferences could be obtained from the findings of patients with rheumatic diseases, but they needed to be confirmed with further studies.[12]

In a recent study, the immunosuppressive treatments used by patients with rheumatic or musculoskeletal diseases who had COVID-19 infection did not seem to protect against the severe course of COVID-19 infection.[13] It was further stated that patients with rheumatic or musculoskeletal diseases using DMARDs did not indicate that stopping immunosuppressive medications could prevent COVID-19 or other infections, as it did not have a worse outcome than non-rheumatic controls. They also concluded that patients with an advanced age that had rheumatic or musculoskeletal diseases and comorbidities were at risk for a more severe course of COVID-19 infection.

There is little evidence surrounding factors associated with COVID-19 in patients with underlying inflammatory-rheumatic diseases. In this respect, studies that examine the clinical course of patients with rheumatic diseases after COVID-19 infection are needed. In this study, we aimed to investigate the differences between patients with rheumatic diseases who had COVID-19 infection during the pandemic period and those without rheumatic diseases in terms of basic clinical characteristics, laboratory findings, prognosis, length of stay in hospital, and treatment.

PATIENTS AND METHODS

This retrospective, observational, paired case-control study was conducted at Sakarya University School of Medicine, Department of Rheumatology and Department of Infectious Diseases and Clinical Microbiology between April 16th, 2020 and March 16th, 2021. A total of 101 patients (30 males, 71 females; mean age: 48±14.4 years; range, 42 to 48 years) with the rheumatic diseases diagnosed with COVID-19 infection were included. A total of 102 age- and sex-matched patients (35 males, 67 females; mean age: 44±14.4 years; range, 28 to 44 years) who were diagnosed with COVID-19 infection and had no history of rheumatic disease in the same period were included as the control group. Patient data were obtained from patient's medical records and electronic patient data monitoring systems.

Patients in the group with rheumatic diseases who we detected as positive for SARS-CoV-2 by means of polymerase chain reaction (PCR)

performed in our center included all of the adult patients diagnosed with spondyloarthritis (SpA), rheumatoid arthritis (RA), psoriatic arthritis (PsA), familial Mediterranean fever (FMF) and connective tissue diseases (systemic lupus erythematosus, Sjögren syndrome and systemic sclerosis, etc.) and others (polymyalgia rheumatic, gout, Behçet's disease, and reactive arthritis). The control group data were taken from the databases of the center where participants that were matched on a 1 to 1 basis with the patients with rheumatic diseases at the time of diagnosis of COVID-19 infection in terms of sex, age, and comorbidity were treated.

The diagnosis of COVID-19 was made by PCR tests. For this purpose, SARS-CoV-2 was investigated by PCR tests by way of taking oropharyngeal and nasopharyngeal swab samples simultaneously from patients who presented with COVID-19 infection compatible complaints such as fever, cough, headache, muscle joint pain. Complaints and symptoms of the patients such as fever (temperature >38°C), cough, shortness of breath, myalgia, arthralgia, fatigue, flu, nausea, vomiting, headache, diarrhea, dysgeusia, and anosmia were recorded. The laboratory data of the patients at the time of diagnosis were also taken from the patient files. The time from the onset of symptoms to the PCR test and the presence and degree of lung involvement on radiological imaging were also recorded.

The diagnosis group, duration of the disease, and treatments administered before COVID-19 disease were recorded among the specific factors for rheumatic diseases. Treatments administered before COVID-19 disease were grouped as follows: conventional synthetic disease-modifying antirheumatic drugs (csDMARD), (i.e., hydroxychloroquine, chloroquine, methotrexate, leflunomide, sulfasalazine cyclophosphamide, cyclosporine, and azathioprine) or targeted synthetic or biologic disease-modifying antirheumatic drugs (ts/bDMARD) (tumor necrosis factor-alpha [TNF-α], IL-1, IL-6 or IL-23/IL-17 inhibitors, abatacept, rituximab, Janus kinase inhibitors [JAK]) and others (glucocorticoids, non-steroidal anti-inflammatory drugs and those not administering treatment).

The treatment administered to patients with COVID-19 was also recorded. The most commonly used treatments in COVID-19 infection offered in our center were hydroxychloroquine, antivirals (favipiravir and oseltamivir), glucocorticoids, plasma, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, supplementary oxygen, and low-molecular-weight heparin anti-cytokines (anti-IL-1 and anti-IL-6).

Patients with any malignancy and recent infection were excluded from all of the study. Patients with chronic inflammatory-rheumatic diseases were excluded from the control group.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to examine whether continuous numerical variables showed a normal distribution. Descriptive data were expressed in mean ± standard deviation (SD) or median (interquartile range [IQR]) or number and frequency. The significance was compared using the chi-square (χ^2) test for categorical variables and the Mann-Whitney U test for continuous variables for differences in disease-specific characteristics between cases and controls. A p value of <0.05 was considered statistically significant.

