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Rheumatology

Musculoskeletal symptoms and related factors in postacute COVID-19 patients

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Abstract

Aim: There is a lack of an overview of the factors associated with postacute COVID-19 musculoskeletal symptoms. The aims of this study were as follows: 1- to evaluate the most frequent admission symptoms and the frequency of musculoskeletal symptoms in postacute COVID-19 patients; and 2- to determine the related factors with the postacute COVID-19 musculoskeletal symptoms.

Methods: A total of 280 postacute COVID-19 patients (183 females, 97 males) were enrolled and divided into two groups: 1- patients whose musculoskeletal symptoms initiated with or were aggravated by COVID-19 (n = 240); and 2- patients whose musculoskeletal symptoms did not change with COVID-19 (n = 40). The variables were demographic and treatment data, symptoms on admission, postacute COVID-19 symptoms, laboratory results (complete blood count, erythrocyte sedimentation rate, C-reactive protein, ferritin and D-dimer), chest computed tomography findings and symptoms during acute COVID-19.

Results: Most of the patients have fatigue (71.8%), spine pain (70.7%) and myalgia (60.7%). The most common pain region was the back (30.4%). The frequency of dyspnoea was 30%, cough 18.5% and chest pain 10.7%. Having any chronic disease (P = .031), the duration of hospital stay (P = .016), frequency of back pain during acute COVID-19 (P = .018), tomography findings and D-dimer (P = .035) levels were significantly higher, and lymphocyte (P = .024) levels were significantly lower in the patients whose symptoms began with or were aggravated by COVID-19.

Conclusion: Back pain was the most frequent symptom on admission. The most common postacute COVID-19 musculoskeletal symptoms were fatigue, spine pain and myalgia. Lower lymphocyte and higher D-dimer levels, the presence of COVID-19 findings in tomography and back pain during acute COVID-19 infection, higher duration of hospital stay and having chronic diseases were related to post-COVID-19 musculoskeletal symptoms.

1 | INTRODUCTION

COVID-19 leads to long-term effects in multiple biological systems, including the musculoskeletal system. These long-term effects are said to result from "post acute COVID-19". In recent guidelines, postacute COVID-19 patients, who have persistent symptoms, have been divided into two groups: (i) 4-12 weeks after the onset of acute COVID-19: ongoing symptomatic COVID-19 patients, and (ii) 12 weeks after the onset of acute COVID-19: chronic COVID-19 patients (post-COVID-19 syndrome).[1]

Recently, many papers have been published about the symptoms of postacute COVID-19 patients.[2-5] However, there are only a few studies investigating the effect of postacute COVID-19 on the musculoskeletal system. These studies examined the most frequent symptoms. For example, Karaarslan et al[4] reported the most frequent musculoskeletal symptoms as "fatigue and back pain", while Numan et al[5] reported the most common symptom to be "pain in the lower limb". These results are conflicting, and the relationship between prognostic factors, such as laboratory and chest computed tomography (CT), and postacute COVID-19 musculoskeletal symptoms has not yet been investigated to the best of our knowledge.

The aims of this study were as follows: (i) to evaluate the most frequent admission symptoms to physical medicine and rehabilitation (PMR) outpatient clinics and the frequency of musculoskeletal problems in postacute COVID-19 patients; (ii) to determine which factors are most related to the postacute COVID-19 musculoskeletal symptoms such as disease symptoms, laboratory results and chest computed tomography in acute infection.

2 | MATERIALS AND METHODS

This retrospective cross-sectional study was carried out with the records of 280 postacute COVID-19 patients who were admitted to the PMR outpatient clinic between December 2020 and May 2021. The inclusion criteria were being 18 years or older, and having COVID-19 treatment (home quarantine/hospital/intensive care unit) according to a positive polymerase chain reaction (PCR) test in a nasopharyngeal + oropharyngeal swab or chest CT. Patients who have both negative PCR test and chest CT, patients who did not have recorded musculoskeletal symptoms (admission symptoms and musculoskeletal symptoms such as fatigue and spine/joint/muscle pain/numbness) in patients files and also acute COVID-19 patients whose symptoms have started less than 1 month previously were excluded.

