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Orijinal Araştırma / Original Article

Relationship Between Myalgia and Laboratory Parameters in Hospitalized Patients with COVID-19

COVID-19 Tanılı Hospitalize Hastalarda Miyalji ve Laboratuvar Parametreleri Arasındaki İlişki

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Abstract

Aim: Myalgia is among the first and most common symptoms in patients with COVID-19. A limited number of studies have been found evaluating the frequency of myalgia and the laboratory findings associated with this condition. In this study, we aimed to evaluate the prevalence of myalgia and the relationship between myalgia and laboratory parameters in patients who were hospitalized due to COVID-19.

Material and Method: Three hundred fifty-eight patients with confirmed diagnoses of COVID-19 who were hospitalized between March 2020 and January 2021 were included in the study. The patients were divided into two groups according to the presence and absence of myalgia. Demographic characteristics, medical history, symptoms, clinical findings, and laboratory findings were evaluated retrospectively.

Results: A total of 358 patients, 192 (42.9%) females and 166 males, were included in the study. The mean age of the patients was 60.3±15.2 years. When the laboratory findings of the 166 patients with myalgia and 192 patients with no myalgia were compared, no difference was found between the groups in terms of white blood cell, neutrophil, lymphocyte, monocyte, and platelet counts, C-reactive protein, ferritin D-dimer, and troponin levels. However, creatine kinase (CK) levels were found to be significantly higher in the group with myalgia compared with the group without myalgia ($p<0.001$). In 92 (25.6%) of 358 patients, the CK level was found to be higher than 200 U/L. The median value for CK was 55 U/L in the group without myalgia and 221 U/L in the group with myalgia.

Conclusion: Myalgia is one of the most common symptoms in COVID-19. In patients with myalgia, the CK level is higher than in patients without myalgia. These patients should be closely monitored in terms of the risk of rhabdomyolysis because high CK is an indicator of muscle damage.

Keywords: COVID-19, myalgia, creatine kinase, rhabdomyolysis

Öz

Amaç: COVID-19 hastalarında miyalji ilk ve en yaygın semptomlar arasında yer almaktadır. Miyalji sıklığını ve bu durumla ilişkili laboratuar bulgularını değerlendiren sınırlı sayıda çalışmaya rastlanılmıştır. Bu çalışmada hastalığı daha şiddetli olması sebebiyle hospitalize takip edilen hastalarda miyalji sıklığını ve miyalji ile laboratuar parametreleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya Mart 2020- Ocak 2021 tarihleri arasında hastanede yatırılarak takip edilen COVID-19 tanısı doğrulanmış 358 hasta dahil edilmiştir. Miyalji varlığı ve yokluğuna göre hastalar 2 gruba ayrılmıştır. Demografik özellikler, tıbbi geçmiş, semptomlar, klinik bulgular ve laboratuvar bulguları retrospektif olarak değerlendirildi.

Bulgular: Bu çalışmaya 192'si (% 42,9) kadın, 166'sı erkek olmak üzere toplam 358 hasta dahil edildi. Hastaların yaş ortalaması 60,3±15,2 idi. Miyalji tarifleyen 166 hasta ve tariflemeyen 192 hastanın laboratuar bulguları karşılaştırıldığında, white blood cell (WBC), neutrophil, lymphocyte, monocyte, platelet değerleri, C reactive protein (CRP), ferritin D-dimer, troponin düzeyleri arasında gruplar arası fark saptanmadı. Ancak miyalji olan grupta olmayan gruba göre creatine kinase (CK) düzeyleri anlamlı yüksek saptandı ($p<0.001$). 358 hastanın 92'sinde (%25,6) CK düzeyi 200 U/L 'den yüksek saptanmıştır. CK için ortanca değer miyaljisi olmayan grupta 55 U/L iken miyaljisi olan grupta 221 U/L olarak elde edilmiştir.

