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ORIGINAL ARTICLE

COVID-19 AMONG A SAMPLE OF IRAQI PATIENTS WITH RHEUMATIC DISEASES: A MULTICENTER STUDY

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Summary

Background: There are scarce data on disease characteristics and severity of coronavirus 2019 (COVID-19) among Iraqi patients with rheumatic diseases (RDs). In this study, we aimed to report the disease characteristics and variables associated with COVID-19 outcome among patients with RDs.

Methods: Between October 2020 and April 2021, rheumatic diseases (RDs) patients with COVID-19 were registered from different centres in Iraq. The patient's demographics, rheumatological history, COVID-19 symptoms, severity, and management, if any, their disease progress and outcome have been assessed. Binary logistic regression analysis was performed to determine predictors of disease severity.

Results: 253 patients were included in the study, and most were females. The commonest rheumatic disease was rheumatoid arthritis (RA), followed by systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) (95, 52 and 20 patients respectively). It has been found that 50.6% of patients had mild COVID-19, and 49.4% had moderate disease; 18% of patients required oxygen support, no patient was treated in hospital, and there was no reported death. Patients with moderate COVID-19 had significantly higher age than mild type (p= 0.022); with more BMI (p=0.03), more in the number of comorbidities (p<0.001), more steroids users (p=0.012), higher steroid dose (P=0.034), had longer steroid duration, longer duration of conventional disease-modifying antirheumatic drugs (cDMARDs) (p=0.018), and biologic Disease-modifying Antirheumatic Drug (bDMARDs) in months (p=0.025). Increasing body mass index (BMI), duration of biological DMARDs use, and an increasing number of comorbidities were significant independent factors that increase the risk of having more severe COVID-19, (p<0.05).

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Conclusion: COVID-19 infection rheumatic patients tend to have mild-moderate disease course; BMI, duration of biological DMARDs use, and many comorbidities were significant independent factors that increase the risk of having more severe COVID-19.

Key words: SARS-CoV-2; COVID-19; DMARDs; rheumatic diseases; rheumatoid arthritis

Introduction

"Coronavirus disease 2019 (COVID-19)", caused by the "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), has a wide range of symptoms, ranging from subclinical infection with a benign outcome to multi-organ failure and death (1). "COVID-19" can affect people of all ages and patient populations, but those who are older and have co-morbidities are at a higher risk of developing the more severe disease (2). Rheumatic diseases (RDs) have been a source of concern for a variety of reasons. Immune dysregulation caused by RDs or the drugs used to treat them may have an impact on innate immune responses, which are important in limiting viral replication and developing an adaptive immune response (3). COVID-19 outcome may be influenced by medications used to treat RDs. Antiviral effects were suggested for some anti-rheumatic drugs like hydroxychloroquine, and chloroquine, and patients taking these medications were thought to be less likely to have severe COVID-19 outcomes due to lower viral replication during the early phase (4).

Given the lack of data on COVID-19 in patients with "rheumatic diseases" in our region, we undertook this investigation to assess general patterns and health outcomes of COVID-19 among such patients, as well as determinants of COVID-19 seriousness.

Patients and Methods

This was a multi-centre observational cross-sectional descriptive study of patients with rheumatic disease in Iraq. The study was conducted in keeping with the principles stated in the "Helsinki Declaration", and before the study, written informed approval was taken from all participants. The study protocol was approved as a research plan for the period 2020 - 2021 and was registered in the Department of Medicine, College of Medicine, the University of Babylon with a number 38 and the date of 7/12/2020.

