

Musculoskeletal Symptoms in Patients Recovering from COVID-19

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SUMMARY

Background. Muscle and joint problems are recognized complications following acute infection of coronavirus infection. Long Covid is the recognized term now that is given to symptoms like fatigue, myalgia, respiratory and neurological problems that occur or persist in recovery phase.

Objective. The objective of the present study is to identify the long term musculoskeletal complications of SARS-CoV2 infection in a sample of 367 individuals and to analyze the relation between the intensity of these complications and severity of illness.

Methods. COVID PCR positive patients were enrolled in this study. COVID-19 symptoms at the time of infection and musculoskeletal symptoms like fatigue, myalgia, arthralgia, muscle weakness, cracking or popping sound from joints and muscle stiffness in recovery period were asked from patients. The intensity of these symptoms was also recorded for these symptoms. The data was described in frequency and percentages mostly where P-value < 0.05 was considered significant.

Results. 187 hospitalized and 180 non hospitalized patients were analyzed in this study. Results showed that a quite large percentage of the enrolled patients suffered from fatigue (55%), myalgia (39%), arthralgia (25%), and muscle weakness (12%) during the 6 months following the confirmed date of COVID 19 infection. No relation between severity of COVID 19 infection and musculoskeletal complications was identified.

Conclusions. Most patients had at least one or more symptoms which emphasize the persistence of musculoskeletal problems after recovery from acute illness. The health-care workers need to be vigilant about such problems and plan further steps such as providing rehabilitation for such individuals.

KEY WORDS

Arthralgia; myalgia; fatigue; muscle weakness; popping/cracking joint.

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to a group of respiratory viruses that are responsible for a wide spectrum of problems related to the respiratory system and can cause mild, moderate or severe disease that may require mechanical ventilation. In addition to the respiratory system, coronavirus disease 2019 (COVID-19) can also affect the neurological, musculoskeletal and gastrointestinal systems (1). Musculoskeletal manifestations are common in patients with COVID-19. It is possible

that these symptoms, which include muscle weakness and arthralgia, are due in part to prolonged immobilisation (2). Long-term effects of SARS-CoV-2 infection, including persistent fatigue, muscle dysfunction and dyspnoea, in people who were admitted to an intensive care unit are also referred to as post-intensive care syndrome (3). Patients who have mild to moderate symptoms can also have long-term sequelae. Notably, individuals who are homebound tend to develop a sedentary lifestyle, and this physical inactivity leads to attenuated muscle and joint function (4).

Social isolation and functional limitations contribute to the appearance of musculoskeletal symptoms like facial muscle pain and pain in joints, especially in patients who have autoimmune diseases such as rheumatoid arthritis, spondyloarthropathy and systemic lupus erythematosus. Moreover, patients with fibromyalgia tend to develop exaggerated symptoms of fatigue, possibly due to stress and anxiety associated with these social restrictions (5). Thus, physiotherapists must face both the complications of having fewer resources for physical therapy and patients' limitations in performing the prescribed exercises. Patients recovering from SARS-CoV-2 infection may face both short- and long-term complications (6).

Studies carried out in survivors of severe acute respiratory syndrome showed reduced cardiorespiratory capacity, musculoskeletal limitations and reduced quality of life even after the end of the disease, which shows the need for rehabilitation to enable full recovery (7). Another study revealed that the majority of individuals who were previously affected by COVID-19 experienced persistence of at least one symptom. Patients were re-evaluated within three months after discharge, and it was found that many had on going fatigue and joint pain (8).

The persistent musculoskeletal symptoms in coronavirus survivors should be identified so that they can be addressed with proper rehabilitation (9). This study will help characterise the long-term musculoskeletal complications in our population in relation to prior severity of illness. This research has important implications for addressing the long-term health issues of patients who were affected in this pandemic, as it could help ensure their proper care and complete recuperation. The long-term joint and muscular problems in long COVID have not been widely studied; thus, this study is a very powerful source of information.

