The severity of symptoms and outcomes of patients admitted with rheumatic diseases and COVID-19; a prospective cohort study in Iran

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Abstract

Introduction: In severe COVID-19 patients, a pre-inflamatory condition leads to a cytokine storm syndrome. This may signify the need for using immunomodulatory drugs. Patients with rheumatic diseases (RDs) are prone to severe infectious diseases.
Objectives: Whether the presence of the RD itself or the use of its drugs in patients with COVID-19 increases the severity of symptoms and outcomes remains largely unknown.
Patients and Methods: In a prospective cohort study conducted in Khorshid hospital of Isfahan, Iran, 219 patients with COVID-19 were enrolled and divided into two groups of patients with a positive history for RD (n=19) and those without this history (NRD, n=200). The severity of symptoms and outcomes was compared between the groups.
Results: Shortness of breath ($P=0.001$), cough ($P=0.019$), and weakness ($P=0.001$) were significantly higher in the RD than the NRD group after, but not before, recovery. All the patients in the RD group had comorbid diseases (hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular disease), the number of which was significantly higher than that of the NRD group ($P<0.001$). The Charlson Comorbidity Index (CCI) was used to predict 10-year survival in patients with multiple comorbidities. It was significantly lower in the RD group as opposed to the NRD group ($P<0.001$). Logistic regression also showed a non-significantly higher chance of the composite outcome (ICU admission, death status, and intubation status) in the RD group as opposed to the NRD group, both before and after adjustment for confounding factors. However, no difference was found between the RD patient who received corticosteroid as a treatment (RD-CS) and those who did not (RD-NCS).
Conclusion: The results showed an increased risk for severe forms of COVID-19 in RD patients. This risk is possibly attributable to a high prevalence of comorbidities in these patients.

Introduction

In the last two decades, there have been three major global outbreaks of acute respiratory illnesses caused by coronaviruses, the most dangerous of which is the current pandemic, first observed in Wuhan, China in December 2019 (COVID-19). The disease has spread to six continents, with more than 118 million cases and over 2/6 million deaths, making it a major public health emergency in the world (1).

A pre-inflammatory condition with an increase in the IL-1β, tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (G-CSF), IP10/CXCL10, monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 1-α (MIP-

Key point

It remains unresolved whether the rheumatic disease (RD) itself or the use of glucocorticoids and disease-modifying antirheumatic drugs in patients with concurrent rheumatic diseases and COVID-19 increases or decreases the severity of symptoms and outcome. An increased risk for severe forms of COVID-19 in patients with RD is shown in our study. This may be attributed to a high prevalence of comorbidities in these patients.

1) levels has been reported in COVID-19 patients, leading to a cytokine storm syndrome in those in need of intensive care. This may signify the need for using immunomodulatory drugs in severe cases (2). Nevertheless, patients with a suppressed

immune system might not be able to combat the virus properly due to the lack of immediate immunological response and are more likely to develop COVID-19 complications (3).

Evidence suggests that patients with rheumatic diseases (RDs) are prone to severe infectious diseases. However, the disease itself and RD-related genetic and environmental factors, such as susceptible genes and living habits, and the use of glucocorticoids and conventional or biologic disease-modifying antirheumatic drugs (DMARDs) may reduce host defense against infection (4,5). It has been found that altered immunological function, disability, immobility, and joint surgery which occur in patients with RD contribute to the increased susceptibility to infections in these patients (6).

Furthermore, glucocorticoids such as methylprednisolone and prednisone, and several conventional and biologic DMARDs, including hydroxychloroquine and chloroquine, have the potential to modulate the cytokine storm in patients with concurrent severe COVID-19 and rheumatoid arthritis (7). However, evidence emerging from studies is mixed and controversial, as DMARDs are shown to be associated with an increased risk of tuberculosis, forms of pneumonia and pyogenic bacterial infections, herpes zoster, and infections after orthopedic surgeries in patients with RDs (6).

