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ORIGINAL ARTICLE

A new cystatin C based model for predicting COVID-19- associated mortality

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Abstract

Background: This study aimed to investigate the effect of the Cystatin C based model on kidney function and the value of this model on predicting mortality in patients with the recent novel coronavirus disease (COVID-19).

Methods: Demographic characteristics, clinical manifestations, and laboratory measurements were measured in critically ill patients with COVID-19 infection. Patients were monitored until they were discharged from the hospital or died.

Results: 105 patients participated in this study. 29 of 105 patients were treated in the intensive care unit. Acute kidney injury developed in nearly all of these patients and developed in 6 other non-intensive care unit patients. 21 of the patients in the intensive care unit had exitus.

Conclusion: The cystatin C (sCys C)based model may be used to predict mortality in severe COVID-19 infections.

Keywords: Acute Kidney Injury, Cystatin-C, Mortality.

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INTRODUCTION

The kidney is one of the most frequently affected organs, as are the respiratory and immune systems, in coronavirus disease-2019 (COVID-19) infection. It is critical to diagnose whether COVID-19 patients develop acute kidney injury (AKI), affecting their prognosis by increasing morbidity, mortality and healthcare costs (1). Several direct and indirect factors that cause kidney damage have been identified in COVID-19. However, difficulties remain in recognizing kidney damage since creatinine and urine output are not enough to diagnose AKI timely (2). Consequently, researchers are in search of new biomarkers for early diagnosis of AKI.

sCys C is a valuable biomarker for detecting AKI and has been shown to include advantages over creatinine, notably in patients with a critical illness. It is a low molecular weight (13.3 kDa) proteinase inhibitor present in all extracellular fluids and is produced continuously by nucleated cells (3). Serum sCys C is a biochemical marker with high sensitivity and specificity to estimate kidney functions and is unaffected by age, gender, weight and inflammation. Several clinical and experimental studies have shown that this biomarker is a better indicator than creatinine of glomerular filtration rate (GFR) measured (4,5). Moreover, the level of circulating sCys C has shown to be strongly associated with critical illness such as increased risk of coronary heart disease, ischemic stroke, and heart failure. Additionally, it has been reported that sCys C a good parameter for evaluating the survival rates of patients with sepsis in the intensive care unit (6,7).

No previous study has been conducted on serum cystatin levels in intensive care patients with COVID-19 infection. The purpose of this study was to investigate the effect of COVID-19 on kidney function and to evaluate the predictive value of sCys C for mortality risk in critically ill patients with COVID-19.

MATERIALS AND METHODS

This is a prospective study performed at Medical Faculty Department of Intensive Care and State Hospital. After the study was approved by the local ethics committee, data collection was carried out between November 2020 and March 2021. Those found to have COVID-19 infection were included. Only COVID-19 infected patients identified by throat swab samples were included in the current study. Patients with chronic kidney diseases (G4–G5 according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria) and history of renal transplant were excluded. 105 hospitalized COVID-19 patients, aged ≥ 18 years were enrolled in the study.

Demographic characteristics (age, gender), comorbid disease, clinical manifestations (fever, cough, sore throat, dyspnea), laboratory parameters (white blood cell, platelet, hemoglobin, C-reactive protein, procalcitonin, sCys C, blood urea nitrogen, creatinine, albumin, fibrinogen, D-dimer, lactate dehydrogenase, ferritin) were recorded. All data were obtained from the first admission to the hospital. Patients were monitored until hospital discharge or death.

COVID-19 was diagnosed based on World Health Organization guidance (8). The real-time reverse transcription-polymerase chain reaction was used to confirm COVID-19 infection in accordance with the manufacturer's protocol (Beijing Genomics Institution and Geneodx Biotechnology Co., Ltd.). The diagnosis of COVID-19 infection was confirmed by polymerase chain reaction (PCR) from nasopharyngeal and oropharyngeal swab samples. Daily biochemical parameters of the patients were recorded. AKI was defined as per KDIGO criteria: a change in the serum creatinine of 0.3 mg/dL over a 48-hour period or 50% increase in baseline creatinine. AKI stages were defined using KDIGO. Description of AKI stages based on creatinine levels were as follows:

Stage 1 is an increase of ≥ 0.3 mg/dL in serum creatinine or an increase to ≥ 1.5–1.9 times the baseline serum creatinine,

Stage 2 is an increase to > 2–2.9 times from the baseline serum creatinine,

Stage 3 is an increase to > 3 times baseline serum creatinine or a peak serum creatinine ≥ 4.0 mg/dL or if the patient received renal replacement therapy during admission (9,10).

