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Clinical course, chest computed tomography severity score and outcome of coronavirus disease 2019 (COVID-19) in patients with rheumatic diseases

Kamal Esalatmanesh [a], Javid Azadbakht [b], Mehrzad Hajialilo [c], Mohsen Soroush [d], Roozbeh Esalatmanesh [e], Zahra Soleimani [f], Alireza Khabbazi [c,*]

[a] Department of Rheumatology, Autoimmune Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran
[b] Department of Radiology, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[c] Department of Rheumatology, Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, University Street, Tabriz, Iran
[d] Rheumatology Section, Department of Internal Medicine, AJA University of Medical Sciences, Tehran, Iran
[e] Autoimmune Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran
[f] Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran

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ABSTRACT

Aim of the work: To assess the clinical manifestations, imaging findings and outcomes of corona virus disease 2019 (COVID-19) in patients with rheumatic diseases.

Patients and methods: In a three-center study, patients with rheumatic diseases who developed COVID-19 were included. Patients were classified into two groups, i) inflammatory arthritis including rheumatoid arthritis (RA), spondyloarthritis (SpA) and undifferentiated arthritis, ii) connective tissue diseases (CTDs) including systemic lupus erythematosus (SLE), vasculitis and others. COVID-19 outcomes were assessed based on chest computed tomography severity score (CT-ss), the level of care, the number of patients who died and flare of underlying rheumatic disease.

Results: One hundred ninety-six patients with a mean age of 47.9 ± 15.1 years, 73.5% female, were included. Underlying rheumatic diseases were RA (57.7%), SLE and other CTDs (17.9%), SpA (11.2%), vasculitis (11.2%) and undifferentiated arthritis (2%). Myalgia, malaise and fever were the most common clinical manifestations of COVID-19. Pneumonia on computerized tomography (CT), hospitalization, admission in intensive care unit and need to mechanical ventilation were observed in 75.5, 37.2%, 10.7% and 6.6% of patients, respectively. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, diabetes and underlying pulmonary disease were predictors of moderate to severe pneumonia and hospitalization. Fifteen (7.6%) patients died. Flare of underlying rheumatic disease occurred in 16.3% of patients. Flare of disease in patients with CTDs was significantly more than other rheumatic diseases.

Conclusions: In rheumatic patients, treatment with NSAIDs or prednisolone, diabetes and pulmonary disease are risk factors of moderate to high CT-ss and hospitalization during COVID-19.

1. Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to an outbreak of coronavirus disease 2019 (COVID-19) pneumonia in China that rapidly spread across the planet. The confirmed cases were over 270 million globally, with more than 5 million casualties [1]. SARS-CoV-2 is the seventh member of the family of coronaviruses that infects mostly the human upper respiratory tracts, causing dry cough and shortness of breath [2]. As this corona virus pandemic broadens, rheumatologists having a strong background in understanding the immune system and well trained with utilizing biologics are well positioned to assist in management. Such cooperative effort should help reduce mortality during these trying times [3]. Potential changes in rheumatology outpatient practice evolved since the COVID-19 pandemic [4] and patients with rheumatoid arthritis (RA) faced remarkable difficulty to obtain their medications with

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* Corresponding author at: Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Iran.
E-mail address: dr.khabazi@gmail.com (A. Khabbazi).

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subsequent change in their disease status. The challenges of the pandemic have hastened changes in the way we deliver health care [5]. Never the less the COVID-19 pandemic has remarkably affected the quality of life of RA patients [6]. Accordingly, there is an agreement among rheumatologists that the rheumatic disease patients should be vaccinated against COVID-19 [7]. Among adults with systemic rheumatic disease who received COVID-19 vaccination, patient-reported adverse events were typical of those reported in the general population. Most patients were willing to temporarily discontinue DMARDs to improve vaccine efficacy. The relatively low frequency of rheumatic disease flare requiring medications was reassuring [8].

Patients with various rheumatic diseases are at risk of infectious diseases because of the effects of the immune system dysfunction, various comorbidities such as end organ damage, diabetes mellitus, and hypertension as well as the chronic use of immunosuppressants [9,10]. *Ferri et al.* reported a higher frequency of COVID-19 in patients with various systemic autoimmune diseases compared with general population of Italy [11]. Meta-analysis of case–controlled studies showed a higher risk of COVID-19 in patients with autoimmune diseases [12].