RESULTS

There were 101 (49.7%) patients in the group with rheumatic diseases and 102 (51.3%) in the group without rheumatic diseases. The mean ages and sex of the groups were not significantly different (p=0.951 and p=0.582). The smoking rate of patients without rheumatic diseases was two (4%), while the smoking rate of patients with rheumatic diseases was seven (13%). Comorbidities were hypertension in 16 patients (30%), diabetes in seven (13%), cardiovascular disease in two (4%), and lung disease in two patients (4%) in the group with rheumatic diseases. Comorbidities took the form of hypertension in 16 patients (31%), diabetes in 12 (23%), cardiovascular disease in 12 (23%), and lung disease in five patients (10%) in the group without rheumatic diseases. In the group with rheumatic diseases, hypertension in 16 (30%) patients, diabetes in seven (13%), cardiovascular disease in two (4%), and lung

disease in two (4%) patients were recorded as comorbid disorders, while in the other group they were in 16 (31%), 12 (23%), in 12 (23%), and five (10%), respectively. Patients with COVID-19 infection but without rheumatic disease were under the medical treatment with anti-rheumatic drugs such as csDMARD in 41 (76%), bDMARD, 15 (%28) and low-dose glucocorticoid (10 mg/day) 13 (%23). Overall characteristics and laboratory data of the groups participating in the study are shown in Tables 1 and 2. The patients included

Table 1. Baseline demographic and clinical characteristics of COVID-19 patients with and without rheumatic disease

		Rheumatic group					Non-rheumatic group				
	n	n	%	Median	IQR	n	n	%	Median	IQR	*p*
Age (year)	101			101	48-42	102			102	44-28	0.007
Age (>60 year)	101	19	19			102			22	22	0.625
Sex											
Female	101	71	70			102			67	66	0.481
Smoking	101	14	14			102			8	8	0.168
Alcohol	101	4	4			102			2	2	0.4
Comorbidity	101	38	38			102	35	34			0.623
Hypertension	101	25	25			102	21	21			0.479
Diabetes	101	12	12			102	16	16			0.432
Heart disease	101	4	4			102	9	9			0.157
Pulmonary disease	101	3	3			102	5	5			0.479
Liver disease	101	1	1			102	1	1			0.994
Kidney disease	101	0	0			102	4	4			0.121
No. of comorbidities	101			101	0-0	102			102	0-0	0.993
Disease duration (year)	99			99	7-4	-			-	-	-
Laboratory tests (peak value)											
White blood cell count ($\times 10^9$/L)	53			53	6-5	91			91	5-4	0.053
Red blood cell ($\times 10^9$/L)	53			53	4-4	87			87	5-4	0.163
Hemoglobin (g/dL)	53			53	13-12	89			89	13-12	0.092
Hematocrit (%)	53			53	39-37	87			87	41-37	0.299
Lymphocyte count ($\times 10^9$/L)	57			57	2-1	92			92	1-1	0.031
Neutrophil count ($\times 10^9$/L)	53			53	3-3	88			88	3-3	0.689
Platelet count ($\times 10^9$/L)	52			52	204-159	92			92	179-146	0.052
Mean platelet volume (fL)	58			58	8-7	89			89	8-8	0.152
Platelet distribution width	58			58	19-16	52			52	18-17	0.465
Neutrophil-lymphocyte ratio	50			50	2-1	88			88	2-2	0.112
Thrombocyte-lymphocyte ratio	52			52	121-79	92			92	132-99	0.221
Ferritin (ng/mL)	48			48	260-136	87			87	136-40	0.01
D-dimer (ng/mL)	42			42	529-229	87			87	311-127	0.02
Urea (mg/dL)	52			52	28-20	90			90	24-19	0.163
Serum creatinine (mg/dL)	51			51	1-1	89			89	1-1	0.047
Lactate dehydrogenase (U/L)	42			42	266-200	86			86	237-192	0.573
Aspartate aminotransferase (U/L)	53			53	28-20	90			90	27-21	0.988
Alanine aminotransferase (U/L)	53			53	30-24	91			91	23-15	0.004
C-reactive protein (mg/dL)	52			52	33-9	88			88	11-3	0.029
Time to consult a doctor from the onset of symptoms	33			33	2-1	80			80	3-2	0.379

IQR, interquartile range; Quantitative measures, the Mann-Whitney U test; Categorical variables, the chi-square test.

