

RESEARCH ARTICLE

Post-COVID-19 arthritis: is it hyperinflammation or autoimmunity?

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ABSTRACT. Background: Various musculoskeletal and autoimmune manifestations have been described in patients with coronavirus disease 2019 (COVID-19). **Objectives:** This study aims to investigate the prevalence and etiology of arthritis in post-COVID Egyptian patients. **Methods:** We included 100 post-COVID Egyptian patients who recovered 6 months ago and assessed several inflammatory and autoimmune markers. **Results:** The prevalence of post-COVID arthritis was 37%. Ankle, knee, and wrist were the most commonly affected joints. Old age ($P = 0.010$), smoking ($P = 0.001$), and arthralgia ($P = 0.049$) were all linked with post-COVID arthritis. Levels of pretreatment (baseline) interleukin (IL)-6 (46.41 ± 3.67 vs. 24.03 ± 2.46 ; $P = 0.001$), as well as 6-month post-COVID C-reactive protein (CRP; 98.49 ± 67.55 vs. 54.32 ± 65.73 ; $P = 0.002$), and erythrocyte sedimentation rate (ESR; 109.08 ± 174.91 vs. 58.35 ± 37.87 ; $P = 0.029$) were significantly higher in patients with arthritis compared to those without. On the other hand, complement C3 ($P = 0.558$) and C4 ($P = 0.192$), anti-nuclear antibodies ($P = 0.709$), and anti-cyclic citrullinated peptides (anti-CCP; $P = 0.855$) did not show significant differences. Only pretreatment IL-6 level was the significant single predictor of post-COVID arthritis with an odds ratio (95% confidence interval) of 3.988 (1.460–10.892) and a P -value of 0.007. **Conclusion:** The strong association observed with inflammatory markers (ESR and CRP) and the insignificant association with serologic markers of autoimmunity (ANA and anti-CCP) in our study support the notion that the underlying mechanism of post-COVID-19 arthritis is primarily due to the hyperinflammatory process associated with COVID-19 infection, and not the result of an autoimmune reaction. IL-6 levels before therapy can predict post-COVID arthritis allowing for early management.

Keywords: Autoimmunity, Hyperinflammation, Musculoskeletal, Arthritis, Post-COVID, Rheumatology

The new coronavirus 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has swept the globe since its discovery in Wuhan, China [1]. As of September 27, 2021, the Egyptian Ministry of Health has documented over 300,000 confirmed COVID-19 cases, nearly 17,000 deaths, and around 15 million administered vaccine doses [2]. In critically ill patients with COVID-19, many organs could be affected because of the increased production of proinflammatory cytokines to

either fight the virus or cause a “cytokine storm” that can worsen patients’ condition [3, 4]. The widespread expression and tissue distribution of angiotensin-converting enzyme 2, the primary SARS-CoV-2 entrance receptor, may also explain the observation of COVID-19 signs and symptoms beyond the respiratory tract [5], particularly in the intestine, small blood vessels, muscles, and synovial tissue [6]. In addition, SARS-CoV-2 can activate the immune system to produce autoantibodies leading to a systemic autoimmune response [7].

Conquering the early symptoms of COVID-19 may simply be the start of a long and challenging road to recovery as a substantial number of patients “long haulers” may have persistent post-COVID-19 symptoms [8-11]. Several studies reported post-COVID-19 reactive arthritis, vasculitis, and connective tissue illnesses, including lupus and inflammatory myositis [12, 14]. Others documented that patients with

Abréviations

anti-CCP	Anti-cyclic citrullinated peptides
ANAs	Anti-nuclear antibodies
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
IL	Interleukin

COVID-19 with preexisting rheumatic disorders may worsen or develop new autoimmune characteristics [15]. In this context, patients recovering from COVID-19 must be closely monitored for autoantibody production and rheumatic symptoms.

In this study, we aimed to determine the prevalence of arthritis along with its risk factors among 6-month post-COVID-19 Egyptian patients by evaluating multiple inflammatory and autoimmune markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complement C3, and C4, anti-nuclear antibodies (ANAs), anti-cyclic citrullinated peptides (anti-CCP), and rheumatoid factor].

METHODOLOGY

Ethical considerations

We followed the principles mentioned in the Declaration of Helsinki of the World Medical Association in this study. Ain Shams University Research Ethics Committee approved the work. Each participant provided written informed consent after being told of the purpose of the study.

Study design and subjects

In this single-center cross-sectional study, 100 patients (age ≥ 18 years) who recovered from COVID-19 6 months ago were recruited from the post-COVID-19 clinic of Ain Shams University Hospitals. All patients had a history of confirmed SARS-CoV-2 infection. Patients unwilling to participate and those with known autoimmune disease or any rheumatologic complaints before COVID-19 were excluded from the study.

