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Clinical characteristics associated with hospitalization and mortality of coronavirus disease-2019 (COVID-19) infection in rheumatic patients: a cross-sectional study from Iran

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This study was designed to describe COVID-19 infection in rheumatic patients and to investigate possible risk factors for hospital admission and death related to COVID-19 infection considering the type of rheumatic disease and medications used to treat it. In this observational cross-sectional study, patients under follow-up in Kermanshah rheumatology units were investigated in a 6-month period between February 18 and August 22, 2020. Confirmed COVID-19 cases were collected. The following data was obtained: age, sex, rheumatic disease diagnosis, rheumatic disease medication (glucocorticoids, csDMARDs, ts/bDMARDs). Rheumatic patients were divided into two groups of hospitalized and non-hospitalized. The data from the two groups were compared.

In total, 221 patients were enrolled in this study. Of these, 38 patients (17.19%) were hospitalized, and 9 patients (4.07%) died. No significant difference was observed between hospitalized and non-hospitalized patients except for vasculitis and prior use of Janus kinase inhibitors (Tofacitinib). A greater rate of hospitalized patients had vasculitis (6 (15.79%) vs. 1 (0.55%), $p <$ 0.0001). A greater rate of them were on Tofacitinib therapy (2 (1.09%) vs. 0, *p value* = 0.03). A greater rate of patients who died used Tofacitinib (2 (22.22%) vs. 0, *p value* = 0.001) and Mycophenolate Mofetil (4 (44.44%) vs. 23 (10.85%), *p value* = 0.014).

Hospitalization and mortality rates in rheumatic patients are comparable to the general population. A higher risk for hospitalization was observed only in vasculitis patients and users of Tofacitinib, and a higher risk for mortality was seen only in users of Mycophenolate Mofetil and Tofacitinib, though this finding should be interpreted with caution due to the small size of these subgroups. In conclusion, most rheumatic patients do not seem to be at higher risk for severe COVID-19.

Keywords: COVID-19, Hospitalization, Iran, Rheumatic diseases, SARS COV-2 infection

Introduction

Novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan, China, in December 2019. Soon, the World Health Organization declared the coronavirus disease 2019 (COVID-19) a pandemic. Hospitalization and mortality rates related to COVID-19 seemed to be higher in patients with certain risk factors, such as advanced age and specific underlying diseases (heart disease, respiratory diseases, hypertension, diabetes mellitus, etc.) [1]. It is still unknown whether patients with rheumatic diseases are more vulnerable for severe SARS-CoV-2 infection or whether they have higher odds of hospitalization and mortality. On the one hand, rheumatic patients are potentially more susceptible to severe infection due to the rheumatic disease and its treatment [2-4]. On the other hand, some studies have shown the potential role of some immune modifying therapies in the prevention and treatment of COVID-19 infection [5-6].

The current study aimed to investigate the outcomes of COVID-19 infection in rheumatic patients and compare them with rheumatic patients who have been hospitalized or have died due to COVID-19 and patients who have recovered from it while considering the type of rheumatic disease and medications used to treat it.

Materials and Methods

This observational cross-sectional study was performed in Kermanshah, Iran. Convenience sampling was done to acquire the study population. Patients attending outpatient rheumatology clinics and the rheumatology or COVID-19

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wards of Emam Reza and Golestan hospitals were enrolled. All rheumatic patients meeting the American College of Rheumatology classification or European League Against Rheumatism criteria and diagnosed with COVID-19 infection were included. COVID-19 confirmed cases were considered those with positive RT-PCR testing, radiological infiltrates consistent with viral pneumonia, elevated levels of serum coronavirus IgM and IgG, or those with clinical symptoms and a contact history with a patient diagnosed with COVID-19 infection.

The endpoint of the study was the determination of characteristics associated with hospitalization and mort-ality due to COVID-19 infection regarding the type of rheumatic disease and medications used to treat it. The number of follow-up days of patients varied depending on the severity of COVID-19 infection, and each patient was followed until recovery, discharge from the hospital, or death.