For enrollment, a rheumatologist-confirmed assessment of rheumatic disease and a COVID-19 assessment using at least three of the independent parameters were necessary: "SARS-CoV-2 RNA" was detected using "reverse-transcription polymerase chain reaction (RT-PCR)". (ii) the existence of antibodies against SARS-CoV-2, or (iii) symptoms and "computed tomography (CT)" findings consistent with COVID-19. Patients having a presumptive assessment based only on symptoms were excluded. The severity of COVID-19 was determined using the WHO classification (5). COVID-19 infection was classified into mild, moderate or severe infection. In mild infection, there are no signs or symptoms of pneumonia or hypoxia; moderate infection defined as presence of clinical and radiological evidence of pneumonia with SpO_2 ≥90% on room air, while severe infection is defined by the presence of pneumonia and one of the following: respiratory rate >30 breaths/min or SpO_2 <90% on room air (5). We included all patients who met our inclusion criteria in the study during the period between October 2020 and April 2021.

Data were collected using questionnaires including the patients' demographic data such as age, gender, "body mass index" (BMI), smoking history, and comorbidities. In addition, rheumatic disease characteristics were included, such as the type of rheumatic disease and its duration, steroid use (dosage and duration), and the usage and duration of "disease-modifying anti-rheumatic medications (DMARDs)", including biological DMARDs, at the time of diagnosis. We also gathered information about COVID-19, including clinical features, way of diagnosis, history of exposure, previous COVID-19 infection, drugs used for COVID-19, need for "hospitalization, oxygen therapy, continuous positive airway pressure (CPAP), or invasive ventilation, and outcome".

Statistical analysis

Data were presented as "median (interquartile range) for non-normally distributed continuous variables", and number (percentages) for "categorical variables. Mann-Whitney test" was utilized to distinguish the differences between continuous variables and Chi-square test for categorical variables. Correlation between patients' demographics, rheumatic disease duration, medications used, and comorbidities with COVID-19 severity was measured using Spearman correlation. Binary logistic regression analysis was done to predict the severity of COVID 19 in rheumatic diseases. P value less than 0.05 was considered statistically significant. "All statistics were performed using SPSS 26 (IBM Corp, USA, 2019) and Microsoft excels 2019".

Results

A total of 253 patients with rheumatic disease infected with COVID-19 were involved in the study. Of those 187 were female and 66 were male. The median (interquartile range) age of patients was 45 (35-55) years. The median (IQR) of BMI was 27(24-30) kg/m^2. Fifty patients were smokers, 210 had a previous history of exposure, and six patients were previously infected with COVID19. The median (IQR) duration of rheumatic diseases was 4 (3-6) years; Steroid users were 182 patients with a median (IQR) dose of 5 (5-10) mg/ day with a median duration of steroids use of 9 (5-24) months. Most of the patients (120) were taking cDMARDS with a median (IQR) duration of 2 (1-4) years. In addition, 101 patients were taking biological DMARDs with a median duration of 6 (6-18) months. Most of the patients had more than one comorbidity, as shown in table 1.

Table 1. Covid-19 patient basic features based on severity in patients with rheumatic illnesses (n=253).

Variables		Total	Mild	Moderate	p
Age in years, Median (IQR)		45 (35-55)	35(30-55)	45(35-55)	0.022
Gender, n(%)	Male	66(100%)	36 (54.5%)	30 (45.5%)	0.455
	Female	187 (100%)	92(49.2%)	95 (50.8%)	
BMI kg/m^2, Median (IQR)		27(24-30)	26.28(23-29)	27(24-30)	0.03
Smoking Hx positive, n(%)		50(100%)	28 (56.0%)	22 (44%)	0.432
Number of comorbidities, n(%)	0	124(100%)	81(65.3%)	43(34.7%)	<0.001
	1	77(100%)	38(49.4%)	39(50.6%)	
	2	38(100%)	6(15.8%)	32(84.2%)	
	3	11(100%)	3(27.3%)	8(72.7%)	
	4	3(100%)	0(0.0%)	3(100%)	
Hx of exposure positive, n(%)		210 (100%)	107(51.0%)	103(49.0%)	0.868
Previous infection positive, n(%)		6(100%)	3(50%)	3(50%)	1.000
Duration of rheumatic disease yrs, Median (IQR)		4 (3-6)	4(2-6)	4(3-6)	0.05
Steroid users, n(%)		182 (100%)	83 (45.6%)	99 (54.4%)	0.012
Steroid dose mg, Median (IQR)		5(5-10)	5(5-5)	5(5-15)	0.034
Duration of steroids in months, Median (IQR)		9 (5-24)	6 (5-18)	12 (6-24)	0.001
Number of cDMARds, n(%)	0	33(100%)	19(57.6%)	14(42.4%)	0.614
	1	142(100%)	70(49.3%)	72(50.7%)	
	2	74(100%)	38(51.4%)	36(48.6%)	
	3	4(100%)	1(25.0%)	3(75.0%)	
Durations of cDMARDs in years, Median (IQR)		2 (1-4)	2 (1-3)	2.5 (2-4)	0.018
Biologic users, n(%)		101(100%)	44(43.6%)	57(56.4%)	0.074
Duration of biologics in months, Median (IQR)		6 (6-18)	6 (6-12)	6 (6-24)	0.025

