Journal of Medicine in Scientific Research

Volume 5 | Issue 3 Article 18

Subject Area:

Characteristic clinical features of rheumatic patients with COVID-19 infection in mataria teaching hospital

Wael Mahmoud Hossameldin
Cairo University

Wessam Eissa Hamed
Cairo University, wessameissa2007@gmail.com

Recommended Citation

Hossameldin, Wael Mahmoud and Hamed, Wessam Eissa (2022) "Characteristic clinical features of rheumatic patients with COVID-19 infection in mataria teaching hospital," *Journal of Medicine in Scientific Research*: Vol. 5: Iss. 3, Article 18.
DOI: https://doi.org/10.4103/jmisr.jmisr_1_22

Original Article

Characteristic clinical features of rheumatic patients with COVID-19 infection in Mataria teaching hospital

Wessam Eissa Hamed[a], Wael Mahmoud Hossameldin[b]

Departments of [a]Rheumatology and Rehabilitation, [b]Anesthesiology, Cairo University, Cairo, Egypt

Abstract

Objective

The patients who have rheumatic diseases and have coronavirus disease 2019 (COVID-19) infection, their clinical features have not been reported. This study aims to identify the characteristic clinical features of COVID-19 in patients with rheumatic diseases admitted either inside or outside the ICU and present data to handle these conditions in clinical practice.

Patients and methods

We conducted a retrospective study, including data about the sex, age, laboratory and radiographic findings, clinical symptoms and signs, ICU admission, and drug history, from 180 patients having COVID-19 infection, and includes 61 patients having in combination of rheumatic diseases, in the period between April and June 2020 in Mataria Teaching Hospital.

Results

The risk of admission in the ICU in the rheumatic group 20 (32.8%) did not exceed those expected in the nonrheumatic group 59 (49.6%). Nevertheless, the mortality of these patients was lower three (15%) than nonrheumatic group who were admitted in the ICU 33 (55.9%). Patients with rheumatic diseases presented with less symptoms and signs of respiratory failure, in comparison with those not having rheumatic diseases (rheumatic group vs. nonrheumatic group: 34.4 vs. 49.6%, $P < 0.005$). Comorbidities were similar in those with rheumatic diseases and comparators [25 (41.0%) vs. 48 (40.3%), respectively]. Symptoms of fever, fatigue, and diarrhea were seen in 55.7, 78.7, and 41% of patients, respectively. Nine patients with rheumatic diseases developed rheumatic disease flare during their hospital stay, represented in muscle aches, rash, and pain in the back and joints. Lymphocytopenia was seen in 16.7% of patients with rheumatic diseases, but 14.8% of patients presented with leukopenia. Patients with rheumatic diseases experienced same radiographic findings of ground-glass opacity and consolidation. Patients who have preexisting interstitial lung disease presented at an early stage with massive fibrous stripes and crazy-paving signs.

Conclusions

Symptoms of respiratory failure were less common in patients with rheumatic diseases infected with COVID-19. The ICU admission in the rheumatic group did not exceed those expected in the nonrheumatic group. Differential diagnosis should be considered between COVID-19 infection and rheumatic disease flare.

Keywords: Rheumatic patients, Covid – 19, Intensive care unit, Respiratory failure

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19), has spread so fast into a pandemic worldwide. The estimates of mortality ranges from 1 to 20% in different areas [1]. It is critical for the immune response to defense against SARS-CoV-2 functionally and effectively. Activated follicular

Correspondence to: Wessam Eissa Hamed, MD, Rheumatology and Rehabilitation, Cairo University, El-Mataria Teaching Hospital, Cairo, Egypt.
Tel: +01007161659;
E-mail: wessameissa2007@gmail.com

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/jmisr.jmisr_1_22

Submitted: 08-Jan-2022 **Revised:** 17-Jan-2022 **Accepted:** 26-Jan-2022 **Published:** 23-Nov-2022

How to cite this article: Hamed WE, Hossameldin WM. Characteristic clinical features of rheumatic patients with COVID-19 infection in mataria teaching hospital. J Med Sci Res 2022;5:316-25.

helper T cells and antibody-secreting cells, which are subsets of immune effector cells that are responsible for the immunity against the virus, were increased prior to the clearance and the symptomatic recovery of SARS-CoV-2, suggesting that the antiviral immune response is important for the clearance of SARS-CoV-2 [2].

The manifestation of excess release of inflammatory cytokines, especially the upregulation of interleukin (IL)-2, IL-6, IL-10, IL-12 and tumor necrosis factor-α (TNF-α) was associated with progression of acute respiratory distress syndrome in COVID [3]. COVID-19 infected patients, especially those who are severely ill patients, beside increased levels of inflammatory cytokines in plasma, they have also in parallel increase in the level of tissue damage markers such as creatine kinase-MB, hypersensitive troponin I, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase [4]. In April 2020, a number of patients infected with COVID-19 and have rheumatic diseases were diagnosed at Mataria Teaching Hospital (MTH), a hospital where moderately to critically ill patients with COVID-19 receive care. In this observational retrospective study, we demonstrate patients' clinical features and medication history before hospitalization for COVID-19, to help determine the clinical, laboratory and radiographic characteristics, medical history and the outcome of those patients who have rheumatic diseases and infected with COVID-19.

