



# Clinical characteristics and outcome of COVID-19 in patients with rheumatic diseases

Zeyad A. Alzahrani<sup>1,2,4</sup> · Khalid Abdullah Alghamdi<sup>2,4</sup> · Ahmed Saeed Almaqati<sup>3,4</sup>

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## Abstract

This study aimed to assess the baseline characteristics and clinical outcomes of coronavirus disease 2019 (COVID-19) in patients with rheumatic diseases and identify the risk factors associated with severe COVID-19 pneumonia. This was a retrospective study in a tertiary care center conducted through the period between March 2020 and November 2020 and included all adult patients with rheumatic diseases who tested positive on the COVID-19 polymerase chain reaction (PCR) test. We assessed the patients' demographic data, history of rheumatic disease, COVID-19 symptoms and experimental treatment, if any, their disease course, and outcome. In all, 47 patients were included, and most were females. The commonest rheumatic diseases were rheumatoid arthritis (53.2%), followed by systemic lupus erythematosus (21.3%), and psoriatic arthritis (10.6%). Methotrexate and hydroxychloroquine were the most commonly used disease-modifying anti-rheumatic drugs in 36.1% and 25.5%, respectively. Out of 47 patients, 48.9% required hospitalization with a median hospital stay of 7 days. Severe COVID-19 pneumonia, defined as clinical signs of pneumonia plus one of the following: respiratory rate > 30 bpm, severe respiratory distress, or oxygen saturation < 90% in room air was observed in 19.1% of the patients, and one patient died. We found that elderly patients with a mean age of 65.3 years were more likely to develop severe COVID-19 pneumonia and that was statistically significant. Our study showed that elderly patients with a mean age of 65 years and having rheumatic diseases had an increased risk of hospital admission and development of severe COVID-19 pneumonia.

**Keywords** COVID-19 · Rheumatic diseases · Antirheumatic drugs

## Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic. It was first reported in Wuhan, China, after a cluster of cases of community-acquired pneumonia showed similar clinical and biochemical

characteristics. COVID-19 symptoms and outcomes range from asymptomatic with a benign course to multi-organ failure and acute respiratory distress syndrome (ARDS) and death [1]. To date, more than 100 million cases have been reported, with more than 2.2 million deaths worldwide [2]. The World health organization (WHO) has defined the severity of COVID-19 in adult patients based on the clinical and radiological presentations into mild, moderate, severe, and critical. Mild COVID-19 is defined as symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. Moderate disease is defined as the presence of clinical signs of pneumonia, e.g., fever, cough, dyspnea, high respiratory rate, without signs of severe pneumonia, including SpO<sub>2</sub> of ≥ 90% in room air. Severe COVID-19 pneumonia is defined as the presence of clinical signs of pneumonia plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO<sub>2</sub> < 90% in room air. Finally, critical disease is considered as the development of sepsis, septic shock, ARDS, or acute thrombosis [3]. Multiple poor prognostic factors have

✉ Ahmed Saeed Almaqati  
almaqatias@gmail.com

<sup>1</sup> Medicine/Rheumatology, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia  
<sup>2</sup> Department of Rheumatology, King Abdulaziz Medical City, Ministry of National Guard-Health Affairs, Jeddah, Saudi Arabia  
<sup>3</sup> Department of Internal Medicine, King Abdulaziz Medical City, Ministry of National Guard-Health Affairs, Jeddah, Saudi Arabia  
<sup>4</sup> King Abdullah International Medical Research Center, Jeddah, Saudi Arabia

been identified, including advanced age, obesity, smoking history, diabetes mellitus, and immunosuppression [4].

Patients with rheumatic diseases are predisposed to infections due to their disease background, especially when they have active disease and when they are on immunosuppressive medications. However, during the COVID-19 pandemic, conflicting results of the clinical course were seen in patients with connective tissue diseases infected with SARS-CoV-2. A study by Pablos et al. found that patients with connective tissue diseases are more likely to develop severe COVID-19 [5]. In contrast, a case series from New York showed that there was no difference in the rate of hospitalization between patients with immune-mediated inflammatory diseases and the general population [6].

In patients with connective tissue diseases, available data from the COVID-19 Global Rheumatology Alliance physician-reported registry found that the use of conventional disease-modifying anti-rheumatic drugs (DMARDs) alone or in combination with biologics/Janus Kinase inhibitors was not associated with an increased rate of hospitalization [7].