The local Clinical Research Ethics Committee approved the study protocol (approval number IR.KUMS.REC-.1399.912). This study was performed according to the principles of the Declaration of Helsinki, and patient consent was obtained.

Between February 18 and April 2, 2020, we identified 221 rheumatic patients diagnosed with COVID-19 infection. Patient data was obtained. Recorded variables were: (1) Demographical characteristics including sex and age; (2) Type of rheumatic disease (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSC), axial spondyloarthritis (SPA), psoriatic arthritis (PSA), Sjogren's syndrome, vasculitis, inflammatory myositis, relapsing polychondritis, sarcoidosis, anti-phospholipid syndrome (APS)); (3) Medication for rheumatic disease comprising glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs); conventional synthetic disease modifying anti-rheumatic drugs (csD-MARDs) including hydroxychloroquine (HCQ), leflunomide, mycophenolate mofetil, azathioprine, methotrexate, sulfasalazine and cyclosporine; targeted synthetic/biologic DMARDs (ts/bDMARDs) including antitumor necrosis factor (TNF)-alpha drugs (adalimumab, etanercept, infliximab) and other ts/bDMARDs such as rituximab and Janus kinase (JAK) inhibitors (tofacitinib); other medication including cyclophosphamide, colchicine, aspirin, warfarin, calcium channel blocker, 5-phosphodiesterase inhibitor, and endothelin antagonist; (4) Covid-19 clinical outcomes (recovery without hospitalization, recovery with hospitalization, intensive care admission and death).

The subjects were divided into two groups of hospitalized and non-hospitalized patients during the 6 months of the study.

Statistical Analysis

Data of the study was analyzed in SPSS version 25 (IBM). Mean and standard deviation [SD] of quantitative variables were reported. The non-parametric Mann-Whitney test was used to compare variables. Categorical variables were reported as number (percentage), and contingency tables were used to compare them. Moreover, *p*-values were calculated with the $\chi 2$ test with Yates' correction between hospitalized and non-hospitalized groups or Fisher's exact tests for variables less than five. A *p value* less than 0·05 was considered significant. Odds ratios (ORs) with 95% CI were calculated for each item.

Results

In total, 221 rheumatic patients were identified with a diagnosis of COVID-19 infection, most of whom were female (81.9%). Mean patient age was 43.32. The main diagnosis was rheumatoid arthritis (78 patients, 35.29%), followed by systemic lupus erythematosus (54 patients, 24.43%), axial spondyloarthritis (33 patients, 14.93%), systemic sclerosis (24 patients, 10.85%), PSA (8 patients, 3.61%), vasculitis (7 patients, 3.16%), Behcet's disease (4 patients, 1,80%), SLE+RA (4 patients, 1,80%), Inflammatory myositis (2 patients, 0.9%), SLE+SSC (1 patient, 0.45%), Sjogren 's syndrome (1 patient, 0.45%), relapsing polychondritis (1 patient, 0.45%), and SLE+APS (1 patient, 0.45%). About three quarters of the patients were taking glucocorticoids (170 patients, 76.92%), and about half of them were taking NSAIDs (116 patients, 52.48%). A large majority of patients were taking at least one of the conventional synthetic disease-modifying anti-rheumatic drugs (Methotrexate: 83 patients, 37.55%; sulfasalazine: 50 patients, 22.62%; azathioprine: 41 patients, 18.55%; mycophenolate mofetil: 27 patients, 12.21%; leflunomide: 19 patients, 8.59%). Furthermore, 80 patients (36.19%) were taking hydroxychloroquine, and 39 patients (17.64%) were taking ts/bDMARDs. Adalimumab was the most frequently taken bDMARD (26 patients, 11.76 %), followed by infliximab (7 patients, 3.16 %), etanercept (3 patients, 1.35 %), tofacitinib (2 patients, 0.9%), and rituximab (1 patient, 0.45%).