Sonuç: COVID-19'da miyalji en sık gözlenen bulgulardan biridir. Miyalji tarifleyen hastalarda CK düzeyi miyalji olmayan hastalara göre yüksektir. CK yüksekliği kas hasarı göstergesi olduğundan bu hastalar rabdomiyoliz riski açısından yakın izlenmelidir.

Anahtar Kelimeler: COVID-19, kreatin kinaz, miyalji, rabdomiyoliz

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INTRODUCTION

The infection that was first detected in December 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was named coronavirus 2019 (COVID-19) by the World Health Organization (WHO) and declared a pandemic. As of April 2021, COVID-19 has infected more than 153.1 million people in 216 countries and killed more than 3.2 million people worldwide.[1]

The clinical manifestations of patients infected with COVID-19 range from mild symptoms to severe pneumonia and multiorgan failure. Although COVID-19 specifically targets the respiratory system, neurologic symptoms may also frequently accompany.[2] These include central nervous system involvement such as encephalitis, acute disseminated encephalomyelitis (ADEM), encephalopathy, steroid-sensitive encephalopathy, posterior reversible encephalopathy syndrome (PRES), and meningitis, as well as peripheral findings such as hyposmia/agusia, ophthalmoparesis, facial paresis, and Guillain-Barre syndrome. Neuromuscular findings such as neuropathy, critical illness myopathy, myalgia, myositis, and rhabdomyolysis have also been described.[3]

Myalgia, in particular, may be among the first and most common symptoms. In a meta-analysis evaluating 1995 patients with COVID-19 from 10 countries, the prevalence of myalgia was found as 35.8%.[4] The presence and severity of myalgia can adversely affect activities of daily living and prevent patients from maintaining their quality of life during the illness.[5] In addition, studies are showing that the presence of myalgia is closely related to disease severity and respiratory distress.[6,7] A limited number of studies have been found evaluating the frequency of myalgia and the laboratory findings associated with this condition.

In this study, we aimed to evaluate the prevalence of myalgia and the relationship between myalgia and laboratory parameters in hospitalized patients.

MATERIAL AND METHOD

This study was a single-center retrospective study, and patients with confirmed COVID-19 diagnoses who were hospitalized between March 2020 and January 2021 were included. It was planned to include 400 patients in the study, but 358 patients were included in the study; 42 patients were excluded because they did not meet the inclusion criteria. The patients were divided into two groups according to the presence and absence of myalgia. All patients with COVID-19 in this study were diagnosed according to the WHO guideline.[8] The inclusion criteria were as follows: age over 18 years, positive SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (rRT-PCR) in a nasopharyngeal swab, lung tomography compatible with viral pneumonia, and hospitalization. Patients with a history of malignancy, a history of rheumatologic disease, and patients transferred to the intensive care unit (ICU) due to the need for intensive care were not included in the study.

Demographic characteristics, medical history, comorbid diseases, initial symptoms, clinical, laboratory, and imaging findings of hospitalized patients were evaluated retrospectively from electronic medical records. Approval was obtained from the Local Ethics Committee (Protocol No: 2021-026) and the Ministry of Health for this study.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for the Social Sciences V23 software (SPSS Inc.; Chicago, IL, USA). Normal distribution of the laboratory values according to the presence of myalgia was examined using the Kolmogorov-Smirnov test. The difference between the groups was examined using the Mann-Whitney U test because the quantitative data did not show normal distribution. The Chi-square test was used to analyze categorical data. The independent samples t-test was used to compare the ages. Univariate and multivariate binary logistic regression analyses were used to determine the risk factors affecting the presence of myalgia. The cut-off values for creatine kinase (CK) values in diagnosing myalgia were analyzed using receiver operating characteristics (ROC) curve analysis. The level of significance was accepted as $p<0.05$.

RESULTS

A total of 358 patients, 192 (42.9%) females and 166 males, were included in the study. The mean age of the patients was 60.3±15.2 years. The most common presenting symptom was fatigue (n=176, 49.1%), followed by myalgia, cough, fever, shortness of breath, and headache. The most common comorbidity in patients was hypertension (HT) with 31.2%, followed by diabetes mellitus (DM) with 29.6%, and asthma with 9.5%. Of the patients, 42 (11.7%) were smokers (**Table 1**).

