Original Research Article

Skeletal Muscle Manifestations and Creatine Kinase in COVID-19

The Neurohospitalist
2022, Vol. 12(4) 597–606

DOI: 10.1177/19418744221105961
journals.sagepub.com/home/nho
SAGE

Sarah A. Friedman, MD[1,2], Zeinab Charmchi, MD[1], Michael Silver, MS[1], Nuri Jacoby, MD[1], Jonathan Perk, MD, PhD[1], and Yaacov Anziska, MD, MPH[1]

Abstract

Background and Purpose: Skeletal muscle symptoms and elevated creatine kinase (CK) levels have been consistently reported as part of the COVID-19 disease process. Previous studies have yet to show a consistent relationship between CK levels and skeletal muscle symptoms, disease severity, and death from COVID-19. The purpose of this study is to determine whether elevated CK is associated with a COVID-19 course requiring intubation, intensive care, and/or causing death. Secondary objectives: To determine if there is a relationship between elevated CK and (1) skeletal muscle symptoms/signs (2) complications of COVID-19 and (3) other diagnostic laboratory values. **Methods:** This is a retrospective, single center cohort study. Data were collected from March 13, 2020, to May 13, 2020. This study included 289 hospitalized patients with laboratory-confirmed SARS-CoV-2 and measured CK levels during admission. **Results:** Of 289 patients (mean age 68.5 [SD 13.8] years, 145 [50.2%] were men, 262 [90.7%] were African American) with COVID-19, 52 (18.0%) reported myalgia, 92 (31.8%) reported subjective weakness, and 132 (45.7%) had elevated CK levels (defined as greater than 220 U/L). Elevated CK was found to be associated with severity of disease, even when adjusting for inflammatory marker C-reactive protein (initial CK: OR 1.006 [95% CI: 1.002-1.011]; peak CK: OR 1.006 [95% CI: 1.002-1.01]; last CK: 1.009 [95% CI: 1.002-1.016]; q = .04). Creatine kinase was not found to be associated with skeletal muscle symptoms/signs or with other laboratory markers. **Conclusions:** Creatine kinase is of possible clinical significance and may be used as an additional data point in predicting the trajectory of the COVID-19 disease process.

Keywords

myalgia, myopathy, SARS-CoV-2, coronavirus, COVID-19, creatine kinase, CK, Creatine Phosphokinase

Introduction

Coronavirus disease 2019 (COVID-19) was first identified in December 2019 in Wuhan, China and spread throughout the world, leading to a global pandemic. Typical manifestations of COVID-19 include fever, fatigue, cough, and respiratory symptoms that can become fatal.[1] In addition, between 11-51% of patients with COVID-19 in various cohorts experienced muscle aches and muscle fatigue.[1-10] Creatine kinase (CK) is released from muscles in the case of muscle membrane dysfunction and/or direct muscle destruction.[11] This is often seen in conjunction with an exaggerated inflammatory response, like in the well-documented cytokine release storm seen with COVID-19.[10,12] However, elevations in CK can also be seen with muscle destruction that is independent of inflammation, for example in muscular dystrophy.

Creatine Kinase and Myopathies

Increased CK has been reported in 9-33% of patients with COVID-19.[2,4,5,8-10] Skeletal muscle injury and myopathies in the setting of COVID-19 have been seen in association with increased neutrophils, lymphopenia, increased C-reactive protein (CRP), increased D-dimer levels, length of ICU stay, and more severe disease.[10,12] However, other studies have linked patient-reported myalgia with more mild disease and reported them as an independent risk factor for improvement.[13,14]

Myositis, a subset of myopathy due to inflammation of muscle fibers, has also been reported in patients with COVID-19 in association with elevated CK values.[15-18] Many initially postulated that myositis might be secondary to direct invasion

[1]Department of Neurology, SUNY Downstate Medical Center, SUNY Downstate Health Sciences University, Brooklyn, NY, USA
[2]Department of Neurology, New York Presbyterian and Weill Cornell Medicine, New York, NY, USA

Corresponding Author:
Sarah A. Friedman, Department of Neurology, New York Presbyterian and Weill Cornell Medicine, 525 E 68th Street, New York, NY 10065-4870, USA.
Email: saf9137@nyp.org

of the virus into muscle tissue through the angiotensin coverting enzyme-2 (ACE-2) receptor present on muscle cells, however this has not been reported.[10,19] This, in association with findings of elevated inflammatory cytokines has led to the hypothesis that COVID-19-induced myopathy may be a result of the inflammatory cascade.[20]

Patients who presented with weakness and myalgia in association with elevated CK levels often experienced concurrent renal involvement, including acute kidney injury (AKI) and rhabdomyolysis. Acute kidney injury is often seen in association with rhabdomyolysis, but can also occur independent of muscle injury. Rhabdomyolysis, defined as CK greater than 5 times the upper limit of normal, has been reported both as an initial presentation of COVID-19 and as a late complication, also often in association with elevated inflammatory markers.[21-24] Similar cases of myopathies with elevated CK levels and rhabdomyolysis have been seen with SARS-CoV-1 and other coronaviruses; and subsequent autopsies have revealed focal myocyte necrosis in skeletal muscle.[5,25-28] One investigation isolated SARS-CoV-1 virus in 12% of post-mortem muscle samples.[29] To date, the SARS-CoV-2 virus has not been detected in muscle in post-mortem samples.[9,30]

Prognostic Value of CK and Contributing Factors

Previous literature has been conflicted, reporting both the presence of a relationship between elevated CK values and severity of disease,[10,11,31-36] as well as the lack of an association.[6,37,38] In addition, patients who died during admission have been reported to have elevated CK values,[39-42] under the assumption that it is part of the inflammatory cascade and related to the cytokine storm. While one study reported elevations in CK in conjunction with other inflammatory markers,[34] the relationship between CK and the inflammatory cascade in COVID-19 has not been thoroughly investigated.

