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The Impact of the COVID-19 Pandemic on Inflammatory Rheumatic Diseases

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ABSTRACT

Objective: The objective of this study was to investigate the impact of the Coronavirus Disease 2019 (COVID-19) on inflammatory rheumatic diseases (IRD) by comparing them with non-IRD (nIRD) and healthy controls (HC).

Materials and Methods: In this cross-sectional study, subjects were screened for contact with COVID-19, new-onset symptoms, and adherence to precautionary measures against COVID-19. The Impact of Event Scale-Revised (IES-R) and Depression Anxiety and Stress Scales (DASS-21) were used to evaluate the psychological effect of the pandemic and health status. Additionally, therapy adherence and clinical characteristics were noted.

Results: A total of 279 subjects were recruited (IRD 47.3%; nIRD 29.7%). The number of patients who believed that the risk of COVID-19 increased due to their diseases or received therapy was higher in IRD than nIRD (38.6% vs 7.2%). Maintaining physical distancing was highest in the IRD and lowest in HC (p=0.037). Approximately 40% of the patients discontinued or extended the dose interval of Tumor Necrosis Factor Inhibitor (TNFi) without obtaining physician's advice. DASS-21 anxiety, depression and stress rates were lowest in IRD. COVID-19 contact history was an independent risk factor for DASS-21 stress and anxiety, while female gender was an independent risk factor for DASS-21 anxiety.

Conclusion: Confirmed COVID-19 infection was similar in HC, IRD, and nIRD. HC were substantially more likely to experience mental health issues than other groups. Most patients with IRD discontinued or extended the ongoing treatment without physician's recommendation during the COVID-19 outbreak. Therefore, patient adherence and disease control could be improved through closer monitoring and recognition of early signs of psychological discomfort during the COVID-19 pandemic.

Keywords: COVID-19, rheumatic diseases, mental health, spondyloarthritis.

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19), which first appeared in the city of Wuhan, China's Hubei Province, on December 31, 2019, rapidly spread to many countries, turning into a pandemic. By 2021, the global mortality rate had reached 0.15% with 1.5–2.0 billion infections.[1] The severity of this viral infection ranges from mild common cold symptoms to life-threatening severe acute respiratory failure. Studies have indicated that COVID-19 tends to progress more rapidly and have a more severe course, especially in the elderly (>65 years), individuals with chronic diseases such as diabetes and cardiovascular diseases, and those using immunosuppressive drugs.[2]

Inflammatory or autoimmune disorders have been associated with an increased risk of infection and a more severe disease course, attributed to the disease itself, comorbidities, and immunosuppressive treatments, particularly corticosteroids.[3] Additionally, advanced age (>60 years), high disease activity, and comorbidities (such as pulmonary diseases and chronic kidney failure) further increase the risk of infection, hospitalization, and mortality in individuals with rheumatologic conditions.[4] However, recent findings have suggested that patients with inflammatory rheumatologic disorders (IRD) do not have a significantly higher rise of COVID-19 infection, contrary to initial expectations.[5]

Clinical studies have revealed an increase in the incidence of various psychological symptoms and disorders, including denial, loneliness, insomnia, hopelessness, irritability, depression, anxiety, and post-traumatic stress disorder, among individuals diagnosed with or suspected of having COVID-19, as well as among healthcare workers primarily involved in their treatment.[6,7] Furthermore, it has been shown that individuals in isolation due to suspected COVID-19 cases may develop anxiety and obsessive-compulsive symptoms due to the uncertainty surrounding their health status during the pandemic.[7,8]

Many international and national treatment guidelines on the management of inflammatory rheumatic diseases (IRD) have been published during the COVID-19 pandemic.[9–11] However, there are still many unanswered questions regarding the impact of the COVID-19 pandemic on mood disorders, changes in disease activity, behavioral attitudes towards epidemic measures, and treatment adherence. To the best of our knowledge, no adequate research has been conducted to address these questions, especially including non-inflammatory rheumatic diseases (nIRD) and healthy volunteers as control groups. Therefore, in this study, we aimed to investigate the psychological burden of COVID-19, behavioral attitudes towards COVID-19, disease activity, and treatment compliance in IRD by comparing them with nIRD and healthy controls (HC).

MATERIALS AND METHODS

This cross-sectional, controlled study was conducted in the Black Sea region of Türkiye, which was identified by the Ministry of Health as one of the regions with the highest risk of coronavirus transmission between September 1, 2020 (the start of the second peak), and March 31, 2021.

