Musculoskeletal symptoms and relationship with laboratory findings in patients with COVID-19

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Abstract
Aim: To investigate the frequency of fatigue and musculoskeletal symptoms and their correlation with laboratory data in patients with COVID-19.

Methods: This study included 80 patients hospitalised and treated for COVID-19 in the infectious diseases clinic between March 2020 and May 2020. Data analysis was performed retrospectively from the hospital medical charts. Demographic data, clinical symptoms, and laboratory findings were noted. Clinical symptoms and correlations with laboratory results were assessed. Besides, an analysis of patients with and without chronic disease was performed for clinical symptoms and laboratory findings.

Results: The frequencies of myalgia and fatigue were 46.1% and 50%, respectively. In the laboratory data, there was a significant increase in creatinine kinase (CK) level and lymphocyte count in the patients with myalgia symptoms (P < .05). There were no other significant results in the laboratory data. Of the patients with chronic disease, it has been shown that hemoglobin levels were significantly decreased (P < .05), while D-dimer was markedly increased (P < .05).

Conclusion: The laboratory findings of COVID-19-related myalgia suggested that patients might have a risk of progressive muscle injury. Therefore, these patients should also be followed up in terms of the myopathic process.

What’s known
• It is known that myalgia and fatigue are most common complaints in COVID-19.
• However, the prevalence of these symptoms has not been systematically evaluated in the literature.
• In addition to this, there is no data evaluating its relationship with laboratory findings.

What’s new
• This article is the first study that evaluated the musculoskeletal symptoms and relationship with laboratory results.
• Our clinical and laboratory results confirmed that COVID-19 related myalgia patients might have a risk of progressive muscle injury.
1 | INTRODUCTION

The new coronavirus (COVID-19), which causes severe pneumonia, was first identified in Wuhan, China, in January 2020. The virus spread rapidly worldwide and became a pandemic and created a serious health problem.\(^1\) Infection is spread by the droplet inhalation of coughs and sneezes of symptomatic or asymptomatic individuals, or after nasal, eye-mouth contact with dirty hands, or faecal-oral transmission. Patients may be infectious during the symptomatic period, or even the asymptomatic patients may spread the virus.\(^2\) The initial symptoms are mainly fever, cough, dyspnea, myalgia, and fatigue. Besides, there may be symptoms such as loss of taste and smell, diarrhoea, and headache. While mild symptoms are observed in most of the COVID-19 patients, the disease is more severe, especially in patients with advanced age and chronic diseases such as hypertension, diabetes, asthma, chronic obstructive pulmonary disease, and malignancy.\(^3\) Intensive care support is required for at least one in five of the patients. The mortality rate was reported to be 13.9% in patients receiving intensive care support in a recent meta-analysis.\(^7\) As of November 2020, there have been 57,882,183 confirmed cases of COVID-19, including 1,377,395 deaths reported by WHO.\(^5\) The inflammatory mediator cascade causes influenza-like symptoms of the disease. Plasma IL-6 and TNF-alpha levels were found to be associated with viral replication in the presence of fever, upper respiratory symptoms, and musculoskeletal complaints.\(^6,7\)

Myalgia and fatigue are one of the most common symptoms at the onset of the disease, which occurs as a result of IL-6 upregulation.\(^8,9\) A study related to pain in COVID-19 infection demonstrated that myalgia symptoms indicated the general inflammation and cytokine response in the disease.\(^10\) Although fatigue and myalgia are common symptoms of COVID-19, data on their prevalence are not yet precise.\(^11,13\) Besides, as far as we know, there is currently no study examining the relationship between musculoskeletal symptoms and laboratory data. In our study, we aimed to investigate the frequency of fatigue and musculoskeletal symptoms and their correlation with laboratory data in patients treated with COVID-19 infection in our hospital.

2 | PATIENTS AND METHODS

Before the study, 250 patients were screened. Of these, 110 patients had incomplete data and 60 patients did not meet the inclusion criteria. In total 80 patients diagnosed with COVID-19 and hospitalised between March 2020 and May 2020 were included in this study. The data were obtained retrospectively from the hospital records. The patients were called by phone and the data were provided, in case of missing data. Patients’ demographic characteristics, symptoms, and laboratory results were noted. The frequency of symptoms and correlation with the laboratory data were examined. Before the study, approval was obtained from the institutional review board (No:2020/16) and the General Directorate of Health Services of the Republic of Turkey (No: 2020-06-16T10-26-57).

Criteria for inclusion in the study; Adult patients over 18 years of age, who meet the diagnosis and treatment criteria\(^14\) defined for COVID-19 mentioned below: (a) clinical signs such as fever, fatigue, dry cough, dyspnea, and pneumonia findings in imaging, (b) the history of travel to the risky regions 14 days before symptoms start, (c) the history of close contact with the sick people, (d) the confirmation of diagnosis by the nucleic acid real time-polymerase chain reaction (RT-PCR) test. All patients’ chronic diseases such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, malignancy that may cause comorbidity were noted. Furthermore, the patients were divided into two groups according to the presence or absence of comorbidity, and their symptoms and correlations with laboratory findings were also examined.