Table 2. Symptoms, clinical course and treatments of COVID-19 patients with and without rheumatic disease

	Rheumatic group (n=101)				Non-rheumatic group (n=102)				
	n	%	Median	IQR	n	%	Median	IQR	*p*
COVID-19 symptoms									
Fever	27	27			34	33			0.305
Headache	51	50			38	37			0.057
Anosmia	45	45			30	29			0.025
Ageusia	51	50			27	26			<0.001
Sore throat	16	16			22	22			0.296
Cough	55	54			53	52			0.722
Shortness of breath	45	45			35	34			0.135
Nausea	29	29			23	23			0.314
Vomiting	16	16			14	14			0.671
Diarrhea	25	25			14	14			0.046
Myalgia-Arthralgia	81	80			50	49			<0.001
Asthenia-Fatigue	26	26			78	76			<0.001
COVID-19 therapy									
Hydroxychloroquine	11	11			35	35			<0.001
Favipiravir	91	90			62	61			<0.001
Oseltamivir	3	3			10	10			0.047
Antibiotics	21	21			27	26			0.341
Glucocorticoids	12	12			19	19			0.182
Plasma	0	0			7	7			0.007
Non-steroidal anti-inflammatory drugs	6	6			24	24			<0.001
Acetylsalicylic acid	8	8			52	51			<0.001
Supplementary oxygen	6	6			25	25			<0.001
Low molecular weight heparin	28	28			42	41			0.044
Number of treatments applied			100	1-1			52	3-2	<0.001
Radiographic pneumonia	40	40			50	49			0.177
Hospitalized	31	31			38	37			0.324
Intensive care	1	1			2	2			0.567

COVID-19: Coronavirus disease-19; IQR, interquartile range; Quantitative measures, the Mann-Whitney U test; Categorical variables, the chi-square test.

Table 3. Baseline characteristics of patients with rheumatic diseases

	n	%
Rheumatic diagnosis		
Spondyloarthropathies	30	29.7
Connective tissue diseases	23	22.8
Psoriatic arthritis	22	21.8
Rheumatoid arthritis	15	14.9
Familial Mediterranean Fever	5	5.0
Behçet's disease	6	5.9
Regular medications		
csDMARD	54	53.5
Methotrexate	22	21.8
Hydroxychloroquine	18	17.8
Colchicine	13	12.9
Sulfasalazine	9	8.9
b/tsDMARD	31	30.7
Anti-TNF-alpha	24	23.8
Rituximab	3	3.0
Secukinumab	2	2.0
JAK Inhibitor	2	2.0
Low-dose glucocorticoid	11	10.9
No-treatment	8	7.9

DMARD: Disease-modifying antirheumatic drug; csDMARD: Conventional synthetic DMARD; b/tsDMARD: Biological/targeted synthetic DMARD; TNF: Tumor necrosis factor.

in the study were well balanced by age, sex, comorbidity, and smoking.

The diagnoses of patients with rheumatic diseases were SpA (n=15, 27%), connective tissue diseases (CTD) (n=11, 21%), PsA (n=9, 17%) and RA (n=7, 13%). The mean duration of the rheumatic disease was 7.6±5.96 years (Table 3). Most of the patients with previous rheumatic diseases were using biological agents (n=26, 48%) and csDMARD (n=22, 40%) (Table 3). None of the patients in the group without rheumatic diseases were taking any of these drugs.

In terms of laboratory values, lymphocyte count (median (IQR)=2 (1-2), p=0.025) and white blood cell count (median (IQR)=7 (6-9), p=0.025) were statistically higher in patients with rheumatic diseases. Only neutrophil-to-lymphocyte ratio (NLR) (median (IQR)=2 (2-4), p=0.048) was higher in the group without rheumatic diseases. There was no significant difference between the groups in terms of other laboratory values.

Table 4. The relationship between rheumatic drugs and COVID-19 laboratory parameters

	no DMARD (n=14)			csDMARD (n=50)			b/tsDMARD (n=37)			
	n	Median	IQR	n	Median	IQR	n	Median	IQR	*p*
Laboratory tests (peak value)										
White blood cell count (×10^9/L)	7	7	6-10	27	5	5-7	19	6.19	5.58-7.63	0.064
Red blood cell (×10^9/L)	7	4	4-5	27	4.4	4-5	19	5	4-5	0.373
Hemoglobin (g/dL)	7	12	12-12	27	12	11-14	19	12.9	12-14	0.634
Hematocrit (%)	7	38	34-39	27	39	36-42	19	41	39-44	0.02
Lymphocyte count (×10^9/L)	8	2	1-2	29	2	1-2	20	2	2-2	0.647
Neutrophil count (×10^9/L)	7	3	2-5	28	3	2-4	18	4	3-4	0.512
Platelet count (×10^9/L)	7	65	33-265	27	195	172-232	18	237	195-285	0.044
Mean platelet volume (fL)	9	8	7-9	30	8	8-9	19	8	7-9	0.56
Platelet distribution width	9	19	19-21	30	18	16-20	19	18	13-20	0.49
Neutrophil-lymphocyte ratio	7	2	1-8	26	2	2-4	17	2	2-3	0.921
Thrombocyte-lymphocyte ratio	7	64	15-130	27	143	76-188	18	128	98-156	0.086
Ferritin (ng/mL)	6	389	75-855	23	248	143-408	19	271	117-358	0.76
D-dimer (ng/mL)	5	317	275-351	21	543	286-1250	16	538	156-1155	0.565
Urea (mg/dL)	7	24	0.89-37	27	25	20-33	18	31	24-40	0.437
Serum creatinine (mg/dL)	6	1	1-202	27	1	1-1	18	1	1-1	0.292
Lactate dehydrogenase (U/L)	5	333	217-430	22	209.5	195-337	15	286	227-360	0.299
Aspartate aminotransferase (U/L)	7	30	20-48	27	28	21-33	19	28	20-36	0.822
Alanine aminotransferase (U/L)	7	30	21-36	27	33	24-43	19	29	21-39	0.731
C-reactive protein (mg/dL)	6	72	37-112	27	32	10-82	19	16	8-72	0.2
Time to consult a doctor from the onset of symptoms	7	3	1-7	17	3	1-5	9	2	1-3	0.591
Number of treatments applied	14	1	1-3	49	1	1-2	37	1	1-3	0.988

