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Acute Kidney Injury in Cases of COVID-19 Without Existing Kidney Disease: Does It Differ at Various Stages of the Disease?

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Abstract

Objective: Kidney involvement in coronavirus disease 19 may manifest as acute kidney injury. This study aimed to analyze and compare acute kidney injuries in different stages of coronavirus disease 19 on patients without previous kidney diseases.

Methods: A total of 1056 hospitalized coronavirus disease 19 patients were retrospectively evaluated, and 89 patients who developed acute kidney injury but did not have prior kidney diseases were involved in the final analysis. Acute kidney injury was defined according to Kidney Diseases: Improving Global Outcomes criteria. Patients were classified into 3 groups, those who had acute kidney injury on admission, those who developed acute kidney injury in the first week, and those who developed acute kidney injury starting from the seventh day. Electrolytes, acid–base status, and changes in the inflammatory markers were compared.

Results: Twenty-nine patients (33%) had acute kidney injury on admission, 33 (37%) patients developed acute kidney injury in the first week, and 27 (30%) developed acute kidney injury after the first week. Acute kidney injuries that were seen on hospital admission day were generally transient. Patients who developed acute kidney injury after the seventh day had higher peak C-reactive protein (CRP) and D-dimer levels and lower nadir lymphocyte counts (P = .000, .004, and .003, respectively). Patients who developed acute kidney injury after the first week had significantly more intensive care unit admission and higher mortality, reaching as high as 62% and 44%, respectively (P = .001 and .009). Cox regression analysis revealed that increasing creatinine (P = .02; OR = 2.83; 95% CI: 1.45-5.53) and ferritin levels (P = 0.04; OR = 1.62; 95% CI: 1.16-2.05) were related to the mortality.

Conclusion: Acute kidney injury in different stages of coronavirus disease 19 may have different characteristics and outcomes. Acute kidney injury that develops later tends to present with higher creatinine levels and has a worse prognosis.

Keywords: Acute kidney injury, AKI, COVID-19, cytokine release, electrolytes

The clinical course of coronavirus disease 19 (COVID-19) patients who needed hospital admission may be examined in 3 consecutive stages: stage 1 as the early infection period (first 3 days after being infected by the virus), stage 2 as the intermediate period (until the seventh day of the illness) with pulmonary involvement, and stage 3 as the systemic hyper-inflammation phase. Stage 3 is generally accepted to start within the second week of the disease course.[1] While COVID-19 is mainly a respiratory illness, kidneys may also be involved. Multiple pathologic mechanisms have been proposed to explain the cause of kidney involvement including fluid balance disturbances, angiotensin II pathway activation, endotheliitis with intravascular coagulation, lung–kidney and heart–kidney cross talks, cytokine release syndrome, and drug nephrotoxicity.[2,3]

Kidney involvement in COVID-19 may be manifested as acute kidney injury (AKI). Previous studies generally evaluated all forms of AKIs together. However, AKIs may have different characteristics depending on the timing and etiologies. This study aims to analyze the characteristics of AKI in different phases of the disease among hospitalized COVID-19 patients without prior kidney diseases.

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Methods

Setting

Patients who were admitted to the designated COVID wards in our tertiary healthcare center, between March 15 and July 1, 2020, were retrospectively analyzed. This period has been the first wave of the pandemic, and symptomatic patients were admitted immediately. Hospitalized COVID-19 patients whose disease status was confirmed by a real-time polymerase chain reaction (RT-PCR) test for severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) were involved in the study. Kidney transplant patients and those who were younger than 18 years old were excluded from the study. As glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 was already shown to be related to mortality,[4] these patients were also excluded (Figure 1).