2.1 | Statistical analysis

All statistical analyses were performed with IBM SPSS Version 22. Descriptive statistics for numerical variables are presented as mean ± standard deviation, and statistics for categorical variables are presented as frequency (n) and percentage (%). Relationships between laboratory findings and myalgia and fatigue were performed at the level of 2 × 2 cross-table, with Yates continuity corrected chi-square test and Fisher’s exact test, and at 2 × 3 cross-table level, with Exact test. \(P < .05\) was considered statistically significant.

3 | RESULTS

Of the 80 cases included in the study, 31 (38.8%) were female and 49 (61.1%) were male. The average age was 44.93 ± 15.55 (18-79) and the most common symptoms were cough (61.3%), fatigue (50%), myalgia (46.3%), and fever (37.5%), respectively. Lung involvement was present in 38.8% of the patients. Hypertension (26.2%), diabetes (21.4%), and asthma (21.4%) were the most common accompanying comorbid diseases. Other demographic data of the patients are summarised in Table 1.

When the laboratory data of the patients were examined, white blood cell count was normal in 77.5%. However, neutrophil, lymphocyte, and platelet counts were decreased in 11.3%, 12.5%, and 16.3% of the patients, respectively. High levels of neutrophil, lymphocyte, and platelet counts were 16.3%, 21.3%, and 2%, respectively. The C-reactive protein was high in 48.8% of patients, while the d-Dimer value was high in 40% of patients. Data on other laboratory data are given in Table 2.
The lymphocyte count of patients with myalgia symptoms was significantly higher than those without myalgia symptoms ($\chi^2 = 9.368, P = .008$). Similarly, creatine kinase levels in patients with myalgia symptoms were significantly higher than those without myalgia ($\chi^2 = 14.424, P < .001$). No statistically significant relationship was found between other laboratory findings and myalgia symptoms ($P > .05$) (Table 3).

When the laboratory data of patients with and without comorbidity were compared, a statistically significant difference was found in hemoglobin, D-Dimer, and ferritin levels ($P < .05$) (Table 4). There were no differences in myalgia and fatigue symptoms between the groups ($P$ values for myalgia and fatigue were .249 and .999, respectively).

## DISCUSSION

In this study, we found a 46.3% frequency for myalgia, which was one of the most common complaints in patients hospitalised for COVID-19. This result was in line with some studies in the literature.\textsuperscript{15-17} In these studies myalgia frequencies were 52%, 55%, and 42%, respectively. We found fatigue frequency, which was also one of the most common symptoms, as 50% in our study. This rate was the same as in the study by Chen et al in the literature.\textsuperscript{18} However, currently, the frequency of myalgia and other symptoms in the COVID-19 positive patients were variable in the literature. The

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### Table 1: Demographic, clinical, and treatment characteristics of patients diagnosed with COVID-19

| Characteristics                  | Results (n = 80) |
|----------------------------------|-----------------|
| Age (y), mean ± SD (min-max)     | 44.93 ± 15.55 (18-79) |
| Gender, n (%)                    |                 |
| Female                           | 31 (38.8)       |
| Male                             | 49 (61.2)       |
| Symptoms, n (%)                  |                 |
| Cough                            | 49 (61.3)       |
| Fever                            | 30 (37.5)       |
| Sore throat                      | 19 (23.8)       |
| Dyspnea                          | 16 (20)         |
| Myalgia                          | 37 (46.3)       |
| Fatigue                          | 40 (50)         |
| Headache                         | 11 (13.8)       |
| Diarrhoea                        | 4 (5)           |
| Loss of taste                    | 5 (6.3)         |
| Loss of smell                    | 3 (3.8)         |
| Additional Disease, n (%)        | 28 (35)         |
| Hypertension                     | 11 (26.2)       |
| Diabetes                         | 9 (21.4)        |
| Asthma                           | 9 (21.4)        |
| Cardiovascular diseases          | 5 (11.9)        |
| COPD                             | 4 (9.5)         |
| Rheumatic disease                | 2 (4.8)         |
| Malignancy                       | 1 (2.4)         |
| Chronic renal failure            | 1 (2.4)         |
| Lung Involvement, n (%)          |                 |
| Unilateral                       | 14 (17.5)       |
| Bilateral                        | 31 (38.8)       |
| No                               | 35 (43.7)       |
| Treatment, n (%)                 |                 |
| Hydroxychloroquine               | 23 (28.8)       |
| Hydroxychloroquine + antiviral   | 10 (12.5)       |
| Hydroxychloroquine + antiviral + antibiotic | 39 (48.8) |
| Hydroxychloroquine + antiviral + antibiotic + corticosteroid | 4 (5) |
| Hydroxychloroquine + antibiotic  | 4 (5)           |
| Hospitalisation Status, n (%)    |                 |
| Discharged                       | 80 (100)        |
| Hospitalisation days, mean ± SD (min-max) | 8.10 ± 3.92 (1-30) |

Note: Data were presented as mean ± SD (min-max) and frequency (n) in percent (%).

