



Lifting the Mask on Musculoskeletal Manifestations of COVID-19: Results of an Interview-Based Study

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Background: Coronavirus disease of 2019 (COVID-19) is considered a multi-system disease that might present with or develop complications during the acute phase of illness. The aim of this study was to describe the characteristics of musculoskeletal (MSK) manifestations in patients with COVID-19 infection and investigate their clinical correlations.

Methods: This study was carried out on 110 patients with a history of RT-PCR confirmed COVID-19 infection. They completed a questionnaire that covered detailed information on their sociodemographic characteristics, clinical data of COVID-19 infection in addition to MSK discomfort form based on the Nordic MSK Questionnaire.

Results: The mean age of the patients was 37.7 years (SD 12.9), 72.7% were females. The majority of patients (90.9%) reported MSK symptoms that occur during or shortly after the acute attack of COVID-19 infection. The median duration of onset of MSK symptoms was 2 days from the first day of COVID-19 infection (min-max: 0–45 days) with a median duration of MSK symptoms of 7 days. Myalgia was the main complaint (85.5%) followed by arthralgia 90 (81.8%). However, swollen joints were reported in only 9 patients (8.2%). According to the body areas, maximum number of patients felt pain at the lower back (60%), followed by neck (39.1%), and upper back (32.5%) followed by right and left shoulder (20.9%). Patients with MSK manifestations were associated higher severity of COVID-19 infection ($p < 0.001$), prolonged duration of COVID-19 symptoms ($p < 0.001$) and higher prevalence of fatigue ($p < 0.001$).

Conclusion: MSK manifestations are common in COVID-19 patients and related to disease severity, duration and fatigue.

Keywords: musculoskeletal, COVID-19, Nordic MSK Questionnaire

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new form of coronavirus was discovered in Wuhan, China, and has since spread throughout the world.¹ The virus can cause asymptomatic infection or flu-like symptoms such as fever, cough, and shortness of breath.¹ The condition can also lead to severe acute respiratory syndrome, pneumonia, and death in certain cases.²

Coronavirus disease of 2019 (COVID-19) is considered a multi-system disease that might present with or develop complications during the acute phase of illness. These complications include not only respiratory,³ but also cardiovascular,⁴ renal,⁵ gastrohepatic, thromboembolic,⁶ neurological,⁷ cerebrovascular,⁸ and autoimmune diseases.⁹

Patients with moderate and severe COVID-19 infection have also reported a significant musculoskeletal (MSK) burden, including skeletal muscle, bone, and joint abnormalities.¹⁰ Symptoms involving myalgia, arthralgia and muscle weakness can make it difficult for patients to perform activities of daily living like walking.¹¹ Ironically, some of these MSK manifestations may occur before the most prevalent COVID-19 symptoms in some patients.³ The magnitude of viral replication, fever, and respiratory and systemic symptoms, including MSK manifestations, are directly correlated with interleukin-6 (IL-6) and tumor necrosis factor α (TNF α) levels in plasma and upper respiratory secretions.¹² Also,

proinflammatory conditions associated with prolonged ventilator times have been linked to muscle and bone manifestations.¹³

Identifying the MSK characteristics of the disease would be valuable and could provide further information to help with COVID-19 diagnosis and patient management. Thus, the aim of this study was to determine the frequency and pattern of MSK manifestations in patients with COVID-19 infection and investigate their clinical correlations.

Methods

Study Population

This interview-based cross-sectional study was conducted at the period from 25th July to 10th August 2021 at Internal Medicine department, Mansoura University Hospital. The work adhered to the 1995 Helsinki Declaration's ethical standards and was approved by the Institutional Research Board of the Faculty of Medicine, Mansoura University (approval registration number: R.21.10.1469).

The study involved one hundred and ten patients (80 females, 23 males) from those who visited general medical outpatient clinic (follow-up or new cases). The inclusion criteria included patients aged >18 years old with a history of confirmed COVID-19 infection (by positive RT-PCR for COVID-19) in the last 8 months. Patients who had malignancies or any chronic rheumatic, MSK, or neurological disease before COVID-19 infection were excluded from the start. The study was explained to all participants, and written informed consent was obtained from all of them.

