Clinical Features of Admitted Patients with COVID-19 and Underlying Rheumatic Diseases

Jeonghun Heo* Minyoung Her, MD**

ABSTRACT

Objective: This study aimed to describe the clinical manifestations of admitted patients with coronavirus disease 2019 (COVID-19) who had underlying rheumatic diseases.

Methods: This study is a retrospective and case–control matched study. Demographic data were collected from 4,966 patients admitted for COVID-19 in Busan Medical Center from February 2020 to November 2021. Among these patients with COVID-19, we identified those who had underlying rheumatic disease through a medical record review. The controls without underlying rheumatic diseases were randomly sampled and matched by age and sex at a 1:4 ratio. The clinical, laboratory and radiographic findings of COVID-19 were compared between the two groups. To evaluate the risk for severe/critical COVID-19, multivariable logistic regression models were applied.

Results: Altogether, thirty-eight patients with rheumatic diseases and one hundred fifty-two matched controls were included. The mean age was 53.9 years old, and the female sex was 73.7% in both groups. More patients with underlying rheumatic diseases showed some COVID-19 manifestations, such as cough, sputum, dyspnea and chest discomfort, than the control group ($p<0.01$). The proportion of severity of COVID-19 and number of deaths were not significantly different between patients with rheumatic disease and control subjects. There was no significant difference in laboratory findings between the groups. All patients were given chest X-ray examinations, and the proportion of patients with lung infiltration on chest X-ray at admission was not different in either group. The risk for severe/critical COVID-19 was more than 60 years old, cardiovascular diseases and diabetes, but not rheumatic diseases.

Conclusions: Our data suggested that COVID-19 patients with underlying rheumatic diseases showed similar courses compared to patients without rheumatic diseases.

Keywords: COVID-19, Rheumatic diseases, Admission, Clinical features

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to unprecedented global health crises for the last several years. There have been some data regarding immunologic dysfunctions in COVID-19 patients[1,2]. Hyperactivation of immune cells and release of cytokines in the alveoli is regarded as a pathogenesis of COVID-19[1,2]. COVID-19 patients develop mostly respiratory symptoms such as cough, sore throat, and pneumonia but can also develop hyperinflammatory responses such as vasculitis, arthritis, and multisystem inflammatory syndrome[3]. The development of rheumatic diseases following COVID-19 infection in some cases raised concern regarding the correlation between COVID-19 and autoimmune-related manifestations[4].

Risk factors such as old age, cardiovascular diseases, cancer, chronic kidney diseases, cerebrovascular diseases, chronic lung disease, and diabetes were associated with higher morbidity and mortality for COVID-19[5]. In some studies, COVID-19 patients with various underlying rheumatic diseases showed more severe courses and higher mortality than patients without rheumatic diseases[6,7], but the findings of the studies were not consistent[8,9].

Here, we compared the clinical characteristics of admitted patients with COVID-19 underlying rheumatic diseases versus controls without rheumatic diseases to investigate the relationship between COVID-19 and rheumatic diseases.

PATIENTS AND METHODS

This study is a retrospective and matched case–control study. Demographic data were collected from 4,966 patients older than 18 years who were admitted for COVID-19 in Busan Medical Center from the 21st of February 2020 to the 18th of November 2021. During the COVID-19 pandemic, the Busan Medical Center, which was originally a secondary care hospital, was designated and worked as a dedicated

* Division of Pulmonology
Department of Internal Medicine
Busan Medical Center, Busan, Korea.
** Department of Internal Medicine
Busan Medical Center
Division of Rheumatology, Department of Internal Medicine
Haeundae Paik Hospital, Inje University
Busan, South Korea.
E-mail: alsdud92@gmail.com

COVID-19 center by the Ministry of Health and Welfare of South Korea. The diagnosis of COVID-19 was determined by the central task force team by real-time polymerase chain reaction, and the patients were referred to each hospital[10].

