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Skeletal Muscle Injury during COVID-19: A Cohort of 873 Patients

COVID-19 Sırasında İskelet Kası Hasarı: 873 Hastalık Bir Kohort

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Abstract

Objective: The aim of the present study was to determine the prevalence of skeletal muscle injury in the clinical course of coronavirus disease-2019 (COVID-19) using creatine kinase (CK) levels.

Materials and Methods: The medical records of all patients with COVID-19 cases were retrospectively retrieved. These comprised two groups: patients with high CK levels and patients with normal CK levels. The CK level and its relationship with other clinical features and outcome were analyzed.

Results: In the study period, 994 patients who were hospitalized with COVID-19 were identified. Of them, CK was measured in 873 patients. There were 74 patients with CK >500 IU/l and 33 patients with CK >1,000 IU/l. Seventeen patients had weakness and CK >500 IU/l. Use of favipiravir and hospitalization in the intensive care unit were the risk factors for high CK levels. The CK levels positively correlated with age, duration of hospitalization, duration in intensive care, and levels of liver function tests, serum urea, D-dimer, and ferritin levels, and negatively correlated with oxygen saturation and thrombocyte levels.

Conclusion: This study showed that the use of favipiravir is a potential risk factor for elevated CK levels. Severe systemic inflammation, disseminated intravascular coagulation, and thrombosis may facilitate skeletal muscle damage. Prolonged intensive care is probably related to more severe inflammatory and coagulation response.

Keywords: COVID-19, creatine kinase, SARS-CoV-2, skeletal muscle damage, myopathy

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) seyri sırasında, kreatin kinaz (CK) düzeyini kullanarak iskelet kas hasarı prevalansını belirlemeyi amaçladık.

Gereç ve Yöntem: Tüm COVID-19 hastalarının kayıtlarını retrospektif olarak inceledik. CK düzeyi yüksek hastalar ve normal CK düzeyi olan hastalar olmak üzere iki grup oluşturduk. İskelet kas hasarı prevalansını, diğer klinik özelliklerle ilişkisini ve sonuçları analiz ettik.

Bulgular: Çalışma döneminde COVID-19 nedeniyle hastaneye yatırılan 994 hasta belirledik. Bunlardan 873 hastada CK düzeyi ölçülmüştü. CK seviyeleri 500 IU/L'nin üzerinde olan 74 hasta ve 1.000 IU/l'nin üzerinde olan 33 hasta bulunmaktaydı. CK seviyeleri 500 IU/l'den yüksek olan 17 hastada kas güçsüzlüğü yakınması vardı. Favipiravir kullanımı ve yoğun bakım ünitesinde yatış, yüksek CK seviyeleri için risk faktörleriydi. CK düzeyleri yaş, hastanede kalış süresi, yoğun bakımda kalma süresi, karaciğer fonksiyon testleri, serum üre, D-dimer ve ferritin düzeyleri ile pozitif; oksijen satürasyonu ve trombosit düzeyleri ile negatif korelasyon gösterdi.

Sonuç: Bu çalışma, favipiravir kullanımının yüksek CK seviyeleri için potansiyel bir risk faktörü olduğunu göstermiştir. Şiddetli sistemik enflamasyon, yaygın damar içi pıhtılaşma ve tromboz, iskelet kası hasarını kolaylaştırabilir. Uzun süreli yoğun bakım yatışı muhtemelen daha şiddetli enflamatuvar ve pıhtılaşma yanıtı ile ilişkilidir.

Anahtar Kelimeler: COVID-19, kreatin kinaz, SARS-CoV-2, iskelet kas hasarı, miyopati

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Introduction

Coronavirus disease-2019 (COVID-19) is caused by a new type of coronavirus in the class of betacoronaviruses, which is known for its potential for neurological involvement (1). The virus can enter the cell by binding to the angiotensin-converting enzyme-2 receptor (ACE-2) (2). The ACE-2 receptor is found in many tissues in the human body, including the central and peripheral nervous system (3,4,5). Since the first COVID-19 case, studies and case reports have described many neurological manifestations, including stroke, encephalitis, Guillain–Barré syndrome, hyperCKemia, and others (6,7,8,9,10,11,12). Among neurological complications, one of the most common and interesting manifestations is muscle involvement. Reports from China indicate that myalgia is present in 35%–52% of patients with COVID-19 (8,9,10,11,12). Additionally, increased creatine kinase (CK) levels were found in 9%–33% of patients (9,12,13). Two recent cases had acute onset of severe muscle weakness with CK >10,000 U/l, suggesting that COVID-19 could trigger autoimmune myositis and cause rhabdomyolysis (14,15).