Patients were grouped according to the presence of myalgia. Demographic characteristics and laboratory findings of 166 patients with myalgia and 192 patients with no myalgia were compared. No difference was found between the groups in terms of age, gender and comorbid diseases (**Table 2**). No difference was found between the groups with and without myalgia in terms of steroid use during hospitalization ($p = 0.078$). All patients included in the study were discharged, and the mean hospital stay was 8.1±3.52 days.

When the groups were compared in terms of laboratory findings, no difference was found between the groups in terms of white blood cell (WBC), neutrophil, lymphocyte, monocyte, and platelet counts, C reactive protein (CRP), ferritin D-dimer, and troponin levels. However, creatine kinase (CK) levels were found to be significantly higher in the group with myalgia compared to the group without myalgia ($p<0.001$) (**Table 2**).

Table 1. Demographic and Clinical Features

Characteristics	Results (n=358)	
	Mean± SD	Median (min-max)
Age (years)	60.3±15.2	61 (20-88)
	n	%
Sex		
Male	192	53.6
Female	166	46.4
Symptom at admission		
Cough	130	36.3
Fever	104	29
Myalgia	166	46.3
Fatigue	176	49.1
Headache	70	19.5
Dyspnoea	80	22.3
Loss of taste and smell	30	8.3
Diarrhea	14	3.9
Comorbid diseases		
Hypertension	118	31.2
Diabetes mellitus	112	29.6
Asthma	36	9.5
Chronic obstructive pulmonary disease (COPD)	26	7.2
Cardiovascular diseases	28	7.8
Other Diseases	36	10.1
Smoking	42	11.7
Discharge from the hospital	358	100
Steroid treatment during hospitalization	278	77.6
Length of stay (days), mean±SD (min-max)	8.1± 3.52	4-29

*Significant at 0.05 level; Chi-square test for categorical variables, Student's t-test for age. Abbreviations: SD, standard deviation.

In 92 (25.6%) of 358 patients, the CK level was found to be higher than 200 U/L. In patients describing myalgia, this rate was 31.9% (53/166). The median value for CK was 55 U/L in the group without myalgia and 221 U/L in the group with myalgia. The cut-off value for CK was 123.5 U/L and the area under the ROC curve (AUC) was determined as 88.5%. According to the cut-off value of 123.5 U/L, the sensitivity was 85.4%, the specificity was 87.9%, the positive predictive value (PPV) was 89.1%, the negative predictive value (NPV) was 83.9%, and the correct classification rate was 86.6%. The ROC curve analysis is presented in **Figure 1**.

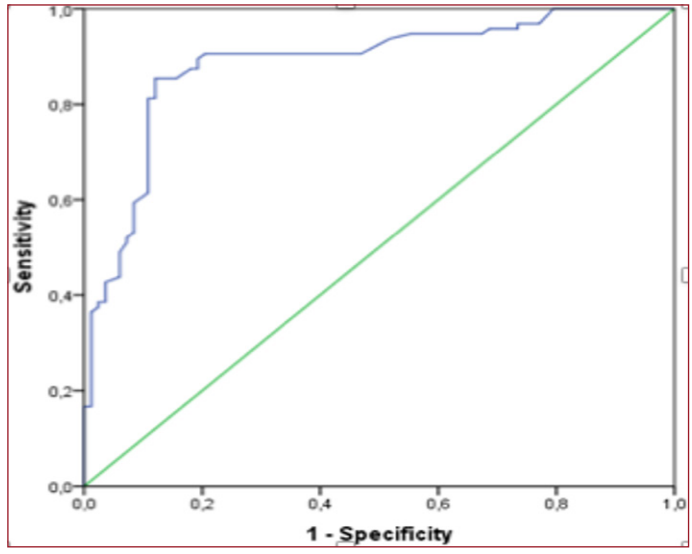

Figure 1. ROC curve analysis of CK value

Table 2. Comparison of demographic characteristics and laboratory parameters in the groups with and without myalgia