For the identification of rheumatic disease, the electronic health records were searched via the international classification of disease codes and manual review of the patients' medical record charts. Through those processes, we identified thirty-eight patients who had underlying rheumatic disease. The control group was selected from patients without underlying rheumatic diseases matched for sex and age at a 1:4 ratio.

Clinical findings and laboratory and radiographic results were extracted from a manual review of electronic medical records. Clinical findings such as various symptoms related to COVID-19, the severity of COVID-19, comorbid diseases, the use of oxygen therapy, and the number of deaths were evaluated. The severity of COVID-19 was defined according to the National Institutes of Health (NIH) clinical spectrum[11]. (1) Mild: patients who have various signs and symptoms of COVID-19 but do not have shortness of breath, dyspnea, or abnormalities on chest imaging; (2) Moderate: patients who have evidence of lower respiratory tract diseases on clinical symptoms or chest image and who showed an oxygen saturation ≥94% on room air measured by pulse oximetry; (3) Severe: patients whose oxygen saturation was < 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 mmHg, a respiratory rate>30 breath/minutes, or lung infiltration >50% of the chest image; and (4) Critical: patients who showed respiratory failure, septic shock, and/or multiple organ failure. The study protocol was approved by the ethics committee of Busan Medical Center and was performed in accordance with the Helsinki human research declaration (IRB No. 2022-11-001-(002)).

Laboratory findings such as white blood count, C-reactive protein, aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), pro-brain natriuretic peptide (Pro-BNP), prothrombin (PT), D-dimer, and fibrinogen level were extracted. The chest X-ray findings at admission were reviewed.

Continuous variables with normal distributions are reported as the mean ± standard deviation. We used independent t tests, chi-square tests and Fisher's exact tests to compare the differences between two groups. The factors associated with severe/critical severity were subjected to binary logistic regression models. Covariates included rheumatic diseases, sex and comorbidities, which are known as poor prognostic factors for COVID-19, such as age older than 60 years, cardiovascular diseases, hypertension, diabetes, cancer, obesity, cerebrovascular diseases and chronic lung diseases. The predictive factors for severe/critical severity with p values of <0.1 in univariate analysis were included in a multivariable regression analysis. A backward elimination technique was applied. P values less than 0.05 were considered statistically significant. Case control matching and statistical analysis were performed by SPSS software version 25 (IBM, Inc., USA).

RESULTS

Among the 4,966 admitted patients with COVID-19, thirty-eight patients were identified as having an underlying rheumatic disease. One hundred fifty-two patients without rheumatic diseases matched for sex and age were selected. The basic characteristics of this study population are described in Table 1. The mean age was 53.9 ± 15.9 years in the patients with underlying rheumatoid disease and 53.9 ± 15.8 years in the controls. A total of 73.7% were female in both groups.

Table 1: Demographics of the patients with COVID-19 and underlying rheumatic diseases (N=38) and controls (N=152)

	Underlying Rheumatic diseases (N=38)	Controls (N=152)	P value
Sex; Female (%)	28 (73.7)	40 (73.7)	1.0
Age (mean +SD)	53.9 ± 15.9 (22~79 years old)	53.9 ± 15.8 (22~79 years old)	1.0
Other comorbidities, n (%)			
Hypertension	6 (15.8)	40 (26.3)	0.17
Diabetes	6 (15.8)	15 (9.9)	0.29
Cardiovascular	3 (7.9)	5 (3.3)	0.19
Cancer	3 (7.9)	0	<0.01
Cerebrovascular	1 (2.6)	5 (3.3)	1.0
Chronic lung diseases	2 (5.3)	0	0.03
Rheumatic Diseases			
Rheumatoid arthritis	23 (60.5)		
Ankylosing spondylitis	5 (13.2)		
Sjogren's syndrome	4 (10.5)		
Behcet's diseases	4 (10.5)		
Scleroderma	1 (2.6)		
Polymyalgia Rheumatica	1 (2.6)		
Antirheumatic medications	N=33, missing=5		
Methotrexate	10 (30.3)		
Antimalarial agent	7 (21.2)		
Sulfasalazine	7 (21.2)		
Calcineurin inhibitors	5 (15.1)		
Oral glucocorticoids	20 (60.6)		
Biologic agents	3 (9.1)		

SD: standard deviation
n (%) presented unless otherwise specified
We bolded significant **P values (p<0.05)**
Comparisons between groups were made by the chi-squared test and independent t test.