Patients and methods

We conducted a retrospective study. Inclusion criteria: (a) we included patients having rheumatic diseases and patients not having rheumatic disease who not admitted in ICU (mild and moderate cases) and those who are admitted in ICU (severe cases), that were admitted at MTH in the period between April and June 2020. (b) We included patients aged more than or equal to 17 years old seen at MTH and tested positive for COVID-19 by PCR clinical assay. We matched data of patients with rheumatic diseases and have positive PCR tests to the other nonrheumatic patients. Data on demographics (age, sex), clinical (symptoms and signs, respiratory failure status, medical history and disease outcome), laboratory information (leukocyte/lymphocyte counts, hemoglobin, and so on), radiological [characteristics of chest computed tomography (CT) scans], and management prior and after COVID-19 infection, collected from MTH electronic information system. Because of the rapid spread of COVID-19 infection, written informed consent was ignored.

Identification of a case with rheumatic disease

To identify patients that have a possible rheumatic disease with confirmed COVID-19, we searched the hospital electronic health record. Diagnosis of rheumatic disease was confirmed by manual review of the electronic health record. Exclusion criteria: (a) we excluded cases that did not need any hospitalization or any referral to hospital emergency departments. (b) Patients having osteoarthritis, fibromyalgia or crystalline arthropathy were not included also, because they do not represent a typical systemic autoimmune rheumatic disease (or managed by systemic immune-modulators) [5]. We excluded also: cases of antiphospholipid antibody syndrome or sarcoidosis with no prior administration of immunosuppressive medication, and cases of polymyalgia rheumatica.

Identification of a nonrheumatic disease comparator

We matched every patient with a rheumatic disease to comparators having no rheumatic disease from MTH population who are positive for COVID-19, on the basis of age and sex.

Data collection

We collected data on the demographic features (sex, age), clinical features (drug history, disease severity grading, clinical symptoms and signs, status of respiratory failure and outcome of disease), radiographic features (scans of CT chest) and laboratory findings (hemoglobin, leukocyte/lymphocyte counts, so on), and management prior and after COVID-19 infection from MTH electronic information system. CT scan images of patients with rheumatic diseases were collected from the Department of Radiology in MTH. Radiological features of ground-glass opacity (GGO), pleural lesions and consolidative patches in each case were assessed independently by two radiologists at least.

Ethical considerations

Ethical Committee approval was taken.

Statistical analysis

We use the Statistical Package for Social Science (IBM SPSS statistics for windows. Version 23.0. Armonk. New York: IBM Corp. Released 2015), version 23 to collect, revise, and enter data. We presented the quantitative data as mean, SDs, and ranges when parametric. Also, we presented qualitative variables in the form of number and percentages.

We use the χ^2 test and/or Fisher exact test to compare between groups regarding qualitative data when the expected count in any cell found less than 5. We use the independent t test to compare between two groups regarding quantitative data and parametric distribution.

We set the confidence interval to be at 95% and we accept the margin of error to be at 5%. So, we consider the *P* value significance as follows:

P value less than 0.01: highly significant, *P* value less than 0.05: significant, *P* value more than 0.05: nonsignificant.

Results

Basic information of patients with rheumatic diseases

In the period between April and June 2020, 180 patients infected with COVID-19 were admitted to MTH, 61 (33.9%) patients had rheumatic diseases. In these 61 patients with rheumatic diseases, there were 43 (23.9%) rheumatoid arthritis (RA) cases, nine (5.0%) systemic lupus erythematosus (SLE) cases, one (0.6%) primary Sjögren's syndrome (pSS) case, six (3.3%) psoriatic arthritis (PsA) cases, one (0.6%)

inflammatory bowel disease case, and one (0.6%) ankylosing spondylitis case. In comparison with 119 (66.1%) patients with no rheumatic disease, female patients ratio was higher in the group of rheumatic diseases and significant [rheumatic group vs. nonrheumatic group: 54 (88.5%) vs. 61 (51.3%)]. The risk of ICU admission in the rheumatic group 20 (32.8%) were also compared with those in the nonrheumatic group [59 (49.6%)] (Table 1).

Study population

Between April and June 2020, 180 patients were diagnosed with COVID-19 disease at MTH. Sixty one (33.9%) patients was complaining from rheumatic disease. We matched those rheumatic patients to 119 (66.1%) comparators (Fig. 1); the mean of age was 48 (48.74 ± 13.25) years in the rheumatic disease group and 54 (54.18 ± 17.00) years in the nonrheumatic group, and 88.5% accounts for female patients in the rheumatic group (Table 1). In the group of patients with rheumatic diseases, the rheumatic disease distributed broadly, and included 43 (23.9%) RA cases, nine (5.0%) SLE cases, six (3.3%) PsA cases, one (0.6%) pSS case, six (3.3%) PsA cases, one (0.6%) inflammatory bowel disease case, and one (0.6%) ankylosing spondylitis case (Table 2). Rheumatic patients were on some immunomodulatory drugs: 59 (32.8%) were on conventional synthetic DMARDs, 15 (24.6%) were on biologic DMARDs, and no one were on targeted synthetic DMARDs. Of those on conventional synthetic DMARDs also were on oral glucocorticoids (59; 32.8%), the median prednisone-equivalent dose was 5 mg/day.

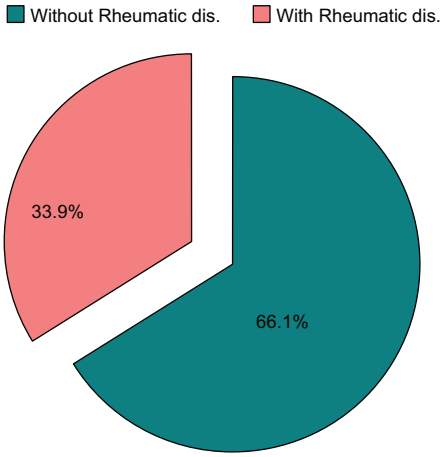

Figure 1: Distribution of patients with rheumatic and nonrheumatic diseases.

