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Clinical signs, symptoms, and severity of COVID-19 in patients with rheumatic diseases during the COVID-19 epidemic

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Abstract

Introduction: Recent studies have shown that patients with rheumatic diseases are more likely to experience severe cases of COVID-19. Additionally, certain anti-inflammatory medications have been linked to a reduction in the severity of COVID-19 symptoms.
Objectives: This cross-sectional study aimed to determine the frequency of clinical signs, symptoms, and severity of COVID-19 in outpatients with rheumatic diseases.
Patients and Methods: A total of 77 patients with rheumatic disorders who were diagnosed with COVID-19 and referred to Isfahan rheumatology clinics in 2020 were selected for this study. The study investigated their clinical signs, symptoms, severity of COVID-19, type of rheumatic disease, and the medications they were using. Furthermore, the study examined the relationship between the severity of COVID-19 and the type of rheumatic disease.
Results: Among the 77 patients, 79.2% had rheumatoid arthritis (RA), 9.1% had systemic lupus erythematosus (SLE), 9.1% had Sjogren's syndrome, and 2.6% had other rheumatic disorders. The severity of COVID-19 was classified as mild in 40.3% of cases, moderate in 44.2%, and severe in 15.6%. There was no statistically significant relationship between the type of rheumatic disease and the severity of COVID-19 ($P=0.093$).
Conclusion: The findings suggest that patients with rheumatic diseases are more likely to experience severe cases of COVID-19. Conversely, the combination of hydroxychloroquine, sulfasalazine, and prednisolone has been associated with a lower prevalence of severe cases of COVID-19. In contrast, the administration of methotrexate and prednisolone has been linked to a higher prevalence of severe cases of COVID-19.

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Introduction

The COVID-19 pandemic, which lasted from the end of 2019 to the end of 2022, significantly impacted Iran and the world. The disease's prevalence surged, with approximately 20% of patients requiring hospitalization and 15-5% needing specialized care, while the remaining patients received outpatient treatment (1). The global fatality rate varied between 1-20% in different regions (1-4). Despite having a lower mortality rate than Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), the number of deaths was higher due to its widespread prevalence (2).

COVID-19 poses a higher mortality risk for older individuals, those with weakened immune systems, and those with underlying chronic conditions. Some patients experience hospitalization, while others succumb to acute respiratory distress syndrome (ARDS) or multi-organ dysfunction syndrome (5-7). These patients often exhibit clinical signs and symptoms indicative of cytokine storm syndrome, such as fever, confusion, and coagulopathy. Laboratory findings in hospitalized patients reveal elevated liver enzymes, C-reactive protein (CRP), Serum ferritin, interleukin (IL)-2, D-dimer, coagulation tests (prothrombin time, activated partial thromboplastin time), and lactate dehydrogenase (LDH), alongside decreased platelet and lymphocyte counts (1,8).

Several studies have reported that

Key point

Patients with rheumatic diseases have a higher prevalence of severe cases of COVID-19. The combination of hydroxychloroquine, sulfasalazine, and prednisolone is associated with a lower prevalence of severe cases of COVID-19.

individuals with rheumatic diseases experience more severe symptoms and are at a higher risk of developing ARDS compared to healthy individuals. It has also been observed that pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), IL-1, and IL-6, which play a pathological role in rheumatic diseases, are elevated in COVID-19 patients, leading to tissue damage in various organs (8-12).

The efficacy of chloroquine and its derivative, hydroxychloroquine, has been evaluated in numerous studies for treating COVID-19 patients. These drugs have shown promise in improving pneumonia symptoms and laboratory test results and reducing the likelihood of disease progression to severe or critical conditions. However, some studies have questioned their effectiveness and highlighted potential side effects. Additionally, drugs like methotrexate and cyclophosphamide, which have immunosuppressive properties, may exacerbate disease progression (13,14).

Given the complexities surrounding rheumatic diseases and the lack of sufficient research on the impact of specific drugs on clinical signs, symptoms, and disease severity in COVID-19 patients, it is crucial to consider the implications for decision-making and treatment management of patients with rheumatic diseases who contract COVID-19. Failure to diagnose COVID-19 promptly and drug misuse can jeopardize many rheumatic patients' lives. Therefore, conducting comprehensive research to determine the relative frequency of clinical signs, symptoms, and disease severity in outpatients with rheumatic diseases is deemed necessary.

