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ORIGINAL RESEARCH

COVID-19 in Patients with Rheumatic Disease Using Immunomodulatory Drugs: Imaging Findings and Predictors of Hospitalization

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ABSTRACT

Introduction: SARS-CoV-2 causes more severe symptoms in most chronic diseases, and rheumatic disease is no exception. This study aims to investigate whether there is an association between the use of immunomodulatory medications, including conventional disease-modifying agents (csDMARDs), glucocorticoids, and biologic DMARDs, and outcomes such as hospitalization and lung involvement in patients with rheumatic disease with COVID-19.

Methods: We performed a cross-sectional study on 177 COVID-19 cases with rheumatologic diseases using immunomodulatory drugs as their regular treatment. All patients were evaluated regarding their initial chest computed tomography (CT) scan, COVID-19 symptoms, and comorbidities. We ran predictive models to find variables associated with chest CT-scan involvement and hospitalization status.

Results: CT findings showed lung involvement in 87 patients with chest CT-scan severity score (C-ss) of less than 8 in 59 (33%) and more than 8 in 28 (16%) of our patients. Of all patients, 76 (43%) were hospitalized. Hospitalized patients were significantly older and had more comorbidities ($P = 0.02$). On multivariate analysis, older age [odds ratio (OR) 1.90, 95% confidence interval (CI) 1.31–3.08] and comorbidity (OR 2.75, 95% CI 1.06–3.66) were significantly associated with higher odds of hospitalization ($P = 0.03$). On multivariate analysis, older age (OR 1.15, 95% CI 0.94–2.01), pulmonary diseases (OR 2.05, 95% CI 1.18–3.32), and treatment with csDMARDs (OR 1.88, 95% CI 0.37–1.93) were associated with higher C-ss ($P = 0.039$).

Conclusions: This study found that advanced age and comorbidities, similar to the general population, are risk factors for hospitalization in patients with COVID-19 with rheumatic disorders. Administration of csDMARDs, older age, and pulmonary disorders were linked to increased risk of COVID-19 pneumonia in these individuals.

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Key Summary Points

The results of this study have confirmed that advanced age and comorbidities are predictive risk factors for hospitalization for patients with rheumatic diseases, just as they are for the general population.

Patients with rheumatic disease with COVID-19 treated with csDMARDs prior to the disease had higher C-ss on initial chest CT scan.

Higher C-ss is significantly associated with higher rates of hospitalization and mortality in patients with rheumatic disease with COVID-19.

Older patients and those with pulmonary diseases had higher rates of C-ss on their initial chest CT scans.

INTRODUCTION

In December 2019, the novel coronavirus was recognized as the cause of disease outbreak in China [1]. It is still a global concern, for as the pandemic progresses, new mutations emerge, prolonging the situation. Although most people have mild to moderate flu-like symptoms, the disease becomes more severe in vulnerable populations like patients with underlying hypertension, lung disease, diabetes, cardiovascular diseases, or end-stage renal disease [2]. It can induce severe pneumonia leading to acute respiratory distress syndrome (ARDS) and respiratory failure or multiple organ failure and death in severe cases [3, 4]. The severity of lung involvement on initial chest CT scans is reported to be associated with higher rates of adverse outcomes in patients with COVID-19 [5]. Moreover, it has been shown that older male adults with comorbidities are more likely to be infected with SARS-CoV-2 owing to their weaker immunity [6].

Rheumatic diseases are a group of immune-mediated inflammatory conditions, and most have an autoimmune mechanism [7]. As SARS-CoV-2 causes more severe symptoms in most chronic diseases, it is hypothesized that rheumatic diseases are no exception. The use of immunosuppressive drugs that can weaken the immune system is a concern, as it is unclear whether the body can deal effectively with the unknown infection [8]. On the other hand, immunosuppressive drugs might be beneficial in SARS-CoV-2 infection, especially in severe cases, by diminishing the cytokine storm and hyperinflammation it causes, leading to reduced risk of acute respiratory distress syndrome (ARDS) and hemophagocytic lymphohistiocytosis, which are the main causes of death in patients with COVID-19 [9, 10]. Examples of drugs with this potential are some disease-modifying antirheumatic drugs (DMARDs), including hydroxychloroquine, azathioprine, and methotrexate [11, 12]. Glucocorticoids used in rheumatic diseases are other drugs that have shown convincing effects in patients with COVID-19, reducing mortality [13]. According to the data currently available, it can be concluded that rheumatic diseases appear to be linked to a small increased risk of SARS-CoV-2 infection [14, 15].

