The Profile of COVID-19 in Patients with Autoimmune Disease: A Case Series

Zubairi Djoerban[1,2], Muhammad Alkaff[2,3], Dimas Priantono[1,2], Dyah Agustina Waluyo[2], Jessica Marsigit[2,4], Chairina Azyka Noor[2,4], Oemar Ichsan[2], Kevin Yonathan[2], Matdoan Rifikah Aisyah[2,4], Andy William[2], Uva Rahmah[2], Wahyu Permatasari[2,4]

[1] Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
[2] Kramat 128 General Hospital, Jakarta, Indonesia.
[3] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Persahabatan General Hospital, Jakarta, Indonesia.
[4] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.

Corresponding Author:
Prof. Zubairi Djoerban, MD., PhD. Hematology-Oncologist Consultant, Internal Medicine Specialist, Kramat 128 Hospital. Jl. Kramat Raya, Jakarta 10430, Indonesia. Email: zubairi_djoerban@yahoo.com.

ABSTRACT

Autoimmune diseases are known to be a risk factor for severe COVID-19 infection. This is the first case series of patients with autoimmune disease suffering from COVID-19 infection in Jakarta, Indonesia. There were 12 confirmed cases of COVID-19 infection in autoimmune patients from March 2020 until February 2021. We select 5 patients in this case series. Three of them had systemic lupus erythematous (SLE), one of them had rheumatoid arthritis, and one of them had ankylosing spondylitis. Three of them had high BSR Risk Stratification. Most of them had used daily steroid therapy. Fatigue, abdominal pain, diarrhea, and cough were the common symptoms found. None of the patients were admitted to ICU, used mechanical ventilators, and all of them survived. Most of the patients were prescribed anti-coagulant therapy. This first comprehensive case series can provide valuable information regarding the clinical characteristics of COVID-19 infection in the Indonesian autoimmune disorder patient population.

Keywords*: autoimmune diseases, COVID-19, case series, Indonesia.*

INTRODUCTION

Coronavirus Disease-19 (COVID-19) is a new global pandemic that started in Wuhan, China, at the end of 2019. It is caused by a new virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The virus is transmitted via droplets, and its spike protein (protein S) can infect the respiratory cells as it has Angiotensin-converting enzyme-2 (ACE-2) receptors. In addition to causing respiratory symptoms, it can also manifest in other organ systems, for example kidney injury, heart damage, and coagulation in the blood vessels. Based on the latest number in Indonesia, there are more than 1 million cases of COVID-19 infection with mortality cases over

25,000 (2.9% mortality rate).[2] The spectrum of severity in COVID-19 is variable, ranging from asymptomatic, mild symptoms, moderate symptoms, and life-threatening conditions such as acute respiratory distress syndrome (ARDS) and multi-system organ failure. Patients with chronic comorbid conditions have a higher risk of morbidity and mortality of COVID-19.[3] The severity of COVID-19 is related to a combination between uncontrolled inflammation and dysfunctional lymphocyte response.[4]

Autoimmune disease is a known risk factor for severe COVID-19 infection as patients usually receive immunosuppressive therapy to control the disease.[5] Autoimmune disease occurs when the immune system attacks the body's cells due to immunologic tolerance breakdown towards autoreactive immunity. It is a multifactorial disease that is usually related to genetics, environments, and infections. Common examples of autoimmune disease include systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, etc.[6] Steroids are currently used in treating COVID-19 infection, and it may have a dual effect on the patient. Steroids can either exacerbate the infection or protect the host from cytokine storms resulting from the viral clearance in the early stages.[7] Current prevalence of the autoimmune disease in Indonesia is expected to be more than 2000 patients, and the number is increasing annually, yet the exact number is still unknown.[8]

To our knowledge, this is the first comprehensive case series in Indonesia reporting the characteristics and clinical course of COVID-19 in patients with autoimmune diseases.