Objectives
It remains to be resolved whether the presence of the disease itself or the use of glucocorticoids and DMARDs in patients with concurrent RD and COVID-19 increases or decreases the severity of symptoms and outcome. This prospective study aimed to find a proper answer to this question.

Patients and Methods
Study design
In a prospective cohort study conducted in the emergency department of Khorshid hospital of Isfahan, Iran, between February and May 2020, 219 patients with COVID-19 were enrolled using the convenience sampling method. The patients were divided into two groups of patients with a positive history for RD and those without this history (NRD), then the severity of symptoms and outcomes was compared between the groups.

The inclusion criteria were 1) definite diagnosis of COVID-19 confirmed by positive polymerase chain reaction (PCR) test or imaging findings compatible with COVID-19 (8), and 2) informed self-consent to participate in the study. Patients were excluded from this study if they did not meet the inclusion criteria.

Upon admission, all the patients were examined by an expert rheumatologist and the presence/absence and type of RDs were determined according to the EULAR/ACR (European League Against Rheumatism /American College of Rheumatology) criteria (https://www.eular.

org). Then, the patients' demographic data such as age and gender, and clinical data including signs, symptoms, recent travel history, drug history, history of RDs, concomitant illnesses, symptom onset to admission time, hospitalization and admission to the intensive care unit (ICU) duration, and mortality rate (in- and outpatients) were recorded. Circulating biochemical factors such as complete blood count (CBC), aspartate transaminase (AST), alanine transaminase (ALT), calcium (Ca), and phosphorous (P) levels, oxygen saturation (SaO_2), and the high-resolution computed tomography (HRCT) score, were obtained. The results were compared between the RD and NRD groups, and also between the RD patients who received corticosteroid as a treatment (RD-CS) and those who did not (RD-NCS).

The patients were followed-up by several members of the research team by phone calls 1, 4, and 12 weeks after discharge to ensure their condition (complete resolution, re-hospitalization, or death). The Charlson Comorbidity Index (CCI) was used to predict 10-year survival in patients with multiple comorbidities which was compared between the groups (9).

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study. The Institutional Ethical Committee at Isfahan University of Medical Sciences approved all study protocols (IR.MUI.MED.REC.1399.306). Written informed consent was obtained from all the participants before any intervention. This study was based on a research project at Isfahan University of Medical Sciences (proposal# 199140).

Data analysis
The data were analyzed using SPSS 22 (IBM Corporation, Armonk, NY). Descriptive data are shown as mean±standard deviation (SD) or frequencies (%). The qualitative variables were compared using the χ^2 test, and the Fisher's exact test was performed when the data were limited. The quantitative variables were compared using an independent t-test when the data were normally distributed; otherwise, the Mann-Whitney U test was used. Logistic regression was used to identify confounding variables (Model 1) and then to determine the 95% odds ratio (OR) for the composite event (ICU admission, intubation, and death) in the RD group as opposed to the NRD group (models 2 and 3). $P < 0.05$ was considered statistically significant.

Results
A total of 219 patients with COVID-19 were enrolled. Subsequently, 19 (8.67%) patients were categorized into the RD group and 200 (91.32%) patients into the NRD group. In the RD group, two (10.52%) patients had systemic lupus erythematosus (SLE) and 17 (89.48%) patients

had rheumatoid arthritis (RA). The demographic data and the clinical and paraclinical findings of the RD and NRD groups are given in Table 1. We found no significant difference in the clinical and paraclinical findings between the groups except for shortness of breath ($P=0.001$), cough ($P=0.019$), and weakness ($P=0.001$) which were significantly higher in the RD group than the NRD group after, but not before, recovery. All the patients in the RD group had comorbid diseases (hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular disease), the number of which was significantly higher than that of the NRD group ($P<0.001$). Additionally, the

Table 1. Demographic, clinical, and paraclinical findings of the patients with and without a history of rheumatologic diseases. Data are shown as mean ± SD or numbers (%)

