

## The prevalence of Covid-19 in patients with Rheumatoid Arthritis receiving classic Disease-Modifying Anti Rheumatic Drugs

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The aim of the current study was to investigate the prevalence of Covid-19 in patients with rheumatoid arthritis who used classic disease-modifying anti-rheumatic drugs (DMARDs). In this descriptive study that was performed in Loghman-Hakim Hospital (Tehran, Iran) between 2011 and 2020, patients with RA who were referred to the hospital were assessed based on age, sex, medications, comorbidities, smoking, duration of RA, history of Covid-19 in a first-degree relative, history of Covid-19 in the patient, and Covid-19 symptoms.

Of one thousand patients with RA, the mean age was 53.84 years old, and 72.3% were female. Covid-19 prevalence among patients with RA was 10.4%. The prevalence of Covid-19 in patients who used sulfasalazine was significantly higher (14.3%) than in patients who did not take it (8.9 %) (OR = 1.72; 95% CI,  $p$  value = 0.011). Hydroxychloroquine was the most generally utilized drug among Covid-19 patients. However, there was no correlation between the prevalence of Covid-19 and the use of hydroxychloroquine ( $p$  value = 0.779). In RA, self-quarantine lowered the risk of Covid-19 by around 60% (OR = 0.382; 95% CI (0.225 - 0.650)). In these patients, cardiac disease exhibited a significant correlation with Covid-19 prevalence ( $p$  value < 0.001). Covid-19 has no higher prevalence in RA patients taking classic DMARDs than in the general population. The most common medicine among RA patients was hydroxychloroquine, which could be one of the reasons why these people did not develop Covid-19.

**Keywords:** Antirheumatic agents, Arthritis drug therapy, COVID-19, Rheumatoid arthritis

### Introduction

In December 2019, a new type of pneumonia caused by the intervention of a new member of the CORONOVIRIDAE family, SARS-COV-2 (Acute Respiratory Syndrome Coronavirus 2), was identified in Wuhan Province, China [1]. SARS-COV-2 disease is characterized by dry cough, fever, shortness of breath, fatigue, anosmia, dysgeusia, and lymphopenia [2-4]. In more severe cases (15-20% of patients), onset may become more complicated with interstitial pneumonia with alveolar injury, which can clinically lead to acute respiratory distress syndrome (ARDS) and even death [5]. Coronavirus became a pandemic and forced the World Health Organization (WHO) to address the disease as a public health emergency and international concern on January 30, 2020 [6]. People with inflammatory diseases such as rheumatoid arthritis (RA)

need special attention against acute coronavirus 2 (SARS-COV-2), especially against inflammatory-induced agents following coronavirus. Many of these people are at risk of severe infection, because they use immunosuppressive medications [7-9]. Patients with rheumatic disorders who are using immunosuppressive agents in the Covid-19 period may also be at risk [10]. However, some disease-modifying drugs commonly used to treat rheumatic diseases, including hydroxychloroquine, have been used as possible treatments for Covid-19 [11]; however, more research is needed on whether immune-suppressive drugs increase the risk of severe SARS-COV-2 infection in people with rheumatoid arthritis [12]. Assessing the prevalence of COVID-19 in patients with RA is important, because these patients use immunosuppressive medications such as classic disease-

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modifying antirheumatic drugs (DMARDs), and it had said that immunosuppression is one of the risk factors for higher mortality in corona disease [13-14]. The current study aimed to investigate the prevalence of Covid-19 in RA patients receiving classical DMARDs in Iran.

## Materials and Methods

This descriptive study was performed on all patients with RA who took classic DMARDs and referred to Loghman-Hakim Hospital (Tehran, Iran) from 2011 to 2020.

Inclusion criteria were taking classic DMARDs (hydroxychloroquine, methotrexate, leflunomide, sulfasalazine), RA involvement, referring to the hospital within the study period, and older than 18 years of age. Exclusion criteria were using biological DMARDs and having any other rheumatologic disorder.