CASE ILLUSTRATION

Cases were collected retrospectively from medical records between March 2020 until February 2021. Cases were confirmed by RT-PCR (qRT-PCR) detection of SARS-CoV-2 RNA through analysis of nasopharyngeal swabs. The severity of COVID-19 infection was classified based on the Indonesia National Guideline of COVID-19.[9] The specific diagnosis of autoimmune diseases was made based on the revised classification criteria of the American College of Rheumatology. British Society of Rheumatology (BSR)- Risk Stratification was used to know whether the patient had a low-moderate risk of COVID-19 infection (score less than three) or clinically extremely vulnerable (score three or more).[10] Acute Respiratory Distress Syndrome (ARDS) was diagnosed using Berlin's criteria.[11] Data was analyzed using SPSS software. The results were presented in percentage, mean and standard deviation if data distribution was normal or median and interquartile range if data were not normally distributed.

Ethical approval was obtained from Director of Kramat 128 Hospital. Informed consent was obtained from all patients for being included in the study. Proxy consent occurs when an individual was provided with the legal right to make decision on behalf of another, for example in patient with altered mental status. The patients also give written inform consent for publishing their clinical records.

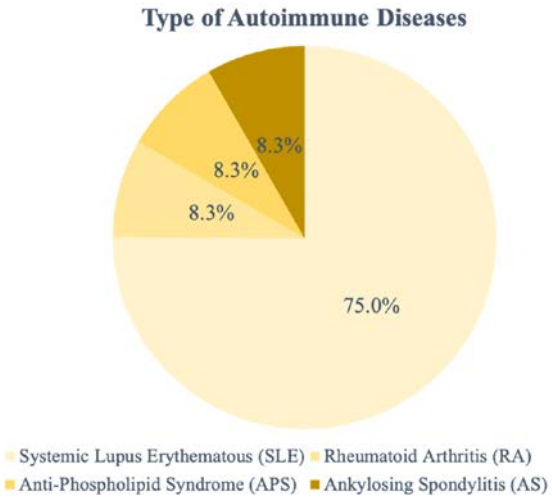

Figure 1. Type of autoimmune diseases

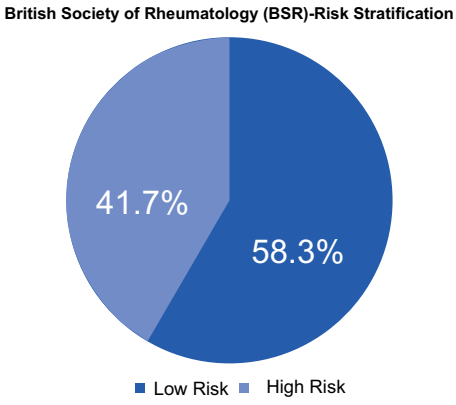

Figure 2. British Society of Rheumatology (BSR) – risk stratification.

There were 60 autoimmune patients who were hospitalized between March 2020 until February 2021, with 12 confirmed cases of COVID-19 infection. Most of the patients (75.0%) had systemic lupus erythematosus (SLE) (**Figure 1**).

Based on the British Society of Rheumatology (BSR)- Risk Stratification, more than 50% of the patients had low-moderate risk (**Figure 2**).

8 out of 12 patients were categorized as moderate COVID-19 infection, three as mild COVID-19 infection, and only one patient without any symptoms (**Figure 3**).

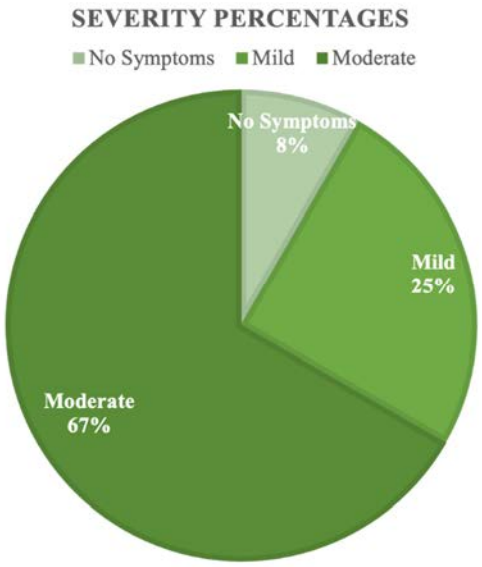

Figure 3. Severity percentages.