MATERIALS AND METHODS

In this random consecutive cross-sectional study, patients who had symptomatic laboratory-confirmed SARS-CoV-2 infection in the last 6 months were enrolled from 31/12/2020 to 31/3/2021. Ethical approval was obtained from Shaikh Zayed Federal Postgraduate Medical Institute on, Lahore, Pakistan on 31/12/2020 (SZMC/internal/0093/2020) with respect of protocol of Helsinki. The patients who were not admitted were reached through social media, relatives and colleagues of healthcare workers. The studied population was approached at different points in time during the 6 month recovery period after their positive PCR test for SARS-CoV-2. Informed consent was obtained from all patients, following which they were asked about their COVID symptoms, which were catego-

rised as mild (patients with mild respiratory symptoms of low-grade fever (< 100 °F), cough, flu), moderate (shortness of breath in addition to fever (> 100 °F), cough with or without sputum, flu) or severe (respiratory failure, shock, multi-organ dysfunction or requiring ventilation) (10). Patients were also asked about the presence of symptoms like myalgia (11), fatigue (12), arthralgia (13), muscle weakness (14), cracking/popping from joints and muscle stiffness. In addition, patients were asked to describe the intensity of their myalgia, fatigue, arthralgia and muscle weakness to the best of their understanding, and the severity of each of these symptoms was categorised as follows: none (no problem), mild (symptom is present, but infrequently (*i.e.*, not on a daily basis), moderate (symptom present daily and exacerbated with exercise) and severe (persistent symptom that prevents the patient from doing routine activities). The data was carefully entered into a well-designed questionnaire. Patients were also asked about joint pain, and any joints that were swollen, warm, red and painful to touch without recent history of trauma or long-standing joint disorders were labelled as having arthritis. Patients reporting arthritis were asked whether they had already visited a doctor and received a diagnosis for this complaint, and those who had not were advised to see one immediately and were contacted later for their diagnosis. In addition, their treating physician was contacted to confirm the diagnosis.

Patient's ≥ 20 years of age with a laboratory-confirmed case of COVID-19 in the last 6 months were included in the study. Patients who had had a positive PCR test for SARS-CoV-2 within the last month or who had diabetes mellitus (15) for more than 10 years, a cerebrovascular accident (16) in their history or a known case of joint disorder (17) were excluded from the study. Data on age, hospital stay and time to recovery is presented as mean \pm SD if normally distributed and median (IQR) otherwise. Data on age, gender, occupation, severity of COVID-19, and symptoms like fatigue, myalgia, arthralgia, muscle weakness, cracking or popping sound in joints, muscle stiffness and arthritis is presented as frequencies and percentages. Pearson's correlations were performed to determine whether the conditions listed above were associated with age, gender and severity of COVID-19. A P-value of < 0.05 was considered statistically significant. SPSS 25.0 was used for detailed analysis.

RESULTS

The demographic details of patients enrolled in this study are presented in **table I**. The mean age was 42.73 ± 15.84 years, and the sample consisted of 48.3% women and 51.7% men. Information on participants' age, gender, and occupation and hospitalisation record is presented in tabulated

form (**table I**). There were more male participants, predominantly of younger age group between 25 and 35 years of age, over half of them were employed and the majority were hospitalised for COVID-19 infection. Of the 367 total patients, 187 were admitted to a care facility and 180 were treated at home. The COVID-19 cases were defined as described in the methods section; of the total, 57% of survivors had mild disease, 38% had moderate disease and 5% had severe disease at the time of illness.

Analysis of comorbidities according to organ involvement revealed that patients with disorders of the endocrine system such as diabetes of less than 10 years and thyroid dysfunction comprised 11% of the total study population. In addition, 8% had cardiovascular problems. Seventy-nine percent had no comorbidities at the time of question in regards to this research. When all of the rheumatological symptoms were grouped according to gender, it was noted that for mild fatigue, 29% of men and 28.8% of women

were affected with this symptom during the recovery period. Regarding severe arthralgia and myalgia, 0.5% of men and 2%–3% of women were symptomatic in the next six months after infection. The details of all symptoms according to gender are provided in **table II**.

Most of the patients in this study had some degree of fatigue and myalgia at some point in time during the convalescent phase of 6 months after SARS-CoV-2 infection. Overall, 15.3% reported persistent arthralgia and only 8.8% complained of muscle weakness. Of the studied population, 55% had fatigue, 39% had myalgia, 25% had arthralgia and 12% had muscle weakness. Twenty-six percent of the patients who had mild COVID-19 had mild myalgia, while 5.6% of those with severe COVID-19 had mild myalgia; thus, no correlation could be detected between COVID-19 severity and mild myalgia symptoms. Similarly, 31% of patients with mild COVID-19 and 16% of patients with severe COVID-19 suffered from mild fatigue (**table III a**).

Table I. Demographic details of study population.

