

Editorial

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Is creatine kinase associated with outcome in COVID-19?

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The new “severe acute respiratory syndrome” (SARS)-correlated coronavirus (SARS-CoV-2), first isolated from three patients from Wuhan (China), has been spreading worldwide since the end of 2019, emerging as an exceptional global crisis. This disorder was called “coronavirus disease 2019” or COVID-19. Clinical features are highly variable, and the clinical severity ranges from asymptomatic to fatal. The understanding of SARS-CoV-2 infection is ongoing. Several neurological symptoms were identified as part of the COVID-19 spectrum, including muscle pain, confusion, and headache^[1].

A study performed on 113 patients who deceased from COVID-19 revealed that acute respiratory distress syndrome with respiratory failure, sepsis, heart failure and subsequently hypoxic encephalopathy were the most common severe complications. The median age of the deceased patients was 68 years and male gender was predominant (73%). Hypertension and other cardiovascular disorders were more frequent among the patients who died. Dyspnea, chest tightness and altered consciousness were more frequent in the deceased patients, as well as hyperCKemia (increased levels of creatine kinase, CK)^[2].

Other retrospective studies provided partly similar results regarding CK, but data on this marker of muscle damage were only briefly mentioned in most papers, and a detailed literature review is not available to date. This exploratory literature review aimed to summarize early findings on the relevance of CK as a marker potentially associated with outcome in patients infected by Sars-CoV-2.

PubMed was searched up to May 13, 2020 for all articles about “(sars* OR covid* OR coronavirus) and (CK OR CPK OR creatine kinase OR creatine phosphokinase OR muscular OR muscle OR retrospective



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OR series)”, and the abstracts were reviewed to identify all the relevant publications. The full text of all the retrospective case series or cohort studies which were identified according to this search were then screened for the following words: “kinase” or “CK” or “CPK”. All the studies reporting data on CK levels (in any form) were included in this analysis and summarized in [Table 1](#). Retrospective studies including only children or pregnant women were not considered. We mainly focused on the publications where there was a distinction between less severe and more severe cases (defined in any possible way, see [Table 1](#)) which could work as an outcome measure. These references, allowing an evaluation of CK as a marker potentially associated with outcome, are underscored in [Table 1](#).

Twenty-one retrospective studies which included data on CK were identified [[Table 1](#)]^[1-21]. Among these 21 papers, 12 (underscored in [Table 1](#))^[2,4,6,7,9,10,14,15,18-21] provided a measure of severity potentially useful to serve as an outcome measure. Eleven of these studies were from China and one from South Korea.

There is marked heterogeneity between these studies. In some instances, CK data were provided as a continuous variable, whereas other studies showed the fraction of patients with CK higher than a given value (different from study to study). In some cases, CK levels were presented as a mean, in others as a median. Furthermore, the definition of severe cases, and their percentage, mean (or median) age and gender proportion were also markedly different from study to study. Blood was sampled at admission in most of these retrospective studies (but not in all of them). These evident differences precluded further statistical analysis and a formal meta-analysis.

However, some conclusions could be drawn. In 11 of the 12 studies considered, CK levels were higher in the more severe group of COVID-19 patients^[2,4,6,7,9,10,14,18-21]. Among these 11 studies, the difference reached statistical significance in 7 studies^[2,7,14,18-21], while there was no statistical significance in 4. The significant studies included an average of 249 patients, compared with 69 patients in the other studies. Therefore, the lower power of the smaller studies could explain the fact that the difference did not reach statistical significance in some of these studies.

The five larger studies, each involving more than 160 patients, showed similar findings.

Chen and coworkers observed that CK levels at admission were markedly higher in the patients who subsequently died (median 189 U/L) compared with the ones who recovered (median 84 U/L)^[2].

Mao and coworkers reported that CK was higher in the patients with more severe pneumonia; unfortunately, this study did not explicitly specify when CK was tested^[14].

Zhang *et al.*^[19] reported that mean CK was higher in the patients with pneumonia compared with the patients with no radiological evidence of pneumonia; in the pneumonia group, higher CK could predict a more severe clinical picture.

Zheng *et al.*^[20] showed that median CK levels at admission were higher in the more severe group; hyperCKemia (> 190 U/L) was present in 30% of the more severe cases vs. 6% of the others (significant difference).

Zhou *et al.*^[21] observed that median CK at admission was higher in the patients who subsequently died than in the subjects who were discharged; hyperCKemia (> 185 U/L) was observed in 21% of the deceased persons compared with 9% of the others, and was associated with death (univariate odds ratio 2.56, 95% confidence interval 1.03-6.36).