The goal of this study is to determine whether the use of immunomodulatory medications is linked with adverse outcomes such as hospitalization or lung involvement in patients with rheumatic disease with COVID-19 when adjusted for their demographic characteristics.

METHODS

Study Design and Participants

This is a cross-sectional, single-center study in Qom, Iran, carried out between January 2020 and September 2021 at a large urban hospital center (Shahid Beheshti Hospital). The study protocols were developed following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

In the current study, a consecutive sample of patients from Shahid Beheshti Hospital was enrolled (including hospitalized patients and outpatients). In the current study, hospitalized patients and outpatients were enrolled from Shahid Beheshti Hospital. The patients were diagnosed with COVID-19 infection using positive reverse-transcription polymerase chain reaction (RT-PCR) for COVID-19 RNA or chest CT-scan results suggestive of COVID-19. We included all patients with rheumatic disease whose records showed that they were using immunomodulatory drugs. Patients without chest CT-scan imaging or positive RT-PCR and those without informed consent were excluded from the study. Patients with O_2 saturation lower than 93% on room air, $PaO_2/FiO_2 < 300$ mmHg, respiratory rate of > 30 breaths per minute, and significant lung involvement on initial chest CT scan were hospitalized. An expert rheumatologist investigated the participants for age, gender, rheumatologic disease, comorbidities, medications, imaging findings, hospitalization status, and duration of illness.

All chest CT scans were performed at the patient's initial admission ($\pm$ 8 h) and before their COVID-19 treatment was initiated. The chest CT scans were reported by one expert radiologist and rechecked by a second expert radiologist. The radiologists were blinded to the clinical features of the patients. The CT scans were evaluated regarding ground-glass opacity, consolidation, and bronchial and pleural wall thickening, and the CT-scan severity score (C-ss) was calculated on the basis of the method from previous studies [16, 17], where a score of 0 points indicates no involvement, 1 point indicates 1–25% involvement, 2 points indicates 25–50% involvement, 3 points indicates 50–75% involvement, and 4 points indicates 75–100% involvement for each lobe of a lung. The C-ss was calculated by summing the scores of five lobes for each lung, and the total amount was 40. The C-ss for each patient was compared with the possible risk factors of lung involvement using statistical tests.

Bias

To avoid misinterpretation of chest involvement on imaging, we consulted a second radiologist. Moreover, all the missing data were filled by phone calls to the discharged patients.

Statistical Analysis

Quantitative data were expressed as mean $\pm$ standard deviation or median and interquartile range. The normal distribution of data was assessed using the Kolmogorov–Smirnov test. Categorical variables were expressed as numbers and percentages. the weighted kappa coefficient was used to compare the consistency of two observers in each lung. Interrater reliability was evaluated using intraclass correlation coefficient (ICCs). Independent-sample *t*-test and chi-square test were used to determine whether there is an association between the demographic (i.e., age and sex) and clinical features (immunomodulatory medication type and rheumatic disease) of the patients and their hospitalization status. Patients with missing values for any of the above-mentioned variables were excluded from the analysis. The association between the patient's characteristics and their hospitalization status was assessed using a multinomial logistic regression method with age, sex, common comorbidities, rheumatoid diseases [rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and sarcoidosis] and type of immunomodulatory medication (csDMARDs, b-DMARDs, glucocorticoids) as covariates. The results are shown as odds ratio (OR) and 95% confidence interval (95% CI). Another multiple logistic regression model was fit to estimate the impact of patient's demographic features, comorbidities [hypertension (HTN) and cardiovascular diseases, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and asthma] and types of immunomodulatory medication (csDMARDs, b-DMARDs, glucocorticoids) on CT-scan severity score (C-ss). The results are shown as odds ratio (OR) and 95% confidence interval (95% CI). Results were considered statistically significant for *P*-values < 0.05. All analyses were conducted using IBM SPSS Statistics for

Windows, version 26 (IBM Corp, Armonk, NY, USA).

