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Autoimmune rheumatic manifestations in a cohort of Egyptian COVID-19 patients

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic had significant global health impact. Like systemic autoimmune diseases, COVID-19 may manifest with systemic and heterogenous clinical presentations. This study aimed to evaluate the prevalence of autoimmune rheumatic manifestations among a cohort of Egyptian patients with COVID-19 infection. The study included 90 adult confirmed COVID-19 patients as determined by the polymerase chain reaction test. They were subjected to the following assessments: detailed medical history, full clinical and rheumatological examination, routine laboratory investigations, a panel of autoimmune markers, and high-resolution computed tomography chest. Then the patients studied were divided according to the positivity of autoimmune markers into positive and negative groups. According to the COVID-19 disease severity, patients were divided into mild, moderate, severe, and critical groups. The mean age of the study population was 54.60 ± 10.72 years, and 53.3% of them were females and 46.7% males. Of the patients studied 13.3% had positive antinuclear antibodies (ANA), 15.6% positive for rheumatoid factor (RF), 8.9% positive for anticardiolipin (ACL) IgM, and 5.6% positive for ACL IgG. The autoimmune markers were not statistically different however, all cases with positive ANA were present among severe and critical COVID-19 cases. All cases with positive RF, ACL IgM, or ACL IgG were found among moderate, severe, and critical patients. In conclusion, COVID-19 disease is associated with variable autoimmune manifestations. Autoimmune rheumatic manifestations, either clinical or autoimmune markers, are more evident in severe and critical COVID-19 cases. COVID-19 patients with positive ANA or RF are more likely to develop cutaneous, musculoskeletal, and vascular manifestations.

Keywords: Autoimmune; COVID-19; antinuclear antibodies; rheumatoid factor; anticardiolipin; high-resolution computed tomography.

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Introduction

In January 2020, severe acute respiratory virus 2 (SARS-CoV-2) was identified as the cause of the novel coronavirus disease 2019 (COVID-19),[1] representing the third major coronavirus infection of the 21 St century after severe acute respiratory syndrome (SARS),[2] and Middle East respiratory syndrome (MERS).[3]

Cough, fever, dyspnea, myalgia, and exhaustion are the hallmarks of COVID-19, although patients may also have gastrointestinal

symptoms and complications involving many organs.[4] Clinical manifestations and disease course of COVID-19 would depend on a delicate balance between SARS-CoV-2 virulence and the host's characteristics.[5] Importantly, the efficiency of the immune response is critical for the control of SARS-CoV-2 infection, however, excessive inflammation has also been associated with severe COVID-19 outcomes.[5]

The finding of signs and symptoms of COVID-19 extending beyond the respiratory tract can be explained by the ubiquitous expression and tissue distribution of angiotensin-converting enzyme 2 (ACE2), the major SARS-CoV-2 entry receptor.[5] ACE-2 is also present in the bowel, skeletal muscles, smooth muscles, synovial tissue, and the endothelium of small blood vessels.[6]

It is therefore not unexpected that, besides cough and dyspnea, COVID-19 patients often experience fever, fatigue, muscle pain, or arthralgia.[7] Immune-mediated manifestations have been described in COVID-19 patients and may occur during recovery or represent the first clue of infection in otherwise healthy individuals.[7] Viruses can be direct etiologic agents of acute and chronic arthritis,[8] and of different forms of vasculitis, and other autoimmune manifestations.[9] Thus, from the point of view of a rheumatologist, evaluating the role of SARS-CoV-2 in inflammatory arthritis is essential for its diagnosis.[8] Serological tests could be useful to establish a diagnosis, but the possibility that low-titer positivity for autoantibodies [such as rheumatoid factor (RF) or antinuclear antibody (ANA)] could be detected in viral arthritis must also be considered.[8]

Similarly, an association between COVID-19 and thrombotic events, along with detection of anti-phospholipid antibodies (APLA), has also been reported.[10] APLA, including anti-cardiolipin and anti-β2-glycoprotein antibodies, were detected in the sera of COVID-19 patients, but their contribution to thrombosis is uncertain.[11]

In the study, we evaluated the prevalence of autoimmune rheumatic manifestations among a cohort of Egyptian patients with confirmed COVID-19 infection by the polymerase chain reaction (PCR) test.

