Original Article

Cystatin C and Neutrophil Gelatin-associated Lipocalin (NGAL) Can Predict Acute Kidney Injury and In-Hospital Mortality in COVID-19 Patients

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Abstract

Background: Prediction and early diagnosis of acute kidney injury (AKI) in critically ill Coronavirus disease 2019 (COVID-19) patients are of great importance. Therefore, using promising renal biomarkers such as cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) to identify the risk of future AKI is crucial.

Materials and Methods: A total of 89 adult patients with COVID-19 were included in this study. Serum cystatin C and NGAL concentration were assessed on intensive care unit (ICU) admission then repeated after 48 hours. Serum creatinine was followed for 7 days to report the development of AKI.

Results: Among the COVID-19 patients, 28.1% developed AKI. Although admission serum creatinine was not significantly different between the AKI group and the non-AKI group (p=0.375), admission Cystatin C (p=0.018), and NGAL (p<0.001) were significantly different between both groups. After 48 hours, a change in Cystatin C level (p<0.001) but not NGAL (p=0.4) was a predictor for AKI. Logistic regression model including age (p=0.031), Cystatin C on 48 hrs (p=0.003) and NGAL on admission (p=0.015) could predict AKI in COVID-19 patients.

Conclusion: Serum Cystatin C and NGAL in ICU could be used to predict AKI in COVID-19 patients. A logistic regression model including age, Cystatin C on 48hrs, and NGAL on admission might be a tool for individualized risk estimation of AKI in COVID-19 patients.

Keywords: Cystatin C, NGAL, Acute kidney injury, COVID-19, In-Hospital mortality

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Introduction

Coronavirus disease 2019 (COVID-19) has spread rapidly worldwide and resulted in a global pandemic after its diagnosis in Wuhan in December 2019. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly affects the respiratory system; however, studies have reported variable prevalence of acute kidney injury (AKI) among COVID-19 patients during their hospital stay (1-3). Pathophysiology of COVID-19 associated AKI involves different mechanisms such as cytokine storm due to secondary inflammatory response, development of microthrombi,

and direct viral invasion of the kidney (4). AKI is an established risk factor for mortality in an intensive care unit (ICU) (5). Therefore, early diagnosis of kidney injury and early control of potential risk factors for AKI might improve patients' survival.

Protocol of management of AKI in patients with COVID-19 is generally the same as the protocol adopted for managing AKI in critically ill patients. It is mainly supportive according to the current guidelines and consensus recommendations of AKI. Some recommendations should be considered specifically as using low positive end-expiratory pressure (PEEP) if possible and early kidney replacement therapy (4).

An increasing body of evidence suggests that our existing approach to kidney assessment using serum creatinine has very significant limitations in hospitalized patients (6). Elevated serum creatinine or oliguria are neither specific nor sensitive for early AKI diagnosis. Moreover, they are reflecting established kidney damage rather than predicting its development. Other tools like novel kidney biomarkers can be used as alternative blood markers for identifying early kidney dysfunction (7). Cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) are available biomarkers that have been previously investigated in the context of AKI in critically ill patients for the last decade. Both markers were good detectors of early renal injury either in sepsis, in renal nephrotoxicity, or after cardiac surgery (8-10).

Cystatin C is a cysteine protease inhibitor widely expressed in body tissues. It is filtered by the glomerular capillaries and reabsorbed by the proximal convoluted tubules, but not secreted. Thus, it is normally not present in the urine (11). Cystatin C is more sensitive and specific than creatinine as it is less affected by gender, age, or other extra-renal factors. Studies have shown that serum cystatin C mainly reflects glomerular filtration rate (GFR), and it can be more accurate than serum creatinine for this purpose (12, 13).

NGAL is a 25 KDa protein produced by thick ascending and collecting ductal cells of the kidney. Thus, it is considered a marker of renal tubular function. It reaches its peak level 6 hours after renal injury (14, 15).

To show the dynamic pattern of cell injury during AKI development, we thought that measuring 2 biomarkers at 2-time points would be more effective for early diagnosis rather than a single reading of a single marker. Therefore, in the present study, we measured the serum level of cystatin C and NGAL in patients with COVID-19 twice: on admission to ICU and after 48 hours. Then, we evaluated their ability to predict AKI development during the following 7 days of admission.