Variables	N	%	χ^2 -value	P-value	Mean \pm SD
Occupation					
None	79	22			
Business	14	4			
Employed	126	34			
House Wife	54	15			
Professional	94	26			
Gender			10.14	0.001	
Male	214	58.3			
Female	153	41.7			
Age (years)			83.26		42.73 \pm 15.84
15-25	24	7			
25-35	131	36			
35-45	76	21			
45-55	56	15			
> 55	80	22			
Hospitalized			0.134	0.715	
No	180	49			
Yes	187	51			
Hospitalized Days					
No Stay at Hospital	180	49	359.3	< .001	
1-7 (one week)	12	3			
8-14 (two week)	46	13			
15-21 (three week)	96	26			
22-28 (four week)	18	49			
> 28 (more than one month)	15	4			

This table gives the detail of participants based on their age group, gender, occupation, hospitalization and days of hospital stay if admitted.

Table II. Rheumatological symptoms distributed according to gender.

Symptoms	Gender		Total	χ^2 -value (df)	P-value
	Male n (%)	Female n (%)			
Myalgia				18.09 (3)	< .001
None	149 (69.6)	75 (49.0)	224 (61.0)		
Mild	43 (20.1)	43 (28.1)	86(23.4)		
Moderate	21 (9.8)	32 (20.9)	53(14.4)		
Severe	1 (0.5)	3 (2.0)	4 (1.1)		
Total	214 (100)	153 (100)	367 (100)		
Arthralgia				15.32 (3)	.002
None	176 (82.2)	100 (65.4)	276 (75.2)		
Mild	29 (13.6)	37 (24.2)	66 (18.0)		
Moderate	8 (3.7)	11 (7.2)	19 (5.2)		
Severe	1 (0.5)	5 (3.3)	6 (1.6)		
Total	214 (100)	153 (100)	367 (100)		
Fatigue				13.067 (3)	.004
None	111 (51.9)	56 (36.6)	167 (45.5)		
Mild	62 (29.0)	44 (28.8)	106 (28.9)		
Moderate	37 (17.3)	49 (32.0)	86 (23.4)		
Severe	4 (1.9)	4 (2.6)	8 (2.2)		
Total	214 (100)	153 (100)	367 (100)		
Muscle Weakness				8.88 (3)	.031
None	197 (92.1)	128 (8.7)	325 (88.6)		
Mild	15 (7.0)	17 (11.1)	32 (8.7)		
Moderate	2 (0.9)	6 (3.9)	8 (2.2)		
Severe	0 (0)	2 (1.3)	2 (0.5)		
Total	214 (100)	153 (100)	367 (100)		
Cracking or popping sound				8.972 (3)	.003
Absent	207 (96.7)	136 (88.9)	343 (93.5)		
Present	7 (3.3)	17 (11.1)	24 (6.5)		
Total	214 (100)	153 (100)	367 (100)		
Joint stiffness				1.238	.266
Absent	201 (93.9)	139 (90.8)	340 (92.6)		
Present	13 (6.1)	14 (9.2)	27 (7.4)		
Total	214 (100)	153 (100)	367 (100)		
Arthritis				0.699 (3)	.403
Absent	212 (99.1)	150 (98.0)	362 (98.6)		
Present	2 (0.9)	3 (2.0)	5 (1.4)		
Total	214 (100)	153 (100)	367 (100)		

The rheumatological problems are distributed according to male and female gender and percentages of these symptoms present in all the population is given in detail.

Similar discrepancies were observed for other variables (*i.e.*, arthralgia and muscle weakness). A cracking or popping sound in joints was observed in 7% of the individuals in the study; likewise, 7% experienced muscle stiffness during their recovery phase. No links could be established between the severity of disease and the problems of noisy joints and muscle stiffness. One percent of the studied population had developed arthritis (*i.e.*, warm, red, painful and swollen joints). Of these five individuals, two had ankle joint arthritis, one had arthritis in a single wrist joint, one had knee

ity of COVID-19 (**tables III, IV**). Pearson's correlation was performed to measure associations between COVID-19 severity and the intensity of musculoskeletal symptoms (**table V**). Notably, of the eight patients with severe fatigue, seven had moderate and one had severe COVID-19. Arthritis was found in only five patients ($p = 0.699$). These patients were followed long term (for 6 months after COVID-19) and it was discovered that the patient with swelling of the small joints of the hand had developed rheumatoid arthritis, one of the patients with ankle arthritis had

Table III. Association of Covid 19 case and musculoskeletal symptoms.

a)