Of these thirty-eight patients, twenty-three had rheumatoid arthritis, five had ankylosing spondylitis, four had Sjogren syndrome, and four had Behcet's syndromes. The remaining patients had been diagnosed with other rheumatic diseases (Table 1). Patients with underlying rheumatic diseases had more other comorbid diseases, such as malignancies and chronic respiratory diseases (p<0.05), but the number of patients was small. Information about previous prescriptions for rheumatic diseases was available for thirty-three patients and was missing for five patients. Methotrexate was prescribed for ten patients, hydroxychloroquine was prescribed for seven patients, and oral glucocorticoids were given for twenty out of thirty-three patients. In regard to biologic agents, one patient was treated with tocilizumab for rheumatoid arthritis, and two patients were treated with adalimumab for ankylosing spondylitis.

The common symptoms of COVID-19 were cough, sputum production, sore throat, myalgia and fever (Table 2). There were significant differences in the frequency of some clinical manifestations of COVID-19 in patients with rheumatic diseases compared with controls, including cough, sputum, dyspnea, myalgia, sore throat, chest pain/chest discomfort and diarrhea (P < 0.01). Those symptoms were more prevalent in COVID-19 patients with underlying rheumatic diseases than in controls.

Table 2: Clinical and laboratory findings of the patients with COVID-19 and underlying rheumatic diseases (N=38) and controls (N=152)

	Underlying Rheumatic diseases (N=38)	Controls (N=152)	P value
Clinical features of COVID-19, n (%)			
Fever	11 (28.9)	30 (19.7)	0.21
Myalgia	14 (36.8)	27 (17.8)	0.01
Sore throat	17 (44.7)	18 (11.8)	<0.01
Headache	6 (15.8)	29 (19.1)	0.51
Cough	28 (73.7)	39 (25.7)	<0.01
Sputum	18 (47.4)	20 (13.2)	<0.01
Rhinorrhea	2 (5.3)	9 (5.9)	0.1
Dyspnea	6 (15.8)	4 (2.6)	<0.01
Chest pain/discomfort	6 (15.8)	3 (2.0)	<0.01
Diarrhea	7 (18.4)	8 (5.3)	<0.01
Anosmia/taste loss	4 (10.5)	8 (5.3)	0.2
Severity of COVID-19, n (%)			0.88
Mild	21 (55.3)	92 (60.5)	
Moderate	11 (28.9)	42 (27.6)	
Severe	5 (13.2)	14 (9.2)	
Critical	1 (2.6)	4 (2.6)	
Number of patients who need oxygen	6 (15.8)	19 (12.5)	0.59
Low flow 02	5 (13.2)	17 (11.2)	
High flow 02	1 (2.6)	4 (2.6)	
Mechanical ventilator	0	2 (1.3)	
Number of deaths	0	2 (1.3)	1.0
Lung infiltration on chest X ray at admission	14 (36.8)	54 (35.5)	0.87
Laboratory findings of COVID-19, n (%)			
Leukopenia	14 (36.8)	51 (33.6)	0.70
Increased CRP	15 (39.5)	61 (40.1)	0.94
Increased AST	8 (21.1)	22 (14.5)	0.32
Increased ALT	10 (26.3)	26 (17.1)	0.19
Increased LDH	11 (28.9)	39 (25.8) out of 151	0.69
Increased BNP	3 (7.9)	10 (7.1) out of 140	1.0
Prolonged PT	3 (7.9)	10 (6.6) out of 151	0.72
Increased fibrinogen	10 (26.3)	21(13.9) out of 151	0.06
Increased D-dimer	6 (16.2) out of 37	21(15.9) out of 132	0.96

We bolded significant **P values (p<0.05)**
Comparisons between groups were made by the chi-squared test.

