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ORIGINAL ARTICLE

Outcomes of coronavirus disease 19 patients with a history of rheumatoid arthritis: A retrospective registry-based study in Iran

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Abstract

Background: We aimed to study the outcomes of coronavirus disease 2019 (COVID-19) in patients with a history of rheumatoid arthritis (RA) in Iran, where most patients receive corticosteroids and are at high risk for COVID-19 infection.

Method: We collected the demographic, diagnostic, and treatment data of all COVID-19 patients by the clinical COVID-19 registry system. We recruited 38 RA patients and 2216 non-RA patients from the COVID-19 registry. The primary outcome was mortality due to COVID-19. We also studied the risk of intensive care unit admission and intubation in RA patients compared to non-RA patients. We used multiple logistic regression analysis to study the association between RA and the risk of COVID-19 outcomes.

Result: We recruited 38 RA patients and 2216 non-RA patients from the COVID-19 registry. The RA patients had a higher mean age (59.9 years) than the non-RA patients (57.7 years). The group of RA patients had a larger proportion of women (76.3%) than the non-RA patients (40.8%). The death rate due to COVID-19 was significantly higher in RA patients than non-RA patients (odds ratio [OR] = 2.69, 95% confidence interval [CI] = 1.24-5.81). The OR was higher among those who received prednisolone than among those who did not (OR = 3.59, 95% CI = 1.54-7.81). The odds of intubation were statistically significant among patients who received corticosteroid therapy (OR = 2.58, 95% CI = 1.07-6.18).

Conclusion: The risk of COVID-19 outcomes was higher in RA patients than non-RA patients, especially for RA patients who received a low dose of prednisolone. The results of this study can be used to triage RA patients who get infected by COVID-19. Further studies with larger sample sizes are required to more precisely define the high-risk groups.

KEYWORDS
COVID-19, outcome, pandemic, rheumatoid arthritis

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1 | INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) has caused a global pandemic, experienced by more than 200 countries, and resulted in more than 4 million deaths.[1] About 5 million people contracted COVID-19 disease in the Islamic Republic of Iran from February 1, 2020, to June 10, 2021, and more than 100 000 patients died due to this disease.[2]

Clinical features and outcomes of COVID-19 patients are associated with different risk factors, including gender, age, comorbidity, the severity of disease, and oxygen saturation at admission.[3] The most important comorbidities associated with poor outcomes in these COVID-19 patients include diabetes, hypertension, cardiovascular disease, obesity, chronic liver disease, chronic kidney disease, and asthma.[4]

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disorder, and RA patients usually take immunosuppressive agents. Because of the impairment of the immune system and the iatrogenic effect of corticosteroids and immunosuppressive medicine, these patients may be at high risk for severe infections. Available evidence indicates a small elevation in the risk of infection in RA patients compared to the general population.[5] However, some studies showed no association between a history of rheumatologic diseases and risk of COVID-19 infection.[6] A meta-analysis of 23 studies showed that the relative risk of COVID-19 infection among patients with a history of rheumatologic diseases was 1.52 (95% 1.16-2.00) compared to the general population. Some studies showed that the risk of COVID-19 infection was higher than the risk of developing other rheumatologic diseases in China, Spain, Italy, the UK, and the USA.[5,7]

Therefore, COVID-19 patients with a history of RA would require more attention and probably intensive care when admitted to the hospitals than the general population.[5,7] Several studies reported that COVID-19 patients with rheumatologic diseases had a higher risk of COVID-19 outcomes than other COVID-19 patients.[5] However, the data on COVID-19 outcomes among RA patients are limited, especially in low and middle-income countries, where the treatment regimens of rheumatic diseases and the management of COVID-19 are different from those in high-income countries. In Iran, most RA patients receive low-dose daily corticosteroids, which may increase the risk of severity of COVID-19 infection and outcomes in these patients.