The most common method of diagnosing COVID-19 infection was based on symptoms and contact history (31.67%), followed by PCR testing (27.14%) and chest CT scan (23.52%). Of 221 patients diagnosed with COVID-19, 38 (17.19%) were hospitalized, 8 (3.61%) were admitted to ICU, and 9 patients (4.07%) died.

Demographical (sex and age) and clinical characteristics (type of rheumatic disease and rheumatic disease medication) between hospitalized and non-hospitalized patients were compared. Details are available in Tables 1 and 2. Similar rates of patients had different types of rheumatic diseases, except vasculitis: RA (11 (28.95%) vs. 67 (36.61%)), SLE (9 (23.68%) vs. 45 (24.59%)), SPA (4 (10.53%) vs. 29 (15.55%)), SSC (7 (18.42%) vs. 17 (9.29%)), Behcet's (0 vs. 4 (2.18%)), PSA (0 vs. 8 (4.37%)), SLE+RA (0 vs. 4 (2.18%)), inflammatory myositis (1 (2.63%) vs. 1 (0.55%)), Sjogren 's syndrome (0 vs. 1 (0.55%)), SLE+SSC (0 vs. 1 (0.55%)), relapsing polychondritis (0 vs. 1 (0.55%)), and SLE+APS (0 vs. 1 (0.55%)). A greater rate of hospitalized patients had vasculitis (6 (15.79%) vs. 1 (0.55%), *p value*< 0.0001).

No differences were observed in medication use prior to COVID-19 infection except for Janus kinase (JAK) inhibitors (tofacitinib) (2 (1.09%) vs 0, *p value*=0.03). Other differences in rheumatic disease medication were not

statistically significant: glucocorticoids (33 (86.84%) vs. 137 (74.86%)), hydroxychloroquine (16 (42.10%) vs. 64 (34.97%)), methotrexate (14 (36.84%) vs. 69 (37.70%)), sulfasalazine (5 (13.16%) vs. 45 (24.59%)), azathioprine (7 (18.42%) vs. 34 (18.58%)), mycophenolate mofetil (7 (18.42%) vs. 20 (10.93%)), leflunomide (4 (10.53%) vs. 15 (8.20%)), adalimumab (2 (5.26%) vs. 24 (13.11%)), etanercept (1 (2.63%) vs. 2 (1.09%)), infliximab (1 (2.63%)) vs. 6 (3.29%)), rituximab (0 vs. 1 (0.55%)), cyclophosphamide (2 (5.26%) vs. 3 (1.64%)), NSAID (16 (42.10%) vs. 100 (54.64%)), aspirin (5 (13.16%) vs. 18 (9.84%)), colchicine (0 vs. 3 (1.64%)).

Table 1. Different types of rheumatic disease compared between hospitalized and non-hospitalized patients (Variables are presented as number (percentage))

Different types of rheumatic disease	**Not hospitalized number = 183 (percent)**	**Hospitalized number = 38 (percent)**	***P value***	**OR**	**95% CI**
female	148	33	0.52		
Age(mean,SD)	42.86,11.33	45.45,14.54	0.22		
Systemic lupus erythematosus	45 (24.59)	9 (23.68)	0.91	1.05	0.46-2.39
Rheumatoid Arthritis	67 (36.61)	11 (28.95)	0.47	1.42	0.66-3.04
SLE + RA	4 (2.18)	0	>0.99		
Systemic Sclerosis	17 (9.29)	7 (18.42)	0.17	0.45	0.17-1.18
SLE + SSC	1 (0.55)	0	>0.99		
axial spondyloarthritis	29 (15.55)	4 (10.53)	0.61	1.6	0.53-4.85
Psoriatic arthrtis	8 (4.37)	0	0.36		
Sjogren's syndrome	1 (0.55)	0	>0.99		
Behcet	4 (2.18)	0	>0.99		
Inflammatory myositis	1 (0.55)	1 (2.63)	0.31	0.2	0.01-3.32
Vasculitis	1 (0.55)	6 (15.79)	**<0.0001**	**0.03**	**0-0.25**
Relapsing Polychondritis	1 (0.55)	0	>0.99		
SLE + APS	1 (0.55)	0	>0.99		
other	3 (1.64)	0	>0.99		

