


# Early predictors of acute kidney injury in COVID-19 patients

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## Abstract

**Aim:** This study aims to determine the frequency of COVID-19 related AKI and to identify the early predictors of AKI.

**Methods:** This study is a single-center, retrospective, observational study. Hospitalized COVID-19 patients between 24/03/2020 and 31/05/2020 were included in the study. All patients were evaluated for renal dysfunctions with urine dipstick, protein/creatinine ratio, albumin/creatinine ratio in spot urine, serum cystatin C, serum creatinine level on hospital admission, and 28th day of hospital admission. To assess the utility of these parameters to predict AKI, a receiver-operating characteristic curve was generated and the area under the curve (AUC) was calculated.

**Results:** 348 patients were included. The average incidence of AKI was 4.9% (n = 17). The incidence of AKI in mild, moderate and severe COVID-19 cases was 1.3% (n = 4), 9.0% (n = 3) and 76.9% (n = 10), respectively. Proteinuria was detected in 7.8% (n = 27) of patients with a urine dipstick test. In spot urine analysis, proteinuria was found in 20.1% (n = 70) of patients. The frequency of persistent proteinuria was 5.2% (n = 18). The AUC value of serum cystatin C, D-dimer and albumin/creatinine ratio to predict COVID-19 related AKI were 0.96 (0.90 to 1.0), 0.94 (0.89–0.98), and 0.95 (0.91–0.98).

**Conclusion:** In COVID-19 patients with normal serum creatinine levels on hospital admission, albuminuria, serum cystatin C and D-dimer levels may be an early predictor of COVID-19 related AKI and these patients should be monitored closely for AKI. Since the sample size in the AKI group was small, our study results should be confirmed with larger cohort studies.

## KEYWORDS

acute kidney injury, COVID-19, cystatin C, D-dimer, proteinuria

## 1 | INTRODUCTION

As of September 2020, COVID-19 has become a worldwide epidemic, with over 28 million reported cases and over 900 000 reported deaths.<sup>1</sup> In Turkey, the reported number of confirmed COVID-19 cases is over 300 000 as of the same date. The actual data suggest that approximately 20% of COVID-19 patients require hospital admission, and approximately 5% require intensive care unit (ICU) admission.<sup>2</sup> The fact that COVID-19-related hospitalizations were generally

in acute respiratory failure led to focusing on pulmonary involvement and complications in these patients. However, increasing the frequency of extrapulmonary system involvement is still reported.<sup>3</sup> In current studies, cardiac, gastrointestinal, hepatic, renal, neurological, ocular, cutaneous, haematological findings have all been described in COVID-19 patients.<sup>3</sup>

Renal involvement of COVID-19 can range from abnormal urine analysis results in AKI requiring renal replacement therapy. The incidence of AKI associated with COVID-19 was initially considered to be

low and negligible.<sup>4</sup> However, a recent meta-analysis shows that the incidence of AKI varies between 1.3% and 36.4% based on the severity of COVID-19.<sup>5</sup> Depending on the pathophysiology of AKI and disease duration of COVID-19, the incidence of AKI can be varied. Cytokine release syndrome and acute respiratory distress syndrome (ARDS) increase the frequency of AKI in COVID-19 patients.<sup>6</sup> Especially in those patients requiring intensive care support, AKI is associated with poor prognosis and increased risk of mortality.<sup>5-8</sup> Therefore, early predicting COVID-19-related renal dysfunction may affect the prognosis of COVID-19 as well as reducing the risk of AKI.

Cystatin C is a low-molecular weight endogenous protein that is not reabsorbed after filtering through glomeruli.<sup>9</sup> Serum cystatin C levels are more closely correlated with glomerular filtration rate (GFR) compared to serum creatinine levels.<sup>9-11</sup> Serum cystatin C can be used earlier than serum creatinine levels especially in detecting mild to moderate GFR changes.<sup>10</sup> Serum cysteine C levels can be used in the early prediction of AKI in COVID-19 patients.

In this study, we aimed to determine the incidence of COVID-19-related renal dysfunctions and to evaluate the effectiveness of cystatin C and other biomarkers in the early prediction of AKI.

## 2 | METHODS

### 2.1 | Study design

The study was conducted as a single-centre, retrospective, observational cohort study between 24 March 2020 and 31 May 2020 in hospitalized COVID-19 patients. This study was conducted at a university hospital located in the central part of Turkey. The study protocol was approved by the Gazi University Clinical Research Ethics Committee on 8 June 2020 (Decision No: 360).