In this work, we compared the COVID-19 outcomes of RA patients with those of non-RA patients in Iran. To the best of our knowledge, this is the first study to evaluate the outcome of RA patients in a low- or middle-income country.[8]

2 | MATERIALS AND METHODS

2.1 | Patients

We used data from the Clinical COVID-19 Registry of Imam Khomeini Hospital between February 1, 2020, and June 10, 2021. We registered 2254 COVID-19 patients in the program, of whom 38 had a history of RA. We confirmed COVID-19 infection by clinical evaluation, computed tomography scan, or reverse transcription polymerase chain reaction (RT-PCR) test. We included only those patients who had positive RT-PCR test results and excluded patients whose RT-PCR test results were negative (n = 786, 25%) or unknown (n = 106, 3.4%). We reviewed the patient files and contacted the RA patients or their next of kin to confirm their diagnosis and collect additional data related to their condition, including their treatment history.

2.2 | Statistical analysis

We used descriptive statistics to study the distribution of the patients' characteristics. Because the follow-up time was very short, the hazard was not proportional during the follow-up period. Therefore, we performed multivariate logistic regression models and estimated crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI). ORs were adjusted for age, gender, comorbidities, and oxygen saturation level. We considered patients' histories of cancer, liver diseases, chronic kidney disease, diabetes, heart disease, hypertension, neurologic disease, stroke, lung disease, human immunodeficiency virus infection, autoimmune diseases, and organ transplantation; we also created a summary variable to adjust for comorbidities. We performed logistic regression analyses for different outcomes, including death, intensive care unit (ICU) admission, and intubation. All analyses were performed in Stata14 (Stata Statistical Software: Release 14, College Station, TX, USA).

3 | RESULTS

We recruited 38 RA patients and 2216 non-RA patients from the COVID-19 registry (Table 1). The RA patients had a higher mean age (59.9) than non-RA patients (57.7), as well as a higher proportion of women (76.3% vs 40.8%). Multivariate analyses showed that the odds of death due to COVID-19 were 2.69 times higher in RA patients than non-RA patients (OR = 2.69, 95% CI = 1.24-5.81) (Table 2). The OR was especially high among RA patients who received prednisolone (OR = 3.59, 95% CI = 1.54-7.81). Although the excess risk of ICU admission was not statistically significant, we found that the odds of intubation were statistically significant among patients who received corticosteroid therapy (OR = 2.58, 95% CI = 1.07-6.18).

4 | DISCUSSION

RA patients have a slightly increased risk of COVID-19 infection compared with non-RA patients because their immune systems are impaired.[5] Moreover, the risk of infection is a side effect of corticosteroids commonly used to treat RA.[9-11] We found a higher risk of death and intubation in RA patients compared to non-RA patients,

especially among patients who received low-dose corticosteroid therapy.

A few previous studies on RA patients presented similar results. The risk of death due to COVID-19 was 35% higher in RA patients than in non-RA patients in a study conducted in the US.[12] A UK-based study revealed that RA patients had severe COVID-19 outcomes.[13] A retrospective study showed that old age and the use of glucocorticoids were risk factors for severe COVID-19 outcomes but that the use of other classes of disease-modifying antirheumatic drugs was not. Similarly, among 600 cases in England, 46% required hospitalization. Old age and underlying conditions were associated with hospitalization.

Another study showed that hydroxychloroquine use has no association with hospitalization, but the use of high-dose glucocorticoids (more than 10 mg per day of prednisolone) influenced the mortality rate. Patients who received disease-modifying antirheumatic drugs were less likely than others to be hospitalized.[14] Another British retrospective study of 3729 RA patients found that COVID-19-related deaths were associated with factors such as old age, male gender, some comorbidities, and disease activity.[15] Although initial publications warned about increasing mortality rates in immune-suppressed cases, a recent analysis indicated that immune-suppressed patients had similar or even lower mortality rates than the general population.[16] Moreover, data about the pathophysiology of COVID-19 infection shows that some anti-rheumatoid medicines can manage COVID-19.[7]

A major strength of this study is that it considered a large, high-quality COVID-19 registry that allowed us to adjust for several important confounding factors, such as age, gender, oxygen saturation, and several comorbidities. We also actively reviewed the patient files and contacted the RA patients to confirm their history of RA and their use of different treatment regimens.