Out of the 1264 patients who referred to the clinic or rheumatology department of Loghman Hospital, 1000 patients were enrolled in the study during the ten years; others were not enrolled due to reasons like death, unwillingness to participate, having other rheumatologic diseases, or using biological drugs. RA for all patients was diagnosed according to ACR criteria (1987) from clinical or admission data. After extracting the information of RA patients receiving classical DMARDs who had referred to the hospital clinic, the patients were contacted by phone. After each patient gave consent to participate in the study and was ensured of the confidentiality of their information, questions about demographic information, medications, comorbidities, smoking, duration of RA, history of Covid-19 in first-degree relatives, history of Covid-19 in the patient, Covid-19 symptoms (including dry cough, shortness of breath, fever, headache, chest pain, sore throat, olfactory and taste disturbances, headache, muscle aches, bruising or fatigue, diarrhea, nausea and vomiting, or abdominal pain) were asked of all patients. Patients were also asked about the diagnostic test used, if any (including PCR from nasal swab, blood immunoglobulin test (IgG and IgM), and lung CT scan). If the patient had not had diagnostic testing done, they were invited to the hospital for serological tests (IgG and IgM), nasal swab PCR, and lung CT scan. Patients were also asked about self-quarantining during this period. The research procedure was accepted by the ethics committee (IR.SBMU-.MSP.REC.1399.329) of Shahid Beheshti University of Medical Sciences.

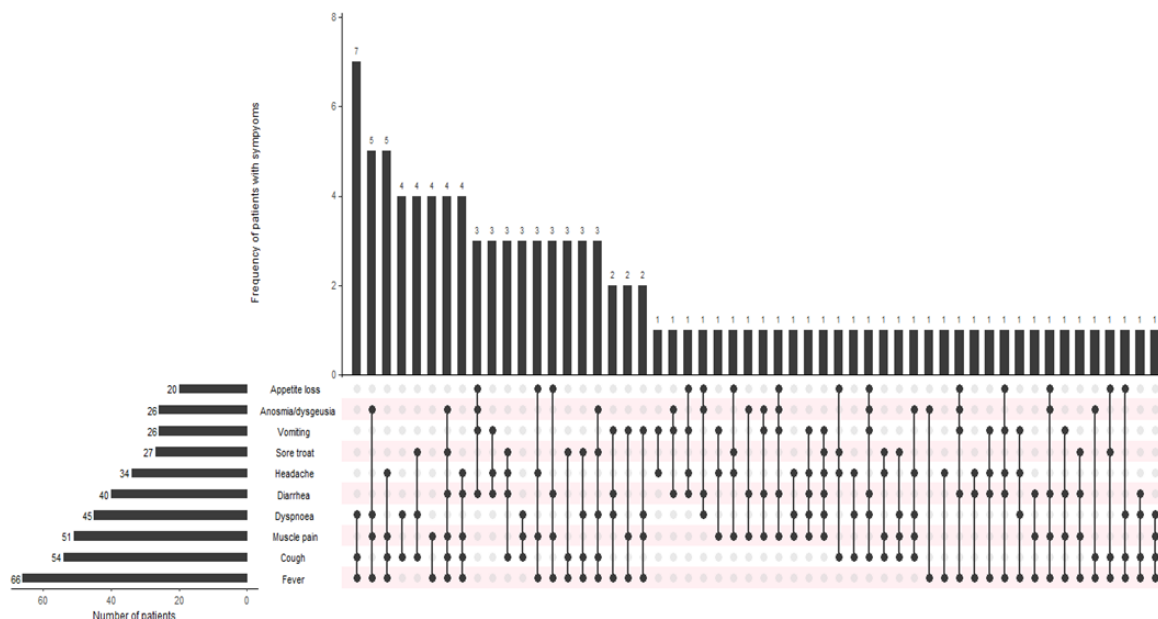
## Statistical Analysis

Quantitative data was displayed using mean and standard deviation, and qualitative data was displayed using frequency and percentage. Independent t-test and chi-square test were used to analyze the data. If necessary, the *p* value of Fisher's exact test was reported. Univariate logistic regression was used to estimate the odds ratio of Covid-19. Moreover, the

upset plot was used to show the symptoms of patients with Covid-19. The significance level was considered 0.05 for statistical tests. SPSS statistical software version 20 and R version 3.6.1 were used for data analysis.

