

The Role of Immunosuppression in the Development of COVID-19 in Systemic Lupus Erythematosus Patients: A Brief Report

Mohammadrafi Damirchi¹, MD; Mehrdad Aghaie¹, PhD; Sima Sedighi¹, PhD; Samaneh Tavassoli¹, PhD; Gholamreza Roshandel², PhD; Mohammadjavad Hassani¹, MD; Nafiseh Abdolahi¹, PhD

¹Golestan Rheumatology Research Center, Golestan University of Medical Sciences, Gorgan, Iran;

²Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran

Correspondence:

Nafiseh Abdolahi, PhD;
Golestan University of Medical sciences,
Gorgan-Sari Highway,
Postal Code: 49189-36316,
Gorgan, Iran

Tel: +98 9113712041

Fax: +98 17 32430310

Email: N_abdolahi2002@yahoo.com

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What's Known

- Immunosuppressive drugs can make rheumatic patients susceptible to infectious diseases, and patients receiving these drugs are more prone to viral, bacterial, and fungal infections.
- The immunosuppression state is a risk factor for a severe form of common viral infections and is associated with poorer outcomes. However, this is not the case for the coronavirus family.

What's New

- In our study population, immunosuppressed systemic lupus erythematosus patients had fewer clinical symptoms or were less affected by COVID-19 than non-immunosuppressed patients.
- Pending further studies, it is suggested that immunosuppression is not only not a risk factor, but also contributes to better patient prognosis.

Abstract

Recently, due to the coronavirus disease 2019 (COVID-19) pandemic, much concern has been raised about patients with chronic diseases who may become more susceptible to the disease. The present cross-sectional study aimed to characterize the clinical course of COVID-19 in patients with systemic lupus erythematosus (SLE). In addition, a possible correlation between the immunosuppression state and the incidence of COVID-19 is investigated. In May 2020, 500 SLE patients registered in the database of Golestan Rheumatology Research Center (Golestan province, Iran) were selected for this cross-sectional study. Using a questionnaire, patients were contacted by telephone to collect data including demographic characteristics, disease status, drug use, and new clinical symptoms. Data were analyzed using SPSS software version 24.0. Of the 500 selected patients, 355 responded to the phone calls and subsequently enrolled in the study. Among the enrolled patients, 25 were classified as COVID-19 positive, including eight hospitalized patients, of which two required intensive care and subsequently died. COVID-19 incidence was significantly lower in the immunosuppressed patients (2.2% vs. 10%, $P=0.01$). There was no significant correlation between hydroxychloroquine consumption and the incidence of COVID-19 in SLE patients. Fever, fatigue, dyspnea, and dry cough were the most common clinical symptoms. Our results showed that COVID-19 incidence was lower in immunosuppressed than the non-immunosuppressed SLE patients. Further studies are required to substantiate the role of immunosuppression in the development of COVID-19.

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Keywords • COVID-19 • Systemic lupus erythematosus • Hydroxychloroquine • Immunosuppression • SARS-COV2

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that may involve any of the organs of the human body in its clinical course. The pathogenesis of SLE is not clearly known, but it is thought to be related to the production of high levels of an immunogenic form of nucleic acids and other self-antigens,

which drive autoimmune-inducing activation of innate immunity, autoantibodies, and T cells. SLE can manifest with a wide range of clinical signs and symptoms.¹ Common manifestations may include arthralgia and arthritis, malar and other skin rashes, pleuritis, pericarditis, renal or central nervous system involvement, and hematologic abnormalities.² Patients with SLE are more prone to develop infections and may present more severe forms than the normal population. Some of these patients are also on immunosuppressants, which makes them more susceptible to infections.³ One of the most common causes of death in these patients is infection.⁴

The Coronavirus disease 2019 (COVID-19) first emerged in Wuhan (China) and rapidly spread to other countries and became an international concern to the extent that it was declared a global pandemic. The most common symptoms of COVID-19 are fever, cough, fatigue, and dyspnea. Other symptoms include diarrhea, vomiting, nausea, rhinorrhea, sore throat, headache, sputum, anosmia, dysgeusia, anorexia, and muscle pain.⁵