We select five COVID-19 patients with autoimmune diseases included in this case series. Three of them had systemic lupus erythematous as the base autoimmune diseases, one with rheumatoid arthritis, and one with ankylosing spondylosis. **(Table 1)**

Case 1

Female, 46 years old, had Systemic Lupus Erythematous (SLE) with hypertension and hyperthyroidism came into the ER with moderate COVID-19 severity. She used Methylprednisolone 2x4 mg daily with BSR Risk Stratification categories of high. She had symptoms such as fever, chills, muscle pain, joint pain, abdominal pain, diarrhea, nausea, cough, fatigue, and dyspneu. Upon hospital admission, she was hypertensive (177/96 mmHg), tachycardic (107x/minute), and feverish (37.6^{o}C). She was given oxygen supplementation of 5 liter/minute using nasal cannule and her oxygen saturation was 98%. She had body mass index category of overweight (22.1 kg/m2). She had absolute lymphocyte count (ALC) of 1317/uL with Neutrophil-Lymphocyte Ratio (NLR) of 1.93. She had normal D-dimer result with ground glass opacity as found in the thorax CT-Scan. She was treated with vitamins, intravenous Remdesivir, and Heparin prophylaxis dose (2x5000U).

Case 2

Female, 46 years old, had Rheumatoid Arthritis (RA) with hypertension, heart disease, hyperthyroidism, and chronic kidney disease came into the ER with moderate COVID-19 severity. She used Methylprednisolone 1x4 mg daily with Sulfasalazine three times a day. She had low BSR Risk Stratification. She

Table 1. Patient's characteristics.

Patient No.	Sex	Age	Auto-immune Disease	Comorbidities	Autoimmune Medication	Prednisolone Equal Dose (mg/ day)	BSR Risk Stratification	Charlson Comorbidity Index	Length of Stay	COVID Severity
1	F	46	SLE	HT, Thyroid	Glucocorticoid	10	High	0	7	Moderate
2	F	46	RA	HT. Heart Disease, Thyroid, CKD	Glucocorticoid, Sulfasalazine	5	Low	5	10	Moderate
3	F	36	SLE	Heart disease, Tuberculosis	Glucocorticoid	10	High	2	15	Moderate
4	M	33	AS	HT, Obesity	None	N/A	Low	0	0	Mild
5	F	27	SLE	Lymphadenitis TB	Glucocorticoid	20	High	0	8	Mild

had symptoms such as sore throat, joint pain, abdominal pain, diarrhea, cough, fatigue, and dyspneu. Upon hospital admission, she was normotensive (122/75 mmHg), bradycardic (58x/minute), and her oxygen saturation was 98% in room air. She had body mass index category of overweight (22 kg/m^2). She had absolute lymphocyte count (ALC) of 1644/uL with Neutrophil-Lymphocyte Ratio (NLR) of 1.15. She had normal D-dimer result with normal thorax x-ray. She was treated with vitamins and Heparin prophylaxis dose (2x5000 U).

Case 3

Female, 36 years old had Systemic Lupus Erythematous (SLE) with congestive heart failure with (Ejection Fraction of 55%), and hypercoagulable state came into the ER with moderate COVID-19 severity. She used Methylprednisolone 2x4 mg, Aspirin 1x80 mg, Nitroglycerine 1x2.5 mg, Furosemide 1x40 mg, Spironolactone 1x100 mg, and Diltiazem 1x200 mg. She had high BSR Risk Stratification. She had symptoms such as fever, headache, fatigue, ageusia, abdominal pain, nausea, vomiting, and diarrhea. Upon hospital admission, she was normotensive (120/80 mmHg), heart rate was 100x/minute, and her oxygen saturation was 97% on room air. She had body mass index category of obese (28 kg/m^2). She had absolute lymphocyte count (ALC) of 2034/uL with Neutrophil-Lymphocyte Ratio (NLR) of 2.03. She had increased D-Dimer of 1400 with bilateral infiltrate on the thorax x-ray. She was treated with vitamins and Heparin prophylaxis dose (2x5000 U).