Several medications that are used in the treatment of different rheumatic diseases have been explored for the treatment of COVID-19, e.g., hydroxychloroquine [8], corticosteroids [9], tocilizumab [10], and anti-TNF with variable results. A systematic review and meta-analysis by Michael Putman et al. that included 45 articles reporting the use of anti-rheumatic therapies in COVID-19 treatment found that hydroxychloroquine did not significantly change the COVID-19 outcome. Two cohort studies with a high risk of bias showed that anakinra were associated with decreased mortality rate. Evidence about other anti-rheumatic therapies in the treatment of COVID-19 was inconclusive [11].

Therefore, due to a paucity of research data about COVID-19 in patients with rheumatic diseases in our region, we conducted this study to assess the baseline characteristics and clinical outcomes of COVID-19 in these patients and determine the risk factors associated with the development of severe COVID-19.

## Methods

This was a single-center study conducted in a tertiary care center in the Western Region of Saudi Arabia.

## Patients

The study included all adult patients aged  $\geq 18$  years who tested positive on the COVID-19 polymerase chain reaction (PCR) test and had been diagnosed with rheumatic diseases based on the approved classification criteria. We included patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriatic arthritis (PsA), mixed

connective tissue disease (MCTD), Sjogren's syndrome, dermatomyositis, polymyositis, spondyloarthritis (SpA), and juvenile idiopathic arthritis (JIA). Patients with crystal-induced arthritis, fibromyalgia, and osteoarthritis were excluded from the study as the management of these conditions does not include immunosuppressive medications.

We included all patients who met our inclusion criteria in the study during the period between March 2020 and November 2020. The patients' electronic medical records were reviewed, and their demographic and clinical data were collected by trained rheumatologists.

## Main outcome variable

There is no age cut-off defined by the WHO to categorize the elderly population; however, the United Nations (UN) refers to elderly individuals as those aged 60 years and above. We considered this age as the cut-off to define advanced age in our cohort [12]. We defined severe COVID-19 pneumonia based on the WHO guidance as the presence of clinical signs of pneumonia plus one of the following: respiratory rate  $> 30$  bpm, severe respiratory distress, or oxygen saturation  $< 90\%$  in room air.

Our data collection sheet included the patients' demographic data, history of rheumatic disease, COVID-19 symptoms, COVID-19 experimental treatment, the clinical course of the disease, and outcome. The patients' demographic data included age, sex, body mass index (BMI), and history of smoking and diabetes. In addition, details of the rheumatic disease, including the type of rheumatic disease, intake of steroids or disease-modifying anti-rheumatic drugs (DMARDs) at the time of diagnosis, and whether if it were held during COVID-19 illness or not. We also collected data about the course of COVID-19, including receiving experimental treatment, need for hospitalization, ICU admission, oxygen therapy or invasive ventilation, and/or death.

## Procedures

The diagnosis of COVID-19 was confirmed as a positive test of samples obtained by nasopharyngeal swab and tested on the approved diagnostic reverse transcription-polymerase chain reaction (RT-PCR) test, the RealStar<sup>®</sup> SARS-CoV-2 RT-PCR kit 1.0 (Altona Diagnostics, Hamburg, Germany).

## Statistical analysis

Descriptive statistics are presented as numbers, percentages, mean, standard deviation, and median (min–max) whenever appropriate. Between comparisons, Fisher's Exact test, independent *t*-test, or Mann Whitney *U* test were applied, and a *p* value  $< 0.05$  was considered statistically significant. The normality of variables was tested using the

Kolmogorov–Smirnov test, as well as the Shapiro–Wilk test. The data showed normal distribution; thus, parametric methods were applied. All data analyses were performed using Statistical Packages for Social Sciences (SPSS) version 21 Armonk, NY: IBM Corporation.

## Results

We analyzed the clinical characteristics of 47 patients with an established diagnosis of rheumatic disease who tested positive for COVID-19. The mean age of the patients was  $50.8 \pm 17.1$  years, and most of them were females (87.2%). The median BMI value was  $28 \text{ kg/m}^2$  (14–59  $\text{kg/m}^2$ ). The prevalence of smoking was 8.5%, and that of diabetes was 14.9%. The proportion of patients taking steroids was 44.7%, while that of those taking DMARDs was 93.6%. However, almost 60% of the patients had discontinued medication due to COVID-19 illness, as shown in Table 1.

In the study cohort, the most prevalent rheumatic diseases were RA (53.2%), followed by SLE (21.3%), and PsA (10.6%). The mean rheumatic diseases duration was  $7 \pm 4$  years. The most commonly used DMARDs were methotrexate (36.1%) followed by hydroxychloroquine (25.5%), as presented in Table 1.