Objectives

This study aimed to determine the relative frequency of clinical signs, symptoms, and disease severity in outpatients with rheumatic diseases who contracted COVID-19.

Patients and Methods

Study design

This study is a cross-sectional study that received approval from the Isfahan university of medical sciences and was conducted in 2020 at the Rheumatology clinics of Isfahan. The target population consisted of patients with rheumatic diseases who sought treatment at the rheumatology clinics in Isfahan during the COVID-19 pandemic in 2020.

Inclusion criteria included individuals who had a rheumatic disease, were diagnosed with COVID-19 through a polymerase chain reaction (PCR) test or confirmed by lung high-resolution computed tomography (HRCT), and were above 18 years of age. Exclusion criteria encompass incomplete information and the unavailability of the patient, family, or medical records required to rectify any deficiencies.

The sampling method employed was a census, whereby all rheumatism patients with COVID-19 who visited the rheumatology clinics in Isfahan city during the fall of 2019 were examined and included in the study if they met the necessary conditions.

The procedure involved designing a checklist that encompassed the required information. This checklist was completed either in person or via phone, after obtaining informed consent from the patients, by a trained researcher under the supervision of an experienced rheumatology subspecialist. The checklist included questions pertaining to demographic characteristics, clinical signs and symptoms, disease severity, underlying diseases, and medications used. The information was gathered from patient files and through direct questioning.

According to the current guidelines, the severity of COVID-19 is classified into three categories: mild, moderate, and severe. Mild disease is characterized by symptoms such as fever, cough, fatigue, anorexia, body aches, sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, loss of taste, and loss of smell, without evidence of pneumonia or hypoxia (15-17). Moderate disease includes mild symptoms accompanied by shortness of breath and hypoxia (O2 saturation ≥90%) (15-18). Severe disease is defined as moderate symptoms accompanied by either O_2 saturation <90% or severe respiratory distress (15-18).

Statistical analysis

Upon collecting the study data, it was entered into IBM SPSS software version 26. Initially, we assessed the normality of the data using the one-sample Kolmogorov-Smirnov test. The data were then analyzed using chi-square and *t* tests. A *P* value of less than 0.05 was considered statistically significant.

Results

This study included a total of 77 patients diagnosed with COVID-19 in the autumn of 2020, all of whom were suffering from rheumatic diseases. The age of the patients ranged from 29 to 67 years, with a mean age of 44.83 ± 8.43 years. Among the participants, 53 (68.8%) were women and 24 (31.2%) were men. The average age for men was 44.62 ± 8.1 years, while for women it was 45.29 ± 9.3 years. However, there was no significant difference observed between the two groups ($P=0.75$).

Out of the 77 patients studied, 61 individuals (79.2%) had rheumatoid arthritis (RA), 7 individuals (9.1%) had systemic lupus erythematosus (SLE), 7 individuals (9.1%) had Sjogren's syndrome, and 2 individuals (2.6%) had other rheumatic disorders (1 case of GPA and 1 case of Takayasu). As shown in Table 1, there was a significant difference in the average age of patients based on the type of rheumatic disease ($P=0.011$). However, there was no significant difference observed in the gender distribution of patients according to the type of disease ($P=0.99$; Table 1).

The most prevalent clinical symptom observed in patients was cough, with a frequency of 48 cases (62.3%).

Table 1. Age and gender distribution based on the kind of rheumatoid diseases

Kind of the diseases	Mean (±SD) of age (y)	Gender	
		Male	Female
RA	46.05 ± 8.82	20 (32.8)	41 (67.2)
SLE	36.29 ± 6.24	2 (28.6)	5 (71.4)
Sjogren's syndrome	45.29 ±7.18	2 (28.6	5 (71.4)
Other	36 ± 8.49	0 (0)	2 (100)
P value	0.011	0.99	

RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus.

Table 2. Frequency distribution of the severity of COVID-19 according to the type of autoimmune disease

Kind of disease	COVID-19 severity			*P* value
	Mild	Moderate	Severe	
RA	21(34.4)	29 (47.5)	11 (18)	0.093
SLE	4 (57.1)	3 (42.9)	0 (0)	
Sjogren's syndrome	6 (85.7)	1 (14.3)	0 (0)	
Other	0 (0)	1 (50)	1 (50)	
Total	31 (40.3)	34 (44.2)	12 (15.6)	

RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus.