The Questionnaire

The questionnaire was created by the present authors and then revised and refined ([Supplementary Data 1](#)). It was distributed to the patients in Arabic version. The questions were written in an attempt to be as straightforward as possible. Answers were limited to yes/no questions (closed-ended questions). The questions covered detailed information on demographic and socioeconomic data including gender, age, marital status, residence, occupation, education, smoking habit and socioeconomic level. Participants were asked to indicate if they had ever been told by a doctor that they had any of the following conditions: diabetes mellitus, hypertension, chronic kidney disease or chronic lung disease, using a yes/no answer.

Participants were also enquired about their contact with a known COVID-19 case before getting infected. They were asked to mark the manifestations they were having at the time of COVID-19 infection and the positive investigations that confirmed their diagnosis. Additionally, they were questioned about the severity of COVID-19 infection, their need for oxygen supply or hospital admission and the duration of COVID-19 infection (from the first day until symptoms resolved).

The questionnaire also included questions about the MSK manifestations experienced by the patients during or shortly after infection with COVID-19, their onset (from the first day of COVID-19 infection), severity and duration.

The final part of the questionnaire is based on the Nordic Musculoskeletal Questionnaire, which has already been validated¹⁴ to determine the distribution of these MSK manifestations. It explores the prevalence of MSK disorders or discomfort in the neck, shoulder, elbow, wrist/hand, upper and lower back, ribs, hip/thigh, knee, leg or ankle and foot.

A team of six Internal Medicine staff members evaluated the generated questionnaire for input, critical appraisal, and content validation. On this premise, no new items were added, four were eliminated, and three were reworded. Following that, a preliminary questionnaire was developed and tested in a small group of participants (n = 15). The internal consistency of the questionnaire was determined using Cronbach's alpha. The reliability coefficient was 0.83, indicating that the internal consistency was good.

Patients were contacted (in person) and informed about the questionnaire. Patients with a low level of education were given instructions on how to complete the questionnaire. The responses were then recorded into a Microsoft Excel spreadsheet.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp). After examining the distribution of continuous variables for normality using the Shapiro–Wilk test, continuous variables with a normal distribution were described in mean \pm standard deviation (SD) while those with abnormal distribution in median (minimum–maximum). Categorical variables were described in frequency (n) and percentage (%). For normally distributed data, the significance of differences between two groups was tested using the independent samples *t*-test, and for non-parametric variables, the Mann–Whitney test. For comparisons between qualitative variables, Chi-square or Fisher exact tests were used, as appropriate. The statistical significance level was $p \leq 0.05$.

Results

A total of 110 patients with a history of confirmed COVID-19 infection were included in this study (Table 1), with a mean age of 37.7 years (SD 12.9), 72.7% were females and most of them were employed (60%). Ninety-two patients (83.6%) were nonsmokers, while about 31 (28.2%) had associated comorbid conditions. The majority of patients (90.9%) reported MSK symptoms (pain, discomfort, numbness) that occurred during or shortly after the acute attack of COVID-19 infection.

As shown in Table 2, the median duration of onset of MSK symptoms was 2 days from the first day of COVID-19 infection (min-max: 0–45 days). The median duration of MSK symptoms was 7 days with maximum duration up to 7

Table 1 Demographic, Clinical Data of the Study Patients According to Musculoskeletal Manifestations

Variables	All Patients (n=110)	Without MSK Manifestations (n=10)	With MSK Manifestations (n=100)	P
Demographic Characteristics				
Gender, n (%)				
Female	80 (72.7)	7 (70)	73 (73)	1
Male	23 (27.3)	3 (30)	27 (27)	
Age (years), mean \pm SD	37.7 \pm 12.9	36.1 \pm 12.46	38.5 \pm 13.01	0.693
Marital status, n (%)				
Single/divorced/widowed	38 (34.5)	4 (40)	34 (34)	0.735
Married	72 (65.5)	6 (60)	66 (66)	
Occupation				
Not employed	17 (15.5)	0 (0)	17 (17)	0.512
Employed	66 (60)	8 (80)	58 (58)	
Retired	7 (6.4)	0 (0)	7 (7)	
Not able to work	1 (0.9)	0 (0)	1 (1)	
Student	19 (17.3)	2 (20)	17 (17)	
Residence, n (%)				
Urban	93 (84.5)	8 (80)	85 (85)	0.651
Rural	17 (15.5)	2 (20)	15 (15)	
Education, n (%)				
Middle school	3 (2.7)	0 (0)	3 (3)	0.732
High school	6 (5.5)	0 (0)	6 (6)	
College degree	85 (77.3)	9 (90)	76 (76)	
Post-graduate	16 (14.5)	1 (10)	15 (15)	

(Continued)

Table 1 (Continued).

