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ORIGINAL ARTICLE

Pandemic of the century: COVID-19 in inflammatory rheumatic diseases of a national cohort with 3,532 patients

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ABSTRACT

Objectives: This study aimed to assess the clinical outcomes and risk factors for severe coronavirus disease 2019 (COVID-19) in patients with inflammatory rheumatic disease (IRD) of a national cohort.

Patients and methods: The multicenter cross-sectional study was carried out between July 15, 2020, and February 28, 2021. Data collection was provided from a national network database system, and 3,532 IRD patients (2,359 males, 1,173 females; mean age: 48.7±13.9 years; range; 18 to 90 years) were analyzed. Demographics, clinics about rheumatic disease, comorbidities, smoking status, being infected with COVID-19, and the course of the infection were questioned by rheumatology specialists.

Results: One hundred seventeen patients were infected with COVID-19, the hospitalization rate due to COVID-19 was 58.9%, and the mortality rate was 1.7%. There was no difference between the COVID-19 positive and negative groups in terms of rheumatic disease activities and receiving drugs. It was observed that patients with COVID-19 had worse compliance with isolation rules, and bacillus Calmette-Guérin (BCG) vaccination was less common. The mean age and the rate of smoking of hospitalized COVID-19 patients were higher than those without hospitalization.

Conclusion: In this cohort, in which real-life data were analyzed, COVID-19 rates in IRD patients were similar to the general population for the same period. Compliance with the isolation rules and BCG vaccination attracted attention as components that reduce the risk of COVID-19 infection. The risk factors for hospitalization were older age and smoking.

Keywords: Disease-modifying antirheumatic drugs, hospitalization, mortality rate, rheumatic diseases, severe acute respiratory syndrome coronavirus 2.

The ongoing coronavirus disease 2019 (COVID-19) pandemic has created a significant health threat worldwide for more than two years. Due to the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection in a growing number of countries, a total of more than 750,000,000 cases and more than 6 million deaths have been reported since COVID-19 was confirmed as a global epidemic on 11 March 2020.[1,2] The course of the infection may be mild, moderate, or severe. Sepsis, septic shock, acute respiratory distress, or acute thrombosis are considered fatal critical illnesses. Older age, smoking history, diabetes mellitus, obesity, and immunosuppression can be considered among the poor prognostic factors.[3] While COVID-19 is asymptomatic or mild in many patients, a severe and life-threatening disease course is observed in up to 5 to 10% of patients. Mortality rates have been reported to be about 2% in the general population.[4]

The patient's immune response has an essential role in the resolution of COVID-19, but it also plays a role in the development of cytokine storm syndrome with abnormal production of proinflammatory cytokines, mostly in more severe patients. To date, biologic disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs are used in the treatment in the case of the mortal cytokine storm due to COVID-19.[5] The clinical course of viral infection can be affected by both autoinflammatory diseases and immunosuppressive treatments.[3] It has been identified that patients with inflammatory rheumatic disease (IRD) have higher risk of infections associated with comorbidities, disease activity, and receiving DMARDs. However, contradictory outcomes of the SARS-CoV-2 infection have been seen in patients with inflammatory diseases. Impaired immunological background and various antirheumatic treatments are thought to be the cause of different responses to SARS-CoV-2 infection in inflammatory diseases. Several studies have particularly emphasized that patients with inflammatory diseases receiving biologic DMARDs may have higher risk of being infected with COVID-19 than the general population but not at increased risk of admission to intensive care units or death.[5]

It is known that there is a multifaceted relationship between viral infections and IRD, and viral infections are known to be associated with triggering or exacerbation of rheumatic disease. Surveys about the relationship between IRD and COVID-19 throughout the pandemic have reached inconsistent outcomes.[5,6] Management of the SARS-CoV-2 infection process in those with inflammatory diseases during the pandemic and continuation of DMARDs represented a difficult challenge for physicians in the field of rheumatic diseases. Therefore, this study aimed to assess the clinical outcomes and management of rheumatic therapies and risk factors for severe COVID-19 in patients with IRD of a national cohort.