During clinical examinations, it was found that 34 patients (44.2%) had a blood oxygen saturation level of 90% and above, while 11 patients (14.3%) had a blood oxygen saturation level below 90%. Among the patients studied, 4 individuals (5.2%) experienced respiratory distress. Based on the obtained results, the severity of COVID-19 was classified as mild in 31 individuals (40.3%), moderate in 34 individuals (44.2%), and severe in 12 individuals (15.6%) (Figure 1).

According to Table 2, out of the 61 patients with RA, 11 individuals (18%) were infected with the severe form of COVID-19. However, among the 7 patients with SLE and the 7 patients with Sjogren's syndrome, no cases of severe COVID-19 were observed. On the other hand, the mild form of the disease was more common in patients with Sjogren's syndrome, as 6 patients (85.7%) had a mild form of the disease. Nevertheless, Fisher's exact test did not reveal a statistically significant relationship between the severity of COVID-19 and the type of autoimmune disease ($P=0.093$).

The mean age of patients with mild, moderate, and severe COVID-19 was 46.1 ± 8, 43.8 ± 8.7, and 44.7 ± 9.1 years, respectively. No significant correlation was found between age and the severity of COVID-19 ($P=0.55$). Additionally, the severity of COVID-19 was distributed as follows: mild in 10 men and 21 women (32.3% versus 67.7%), moderate in 12 men and 22 women (35.3% versus 64.7%), and severe in 2 men and 10 women (16.7% versus 83.3%). There was no significant difference in the severity of the disease based on gender ($P=0.51$).

Table 3 presents the frequency distribution of clinical symptoms according to the type of autoimmune disease. The table indicates a significant difference in the presence of cough among patients with different autoimmune diseases, with a higher occurrence of cough in patients with RA.

Considering that each patient was using multiple medications simultaneously, an analysis was conducted to categorize the medications used and investigate their relationship with the severity of COVID-19. The results showed that 14 patients (18.2%) were receiving methotrexate + prednisolone, 20 individuals (26%) were taking hydroxychloroquine + sulfasalazine + prednisolone, 5 individuals (6.5%) were on leflunomide + prednisolone, 24 individuals were using methotrexate + hydroxychloroquine + sulfasalazine + prednisolone, 8 individuals (10.4%) were prescribed anti-TNF + prednisolone, and 6 individuals (7.8%) were using a combination of anti-TNF + methotrexate + prednisolone (Figure 2).

Table 4 presents the frequency distribution of drug categories used based on the severity of COVID-19.

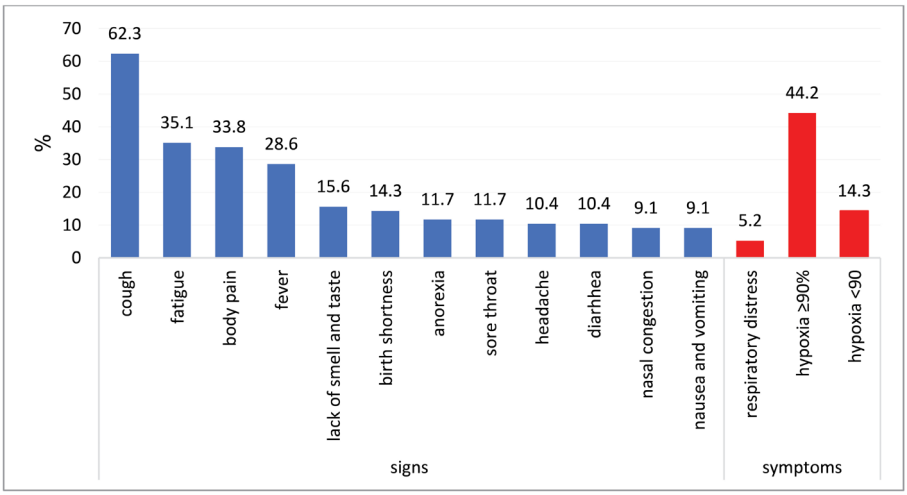

Figure 1. Frequency percentage of clinical signs and symptoms in all studied patients.