Variables	All Patients (n=110)	Without MSK Manifestations (n=10)	With MSK Manifestations (n=100)	P
Smoking habit, n (%)				
Current smoker	9 (8.2)	0 (0)	9 (9)	0.341
Nonsmoker	92 (83.6)	10 (100)	82 (82)	
Ex-smoker	9 (8.2)	0 (0)	9 (9)	
Family income, n (%)				
Not enough	6 (5.5)	0 (0)	6 (6)	0.719
Enough but no saving	60 (54.5)	6 (60)	54 (54)	
Enough and saving	44 (40)	4 (40)	40 (40)	
Socioeconomic status, n (%)				
Low	6 (5.5)	1 (10)	5 (5)	0.588
Average	90 (81.8)	7 (70)	83 (83)	
High	14 (12.7)	2 (20)	12 (12)	
Active lifestyle, n (%)	74 (67.3)	9 (90)	65 (65)	0.108
Clinical data				
Weight (Kg), mean ± SD	80.33±18.21	71.45 ±19.3	81.25 ±17.95	0.106
Height (Cm), mean ± SD	165.63±26.41	165.1 ±9.72	165.68 ±9.42	0.853
Body mass index (Kg/m²), mean ± SD	29.07±5.41	26.08±6.1	29.39±5.27	0.065
Comorbidities, n (%)				
Any comorbidity	31 (28.2)	2 (20)	29 (29)	0.722
Diabetes mellitus	9 (8.2)	0	9 (9)	1
Hypertension	14 (12.7)	2 (20)	12 (12)	0.613
Chronic kidney disease	2 (1.8)	0	2 (2)	1
Chronic lung disease	6 (5.5)	0	6 (6)	1

Table 2 Musculoskeletal and Rheumatic Manifestations Associated with COVID-19 Infection

Variables	Study Group (n=110)
Onset from the first day of COVID-19 infection (days), median (min-max)	2 (0–45)
Duration of musculoskeletal /rheumatic manifestations (days), median (min-max)	7 (0–210)
Musculoskeletal manifestations, n (%)	
Arthralgia	90 (81.8)
Myalgia	94 (85.5)
Muscle weakness	45 (40.9)
Facial muscle pain	8 (7.3)
Swollen joints	9 (8.2)
Widespread musculoskeletal pain	66 (60)
Infectious arthritis	0
Mucocutaneous manifestations, n (%)	
Persistent dryness of the mouth	21 (19.1)

(Continued)

Table 2 (Continued).

Variables	Study Group (n=110)
Persistent dryness of the eyes	37 (33.6)
Skin rash	8 (7.3)
Severity of COVID-19 related arthralgia, n (%)	
No	20 (18.2)
Mild	20 (18.2)
Moderate	36 (32.7)
Severe	26 (23.6)
Very severe	8 (7.3)
Severity of COVID-19 infection related myalgia, n (%)	
No	16 (14.5)
Mild	28 (25.5)
Moderate	37 (33.6)
Severe	23 (20.9)
Very severe	6 (5.5)
The maximum musculoskeletal pain score, median (min-max)	7 (0–10)

months. Myalgia was the main complaint (85.5%) followed by arthralgia 90 (81.8%). However, swollen joints were reported in only 9 patients (8.2%). No one reported infectious arthritis. The severity of arthralgia ranged from mild (18.2%), moderate (32.7%), severe (23.6%) and very severe (7.3%).

The distribution of MSK symptoms is shown in Figure 1. According to the body areas, maximum number of patients felt pain at the lower back (60%), followed by neck (39.1%), and upper back (32.5%) followed by right and left shoulder (20.9%). Left and right elbows were the least affected body areas (9.1% and 8.2% respectively).