Data collection

All the included 6-month post-COVID-19 patients were subjected to a thorough clinical examination. A case record form was constructed to collect baseline patients' information, such as demographics, smoking, pretreatment laboratory findings [including interleukin (IL)-6, complete blood count with differential, albumin, serum creatinine, ferritin, lactate dehydrogenase, D-dimer, alanine aminotransferase, and aspartate aminotransferase levels], post-COVID-19 infection severity according to the WHO interim guidance [16], and rheumatologic symptoms that first appeared during COVID-19 infection or after patient's recovery and were persisting at the time of evaluation (6-month post-COVID-19) such as fatigue, arthritis (≥ 2 joints to exclude septic arthritis), arthralgia, myalgia, myositis, cutaneous vasculitis, and Raynaud phenomenon.

Blood samples collection and laboratory investigations

From each included 6-month post-COVID-19 patient, 5 mL blood was collected under aseptic conditions and divided into two vacuum tubes; a plain gel tube with clot activator for serum separation by centrifugation and a liquid sodium citrate tube for ESR determination by the Westergren method [17]. Sera were used to analyze serologic markers by standard methods at

Central Laboratories of Ain Shams University Hospitals; anti-CCP, CRP, complement C3, and C4, and rheumatoid factor by COBAS e411 and C311 auto-analyzers (Roche Diagnostics GmbH, Mannheim, Germany). We assessed the ANA by indirect immunofluorescence technique using commercial HEp-2 slides (ANAFLUORTM; DiaSorin, Stillwater, MN, USA) at a dilution of 1:80 according to manufacturer instructions.

Statistical analysis

We used IBM SPSS version 23 (IBM, Armonk, NY, USA) to analyze the data. After descriptive statistics, The Chi-squared test was used to compare qualitative data between groups. The independent *t* test was used to compare two independent groups with quantitative data and parametric distribution, while the Mann-Whitney test was used for nonparametric data. The odds ratio (OR) and 95% confidence interval (CI) for post-COVID-19 arthritis were determined using univariate and multivariate logistic regressions. The accepted margin of error was set to 5.0%.

RESULTS

This study included a total of 100 patients, their mean (\pm SD) age was 57.00 ± 15.74 years with a range of 18 to 74 years. Of them, 61.0% were males and 39.0% were females. The frequency of arthritis among the included post-COVID-19 patients was 37.0% (figure 1), with no significant differences according to the male-to-female ratio ($P = 0.855$) or COVID-19 severity ($P = 0.408$). The most commonly affected joints were the knee (72.0%), ankle (67.0%), and wrist (50.0%). When compared with patients without arthritis, post-COVID-19 arthritis was significantly associated with older age (63.06 ± 12.33 years vs. 50.93 ± 19.95 years; $P = 0.010$), and smoking [14 (37.8%) vs. 0 (0.0%); $P < 0.001$]. Other rheumatologic manifestations, except arthralgia ($P = 0.049$), were not significantly associated with post-COVID-19 arthritis, such as myalgia ($P = 0.954$), myositis ($P = 0.954$), cutaneous vasculitis ($P = 0.521$), and Raynaud phenomenon ($P = 0.521$). table 1 summarizes characteristics of the included patients 6-month post-COVID-19 compared according to the presence of arthritis.

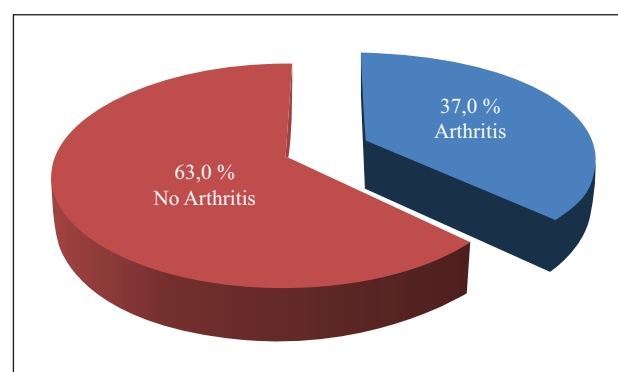


Figure 1

Arthritis frequency among the studied post-COVID-19 patients. Blue: positive; Red: negative.