The case population included adult patients (>18 years old) diagnosed with IRD (such as spondyloarthritis (SpA), rheumatoid arthritis (RA), connective tissue disease (CTD), vasculitis, and others) at the rheumatology clinic of the university hospital. For the nIRD control group, patients with mechanical or degenerative diseases were consecutively recruited from our physical therapy and rheumatology clinic during the same time period. Volunteers over the age of 18 without any inflammatory or non-inflammatory diseases were included in the healthy control group. Participants who were pregnant, lactating/breastfeeding, had malignancies, or systemic infectious diseases were excluded. Approval for the research protocol was obtained from both the medical research ethics committee of the university and the Ministry of Health (approval date: 17.07.20, issue number: 24237859-479). Written informed consent was obtained from all study participants prior to their inclusion in the research.

Assessment

The baseline clinical and demographic characteristics of the study were recorded. A structured questionnaire was utilized to investigate several clinically significant issues during the COVID-19 outbreak, including contact history with suspected or confirmed COVID-19 cases, adherence to precautionary measures (such as wearing masks and practicing physical distancing) in response to COVID-19, and treatment adherence. Physical distancing was defined by the World Health Organization (WHO) as maintaining a distance of at least 1 m (3 feet) from others. Additionally, patients were asked if they believed their current rheumatic disease or treatment increased their risk of contracting COVID-19 compared to the general population.

The psychological impact of the COVID-19 pandemic and quarantine measures was assessed using the Impact of Event Scale-Revised (IES-R) and the Depression, Anxiety, and Stress Scales (DASS)-21.[12,13] The IES-R consists of 22 items and three subscales (intrusion, avoidance, and hyperarousal). The total IES-R score is categorized into four groups: 0 to 23 (normal), 24 to 32 (mild), 33 to 36 (moderate), and above 37 (severe).[14] The DASS-21 questionnaire includes seven items for each of the three subcategories: depression, anxiety, and stress. Scores for each subscale are calculated by summing the scores of the relevant items, with higher scores indicating a more severe level of negative emotional symptoms.

Table 1. Demographic and clinical features of inflammatory and non-inflammatory rheumatic diseases and healthy controls

	(1) IRD (n=132)		(2) nIRD (n=83)		(3) HC (n=64)		p
	n	%	n	%	n	%	
Age, years, (Mean±SD)	45.1±13.5		44.7±15.3		35.3±12.0		<0.0001
							1 vs 2: 0.999
							1 vs 3: <0.001
							2 vs 3: <0.001
Gender, Male	66	50.0[b]	27	32.5[a]	33	51.6[a,b]	0.022
BMI, kg/m^2, (Mean±SD)	28.2±5.3		27.2±5.5		25.3±4.8		0.002
							1 vs 2: 0.498
							1 vs 3: 0.001
							2 vs 3: 0.094
Educational level							<0.001
Secondary school or below	80	60.6[b]	34	41.0[c]	3	4.7[a]	
High school	25	18.9[a]	24	28.9[a]	11	17.2[a]	
University or high	27	20.5[b]	25	30.1[b]	50	78.1[a]	
Cigarette smoking status							0.442
Current smoker	30	22.7[a]	14	16.9[a]	18	28.1[a]	
Ex-smoker	30	22.7[a]	16	19.3[a]	14	21.9[a]	
Non-smoker	72	54.5[a]	53	63.8[a]	32	50.0[a]	
COVID-19 contact history	18	13.6[b]	12	14.5[b]	20	31.3[a]	0.007
Applying on suspicion of COVID-19	17	13.6[a,b]	8	9.6[b]	17	26.6[a]	0.012
Positive COVID-19 PCR	8	6.1[a]	3	3.6[a]	3	4.7[a]	0.827
Preventative measures for COVID-19							
Hand wash: Always	83	62.9[a]	52	62.7[a]	40	62.5[a]	0.999
Wearing a mask: Always	92	69.7[a]	59	71.1[a]	53	82.8[a]	0.134
Avoiding external surface contact: Always	77	58.3[a]	53	63.9[a]	30	46.9[a]	0.113
Avoiding handshakes and hugs: Always	98	74.2[a]	63	75.9[a]	48	75.0[a]	0.961
Keeping physical distance: Always	83	62.9[a]	46	55.4[a,b]	34	53.1[b]	0.037

HC: Healthy controls; IRD: Inflammatory rheumatic diseases; nIRD: Non-inflammatory rheumatic diseases; COVID-19: Coronavirus Disease 2019; PCR: Polymerase chain reaction; BMI: Body mass index; Statistical test: ANOVA, and Pearson's Chi-square; Each superscript letter denotes a subset of patient groups whose column proportions do not differ significantly from each other at the 0.05 level.