Methods

Patients: The study was approved by the Ethical Committee of Faculty of Medicine, Ain Shams University, Cairo, Egypt. The protocol was registered in ClinicalTrials.gov (NCT04603664). Patients from Ain Shams University specialized hospital (Obour city) were recruited from November 2020 to June 2021. Written informed consent from the patients or their legal guardians was taken.

Inclusion criteria involved age ≥ 18 years, need for oxygen therapy, and admission to ICU after diagnosis of COVID-19 by either nasopharyngeal or oropharyngeal swab. AKI development was assessed according to Kidney Disease Improved Global Outcome (KDIGO) criteria that include the serial increase of serum creatinine ≥ 0.3 mg/dl within 48 h or an increase in serum creatinine ≥1.5 times from baseline within 7 days (16). The exclusion criteria included: end-stage renal disease (ESRD) or on regular chronic dialysis, elevated creatinine>1.2 mg/dl or anuria at the time of admission, history of chronic kidney disease, severe urinary tract infection, kidney malignancy, or renal transplantation.

History and clinical data: Age, sex, and comorbidities such as hypertension, diabetes, cardiovascular diseases, or cerebrovascular diseases were recorded. On admission, total leucocytes count (TLC), lymphocytes count, and other inflammatory biomarkers such as C reactive protein (CRP), procalcitonin, LDH, ferritin, and D dimer were recorded.

Blood Sampling: Peripheral blood samples (7 ml) were taken on admission (baseline) then repeated after 48 hours. After clotting, samples were centrifuged at 3000 rpm for 5 min, and then sera were separated,

divided into aliquots, and stored at - 80ºC.

Laboratory investigations: Serum creatinine on admission and 48 hours was measured colorimetrically (17). The reference for serum creatinine in the study laboratory ranges from 0.5 to 1.2 mg/dl. Cystatin C and NGAL were determined on admission and 48 hours by enzyme-linked immunosorbent assay (ELISA) assay using commercially available kits: Human E1719Hu and E1014Hu, respectively, from Bioassay Technology Laboratory (Shanghai, China).

Statistical Analysis: In this study, 100 patients were enrolled over 8 months. Eleven patients were excluded after enrollment; 4 were referred to other hospitals, and 7 died within 7 days from admission. Data were collected, coded, tabulated, and then analyzed using the SPSS software package (SPSS for Windows, version 16.0. Chicago, SPSS Inc.). Continuous variables were presented as mean±standard deviation, skewed variables were presented as median and 25^{th} - 75^{th} percentiles, and categorical variables were presented as numbers and percentages. Between-groups comparisons were made using unpaired t-test, Mann-Whitney U test, and Fisher's exact test; for continuous variables, skewed variables, and categorical variables, respectively. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the ability of Cystatin C and NGAL to predict AKI and mortality. A backward stepwise (conditional)-Logistic regression model to predict AKI was performed. Any difference with a p-value ⩽0.05 is considered statistically significant.

Results

Patients' characteristics

Using KDIGO criteria, a total of 28.1% (n=25/89) of patients developed AKI. Only 2 patients (8%) developed AKI before 48 hours of admission. In-hospital mortality was significantly higher among AKI patients (53.8% (n=14/25)) compared to non-AKI patients (18.8% (12/64)) at p<0.001.

Demographic characteristics and admission laboratory values of subjects with AKI were compared with those without AKI (Table 1). Statistically, a significant difference was noted in age (p=0.004), TLC (p=0.002), need for dialysis (p<0.001), and mechanical ventilation (p<0.001). However, no significant differences were seen in sex, comorbidities, lymphocyte count, CRP, procalcitonin, LDH, ferritin, D dimer, and urea.