Many medications can contribute to the development of myopathies and can affect CK levels. These include lipid lowering medications (particularly statins), antimalarial medications, antipsychotic medications, colchicine, antiretroviral medications, propofol, and TNF-α inhibitors.[43-45] Of particular consideration here are chloroquine and hydroxychloroquine, both of which have been widely used in the treatment of COVID-19.[5,46]

Hypotheses

The objective of this study was to evaluate the relationship between CK levels and severity of COVID-19 and death. Severe disease was defined as patients who required intubation, admission to the intensive care unit, or who expired during the hospital course. Secondary objectives of this study included an evaluation of the relationship between CK levels and other complications of COVID-19 (development of hypercoagulable sequela, acute respiratory distress syndrome [ARDS], or AKI), skeletal muscle symptoms/signs, and laboratory markers CRP and ferritin.

Methods

Study Design and Participants

This is an observational retrospective cohort study designed to examine the relationship between CK levels in hospitalized patients with COVID-19 and skeletal muscle symptoms/signs, disease severity, complications, and death. This study included patients who were admitted to University Hospital of Brooklyn (UHB) with laboratory confirmed SARS-CoV-2 and measured CK levels. The electronic medical record system was used to screen for eligible patients. Inclusion criteria were age > 18 years, CK levels measured, admission to UHB between March 13, 2020 – May 13, 2020, and laboratory-confirmed SARS-CoV-2 testing on admission. Two hundred eighty-nine patients fulfilled the criteria and were included in the study. We observed that CK levels were increasingly ordered as time progressed. This was due to a change in institutional policy and also likely influenced by increased understanding of the COVID-19 disease process. This study was approved by the Institutional Review Board at SUNY Health Sciences University and a HIPAA waiver was obtained for this study.

Data Collection

Clinical data, laboratory values, and imaging results were collected from the electronic medical record (HealthBridge used at UHB). The following data were collected: patient's age, sex, race, past medical history, home medications, date of positive SARS-CoV-2 PCR result, vital signs on admission, initial symptoms, duration of symptoms prior to admission, physical examination (particularly documented clinical weakness) on presentation, length of hospital admission, medications given during admission, laboratory values including white blood cell count, hemoglobin, platelets, potassium, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate transaminase, alkaline phosphatase, total bilirubin, lactate dehydrogenase, CRP, estimated sedimentation rate, troponin, D-dimer, ferritin, procalcitonin, anti-nuclear antibody, double-stranded DNA antibody, imaging findings including chest x-rays and CT Chest, clinical course, and disposition. Only those who had generalized weakness specifically stated in their medical documentation, not fatigue and/or tiredness, were included in the generalized weakness group. While D-Dimer values were collected, they were unavailable for statistical analysis due to variations in laboratory testing during the period of interest. Elevated CK was defined as > 220 U/L, based on the upper limit of normal used at our institution. This cutoff value is based on Beckman Coulter Inc. data on samples collected from 200 blood donors

in North Texas.[47] As defined by the widely accepted textbook *Neuromuscular Disorders*,[48] rhabdomyolysis was defined as CK greater than 5 the upper limit of normal, or 1100 U/L. Acute kidney injury was defined as creatinine greater than 2 times the patient's baseline, as defined as stage 2 AKI by Kidney Disease: Improving Global Outcomes.[49] Severe disease was defined as patients who required intubation, admission to the intensive care unit, or who expired during the hospital course.

Data Analysis

All continuous variables were tested for symmetry and normality and summarized with median and IQR. All categorical variables were summarized with frequency and percentage. Creatine kinase levels shown in Table 3 are reported as 25th percentile – 75th percentile. The relationship of CK levels was assessed with 3 main outcomes (severity of infection, death, and complications [hypercoagulable sequela, ARDS, and AKI]), and presence of skeletal muscle systems using a Wilcoxon rank sum test. Pearson Correlation coefficients were generated to investigate the relationship between CK levels with CRP and ferritin. To account for statistical correction for multiple comparisons, a positive-false discovery rate was used to calculate a q-value. "Q-values" are adaptive adjusted *P*-values for strong control of the false discovery rate when the *P*-values corresponding to the true null hypothesis are independent and uniformly distributed. Logistic regression models were created to control for the effect of CRP on the odds ratios.