Furthermore, patient's global assessment (PtGA), physician's global assessment (PhGA), visual analogue scale (VAS) for pain and fatigue, tender joint count (TJC), swollen joint count (TJC), Disease Activity Score-28 (DAS-28), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and acute phase reactants (APR) were also recorded during the last visit after the COVID-19 pandemic in patients with IRD.[15,16]

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS v23, IBM, Armonk, NY). The normality of variable distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were used to calculate proportions for categorical variables and means, 95% confidence intervals (CI), and standard deviations (SD) for continuous variables. Student's t-test was performed to compare groups (IRD vs nIRD), while Analysis of Variance (ANOVA) was used to compare IRD vs nIRD and HC groups. Bonferroni post-hoc test was applied for multiple group comparisons. Pearson's Chi-square test was employed to compare proportions. Adjustments for age and gender were made using Analysis of Covariance (ANCOVA) for continuous variables. Multiple binary logistic regression analy-

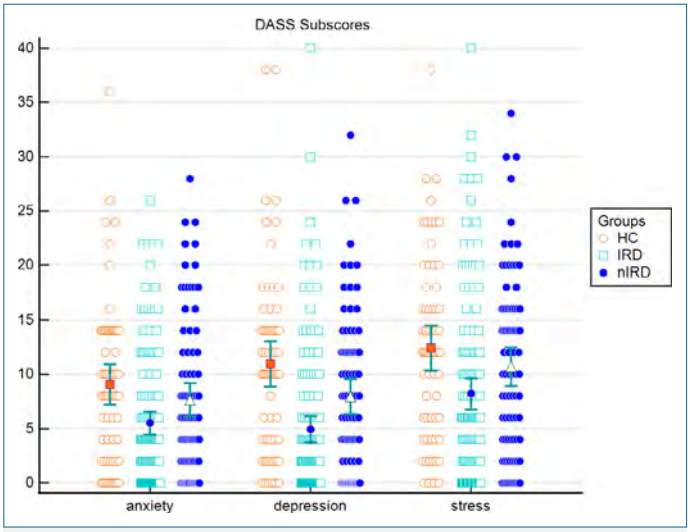

Figure 1. Comparison of crude mean DASS-21 subscores (anxiety, depression, and stress) between HC, IRD, and nIRD ($p<0.01$).

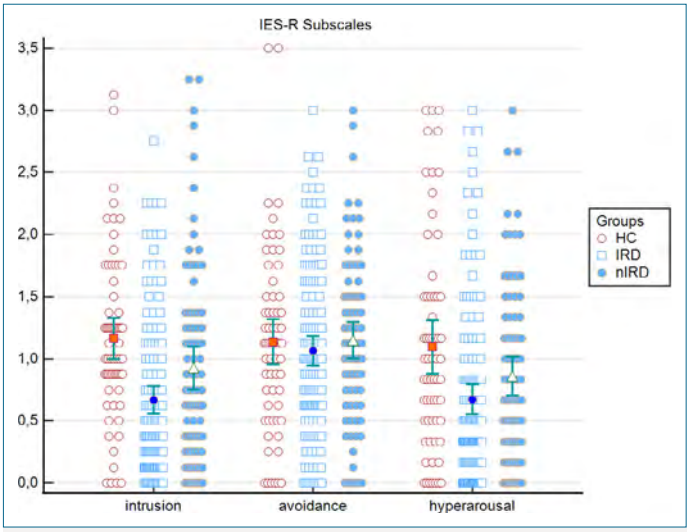

Figure 2. Comparison of crude mean IES-R subscores (intrusion, avoidance, and hyperarousal) between HC, IRD, and nIRD ($p<0.05$).

ses were conducted to identify risk factors associated with DASS-21 subscores for anxiety, depression, and stress. DASS-21 was converted into binary mode, with negative anxiety, depression, and stress recoded as 0, and mild, moderate and severe anxiety, depression, and stress recoded as 1. Backward stepwise model was applied for binary logistic regression analysis. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

A total of 279 subjects (45.2% male, 54.8% female) were included in the study, with 132 (50% male) having IRD (75 SpA; 30 RA; 11 connective tissue disease; 7 vasculitis; 9 others), 83 (32.5% male) having nIRD (23 myofascial pain syndrome; 16 osteoarthritis; 30 mechanical back pain; 14 other), and 64 (51.6% male) serving as HC. The mean age of all the subjects was 42.8±14.3 years, and the mean Body Mass Index (BMI) was 27.2±5.3 kg/m^2. The mean age and body mass index were similar between the IRD (45.1±13.5 and 28.2±5.3, respectively) and nIRD (44.7±15.3 and 27.2±5.5, respectively) groups. Symptom duration was significantly longer in the inflammatory group compared to the non-inflammatory group (11.3±8.2 years vs 5.6±7.8 years, $p<0.0001$). Systemic comorbidities (such as cardiovascular disease, diabetes mellitus, and chronic liver disease) were comparable between the inflammatory and non-inflammatory rheumatic disease groups. Demographic and clinical features of inflammatory and non-inflammatory rheumatic diseases and healthy controls are shown in Table 1.