### 2.2 | Study population

Hospitalized COVID-19 patients aged  $\geq 18$  years were enrolled in the study. The diagnosis of COVID-19 infection was confirmed by polymerase chain reaction (PCR) from nasopharyngeal and oropharyngeal samples. In patients with recurrent hospitalizations, only the first hospitalization was considered. Patients with chronic kidney diseases (G4-G5 according to Kidney Disease: Improving Global Outcomes criteria), history of renal transplant and unable to achieve two different serum creatinine levels within the last year, at least one of which was 7 days before hospitalization in the electronic health record, were excluded from this study (Figure 1).<sup>12</sup>

### 2.3 | Data collecting

The electronic health records of the patients were evaluated in terms of the inclusion and exclusion criteria mentioned above. The evaluation of the electronic records was carried out by the infectious

### SUMMARY AT A GLANCE

This observational single-center study assessed the frequency and predictors of acute kidney injury in 348 hospitalized patients with COVID-19. In this cohort, AKI was diagnosed in 4.9% of patients and proteinuria (spot urine analysis) in 20%. Albuminuria/creatinine ratio, cystatin C and D-dimer were identified as potential predictors of AKI on admission.

diseases specialist in the study team, and the data obtained were checked by the nephrologist before the analysis.

### 2.4 | Definitions

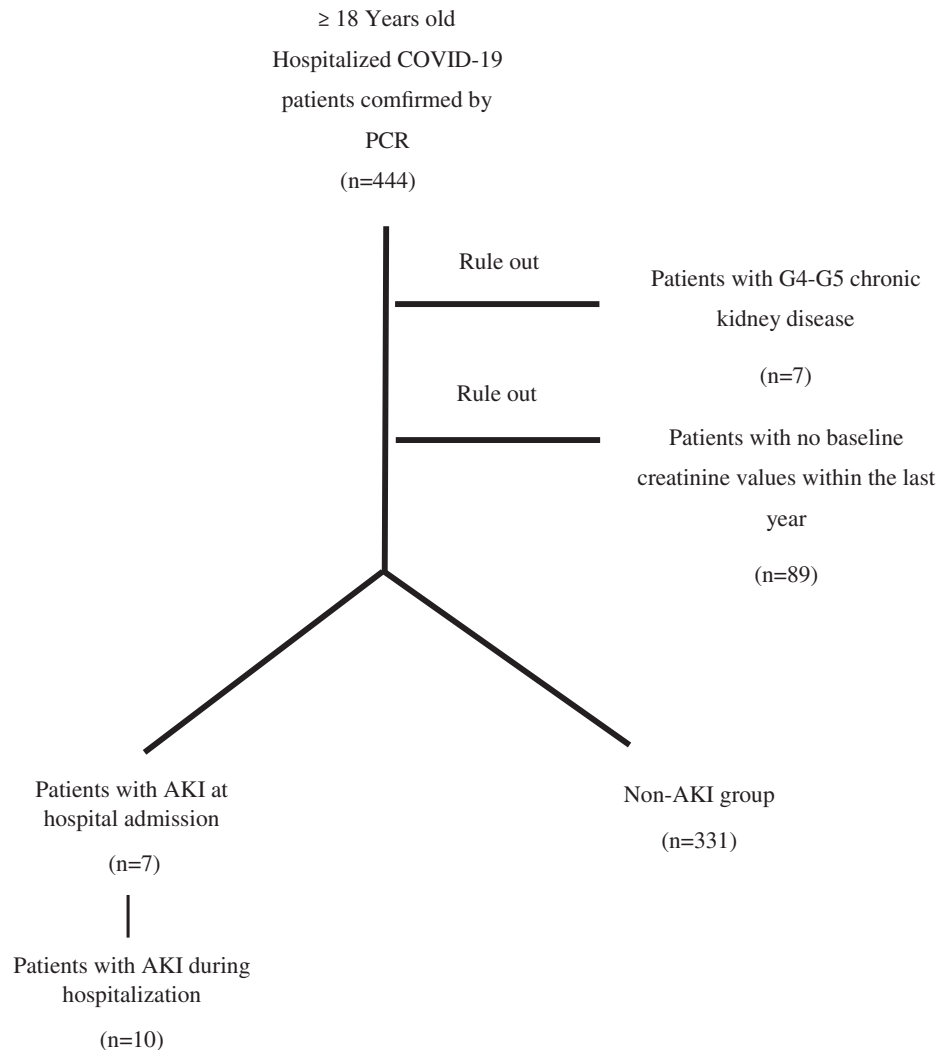
AKI was defined as per Kidney Disease Improving Global Outcomes (KDIGO) criteria: a change in the serum creatinine of 0.3 mg/dL over 48 h period or 50% increase in baseline creatinine.<sup>13</sup> Serum creatinine in the 7-365 days before admission was considered the baseline creatinine.<sup>8</sup> The serum creatinine values of all patients at hospital admission and during their stay in hospital were recorded. AKI definition was made by comparing creatinine values at hospital admission or during hospitalization with baseline serum creatinine values (Figure 1).