However, this study also suffered from some limitations. Unfortunately, detailed data for RA, such as disease duration and severity, medications taken before hospitalization, rheumatoid factor level, and cyclic citrullinated peptide levels, were not available. In addition, we did not have sufficient power to carry out sub-group

TABLE 1 Characteristics of COVID-19 patients with rheumatoid arthritis (RA COVID-19) and without rheumatoid arthritis (non-RA COVID-19) at Imam Khomeini Hospital, Tehran, Iran

Variable	RA COVID-19 n (%)[a]	Non-RA COVID-19 n (%)
Number of patients	38	2216
Mean age (SD), in y	59.9 (±11.9)	57.7 (±16.9)
Gender, female	29 (76.3)	904 (40.8)
Comorbidity	20 (53.6)	1417 (63.9)
Mortality	12 (31.6)	424 (19.1)
Intensive care unit admission	10 (26.3)	463 (20.9)
Intubation	8 (15.7)	265 (12.0)
Abnormal computed tomography scan	34 (89.47)	1820 (82.5)
Mean duration of stay, (SD), in d	5.68 (±4.59)	6.53 (±7.84)
Mean O_2 saturation percentage (SD)	88.6 (±6.8)	88.9 (±8.0)
RA drug history		
Hydroxychloroquine	18 (47.4)	–
Methotrexate	20 (52.6)	–
Prednisolone	31 (81.6)	–

[a]We reported percentages in parenthesis, unless otherwise noted.

TABLE 2 COVID-19 outcomes in rheumatoid arthritis patients and non-rheumatoid arthritis patients with positive reverse transcription polymerase chain reaction COVID-19 tests

Outcome	Patient group	No. outcome (%)	Crude OR	Adjusted OR (95% CI)[a]	*P* value
Death	Non-RA COVID-19	424 (19.7)	Reference	Reference	–
	RA COVID-19	12 (31.6)	1.95 (0.98-3.90)	**2.69 (1.24-5.81)**	**0.012**
	Hydroxychloroquine	5 (27.8)	1.61 (0.57-4.54)	2.61 (0.81-8.41)	0.11
	Methotrexate	6 (30)	1.80 (0.68-4.70)	2.13 (0.76-6.00)	0.15
	Prednisolone	11 (35.5)	**2.32 (1.11-4.89)**	**3.59 (1.54-7.81)**	**0.003**
Intensive care unit admission	Non-RA COVID-19	463 (24.5)	Reference	Reference	
	RA COVID-19	10 (29.4)	1.28 (0.61-2.71)	1.4 (0.67-3.23)	0.34
	Hydroxychloroquine	6 (37.5)	1.85 (0.67-5.12)	2.5 (0.82-4.70)	0.11
	Methotrexate	6 (33.3)	1.54 (0.58-4.12)	1.69 (0.60-4.70)	0.32
	Prednisolone	9 (32.1)	1.46 (0.66-3.25)	1.80 (0.76-4.20)	0.18
Intubation	Non-RA COVID-19	327 (14.8)	Reference	Reference	
	RA COVID-19	8 (21.1)	1.54 (0.70-3.39)	1.81 (0.79-4.17)	0.16
	Hydroxychloroquine	3 (16.7)	1.15 (0.33-3.98)	1.50 (0.39-5.70)	0.56
	Methotrexate	4 (20.0)	1.44 (0.48-4.32)	1.51 (0.48-4.76)	0.48
	Prednisolone	8 (25.8)	2.02 (0.89-4.54)	**2.58 (1.07-6.18)**	**0.03**

Note: Bolded estimates indicate that the results were statistically significant.