The proportion of patients who believed that their diseases or received therapy increased the risk of COVID-19 was significantly higher in the inflammatory group compared to the non-inflammatory group (38.6% vs. 7.2%, respectively, $p<0.0001$). Fifty subjects (17.9%) had a history of close contact with a COVID-19 patient. A total of 42 individuals (15.1%) were admitted to COVID-19 clinics with suspicion of COVID-19. Polymerase Chain Reaction (PCR)-confirmed cases of COVID-19 infection were 8 (6.1% of all IRD patients) in the inflammatory group, 3 (3.6% of all nIRD patients) in the non-inflammatory group, and 3 (4.7% of all HC) in the HC group. No severe complications were observed, and none of the cases resulted in hospitalization or death.

The groups' compliance with preventive measures for COVID-19, such as handwashing, wearing masks, avoiding touching surfaces, shaking hands, and hugging, were found to be similar, except for maintaining physical distancing ($p>0.05$) (Table 1). Maintaining physical distancing was highest in the inflammatory group and lowest in the healthy control group ($p=0.037$).

Changes in rheumatic disease-related treatment during the COVID-19 pandemic were summarized in Table 2. During this period, 20.8% of patients using Tumor Necrosis Factor Inhibitor (TNFi) did not change their treatment. Approximately 40% of these patients discontinued or extended the dose interval of TNFi without obtaining physician's advice. More than 60% of patients receiving tofacitinib, interleukin 17 inhibitor (IL-17i), or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (such as methotrexate, leflunomide, sulfasalazin, hydroxychloroquine, etc.) did not modify their treatment.

Table 2. Treatment modification during the COVID-19 pandemic in patients with rheumatic diseases

	TNFi		IL17i		IL6i		ABT		MTX		LEF		SLZ		HCQ		CS		TOF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No modification	29	20.8	2	66.7	1	50.0	1	33.3	13	72.2	6	66.7	8	72.7	9	64.3	15	68.2	3	75.0
Treatment discontinuation voluntarily	13	18.3	–	–	1	50.0	1	33.3	–	–	1	11.1	1	9.1	3	21.4	2	9.1	1	25.0
Treatment discontinuation with doctor's recommendation	10	14.1	1	33.3	–	–	–	–	2	11.1	2	22.2	2	18.2	2	14.3	4	18.2	–	–
Dose reduction voluntarily	–	–	–	–	–	–	–	–	1	5.6	–	–	–	–	–	–	–	–	–	–
Dose reduction with doctor's recommendation	2	2.8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	4.5	–	–
Dose interval extended voluntarily	15	21.1	–	–	–	–	1	33.3	–	–	–	–	–	–	–	–	–	–	–	–
Dose interval extended with doctor's recommendation	2	2.8	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

TNFi: Tumor necrosis factor inhibitor; IL17i: Interleukin-17 inhibitor; IL6i: Interleukin-6 inhibitor; ABT: Abatacept; MTX: Methotrexate; LEF: Leflunomide; SLZ: Sulfasalazine; HQC: Hydroxychloroquine; CS: Corticosteroids; TOF: Tofacitinib. Statistical test: descriptive statistics.

Table 3. Comparison of age and sex-adjusted IES-R and DASS-21 subscores of three groups

New	(1) IRD		(2) nIRD		(3) HC		p
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
DASS-21 stress	9.36	8.54–10.18	10.32	8.87–11.77	11.45	10.00–12.90	1 vs 2=0.190, 1 vs 3=0.012, 2 vs 3=0.386
DASS-21 depression	6.04	5.14–6.94	7.37	6.72–8.02	8.83	7.72–9.94	1 vs 2=0.124, 1 vs 3=0.001, 2 vs 3=0.116
DASS-21 anxiety	6.24	5.45–7.03	7.23	6.13–8.33	7.20	6.75–7.65	1 vs 2=0.076, 1 vs 3=0.132, 2 vs 3=0.785
IES-Intrusion	0.78	0.67–0.88	0.89	0.80–0.97	0.93	0.87–0.99	1 vs 2=0.092, 1 vs 3=0.094, 2 vs 3=0.756
IES-Avoidance	1.08	0.97–1.19	1.13	0.99–1.26	1.13	0.96–1.31	1 vs 2=0.364, 1 vs 3=0.442, 2 vs 3=0.654
IES-Hyperarousal	0.72	0.57–0.87	0.84	0.78–0.94	0.97	0.84–1.10	1 vs 2=0.098, 1 vs 3=0.002, 2 vs 3=0.256

IRD: Inflammatory rheumatic diseases; non-IRD: Non-inflammatory rheumatic diseases; HC: Healthy controls; CI: Confidence intervals; IES: Impact of Event Scale; DASS-21: Depression Anxiety Stress Scale-21. Statistical test: ANCOVA.