AKI stages were defined using the KDIGO AKI stage creatinine definitions: stage 1 as an increase in serum creatinine of  $\geq 0.3$  mg/dL or increase to  $\geq 1.5-1.9$  times baseline (serum creatinine, stage 2 as an increase to  $>2-2.9$  times from baseline serum creatinine, and stage 3 as an increase to more than three times baseline serum creatinine or a peak serum creatinine  $\geq 4.0$  mg/dL or if the patient received renal replacement therapy during admission.<sup>8,13</sup>

Proteinuria evaluation was made with urine dipstick test, protein/creatinine, and albumin/creatinine ratio in spot urine at hospital admission. Albuminuria was described as an albumin creatinine ratio is over 30 mg/g. Proteinuria was described as protein creatinine excretion rate is over 150 mg/g or 1+ proteinuria or higher on the dipstick.<sup>14</sup> Serum creatinine level and urine analysis results were re-evaluated on the 28th day of hospitalization and compared with initial test results at hospital admission. Persistent proteinuria was defined as the persistence of proteinuria in the second urine sample taken at least 28 days apart. Haematuria was defined as 1+ or higher on dipstick or urinalysis.<sup>8</sup> In automatized urine microscopy, the presence of  $>5$  red blood cells was considered as haematuria.

Patients diagnosed with COVID-19 were divided into three groups as mild, moderate, and severe disease to evaluate the relationship between disease severity and AKI. Patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate  $>30$  breaths/min; severe respiratory distress; or SpO<sub>2</sub>  $< 90\%$  on room air were considered as severe cases. Patients with pneumonia and have no above severity criteria were considered as moderate cases. Symptomatic patients without evidence of viral pneumonia or hypoxia were considered as mild cases.<sup>15</sup>

**FIGURE 1** Flowchart of the study



## 2.5 | Study protocol

During the study period, all eligible participants were enrolled consecutively. On admission of all patients, demographical-clinical characteristics (sign and symptoms, symptoms duration, physical exams evaluations), home medications, routine laboratory results including hemogram, liver and renal function tests, urine analysis results, protein creatinine ratio, and albumin creatinine ratio in early morning urine samples, D-dimer, fibrinogen, ferritin, C-reactive protein (CRP) and serum cystatin C levels, treatments, and outcomes of patients were recorded to the study form. Laboratory results such as renal function tests and urine analysis results on 28 days after the first assessment were also recorded.

## 2.6 | Statistical analysis

All data were analysed by IBM SPSS Statistics, version 20.0 X (IBM Corp., Armonk, NY, USA). The normality of the data distribution was determined by the Shapiro–Wilk test, histogram, and Q-Q plots. The categorical values of the patients were expressed as a number and a

percentage and were analysed with a Chi-square test. Continued values were presented as a mean and standard deviation (SD) or median values and an interquartile range (IQR) of 25%–75%. The non-parametric values were analysed using the Mann–Whitney U, and the parametric ones with a Student t-test. Comparison of creatinine, blood urea nitrogen (BUN) test, GFR, Cystatin C, albumin/creatinine and protein/creatinine ratios between hospital admission and 28th days of hospital admission were made by paired Student t-test for normal distribution variables and Wilcoxon test for variables that did not show a normal distribution. To assess the diagnostic utility of several biomarkers at varying cut-off values for predicting AKI, a receiver-operating characteristic (ROC) curve was generated, and AUC was calculated. The 95% confidence intervals (95% CIs) were also calculated when appropriate, and a *p*-value < .05 was considered statistically significant.

## 3 | RESULTS

In the study, 444 patients were evaluated. Seven patients were excluded because they had G4-G5 chronic kidney disease (G4 chronic

