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COVID-19 and autoimmune rheumatic diseases

COVID-19 y enfermedades reumáticas autoinmune

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SUMMARY

Background: *Coronavirus disease 2019 (COVID-19) was declared a pandemic since it rapidly spread worldwide. COVID-19 has various manifestations, ranging from asymptomatic to life-threatening conditions. During the pandemic, patients with autoimmune rheumatic diseases (ARD) were included in the population at risk. In addition, the use of immunosuppressants or disease-modifying antirheumatic drugs (DMARDs) was considered to increase the susceptibility to infection. Studies have reported that COVID-19 and ARD have similarities in their clinical findings and immune responses. This study aims to understand the profile of patients with ARD infected with COVID-19 at Dr. Soetomo Hospital in 2020–2022.*
Methods: *An observational cross-sectional study using the medical records of ARD patients was carried out in the rheumatology outpatient clinic at Dr. Soetomo Hospital, Surabaya.*
Results: *This study included 200 patients. Of these, 49 (24.5 %) were infected with COVID-19. The study population was predominantly female (93.9 %), with a mean age of 43±14.3 years old. Methylprednisolone was the most frequent medication used. A total of 63.2 % of the samples had asymptomatic–mild COVID-19 conditions, while the others had moderate–severe COVID-19 conditions. There were 14 cases (28.6 %) that developed ARD post-COVID-19 infection.* **Conclusion:** *The proportion of COVID-19 among ARD patients was 24.5 %.*

Keywords: *Autoimmune rheumatic disease, COVID-19, humans and health.*

RESUMEN

Antecedentes: *La enfermedad por coronavirus 2019 (COVID-19) fue declarada pandemia debido a que se propagó rápidamente por todo el mundo. La COVID-19 tiene varias manifestaciones, que van*

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desde condiciones asintomáticas hasta condiciones que amenazan la vida. Durante la pandemia, los pacientes con enfermedades reumáticas autoinmunes (ERA) se incluyeron en la población de riesgo. Además, se consideró que el uso de inmunosupresores o fármacos antirreumáticos modificadores de la enfermedad (FAME) aumentaba la susceptibilidad a la infección. Los estudios han indicado que COVID-19 y ARD tienen similitudes en sus hallazgos clínicos y respuestas inmunes. El objetivo de este estudio es comprender el perfil de los pacientes con ERA infectados con COVID-19 en el Hospital Dr. Soetomo en 2020-2022. **Métodos:** *Se llevó a cabo un estudio transversal observacional utilizando los registros médicos de pacientes con ERA en la consulta externa de reumatología del Hospital Dr. Soetomo, Surabaya.* **Resultados:** *Este estudio incluyó a 200 pacientes. De estos, 49 (24,5 %) estaban infectados con COVID-19. La población de estudio fue predominantemente femenina (93,9 %), con una edad media de 43±14,3 años. La metilprednisolona fue el medicamento más frecuentemente utilizado. Un total de 63,2 % de las muestras tenían condiciones de COVID-19 asintomático-leve, mientras que el resto tenían condiciones de COVID-19 moderadas-graves. Hubo 14 casos (28,6 %) que desarrollaron ERA post-infección por COVID-19.* **Conclusión:** *La proporción de COVID-19 entre los pacientes con ERA fue del 24,5 %.*

Palabras clave*: Enfermedad reumática autoinmune, COVID-19, humanos y salud.*

INTRODUCTION

The Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) was discovered as pneumonia cases in Wuhan City, China, in December 2019. The World Health Organization (WHO) officially named the disease resulting from the infection of SARS-CoV-2 as coronavirus disease 2019 (COVID-19). As the disease rapidly spread worldwide, the WHO then declared COVID-19 a pandemic. In the early days of the pandemic, few studies were conducted related to this disease. However, based on the observations, COVID-19 appeared to have various manifestations, ranging from asymptomatic to life-threatening conditions. Autoimmune rheumatic diseases are characterized by a dysregulation of the immune systems and immune-mediated inflammation against joints, bones, muscles, and connective tissues, predominantly. Patients with ARD were included in the population at risk of COVID-19. ARD patients are dependent on immunosuppressants or DMARDs, which have effects on the immune system to control disease progression. Therefore, an increased risk for worse COVID-19 disease outcomes may be observed in immune-compromised populations (1). It was reported that COVID-19 was twice as common in people with autoimmune diseases compared to the general population (2). Although it seems that the COVID-19 pandemic puts ARD patients at risk, several studies have reported that COVID-19 and ARD have similarities in their clinical findings and immune-mediated injuries, such as cytokine storm and tissue damage (1).