Outcomes of patients with rheumatic disease infected with coronavirus disease 2019

We assessed the outcome of patients with inflammatory rheumatic diseases who admitted to the ICU, and we found that the risk of ICU admission in the rheumatic group 20 (32.8%) did not exceed those expected in the nonrheumatic group 59 (49.6%) (Fig. 2). Nevertheless, the mortality of these rheumatic patients who admitted in ICU was lower (15%) than nonrheumatic patients who also admitted in ICU (55.9%) (Fig. 3). In comparison with nonrheumatic patients, we found that rheumatic patients presented with less respiratory failure (rheumatic group vs. nonrheumatic group: 34.4 vs. 49.6%), *P* value less than 0.005 (Table 1, Fig. 4).

Table 1: The demographic and clinical features in both patients with and without rheumatic disease and coronavirus disease 2019

	Without rheumatic disease *n*=119	With rheumatic disease *n*=61	Test value	*P*	Significance
Age					
Mean±SD	54.18±17.00	48.74±13.25	2.184•	0.030	S
Range	17–82	17–79			
Sex [*n* (%)]					
Female	61 (51.3)	54 (88.5)	24.273*	0.000	HS
Male	58 (48.7)	7 (11.5)			
ICU admission [*n* (%)]					
Non-ICU	60 (50.4)	41 (67.2)	4.618*	0.032	S
ICU	59 (49.6)	20 (32.8)			
Respiratory failure [*n* (%)]					
No	(50.4)	(65.6)			
Yes	(49.6)	(34.4)			
Mask	9 (7.6)	10 (16.4)			
HFNC	8 (6.7)	6 (9.8)			
CPAP	21 (17.6)	5 (8.2)	18.407*	0.005	HS
Ventilator	14 (11.8)	0			
Nasal	6 (5.0)	0			
Tracheostomy tube	1 (0.8)	0			

*Chi-square test (It means that the test used was the Chi-square test), •Independent t-test (It means that the test used was the Independent t-test).
CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula.

Comorbidities [25 (41.0%)] versus 48 (40.3%) were similar in those with rheumatic diseases and comparators respectively. From the 61 rheumatic patients, 25 (41.0%) were having comorbid conditions, distributed as follow: hypertension, ischemic heart disease, chronic kidney disease, diabetes mellitus and interstitial lung disease (ILD). The most common comorbid condition was hypertension, affecting 24 (39.3%) out of the 61 rheumatic patients (Table 3), but mortality generally was lower in rheumatic group three (4.9%) versus nonrheumatic group: 33 (27.7%) with statistically significant *P* value ($P < 0.000$) (Table 4, Fig. 5). Both rheumatic and nonrheumatic patients represent age structures with more than 40 years old (rheumatic group: 48.74 ± 13.25; nonrheumatic group: 54.18 ± 17.00) at the time of diagnosis with COVID-19.

Table 2: Distribution of rheumatic diseases among rheumatic group

	Without rheumatic disease [*n* (%)]	119 (66.1)
Rheumatic disease	RA [*n* (%)]	43 (23.9)
	PsA [*n* (%)]	6 (3.3)
	SLE	9 (5.0)
	AS	1 (0.6)
	Sjogren $	1 (0.6)
	IBD	1 (0.6)

AS, ankylosing spondylitis; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

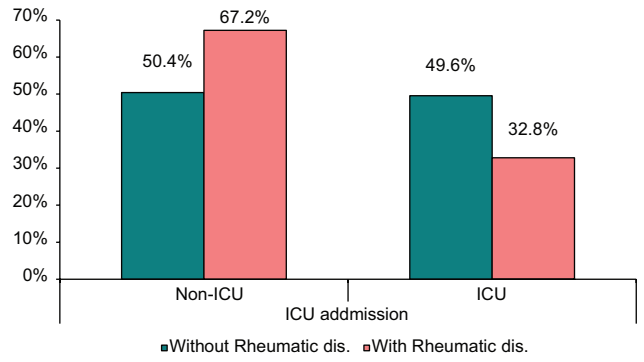

Figure 2: ICU admission in rheumatic and nonrheumatic patients with COVID-19. COVID-19, coronavirus disease 2019.

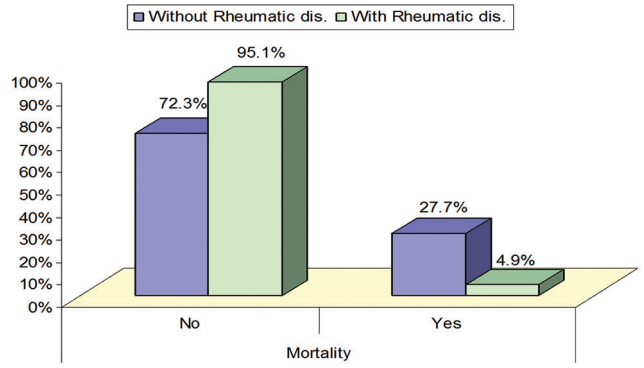

Figure 4: Basic information of respiratory failure in rheumatic and nonrheumatic cases.