It was unclear if COVID-19 causes viral myositis by directly infecting muscle fibers until recent evidence suggested a direct severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) muscle infection (16). On the other hand, viruses are shown to trigger an inflammatory response and cause an accumulation of cytokines around or in the muscle fibers (17,18).

Causes of myopathies in systemic infectious diseases could be multifactorial. Hypoxia, multiorgan failure, and critical illness myopathy are some of the possible pathogenic mechanisms (13). However, if a patient develops an acute onset of severe muscle weakness with increased CK levels (>10,000 U/l) and elevated inflammatory biomarkers, it is highly suggestive of an autoimmune inflammatory myopathy, which is one of the necrotizing autoimmune myositis spectrum disorders (19,20). Another important factor in the case of COVID-19 in Türkiye is the medication used, such as chloroquine or hydroxychloroquine, antiviral agents, or corticosteroids. It is known that patients taking chloroquine or hydroxychloroquine may develop slowly progressive, painless, proximal weakness and atrophy, especially in the legs (21,22), and some antiviral agents have been shown to cause toxic myopathy when combined with statins (23,24,25).

The aim of this study was to determine the prevalence of patients with muscle weakness and increased CK levels that would be attributed to muscle damage in the presentation or in the clinical course of COVID-19. A secondary analysis aimed to define the clinical and laboratory features of COVID-19 associated with muscle damage.

Patients and Methods

This was a retrospective study. The medical records of all patients with COVID-19 cases who were followed in the subject hospital between March 21 and June 7, 2020, were retrieved. The diagnosis of COVID-19 was done according to the guidelines of the National Health Ministry (https://covid1pcr9.saglik.gov.tr/?_Dil=2. The Turkish version includes the guidelines). All hospitalized patients treated as COVID-19 with typical clinical, laboratory, and radiological findings were included. The diagnosis was made even in the case of polymerase chain reaction (PCR) negativity when clinical findings and thorax computerized tomography (CT) were concordant with COVID-19. Patients who did not have at least one measurement of the CK level throughout the hospitalization were excluded. Patients with high CK levels, that were attributed to confirmed myocardial origin were also excluded. The Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Local Ethics Committee approved the study (05/08/2020-100286).

During hospitalization, all patients underwent daily clinical and laboratory examinations. If needed, daily neurological consultations were conducted. Daily laboratory investigations included complete blood count, urea, creatinine, electrolytes, fibrinogen, D-dimer, CK, troponins, liver function tests, ferritin, and C-reactive protein (CRP). Viral PCR and thorax CT were performed on admission, and PCR was repeated during the hospitalization. The national guidelines for treatment and recommendation for the intensive care unit (ICU) were followed (https://covid19.saglik.gov.tr/?_Dil=2, The Turkish version includes the guidelines).

Main Outcome Measures

The main outcome measures were the CK levels and muscle weakness at admission and the highest CK levels and muscle weakness during the hospital stay and in the ICU.

- Two groups were created: patients with moderate–high CK levels and patients with normal CK levels. Moderate–high CK level was defined as >500 IU/l, which has a considerable sensitivity for myopathy (26).
- To increase sensitivity, a cut-off CK value of 1,000 IU/l, which is associated with a high likelihood of myopathy according to Abraham et al. (27), was selected, and a second comparison was done between patients with CK <1,000 IU/l and CK >1,000 IU/l.
- A third group was formed: patients with high CK levels with muscle weakness.

Clinical Evaluation

Data retrieved from the medical records were details of age, gender, fever, cough, dyspnea, myalgia, headache, hyposmia, diarrhea, low blood pressure, high blood pressure, arrhythmia, hypoxemia on admission, hypoxemia during hospitalization, comorbid conditions, medications used for COVID-19 during hospitalization (hydroxychloroquine, azithromycin, favipiravir, oseltamivir, lopinavir/ritonavir, tocilizumab, corticosteroids, anticoagulation, oxygen replacement, and plasma exchange). The comorbid disorders were classified as hypertension, diabetes mellitus, malignancy, asthma/chronic obstructive pulmonary disorder, cardiac disorders, chronic renal disorders, cirrhosis, rheumatological diseases, myopathies, other neurological disorders (stroke, Parkinson's disease, other parkinsonisms, and dementias), immune deficiencies (human immunodeficiency virus and hereditary immune deficiencies), and other disorders. The need for intensive care, duration of the hospital stay (days), duration in an ICU (days), the need for mechanical ventilation, and outcome data were also provided from the records.