PATIENTS AND METHODS

This multi-center, cross-sectional study was conducted at 16 centers, Department of Rheumatology and Physical Medicine and Rehabilitation (PMR) outpatient clinics between July 15, 2020 and February 28, 2021. Patients who were regularly followed up for at least six months in the rheumatology or physical medicine and rehabilitation outpatient clinics were examined for the dates they applied for their routine controls. A total of 3,532 IRD patients (2,359 males, 1,173 females; mean age: 48.7±13.9 years; range; 18 to 90 years) were included in the study. Demographics, clinics about rheumatic disease, comorbidities, smoking status, being infected with COVID-19, and the course of infection were questioned by rheumatology specialists. Patients with COVID-19 symptoms were referred to COVID-19 outpatient clinics and followed up. Patients were asked whether they followed the isolation rules. Diagnostic method recorded in patients with COVID-19 (positive SARS-CoV-2 real-time polymerase chain reaction test and chest computed tomography images in accordance with typical signs). Management of infection and outcomes, including hospitalization, need for oxygen support, death, and complications (secondary infection, sepsis, disseminated intravascular coagulation, acute respiratory distress syndrome, renal failure, myocarditis, macrophage activation syndrome, and thromboembolism), were noted. Electronic case report forms were composed with the

obtained data. Data collection was provided from a national network database system (https://www.trasd-network.org), emerged by the Turkish League Against Rheumatism. Sixteen centers (20 researchers) from several provinces of Türkiye attended the database.

Statistical analysis

Data were analyzed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Results were demonstrated as means (standard deviations), mean differences (95% confidence intervals), numbers, and percentages. The Kolmogorov-Smirnov test was used for the normality assessment. Comparisons between groups were analyzed by the independent sample t-test, chi-square test, and Fisher exact test. Statistical significance was set at $p<0.05$.

RESULTS

The most common rheumatic diseases in the study group are listed as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, and familial Mediterranean fever. Among the IRD subgroups, systemic sclerosis (10.2%), vasculitis (10.3%), and inflammatory myopathies (10.5%) were most frequently diagnosed with COVID-19 (Table 1).

One hundred seventeen patients were infected with COVID-19, and the diagnosis was corroborated with real-time polymerase chain reaction or chest computed tomography findings. Age, sex, and smoking status of the patients with and without COVID-19 diagnosis were similar. There was no difference between

Table 1. Diagnosis of the patients with IRDs

	Patients IRD (n=3,532)	IRD Patients with COVID-19 (n=117)	
	n	n	%
Rheumatoid arthritis	1,229	42	3.41
Axial spondyloarthritis	971	32	3.29
Psoriatic arthritis	238	7	2.94
Systemic lupus erythematosus	185	6	3.24
Familial Mediterranean fever	163	6	3.68
Other peripheral spondyloarhtritis	146	1	0.68
Primer Sjögren syndrome	129	5	3.87
Behçet's disease	117	2	1.71
Mixed connective tissue disease	87	2	2.29
Systemic sclerosis	39	4	10.25
Polymyalgia rheumatica	33	0	0
Vasculitis	29	3	10.34
Gout	25	0	0
Inflammatory myopathy	19	2	10.52
Antiphospholipid antibody syndrome	15	1	6.66
Juvenile idiopathic arthritis	18	0	0
Sarcoidosis	13	0	0
Giant cell arteritis	4	0	0
Still's disease	4	0	0
Other inflammatory arthritis*	68	4	5.88

IRD: Inflammatory rheumatic diseases; * Crystal arthropathies, acute rheumatic fever, ocular inflammation (uveitis), recurrent polychondritis, chronic recurrent multifocal osteomyelitis, undifferentiated connective tissue disease, discoid lupus erythematosus, other autoinflammatory arthritis.

the two groups in terms of rheumatic disease activities receiving steroids and DMARDs. The most commonly used synthetic DMARD was methotrexate, while the most common biologic DMARDs were anti-tumor necrosis factor (TNF) drugs. It was observed that patients with COVID-19 infection had worse compliance with isolation rules, and bacillus Calmette-Guérin (BCG) vaccination was less common. Of the patients, 17.1% did not continue their rheumatic treatment during COVID-19 infection (Table 2).