The immune system plays a major role in the development of COVID-19. The innate immune response to pulmonary tissue damage caused by the virus can lead to acute respiratory distress syndrome (ARDS), which can cause death in these patients.^{6, 7} It is therefore possible that weakness of the immune system in immunosuppressed patients has some advantages in relation to COVID-19. On the other hand, hydroxychloroquine (HCQ) is one of the most common drugs used in the treatment of SLE patients, and there are some reports claiming the beneficial effect of HCQ in treating COVID-19 patients.^{8, 9}

Given the above, the objective of the present study is to investigate the clinical course of COVID-19 in SLE patients and evaluate the effect of HCQ on the development of COVID-19. In addition, a possible correlation between immunosuppression status and the incidence of COVID-19 is investigated.

Patients and Methods

In May 2020, 500 patients registered in the database of the Golestan Rheumatology Research Center (Golestan province, Iran) were selected for this cross-sectional study. The inclusion criteria were the diagnosis of SLE according to the 2019 European League Against Rheumatism (EULAR) or the 1997 American College of Rheumatology (ACR) classifications, and willingness to participate in the study.^{10, 11}

Eventually, 355 patients were willing to participate and were included in the study. A data collection form was designed to classify patients according to the World Health Organization (WHO) COVID-19 case definitions.¹² Collected data included demographic characteristics, disease status, medications used, and new clinical symptoms. Through phone calls, the 355 participants were asked about their COVID-19-related symptoms, laboratory tests, clinical imaging, and hospitalizations. In accordance with the WHO definitions and based on the collected information, the patients were divided into three groups, namely suspected cases, probable cases, and confirmed cases. In the course of the study, we were unable to visit the SLE patients in person due to the imposed social distancing protocols, consideration for their health status, and measures to prevent the spread of COVID-19. Consequently, we could not perform laboratory tests to assess the SLE activity in these patients. Instead, the following criteria were used to determine active disease status.

1. The presence of SLE-related clinical symptoms within the previous two weeks, as confirmed by the patient's rheumatologist.

2. Recent admission to hospital due to major SLE-related organ involvement.

3. Patients taking corticosteroids >15 mg per day.

4. Patients undergoing treatment with cyclophosphamide.

5. Patients taking mycophenolate mofetil >1500 mg per day.

We considered those using azathioprine, mycophenolate mofetil, or methotrexate >12.5 mg per week as immunosuppressed patients.

This study was approved by the Ethics Committee of Golestan University of Medical Sciences (code: IR.GOUMS.REC.1399.034). Written informed consent was obtained from all participants.

Statistical Analysis

Data were analyzed using SPSS software, version 24.0 (IBM Corp., USA). Quantitative data were expressed as mean±SD (standard deviation) and qualitative data as numbers and percentages. The Chi square test was used to assess the relationship between COVID-19 and qualitative variables. Student *t* test was used to assess the relationship between COVID-19 and quantitative variables with normal distribution. Mann-Whitney U test was used to assess the relationship between COVID-19 and quantitative variables that did not have a normal distribution. $P < 0.05$ was considered statistically significant.

Results

The mean age of the 500 selected patients was 40.8±11.9 years, 458 (91.6%) of whom were women. We successfully contacted 355 (71%) of the patients to collect the required information. The mean age of the participants was 40.1±11.5 years, 326 (91.8%) of whom were women. Table 1 shows the demographic characteristics, disease status, comorbidities, medications, and organ involvement of the respondents.

Based on the WHO case definitions, 25 (7%) patients were classified as COVID-19 positive group, of which 11 (44%) were suspected cases, 11 (44%) were probable cases, and 3 (12%) were confirmed cases. The mean age of the COVID-19 positive group was 43.4±13.2 years, 23 (92%) of whom were women. Figure 1 shows the frequency distribution of COVID-19-related clinical symptoms in this group. Fever (68%), fatigue (68%), dyspnea (68%), and dry cough (64%) were the most common symptoms.

