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Characteristics of Patients with Autoimmune Rheumatic Disease in the Era of COVID-19 Pandemic in Indonesia

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ABSTRACT

Background Coronavirus Disease 2019 (COVID-19) could be fatal high-risk patient including autoimmune rheumatic patien Nowadays, the management of these patients becomes dilem because the use of steroids and disease-modifying anti-rheuma drugs could suppress the immune system however, poor control of t underlying disease increases the infection risk. Understanding t characteristics of these patients in the COVID-19 pandemic essentials to establish management guidelines and identify patie who are more susceptible to COVID-19. This study aimed to determi the characteristics of autoimmune rheumatic patients in the era COVID-19 pandemic in Indonesia. **Methods** A descriptive study usi national scale survey method was conducted. The subjects w autoimmune rheumatic patients in Indonesia and recruited usi consecutive sampling. The variables evaluated in this study w demographic data, history of disease, current medications taken, da activities in the COVID-19 pandemic, and also data related to COVI 19. The surveys distributed in online form to patients w autoimmune rheumatic disease in Indonesia. **Results** During COVI 19 pandemic, 76.5% respondents still do normal activities/work a only 53.2% use personal protective equipment. Eleven of 5 respondents had positive PCR test and confirmed to COVID-19. T risk of COVID-19 infection based on British Society of Rheumatolc (BSR) scoring system showed that 57.9%, 28.6%, and 13.5% patie in high, moderate and low risk, respectively. **Conclusion** Patients w autoimmune rheumatic diseases might be more susceptible to COVI 19 than the general population.

1. Introduction

Coronavirus Disease 2019 (COVID-19) is caused by the Coronavirus-2 Severe Acute Respiratory Syndrome (SARS-CoV-2) and WHO had stated that COVID-19 became a pandemic on 12 March 2020.[1] The first case of COVID-19 was found in China and now has been spread to 213 countries and territories. Globally, as of 15 July 2020, there have been 13,150,645 confirmed cases of COVID-19, including 574,464 deaths, reported to WHO.[2] On the same date, there have been 80,094 positive cases and 3,797 deaths in Indonesia.[3] Compared to the other types of coronavirus, SARS-CoV-2 has faster ability to spread and higher transmission rate.[4] Although COVID-19 is reported to have low mortality rate, it could be fatal in high-risk patients.[5] Moreover, up to now there is no vaccine and special treatment for COVID-19 yet.[6]

During the COVID-19 pandemic, patients with autoimmune rheumatic disease need special attention. Autoimmune rheumatic patients are included in high-risk groups for infections due to immunocompromised. The management of autoimmune rheumatic disease nowadays become a dilemma because the use of steroids and disease-modifying anti-rheumatic drugs are able to suppress the body's immune system. On the other hand, poor control of the underlying disease also increases the risk of infection.[7] Besides, when autoimmune rheumatic patients are infected with COVID-19, this group is more susceptible to higher severity of infection, sepsis or even shock. Mortality of autoimmune rheumatic patients due to infection is also higher compared to normal individuals.[8] Up to now, the effectivity of using immunosuppressive drugs in COVID-19 patients with autoimmune rheumatic diseases to reduce the severity of infection is still unknown due to lack of clinical evidence.[7]

Understanding the characteristics of autoimmune rheumatic patients in the era of COVID-19 pandemic is important to establish patient management guidelines and to identify groups of patients who are more susceptible to SARS-CoV-2 infection. The International Rheumatology Community has established the COVID-19 Global Rheumatology Alliance to gather the characteristics and basic data of autoimmune rheumatic patients in the COVID-19 pandemic.[9] However, no similar studies have been conducted in Indonesia. Thus, the aim of this study was to determine the characteristics of autoimmune rheumatic patients in the era of COVID-19 pandemic in Indonesia, and the results are able to be considered for establishing management guidelines or as a basis for further research.

2.Methods

This study was a descriptive study using national scale survey method, involving autoimmune rheumatic patients in Indonesia, done in April 2020. Subjects were recruited using consecutive sampling. The inclusion criteria of this study are patients who have been diagnosed with autoimmune rheumatic disease until April 2020 and we excluded patients who filled out the survey with incomplete data. The variables collected in this study consist of (1) demographic data (sex, age, occupation, address and hospital where the patient used to follow up); (2) history of disease (diagnosis of autoimmune rheumatic disease and comorbidities); (3) current medication taken (type or name of drugs, dosage and compliance to medication); (4) daily activities in the COVID-19 pandemic (activities, the use of personal protective equipment and self-isolation); also (5) data related to COVID-19 (history of taking COVID-19 diagnostic tests either PCR from swab or rapid antibody test and the status of large-scale social limitation in their city).