The most common initial symptoms of COVID-19 were myalgia, arthralgia, and fatigue. It was noted that patients who were positive for COVID-19 received antiviral, antimalarial, and anticoagulant treatments (74%, 58.1%, and 58.1%, respectively). It was seen that 69 of the

Table 2. Demographics, disease characteristics, and comorbidities in patients with IRDs

	IRD patients without COVID-19 (n=3,415)			IRD Patients with COVID-19 (n=117)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			48.7±13.9			48.1±13.1	0.587
Females	1,133	33.2		39	33.3		0.972
Smoking habit							0.294
Never	2,000	58.6		65	55.5		
Ex-smoker	545	15.9		20	17.1		
Smoking	870	25.5		32	27.4		
Comorbidities							*0.960
None	2,057	60.2		77	65.8		
Diabetes mellitus	1	0.03		0	0		
Hypertension	789	23.1		20	17.1		
Cardiovascular disease	207	6.1		7	5.9		
COPD	41	1.2		2	1.7		
Interstitial lung disease	0	0		2	1.7		
Chronic renal failure	23	0.7		3	2.6		
Cancer	37	1.1		2	1.7		
Transplantation	4	0.1		0	0		
Pregnancy	15	0.47		0	0		
Disease severity							0.375
Remission	1,141	33.4		41	35.0		
Mild	1,294	37.9		41	35.0		
Moderate	852	24.8		32	27.3		
Severe	130	3.8		3	2.6		
BCG vaccinated	2,895	84.8		87	74.4		0.002
Isolation	2,514	73.6		71	60.7		0.002
Medications							0.267
Glucocorticoids	1,081	31.7		35	29.9		
TNF inhibitors	877	25.6		25	21.3		
Anti-CD20 antibody	71	2.1		4	3.4		
IL-1 inhibitor	23	0.7		0	0		
IL-6 inhibitor	44	1.3		0	0		
IL-17 inhibitor	43	1.3		2	2		
Janus kinase inhibitor	42	1.2		2	2		
Hydroxychloroquine	748	21.9		34	29.1		
Methotrexate	862	25.2		35	29.9		
Leflunomide	342	10.1		13	11.1		
Cyclophosphamide	0	0		5	4.2		
Cyclosporine	0	0		4	3.4		
Mycophenolate	36	1.1		1	0.8		
Sulfasalazine	413	12.1		14	11.9		
Stopped DMARD therapy during COVID 19 infection	-	-		20	17.1		

IRD: Inflammatory rheumatic disease; COVID-19: Coronavirus disease 2019; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease; TNF: Tumor necrosis factor; IL: Interleukin; * P value for comorbidity none and present.

Table 3. COVID-19 findings in IRD

	IRD patients with COVID-19 (n=117)	
	n	%
COVID-19 diagnosis methods		
Positive PCR test	89	76.1
Positive CT findings	28	23.9
COVID-19 symptoms		
Asymptomatic	8	6.8
Fever	51	43.5
Headache	39	33.3
Throat ache	34	29.1
Cough	53	45.3
Dyspnea	35	29.9
Arthralgia	57	48.7
Myalgia	61	52.1
Fatigue	58	49.6
Diarrhea	15	12.8
COVID-19-related medications		
Antiviral agents	87	74.3
Antibacterial agents	19	16.2
Antimalarial drugs	68	58.1
Corticosteroids	6	5.2
IL-6 inhibitors	2	1.7
Intravenous immunoglobulin	2	1.7
Anticoagulants	69	58.9
COVID-19 severe outcomes		
Hospitalization	69	58.9
Oxygen support	69	58.9
Death	2	1.7
Complications		
ARDS	2	1.7
Sepsis	2	1.7
MAS	2	1.7
Seconder infection	1	0.8
Thromboembolism	0	0

IRD: Inflammatory rheumatic diseases; COVID-19: Coronavirus disease 2019; PCR: Polymerase chain reaction; CT: Computed tomography; IL: Interleukin; ARDS: Acute respiratory distress syndrome; MAS: Macrophage activating syndrome.

COVID-19 patients were hospitalized, and the number of reported deaths was two (Table 3).

It was observed that the mean age and the rate of smoking were higher in hospitalized COVID-19 patients. Disease activity and receiving DMARDs were similar. Table 4 summarizes the characteristics of hospitalized and nonhospitalized patients. A plot of the variables with odd ratios for the predictors of hospitalization is shown in Figure 1.