Table 1: Demographics, primary disease status, comorbidities, medications, and organ involvement in our patient group.

Variables	Respondents (n=355)	
Age (years, mean±SD)	40.1±11.5	
Sex	Female	326 (91.8%)
	Male	29 (8.2%)
Duration of SLE (years, mean±SD)	8.9±6.3	
Active disease	34 (9.6%)	
Comorbidities	Diabetes mellitus	25 (7%)
	Respiratory diseases	17 (4.8%)
	Cardiovascular diseases	30 (8.5%)
	Hypertension	76 (21.4%)
Medications	Prednisolone	273 (76.9%)
	HCQ	247 (69.6%)
	Methotrexate	94 (26.5%)
	Azathioprine	80 (22.5%)
	Mycophenolate mofetil	42 (11.8%)
	Organ involvements	Mucocutaneous
Musculoskeletal		305 (85.9%)
Renal		118 (33.2%)
Hematologic abnormalities		155 (43.7%)
Nervous system		104 (29.3%)
Pulmonary		51 (14.4%)
Eye		101 (28.5%)
Cardiac		32 (9%)

HCQ: Hydroxychloroquine; SLE: Systemic lupus erythematosus

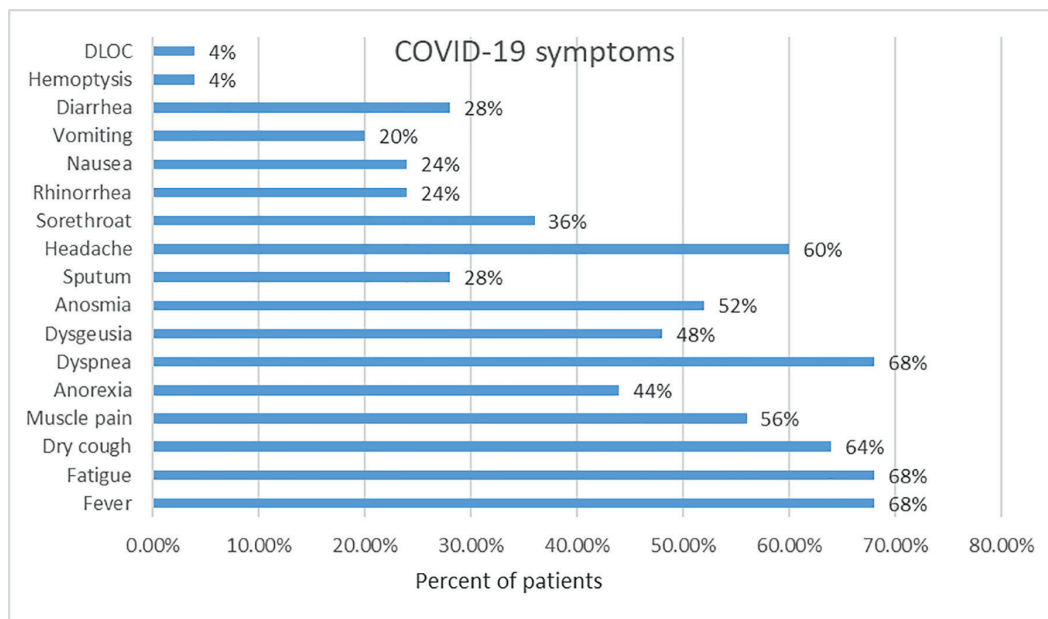


Figure 1: The figure shows the frequency distribution of clinical symptoms in the COVID-19 positive group. DLOC: Decreased level of consciousness

Table 2: Characteristics of the patients in the COVID-19 positive and COVID-19 negative groups