The national scale surveys distributed in online

form to patients with autoimmune rheumatic disease in Indonesia. Subjects were invited to fill out the survey by using an online form survey. Informed consent has been included in the survey. The results of the study were analyzed to get the proportion of each variables and presented in tables. We stratified our rheumatic disease patients based on risk stratification by British Society of Rheumatology (BSR). The scoring system to stratify the risk of infection in patients with rheumatic autoimmune disease. The risk stratification could be divided into 3 groups, [1] low risk (patients to shield), [2] moderate risk (patients to self-isolate or maintain social distance at their discretion) and [3] high risk (patients to maintain social distance).[10] The analysis was performed with SPSS software version 20.0. The protocol of this study has been reviewed and approved by Ethical Committee of Faculty of Medicine, University of Indonesia.

3.Results

Total participants who fulfilled the inclusion criteria were 570 patients. Table 1 showed the characteristics of patients with autoimmune rheumatic diseases in Indonesia. The highest percentage of autoimmune rheumatic diseases is systemic lupus erythematosus (62.8%). There are 166 respondents (29.1%) have other illness besides the autoimmune rheumatic diseases. The most common comorbidities among patients are asthma, dyspepsia or gastroesophageal reflux disease (GERD), diabetes mellitus type 2 and hypertension. In this study, almost one-third patients (177 patients) took hydroxychloroquine or chloroquine and most of them had good compliance (88.1%). Among respondents who took hydroxychloroquine or chloroquine medication, 21 of them did not take the medication routinely because of several reasons include (1) low availability, (2) unaffordable, (3) pregnancy, (4) experiencing side effect of hydroxychloroquine or chloroquine, (5) not going to out-patient care routinely, (6) forget to take the pills and (7) feeling healthy already.

In the era of COVID-19 pandemic, patient with autoimmune rheumatic diseases might be at higher risk for severe illness from COVID-19. Thus, minimizing the interaction to other people and using personal protective equipment are important steps besides medication to limit the COVID-19 transmission. Although, 76.5% respondents still did usual activities or work in several places include government offices, bank, school, factories, convection, mosque, shops, minimarkets, hospitals, clinics, pharmacies, medical laboratories and cemetery. There were 295 respondents (51.8%) who never or sometimes use personal protective equipment in the era of COVID-19 pandemic because of several reasons include (1) the activities are only at home, (2) feeling uncomfortable (3) do not have personal protective equipment.

British Society of Rheumatology (BSR) proposed scoring system to stratify the risk of infection in patients with rheumatic autoimmune disease based on the patients' comorbidities and the immunosuppressive medications. Figure 1 showed our patients' risk stratification group using BSR scoring system.

Table 1. The characteristics of autoimmune rheumatic patients in Indonesia

Characteristic	Frequency (n = 570)
Sex	
Male	35 (6.1%)
Female	535 (93.9%)
Age (years old)	35 (3-72) *
<60	554 (97.2%)
≥60	16 (2.8%)
Occupation	
Housewife	201 (35.3%)
Private employee	100 (17.5%)
Government employee	89 (15.6%)
Entrepreneur	67 (11.8%)
Unemployment	42 (7.4%)
Student	40 (7.0%)
Medical staff	23 (4.0%)
Retired	8 (1.4%)
Domicile	
Java	439 (77.0%)
Bali	44 (7.7%)
Kalimantan	41 (7.2%)
Sumatra	24 (4.2%)
Nusa Tenggara	11 (1.9%)
Sulawesi	8 (1.4%)
Other	3 (0.5%)
Doing normal activities/ working during COVID-19 pandemic	
Yes	436 (76.5%)
No	134 (23.5%)
The use of personal protective equipment	
Routine	275 (48.2%)
Sometimes	28 (4.9%)
No	267 (46.8%)
Type of personal protective equipment	
Cloth woven mask	235 (41.2%)
Surgical mask	98 (17.2%)
Medical glove	72 (12.6%)
Face shield	23 (4.0%)
Goggles	21 (3.7%)
Medical gown	20 (3.5%)
N95 respirator mask	7 (1.2%)
Status of large-scale social limitation in the city	
Yes	310 (54.4%)
No	260 (45.6%)

Notes: COVID-19 = Coronavirus Disease 2019. *Not normally distributed, data presented in median (range)