The typical findings of the chest CT were as follows: bilateral, multifocal and peripheral ground glass opacities with/without consolidation, including fissures, close to visceral pleural surfaces. The COVID-19 Reporting and Data System (CO-RADS) was used for chest CTs. CO-RADS assigns scores from 1 (very low suspicion of COVID-19) to 5 (very high suspicion of COVID-19).[6]

A detailed anamnesis was recorded about age, gender, body mass index, education, employment history, the presence of any chronic disease (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, cardiac disease, cancer, rheumatological disease, etc), smoking, duration of symptoms, usage of vitamin supplements such as vitamin D, C, zinc etc, place of treatment (home quarantine, hospital and intensive care unit), duration of home quarantine and hospital treatment, the number of months since the onset of COVID-19 symptoms and the usage of anticoagulants and treatment drugs such as hydroxychloroquine and favipiravir.

The symptoms of all patients on admission to outpatient clinics were recorded, including local or radicular back/lower back/neck pain, fatigue, myalgia, knee/hip/ankle/foot pain, shoulder/elbow/wrist/hand pain, chest pain and numbness. Furthermore, all patients have musculoskeletal symptom records in detail, including fatigue, spine pain, myalgia, arthralgia and numbness. Neck/back/lower back pain, both radiating or not, was accepted as spine pain. Widespread myalgia was accepted as pain in more than one site (shoulder girdle, arm, thigh and lower leg). Joint pain in any joint was accepted as arthralgia and also the region of joint pain was recorded. The presence of numbness was also recorded. Moreover, it was also recorded whether these musculoskeletal symptoms have begun with or been aggravated by the COVID-19 infection or have not changed with the COVID-19 infection.

The laboratory values of 182 patients, the presence of chest CT findings of 206 patients and the symptoms of all patients during the period of the COVID-19 infection were recorded. Laboratory values of haemoglobin, leucocyte, lymphocyte, platelet, C-reactive protein, erythrocyte sedimentation rate, ferritin and D-dimer were recorded. Also, the symptoms experienced during the period of the COVID-19 infection were recorded from the patient files, including cough, fever, dyspnoea, chest pain, loss of smell and taste, sore throat, headache as well as no symptoms and any musculoskeletal symptoms such as muscle, lower back, back and/or joint pain. Moreover, concomitant

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What's known?

- The majority of postacute COVID-19 patients have at least one symptom.
- Fatigue was the most common symptom in postacute COVID-19 patients.

What's new?

- This study described the factors associated with postacute COVID-19 musculoskeletal symptoms.
- The most frequent admission symptom to physical medicine and rehabilitation outpatient clinic was back pain.
- The presence of lower lymphocyte, higher D-dimer levels, presence of COVID-19 in chest computed tomography and back pain during acute COVID-19 infection, higher duration of hospital stay and having chronic diseases, all seem to contribute to postacute COVID-19 musculoskeletal symptoms.

respiratory tract symptoms in the post-COVID-19 period, such as cough, dyspnoea and chest pain, were also recorded.

Ethics approval was received from the local ethics committee (date: 30.03.21, decision number: 04).

2.1 | Statistical analysis

The distribution of each continuous variable was tested for normality using the Shapiro-Wilk test. Non-normally distributed variables were compared using the Mann-Whitney *U*-test and expressed as median values (25%-75%). Normally distributed variables were performed using the *t*-test and they were expressed as mean ± standard deviation. Categorical variables are expressed as frequencies and percentages and they were compared using the Chi-square test. A *P*-value of <.05 was considered significant. All analyses were performed using the SPSS version 22.0 software (SPSS Inc, Chicago, IL, USA).

3 | RESULTS

Five patients were excluded because of having negative PCR and normal chest CT. A total of 280 post-COVID-19 patients (183 women, 97 men) (mean age 47.45 ± 13.92) were recorded. While 277 of them have positive PCR, 3 of them have negative PCR, but their chest CTs were CO-RADS-5. None of them had rheumatological disease such as rheumatoid arthritis, ankylosing spondylitis, etc All patients have at least one musculoskeletal symptom. The most common admission symptom was back pain (28.6%). All admission symptoms are given in Table 1.