Variable	Total (n = 219)	Group		P value
		RD (n = 19)	NRD (n = 200)	
Demographic data				
Age (years)	54.41±16.41	58.26±12.77	54.05±16.70	0.286
Gender (male)	144 (65.8%)	5 (26.3%)	139 (69.5%)	0.001
Laboratory Findings (before recovery)				
White blood cell count (cells/µg)	5778.10±2783.86	5925.00±2398.19	5765.99±2818.40	0.827
Lymphocyte (%)	20.81±9.63	22.86±9.64	20.64±9.64	0.379
Lymphocyte (categorized, <1000 cells/µg)	21 (9.6%)	0 (0.0%)	21 (10.5%)	0.380
Platelet count (cells/µg)	184.35±68.84	213.25±85.65	181.97±66.98	0.081
ALT (U/L)	33.87±31.66	27.41±13.10	34.49±32.85	0.380
ALT>60 (U/L)	20 (9.1%)	0 (0.0%)	20 (10.0%)	0.226
AST (U/L)	46.53±33.40	44.00±21.37	46.78±34.37	0.744
AST >40 (U/L)	94 (42.9%)	9 (47.4%)	85 (42.5%)	0.801
Ca (mg/dL)	8.50±0.76	8.72±0.99	8.47±0.73	0.196
P (mg/dL)	2.91±0.73	3.01±0.63	2.90±0.74	0.550
SaO$_2$ (%)	89.69±7.02	89.95±5.08	89.67±7.18	0.868
SaO$_2$ (categorized, <90%)	73 (33.3%)	6 (31.6%)	67 (33.5%)	0.998
Laboratory Findings (after recovery)				
White blood cell count (cells/µg)	7395.38±4394.80	6462.50±3810.86	7243.44±4439.96	0.628
Lymphocyte (%)	21.70±12.82	25.74±13.16	21.43±12.81	0.359
Lymphocyte (categorized, <1000 cells/µg)	31 (14.2%)	1 (5.3%)	30 (15.0%)	0.679
Platelet count	204.75±87.88	196.00±111.17	205.32±86.67	0.773
ALT	72.83±45.78	56.33±44.43	74.33±46.27	0.522
ALT (categorized, >60)	19 (8.7%)	1 (5.3%)	18 (9.0%)	0.593
AST	57.94±32.77	69.25±58.96	56.58±29.39	0.473
AST (categorized, >40)	27 (12.3%)	3 (15.8%)	24 (12.0%)	0.998
Ca	8.34±0.79	8.89±1.87	8.28±0.57	0.055
P	3.17±0.81	3.01±0.38	3.19±0.85	0.409
SaO2	92.60±3.53	93.68±3.73	92.48±3.49	0.159
SaO2 (categorized, <90)	22 (10.0%)	1 (5.3%)	21 (10.5%)	0.702
Signs and symptoms (before recovery)				
Fever	164 (74.9%)	11 (57.9%)	153 (76.5%)	0.079
Cough	172 (78.5%)	11 (57.9%)	161 (80.5%)	0.053
Shortness of Breath	139 (63.5%)	10 (52.6%)	129 (64.5%)	0.593
Rhinorrhea	24 (11.0%)	3 (15.8%)	21 (10.5%)	0.452
Sore throat	44 (20.1%)	5 (26.3%)	39 (19.5%)	0.569
Weakness	123 (56.2%)	11 (57.9%)	112 (56.0%)	0.998
Signs and symptoms (after recovery)				
Fever	1 (0.5%)	1 (5.3%)	0 (0.0%)	0.061
Cough	4 (1.8%)	2 (10.5%)	2 (1.0%)	0.019
Shortness of breath	5 (2.3%)	5 (26.3%)	0 (0.0%)	0.001
Rhinorrhea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.694