Table 3. Frequency distribution of clinical symptoms according to the type of autoimmune disease

COVID-19 Symptoms	Rheumatic disease				*P* value
	RA	SLE	Sjogren's	Other	
Fever	16 (26.2)	2 (28.6)	2 (28.6)	2 (100)	0.2
Cough	42 (68.9)	1 (14.3)	3 (42.9)	2 (100)	0.008
Fatigue	27 (39.3)	3 (42.9)	0 (0)	0 (0)	0.13
Anorexia	6 (9.8)	2 (28.6)	1 (14.3)	0 (0)	0.39
Body pain	21 (34.4)	1 (14.3)	4 (557.10	0 (0)	0.29
Sore throat	7 (11.5)	2 (28.6	0 (0)	0 (0)	0.50
Nasal congestion	6 (9.8)	1 (14.3)	0 (0)	0 (0)	0.82
Headache	7 (11.5)	1 (14.3)	0 (0)	0 (0)	0.99
Diarrhea	5 (8.2)	1 (14.3)	2 (28.6)	0 (0)	0.33
Nausea and vomiting	5 (8.2)	0 (0)	1 (14.3)	1 (50)	0.22
Lack of smell and taste	7 (11.5)	3 (42.9)	2 (28.6)	0 (0)	0.089
Shortness of breath	11 (18)	0 (0)	0 (0)	0 (0)	0.55
SPO2 ≥ 90	29 (47.5)	2 (28.6)	1 (14.3)	2 (100)	0.11
SPO2 < 90	11 (18)	0 (0)	0 (0)	0 (0)	0.55
Respiratory distress	4 (6.6)	0 (0)	0 (0)	0 (0)	0.99

RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus.

According to the table, the mildest cases of COVID-19 were predominantly associated with the drug category of hydroxychloroquine + sulfasalazine + prednisolone, accounting for 54.8% of mild cases. Interestingly, this drug category, along with several others, had zero frequency in severe COVID-19 cases. On the other hand, the most severe cases of COVID-19 were linked to the drug category of methotrexate + prednisolone, representing 83.3% of severe COVID-19 cases. Furthermore, Fisher's exact test conducted on this data revealed a significant difference in the frequency distribution of COVID-19 severity based on the type of drug category used (P<0.001).

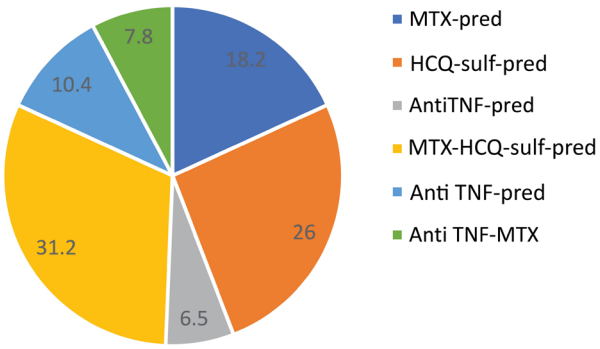

Figure 2. Types of drug combinations used by the studied patients. MTX, Methotrexate; pred, Prednisolone; HCQ, Hydroxychloroquine.

Discussion

With the COVID-19 pandemic reaching its peak and spreading rapidly, there has been a notable increase in severe cases and fatalities attributed to the development of inflammatory factors. As a result, the use of anti-inflammatory drugs commonly prescribed for rheumatic diseases, such as prednisolone and hydroxychloroquine, has taken center stage in the treatment and prevention protocols for this disease. Additionally, it has been observed that patients with pre-existing rheumatic conditions tend to experience more severe symptoms of COVID-19 and are at a higher risk of developing ARDS. This study was conducted with the objective of determining the relative frequency of clinical signs, symptoms, and the severity of COVID-19 among outpatients with rheumatic diseases

Table 4. Frequency distribution of drug category according to the severity of COVID-19

Drugs combination	COVID-19 severity			*P* value
	Mild	Moderate	Severe	
Prednisolone-MTX	0 (0)	4 (11.8)	10 (83.3)	<0.001
Hydroxychloroquine–sulfasalazine-prednisolone	17 (54.8)	3 (8.8)	0 (0)	
Prednisolone–Anti-TNF	4 (12.9)	1 (2.9)	0 (0)	
MTX-hydroxychloroquine, sulfasalazine-prednisolone	3 (9.7)	19 (55.9)	2 (16.7)	
Prednisolone–Anti TNF	6 (19.4)	2 (5.9)	0 (0)	
Anti-TNF–MTX	1 (3.2)	5 (14.7)	0 (0)	

MTX, Methotrexate; TNF, Tumor necrosis factor.

who were referred to rheumatology clinics in Isfahan city in 2020.