	With myalgia (n=166)		Without myalgia (n=192)		P
Age (Mean±SD)	60.4±14.8		60.3±15.7		0.960
Sex-Male, n (%)	104 (55.9)		110 (64)		0.302
Female	62 (36)		82 (44.1)		
Comorbid disease					
Hypertension	44 (26.5)		74 (38.5)		0.088
Diabetes mellitus	60 (36.1)		52 (27.1)		0.192
Asthma	20 (12)		16 (8.3)		0.243
Chronic obstructive pulmonary disease (COPD)	12 (7.2)		14 (7.3)		0.999
Cardiovascular diseases	14 (8.4)		12 (6.3)		0.785
Other Diseases	15 (9)		21 (10.9)		0.656
Smoking	20 (12)		22 (11.5)		0.862
Steroid treatment during hospitalization	122 (73.4)		156 (81.2)		0.078
Laboratory findings	**Mean±SD**	**Median (Min-Max)**	**Mean±SD**	**Median (Min-Max)**	
White blood cells, ×103/μL	7.8±3.1	6.8 (3.3 - 17.2)	7.5±3.3	6.7 (3.3 - 23.8)	0.379
Neutrophils, ×103/μL	5.7±3	4.9 (1.7 - 15.7)	5.4±2.9	4.4 (1.7 - 15.9)	0.456
Lymphocytes, ×103/μL	1.3±0.6	1.2 (0.3 - 2.8)	1.4±0.7	1.3 (0.3 - 5.6)	0.319
Monocytes, ×103/μL	0.9±2.9	0.5 (0.1 - 27)	1.5±6.8	0.5 (0.1 - 57)	0.706
Platelets ×103/μL	238.9±93.6	220 (97 -624)	239.9±88.5	212.5 (71 -581)	0.808
C-reactive protein (CRP), mg/L	91.8±119.6	56 (3.1 - 869)	65.3±59.3	49.5 (1.5 - 322)	0.292
Ferritin, ng/mL	322±304.6	197 (7.6-1500)	227±215.9	149 (7.6-1146)	0.061
D-dimer, ng/mL	1.4±4.1	0.4 (0.1-29.3)	0.9±2.7	0.3 (0 - 25.4)	0.115
Troponin, ng/mL	14.7±32.9	6.8 (1.3-255)	11.5±21.5	5.3 (0.4 - 175)	0.617
Creatine kinase (CK), U/L	77.6±80.9	55 (4 - 540)	364±459.8	221 (25 - 3550)	<0.001

*Significant at 0.05 level; Mann-Whitney U test for numerical variables; SD, standard deviation

Risk factors affecting the presence of myalgia were determined as a result of univariate analysis (**Table 3**). According to the analysis, the increase in the CK value indicated the presence of myalgia (p<0.001). No other variables were determined as risk factors (p>0.05). In multivariate analysis, the increase in CK value increased the presence of myalgia 1.016 times (p<0.001). No other variables were identified as risk factors for the presence of myalgia (**Table 3**).

DISCUSSION

In this study, among 358 patients who were hospitalized over a 10-month period and whose diagnoses of COVID-19 were confirmed clinically, and whose laboratory tests were evaluated, the frequency of myalgia was found as 46.3% (166/358). When the literature was reviewed, the prevalence of myalgia was found as 37.5% in a study in which 294 hospitalized patients with COVID-19 were evaluated,[9] and the prevalence of myalgia was found as 59% in a study examining the data of 417 patients with COVID-19 from 12 European hospitals.[10] In a study on the function of smell and taste in patients with COVID-19, myalgia was found in more than 50% of the patients.[11] The rate found in our study was similar to the literature consisting of large case series.

In a study conducted on 1420 European patients with COVID-19, myalgia was found at a higher rate in older patients compared with younger patients with prominent ear, nose, and throat symptoms.[12] However, when the groups with and without myalgia were compared in our study, no difference was found in terms of age.