Case 4

Male, 33 years old had ankylosing spondylitis (AS) with hypertension came into the ER with mild COVID-19 severity. He did not use any routine medications. He had low BSR Risk Stratification. He had symptoms of cough, runny nose, fatigue, muscle pain, joint pain, and diarrhea. Upon hospital admission, he was hypertensive (149/94 mmHg), heart rate was 72x/minute, and her oxygen saturation was 99% on room air. He had body mass index category of obese (28 kg/m^2). He had absolute lymphocyte count (ALC) of 3400.3/uL with Neutrophil-Lymphocyte Ratio (NLR) of 1.43. He had normal D-dimer result with normal thorax x-ray. He was treated with vitamins and sent to do self-isolation.

Case 5

Female, 27 years old had Systemic Lupus Erythematous (SLE) with tuberculosis of the glands came into the ER with mild COVID-19 severity. She used Methylprednisolone 16 mg daily. She had high BSR Risk Stratification. She had symptoms of fever, headache, runny nose, anosmia, ageusia, fatigue, and joint pain. Upon hospital admission, she was normotensive (107/68 mmHg), heart rate was 76x/minute, and her oxygen saturation was 99% on room air. She had body mass index category of overweight (22 kg/m^2). She had absolute lymphocyte count (ALC) of 2125.2/uL with Neutrophil-Lymphocyte Ratio (NLR) of 7.64. She had normal D-dimer result with normal thorax x-ray. She was treated with vitamins and Heparin prophylaxis dose (2x5000 U). She had increased D-Dimer (800) with normal thorax x-ray. She was treated with Methylprednisolone high dose (2x125 mg) for 2 days due to increased disease activity and Heparin continuous drip 10.000 unit/24 hour.

DISCUSSION

There have been several studies investigating the impact of the presence of autoimmune diseases in COVID-19. Below we highlighted several studies and correlating them with the results from our case series.

Risk of Developing COVID-19

Autoimmune diseases have been postulated as risk factors for developing infection through the generation of autoantibody to cytokines. For example, autoantibody to IFN-γ is associated with an increased risk of tuberculosis infection.[12] Autoimmune disease, primarily systemic connective tissue disease such as systemic lupus erythematosus (SLE), was associated with delayed type 1 interferon response. This dysfunctional interferon response could predispose to a higher risk of SARS-CoV-2 infection and worse outcome.[13]

Several studies reported that patients with autoimmune diseases were at higher risk of developing COVID-19 than general population. Pablos JL et al. conducted a retrospective observational study from seven hospitals in Spain, investigating the difference between the prevalence of PCR + COVID-19 in rheumatology patients compared with matched reference populations from the same hospitals.[14] The results showed that patients with chronic inflammatory diseases had higher odds of developing COVID-19 (OR 1.3, 95% CI 1.15-1.52) compared with the reference population. This higher prevalence was observed in systemic autoimmune or immune-mediated diseases, except for inflammatory arthritis or SLE. Besides, patients receiving biologic or targetted synthetic disease-modifying antirheumatic drugs (bDMARD or tsDMARD) but not conventional-synthetic DMARD (csDMARD) had a higher prevalence than the reference population.[14] Similarly, a meta-analysis of 62 observational studies showed that patients with autoimmune diseases were at higher risk of developing COVID-19 than the control patients (OR 2.19; 95% CI 1.05 - 4.58). Unlike the previous study, the SLE/ Sjögren's syndrome/ Systemic sclerosis subgroup had a higher prevalence of COVID-19 than other disease subgroups. The meta-regression analysis results also showed that studies with a higher proportion of steroid use had a higher prevalence of COVID-19. Meanwhile, the use of DMARDs was not associated with increased risk.[15]

However, not all studies supported those results. An online survey involving 1,381 respondents with rheumatic diseases in Ireland reported that the COVID-19 PCR positivity rate was 0.46%, similar to general Irish population positivity rate.[16] Similarly, a large cross-sectional study performed in Italy reported no difference in the incidence of COVID-19 between patients with autoimmune disease and those with no autoimmune disease.[17] Recommendation from European League Against Rheumatism (EULAR) also stated that so far, there had been not enough evidence that autoimmune diseases increased the risk of COVID-19.[18]

