

Myalgia Frequency in Patients with COVID-19 and Its Relationship with Creatine Kinase Levels

COVID-19 Hastalarında Myalji Sıklığı ve Kreatin Kinaz Düzeyleri ile İlişkisi

Nimet UÇAROĞLU CAN

 0000-0003-1307-3578

Özgecan KAYA

 0000-0003-4328-8932

Dilcan KOTAN

 0000-0002-8624-6321

Sakarya University Faculty of
Medicine Department of Neurology,
Sakarya, Turkey

ABSTRACT

Aim: Many studies have showed that myalgia is a common onset symptom in coronavirus disease 2019 (COVID-19). This study aimed to determine the frequency of muscle pain in patients followed with COVID-19 diagnosis, and to investigate the relationship between muscle pain and creatine kinase (CK), pH, lactate and lactate dehydrogenase (LDH) levels.

Material and Methods: One hundred ten patients diagnosed with COVID-19 in our hospital were included retrospectively in this study. Presence of myalgia at the time of admission and on the 14th day of control were investigated. The first admission laboratory findings, 3rd day CK values and 14th day control CK values of all patients were recorded retrospectively from their files.

Results: The study included 110 patients diagnosed with COVID-19. Fifty patients (45.5%) had muscle pain at the time of admission, and it was one of the most common musculoskeletal complaints. High CK results were obtained in 48 (43.6%) of the 110 patients at the time of admission. Thirty-two (66.7%) of 48 patients with high CK had muscle pain ($p<0.001$). In the patients with muscle pain, the CK levels observed on 1st, 3rd, and 14th day of the disease were found to be significantly higher than in those without muscle pain ($p<0.001$, $p=0.003$, $p=0.029$). No significant relationship was found between complaints of muscle pain and lactate, pH, and LDH values.

Conclusion: Since some patients may only present with musculoskeletal symptoms such as myalgia, it is important that clinicians consider COVID-19 in patients presenting with myalgia and high CK levels.

Keywords: COVID-19; myalgia; creatine kinase.

ÖZ

Amaç: Birçok çalışma miyaljinin koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19)'da sık görülen bir başlangıç semptomu olduğunu göstermiştir. Bu çalışmada COVID-19 tanısıyla takip edilen hastalarda kas ağrısı sıklığının belirlenmesi ve kas ağrısı ile kreatin kinaz (creatine kinase, CK), pH, laktat ve laktat dehidrogenaz (LDH) düzeyleri arasındaki ilişkisinin araştırılması amaçlandı.

Gereç ve Yöntemler: Bu çalışmaya hastanemizde COVID-19 tanısı almış olan 110 hasta geriye dönük olarak dahil edildi. Başvuru sırasında ve 14. gün kontrolde miyalji yakınlığı olup olmadığı incelendi. Tüm hastaların ilk başvurudaki laboratuvar bulguları, 3. gün CK değerleri ve 14. gün kontrolündeki CK değerleri dosyalarından geriye dönük olarak kaydedildi.

Bulgular: COVID-19 tanısı almış 110 hasta çalışmaya alındı. Elli hastada (%45,5) başvuru anında kas ağrısı vardı ve en sık görülen kas iskelet sistemi şikâyetlerinden biriydi. Yüz on hastanın 48'inde (%43,6) başvuru anında CK yüksekliği saptandı. CK yüksekliği saptanan 48 hastanın 32'sinde (%66,7) kas ağrısı vardı ($p<0,001$). Kas ağrısı olan hastalarda 1., 3. ve 14. günde bakılan CK düzeyleri kas ağrısı şikâyeti olmayanlara göre anlamlı derecede yüksek bulundu ($p<0,001$; $p=0,003$; $p=0,029$). Kas ağrısı yakınlığı ile laktat, pH ve LDH değerleri arasında anlamlı ilişki bulunmadı.

Sonuç: Başvuru sırasında yalnızca miyalji gibi kas iskelet sistem semptomları bulunan hastalar olabileceğinden, miyalji ile başvuran ve CK yüksekliği saptanan hastalarda COVID-19'un akılda tutulması önem arz etmektedir.

Anahtar kelimeler: COVID-19; miyalji; kreatin kinaz.