Patients and Methods

This cross-sectional study included a random sample of 90 adult Egyptian patients with confirmed COVID-19 infection, admitted to the Quarantine Hospitals of Ain Shams University. The age of the patients studied ranged between 18 and 65 years. Patients with a known history of autoimmune disease prior to infection with COVID-19 virus and patients with a known history of hepatitis C virus (HCV) infection were excluded from the study.

All patients were subjected to a full medical history, clinical and rheumatological examination, and several laboratory investigations were conducted. Blood samples were taken from each patient and were evaluated using the Ain Shams University Hospital's standard procedures. Complete blood count (CBC) by Beckman Coulter, erythrocyte sedimentation rate (ESR) by the Westergren method, C-reactive protein (CRP) by agglutination test. Liver and kidney function tests, serum ferritin, D-dimer, LDH, CK Total, CK MB were assessed by calorimetric methods. HCV antibodies by an enzyme linked immunosorbent assay (ELISA). Autoimmune markers: ANA by the indirect immunofluorescence test, ACL IgG and IgM by ELISA, and RF titer test by the latex agglutination test. In addition to the COVID-19, the real-time reverse transcription polymerase chain (RT-PCR) test was performed for the qualitative detection of nucleic acid from SARS-COV-2 in nasopharyngeal or oropharyngeal swabs. Finally, a high-resolution computed tomography (HRCT) of the chest without contrast using a 128-slice MDCT scanner (GE Healthcare) equipment for all the patients' high-resolution CT scans. During breath-holding at full inspiration, all patients were scanned in the supine position without the use of an intravenous contrast. From the apices of the lungs to the bases of the lungs, the chest was inspected. They were examined to identify various chest CT presentations in COVID-19 patients. The degree of COVID-19 disease suspicion was assessed according to the COVID-19 Reporting and Data System (CO-RADS) classification[12]; with the range of suspicion

being very low (CO-RADS 1) to very high (CO-RADS 5).

Statistical Analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) (IBM Inc., Chicago, IL, USA). Categorical variables are expressed as percentages, and continuous variables expressed as mean and standard deviation. For normally distributed values the t-test was used for independent samples, categorical data were compared using the Chi-Square test. Data are presented as mean ± standard deviation (±SD), number (N), and percentage (%). A $p<0.05$ was considered statistically significant.

Results

This study included 90 patients diagnosed with COVID-19 infection with a mean age of 54.60 ± 10.72 years. Of these, 48 of patients (53.3%) were females, 42 (46.7%) males and 37.8% smokers as shown in Table 1.

Most of the patients (80%) had multiple co-morbidities and 20% had no comorbidities as shown in Table 2.

Table 1. Demographic data and characteristics of the 90 patients studied.

Demographic Data		No. (%)
Age	Mean ± SD	54.60 ± 10.72
	Range	21 – 65
Sex	Female	48 (53.3%)
	Male	42 (46.7%)
Special habits (smoking)	No	56 (62.2%)
	Yes	34 (37.8%)
Abortions/miscarriages	No	79 (87.8%)
	Yes	11 (12.2%)

Table 2. Co-morbidities of the 90 patients studied.

Co-morbidities	No. (%)
Multiple co-morbidities	72 (80.0%)
DM	39 (43.3%)
HTN	48 (53.3%)
IHD	13 (14.4%)
CKD	6 (6.7%)
COPD	3 (3.3%)
AF	8 (8.9%)
HF	4 (4.4%)
Asthma	4 (4.4%)

DM (diabetes mellitus), HTN (hypertension), IHD (ischemic heart disease), CKD (chronic kidney disease), COPD (chronic obstructive pulmonary disease), AF (atrial fibrillation), HF (heart failure)

Patients were classified according to the World Health Organization (WHO)[13] into mild group, moderate, severe, and critical groups as shown in Figure 1.

Table 3 shows the classification of high resolution chest computed tomography and COVID-19 Reporting and Data System score (CO-RADS) of the studied patients.