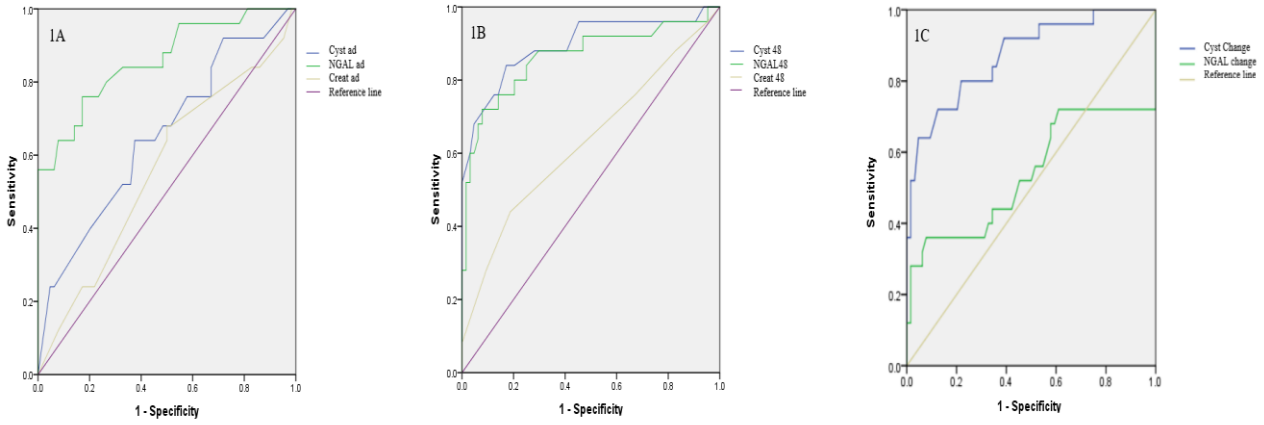

Figure 1. ROC curve of serum Cystatin C, NGAL and creatinine for prediction of AKI in COVID-19 patients (A) serum markers on admission to ICU (B)serum markers on 48 hrs after admission.

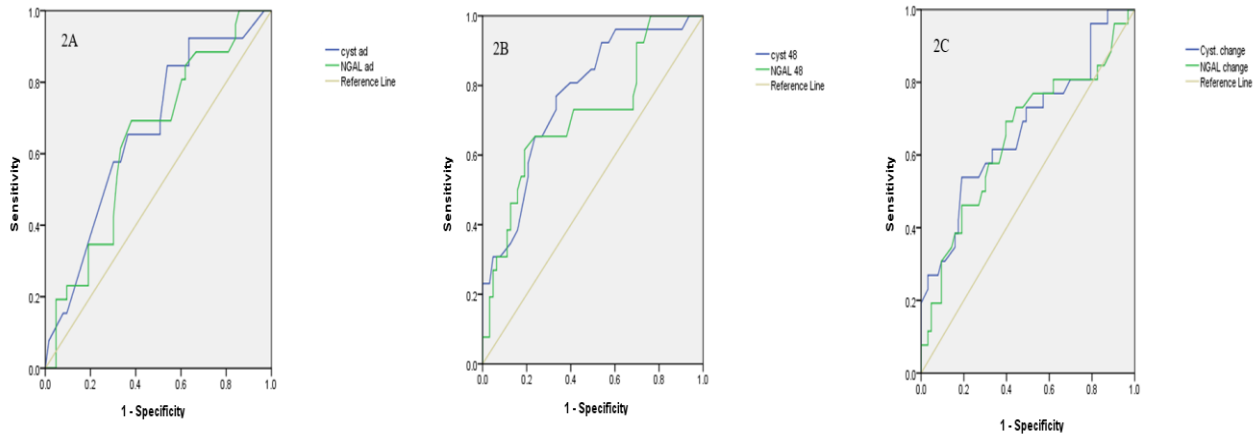

Figure 2. ROC curve of serum Cystatin C and NGAL for prediction of mortality in COVID-19 patients (A) serum markers on admission (B) serum markers on 48 hrs after admission (C) change in serum markers between admission and 48 hrs.

Serum Cystatin C and NGAL values compared to serum creatinine: Regarding Cystatin C and NGAL values on admission, there was a significant difference between AKI and non-AKI patients. AKI patients had significantly higher Cystatin C (1.1±0.25 vs 0.9 ±0.23mg/l, p=0.018) and NGAL levels (285 (240-335) vs 227 (182-238) ng/ml, p<0.001). Admission creatinine was not significantly different between the AKI and non-AKI patients (1.00 (0.90-1.05) vs 0.97 (0.90-1.00), p=0.375) (Table 1).