Table 1. Retrospective studies on COVID-19 including data on CK

Author	Country	Definition of severe cases	Severe/total cases	Mean age (or median)	Males (%)	How CK is reported	When blood was sampled	Results (concerning CK)
Bhatraju <i>et al.</i> ^[3]	United States	Mechanical ventilation	18/24	64	63%	No. of cases with CK U 100 U/L	During the first 3 days in ICU	CK performed on only six ICU patients (increased in three of them)
Chen <i>et al.</i> ^[1]	China	Death	11/99	56	68%	% of cases with CK > 310 U/L	Admission	Elevation of CK in 13 (13%) patients, one of whom had CK 6,280 U/L
Chen <i>et al.</i> ^[4]	China	More severe respiratory insufficiency	11/21	56 (median)	81%	Continuous value (U/L)	Admission	Median CK 214 U/L in severe cases vs. 64 U/L in moderate cases (n.s.)
Chen <i>et al.</i> ^[2]	China	Death	113/274	62	62%	Continuous value (U/L)	Admission	CK was markedly higher in deceased patients (median 189) than in recovered ones (median 84) (sign.)
Chen <i>et al.</i> ^[5]	China	?	?/78	45 (median)	50%	?	?	? (CK data cited in the results but not shown in detail)
Chen <i>et al.</i> ^[6]	China	Death	19/55	74	62%	Continuous value (U/L)	Admission	Median CK 213 U/L in deceased cases vs. 106 U/L in others (n.s.)
Chen <i>et al.</i> ^[7]	China	More severe respiratory insufficiency	43/145	48	55%	Continuous value (U/L)	?	Severely ill patients had higher CK (90 vs. 60 U/L) (sign.)
Du <i>et al.</i> ^[8]	China	Death	85/85	66 (median)	73%	% of cases with CK > 170 U/L	Admission	Increased CK in 37%
Hong <i>et al.</i> ^[9]	South Korea	ICU	13/98	55	39%	continuous value (U/L)	Admission	Mean CK 132 in ICU patients and 101 in non-ICU (n.s.)
Hou <i>et al.</i> ^[10]	China	"Clinically advanced pneumonia", ICU, death	17/101	51 (median)	44%	Continuous value (U/L)	Admission	CK higher in the more severe group (96 vs. 75 U/L) but not statistically significant (n.s.)
Huang <i>et al.</i> ^[11]	China	ICU	8/34	56	41%	?	?	CK increased in one of the 12 patients in whom it was tested
Lescure <i>et al.</i> ^[12]	France	Death	1/5	46 (median)	60%	Continuous value (U/L)	Admission	Normal in 4 subjects; not tested in the deceased patient
Liu <i>et al.</i> ^[13]	China	Death	16/137	55	45%	?	?	? (CK data not provided in the results differently than declared in the methods)
Mao <i>et al.</i> ^[14]	China	More severe pneumonia	88/214	53	41%	Continuous value (U/L)	?	Median CK higher in the severe patients: 83 vs. 59 U/L (sign.)
Mo <i>et al.</i> ^[15]	China	No remission in 10 days ("refractory")	85/155	54 (median)	55%	Continuous value (U/L)	Admission	Median CK 89 U/L in "refractory" patients and 100 U/L in the other patients (n.s.)
Yang <i>et al.</i> ^[16]	China	?	0/149	45	54%	% of cases with CK > 200 U/L	Admission	CK increased in 12 cases (8%)
Zangrillo <i>et al.</i> ^[17]	Italy	Invasive ventilation	73/73	61 (median)	84%	Continuous values	Admission	Median (quartile 25% - quartile 75%) CK 128 U/L (101-471)
Zhang <i>et al.</i> ^[18]	China	ICU/mechanical ventilation or death ("composite end-point")	32/95	49 (median)	56%	% of cases with CK < 200 (normal) or 200-400 or 400-600 or >600 U/L	Highest levels during hospitalization	For < 200 U/L group, 17.9% of the patients reached the composite endpoint. For 200-400 U/L group, 41.7% of the patients reached the composite endpoint. For 400-600 U/L group, 44.4% of the patients reached the composite endpoint. For > 600 U/L group, 57.1% of the patients reached the composite endpoint. (sign.) Higher CK activity correlated strongly with severe pneumonia and composite endpoint. (sign.)