The medical files and neurology consultations were reviewed to find any weakness that could be attributed to muscle damage, and phone consultations were made with patients who had high CK levels to learn about their weakness. Phone consultations were performed using a standardized questionnaire (the Turkish version

of INQoL) (28). Electromyography could not be done due to the assignment of the physicians to shifts at pandemic clinics.

Laboratory Evaluation

The complete blood count, urea, creatinine, electrolytes, fibrinogen, D-dimer, troponins, serum alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), CRP, ferritin level, fibrinogen, CT finding, oxygen saturation (SpO_2), and PCR finding on admission and during hospitalization were recorded.

Statistical Analysis

The prevalence of (i) patients with moderate–high CK levels, (ii) patients with high CK levels, and (iii) patients with weakness that could be attributed to muscle damage was analyzed.

The clinical and laboratory findings were compared, as well as the outcome data of COVID-19 between patients with high CK levels (>1,000 IU/l) and patients with normal CK levels. A correlation analysis between the CK levels and the duration of the hospital stay, duration of ICU stay, and other laboratory parameters was also performed.

Data analyses were performed using the SPSS™ v20.0 software statistical package (IBM® Inc., Chicago, IL, USA). For quantitative variables, when the data were non-normally distributed, comparisons were made using the Mann–Whitney U test. When the data were homogenous, the t-test was used. For qualitative variables, the chi-squared test was used. To determine the risk factors, a logistic regression analysis was performed. The factors entered in the model were gender, clinical findings on admission (fever, cough, dyspnea, myalgia, headache, hyposmia, and diarrhea), hypoxemia on admission, hypoxemia during hospitalization, comorbid conditions, medications (hydroxychloroquine, lopinavir/ritonavir, tocilizumab, oseltamivir, favipiravir, corticosteroids, azithromycin, anticoagulation, oxygen replacement, and plasma exchange), need for ICU, need for mechanical ventilation, abnormal CT finding, and PCR finding. For correlation analysis, the Spearman's correlation test was used. A P value ≤ 0.05 was deemed significant.

Results

General Information about Patients with COVID-19

In the study period, 994 patients who were hospitalized with COVID-19 were identified. Of them, CK was measured in 875 patients. Two patients did not accept phone consultations. The mean age was 53.9 ± 20.2 years (range 0–98 years) in 873 patients. There were 469 male patients. The SARS-CoV-2 PCR test was positive for 356 patients. A total of 150 patients required intensive care. The most common symptoms were cough (41.6%), fever (36.3%), and dyspnea (31%), followed by fatigue/myalgia (25.3%) and nausea/vomiting (7.6%). The PCR test was positive in 48.4% of cases.

Patients with High CK Levels

There were 74 (8.5%) patients with CK >500 IU/l and 33 (3.8%) patients with CK >1,000 IU/l during the hospital stay. Among them, six had CK >5,000 IU/l, including two with >10,000 IU/l. Only seven patients had CK >500 IU/l at admission. All others had increased levels during the hospital stay. Seventeen (1.9%) patients had muscle weakness and CK >500 IU/l. The mean CK in patients with weakness was 1,412.6 ± 2,382.7 IU/l.

The prevalence of high CK levels was 20.7% in patients who required intensive care, whereas it was 5.8% in patients who did not need intensive care (P < 0.001). However, only three patients had elevating CK levels during the course of the ICU stay. Three patients with mitochondrial myopathy did not have high CK levels or weakness at all.

The proportion of individuals with a positive PCR result at admission was similar between patients with high and normal CK (41.7% vs. 43.1%, P = 0.573). The percentage of patients using hydroxychloroquine, lopinavir/ritonavir (200 mg/50 mg), oseltamivir, corticosteroid, and anticoagulation was not different between patients with high CK and normal CK. However, tocilizumab and favipiravir were more commonly used in patients with high CK than in patients with normal CK (P = 0.004 and P = 0.000, respectively) whereas the use of azithromycin was more common in patients with normal CK than high CK (P = 0.011).

