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BRIEF REPORT

# Factors associated with COVID-19 and its outcome in patients with rheumatoid arthritis

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## Abstract

**Objective** We assessed the factors associated with COVID-19, clinical manifestations, and a 30-day-prognosis of COVID-19 in a cohort of rheumatoid arthritis (RA) patients compared with the index population.

**Methods** In a cross-sectional study, RA patients were followed in rheumatology clinics of Tabriz University of Medical Sciences, and a group of patients diagnosed with COVID-19 from index population were recruited. Outcomes of COVID-19 were assessed by the hospitalization rate and need to intensive care unit (ICU) and mortality. During a period of 12 weeks, 128 RA patients diagnosed with COVID-19, 760 RA control group, and 92 COVID-19 patients from index population were enrolled.

**Results** Being female, obese, and diabetic, having pulmonary disease and chronic kidney disease (CKD), and treatment with prednisolone > 5 mg/d and TNFα inhibitors (TNFis) were independent predictors of COVID-19 in RA patients. Dyspnea, anosmia, and taste loss were more common in RA patients compared with the index population. Admission in hospital, need to ICU care, and mortality occurred in 38, 11.9, and 8.6 percent of RA patients, respectively. Although hospitalization rate in RA patients was more than the index population, there were no significant differences in need to ICU care and mortality between the two groups.

**Conclusions** Treatment with prednisolone and TNFis and having comorbidities including obesity, diabetes, pulmonary disease, and CKD increase the risk of COVID-19 in RA patients. Although some differences exist in the clinical manifestations of COVID-19 in RA patients and index population, prognosis of COVID-19 in RA patients is not any worse.

**Key Points**

- *Being female, obese and diabetic, having pulmonary disease, chronic kidney disease (CKD), treatment with prednisolone > 5 mg/d and TNFα inhibitors (TNFis) were independent predictors of COVID-19 in RA patients.*
- *Dyspnea, anosmia and taste loss were more common in RA patients compared with the index population.*
- *Although COVID-19 related hospitalization was higher in RA patients than in the index population, there was no significant differences in the need to ICU care and mortality between the two groups.*

**Keywords** Clinical manifestations · COVID-19 · Outcomes · Rheumatoid arthritis · Risk factors

## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune rheumatic disease (SARD). Many reports showed that patients with SARDs are in danger of coronavirus disease 2019 (COVID-19) and its worse prognosis, including hospitalization and need to intensive care unit (ICU) care [1–3]. However, SARDs are a heterogeneous group of diseases, and the information on the prevalence and prognosis of COVID-19 in SARDs obtained from these studies cannot be generalized to any of these diseases.

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**Table 1** Comparison of demographic characteristics, factors associated with COVID-19, medications and clinical manifestations, and outcomes of COVID-19 in the studied group