This study was approved by the clinical research ethics committee of the Erciyes University, (Date: 20.05.2020 no:2020/252), and written consent was obtained from all patients participating in the study.

Statistical Analysis

Histogram and q-q plots were plotted and Shapiro-Wilk's test was used to assess the data normality. Continuous variables were summarized as mean and standard deviation or median and interquartile ranges, depending on the data distribution. Categorical variables were summarized as numbers and percentages. The sCys C variable was dichotomized, and then survival probabilities were estimated with the Kaplan–Meier method and compared between groups using the log-rank test. The optimal cut-off value was determined by maximizing the Log-rank chi-square statistic after a grid search of all sCys C values. Furthermore, univariate Cox regression analysis was used to assess the risk of clinical variables on the overall survival of the Covid-19 patients. Significant variables at $p < 0.25$ were included into the multiple model and forward elimination was performed using likelihood ratio statistics to identify the independent risk factors. Two separate multiple models were built for continuous (Model-1) and binary variables of sCys C (Model-2). Hazard ratios were calculated with 95% confidence intervals. p values less than 5% were considered as statistically significant. All analyses were conducted using R 3.6.0 (www.r-project.org) and TURCOSA (Turcosa Analytics Ltd. Co., Turkey, www.turcosa.com.tr) software.

RESULTS

Patients demographic and biochemical parameters are shown in Table 1. 105 patients participated in this study and 54 were male. The mean age of the patients was 53.04 ± 19.83 years. 25 (25.3%) of the patients were diabetic and 24 (24.3%) were hypertensive patients. 29 of 105 patients were treated in the intensive care unit. AKI developed in nearly all of these patients and in 6 non-intensive care unit patients. 21 of the patients treated in the intensive care unit had exitus.

Table 1. The distribution of clinical variables in Covid-19 patients

Variables	Statistics
Age (years)	53.04 ± 19.83
Gender (male)	54 (52.4%)
Diabetes mellitus (present)	25 (24.3%)
Hypertension (present)	24 (23.3%)
CRP	11.25 (3.83-76.75)
Sodium	136±3.2
Potassium	4.2±0.7
Calcium	8.9±1.3
Creatinine	1.17 (0.60-2.23)
Procalcitonin	0.19 (0.08-0.37)
Fibrinogen	367.62±141.89
D-dimer	350.0 (197.50-822.50)
Albumin	3.71±0.73
LDH	214.0 (174.75-317.50)
Ferritin	190.0 (93.00-440.00)
Cystatin C	1.00 (0.88-2.16)

Values are expressed as n(%), mean±SD or median(1^{st}-3^{rd} quartiles).

In univariate analysis of all patients (Table 2) sCys C was positively correlated with ferritin, procalcitonin, hs-CRP, and D-dimer. However, sCys C negatively correlated with albumin. Univariate and multiple Cox regression results in predicting survival in COVID-19 patients are shown in Table 3.

Table 2. Univariate correlates of selected markers in all 105 study participants

	Cystatin		Ferritin		Procalcitonin		Crp		D-dimer		Fibrinojen		Albumin	
	p	r	p	r	p	r	p	r	p	r	p	r	p	r
Cystatin	----		0.06	0.223	0.001	0.371	0.001	0.515	0.008	0.401	0.51	0.060	0.03	-0.329
Ferritin	0.06	0 .223	-----		0.001	0.387	0.001	0.366	0.09	0.179	0.078	0.190	0.001	-0.447
Procalsitonin	0.001	0.371	0.001	0.387	-----		0.020	0.248	0.07	0.185	0.848	0.020	0.001	-0.424
Crp	0.001	0.515	0.001	0.366	0.020	0.248	----		0.001	0.665	0.042	0.208	0.001	-0.651
D-dimer	0.008	0.401	0.09	0.179	0.07	0.185	0.001	0.665	----		0.034	0.214	0.07	-0.188
Fibrinojen	0.514	0.060	0.078	0.190	0.848	0.020	0.042	0.208	0.034	0.214	----		0.501	-0.068
Albumin	0.03	-0.329	0.001	-0.447	0.001	-0.424	0.001	-0.651	0.07	-0.188	0.501	-0.068	----	