Results

Demographics and Clinical Characteristics

Two hundred eighty-nine hospitalized patients with laboratory-confirmed SARS-CoV-2 and measured CK levels were included in the analysis. Patients' demographics and medical history are included in Table 1. Their mean age was 68.5 (SD: 13.8) years and 145 (50.2%) were men. 262 (90.7%) were African American, 236 (81.7%) had hypertension, 145 (50.2%) had diabetes, 119 (41.2%) had hyperlipidemia, 67 (23.2%) had chronic kidney disease (20 [6.9%] end stage renal disease on hemodialysis), 49 (17.0%) had lung disease (32 [11.1%] with asthma and 21 [7.3%] with chronic obstructive pulmonary disease), and 4 (1.4%) had a history of neuromuscular disease (1 [.3%] patient each with a history of Guillain-Barré syndrome, inflammatory myopathy, muscular dystrophy and myasthenia gravis). 92% of subjects had at least 1 comorbidity, 72% of subjects had greater than 2 comorbidities, and 54% had 3 or more comorbidities**.** Home medications included statins (140 [48.1%] patients), ACE inhibitors or angiotensin II receptor blockers (120 [41.5%]

Table 1. Baseline demographics of study participants – COPD: Chronic obstructive pulmonary disease. SLE: systemic lupus erythematosus. ACE: angiotensin-converting enzyme. ARBs: angiotensin II receptor blockers.

Baseline Demographics of Study Participants	
Characteristic	No. (%)
Age (years)	68.5
Sex	
Male	145 (50.2%)
Female	144 (49.8%)
Race/Ethnicity	
African American	252 (90.7%)
Caucasian	14 (4.8)
Asian	1 (.3%)
Other or combination	8 (2.8%)
Not available	4 (1.4%)
Past Medical History	
Hypertension	235 (81.7%)
Diabetes	145 (50.2%)
Hyperlipemia	119 (41.2%)
Chronic kidney disease	67 (23.2%)
End stage renal disease	20 (6.9%)
Coronary Artery Disease	54 (18.7%)
Previous stent placement	16 (5.5%)
Coronary artery bypass graft	6 (2%)
Myocardial infarction	13 (4.5%)
Lung disease	49 (17.0%)
Asthma	32 (11.1%)
COPD	21 (7.3%)
Cerebrovascular accident	33 (11.4%)
Malignancy	23 (8.0%)
Endocrinological disease	19 (6.6%)
Hypothyroidism	15 (5.2%)
Hyperthyroidism	3 (1.0%)
Cardiomyopathy	15 (5.2%)
Rheumatological disease	11 (3.8)
SLE	7 (2.4%)
Rheumatoid arthritis	5 (1.7%)
Seizures	11 (3.8%)
Neuromuscular disease	4 (1.4%)
Guillain-Barré syndrome	1 (.3%)
Inflammatory myopathy	1 (.3%)
Muscular dystrophy	1 (.3%)
Myasthenia gravis	1 (.3%)
Home Medications	
Statins	140 (48.1%)
ACE inhibitors or ARBs	120 (41.5%)
Beta blockers	94 (32.5%)
Glucocorticoids	24 (8.3%)
Hydroxychloroquine	7 (2.4%)
Anti-retroviral medication	5 (1.7%)
Colchicine	2 (.7%)
Fibrates	1 (.3%)

patients), beta blockers (94 [32.5%] patients), glucocorticoids (24 [8.3%] patients), hydroxychloroquine (7 [2.4%] patients), anti-retroviral medication (5 [1.7%] patients), colchicine (2 [.7%] patients), and fibrates (1 [.3%] patient). Of the 7 patients who were prescribed hydroxychloroquine prior to admission, 5 were for rheumatological disease and 2 were for the treatment of COVID-19.

Initial Presentation and Hospital Course

Table 2 describes patients' initial clinical picture and hospital course. Upon initial presentation, 52 (18.0%) patients reported myalgia and 92 (31.8%) patients reported subjective weakness. The mean (SD) duration of symptoms prior to presentation was 3.9 (3.8) days. Physical examination revealed documented clinical weakness in 30 (10.4%) patients. Initial CK levels were elevated in 132 (45.7%) patients. Initial CK was measured at a mean (SD) of 1.6 (3.4) days from presentation. 30 (10.4%) patients presented with rhabdomyolysis and 78 (27.0%) patients with AKI.

Intensive care was required for 79 (27.3%) patients and supplemental oxygen was required for 224 (77.5%) patients. Of those requiring supplemental oxygen, 100 (44.6%) were given intermediate oxygen support including high flow nasal cannula and/or bilevel positive airway pressure (BiPAP) and 55 (24.6%) were intubated. Another 62 (21.5%) patients likely would have been intubated, but expired soon after admission. Evidence of ARDS developed in 63 (21.8%) patients.

Patients received varying treatments during hospitalization including hydroxychloroquine (180 [62.3%] patients), glucocorticoids (78 [27.0%] patients), and tocilizumab (23 [8.0%] patients). Some patients developed hypercoagulable sequela including deep vein thrombosis (documented in 5 [1.7%] patient charts), pulmonary embolism (documented in 10 [3.5%] patient charts), and myocardial infarction (documented in 6 [2.1%] patient charts). Throughout their hospital course, 62 (21.5%) patients developed renal failure and 9 (3.1%) patients developed rhabdomyolysis after admission. 116 (40.1%) patients expired during admission.