Regarding the psychological status of the participants, DASS-21 results showed that the proportion of individuals with moderate or higher depression rates was 37.5% in the HC group, 21.7% in the nIRD group, and 13.0% in the IRD group (p=0.0004). Moderate or higher anxiety rates were 47.6% in the HC group, 32.5% in the nIRD group, and 22.7% in the IRD group (p=0.002). Additionally, moderate or higher stress rates were 21.9% in the HC group, 16.8% in the nIRD group, and 13.6% in the IRD group (p=0.045). The psychological status of the participants, assessed by crude DASS-21 subscores, is represented in Figure 1. Age and sex-adjusted DASS-21 subscores are summarized in Table 3. Mean adjusted DASS stress and depression scores were higher in the healthy control group compared to the non-inflammatory and inflammatory groups.

The IES-R crude subscores were summarized in Figure 2. The proportion of individuals with mild or higher psychological impact rates was 23.8% in the HC group, 20.5% in the nIRD group, and 14.1% in the IRD group (p<0.05). Age and sex-adjusted IES-R subscores are presented in Table 3. Mean adjusted intrusion, avoidance, and hyperarousal subscale scores were lowest in the IRD group.

Univariate analysis revealed seven variables related to DASS-21 anxiety, depression, and stress, including IES-intrusion, IES-hyperarousal, VAS-pain, PhGA, gender, COVID-19 contact history, and educational status (Table 4). Furthermore, multiple binary logistic regression analysis of the entire group showed that independent risk factors for DASS-21 anxiety were IES-hyperarousal subscores (Odds Ratio (OR), 5.18; 95% Confidence Interval (CI), 2.91–9.24; p<0.0001), female gender (OR, 2.46; 95% CI, 1.20–5.04; p=0.015), COVID-19 contact history (OR, 2.92; 95% CI, 1.15–7.45; p=0.025), and VAS-pain (OR, 1.16; 95% CI, 1.01–1.35; p=0.043). The independent risk factor for DASS-21 depression was IES-hyperarousal subscores (OR, 5.62; 95% CI, 3.27–9.69; p<0.0001). Additionally, independent risk factors for DASS-21 stress were COVID-19 contact history (OR, 2.64; 95% CI, 1.04–6.71; p=0.042) and IES-hyperarousal subscores (OR, 5.04; 95% CI, 2.92–8.68; p<0.0001).

DISCUSSION

This study adopted a novel approach by comparing the impact of COVID-19 infection on three different groups: IRD, nIRD, and HC. Our findings indicate that the rate of confirmed COVID-19 infection was similar across all groups. The psychological burden of the COVID-19 outbreak was not uniformly perceived throughout the society, with healthy volunteers being significantly more affected by mental health issues than the other groups. Among the behavioral attitudes towards preventive measures against COVID-19, patients with IRD showed more attention to physical distancing.

In this study, at least 6.1% of patients with IRD and 3.6% of patients with nIRD had confirmed COVID-19 infection. These figures are higher than the reported proportions of COVID-19 cases in rheumatic diseases in France (1.8%), Italy (0.2–0.6%), Spain (0.48%), and Germany (2.2%).[17–19] Recent studies have suggested that the risk of COVID-19 infection in autoimmune IRD is similar or slightly higher compared to the general population.[20,21] Our findings indicate that the frequency of COVID-19 in IRD is comparable to that of nIRD and HC. Thus, there appears to be no significant increase in the risk of COVID-19 infection in rheumatic diseases, contrary to initial expectations.

Regarding preventive measures for COVID-19, although maintaining physical distancing was highest in the inflammatory group, the number of patients with positive COVID-PCR was similar across the groups. Several factors may explain this finding. Firstly, in our study, maintaining physical distancing was assessed only in public areas, and we were unable to quantify ventilation within rooms or close contact with potentially infected family members at home. Secondly, besides physical distancing, other individual or public preventive interventions could be contributing to the occurrence of COVID-19.[22] Therefore, it is challenging to determine the exact relationship between physical distancing and COVID-19 infection in this cross-sectional investigation.