Table 3. Univariate and multiple Cox regression results in predicting survival in Covid-19 patients

Variables	Univariate		Multiple-1		Multiple-2	
	HR(95% CI)	p	HR(95% CI)	p	HR(95% CI)	p
Age (years)	1.05(1.01-1.09)	0.008	1.04(1.01-1.08)	0.048	1.05(1.01-1.09)	**0.043**
Gender (male)	2.13(0.72-6.33)	0.175	-	-	-	-
Diabetes mellitus (present)	1.33(0.62-2.84)	0.468	-	-	-	-
Hypertension (present)	1.30(0.60-2.79)	0.503	-	-	-	-
CRP	1.00(0.99-1.01)	0.534	-	-	-	-
Creatinine	1.72(1.20-2.47)	0.003	-	-	-	-
Prokalsitonin	1.59(1.01-2.48)	0.043	-	-	1.98(1.08-3.60)	**0.026**
Fibrinojen	1.00(0.99-1.01)	0.896	-	-	-	-
D-dimer (1/100 ng/mL)	1.00(0.99-1.01)	0.217	-	-	1.04(1.01-1.08)	**0.027**
Albumin	0.76(0.43-1.35)	0.351	-	-	-	-
LDH	1.01(1.00-1.01)	0.041	-	-	-	-
Ferritin	1.00(0.99-1.01)	0.437	-	-	-	-
Cystatin C	1.46(1.18-1.82)	<0.001	1.34(1.04-1.71)	**0.022**	-	-
Cystatin C (>2.715 mg/l)	4.39(1.94-9.94)	<0.001	-	-	4.93(1.87-12.98)	**<0.001**

HR: Hazard ratio, CI: Confidence interval

Two separate Cox proportional hazard regression models were built for continuous (Model-1) and binary variables of sCys C (Model-2). In these formulae, is called the baseline hazard function, while is the hazard at time *t* for a given set of independent variables, ***X***. With a given specification of age, sCys C, D-dimer, and procalcitonin variables; the hazard at time *t* for an individual can be predicted using these models (Table 3). Procalcitonin levels [HR (95% CI): 1.98 (1.08 - 3.60), p: 0.026], and D-dimer [HR (95% CI): 1.04 (1.01 - 1.08) p: 0.027] predicted mortality in these patients. Moreover, sCys C [HR (95% CI): 4.93 (1.87 - 12.98) p: < 0.001] predicted mortality in patients with severe COVID-19 infection.

Model 1: $\hat{h}(t, \boldsymbol{X}) = \hat{h}_0(t) * e^{0.036 x age \ + 0.289 x Cystatin\ C}$

Model 2: $\hat{h}(t, \boldsymbol{X}) = \hat{h}_0(t) *$

$e^{0.046 x age + 0.681 x Procalcitonin + 0.000416 x Ddimer + 1.594 x Cystatin\ C\ group}$

In model 2, the sCys C group, was coded as "1" if the numerical value of sCys C is greater than 2.715. Otherwise, the sCys C group was coded as "0".

DISCUSSION

In this study, we firstly evaluated the factors affecting COVID-19-related mortality. Secondly, we performed a new model for predicting survival and showed the relationship between several factors including sCys C, procalcitonin, D-dimer, and survival rate.

sCys C has been claimed to be more strongly associated with cardiovascular events and death compared to creatinine. Additionally, it has been reported that the sCys C-based GFR is associated with all-cause mortality and cardiovascular events, regardless of both the measured and creatinine-based GFR (11-13).

Critical patients are at risk of decline in GFR due to several causes such as nephrotoxicity and sepsis, partly related to individual initial risk. In a prospective study of 442 critically ill patients, Nejat et al. (14) showed sCys C and creatinine at admission and daily series sustains AKI. They observed an earlier increase of sCys C levels than in creatinine. Similarly, this trend was found in subgroups with chronic kidney failure cardiac surgery, and sepsis. sCys C levels also rise earlier than serum creatinine levels in Intensive care unit (ICU) patients (15). In one study, a similar relationship was found between sCys C levels and COVID-19 associated AKI. According to the results, in patients with normal serum creatinine values at the time of hospitalization, AKI could be predicted by using a cutoff value of 1 mg / L and sCys C levels in the early period (16).