Definitions

To define AKI, Kidney Disease Improving Global Outcomes (KDIGO) criteria were used; an absolute increase of 0.3 mg/dL in creatinine levels in 48 hours or 50% increase in creatinine levels

in the last 7 days or when urine output is less than 0.5 mL/kg/h for the previous 6 hours.[5]

We observed the progression of creatinine values in all patients who were admitted with COVID-19 diagnosis. In patients with an increase in creatinine levels, we directly applied the Kidney Diseases: Improving Global Outcomes criteria (KDIGO) criteria. The first calculated creatinine level after being admitted to the hospital was taken as the baseline creatinine level for these patients. For patients with a decrease in their creatinine levels following hospital admission, KDIGO criteria were applied according to patients' previous creatinine levels. When there was no previous data 7 to 365 days prior to hospital admission, baseline creatinine levels were calculated backward using the Modification of Diet in Renal Disease $(MRD)_{75}$ formula.[5,6]

Stage of the AKI was also defined according to KDIGO criteria; 1.5-1.9 times baseline creatinine or 0.3 mg/dL absolute increase as stage 1 AKI; 2.0-2.9 times baseline creatinine as stage 2 AKI, and more than 3.0 times baseline creatinine or increase to more than 4.0 mg/dL as stage 3 AKI.

Estimated glomerular filtration rate (eGFR) was used to define the kidney functions, and it was calculated by Chronic Kidney Diseases Epidemiology Collaboration (CKD-EPI) formula.

Hematuria was defined as the presence of more than 3 red blood cells per high power field in the urine sediment. Proteinuria was detected semi-quantitatively by a fully automated urine dipstick test. The level of proteinuria was graded as +1, +2, or +3; indicating levels between 30 and 100 mg/dL, between 100 and 300 mg/dL, and over 300 mg/dL, respectively.

Hyponatremia (<135 mmol/L), hypernatremia (>145 mmol/L), hypochloremia (<98 mmol/L), hyperchloremia (>107 mmol/L), hypokalemia (<3.5 mmol/L), hyperkalemia (5.1 mmol/L), hypophosphatemia (<2.5 mg/dL), hyperphosphatemia (>4.5 mg/dL), acidosis (pH < 7.35), and alkalosis (pH > 7.45) were all described according to the reference range of respective laboratory measurements.

We defined 3 groups on the basis of the timing of AKI; those seen on admission, those developed in the first week, and those developed after the first week.

Severity of COVID-19

Clinical pictures of COVID-19 patients were classified according to a scale that included the following categories: Mild (symptoms of upper respiratory tract infection or digestive symptoms), moderate (pneumonia without hypoxemia), severe (pneumonia with hypoxemia), and critical (acute respiratory distress syndrome, shock).[7]

Acquisition of data and statistical analysis

Hospital electronic health records and patient files were used to collect the data. Admission day to the COVID ward was accepted as day 0 of the patient follow-up. Data were expressed as means ± standard deviation. Continuous variables were compared by independent samples *t*-test. Categorical variables were compared either by Pearson chi-square or Fisher's exact test. For the comparison of