Despite general agreement that COVID-19 is more prevalent in patients with rheumatic diseases, there is less consensus on the course and prognosis of COVID-19 in these patients.

The aim of the current study was to assess the clinical manifestations, imaging findings and outcomes of COVID-19 in patients with rheumatic diseases.

2. Patients and methods

In this study, patients with rheumatic diseases who developed COVID-19 were recruited. These patients were followed at the rheumatology clinics of Kashan University of Medical Sciences, Tabriz University of Medical Sciences, and Army Hospital of Tehran. Adult patients were included if they were diagnosed with rheumatic diseases according to the clinical criteria and had COVID-19 according to clinical manifestations consistent with the infection plus positive polymerase chain reaction (PCR) or chest computerized tomography (CT) scan findings of COVID-19 pneumonia [13,14] and ruling out other causes of pneumonia. The ethical committee approval (IR.KAUMS.MEDNT.REC.1399.166) was attained and written informed consent was obtained from all participants. The study was performed according to the Helsinki humanity research declaration (2008).

Demographic, clinical and medications data of the patients were extracted using a questionnaire for patients receiving outpatient care and review of electronic medical records in hospitalized patients. Patients with a diagnosis of COVID-19 were invited to visit in a multidisciplinary clinic. Disease activity was assessed by a rheumatologist and diagnosis of COVID-19 was evaluated by an infectious disease specialist. Two radiologists who were confident and experienced with thoracic imaging, blinded to the demographic and clinical data, reviewed the chest CT images on a same diagnostic monitor independently and discrepancies were resolved in consensus. The CT images were reviewed on both lung and mediastinal windows. Based on the parenchymal involvement extension, semi-quantitative CT severity score (CT-ss) was calculated and assigned to each patient following instructions in previous studies [13,14]. A score of 0–5 was given based on the extension of the ground glass opacity, consolidation and crazy-paving pattern in each lung lobe (according to the anatomical definition provided by the Fleischner Society glossary of terms for thoracic imaging). These scores were graded according to the extent of parenchymal involvement: score 0 (no involvement); score 1 (<5%); score 2 (5–<25%); score 3 (25–<50%); score 4 (50–<75%) and score 5 (75–100%) [15]. The summation of the scores were considered as CT-ss (on a scale of 0–25) and patients were stratified into four groups based on their CT-ss: normal CT (CT-ss 0), mild pneumonia (CT-ss 1–10), moderate pneumonia (CT-ss 10–15) and severe pneumonia (CT-ss 15–25).

The COVID-19 outcomes were assessed based on the level of care, the number of patients who died and flare of the underlying rheumatic disease. Four levels of care were identified including outpatient care, hospitalization, need to intensive care unit (ICU) care and need to mechanical ventilation. Rheumatic diseases were classified as rheumatoid arthritis (RA); systemic lupus erythematosus (SLE) and other inflammatory connective tissue disorders including Sjogren's syndrome, idiopathic inflammatory myopathies, systemic sclerosis, overlap syndromes and undifferentiated connective tissue disorders; seronegative spondyloarthritis (SpA); vasculitis as well as undifferentiated inflammatory arthritis (UIA). In order to facilitate comparison of our results with other studies, patients were further classified into two groups, i) inflammatory arthritis group including RA, SpA and undifferentiated arthritis and connective tissue disorders (CTDs) including SLE, vasculitis and others.

Statistical analysis: Data analysis was performed using SPSS 16.0 software (SPSS, Chicago, IL). The normal distribution of data was assessed using the Kolmogorov-Smirnov test. Variables were presented as mean ± standard deviation (SD), median (25–75% interquartile range [IQR]) or frequency (percentage). Variables were compared using the independent sample *t*-test, Mann-Whitney test and Chi-squared test, respectively. The parameters associated with hospitalization of patients were subjected to univariate analysis. The predictive factors of hospitalization with P-values of <0.1 in univariate analysis were included in a multivariate regression analysis. They were then expressed as odds ratio (OR) and 95% confidence interval (95% CI). Variables were selected using a backward stepwise method based on P-value. $P < 0.05$ was considered significant.