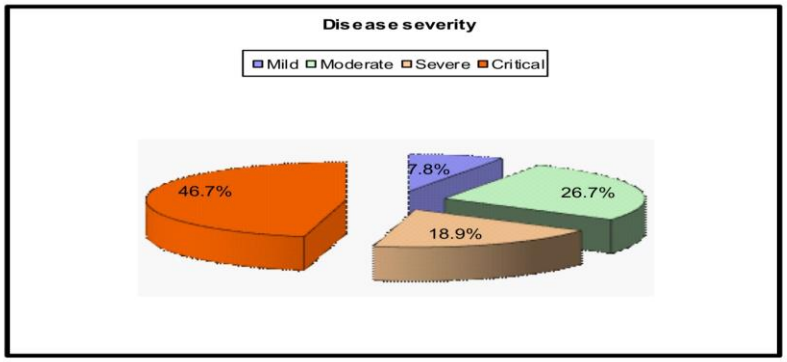

Figure 1. Classification of the 90 patients studied according to coronavirus disease 2019 (COVID-19) severity.

Table 3. High Resolution Computed Tomography (HRCT) chest (CO-RADS grade) of the 90 patients studied.

HRCT chest (CO-RADS grade)	No. (%)
I	3 (3.3%)
II	9 (10.0%)
III	9 (10.0%)
IV	2 (2.2%)
V	67 (74.4%)

HRCT (High Resolution Computed Tomography).

The clinical and autoimmune rheumatological manifestations of COVID-19 found in the studied 90 patients are shown in Table 4 and Table 5.

Table 4. Coronavirus disease 2019 (COVID-19) manifestations in the 90 studied patients.

COVID-19 manifestations		No. (%)
Constitutional	Fever	79 (87.8%)
	Malaise	82 (91.1%)
	Dizziness	62 (68.9%)
	Headache	55 (61.1%)
Upper respiratory tract	Sore throat	53 (58.9%)
	Nasal discharge	13 (14.4%)
	Loss of smell/taste	51 (56.7%)
Cardiopulmonary	Cough	78 (86.7%)
	Dyspnea	85 (94.4%)
	Wheezes	17 (18.9%)
	Orthopnea	9 (10.0%)
	PND	6 (6.7%)
	Hemoptysis	10 (11.1%)
	Chest pain	31 (34.4%)
	Palpitations	35 (38.9%)
	Syncope	8 (8.9%)
	Edema	16 (17.8%)
GIT	Nausea/Vomiting	33(36.7%)
	Diarrhea	33(36.7%)
Musculoskeletal	Myalgia	70 (77.8%)
	Arthralgia	52 (57.8%)
	Arthritis	18 (20.0%)

PND: Paroxysmal Nocturnal Dyspnea.

Table 5. Autoimmune rheumatological manifestations in the 90 patients studied.

Autoimmune rheumatic manifestations			No. (%)
Renal	Hematuria		6 (6.7%)
	Oliguria		9 (10.0%)
	Frothy urine		9 (10.0%)
	Edema		19 (21.1%)
	AKI (rising creatinine)		23 (25.6%)
Hematological	Bleeding/ orifices (hematuria and bloody diarrhea)		13 (14.4%)
	Hematomas		3 (3.3%)
	Purpura / Petechiae		7 (7.8%)
	Ecchymosis		44 (48.9%)
	Anemic symptoms		21 (23.3%)
Vascular	Raynaud's		8 (8.9%)
	Blue toes/fingers		4 (4.4%)
	Fingers/toes gangrene		4 (4.4%)
	Limb gangrene (LL)		1 (1.1%)
	Claudication (LL)		3 (3.3%)
	PE		6 (6.7%)
	MI		2 (2.2%)
	Venous thrombosis (DVT (LL) +PVT)		8 (8.9%)
Neurological	Ischemic stroke		3 (3.3%)
	Hemorrhagic stroke		1 (1.1%)
	Mononeuropathy		3 (3.3%)
	GBS		3 (3.3%)
GIT	Abdominal pain		24 (26.7%)
	Bloody diarrhea		2 (2.2%)
Mucocutaneous	Oral ulcers		13 (14.4%)
	Genital ulcers		4 (4.4%)
	Photo sensitivity		10 (11.1%)
	Skin rash		36 (40.0%)
	Types of skin rash	Maculopapular	5 (5.6%)
		Malar rash	13 (14.4%)
		Urticarial	10 (11.1%)
		Palpable purpura	9 (10.0%)
		Non-Palpable purpura (thrombocytopenic)/ petechiae	7 (7.8%)
		Erythematous, vesicular, crusted	1 (1.1%)
		Heliotrope rash	1 (1.1%)
	Dry eye and dry mouth		27 (30.0%)
	Gottron papules/ sign and Shawl/v sign		1 (1.1%)
	Periungual erythema		17 (18.9%)
	Chilblain fingers/ toes		18 (20.0%)
	Splinter hemorrhage		2 (2.2%)
	Proximal weakness		7 (7.8%)