Ethics

The ethics committee of Qom University of Medical Sciences approved this study, and it fulfilled the guidelines of the Helsinki Declaration. The institutional review board (IRB) number for this study is **IR.MUQ.REC.1399.229**. All participants completed and signed a written informed consent form, and all personal information was kept private.

RESULTS

Participants' Characteristics

A total of 177 patients were included in the present study during the 2 years of the COVID-19 pandemic, of which 81% were female and the mean age was 49.1 ± 14.2 years (range, 20–92 years). Demographic and clinical features are presented in Table 1. All patients were diagnosed with COVID-19 either via PCR testing (134, 75%), or chest CT-scan results (87, 49%). Fever (72%), cough (39%), and shortness of breath (27%) were the most frequent symptoms in the population, and 22% also had gastrointestinal manifestations, mostly abdominal pain. Recorded rheumatic diseases were rheumatoid arthritis (122, 69%), systemic lupus erythematosus (30, 17%), ankylosing spondylitis (13, 7%), and sarcoidosis (12, 7%). Comorbidities, including hypertension (HTN), diabetes mellitus (DM), cardiovascular, pulmonary diseases, and renal insufficiency, were detected in 97 (55%) patients. Nine patients had hypothyroidism and were being treated with levothyroxine. Seventy-six (43%) patients were hospitalized, eight of whom were reported to be deceased by the end of the study. The mean number of days for COVID-19 illness from the beginning of the symptoms to resolution or death was 17.3 ± 11 days. The intraclass correlation coefficient for radiologic reports was good (ICC, 0.7). Of 87 patients with positive chest CT-scan results, 28 (32%) had radiologic

Table 1 Demographic characteristics, comorbidities, symptoms, history of hospital admission, and DMARD use for participants with rheumatic disease and COVID-19 (n = 177)

	N **(%)**
Female	143 (81%)
Age (years)	
20–39	49 (28%)
40–59	81 (45%)
60–80	43 (21%)
> 80	4 (6%)
Rheumatic diseases	
Rheumatoid arthritis	122 (69%)
Systemic lupus erythematosus	30 (17%)
Spondyloarthritis	13 (7%)
Sarcoidosis	12 (7%)
Comorbidities	
Hypertension and cardiovascular disease	37 (21%)
Diabetes	24 (13%)
Obstructive pulmonary diseases	36 (20%)
Medication	
No immunomodulatory	50 (28%)
csDMARDs	108 (61%)
b-DMARDs	27 (15%)
Glucocorticoids	97 (55%)
Chest CT-scan findings	
No lung involvement	90 (51%)
C-ss less than 8	59 (33%)
C-ss more than 8	28 (16%)
Ground-glass opacity	152 (86%)
Consolidation	139 (78%)
Bronchial and pleural wall thickening	74 (41%)
Hospitalized	76 (43%)
Duration of COVID-19 illness (median)	10–21 days

Table 1 continued

	N (%)
Extrapulmonary manifestations of COVID-19	86 (48%)

*csDMARDs medications included: antimalarial (hydroxychloroquine, chloroquine),
azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, mycophenolate mofetil/mycophenolic acid, sulfasalazine, tacrolimus;
b-DMARD biologic or targeted synthetic DMARD, csDMARDs conventional synthetic
b-DMARD included: infliximab, adalimumab, rituximab, CD-20 inhibitors, IL-1 inhibitors, IL-6 inhibitors, IL-12/IL-23 inhibitors, anti-TNF, and Janus kinase inhibitors
RA, rheumatoid arthritis; SpA, spondyloarthritis;
SLE, systemic lupus erythematosus; DM, diabetes mellitus

C-ss more than 8, and mean (IQR) C-ss in nonhospitalized and hospitalized patients was 8 and 12, respectively, and significantly different ($P = 0.01$).