A total of 247 (88.2%) of the 280 patients have at least one or more symptom, no difference was found according to gender (*P* = .165). A total of 240 (85.7%) of the 280 patients have at least one or more musculoskeletal symptoms, which began with or were aggravated by their COVID-19 infection, while the musculoskeletal problems of 40 (14.3%) of the 280 patients did not change after being infected with COVID-19. Also in these 240 patients, no difference was found according to gender (*P* = .343). Most of the patients have fatigue (71.8%), spine pain (70.7%) and widespread myalgia (60.7%). The most common site of spine pain was the back (30.4%). Furthermore, most of these symptoms began with or were aggravated by the COVID-19 infection. The frequency of dyspnoea was 30%, cough 18.5% and chest pain 10.7%. The frequency of respiratory tract and musculoskeletal symptoms and starting/increasing with the COVID-19 infection are given in Table 2.

The patients were divided into two groups: (i) patients whose musculoskeletal symptoms began with or were aggravated by COVID-19 (n = 240), and (ii) patients whose musculoskeletal symptoms did not change with COVID-19 (n = 40). Comparison of demographic and treatment parameters of these two groups showed that

TABLE 1 Symptoms of admission to physical medicine and rehabilitation outpatient clinic in postacute COVID-19 patients

	Frequency n (%)
Admission symptoms	
Back pain	80 (28.6%)
Fatigue	34 (12.1%)
Low back pain	30 (10.7%)
Neck pain	27 (9.6%)
Spinal pain more than one site	17 (6.1%)
Knee pain	15 (5.4%)
Joint pain more than one site	13 (4.6%)
Shoulder pain	11 (3.9%)
Widespread myalgia	11 (3.9%)
Radicular neck pain	6 (1.4%)
Chest pain	6 (1.4%)
Numbness	5 (1.8%)
Other symptoms[a]	25 (8.9%)
Total	280 (100%)

[a] Other symptoms n (%): radicular low back pain: 4 (1.4%), hand/wrist pain: 4 (1.4%), hip pain: 4 (1.4%), foot/ankle pain: 4 (1.4%), elbow pain: 3 (1.1%), cramp: 2 (0.7%), vertigo: 2 (0.7%), tremor: 1 (0.4%) and headache: 1 (0.4%).

age, body mass index, smoking, employment status, education level, duration of symptoms, using vitamin supplements (vitamin D and/or vitamin C and/or zinc), anticoagulant treatment, the duration after the onset of COVID-19 symptoms and places of treatment were all similar. However, the frequency of any chronic disease (*P* = .031) and the duration of the treatment in hospital (*P* = .016) were higher in those patients whose symptoms began with or were aggravated by COVID-19. The duration of home quarantine was 10 days in all patients who were treated at home. When patients were evaluated in terms of drug treatment, the musculoskeletal symptoms began with or were aggravated by COVID-19 in 3 (30%) of 10 patients who refused to use any drug and in 216 (90%) of 241 patients who used favipiravir, as well as in 8 (80%) of 10 patients who used hydroxychloroquine (Table 3).

Comparison of the symptoms during the COVID-19 infection showed that only back pain (*P* = .018) was significantly higher in patients whose musculoskeletal symptoms began with or were aggravated by COVID-19. On the other hand, the asymptomatic rate was significantly higher (*P* = .046) in patients whose symptoms did not change with COVID-19. A total of 206 of the patients have chest CTs, and the presence of COVID-19 findings in tomography were significantly higher in patients whose musculoskeletal symptoms began with or were aggravated by COVID-19 (*P* = .048). A total of 182 of all the patients have laboratory findings during the infection. When the patients were evaluated in terms of laboratory parameters, only the lymphocyte count (*P* = .024) was significantly lower, while D-dimer (*P* = .035) was significantly higher, in those patients