[a]All ORs (odds ratios) are adjusted for age, gender, comorbidities, and O_2 saturation.

analyses. Studies large enough to allow sub-group analyses should be conducted in the future.

5 | CONCLUSION

The risk of death due to COVID-19 infection is higher in RA patients than in non-RA patients, especially among those who receive corticosteroid therapy. The results of this study can be considered when triaging RA patients who contract COVID-19. Further studies with larger sample sizes are required to more precisely define high-risk groups.

AUTHOR CONTRIBUTIONS

MZ, AR, and KZ designed the study. MZ and MSS collected the data. KZ and MSS analyzed the data. MZ and MSS prepared the first draft of the manuscript. All authors were involved in the interpretation of the results and approval of the final version. MZ wrote the first draft of the paper and implemented the comments and suggestions from other authors and prepared the final draft of the paper. AR, SM, and KZ took full responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors have met authorship criteria.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3
2. Anastassopoulou C, Russo L, Tsakris A, Siettos C. Data-based analysis, modelling and forecasting of the COVID-19 outbreak. *PLoS One*. 2020;15(3):e0230405. doi:10.1371/journal.pone.0230405
3. Li X, Marmar T, Xu Q, et al. Predictive indicators of severe COVID-19 independent of comorbidities and advanced age: a nested case–control study. *Epidemiol Infect*. 2020;148:e255. doi:10.1017/S0950268820002502
4. Sutter W, Duceau B, Vignac M, et al. Association of diabetes and outcomes in patients with COVID-19: propensity score-matched analyses from a French retrospective cohort. *Diabetes Metab J*. 2021;47(4):101222. doi:10.1016/j.diabet.2020.101222
5. Grainger R, Kim AH, Conway R, Yazdany J, Robinson PC. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. *Nat Rev Rheumatol*. 2022;18(4):191-204. doi:10.1038/s41584-022-00755-x
6. Jung Y, Kwon M, Choi HG. Association between previous rheumatoid arthritis and COVID-19 and its severity: a nationwide cohort study in South Korea. *BMJ Open*. 2021;11(10):e054753. doi:10.1136/bmjopen-2021-054753
7. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: faraway, so close! *Autoimmun Rev*. 2020;19(5):102523. doi:10.1016/j.autrev.2020.102523
8. Wallace DJ. COVID-19 in patients with rheumatic disease: finally, a denominator. *Lancet Rheumatol*. 2021;3(7):e462-e463. doi:10.1016/S2665-9913(21)00121-1
9. Smolen JS, Landewé RB, Bijlsma JW, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685-699. doi:10.1136/annrheumdis-2019-216655
10. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2007;21(5):885-906. doi:10.1016/j.berh.2007.06.002
11. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology*. 2013;52(1):53-61. doi:10.1093/rheumatology/kes305
12. England BR, Roul P, Yang Y, et al. Risk of COVID-19 in rheumatoid arthritis: a National Veterans Affairs matched cohort study in at-risk individuals. *Arthritis Rheumatol*. 2021;73(12):2179-2188. doi:10.1002/art.41800
13. Topless RK, Phipps-Green A, Leask M, et al. Gout, rheumatoid arthritis, and the risk of death related to coronavirus disease 2019: an analysis of the UK Biobank. *ACR Open Rheumatol*. 2021;3(5):333-340. doi:10.1002/acr2.11252
14. Hyrich KL, Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. *Nat Rev Rheumatol*. 2021;17(2):71-72. doi:10.1038/s41584-020-00562-2
15. Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis*. 2021;80(7):930-942. doi:10.1136/annrheumdis-2020-219498
16. Shadmanfar S, Jonaidi-Jafari N, Jafari R, Rastgar-Moqaddam Z, Saburi A. COVID-19 in rheumatoid arthritis cases: an Iranian referral center experience. *Clin Rheumatol*. 2021;40(7):2979-2984. doi:10.1007/s10067-020-05464-y

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