3. Results

Between Feb 2020 to March 2021, 196 adult patients with rheumatic diseases who developed COVID-19 were included in the study. Diagnosis was made according to positive PCR in 164 (83.7%) patients and clinical criteria in 32 (16.3%) of the cases. Demographic characteristics of patients are presented in Table 1. The underlying rheumatic disease was active in 86 (43.9%) patients at the time of developing COVID-19. Except for 3 patients, the rest were treated with prednisolone and/or conventional or biologic disease-modifying anti-rheumatic drugs (DMARDs).

According to the National Protocol of the Ministry of Health, all cases with COVID-19 who had PO_2 saturation $\leq$90–93% on ambient air or dyspnea or respiratory rate $\geq$30 were considered for hospitalization. DMARDs and nonsteroidal anti-inflammatory drugs (NSAIDs) were discontinued during active infection. Patients that were on of glucocorticoids (GCs) received stress dose of GC. All inpatient cases received oxygen and supportive treatment. Patients with respiratory distress, unstable hemodynamic, decreased consciousness or PO_2 saturation $\leq$90 despite oxygen therapy were considered for ICU care and were treated with dexamethasone 8 mg/d and remdesivir. Myalgia, malaise and fever were the most common clinical manifestations of COVID-19. The outcomes of COVID-19 in the studied patients were assessed (Table 2).

The hospitalization rate and need to ICU care tended to be higher in patients with inflammatory arthritis than patients with CTDs while the need for mechanical ventilation and the mortality was comparable. Yet flare of underlying disease was significantly higher in patients with CTDs (Table 3). Mild, moderate and severe

Table 1
Demographic characteristics, risk factors and medications of patients with rheumatic diseases who developed coronavirus disease 2019 (COVID-19).

Characteristic mean ± SD, median (IQR) or n (%)	RD with COVID-19 (n = 196)
Age (year)	47.9 ± 15.1
Females	144 (73.5)
Disease duration (month)	70 (36–129)
Rheumatic disease	
RA	113 (57.7)
SpA	22 (11.2)
Undifferentiated inflammatory arthritis	4 (2)
CVD	35 (17.9)
SLE	30 (15.3)
DM	3 (1.5)
SSc	1 (0.5)
SS	1 (0.5)
Vasculitis	22 (11.2)
PMR	3 (1.5)
BD	2 (1.0)
GPA	2 (1.0)
Risk factors of COVID-19	
Obesity	59 (30.1)
Hypertension	45 (30.0)
Age $\geq$ 65	31 (15.8)
Diabetes	28 (14.3)
Pulmonary disease	17 (8.7)
Smoking	13 (6.6)
Chronic kidney disease	12 (6.1)
Cardiac disease	5 (2.5)
Malignancy	4 (2.0)
Medications	
Prednisolone	151 (77)
Hydroxychloroquine	106 (54.1)
Methotrexate	99 (50.9)
Sulfasalazine	31 (15.8)
NSAIDs	26 (13.6)
Leflunomide	18 (9.2)
Mycophenolate mofetil	16 (8.2)
Azathioprine	14 (7.1)
Cyclophosphamide	3 (1.5)
Calcineurin inhibitors	1 (0.5)
Biologics	30 (15.3)
TNFi	25 (12.8)
Rituximab	4 (2.0)
Interferon α	2 (1.0)

RA: rheumatoid arthritis, SpA: spondyloarthritis, CVD: collagen vascular disease, SLE: systemic lupus erythematosus, DM: dermatomyositis, SSc: systemic sclerosis, SS: Sjogren's syndrome, PMR: polymyalgia rheumatica, BD: Behcet's disease, GPA: granulomatosis with polyangiitis, BMI, body mass index; TNFi: TNFα inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs.

Table 2
Clinical manifestations and outcomes of patients with various rheumatic diseases who developed coronavirus disease 2019 (COVID-19).