Predictors of Lung Involvement in Multivariate Analysis

Multiple logistic regression (Table 2) model revealed that older age ($P = 0.007$, OR 1.15, 95% CI 0.94–2.01) and treatment with csDMARDs are related to odds of higher C-ss in patients with rheumatic disease with COVID-19 ($P = 0.039$, OR 2.06, 95% CI 1.09–3.89). Table 2 also shows that patients with pulmonary diseases including asthma and chronic obstructive pulmonary disease (COPD) show higher rates of abnormalities on their chest CT ($P = 0.020$, OR 2.05, 95% CI 1.18–3.32).

Table 2 Effect of medications and demographic findings of patients with rheumatic disease with COVID-19 on chest CT-scan severity score (C-ss)

	Number of lung involvement cases/ Number of cases (%)	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	***P*-value**
Age (years)		**1.85 (0.82–2.98)**	**1.15 (0.94–2.01)**	**0.007**
Sex (female)	78/143 (54%)	0.94 (0.35–2.56)	1.82 (0.38–3.08)	0.882
Comorbidities				
HTN and cardiovascular diseases	25/97 (26%)	1.41 (0.36–1.54)	1.32 (0.57–3.09)	0.513
Diabetes mellitus	13/97 (14%)	2.03 (1.25–4.55)	1.65 (1.01–2.66)	0.079
Obstructive pulmonary disorder	20/97 (21%)	**2.11 (0.89–3.89)**	**2.05 (1.18–3.32)**	**0.02**
csDMARDs	58/108 (54%)	**1.78 (0.38–1.62)**	**1.88 (0.37–1.93)**	**0.039**
b-DMARDs	12/27 (44%)	1.18 (0.68–4.68)	1.09 (0.65–5.11)	0.251
Glucocorticoids (prednisolone equivalent)	40/97 (41%)	1.06 (0.51–2.12)	0.96 (0.42–2.18)	0.927

Table 3 Characteristics based on hospitalization status of patients with rheumatic disease and COVID-19

	Hospitalized, 76	Not hospitalized, 101	*P* value
Female	61	82	0.87
Age (mean), years	53.8	45.4	**0.01**
Rheumatic diseases			0.64
Rheumatoid arthritis	56	66	0.26
Systemic lupus erythematosus	8	22	0.15
Other rheumatoid diseases	12	13	0.3
Comorbidities			
Hypertension, cardiovascular disease, diabetes, obstructive pulmonary diseases	51	46	**0.02**
Medication			
No immunomodulatory	21	29	0.14
csDMARDs	48	60	0.21
b-DMARDs	11	16	0.67
Glucocorticoids (prednisolone equivalent)	41	56	**0.04**

Hospitalized versus Nonhospitalized Participants

Table 3 presents our patients' demographic and clinical characteristics stratified by their hospitalization status. Hospitalization outcomes did not differ significantly between males and females ($P = 0.87$). Hospitalized patients were significantly older than the nonhospitalized group ($P = 0.01$). comorbidities were more frequent among hospitalized patients ($P = 0.02$). The use of glucocorticoids (prednisolone equivalent) was associated with hospitalization ($P = 0.04$). Univariable analysis showed no significant difference between hospitalized and nonhospitalized groups regarding their rheumatic diseases, duration of COVID-19 symptoms, and use of csDMARDs or b-DMARDs (*P*-value > 0.05 for all). Higher CT severity score and hospitalization were also correlated in our patients ($P = 0.01$).

However, on multivariable analysis (Table 4), the effect of glucocorticoids became insignificant when adjusted for the use of either csDMARDs or b-DMARDs ($P = 0.07$), adjusted (OR 1.62, 95% CI 0.53–2.05). The odds of being hospitalized for older age (OR 1.90, 95% CI 1.31–3.08) and patients with comorbidity (OR 2.75, 95% CI 1.06–3.66) remained significantly high after adjusting for other covariates ($P = 0.03$). Since 43% of our patients in the csDMARDs-treated group were taking hydroxychloroquine, we also performed the analysis with this group being separated as a variable, but the result did not significantly change.