**TABLE 1** Characteristics, clinical findings, and outcomes of patients with COVID-19 at hospital admission

Variables	AKI (n = 17)	Non-AKI (n = 331)	p-value
Age, median (IQR 25–75%)	72 (66–76.5)	37 (29–45)	<.001
<b>Gender, n (%)</b>			
Male	12 (70.6)	146 (44.1)	.032
<b>Comorbidities, n (%)</b>			
Chronic hypertension	13 (76.5)	21 (6.3)	<.001
Diabetes mellitus	5 (29.4)	17 (5.1)	<.001
Malignancy	2 (11.8)	6 (1.8)	.053
Chronic heart disease	7 (41.7)	9 (2.7)	<.001
Chronic respiratory disease	3 (17.6)	17 (5.1)	.6
Patients with at least one comorbidity, n(%)	12 (70.6)	47 (14.2)	<.001
Patients with at least two comorbidities, n(%)	11 (64.7)	15 (4.5)	<.001
Baseline serum creatinine, mg/dl	<b>0.89 (0.73–1.14)</b>	<b>0.70 (0.65–0.80)</b>	<.001
<b>Home medicines, n (%)</b>			
ACE inhibitors or ARB	9 (52.9)	14 (4.2)	<.001
Other anti-hypertensives	4 (23.5)	5 (1.5)	<.001
Statins	3 (17.6)	9 (2.7)	.016
Immunosuppressive agents	1 (5.9)	8 (2.4)	.3
NSAID	1 (5.9)	0	N/A
<b>Current smoker, n (%)</b>	5 (29.4)	78 (23.6)	.51
<b>Symptoms on admission n (%)</b>			
Fever>38°C	9 (52.9)	39 (11.8)	<.001
Cough	6 (35.3)	51 (15.4)	.031
Dyspnea	11 (64.7)	32 (9.7)	<.001
Sputum	5 (29.4)	4 (1.2)	<.001
Headache	1 (5.9)	19 (5.7)	1.0
Sore throat	1 (5.9)	31 (9.4)	.524
Myalgia and arthralgia	3 (17.6)	31 (9.4)	.3
Diarrhea	3 (17.6)	10 (3.0)	.020
<b>Severity of disease</b>			
Mild COVID-19	4 (23.5)	298 (90)	<.001
Moderate COVID-19	3 (17.6)	30 (9.1)	
Severe COVID-19	10 (58.8)	3 (0.9)	
<b>Treatment, n(%)</b>			
NO drugs for COVID-19	1 (5.9)	17 (5.1)	<.001
Favipiravir	3 (17.6)	1 (0.3)	
HQ	6 (35.3)	307 (92.7)	
HQ + favipiravir	7 (41.2)	6 (1.8)	
Tocilizumab,n (%)	5 (29.4)	0	N/A
<b>Outcomes, n (%)</b>			
Length of hospitalization, day, median (IQR 25–75)	9 (4–18.5)	2 (1–4)	.01
ICU support	9 (52.9)	3 (0.9)	<.001
Mortality	5 (29.4)	0	N/A

Note: Bold values indicates statistical significance ( $p < 0.05$ ).

Abbreviations: ACE, Angiotensin-converting enzyme; AKI, acute kidney injury; ARB, Angiotensin receptor blocker; HQ, hydroxychloroquine; ICU, intensive care unit; IQR, inter-quartile range; N/A, not applicable; NSAID, non-steroidal anti-inflammatory drug.

**TABLE 2** Laboratory findings of COVID-19 patients at hospital admission, median (IQR 25–75)

Variables	AKI (n = 17)	Non-AKI (n = 331)	p value
White blood cell, mm <sup>3</sup>	6.1 (5.1–8.1)	7.1 (5.8–8.7)	.1
Leukocyte, mm <sup>3</sup>	4.3 (3.3–5.8)	4.3 (3.2–5.6)	.7
Lymphocyte, mm <sup>3</sup>	0.9 (0.6–1.3)	1.95 (1.46–2.47)	<.001
Haemoglobin, g/dl	11.7 (11–13.1)	13.9 (12.9–15.0)	<.001
Platelet, x 10 <sup>3</sup> /mm <sup>3</sup>	209 (156–256)	247 (210–287)	.03
ALT, U/L	23 (14.5–31.5)	20 (14–29)	.503
AST, U/L	33 (21.5–46)	22 (18–27)	.003
Sodium, mmol/L	135 (132.5–136.5)	139 (138–140)	<.001
Potassium, mmol/L	4.06 (3.7–4.4)	4.1 (3.9–4.3)	.6
Chloride, mmol/L	101 (99–103)	105 (103–106)	<.001
D-dimer >0.5 µg/ml, n(%)	14 (82.4)	44 (13.3)	<.01
Fibrinogen, mg/dl	554 (337–735)	293 (249–342)	<.001
Ferritin, ng/ml	180 (41–680)	34 (14.2–99)	<.001
LDH, U/L	407 (219–629)	201 (174–236)	<.001
CK, U/L	146 (73–293)	96 (69–138)	.093
CRP, mg/dl	67 (20.2–106.7)	2.96 (1.74–5.70)	<.001
Serum creatinine, mg/dl	1.2 (1.08–1.81)	0.74 (0.62–0.86)	<.001
eGFR, ml/min per 1.73 m <sup>2</sup>	51 (37–77)	90	<.001
Cystatin C, mg/L	1.64 (1.17–2.07)	0.78 (0.72–0.87)	<.001
<b>Proteinuria, n(%)</b>			
Negative	6 (35.3)	315 (95.2)	<.001
1+	6 (35.3)	7 (2.1)	
2–3+	5 (29.4)	9 (2.7)	
<b>Albumin/creatinine ratio (mg/g), n(%)</b>			
<30	4 (23.5)	291 (87.9)	<.001
30–300	8 (47.1)	35 (10.6)	
>300	5 (29.4)	5 (1.5)	
<b>Protein/creatinine ratio (mg/g)</b>			
<150	3 (17.6)	275 (83.1)	<.001
150–500	7 (41.2)	41 (12.4)	
>500	7 (41.2)	15 (4.5)	
<b>Haematuria with urine dipstick, n(%)</b>	<b>11 (64.7)</b>	<b>143 (43.2)</b>	<b>.08</b>
Positive with red blood cells > 5 with automated urine microscopy, n(%)	<b>6 (35.3)</b>	<b>38 (11.5)</b>	<b>.013</b>