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

### Table 2: Laboratory findings of patients diagnosed with COVID-19

| Laboratory findings (Normal range) | Finding levels [n (%)]* |
|------------------------------------|------------------------|
| White blood cell (3.5-10.5 K/µL)   | Normal (32 (77.5)), High (15 (18.8)), Low (3 (3.8)) |
| Neutrophil count (1.7-7 K/µL)     | Normal (58 (72.5)), High (13 (16.3)), Low (9 (11.3)) |
| Lymphocyte count (0.90-2.90 K/µL) | Normal (53 (66.3)), High (17 (21.3)), Low (10 (12.5)) |
| Hemoglobin (12-15.5 g/dL)         | Normal (60 (75)), Low (20 (25)) |
| Platelet (150-450 K/µL)           | Normal (65 (81.3)), High (2 (2.5)), Low (13 (16.3)) |
| Creatine kinase (30-145 U/L)      | Normal (67 (83.8)), High (10 (12.5)), Low (3 (3.8)) |
| C-reactive protein (0-8 mg/L)     | Normal (41 (51.3)), High (39 (48.8)) |
| D-dimer (0-500 ng/mL)             | Normal (48 (60)), High (32 (40)) |
| Prothrombin time (0.8-1.2 INR)    | Normal (76 (95)), High (1 (1.3)), Low (3 (3.8)) |
| Procalcitonin (0-0.5 µg/L)        | Normal (79 (98.8)), High (1 (1.3)) |
| Aspartate aminotransaminase (0-55 U/L) | Normal (76 (95)), High (4 (5)) |
| Alanine aminotransaminase (0-55 U/L) | Normal (67 (83.8)), High (13 (16.3)) |
| Lactate dehydrogenase (125-243 U/L) | Normal (46 (57.5)), High (33 (41.3)), Low (1 (1.3)) |
| Ferritin (11-306 ng/mL)           | Normal (58 (72.5)), High (8 (10)), Low (14 (17.5)) |

*Data were presented in frequency (n) as percentages (%).
### TABLE 3  
Comparison of laboratory findings with symptoms of myalgia and fatigue

| Laboratory findings          | Myalgia              | Fatigue              |   |
|------------------------------|----------------------|----------------------|---|
|                              | Positive (n = 37)    | Negative (n = 43)    | P  |
| White blood cell             |                      |                      | .118 |
| Normal (3.5-10.5 K/µL)       | 26 (70.3)            | 36 (83.7)            | .118 |
| High                         | 8 (21.6)             | 7 (16.3)             | 0.051 |
| Low                          | 3 (8.1)              | 0 (0)                | 0.051 |
| Neutrophil count             |                      |                      | .627 |
| Normal (1.7-7 K/µL)          | 25 (67.6)            | 33 (76.7)            | .298 |
| High                         | 7 (18.9)             | 6 (14)               | .556 |
| Low                          | 5 (13.5)             | 4 (9.3)              | .556 |
| Lymphocyte count             |                      |                      | .008* |
| Normal (0.90-2.90 K/µL)      | 18 (48.6)            | 35 (81.4)            | .556 |
| High                         | 12 (32.4)            | 5 (11.6)             | .556 |
| Low                          | 7 (18.9)             | 3 (7)                | .556 |
| Hemoglobin                   |                      |                      | .999 |
| Normal (12-15.5 g/dL)        | 28 (75.7)            | 32 (74.4)            | .796 |
| Low                          | 9 (24.3)             | 11 (25.6)            | .796 |
| Platelet count               |                      |                      | .617 |
| Normal (150-450 K/µL)        | 30 (81.1)            | 35 (81.4)            | .063 |
| High                         | 0 (0)                | 2 (4.7)              | .063 |
| Low                          | 7 (18.9)             | 6 (14)               | .063 |
| Creatine kinase              |                      |                      | <.001* |
| Normal (30-145 U/L)          | 26 (70.3)            | 41 (95.3)            | .085 |
| High                         | 10 (27)              | 0 (0)                | .085 |
| Low                          | 1 (2.7)              | 2 (4.7)              | .085 |
| C-reactive protein           |                      |                      | .836 |
| Normal (0-8 mg/L)            | 18 (48.6)            | 23 (53.5)            | .999 |
| High                         | 19 (51.4)            | 20 (46.5)            | .999 |
| D-dimer                      |                      |                      | .436 |
| Normal (0-500 ng/mL)         | 20 (54.1)            | 28 (65.1)            | .819 |
| High                         | 17 (45.9)            | 15 (34.9)            | .819 |
| Prothrombin time             |                      |                      | .779 |
| Normal (0.8-1.2 INR)         | 35 (94.6)            | 41 (95.3)            | .999 |
| High                         | 0 (0)                | 1 (2.3)              | .999 |
| Low                          | 2 (5.4)              | 1 (2.3)              | .999 |
| Procalcitonin                |                      |                      | .463 |
| Normal (0-0.5 µg/L)          | 36 (97.3)            | 43 (100)             | .999 |
| High                         | 1 (2.7)              | 0 (0)                | .999 |
| Aspartate aminotransaminase  |                      |                      | .331 |
| Normal (0-55 U/L)            | 34 (91.9)            | 42 (97.7)            | .116 |
| High                         | 3 (8.1)              | 1 (2.3)              | .116 |
| Alanine aminotransaminase    |                      |                      | .366 |
| Normal (0-55 U/L)            | 29 (78.4)            | 38 (88.4)            | .069 |
| High                         | 8 (21.6)             | 5 (11.6)             | .069 |
| Lactate dehydrogenase        |                      |                      | .650 |