Our study aimed to describe the special interplay between COVID-19 and ARD, which began with data collection of the profile of patients with ARD infected with COVID-19 at Dr. Soetomo Hospital in 2020-2022, including the demographics data, clinical characteristics of ARD patients, their COVID-19 infection, and vaccination history.

METHODS

We conducted a retrospective observational cross-sectional study, including patients with autoimmune rheumatic diseases who were infected with SARS-CoV-2, and who attended the rheumatology outpatient clinic at Dr. Soetomo Hospital, Surabaya.

We obtained the following data from the medical records: demographics, comorbidities, ARD patients' current diagnoses and treatments, and their COVID-19 infection and vaccination history. A diagnosis of SARS-CoV-2 infection was considered if the patients had a positive polymerase chain reaction (PCR) test, a positive antigen test (3), and high suspicions of infection following the clinical symptoms' scoring (4). The COVID-19 severity was determined based on the COVID-19 Treatment Guidelines of the National Institutes of Health (5), which categorized the disease as asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness.

After collecting the data by total sampling, 49 of 200 patients were eligible for this study. The results of the descriptive analyses are presented in Table 1 using frequencies and percentages for the qualitative variables and median values for continuous variables. The Mann–Whitney test was used to conduct a bivariate analysis of the predictive factors that could determine the severity of the COVID-19 manifestations.

RESULTS

Our study identified 49 patients from a total population of 200, through the inclusion and exclusion criteria. The proportion of ARD patients infected with COVID-19 was 24.5 % (Table 1).

Table 1. COVID-19 History

COVID-19 Infection History	Frequency (n = 200)
History of infection	
Never getting infected	151 (75.5 %)
Infected	49 (24.5 %)

The patients' characteristics are presented in Table 2, including the demographic data, in which females were the majority, and the patients had a mean age of 43±14.3 years. The most common primary ARD diagnoses were undifferentiated spondyloarthritis (SpA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis, accounting for 44.9 %, 32.7 %, 16.3 %, and 4.1 %, respectively. The frequency of the undifferentiated SpA was higher than the SLE in the sample compared to the population data. There were various ARD-related current medications including methylprednisolone (65.3 %), methotrexate (32.7 %), chloroquine/hydroxychloroquine (26.5 %). The most notable comorbidities among the ARD patients were hypertension (24.5 %), cardiovascular disease (16.3 %), and diabetes mellitus (6.1 %).

Table 2. Characteristics of the ARD Patients Infected with COVID-19

Characteristics of the ARD Patients Infected with COVID-19	Frequency (n = 49)
Sex	
Female	46 (93.9 %)
Male	3 (6.1 %)
Age (years)	43±14.3
≤ 30	13 (27 %)
31 – 40	10 (20 %)
41 – 50	11 (22 %)
51 – 60	8 (16 %)
≥ 61	7 (14 %)
ARD diagnosis	
Undifferentiated spondyloarthritis	22 (44.9 %)
Systemic lupus erythematosus	16 (32.7 %)
Rheumatoid arthritis	8 (16.3 %)
Psoriatic arthritis	2 (4.1 %)
Scleroderma	1 (2.0 %)
ARD current medication	
Not receiving any current medication	2 (4.1 %)
Methylprednisolone	32 (65.3 %)
Methotrexate	16 (32.7 %)
Chloroquine/Hydroxychloroquine	13 (26.5 %)
Sulfasalazine	10 (20.4 %)
NSAIDs	8 (16.3 %)
Mycophenolate sodium	7 (14.3 %)
Azathioprine	4 (8.2 %)
Leflunomide	3 (6.1 %)
Comorbidities	
Hypertension	12 (24.5 %)
Cardiovascular disease	8 (16.3 %)
Diabetes Mellitus	3 (6.1 %)

Table 3 describes the history of COVID-19 infections. More than half of the ARD patients with COVID-19 had asymptomatic–mild COVID-19 clinical conditions (63.2 %), and 36.7 % had moderate–severe clinical conditions. The patients carried out self-isolation (69.4 %) and underwent hospital admission (30.6 %). Only 22.4 % had received the COVID-19 vaccine; two people had been vaccinated once, six people had received two doses, and three people had received three. Despite the infection, 57.1 % of the ARD patients chose to continue their ARD medication, and 14.3 % chose to stop. For those who chose to continue their ARD medication, it was mostly due to the lack of knowledge and information regarding this issue.