The need for the ICU was higher among patients with high CK compared with those with normal CK (43.1% vs. 15.3%, P < 0.001). The need for mechanical ventilation was also higher in these patients (14.1% vs. 6.2, P = 0.017). The fatality rate among patients with high CK was also higher compared with those with normal CK (28.3% vs. 8.3%, P < 0.001). The hospital stay and duration of stay in the ICU were also longer in patients with high CK than the corresponding durations in patients with normal CK (Table 1).

Among comorbid disorders, malignancy was more common among patients with high CK compared with those with normal CK (P = 0.035). The duration in the ICU was longer among patients with CK >1,000 IU/l compared with those with CK <1,000 IU/l, (6.0 ± 9.8 vs. 1.4 ± 5.2 days, P < 0.001). The need for the ICU was also more frequent among patients with CK > 1,000 IU/l (48.5% vs. 16.4%, P < 0.001).

The AST, ALT, highest urea during the hospital stay, creatinine at admission, highest creatinine during the hospital stay, LDH at admission, highest LDH during the hospital stay, ferritin at admission, highest ferritin during the hospital stay, CRP at admission, and highest CRP during the hospital stay were higher among patients with CK >1,000 IU/l when compared with those with CK <1,000 IU/l. However, thrombocyte level, the highest D-dimer during the hospital stay, and the highest fibrinogen during the hospital stay were lower among patients with CK >1,000 IU/l.

Comparison of the groups with normal CK levels, high CK levels, and high CK levels with weakness revealed there were no major differences between patients with high CK and high CK with weakness. The age and duration of the hospital stay were not different across groups.

Regarding COVID-19 symptoms and comorbid disorders, there were no differences between patients with CK >1,000 IU/L and those with CK <1,000 IU/l or patients with weakness. However, use of favipiravir (P = 0.002) and tocilizumab (P = 0.036) were more common among patients with CK >1,000 IU/l.

Logistic regression analysis disclosed that the use of favipiravir (P < 0.001, B = 4.805) and hospitalization in the ICU (P = 0.027, B = 2.814) were the risk factors for moderate–high CK levels. For high CK levels, favipiravir (P = 0.019, B = 3.247) and hospitalization in the ICU (P = 0.010, B = 3.539) were the risk

factors. The number of patients with muscle weakness was too low to conduct a logistic regression analysis.

The CK levels positively correlated with age, duration of the hospital stay, duration in the ICU, levels of liver function tests, urea level at admission, highest urea level during hospitalization, LDH level at admission, highest LDH level during hospitalization, highest D-dimer level during hospitalization, ferritin level at admission, highest ferritin level during hospitalization, hematocrit, neutrophil, and highest fibrinogen during hospitalization (Table 2).

The CK levels negatively correlated with the hemoglobin SpO_2 level at admission, the lowest SpO_2 level during hospitalization, and the thrombocyte levels (Table 2).

Discussion

The present study revealed that the prevalence of any kind of muscle injury was below 10% in hospitalized patients with COVID-19. Using favipiravir and the need for ICU may be the risk factors for CK level elevation and muscle injury.

It is clear that skeletal muscles are involved in the clinical course of COVID-19. However, according to the present study, it is relatively uncommon. The prevalence of skeletal muscle involvement may change, probably depending on the method of diagnosis. Since the start of the pandemic, multiple studies have reported clinical features. For example; Huang et al. (9) reported myalgia or fatigue, which are common symptoms in COVID-19, in 44% of 41 patients. Myalgia and fatigue were also common among the patients in the present study, and their frequency was similar to that reported in the literature (9,29). Mao et al. (6) reported skeletal muscle injury in around 10% of 217 patients by measuring CK levels; however, the frequency doubled among patients with severe infection, whereas it was around 5% among patients with non-severe infection. The figures were also similar in the present study. Functional investigation methods, such as electromyography, or structural investigation methods, such as CT or ultrasonography, may further change the understanding of prevalence of muscle involvement in COVID-19.