| Parameters | RA patients with COVID-19 (n = 128) | Control RA patients (n = 760) | p-value* | Index population (n = 92) | p-value* |
|---|---|---|---|---|---|
| Female, n (%) | 107 (83.6) | 578 (76.1) | **0.036** | 39 (42.4) | **0.001** |
| Age (mean ± SD) | 52.3 ± 13.9 | 52.4 ± 12.5 | 0.929 | 48.4 ± 16.2 | 0.058 |
| RA disease duration, median (IQR) | 97 (47, 150) | 78 (38, 132) | **0.083** | - | - |
| Active RA disease, n (%) | 35 (27.3) | 195 (25.7) | 0.377 | - | - |
| Factors associated with COVID-19 | | | | | |
| Obesity (BMI > 30), n (%) | 50 (39.1) | 136 (17.9) | **0.001** | 27 (29.3) | 0.112 |
| Hypertension, n (%) | 34 (26.7) | 177 (23.3) | 0.247 | 29 (31.5) | 0.302 |
| Diabetes, n (%) | 24 (18.8) | 73 (9.6) | **0.004** | 19 (20.7) | 0.447 |
| Pulmonary disease†, n (%) | 9 (7.0) | 14 (1.8) | **0.004** | 14 (15.2) | 0.082 |
| Chronic kidney disease‡, n (%) | 6 (4.7) | 7 (0.9) | **0.010** | 11 (12.0) | 0.049 |
| Malignancies, n (%) | 3 (2.3) | 5 (0.7) | 0.082 | 6 (6.5) | 0.127 |
| Smoking, n (%) | 4 (3.1) | 71 (9.3) | **0.018** | 22 (23.9) | **0.001** |
| Heart disease§, n (%) | 4 (3.1) | 17 (2.1) | 0.444 | 9 (9.8) | 0.079 |
| Transplantation, n (%) | 0 | 0 | - | 5 (5.4) | - |
| Medications used for the treatment of RA | | | | | |
| NSAIDs, n (%) | 19 (14.8) | 105 (13.8) | **0.048** | - | - |
| Prednisolone, n (%) | 97 (75.8) | 471 (62.0) | **0.001** | - | - |
| Methotrexate, n (%) | 93 (72.7) | 580 (76.3) | 0.210 | - | - |
| Hydroxychloroquine, n (%) | 88 (68.8) | 577 (75.9) | 0.055 | - | - |
| Sulfasalazine, n (%) | 28 (21.9) | 109 (14.3) | **0.025** | - | - |
| Leflunomide, n (%) | 24 (18.8) | 114 (15.0) | 0.170 | - | - |
| Azathioprine, n (%) | 4 (3.1) | 6 (0.8) | **0.045** | - | - |
| Calcineurin inhibitors, n (%) | 1 (0.8) | 5 (0.7) | - | - | - |
| TNFis, n (%) | 17 (13.3) | 28 (3.7) | **0.001** | - | - |
| Clinical manifestations of COVID-19 | | | | | |
| Fever, n (%) | 85 (66.4) | - | - | 68 (73.9) | 0.073 |
| Malaise, n (%) | 108 (84.4) | - | - | 84 (91.3) | 0.136 |
| Myalgia, n (%) | 106 (82.8) | - | - | 79 (85.9) | 0.112 |
| Sore throat, n (%) | 49 (38.3) | - | - | 40 (44.6) | 0.163 |
| Rhinorrhea, n (%) | 22 (17.2) | - | - | 25 (27.2) | **0.049** |
| Cough, n (%) | 92 (71.9) | - | - | 83 (90.2) | **0.001** |
| Dyspnea, n (%) | 72 (56.3) | - | - | 42 (45.7) | **0.048** |
| Diarrhea, n (%) | 30 (23.4) | - | - | 41 (44.6) | **0.001** |
| Anosmia, n (%) | 76 (59.4) | - | - | 38 (41.3) | **0.019** |
| Taste loss, n (%) | 67 (52.3) | - | - | 33 (35.9) | **0.031** |
| Pneumonia in CT, n (%) | 88 (68.8) | - | - | 57 (62.0) | 0.229 |
| Outcomes of COVID-19 | | | | | |
| Admission in hospital, n (%) | 49 (38.3) | - | - | 22 (23.9) | **0.002** |
| ICU care, n (%) | 14 (10.9) | - | - | 9 (9.8) | 0.546 |
| Mortality, n (%) | 11 (8.6) | - | - | 5 (5.4) | 0.161 |

We bolded significant P-values ($p < 0.05$)

*Comparisons between groups was made by chi-squared test, independent sample t test and U Mann–Whitney test, as appropriate

†Asthma, chronic obstructive pulmonary disease, interstitial lung disease and cystic fibrosis

‡Decrease in glomerular filtration rate over a period of ≥ 3 months

§Ischemic heart disease, congestive heart failure, valvular heart disease

*RA*, rheumatoid arthritis; *n*, number; *SD*, standard deviation; *BMI*, body mass index; *IQR*, interquartile range; *NSAIDs*, non-steroidal anti-inflammatory drugs; *CT*, computed tomography; *TNFis*, TNFα inhibitors; *ICU*, intensive care unit