Patients with moderate COVID-19 had significantly higher age than mild type [45 (35-55) vs. 35(30-55), p= 0.022) years; with more BMI (27(24-30)vs. 26.28(23-29), p=0.03], more in number of comorbidities (p<0.001), more steroids users (99 (54.4%)vs. 83 (45.6%), p=0.012], higher steroid dose (0.034), with longer steroid duration (12 (6-24)vs 6 (5-18), had longer duration of cDMARDs (2.5 (2-4) vs 2 (1-3),p=0.018), longer duration of bDMARDs in months(p=0.025).

Most of the patients had rheumatoid arthritis (RA) (95 patient), second in frequency had systemic lupus erythematosus (SLE) (52 patients), and third in frequency had ankylosing spondylitis (AS) (20 patients). Other rheumatic diseases are shown in Figure 1.

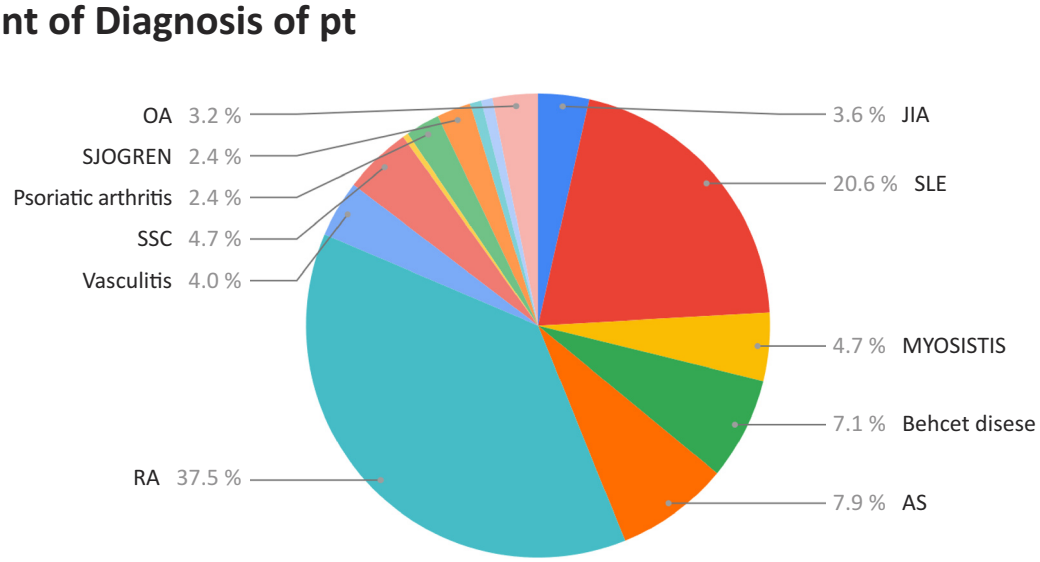

Figure 1. Distribution of COVID -19 patients among rheumatic diseases. OA= osteoarthritis; SSc= systemic sclerosis; RA= rheumatoid arthritis, JIA= juvenile idiopathic arthritis; SLE= systemic lupus erythematosus; AS= ankylosing spondylitis

The most common manifestation of COVID-19 in rheumatic diseases was fever 241, (96%), the second was Cough 229 (91.2%), then myalgia and arthralgia (75%), loss of taste 155 (61.8%), and next SOB 120 (50.2%), then other manifestations as in figure 2.