PND (Paroxysmal Nocturnal Dyspnea), GIT (Gastrointestinal Tract), AKI (Acute kidney Injury), LL (Lower Limb), PE (Pulmonary Embolism), MI (Myocardial infarction), DVT (deep venous thrombosis), PVT (portal vein thrombosis), GBS (Guillain-Barre' Syndrome)

Laboratory data indicated that 82.2% of the studied patients had lymphopenia, 31.1% had thrombocytopenia, 96.7% with high CRP, 72.2% had high D-Dimer, and 78.9% of patients had hyperferritinemia.

The results of the autoimmune markers indicated that 13.3% of the COVID-19 patients studied had positive ANA, 15.6% had positive RF, 8.9% had positive ACL IgM, and 5.6% had positive ACL IgG as shown in Figure 2.

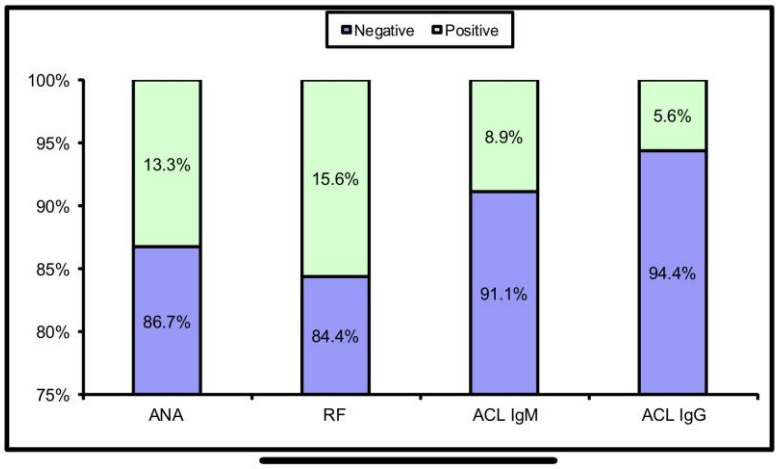

Figure 2. Results of autoimmune markers in the COVID-19 patients studied.

When we compared the severity group of the COVID-19 patients we found a statistically significant difference between the different groups (p<0.01) (Table 6). We compared autoimmune markers among disease severity groups of the COVID-19 patients studied. There was no statistically significant difference in the results of ANA, RF, ACL IgM and IgG between the different severity groups. However, all cases with positive ANA were present among severe and critical COVID-19 cases and all cases with positive RF, ACL IgM, or ACL IgG were among moderate, severe, and critical cases as shown in Table 6.

Table 6. Comparison of autoimmune markers between different severity groups in the patients studied.

Autoimmune Markers		Disease severity				^{X2}p-value
		Mild	Moderate	Severe	Critical	
		No. = 7	No. = 24	No. = 17	No. = 42	
ANA	Negative	7 (100.0%)	24 (100.0%)	14 (82.4%)	33 (78.6%)	NS
	Positive	0 (0.0%)	0 (0.0%)	3 (17.6%)	9 (21.4%)	
RF	Negative	7 (100.0%)	22 (91.7%)	12 (70.6%)	35 (83.3%)	NS
	Positive	0 (0.0%)	2 (8.3%)	5 (29.4%)	7 (16.7%)	
ACL IgM	Negative	7 (100.0%)	24 (100.0%)	16 (94.1%)	35 (83.3%)	NS
	Positive	0 (0.0%)	0 (0.0%)	1 (5.9%)	7 (16.7%)	
ACL IgG	Negative	7 (100.0%)	23 (95.8%)	16 (94.1%)	39 (92.9%)	NS
	Positive	0 (0.0%)	1 (4.2%)	1 (5.9%)	3 (7.1%)	

ANA: antinuclear antibodies; RF: rheumatoid factor; ACL: anticardiolipin. $p > 0.05$ is not significant (NS).