Table 1
Clinical and demographic characteristics of the included patients compared according to the presence of post-COVID-19 arthritis

Parameters		Total (<i>n</i> = 100)		Post-COVID-19 arthritis					
				Positive (<i>n</i> = 37)		Negative (<i>n</i> = 63)		Chi square test/ Independent <i>t</i> test	
Age (years)	Mean ± SD	57.00 ± 15.74		63.06 ± 12.33		50.93 ± 19.95		4.878	0.010
	Range	18–74		30–74		18–71			
Sex, <i>n</i> (%)	Male	61	61.0%	23	62.2%	38	60.3%	0.033	0.855
	Female	39	39.0%	14	37.8%	25	39.7%		
COVID-19 severity, <i>n</i> (%)	Nonsevere	38	38.0%	16	43.2%	22	34.9%	0.685	0.408
	Severe	62	62.0%	21	56.8%	41	65.1%		
Smoking, <i>n</i> (%)	No	86	86.0%	23	62.2%	63	100.0%	27.718	<0.001
	Yes	14	14.0%	14	37.8%	0	0.0%		
Associated rheumatologic manifestations, <i>n</i> (%)	Fatigue	32	32.0%	7	18.9%	25	39.7%	4.618	0.032
	Arthralgia	35	35.0%	17	45.90%	45	28.60%	3.093	0.049
	Myalgia	24	24.0%	9	24.30%	15	23.80%	0.003	0.954
	Myositis	24	24.0%	9	24.30%	15	23.80%	0.003	0.954
	Cutaneous vasculitis	5	5.0%	1	2.70%	4	6.30%	4.175	0.521
	Raynaud phenomenon	5	5.0%	1	2.70%	4	6.30%	4.175	0.521

Significance was set at <0.05 and indicated by bold *P*-values.
COVID-19: Coronavirus disease 2019; SD: Standard deviation.

Tables 2, 3 summarize the laboratory findings of the included patients. Levels of pretreatment IL-6 (46.41 ± 3.67 vs. 24.03 ± 2.46 ; $P = 0.001$), as well as 6-month post-COVID-19 CRP (98.49 ± 67.55 vs. 54.32 ± 65.73 ; $P = 0.002$), and ESR (109.08 ± 174.91 vs. 58.35 ± 37.87 ; $P = 0.029$) were significantly higher in patients with arthritis compared to those without arthritis. In addition, the frequency of positive rheumatoid factor was higher among patients with post-COVID-19 arthritis [11 (29.7%) vs. 8 (12.7%); $P = 0.036$]. On the other hand, complement C3 ($P = 0.558$) and C4 ($P = 0.192$), ANA ($P = 0.709$), and anti-CCP ($P = 0.855$) did not show significant differences between patients with post-COVID-19 arthritis and those without arthritis.

Finally, we performed a logistic regression analysis to discover significant predictors of post-COVID-19 arthritis. The multivariate analysis showed that only pretreatment (baseline) IL-6 level was the significant single predictor of post-COVID-19 arthritis with an OR (95% CI) of 3.988 (1.460–10.892) and a *P*-value of 0.007 (table 4).

DISCUSSION

The COVID-19 is a disease with a wide range of symptoms, from asymptomatic to multiorgan failure. Both inflammation and autoimmunity have been reported as contributing factors in its pathogenesis [18]. It can cause pulmonary, neurologic, cardiovascular, rheumatologic, dermatologic, and other disturbances [19]. How these disorders progress and if they are reversible are still unknown.

This study aimed to discover how common post-COVID-19 arthritis was in a group of 6-month

recovered Egyptian patients. We looked at some immunologic and inflammatory markers to better understand the underlying mechanism, which may lead in the future to better preventive therapies and early control of post-COVID-19 arthritis.

Our results reveal that post-COVID-19 arthritis was the most prevalent rheumatologic manifestation among our included patients (37.0%) followed by arthralgia and fatigue (35.0% and 32.0%, respectively), with a significant link to old age and smoking. Still, it was not associated with COVID-19 severity, patients' gender, and the other rheumatologic manifestations except arthralgia and fatigue. The most commonly affected joints were the knee, ankle, and wrist.

Similarly, Colatutto and colleagues [20] reported that articular involvement in COVID-19 can be nonspecific arthralgia or acute arthritis that arises during hospitalization or after recovery. They also noted that anti-inflammatory medicines usually relieve these symptoms, but steroids are sometimes required. In addition, Gasparotto et al. [21] and Ono et al. [22] reported that COVID-19-related articular affection usually manifests as nonspecific arthralgia during the active phase of the infection. Still, it can progress to acute arthritis during the healing phase.