There was no significant difference between patients with MSK symptoms and those without regarding their socio-demographic data. However, patients with MSK manifestations were associated with a more severe COVID-19 infection ($p < 0.001$). Additionally, significant difference existed between both groups regarding the presenting manifestations of

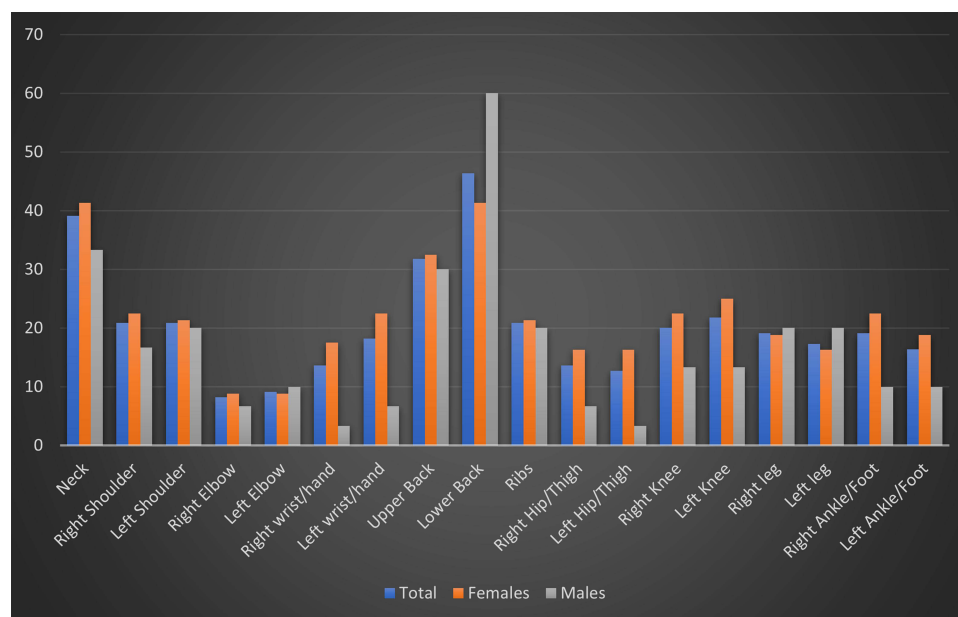


Figure 1 Distribution of MSK manifestations (pain, discomfort, numbness) associated with COVID-19 infection.

COVID-19 infection such as shortness of breath ($p = 0.006$), loss of taste ($p < 0.001$), loss of smell ($p = 0.001$), loss of appetite ($p = 0.001$), headache ($p < 0.001$) and fever (0.013). Patients with MSK symptoms were also associated with prolonged duration of COVID-19 symptoms ($p < 0.001$) and higher prevalence of COVID-19-related fatigue ($p < 0.001$) as illustrated in Table 3.

Table 3 COVID-19 Infection Data According to Musculoskeletal Manifestations

Variables	All Patients (n=110)	Without MSK Manifestations (n=10)	With MSK Manifestations (n=100)	P
Contact to a symptomatic case in 14 days, n (%)	73 (66.4)	6 (60)	67 (67)	0.730
Severity of COVID-19 infection, n (%)				
Mild	26 (23.6)	8 (80)	18 (18)	<0.001*
Moderate	52 (47.3)	1 (10)	51 (51)	
Severe	32 (29.1)	1 (10)	31 (31)	
Presenting manifestations, n (%)				
Shortness of breath	58 (52.7)	1 (10)	57 (57)	0.006*
Loss of taste	59 (53.6)	0 (0)	59 (59)	<0.001*
Cough	60 (54.5)	3 (30)	57 (57)	0.181
Loss of smell	68 (61.8)	1 (10)	67 (67)	0.001*
Loss of appetite	52 (47.3)	0 (0)	52 (52)	0.001*
Headache	83 (75.5)	1 (10)	82 (82)	<0.001*
Sore throat	48 (43.6)	0 (0)	48 (48)	0.005*
Diarrhea	37 (33.6)	0 (0)	37 (37)	0.016*
Dizziness	58 (52.7)	0 (0)	58 (58)	<0.001*
Fever	67 (60.9)	2 (20)	56 (56)	0.013*
Pneumonia	23 (20.9)	2 (20)	21 (21)	1
Investigations done to confirm the diagnosis of COVID-19 infection, n (%)				
X-Ray chest	15 (13.6)	0 (0)	15 (15)	0.352
HRCT chest	20 (18.2)	2 (20)	18 (18)	1
PCR-COVID-19	110 (100)	10 (10)	100 (100)	1
Antibodies for COVID-19	12 (10.9)	0 (0)	12 (12)	0.597
Complete blood count	37 (33.6)	2 (20)	35 (35)	0.49
O ₂ requirement, n (%)	11 (10)	1 (10)	10 (10)	1
Hospital admission, n (%)	10 (9.1)	1 (10)	9 (9)	1
Duration of COVID-19 symptoms (from the first day until symptoms resolved) (days), median (min-max)	10 (1–150)	2.5 (1–17)	12 (1–150)	<0.001*
Outcome of COVID-19 infection in the first 2 weeks, n (%)				
Improvement	84 (76.4)	10 (100)	74 (74)	0.113
Deterioration	26 (23.6)	0 (0)	26 (26)	
Mucocutaneous manifestations, n (%)				
Persistent dryness of the mouth	21 (19.1)	1 (10)	20 (20)	0.684
Persistent dryness of the eyes	37 (33.6)	0 (0)	37 (37)	0.016*
Skin rash	8 (7.3)	0 (0)	8 (8)	1
Severity of COVID-19 infection related fatigue, n (%)				
No	11 (10)	8 (80)	3 (3)	<0.001*
Mild	14 (12.7)	1 (10)	13 (13)	
Moderate	37 (33.6)	1 (10)	36 (36)	
Severe	31 (28.2)	0 (0)	31 (31)	
Very severe	17 (15.5)	0 (0)	17 (17)	