Corresponding Author

Sorumlu Yazar

Nimet UÇAROĞLU CAN
nimetucaroglu37@hotmail.com

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by a new type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This coronavirus has genetic similarities with severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), which was responsible for the epidemic of severe acute respiratory syndrome (SARS) in 2003. SARS-CoV-2 first emerged in China in December 2019 and soon spread to the rest of the world. The most common symptoms in adults are fever, cough, fatigue, dyspnea, anorexia, diarrhea, and myalgia (1,2). Many studies have shown that myalgia is a common (36%) onset symptom in COVID-19 (3).

Similar to other types of coronavirus causing acute respiratory failure, the spike (S) proteins of SARS-CoV-2 bind to the angiotensin-converting enzyme 2 (ACE2) receptors, and proteolytic cleavage occurs via the serine protease transmembrane protease serine 2 (4-6). ACE2 receptors have been shown in the brain, kidney, vascular smooth muscle, and skeletal muscles (7,8). SARS-CoV-2 can spread through the bloodstream or vascular endothelium, causing infection in all ACE2 receptor-containing tissues, including the musculoskeletal system. SARS-CoV-2 can affect skeletal muscle cells by binding with ACE2 alone or with the proinflammatory cytokines interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor- α (TNF- α). Increased creatine kinase (CK) and lactate dehydrogenase (LDH) levels during COVID-19 infection are indicative of muscle involvement. As a result of cell damage, lactate levels increase (7), and the oxygen-carrying capacity of erythrocytes and the transport of oxygen to tissues are significantly reduced due to hyperlactatemia. The muscles, therefore, remain ischemic during the COVID-19 infection period (9). The expression of growth factors and inflammatory cytokines increases in the ischemic muscle tissue, and these endogenous substances cause excessive stimulation of the dorsal root ganglions. This stimulation is interpreted as pain by projection into the thalamus and cortex via ascending pathways (10). Myalgia is thought to reflect the systemic inflammation and cytokine response found in patients with COVID-19 (11). In addition, TNF- α is responsible for the intense fragmentation of muscle proteins by direct action (12). This can cause focal muscle fiber necrosis and diffuse muscle fiber atrophy, as previously demonstrated in studies of SARS-CoV-1 infection (13,14). Muscle pain that does not respond to classic analgesics decreases with a reduced viral load, decreased inflammation, and lower muscle lactate levels. This study aimed to determine the frequency of muscle pain in patients followed with a diagnosis of COVID-19 and to investigate the relationship between muscle pain and CK, pH, lactate, and LDH levels.

MATERIAL AND METHODS

In this retrospective single-center study, the medical records of patients diagnosed with COVID-19 between April and May 2020 in our hospital were screened retrospectively. In total, 110 patients with confirmed diagnosis of COVID-19 by reverse-transcription polymerase chain reaction (RT-PCR) assays from throat and nasal swab samples used for SARS-CoV-2 virus analysis and chest computed tomography findings were

included in the study. The demographic, clinical, and laboratory findings of the patients were recorded in their files. The patients were asked about the presence of myalgia at the time of admission and on the 14th day of control. The CK, LDH, lactate, and pH laboratory findings of all the patients were recorded on the 3rd day and again on the 14th day of control and reviewed retrospectively. CK values over 171 U/L are considered high in our laboratory. The relationship between myalgia and the laboratory parameters was examined. The study was carried out in accordance with the principles of the Declaration of Helsinki with the approval of the Ministry of Health following approval by the local ethics committee. The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (10.07.2020, 416).

Statistical Analysis

Kolmogorov-Smirnov test was used to evaluate whether the distribution of numerical variables was normal. Accordingly, Mann-Whitney U test was used to compare the numerical variables, and Chi-square test was used to compare the categorical variables between the groups. The numerical variables were presented as median, interquartile range, minimum-maximum, and categorical variables were presented as a count and percentage. A p-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics v.22.