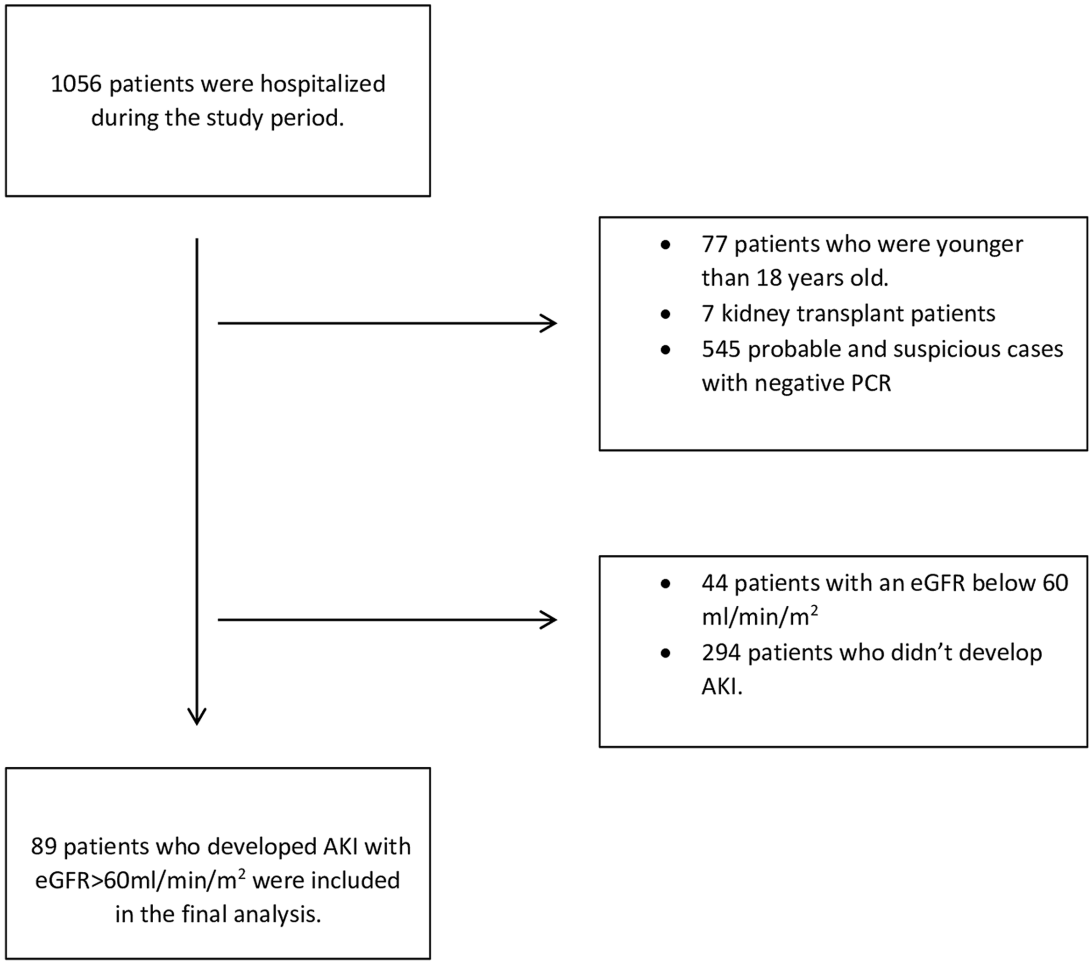

Figure 1. Flowchart of inclusion and exclusion criteria of the patients.
PCR, polymerase chain reaction; eGFR, estimated glomerular filtration rate.

3 groups that were created according to the timing of AKI, analysis of variance test was performed. Tukey Honest Significance Test (HSD) test was used for post hoc analysis. Survivals of patients in different groups were compared by log-rank test via Kaplan–Meier analysis. Cox regression analysis was used to define variables that were related to mortality. All tests were applied using Statistical Package for the Social Sciences for Windows, version 22.0 software (IBM SPSS Corp.; Armonk, NY, USA). *P* values less than .05 were accepted as statistically significant.

Results

A total of 1056 patients were admitted in this specified period. A total of 427 patients were confirmed by RT-PCR, 104 of these PCR-confirmed COVID-19 patients experienced AKI (24,3%), and 89 AKI patients who had baseline eGFR of over 60 mL/min/1.73 m^2 were included in the final analysis (Figure 1). Patients were 62.4 ± 14.2 years old and there was a male predominance (67 males, 75%).

In total, 29 (33%) patients had AKI on admission, 33 (37%) developed AKI during the first week of admission, and 27 (30%) developed AKI after the first week. For patients who developed AKI later than the hospital admission date, AKI developed on the 6.7th ± 5.4th day of the admission.

Urine analysis

Urine analysis was available in a total of 35 patients. Hematuria was the most prominent finding, which was seen in 21 of them. Proteinuria was documented in 9 patients, and they were all 1+ semiquantitative. Proteinuria was going along with hematuria in 7 patients, while 2 patients had isolated proteinuria.

