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The prognostic value of elevated creatine kinase as an Independent Prognostic Factor for COVID-19 mild infection

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Abstract:

Background: Creatine kinase (CK), which is a marker of muscle damage, was also often found to be elevated in deceased COVID-19 patients and those with severe disease, Therefore, higher CK could be used as a prognostic marker to indicate a more severe clinical picture of COVID-19. **Patients and methods:** This study included 225 out-hospitalized patients with confirmed COVID-19 infection, these study subjects were randomly selected irrespective of the age group and both genders were included, Assay procedure as manufactory instructions and Reagents of Spectrum diagnostics, optimized DGKC/IFCC liquid reagent, Egypt are used. **Results:** This study showed male gender was more frequent (n=135, 60%) than the female gender (n=90, 40%). This study reveals high serum CK levels in 45 patients (20%), which has a sensitivity of 20% as a biomarker for COVID-19 diagnosis in out-hospitalized patients (Outpatients and patients under home observation), with a p-value is <0.001 which is less than 0.05. **Conclusion:** CK has a sensitivity of 20% in out-hospitalized patients (Outpatients and patients under home observation), thus elevated CK is best used as a rule-in test rather than a rule-out test.

Keywords: CK, creatine kinase, COVID-19, out-hospitalized patients, biomarker.

1. Introduction:

The coronavirus disease 2019 (COVID-19) outbreak started in December 2019 in China and has spread sharply all over the world. COVID-19 is a disease that could cause multiple organ injuries, several neurological and neuromuscular symptoms have been identified as part of the COVID-19 spectrum, including muscle pain and fatigue⁽¹⁾.

Skeletal muscle injury has originally been defined by muscle pain associated with elevated serum creatine kinase (CK) levels⁽²⁾, Early reports from Asia, have suggested that increased serum levels of the muscular

enzyme creatine (phospho)-kinase (CK or CPK) could be linked with a worse prognosis, this observation has been further confirmed by most recent retrospective studies⁽³⁾.

Creatine kinase (CK), which is a marker of muscle damage, was also often found to be elevated in deceased COVID-19 patients and those with severe disease^(4,5), Therefore, higher CK could be used as a prognostic marker to indicate a more severe clinical picture of COVID-19.

This study aimed to evaluate the prognostic performance of elevated Creatine kinase (CK) in

patients with COVID-19, Outpatients and patients under home observation are included in this study, while hospitalized patients are not included, Because CK levels can also raise during cardiac disorders, so we selected patients without any reported history of myocarditis or peritonitis.

2. Patients and methods

2.1. Study population Patients

This study included 225 mild infected (patients under home observation out-hospitalized) patients with confirmed COVID-19 infection, these study subjects were randomly selected irrespective of the age group and both genders were included.

It was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All the studied population was informed about the purpose of sample collection. Patients were free to refuse sample collection.

2.2. Data collection

In this cross-sectional study, we obtained data regarding 225 non hospitalized patients with confirmed COVID-19 via real-time reverse transcription-polymerase chain reaction (PCR), they came to Alyamenny laboratory in Alexandria, Egypt for biomarkers and complete blood count investigations, we reviewed the medical records and compiled data between January 12 and May 30, 2021.

2.3. Collection and processing of blood samples:

1 ml blood sample was collected for performing serum Creatine kinase (CK) test (Spectrum diagnostics, optimized DGKC/IFCC liquid reagent, Egypt) on 225 Positive COVID-19 patients for individuals matching in age and gender.

2.4. Assay procedure as manufactory instructions:

Reagents of Spectrum Diagnostics kit human CK test and samples allowed to be at room temperature before testing, (serum was separated from a blood sample by centrifugation), considered normal serum CK level for men is 24-204 U/L, and for women 24 – 173 U/L.

2.5. Statistical analysis

Data were analyzed using SPSS statistical software, version 20.0(SPSS, Chicago, Illinois, USA). All continuous data are presented as means and standard deviations, while categorical data are presented as numbers and percentages. A chi-square test was used to compare categorical variables. Multivariate regression analysis was performed to analyze relationships between COVID-19 infected patients and serum CK levels, this model was generated using independent variables achieving a p-value of 0.10 during bivariate analysis. Then, the best-fit model was generated without interaction variables. For all calculations, a p-value of less than 0.05 was considered statistically significant.