Data from the COVID-19 Global Rheumatology Alliance (C19-GRA) registry showed that the most common SARD with COVID-19 is RA [4]. A recent report from the USA found that RA increases the risk of COVID-19 by 25% [5]. However, information on the impact of COVID-19 on RA patients is scant. In this study, we assessed the factors associated with COVID-19, clinical manifestations, and a 30-day-prognosis of COVID-19 in a cohort of RA patients compared with the index population.

## Patients and methods

In an observational study, RA patients were followed in rheumatology clinics of Tabriz University of Medical Sciences (TUOMS), and a group of patients diagnosed with COVID-19 from the index population were recruited. The study protocol was approved by the ethics committee of TUOMS and was conducted in accordance with the Helsinki humanity research declaration. Written informed consents were received from subjects. Inclusion criteria for RA control group were (i) diagnosis of RA according to ACR/EULAR classification criteria [6], (ii) age ≥ 16 at disease onset, and (iii) disease onset before COVID-19 outbreak. Information about developing COVID-19 was obtained by telephone interview. RA patients diagnosed with COVID-19 were invited to the rheumatology clinic of TUOMS, and electronic medical records in hospitalized patients were reviewed. RA disease activity was assessed by a rheumatologist, and diagnosis of COVID-19 was re-evaluated by an infectious disease specialist. Remission was defined as ACR/EULAR definitions of remission [7]. The RA control group was selected from the patients who had visited the rheumatology clinic of TUOMS from 14 December 2020 to 14 March 2021. As a control group from the index population, we enrolled 92 patients diagnosed with COVID-19 who were followed up at the Infectious Diseases Clinic of TUOMS from 14 December 2020 to 14 March 2021.

Diagnosis of COVID-19 was made in patients with symptoms suggestive of COVID-19 and meeting one of these three criteria: (i) positive polymerase chain reaction (PCR), (ii) chest computerized tomography scan findings of COVID-19 pneumonia and ruling out other causes of pneumonia, and (iii) symptoms onset after close contact with a known PCR-confirmed COVID-19 patient. Outcomes of COVID-19 were assessed within 30 days of COVID-19 diagnosis by hospitalization rate, need to ICU care, and mortality.

### Statistical analysis

Statistical analysis was performed using SPSS software version 16.0 (SPSS, Inc., USA). Continuous variables with

**Table 2** Factors associated with COVID-19 in RA patients

| Parameters | Univariate analysis | | Multivariate analysis* | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Age ≥ 65 | 0.80 (0.50–1.29) | 0.361 | | |
| Female sex | 1.60 (0.94–2.72) | 0.062 | 2.03 (1.10–3.72) | **0.023** |
| Obese | 2.63 (1.6–4.19) | 0.001 | 3.01 (1.92–4.73) | **0.001** |
| Being a smoker | 0.32 (0.10–0.95) | 0.041 | 0.55 (0.18–1.84) | 0.310 |
| Diabetes | 2.19 (1.29–3.71) | 0.003 | 1.77 (1.01–3.12) | **0.050** |
| Hypertension | 1.18 (0.76–1.96) | 0.428 | | |
| Pulmonary diseases | 4.12 (1.67–10.19) | 0.002 | 3.74 (1.29–10.77) | **0.014** |
| Heart disease | 1.36 (0.39–4.68) | 0.713 | | |
| Chronic kidney disease | 5.52 (1.17–18.41) | 0.005 | 4.35 (1.09–17.40) | **0.038** |
| Malignancy | 3.39 (0.87–13.56) | 0.080 | 2.17 (0.41–11.49) | 0.362 |
| Active disease | 1.28 (0.77–2.12) | 0.338 | | |
| Disease duration > 10 years | 1.41 (0.95–2.09) | 0.085 | 1.01 (0.64–1.61) | 0.956 |
| NSAIDs | 0.79 (0.58–1.12) | 0.167 | | |
| Prednisolone dose > 5 mg/d | 1.92 (1.25–2.95) | 0.003 | 2.58 (1.57–4.25) | **0.001** |
| Hydroxychloroquine | 0.69 (0.45–1.06) | 0.090 | 0.84 (0.49–1.43) | 0.524 |
| Methotrexate | 0.82 (0.54–1.25) | 0.361 | | |
| Sulfasalazine | 1.79 (1.09–2.94) | 0.022 | 1.38 (0.77–2.46) | 0.279 |
| Leflunomide | 1.31 (0.80–2.13) | 0.280 | | |
| TNFis | 3.93 (2.08–7.42) | 0.001 | 5.28 (2.62–10.65) | **0.001** |