In 48 hours, serum levels of Cystatin C remained significantly elevated in the AKI group compared to the non-AKI group (1.79 ± 0.58 vs 1.01± 0.24, p<0.001). Serum NGAL was also significantly elevated in the AKI group compared to the non-AKI group (307 (242- 354) vs 212 (191-232), p<0.001). Serum creatinine levels showed insignificant difference between AKI and non-AKI groups (1.00 (0.95-1.20) vs 1.00 (0.90-1.00), p=0.075) (Table1).

Diagnostic value of Cystatin C and NGAL compared to creatinine: On admission, Cystatin C had AUC=0.65 (95%CI 0.52–0.78, p =0.02)) with 65.4% sensitivity and 63.5% specificity at cut off value 0.99 mg/l. NGAL showed a higher diagnostic value where AUC was 0.85 (95%CI 0.76–0.95, p <0.001) with a sensitivity of 76% and specificity of 82.8% at the cut-off value of 242.5 ng/ml. Admission serum creatinine did not have a significant AUC (p=0.38) (Figure 1A).

In 48 hours, the diagnostic values of Cystatin C and NGAL were comparable. Cystatin C had AUC=0.86 (95%CI=0.76-0.96, p<0.001) with sensitivity of 84% and 82.8 specificity at the cut-off value of 1.26 mg/l. While, NGAL showed AUC=0.89 (95%CI=0.81-0.98, p<0.001) with a sensitivity of 84% and 75% specificity at cut off value 231ng/ml. Serum creatinine at this time point failed to have a significant diagnostic value to discriminate between AKI and non-AKI patients (p=0.07) (Figure 1B).

The change of Cystatin C after 48 hours had AUC= 0.87(95%CI 0.78–0.95) with a sensitivity of 80% and specificity of 78.1%. at cut off value 0.29 mg/l. In comparison, the AUC of the change of NGAL level was an insignificant predictor for AKI (AUC=0.53, p =0.4) (Figure 1C).

Multivariate regression analysis for prediction of AKI in COVID-19 patients To investigate the usefulness of these biomarkers as early independent predictors of AKI in COVID-19 patients, we performed a binary backward-conditional logistic regression model including age, TLC, Cystatin C on 48 hrs and NGAL on admission. Regression analysis revealed that the age, Cystatin C on 48 hr, and NGAL on admission could form a model that significantly predicts AKI in COVID-19 patients (Table 2).

The logistic model is:

$$z = 0.113\times\text{age (y)} + 0.037\times\text{NGAL, admission} + 4.926\times\text{Cystatin,4h hrs} - 23.239$$

Table 1: Patients characteristics of AKI and non-AKI groups.

Characteristics	AKI (n=25)	Non-AKI (n=64)	P-Value
Age, years	65 (61-71)	60(56-64)	0.004
Sex, male, no (%)	14 (56%)	37 (57.8%)	1.000
Diabetes	18 (72%)	32 (50%)	0.095
Hypertension	17 (68%)	8 (32%)	0.346
Cardiovascular Disease	7 (28%)	16 (25%)	0.792
Cerebrovascular Disease	7 (28%)	8 (12.5%)	0.114
Total leucocyte count, $x10^9$/l	9.60 (7.60-15.20)	7.45 (5.65-9.90)	0.002
Lymphocytes, $x10^9$/l	0.90 (0.80-1.15)	1.10 (0.80-1.40)	0.182
C-reactive Protein, mg/l	90 (58-135)	104 (44-160)	0.935
Procalcitonin, ng/ml	0.40 (0.23-1.2)	0.21 (0.18-0.88)	0.060
Urea, mg/dl	29.84±8.71	27.59±8.05	0.251
D-dimer, ng/ml	2200 (905-3650)	900 (400-3250)	0.057
Ferritin, ng/ml	670 (331-1120)	602 (157-1100)	0.674
Lactate dehydrogenase, U/l	330 (191-515)	308 (167-498)	0.648
Creatinine on admission, mg/dl	1.00 (0.90-1.05)	0.97 (0.90-1.00)	0.375
Serum creatinine 48 hrs, mg/dl	1.00 (0.95-1.20)	1.00 (0.90-1.00)	0.075
Peak Creatinine, mg/dl	2.50 (1.90-4.35)	1 (0.82-1.2)	<0.001
Cystatin C on admission, mg/l	1.06 ± 0.25	0.93 ± 0.23	0.018
Cystatin C 48 hrs, mg/l	1.79 ± 0.58	1.01 ± 0.24	<0.001
NGAL on admission, ng/ml	285 (240-335)	227 (182-238)	<0.001
NGAL 48 hrs, ng/ml	307 (242- 354)	212 (191-232)	<0.001
Mechanical Ventilation, no (%)	12 (48%)	8 (12.5%)	<0.001
Vasopresser, no (%)	6 (24%)	5 (7.8%)	0.067
Dialysis, no (%)	5 (20%)	0 (0%)	<0.001
In hospital death, no (%)	14 (53.8%)	12 (18.8%)	<0.001