Regarding the severity of COVID-19, severe/critical patients accounted for 15.8% of patients with rheumatic diseases and 11.8% of controls, but there was no significant difference in the proportion of severity of COVID-19 between the two groups (Table 2). The proportion of patients who needed oxygen therapies was not significantly different. Six patients (15.8%) received oxygen therapy in the rheumatic disease group, and nineteen patients (12.9%) received oxygen in the control group. In the rheumatic disease group, a single patient received treatment in the intensive care unit for organ failure and shock, but all patients had a successful recovery and were discharged. None of the patients underwent mechanical ventilation or extracorporeal membrane oxygenation. In the control groups, two patients died of respiratory failure, but there was no significant difference in death between the two groups.

There was no difference in laboratory findings, such as the proportion of patients with leukopenia and increased AST, ALT and LDH levels, between the groups. There was no difference in the proportion of patients with abnormal coagulation tests, such as PT, fibrinogen and D-dimer, in both groups (Table 2).

All one hundred ninety patients underwent chest X-ray examinations at admission. Fourteen patients (36.8%) with underlying rheumatic diseases showed lung infiltration on chest X-ray at admission, and fifty-four patients (35.5%) in the control group showed lung infiltration on chest X-ray at admission. There was no significant difference in the proportion of patients who had lung infiltration on chest X-ray at admission. During admission, eighteen patients with underlying rheumatic diseases showed abnormal findings on chest X-ray. Thirteen patients with underlying rheumatic diseases underwent chest computed tomography (CT) scans. Ground glass opacities were found on the chest CT scans of twelve patients.

In the regression analysis for risk factors associated with severe/critical COVID-19, being more than 60 years old, diabetes, cardiovascular diseases and hypertension were risk factors for severe/critical COVID-19 in univariate analysis (Table 3). However, the presence of rheumatic diseases was not associated with severe/critical COVID-19. In multivariable analysis, being older than 60 years, cardiovascular diseases and diabetes were risk factors for severe/critical COVID-19.

Table 3: Regression analysis of factors associated with severe/critical COVID-19

Factors	OR (95% CI) Univariate	P value	OR (95% CI) Multivariable	P value
Age> 60 years old	5.75 (2.04~16.17)	<0.01	3.66 (1.13~11.81)	0.03
Cardiovascular	8.1 (1.87~34.93)	<0.01	5.61 (1.1~28.4)	0.03
Cerebrovascular	1.40 (0.15~12.52)	0.76		
Diabetes	5.88 (2.12~16.32)	<0.01	3.20 (1.04~9.83)	0.04
Rheumatic diseases	1.39 (0.51~3.79)	0.51		
Hypertension	3.16 (1.30~7.67)	0.01	1.18 (0.41~3.41)	0.74
Male	1.2 (0.4~3.0)	0.73		

Odds ratios and 95% confidence intervals (95% CIs) are expressed.

DISCUSSION

This manuscript discusses the clinical characteristics of COVID-19 in patients with rheumatic diseases. Among 4,966 patients, thirty-eight patients (0.7%) were identified as having an underlying rheumatic disease. The clinical characteristics of COVID-19 patients with underlying rheumatic diseases were compared with those of patients without rheumatic diseases through case–control matching. In our study, interestingly, more patients with underlying rheumatic diseases showed some clinical manifestations of COVID-19, such as cough, sputum, sore throat, dyspnea, chest discomfort and diarrhea, than

controls. However, there was no difference between groups in the severity of COVID-19. Most patients in both groups showed a mild or moderate course. The proportion of patients who needed oxygen and the proportion of patients with lung infiltration on chest X-ray at admission were not significantly different between groups. The proportion of patients with abnormal laboratory findings, including increased C-reactive protein and abnormal coagulation profiles, was not significantly different. Throughout the results regarding severity, the number of deaths, laboratory and imaging studies, admitted COVID-19 patients with underlying rheumatic diseases showed similar courses to controls without rheumatic diseases in this study.