The mechanism of muscle-joint pain in viral diseases has not yet been revealed, and when the possible myalgia mechanisms due to COVID-19 are evaluated, the angiotensin-converting enzyme 2 (ACE2) receptor used by the virus to enter the cell has been highlighted. It is thought that SARS-coV-2 may cause skeletal muscle damage via ACE2 receptors in muscles or due to proinflammatory cytokine increase.[13,14] It is thought that interferon (IFN)-γ, interleukin (IL)-1β, IL-6, IL-17, and tumor necrosis factor (TNF)-α, which are known to be elevated in patients with COVID-19, can directly induce muscle fiber proteolysis and decrease protein synthesis.[15] Satellite cells, thought to be important in the recovery process of COVID-19, are progenitor cells that directly contribute to muscle fiber growth. It is thought that IL-1β and TNF-α can inhibit the proliferation and differentiation of these cells, and IL-1β and IL-6 can induce muscle fibroblast activity and lead to fibrosis.[16,17]

There are a limited number of studies evaluating musculoskeletal symptoms and parameters related to infection and inflammation. In a meta-analysis performed by Cipollaro et al.[18] it was recommended to evaluate the relationship between musculoskeletal symptoms and inflammatory and infection-related parameters (IL-6, C-reactive protein) and laboratory findings. In a study evaluating laboratory parameters associated with myalgia and fatigue in patients with COVID-19, a higher lymphocyte count was observed in the group with myalgia compared with those without myalgia.[19] In our study, however, no difference was found between the groups with and without myalgia in terms of inflammatory parameters such as white blood cell counts, lymphocyte and neutrophil counts, and C-reactive protein.

Table 3. Logistic regression analysis results of risk factors affecting the presence of myalgia

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.999 (0.98 - 1.019)	0.959	0.968 (0.929 - 1.008)	0.115
Sex, Female	2.250 (1.234 - 4.1059)	0.088	1.064 (0.369 - 3.066)	0.908
Sex, Male	1.476 (0.769 - 2.833)	0.242	1.964 (0.655 - 5.894)	0.229
Comorbid disease	1.007 (0.553 - 1.836)	0.981	0.449 (0.09 - 2.228)	0.327
Diabetes mellitus	0.656 (0.348 - 1.238)	0.193	0.863 (0.263 - 2.83)	0.808
Hypertension	1.739 (0.919 - 3.29)	0.089	3.849 (1.081 - 13.7)	0.057
Cardiovascular diseases	1.009 (0.325 - 3.132)	0.987	0.56 (0.094 - 3.349)	0.525
Asthma	0.724 (0.233 - 2.246)	0.576	0.907 (0.132 - 6.248)	0.921
COPD	1.182 (0.654 - 2.138)	0.580	0.53 (0.185 - 1.52)	0.238
Other additional diseases	1.269 (0.606 - 2.659)	0.527	1.251 (0.336 - 4.655)	0.738
White blood cell, $\times10^3/\mu L$	0.971 (0.886 - 1.064)	0.530	0.904 (0.594 - 1.376)	0.638
Neutrophil, $\times10^3/\mu L$	0.963 (0.871 - 1.065)	0.465	1.106 (0.687 - 1.783)	0.678
Lymphocyte , $\times10^3/\mu L$	1.278 (0.782 - 2.09)	0.328	0.757 (0.225 - 2.548)	0.653
Monocyte, $\times10^3/\mu L$	1.028 (0.959 - 1.101)	0.435	1.029 (0.874 - 1.211)	0.735
Platelet $\times10^3/\mu L$	1 (0.997 - 1.003)	0.941	0.998 (0.993 - 1.004)	0.561
CRP, mg/L	0.996 (0.992 - 1)	0.073	0.995 (0.987 - 1.003)	0.232
Ferritin, ng/mL	0.999 (0.997 - 1)	0.021	0.999 (0.997 - 1.001)	0.283
D-dimer, ng/ml	0.952 (0.863 - 1.05)	0.326	1.008 (0.898 - 1.133)	0.888
Troponin, ng/mL	0.996 (0.984 - 1.007)	0.441	0.998 (0.976 - 1.021)	0.887
Creatine kinase (CK), U/L	1.016 (1.011 - 1.021)	<0.001	1.016 (1.011 - 1.022)	<0.001

* Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; SD, standard deviation.