During the initial phase of the COVID-19 outbreak, the management of IRD posed challenges for both patients and rheumatologists. Immunosuppressive drugs were seen as double-edged swords at that time. Although disease activity was effectively controlled with immunosuppressive therapy, concerns arose regarding the increases risk of COVID-19 infection and its impact on related outcomes. Despite these concerns about the care of patients with IRD, many international and national treatment guidelines have recommended maintaining regular medical therapy for patients without suspected or confirmed COVID-19.[9–11] Furthermore, according to the Global Rheumatology Alliance registry, patients who received biologic Disease-Modifying Antirheumatic Drug/JAK Inhibitor (bDMARD/JAKi) monotherapy shortly before being diagnosed with COVID-19 had a decreased risk of hospitalization compared to those who did not receive DMARD therapy.[23] Today, the pathogenesis of COVID-19 infection is better understood, leading to the use of certain immune-modulating treatments (such as corticosteroids, tocilizumab, anakinra) as potential therapies for cytokine release syndrome in COVID-19 patients.[24]

Most previous studies have primarily investigated treatment decisions for systemic rheumatic diseases from the physician's perspective.[9,10] However, there is limited data concerning patients' perceptions regarding treatment adherence or usual drug modifications in patients with IRD during the COVID-19 pandemic.

Table 4. Results of univariate and multiple binary logistic regression analysis for DASS-21 subscores [Exp(B) (95% CI)]

	DASS-21 depression		DASS-21 anxiety		DASS-21 stress	
	Univariate	**Multiple**	**Univariate**	**Multiple**	**Univariate**	**Multiple**
Gender, Female	1.40 (0.85–2.29)		2.15 (1.31–3.52)	2.46 (1.20–5.04)	1.27 (0.73–2.19)	
	p=0.185		p=0.003	p=0.015	p=0.398	
Educational status						
Secondary school or below	1		1		1	
High school	2.06 (1.08–3.94)		1.68 (0.89–3.18)		1.52 (0.77–3.00)	
	p=0.029		p=0.108		p=0.230	
University or high	1.83 (1.04–3.22)		1.49 (0.86–2.57)		0.83 (0.44–1.57)	
	p=0.035		p=0.157		p=0.574	
VAS-pain	1.17 (1.04–1.32)		1.21 (1.08–1.36)	1.16 (1.01–1.35)	1.09 (0.96–1.23)	
	p=0.012		p=0.002	p=0.043	p=0.198	
PhGA	1.14 (1.01–1.28)		1.20 (1.07–1.35)		1.06 (0.93–1.20)	
	p=0.034		p=0.002		p=0.379	
COVID-19 contact history	1.58 (0.85–2.93)		3.15 (1.66–7.97)	2.92 (1.15–7.45)	2.33 (1.22–4.44)	2.64 (1.04–6.71)
	p=0.150		p<0.0001	p=0.025	p=0.010	p=0.042
IES-Intrusion	4.16 (2.71–6.38)		4.12 (2.68–6.32)		3.12 (2.08–4.68)	
	p<0.0001		p<0.0001		p<0.0001	
IES-Hyperarousal	3.83 (2.55–5.77)	5.62 (3.27–9.69)	4.52 (2.92–7.00)	5.18 (2.91–9.24)	3.38 (2.28–5.00)	5.04 (2.92–8.68)
	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001

CI: Confidence intervals; VAS: Visual Analog Scale; PhGA: Physician's Global Assessment; COVID-19: Coronavirus disease 2019; IES: Impact of Event Scale; DASS-21: Depression Anxiety Stress Scale-21; Statistical test: Univariate and multiple binary logistic regression analysis.

A longitudinal study conducted in New York during the height of the COVID-19 pandemic focused on this issue. The study demonstrated that nearly 11–14% of patients with systemic rheumatic disease reported self-imposed or physician-directed treatment modifications.[25] In another study examining the effects of the COVID-19 pandemic on the daily management of rheumatic diseases, it was found that over 30% of patients with IRD had one of their medication doses reduced or discontinued. The most commonly modified drugs were Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (41.6%), followed by bDMARDs (17.4%), Conventional Disease-Modifying Antirheumatic Drugs (cDMARDs) (12.0%), and corticosteroids (12.0%).[17] Our study revealed significant changes in treatment adherence among the inflammatory disease group during the lockdown period. Approximately 40% of the patients discontinued TNFi or extended the dosing interval without obtaining physician's advice. The rate of discontinuation or modification of ongoing therapy was higher than previously reported.[17,25] Various factors may contribute to poor medication adherence in patients with chronic inflammatory disease. One factor could be apprehension regarding COVID-19 infection, as many patients receiving immunosuppressive drugs may have been concerned about their susceptibility to COVID-19 and potential poor outcomes during the early stages of the pandemic.[26] Another factor could be limited accessibility to healthcare services during the pandemic. Additionally, patients' perceptions or beliefs about their own disease may influence treatment adherence. In this study, nearly 39% of patients with inflammatory rheumatic disease believed that their diseases or the therapy they were using may have increased the risk of COVID-19 infection.