COVID-19 Case	Myalgia				Fatigue			
	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Mild	133 (63)	57 (27.0)	21 (10.0)	0 (0)	103 (48.8)	66 (31.3)	42 (19.7)	0 (45.5)
Moderate	81 (58.7)	28 (20.3)	27 (19.6)	2 (1.4)	59 (42.8)	37 (26.8)	35 (25.4)	7 (28.9)
Severe	10 (55.6)	1 (19.3)	5 (27.8)	2 (11.1)	5 (27.8%)	3 (16.7%)	9 (50.0%)	1 (23.4)
Total	224 (61.0)	86 (1.4)	53 (14.4)	4 (1.1)	167 (45.5)	106 (28.9)	86 (5.6)	8 (2.2)

χ^2 -value = 31.26, $p < .001$ for Myalgia; χ^2 -value = 14.13, $p = .028$ for Fatigue; χ^2 -value = 21.13, $p = .002$ for Arthralgia; χ^2 -value = 52.62, $p < .001$ for Muscle Weakness.

b)

COVID-19 Case	Arthralgia				Muscle Weakness			
	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Mild	159 (75.4)	44 (20.9)	7 (3.3)	1 (5)	192 (91.0)	19 (9.0)	0 (0)	0 (0)
Moderate	106 (76.8)	19 (13.8)	9 (6.5)	4 (2.9)	118 (85.5)	12 (8.7)	8 (5.8)	0 (0)
Severe	11 (61.6)	3 (16.7)	3 (16.7)	1 (5.6)	15 (83.3)	1 (5.6)	0 (0)	2 (11.1)
Total	276 (75.2)	66 (18.0)	19 (5.2)	6 (1.6)	325 (88.6)	32 (8.7)	8 (2.2)	5 (5)

arthritis and one developed arthritis of all small joints of both hands (**table III b**).

Two patients with severe myalgia had moderate COVID-19 and two had severe COVID-19, suggesting that the intensity of myalgia symptoms is not directly related to the sever-

actually experienced a gout episode for the first time (identified by synovial aspirate) and the patient with swelling of the knee joint was told by his doctor that it was due to his osteoarthritis precipitated by recent strenuous exercise. No cause could be identified for the patient with wrist swell-

Table IV Association between Cracking/popping of joints, Muscle stiffness and Arthritis to severity of Covid 19 illness.

Covid 19 case	Cracking/ Popping of joints		Muscle Stiffness		Arthritis	
	Present	Absent	Present	Absent	Present	Absent
Mild	202 (95.7%)	9 (4.3%)	198 (93.8%)	13 (6.2%)	209 (99.1%)	2 (0.9%)
Moderate	126 (91.3%)	12 (8.7%)	127 (92.0%)	11 (8.0%)	136 (98.6%)	2 (1.4%)
Severe	12 (8.7%)	3 (16.7)	15 (83.3%)	3 (16.7%)	17 (94.4%)	1 (5.6%)
Total	343 (93.5%)	24 (6.5%)	340 (92.6%)	27 (7.4%)	36 (98.6%)	5 (4%)

This table demonstrates the symptoms of rheumatological disease spectrum like cracking or popping sound from joints, muscle stiffness and arthritis with the severity of Covid 19 infection.

Table V. Pearson correlation between Covid 19 symptoms and musculoskeletal problems.

Musculoskeletal symptoms	Myalgia	Arthralgia	Fatigue	Muscle Weakness	Muscle stiffness	Cracking/popping sound from joints	Arthritis
Pearson Correlation value	31.260*	14.131*	21.134*	52.622*	2.808**	5.856*	2.633**

*P-value < 0.05; **P-value > 0.05.

ing or the second patient with ankle joint swelling, both of which resolved with a few weeks of non-steroidal anti-inflammatory drug intake. Overall, a random distribution of symptoms was seen based on patients' perception of their disease.

DISCUSSION

This study shows that many people who were affected by COVID-19 had persistence of musculoskeletal symptoms and continued to suffer from fatigue, myalgia, arthralgia and muscle weakness during their recovery, which had huge impact on their lives. Some had muscle stiffness and a popping/cracking sound coming from their joints; in addition, though rare, some patients developed arthritis leading to functional limitation. Arthritis may result from this viral infection itself or from an unidentified problem; to our knowledge, this has not yet been studied in COVID-19 patients. These musculoskeletal symptoms should be identified and addressed carefully to build patient confidence and meet their rehabilitation needs in order to prevent muscle wasting from prolonged disuse. Moreover, it is important to recognise the long-term implications of these symptoms and address these complications to improve patients' quality of life during the current pandemic, which can be challenging. Previous studies have reported the persistence of fatigue in 52.3% and 55% of patients at 2 and 6 months after initial SARS-CoV-2 infection, respectively (18); these findings are similar to our finding that 55% of patients experienced fatigue in the 6 months after COVID-19 diagno-