Electrolyte and acid/base disturbances

Hypochloremia and hyponatremia were the most common electrolyte abnormalities. In total, 65 of the 89 patients (73%) had hypochloremia and 50 (56.1%) of the patients had hyponatremia. Hypernatremia and hyperchloremia were seen in 22 (24.7%) and 18 (20.2%) of the patients, respectively. Among potassium abnormalities, hyperkalemia developed in 35 (39.3%) of the patients, while hypokalemia was seen in 16 (17.9%) of them. Among patients for whom phosphorus levels were evaluated (79 patients), 22 had hypophosphatemia (27.8%) and 20 patients (25.3%) had hyperphosphatemia. Acidosis (respiratory and/or metabolic) developed in 23 (25.8%) of the patients, and respiratory alkalosis was seen in 38 (42.6%) of them.

Treatment modalities

Although there is no specific validated treatment for COVID-19 yet, some antiviral therapies were applied in accordance with the ministry of health (MoH) treatment guidelines. These included different combinations of hydroxychloroquine, favipiravir, and lopinavir. Anti-IL-6 receptor antibody tocilizumab or steroids were used in patients who had a high inflammatory response. Low-molecular-weight heparin was prescribed for all patients in line with the MoH guidelines.[8] Continuous renal replacement therapy (CRRT) in intensive care unit (ICU) setting was performed with Prismaflex® system in a citrate anticoagulated circuit, aiming a blood flow of around 20 mL/kg/h.

Comparison according to the timing of AKI

Patients of the 3 groups (AKI on admission, AKI in the first week, and AKI after the first week) were of similar age. Duration of hospital stay, ICU requirement, and mortality were higher when AKI developed later in the disease course, especially after the seventh day. Patients who develop AKIs later had lower serum albumin levels as well as lower arterial O_2 pressure and lower oxygen saturation levels. Pre-dominant stage of AKI was stage 1; however, stage 2 & 3 AKIs, which have a worse prognosis, tend to increase with AKIs that occurred later. Similarly, COVID-19 was more severe in patients who had AKIs later (Table 1).

Patients of 3 groups had a similar baseline mean arterial pressure, creatinine, and hemoglobin levels. Co-morbidities such as diabetes, hypertension, malignancies, and ischemic heart diseases/heart failure were also similar between 3 groups. CRP and D-dimer levels on admission did not differ between the groups. Patients who had AKI on admission day had higher initial uric acid levels and had lower urea-to-creatinine ratios. All initial laboratory values of the patients are given in Table 2.

While there were no significant differences between the initial inflammatory markers of the 3 groups, the comparison of changes put forth significant differences. Nadir lymphocyte counts were significantly lower, while peak CRP and peak D-dimer levels were significantly higher in patients who developed AKI later in the disease course (Table 3). Although it could not reach statistical significance, peak ferritin levels were also higher in patients who developed AKI later.

Sodium, chlorine, and potassium abnormalities were more common in patients who developed AKI later (Table 3).

Treatment modalities were similar in all groups. renal replacement therapy (RRT) had to be performed in 6 patients who developed AKI later (2 among the first week AKIs and 4 among the AKIs developed after the first week), but none of the patients who had AKI on admission needed RRT.

Comparison between survivors and non-survivors

Duration of hospital stay was not different for survivors and non-survivors. Those who died were older. Patients who survived and who did not have similar rates of diabetes or hypertension, while concomitant malignancies were more frequent in patients who died (Table 4).

AKI had 24.7% mortality in our patients who had baseline eGFRs of above 60 mL/min/1.73 m^2. AKI developed later in non-survivors and it lasted longer. Non-survivors had significantly higher initial CRP, LDH, ferritin, and D-dimer levels while their hemoglobin and lymphocyte counts were significantly lower (Table 4).

Patients who died had lower serum albumin levels than those who survived. Hematuria or proteinuria (*P* = .001; OR = 2.4; 95% CI: 1.4-3.8 and *P* = .015; OR = 4.34; 95% CI: 1.3-14.3, respectively) was more common in patients who died.