Clinical features of rheumatic patients infected with coronavirus disease 2019

The clinical spectrum of COVID-19 infection is broad, ranges from no symptoms to fatal symptoms or life-threatening condition. COVID-19 clinical presentation ranges from asymptomatic form of pneumonia to severe form. Based on the analysis done by WHO for confirmed cases, the common symptoms of the infection are fever, dry cough and fatigue. From the typical symptoms also myalgia and arthralgia [6]. The major cause of morbidity and mortality is the acute bilateral interstitial pneumonia in COVID-19 infection (Table 5) summarizes the manifestations that mimic rheumatic syndromes which may associate COVID-19 infection. Fever was noticed in 34 rheumatic patients out of the 61 ones. The temperatures ranged between 37.7 and 41°C in 55.7%, with a mean of 38.39 ± 0.70. At least one respiratory symptom was found in most of the rheumatic cases, but with different patterns in the patients: cough, expectoration, chest pain, and dyspnea were found in 31.1, 8.2, 31.1, and 26.2% of rheumatic patients, respectively (Table 6).

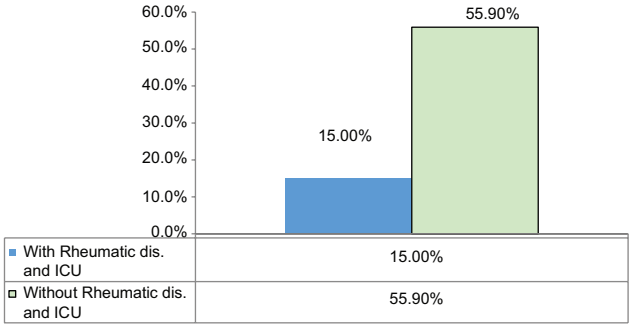

Figure 3: Mortality rate in rheumatic and nonrheumatic patients with COVID-19 admitted in ICU. COVID-19, coronavirus disease 2019.

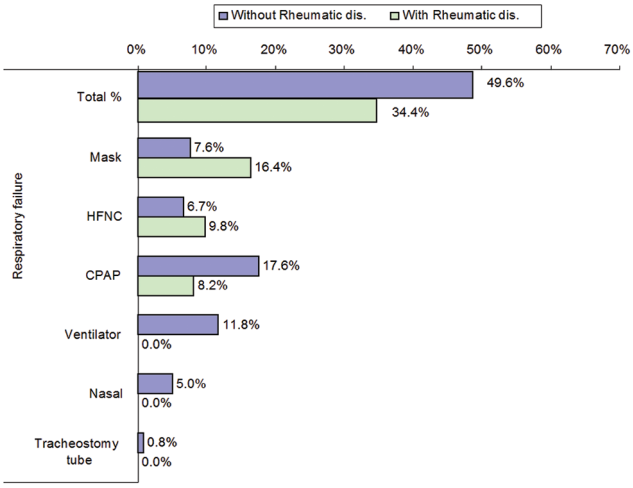

Figure 5: Mortality rate in rheumatic and nonrheumatic patients with COVID-19. COVID-19, coronavirus disease 2019.

Table 3: Comorbidities in rheumatic and nonrheumatic patients with coronavirus disease 2019

	Without rheumatic disease [*n* (%)]	With rheumatic disease [*n* (%)]	Test value	*P*	Significance
	n=119	*n*=61			
Comorbidities					
No	71 (59.7)	36 (59.0)	0.007*	0.933	NS
Yes	48 (40.3)	25 (41.0)			
Fits	1 (0.8)	0	0.515*	0.473	NS
Dehydration	1 (0.8)	0	0.515*	0.473	NS
ILD	0	1 (1.6)	1.962*	0.161	NS
Asthma	4 (3.4)	3 (4.9)	0.261*	0.609	NS
DM	14 (11.8)	14 (23.0)	3.842*	0.050	NS
HTN	33 (27.7)	24 (39.3)	2.513*	0.113	NS
IHD	3 (2.5)	2 (3.3)	0.086*	0.770	NS
CKD	1 (0.8)	0	0.515*	0.473	NS

*Chi-square test; It means that the test used was the Chi-square test. CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; ILD, interstitial lung disease.

Table 4: Mortality rate in rheumatic and nonrheumatic patients with coronavirus disease 2019

	Without rheumatic disease [*n* (%)]	With rheumatic dis ease [*n* (%)]	Test value*	*P*	Significance
Mortality					
No	86 (72.3)	58 (95.1)	13.118	0.000	HS
Yes	33 (27.7)	3 (4.9)			

*Chi-square test; It means that the test used was the Chi-square test.

Table 5: Features associated with (coronavirus disease 2019) infection and mimic rheumatic syndromes

1. Joint pain and muscle pain
2. Decreased leukocytic count (predominantly decreased lymphocytes); and decreased thrombocytes
3. Acute interstitial pneumonia-like presentation
4. Inflammation of cardiac muscles (myocarditis)
5. Cytokine storm
6. A possible great risk of venous thromboembolic manifestation

In addition to these respiratory manifestation, a large number of patients who have rheumatic diseases presented with fatigue 48 (78.7%) in our study and/or diarrhea 25 (41%), which could be found in both COVID-19 infection and the active state of rheumatic diseases. In many cases of COVID-19 infection, we observed that fatigue and diarrhea were initial symptoms. Also, fatigue is considered a complaint that occur most commonly in systemic autoimmune rheumatic diseases [7]. But, diarrhea might occur due to either certain antirheumatic drugs like leflunomide [8] or because of the rheumatic disease itself like Ehlers-Danlos syndrome and Behçet disease [9]. Also, severe course of SARS-CoV-2 infection is typically associated with lymphopenia, leucocytosis and high neutrophil–lymphocyte ratio. In SLE and Sjogren's syndrome, features of acute interstitial pneumonia, thrombocytopenia and lymphopenia could also be seen in the state of disease activity. So, these clinical situations may cause clinical confusion in patients whether the condition is autoimmune in origin or infective.