Table 2. Diagnosis and medication of autoimmune rheumatic patients in Indonesia

Characteristic	Frequency (n = 570)
Autoimmune rheumatic disease	
Systemic lupus erythematosus	358 (62.8%)
Rheumatoid arthritis	115 (20.2%)
Scleroderma/ systemic sclerosis	25 (4.4%)
Overlap syndrome	18 (3.2%)
Sjogren syndrome	16 (2.8%)
Spondylarthritis	10 (1.8%)
Ankylosing spondylitis	9 (1.6%)
Psoriatic arthritis	4 (0.7%)
Mixed connective tissue disease	4 (0.7%)
Polymyositis	3 (0.5%)
Undifferentiated connective tissue disease	3 (0.5%)
Vasculitis	2 (0.4%)

Other	3 (0.5%)
Comorbidities	
Yes	166 (29.1%)
No	404 (70.9%)
Autoimmune rheumatic disease medication	
Glucocorticoids	400 (70.2%)
Low dose	300 (52.6%)
Moderate dose	88 (15.4%)
High dose	9 (1.6%)
Very high dose	3 (0.5%)
Hydroxychloroquine/ Chloroquine	177 (30.5%)
Methotrexate	98 (17.2%)
Mycophenolate	84 (14.7%)
Azathioprine	81 (14.2%)
Cyclophosphamide	43 (7.5%)
Cyclosporine	35 (6.1%)
Anti TNF	31 (5.4%)
Characteristic	**Frequency (n = 570)**
Leflunomide	29 (5.1%)
Sulfasalazine	27 (4.7%)
IL-6 Tocilizumab	12 (2.1%)
Anti IL17	8 (1.4%)
Anti IL12-IL23	6 (1.1%)
Rituximab	3 (0.5%)
Compliance to Hydroxychloroquine/ Chloroquine medication	
Yes	156 (88.1%)
No	21 (11.9%)

Notes: IL = Interleukin, TNF = Tumor Necrosis Factor

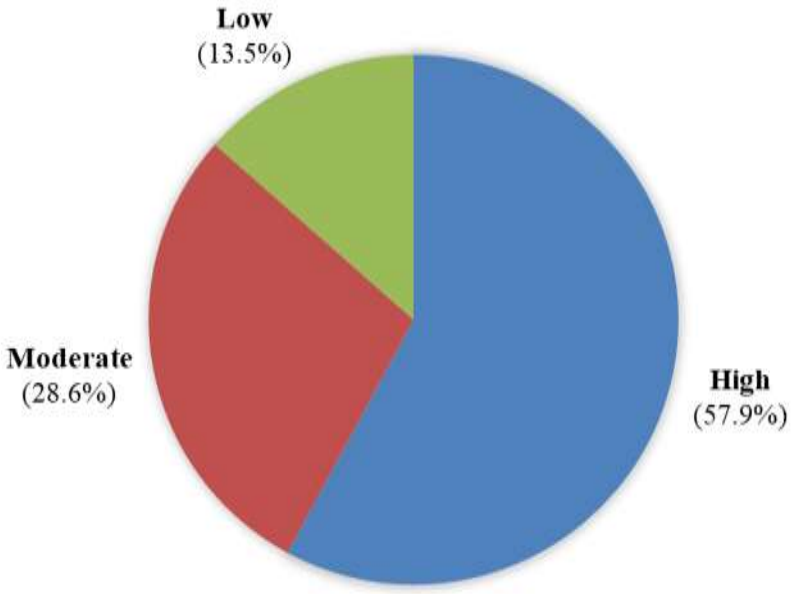

Figure 1. The risk stratification group in patients with autoimmune rheumatic disease

Table 3. Data of patients confirmed COVID-19

Patient No.	Sex	Age	Autoimmune rheumatic disease	Comorbidity	Medication	The Usage of PPE	BSR Risk Stratification	Patient Care	Source of Transmission
1	F	36	Systemic lupus erythematosus	None	Azathioprine	No	Moderate	Outpatient	Contact with confirmed case
2	F	64	Scleroderma	None	Cyclosporine	No	Low	Inpatient	Travelling abroad
3	F	26	Systemic lupus erythematosus	None	Low dose corticosteroid Azathioprine	Sometimes	High	Inpatient	Contact with confirmed case
4	M	47	Systemic lupus erythematosus	None	None	Routine	Low	Inpatient	Not identified
5	F	40	Rheumatoid arthritis	None	Methotrexate	Routine	Low	Inpatient	Contact with confirmed case
6	F	33	Systemic lupus erythematosus	Pregnancy	Hydroxychloroquine	Routine	Low	Inpatient	Unidentified
7	F	43	Spondylarthritis	Type 2 Diabetes Mellitus	Low dose corticosteroid Methotrexate	Sometimes	High	Outpatient	Unidentified
8	F	54	Systemic lupus erythematosus	None	Low dose corticosteroid	Routine	High	Outpatient	Unidentified
9	M	62	Ankylosing spondylitis	None	Methotrexate	Sometimes	Low	Outpatient	Unidentified
10	F	40	Systemic lupus erythematosus	None	Chloroquine Moderate corticosteroid Mycophenolate	Routine	High	Inpatient	Unidentified
11	F	57	Systemic lupus erythematosus	Hypertension	Low dose corticosteroid	No	High	Outpatient	Unidentified