Relationship Between CK and Other Variables

Duration of symptoms at the time of presentation did not have an association with CK levels. When initial, peak, and last CK levels were compared between patients with and without skeletal muscle symptoms/signs, there was not a statistically significant difference (see Table 3). A significant relationship was found between AKI and peak CK [25th percentile – 75th percentile] (277.5 U/L [152-875] vs 192 U/L [96-509], P = .03, shown in Table 3), indicating that elevated CK levels and AKI co-occur. No relationship was found between CK levels and ARDS or the development of hypercoagulable sequela during admission (see Table 3).

Initial, peak, and last CK levels were all found to be significantly associated with the development of severe

Table 2. Presentation and Hospital course - Rhabdomyolysis defined as creatine kinase greater than 5 times the upper limit of normal, or 1100 U/L. Acute kidney injury defined as creatinine greater than 2 times the patient's baseline. Acute respiratory distress syndrome defined as PaO2/FiO2 < 200. Intermediate oxygen therapy included nasal cannula and/or bilevel positive airway pressure (BiPAP).

Presentation and Hospital Course	
Symptoms at Presentation	No. (%)
Myalgia	52 (18.0%)
Subjective weakness	92 (31.8%)
Shortness of breath	194 (67.1%)
Fever	165 (57.1%)
Cough	155 (53.6%)
Dysphagia	4 (1.4%)
Physical Examination at Presentation	
Measured fever	87 (30.1%)
Objective weakness	30 (10.4%)
Initial Laboratory Findings	
Creatine kinase > 220 U/L	132 (45.7%)
Rhabdomyolysis	30 (10.4%)
Acute kidney injury	78 (27.0%)
Hospital Course	
Intensive care	79 (27.3%)
Supplemental oxygen	224 (77.5%)
Intermediate oxygen support	100 (34.6%)
Intubation	55 (19.0%)
Percutaneous endoscopic gastrostomy (PEG)	10 (3.5%)
Acute respiratory distress syndrome	63 (21.8%)
Medications Given During Admission	
Hydroxychloroquine	180 (62.3%)
Glucocorticoids	78 (27.0%)
Tocilizumab	23 (8.0%)
Complications During Admission	
Deep vein thrombosis	5 (1.7%)
Pulmonary embolism	10 (3.5%)
Myocardial infarction	6 (2.1%)
Renal failure	62 (21.5%)
Rhabdomyolysis	9 (3.1%)
Disposition	
Discharged	173 (59.9%)
Home	146 (50.1%)
Nursing home	14 (4.8%)
Subacute rehabilitation facility	11 (3.8%)
Acute rehabilitation facility	1 (.3%)
Hospice	1 (.3%)
Expired	116 (40.1%)

Table 3. Relationship of Creatine Kinase with Other Variables – Skeletal muscle symptoms/signs defined as muscle pain, subjective weakness or documented weakness on physical examination. Acute kidney injury defined as creatinine greater than 2 times the patient's baseline. Acute respiratory distress syndrome defined as PaO2/FiO2 < 200. Development of hypercoagulable sequela defined as documented myocardial infarction, pulmonary embolism or deep vein thrombosis during admission. Severe disease defined as need for intubation, admission to intensive care unit and/or death. Q-values reported adjust for the effect of CRP on CK values using pFDR. Data reported as mean value (25th percentile – 75th percentile) with units of U/L.

Relationship of Creatine Kinase with Other Variables				
Timing of CK Measurement	Yes	No	*P*-value	q-value
Skeletal Symptoms/Signs				
Initial CK	183 (97-556)	198 (91-531)	.92	.92
Peak CK	193 (112-579)	251 (100-546)	.82	.82
Last CK	155 (79-329)	168 (70-426)	.73	.73
Acute Kidney Injury				
Initial CK	260 (128-796)	183.5 (89-480)	.10	.14
Peak CK	277.5 (152-875)	192 (96-509)	.03	.07
Last CK	181 (94-353)	152.5 (71-352)	.21	.21
Acute Respiratory Distress Syndrome				
Initial CK	271 (118-729)	240 (107-877)	.78	.78
Peak CK	329 (120-801)	263.5 (137-966)	.89	.89
Last CK	151 (62-333)	177.5 (107-724)	.15	.18
Hypercoagulable Sequela				
Initial CK	191 (97-489)	195 (92-532)	.76	.76
Peak CK	196.5 (116-801)	214 (104-561)	.64	.64
Last CK	180.5 (104-489)	159 (71-331)	.19	.19
Severe Disease				
Initial CK	266 (118-770)	163 (76-371)	.001	.003
Peak CK	307 (137-801)	169 (79.5-460.5)	< .001	< .001
Last CK	191 (89-507)	133 (67-252.5)	< .001	.002
Death				
Initial CK	209 (109-625)	186.5 (88-489)	.18	.19
Peak CK	261.5 (135-715)	197 (89-531)	.05	.08
Last CK	188.5 (94-509)	142.5 (67-292)	.002	.004

Abbreviation: CRP, C-reactive protein; pFDR, positive-false discovery rate.

disease (initial CK: 266 U/L [118-770] vs 163 U/L [76-371], $P = .001$; peak CK: 307 U/L [137-801] vs 169 U/L [79.5-460.5], $P < .001$; last CK: 191 U/L [89-507] vs 133 U/L [67-252.5], $P < .001$, shown in Table 3 and Figure 1). Peak and last CK levels were associated with death (peak CK: 261.5 U/L [135-715] vs 197 U/L [89-531], $P = .05$; last CK: 188.5 U/L [94-509] vs 142.5 U/L [67-292], $P = .002$, shown in Table 3). When accounting for patients taking medications that can affect CK levels, these associations remained.