With respect to the COVID-19 symptoms and receiving experimental treatment, only one patient was asymptomatic, as shown in Table 2. The most commonly reported symptoms were fever and myalgia (78.7% each), followed by cough (74.5%) and arthralgia (70.2%). The incidence of gastrointestinal symptoms was the lowest, with nausea and vomiting seen in 25.5% of the patients. Furthermore, 19.1% of the patients received experimental treatment for COVID-19, with dexamethasone being the most commonly prescribed medication (66.7%).

Almost 50% of the patients were admitted to the hospital with a median hospital stay of 7 days (1–111). Only 16 patients (34%) had evidence of pneumonia, of which only nine met the guidance criteria for severe COVID-19 pneumonia. Five patients (10.6%) were admitted to the intensive care unit (ICU), and three patients required invasive ventilation (6.4%). One elderly patient with RA who was on rituximab therapy died during the course of the study.

All the three patients who required invasive ventilation were females who were on baseline DMARDs: rituximab, adalimumab, and etanercept, respectively, which were discontinued during the COVID-19 illness. Of these, the patient who died had received her rituximab dose five months prior to the COVID-19 infection.

On analyzing the characteristics of patients with severe COVID-19 pneumonia, it was found that advanced age with a mean of 65.3 years was the only statistically significant factor ( $p = 0.003$ ). This was about 18 years older than those

**Table 1** Baseline characteristics of the patients ( $n = 47$ )

Study variables	N (%)
Age in years (mean $\pm$ SD)	$50.8 \pm 17.1$
BMI $\text{kg/m}^2$ [median (min–max)]	28.0 (14–59)
Gender	
Male	6 (12.8%)
Female	41 (87.2%)
Smoking	
Yes	4 (08.5%)
Diabetes	
Yes	7 (14.9%)
Steroids use	
Yes	21 (44.7%)
Disease-modifying anti-rheumatic drugs (DMARDs) use	
Yes	44 (93.6%)
Stopped medications during COVID-19 illness	
Yes	28 (59.6%)
Type of rheumatic disease	
Rheumatoid arthritis	25 (53.2%)
Systemic lupus erythematosus	10 (21.3%)
Psoriatic arthritis	5 (10.6%)
Mixed connective tissue disease	2 (4.3%)
Sjogren's syndrome	1 (2.1%)
Dermatomyositis	1 (2.1%)
Polymyositis	1 (2.1%)
Spondyloarthritis	1 (2.1%)
Juvenile idiopathic arthritis	1 (2.1%)
Rheumatic diseases duration in years (mean $\pm$ SD)	$7 \pm 4$
Baseline DMARDs	
Methotrexate	17 (36.1%)
Hydroxychloroquine	12 (25.5%)
Methotrexate plus adalimumab	4 (8.5%)
Adalimumab	2 (4.3%)
Hydroxychloroquine plus azathioprine	1 (2.1%)
Hydroxychloroquine plus rituximab	1 (2.1%)
Methotrexate plus etanercept	1 (2.1%)
Canakinumab	1 (2.1%)
Secukinumab	1 (2.1%)
Etanercept	1 (2.1%)
Tocilizumab	1 (2.1%)
Azathioprine	1 (2.1%)
Rituximab	1 (2.1%)
Off DMARDs	3 (6.4%)

who did not develop severe disease. Other baseline characteristics did not significantly influence the course of the disease (all  $p > 0.05$ ), as presented in Table 3. Among those with severe COVID-19, 8 out of 9 patients were females. None of the nine patients were smokers, and all of them were on DMARDs; however, seven patients (77.8%) had

**Table 2** COVID-19 symptoms and experimental treatment ( $n = 47$ )

Variables	<i>N</i> (%)
Asymptomatic	
Yes	1 (2.1%)
Symptoms <sup>a</sup>	
Fever	37 (78.7%)
Myalgia	37 (78.7%)
Cough	35 (74.5%)
Arthralgia	33 (70.2%)
Dyspnea	29 (61.7%)
Loss of smell	29 (61.7%)
Headache	29 (61.7%)
Loss of taste	28 (59.6%)
Sore throat	22 (46.8%)
Diarrhea	18 (38.3%)
Nausea and/or vomiting	12 (25.5%)
Received COVID-19 experimental treatment	
Yes	9 (19.1%)
COVID-19 experimental treatment ( $n = 9$ )	
Dexamethasone	6 (66.7%)
Tocilizumab	1 (11.1%)
Dexamethasone + tocilizumab	1 (11.1%)
Hydroxychloroquine + azithromycin	1 (11.1%)

<sup>a</sup>Variable with multiple responses

discontinued their medications due to COVID-19 illness. RA was the most prevalent rheumatic disease (55.6%), followed by PsA (22.2%), while the most commonly used DMARDs were hydroxychloroquine, methotrexate, and the combination of methotrexate with adalimumab (22.2% each).