Different reports revealed rhabdomyolysis and high CK levels (30,31), which were presenting symptoms in patients without any respiratory complaints (32). Although almost half of the cases had mild to moderate increases in CK levels, there were also patients with high and even very high CK levels, suggesting rhabdomyolysis in the present series. Myalgia and fatigue were not predictive of high CK levels. There is also a previous report

Table 1. The comparison of clinical and laboratory parameters between patients with high CK and patients with normal CK

	Patients with high CK n = 74	Patients with normal CK n = 799	*P*
Age, year	58.0 ± 18.4	53.5 ± 20.3	0.069
Duration of hospitalization, days	12.0 ± 8.9	8.5 ± 6.8	<0.001
Duration of ICU stay, days	4.8 ± 8.3	1.3 ± 5.1	<0.001
CK levels, IU/l	1,674.5 ± 1,972.9	120.8 ± 111.8	<0.001
SpO_2 level at admission, %	84.5 ± 26.7	87.8 ± 24.7	0.017
Lowest SpO_2 level during hospitalization, %	85.3 ± 17.0	87.1 ± 20.0	<0.001
AST, IU/l	206.9 ± 642.1	68.0 ± 226.3	<0.001
ALT, IU/l	80.3 ± 208.6	37.2 ± 83.4	<0.001
Urea level at admission, mg/dl	45.6 ± 35.0	40.1 ± 35.3	0.027
Highest urea level during hospitalization, mg/dl	85.1 ± 74.3	54.8 ± 49.6	<0.001
Creatinine level at admission, mg/dl	1.1 ± 0.6	1.2 ± 2.1	0.004
Highest creatinine level during hospitalization, mg/dl	1.8 ± 1.4	1.4 ± 1.8	<0.001
LDH level at admission, IU/l	453.3 ± 476.3	297.2 ± 241.5	<0.001
Highest LDH level during hospitalization, IU/l	794.4 ± 731.5	436.3 ± 358.9	<0.001
D-dimer level at admission, ng/ml	116.9 ± 948.9	35.5 ± 507.3	0.003
Highest D-dimer level during hospitalization, ng/ml	311.2 ± 1,389.9	100.2 ± 817.2	<0.001
Ferritin at admission, ng/ml	692.9 ± 623.4	559.3 ± 1,679.1	<0.001
Highest ferritin during hospitalization, ng/ml	1,057.8 ± 886.5	821.4 ± 2,100.1	<0.001
Neutrophil, 10^3/µl	11.7 ± 20.5	9.3 ± 17.3	0.014
Thrombocyte, 10^3/µl	217.0 ± 146.6	241.8 ± 142.6	0.003
CRP at admission, mg/l	93.2 ± 80.4	62.8 ± 75.2	<0.001
CRP during hospitalization, mg/l	170.9 ± 104.7	105.8 ± 341.7	<0.001
Highest fibrinogen during hospitalization, mg/dl	643.8 ± 181.5	684.7 ± 3,309.7	<0.001

All data is given as mean ± standard deviation. CK: Creatine kinase; ICU: Intensive care unit; SpO_2: Oxygen saturation; AST: Aspartate transaminase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein

showing no association between CK levels and myalgia (33). Therefore, measuring CK levels in all patients is suggested.

The need for the ICU was highly associated with skeletal muscle injury. This association is mutual. It is accepted that some of the invasive or semi-invasive procedures in the ICU may increase CK levels. However, it is generally associated with mild to moderate increases. Previously, severe COVID-19 disease was determined as a risk factor for high CK levels in meta-analyses (34). Nevertheless, those authors attributed their findings to myocardial inflammation or myocarditis. It is suggested that severe systemic inflammation, disseminated intravascular coagulation, and thrombosis generally seen in COVID-19 may facilitate skeletal muscle damage. Unfortunately, because of the pandemic conditions, the autopsy findings of skeletal muscles are limited to the lungs and heart. Yet, another finding supporting the hypothesis of systemic inflammation and coagulation comes from the study of Mao et al. (6), who compared patients without muscle injury and patients with muscle injury regardless of their severity. Patients with muscle injury had higher neutrophil counts, lower lymphocyte counts, higher CRP levels, and higher D-dimer levels. These abnormalities were manifestations of increased inflammatory response and blood coagulation function. It was also found that patients with muscle injury had multiorgan damage, including more serious liver (increased LDH, ALT, and AST levels) and kidney (increased blood urea nitrogen and creatinine levels) damage, in addition to the higher systemic inflammatory response. However, the role of critical disease myopathy in the ICU or in patients with severe disease should be acknowledged.