Characteristics	Condition	COVID-19 positive (n=25)	COVID-19 negative (n=330)	P value		
Age (years, mean±SD)		43.4±13.2	39.8±11.4	0.13*		
Women		23 (7.1%)	303 (92.9%)	0.97**		
Duration of SLE (years, median [IQR])		7 (9)	8 (9)	0.51***		
Active disease	Active	1 (2.9%)	33 (97.1%)	0.32*		
	Inactive	24 (7.5%)	297 (92.5%)			
Comorbidities	Diabetes mellitus	Positive	2 (8%)	23 (92%)	0.84*	
		Negative	23 (7%)	307 (93%)		
	Cardiovascular	Positive	0 (0%)	30 (100%)	0.11*	
		Negative	25 (7.7%)	300 (92.3%)		
	Hypertension	Positive	6 (7.9%)	70 (92.1%)	0.743*	
		Negative	19 (6.8%)	260 (93.2%)		
	Respiratory disease	Positive	5 (29.4%)	12 (70.6%)	<0.001*	
		Negative	20 (5.9%)	318 (94.1%)		
Organ involvement	Mucocutaneous	Positive	15 (6.5%)	217 (3.5)	0.56*	
		Negative	10 (8.1%)	113 (91.9%)		
	Musculoskeletal	Positive	23 (7.5%)	282 (92.5%)	0.36*	
		Negative	2 (4%)	48 (96%)		
	Renal	Positive	8 (6.8%)	110 (93.2%)	0.89*	
		Negative	17 (7.2%)	220 (92.8%)		
	Hematologic abnormalities	Positive	9 (5.8%)	146 (94.2%)	0.42*	
		Negative	16 (8%)	184 (92%)		
	Nervous system	Positive	10 (9.6%)	94 (90.4%)	0.22*	
		Negative	15 (6%)	236 (94%)		
	Eye	Positive	7 (6.9%)	94 (93.1%)	0.95*	
		Negative	18 (7.1%)	236 (92.9%)		
	Pulmonary	Positive	5 (9.8%)	46 (90.2%)	0.40*	
		Negative	20 (6.6%)	284 (93.4%)		
	Cardiac	Positive	3 (9.4%)	29 (90.6%)	0.58*	
		Negative	22 (6.8%)	301 (93.2%)		
	Medications	HCQ	Positive	15 (6.1%)	232 (93.9%)	0.28*
			Negative	10 (9.3%)	98 (90.7%)	
		Prednisolone	Positive	16 (5.9%)	257 (94.1%)	0.11*
			Negative	9 (11%)	73(89%)	
Methotrexate		Positive	10 (10.6%)	84(89.4%)	0.11*	
		Negative	15 (5.7%)	246 (94.3%)		
Immunosuppressive drugs		Positive	3 (2.2%)	133 (97.8%)	0.01*	
		Negative	22 (10%)	197 (90%)		

*Chi square test; **Student t test (P<0.05 was considered significant); ***Mann-Whitney U test; HCQ: Hydroxychloroquine; IQR: Interquartile range

Of the 25 patients in the COVID-19 positive group, 8 (32%) needed hospitalization, of which two were admitted to the intensive care unit and later died. One of the deceased patients was a 63-year-old man with a two-year history of SLE. He had a history of respiratory disease and was using mycophenolate mofetil (1.5 g/d), prednisolone (15 mg/d), HCQ (400 mg/d), and methotrexate (10 mg/w). He also had SLE-related pulmonary involvement. The other deceased patient was a 63-year-old woman with a three-year history of SLE. She was using prednisolone (10 mg/d) and methotrexate (5 mg/w). The remaining patients (n=23) recovered from COVID-19. Table 2 shows the characteristics of the patients in the COVID-19