Table 1. Continued

Variable	Total (n = 219)	Group		P value
		RD (n = 19)	NRD (n = 200)	
Weakness	4 (1.8%)	3 (15.8%)	1 (0.5%)	0.001
Temperature before recovery	37.57±1.03	37.38±0.83	37.62±1.06	0.361
Temperature before recovery (categorized, >38)	33 (15.1%)	4 (21.1%)	29 (14.5%)	0.587
Temperature after recovery	36.78±0.57	36.64±0.47	36.79±0.57	0.303
Hospitalization duration (days)	6.42±6.02	7.74±5.10	6.29±6.02	0.319
Admission to ICU (yes)	36 (16.4%)	2 (10.5%)	34 (17.0%)	0.746
HRCT score	8.66±5.01	10.10±4.95	8.50±5.01	0.319
HRCT score (categorized, >6)	76 (34.7%)	9 (47.4%)	67 (33.5%)	0.501
HRCT score (categorized, >7)	71 (32.4%)	8 (42.1%)	63 (31.5%)	0.747
Symptoms duration before admission (days)	7.53±5.20	8.63±7.36	7.41±4.95	0.489
Mortality rate (yes)	17 (7.8%)	1 (5.3%)	16 (8.0%)	0.998
Smoking (yes)	17 (7.8%)	2 (10.5%)	15 (7.5%)	0.879
Influenza vaccine (yes)	4 (1.8%)	1 (5.3%)	3 (1.5%)	<0.001
Comorbidity disease * (yes)	19 (8.7%)	19 (100%)	0 (0.0%)	<0.001
CCI	1.30±1.52	0.69±0.31	1.36±1.58	<0.001

HTN, HF, IHD, CVD, COPD, Asthma, Lung Fibrosis, Diabetes, Immune-compromised, Cancer, CKD, Dialysis, HIV, Organ transplant, Chemotherapy, HLP, ESRD, Hypothyroidism. HTN, hypertension; HF, heart failure; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HIV, human immunodeficiency virus; HLP, hyperlipidemia; ESRD, end-stage renal disease; RD, rheumatologic disease; NRD, no rheumatologic disease; ALT, alkaline transaminase; AST, aspartate transaminase; Ca, calcium; P, phosphate; Sa, saturation; ICU, intensive care unit; HRCT, high-resolution computed tomography; CCI, Charlson comorbidity index.

CCI was significantly lower in the RD group as opposed to the NRD group (*P* < 0.001). Besides, the number of patients who received influenza vaccination was remarkably low in the RD group than the NRD group (*P* < 0.001).

We found no difference in the radiologic findings of patients in the RD and NRD groups except for distribution patterns (upper versus lower, *P* = 0.008) and peripheral versus central (*P* = 0.001; Table 2).

Further, the analysis showed no difference in terms of demographic, clinical, and paraclinical findings between the RD-CS and RD-NCS groups (Table 3).

We supposed three logistic regression models, the response variable being the composite event (the combination of death, ICU admission, and intubation status) in all of them. In the first model, the chance of occurrence of at least one of the events was found to be almost 90% higher in the patients of the RD group than those in the NRD group. According to the second model and by eliminating the confounding effects of age and gender, the chance was almost doubled. By adding other confounding variables to the model described above, this chance was 13% higher in the RD group than in the NRD group (Table 4). However, none of these changes was significant.

Discussion

In our study, a majority of RD patients (89.48%) had RA. This study showed that dyspnea, cough, and weakness were significantly higher in the RD group than in the NRD group. The results indicated that patients with RD had a significantly higher number of comorbid diseases compared with the NRD. Our findings also revealed that the CCI was remarkably higher in the RD group than the NRD group, predicting lower 10-year survival rates in the former. Further, logistic regression demonstrated a non-significantly higher chance of the composite outcome (ICU admission, death status, and intubation status) in the RD group as opposed to the NRD group, both before and after adjustment for confounding factors. However, no difference was found between the RD-CS and RD-NCS groups in this regard.