There have been some published data regarding the outcome of COVID-19 underlying rheumatic diseases. In the primary care database of the United Kingdom, deaths related to COVID-19 in combined groups of patients with rheumatoid arthritis, psoriasis, or lupus were higher than those in the general population[6]. In another large population study, the United Kingdom Biobank cohort, which consisted of 5,409 people with rheumatoid arthritis and 467,730 people without rheumatoid arthritis, showed that rheumatoid arthritis was associated with the risk of death related to COVID-19[7]. However, the results were not consistent among studies[9]. Serling-Boyd et al showed that in a cohort study including 143 patients with rheumatic and musculoskeletal diseases and 688 comparators, hospitalization, intensive care unit admission, and death were not significantly different between the two groups[12].

Rheumatic diseases include a variety of different diseases, and their immune status, activity and medications vary. For example, the status of immunity in young men with ankylosing spondylitis who take nonsteroidal anti-inflammatory drugs could be different from that in women with active rheumatoid arthritis and interstitial lung diseases who are treated with biologic agents. One multicenter cohort study, which was composed of 456 rheumatic and nonrheumatic patients, showed that having connective tissue diseases such as lupus was associated with severe COVID-19 but not chronic inflammatory arthritis such as rheumatoid arthritis[13]. In our study, lupus, inflammatory myositis or vasculitis were not included compared to other studies of rheumatic diseases[12,13]. The heterogeneity of rheumatic diseases in various COVID-19 studies might affect the outcome of COVID-19 differently.

Since patients with rheumatic diseases are treated with various immunomodulatory agents or anti-cytokine therapies for rheumatic diseases, there is concern about poor outcomes in COVID-19 patients with underlying rheumatic diseases. In 2,869 patients with COVID-19 and rheumatoid arthritis, patients who were treated with Janus kinase inhibitors or rituximab before developing COVID-19 showed poorer outcomes than patients treated with tumor necrosis factor inhibitors[14]. In our study, only three patients were treated with biologic agents, and this number is smaller than that in other studies[12,14]. Two patients were treated with adalimumab for ankylosing spondylitis and one patient was treated with tocilizumab for rheumatoid arthritis. A possible explanation for the low number of patients with biologic agents in our study is that in South Korea, the prescription paper that was distributed to patients did not include the injection material. Therefore, there is a possibility of missing data regarding biologic agents. However, there is another possibility that patients in our study might be in moderate/mild activity of rheumatic diseases that did not need biologic agents. High disease activity of rheumatic diseases could be related to poorer outcome in COVID-19 underlying rheumatic disease[15], and the outcome of the patients with rheumatic diseases in our study could be partially influenced by the activity of rheumatic diseases. However, since the data regarding the activity of rheumatic disease were not evaluated in this study, no affirmation could be made.

In the rheumatic group, one patient who was in a critical condition in the intensive care unit presented with congestive heart failure and acute renal injury, but she recovered successfully in the end. Two patients in the control group died of respiratory failure, and there was no significant difference in death in either group in our study. In contrast to our study, in Mass General Brigham cohorts that included two tertiary hospitals, the case fatality rate in rheumatic diseases was reported to be up to 8%[12]. Compared to other studies about rheumatic diseases[12,15], the case fatality of rheumatic diseases in our study is low. During the pandemic, the Busan Medical Center, which was originally a secondary care hospital, was designated the main referral center for COVID-19. The referral of patients for COVID-19 was decided by the central task force system[10]. Therefore, there is a possibility that more critical patients were referred to tertiary referral hospitals instead of the Busan Medical Center.