Laboratory indices

Information on laboratory indices is shown in Table 7. In our study, we found that the lymphocytic count was declined in 16.7% of patients with rheumatic diseases but, leucopenia was found in 14.8%. Elevated count of neutrophils was observed in 57.4% of patients, while hemoglobin level ranges between 9.2 and 15.5 with a mean ± SD: 11.82 ± 1.21, 13 (21.3%) of 61 patients showed anemia.

Liver function was also disturbed. Liver enzymes such as alanine aminotransferase and aspartate aminotransferase were increased, respectively, in 16 (26.2%) and 14 (23%) of patients, while elevated lactate dehydrogenase and serum ferritin were observed in 21 (34.4%) and in 35 (57.4%), respectively. Coagulation and anticoagulation system found to be activated in most cases of rheumatic diseases: we found that D-dimer level was elevated in 16 (37.2%) of patients with rheumatic diseases. Increased D-dimer, elevated fibrinogen, and increasing prothrombin time are abnormalities of the coagulation system that are increasingly reported in hospitalized patients with COVID-19 infection, and the increase in D-dimer concentration is the most typical finding in patients infected with COVID-19 [10].

The increase in the incidence of venous thromboembolism, which includes deep venous thrombosis and pulmonary embolism, has been associated with (COVID-19) infection. It is unclear what is the underlying mechanism for this phenomenon but it is suggested that antiphospholipid antibody production upregulation and cytokine storm related hypercoagulability are causes induced by the viral infection [11].

Table 6: Symptoms and signs of rheumatic and nonrheumatic patients with coronavirus disease 2019

	Without rheumatic disease [*n* (%)]	With rheumatic disease [*n* (%)]	Test value	*P*	Significance
	n=119	*n*=61			
Fever					
No	30 (25.2)	27 (44.3)	6.765*	0.009	HS
Yes	89 (74.8)	34 (55.7)			
Mean±SD	38.60±0.68	38.39±0.70	1.527•	0.129	NS
Range	37.7–40	37.7–41			
Chest pain					
No	59 (49.6)	42 (68.9)	6.083*	0.014	S
Yes	60 (50.4)	19 (31.1)			
Shortness of breath					
No	46 (38.7)	45 (73.8)	19.893*	0.000	HS
Yes	73 (61.3)	16 (26.2)			
Abdominal pain nausea and vomiting					
No	95 (79.8)	37 (60.7)			HS
Nausea	18 (15.1)	1 (1.6)			
Abdominal pain	1 (0.8)	20 (32.8)	47.086*	0.000	
Vomiting	3 (2.5)	1 (1.6)			
Cough					
No	48 (40.3)	37 (60.7)			S
Dry cough	60 (50.4)	19 (31.1)	6.989*	0.030	
Productive cough	11 (9.2)	5 (8.2)			
Fatigue	100 (84.0)	48 (78.7)	0.788*	0.375	NS
Arthralgia	7 (5.9)	9 (14.8)	3.919*	0.048	S
Myalgia	52 (43.7)	24 (39.3)	0.313*	0.576	NS
Diarrhea	19 (16.0)	25 (41.0)	13.666*	0.000	HS
headache	30 (25.2)	13 (21.3)	0.337*	0.561	NS
Sore throat	42 (35.3)	20 (32.8)	0.112*	0.738	NS
Loss of taste	22 (18.5)	9 (14.8)	0.394*	0.530	NS
Anosmia	33 (27.7)	21 (34.4)	0.861*	0.354	NS

*Chi-square test (It means that the test used was the Chi-square test), •Independent t-test (It means that the test used was the Independent t-test).

The internal milieu of rheumatic cases was relatively pro-inflammatory: a great number of cases reported an increase in the levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in 57 (96.6%) and 56 (91.8%), respectively.

Radiological characteristics

The most common sign in patients with rheumatic diseases and have COVID-19 infection was GGO, which was reported in 23% of rheumatic patients. The presence of consolidative patchy shadows (16.4%) were also noticed. Signs of GGO, consolidative and patchy shadows were found at earlier stage combined with massive fibrous stripes and crazy-paving signs, in one (1.6%) case with preexisting RA-associated ILD. These crazy-paving signs and fibrous stripes remained after consolidation and GGO absorption on images of CT scans which suggest a feature of ILD.

Drugs

Prior to the diagnosis of COVID-19 infection, patients were administered a variety of medication such as glucocorticoids, NSAIDs, leflunomide, methotrexate, hydroxychloroquine (HCQ) according to the type of the rheumatic disease found and its status, while 15 (24.5%) of rheumatic patients were administered biologics. During hospital stay, nine (14.8%) of 61 cases developed a flare of their rheumatic disease, and received therapeutic medications such as HCQ, mycophenolate mofetil, NSAIDs, and prednisone with a high-dose (40 mg/day) were given according to the type of the rheumatic disease present to control disease activity. Among the nine cases of rheumatic flare, four (RA) patients developed pain in joints and muscle aches, two (SLE) patients presented with rash and arthralgia, three (PsA) patients presented with pain in the back and ankle.