DISCUSSION

In this cohort of 3,532 inflammatory rheumatic patients, in which real-life data were analyzed, approximately 3.3% of COVID-19 infections were detected at the end of the first peak of the pandemic. While age, sex, comorbidities, and rheumatic disease activity were similar between patients with and without COVID-19, higher rate of BCG vaccination and lower compliance with isolation rules were detected in COVID-19 patients. The hospitalization rate due to COVID-19 was 58.9%. The mortality rate was 1.7%, which is lower than the COVID mortality rate in the general population reported at similar times.[4] The factors that could predict hospitalization were older age and smoking.

There is a multifaceted relationship between viral infections and rheumatic diseases. Viruses have been associated with genetic and

Table 4. Comparison of demographics and clinical characteristics between hospitalized and nonhospitalized IRD patients with COVID-19

	Hospitalized (n=69)			Non-hospitalized (n=48)				
	n	%	Mean±SD	n	%	Mean±SD	Mean difference (95% CI)	*p*
Diagnosis								0.539
Axial spondyloarthritis	20	28.9		12	25			
Psoriatic arthritis	6	8.6		1	2.1			
Other peripheral spondyloarhtritis	0	0		1	2.1			
Rheumatoid arthritis	22	31.8		20	41.6			
Familial Mediterranean fever	5	7.2		1	2.1			
Behçet's disease	1	1.4		1	2.1			
Primer Sjögren syndrome	2	0		3	6.3			
Systemic lupus erythematosus	5	7.2		1	2.1			
Mixed connective tissue disease	1	1.4		1	2.1			
Systemic sclerosis	2	2.9		2	4.2			
Vasculitis	2	2.9		1	2.1			
Inflammatory myopathy	0	0		2	4.2			
Antiphospholipid antibody syndrome	1	1.4		0	0			
Other inflammatory arthritis	2	2.9		2	4.2			
Age (year)			51.9±13.2			45.4±12.5	6.5 (1.7-11.2)	**0.008**
Females	21	30.4		18	37.5			0.425
Smoking habit	12	17.4		5	10.4			**0.049**
BGC	56	81.2		31	64.5			0.065
Isolation	50	72.4		21	43.7			<0.001
Comorbidities								**0.030**
None	55	79.7		22	45.8			
Diabetes mellitus	2			6				
Hypertension	6			14				
Cardiovascular disease	1			6				
Interstitial lung disease	2			0				
Disease severity								0.329
Remission	25	36.2		16	33.3			
Mild	25	36.2		16	33.3			
Moderate	19	27.6		13	27.1			
Severe	0	0		3	6.3			
Medications								
Glucocorticoids	17	24.6		18	37.5			0.303
TNF inhibitors	15	21.7		10	20.8			0.906
Anti-CD20 antibody	2	2.9		2	4.2			0.710
Janus kinase inhibitor	1	1.4		1	2.1			0.795
Hydroxychloroquine	15	21.7		19	39.6			0.037
Methotrexate	23	33.3		12	25			0.334
Leflunomide	6	8.7		7	14.6			0.319
Azathioprine	2	2.9		2	4.2			0.710
Mycophenolate	0	0		1	2.1			0.410
Sulfasalazine	4	5.8		10	20.8			0.014

IRD: Inflammatory rheumatic disease; COVID-19: Coronavirus disease 2019; SD: Standard deviation; BGC: Bacillus Calmette-Guérin; TNF: Tumor necrosis factor.

environmental risk factors in the pathogenesis of rheumatic diseases and dysfunctions of the immune system. In addition, infections can alter the course of autoimmune diseases and increase the risk of mortality. Therefore, it is important to establish a clear opinion of the interaction between viral infections and IRD.[6]

While IRD is predominantly characterized by musculoskeletal involvement, it is a wide spectrum of diseases that can affect many different tissue and organ systems. Immune complexes, autoantibodies, and abnormal T-lymphocyte responses all play a role in the pathogenesis, and many cytokines are involved.[6] COVID-19