The results of the current investigation revealed that out of the 77 individuals with rheumatic conditions who contracted COVID-19, 15.6% experienced a severe manifestation of the illness. This percentage is notably higher compared to the proportion of individuals without any underlying health conditions who develop a severe form of the disease (5-7). Researchers have attributed this disparity to various factors, including elevated levels of inflammatory markers and the occurrence of a cytokine storm (3). These factors can contribute to the development of life-threatening complications and disorders such as ARDS.

The study findings indicate that there is no statistically significant correlation between the severity of COVID-19 and the specific type of rheumatic disease. However, it is worth noting that the frequency of severe COVID-19 cases is significantly higher among patients with RA, which aligns with the results of a study conducted by Mukarram et al (19). Additionally, the research conducted by Freites et al has demonstrated that rheumatic patients experience a higher incidence of severe COVID-19, resulting in prolonged hospitalization (20). Conversely, a study by Jung et al did not observe a significant statistical relationship between the severity of COVID-19 and RA (21).

Regarding clinical signs and symptoms, the present study found a higher prevalence of certain indicators of COVID-19, such as cough, oxygen saturation drops (sat o2), and respiratory distress, among patients with RA. These findings are consistent with the results of Freites' study, which reported a greater decrease in oxygen saturation among rheumatic patients compared to those without underlying diseases (20).

Our study findings revealed a significantly higher incidence of severe COVID-19 cases among patients who were taking methotrexate + prednisolone. In other words, the use of this combination of medications exacerbated the severity of COVID-19 in rheumatic patients. This aligns with a study conducted by Brownstone, which reported an increased risk of COVID-19 infection associated with the administration of methotrexate in rheumatic patients (22). Another study by Sparks and Tedeschi indicated that discontinuing methotrexate usage improves the immunogenicity of the coronavirus vaccine (23). However, the definitive impact of methotrexate on COVID-19 has not been established in studies, and there are differing opinions on this matter (23).

Furthermore, our study demonstrated that the frequency of severe COVID-19 cases was significantly lower among users of hydroxychloroquine + sulfasalazine + prednisolone compared to patients who did not use these drugs.

Numerous studies and experiences have investigated the use of drugs such as hydroxychloroquine, prednisolone, and tocilizumab for the treatment of COVID-19. However, it is important to note that these findings are preliminary, and further research is needed to understand how to protect and manage COVID-19 in patients taking immunosuppressive drugs. The evidence for treatment decisions is still incomplete, and uncertainties remain regarding the continuation and initiation of immunosuppressive medications. RA is the most common immune-related disorder observed in COVID-19 patients, and this review has discussed how commonly used drugs in rheumatic diseases can affect patients' susceptibility to this infection. Additionally, it is crucial to acknowledge the limitations of this study, such as the small sample size and the absence of a control group, which make it challenging to generalize the results to the entire patient population. Therefore, further research in this field is necessary.

Conclusion

The findings of this study suggest that patients with rheumatic diseases have a higher prevalence of severe cases of COVID-19. Additionally, the use of drugs such as hydroxychloroquine + sulfasalazine + prednisolone is associated with a lower incidence of severe COVID-19 cases. Conversely, the use of methotrexate + prednisolone has been linked to an increased prevalence of severe COVID-19 cases.

Limitations of the study

The study is subject to certain limitations, including a small sample size. Therefore, it is recommended that further research be conducted in this field to validate and expand upon these findings.