RESULTS

The study included 110 patients (63 male, 47 female) who had been diagnosed with COVID-19. The mean age of the patients was 47.13 \pm 15.06 (range, 18-73) years. The demographic characteristics of the patients are shown in Table 1. Fifty (45.5%) patients had muscle pain at the time of admission, and it was one of the most common musculoskeletal complaints. On the 14th day, 12 (10.9%) patients had ongoing muscle pain. In our study, 5 (4.5%) patients had only myalgia at the time of admission. High CK results were obtained in 48 (43.6%) of the 110 patients at the time of admission. Thirty-two (66.7%) of these patients had muscle pain (p<0.001).

Table 1. Demographic and clinical features of the patients

Patients diagnosed with COVID-19	n (%)
Gender	
Male	63 (57.3)
Female	47 (42.7)
CK level at admission	
High	48 (43.6)
Normal	62 (56.4)
CK level on 3 rd day	
High	31 (28.2)
Normal	79 (71.8)
CK level on 14 th day	
High	13 (11.8)
Normal	97 (88.2)
Myalgia at admission	
Yes	50 (45.5)
No	60 (54.5)
Myalgia on the 14 th day	
Yes	12 (10.9)
No	98 (89.1)

COVID 19: coronavirus disease 2019, CK: creatine kinase

A significant difference was not observed on admission and on the 14th day of control according to the gender ($p=0.360$ and $p=0.188$, Table 2). On days 1 and 3, the CK values for the male patients were significantly higher than those of the female patients (both $p<0.001$). On day 14, there was no significant difference in CK values between the female and male patients.

The median CK values observed on days 1, 3, and 14 of control were 248.5, 150.5 and 80.0 U/L in the patients with muscle pain, respectively, while the median CK values of those without muscle pain were 96.0, 74.5 and 68.0 U/L respectively. In the patients with muscle pain, the CK levels observed on days 1, 3, and 14 of the disease were found to be significantly higher than in those without muscle pain ($p<0.001$, $p=0.003$, $p=0.029$). No significant relationship was found between complaints of muscle pain and lactate, pH, and LDH values (Table 3).

In the patients with muscle pain, high CK results were observed on 1st, 3rd, and 14th day of the disease to be significantly higher than in those without muscle pain ($p<0.001$, $p=0.001$, $p=0.003$, Table 4).

DISCUSSION

The biochemical parameters used in the diagnosis of COVID-19 play a major role in predicting the course and prognosis of the disease and directing its treatment. Since the emergence of the pandemic, researchers have concentrated their work on determining easily applicable practical parameters. Myalgia is known to be common in the early stages of COVID-19. We therefore evaluated CK levels, which we predicted could be a favorable parameter for evaluating myalgia.

Myalgia can occur as a symptom of many diseases, and viral infections are one of the main causes. In the course of a viral infection, IL-6 most frequently mediates myalgia (15). Since the SARS-CoV-2 agent causes a strong inflammatory response, high cytokine levels (IL-6, IL-10, and TNF- α) are detected, especially in patients with a moderate or severe disease course (16,17). Although the exact mechanism of myalgia during viral infection is not known, it is thought that proinflammatory cytokines cause muscle pain directly (i.e., TNF- α on muscle proteins) and indirectly (i.e., PGE2 stimulates nociceptive pathways causing a pain sensation). Myalgia caused by COVID-19 lasts longer and is more severe than myalgia caused by other viral infections. In patients with COVID-19, myalgia and fatigue do not respond to classic analgesics.

There is a relationship between high CK levels and muscle damage. CK levels begin to rise approximately 2-12 hours after the onset of muscle damage and start to decrease to their basal values in 3-5 days (18).

In our study, 110 patients diagnosed with COVID-19 were evaluated retrospectively. Among these, 50 (45.5%) patients had myalgia on admission, and 48 (43.6%) patients had CK elevation on admission. The control CK values on days 1, 3, and 14 were higher among the patients presenting with myalgia than those without myalgia. Although we found a significant relationship between myalgia and high CK levels, there was no significant relationship between myalgia and lactate, pH, and LDH values.