## Results

This study evaluated 1000 RA patients, the mean age of whom was 53.84 years with a standard deviation of 13.51 years. The youngest patient was 19 years old, and the oldest patient was 84 years old. Among the subjects, 227 (27.7%) were male, and 723 (72.3%) were female. Forty-two patients were smokers (4.2%). The duration of RA disease was less than five years among 308 patients, between five and ten years among 217 patients, between ten and 15 years in 199 patients, and over 15 years for 276 patients. The DMARDs with the highest frequency of use by patients were hydroxychloroquine (622 patients) and methotrexate (574 patients). Two hundred and seventy-nine patients were taking sulfasalazine, and 220 were taking leflunomide. Approximately 81% of the patients used NSAIDs, and 80.1% of patients used prednisolone. Six hundred and eighty patients had at least one underlying disease. The most common underlying diseases among patients were pulmonary (46.7%), hypertension (23.2%), hyperlipidemia (12.9%), diabetes (10.5%), cardiac disorders (8.4%), cancer (0.5%), and other diseases (8.8%), respectively. One hundred and thirteen patients reported having at least one of the symptoms of Covid-19 disease, and 104 of whose Covid-19 diagnosis was confirmed (the blood test of nine others was negative). The prevalence of Covid-19 among patients with RA was 10.4%. The definitive diagnoses were made by blood serology tests in 48 patients, CT scans in 31 patients, and the swab method in 25 patients. Among patients with Covid-19, 11 (10.6%) had two symptoms, 30 (28.8%) had three, 44 (42.3%) had four, 9 (8.7%) had five, and 10 people (9.6%) had six symptoms, respectively. Symptoms included fever, cough, muscle pain, dyspnea, sore throat, loss of sense of smell and taste (dysgeusia and anosmia), headache, anorexia, diarrhea, and vomiting. Among patients diagnosed with Covid-19, 66 (63.5%) had a fever, 54 (51.9%) had a cough, 51 (49%) had body aches, 45 (43.3%) shortness of breath, 26 (25%) sore throat, 34 (32.7%) headache, 20 (19.2%) anorexia, 40 (38.5%) diarrhea, 26 (25%) vomiting, and 26 (25%) had dysgeusia and anosmia. In terms of the concurrence of symptoms, five Covid-19 patients had fevers, coughs, and dyspnea; five Covid-19 patients had fevers, coughs, muscle pain, and headaches; four patients had a fever, cough, muscle pain, sore throat, dysgeusia, anosmia, and diarrhea; four patients had a fever, cough, muscle pain, dyspnea, headache, and diarrhea; four patients had a cough, dyspnea, and sore throat; four people had a fever and muscle pain; four people had a cough and dyspnea ([Figure 1](#)).



**Figure 1.** The upset diagram shows symptoms in patients with Covid-19. Each vertical line at the end of the graph is related to the combination of complications observed between patients. Each of the circles on the vertical lines indicates the presence of a symptom in the person. Each vertical bar at the top of the figure represents the frequency of the number of patients by combining the symptoms shown at the bottom. The frequency distribution of each symptom among patients is shown in the lower-left horizontal bars.

Nine of the symptomatic patients did not have Covid-19 based on three diagnostic tests that were mentioned in the methods section. None of these nine patients were in contact with Covid-19, and only two did not observe quarantine. All of them reported dyspnea. Muscle pain, anorexia, and diarrhea occurred in two of these patients. None of these patients lost their sense of smell or taste, and none had headache, vomiting, or fever.