4.Discussion

Baseline characteristics

In this study, the mean age of SSc patients was 42 years old. This was echoed the findings in the other studies which stated that the highest SSc onset was on the third until fourth decade of life.[14] A study in Indonesia conducted by Salim et al shown that the average age of SSc patients was 41 ± 11 years.[9] Similar findings were also reported in a cohort study by Sujau et al from Malaysia which involved 90.3% female subjects with the mean age of 42.6 years old.[15] Another study conducted in Singapore by Low et al reported mean age of 46 ± 14.9 years in their subjects.[16]

Range of mRSS value in this study was 5-45 with the mean score of 23. It was in accordance with a cohort study from Egypt which showed mRSS value ranged from 4 until 45.[17] Mean FVC value of the subjects was 52%. It was quite consistent with the findings from Salim et al study which stated FVC value of 58.2 ± 10.8 %.[9] Classification of restrictive lung disorder based on FVC value in this study were mostly severe restrictive lung disorder (74.1%), whilst the rest of the subjects (25.9%) had mild to moderate restrictive lung disorder. This was in accordance with study by Steen et al which shown moderate to severe restrictive lung disorder in 40% of subjects.[18]

KL-6 serum with FVC value

This study was the first study in Indonesia to analyze the correlation between KL-6 serum with FVC value and mRSS. In this study, there was no correlation between KL-6 serum and FVC value. It was different with another study from Benyamine et al and Bonela et al which showed a significant negative correlation between KL-6 serum and FVC value.[19,20] Benyamin et al reported in their study that KL-6 serum significantly correlated with FVC value ($r = -0.418$; $p = 0.001$) on SSc patients in France.[20] Study in Italy by Bonela et al also showed a significant negative correlation between KL-6 serum and FVC value ($r=-0.47$, $p<0.05$).[19] Both Benyamin et al and Bonela et al used HRCT and PFT to assess pulmonary fibrosis on SSc patients.

The difference on KL-6 serum with FVC value between this study and previous studies might happen due to several things. First, the subjects of this study have different degree of skin thickening on chest area. This altered the ability of chest cavity to expand, hence disrupting accuracy of spirometry test. The decrease in FVC value due to lung fibrosis is the one that was supposed to be measured. In addition to that, the mean age of subjects in this study was 42 years old, in which their volume of lungs might had already decreased. Secondly, KL-6 serum in this study was measured using ELISA method instead of chemiluminescent enzyme immunoassay (CLEIA) method which was used in most of KL-6 studies in the other countries. However, in Indonesia, CLEIA method was not possible to be

performed on daily clinical practice.

KL-6 serum with mRSS

This study also showed no significant correlation between KL-6 serum and mRSS. This was consistent with cohort study from Cao et al in China who reported lack of correlation between KL-6 serum and mRSS score in 141 SSc patients (60 dSSc patients and 81 lSSc).[21] This lack of correlation was also reported in Hant et al study, named Scleroderma Lung Study (SLS), in North America.[22] Benyamin et al also reported that there was no significant level of KL-6 serum in dSSc patients compared to lSSc.[20]

On the other hand, Bonella et al reported different results. They reported that there was a significant correlation between KL-6 and mRSS score ($r= 0.71$, $p<0.0001$).[19] However, they include 10 lSSc and only 15 dSSc patients, a fewer amount of subjects compared to the other studies.

We could not differentiate whether the restrictive lung disorder was caused by lung fibrosis or caused by skin fibrosis on chest area, which might affect the results of this study. The measurement of KL-6 serum in this study used KL-6 / Human MUC-1, in which has not been used in any published study and might need some calibrations.

5.Conclusion

There was no correlation between serum KL-6 levels with FVC and mRSS value of patient with restritive lung disease in diffuse type systemic sclerosis. Further study analyzing KL-6 serum with lung fibrosis in SSc patients, diffuse and limited type, using HRCT is warranted.

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