We bolded significant P-values ($p < 0.05$)

*Backward stepwise method was used

*RA*, rheumatoid arthritis; *OR*, odds ratio; *CI*, confidence interval; *NSAIDs*, non-steroidal anti-inflammatory drugs; *TNFis*, TNFα inhibitors

normal distribution were reported as mean ± standard deviation (SD), and non-normally distributed continuous variables were reported as median (25–75% interquartile range [IQR]). Categorical variables were reported as frequency and percentage. The factors associated with COVID-19 in RA were subjected to univariate analysis. The predictive factors for COVID-19 with p-values of < 0.1 in univariate analysis were included in a multivariate regression analysis and were expressed as hazard ratio and 95% confidence interval (95% CI). P-values less than 0.05 were considered as statistically significant.

## Results

During a period of 12 weeks, 128 RA patients diagnosed with COVID-19, 760 RA control group, and 92 patients with COVID-19 from index population were enrolled in this study. Diagnosis was based on positive PCR in 102 (79.7%) and clinical criteria in 26 (20.3%) RA patients. These figures for index population were 64 (69.6%) and 28 (30.4%), respectively. Demographic, clinical characteristics, and medications of the RA patients with COVID-19, RA control group, and index population were compared (Table 1). There were significant differences in the frequency of some manifestations of COVID-19 in RA patients compared with the index population, including rhinorrhea, cough, dyspnea, diarrhea, anosmia, and taste loss (Table 1).

We assessed factors associated with COVID-19 in the RA patients. Being female, obese, diabetic, having pulmonary disease, having chronic kidney disease (CKD), treatment with prednisolone > 5 mg/d, and treatment with TNFα inhibitors (TNFis) were the independent risk factors for developing COVID-19 (Table 2). In addition, we assessed the outcomes of COVID-19 in the studied groups. Exacerbation of RA happened in 20 (15.6%) patients. Hospitalization rate in RA patients with COVID-19 was more than the index population. However, there were no significant differences in ICU care and mortality between the two groups (Table 1).

We compared the demographic and clinical characteristics of the hospitalized RA patients with the RA patients treated in outpatient (Table 3). Age ≥ 65 years, diabetes,