Discussion

The condition of patients with rheumatic diseases who have COVID-19 infection is worrisome. In our study, we found that patients in the rheumatic group presented with less severe respiratory manifestations when having COVID-19 infection, with risk of respiratory failure lower than that of the nonrheumatic group. This finding was supported with a study done by Moiseev *et al*. [12] in which he reported that the total prevalence of patients that have rheumatic diseases and developed pneumonia due to COVID-19 infection and admitted to ICU was low. Several studies reported

Table 7: Laboratory indices of rheumatic and nonrheumatic patients with coronavirus disease 2019

	Without rheumatic disease [*n* (%)] *n*=119	With rheumatic dis ease [*n* (%)] *n*=61	Test value	*P*	Significance
ESR (mm/h)					
Normal	11 (9.2)	2 (3.4)	1.997*	0.158	NS
Increased	108 (90.8)	57 (96.6)			
CRP (mg/dl)					
Normal	18 (15.1)	5 (8.2)	1.737*	0.187	NS
Increased	101 (84.9)	56 (91.8)			
White cell count (K/µl)					
Normal	108 (90.8)	52 (85.2)	1.240*	0.266	NS
Decreased	11 (9.2)	9 (14.8)			
Lymphocytes %					
Normal	96 (80.7)	50 (83.3)	0.188*	0.665	NS
Increased	23 (19.3)	10 (16.7)			
Serum ferritin (µg/l)					
Normal	45 (37.8)	26 (42.6)	0.390*	0.532	NS
Increased	74 (62.2)	35 (57.4)			
LDH (U/l)					
Normal	79 (66.4)	40 (65.6)	0.012*	0.913	NS
Increased	40 (33.6)	21 (34.4)			
Neutrophils %					
Normal	36 (30.3)	26 (42.6)	2.733*	0.098	NS
Increased	83 (69.7)	35 (57.4)			
Hemoglobin (g/dl)					
Nonanemia	99 (83.2)	48 (78.7)	0.547*	0.460	NS
Anemia	20 (16.8)	13 (21.3)			
Serum ALT (U/l)					
Normal	70 (58.8)	45 (73.8)	3.905*	0.048	S
Increased	49 (41.2)	16 (26.2)			
Serum AST (U/l)					
Normal	74 (62.2)	47 (77.0)	4.044*	0.044	S
Increased	45 (37.8)	14 (23.0)			
D-dimer (ng/ml)					
Normal	36 (67.9)	27 (62.8)	0.277*	0.598	NS
Increased	17 (32.1)	16 (37.2)			

*Chi-square test; It means that the test used was the Chi-square test. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; K/µl, thousands per microliter; LDH, lactate dehydrogenase. Normal references: white cell count: 4.5-11.0 K/µl; hemoglobin: 11.5-17.5 g/dl; lymphocytes: 20-40%; neutrophils: 40-60%; ferritin: 20-300 µg/l; D-dimer: less than 500 ng/ml; LDH: less than 240 µ/l; AST: 10-40 U/l; ALT: 10-40 U/l; ESR: less than 13 mm/h in male, less than 20 mm/h in female; CRP: less than 6 mg/l.

recently that pro-inflammatory cytokines like IL-1, IL-6 and TNF-α, which play a role in different rheumatic diseases as pathogenic factors, may be a cause also for multiple organs failure in patients having COVID-19 infection. One of the major causes that is responsible for acute respiratory distress syndrome (ARDS) and multiple-organ tissue damage is the cytokine storm [13]. It has an important role in the aggravation of disease. Clinical studies have detected a cytokine storm in critical patients with COVID-19. Therefore, the effective suppression of the cytokine storm is a very important way to stop the rapid patients' deterioration and will help save their lives [14].

The long-term use of immunosuppressive treatment and/or glucocorticoids increases the chance of infection by microbes also [15]. At the pathogenic mechanism level, both COVID-19 infection and rheumatic diseases can affect each other and can cause catastrophic deterioration to patients' health at the end. Thus, identification of the rheumatic disease active state in COVID-19 infection should be taken into consideration seriously, and vice versa. There are common clinical features between COVID-19 infection and a flare of rheumatic disease, like fever, fatigue, and abnormal laboratory tests (CRP, ESR, decreased lymphocytic count, and so on), and concerning images of CT (we can see GGO commonly in patients with rheumatic diseases and have lung affection). Presence of these clinical symptoms may cause misdiagnosis of the flare of rheumatic disease and further delay in the diagnosis of COVID-19 infection. Fever also may be masked by the glucocorticoid use. A well-known recognized symptom of COVID-19 infection by the general population. Also,

inflammatory biomarkers and lymphocytopaenia which are laboratory indices that used commonly in COVID-19 assessment, are very similar in both condition of rheumatic disease flare and COVID-19 infection.

In our study, we observed lymphocytopaenia in 16.7% of cases, while increased levels of CRP, ESR, lactate dehydrogenase and ferritin was reported in 91.8, 96.6, 57.4, and 34.4% of cases, respectively although it is hard to make a distinguish for the precise origin for these clinical features, combined with the other immune-related parameters. Chest CT images of patients with rheumatic diseases who have COVID-19 infection should also be evaluated in a careful way. Generally, there was no difference between radiographic features of the chest CT images of patients with rheumatic diseases who have COVID-19 infection and those of nonrheumatic group. They include features of GGOs, consolidative and patchy shadows. However, there are many systemic diseases including rheumatic diseases that can affect the lungs as target organs. ILD that is associated with connective tissue disease (CTD-ILD) is seen commonly in diseases like RA, scleroderma and pSS [16]. So, to help identify the origin of interstitial lesions, a differential diagnosis should also be done.