Our case series was not designed to estimate the risk of SARS-CoV-2 infection in autoimmune disease patients. Thus, we were unable to draw any conclusion regarding the risk of infection in our patient population. Our study identified 12 patients with autoimmune diseases and confirmed COVID-19. Although men have a higher risk of SARS-CoV-2 infection in the general population, most of our subjects were female because they had higher risk of developing autoimmunity. Based on the BSR risk score, about half of the patients in this series were classified as low risk and the other half as high risk. Two of the patients were healthcare workers. Although one of them (patient no. 9) was classified as BSR low risk, they were at higher risk of SARS-CoV-2 exposure than the general population due to their clinical duty.

Clinical Characteristics

The most common symptom was fatigue, a non-specific symptom, followed by anorexia, fever, and cough. This finding was pretty similar to a case series in New York, where the most common symptom in the patient population of autoimmune diseases and COVID-19 was fever, followed by cough and dyspnea.[19] Similarly, data from the German national registry for patients with rheumatic diseases and COVID-19 showed that the patients' common symptoms included cough, fever, and fatigue.[19]About 40% of patients in our case series experienced arthralgia, which might reflect the underlying rheumatic disease activity or disease flares triggered by SARS-CoV-2 infection. In our case series, the most common autoimmune disease was SLE, which was similar to an online survey performed by the Indonesian Rheumatology Association where 63.6% of subjects with confirmed COVID-19 in that study had SLE.[20] One patient in our series had asymptomatic COVID-19 and was hospitalized due to other reasons.

The most prevalent comorbidity in our patient population was hypertension, similar to findings from other studies.[19] However, surprisingly, the prevalence of tuberculosis (TB) was relatively high in our case series (4/12 patients). Three of them had pulmonary tuberculosis, while one patient had lymphadenitis TB. Two of them had active pulmonary TB, and one required streptomycin injection as part of

the TB treatment regimen.

Tuberculosis in COVID-19 has not been extensively reviewed. Past studies about tuberculosis in SARS infection showed that the SARS-CoV infection suppressed cellular immunity, thus causing the reactivation or new infection of *M. tuberculosis*.[21] Besides, tuberculosis patients who suffered from influenza infection had a higher risk of mortality with symptoms lasting for more than seven days. Moreover, tuberculosis is an independent risk factor for hospitalization caused by influenza-associated illness.[22] A systematic review and meta-analysis investigating the relationship between tuberculosis and COVID-19 by Gao et al. stated that the prevalence of tuberculosis was higher in severe COVID-19 patients than non-severe COVID-19 patients (OR=2.10; 95% CI: 0.61-7.18).[22] However, this result was not statistically significant. There was still conflicting data regarding whether tuberculosis affects the mortality rate in patients with COVID-19 or not. One possible mechanism is that active tuberculosis infection can increase the proinflammatory cytokines, such as IFN type I and III, which are upregulated in both COVID-19 and tuberculosis infection.[23] More high-quality studies providing a clear relationship between tuberculosis and COVID-19 are still needed.

Risk of Hospitalization in Patients with Autoimmune Diseases and COVID-19

The COVID-19 Global Rheumatology Alliance (C-19 GRA) is a global physician-reported registry gathering data on patients with rheumatic diseases diagnosed with COVID-19. There have been several publications based on the data, which helped clarify the relationship between rheumatic diseases and the risk or clinical course of COVID-19. One of the earlier publications from the C-19 GRA registry investigated factors associated with increased risk of hospitalizations in autoimmune patients with COVID-19. Around 600 patients from 40 countries were included in the study. The study results showed that older age, comorbidities, and steroid use with a prednisolone-equivalent dose of ≥ 10 mg/day were associated with higher odds of hospitalization. Neither antimalarial use (such as hydroxychloroquine) nor NSAID uses positively or negatively impacted the odds of hospitalization. In contrast, the use of bDMARD or tsDMARD monotherapy was associated with lower odds of hospitalization (OR 0.46; 95% CI 0.22-0.93). This finding was especially true for anti-TNF, as the number of patients who used other classes of drugs was too small to draw conclusions.[24]

The number of patients whose age was ≥ 60 years old in our study was just one patient, and she had a mild course of COVID-19. The age range of patients who had moderate COVID-19 in our study was 28-59 years old. None had a severe course of COVID-19. Half of our patients had taken steroids with a prednisolone-equivalent dose of ≥ 10 mg/day, which was associated with a higher hospitalization rate and worse clinical outcomes.