**Table 3** Factors associated with COVID-19-related hospitalization in RA patients

| Parameters | Hospitalized RA patients with COVID-19 (N = 49) | Outpatient RA patients with COVID-19 (N = 79) | p-value* |
|---|---|---|---|
| Female, n (%) | 43 (87.8) | 64 (81.0) | 0.227 |
| Age ≥ 65, n (%) | 16 (32.7) | 6 (7.6) | **0.001** |
| Obesity (BMI > 30), n (%) | 25 (51.0) | 25 (31.6) | **0.024** |
| Hypertension, n (%) | 16 (32.7) | 18 (22.8) | 0.128 |
| Diabetes, n (%) | 16 (32.7) | 8 (10.1) | **0.001** |
| Pulmonary disease, n (%) | 5 (10.2) | 4 (5.1) | 0.188 |
| Chronic kidney disease, n (%) | 3 (5.6) | 3 (0.9) | 0.084 |
| Malignancies, n (%) | 3 (6.1) | 0 | - |
| Smoking, n (%) | 0 | 4 (5.1) | - |
| Heart disease, n (%) | 3 (6.1) | 1 (1.3) | - |
| Having ≥ 2 COVID-19 risk factors, n (%) | 21 (42.9) | 12 (15.2) | **0.004** |
| RA disease duration, median (IQR) | 84 (37, 128) | 72 (36, 120) | 0.321 |
| Active RA disease, n (%) | 16 (34.7) | 19 (24.1) | 0.228 |
| Medications | | | |
| NSAIDs, n (%) | 14 (28.6) | 5 (6.3) | **0.002** |
| Prednisolone, n (%) | 45 (91.8) | 52 (65.8) | **0.001** |
| Prednisolone dose (mg/d) | 5 (5, 7.5) | 5 (2.5, 5) | **0.001** |
| Hydroxychloroquine, n (%) | 37 (75.5) | 51 (64.5) | 0.135 |
| Methotrexate, n (%) | 38 (77.6) | 55 (69.6) | 0.220 |
| Sulfasalazine, n (%) | 11 (22.2) | 17 (21.5) | 0.534 |
| Leflunomide, n (%) | 7 (14.3) | 17 (21.5) | 0.217 |
| TNFis, n (%) | 6 (12.2) | 11 (13.9) | 0.372 |

We bolded significant P-values ($p < 0.05$)

*Comparisons between groups was made by chi-squared test, independent sample t test, and U Mann–Whitney test, as appropriate

*RA*, rheumatoid arthritis; *n*, number; *BMI*, body mass index; *IQR*, interquartile range; *NSAIDs*, non-steroidal anti-inflammatory drugs; *TNFis*, TNFα inhibitors

having ≥ 2 COVID-19 risk factors, and treatment with NSAIDs and prednisolone were significantly more common in the hospitalized patients (Table 3).

## Discussion

RA patients are at a higher risk of COVID-19 and COVID-19-related hospitalization [5]. Our study showed that some *common factors* (*being female*, *being obese*, *being diabetic*, *having underlying pulmonary disease* and *CKD*) and *RA-specific factors* (*treatment with prednisolone > 5 mg/d or TNFis*) were independently associated with COVID-19 in RA. In England et al. report treatment with csDMARDs, bDMARDs, and prednisone, black race, Hispanic ethnicity, and having several comorbidities were associated with COVID-19 [5]. COVID-19 resulted in hospitalization in 38% of RA patients in our study. This figure was 49% and 24% in the C19-GRA registry for patients with rheumatic diseases [4] and England et al. [5] reports, respectively.

Our findings on factors associated with hospitalization in RA patients differ in some respects from reports in other countries. In our study, *common factors including age ≥ 65 years, diabetes, and having ≥ 2 COVID-19 risk factors* and *RA-specific factors including treatment with NSAIDs and prednisolone* were associated with hospitalization in RA patients. Contrary to our results, in Pablos et al. report, treatment with glucocorticoids was not associated with a poor outcome of COVID-19 [8]. Analysis of C19-GRA data showed a higher OR of hospitalization in patients treated by prednisone dose ≥ 10 mg/day [8]. However, treatment with NSAIDs was not associated with hospitalization, and TNFis use was associated with a reduced OR of hospitalization [9].

Despite data showing a positive correlation between risk of infection and disease activity in RA patients [10, 11], having active disease was not associated with COVID-19 development or hospitalization in our cohort.

Overall, treatment with prednisolone and TNFis and having comorbidities including obesity, diabetes, pulmonary disease, and CKD increase the risk of developing COVID-19 in RA patients. Although some differences exist in the clinical manifestations of COVID-19 in RA patients and index population, prognosis of COVID-19 in RA patients is not any worse.

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**Data availability** Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

## Declarations

**Conflict of interest** The authors declare no competing interests.

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