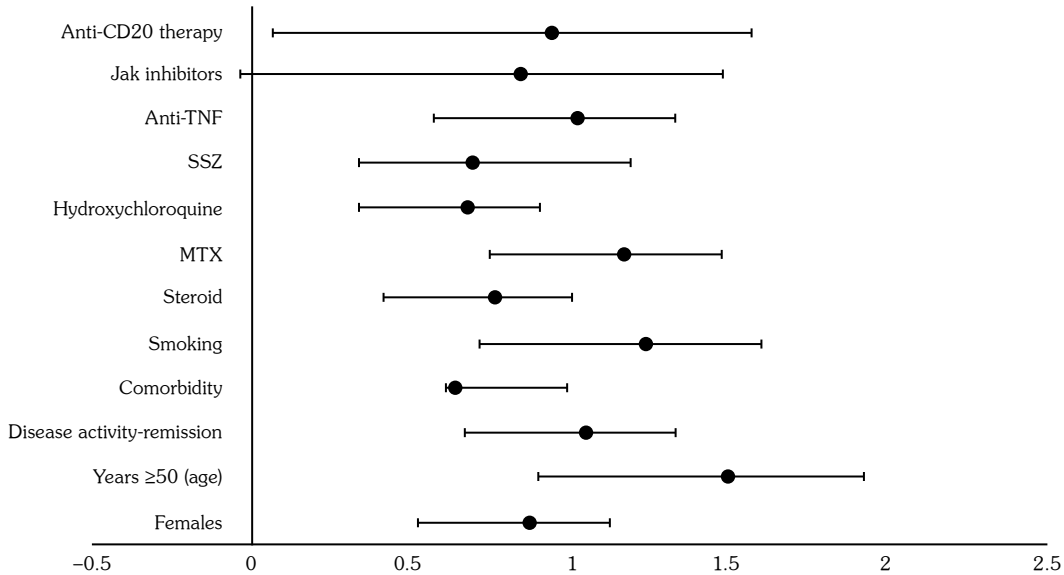

Figure 1. Plot of adjusted odds ratios and 95% confidence intervals for predictors of hospitalization.
TNF: Tumor necrosis factor; SSZ: Sulfasalazine; MTX: Methotrexate.

infection is known to cause hyperinflammation that is dependent on the host response, and it has been suggested that it may be similar to other cytokine storm states, such as macrophage activation syndrome. The prevalence of severe COVID-19 infection in patients with preexisting autoimmune or inflammatory diseases has been a subject of attention.[7] Although conflicting results have been published, this patient group is not at risk of susceptibility or severity of COVID-19.[8-15] As far as we know, there is no COVID-19 prevalence study in our country for the first peak period of the pandemic. However, in a similar period, a study from Italy, a southern European country, the prevalence of COVID-19 was reported as 4%.[16] The present study yielded a lower COVID-19 frequency of 3.32% in IRD patients. In addition, in a paper conducted with 822 patients with familial Mediterranean fever from our country, the frequency of COVID-19 was 7%, higher than the present study.[17] Results from our cohort indicate that patients with IRD do not have an increased risk of contracting COVID-19.

In the study of Pablos et al.,[7] the COVID-19 rates in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients were similar to the reference population, whereas the frequency of COVID-19 was found to be higher in autoimmune or immune-mediated disease, Sjögren's syndrome, and systemic sclerosis. In addition, when the medications of the patients were analyzed, it was found that the frequency of COVID-19 was higher in patients receiving tsDMARD and bDMARDs compared to conventional DMARDs.[7] In a study from the World Health Organization pharmacovigilance database with 398 IRD patients, it was observed that the majority of COVID-19-positive patients received TNF-alpha inhibitors. It was concluded that interleukin (IL)-6 and Janus kinase inhibitors potentially have a better safety profile in terms of COVID-19.[18] Malek Mahdavi et al.[13] showed that TNF inhibitors were among the factors associated with COVID 19 in their analysis with RA patients. In an analysis from France, 655 patients with, spondyloarthritis (SpA), and PsA were evaluated, and the incidence of COVID-19 was found to be similar between the three groups.[19] In addition, no relationship was found between the COVID-19 frequency and biologic DMARD use in these patients. Several rheumatic diseases were included in our cohort, with the predominant diseases being RA and SpA. It was seen that the frequency of COVID-19 is nearly similar among these diseases. The frequency of COVID-19 was found to be higher in patients with systemic sclerosis, vasculitis, and inflammatory myopathy

compared to other groups; however, the low number of patients in these groups compared to RA and SpA complicates a certain conclusion. Age, sex, comorbidity, and medications were not associated with COVID-19 positivity in our patients with IRD. It is noteworthy that a significant factor associated with the prevalence of COVID-19 was noncompliance with isolation rules. While this special patient group has persistent immune disorders and indispensable medications, it has been confirmed once again in this study that the risk of infection can be reduced by simple methods such as providing personal protection and isolation conditions.