DISCUSSION

In this current study of 177 rheumatic diseases with SARS-CoV-2 infection confirmed either with PCR test or chest CT scan, we found the following outcomes: the risk of hospitalization was higher among patients with older age and those with comorbidities including hypertension, cardiovascular diseases, diabetes, and obstructive pulmonary diseases. Besides, the use of csDMARDs and b-DMARDs was not

Table 4 Association between demographic and clinical characteristics and hospitalization status in patients with rheumatic disease with COVID-19 using multinomial regression

	Hospitalized/number of cases (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*-value
Sex (female)	61/143 (42%)	1.14 (0.54–2.86)	0.85 (0.38–1.89)	0.87
Age (mean)		**2.53 (1.22–4.46)**	**1.90 (1.31–3.08)**	**0.04**
Comorbidities	51/97 (52%)	**2.03 (1.71–4.87)**	**2.75 (1.06–3.66)**	**0.03**
csDMARDs	47/107 (44%)	1.15 (0.56–2.43)	1.56 (0.79–2.38)	0.37
b-DMARDs	11/27 (40%)	0.99 (0.69–2.56)	0.78 (0.31–2.09)	0.54
Glucocorticoids (prednisolone equivalent)	49/97 (50%)	**2.04 (1.56–3.04)**	1.62 (0.53–2.05)	0.09
Rheumatoid arthritis	55/122 (47%)	0.75 (0.45–1.11)	0.89 (0.60–1.05)	0.86
Systematic lupus erythematosus	9/30 (40%)	1.10 (0.89–1.50)	1.21 (0.92–1.40)	0.2
Other rheumatoid diseases	12/25 (48%)	0.89 (0.44–2.44)	0.69 (0.35–1.88)	0.61

associated with higher hospitalization; however, the use of glucocorticoids increases the hospitalization rate when not adjusted for csDMARDs or b-DMARD. Furthermore, patients using csDMARDs before infection with COVID-19 demonstrated a higher degree of lung involvement on their chest CT scan, which was not significant for other rheumatoid drug types or other risk factors except for older age.

The risk factors of hospitalization in patients with COVID-19, in the general population, were demonstrated to be advanced age, male sex, and comorbidities including hypertension, diabetes, and obesity [18]. These risk factors can also increase the risk of severe disease and death [8]. Other studies examining rheumatic diseases found a higher death rate and hospitalization [4, 11] with the same risk factors (in addition to comorbidities such as hypertension, cardiovascular disease, and obstructive pulmonary diseases) for patients with underlying rheumatic diseases, of which old age and presence of comorbidities were consistent with our study as risk factors for hospitalization. The hospitalization rate in our study (43%) is similar to that reported in a study from the COVID-19 Global Rheumatology Alliance registry that investigated 600 patients from different countries [19]. It seems that comparable composition of studied populations regarding the number of patients with each rheumatoid disease (e.g., RA, SLE, and AS) and also the prevalence of certain comorbidities (e.g. HTN, DM, and COPD) are responsible for such similarities [20]. These two factors are also shown to be important when it comes to defining which medication group is a risk factor for hospitalization and other adverse outcomes in patients with COVID-19 with

rheumatoid diseases [21]. A notable example is a large-scale Italian nested case–control study in which the use of hydroxychloroquine was not related to higher hospitalization outcomes until the study was restricted to only patients with RA and SLE [22].