The severe and critical groups of COVID-19 patients were included as one group and autoimmune markers compared statistically to mild and moderate groups. We found that there was a statistically significant higher percentage of COVID-19 with positive ANA among severe/critical groups (20.3%) than in mild (0%) and moderate groups (0%) as shown in Table 7.

Table 7. Comparison of autoimmune markers between Severe/Critical groups of COVID-19 patients included as one group and other groups.

Autoimmune Markers		Clinical severity			^{X2}*p*-value
		Mild	Moderate	Severe/ Critical	
		No. = 7	No. = 24	No. = 59	
ANA	Negative	7 (100.0%)	24 (100.0%)	47 (79.7%)	0.026
	Positive	0 (0.0%)	0 (0.0%)	12 (20.3%)	
RF	Negative	7 (100.0%)	22 (91.7%)	47 (79.7%)	NS
	Positive	0 (0.0%)	2 (8.3%)	12 (20.3%)	
ACL IgM	Negative	7 (100.0%)	24 (100.0%)	51 (86.4%)	NS
	Positive	0 (0.0%)	0 (0.0%)	8 (13.6%)	
ACL IgG	Negative	7 (100.0%)	23 (95.8%)	55 (93.2%)	NS
	Positive	0 (0.0%)	1 (4.2%)	4 (6.8%)	

ANA: antinuclear antibody; RF rheumatoid factor; ACL: anticardiolipin. $p > 0.05$ is not significant (NS).

All the COVID-19 patients studied were classified according to the result of ANA into negative and positive groups and both groups statistically compared to each other. All the COVID-19 patients studied were classified according to the result of RF into negative and positive groups and both groups were compared statistically to each other. There was a statistically significant difference in the age between the COVID-19 patients studied with positive and negative RF (*p*=0.031). In addition, there was a statistically significant difference in sore throat, chest pain, urticarial rash, acute kidney injury, Lower limb claudication and hemorrhagic stroke between the two groups.

The COVID-19 positive group had significantly higher sore throat in 85.7% of patients versus 53.9% in negative group (*p*=0.026). Similarly, chest pain in 64.3% of patients versus 28.9% in the negative group (*p*=0.011), urticarial rash in 42.9% of patients versus 5.3% in the negative group (p<0.001), acute kidney injury in 50% of patients versus 21.1% in the negative group (*p*=0.022), lower limb claudication in 14.3% of patients versus 1.3% in the negative group (*p*=0.013) and hemorrhagic stroke in 7.1% of patients versus (0%) in negative group (*p*=0.19).

All the COVID-19 patients studied were classified according to the result of ACL IgM into negative and positive groups and both groups statistically compared to each other. There was a statistically significant higher percentage of female COVID-19 patients among positive group 87.5% than the negative group (50%) (p=0.042). Also, all COVID-19 patients with positive ACL IgM were non-smokers (100%) (*p*=0.021). Also, there was a statistically significant difference between the two groups regarding fever. The negative group had fevers in 90.2% of patients versus 62.5% in positive group (*p*=0.022). In addition, there was a statistically significant difference between the two groups as regards finger/toe gangrene (25%), genital ulcers (25%), myocardial infarction (MI) (12.5%), maculopapular rash (25%), dry eye and dry mouth (62.5%) and arthritis (50%) being among the positive group.

All the COVID-19 patients studied were classified according to the result of ACL IgG into negative and positive groups and both groups were compared statistically to each other. There was a statistically significant higher percentage of abortions among female COVID-19 patients with positive ACL IgG group (60%) than negative group (9.4%) (*p*=0.001). Also, there was statistically significant difference between COVID-19 studied patients with positive and negative ACL IgG groups as regard MI (20%), genital ulcers (40%), LL claudication (20%) and bloody diarrhea (20%) being among the positive group.