TABLE 2 Symptom frequency of patients in postacute COVID-19 period

	Frequency n (%)
Musculoskeletal system	
Fatigue	
Initiated or were aggravated with COVID-19	156 (55.7%)
Total	201 (71.8%)
Spine pain	
Neck pain	32 (11.4%)
Back pain	85 (30.4%)
Low back pain	45 (16.1%)
Spine pain more than one site	36 (12.8%)
Initiated or aggravated with COVID-19	160 (57.1%)
Total	198 (70.7%)
Muscle pain more than one site	
Initiated or aggravated with COVID-19	143 (51.1%)
Total	170 (60.7%)
Arthralgia	
Hand/wrist	9 (3.2%)
Elbow	2 (0.7%)
Shoulder	16 (5.7%)
Hip	4 (1.4%)
Knee	34 (12.1%)
Foot/ankle	5 (1.8%)
Joint pain more than one site	52 (18.6%)
Initiated or aggravated with COVID-19	101 (36.1%)
Total	122 (43.6%)
Numbness	
Initiated or aggravated with COVID-19	55 (19.6%)
Total	66 (23.6%)
Any musculoskeletal symptom which initiated or aggravated with COVID-19	240 (85.7%)
Respiratory tract system	
Dyspnoea	82 (30%)
Cough	52 (18.5%)
Chest pain	30 (10.7%)
Patients with at least one symptom which initiated or aggravated with COVID-19	247 (88.2%)
All patients	
Total	280 (100%)

Note: Most of the patients have more than one symptom.

whose musculoskeletal symptoms began with or were aggravated by COVID-19 (Table 4).

All the respiratory tract symptoms of the patients were found to have begun with their COVID-19 infection. The comparison of the frequency of respiratory tract symptoms between the groups showed that the frequency of dyspnoea ($P = .015$) and any respiratory tract symptom ($P = .014$) was significantly higher in patients whose musculoskeletal symptoms began with or were aggravated by COVID-19. However, the frequency of cough and chest pain was similar between the groups (Table 5).

4 | DISCUSSION

This study described the frequency of both musculoskeletal and respiratory tract symptoms in postacute COVID-19 patients who were admitted to a PMR clinic and also the factors associated with postacute COVID-19 musculoskeletal symptoms.

The common result from previous studies about post-COVID-19 symptoms was that the majority of patients have at least one symptom.[2-4] Consistent with these studies, 88.2% of our patients have at least one symptom, while 85.7% of our patients have at least one musculoskeletal symptom. Most of the previous studies have focused on whole body symptoms[2,3,7] after COVID-19. Different from these studies, the present study focused on musculoskeletal symptoms. The most common musculoskeletal symptoms were fatigue, spine pain and myalgia. The frequency of respiratory tract symptoms was lower than that of musculoskeletal symptoms, and the most common respiratory tract symptom was dyspnoea. Similar to our study, other studies have reported that dyspnoea was present in one-quarters of postacute COVID-19 patients.[4,7]

To the best of our knowledge, this is the first study that describes how factors such as disease symptoms and laboratory and chest CT related to postacute COVID-19 musculoskeletal symptoms. To evaluate these related factors, comparison was made between patients whose musculoskeletal symptoms began with or were aggravated by COVID-19 and patients whose musculoskeletal symptoms did not change with COVID-19. This comparison showed that the presence of back pain, lower lymphocyte and higher D-dimer levels; the presence of COVID-19 findings in chest CT during acute COVID-19 infection; a longer duration of hospital stay and having chronic diseases were more related to postacute COVID-19 musculoskeletal symptoms. The probable pathophysiologic mechanisms of musculoskeletal symptoms in COVID-19 are systemic immune response with inflammation, direct viral toxicity, hypercoagulability and microvascular injury.[8] The results of the present study support these pathophysiologic mechanisms with lower lymphocyte and higher D-dimer levels in patients whose musculoskeletal symptoms began with or were aggravated by COVID-19. The reduction in lymphocytes is related to the consumption of lymphocytes in inflamed regions while fighting against COVID-19.[9] This reduction has also been shown to be associated with poor outcomes.[10,11] In addition, hyperinflammation seems to contribute to COVID-19-related coagulopathy, and microthrombosis was reported to occur in almost every system, including the musculoskeletal system.[12] Not only lower lymphocyte levels but also elevated levels of D-dimer are related to poor outcomes[13] and this elevation may be related to this coagulopathy

TABLE 3 Comparison of demographic parameters and treatment characteristics between the patients whose musculoskeletal symptoms initiated or were aggravated with COVID-19 and the patients whose musculoskeletal symptoms did not change with COVID-19