Parameter n (%)	RD with COVID-19 (n = 196)
Findings	
Myalgia	163 (83.2)
Malaise	162 (82.7)
Fever	135 (68.9)
Cough	135 (68.9)
Anosmia	110 (56.1)
Dyspnea	106 (54.1)
Taste loss	96 (50.0)
Sore throat	72 (36.7)
Diarrhea	39 (19.9)
Rhinorrhea	29 (14.8)
Pneumonia on CT	148 (75.5)
Outcomes	
Hospitalized	73 (37.2)
Need to ICU	21 (10.7)
Need to MV	13 (6.6)
Death	15 (7.7)
Flare of RD	32 (16.3)

COVID-19: coronavirus disease 2019; RD: rheumatic disease, CT: computed tomography; ICU: intensive care unit; MV: mechanical ventilation.

pneumonia was observed in 50 (25.5%), 62 (31.6%) and 36 (18.4%) patients, respectively. In multivariate regression analysis (Table 4), treatment with NSAIDs and GCs, diabetes and underlying pulmonary disease were the independent factors associated with moderate to severe pneumonia and the parameters associated with hospitalization included treatment with NSAIDs, with GCs and diabetes. Fifteen (7.6%) patients died. The causes of death were respiratory failure in 7, septic shock in 4, multiple organ failure in 3 and pulmonary thromboembolism in 1 patient. Exacerbation of underlying rheumatic disease occurred in 32 (16.3%) patients (Table 5).

4. Discussion

Due to concerns about underlying immune dysregulation and immunosuppression, patients with systemic rheumatic diseases might modify their medications at the time of COVID-19 vaccination to optimise their immune response and mitigate vaccine side-effects [16]. In a previous study from another region in Iran, it was found that most rheumatic diseases do not seem to be a risk factor for developing COVID-19 infection and despite immunosuppressive therapies, there is no poorer outcome. Only, patients using prednisolone >20 mg/d are at higher risk of developing COVID-19 infection [17]. Yet, it has been reported that it is necessary to be aware of the development of SLE in COVID-19 infected patients as prompt diagnosis and treatment is important to improve the outcome [18].

The clinical, CT-ss and outcomes of COVID-19 in patients with rheumatic diseases were assessed. Current findings on the prognostic factors of COVID-19 in patients with rheumatic diseases differ in some respects from reports in other countries (Table 6). In the data published by COVID-19 Global Rheumatology Alliance (GRA) registry on 7263 patients with inflammatory rheumatic diseases, 76% of the patients were female and RA (41%) was the most common disease [19,20]. Most common symptom of COVID-19 was fever [19,20]. Hospitalization and mortality rates were comparable to current results [19,20]. In *Haberman et al.* report on 103 patients with inflammatory arthritis having active rheumatic disease at the time of developing COVID-19 was more common [21]. RA patients hospitalized significantly more than SpA patients (38% versus 16%) [21]. The lower hospitalization and mortality rates in this study compared to our study may be related to lower prevalence of comorbidities and differences in the type of rheumatic diseases in this study. All patients included in this study had RA or SpA [21] and the hospitalization and mortality rates in *Nunez et al.* report [22] was comparable. In agreement, having connective tissue diseases was significantly associated with hospitalization. *Montero et al.* reported a higher hospitalization rate [23]. They did not find any association between baseline rheumatic disease and DMARDs with hospitalization rate.

Present findings on the effect of medications used to treat rheumatic diseases on the outcomes of COVID-19 have similarities and differences with other studies. In *Haberman et al.* study hospitalization rate in patients treated with GCs (OR 21) and JAK inhibitors (OR 6) was more common [21]. In a report from National registry for patients with inflammatory rheumatic diseases from Germany, in accordance to the present work, hospitalization rate in patients treated with GCs and patients with comorbidities was higher [24]. However, in patients treated with bDMARDs hospitalization rate

Table 3
Predictors of moderate and severe pneumonia on computed tomography scan and factors associated with hospitalization in patients with rheumatic disease who developed coronavirus disease 2019 (COVID-19).

