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A Parameter and complication to be followed in COVID-19 patients: creatine kinase and rhabdomyolysis

Nevsun Pihtili Tas[1], Selda Telo[2]

[1]Elazig Fethi Sekin City Hospital, Medicine and Rehabilitation, Department of Physical, Elazig, Turkey
[2]Firat University, Faculty of Dentistry, Department of Biochemistry, Elazig, Turkey

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Abstract

This study aims to reveal the relationship between imaging findings obtained from computed tomography (CT), and CK levels in addition to other biochemical parameters in individuals diagnosed with COVID-19. The study also aims to draw awareness to the fact that COVID-19 may have various organ involvements apart from the lung. Two hundred and thirty patients with CT findings indicating COVID-19, and 119 control subjects without COVID-19 diagnosis, who had CT scans for other reasons, were included in this retrospective study. The patients were divided into three groups as those with ground-glass opacity (GGO) on CT, those with signs of consolidation (CONS) on CT, and the control group with normal CT findings. Then, the imaging and laboratory findings of the patients were evaluated. Of the CT-positive patients, 113 were females and 117 were males. There was no statistically significant difference between the groups in terms of the age variable (p=0.43). Ground-glass opacities were found on CT findings in 113 (32.3%) patients, and consolidation findings were found in 117 (33.7%) patients. Serum CK levels were 162.6 (U/L) (13-765) in the group with GGO while these levels were 162 (U/L) (6-731) in the CONS group and 94.27 (U/L) (11-400) in the normal CT group. CK levels were statistically increased in GGO and CONS groups compared to the normal CT group (p=0.000). In the initial admission of the patients with COVID-19 diagnoses, all the laboratory parameters should be evaluated carefully, and risky patients should be followed up considering complications, such as myositis and rhabdomyolysis that may affect mortality.

Keywords: COVID-19, rhabdomyolysis, consolidation, ground-glass opacity

Introduction

COVID-19 disease, which began in China in December 2019, spread rapidly, and caused a pandemic in the world. Initially, it was revealed that while lung findings were at the forefront, over time, it caused potentially fatal involvement in other organs [1-3]. Therefore, it is important to determine the early diagnosis and prognosis of patients in the COVID-19 pandemic, which is a medical and social problem. The necessity of determining effective laboratory biomarkers that can help in early diagnosis is increasing day by day [2, 4].

Rhabdomyolysis, which is serious damage to the skeletal muscle, may present as a clinical manifestation of COVID-19. Myositis is usually self-limiting in viral diseases and lasts an average of three days or may cause rhabdomyolysis at the end [5]. Skeletal muscle damage followed by the release of degraded products into the blood can cause acute renal damage [5-8]. Muscle destruction and related rhabdomyolysis may occur as a result of the viral invasion effect, muscle destruction due to the cytokine storm caused, and the mechanisms that suggest direct destruction of the muscle cell membrane by the effect of viral toxins [6, 9].

Creatine kinase (CK) is the best-known laboratory marker of muscle damage that is used to confirm rhabdomyolysis [10]. The values five times higher than the upper limit of normal values (≥1,000 U/L) are recognized as markers for the diagnosis of rhabdomyolysis [11-12].

However, the mechanisms of muscle damage, increased CK levels, and rhabdomyolysis in COVID-19 have not been clarified yet. Although many case reports have been presented in this regard, studies investigating these complications are required in patients diagnosed with COVID-19 to investigate the matter further.

This study aimed to evaluate the relationship between imaging findings of computed tomography (CT) and CK levels in addition to other biochemical parameters in individuals diagnosed with COVID-19. The study also aims to draw attention to other complications that may occur other than lung findings.

***Corresponding Author:** Selda Telo, Firat University, Faculty of Dentistry, Department of Biochemistry, Elazig, Turkey
E-mail: drseldatelo@hotmail.com

Materials and Methods

Patient population and study design

Patients who applied to our Pandemic Outpatient Clinic between April 2020 and October 2020 were included in the study. Laboratory diagnostic tests and radiological findings (lung radiography and/or CT) of cases with PCR positivity, who presented with a pre-diagnosis of COVID-19, were evaluated retrospectively. As the control group, individuals who did not have any abnormalities (pneumonia, etc.) in imaging and laboratory tests were included in the study. Additionally, patients older than 18 years were included in the study. The exclusion criteria were history of trauma, muscle disease, connective tissue disease, and seizures.