If striated muscle cells are damaged and membrane integrity changes, CK begins to rise in the blood after about 2-12 hours and decreases to baseline values within 3-5 days. In conclusion, high CK is closely related to the intensity of striated muscle damage.[20] In studies, an increase in CK levels has been reported, varying between 9.6% and 27%.[21,22] In our study, the CK level was found to be higher than 200 U/L in 92 (25.6%) of 358 patients. This rate was found to be 31.9% in patients describing myalgia. The high percentage of CK in our study can be explained by the inclusion of hospitalized patients with a more severe course, similar to the study of Pitscheider et al.[22] It was reported that patients with COVID-19 with very high CK levels developed rhabdomyolysis following viral myositis.[23] Patients with rhabdomyolysis can present with elevated CK levels without myalgia and typical COVID-19 symptoms. Although very high CK levels were detected in only three patients in our study, a rapid decrease was observed in the follow-up and renal functions remained within normal limits. Careful monitoring of kidney functions and muscle enzymes in SARS-CoV-2 infection, and closer follow-up of patients with myalgia and high CK for the development of rhabdomyolysis have been recommended.[23]

In another study involving 161 adults with COVID-19, 17 patients had CK levels higher than 190 U/L and 18 had myalgia. However, no association was found between CK levels and myalgia.[24] In another study investigating the relationship between myalgia and CK levels in patients with COVID-19, a significant relationship was found between high CK results and myalgia in 140 of 239 patients.[25] In our study, the median value for CK was 55 U/L in patients without myalgia and 221 U/L in patients with myalgia, and a significant increase was found in CK values in patients with myalgia symptoms compared with patients without myalgia symptoms. The cut-off value for CK was 123.5 U/L, with a sensitivity of 85.4% and a specificity of 87.9%.

The presence of muscle-joint pain has been associated with the severity of the disease. In one study, increased CK was observed in 40% of severely affected patients (for example, those admitted to the ICU) and only 24% of patients with mild disease.[26] In another study, it was reported that CK was higher in patients with abnormal findings on lung imaging.[26] It has been stated that CK can indicate the severity of the disease, but it is not a prognostic indicator. No comment can be made on this issue because patients who were followed in the ICU or transferred to the ICU during the follow-up were not included in our study.

It is known that corticosteroids used in the treatment of COVID-19 affect the musculoskeletal system negatively and it is recommended that patients who receive corticosteroid treatment should be monitored in terms of musculoskeletal symptoms.[27] There is no study in the literature searching the relation between steroid use and myalgia in patients with COVID-19. In our study, steroid use was evaluated in groups with and without myalgia. In our study, our patients were mostly followed up with moderate-to-severe pneumonia, so they were receiving corticosteroids. However, there was no difference between the groups with and without myalgia in terms of steroid use.

This study had some limitations such as being a single-center study, having a limited number of patients, being a retrospective study, not being able to perform advanced etiologic examinations such as electromyoneurography (ENMG) and muscle biopsy, not including patients in the ICU, and not being able to perform advanced laboratory investigations such as measuring IL levels. It is thought that more data are needed in this area to determine the contribution of processes involved in the pathogenesis of myalgia in patients with COVID-19, and multicenter clinical studies with a larger number of patients are needed.

CONCLUSION

Myalgia is one of the most common symptoms in COVID-19. The CK level in patients describing myalgia is higher than in patients without myalgia. These patients should be closely monitored in terms of the risk of rhabdomyolysis because high CK is an indicator of muscle damage. In addition, cohort studies focusing on the health of the musculoskeletal system of recovering patients will make an important contribution to more clearly determining the long-term consequences of this devastating disease..

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee (Protocol No: 2021-026) and the Ministry of Health for this study.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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