Predictors	Regression analysis in RD patients during the COVID-19 infection (n=196)							
	Pneumonia				Hospitalization			
	univariate		*multivariate*		*univariate*		*multivariate*	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age > 65 y	3.6 (1.5–8.6)	**0.004**	2.1 (0.8–5.6)	0.16	2.8 (1.3–6.1)	**0.01**	1.8 (0.7–4.8)	0.24
Male sex	0.8 (0.4–1.8)	0.56			0.9 (0.4–1.7)	0.65		
Co-morbidity								
Smoking	3.4 (0.7–17.4)	0.14			0.8 (0.2–3)	0.78		
Diabetes	6.3 (2.9–13.7)	**0.001**	5.4 (2.1–13.5)	**0.001**	6.2 (2.3–16.3)	**0.001**	4.6 (1.7–12.9)	**0.004**
Obsetiy	1.9 (1.1–3.5)	**0.02**	1.3 (0.6–2.5)	0.51	1.9 (1–3.6)	0.06	1.9 (0.9–3.9)	0.08
Hypertension	2.2 (0.95–5)	0.07	1.5 (0.6–4.3)	0.42	1.6 (0.8–3.3)	0.19		
Pulmonary disease	4.67 (1–22.6)	0.06	3.3 (1.1–9.7)	**0.049**	3.3 (1.1–10.2)	**0.035**	2.9 (0.8–10)	0.09
Cardiac disease	0.53 (0.1–3)	0.47			4.7 (0.5–45.9)	0.19		
CKD	4.3 (1.4–13.6)	**0.01**	0.9 (0.2–3.6)	0.82	7.6 (1.6–36.4)	**0.01**	2.7 (0.5–15)	0.27
IA *vs* CTDs	1.13 (0.5–2.5)	0.76			1.5 (0.8–2.8)	0.22		
Treatment								
NSAIDs	2.6 (1.2–5.5)	**0.01**	5.2 (2.2–14)	**0.001**	2.2 (0.9–5.1)	0.07	2.8 (1.2–2.8)	0.05
Steroids	3.01 (0.9–9.7)	0.07	4.8 (1.1–20.1)	**0.03**	6.6 (2.5–17.5)	**0.001**	5.3 (1.9–14.8)	**0.001**
HCQ	0.7 (0.4–1.3)	0.3			1.4 (0.8–2.5)	0.3		
SAZ	0.9 (0.5–1.7)	0.74			0.8 (0.3–1.7)	0.53		
MTX	1.5 (0.8–2.6)	0.21			1.6 (0.9–2.8)	0.13		
LFN	0.8 (0.3–2.3)	0.72			0.8 (0.3–2.3)	0.72		
AZA	1.9 (0.8–4.4)	0.14			3.3 (1.1–10.3)	**0.038**	2.6 (0.7–9.5)	0.15
MMF	0.8 (0.3–2.4)	0.69			1.3 (0.5–3.8)	0.57		
Biologics	0.8 (0.4–1.8)	0.56			0.6 (0.2–1.4)	0.2		
Activity	1.6 (0.8–2.9)	0.18			2.5 (1.2–5.2)	**0.016**	2 (0.9–4.7)	0.11

RD: rheumatic disease, COVID-19: coronavirus disease 2019, OR: odds ratio; CKD: chronic kidney disease; IA: inflammatory arthritis, CTDs: connective tissue diseases, NSAIDs; nonsteroidal anti-inflammatory drugs, HCQ: hydroxychloroquine, SAZ: sulfasalazine, MTX: methotrexate, LFN: leflunomide, AZA: azathioprine, MMF: mycophenolate mofetil. Bold values are significant at $p < 0.05$

Table 4
Coronavirus disease 2019 (COVID-19) outcomes in patients with rheumatic diseases.

Outcome	RD with COVID-19 (n = 196)		
	IA (n = 139)	CTDs (n = 57)	p
Hospitalization	48 (34.5)	25 (43.9)	0.14
ICU care	12 (8.6)	9 (15.8)	0.11
Need to MV	10 (7.2)	3 (5.3)	0.6
Mortality	11 (7.9)	4 (7.0)	0.55
Flare of RD	14 (10.8)	18 (31.6)	**0.04**

IA: inflammatory arthritis including rheumatoid arthritis, seronegative spondyloarthritis and undifferentiated inflammatory arthritis; CTDs: connective tissue diseases including SLE: systemic lupus erythematosus, vasculitis and others, ICU: intensive care unit, MV: mechanical ventilation. Bold values are significant at $p < 0.05$.