Three groups were formed as those with ground-glass opacity (GGO) on CT, those with signs of consolidation (CONS) on CT, and the control group with normal CT findings. Ethical approval of the institutional review board and permission from the Ministry of Health were obtained for the study (4.12.2020/16-19).

Statistical Analysis

Statistical analyses were conducted by SPSS version 22.0 (SPSS Inc., IL). The data without normal distribution were presented as median and minimum/maximum values. One-way analysis of variance (ANOVA) was used to compare the groups. Correlations between the variables were investigated by the Spearman correlation analysis. The level of statistical significance was considered as $p<0.05$.

Results

Two hundred and thirty patients with findings of COVID-19 pneumonia in computed tomography, and 119 patients, who applied to our outpatient clinic for various reasons and did not have COVID-19 findings, complaints, and did not have COVID-19 pneumonia in CT, were included in the study. Of the patients with CT positive, 113 were females and 117 were males. No statistically significant differences were observed between the groups in terms of the age variable (p=0.43) (Table 1). Ground-glass opacities were found on CT findings in 113 (32.3%) patients, and consolidation findings were found in 117 (33.7%) patients. Laboratory variables of the groups were presented in Table 1.

Positive correlations were observed between urea and signs of consolidation (r=0.02, p=0.000) (Table 2). We also discovered a more pronounced positive correlation in D-dimer and ferritin values in patients with consolidation findings (r=0.30, p=0.000; r=0.37, p=0.000, respectively) (Table 2). A positive correlation was determined between Crp and ground-glass opacity and the presence of consolidation, which had a stronger correlation with the consolidation findings (r=0.21, p=0.000; r=0.35, p=0.000, respectively) (Table 2). CK levels were positively correlated with ferritin and D-dimer levels (r=0.21, p=0.000; r=0.11 p=0.03, respectively) (Figure 1).

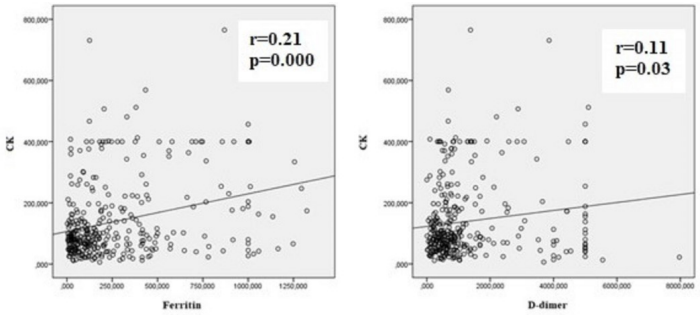

Figure 1. Correlation between CK with ferritin and D-dimer

Table 1. Comparison of demographic and laboratory parameters between groups

	GGO n=113 Mean(Min-Max)	CONS n=117 Mean(Min-Max)	NORMAL CT n=120 Mean(Min-Max)	p
Age, (years)	53.92(19-87)	57.67(21-92)	56.57(18-85)	0.06
Sex, (male/female)	61/52	57/60	53/67	0.43
CK, U/L	162.6(13-765)	162(6-731)	94.27(11-400)	0.000
LDH, U/L	325.04(30-640)	355.28(30-820)	227.2(30-934)	0.000
AST, U/L	50(14-283)	62(13-261)	28(11-325)	0.000
ALT, U/L	57.53(1-1443)	59.9(1-294)	22(5-95)	0.02
GGT, U/L	63.9(9-299)	85.7(10-565)	27.5(8-239)	0.000
Urea, mg/dl	50.7(2.26-261)	64.3(0.7-338)	33.45(12-80)	0.000
Creatine, mg/dl	1.68(0.4-54)	1.97(0.18-64)	0.81(0,28-9)	0.000
Uric Acid, mg/dl	5.3(0.8-13)	5.7(1.09-16,2)	4.67(2-9,26)	0.001
Total Protein, g/l	65.1(6-87)	64.04(41-78)	70.31(53-79)	0.000
Albumin, g/l	35.58(20-89)	32.8(15-48)	40.87(26-50)	0.000
Ferritine, µg/l	294.6(5-1012)	405.8(15-1324)	98.11(2-1030)	0.000
D-dimer, µg/l	1310.3(16.2-5550	1860.1(100-7970)	608.38(3-5000)	0.000
Procalsitonin, µg/l	5.19(0.02-200)	6.02(0.003-200)	0.01(0.006-0.016	0.948
CRP, mg/l	65.16(1.6-353)	84.04(1-373)	12.05(0.5-192)	0.000