In our study, a massive fibrous stripes and crazy-paving signs were observed on CT images of patients who have CTD-ILD at an earlier stage, which supposed to be found later [17,18]. These signs more importantly, remained with no change after the recovery of symptoms and the absorption of GGO/consolidative patches. So, we can consider these features during the differential diagnosis between ILD and COVID-19. In clinical practice, there is another important task, which is how to balance between the medication of antirheumatic and antivirus therapy. In this study, no case that was on HCQ medication for long-term and reached to a critical stage of illness. There is a recent human trial and *in vitro* studies support the antiviral activity of chloroquine and HCQ medications [19]. Chloroquine proved its high effectiveness in controlling COVID-19 infection in vitro. Other than the direct effect of its activity against viral infection, HCQ proved to be a safe and a successful anti-inflammatory drug that extensively used in autoimmune diseases producing a significant decrease in the production of pro-inflammatory cytokines [20,21]. In randomized clinical trials in China, use of HCQ in patients having COVID-19 infection has led to improvement of pneumonia and laboratory results and decrease the progression to a severe/critical state of illness [22,23]. However, some other reports did not show any benefits [24], even side effects [25], from its use in COVID-19 infection. Some other studies reported high frequency of side effects that may occur (e.g., cardiotoxicity) in patients with COVID-19 infection and treated with chloroquine or HCQ, especially with high doses [26,27]. Therefore, in COVID-19 infection HCQ/chloroquine use is still controversial, and we need to do further investigations to evaluate the efficacy of HCQ medication and its safe use in COVID-19 infection.

Currently, in this pandemic, we are in an urgent need for timely investigations to help assess rheumatic patients' clinical course who having with COVID-19 infection. The biological disease-modifying antirheumatic drugs b (DMARDs) like tocilizumab (TCZ) proved to have a benefit in managing the hyper inflammatory state of severe cases of COVID-19 [28,29]. TCZ, a recombinant humanized, monoclonal antibody that has the ability to bind to the soluble and membrane-bound form of IL-6 receptors, has been approved for treating rheumatic diseases, including juvenile idiopathic arthritis and RA [30]. An Italian study recently, reported that among 530 rheumatic patients treated with biological drugs such as TCZ and anti-TNFs, three patients only were diagnosed with COVID-19 infection, and they all were mild cases [31]. Another study also stated that no progression to a severe form of respiratory complications or death occurred in any of the four confirmed cases of COVID-19 infection that were treated by biological or targeted synthetic DMARDs for RA [32]. In our study, one RA patient has received TCZ during his stay in the hospital due to severe form of COVID-19 infection and an elevated level of serum IL-6. His COVID-19 status improved, and no disease flare happened during his stay in the hospital. Within 15 days after his admission, he finally recovered and was discharged. However, these previous studies were all observational and have no appropriate control populations. Hopefully, conduction of randomized controlled trials may help provide a real direct evidence for the degree of safety and efficacy of TCZ use in COVID-19 infection.

We assume that patients who are immunocompromised and are complaining from systemic autoimmune rheumatic diseases, present with a more severe state of COVID-19 infection that may require oxygen support and possibility for ICU admission. However, in our study the total prevalence of rheumatic patients having SARS-CoV-2 pneumonia and admitted to ICU was low (32.8%) and was not exceeding that in the general population (49.6%). Moreover, some predictors of unfavorable outcomes of SARS-CoV-2 pneumonia were found in most patients with rheumatic disease who develop a critical state of illness, such as CVD, diabetes mellitus and obesity, which are a major cause for ARDS. These comorbidities were the same comorbidities that had been identified previously in the general population affected by COVID-19 as risk factors and may lead also to worse outcome [33]. This comment confirms that patients having rheumatic diseases might not suffer from a bad prognosis and outcome during COVID-19 infection and the severity of the infection might be influenced by the underlying concomitant cardiovascular comorbidities. Patients with rheumatologic diseases complain from frequent comorbidities, even these comorbidities can occur at younger age in comparison with the control populations, and these might lead to an increased risk of developing a severe form of COVID-19 infection [34].

Obviously, because we do not know the total number of rheumatic patients having COVID-19 infection in Egypt, we cannot be sure of a definite conclusion regarding the risk of severe COVID-19

in those patients. Of note, any patient complains of chronic diseases can easily be at increasing risk of contracting respiratory infections because of the more frequent visits to the outpatient clinics where there are infected individuals they can contact infection from them. There is an accumulating evidence that a number of patients with severe COVID-19 pneumonia have a cytokine storm, this cytokine storm is the main leading cause of mortality [28]. Some of the anti-inflammatory medications can improve cytokine profile, decrease hyperinflammation and, therefore may prevent progression to ARDS induced by COVID-19 infection in patients [35]. Many antirheumatic agents, like HCQ, anakinra, TCZ and colchicine, are currently used in managing patients with COVID-19 infection. TCZ appears to be one of the most promising agents for SARS-CoV-2-induced ARDS prevention and treatment.

In brief, our study reported that rheumatic patients were less represented in the group of patients who admitted in ICU due to SARS-CoV-2 pneumonia and developed ARDS. These information support in an indirect way the current recommendation not to discontinue or stop medications used in patients with rheumatic diseases to avoid occurrence of rheumatic disease flare [36].