Initial CRP levels were also found to be statistically associated with the severity of disease ($P = .001$). However, when initial, peak, and last CK values were compared to CRP, there was no relationship that could be established (r = approximately 0 for all 3 comparisons). There was also a lack of association between CK values and ferritin, another marker of inflammation (r = .03). When the association of CK on outcomes of interest was adjusted for the effect of CRP, the relationship remained between initial, peak, and last CK and severe disease (initial CK: OR 1.006 [95% CI: 1.002-1.011]; peak CK: OR 1.006 [95% CI: 1.002-1.01]; last CK: 1.009 [95% CI: 1.002-1.016]; q = .04, further statistics shown in Table 4). However, when accounting for CRP, the relationship between peak and last CK with death is no longer significant (q = .17, q = .10, further statistics shown in Table 4).

Discussion

Skeletal Muscle Symptoms/Signs and CK Levels

The proportion of patients who presented with myalgia and weakness in our study was consistent with other cohorts.[1-10] The percentage of patients who had elevated initial CK levels was greater than previously reported: 48% vs 9-33%.[2,4,8-10] This may be due, in part, to more severe infection in this cohort, inconsistencies in sending CK levels due to differences in individual provider practice, changes in clinical care as our understanding of COVID-19 progressed, and/or inherent cohort differences. This cohort

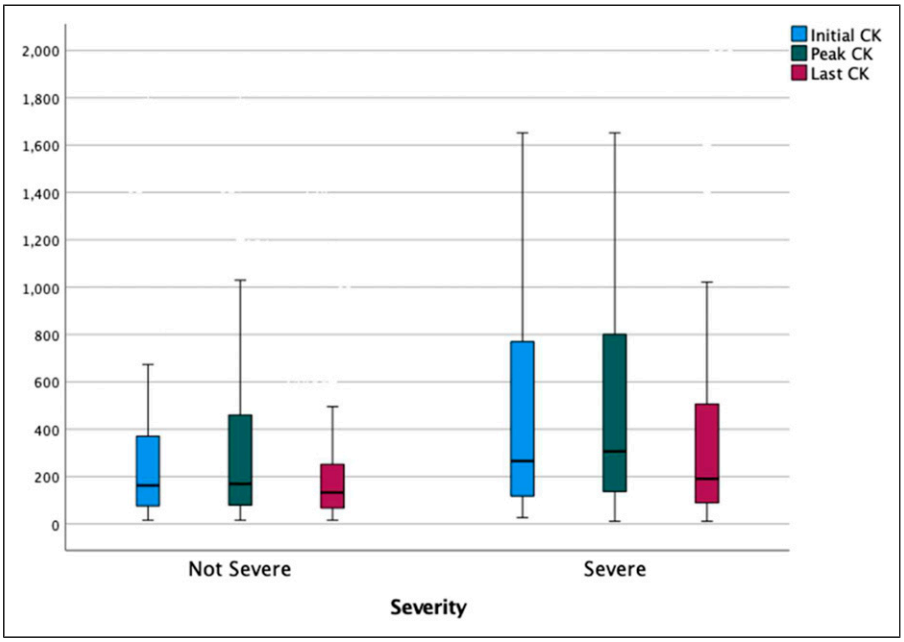

Figure 1. Creatine Kinase and Severity of COVID-19 – This boxplot shows range of creatine kinase in subjects with non-severe COVID-19 vs severe COVID-19. The difference between creatine kinase in each category (initial, peak, and last CK) compared between the 2 groups reached statistical significance with $P < .05$. Severe COVID-19 is defined as those who were intubated, admitted to the ICU, or died during admission. Outliers outside the 95% range are excluded in this image.

was predominantly African American, which may have contributed to the higher proportion of patients with elevated CK levels, as African Americans tend to have increased baseline CK levels compared to other populations. On the contrary, our cohort was generally older, with an average age of 69 years, and CK is inversely correlated with age.[50] Further, a strength of our study was the unique ability to study a predominantly African American population, a community that has been underrepresented in the literature on COVID-19.

The relationship between skeletal muscle symptoms/signs of COVID-19 and CK levels remains unclear. Both a significant relationship[10,51] and a lack of relationship have been reported.[52] Our cohort is consistent with the lack of a statistically significant relationship. There are a multitude of factors that may contribute to this finding. It is possible that there was a lack of subjective reporting of muscle complaints by patients due to the severity of other alarming symptoms, such as respiratory distress. This may also explain the lack of documented strength testing by clinicians in the wake of other urgent signs to document.

Severity of Disease, Death, and CK Levels

The literature remains undecided in regards to the relationship between elevated CK and severity of disease, with some studies reporting increased severity of disease with elevated CK,[10,12,30-34] and others a lack of relationship.[7,35,36] These differences may be due in part to differing definitions of severity, confounding variables, and/or inherent cohort differences. We report an association between elevated CK levels and severe COVID-19 in our cohort. This relationship was true for initial, peak, and last CK levels, indicating that when CK is measured is not particularly important. Interestingly, after accounting for CRP (as a marker of inflammation), severity of disease was the only factor that remained statistically correlated with CK levels. This may be because severe disease encompasses other sub-contributors to disease.