Note: * $p < 0.05$.

Discussion

It has been demonstrated that coronavirus infections, like other respiratory illnesses, can cause MSK symptoms that range from arthralgia to spurious and chronic arthritis.¹⁵ However, COVID-19-related MSK complaints may not be linked to the development of pneumonia. Therefore, clinicians should be aware of COVID-19 variable onset to prevent missing a diagnosis, especially when respiratory symptoms are absent at the time of presentation.¹⁶

This is the first detailed study of MSK manifestations encountered by patients with COVID-19 infection, which utilizes Nordic MSK Questionnaire. The study includes those diagnosed with COVID-19 infection and provides data on the relation between MSK symptoms and clinical parameters in these patients.

The present study revealed that COVID-19 patients had a heavy MSK symptom burden. Also, the high prevalence of MSK symptoms was associated with higher severity of COVID-19 infection ($p < 0.001$), prolonged duration of COVID-19 symptoms ($p < 0.001$) and higher prevalence of fatigue ($p < 0.001$).

The most important result in this study is the high prevalence (90.9%) of MSK symptoms (pain, discomfort, numbness) related to COVID-19 infection. These results are much more higher than that of other studies, in which post-COVID-19 myalgia was found to be from 4.5% to 36% common, while post-COVID-19 arthralgia was shown to be from 6% to 27% common.¹⁷

This study confirmed the high prevalence of fatigue in COVID-19 patients, which was reported in almost all surveyed patients (90%). There is increasing concern regarding this point as recent research has found that more than half of patients suffer from fatigue, while other studies have found greater rates of arthralgia/myalgia symptoms.^{18,19}

COVID-19 individuals may experience myalgia that lasts longer than typical viral infections and is resistant to conventional analgesics.²⁰ This study found that the median duration of onset of MSK symptoms was 2 days from the first day of COVID-19 infection (min-max: 0–45 days). The MSK manifestations persisted up to 7 months in some patients.

The current study determined that myalgia was the main complaint (85.5%) followed by arthralgia (81.8%). These results are in accordance with recent studies indicating that myalgia is the most common MSK manifestation in COVID-19 patients.^{21,22} According to the Office for National Statistics, people infected with the new variant of COVID-19 found in the South East of England (known as B.1.1.7 or VUI 202012/01) are more likely to develop myalgia than those infected with other versions.²³

Myalgia is the result of a cytokine response and widespread inflammation,²⁴ as it is usually linked to MSK pain in the acute phase of COVID-19 infection.²⁵ Additionally, it is associated with a higher risk of postoperative death among these patients.²⁶

Arthralgia is also one of the symptoms that people with COVID-19 experience.²⁷ Myalgias and arthralgias have been lumped together as a single entity in COVID-19 studies.¹⁶ In COVID-19, viral arthralgia is less common than myalgia, but it has been reported in other coronavirus infections.^{28,29} Patients with COVID-19 presented with acute arthralgia are typically younger, with no previous arthritic episodes or inflammatory joint effusions.¹⁶

The severity of arthralgia in the surveyed patients ranged from mild (18.2%), moderate (32.7%), severe (23.6%) and very severe (7.3%). COVID-19 arthralgia is usually more severe and has a variable onset, whereas generalized body pain and myalgia are usually milder and occur in association with fever or respiratory symptoms.¹⁶