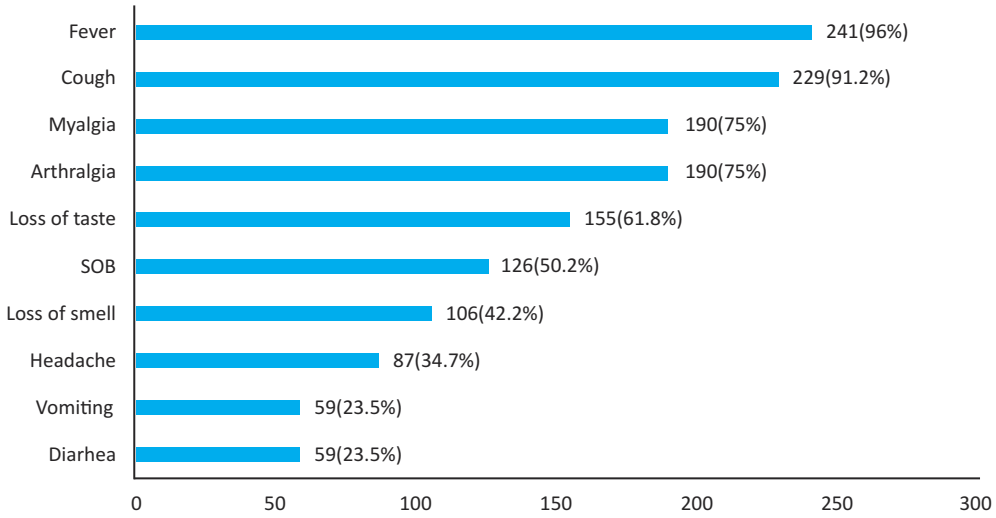

Figure 2. Symptoms of COVID-19 in rheumatic diseases.

There was significant positive correlation between age(r=0.144, p=0.022), BMI(r=0.137, p=0.029), duration of rheumatic diseases(r=0.125, p=0.049), dose of steroids used(r=0.127, p=0.044), duration of cDMARds used(r=0.151,p=0.017), duration of bDMARDs (r=0.142,p=0.025), and number of comorbidities (r=0.345, p<0.0001) with COVID-19 severity (Table 2).

On Using binary logistic regression analysis to control confounders and to predict severity of COVID-19, we found that increasing BMI, duration of biological DMARDs use, and the increasing number of comorbidities were significant independent factors that increase the risk of having more severe COVID-19 (p<0.05, Table 3).

Table 2. Correlation between patients' demographics, rheumatic diseases duration, medications used, and comorbidities with COVID-19 severity.

Variable	Covid19 severity Spearman ρ	P value
Age	0.144	0.022
BMI	0.137	0.029
Duration of rheumatic disease	0.125	0.049
The dose of steroid used	0.127	0.044
Duration of steroids	0.201	0.001
Duration of cDMARDs used	0.151	0.017
Duration of bDMARDs used	0.142	0.025
Number of comorbidities	0.345	<0.0001

Table 3. Binary logistic analysis to predict severity of COVID 19 in rheumatic diseases.

Predictor	p	Odds ratio	95%CI Lower	Upper
Age of the patient	0.733	1.0039	0.98187	1.026
BMI	0.033	1.0762	1.00587	1.151
Duration of diease rheumatic condition	0.780	0.9812	0.85842	1.121
Duration of steroid months	0.516	0.9931	0.97267	1.014
Duration of cDMARD years	0.472	1.0780	0.87845	1.323
Duration of biologics use mth	0.004	1.0394	1.01264	1.067
Steroid use :				
Yes – No	0.244	1.5214	0.75116	3.081
Comorbidity N.				
1 compared to 0	0.076	1.7617	0.94150	3.296
≥2 compared to 0	<.001	8.0546	3.28566	19.745
The dose of steroid used	0.141	1.0277	0.99101	1.066

P of the model <0001; Accuracy of the prediction = 0.70.