sis. The prevalence of myalgia was reported to be 19% in a previous article (2), while the current study reported a rate of 38%. Halpin *et al.* recently reported the results of a structured telephone interview about symptoms after the acute infection phase in which 100 patients were evaluated approximately 48 days after discharge from the hospital; in their study, fatigue was the most commonly reported symptom, with 72% of those who were in the ICU and 60.3% of those admitted to a ward reporting fatigue (19). Lechien *et al.* also reported on 417 COVID-19 patients from 12 European hospitals and found myalgia in 246 and arthralgia in 129 of these patients (20). Jacob *et al.* reported musculoskeletal symptoms in greater than 50% of patients, with the prevalence of fatigue ranging from 8% to 47% and higher values for arthralgia/myalgia symptoms 50% and 59% respectively. The prevalence of musculoskeletal symptoms in studies from Europe reached high values of approximately 50% (21).

The pathophysiology behind the development and persistence of these symptoms is largely unknown. However, systemic inflammation has been studied in the context of bone and joint tissue physiology in patients with active COVID-19. The cytokines that might have a role in decreased formation and destruction of bone and joints, respectively, include CXC motif chemokine ligand 10 (CXCL10), interleukin (IL)-17 and tumour necrosis factor alpha (TNF- α), which lead to a net reduction in bone mineral density. IL-1 β , IL-6 and TNF- α cytokines cause chondrolysis, resulting in arthralgia in elderly. Additionally, IL-1 β , IL-17 and TNF- α are thought to promote inflamma-

tion in tendons, resulting in impaired matrix remodelling and possible exacerbation of degenerative tendon disorders (22, 23). Muscular and neuropathic pain can result from a direct effect of viral proteins, macrophages circulating in the blood and effects on sensory nerve endings in addition to systemic inflammatory markers (24). Notably, the important role played by human leukocyte antigen (HLA) molecules in the immune response, especially through peptide presentation of the pathogen responsible for causing disease, and the huge molecular variability of HLA alleles in human populations could be responsible for the differences in severity of infection and patients' symptoms following coronavirus infection (25). These changes in the body may lead to long-term effects and prolongation of musculoskeletal symptoms. Interestingly, few patients coming to out-patient clinic presented biological abnormalities like increased C-reactive protein and, in rare instances, scarce infection on chest computed tomographic scan. Whereas nasopharyngeal PCR can still be positive even 30 days after symptom onset (26), a previous study reported that approximately 60 days after onset of the first COVID-19 symptom, only 13% of the previously hospitalised COVID-19 patients were completely free of any COVID-19-related symptom: 32% had 1 or 2 symptoms and 55% had 3 or more (27). A randomised controlled trial of 133 patients with SARS demonstrated that a 1.5-month course of an aerobic and resistance training program consisting of 1- to 1.5-hour sessions 5 times per week could improve strength and function of muscle and joints (28). This post-COVID-19 entity is worth addressing: we are facing an unprecedented pandemic, and suddenly, many who were affected at the same time are seeking care for what might otherwise be considered a chronic fatigue syndrome.

Limitations of this study include the small sample size, which could lead to alteration in results. In addition, because the findings are scored, as mild moderate or severe, based solely on patients' assessment of their symptom severity, the problems are subject to their feelings and emotional stresses. Lack of availability of hospital record charts to assess the severity of COVID-19 during each patient's hospital stay is a further limitation. The possibi-

ty of undetected pre-COVID abnormalities in the patients, lack of knowledge about SARS-CoV-2 variants, the exclusion of some patients with severe comorbidities and the absence of documentary evidence are additional limitations of this study.

CONCLUSIONS

Here, we conclude that more than half of COVID-19 patients have persistent musculoskeletal symptoms that require special attention (*i.e.*, physical rehabilitation) while maintaining social isolation; this will require physical therapists working outside the hospital to provide treatment measures in accordance with COVID restrictions. Early post-acute evaluation of symptoms and their impact on function is necessary to plan community-based services like post-acute medical, psychological and physical services to enable full recovery and ensure patients' early return to work.

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DATA AVAILABILITY

The data in CSV file will be available on request.

CONTRIBUTIONS

All authors: ethical approval, data collection and research writing.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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