Table 2. Correlation between laboratory parameters and CT groups

	Correlation	GGO	CONS
Urea	r	0.02	0.234
	p	0.7	0.000
D-Dimer	r	0.134	0.305
	p	0.012	0.000
Ferritine	r	0.162	0.372
	p	0.02	0.000
Crp	r	0.217	0.356
	p	0.000	0.000

Discussion

In our study, CK levels were significantly higher in patients diagnosed with COVID-19. Furthermore, we found that the mean CK values of patients with normal CT findings were 94.27 (U/L), while the CK levels of patients with ground-glass opacity or signs of consolidation were higher than 160 (U/L). We also determined that CK levels were positively correlated with the D-dimer and ferritin levels, which affect the survival rates.

The mechanisms of muscle damage in COVID-19 have not been fully elucidated. The first hypothesis is via direct viral muscle invasion [11] and the second hypothesis suggests that skeletal muscle damage could be caused by the host "cytokine storm"-like immune response [9].

High CK levels before the onset of myalgia and typical COVID-19 symptoms can be observed in patients diagnosed with COVID-19. Cases of viral myositis caused by the virus with very high CK levels due to direct muscle damage [13]. Although certain data stated that myalgia did not increase with the severity of COVID-19, myalgia was reported as an important predictor of disease severity in patients with abnormal CT or radiographic image of the lungs [4]. In a meta-analysis of three large studies comparing survivors and non-survivors in COVID-19 patients, significant increases in serum ferritin, WBC count, and IL-6, as well as total bilirubin and CK, were reported in non-survivors compared to survivors [2, 4].

In a study conducted with 214 patients, who were hospitalized due to COVID-19 in Wuhan, it was found that 9% of the patients had CK levels higher than 200 (U/L) while the highest value was 12.216 (U/L) [14]. It is important to be able to evaluate clinical markers and laboratory parameters together. Since we made a retrospective evaluation, we could not evaluate the patients' application complaints clearly, especially the frequency of myalgia. However, we examined the CT findings of our patients. Imaging has a major role in the diagnosis and treatment of COVID-19 pneumonia. CT is used in the diagnosis of suspicious cases as the first-line imaging method. It is also used to monitor imaging changes during treatment [15].

Rhabdomyolysis may occur due to the viruses that cause myositis. The most frequent cause of infection that causes viral myositis and rhabdomyolysis is influenza A and B while less common viruses include the enteroviruses, Epstein-Barr virus, human immunodeficiency virus, Cytomegalovirus, Herpes Simplex Virus, and Chickenpox-zoster. Approximately 3% of patients with influenza-induced myositis developed rhabdomyolysis according to a literature review of 300 cases [16].

In another study, a late complication of rhabdomyolysis in one patient with COVID-19 in Wuhan, China was reported. This is the first case of rhabdomyolysis in COVID-19 patients with both early and late presentations [8]. Acute renal failure is a serious complication of severe rhabdomyolysis, particularly in cases with serum CK elevation higher than 16000 U/L [17].

In another study, it was reported that patients with rhabdomyolysis got worse compared to patients without rhabdomyolysis and constituted a greater percentage of those admitted to the intensive care unit and patients who are mechanically ventilated. It was also reported that creatine kinase (CK) levels higher than1000 IU/L and serum myoglobin (MYO) concentrations higher than 1000 ng/mL were independent risk factors for in-hospital death in COVID-19 patients with rhabdomyolysis [18].

Chu et al. demonstrated that in the 2003 coronavirus (CoV) pandemic that caused severe acute respiratory syndrome (SARS), 6.7% of patients developed kidney failure within an average of 20 days after the onset of infection. Renal dysfunction has been frequently detected among patients with confirmed CoV-associated SARS hospitalized during clinical observations. Impaired renal functions were observed in the follow-up of patients who did not have any problems in the early period [19]. We found increased BUN and creatinine levels in patients with pulmonary involvement compared to those without COVID-19 diagnoses. In the current study, it was thought that rhabdomyolysis was a diagnosis that should not be missed, considering the relationship between renal dysfunction and high CK. Early aggressive fluid resuscitation is the main therapy in the prevention and treatment of acute renal failure [20].