BMI - body mass index; cDMARDs - conventional disease-modifying anti-rheumatic drugs

Discussion

To the best of our knowledge, the current study is the first in Iraq that reports the baseline characteristics of rheumatic diseases patients who were infected with "SARS-CoV-2. The median age of moderately-ill cases was statistically higher compared with mild disease, and there was a suggestive reciprocity between age and disease severity. Our discovery was consistent with multiple previously reported studies (6-8).

Female gender was more prevalent (73.9%) as per overall cases, however, this finding is reciprocal to the proportional higher prevalence of rheumatic disease cases in female compared to male. Nonetheless, there was apparently no statistical correlation between gender and disease severity. Our findings were consistent with those reported in earlier studies from various geographical locations (9,10). According to the COVID-19 "Global Rheumatology Alliance physician-reported registry (GRA)", there was no indicative variation in the degree of hospitalization rates regarding male-to-female ratio (11).

In the current study RA was the most common rheumatic disease, followed by SLE and ankylosing spondylitis. A systematic review and meta-analysis done by Xu showed that the utmost prevailing rheumatic disease was RA (33.7%), superseded by Spondyloarthritis (22.0%) and SLE (14.3 %) (12). In their cohort study, Esatoglu *et al.,* (2021) found that RA is the most common "rheumatic disease" (36 %), followed by Spondyloarthritis (25%) and Connective tissue disease (18%) (13).

Among the "COVID-19 symptoms, fever, cough, myalgia, and arthralgia were the most commonly reported symptoms by our patients" (96%, 91.2%, 75%, and 75%, respectively). In the study conducted by Alzahrani *et al*., (2021), "fever, myalgia, and cough" were the utmost prevailing divulged symptoms (78.7%, 78.7%, and 74.5 percent, respectively) (8). A report from the German registry showed that the utmost prevailing divulged symptoms of COVID-19 included cough (69%), fever (59%), and fatigue (42%) (9). This finding is in accordance with another Unicenter Iraqi study conducted by Darweesh *et al*., 2021, which confirmed that most cases are mild upon admission (14).

In the current study, 50.6% of patients had mild COVID-19, and 49.4% had the moderate disease; 18% of patients required oxygen support, no patient was treated in hospital, and there was no reported death. A further Unicenter Iraqi research by Darweesh *et al.,* 2021 revealed similar symptoms (14). A systematic review of studies conducted by Sood *et al*., (2021) Evaluating the result of COVID-19 infection in the treatment and biologics of rheumatic patients revealed that Most patients had a benign clinical course, with low case fatality (15). According to this study, patients with moderate disease tended to be more steroid users, with higher doses and longer duration of steroid usage compared with a mild one.

Data from COVID-19 GRA physician-reported registry showed that glucocorticoids increase the risk of severe disease. Unlike GRA, where only a prednisolone dose of 10 mg or higher was delineated to be conjoin with an exaggeration of plunge for severe illness, any glucocorticoid dose was associated with a poorer outcome in a Turkish cohort study (11, 13). Glucocorticoids could have an anti-inflammatory impact to reduce the serious symptoms of the hyper-inflammatory phase; nevertheless, they may augment viral proliferation in the disease in its early stage by weakening innate immune (13).