Zhang <i>et al.</i> ^[19]	China	Radiological evidence of pneumonia	573/665	47 (pneumonia) 35 (others) (sign.)	51%	Continuous value (U/L)	?	Mean CK 73 U/L (patients with pneumonia) vs. 63 U/L (others) (sign.) In the pneumonia group, higher CK could predict a more severe clinical picture (univariate OR 1.001 with confidence interval 1.000-1.002) (sign.)
Zheng <i>et al.</i> ^[20]	China	More severe respiratory insufficiency	30/161	45 (median)	50%	Both continuous values (U/L) and % of cases with CK > 190 U/L	Admission	Median CK higher in severe patients (100 vs. 69 U/L) (sign.) HyperCKemia present in 30% of the more severe cases vs. 6% of the others (sign.)
Zhou <i>et al.</i> ^[21]	China	Death	54/191	56 (median)	62%	Both continuous values (U/L) and % of cases with CK > 185 U/L	Admission	Median CK overall 21.5 U/L: 39 U/L in the patients who died and 18 U/L in subjects who were discharged (sign.) HyperCKemia (> 185 U/L): 22/168 (13%) overall: 11/52 (21%) in deceased subjects vs. 11/116 (9%) of the other patients (sign.) HyperCKemia was associated with death: univariate OR (95%CI) 2.56 (1.03-6.36) (sign.)

?: data not provided in the given article; CK: creatine kinase; ICU: intensive care unit; n.s.: not significant difference; OR: odds ratio; Ref.: see reference list; Sign.: statistically significant difference

Taken together, the retrospective studies available to date (especially the larger ones) showed some association between CK levels and the clinical outcome of patients infected by SARS-CoV-2. CK was determined at hospital admission in most cases.

This preliminary review showed the limitations typical of all the systematic reviews based on retrospective studies. It is not possible to rule out the influence of various confounding factors in the original studies. Some of the included studies did not fully clarify inclusion criteria, course of disease and severity of disease. Lastly, most of these studies were performed in China, and this could lead to geographic and ethnicity biases.

Furthermore, data on CK levels were only briefly mentioned in most papers, and possible correlations with other clinical features (such as muscle pain) were not researched.

Only the retrospective study performed in Wuhan^[14] reported that “skeletal muscle injury” (defined in the following way: “when a patient had skeletal muscle pain and elevated serum CK”, greater than 200 U/L) was significantly more frequent in severe COVID-19, compared with less severe diseases (19% vs. 5%). Median CK levels were higher in the more severe group: 83 U/L (range 9-12,216) vs. 59 U/L (19-1,260). Interestingly, patients with “muscle injury” had multiorgan damage, including more severe liver and kidney abnormalities^[14].

Another Chinese retrospective work performed on compromised patients reported that muscle pain was an onset symptom in 22%^[2]. Interestingly, a European study performed on patients with much milder symptoms reported a higher prevalence of muscle pain (63%)^[22].

Furthermore, severe rhabdomyolysis is a possible, rare complication of COVID-19^[23].

A third of patients with other coronavirus infections (namely SARS) have manifested myalgia and elevated CK, and in some instances rhabdomyolysis^[24]. Therefore, even if electromyography (EMG), muscle imaging

Table 2. Typical neurological features associated with mild and severe COVID-19

Neurological features typical of mild/initial cases	Neurological features typical of severe cases
Headache	Delirium
Smell impairment	Impaired consciousness
Myalgia/muscle pain	Pyramidal signs
	Ischemic stroke (rare)
	Muscle damage with increased CK

CK: creatine kinase

or muscle histopathology is not available to date, coronavirus infections may possibly cause viral myositis on the basis of the above reported data^[24]. Immune-mediated mechanisms should also be considered^[25]. Furthermore, severely ill patients may develop weakness due to muscle atrophy from disuse and/or critical illness myopathy (and/or polyneuropathy), so specifically designed studies are needed^[24].

The most common neurological features associated with COVID-19 are presented in Table 2. Muscle pain is common in both mild and severe cases, and in the most compromised patients, it is accompanied by increased CK levels and possibly true myopathic damage.

Interestingly, angiotensin converting enzyme 2, which was identified as the functional receptor for SARS-CoV-2, is present in multiple human tissues, including skeletal muscle and nervous system^[14]. Therefore, the longitudinal follow-up of people who have been infected by SARS-CoV-2 should include a careful assessment of the neuromuscular system. There is a strong need for prospective and specifically designed studies, including EMG, muscle imaging, muscle histopathology and PCR assay for detection of SARS-CoV-2 in muscle tissue.

In conclusion, some association between CK levels and the clinical outcome of patients infected by SARS-Cov-2 seems to exist, but the precise mechanisms are still unknown. The influence of this novel coronavirus on voluntary muscle really needs to be clarified.

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