	Initiated or were aggravated with COVID-19 (n = 240) n (%)	No change with COVID-19 (n = 40) n (%)	P
Age[a]	47 (39-58)	43 (33.25-56.50)	.219
Gender (female/male) (n)	160/80	23/17	.343
Body mass index[a]	27.55 (24.99-30.89)	26.59 (23.33-30.12)	.266
Education			
Primary school and lower	130 (54.2%)	20 (50%)	.751
High school and higher	110 (45.8%)	20 (50%)	
Working	104 (43.3%)	23 (57.5%)	.135
Smoking	40 (16.6%)	7 (17.5%)	.896
Any chronic disease	107 (44.6%)	10 (25%)	**.031**
Duration of symptom (months)[a]	5 (3-12)	12 (2-24)	.277
Using supplemental vitamins	52 (21.7%)	8 (20%)	.976
Treatment place			
Home quarantine	162 (67.5%)	33 (82.5%)	.174
Hospital service	60 (25.0%)	5 (12.5%)	
Intensive care unit	18 (7.5%)	2 (5%)	
Duration of hospital stay (days)[a]	10 (0-12)	0 (0-7.5)	**.016**
Duration after the onset of COVID-19 (months)[a]	4 (3-5)	3.25 (2-6)	.601
Treatment drugs			
No drug	3 (1.3%)	7 (20.6%)	**<.001**
Favipiravir	216 (95.2%)	25 (73.5%)	
Hydroxychloroquine	8 (3.5%)	2 (5.9%)	
Total (n)	227	34	
Usage of anticoagulant treatment	93 (38.75%)	10 (25%)	.131

[a] Median (25%-75%).
Bold values indicate statistical significance of P values.

in those of our patients whose musculoskeletal symptoms began with or were aggravated by COVID-19. Furthermore, similar to the current study, previous studies have reported that having concomitant diseases and extensive chest CT involvement were predictive for COVID-19 outcomes.[14]

Only a limited number of studies could be found evaluating the musculoskeletal features of post-COVID-19 patients. A rehabilitation centre in Bangladesh reported that the frequency of head and neck pain was 27%, pain in the lower limb 34%, back pain 24% and pain in the upper limb 13% in 90 post-COVID-19 patients.[5] In our study, the most common region of pain was the back (30%) and back pain was also the most frequent symptom on admission to the PMR outpatient clinic. Furthermore, back pain in acute COVID-19 was found to be related to postacute COVID-19 musculoskeletal symptoms. Gender and ethnic differences may be the reason for these different results: in our study, 65% of patients were women, whereas 30% of patients were women in the Bangladesh study. In another study in Turkey, phone interviews were conducted with 300 COVID-19 patients (60% male) after hospitalisation (intensive care unit patients were excluded): 72%

of these patients have at least one symptom, while most complaints regarding the musculoskeletal system were fatigue (44%), back pain (22.7%), arthralgia (22%), myalgia (21%) and lower back pain (16%) after 1 month.[4] These frequencies were lower than in our study, and the methodology used was also different. Our study's population was predominantly female and also includes patients who were treated in an intensive care unit. In addition, the population consisted of patients admitted to the PMR outpatient clinic with at least one musculoskeletal symptom after COVID-19. The frequencies recorded in the present study were, thus, higher than those in the other Turkish study. On the other hand, similar to our study, Karaarslan et al[4] also reported that back pain was the most common form of pain, the knee was the most common site of joint pain and that fatigue was the most common symptom.

In acute COVID-19 infections, the most common complaints regarding the musculoskeletal system are fatigue and myalgia.[15] In addition, these complaints seem to continue after acute COVID-19. Consistent with the results of our study, many other studies have reported that fatigue is commonly seen after recovery from

TABLE 4 Comparison of the findings during the period of COVID-19 infection between the patients whose musculoskeletal symptoms initiated or were aggravated with COVID-19 and the patients whose musculoskeletal symptoms did not change with COVID-19