Generally, the COVID-19 process involves overactivation of inflammatory and immune responses in severe cases of the disease, which ultimately result in high mortality for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients (17,18). Several studies have been conducted on COVID-19 patients that evaluated their prognosis. Previous studies revealed that non-survivors from the disease had obvious increase trends in D-dimer, IL-6, serum ferritin, high-sensitivity cardiac troponin, lactate dehydrogenase (LDH), white blood cell (WBC), neutrophil count, blood urea nitrogen, and creatinine, procalcitonin levels, and noticeable lymphopenia when compared with survivors (19-21). In a systematic review and meta-analysis of laboratory test findings of COVID-19, Ghahramani et al. and Akbari et al. reported that cytokine storm might be one of the main causes of COVID-19-related death (22,23) and these studies have shown inflammation, coagulopathy, anemia, and kidney failure as the main causes of COVID-19-related mortality.

It has been reported that sCys C, which is confirmed to predict AKI and death risk in critically ill patients, can also be predictive of the prognosis in COVID-19 patients (24). Circulating sCys C could serve as a potential inflammatory target for preventing COVID-19 from the likely progression of critical illness and in-hospital death. sCys C may also have a role as a potential biomarker of systemic inflammation during the exacerbation of COVID-19, rather than only reflecting renal function in patients infected by SARS-CoV-2. Higher sCys C levels at admission can predict significantly worse outcomes for adult patients with COVID-19 (25).

In another prospective study of 845 critically ill patients, sCys C levels were shown to be independently associated with death in hospital for those with and without AKI; however, the relationship was stronger for those with AKI (26).

Some studies have revealed that patients with COVID-19 associated with renal deterioration and clinical signs include hematuria, albuminuria, and decreased GFR (27,28). Xiang et al. (29) also showed that blood urea nitrogen (BUN), creatinine, and sCys C were increased significantly in severe COVID-19 patients. It has been reported that the incidence of AKI in COVID-19 patients ranges from 0.9% to 29% (30,31). The incidence of AKI is significantly higher in patients, who need intensive care (32). Pei et al. (33) showed that the total mortality rate of patients with renal involvement was 11.2%, while the mortality rate of patients without renal involvement was 1.2%. They also showed that sCys C levels were positively correlated with inflammatory markers, such as IL-1β, IL-6, tumor necrosis factor-α, and hs-CRP (34). Therefore, in the pathological state of COVID-19 invading lung tissue, sCys C is synthesized and released in large quantities, and the level of sCys C is increased, which regulates the cathepsin activity released from necrotic or inflammatory cells. It has been suggested that clinicians should pay close attention to sCys C's level and its changes (35).

In another study, it was concluded that albuminuria, serum sCys C, and D-dimer levels in COVID-19 patients with normal serum creatinine levels at hospitalization might be an early predictor of AKI associated with COVID-19 (16, 36). In a multicenter cohort study of critically ill adults with COVID-19 in the United States, it was found that more than one in five patients developed AKI requiring renal replacement therapy (RRT), of which more than 60% died within 28 days. Approximately one-third of those with AKI-RRT, who survived until discharge from the hospital, remained dependent on RRT (37). Chen et al. showed that elevated sCys C levels were associated with increased inflammatory index levels, including white blood cell count, C-reactive protein, procalcitonin, neutrophil/lymphocyte ratio, and D-dimer, as well as increased lactate levels, and decreased PaO2: FiO2 ratio. In the study, a positive correlation was found between higher sCys C level and increased blood creatinine level and acute physiology and chronic health evaluation II (APACHE II) score. They also revealed that sCys C levels are independently associated with critical illness and death risks in COVID-19. Thus, it has been thought that sCys C could function as a potential biomarker of systemic inflammation during an exacerbation of COVID-19, rather than simply reflecting kidney function in SARS-CoV-2 infected patients (25, 38).

Limitations of our study were: in critically ill patients, since renal failure often develops during intensive care follow-up, its correlation with creatinine should be considered. In addition, the number of patients should be increased.

In conclusion, we performed the new sCys C based model for predicting mortality in severe COVID-19 infection and we think that new algorithms may be used while determining the risk ratios of these patients and making a treatment plan. Further studies are needed to predict the prognosis of COVID-19, since the infection still has significant morbidity and mortality rates.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the Erciyes University, (Date: 20.05.2020 no:2020/252), and written consent was obtained from all patients participating in the study.

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