Table 5
Factors associated with flare of rheumatic diseases in patients who developedcoronavirus disease 2019 (COVID-19).

Parameters	RD with COVID-19 (n = 196)		
	Flare (n = 32)	Quiescent (n = 164)	p
Age ≥ 65 years	6 (18.8)	23 (14.0)	0.22
Male sex	10 (31.3)	52 (31.7)	0.6
Having comorbidity	16 (50)	95 (57.9)	0.44
Active RD	18 (56.3)	30 (18.3)	**0.03**
CTDs	19 (59.3)	38 (23.2)	**0.03**
Pneumonia on CT	26 (81.3)	122 (74.4)	0.45
Hospitalization	16 (50)	57 (34.8)	**0.04**

RD: rheumatic disease; COVID-19, coronavirus disease of 2019; CTDs: connective tissue diseases; CT, computed tomography. Bold values are significant at $p < 0.05$.

was lower. Although TNFα inhibitors has been shown to be protective against severe coronavirus, and in particular COVID-19 related outcomes and it has reduced hospitalization rate according to previous studies [25,26], current data did not support a prognostic role for biologics. In agreement, *Bezzio et al.* did not report any significant association between medications and COVID-19 pneumonia, in a cohort of patients with inflammatory bowel disease [27]. This study showed that treatment with NSAIDs is an independent risk factor for hospitalization in patients with rheumatic diseases. Increased angiotensin converting enzyme 2 expression by NSAIDs, may be an explanation [28]. However, *Thomas et al.* in a prospective study reported that use of various NSAIDs is not associated with worst outcome and mortality in general population [29]. Mortality of studied patients was 7.6%. This figure is 3 time the mortality due to COVID-19 in the general population of Iran [30].

The present results show that patients with CTDs in comparison with other types of rheumatic diseases are in danger of flare of disease during COVID-19 infection. Patients treated with NSAIDs or glucocorticoids and patients with underlying conditions including diabetes and pulmonary disease are in danger of severe COVID 19. The retrospective design and a potential selection bias for more severe cases were main limitations of this study. The results of this study should be interpreted with caution because of heterogenicity of various groups of rheumatic diseases with different demographic and clinical characteristics and medications that affect the analysis.

In conclusion, in patients with rheumatic diseases, treatment with NSAIDs or prednisolone, diabetes and pulmonary disease are risk factors of moderate to high CT-ss and hospitalization during COVID-19.

Table 6
Clinical manifestations and outcomes of coronavirus disease 2019 (COVID-19) in patients with rheumatic diseases in various studies.

Study	Hospitalization in RD with COVID-19 (n = 196)						
	Country	n	Active RD (baseline)	COVID-19 symptoms	Hosp. rate	Associated factors	Mortality rate
GRA [19,20]	–	7263	–	Fever (79%), Cough (77%), Dyspnea (50%)	31%	–	5.6%
Haberman et al [21]	USA	103	62%	Fever (84%), Cough (79%), Dyspnea (63%)	25%	Obesity, HTN, COPD, Steroids/JAKi	4%
Nunez et al[22]	Spain	123	–	–	44%	Older age, Vasculitis, SLE, CTDs	9.8%
Montero et al [23]	Spain	62	–	–	68%	Male sex, Lung disease, Steroids	16%
Hasseli et al [24]	Germany	104	–	Cough (69%), Fever (59%), Fatigue (42%)	32%	–	5.8%
Present study	Iran	196	44%	Myalgia (83%), Malaise (83%), Fever (69%), Cough (69%)	37%	Steroids, NSAIDs, Diabetes	7.6%

RD: rheumatic disease, GRA: Global Rheumatology Alliance, CT: computed tomography, BMI: body mass index; HTN: hypertension, COPD, chronic obstructive pulmonary disease; JAKi: janus kinase inhibitors, SLE: systemic lupus erythematosus; CTD: connective tissue disease; RA: rheumatoid arthritis; SpA: seronegative spondyloarthritis; NSAIDs; nonsteroidal anti-inflammatory drugs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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