Further, in studies that reported an association between CK levels and severity of disease, they hypothesized that CK values were elevated alongside other inflammatory markers, which was statistically found in a study of an Austrian cohort.[35] It has not been statistically evaluated in other cohorts to our knowledge. While we also found an association between CRP and severity of disease, there was not a correlation between CK and other inflammatory markers, CRP and ferritin. As mentioned, when controlling for the effect of CRP, the correlation between CK and severity of disease weakens, however still remains statistically significant. This raises the question of whether there is an alternate pathway by which CK is elevated, whether it be an alternate inflammatory pathway (one that does not raise CRP) or a non-inflammatory pathway. Manazo et al reports a case of COVID-19 associated myopathy caused by a type 1 interferonopathy.[16] Type 1

Table 4. Relationship of Creatine Kinase with Other Variables, adjusted for effect of CRP – Each line represents odds ratios from a logistic regression model that controls for CRP. Skeletal muscle symptoms/signs defined as muscle pain, subjective weakness or documented weakness on physical examination. Acute kidney injury defined as creatinine greater than 2 times the subject's baseline. Acute respiratory distress syndrome defined as PaO2/FiO2 < 200. Development of hypercoagulable sequela defined as documented myocardial infarction, pulmonary embolism or deep vein thrombosis during admission. Severe disease defined as need for intubation, admission to intensive care unit and/or death.

Relationship of Creatine Kinase with Other Variables, adjusted for effect of CRP			
Timing of CK Measurement	OR (95% CI)	Prob Chi Sq	Q-value
Skeletal Symptoms/Signs			
Initial CK	.999 (.997 – 1.001)	.49	.53
Peak CK	1 (.998 – 1.001)	.89	.89
Last CK	1 (.998 – 1.003)	.80	.80
Acute Kidney Injury			
Initial CK	1.001 (.999 – 1.003)	.37	.43
Peak CK	1.001 (.999 – 1.002)	.28	.40
Last CK	1 (.998 – 1.003)	.93	.93
Acute Respiratory Distress Syndrome			
Initial CK	.999 (.997 – 1.001)	.35	.43
Peak CK	.999 (.997 – 1.001)	.25	.40
Last CK	.995 (.989 – 1.001)	.12	.26
Hypercoagulable Sequela			
Initial CK	1 (.997 – 1.003)	.99	.99
Peak CK	1 (.997 – 1.003)	.85	.85
Last CK	1.001 (.997 – 1.005)	.57	.57
Severe Disease			
Initial CK	1.006 (1.002 – 1.011)	.006	.04
Peak CK	1.006 (1.002 – 1.01)	.004	.04
Last CK	1.009 (1.002 – 1.016)	.01	.04
Death			
Initial CK	1.001 (.999 – 1.003)	.16	.29
Peak CK	1.002 (1 – 1.004)	.06	.17
Last CK	1.004 (1 – 1.008)	.03	.10

Abbreviation: CRP, C-reactive protein.

interferons (which include IFN-α, IFN-β, and IFN-ω) upregulate proteins that are toxic to muscle cells, resulting in elevated CK levels.[53] Previous studies in patients with rheumatological diseases have found that type 1 IFN suppresses CRP[54] and others have begun to examine the role of type 1 IFN in SARS-CoV-2 infection.[55,56] This is one potential mechanism that may explain our findings of elevations in CK, independent of CRP.

Consistent with previous studies,[36-39] we also found an association between CK levels and death. In our analysis, both peak and last CK levels were correlated with patient death. When adjusting for CRP, this relationship is lost; suggesting that this relationship might be mediated by an inflammatory response. These results suggest that CK is of potential clinical significance, and if there are no other obvious causes of CK elevation, it can be used as an additional data point to help predict the severity of patient's disease course. Though we caution that it should not be used as an independent proxy of disease severity.

Other Findings and Limitations

While a relationship between CK levels and the development of ARDS and hypercoagulable complications (pulmonary embolism, deep vein thrombosis, and myocardial infarction) was not established, it is important to note that cause of death was not available for us to include in our analysis. Therefore, it is possible that pulmonary emboli and myocardial infarctions may have been the cause of death in many patients but could not be properly evaluated or included for analysis. In addition, autopsies were often not performed during the height of the COVID-19 pandemic in New York City.

It is important to discuss that 40.1% of patients who were hospitalized with COVID-19 at UHB during this time period had CK levels measured. As discussed in the methods section, the proportion of patients who had CK levels measured increased as time progressed. This was due to policy changes at our institution during this period and increased understanding of the COVID-19 disease process. Creatine

kinase was not checked more often in patients with skeletal muscle complaints than in those without skeletal muscle complaints, therefore, we do not feel that this affected the results. Similarly, it is likely that there were differences in the content of clinician interviews and physical examination as our understanding of the disease process grew, likely affecting the documentation of subjective and objective weakness.