3. Results:

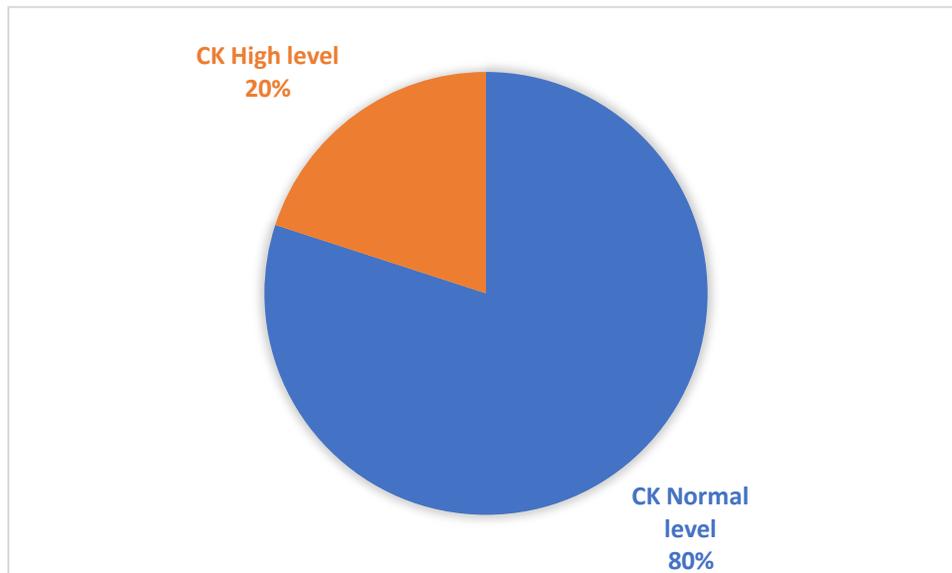
Table (1): shows the percentage of COVID-19 mild infected Patients with the serum CK level, The present study included patients aged from 14 years to 75 years mean age was 44.5 ± 30.5 who were confirmed to have Covid-19 based on real-time reverse transcription-polymerase chain reaction, male gender was more frequent (n=135, 60%) than female gender (n=90, 40%). This study reveals high serum CK levels in 45 patients (20%), which has a sensitivity of 20% as a biomarker for COVID-19 diagnosis in out-hospitalized patients (Outpatients and patients under home observation), with a p-value is <0.001 which is less than 0.05.

Table (1): The association between serum CK level and mild infection of COVID-19 Patients

COVID-19 POSITIVE Patients	Serum CK level				Total	
	*Normal		**High level			
	No.	%	No.	%	No.	%
Male	108	48	27	12	135	60
Female	72	32	18	8	90	40
Total	180		45		225	

The *p*-value is <0.001, Significant at *p* < .05.

Figure (1): CK levels with the mild infection of COVID-19 patients



CK Levels with COVID-19 infection

4. Discussion:

The new coronavirus may cause viral myositis, as seen previously in other coronavirus infections, such as severe acute respiratory syndrome (SARS), and other influenza infections (influenza A and B) ⁽⁶⁾, it is understood that the novel coronavirus (2019-nCoV) uses an angiotensin-converting enzyme 2(ACE-2) receptor to enter human respiratory cells and cause infection. Due to its presence in various tissues, it is possible that the virus directly invades the skeletal muscle and nervous system via the same pathway. The Immune-mediated pathway might also contribute to causing muscle injury in COVID-19 patients. Moreover, muscle atrophy may occur and cause weakness in critically ill patients ⁽⁷⁾, and dehydration and hypovolemia in COVID-19 patients may contribute to renal impairment and subsequent increase in CK levels ⁽⁸⁾.

CK level is an important representative biochemical index of myocardial injury. Several studies found evidence supporting the association between cardiovascular complications and poor prognosis in COVID-19 patients. It is not clear to date if increased CK levels in COVID-19 patients are caused by true myopathic damage. Muscle pain and fatigue are common in both mild and severe cases ⁽⁹⁾.

This study was conducted on 225 mild infected COVID-19 patients (out hospitalized and home observation Patients) who were confirmed to have Covid-19 based on real-time reverse transcription-polymerase chain reaction, This study reveals high serum CK levels in 45 patients (20%), which has a sensitivity 20% as a biomarker for COVID-19 diagnosis in out-hospitalized patients (Outpatients and patients under home observation), thus elevated CK is best used as a rule-in test rather than rule-out test, CK has a sensitivity 20% in mild COVID-19 infection which was less than other biomarkers as ferritin which has a sensitivity of 71.4% ⁽¹⁰⁾, LDH has a sensitivity

67.7% ⁽¹¹⁾, and D.Dimer has a sensitivity 36.4% ⁽¹²⁾ in mild COVID-19 infection.

Reports from Asia (especially from China) confirm that CK levels at admission are higher in COVID-19 patients who later experience more severe outcomes, and hyperCKemia is associated with a worse prognosis ⁽⁴⁾

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 ⁽²⁾.

Zheng *et al.* 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) ⁽¹³⁾.

Conflict of interest

There are no conflicts of interest.

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