Partially consistent with our results, a study by Guan et al. [23] reported that musculoskeletal symptoms were not associated with COVID-19 severity. Arthralgia was found less commonly (15.0%) than myalgia (44%) in patients with COVID-19 [23, 24]. Other studies reported myalgia in 49% to 68% of patients with SARS-CoV-2 [25, 26]. On the other hand, in a study by Mukarram et al. [27], fatigue was the most prevalent rheumatologic symptom among their patients with COVID-19, with a frequency of 73.0%.

Table 2
Laboratory findings of the included patients compared according to the presence of post-COVID-19 arthritis

Pretreatment laboratory parameters	Post-COVID-19 arthritis							
	Total (<i>n</i> = 100)		Positive (<i>n</i> = 37)		Negative (<i>n</i> = 63)		Independent <i>t</i> test	
	Mean	SD	Mean	SD	Mean	SD	<i>t</i>	<i>P</i> -value
IL-6 (pg/mL)	25.52	3.45	46.41	3.67	24.03	2.46	-3.512	0.001
TLC ($\times 10^3/\mu\text{L}$)	10.07	9.74	9.66	6.04	10.33	11.46	-0.329	0.743
Neutrophils ($\times 10^3/\mu\text{L}$)	7.48	7.72	7.57	5.34	7.44	8.92	0.080	0.937
Lymphocytes ($\times 10^3/\mu\text{L}$)	1.59	0.99	1.46	0.88	1.65	1.05	-0.939	0.350
Hemoglobin (g/dL)	10.31	2.41	10.61	2.79	10.11	2.18	1.004	0.318
Platelets ($\times 10^3/\mu\text{L}$)	276.59	148.58	288.22	177.23	271.29	130.82	0.547	0.586
Albumin (g/dL)	2.91	0.50	2.81	0.51	2.99	0.47	-1.826	0.071
Creatinine (mg/dL)	1.14	1.06	1.46	1.58	0.95	0.51	2.390	0.019
Ferritin (ng/mL)	599.13	564.03	693.30	548.58	551.21	572.07	1.217	0.226
LDH (IU/L)	493.42	502.94	621.51	568.35	423.02	451.78	1.925	0.057
D dimer (mg/L)	2.86	3.58	2.95	3.44	2.85	3.70	0.132	0.895
ALT (IU/L)	21.86	13.19	23.62	14.16	20.63	12.59	1.093	0.277
AST (IU/L)	25.49	3.49	25.707	3.499	25.286	3.438	0.598	0.551

Significance was set at <0.05 and indicated by bold *P*-values.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; TLC: Total leukocytic count.

Factors that predispose to arthritis as a result of SARS-CoV-2 infection are unknown; however, a review of medical literature, in line with the results of the current study, suggests that smoking affects mucosal surfaces, including the lungs, as well as synovial membrane and cartilage predisposing to arthritis [28, 29]. In addition, studies reported that the incidence of viral arthritis was dependent on patients' age being more common in adults [30]. The mechanisms of postvirus arthritis are still unknown; they may include joint infection, immunologic complex formation, and immune dysregulation.

Most researchers believe that molecular mimicry between SARS-CoV-2 epitopes and the synovial membrane causes local inflammation; other opinions speculate about the presence of circulating immune complexes or the virus's direct localization on joint tissue [21, 31]. Furthermore, by boosting IL-6-related pathways, SARS-CoV-2 causes cytokine storm and macrophage activation syndrome. Antigen presentation and interferon-dependent routes can both be affected. Those altered inflammatory systems may elicit autoimmune processes in predisposed individuals [20]. Likewise, Lokugamage et al. [32] stated that viral

Table 3
Serological markers of the included patients compared according to the presence of post-COVID-19 arthritis

Serologic markers		Post-COVID-19 arthritis						Chi-squared test	
		Total (<i>n</i> = 100)		Positive (<i>n</i> = 37)		Negative (<i>n</i> = 63)			
		No	%	No	%	No	%	χ^2	<i>P</i> -value
ANA, <i>n</i> (%)	Negative	68	68.0%	26	70.3%	42	66.7%	0.139	0.709
	Positive	32	32.0%	11	29.7%	21	33.3%		
Anti-CCP, <i>n</i> (%)	Negative	61	61.0%	23	62.2%	38	60.3%	0.033	0.855
	Positive	39	39.0%	14	37.8%	25	39.7%		
Rheumatoid factor, <i>n</i> (%)	Negative	81	81.0%	26	70.3%	55	87.3%	4.393	0.036
	Positive	19	19.0%	11	29.7%	8	12.7%		
ESR (mm/hour)	Mean ± SD	77.63	111.94	109.08	174.91	58.35	37.87	2.222	0.029
CRP (mg/L)	Mean ± SD	70.41	69.16	98.49	67.55	54.32	65.73	3.211	0.002
C3 (mg/dL)	Mean ± SD	136.32	53.29	139.92	58.32	133.41	50.50	0.587	0.558
C4 (mg/dL)	Mean ± SD	35.39	18.05	32.22	18.76	37.13	17.63	−1.313	0.192

Significance was set at <0.05 and indicated by bold *P*-values.