COVID-19: Coronavirus disease-19; DMARD: Disease-modifying antirheumatic drug; csDMARD: Conventional synthetic DMARD; b/tsDMARD: Biological/targeted synthetic DMARD; IQR, interquartile range.

Table 5. COVID-19 clinical and treatment parameters according to rheumatic drugs

	no DMARD (n=14)		csDMARD (n=50)		b/tsDMARD (n=37)		
	n	%	n	%	n	%	*p*
COVID-19 symptoms							
Fever	2	14	13	26	12	32	0.42
Headache	6	43	27	54	18	49	0.732
Anosmia	5	36	21	42	19	51	0.531
Ageusia	7	50	22	44	22	59	0.362
Sore throat	4	29	4	8	8	22	0.085
Cough	7	50	33	66	15	41	0.058
Shortness of breath	7	50	24	48	14	38	0.582
Nausea	6	43	13	26	10	27	0.449
Vomiting	2	14	7	14	7	19	0.812
Diarrhea	4	29	12	24	9	24	0.938
Myalgia-Arthralgia	11	79	40	80	30	81	0.979
Asthenia-Fatigue	6	43	9	18	11	30	0.134
COVID-19 therapy							
Hydroxychloroquine	1	7	7	14	3	8	0.608
Favipiravir	13	93	44	88	34	92	0.779
Oseltamivir	0	0	2	4	1	3	0.733
Antibiotics	2	14	12	24	7	19	0.687
Glucocorticoids	3	21	6	12	3	8	0.423
Non-steroidal anti-inflammatory drugs	0	0	3	6	3	8	0.55
Acetylsalicylic acid	0	0	4	8	4	11	0.443
Supplementary oxygen	1	7	4	8	1	3	0.574
Low molecular weight heparin	5	36	13	26	10	27	0.768
Radiographic pneumonia	5	36	22	44	13	35	0.67
Hospitalized	6	43	16	32	9	24	0.423
Intensive care	0	0	1	2	0	0	0.597

COVID-19: Coronavirus disease-19; DMARD: Disease-modifying antirheumatic drug; csDMARD: Conventional synthetic DMARD; b/tsDMARD: Biological/targeted synthetic DMARD; IQR: Interquartile range.

Table 6. COVID-19 laboratory parameters by duration of rheumatic disease

	1-4 year (n=30)			5-9 year (n=33)			10 year and over (n=38)			
	n	Median	IQR	n	Median	IQR	n	Median	IQR	*p*
Laboratory tests (peak value)										
White blood cell count (×10⁹/L)	15	7	4-9	16	6	5-7	22	6	5-8	0.704
Red blood cell (×10⁹/L)	15	4	4-5	16	4	4-5	22	5	4-5	0.679
Hemoglobin (g/dL)	15	12	11-13	16	12	12-13	22	13	12-14	0.164
Hematocrit (%)	15	39	36-43	16	39	27-42	22	40	37-43	0.78
Lymphocyte count (×10⁹/L)	16	2	1-2	19	2	1-2	22	2	1-2	0.535
Neutrophil count (×10⁹/L)	16	3	3-5	15	3	2-4	22	3	3-4	0.229
Platelet count (×10⁹/L)	15	202	148-280	15	217	124-271	22	201	172-259	0.996
Mean platelet volume (fL)	18	8	7-9	18	8	7-9	22	8	7-9	0.924
Platelet distribution width	18	18	15-20	18	19	16-20	22	18	18-20	0.806
Neutrophil-lymphocyte ratio	14	2	1-4	15	2	1-4	21	2	1-3	0.957
Thrombocyte-lymphocyte ratio	15	111	72-201	15	144	95-167	22	117	91-187	0.947
Ferritin (ng/mL)	15	159	30-271	16	262	179-351	17	326	232-422	0.047
D-dimer (ng/mL)	13	543	317-1250	12	691	171-1615	17	519	231-885	0.648
Urea (mg/dL)	15	24	16-30	16	32	21-42	21	28	20-39	0.097
Serum creatinine (mg/dL)	15	1	1-1	16	1	1-1	20	1	1-1	0.926
Lactate dehydrogenase (U/L)	14	212	190-333	12	315	237-414	16	252	210-338	0.233
Aspartate aminotransferase (U/L)	15	29	20-42	16	28	22-39	22	28	20-33	0.79
Alanine aminotransferase (U/L)	15	30	24-43	16	31	24-45	22	31	21-38	0.886
C-reactive protein (mg/dL)	14	12	7-80	16	45	17-75s	22	35	12-82	0.403
Time to consult a doctor from the onset of symptoms	9	2	1-3	12	3	2-5	12	2	1-4	0.391
Number of treatments applied	30	1	1-2	33	1	1-2	37	1	1-3	0.343

COVID-19: Coronavirus disease-19; IQR: Interquartile range.