Excessive fear, stress, or anxiety related to COVID-19 infection is gradually spreading across different segments of society, triggering a wide variety of psychological distress and negatively affecting people's daily lives and social interactions.[6] Previous research has indicated that patients with IRD were more likely to experience psychological distress, with high rates of depression, anxiety, and post-traumatic stress throughout the COVID-19 pandemic.[27,28] The REUMAVID study, which included a larger proportion of patients with rheumatic and musculoskeletal diseases from seven European countries, suggested that the COVID-19 pandemic had an adverse impact on the well-being, mental health, and physical health of many patients.[27] In our study, 22.7% of patients with inflammatory disease had moderate or higher anxiety, and at least 13% of these patients also experienced depression and stress associated with the COVID-19 pandemic. These findings highlight the importance of screening for the impact of the current COVID-19 pandemic on mental health as part of the follow-up care for patients with IRD during this ongoing crisis.

Interestingly, our data revealed that the HC group was significantly more affected by mental health issues related to depression and stress during the COVID-19 pandemic compared to the inflammatory and non-inflammatory groups. Similarly, the HC group exhibited the highest risk of intrusion and hyperarousal. A recent study by Iannuccelli et al.[29] also reported higher stress scores in HC, followed by fibromyalgia and then RA during the COVID-19 outbreak. This unexpected difference within the HC group can be partly explained by varying levels of COVID-19 exposure across society. Healthy controls without chronic diseases may be more susceptible to stress as they are less accustomed to dealing with physical and mental discomfort and the resulting uncertainty. Chronic illness itself can be considered a stressor, and individuals with these conditions may be better adapted to coping with challenging situations.[30] Additionally, during the pandemic, when participants were enrolled in this study, individuals with chronic diseases were placed on administrative leave by the government, allowing them to isolate at home. Therefore, patients with inflammatory diseases were able to stay away from crowded environments such as work and public transportation, which may have led to a decrease in their stress levels. However, healthy volunteers had to continue working and were exposed to social environments, enclosed spaces, and crowded settings during this period, which may partly explain the higher levels of depression and stress observed in this group.

One strength of our study, unlike previous research, was the comparison of the effects of COVID-19 infection on behavioral attitudes towards preventive measures and mental health in patients with IRD, nIRD, and HC. Consequently, we were able to evaluate the changes in the COVID-19-related psychological burden among all three groups. Furthermore, unlike most studies, all of our participants were assessed face-to-face rather than through digital means, such as electronic or online surveys, during the COVID-19 outbreak. However, this study had some limitations. The sample size for each group was limited, and the study was conducted as a cross-sectional study in a tertiary referral center. Therefore, it is not possible to generalize the study results to the entire IRD and nIRD population.

CONCLUSION

In conclusion, except for maintaining physical distancing, behavioral attitudes towards pandemic measures were consistent across all groups. The majority of patients with IRD discontinued or extended their ongoing treatment without physician's recommendation. Contrary to our expectations, healthy volunteers were significantly more likely to experience psychological distress compared to the other two groups. Therefore, close monitoring and early recognition of psychological discomfort during the COVID-19 pandemic could enhance patient adherence and disease control.