RA: Rheumatoid Arthritis

SLE: Systemic lupus erythematosus

SSC: Systemic Sclerosis

APS: Anti Phospholipid syndrome

AS: axial spondyloarthritis

OR: odds ratio

CI: confidence interval

Table 2. Medication of rheumatic disease compared between hospitalized and non-hospitalized patients (Variables are presented as number (percentage))

Medication of rheumatic disease	Not hospitalized number = 183 (percen t)	Hospitalized number = 38 (percen t)	*P value*	OR	95% CI
Prednisolone	137 (74.86)	33 (86.84)	0.17	0.45	0.17-1.22
=< 5mg	111 (60.65)	24 (63.16)	0.92	0.9	0.44-1.85
5mg < dose =<10mg	23 (12.57)	5 (13.16)	0.87	0.95	0.34-2.68
10mg < dose =<20mg	1 (0.55)	1 (2.63)	0.31	0.2	0.01-3.32
> 20mg	3 (1.64)	2 (5.26)	0.20	0.3	0.05-1.86
Hydroxychloroquine	64 (34.97)	16 (42.10)	0.52	0.74	0.36-1.51
Conventional DMARDs					
Methotrexate	69 (37.70)	14 (36.84)	0.93	1.04	0.5-2.14
Sulfasalazine	45 (24.59)	5 (13.16)	0.19	2.15	0.79-5.84
Azathioprine	34 (18.58)	7 (18.42)	0.84	1.01	0.41-2.49
Mycophenolate Mofetil	20 (10.93)	7 (18.42)	0.31	0.54	0.21-1.39
Leflunomide	15 (8.20)	4 (10.53)	0.74	0.76	0.24-2.43
Biologic and targeted synthetic DMARDs	32 (17.49)	7 (18.42)	0.92	0.94	0.38-2.32
Adalimumab	24 (13.11)	2 (5.26)	0.27	2.72	0.61-12.02
Etanercept	2 (1.09)	1 (2.63)	0.43	0.41	0.04-4.63
Infliximab	6 (3.29)	1 (2.63)	>0.99	1.25	0.15-10.73
Tofacitinib	0	2 (1.09)	**0.03**		
Rituximab	1 (0.55)	0	0.17		
Cyclophosphamide	3 (1.64)	2 (5.26)	0.20	0.3	0.05-1.86
NSAIDs	100 (54.64)	16 (42.10)	0.22	1.66	0.82-3.36
Aspirin	18 (9.84)	5 (13.16)	0.75	0.72	0.25-2.08
Colchicine	3 (1.64)	0	>0.99		

DMARD: disease modifying anti-rheumatic drugs

OR: odds ratio

CI: confidence interval

Nine rheumatic patients (all female, mean age: 42.22 years) died of COVID-19, three of whom had rheumatoid arthritis, three had systemic sclerosis, two had systemic lupus erythematosus, and one patient was diagnosed with vasculitis (Takayasu). The demographical and clinical characteristics of these nine patients are reported in Table 3 and compared with those who recovered from COVID-19 in Table 4. No significant difference was observed for age, sex, type of rheumatic disease, or rheumatic disease medications except for prior use of Janus kinase (JAK) inhibitors (tofacitinib) and mycophenolate mofetil. A greater rate of patients who died used these two drugs prior to admission: tofacitinib (2 (22.22%) vs. 0, *p value* = 0.001) and mycophenolate mofetil (4 (44.44%) vs. 23 (10.85%), *p value* = 0.014). Other differences between patients who died of COVID-19 and those who recovered were not statistically significant.