The mean time between the onset of symptoms and the time of referral to the physician was 3.8±3.2 days in patients with rheumatic diseases and 4.6±3.3 days in patients without rheumatic diseases. Besides, 38 (73%) patients without rheumatic diseases were hospitalized due to COVID-19 infection compared to 17 (31%) patients with rheumatic diseases (p<0.001). Similarly, the incidence of radiographic pneumonia was significantly (p=0.012) higher in the group without rheumatic diseases (n=31, 60%). The need for intensive care occurred only in one patient in the group without rheumatic diseases.

In terms of COVID-19 symptoms, myalgia-arthralgia 45 (83%), ageusia 28 (52%), anosmia 23 (43%), shortness of breath 18 (33%), nausea 17 (31%), diarrhea 16 (30%), and vomiting 10 (19%) were seen in the group with rheumatic diseases, and these rates were significantly higher in this group. Only asthenia-fatigue rate was higher in the group without rheumatic diseases, as it was seen in 38 (73%) patients.

Hydroxychloroquine (35%), oseltamivir 10 (10%), antibiotics 27 (26%), acetylsalicylic acid 52 (51%), and supplementary oxygen 25 (25%) treatments which used to cure COVID-19 infection were administered more in the group without rheumatic diseases. Moreover, the number of treatments administered was higher in the group without rheumatic diseases (median (IQR)= 3 (2-3), p<0,001). Only favipiravir 46 (85%) treatment seemed to be administered more in the group with rheumatic diseases. In the study, 14 participants were not receiving medical treatment, 50 participants were using csDMARD, 37 participants were using b/ts DMARD in the rheumatic patients group. Hematocrit and platelet values were significantly higher in the group using b/tsDMARDs. No correlation was found between the clinical parameters of COVID-19 in the rheumatic group according to the medical treatment used (Tables 4 and 5). In the study, the duration of the disease in rheumatic patients was determined as 30 patients between one and four years, 33 patients between five and nine years, and 38 people who were 10 years and older. Ferritin levels were higher in those with a disease duration of 10 years or more. There was no significant difference between

Table 7. Distribution of rheumatic disease by years and COVID-19 clinical and treatment parameters

	1-4 year (n=30)		5-9 year (n=33)		10 year and over (n=38)		
	n	%	n	%	n	%	*p*
COVID-19 symptoms							
Fever	8	27	9	27	10	26	0.996
Headache	11	37	19	58	21	55	0.192
Anosmia	14	47	16	48	15	39	0.72
Ageusia	15	50	21	64	15	39	0.127
Sore throat	7	23	6	18	3	8	0.202
Cough	15	50	17	52	23	61	0.631
Shortness of breath	9	30	14	42	22	58	0.068
Nausea	8	27	12	36	9	24	0.478
Vomiting	6	20	5	15	5	13	0.739
Diarrhoea	6	20	9	27	10	26	0.769
Myalgia-arthralgia	26	87	24	73	31	82	0.369
Asthenia-fatigue	6	20	10	30	10	26	0.643
COVID-19 therapy							
Hydroxychloroquine	6	20	0	0	5	13	0.033
Favipiravir	24	80	31	94	36	95	0.087
Oseltamivir	3	10	0	0	0	0	0.026
Antibiotics	6	20	5	15	10	26	0.508
Glucocorticoids	1	3	4	12	7	18	0.161
Non-steroidal anti-inflammatory drugs	2	7	2	6	2	5	0.97
Acetylsalicylic acid	4	13	0	0	4	11	0.111
Supplementary oxygen	1	3	2	6	3	8	0.731
Low molecular weight heparin	4	13	10	30	14	37	0.091
Radiographic pneumonia	10	33	11	33	19	50	0.253
Hospitalized	7	23	10	30	14	37	0.486
Intensive care	0	0	0	0	1	3	0.433

COVID-19: Coronavirus disease-19; IQR: Interquartile range.

other laboratory parameters. No significant correlation was found between disease duration and clinical parameters in the rheumatic group (Tables 6 and 7).