The severity of COVID-19 could be influenced by the treatment protocol, vaccination and admission availabilities along with the timeline of COVID-19. The outcome of COVID-19 was improved with the accumulation of treatment experience. In a rheumatic cohort study over the course of COVID-19, mechanical ventilation risk in the rheumatic disease group was improved in the later pandemic period versus the earlier pandemic period 6 months apart[12,16]. Since our study was performed from February 2020 to November 2021, these patients might be less impacted by the peak surge of COVID-19 compared to other studies that were performed during the peak of COVID-19[16].

This study has several limitations. First, it is a retrospective study. The inclusion of patients was performed from February 2020 to November 2021. Given the surge in COVID-19, an overwhelming load might lead to a lack of thorough evaluation for rheumatic diseases during the pandemic. The number of patients who had rheumatic diseases was relatively small. Since admission of patients due to COVID-19 was decided by the central task force team, patients who were critical initially tended to be referred to tertiary hospitals, which could lead to selection bias.

However, the study still includes meaningful data. Since the Busan Medical Center was designated a dedicated COVID-19 center, all various aspects, such as severity, clinical data, laboratory findings and imaging data surrounding COVID-19, were captured, although the surge of COVID-19 might affect the quality of data. To determine the whole picture of admitted COVID-19 patients with underlying rheumatic diseases, further analysis including tertiary hospital data is needed.

CONCLUSION

Although patients with rheumatic diseases showed a variable clinical course of COVID-19 in previous studies, most COVID-19 inpatients with underlying rheumatic diseases in our study showed a similar course to inpatients without rheumatic diseases.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflict of Interest: None

Competing Interest: None

Acceptance Date: 05 May 2023

REFERENCES

1. Vályi-Nagy I, Uher F, Rákóczi É, et al. Adaptive Immunity to Viruses: What Did We Learn from SARS-CoV-2 Infection? Int J Mol Sci 2022;23(22):13951.
2. Jin Y, Yang H, Ji W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses 2020;12(4):372
3. Dewanjee S, Kandimalla R, Kalra RS, et al. COVID-19 and Rheumatoid Arthritis Crosstalk: Emerging Association, Therapeutic Options and Challenges. Cells 2021;10(12):3291.
4. Gracia-Ramos AE, Martin-Nares E, Hernández-Molina G. New Onset of Autoimmune Diseases Following COVID-19 Diagnosis. Cells 2021;10(12):3592.
5. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med 2020;383(18):1757-66.
6. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using Open SAFELY. Nature 2020;584(7821):430-6.
7. 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):333-40.
8. Reilev M, Kristensen KB, Pottegård A, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT–PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol 2020;49(5):1468-81.
9. Grainger R, Kim AHJ, Conway R, et al. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. Nat Rev Rheumatol 2022;18(4):191-204.
10. Her M. Repurposing and reshaping of hospitals during the COVID-19 outbreak in South Korea. One Health 2020;10:100137.
11. www.covid19treamentguidline, nih, gov/overview/clincial -spectrum. Clinical Spectrum | COVID-19 Treatment Guidelines (nih.gov)
12. Serling-Boyd N, D'Silva KM, Hsu TY, et al. Coronavirus disease 2019 outcomes among patients with rheumatic diseases 6 months into the pandemic. Ann Rheum Dis 2021;80(5):660-6.
13. Pablos JL, Galindo M, Carmona L, et al. Clinical outcomes of hospitalized patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis 2020;79(12):1544-49.
14. Sparks JA, Wallace ZS, Seet AM, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry. Ann Rheum Dis 2021;80(9):1137-46.
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):930-42.
16. D'Silva KM, Serling-Boyd N, Wallwork R, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. Ann Rheum Dis 2020;79(9):1156-62.