Data are expressed as n (%) or mean ± SD or median (25^{th} -75^{th} percentiles)

The probability of any patient developing AKI is p, where: $p = \frac{1}{1+e^{-z}}$ and e=2.718 approx.

Cystatin C and NGAL in the prediction of in-hospital mortality among COVID-19 patients: On admission, levels of Cystatin C and NGAL were significantly elevated in non-survivors compared to survivors (1.0677±0.23 vs 0.9306±0.24, p=0.022, 242 (224.75-277.75) vs 230 (182-260), p=0.036). On 48 hrs, both serum Cystatin C and NGAL were significantly elevated in non-survivors compared to survivors (1.5950 ±0.62 vs 1.0875±0.37, p<0.001, 255 (200-330) vs 217 (191-240), p=0.001, respectively) (Table 3).

ROC curve demonstrated that admission serum Cystatin C and NGAL had a significant ability to predict mortality in COVID-19 patients. For Cystatin C, AUC was 0.67 with 65% sensitivity and 60% specificity at cut off value 0.98 mg/l (p=0.014). Admission NGAL had AUC of 0.642 with 69.2% sensitivity and 61.9% specificity at cut off value 236 ng/ml (p=0.036) (Fig. 2A).

On 48 hrs, serum Cystain C predicted mortality by AUC of 0.768 with 76.9% sensitivity and 66.7% specificity at cut off value 1.14 mg/l (p<0.001). NGAL on 48 hrs displayed significant AUC of 0.715 with 65.4% sensitivity and 76.2% specificity at cut off value 241 ng/ml (p= 0.001) (Fig. 2B).

The change in Cystatin C levels between

Table 2: Backward (conditional) logistic regression model for predicting AKI in COVID-19 patients.

	Odds Ratio (OR)	95%CI	P value
Age	1.12	1.01-1.24	0.031
Cystatin C, 48 hrs (mg/l)	137.87	5.33-3561.25	0.003
NGAL, ad (ng/ml)	1.04	1.007-1.07	0.015

Variables entered in regression: age, TLC, Cystatin C 48 hrs, NGAL admission

Table 3: Cystatin C and NGAL levels in survivors and nonsurvivors.

Parameter	Survivors (n=63)	Nonsurvivors (n=26)	P-value
Cystatin C on admission, mg/l	0.93±0.24	1.07±0.23	0.022
Cystatin C 48 hrs, mg/l	1.09±0.37	1.60 ±0.62	<0.001
NGAL on admission, ng/ml	230 (182-260)	242 (224.75-277.75)	0.036
NGAL 48 hrs, ng/ml	217 (191-240)	255 (200-330)	0.001

Data are expressed as mean ± SD or median (25^{th} - 75^{th} percentiles)

admission and 48 hrs. also significantly predicted mortality by AUC=0.674 with 61.5% sensitivity and 66.7% specificity with a cut-off increase by 0.27 mg/dl (p=0.01). While the change in NGAL showed a significant diagnostic value by AUC=0.649 with 61.5% sensitivity and 61.9% specificity at cut-off increase=7 ng/ml (p=0.028) (Fig 2C).

Discussion

The close relation between AKI and coronavirus infection was previously identified in the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) epidemics (18). Similarly, AKI is prevalent in hospitalized patients with COVID-19 and has been reported to occur in 19% of COVID-19 patients, and up to 46% of patients admitted to the ICU (19). This single-center prospective observational study demonstrated a 28.1% prevalence of AKI in critically ill COVID-19 patients. Our findings came in line with previous studies (20, 21). However, different studies reported lower prevalence, particularly in China. The prevalence rate varied considerably due to the severity of the disease, presence of coexisting morbidities, different ethnic groups, and other socioeconomic factors (22, 23). Therefore, additional studies are suggested to investigate the incidence of AKI in mild or moderate cases and compare the prevalence of AKI between large cities and rural areas.