DISCUSSION

In the present study, we reported from our center how patients with and without rheumatic diseases were affected by COVID-19 infection in a matched case-control study. In this study, the symptom rates (anosmia, ageusia, shortness of breath, nausea, vomiting, diarrhea, and myalgia-arthralgia) and white blood cell count, from among the laboratory findings, were higher in patients with rheumatic diseases. Asthenia-fatigue and lymphocyte count, ferritin, dimer, CRP count were higher in the group without rheumatic diseases. Patients with the rheumatic disease had less few treatments administered due to COVID-19 infection.

The COVID-19 is a viral infection that manifests itself with systemic involvement and mainly affects the upper respiratory tract and lungs. It is important to clarify the clinical data and factors affecting the prognosis in individuals with autoimmune and autoinflammatory diseases during COVID-19 disease in terms of the course of the disease.[7,12]

In a multi-center study comparing the clinical data in patients with rheumatic diseases and those without rheumatic diseases during COVID-19 disease, there was no significant difference between the groups with and without rheumatic diseases in the rate of hospitalization.[14] Kastritis et al.[15] reported that the risk of COVID-19 infection in patients with systemic autoimmune diseases did not appear to be much higher than in the general population with similar comorbidities and that these two populations did not appear to be different compared to the general population in terms of hospitalization requirements, intensive

care unit admission, or death. Similarly, there was no significant difference in the rate of hospitalization between patients rheumatic diseases and the group without rheumatic diseases in our study. In contrast, Arleo et al.[16] reported that rheumatologic patients with COVID-19 had higher rates of hospitalization and intensive care admission than those without rheumatic disease. However, the rate of hospitalization in patients with rheumatic diseases was stated as 46% in a multi-center study that compiled the hospitalization parameters of patients with rheumatic diseases and with COVID-19 infection in the literature. It was found that there was no relationship between non-steroidal anti-inflammatory drugs (NSAIDs) or antimalarials used by patients with rheumatic diseases and hospitalization due to COVID-19 infection in the same study. Moreover, it was considered that b/tsDMARD monotherapy was associated with a lower probability of hospitalization and a largely anti-TNF-driven effect.[4] In our study, a total of 87 participants from patients with inflammatory disease were using cs or bDMARDs. There was no significant difference between the medical treatments used by rheumatic patients and the clinical symptoms of COVID-19, the treatment of COVID-19 infection, and the incidence of hospitalization. Hasseli et al.[22] showed that some anti-rheumatic drugs such as hydroxychloroquine, anakinra, and IL-6 inhibitors had an interesting role in the course of COVID-19 infection. It was also reported that high-dose corticosteroid use (10 mg and above), advanced age, and comorbidities were factors associated with a higher rate of hospitalization. In the rheumatic disease group, all of the patients with COVID-19 infection were under the medication of low dose corticosteroids (≤10 mg/day).

It is estimated in the literature that lymphocyte counts in COVID-19 disease may give clues about the severity and clinical consequences of the disease.[17] The lymphocyte ratios in patients without rheumatic diseases were found to be higher than in patients with rheumatic diseases in this study. In the literature, lymphocyte rates are low during the COVID-19 disease, particularly in the first two weeks of the disease. There are also studies indicating that a low lymphocyte ratio during COVID-19 disease is associated with a severe form of the disease, namely acute respiratory distress syndrome. It is also stated that if low lymphocyte levels persist for a long time in patients with COVID-19, the disease may become more severe.[18] The lymphocyte ratio in patients without rheumatic diseases was higher than in patients with rheumatic diseases in our study. Unlike the previous study, the rate of hospitalization and oxygen requirement were not in patients without rheumatic diseases than in patients with rheumatic diseases in our study.

The NLR gives information about inflammatory status in patients, and it has prognostic value in diseases such as malignancies, cardiovascular diseases, connective tissue diseases, as well as infections. A high NLR in COVID-19 disease is associated with a high risk of severe disease and mortality.[19] However, in this study, platelet and hematocrit values of participants with rheumatic disease under bDMARD treatment were found to be higher than those who received csDMARDs. However, there was no significant difference in the COVID-19 clinic. Although the rate of NLR in patients with rheumatic diseases was lower, the difference between the groups was not significant; besides, the rate of hospitalization did not significantly differ between the two groups in our study.

Pablos et al.[14] reported that cardiovascular diseases and obesity were detected more in patients with rheumatic diseases. The rate of comorbidity in our patients with rheumatic diseases was 44%, and there was no significant difference between the two groups in the rate of comorbidity in our study. Besides, most of the patients in both groups had no comorbidity. According to the literature data, age and comorbidity correlated positively with hospitalization during COVID-19 infection.[20] The mean age of the patients in our study was lower than in the above-mentioned study, this may explain the lower rate of comorbidity in our patients with rheumatic diseases, and the duration of the rheumatic disease may also increase the incidence of comorbidity. A clear relationship between the duration of rheumatic disease and the clinical progression of COVID-19 has not been reported in the literature. in our study, there was no significant difference between disease duration and clinical progression of COVID-19 in participants with inflammatory disease.