The use of csDMARDs in patients with rheumatoid disease with COVID-19 demonstrated no association with risk of hospitalization or mortality [19]. However, since patients with more severe rheumatic disease are more likely to be treated with csDMARDs, the severity of their condition can be confounded by indication of hospitalization status and mortality [11, 23]. On the other hand, cytokine storm due to mostly IL-6 and TNFα is known to be the cause of severe COVID-19 outcomes such as respiratory failure and intensive care unit (ICU) requirement [24]. Thus, biologically, the use of b-DMARDs should ameliorate the course of COVID-19. We did not find a significant decrease in hospitalization or C-ss in patients treated with b-DMARDs, which in our case consisted mostly of TNFα inhibitors. This was coherent with the findings of other studies [20, 24]. However, Gianfrancesco et al. found lower odds of hospitalization with b-DMARDs compared with csDMARDs [19]. A systematic review recently showed that standard-dose and high-dose b-DMARDs are associated with an increase in serious infections in rheumatoid arthritis, so the potential effect of biological medications should be tested via randomized trials before being advised as a remedy for severe COVID-19 infection.

Immunosuppression therapy was found to reduce the severity of COVID-19 merely in patients with underlying autoimmune diseases. They concluded that this finding was due to the neutralizing effect of immunosuppressive therapy by the inherent lymphocyte activation induced by autoimmune disease [8]. Glucocorticoids are another group of commonly used medications. It has been shown that a prednisolone-equivalent dose of more than 10 mg/day increases the risk of hospitalization and COVID-19-related death [11]; moreover, the risk of infection rises as glucocorticoid dosage increases. Still, in this study, glucocorticoids demonstrated an association with hospitalization, but after adjusting for csDMARDs and b-DMARDs, the association disappeared. It should be noted that, similar to the normal population, late administration of glucocorticoids can be beneficial, while in earlier stages it can increase disease activity [13, 25].

Initial CT-scan severity score (C-ss) can be used to predict adverse outcomes such as hospitalization, ICU admission, and death in patients with rheumatoid disease and COVID-19 [26]. Koc et al. reported that, despite the presence of more atypical findings on chest CT scan, C-ss is not significantly higher in this population compared with other patients with COVID-19 [27]. Still, there is a lack of evidence regarding the predictive value of initial chest CT, especially in patients with rheumatologic diseases. A recent study conducted also in Iran, reported that patients with rheumatoid disease with comorbidities such as pulmonary diseases and diabetes and those who use glucocorticoids have a higher risk for COVID-19 pneumonia and higher C-ss [20]. Our data showed that only older patients with pulmonary diseases and those using csDMARDs have higher C-ss compared with others when adjusted for covariates. Additionally, we did not find a significant connection between the use of csDMARDs and hospitalization or mortality. Since we were not able to measure the severity of the underlying rheumatoid condition, there may have been a confounding effect on pulmonary involvement and higher C-ss. Notably, another study reported that the severity of the rheumatoid condition is not significantly related to hospitalization and adverse outcomes in patients with rheumatoid disease with COVID-19 [19]. Overall, it is not plausible to make therapeutic advice based on these findings [22].

The absence of random sampling makes it difficult to generalize the findings to all patients with rheumatoid diseases. Owing to the observational nature of this study, it is hard to gather data regarding the patients' drug use and whether they use their drugs regularly, on time, and at the prescribed dose. Another limitation is the change in our perception of COVID-19 due to continuously evolving variants and new findings. Therefore, the results of this study should

be interpreted with caution because of the heterogeneity among various groups of rheumatic diseases and different demographic and clinical characteristics and medications.

CONCLUSIONS

This study demonstrated that advanced age and comorbidities are predictive risk factors of hospitalization in patients with rheumatic diseases, like in the general population. Immunomodulatory medications (csDMARDs, b-DMARDs, and glucocorticoids) did not significantly change the course of COVID-19. The exception was the group of patients treated with csDMARDs, who had higher rates of COVID-19 pneumonia. We suggest additional research in larger populations to elucidate the effect of immunomodulatory medications on radiographic findings and their relation with disease outcome.

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Compliance with Ethics Guidelines. The ethics committee of Qom University of Medical Sciences approved this study, and it fulfilled the guidelines of the Helsinki Declaration. The IRB number for this study is **IR.MUQ.REC.1399.229**. All participants completed and signed a written informed consent form, and all personal information was kept private.

Data Availability. The data that support the findings of this study are available from the Qom University of Medical Sciences. Still, restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of Qom University of Medical Sciences.

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