In the current study, swollen joints were reported in only 9 patients (8.2%). Acute arthritis is known to be caused by viral infections.³⁰ Post COVID-19 arthritis has been reported,^{31,32} and arthritis may even be the initial presenting symptom of COVID-19 infection.³³ However, coronaviruses usually cause arthralgia and myalgia rather than clinical arthritis.^{27–29}

Although the pathophysiology of viral-associated arthritis is yet unexplained, molecular mimicry is thought to play a role in the activation of the inflammatory process.³⁴ There have been reports of molecular mimicry in the context of SARS-CoV2, and this mechanism could be involved in the pathogenesis of both the acute systemic infection and the post-infective viral-related immunological repercussions.^{35–37} Also, COVID-19 invasion receptors expressed in the MSK system were thought to be a possible target for the angiotensin-converting enzyme 2 (ACE2) enzyme.^{38,39}

Despite the fact that classical reactive arthritis (ReA) is linked to urogenital and gastrointestinal infections, non-classical ReA can be triggered by a wide range of infections.⁴⁰ ReA can be caused by COVID-19 infection, and few cases of post-COVID-19 ReA have been published since the emergence of COVID-19.^{41–43}

Only one case of septic arthritis induced by *Neisseria meningitidis* in a COVID-19 patient has recently been reported.⁴⁴ However, no one reported infectious arthritis in our surveyed patients.

In this study, when we assessed the distribution of MSK symptoms among COVID-19 patients, maximum number of patients felt pain at the lower back (60%), followed by neck (39.1%), and upper back (32.5%) followed by right and left shoulder (20.9%). In an extension cohort study carried out on COVID-19 patients, joint pain and myalgia were both common; if regional, joint pain was most common in the knee, foot–ankle, and shoulder, while myalgia was most common in the lower leg, arm, and shoulder girdle.⁴⁵ In another single-center cohort study conducted on 300 participants, two phone interviews were conducted (2-week and 1-month after hospitalization) and MSK symptoms were inquired with a standardized questionnaire, the authors found that back pain, arthralgia, myalgia, low back pain, and neck discomfort were the most frequent MSK symptoms.⁴⁶

In this study, there was no significant difference between patients with MSK symptoms and those without regarding their gender or age. In contrast, another study found that fatigue, myalgia, and joint pain were more common in female patients with COVID-19 infection.⁴⁵

SARS patients with moderate and severe infections have a significant MSK burden.^{47–49} The results of the current study indicated that patients with MSK manifestations were associated with higher severity of COVID-19 infection ($p < 0.001$) with prolonged duration of COVID-19 symptoms ($p < 0.001$) and higher prevalence of fatigue ($p < 0.001$). These results are in agreement with those obtained by Bakilan and coauthors⁵⁰ who found that higher frequency of dyspnea, respiratory symptoms in addition to longer duration of hospital stay are related to post-COVID-19 MSK symptoms.

A number of limitations need to be noted regarding the present study. First, the study only included patients who were admitted to an Internal Medicine clinic. Our findings cannot be applied to all COVID-19 patients. Second, the method of data collection, which was based on self-reporting, may have influenced the study outcome. Third, the number of participants was to some extent small to give an acceptable value. Fourth, the majority of the patients in this study were females, which is atypical for COVID-19 infection, and the mean age was younger than in most previously published studies. Finally, the lack of a control group was another limitation.

However, there are many strengths to this study; this is one of the earliest studies conducted in Egypt and addresses the involvement of MSK system in COVID-19 patients. Also, the questionnaire is comprehensive and straightforward, and an in-person interview was conducted.

For future endeavors, improving the population size and involving a control group are highly recommended. Further research is needed to establish the prevalence of MSK manifestations in the general population after COVID-19.

Conclusion

MSK manifestations are common in COVID-19 patients and related to disease severity and duration. Therefore, recognizing the MSK aspects of the disease would be valuable and could provide further information to help with the diagnosis and management of COVID-19 patients.

Abbreviations

COVID-1, coronavirus disease of 2019; IL-6, interleukin-6; MSK, musculoskeletal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; TNF α , tumor necrosis factor α .

Data Sharing Statement

The data are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

A written informed consent was obtained from all participants, and Ethical Approval was obtained from Institutional Research Board of the Faculty of Medicine, Mansoura University (approval registration number: R.21.10.1469).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

No potential conflict of interest was reported by the authors.

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