One hundred patients stated that they did not comply with self-quarantine; the mean and standard deviation of the age of these patients was  $51.99 \pm 16.49$  years, and the mean age of those who complied with self-quarantine was  $54.05 \pm 13.13$  years. There was no statistically significant difference in the mean age of patients between those who complied with self-quarantine and those who did not ( $p$  value = 0.148). Also, 9.8% (71 people) of women and 10.5% (29 people) of men did not comply with self-quarantine. The proportion of people who did not comply with self-quarantine was not statistically significant between the two genders ( $p$  value = 0.759). The prevalence

of Covid-19 was 21% (21 out of 100) among those who did not comply with self-quarantine and 9.2% (83 out of 900) among those who did comply with quarantine ( $p$  value < 0.001). Quarantine reduced the risk of Covid-19 in patients with RA by 62% (OR = 0.382; 95% CI (0.225 - 0.650)).

The mean age of patients with Covid-19 was 52.64 years with a standard deviation of 12.82 years, and the mean age of other patients was 53.98 years with a standard deviation of 13.58 years. The mean age of RA patients with Covid-19 was not significantly different from other patients ( $p$  = 0.339).

There was no statistically significant relationship between sex or smoking and COVID-19 prevalence in these patients (all  $p$  values > 0.05).

The prevalence of Covid-19 was significantly higher among sulfasalazine users (14.3%) than patients taking other drugs (8.9%) (OR = 1.72; 95% CI,  $p$  value = 0.011). The prevalence of Covid-19 among users of other drugs is seen in [Table 1](#).

**Table 1.** Prevalence of COVID-19 by gender, smoking, and medication usage

Variable	Level	Total number	Number of COVID-19 patients	COVID-19 prevalence	<i>P</i> value	Odds ratio (95% confidence interval)
<b>Gender</b>	male	227	28	10.1	0.852	(0.66-1.65)1.05
	female	723	76	10.5		
<b>Smoking</b>	no	958	101	10.5	0.480	(0.198-2.15) 0.653
	yes	42	3	7.1		
<b>Sulfasalazine</b>	no	721	64	8.9	0.011	

Variable	Level	Total number	Number of COVID-19 patients	COVID-19 prevalence	<i>P value</i>	Odds ratio (95% confidence interval)
Methotrexate	yes	279	40	14.3	0.584	(1.01-2.62) 1.72
	no	429	42	9.8		
Hydroxychloroquine	yes	571	62	10.9	0.779	(0.742-1.7) 1.120
	no	378	38	10.1		
Leflunomide	yes	622	66	10.6	0.141	(0.697-1.62) 1.06
	no	780	87	11.2		
NSAID	yes	220	17	7.7	0.069	(0.388-1.15) 0.667
	no	193	27	14		
Prednisolone	yes	807	77	9.5	0.857	(0.405-1.04) 0.649
	no	199	20	10.1		
	yes	801	84	10.5		(0.627-1.75) 1.05

The prevalence of Covid-19 was 11.4% among RA patients whose disease duration was less than 15 years. It was 10.1% among RA patients with a disease duration between five and ten years. Among RA patients with a disease duration between ten and 15 years, it was 6.5%. Among RA patients who had a disease duration of more than 15 years, it was 12.3%. There was no statistically significant difference in the prevalence of patients according to the duration of RA (*p value* = 0.203).

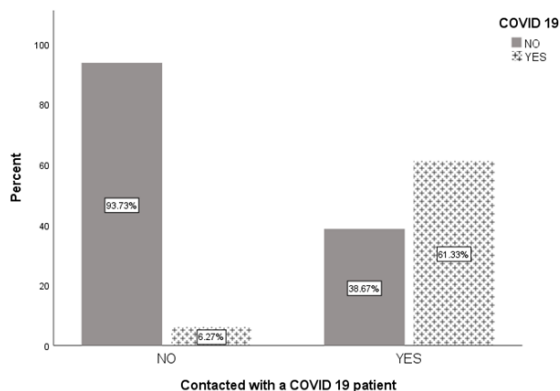
The prevalence of Covid-19 among patients with an underlying disease was 10.1% and in other patients was 10.9%. Accordingly, there was no statistically significant difference in the prevalence of patients with an underlying disease (OR = 0.920; 95% CI (0.598 - 1.41); *p value* = 0.702). The prevalence of Covid-19 among patients with cardiac disorders (22.6%) was statistically significantly higher than other patients (9.3%) (OR = 2.86; 95% CI (1.64 - 4.99); *p value* < 0.001). The results regarding other comorbidities are seen in [Table 2](#).