In our study, interstitial lung involvement in the course of COVID-19 infection (n: 40% *vs.* 50%, p=0.177) was lower in patients with rheumatic diseases compared to patients without rheumatic diseases. In line with our findings, Pablos et al.[14] reported that radiological lung involvement was higher in patients without rheumatic diseases and with COVID-19 infection compared to patients with rheumatic diseases. D'Silva et al.[12] reported that the need for mechanical ventilation during COVID-19 disease was higher in patients with rheumatic diseases than in patients without rheumatic diseases; however, there was no information provided about interstitial lung involvement in that study.

The macrophage-derived cytokine storm seen in the course of COVID-19 disease can damage tissues by causing inflammation. It is also known that cytokine storm causes tissue damage secondary to inflammation with a similar mechanism in rheumatic diseases. Tissue damage that occurs as a result of this pathological inflammatory process may overlap with the radiological findings seen in COVID-19 infection and with the radiological findings related to the current rheumatic disease.[21] Anti-cytokine treatments used by patients with the rheumatic diseases may prevent the release of cytokines that cause lung damage; however, there is no literature data to prove this suggestion.

It was found that COVID-19 infection symptoms such as loss of smell and taste, vomiting, diarrhea, myalgia, and arthralgia were higher in patients with rheumatic diseases than in patients without rheumatic diseases in our study. Fatigue was more prominent in patients without rheumatic diseases. In previous studies, complaints such as cough, fever, fatigue, headache, dyspnea, loss of taste and smell, diarrhea were reported as the main symptoms seen in patients with rheumatic diseases that have COVID-19 infection.[22] However, in the literature, that there was no significant difference between patients with rheumatic diseases and those without rheumatic diseases in clinical symptoms due to COVID-19 infection.[12,14]

Alzahrani et al.[23] reported that fever, myalgia, and cough were the most frequently reported symptoms (78.7%, 78.7%, and 74.5%, respectively) among the symptoms of COVID-19 infection. During the COVID-19 pandemic, hydroxychloroquine, methotrexate, and colchicine were attempted at various stages for the treatment and prophylaxis.[24] There are randomized, observational studies in the literature investigating the potential therapeutic effects of JAK inhibitors and anti-cytokine biological agents in COVID-19 disease.[25] However, there is clinically and prognostically no significant effect of these cs and bDMARDs in patients with rheumatic diseases during COVID-19 infection.[7,15] Jung et al.[26] evaluated with a cohort study patient with rheumatic diseases using hydroxychloroquine and having COVID-19 infection. They reported that hydroxychloroquine use did not reduce the occurrence of COVID-19 in patients with rheumatic diseases before exposure to COVID-19 infection. Hydroxychloroquine was used more in patients in the group without rheumatic diseases as the treatment of COVID-19 infection, and the need for oxygen and antibiotic treatment was higher in this group in our study. In agreement with the literature, there was no significant effect of hydroxychloroquine on prognosis in our study.

Ferri et al.[27] investigated COVID-19 infection in an Italian case series by comparing patients with chronic arthritis and the general population. They found an increased rate of COVID-19 infection in connective tissue diseases in patients with systemic lupus or large vessel vasculitis. Ongoing DMARDs and particularly bDMARDs did not affect the results of symptomatic and generally mild COVID-19 disease in these cases. Montero et al.[28] concluded that more research was needed to evaluate specific immunosuppressive drugs and other comorbidity interactions, but according to the findings and in agreement with the other studies, patients with the rheumatic diseases did not need to discontinue immunosuppressive drugs. They also reported that minimizing glucocorticoid exposure would be important due to its association with poorer outcomes.[2]

Nonetheless, this study has some limitations. Firstly, radiological examinations were not evaluated in some of the patients with mildly symptomatic COVID-19 infection. The other limitation was the heterogeneous structure of our study resulting from its design. The strength of our study was that it was performed in real-life

conditions that allowed us to comprehensively evaluate the baseline clinical characteristics of patients with COVID-19 infection, as well as their laboratory findings and COVID-19 treatment.

In conclusion, it is known that the risk of comorbidity and infection in patients with rheumatic diseases is higher than in the normal population. During the COVID-19 pandemic, it has been a matter of curiosity to what extent patients with rheumatic diseases are at risk, the prognosis of the disease, and how much the treatments would affect the disease. The literature shows that the clinical data of patients with rheumatic diseases that have COVID-19 infection are not significantly different than those of the normal population, but a definitive algorithm for treatment and prognosis is still not created. Evaluation of clinical data and prognostic characteristics of COVID-19 disease in patients with rheumatic diseases should be done carefully. We believe that this study would contribute to the treatment and clinical management of patients with rheumatic diseases during the COVID-19 pandemic.

During the COVID-19 pandemic, high-dose glucocorticoids has been a matter of intention with age and comorbidity in patients with rheumatic diseases. Ongoing csDMARD and bDMARD has no effect on COVID-19 outcomes, anti-rheumatic treatment schedule should be continued without any interruption.