Note: Bold values indicates statistical significance ( $p < 0.05$ ).

Abbreviations: **AKI**, acute kidney injury; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase, **GFR**, glomerular filtration rate, **CK**, creatine kinase; **CRP**, C-reactive protein; **IQR**, inter-quartile range; **LDH**, lactate dehydrogenase.

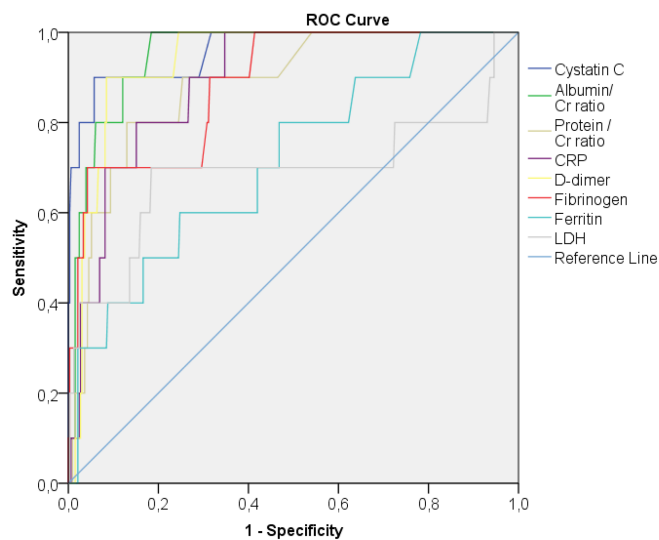
kidney disease (n = 3), G5 chronic kidney disease without renal replacement therapy (n = 1), G5 chronic kidney disease with haemodialysis (n = 3)) and 89 patients were excluded because at least 2 different creatine values could not be reached in the last year. About 348 patients were included in the final analysis. AKI according to KDIGO classification was detected in 4.9% (n = 17) of the patients. The incidence of stage 1, 2, and 3 AKI were 3.45% (n = 12), 0.86% (n = 3), and 0.57% (n = 2), respectively. The frequency of AKI in mild, moderate, and severe COVID-19 cases were 1.3% (n = 4), 9.0% (n = 3), and 76.9% (n = 10), respectively. AKI was detected in

7 (41.2%) of the patients at hospital admission. AKI was detected after hospitalization in 10 (58.8%) of the patients. AKI developed after a median of 7 days (3–19.5, days) after onset of COVID-19-related symptoms. The patients were grouped as AKI and non-AKI and compared in terms of predicting factors for AKI (Tables 1 and 2).

Serum D-dimer levels were 0.92 µg/ml (0.59–2.16), 0.45 µg/ml (0.27–1.14) and 0.24 µg/ml (0.19–0.33),  $p < .001$  in severe, moderate and mild COVID-19 subgroups, respectively. The relationship of serum D-dimer levels with AKI in subgroups with similar disease severity was evaluated. Serum D-dimer levels in the severe COVID-

19 subgroup were 0.84 µg/ml (0.51 to 2.21), 0.92 µg/ml (0.81–2.216),  $p = .398$  in the AKI and non-AKI groups, respectively. Serum D-dimer levels in the moderate COVID-19 subgroup were 1.30 µg/ml (0.84–1.14), 0.41 µg/ml (0.26–1.02),  $p = .064$  in the AKI and non-AKI groups, respectively. Serum D-dimer levels in the mild COVID-19 subgroup were determined as 1.38 µg/ml (0.36–3.40), 0.24 µg/ml (0.18–0.32),  $p = .009$  in the AKI and non-AKI groups, respectively.