Table 2. Correlation between CK values and other clinical and laboratory parameters

	Spearman's rho	*P*
Age, year	0.129	<0.001
Duration of hospitalization, days	0.203	<0.001
Duration of ICU stay, days	0.206	<0.001
CK levels, IU/l	-0.120	0.001
SpO_2 level at admission, %	-0.175	<0.001
Lowest SpO_2 level during hospitalization, %	0.274	<0.001
AST, IU/l	0.218	<0.001
ALT, IU/l	0.175	<0.001
Urea level at admission, mg/dl	0.228	<0.001
Highest urea level during hospitalization, mg/dl	0.300	<0.001
Creatinine level at admission, mg/dl	0.335	<0.001
Highest creatinine level during hospitalization, mg/dl	0.275	<0.001
LDH level at admission, IU/l	0.313	<0.001
d-dimer level at admission, ng/ml	0.160	<0.001
Highest D-dimer level during hospitalization, ng/ml	0.117	0.001
Ferritin at admission, ng/ml	0.116	0.001
Highest ferritin during hospitalization, ng/ml	0.175	<0.001
Hematocrit, %	0.072	0.035
Monocyte, 10^3/µl	-0.139	<0.001
Thrombocyte, 10^3/µl	0.143	<0.001
CRP at admission, mg/l	0.243	<0.001
Fibrinogen at admission, mg/dl	0.189	<0.001

CK: Creatine kinase; ICU: Intensive care unit; SpO_2: Oxygen Saturation; AST: Aspartate transaminase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein

Skeletal muscle injury may also contribute to the patients' prognosis. The involvement of intercostal muscles and the diaphragm may increase morbidity and mortality in COVID-19. Ventilator-induced diaphragm dysfunction was reported due to prolonged mechanical ventilation, and diaphragm ultrasound is recommended in COVID-19 (35).

There was a previous case of acute rhabdomyolysis after ebolavirus infection (36). As mentioned above, rhabdomyolysis may be an initial symptom of COVID-19 (30,32). It is interesting that several rhabdomyolysis cases have been reported related to antiviral treatment (37,38,39). However, a case related to the use of favipiravir, which seemed an independent risk factor for skeletal muscle damage in the present study, could not be found.

In this study, PCR positivity seems to be low. The probability of false negative PCR results varies between 20% and 67%, depending mainly on the duration between symptom onset and sampling time, as reported by Kucirka et al. (40). Furthermore, other possible reasons for relatively low PCR positivity rates in this cohort might have been related to the infrastructural standards, including the non-Dacron swabs used for sampling, the relatively lower viral loads in the upper airways in those with lower respiratory involvement, and lower repeat-testing rates due to the prolonged test-result time at the earliest period of the pandemic. Although these conditions were promptly improved, for the reasons stated, low-dose radiation multi-slice thorax CT imaging was more commonly utilized to establish the diagnosis in patients with typical clinical findings of COVID-19 and defined exposure to the virus.

Study Limitations

There are certain limitations of the present study. The retrospective nature of the study is a major limitation. Because of its retrospective nature, it was not possible to stratify the degree of muscle weakness or exactly specify the duration of weakness. Electromyography and muscle biopsy could not be performed. Thorax CT results were not available in the dataset. As mentioned above, it was not possible to exclude patients with critical disease myopathy that may lead to necrotizing myopathy and high CK levels (41). In addition, urinary myoglobin levels were lacking in patients who had very high CK levels suggesting rhabdomyolysis.

Conclusion

In conclusion, severe skeletal muscle injury is not common in COVID-19. Favipiravir use may be a risk factor for skeletal muscle injury in COVID-19. Severe systemic inflammation, disseminated intravascular coagulation, and thrombosis may facilitate skeletal muscle damage. Prolonged intensive care is probably related to more severe inflammatory and coagulation response.

Ethics

Ethics Committee Approval: Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Local Ethics Committee approved the study (05/08/2020-100286).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.K., N.U., M.K., Design: A.G., Data Collection or Processing: M.H.S., M.A.., R.K., C.B., Ş.B., İ.İ.B., Analysis or Interpretation: A.G., M.A., C.B., M.H.S., Ş.B., Literature Search: M.K.S., Ş.B., Writing: C.B., Ş.B., İ.İ.B., N.U., M.K.

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