In the present study, the BCG vaccination rate was 74.4% in patients with COVID-19, whereas it was 84.8% in COVID-19-negative patients. The low rate of BGC vaccination in patients with COVID-19 was a substantial finding. Studies have provided evidence that BCG vaccine triggers nonspecific cross-protection against unrelated infections. It has been reported that the BCG activates innate immune system cells, which are essential in viral infection control, with its immunomodulatory properties. Borges et al.[20] mentioned that BCG vaccine strains help excite basal defenses and may be used as an accessional defense in future pandemics.[21]

The most common symptoms in the clinical presentation of COVID-19 were high fever (88%) and cough (68%) in the general population.[22] Similarly, the most common symptoms reported in patients with IRD were fever and cough.[10,23] Although the rate of fever and cough was high in our patients, arthralgia, myalgia, and fatigue complaints were also high. It should be kept in mind that newly developed arthralgia, myalgia, and fatigue may be warning signs for viral infections in patients followed in IRD outpatient clinics.

The hospitalization rate was 58.9%, and the mortality rate was 1.7% in the present study. Studies related to the severity of COVID-19 in rheumatic patients reported hospitalization rates between 22.6 and 69% and mortality rates between 0.07 and 19%.[10,14,24-27] Again, a lower hospitalization rate (20.3%) and no mortality were reported in the familial Mediterranean fever patient cohort published from our country.[17] Bower et al.[27] reported that hospital and intensive care unit admission rates due to COVID-19 were lower than the general population in their data on patients with IRD during the first peak period of the pandemic. Moreover, in their analysis, after adjustment for comorbidities and socioeconomic properties, the mortality risk due to COVID-19 in patients with IRD was similar (adjusted hazard ratio: 1.18) to the general population. Although it is not possible to see a complete consensus in the literature on the relationship between the presence of IRD and the severity of COVID-19, as a general opinion, IRD is not considered a clinical factor that increases the severity and mortality of COVID-19.[28] It has been reported that the factors (older age, hypertension, diabetes, chronic renal failure, and chronic respiratory diseases) that increase the severity of COVID-19 in patients with arthritis are similar to the general population.[10,11,14,22,25,29,30] Similar to the literature, we specified higher mean age and smoking rates in patients who needed hospitalization. This result supports that older age may affect the ability to fight infections due to possible disorders in the immune system. Similar to the factors affecting hospitalization and morbidity risk, the low mortality rates compared to the general population may be associated with the low mean age (48.7±13.9 years) and the low rates of comorbid diseases in our patients with IRD.

It has been reported that antirheumatic treatments are not associated with severe COVID-19 risks, although the clarity of data for some drugs is partial.[27] In particular, there are contradictions among publications on glucocorticoids. Akiyama et al.[11] reported that moderate- and high-dose steroids increase the risk of severe COVID-19, whereas Cordtz et al.[8] found no association between treatment with glucocorticoids and hospitalization, and the additional use of time-dependent adjustment for drug exposure did not change their overall findings. Publications have become evident that biologic DMARDs, particularly anti-TNF treatments, do not increase the severity of COVID-19,[11,31] and it has even been mentioned in the literature that cytokine storm due to severe COVID-19 can be prevented with anti-TNF and IL-6 treatments.[30] In line with the literature, no correlation was found between antirheumatic

treatments, steroid use, and hospitalization in our cohort.

In conclusion, the rate of COVID-19 in our patients with IRD was 3.32%, the hospitalization rate due to COVID-19 was 58.9%, and the mortality rate was 1.7%. Among the IRDs, the incidence of COVID-19 was relatively higher in systemic sclerosis, vasculitis, and inflammatory myopathies. Compliance with the isolation rules and BCG vaccination attracted attention as components that reduce the risk of COVID-19 infection. The parameters related to the severity of COVID-19 in IRD patients were similar to the general population. Among these factors, hospitalization, the severity of the disease, older age, and smoking were prominent.

Ethics Committee Approval: The study protocol was approved by the Ankara City Hospital Ethics Committee (date: 02.07.2020, no: 02.07.2020/E1-20-455). 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.

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