To assess the diagnostic utility of several biomarkers at varying cut-off values for predicting AKI, a ROC curve was generated, and AUC was calculated. Accordingly, the AUC values of cystatin C(mg/L), albumin/creatinine ratio, protein/creatinine ratio, CRP (mg/dl), D-



**FIGURE 2** Receiver operating characteristic analysis to differentiate between COVID-19 patients with and without acute renal injury

**TABLE 3** : The values of cystatin C, albumin creatinine ratio, protein creatinine ratio, CRP, D-Dimer, fibrinogen, ferritin, and LDH to the prediction of acute kidney injury in COVID-19 patients at hospital admission<sup>a</sup>

	AUC 95%CI	Cut-off value	Sensitivity (%) 95%CI	Specificity 95%CI	PLR 95%CI	NLR 95%CI	Accuracy 95%CI
Cystatin C	0.96 (0.90–1.0)	1.00	90.0 (55.5–99.75)	88.5 (84.6–91.7)	7.84 (5.45–11.2)	0.11 (0.02–0.71)	88.56 (84.7–91.7)
Albumin/creatinine ratio	0.95 (0.91 to 0.98.9)	30	90.0 (55.5–99.7)	87.9 (83.9–91.2)	7.45 (5.22–10.6)	0.11 (0.02–0.71)	87.9 (84.0–91.2)
Protein/creatinine ratio	0.88 (0.72–0.95)	150	80.0 (44.3–97.4)	83.0 (78.6–86.9)	4.73 (3.2–6.9)	0.24 (0.07–0.83)	82.9 (78.5–86.8)
CRP	0.89 (0.82–0.96)	5	90.0 (55.5–99.7)	69.7 (64.5–74.6)	2.98 (2.29–3.88)	0.14 (0.02–0.90)	70.3 (65.1–75.1)
D-dimer	0.94 (0.89–0.98)	0.5	90.0 (55.5–99.75)	86.7 (82.6–90.2)	6.77 (4.8–9.55)	0.12 (0.02–0.77)	86.8 (82.7–90.2)
Fibrinogen	0.88 (0.79–0.98)	328	90.0 (55.5–97.5)	67.9 (62.5–72.9)	2.81 (2.17–3.64)	0.15 (0.02–0.96)	68.6 (63.4–73.5)
Ferritin	0.72 (0.55–0.88)	36.5	80 (44.3–97.5)	53.1 (47.6–58.6)	1.71 (1.23–2.38)	0.38 (0.11–1.32)	53.9 (48.5–59.3)
LDH	0.68 (0.45–0.92)	260	70.0 (34.7–93.3)	81.2 (76.6–85.3)	3.74 (2.35–5.95)	0.37 (0.14–0.95)	76.3 (76.3–85.0)

Abbreviations: AUC, area under the curve; Cr; creatinine; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

<sup>a</sup>Ten patients without AKI on hospital admission were included.

Dimer (µg/ml), fibrinogen(mg/dl), ferritin (ng/ml) and lactate dehydrogenase (LDH, U/L) are as follows; 0.96 (0.90–1.0), 0.95 (0.91–0.98), 0.88 (0.72–0.95), 0.89 (0.82–0.96), 0.94 (0.89–0.98), 0.88 (0.79–0.98), 0.72 (0.55–0.88) and 0.68 (0.45–0.92), respectively (Figure 2). The best cut-off value of these biomarkers for differentiating between AKI and non-AKI groups and the sensitivity/specificity values in this cut-off level was presented in Table 3.

In hospital admission, proteinuria and haematuria were detected with a urine dipstick test in 27 (7.8%) and 154 (44.3%) patients, respectively. In spot urine analysis, proteinuria (> 150 mg/g) was found in 70 (20.1%) of patients and 68.6% of them were moderate (150–500 mg/g) proteinuria. Albuminuria was found in 51 (14.7%) patients, and ten of them (2.87%) had albuminuria of 300 mg/g and above. A total of 163 patients were re-evaluated mean 28 days after hospitalization. In these patients, Cr, BUN, GFR, cystatin C, albumin/creatinine, and Protein/creatinine ratios values were compared with hospitalization values after a mean of 28 days (Table 4). Compared to spot urine analyses at hospital admission, 74.3% of proteinuria and 72.5% of albuminuria regressed after 28 days. The frequency of persistent proteinuria was 5.2%. Kidney biopsy has not been performed in any of these patients.

The median length of hospital stay was 9 (4–18.5) days in the AKI group and was longer than in the non-AKI group ( $p = .01$ ). The frequency of intensive care support requirement and mortality in the AKI group were 52.9% ( $n = 9$ ) and 29.4% ( $n = 4$ ), respectively, and higher than in the non AKI-group (Table 1).