Discussion

A COVID-19 infection can cause a wide range of symptoms, from moderate, asymptomatic signs to severe symptoms that necessitate ventilatory support and an intensive care unit (ICU). The investigation of the connection between COVID-19 infection and autoimmune diseases has attracted an increasing amount of research.[14] Autoantibodies such as RF, ANA,[8] or APLA [10] have been detected in serum samples of COVID-19 patients. However, the results of these studies are not sufficient to reach an obvious conclusion. So, we did a cross-sectional study including 90 individuals to evaluate the prevalence of autoimmune rheumatic manifestations in a cohort of Egyptian individuals who were diagnosed with COVID-19 infection.

All patients were classified according to results of autoimmune markers, including ANA, RF, ACL IgM, and ACL IgG into positive and negative groups and subjected to correlational analysis to assess the strength of association between each marker, clinical severity of COVID-19 disease and autoimmune rheumatological manifestations. As regards the results of the autoimmune markers, 13.3% of the patients studied had positive ANA, 15.6% had positive RF, 8.9% had positive ACL IgM, and 5.6% had positive ACL IgG.

There was no statistically significant difference in the results of ANA, RF, ACL IgM and IgG between different severity groups of the COVID-19 patients studied. However, all patients with positive RF, ACL IgM, or ACL IgG were found in moderate, severe, and critical COVID-19 cases. While all patients with positive ANA were found in severe and critical cases.

Severe and critical groups of COVID-19 patients were included as one group and autoimmune markers compared statistically to mild and moderate groups. We found that there was a statistically significant higher percentage of COVID-19 with positive ANA among severe/critical groups (20.3%) than in mild (0%) and moderate groups (0%).

These were similar to a study by Stjepanovic et al., 2022,[15] which included 51 patients of confirmed COVID-19 disease and found that ANA positivity was found in 19.6% of patients studied, ACL IgG in 15.7% and ACL IgM in 7.8% of patients and positive RF in 8.2% of patients. The same study also found that none of the tested autoantibodies were associated with disease or pneumonia severity, except for ACL IgG being significantly associated with higher pneumonia severity index. Also the study by Pascolini et al., 2021,[14] reported that the presence of ANA was significantly higher in cases with poor prognosis and patients death.

Moreover, the study by Trahtemberg et al., 2021,[16] reported a high rate of ANA positivity (64%) in patients who were in the ICU and 48% of all the ICU cohort had a positive ACL IgG test. Interestingly, fewer patients (21%) had elevated IgM ACL titers, with only 2 patients (4%) having IgM without IgG but in line with our results they found that positive APA serology had an association with more severe disease regardless of COVID-19 status. However, patients with a positive ACL IgG demonstrated a consistent trend for worse outcomes in every tested measure, but this lacked statistical significance.

In the present study, we compared clinical data in all severity groups of COVID-19 disease. Our study showed statistically significant higher percentages of COVID-19 studied patients that developed sore throat 78.6%, orthopnea 21.4%, hemoptysis 31%, chest pain 52.4%, hematuria 21.4%, oliguria 21.4, bleeding per orifices 26.2%, ecchymosis 64.3%, venous thrombosis 19%, dysphagia 33.3%, abdominal pain 42.9%, oral ulcers 31%, dry eye and dry mouth 45.2%, skin rash 57.1% and arthritis 33.3% in the critical group than in the mild, moderate and severe groups. While finger/toe gangrene 28.6% (2/7) and limb gangrene14.3% (1/7) were found in the mild group.

In this context a study conducted by Monárrez et al., 2021,[17] reported that the prevalence of general symptoms, such as fever, myalgia, arthralgia, headache, and fatigue, increased with COVID-19 severity, reaching 55–70% among the intubated. A similar gradient was seen for respiratory symptoms, including cough and dyspnea, reaching a prevalence of 83% in patients hospitalized or intubated.

Also, the results of a meta-analysis study, by Fu et al., 2020,[18] included 3600 patients from 43 studies, followed a similar pattern. The study

compared critical vs. non-critical illness: namely, the higher prevalence of symptoms in critical patients (i.e., fever 80.8 vs. 71.2%, cough 65.6 vs. 56.7%, dyspnea 49.2 vs. 13.3%, fatigue 41.2 vs. 34.5%, myalgia 17.6 vs. 20.8%, and headache 11.3 vs. 11.9%).