Sociodemographic factors likely contributed to the rate of disease, disease severity, and death rate seen in our cohort. African American communities experience a disproportionate burden of COVID-19, much of which is multifactorial including factors like chronic medical comorbidities, inconsistent access to healthcare, types of employment, public transportation use, and population density.[57]

When designing this study, D-dimer was an important laboratory value that we hoped to include. However, due to variations in laboratory testing of D-dimer at UHB during the period of interest, the data was not optimized for statistical analysis.

Conclusion

Skeletal muscle symptoms and signs are a ubiquitous part of the COVID-19 presentation and their presence may be of important clinical value. The relationship between skeletal muscle symptoms/signs and elevated CK levels remains unclear, as no association was established in this cohort, though has been in others. Our study did reveal that elevated CK values are correlated with the severity of infection; and this association remained after adjusting for inflammatory markers and throughout the hospital course. Thus, CK is a laboratory value with possible clinical significance and may be useful in predicting the trajectory of the COVID-19 disease process in a predominantly African American population. Further studies investigating the pathophysiology of CK and COVID-19 are needed to better understand this correlation.

Acknowledgement

Many thanks to everyone who helped with data collection: Kaitlynne Cunningham, Ron Baazov, Allyson Hernandez, Kush Sharma, MBBS, Mohamed Eldokmak, MBCHB, and Harika Hazal Korkusuz, MD.

Author Note

None of the authors have published, posted, or submitted any related papers from this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sarah A. Friedman https://orcid.org/0000-0001-7667-7905

References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.
2. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol*. 2020;92(6):577-583.
3. Yanga J, Zhenga Y, Goua X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95.
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
5. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. 2020;94(22):959-969.
6. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
7. Gulati A, Pomeranz C, Qamar Z, et al. A Comprehensive Review of Manifestations of Novel Coronaviruses in the Context of Deadly COVID-19 Global Pandemic. *Am J Med Sci*. 2020;360(1):5-34.
8. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
9. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
10. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*. 2020;95(8):e1060-e1070.
11. Foreback CC, Chu JW, Foery RF. Creatine kinase Isoenzymes: Electrophoretic and quantitative measurements. *Crit Rev Clin Lab Sci*. 1981;15(3):187-230.
12. Abenza-Abildua M, Ramirez-Prieto M, Moreno-Zabaleta R, et al. Neurological complications in critical patients with COVID-19. *Neurologia (Engl Ed)*. 2020;35:621-627.
13. Heydari K, Rismantab S, Shamshirian A, et al. *Clinical and Paraclinical Characteristics of COVID-19 patients: A systematic review and meta-analysis*. medRxiv; 2020.
14. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Micro Inf*. 2020;26(6):762-772.