**Table 2.** COVID-19 prevalence according to comorbidities in patients with RA

Comorbidity	Total number	COVID-19 patients	COVID-19 prevalence	<i>P value</i>	Odds ratio (95% confidence interval)
Pulmonary disorders	467	56	12	0.123	(0.916-2.07) 1.38
HTN	232	19	8.2	0.208	(0.426-1.21) 0.717
DM	105	9	8.6	0.516	(0.386-1.62) 0.789
Cardiac disorders	84	19	22.6	<0.001	(1.64-4.99) 2.86
HLP	129	8	6.2	0.094	(0.253-1.13) 0.534
Hypothyroidism	129	9	7	0.172	(0.301-1.25) 0.613
Psychological disorders	16	0	0	0.397	-
Anemia	21	2	9.5	0.999	(0.208-3.94) 0.905
Cancer	5	2	0	0.999	*-
Other disorders	32	2	6.3	0.766	(0.133-2.40) 0.566

Seventy-five (7.5%) of all patients with RA had a history of Covid-19 among their first-degree relatives. The prevalence of Covid-19 was 6.3% among patients who did not have a Covid-19-positive person among their relatives, and 61.3% among patients who did. The risk of developing Covid-19 was 23.71 times higher among those who had a

Covid-19-positive among their relatives (OR = 23.71; 95% CI (13.88 - 40.50); *p value* < 0.001) ([Figure 2](#)).



**Figure 2.** Prevalence of COVID-19 among patients with rheumatoid arthritis in relation to individuals with a history of COVID-19

## Discussion

The aim of this study was to investigate the prevalence of Covid-19 in patients with rheumatoid arthritis who used classic disease-modifying antirheumatic drugs (DMARDs) and their associated factors. This aim is important because in medical practices, these patients were known to think themselves at a higher risk for Covid-19 infection than the general population and they experienced more stress than the general population.

The current study found that the prevalence of Covid-19 among patients with RA was 10.4%. In their study, Fredi et al. found that the prevalence of Covid-19 in rheumatic patients was about 8%, which is similar to the current results. However, the type of rheumatism differed from that in the current study. Fredi et al. examined patients with rheumatic and musculoskeletal disorders, but the current study examined RA patients. In Fredi et al., the most common comorbidity in rheumatic patients with Covid-19 was hypertension; however, among patients with RA in the current study, the most prevalent comorbidity was pulmonary disorders, and among patients with RA who struggled with Covid-19, cardiac disorders were more prevalent. These results are different from those of Fredi et al. [15]. RA affects the lungs; pulmonary involvement is a well-known manifestation in patients with RA. It is the cause of the higher prevalence of pulmonary comorbidities in patients with RA. Causes of higher prevalence of COVID-19 in RA patients with cardiac disorders should be investigated in future studies.

Monti et al. found that among 320 patients with rheumatologic diseases, four patients struggled with Covid-19 diagnosed by rhinopharyngeal swabs, and another four patients were highly suggestive for Covid-19, but they did not perform any diagnostic test. It seems Covid-19 prevalence in patients with rheumatologic disorders is 2.5%. This percentage is very different from the current findings, which indicated the Covid-19 prevalence was 10.4%. One difference between these two studies was the studied population. The current study was performed on patients with RA, but Monti et al. study was performed on patients with rheumatic disorders. Moreover,

the population of the current study comprised 1000 patients, but Monti et al. investigated only 320 patients. Another difference between these two studies was the medications used for the patients. All patients in the present study had received classic DMARDs, but patients in the other study had received biologic, classic, and targeted synthetic DMARDs. Monti et al. mentioned that compared to the general population, patients treated with biologic DMARDs or targeted synthetic DMARDs did not tend to be at an elevated risk of respiratory or life-threatening complications from SARS-CoV-2. The current results indicated no significant difference in such prevalence among the normal population and RA patients [16].