We studied 90 patients as a group of COVID-19 for autoimmune rheumatic manifestations and found that there were statistically significant higher percentages of COVID-19 in the 12 patients studied with positive ANA (Table 6). They developed headache 91.% (11/12), nasal discharge 33.3% (4/12), loss of taste and smell 83.3% (10/12) and chest pain 66.7% (8/12), pulmonary embolism 25% (3/12), hemorrhagic stroke 8.3% (1/12), oral ulcers 41.7%(5/12), genital ulcers 16.7% (2/12), photosensitivity 33.3% (4/12), skin rash 91.7% (11/12) especially malar rash 50% (6/11), arthralgia 100% (12/12) and arthritis 50% (6/12). We found no data available in the literature to be compared with our study findings. We recommend that ANAs must always be evaluated in association with the clinical features, because even healthy subjects can be ANA-positive (25% of the healthy population presents ANA antibodies).[19]

By comparing autoimmune rheumatic manifestations in positive and negative ACL IgM and IgG groups we found that there was a statistically significant higher percentage of COVID-19 studied patients that developed myocardial infarction 12.5% (1/8), maculopapular rash 25% (2/8), dry eye and dry mouth 62.5% (5/8), genital ulcers 25% (2/8) and arthritis 50% (4/8) being among positive group. In addition, there were statistically significant higher percentages of COVID-19 patients with positive ACL IgG that developed lower limb (LL) claudication 20% (1/5), MI 20% (1/5), bloody diarrhea 20% (1/5) and genital ulcers 40% (2/5).

In this context, the study by Liu et al., 2020, [6] concluded that the strong association of APLA with thrombotic events was not observed in most studies, even for patients with double/triple positivity.

Also, in a study by Frapard et al., 2020,[20] which included 37 COVID-19 acute respiratory disease versus 31 pre-pandemic acute respiratory disease controls, reported that 37 patients with COVID-19 exhibited higher thrombotic events in comparison to 31 pre-pandemic controls. Nevertheless, the two groups' incidences of APLA were comparable. Using APLA assays, like our findings, the study by Borghi et al., 2020,[21] reported a low prevalence of APLA in COVID-19 sera and concluded that APLA were not associated with major thrombotic events.

However, this disagrees with the findings of the study conducted by Stjepanovic et al., 2022, [15] who reported 15.7% thrombotic events during COVID-19 disease (7 pulmonary thromboembolism, 1 acute myocardial infarction), but were not associated with ACL antibody positivity.

By comparing autoimmune rheumatic manifestations in positive and negative RF groups, our study demonstrated that there were statistically significant higher percentages of COVID-19 patients that developed sore throat 85.7% (12/14), chest pain 64.3% (9/14), AKI 50% (7/14), LL claudication 14.3% (2/14), hemorrhagic stroke 7.1% (1/14) in the positive RF group than the negative group.

But considering the low percentage of RF positive patients, no further statistical analysis was performed regarding RF to be compared with our results yet. Even so, all studies were conducted on a limited number of individuals so further research is encouraged to corroborate these findings in an independent and larger database.

In conclusion, our study indicated that age, gender, and comorbidities affect the severity of COVID-19 disease. COVID-19 disease is associated with variable autoimmune manifestations. Autoimmune rheumatic manifestations either clinical or autoimmune markers are more with severe and critical COVID-19 cases. COVID-19 cases with positive ANA or RF are more likely to develop cutaneous, musculoskeletal, and vascular manifestations.

Author Contributions

All authors have participated in the concept, design, collection, analysis, and interpretation of data, as well as writing, drafting, and revising the manuscript. All authors read and approved the final manuscript. The authors declare that they have no competing

interests concerning this article. All authors read and approved the final manuscript. All authors have agreed to the conditions noted on the Authorship Agreement Form and have read and approved the final version submitted.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The protocol of the study was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University (FMASU MS 204/2023).

Informed consent

An informed consent was obtained from each patient before being included in the study. .

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