Ethics Committee Approval: The study protocol was approved by the Sakarya University School of Medicine Ethics Committee (E-71522473-050.01.04-25237-246). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: K.N., M.K.U.; Design; E.G., Y.K.; Control/supervision: I.T., K.N.; Data collection and/or processing: A.K., G.D.; Analysis and/or interpretation: N.C., G.D.; Literature review: E.G., K.N., M.K.U., Writing the article: G.D., Y.K.; Critical review: A.K., E.G.; References and fundings: I.T., K.N.; Materials: Y.K., K.N.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. Lancet 2020;395:1763-70.
2. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med 2020;180:1081-9.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62.
4. Gianfrancesco M, Hyrich KL, Al-Adely S, 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.
5. Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: A systematic review and meta-analysis. Lancet 2015;386:258-65.
6. Gianfrancesco MA, Hyrich KL, Gossec L, Strangfeld A, Carmona L, Mateus EF, et al. Rheumatic disease and COVID-19: Initial data from the COVID-19 Global Rheumatology Alliance provider registries. Lancet Rheumatol 2020;2:e250-e253.
7. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American college of rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: Version 1. Arthritis Rheumatol 2020;72:1241-51.
8. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: Current state of the science. Immunity 2020;52:910-41.
9. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-García A, et al. A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. Ann Intern Med 2020;172:819-21.
10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
11. Konig MF, Kim AH, Scheetz MH, Graef ER, Liew JW, Simard J, et al. Baseline use of hydroxychloroquine

in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. Ann Rheum Dis 2020;79:1386-8.
12. D'Silva KM, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravallese EM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: A comparative cohort study from a US 'hot spot'. Ann Rheum Dis 2020;79:1156-62.
13. Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F; Brescia Rheumatology COVID-19 Study Group. COVID-19 in patients with rheumatic diseases in northern Italy: A single-centre observational and case-control study. Lancet Rheumatol 2020;2:e549-e556.
14. Pablos JL, Galindo M, Carmona L, Lledó A, Retuerto M, Blanco R, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: A multicentric matched cohort study. Ann Rheum Dis 2020;79:1544-9.
15. Kastritis E, Kitas GD, Vassilopoulos D, Giannopoulos G, Dimopoulos MA, Sfikakis PP. Systemic autoimmune diseases, anti-rheumatic therapies, COVID-19 infection risk and patient outcomes. Rheumatol Int 2020;40:1353-60.
16. Arleo T, Tong D, Shabto J, O'Keefe G, Khosroshahi A. Clinical course and outcomes of COVID-19 in rheumatic disease patients: A case cohort study with a diverse population. Clin Rheumatol 2021;40:2633-42.
17. He Z, Zhao C, Dong Q, Zhuang H, Song S, Peng G, et al. Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. Int J Infect Dis 2005;9:323-30.
18. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319-25.
19. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020;81:e6-e12.
20. Wang Q, Liu J, Shao R, Han X, Su C, Lu W. Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: A systematic review and meta-analysis. Rheumatol Int 2021;41:851-61.
21. Eslambolchi A, Aghaghazvini L, Gholamrezanezhad A, Kavosi H, Radmard AR. Coronavirus disease 2019 (COVID-19) in patients with systemic autoimmune diseases or vasculitis: Radiologic presentation. J Thromb Thrombolysis 2021;51:339-48.
22. Hasseli R, Mueller-Ladner U, Schmeiser T, Hoyer BF, Krause A, Lorenz HM, et al. National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): A valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. RMD Open 2020;6:e001332.
23. Alzahrani ZA, Alghamdi KA, Almaqati AS. Clinical characteristics and outcome of COVID-19 in patients with rheumatic diseases. Rheumatol Int 2021;41:1097-103.
24. Misra DP, Gasparyan AY, Zimba O. Benefits and adverse effects of hydroxychloroquine, methotrexate and colchicine: Searching for repurposable drug candidates. Rheumatol Int 2020;40:1741-51.
25. Scavone C, Brusco S, Bertini M, Sportiello L, Rafaniello C, Zoccoli A, et al. Current pharmacological treatments for COVID-19: What's next? Br J Pharmacol 2020;177:4813-24.
26. Jung SY, Kim MS, Kim MC, Choi SH, Chung JW, Choi ST. Effect of hydroxychloroquine pre-exposure on infection with SARS-CoV-2 in rheumatic disease patients: A population-based cohort study. Clin Microbiol Infect 2021;27:611-7.
27. Ferri C, Giuggioli D, Raimondo V, L'Andolina M, Tavoni A, Cecchetti R, et al. COVID-19 and rheumatic autoimmune systemic diseases: Report of a large Italian patients series. Clin Rheumatol 2020;39:3195-204.
28. Montero F, Martínez-Barrio J, Serrano-Benavente B, González T, Rivera J, Molina Collada J, et al. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: Clinical characteristics of poor outcomes. Rheumatol Int 2020;40:1593-8.