The etiology of renal dysfunction in COVID-19 patients is multifactorial. Few studies documented direct viral infection of kidney tubules in postmortem kidney specimens (24, 25). This invasion can be induced through angiotensin-converting enzyme 2 (ACE2) receptors which are abundantly present in the human kidney (26). Other predisposing factors for AKI in COVID-19 patients are hypoxia, secondary immune reaction, secondary bacterial or fungal infection, nephrotoxic antibiotics or dyes, vasopressors, and mechanical ventilation (27). Therefore, it is crucial to investigate the possibility of early prediction of renal injury before the rise of serum creatinine. Using renal biomarkers such as Cystatin C and NGAL might help early diagnosis as early management of AKI may decrease the incidence of both morbidity and mortality in COVID-19 patients.

Risk factors for AKI in our patients were increased age, sepsis (as indicated by TLC), and mechanical ventilation. Our findings are consistent with a meta-regression analysis done in Pennsylvania (1). These factors are undoubtedly established risk factors for AKI in other categories of critically ill patients (28).

D-dimer, CRP, ferritin, and LDH are nonspecific inflammatory markers. Studies concluded that these markers were predictors for the severity of

COVID-19 disease (29, 30). In our study, the levels of these markers were not significantly different between AKI and those without AKI.

The mortality rate in this study was 53.8% among AKI patients. These results go with Cheng et al. (31) and Pei et al. (32), who reported increased death incidence among COVID-19 patients with AKI. In a recent observational, retrospective study of 1406 AKI patients with COVID-19, in-hospital mortality was 52% in the ICU (33). The mortality rates increased if the follow-up time was prolonged. However, the criteria for ICU admission were different among the studies, which was another reason for the different mortality rates. Patients with AKI tended to have a multiorgan failure, explaining the increased mortality rate.

Both Cystatin C and NGAL levels on admission predicted AKI development but NGAL showed superior specificity and sensitivity. Our findings are consistent with the findings reported by He L et al.; they demonstrated that combining urinary NGAL and Ground Glass Opacities volume of the lungs can predict AKI and mortality in COVID-19 patients (34). In the current study, the Cystatin C level has changed significantly after 48hrs in comparison to NGAL. The progression of kidney dysfunction can explain Cystatin C level elevation after 48 hours in our patients, increased severity of cytokine storm or addition of nephrotoxic drugs, or positive pressure ventilation in ICU. Increased Cystatin C level may support the evidence of glomerular affection rather than tubular dysfunction (35). This information may help the clinician modify their plan of management and search for suspected causes of glomerular injury rather than tubular injury claimed to occur due to direct viral invasion.

AKI is usually an indicator of more severe disease and multiorgan dysfunction, so kidney function protection should be important for clinical treatment. This study developed a model to accurately predict AKI onset in ICU patients with COVID-19 based on the patient's age, serum NGAL on admission, and serum Cystatin C on 48 hrs. Awareness of these parameters may be a helpful tool to help physicians predict AKI during hospitalization.

As part of predicting AKI in hospitalized COVID-19 patients, this study showed that serum Cystatin C and NGAL can predict mortality in COVID-19 patients. Similar results for Cystatin C were obtained by Li et al. (36) and also for urinary NGAL (34).

Management of AKI includes closer monitoring renal perfusion and hemodynamic parameters and early application of renal protection strategies. Antiapoptotic or antioxidant drugs may also have a role in treating AKI associated with COVID-19.

Conclusion

Measuring serum Cystatin C and NGAL levels on admission then after 48 hours in COVID-19 patients helped develop a simple AKI prediction model. In addition, serum Cystatin C and NGAL are prognostic markers for in-hospital mortality. This may guide the proper management of ICU hospitalized COVID-19 patients.

Limitations of the study were the small size of the sample; therefore, results should be confirmed with larger cohort studies; we did not measure urinary NGAL or cystatin C as it is possible that combining urine markers with serum markers can improve the accuracy of diagnosis, and absence of long-term follow-up to detect later development of chronic kidney disease among discharged patients.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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