ANA: Anti-nuclear antibodies; Anti-CCP: Anti-cyclic citrullinated peptides; C3, C4: Complement C3 and C4; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SD: Standard deviation.

Table 4
Logistic regression analysis for predictors of post-COVID-19 arthritis

Parameter	Univariates				Multivariates			
	P-value	OR	95% CI		P-value	OR	95% CI	
			Lower	Upper			Lower	Upper
IL-6	0.001	10.30	5.02	21.248	0.007	3.988	1.460	10.892
Albumin	<0.001	4.553	2.874	7.213	0.757	1.124	0.536	2.356
Creatinine	<0.001	4.028	2.560	6.337	0.606	0.813	0.370	1.787
Ferritin	0.003	3.297	1.498	7.254	0.481	0.649	0.195	2.161
LDH	<0.001	5.612	2.879	10.939	0.053	2.550	0.987	6.588
D-dimer	<0.001	2.608	1.640	4.149	0.063	2.038	1.023	4.062
ALT	<0.001	3.326	2.125	5.207	0.064	1.964	0.961	4.013
AST	<0.001	4.157	2.629	6.574	0.120	1.998	0.834	4.784

Significance was set at <0.05

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CI: Confidence interval; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; OR: Odds ratio.

arthritis usually presents as a self-limiting bout of symmetric polyarticular arthritis or arthralgia. They also noted that toll-like receptors, which are abundantly expressed in the lung and bronchus, can recognize SARS-CoV-2 to produce IL-6. Thus, patients with COVID-19 may have inflammatory or autoimmune symptoms, such as arthritis.

In terms of inflammatory markers, our study revealed that the multivariate logistic regression analysis revealed that baseline IL-6 levels during COVID-19 infection before treatment and recovery were significantly correlated with the incidence of post-COVID-19 arthritis and were the only significant risk factor for it. ESR and CRP levels measured 6 months after recovery from COVID-19 were also found to be strongly linked to the occurrence of post-COVID-19 arthritis.

Among serologic markers of autoimmunity, our results revealed that only the rheumatoid factor, not complement, ANA, or anti-CCP, was significantly linked with the incidence of post-COVID-19 arthritis. Of our arthritis patients, 29.7% had positive ANA, whereas the rheumatoid factor and anti-CCP were positive in 29.7% and 37.8%, respectively.

In line with our results, Fragata and Mourão [33] stated that viral arthritis usually presents as self-limited symmetric polyarticular arthritis or arthralgia. Auto-antibodies such as rheumatoid factor and ANA can be transiently positive. They also noted that postvirus arthritis usually heals completely and only rarely becomes chronic. Furthermore, Roongta et al. [34] studied five patients with polyarthritis following mild to severe SARS-CoV-2 infection. They concluded that post-COVID-19 arthritis was clinically and serologically similar to rheumatoid arthritis. Still, true rheumatoid arthritis following COVID-19 was just a coincidence, and levels of anti-CCP antibodies were low in those patients. Despite millions of SARS-CoV-2 infections, just one case of postviral arthritis affecting big joints (knee and shoulder) was reported by Yokogawa et al. [35], and two cases of reactive arthritis after COVID-19 infection were reported by Saricaoglu et al. [36] and Ono et al. [22].

In summary, our research found that arthritis and arthralgia were the most common 6-month post-COVID-19 rheumatologic symptoms, with the knee, ankle, and wrist joints most frequently affected. We discovered significant links between post-COVID-19 arthritis and both age and smoking. The strong association observed with inflammatory markers (ESR and CRP) and the insignificant association with serologic markers of autoimmunity (ANA and anti-CCP) in our study supported the fact that the underlying mechanism of post-COVID-19 arthritis is primarily due to the hyperinflammatory process associated with COVID-19 infection and not due to an autoimmune reaction. Furthermore, pretreatment IL-6 levels were a significant independent risk factor for the development of post-COVID-19 arthritis, a finding that could aid in early preventive intervention. Our study's single-center design and small sample size were considerable limitations. Other multicenter studies with bigger sample sizes are advised.

In conclusion, the underlying mechanism of post-COVID-19 arthritis is inflammatory rather than being autoimmune. IL-6 levels before therapy can predict post-COVID-19 arthritis allowing for early management.

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