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REFERENCES

1. Ioannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations. Eur J Clin Invest 2021; 51(5): e13554. [CrossRef]
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323(13): 1239–42. [CrossRef]
3. Jani M, Barton A, Hyrich K. Prediction of infection risk in rheumatoid arthritis patients treated with biologics: are we any closer to risk stratification? Curr Opin Rheumatol 2019; 31(3): 285–92. [CrossRef]
4. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al; COVID-19 Global Rheumatology Alliance. Factors associated with COVID-19-related death in people with rheumatic diseases: Results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021; 80(7): 930–42. [CrossRef]
5. Pablos JL, Galindo M, Carmona L, Lledó A, Retuerto M, Blanco R, et al; RIER Investigators Group; RIER investigators group. 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(12): 1544–9. [CrossRef]
6. Dubey S, Biswas P, Ghosh R, Chatterjee S, Dubey MJ, Chatterjee S, et al. Psychosocial impact of COVID-19. Diabetes Metab Syndr 2020; 14(5): 779–88. [CrossRef]
7. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. Lancet 2020; 395(10227): 912–20. [CrossRef]
8. Bao Y, Sun Y, Meng S, Shi J, Lu L. 2019-nCoV epidemic: address mental health care to empower society. Lancet 2020; 395(10224): e37–8. [CrossRef]
9. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis 2020; 79(7): 851–8. [CrossRef]
10. 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 3. Arthritis Rheumatol 2021; 73(2): e1–12. [CrossRef]
11. Schulze-Koops H, Specker C, Iking-Konert C, Holle J, Moosig F, Krueger K. Preliminary recommendations of the German Society of Rheumatology (DGRh eV) for the management of patients with inflammatory rheumatic diseases during the SARS-CoV-2/COVID-19 pandemic. Ann Rheum Dis 2020; 79(6): 840–2. [CrossRef]
12. Çorapçıoğlu A, Yargıç I, Geyran P, Kocabaşoğlu N. Validity and reliability of Turkish Version of "Impact of Event Scale-Revised" (IES-R). New Symposium J 2006; 44(1): 14–22.
13. Bilgel N, Bayram N. Turkish version of the Depression Anxiety Stress Scale (DASS-42): Psychometric properties. Nöropsikiyatri Arşivi 2010; 47(2): 118–26.
14. Christianson S, Marren J. The Impact of Event Scale - Revised (IES-R). Medsurg Nurs 2012; 21(5): 321–2.
15. Akkoc Y, Karatepe AG, Akar S, Kirazli Y, Akkoc N. A Turkish version of the Bath Ankylosing Spondylitis Disease Activity Index: reliability and validity. Rheumatol Int 2005; 25(4): 280–4. [CrossRef]
16. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum 1989; 32(5): 531–7. [CrossRef]
17. Costantino F, Bahier L, Tarancón LC, Leboime A, Vidal F, Bessalah L, et al. COVID-19 in French patients with chronic inflammatory rheumatic diseases: Clinical features, risk factors and treatment adherence. Joint Bone Spine 2021; 88(1): 105095. [CrossRef]
18. Favalli EG, Monti S, Ingegnoli F, Balduzzi S, Caporali R, Montecucco C. Incidence of COVID-19 in patients with rheumatic diseases treated with targeted immunosuppressive drugs: What can we learn from observational data? Arthritis Rheumatol 2020; 72(10): 1600–6. [CrossRef]

19. Simon D, Tascilar K, Krönke G, Kleyer A, Zaiss MM, Heppt F, et al. Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion. Nat Commun 2020; 11(1): 3774. [CrossRef]
20. Lakota K, Perdan-Pirkmajer K, Hočevar A, Sodin-Semrl S, Rotar Ž, Čučnik S, et al. COVID-19 in association with development, course, and treatment of systemic autoimmune rheumatic diseases. Front Immunol 2021; 11: 611318.
21. Michelena X, Borrell H, López-Corbeto M, López-Lasanta M, Moreno E, Pascual-Pastor M, et al. Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum 2020; 50(4): 564–70. [CrossRef]
22. Lio CF, Cheong HH, Lei CI, Lo IL, Yao L, Lam C, et al. Effectiveness of personal protective health behaviour against COVID-19. BMC Public Health 2021; 21(1): 827. [CrossRef]
23. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al; COVID-19 Global Rheumatology Alliance. 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(7): 859–66. [CrossRef]
24. Liu D, Zhang T, Wang Y, Xia L. Tocilizumab: The key to stop Coronavirus Disease 2019 (COVID-19)-Induced Cytokine Release Syndrome (CRS)? Front Med (Lausanne) 2020; 7: 571597. [CrossRef]
25. Mancuso CA, Duculan R, Jannat-Khah D, Barbhaiya M, Bass AR, Mandl LA, et al. Modifications in systemic rheumatic disease medications: Patients' perspectives during the height of the COVID-19 pandemic in New York City. Arthritis Care Res (Hoboken) 2021; 73(6): 909–17. [CrossRef]
26. Shin YH, Shin JI, Moon SY, Jin HY, Kim SY, Yang JM, et al. Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: a nationwide cohort study. Lancet Rheumatol 2021; 3(10): e698–e706. [CrossRef]
27. Garrido-Cumbrera M, Marzo-Ortega H, Christen L, Plazuelo-Ramos P, Webb D, Jacklin C, et al. Assessment of impact of the COVID-19 pandemic from the perspective of patients with rheumatic and musculoskeletal diseases in Europe: Results from the REUMAVID study (phase 1). RMD Open 2021; 7(1): e001546. [CrossRef]
28. Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. Brain Behav Immun 2020; 89: 531–42. [CrossRef]
29. Iannuccelli C, Lucchino B, Gioia C, Dolcini G, Favretti M, Franculli D, et al. Mental health and well-being during the COVID-19 pandemic: stress vulnerability, resilience and mood disturbances in fibromyalgia and rheumatoid arthritis. Clin Exp Rheumatol 2021; 39 Suppl 130(3): 153–60.
30. Kok AAL, Pan KY, Rius-Ottenheim N, Jörg F, Eikelenboom M, Horsfall M, et al. Mental health and perceived impact during the first Covid-19 pandemic year: A longitudinal study in Dutch case-control cohorts of persons with and without depressive, anxiety, and obsessive-compulsive disorders. J Affect Disord 2022; 305: 85–93. [CrossRef]