Some limitations were found to this study. Firstly, it is done retrospectively from a single-center only with sample size that it is small relatively. So, we are in need for further future investigations of a large sample size and/or multicenter studies to give more informative data. Secondly, in all the 61 rheumatic patients, no one was on targeted small molecule inhibitors like tofacitinib for long term prior to the diagnosis of COVID-19 infection. Thus, we cannot introduce any information about its effect on the susceptibility of COVID-19 infection or its clinical progress. Third, it was not possible to assess the risk of lung damage due to COVID-19 infection in patients with rheumatic diseases and have preexisting ILD because of the very low number of cases that have history of definite CTD-ILD. At last, this study includes a collection of rheumatic diseases. Because each certain type of disease has a small number of patients, we did not do subcategorization of the rheumatic diseases during analyzing and assessing some of the parameters. In summary, our study showed the clinical and demographic features of patients with rheumatic diseases who having COVID-19 infection, in addition to their medication history, laboratory and radiographic findings, which may guide the differentiation between the flare of the rheumatic disease and COVID-19 infection.

Conclusion

We found that respiratory failure was found to be less common in rheumatic patients infected with COVID-19. The ICU admission in the rheumatic group did not exceed those expected in the nonrheumatic group. These findings give reassurance that patients with rheumatic disease may not be at increased risk of developing severe form of COVID-19 infection or at increased risk of death in comparison with the general population. Differential diagnosis should be considered between COVID-19 infection and rheumatic disease flare. Also, this study help introduces some evidence on the antirheumatic drugs usage in management of rheumatic disease activity during COVID-19 infection.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. The Lancet infectious diseases 2020; 20:773.
2. Thevarajan I, Nguyen TH, Koutsakos M, Druce J, Caly L, van de Sandt CE, *et al*. Breadth of concomitant immune responses prior to patient recovery: A case report of non-severe COVID-19. Nature medicine 2020; 26:453-5.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet 2020; 395:497-506.
4. 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; 323:1061-9.
5. Jorge AM, Lu N, Keller SF, Rai SK, Zhang Y, Choi HK. The effect of statin use on mortality in systemic autoimmune rheumatic diseases. The Journal of rheumatology 2018; 45:1689-95.
6. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, *et al*. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. The Lancet 2020; 395:1763-70.
7. Zielinski MR, Systrom DM, Rose NR. Fatigue, sleep, and autoimmune and related disorders. Front Immunol 2019; 10:10.
8. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, *et al*. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Archives of internal medicine 1999;159:2542-50.
9. Kröner PT, Tolaymat OA, Bowman AW, Abril A, Lacy BE. Gastrointestinal manifestations of rheumatological diseases. Official journal of the American College of Gastroenterology| ACG 2019; 114:1441-54.
10. Berger JS, Kunichoff D, Adhikari S, Ahuja T, Amoroso N, Aphinyanaphongs Y, *et al*. Prevalence and outcomes of D-dimer elevation in hospitalized patients with COVID-19. Arterioscler Thromb Vasc Biol 2020; 40:2539–2547.
11. Barnes DH, Lo KB, Bhargav R, Gul F, DeJoy IIIR, Peterson E, *et al*. Predictors of venous thromboembolism in patients with COVID-19 in an underserved urban population: a single tertiary center experience. Clin Respir J 2021; 15:885-91.
12. Moiseev S, Avdeev S, Brovko M, Yavorovskiy A, Novikov PI, Umbetova K, *et al*. Rheumatic diseases in intensive care unit patients with COVID-19. Ann Rheum Dis 2021; 80:e16.
13. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020; 109:102433.
14. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. J Infect 2020; 80:607–613.
15. Vandewalle J, Luypaert A, De Bosscher K, Libert C. Therapeutic mechanisms of glucocorticoids. Trends in Endocrinology and Metabolism 2018 ;29:42-54.
16. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ 2016; 352:h6819.
17. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, *et al*. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology 2020.
18. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for

radiologists on COVID-19: An update—radiology scientific expert panel. Radiology 2020.
19. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56:105949.
20. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell discovery 2020;6:1-4.
21. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al*. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research 2020; 30:269-71.
22. 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; 323:1061-9.
23. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, *et al*. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. bmj 2020;369.
24. Mahévas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, *et al.* No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: Results of a study using routinely collected data to emulate a target trial. medrxiv 2020.
25. Magagnoli J, Narendran S, Pereira F, Cummings TH, Hardin JW, Sutton SS, *et al*. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med 2020;1:114-27.
26. Fihn SD, Perencevich E, Bradley SM. Caution needed on the use of chloroquine and hydroxychloroquine for coronavirus disease 2019. JAMA Netw Open 2020; 3:e209035.
27. Borba MG, Val FF, Sampaio VS, Alexandre MA, Melo GC, Brito M, *et al.* Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. JAMA network open 2020;3:e208857.
28. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The lancet 2020 ;395:1033-4.
29. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. Journal of medical virology 2020;92:814-8.
30. Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B. Tocilizumab (actemra). Human vaccines and immunotherapeutics 2017;13:1972-88.
31. Favalli EG, Ingegnoli F, Cimaz R, Caporali R. What is the true incidence of COVID-19 in patients with rheumatic diseases? Annals of the rheumatic diseases 2021;80:e18.
32. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Annals of the rheumatic diseases 2020;79:667-8.
33. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. The lancet 2020;395:1054-62.
34. Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumatic diseases. Nature Reviews Rheumatology 2015;11:693-704.
35. Lu C, Li S, Liu Y Role of immunosuppressive therapy in rheumatic diseases concurrent with COVID-19. Ann Rheum Dis 2020; 79:737–739.
36. Ceribelli A, Motta F, De Santis M, Ansari AA, Ridgway WM, Gershwin ME, *et al*. Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy. Journal of autoimmunity 2020;109:102442.