Although myalgia and weakness are known as common symptoms of COVID-19, clinicians should be careful considering that rhabdomyolysis may also occur in patients without COVID-19. Treatment of rhabdomyolysis has not been well investigated, and there is no specific treatment that leads to a significant difference in the outcomes. The fluid replacement required in the treatment may lead to heart failure and may trigger respiratory distress, which emphasizes the importance of preventing this complication once again. During the initial admission of the patients, CK and markers showing renal function should be evaluated, and in doubtful cases and CK and renal function markers should be followed. This is because rhabdomyolysis, especially when associated with damaged renal function, poses high mortality rates, and requires high clinical alertness.

Limitations of the study

This study is a single-center study and due to its retrospective nature, the clinical data of the patients could not be fully evaluated. Additionally, the clinical follow-up of the patients could not be performed.

Conclusion

In conclusion, clinicians should be aware that rhabdomyolysis may be the first occurrence of COVID-19 or it may occur at any time during the period of the disease.

Conflict of interests
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial Disclosure
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Ethical approval
Ethical approval of institutional review board and permission from the Ministry of Health was obtained for the study (4.12.2020/16-19).

References

1. Ahmed S.I, Khan S. Coagulopathy and plausible benefits of anticoagulation among COVID-19 Patients. Curr Probl Cardiol. 2020;45:100648.
2. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475–81.
3. Gavriatopoulou M, Korompoki E, Fotiou D, et al. Organ-specific manifestations of COVID-19 infection. Clin Exp Med. 2020;20:493–506.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62.
5. Zhang Q, Shan K.S, Minalyan A,et al. A Rare Presentation of Coronavirus Disease 2019 (COVID-19) Induced Viral Myositis With Subsequent Rhabdomyolysis. Cureus 2019;12:e8074.
6. Suwanwongse K, Shabarek N. (2020). Rhabdomyolysis as a Presentation of 2019 Novel Coronavirus Disease. Cureus. 2020;12:e7561.
7. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361:62–72.
8. Ying-Chao He, Feng C. Rhabdomyolysis as potential late complication associated with COVID-19. Emerg Infect Dis. 2020;26:1618–20.
9. Fadila M, Wool K. Rhabdomyolysis secondary to influenza a infection: A case report and review of the literature. N Am J Med Sci. 2015;7:122.
10. Keltz E, Khan FY, Mann G. Rhabdomyolysis. The role of diagnostic and prognostic factors .Muscles Ligaments Tendons J. 2013;3:303-12.
11. MW Haroun, V Dieiev, J Kang et al. Rhabdomyolysis in COVID-19 patients: a retrospective observational study. Cureus 2021;13:e12552.
12. Jahnke VS, Poloni JAT, Neves CAM,et al. Acute kidney injury associated with rhabdomyolysis in a patient with COVID-19. Braz J Nephrol. 2021; https://doi.org/10.1590/2175-8239-jbn-2020-0170
13. Pedersen S.F, Ho Y-C. SARS-CoV-2: a storm is raging. J Clin Invest. 2020;130:2202–5.
14. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683.
15. Zhao W, Zhong Z, Xie X, et al. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. Am J Roentgenol. 2020;214:1072–7.
16. Crum-Cianflonei N.F. Bacterial, fungal, parasitic, and viral myositis. Clin Microbiol Rev. 2008;21:473–94.
17. Mahmood UA, Mermis JD, Khan NM, Atrouni WE. Rhabdomyolysis With COVID-19. Infect Dis in Clin Pract. 2021:22;129–30.
18. Geng Y, Ma Q, Du YS et al. Rhabdomyolysis is associated with in-hospital mortality in patients with COVID-19. Shock 2021;
19. Chu K.H, Tsang W.K, Tang C.S. et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005;67:698–705.
20. Kellum J.A, Cerda J, Kaplan L.J, et al. Fluids for prevention and management of acute kidney injury. Int J Artif Organs. 2008;31:96–110.