(Continues)
Fatigue and elevated CK is closely related to the intensity of striated muscle damage. As it is well known, CK is released into the blood in cases where the striped muscle cells are damaged and membrane integrity changes. As a result, elevated CK is closely related to the intensity of striated muscle damage. In a study, it was reported that myalgia with elevated CK is common in both moderate and severe cases and may cause a real myopathic injury. The cause of myalgia in COVID-19 may be because of muscle damage caused by the action of released cytokines. Kaiser et al and Misra et al reported that plasma levels of IL-6 and TNF-alpha released during COVID-19 infection may cause musculoskeletal symptoms. Apart from this, in another study conducted in China, the most emphasised cytokine was IL-6, and it was stated that it might be responsible for the cytokine storm that can be seen during the course of the disease. Since there was no kit for IL-6, we did not evaluate the IL-6 levels in this study and can be assessed in future studies.

Our study suggested that hemoglobin values were lower in the group of patients with chronic diseases than those without chronic diseases and d-Dimer values were higher in the chronic diseases group. This finding was in the same line with a study in the literature, and attention has been drawn to the elevated value of d-Dimer and low hemoglobin in patients with chronic disease. The reason for this may be that these patients are at a more advanced age and are prone to coagulation caused by their additional diseases. In this study, ferritin levels were also evaluated and it was observed that ferritin levels were not normal in the group with chronic conditions. However, since the number of patients was not sufficient, we could not make definitive judgements about ferritin levels. In our study, we did not find any difference between patients with and without chronic disease in terms of symptoms.

### LIMITATIONS OF THE STUDY

In this study, patients who received intensive care support were not evaluated. Examination of the musculoskeletal symptoms and laboratory relationships of these patients may be the subject of future studies. The sample size of our research is one of the limitations in terms of the generalisation of the results. Further studies with the participation of more patients are needed. Besides, since there was no kit support in our research, we could not evaluate the relationship between IL-6 level and myalgia, which was determined to be associated with musculoskeletal symptoms.

### TABLE 3 (Continued)

| Laboratory findings | Myalgia | Fatigue |
|---------------------|---------|---------|
|                     | Positive (n = 37) | Negative (n = 43) | P | Positive (n = 40) | Negative (n = 40) | P |
| Normal (125-243 U/L) | 20 (54.1) | 26 (60.5) | 20 (50) | 26 (65) | .326 | .715 |
| High                | 16 (43.2) | 17 (39.5) | 20 (50) | 13 (32.5) | 0 (0) | 1 (2.5) |
| Low                 | 1 (2.7)   | 0 (0)     | 0 (0)   | 1 (2.5)  | .715 | .715 |
| Ferritin            |          |          |        |        |      |      |
| Normal (11-306 ng/mL) | 25 (67.6) | 33 (76.7) | 29 (72.5) | 29 (72.5) | .715 | .715 |
| High                | 3 (8.1)   | 5 (11.6)  | 3 (7.5)  | 5 (12.5) | 0 (0) | 1 (2.5) |
| Low                 | 9 (24.3)  | 5 (11.6)  | 8 (20)   | 6 (15)   | .715 | .715 |

Note: Data were presented in frequency (n) as percentages (%).

*P < .05 is statistically significant.
In our study, we showed that COVID-19 caused a high rate of myalgia and additionally caused CK elevation in the laboratory. The increase of CK in these patients should be a caution about muscle damage and extremely higher values may indicate the progressive myopathic process.

DISCLOSURE

The authors report no conflicts of interest.

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