Table 3. Demographical and Clinical characteristics of rheumatic patients died of COVID-19

Cases	sex	age	type of rheumatic disease	medication prior to admission	comorbidities	Covid diagnosis	other explanations
1	female	15	SLE	prednisolone 40mg daily, HCQ, MM		CT and PCR	she was started on Rituximab for suspected alveolar hemorrhage due to her symptoms (dyspnea and hemoptysis), decrease in hemoglobin and chest CT scan findings
2	female	77	SLE	prednisolone 2.5mg daily, MTX, HCQ	Lupus nephritis, Diadetes Mellitus, Hypertension	CT and PCR	she presented to hospital with CVA and developed pericardial effusion during hospitalization
3	female	30	SSC	Prednisolone 5mg daily, MM, Tadalafil, Bosentan, Diltiazem	Interstitial lung disease	CT	
4	female	50	SSC	Prednisolone 5mg daily, MM, Diltiazem	Interstitial lung disease	contact history	
5	female	50	SSC	Prednisolone 5mg daily, MM, Bosentan, Diltiazem	Interstitial lung disease	CT	
6	female	35	RA	Prednisolone 5mg daily, Infliximab, HCQ, SSZ	Depression	CT and PCR	
7	female	35	RA	prednisolone 5mg daily, MTX, HCQ, Tofacitinib		CT	
8	female	45	RA	prednisolone 5mg daily, MTX, SSZ, Tofacitinib		CT	
9	female	43	Vasculitis (Takayasu)	cyclophosphamide		CT and PCR	

RA: Rheumatoid Arthritis

SLE: Systemic lupus erythematosus

SSC: Systemic Sclerosis

HCQ: Hydroxychloroquine

MM: Mycophenolate Mofetil

SSZ: Sulfasalazine

MTX: Methotrexate

CVA: cerebrovascular attack

CT: chest computed tomography scan

Table 4. Demographical and Clinical characteristics compared between rheumatic patients died of COVID-19 and those who recovered from COVID-19. (Variables are presented as number (percentage))

Demographical and Clinical characteristics	Death number = 9	Remission number = 212	*P value*	OR	95% CI
Age(mean,SD)	42.22,17.08	43.07,11.67	0.83		
Female	9 (100)	172 (81.13)	0.32		
Systemic lupus erythematosus	2 (22.22)	52 (24.52)	>0.99	0.88	0.18-4.36
Rheumatoid Arthritis	3 (33.33)	75 (35.38)	>0.99	0.91	0.22-3.76
Systemic Sclerosis	3 (33.33)	21 (9.90)	0.06	4.55	1.06-19.53
Vasculitis	1 (11.11)	6 (2.83)	0.25	4.29	0.46-39.98
Prednisolone	8 (88.88)	162 (76.41)	0.64	2.47	0.3-20.22
Hydroxychloroquine	4 (44.44)	76 (35.85)	0.73	1.43	0.37-5.49
Methotrexate	3 (33.33)	80 (37.73)	>0.99	0.83	0.2-3.39
sulfasalazine	2 22.22))	48 (22.64)	>0.99	0.98	0.2-4.85
Mycophenolate Mofetil	4 (44.44)	23 (10.85)	0.014	6.57	1.65-26.24
Biologic DMARDs (Infliximab)	1 (11.11)	6 (2.83)	>0.99	0.57	0.07-4.71
Cyclophosphamide	1 (11.11)	4 (1.89)	0.19	6.5	0.65-64.98
Tofacitinib	2 (22.22)	0	0.001		

Discussion

The effects and consequences of COVID-19 infection for patients with underlying rheumatic disease are still unclear; therefore, more surveys are needed to clarify this issue. Herein, data from an observational survey of rheumatic patients with COVID-19 infection is presented, in order to determine which factors in these patients can predict a worse outcome or the need for hospitalization.

Since the beginning of the pandemic, many questions have arisen about contracting a serious or life-threatening infection in patients with rheumatic diseases (RD) [7-9]. Patients with RD are at increased risk of infection because of the nature of the autoimmune disease itself and the use of immunosuppressive drugs [2, 10, 11].