Table 3. COVID-19 Infection History

COVID-19 Infection History	Frequency (n = 49)
COVID-19 diagnosis assessment	
PCR swab, positive	35 (71.4 %)
Clinical symptoms	8 (16.3 %)
Antigen swab, positive	6 (12.2 %)
COVID-19 source of infection	
Family	22 (44.9 %)
Public place	15 (30.6 %)
Workplace / School	12 (24.5 %)
Year of COVID-19 Infection	
2021	30 (61.2 %)
2020	10 (20.4 %)
2022	9 (18.4 %)
COVID-19 clinical condition	
Mild	25 (51 %)
Severe	10 (20.4 %)
Moderate	8 (16.3 %)
Asymptomatic	6 (12.2 %)
Management during COVID-19 infection	
Self-isolation	34 (69.4 %)
Hospital admission	15 (30.6 %)
COVID-19 vaccination history	
Unvaccinated	38 (77.6 %)
Vaccinated	11 (22.4 %)
ARD medication status during COVID-19 infection	
Continued	28 (57.1 %)
Not diagnosed with ARD yet	14 (28.6 %)
Stopped	7 (14.3 %)

The data showed that 28.6 % of the sample had a COVID-19 infection before being diagnosed with ARD. The characteristics of the patients diagnosed with ARD post-COVID-19 infection are presented in Table 4.

Table 4. Post-COVID-19 Infection ARD Diagnosis History

Post-COVID-19 Infection ARD Diagnosis	Frecuency (n = 14)
Sex	
Female	12 (85.7 %)
Male	2 (14.3 %)
COVID-19 clinical condition	
Mild	6 (42.9 %)
Moderate	4 (28.6 %)
Severe	3 (21.4 %)
Asymptomatic	1 (7.1 %)
Management taken during COVID-19 infection	
Self-isolation	9 (64.3 %)
Hospital admission	5 (35.7 %)
ARD current diagnosis	
Undifferentiated spondyloarthritis	7 (50 %)
Rheumatoid arthritis	5 (35.7 %)
Systemic lupus erythematosus	2 (14.3 %)

We conducted a bivariate analysis using the Mann–Whitney test to analyze the predictive factors that might determine the severity of COVID-19. In the beginning, we wanted to conduct multivariate analysis with logistic regression, but the potentially predictive factors were not significantly associated with the outcomes, as seen in Table 5.

Table 5. Analysis of the Factors Potentially Predicting the Severity of COVID-19

Potentially Predictive Factors		Severity of COVID-19				p-value
		Asymptomatic	Mild	Moderate	Severe	
Age	≤ 60 years	6	21	8	7	p=0.332 *
	>60 years	0	4	0	3	
Comorbidity	Hypertension or Diabetes or CVD	2	6	6	3	p=0.334 *
	No comorbidity	4	19	2	7	
Continuing DMARDs during COVID-19	Stopped/no medication	2	11	4	4	p=0.810 *
	Continued	4	14	4	6	
Vaccination	Not vaccinated	6	16	6	10	p=0.392 *
	Vaccinated ≥ 1x	0	9	2	0	

* Not significant using the Mann-Whitney test.

DISCUSSION

In this study, 49 of 200 (24.5 %) ARD patients were infected with COVID-19 during 2020-2022. This number was higher than the results of a study conducted by the Indonesian Rheumatology Association (6) in 2020 of 1.93 %. We need to consider that in the early days of the pandemic, the diagnostic tools were not evenly spread, and studies had not been carried out related to the assessment methods for COVID-19. The prevalence and epidemiological characteristics of COVID-19 in Indonesia from March 2020 to February 2021 showed that 15.7 % were confirmed positive for SARS-CoV-2 (7). Another study from Egypt showed relatively the same proportion as our study, at 25.7 % (8).

The female predominance in this study paralleled a previous cohort study conducted by Alhowaish et al. (9). However, the result was contrary to studies that reported that males were more vulnerable to COVID-19 (10). Yet, because our patients were mostly women, conclusions cannot be drawn. Our patients had a mean age of 43±14.3 years. The average number was similar to that of the study of Alhowaish et al. (9) with 48.3±16 years and the study of Bakasis et al. (11) with 46.6±15.4 years in patients with asymptomatic, mild, or moderate disease. Those studies documented the onset of ARD in COVID-19 patients around the fourth decade.