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Authors' contribution

Conceptualization: Mansour Salesi.
Data curation: Maryam Sedarat.
Formal analysis: Maryam Sedarat.
Funding acquisition: Mansour Salesi.
Investigation: Maryam Sedarat.
Methodology: Mansour Salesi.
Supervision: Mansour Salesi.
Writing–original draft: Mansour Salesi, Maryam Sedarat.
Writing–review and editing: Mansour Salesi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (Ethical code#IR.MUI.MED.REC.1399.883). Accordingly, written informed consent was taken from all participants before any intervention. this study was extracted from a thesis of internal medicine specialty

Maryam Sedarat at this university (Thesis #399786). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295:715-721. doi: 10.1148/radiol.2020200370.
2. Ferro F, Elefante E, Puxeddu I, Baldini C, Bartoloni E, Baratè C, et al. COVID-19: the new challenge for rheumatologists. First update. Clin Exp Rheumatol. 2020;38:373-382. doi: 10.55563/clinexprheumatol/yvn0nh.
3. Cron RQ, Chatham WW. The rheumatologist's role in COVID-19. J Rheumatol. 2020;47:639-642. doi: 10.3899/jrheum.200334
4. Cai J, Sun W, Huang J, Gamber M, Wu J, He G. Indirect virus transmission in a cluster of COVID-19 cases, Wenzhou, China, 2020. Emerg Infect Dis. 2020;26:1343-1345. doi: 10.3201/eid2606.200412.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-1069. doi: 10.1001/jama.2020.1585.
6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-513. doi: 10.1016/S0140-6736(20)30211-7.
7. Chen L, Liu H, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43:E005. Chinese. doi: 10.3760/cma.j.issn.1001-0939.2020.0005.
8. Misra DP, Agarwal V, Gasparyan AY, Zimba O. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. Clin Rheumatol. 2020;39:2055-2062. doi: 10.1007/s10067-020-05073-9.
9. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433. doi: 10.1016/j.jaut.2020.102433.
10. Nocturne G, Mariette X. Advances in understanding the pathogenesis of primary Sjögren's syndrome. Nat Rev Rheumatol. 2013;9:544-56. doi: 10.1038/nrrheum.2013.110.
11. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76:960-977. doi: 10.1136/annrheumdis-2016-210715.
12. Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol. 2016;12:716-730. doi: 10.1038/nrrheum.2016.186.
13. Vandewalle J, Luypaert A, De Bosscher K, Libert C. Therapeutic mechanisms of glucocorticoids. Trends Endocrinol Metab. 2018;29:42-54. doi: 10.1016/j.tem.2017.10.010.
14. Ye C, Cai S, Shen G, Guan H, Zhou L, Hu Y, et al. Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. Ann Rheum Dis. 2020;79:1007-1013. doi: 10.1136/annrheumdis-2020-217627.
15. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. JAMA. 2020;323:2089-2090. doi: 10.1001/jama.2020.6771.
16. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020;71:889-890. doi: 10.1093/cid/ciaa330.
17. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2020;163:3-11. doi: 10.1177/0194599820926473.
18. World Health O. IMAI district clinician manual: hospital care adolescents and adults: guidelines for the management of illnesses with limited resources. Geneva: World Health Organization; 2020.
19. Mukarram MS, Ishaq Ghauri M, Sethar S, Afsar N, Riaz A, Ishaq K. COVID-19: an emerging culprit of inflammatory arthritis. Case Rep Rheumatol. 2021;2021:6610340. doi: 10.1155/2021/6610340.
20. Freites Nunez DD, Leon L, Mucientes A, Rodriguez-Rodriguez L, Font Urgelles J, Madrid Garcia A, et al. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79:1393-1399. doi: 10.1136/annrheumdis-2020-217984.
21. Jung Y, Kwon M, Choi HG. Association between previous rheumatoid arthritis and COVID-19 and its severity: a nationwide cohort study in South Korea. BMJ Open. 2021;11:e054753. doi: 10.1136/bmjopen-2021-054753
22. Brownstone ND, Thibodeaux QG, Reddy VD, Myers BA, Chan SY, Bhutani T, et al. Novel Coronavirus Disease (COVID-19) and Biologic Therapy in Psoriasis: Infection Risk and Patient Counseling in Uncertain Times. Dermatol Ther (Heidelb). 2020;10:339-349. doi: 10.1007/s13555-020-00377-9.
23. Sparks JA, Tedeschi SK. Improving COVID-19 vaccine immunogenicity by interrupting methotrexate treatment. Lancet Respir Med. 2022;10:813-815. doi: 10.1016/S2213-2600(22)00224-7.
24. Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: a systematic review and meta-analysis. Intensive Care Med. 2021;47:521-537. doi: 10.1007/s00134-021-06394-2.