Our findings afford that DMARDs (both conventional and biologic) use was not associated with COVID-19 severity, which is similar to the results of other studies. Estimation of preponderance and magnitute of COVID-19 by epidemiologic surveys betwixt patients handeled with bDMARDs and targeted synthetic DMARDs (tsDMARDs) did not reveal an increased risk owed to these agents (16-19). The GRA registry has shown that the use of bDMARDs or tsDMARDs is not related to hospitalization or death. In fact, a patient treated with TNF-α inhibitors had a 60% lower risk of hospitalization (11). A study conducted by Esatoglu *et al.,* (2021), showed a reduced risk of worse outcomes in RD patients using csDMARD. It is interesting to note the increase in the prevalence of COVID-19 in inflammatory RD patients not using csDMARD in observational, multi-centre studies including 1641 inflammatory RD patients, which suggest that csDMARDs may have a protective effect against COVID-19 (20). Our study showed that the duration of biological DMARDs use was a significant independent factor that fortifies the fortuity of having more sunder COVID-19. We have no clear explanation for that; however, it may be possible that the longer duration of biological DMARDs usage, the greater chance to have more profound immunosuppression, and subsequently higher risk of infection.

In line with previous studies, there was a significant positive correlation between numbers of comorbidities and COVID-19 severity and has been found as significant independent factors that increase the risk of having more severe COVID-19 (11, 21, 22).

Our study revealed that patients with moderate COVID-19 had significantly greater BMI compared with mild disease, and the association remains significant after adjusting for other confounders. The findings in this study are comparable to those of previous reports, which showed that people who are overweight or obese have a plunger fortuity of more sunder COVID-19–related illness (23,24). Obesity is a well-known contributing factor for serious COVID-19 infection. It is thought to be linked to chronic inflammation that changes immunological, thrombogens and obesity-induced lung function (25, 26).

Disease duration is generally considered a risk factor for infections (27). However, disease duration may be confounded with other factors, like age, disease activity, and the presence of comorbidities, and this may explain the significant positive correlation between disease duration and COVID-19 severity in our study; however, it was not found to be a significant independent factor for having more severe COVID-19.

In the current study, there was no association between specific rheumatic disease diagnosis and COVID-19 severity. Three studies found no association between RD diagnoses and a poorer outcome (10, 13, 21), and two other studies reported a higher risk of severe COVID-19 in patients with conditions other than inflammatory arthritis such as vasculitis, connective tissue diseases, and sarcoidosis (22,28).

The main strength of our study is that it is the first to report COVID-19 infection among patients with rheumatic diseases in Iraq. All findings have been detailed by a rheumatologist from several centers in Iraq, which exhort that our discoveries are more global than one-center or local research. The most important limitation of our study is a possible bias towards the inclusion of patients with a more benign course, attending outpatient or private rheumatology clinics. This is evidenced in our cohort's lack of death or hospital admission. We should acknowledge that the majority of patients with COVID-19 preferred to be treated at home, even those with more severe disease courses. Rheumatologists may not be aware of the death of patients that happened at home or in other hospitals. Since the study criteria for the inclusion of people with rheumatic illnesses and COVID-19 were limited, this prevented comparisons between those without rheumatic disease and those without COVID-19 rheumatic disease. This limits our insight into group comparisons and exposes sub-groups that are more at plunge betwixt patients with RD, however they cannot estimate their plunge compared to the broad patient population of COVID-19.

Conclusion

COVID-19 infection betwixt patients with rheumatic diseases tend to have mild-moderate disease course; BMI, duration of biological DMARDs use, and the number of comorbidities were significant independent factors that increase the risk of having more severe COVID-19.

Author contributions

All authors have equally contributed to the study; see details below.

F.I.G; A.A.Y; S.W.M; and N.A.J. designed this study, collected data and wrote this manuscript
A.A. and F.J.M. corrected the final text of the manuscript.
A.MA.M. and M.M.Y. participated in data collection and manuscript writing.
T.A.Q. participated in the retrieval of clinical data.
C.H.M. and N.I.A. dealt with statistical analysis.
M.H.A. and D.S.Y. managed the entire project and the final data processing.
All authors examined and approved the final version of the paper.

Adherence to Ethical Standards

The authors declare that the study is registered and conducted in adherence to ethical standards.

Declaration of interest

No conflict of interest is declared by authors.

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