## Discussion

This study conducted in a tertiary care hospital presents the baseline characteristics of patients with rheumatic diseases who were infected with SARS-CoV-2. Older patients with a mean age of 65.3 years were found to be at a higher risk of getting severe COVID-19 pneumonia, which is consistent with multiple previously reported studies. Data from the French RMD COVID-19 cohort reported that age was a risk factor for severe disease; only 11 patients between the age of 18 and 54 years developed severe COVID-19, while cases increased to 20 between the age of 65 and 74 years and to 45 in patients > 75 years [13]. Furthermore, the mortality rate was higher in the elderly patients, as shown in a recent publication by the COVID-19 Global Rheumatology Alliance physician-reported registry, which found that 68.7% of those who died were > 65 years old [14].

Most of our study subjects were female (87.2%), which is consistent with the natural history of female predominance

in autoimmune diseases. This reflects the higher percentage of females developing severe COVID-19 pneumonia (88.9%) and those who required invasive ventilation in our cohort. This is in contrast to multiple reported papers from different geographical areas [15, 16]. For instance, the COVID-19 Global Rheumatology Alliance physician-reported registry found that there was no significant difference in the rate of hospitalization based on sex [7]. However, sex was not found to be a statistically significant factor for hospital admission or severity of the disease. In addition, we found a low prevalence of smoking in our subjects; however, none of the smokers developed severe COVID-19 pneumonia, which is not in line with a large meta-analysis by Patanavanich et al. who found that smoking was associated with poor prognosis [17]. These differences could be due to the small sample size in our study and the low prevalence of female smokers in the Saudi culture.

In a study by Zhong et al., they traced patients with rheumatic diseases who lived with family members who were tested positive for SARS-CoV-2. They found that patients with rheumatic diseases had a higher predisposition for SARS-CoV-2 infection compared to other family members [18]. Moreover, adjusted multivariable analysis by Freitas Nuñez et al. for sex, age, and comorbidities associated with COVID-19 found that higher age and presence of autoimmune diseases had a higher probability of hospitalization, regardless of other factors [19]. Furthermore, a comparative cohort study by D'Silva et al. found that a history of rheumatic disease was associated with an increased rate of invasive ventilation than the control group, though both had identical clinical features and rates of hospitalization [20]. Nevertheless, no specific rheumatic disease was found to be a statistically significant risk factor for hospitalization or severity of the disease in our study. However, multivariate analysis in a study by Fernandez-Gutierrez et al. showed that some autoimmune diseases, namely Sjogren's syndrome, polyarthritides, Raynaud, and MCTD, are associated with higher rates of hospital admissions [21]. Among risk factors other than rheumatic diseases, the Brescia Rheumatology COVID-19 Study Group found no difference in the comorbidities between deceased or alive patients [22]. In contrast, a recent review concluded that not only rheumatic diseases can affect COVID-19 outcome, but also the other comorbidities those patients have, which necessitates patients stratification based on the presence and number of comorbidities especially during the pandemic to aid in predicting outcome [23].

Our study showed that no specific DMARDs were associated with severe COVID-19 pneumonia, and none of them was found to be statistically significant, which is similar to the results of a study by Santos et al. [24]. Likewise, another publication showed similar findings, wherein baseline rheumatic therapies did not alter the mortality