The most common primary ARD diagnoses were undifferentiated SpA, SLE, RA, and psoriatic arthritis. A previous study showed that subjects with SpA were 27 % more likely to develop COVID-19 than the controls, but the increase did not reach statistical significance (12). The results of this study were different from studies conducted in Saudi Arabia, where rheumatoid arthritis (41.8 %) was the most frequent ARD diagnosis in COVID-19-infected patients (9). Theoretically, ARD patients were included in the population at risk during the pandemic due to the underlying immune-mediated disease and their dependence on immunosuppressive or immunomodulatory treatments. As the first-line treatment for SpA, NSAID use was not associated with the severity of COVID-19, worse in-hospital mortality, critical care admission, or ventilation (13). Our study echoed the cohort study conducted in Saudi Arabia (9) with methylprednisolone, methotrexate, and hydroxychloroquine as the three medications most widely used by ARD patients. Corticosteroids play an important role in immunity and inflammation, especially at low doses (14). This study failed to document the dose-related frequency of steroid use, but a study in France reported that corticosteroids were associated with a higher risk of severe COVID-19 (15). However, as the studies on COVID-19 and its treatment have evolved, the use of corticosteroids for COVID-19 therapy has been considered. Most of our patients continued the use of ARD medications during COVID-19. The correlation between the continuation of ARD medications and the COVID-19 clinical outcome needs to be further investigated, and the data regarding the use of systemic corticosteroids in ARD patients during COVID-19 must be interpreted with caution. Aside from methylprednisolone, methotrexate is also widely used by ARD patients. One study in Spain found no difference in the mortality rates between patients admitted for COVID-19 with DMARD use versus no DMARD use (16). Another previous study suggested that the use of methotrexate did not impact the susceptibility to or severity of COVID-19 (12). As stated before, our patients continued their medications despite COVID-19 infection. Advanced study is needed to confirm whether continuing or discontinuing ARD medications during COVID-19 will have a significant impact. In addition, a prospective study of DMARDs' disruption showed that over half of the participants appeared to have a flare of the underlying systemic ARD in the weeks following acute infection (17).

Regardless, there is controversy over the treatments for ARD patients during the COVID-19 course and its associated comorbidities; this study documented asymptomatic–mild symptoms (fever, fatigue, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, and diarrhea) in more than half of the patients. This result was supported by a current observational cohort study, where most patients had a mild course (11). Around 30.6 % of ARD patients were admitted to the hospital during their COVID-19 infection. The result was lower compared to the data from the Global Rheumatology Alliance (18). However,

the ARD patients did not have a significantly high risk of hospitalization (HR: 0.87, 95 % CI: 0.68–1.11) (19).

From the data on whether to continue ARD medication during COVID-19 infection, 28.6 % of the infected participants were not diagnosed with ARD. This finding was in line with a systematic review analyzing the current data of new-onset systemic and rheumatic autoimmune diseases in COVID-19, which identified 99 patients that fulfilled the classification criteria with the common diagnosis of vasculitis and arthritis (20).

In our study, neither age, comorbidities, continuing DMARDs during infection, nor COVID-19 vaccination affected the severity of the COVID-19 manifestations ($p>0.05$). This was different from many studies. This could be due to the small sample size and the fact that we did not differentiate the variants of the SARS-CoV-2 virus.

Our study had some limitations. First, the numbers of participants were limited. Second, since this study used medical records, which provided some of the data based on information provided by the patients, potential biases were inevitable. Third, this descriptive study could not see the strength of the relationship between variables, so further research is needed.

CONCLUSION

Our study emphasized that the ARD patients with COVID-19 at Dr. Soetomo Hospital were predominantly female, with a mean age of 43±14.3 years old. The most common primary ARD diagnoses were undifferentiated SpA, SLE, RA, and psoriatic arthritis. The proportion of COVID-19 among the ARD patients was 24.5 %, with more than half of the sample having an asymptomatic–mild COVID-19 course. Finally, 28.6 % of the ARD cases were diagnosed after COVID-19 infection.

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Conflicts of Interest

The authors declare no conflict of interest.

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