Patients with concurrent RD and COVID-19 are in need of distinct medical attention; manifestations of COVID-19 may mimic those of RD, and these patients are at risk for serious infections because of their immunosuppressed condition caused by their underlying immune state and the use of glucocorticoids and DMARDs (10). Furthermore, several medications frequently used for the treatment of RDs such as hydroxychloroquine (11), and also those which target interleukin (IL)-6 (e.g., tocilizumab, sarilumab) and IL-1 (e.g., anakinra) are being evaluated in patients with COVID-19 due to their ability to modulate cytokine storm that signals a poorer outcome in these patients (12). The question, however, remains unresolved whether RD patients with immunosuppressive medications are at risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Similar to our findings, in a study by Cheng et al on five patients with concomitant RD (one systemic sclerosis and 4 RA) and COVID-19, fever (80%), cough (80%), dyspnea (40%), and fatigue (20%) were the most frequently detected symptoms. Four patients (80%) had a

Table 2. Radiologic findings of the patients in both groups

Radiologic findings	Total (n=219)	Group		P value
		RD (n=19)	NRD (n=200)	
Ground-glass opacification				
Negative	70 (32.0%)	8 (42.1%)	62 (31.0%)	0.744
Positive	38 (17.4%)	3 (15.8%)	35 (17.5%)	
Ground-glass consolidation				
Negative	53 (24.2%)	5 (26.3%)	48 (24.0%)	0.761
Positive	52 (23.7%)	6 (31.6%)	46 (23.0%)	
Consolidation				
Negative	90 (41.1%)	10 (52.6%)	80 (40.0%)	0.998
Positive	14 (6.4%)	1 (5.3%)	13 (6.5%)	
Centrilobular nodule				
Negative	103 (47.0%)	10 (52.6%)	93 (46.5%)	0.320
Positive	3 (1.4%)	1 (5.3%)	2 (1.0%)	
Bronchial wall thickening				
Negative	99 (45.2%)	10 (52.6%)	89 (44.5%)	0.748
Positive	7 (3.2%)	1 (5.3%)	6 (3.0%)	
Reticular				
Negative	70 (32.0%)	5 (26.3%)	65 (32.5%)	0.280
Positive	35 (16.0%)	6 (31.6%)	29 (14.5%)	
Lymphadenopathy				
Negative	105 (48.0%)	11 (57.9%)	94 (47.0%)	0.998
Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Vascular enlargement				
Negative	94 (42.9%)	10 (52.6%)	84 (42.0%)	0.728
Positive	10 (4.6%)	1 (5.3%)	9 (4.5%)	
Pleural effusion				
Negative	104 (47.5%)	11 (57.9%)	93 (46.5%)	0.648
Positive	2 (0.9%)	0 (0.0%)	2 (1.0%)	
Distribution				
None	36 (16.4%)	5 (26.3%)	31 (15.5%)	0.008
Upper	6 (2.7%)	1 (5.3%)	5 (2.5%)	
Lower	66 (30.1%)	5 (26.3%)	61 (30.5%)	
Transverse				
None	24 (10.9%)	4 (21.1%)	20 (10.0%)	0.001
Peripheral	64 (29.2%)	5 (26.3%)	59 (29.5%)	
Central	4 (1.8%)	2 (10.5%)	2 (1.0%)	
Region				
Unilateral	16 (7.3%)	1 (5.3%)	15 (7.5%)	0.787
Bilateral	89 (40.6%)	10 (52.6%)	79 (39.5%)	
Scattered				
Focal	9 (4.1%)	1 (5.3%)	8 (4.0%)	0.949
Multifocal	95 (43.4%)	10 (52.6%)	85 (42.5%)	
Diffuse	2 (0.9%)	0 (0.0%)	2 (1.0%)	

RD, rheumatologic disease; NRD, no rheumatologic disease. Data are shown as number (%).