In this analysis, hospitalization was considered a factor for a more severe course. Based on the data, the outcomes of COVID-19 infection were overall favorable; only 17.19% of all patients needed hospitalization, and the mortality rate was only 4.07%. Compared to the general population, according to a national cohort study in Iran, the cumulative risk for mortality in hospitalized patients in 30 days was 24.4%, but the high mortality rate in the current study was due to the fact that milder cases were likely excluded, and only hospitalized patients were evaluated [12]. In another large cohort study from Iran, the total case fatality rate (CFR) was 10.05% [13]. Unlike previous studies, the current research showed that age, sex, and dose of glucocorticoid were not associated with risk of hospitalization for rheumatic patients [14-16]. However, most patients in the current study were on chronic treatment for rheumatic disease and taking low-dose prednisolone. The number of patients taking ≥10 mg prednisolone was only 7 persons; therefore, it is not possible to draw definite conclusions about the risk of COVID-19 infection at higher doses of glucocorticoids. At doses less than 10 mg prednisolone, however, the risk of hospitalization and death in patients obviously did not increase.

Based on the systematic reviews, meta-analyses [17-18], and observational studies [19–20-21], the use of immunosuppressive drugs such as ts/bDMARDs has been considered a potential risk for COVID-19 infection [22-23]. The role of these drugs in susceptibility to infection compared with csDMARDs has been well established [24]. Conversely, the current data about bDMARDS was very reassuring, especially about adalimumab, which is the most used bDMARD among the current patients. Regarding tsDMARDs, however, tofacitinib was the only agent used in the current rheumatic patients. Because it is priced much higher than bDMARDs in Iran, it is generally used for patients with severe disease who show a lack of response to other medications. Therefore, the deaths of the two patients who took tofacitinib should be interpreted with caution, and the effect of tofacitinib on COVID-19 infection needs further studies with larger sample sizes.

No significant association was found between csDMARD use and hospitalization, consistent with other studies [14-16]; however, a significant relationship between use of mycophenolate mofetil and death from COVID-19 infection in our patients was seen. In fact, in this study mycophenolate mofetil was used in four of the nine cases of death, three of whom had scleroderma with underlying pulmonary involvement. The fourth patient had active lupus, which was treated with high dose glucocorticoid and rituximab. Therefore, the deaths of these patients cannot be considered a result of taking mycophenolate mofetil alone. In the sub-analysis of different groups among the current patients, vasculitis showed associations with severe COVID-19 and need for hospitalization. This association was in line with large cohort study from Spain [9], but further studies are necessary to more precisely evaluate the association of severity of COVID-19 infection with different types of rheumatic diseases.

The strength of our study is that all patients were treated in one center, and thus treatment strategies for COVID-19 were comparable in all cases, reducing confounding caused by discrepancies in regimens of COVID-19 treatment which might influence the outcome of infected patients. The completeness of data in this study is strong; no data was missing, particularly on the outcome of hospitalization which was recorded after full recovery or death.

The first limitation of this study is the cross-sectional and observational design; based on the data, we could not investigate the potential effects of COVID-19 infection on the course of rheumatic diseases. Another limitation is that the number of cases in many of the subgroups of rheumatic diseases was too low to include specific rheumatic disease and its treatment into the multivariable analysis. Moreover, the impact of disease activity and specific comorbidities like diabetes mellitus, hypertension, and smoking on the outcomes of patients was not investigated. Therefore, it is necessary to continue the investigation of patients with rheumatic diseases and COVID-19 infection to gather more evidence and determine the best therapeutic strategy for these patients.

Conclusion

Hospitalization and mortality rates in rheumatic patients are comparable with those of the general population. A higher risk for hospitalization was observed only in vasculitis patients and users of tofacitinib, and a higher risk for mortality was seen only in users of mycophenolate mofetil and tofacitinib, though this finding should be interpreted with caution due to the small size of these subgroups and limitations of this study. In conclusion, most rheumatic patients do not seem to be at higher risk for developing severe COVID-19 infection.

Acknowledgments

None.

Conflict of interest

The authors have declared that they have no conflicts of interest.

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