## 4 | DISCUSSION

In our study, it was found that AKI was common in COVID-19 patients, its incidence increased with disease severity, and the most

**TABLE 4** Comparison of renal function indicators with an interval of 28 days in COVID-19 patients

	On hospital admission	28th day of hospital admission	p value
Patient with acute kidney injury (n = 16), mean ± SD			
Cr (mg/dl) <sup>a</sup>	1.3 ± 0.50	1.4 ± 1.1	.278
BUN (mg/dl) <sup>a</sup>	27.6 ± 14.6	39.9 ± 29.7	.109
GFR (ml/min per 1.73 m <sup>2</sup> ) <sup>b</sup>	56.3 ± 21.0	58.8 ± 22.4 <sup>a</sup>	.111
Cystatin C (mg/L) <sup>a,c</sup>	1.46 ± 0.5	1.51 ± 0.45	.929
Albumin/creatinine ratio (mg/g) <sup>a,c</sup>	185 ± 177.9	97 ± 108.9	.075
Protein/creatinine ratio (mg/g) <sup>a,c</sup>	486.2 ± 375.5	611.0 ± 544.6	.286
Patient without acute kidney injury (n = 147), mean ± SD			
Cr (mg/dl) <sup>b</sup>	0.74 ± 0.16	0.77 ± 0.48	.419
BUN (mg/dl) <sup>a</sup>	12.7 ± 3.70	12.8 ± 3.40	.605
GFR (ml/min per 1.73 m <sup>2</sup> ) <sup>a</sup>	88.7 ± 5.25	88.8 ± 4.9	.852
Cystatin C <sup>a,d</sup>	0.84 ± 0.19	0.82 ± 0.21	.284
Albumin/creatinine ratio (mg/g) <sup>a,d</sup>	39.8 ± 119.2	26.5 ± 10.1	<.001
Protein/creatinine ratio (mg/g) <sup>a,d</sup>	222.5 ± 475.5	124.2 ± 178.4	<.001

Abbreviations; Cr, creatinine; GFR, glomerular filtration rate; SD, standard deviation.

<sup>a</sup>The Wilcoxon test was used.

<sup>b</sup>Paired student's *t*-test was used.

<sup>c</sup>11 patients were included.

<sup>d</sup>132 patients were included.

common kidney dysfunction was proteinuria. COVID-19-related AKI can be predicted early with serum cystatin C levels, D-dimer levels and albumin/creatinine ratio on hospital admission.

In COVID-19 patients, the most common kidney dysfunction is mild to moderate proteinuria.<sup>16</sup> The frequency of proteinuria ranges from 7% to 63%.<sup>5</sup> Cheng et al was showed that the incidence of proteinuria was 43.9% by urine dipstick test in COVID-19 patients, on hospital admission.<sup>17</sup> However, the urine dipstick test specifically evaluates the excretion of albumin, gives a semi-quantitative estimate of the proteinuria depending on the protein concentration in the urine, and does not reflect the protein excretion rate.<sup>18</sup> The urine dipstick test is not sensitive to detect non-albumin proteinuria.<sup>18</sup> Also, evaluation of proteinuria by urine dipstick tests may be misleading in febrile, oliguric, and critical COVID-19 patients.<sup>19</sup> In our study, the incidence of proteinuria was found to be 7.8% with a dipstick. However, the frequencies of proteinuria and albuminuria are higher with the protein/creatinine ratio in spot urine. The dipstick test appears to be inadequate in the correct identification of proteinuria in COVID-19 patients. Proteinuria often develops as a result of proximal tubular damage in COVID-19 patients.<sup>20</sup> The most common kidney biopsy finding in COVID-19 is acute tubular necrosis (ATN).<sup>5,21</sup> Therefore, non-albumin proteinuria may be the early finding of COVID-19-related tubular dysfunction.<sup>22</sup> In our study, non-albumin proteinuria was found to be the most common proteinuria at hospital admission and follow-up. In addition, a higher frequency of proteinuria was detected in spot urine analysis compared to a dipstick test which supports the presence of non-albumin proteinuria. These findings suggest that proteinuria developing in COVID-19 patients is primarily of tubular origin. However, in some kidney biopsy series, glomerular

pathologies have been described with ATN or rarely alone.<sup>5</sup> In these patients, collapsing glomerulopathy has been described.<sup>19,23</sup> This suggests that some patients with albuminuria accompanying proteinuria may have glomerular damage with tubular damage.<sup>19</sup> In our study, the incidence of proteinuria was higher in the AKI group. As a result, spot urine albumin/creatinine ratio above 30 mg/g can be used as an early marker with high sensitivity and specificity in predicting COVID-19-related AKI in patients who do not meet AKI criteria at hospital admission. In COVID-19 patients, albuminuria should be evaluated routinely with the albumin/creatinine ratio in spot urine at hospital admission.

Haematuria, another urinalysis finding, is frequently detected in COVID-19 patients.<sup>24</sup> In previous studies, the frequency of haematuria is ranged from 26.7 to 63.8% with a urine dipstick.<sup>6,17,24</sup> These studies indicate that haematuria can be used to characterize renal dysfunction in COVID-19 patients.<sup>24</sup> In our study, the frequency of haematuria with urine dipstick or automated microscopy was found to be similar to these studies. The frequency of haematuria was also found to be higher in the AKI group than without AKI.