positive history of other comorbid diseases (most notably hypertension). This study showed that RD patients were more likely to have severe (one-fifth) or critical (two-fifths) COVID-19 illness. These patients had higher levels of IL-1 and IL-6 compared with others, indicating a need for the management of cytokine storm and immune regulation using biological agents such as IL-6 blocker (IVIg, 400 mg) and plasma exchange (400 mL, once or twice) in patients with severe and critical COVID-19 (13). In this light, although the administration of synthetic and biologic DMARDs is linked to a possible further rise in the incidence of life-threatening infections, the poor

management of RA activity is a more important infectious risk factor in patients with RD. Thus, it has been suggested that RA patients should be encouraged to adhere to their medical regimen even during the COVID-19 pandemic. This may decrease a subsequent COVID-19-induced rise in the disease flares, patient burden, disability, poor quality of life, and seeking healthcare attention (14). However, the study by Chen et al was performed on a limited number of patients without a control arm to compare these findings with COVID-19 patients without RD.

Similarly, in a study conducted by Mathian et al on 17 patients with SLE, an increased risk for severe forms

Table 3. Demographic, clinical, and paraclinical findings of the RD patients with and without history corticosteroid treatment

Variable	Groups		P value
	RD-CS (n=10)	RD-NCS (n=9)	
Age (years)	57.50±9.66	59.11±16.14	0.792
Gender (male)	2 (20.0%)	3 (33.3%)	0.628
Laboratory findings			
White blood cell count (cells/µg)	5588.89±2859.83	6357.14±1756.76	0.544
Lymphocyte (%)	21.42±11.67	24.70±6.61	0.519
Platelet count (cells/µg)	213.78±76.38	212.57±102.76	0.979
ALT (U/L)	23.88±9.63	31.37±15.88	0.251
AST (U/L)	42.11±19.78	46.13±24.22	0.712
Ca (mg/dL)	8.92±0.71	8.46±1.28	0.347
P (mg/dL)	3.16±0.56	2.81±0.69	0.248
SaO$_2$ (%)	91.50±1.78	88.22±6.94	0.202
Signs and symptoms			
Fever	5 (50.0%)	6 (66.7%)	0.367
Cough	6 (60.0%)	5 (55.6%)	0.998
Shortness of breath	4 (40.0%)	6 (66.7%)	0.637
Rhinorrhea	2 (20.0%)	1 (11.1%)	0.998
Sore throat	2 (20.0%)	3 (33.3%)	0.593
Weakness	6 (60.0%)	5 (55.6%)	0.604
Temperature (°C)	37.34±0.87	37.42±0.82	0.836
HRCT score	11.13±4.67	7.33±5.51	0.280
Symptoms duration before admission (days)	7.90±4.70	9.44±9.77	0.661
Smoking (yes)	1 (10.0%)	1 (11.1%)	0.998
Influenza vaccine (yes)	1 (10.0%)	0 (0.0%)	0.478
Comorbidity disease* (yes)	10 (100.0%)	9 (100.0%)	-
CCI	0.59±0.37	0.78±0.19	0.143
Hospitalization duration (days)	8.50±7.25	6.89±4.51	0.574
Admission to ICU (yes)	1 (10.0%)	1 (11.1%)	0.998
Intubation status (yes)	0 (0.0%)	1 (11.1%)	0.474
Mortality rate (yes)	0 (0.0%)	1 (11.1%)	0.474

*HTN, HF, IHD, CVD, COPD, asthma, lung fibrosis, diabetes, immune-compromised, cancer, CKD, Dialysis, HIV, organ transplant, chemotherapy, HLP, ESRD, hypothyroidism.

HTN, hypertension; HF, heart failure; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HIV, human immunodeficiency virus; HLP, hyperlipidemia; ESRD, end-stage renal disease; RD, rheumatologic disease; NRD, no rheumatologic disease; ALT, alkaline transaminase; AST, aspartate transaminase; Ca, calcium; P, phosphate; Sa, saturation; ICU, intensive care unit; HRCT, high-resolution computed tomography; CCI, Charlson comorbidity index.

Data are shown as mean ± SD or number (%).