	Initiated or were aggravated with COVID-19 (n = 240)	No change with COVID-19 (n = 40)	P
Symptoms during the period of COVID-19 infection n (%)			
Cough	105 (43.8%)	15 (37.5%)	.571
Fever	59 (24.6%)	8 (20%)	.668
Dyspnoea	85 (35.4%)	10 (25%)	.268
Myalgia	158 (65.8%)	21 (52.5%)	.148
Joint pain	132 (55%)	17 (42.5%)	.195
Low back pain	77 (32.1%)	8 (20%)	.176
Back pain	118 (49.2%)	11 (27.5%)	**.018**
Loss of taste and smell	24 (10%)	4 (10%)	1.000
Chest pain	35 (14.6%)	5 (12.5%)	.917
Sore throat	47 (19.6%)	4 (10%)	.218
Headache	81 (33.8%)	10 (25%)	.362
No symptom	21 (8.8%)	8 (20%)	**.046**
Presence of COVID-19 findings in chest CT (positive/negative) (n = 206) (n)	110/70	10/16	**.048**
Laboratory parameters (n = 182) median (25%-75%)	(n = 157)	(n = 25)	
Haemoglobin[a]	13.35 ± 1.58	13.77 ± 2.14	.246
Leucocyte	6.74 (5.53-8.37)	7.50 (5.86-9.14)	.297
Lymphocyte	1.82 (1.28-2.33)	2.16 (1.61-2.75)	**.024**
Platelet	230 (191-269)	225 (186-285)	.964
C-reactive protein	5.4 (0.6-23)	4.45 (0.2-20.07)	.670
Erythrocyte sedimentation rate	17 (8.5-29)	12 (5-20)	.077
Ferritin	117 (39.5-258.5)	75 (48-110)	.326
D-dimer	0.38 (0.22-0.62)	0.26 (0.15-0.45)	**.035**

Note: Most of the patients have more than one symptom.

Abbreviation: CT, computed tomography.

[a] Mean ± standard deviation.

Bold values indicate statistical significance of *P* values.

TABLE 5 The relationship between musculoskeletal and respiratory tract symptoms in post-COVID-19 period

	Initiated or were aggravated with COVID-19 (n = 240) n (%)	No change with COVID-19 (n = 40) n (%)	P
Cough (n = 52)	48 (20%)	4 (10%)	.198
Dyspnoea (n = 84)	79 (32.9%)	5 (12.5%)	**.015**
Chest pain (n = 30)	26 (10.8%)	4 (10%)	.875
Any respiratory tract symptom (n = 101)	94 (39.2%)	7 (17.5%)	**.014**

Note: Most of the patients have more than one respiratory tract symptom.

Bold values indicate statistical significance of *P* values.

infection.[2-4,7] Perrin et al[16] reported that many acute COVID-19 patients developed chronic fatigue as a part of "post-COVID-19 syndrome". Hives et al[17] showed that pro-inflammatory molecules (interferon gamma, interleukins, etc) are related to chronic fatigue syndrome. Similar molecules may also play a role in postacute COVID-19 fatigue.

In a recently metadata analysis, an ongoing adaptation to COVID-19 evolution showed statistically higher virulence and/or

viral infectivity.[18] This analysis showed that we will continue to fight both with COVID-19 and long-term consequences. It is necessary to develop quick therapeutics that inhibit this infection; also, vaccination of people could control the COVID-19 outbreak.[19]

4.1 | Limitations

The study included patients who were admitted to PMR clinic with at least one musculoskeletal symptom: for this reason, our results cannot be generalised to all postacute COVID-19 patients. Another limitation of our study was the lack of the antibiotic and glucocorticoid intake, invasive ventilation records and laboratory records in postacute period. Further studies are needed to determine the frequency of musculoskeletal symptoms after COVID-19 in the general population.

5 | CONCLUSION

The present study showed that musculoskeletal symptoms were more frequent than respiratory tract symptoms in postacute COVID-19 patients. Specialists in the musculoskeletal field should be a part of multidisciplinary teams. The most frequent symptom on admission to the PMR outpatient clinic was back pain and the most common musculoskeletal symptoms were fatigue, spine pain and myalgia. Each of these was present in more than three-fifths of postacute COVID-19 patients. Furthermore, the presence of back pain, lower lymphocyte and higher D-dimer levels, the presence of COVID-19 findings in chest CT during an acute COVID-19 infection, a longer hospitalisation and having chronic diseases all seem to contribute to post-COVID-19 musculoskeletal symptoms.

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