In the meta-analysis, the average incidence of COVID-19-related AKI was 4.5%, whereas in severe cases requiring ICU, the incidence increased to 36.4%.<sup>5,19</sup> Chan et al. found the incidence of COVID-19-related AKI in ICU patients at 68%.<sup>25</sup> Similarly, in our study, the average incidence of AKI was found to be 4.9%, and the incidence, which was 1.3% in the mild group, was shown to increase up to 76.7% in severe cases requiring intensive care support.

Cystatin C as an endogenous biomarker of renal function is superior to serum creatinine in the definition of renal dysfunction.<sup>26-28</sup> It can be used as an early marker because it is sensitive to mild and early



renal function changes, especially when compared with serum creatinine.<sup>10</sup> Cystatin C levels also increase earlier than serum creatinine levels in ICU patients.<sup>29</sup> In our study, a similar relationship was found between cystatin C level and COVID-19-related AKI. According to our results, in patients with normal serum creatinine values at hospital admission, AKI can be predicted by using serum cystatin C levels with a cut-off value of 1 mg/L in the early period.

Some biomarkers such as CRP, LDH, D-dimer, fibrinogen, ferritin were also evaluated in the prediction of COVID-19-related AKI in our study.<sup>30</sup> When compared with other biomarkers, D-dimer levels can be used to predict COVID-19-related AKI. The data in our study showed that serum D-dimer levels increased with the severity of COVID-19. This is thought to be related to the pathogenesis of the disease characterized by coagulopathy, which is manifested by an increase in D-dimer and fibrin/fibrinogen degradation products.<sup>31</sup> In COVID-19 patients, disseminated intravascular coagulation (DIC)-associated organ infarctions with small vessel thrombosis have been identified in autopsy studies.<sup>32</sup> Renal infarcts may develop as a result of hypercoagulopathy associated with micro thrombosis and embolism.<sup>24,33</sup> Angiotensin-converting enzyme-2 (ACE 2) overactivation, innate/adaptive immune response, endothelitis and microangiopathy resulting from the interaction between complement and coagulation system have been shown to affect AKI severity and disease outcome.<sup>24,31,32</sup> On the other hand, D-dimer also increased secondary to AKI in the moderate and mild subgroups. These results predict that the D-dimer level can be affected not only by the severity of COVID-19 but also by AKI. In previous studies, D-dimer fractions were also found to be higher in patients with renal insufficiency.<sup>34,35</sup>

Detecting the relationship between renal dysfunction and COVID-19 is generally difficult due to the lack of previous renal function evaluation of patients.<sup>17</sup> The strength of our study is to reassess renal functions after 28 days. After all, in the vast majority of affected patients, proteinuria and albuminuria regressed within 1 month in the non-AKI group. This result has been evaluated as evidence of the relationship between proteinuria and COVID-19. In the AKI group, a non-significant decrease was found in albuminuria and proteinuria values. And also, in these patients, no difference was detected in serum creatinine, BUN, cystatin C, and GFR values on day 28. However, recovery of acute kidney damage can take up to 3 months, so there may be a significant regression in the evaluations to be made at the end of the 3rd month in these patients.

Our study has several limitations. The first one is the small number of patients, especially in the AKI group. This situation is related to a high probability of error in statistical comparisons. To reduce this probability, the parameters showing a statistical significance in a univariate analysis could not be evaluated by multivariate analysis. Therefore, our study results need to be confirmed with larger cohort studies. Second, because of the retrospective nature of our study, the 28th day of evaluation records were not available in some patients. Third, factors such as body mass index, presence of malignancy, cholesterol level, hypothyroidism, or hyperthyroidism, which may affect the serum cystatin C levels, could not be evaluated due to the retrospective design of the study.<sup>26</sup>

In conclusion, COVID-19-associated renal dysfunction is quite common. The most common finding of urinary abnormality in these patients is proteinuria and it is usually transient. Albuminuria, which may be associated with glomerular damage, was found more frequently in COVID-19 patients with AKI. In patients with serum creatinine levels within normal limits, the detection of albuminuria should be a stimulus for COVID-19-related AKI and these patients should be monitored closely. Similarly, higher serum cystatin C and D-dimer levels may be early predictors of COVID-19-related AKI.

## ACKNOWLEDGEMENTS

The authors thank all healthcare professionals at Gazi University Hospital for their devoted work in the management of the COVID-19 pandemic.

## CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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**How to cite this article:** Yildirim C, Ozger HS, Yasar E, et al. Early predictors of acute kidney injury in COVID-19 patients. *Nephrology.* 2021;26:513-521. <https://doi.org/10.1111/nep.13856>