Table 4. Estimated ORs and 95% CIs by logistic regression models for the composite outcome (ICU admission, death status, and intubation status)

Model 1*		Model 2*		Model 3*	
OR (95% CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
1.929 (0.427,8.717)	0.393	2.142 (0.453,10.130)	0.336	1.135 (0.220,5.862)	0.880

OR, odds ratio. *Model 1: unadjusted, Model 2: adjusted by age and sex, and Model 3: adjusted by other significant covariates indicated in Table 1.

of COVID-19 was detected. This risk was attributed to a high prevalence of comorbidities such as chronic kidney disease and obesity in patients with SLE (15). In a large-scale study by Gianfrancesco et al on 600 cases (RA (230, 38%), SLE (85, 14%), and psoriatic arthritis (74, 12%)) from 40 countries, almost half of the cases were hospitalized (277, 46%) and 55 (9%) died (higher than the general population). The most frequent comorbidities were hypertension (199, 33%), lung disease (127, 21%), diabetes (69, 12%), and cardiovascular disease (63, 11%). Similar to our study, patients with comorbidities such as hypertension, cardiovascular disease, and diabetes had higher odds of hospitalization. This study found that glucocorticoid exposure of ≥10 mg/d was linked to a higher and anti-TNF with lower hospitalization rates in RD patients. The use of DMARDs or non-steroidal anti-inflammatory drugs was not associated with an increased risk of hospitalization (16). In our study, however, no

difference was detected in paraclinical and clinical findings between the RD-CS and RD-NCS patients.

In a cohort study conducted on 110 patients with concomitant RD and COVID-19, the most common underlying RDs were RA (36%), psoriatic arthritis (17%), and SLE (17%), respectively. The most frequently presented symptoms were fever (79%), cough (77%), and dyspnea (50%). The mortality rate due to COVID-19 was 5%, which was almost equal to that of the general population (5.2%). The five most common comorbid conditions in the deceased patients were hypertension (28%), lung disease (20%), cardiovascular disease (11%), morbid obesity (8%), and diabetes (8%). The results of this study showed no increased risk of death due to COVID-19 in patients with RD compared with those without RD (17). However, this study lacked a proper control arm and was not able to compare the clinical and paraclinical findings with the general population affected by COVID-19. In line with this, Monti et al assessed the clinical course of COVID-19 in 320 patients (68% female, mean age 55±14 years) treated with DMARDs (57% with rheumatoid arthritis, 43% with spondyloarthritis, 52% treated with TNF inhibitors, 48% with other DMARDs). This study showed that RD patients under treatment with DMARDs were not at an increased risk of respiratory or life-threatening complications from SARS-CoV-2 compared with the general population. This might have resulted from the immunomodulatory effects of these treatments in RD patients with COVID-19 who had an aberrant inflammatory and cytokine response induced by the host immune system (18). Similarly, evidence obtained from large population-based studies demonstrated no increased risk of severe COVID-19 disease in patients with RD compared with those with other comorbidities (19,20). These findings are in line with the reports published in SARS and Middle East respiratory syndrome outbreaks, showing that immunocompromised patients with organ transplantation, cancer, or autoimmune diseases are not at an increased risk for coronavirus-induced death and complications (21,22).

Our study had several potential shortcomings that may have affected its outcomes. First, this study was performed on a limited number of patients. Studies with a higher number of RD patients are strictly encouraged. The problem could be tackled by the COVID-19 Global Rheumatology Alliance which helps the generation of rapid data on patients with RD and those using immune-modulating therapies. Second, our study may have suffered from selection bias as patients with more severe diseases are most likely to be captured. Thus, patients with a mild-to-moderate course of the disease are lost.

Conclusion
Our results demonstrated that patients with RD had a significantly higher number of comorbid diseases compared with the NRD. As a result, the CCI was

significantly and the composite outcome (ICU admission, death status, and intubation status) was non-significantly higher in the RD group than the NRD group, both before and after adjustment for confounding factors. Nevertheless, no difference was found between the RD-CS and RD-NCS groups in this regard. These findings should be validated in larger case-control studies.

Limitations of the study
The limitation of our study was its small sample size in the RD group.

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