positive and negative groups. The mean age of the patients in the COVID-19 positive group was higher than the COVID-19 negative group, but the difference was not statistically significant. The incidence of COVID-19 was significantly higher in patients with a history of respiratory diseases than those without this comorbidity (29.4% vs. 5.9%, P<0.001). The results showed no correlation between major organ involvement and COVID-19. Besides, no significant differences were found between SLE activity and developing COVID-19. Furthermore, there was no correlation between HCQ and the incidence of COVID-19. To determine dose-rate effect, patients using HCQ were divided into two groups, namely high dose (>400 mg) and

low dose (<400 mg). Although the incidence of COVID-19 was lower in the high dose group, the difference was not statistically significant (4.8% vs. 6.7%, $P=0.55$). Of the 355 SLE patients, 136 (38.3%) were immunosuppressed patients, and the incidence of COVID-19 was significantly higher in non-immunosuppressed patients (10% vs. 2.2%, $P=0.01$).

Discussion

Similar to other COVID-19 patients, the most common symptoms in the SLE patients in our study were fever, fatigue, dyspnea, and dry cough.⁵ The incidence of COVID-19 was higher in patients with a history of chronic respiratory diseases. Our findings were in line with previous studies reporting that COVID-19 patients with a history of chronic pulmonary diseases develop a more severe clinical course and have poorer outcomes.^{13, 14} Further studies are required to clarify this correlation and evaluate the role of prior chronic respiratory disease as a risk factor for COVID-19.

Several studies have investigated the effect of the immunosuppression state on the clinical course of COVID-19. It is believed that immunosuppressed patients are prone to a more severe clinical course and have poorer outcomes when infected with common viral infections such as adenovirus, rhinovirus, norovirus, influenza, and respiratory syncytial virus.^{15, 16} In contrast, there is no consensus on the effect of the immunosuppression state on the clinical course of infection by coronaviruses. The host immune response appears to be the main cause of damage to lung tissues during the infection. The innate immune response to pulmonary damage caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV2) can lead to acute respiratory distress syndrome, which could be the cause of respiratory failure and death in these patients. Cytokine storm seems to play a major role in severe COVID-19 patients. Hence, in severe cases, blocking interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor (TNF) might be beneficial.^{6, 7}

The majority of viruses that have caused recent epidemics with high mortality rates are bat-related zoonoses. In many of these viruses, including coronavirus, the host response is believed to be a major contributor to the disease process. Bats are a natural host for coronaviruses. It has been suggested that bats' immune system gives them a natural ability to tolerate the infection.¹⁷ This could also be the case with immunocompromised patients infected

with SARS-COV2. During the recent outbreaks of SARS-COV2 and the Middle East respiratory syndrome (MERS), immunosuppression was not a risk factor.^{18, 19}

In a cross-sectional study at a transplantation center in Bergamo (Italy), D'Antiga evaluated 200 children who had undergone a liver transplant and reported that none developed clinical pulmonary disease despite three patients testing positive for COVID-19.¹⁸ In a systematic review and meta-analysis, Minotti and colleagues evaluated 110 immunocompromised patients who were infected with SARS-COV2 and concluded that the outcome of this population was favorable compared to other comorbidities.²⁰ Overall, in line with other studies, we found a lower incidence of COVID-19 and its associated symptoms among immunosuppressed compared to non-immunosuppressed SLE patients.

As the main limitation of the study, we only considered patients with SLE and did not include other confounding factors. This may undermine the generalizability of our findings to other patients with immunosuppression. Especially when taking into account that, generally, immunosuppressed patients strictly adhere to COVID-19 quarantine and social distancing, which could have acted as a confounding factor in our study. To substantiate our findings, it is recommended to conduct further biochemical studies such as comparing cytokine levels between immunosuppressed patients and other patient groups.

Conclusion

Immunosuppression is not a risk factor for severe COVID-19 or increased mortality. Further studies are required to investigate the role of immunosuppression in the development and progression of COVID-19.

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Authors' Contribution

M.D, N.A: Study design, acquisition, and analysis of data. M.A, S.T, S.S, Gh.R, M.H: Acquisition and analysis of data. All authors contributed to the drafting and critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part

of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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