Zhong et al. revealed that the prevalence of Covid-19 in rheumatic patients is 0.43%, which is very different from the current study. In their study, it was seen that hydroxychloroquine had protective effects on rheumatic patients. The current study indicated that taking hydroxychloroquine had no effect on Covid-19 in patients. Zhong et al. concluded there was a significant relationship between higher age and increased Covid-19 prevalence in rheumatic patients, but this issue was not seen in the current study; therefore, there was no significant relationship between age and Covid-19 RA patients [17].

Michelena et al. reported the prevalence of Covid-19 in patients with rheumatic disease who were under biological DMARD treatment to be about 1.5%. In their study, only patients who took biological or targeted synthetic DMARDs were investigated, but the current study examined patients who took classic DMARDs. Perhaps the difference in results is due to the different treatment options [18].

Pablos et al. performed their study on rheumatic patients admitted for rheumatic diseases and assessed the prevalence of Covid-19 in these patients. They observed a higher prevalence of Covid-19 with positive PCR in admitted rheumatic patients (1.32-fold). Accordingly, they found a relationship between DMARD use and a higher prevalence of Covid-19. In contrast, this conclusion was not the case in the current study; there was no significant relationship between DMARD use and Covid-19 prevalence in RA patients (except with sulfasalazine) [19].

In the study of Musca, it was found that hydroxychloroquine had a protective effect against Covid-19; however, the current study found that hydroxychloroquine had no relationship with Covid-19 in patients with RA [20].

According to Kalinova and Rashkov, sulfasalazine should not be used in patients with Covid-19. Similarly, the present study showed that Covid-19 had a higher prevalence in patients who took sulfasalazine with a valuable *p*-value. Hence, these two studies have similar conclusions. This association may be related to the sulfasalazine effect, because it had no immunosuppressive effects, and Covid-19 was higher in patients who took this drug [21, 22].

## Conclusion

The present study revealed that the prevalence of Covid-19 in patients with RA who took classic DMARDs was not

associated with age, sex, or smoking. Covid-19 was more prevalent in RA patients with cardiac disorders than in other patients, so it can be said that underlying diseases (other than cardiac disorders) are not associated with Covid-19 in RA. The duration of RA was not associated with Covid-19. Self-quarantine was shown to reduce the risk of Covid-19 in RA patients by about 62%. This finding confirms that self-quarantine is an effective method for preventing Covid-19 infection. Covid-19 prevalence in patients with a first-degree relative positive for Covid-19 was 10-fold higher than patients who had no relative with a positive Covid-19 test. This finding also shows the self-quarantine is crucial for the prevention of this infection.

Contrary to popular belief that RA patients are at higher risk for Covid-19 infection, the prevalence of Covid-19 in the RA patients studied in the present research has shown this belief to be false. The low prevalence of Covid-19 in RA patients may be due to the use of anti-inflammatory drugs, especially hydroxychloroquine, by these patients. Hydroxychloroquine was the most prevalent drug used by patients in the current study, but the prevalence of Covid-19 infection in patients who used hydroxychloroquine was not high.

### Limitation

Some limitations of this study were the reluctance of patients to participate and the incomplete information some patients submitted, leading to a lack of contact with them.

### Advantages

Of the advantages of this study were the number of people studied and the assessment of associated factors in RA patients who were involved with COVID-19.

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Not applicable.

### Funding

Not applicable.

### Declarations

Ethical approval and consent to participate.

### Conflict of interest statement

The authors declare that they have no competing interests.

### Ethical approval and consent to participate

The research procedure was accepted by the ethical committee (IR.SBMU.MSP.REC.1399.329) of Shahid Beheshti University of Medical Sciences.

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