Risk of Mortality in Patients with Autoimmune Diseases and COVID-19

Strangfeld et al. analyzed 3729 patients with rheumatic diseases from the registry to investigate factors associated with mortality in confirmed or presumptive COVID-19 cases. Rheumatoid arthritis was the most common rheumatic disease in the study, followed by connective tissue diseases such as SLE. Most patients were in remission or had low disease activity. Deaths occurred in 10.5% of patients in the study, and half were hospitalized. More than half of the patients had comorbid disease, the most common being hypertension. Other prevalent comorbidities include chronic lung disease, obesity, other cardiovascular diseases, and chronic kidney disease. Regarding therapy for autoimmune diseases, around 40% of patients only received either csDMARDs, immunosuppressants, or a combination of both. In contrast, approximately 20% of patients did not receive any DMARD or immunosuppressant except for steroids. Almost 40% of patients were treated with steroids, whereby 10% of them received a dose exceeding >10 mg/day.[25]

The results of the multivariate analysis from the study revealed the following factors to be associated with increased risk of deaths: 1) age >65 years old, 2) male sex, 3) chronic lung disease, 4) presence of both CVD and hypertension, 5) patients who did not receive any DMARD, 6)

treatment with rituximab, 7) treatment with sulfasalazine, 8) immunosuppressants, 9) steroid treatment with a prednisolone-equivalent dose of >10 mg/ day, 10) high/ severe/ moderate disease activity. The association between increased age, male sex, and comorbidities had been established as factors that could increase the risk of COVID-related mortality in other populations. High disease activity and absence of DMARD being risk factors highlighted the importance of autoimmune disease control even in patients with COVID. Rituximab worked by depleting B-cells, which could impair immunity to COVID. Likewise, a high dose of steroid and immunosuppressants could cause dysfunction of the host's immune system, leading to a more severe presentation of COVID. The association with sulfasalazine was surprising, given that it was a weak immunosuppressant, but the result was consistent with studies from IBD-COVID patient population. However, as the authors noted, an association was not the same as causation, and further prospective studies were needed.[25]

In our case series, only two patients had taken csDMARD (methotrexate and sulfasalazine) while none had taken bDMARD or tsDMARD. Most of our patients (75%) did have comorbidities that predisposed them to a higher risk of mortality, such as hypertension, cardiovascular disease, and chronic lung disease (tuberculosis). Another factor that might increase mortality in our study was steroid use with a dose of ≥ 10 mg/ day. Despite that, no mortality occurred in our patient population. There were several possible reasons: no patient had severe COVID-19, the autoimmune disease was pretty well controlled without bDMARD or tsDMARD, most patients were <65 years old and were female.

Limitations of our study stemmed from the fact that this was a descriptive case series. Thus we could not perform any statistical analysis. None of our patients in this series had severe COVID-19. Besides, most of our patients had SLE, and patients with other types of autoimmune disorders were underrepresented. No patients in our study received bDMARD or tsDMARD. Therefore, we could not describe the clinical characteristics in those populations. We also did not use a formal scoring system to assess the disease severity. However, although our study was only a descriptive study, our case series provide valuable information regarding the clinical characteristics of COVID-19 in the Indonesian autoimmune disorder patient population. To our knowledge, only one similar study focusing on Indonesian autoimmune disorder patients had been published previously, and most of their subjects did not undergo PCR confirmation of COVID-19.[20] Conversely, all of the COVID-19 diagnoses in our patients were confirmed by PCR testing.

CONCLUSION

This first comprehensive case series provides characteristics of autoimmune patients having positive COVID-19 infection, of which study is still limited in Indonesia. Protecting high-risk group such as autoimmune patients are important, especially during this pandemic.

DATA AVAILABILITY

The data supporting the result of this article will be made available by the authors, without undue reservation.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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