15. Zhang H, Charmchi Z, Seidman RJ, et al. COVID-19-associated myositis with severe proximal and bulbar weakness. *Muscle Nerve*. 2020;62(3):E57-E60.
16. Manzano GS, Woods JK, Amato AA. Covid-19-associated myopathy caused by type 1 interferonopathy. *N Engl J Med*. 2020;383:2389-2390.
17. Beydon M, Chevalier K, Al Tabaa OA, et al. Myositis as a manifestation of SARS-CoV-2. *Ann Rheum Dis*. 2020;80:e42.
18. Zhang Q, Shan KS, Minalyan A, O'Sullivan C, Nace T. A rare presentation of coronavirus disease 2019 (COVID-19) induced viral myositis with subsequent rhabdomyolysis. *Cereus*. 2020; 12(5):e8074.
19. Ferrandi PJ, Always SE, Mohamed JS. The interaction between SARS-CoV-2 and ACE2 may have consequences for skeletal muscle viral susceptibility and myopathies. *J Appl Physiol*. 2020;129(4):864-867.
20. Ozdag Acarli AN, Samanci B, Ekizoglu E, et al. Coronavirus DISEASE 2019 (COVID-19) from the point of view of neurologists: Observation of neurological findings and symptoms during the combat against a pandemic. *Noro Psikiyatr Ars*. 2020;57(2):154-159.
21. Chan KH, Farouji I, Hanoud AA, Slim J. Weakness and elevated creatinine kinase as the initial presentation of coronavirus disease 2019 (COVID-19). *Am J Emerg Med*. 2020;38(7): 1548.e1-1548.e3.
22. Gefen AM, Palumbo N, Nathan SK, Singer PS, Castellanos-Reyes LJ, Sethna CB. Pediatric COVID-19-associated rhabdomyolysis: A case report. *Pediatr Nephrol*. 2020;35(8):1517-1520.
23. Jin M, Tong Q. rhabdomyolysis as potential late complication associated with COVID-19. *Emerg Infect Dis*. 2020;26(7):1618-1620.
24. Taxbro K, Kahlow H, Wulcan H, Fornarve A. Rhabdomyolysis and acute kidney injury in severe COVID-19 infection. *BMJ Case Rep*. 2020;13:e237616.
25. Wang JT, Sheng WH, Fang CT, et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. *Emerg Infect Dis*. 2004;10(5):818-824.
26. Fan CK, Yieh KM, Peng MY, Lin JC, Wang NC, Chang FY. Clinical and laboratory features in the early stage of severe acute respiratory syndrome. *J Microbiol Immunol Infect*. 2006; 39(1):45-53.
27. Tsai LK, Hsieh ST, Chao CC, et al. Neuromuscular disorders in severe acute respiratory syndrome. *Arch Neurol*. 2004;61(11): 1669-1673.
28. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan*. 2005; 14(3):113-119.
29. Farcas GA, Poutanen SM, Mazzulli T, et al. Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus. *J Infect Dis*. 2005;191(2):193-197.
30. Suh J, Mukerhi SS, Collens SI, et al. Skeletal Muscle and Peripheral Nerve Histopathology in COVID-19. *Neurology*. 2021;97(8):e849-e858.
31. Danwang C, Endomba FT, Nkeck JR, Wouna DLA, Robert A, Noubiap JJ. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). *Biomark Res*. 2020;8:37.
32. Duan J, Wang X, Chi J, et al. Correlation between the variables collected at admission and progressiion to severe cases during hospitalization among patients with COVID-19 in Chongqing. *J Med Virol* 2020;92:2616-2622.
33. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. *Clin Chem Lab Med*. 2020;58(7):1021-1028.
34. Khinda J, Janjua NZ, Cheng S, van den Heuvel ER, Bhatti P, Darvishian M. Association between markers of immune response at hospital admission and COVID-19 disease severity and mortality: A meta-analysis and meta-regression. *J Med Virol*. 2020;93:1-21.
35. Pitscheider L, Karolyi M, Burkert FR, et al. Muscle involvement in SARS-CoV-2 infection. *Eur J Neurol* 2021;28(10): 3411-3417.
36. Orsucci D, Trezzi M, Anichini R, et al. Increased creatine kinase may predict a worse COVID-19 outcome. *J Clin Med*. 2021;10(8):1734.
37. Ghahramani S, Tabrizi R, Lankarani KB, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: A systematic review and meta-analysis. *Eur J Med Res*. 2020;25:30.
38. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: A multicenter study of clinical features. *Am J Respir Crit Care Med*. 2020;201(11):1380-1388.
39. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. *BMJ*. 2020;368:m1091.
40. Bonetti G, Manelli G, Patroni A, et al. Laboratory predictors of death from coronavirus disease 2019 (COVID-19) in the area of Valcamonica, Italy. *Clin Chem Lab Med*. 2020;58(7):1100-1105.
41. Chen X, Yan L, Fei Y, Zhang C. Laboratory abnormalities and risk factors associated with in-hospital death in patients with severe COVID-19. *J Clin Lab Anal*. 2020;34(10):e23467.
42. Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. *Eur J Intern Med*. 2020;76:97-99.
43. Doughty CT, Amato AA. Toxic myopathies. *Continuum (Minneap Minn)*. 2019;25(6):1712-1731.
44. Misra DP, Gasparyan AY, Zimba O. Benefits and adverse effects of hydroxychloroquine, methotrexate and colchicine: searching for repurposable drug candidates. *Rheumatol Int*. 2020;40(11):1741-1751.
45. Lonngqvist PA, Bell M, Karlsson T, Wiklund L, Hoglund AS, Larsson L. Does prolonged Propofol sedation of mechanically ventilated COVID-19 patients contribute to critical illness myopathy? *Br J Anaesth*. 2020;125(3):e334-e336.
46. Eadie MJ, Ferrier TM. Chloroquine myopathy. *J Neurol Neurosurg Psychiat*. 1966;29(4):331-337.

47. Beckman Coulter Inc. Data on samples colleceted from 200 blood donors in North Texas. *OSR General Chemistry*. 2009; 6.79(1).
48. Amato AA, Russell JA. Approach to patients with neuromuscular disease. In: AA Amato, JA Russell, eds. *Neuromuscular Disorders, 2e*. New York, New York: McGraw-Hill; 2016.
49. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Inter., Suppl*. 2012; 2:1-138.
50. Neal RC, Ferdinand KC, Ycas J, Miller E. Relationship of ethnic origin, gender, and age to blood creatine kinase levels. *The American Journal of Medicine* 2009;122(1):73-78.
51. Kardas O, Ozturk B, Sonkaya AR. A prospective clinical study of detailed neurological manifestations in patients with COVID-19. *Neurol Sci*. 2020;41(8):1991-1995.
52. Vacchiano V, Riguzzi P, Volpi L, et al. Early neurological manifestations of hospitalized COVID-19 patients. *Neurol Sci*. 2020;41(8):2029-2031.
53. Greenberg SA, Higgs BW, Morehouse C, et al. Relationship between disease activity and type 1 interferon- and other cytokine-inducible gene expression in blood in dermatomyositis and polymyositis. *Genes & Immunity*. 2012;13:207-213.
54. Enocsson H, Sjowall C, Skogh T, Eloranta MJ, Ronnbom L, Wettero J. Interferon-alpha mediates supression of C-Reactive Protein. *Arthritis & Rheumatism*. 2009;60(12):3755-3760.
55. Lei X, Dong X, Ma R, et al. Activation and evasion of type 1 interferon responses by SARS-CoV-2. *Nat Commun*. 2020;11:3810.
56. Lee JS, Shin EC. The type 1 interferon response in COVID-19: Implications for treatment. *Nat Rev Immunol*. 2020;20(10): 585-586.
57. Yancy CW. COVID-19 and African Americans. *JAMA*. 2020; 323(19):1891-1892.