Several studies (19-22) have reported that patients with a diagnosis of COVID-19 and high serum levels of ferritin,

Table 2. Myalgia and creatine kinase levels according to the gender of the patients

	Male (n=63)	Female (n=47)	P
Myalgia at admission	31 (49.2)	19 (40.4)	0.360
Myalgia on the 14 th day	9 (14.3)	3 (6.4)	0.188
High CK level at admission	39 (61.9)	9 (19.1)	<0.001
High CK level on the 3 rd day	27 (42.9)	4 (8.5)	<0.001
High CK level on the 14 th day	12 (19.0)	1 (2.1)	0.007

CK: creatine kinase

Table 3. Comparison of laboratory values of patients with and without myalgia at admission

	M (+) (n=50)	M (-) (n=60)	P
CK at admission	248.5 (459) [39-2103]	96.0 (115) [24-353]	<0.001
CK on the 3 rd day	150.5 (301) [28-1266]	74.5 (83) [22-359]	0.003
CK on the 14 th day	80 (73) [27-315]	68 (54) [20-198]	0.029
Lactate	1.6 (1.2) [0.8-4.3]	1.7 (1.0) [0.2-3.4]	0.794
pH	7.39 (0.06) [7.27-7.47]	7.38 (0.05) [7.30-7.55]	0.693
LDH	235 (95) [151-574]	234 (100) [97-596]	0.147

M (+): patients with myalgia at admission, M (-): patients without myalgia at admission, CK: creatine kinase, LDH: lactate dehydrogenase, descriptive statistics were given as median (interquartile range) [minimum-maximum]

Table 4. Comparison of creatine kinase levels of patients with and without myalgia at admission

	M (+) (n=50)	M (-) (n=60)	P
High CK level at admission	32 (64.0)	16 (26.7)	<0.001
High CK level on the 3 rd day	22 (44.0)	9 (15.0)	0.001
High CK level on the 14 th day	11 (22.0)	2 (3.3)	0.003

M (+): patients with myalgia at admission, M (-): patients without myalgia at admission, CK: creatine kinase

leukocytes, total bilirubin, and IL-6 (CK) have higher mortality rates. Patients with rhabdomyolysis present with myalgia and high CK levels without typical COVID-19 symptoms; however, patients with COVID-19 diagnosed with very high CK levels due to the direct muscle damage caused by the virus have reportedly developed rhabdomyolysis following viral myositis (17). In our study, although very high CK levels were detected in only two patients, a rapid decrease was observed in the follow up, and kidney functions remained within normal limits. Patients with myalgia and high CK should be followed up more closely for the development of rhabdomyolysis.

It is clear that the SARS-CoV-2 virus affects the musculoskeletal system. In 25 of 33 related studies, weakness, myalgia, and increased CK levels, indicating

muscle damage, have been reported as symptoms of COVID-19 (23,24). Similarly, in our study, the incidence of high CK levels accompanying muscle pain was statistically significant.

In several studies from China, CK elevation has been reported in patients with COVID-19 who did not develop rhabdomyolysis. In a study of 91 adults, the CK levels of 14 patients were higher than 190 U/L, and 15 had myalgia (2). However, there was no relationship with myalgia in the patients with CK elevation. In another study involving 161 adults diagnosed with COVID-19, 17 patients had CK levels higher than 190 U/L, and 18 had myalgia (1). However, no relationship was found between the CK levels and myalgia. In contrast to these studies, myalgia and high CK levels were correlated in our series.

In another study on the relationship between myalgia and CK levels in patients diagnosed with COVID-19, 140 of 239 patients had high CK results, and 32 patients with CK elevation had myalgia (25). In the patients with myalgia, the mean CK values were 241.05 ± 137.02 U/L (min 45.00 U/L, max 721 U/L), while the mean CK levels in the patients without myalgia were 139.67 ± 83.80 U/L (min 21 U/L, max 451 U/L). Similarly to our study, the study found a significant relationship between myalgia and increased CK levels.

A limitation of our study was the lack of analgesic responses among the patients with myalgia because of an inadequate filing system. Furthermore, this was a cross-sectional study based on retrospective data. We recommend that it be supported by future multicenter studies with larger patient groups.

CONCLUSIONS

The typical clinical features associated with COVID-19 include fever, cough, and respiratory distress from the first day, but fatigue and myalgia are also common symptoms. Since some patients may only present with musculoskeletal symptoms such as myalgia, it is important that clinicians consider and evaluate COVID-19 in patients presenting with myalgia and high CK levels.

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