**Table 3** Characteristics of severe COVID-19 pneumonia ( $n = 47$ )

Factor	Severe COVID-19		$X^2$	$p$ value <sup>§</sup>
	Yes $N$ (%) ( $n = 09$ )	No $N$ (%) ( $n = 38$ )		
Age in years (mean $\pm$ SD) <sup>a</sup>	65.3 $\pm$ 14.5	47.3 $\pm$ 16.0	3.083	0.003**
BMI kg/m <sup>2</sup> [median (min–max)] <sup>b</sup>	29.5 (22–39)	28.5 (14–59)	0.110	0.925
Gender				
Male	1 (11.1%)	5 (13.2%)	0.027	1.000
Female	8 (88.9%)	33 (86.8%)		
Smoking				
Yes	0	4 (10.5%)	1.035	0.574
No	9 (100%)	34 (89.5%)		
Diabetes				
Yes	3 (33.3%)	4 (10.5%)	2.986	0.084
No	6 (66.7%)	34 (89.5%)		
Steroids use				
Yes	5 (55.6%)	16 (42.1%)	0.533	0.486
No	4 (44.4%)	22 (57.9%)		
DMARDs use				
Yes	9 (100%)	35 (92.1%)	0.759	1.000
No	0	3 (7.9%)		
Stopped medications during COVID-19 illness				
Yes	7 (77.8%)	21 (55.3%)	1.532	0.216
No	2 (22.2%)	17 (44.7%)		
Type of rheumatic disease				
Rheumatoid arthritis	5 (55.6%)	20 (52.6%)		
Psoriatic arthritis	2 (22.2%)	3 (7.9%)		
Systemic lupus erythematosus	1 (11.1%)	9 (23.7%)	7.600	0.517
Polymyositis	1 (11.1%)	0		
Sjogren's syndrome	0	1 (2.6%)		
Mixed connective tissue disease	0	2 (5.3%)		
Dermatomyositis	0	1 (2.6%)		
Spondyloarthritis	0	1 (2.6%)		
Juvenile idiopathic arthritis	0	1 (2.6%)		
Baseline DMARDs				
Hydroxychloroquine	2 (22.2%)	10 (28.6%)	13.692	0.255
Methotrexate	2 (22.2%)	15 (42.9%)		
Methotrexate + adalimumab	2 (22.2%)	2 (5.7%)		
Adalimumab	1 (11.1%)	1 (2.9%)		
Etanercept	1 (11.1%)	0		
Rituximab	1 (11.1%)	0		
Azathioprine	0	1 (2.9%)		
Tocilizumab	0	1 (2.9%)		
Secukinumab	0	1 (2.9%)		
Canakinumab	0	1 (2.9%)		
Methotrexate + etanercept	0	1 (2.9%)		
Hydroxychloroquine + rituximab	0	1 (2.9%)		
Hydroxychloroquine + azathioprine	0	1 (2.9%)		

<sup>a</sup> $p$  value has been calculated using Independent  $t$ -test<sup>b</sup> $p$  value has been calculated using Mann Whitney  $U$  test<sup>§</sup> $p$  value has been calculated using Fischer's exact test\*\*Significant at  $p < 0.05$  level



rate [25]. In contrast, the COVID-19 Global Rheumatology Alliance physician-reported registry found that biological DMARD/targeted synthetic DMARD monotherapy was associated with lower rates of hospital admissions [7]. However, inferred results from a systematic review suggested that patients with rheumatic diseases on chronic immunosuppressive medications are more likely to require ICU admissions and invasive ventilation [26].

Among the COVID-19 symptoms, fever, myalgia, and cough were the most commonly reported symptoms by our patients (78.7%, 78.7%, and 74.5%, respectively), which is consistent with the report of a German registry [15].

During the early days of the pandemic with a lack of evidence-based knowledge about the course of COVID-19 and the prognosis in immunocompromised patients, one of our national policies was to admit all immunocompromised patients diagnosed with COVID-19 for close monitoring, regardless of their disease severity, resulting in a high admission rate in our study (48.9%). However, only 19.1% of these patients had severe COVID-19 pneumonia based on the WHO definition [3]. Similarly, a high rate of admissions for such patients was reported in the literature, one of which was published by Freites Nuñez et al., who reported an admissions rate of 44%; however, our ICU admissions rate was higher [19]. Few of our patients received experimental treatments for COVID-19, with dexamethasone being the most frequently prescribed drug after the release of preliminary findings of the RECOVERY trial [9].

Our cohort showed a significantly low rate of mortality (2.1%) compared to multiple studies worldwide reporting a mortality rate ranging from 6 to 19% [7, 20, 27]. The only deceased patient was an elderly female who was known to have RA and was on rituximab. She was one of the two patients-receiving rituximab as baseline DMARD for their rheumatic disease, which is reported to be associated with increased adverse events and high mortality rates in patients with COVID-19 [28]. The patient's hospital course was complicated with the development of cytokine release syndrome, for which she received an experimental tocilizumab dose and required invasive ventilation.

The following are a few limitations of our study. First, it was a single-centered study with small sample size. However, this is the first paper from our region addressing the baseline characteristics and clinical outcome of COVID-19 in patients with rheumatic diseases. The second limitation is the retrospective study design, which limits our ability to assess for rheumatic disease activity, as the patients were being managed and seen by non-rheumatologists during that COVID-19 illness. Moreover, they were isolated to minimize contact with multiple physicians. Finally, cumulative doses of steroids were not documented due to a lack of data.

## Conclusion

The current study suggests that elderly patients with a mean age of 65 years with rheumatic diseases are more likely to have a poor outcome in terms of developing severe COVID-19 pneumonia. The other variables were not statistically significant. Further large studies are necessary in this field to assess COVID-19 outcomes in patients with rheumatic disease.

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