Among electrolyte disturbances, hyponatremia and hypochloremia were similar between survivors and non-survivors. On the other hand, hypernatremia (*P* = .000, OR = 6.5; 95% CI: 3.0-13.9) and hyperchloremia (*P* = .002, OR = 3.8; 95% CI: 1.7-8.4) were more common in patients who died. Comparison of other electrolytes is given in Table 4.

Patients who died had more secondary bacterial infections (OR = 3.5; 95% CI: 1.9-6.4). However, ferritin levels, as a marker of inflammation, were similar in patients who had secondary bacterial infections and in those who had not (n = 24; 1120 ± 691 vs. n = 62; 976 ± 109; *P* = .548). Urea-to-creatinine ratios checked both on the day of AKI and on the day of worst kidney function were higher in patients who died (*P* = .02 and *P* = .000, respectively).

Survival analysis

In the Kaplan–Meier survival analysis of 3 groups based on the timing of their AKIs (Figure 2), log-rank test did not reveal any difference between the groups (*P* = .65). In multivariate Cox regression

Table 1. Acute Kidney Injury-Related Prognostic Indices of Patients

	AKI on Presentation (n = 29)	AKI in the First Week (n = 33)	AKI After 7 Days (n = 27)	*P*
Co-morbidities (n)	16	18	21	.123
DM (n)	4	10	9	.189
HAT (n)	9	11	11	.729
Malignancy (n)	3	4	6	.398
IHD/HF (n)	8	7	5	.702
Fever (>38°C) (n, %)	14 (48.2)	13 (39.3)	10 (37.0)	.573
AKI stage 1 (n, %)	26 (89.2)	26 (78.7)	16 (59.2)	.058
AKI stage 2 (n, %)	3 (10.3)	3 (9.0)	7 (25.9)	
AKI stage 3 (n, %)	0	4 (12.1)	4 (14.8)	
Severe or critical COVID-19 (n, %)	7 (24)	14 (41)	22 (81)	.000*
Pneumonia in chest CT (n, %)	28 (96)	29 (87)	25 (92)	.446
Secondary bacterial infections (n, %)	6 (20)	8 (24)	12 (44)	.108
Duration of hospital stay (days)	11.3 ± 6.4	11.8 ± 7.9	17.3 ± 6.5	.003*
ICU requirement (n, %)	5 (17)	9 (27)	17 (62)	.001*
pH	N = 20	N = 22	N = 23	.114
	7.41 ± 0.7	7.38 ± 0.98	7.35 ± 0.12	
sPO_2	93.24 ± 2.7	93.04 ± 3.85	87.33 ± 7.5	.000*
Arterial PO_2 (mmHg)	N = 15	N = 15	N = 21	.025*
	65.02 ± 9.53	67.49 ± 14.18	56.95 ± 10.95	
In hospital death (n, %)	4 (13.7)	5 (15)	12 (44)	.009*
Death on (days)	11.75 ± 7.4	10.8 ± 6.3	17.3 ± 8.0	.21

DM, diabetes mellitus; HT, hypertension; IHD/HF, ischemic heart disease and heart failure; CT, computed tomography; ICU, intensive care unit; AKI, acute kidney injury; COVID-2019, coronavirus 2019.
N in the boxes indicates the number of available measurements, when they are not available for all patients.
*Significance results from patients who developed AKI after seventh day.

analysis that included patient age, AKI duration, timing of AKI, peak creatinine, and peak ferritin as co-variates; peak creatinine (*P* = .02; OR = 2.83; 95% CI: 1.45-5.53) and peak ferritin levels (*P* = .04; OR = 1.62; 95% CI: 1.16-2.05) were related to the mortality of the patients. On the other hand, AKI duration, patient age, and group categories based on AKI timing were not found statistically significantly related to survival.

Discussion

Different studies reported variable AKI incidences in COVID-19.[9-12] In the consensus report of the Acute Disease Quality Initiative, AKI incidence was reported to be around 20% for hospitalized patients.[13] Same report underlines that AKI may develop in 50% of the patients who needed ICU support. AKI has been proposed as a poor prognostic factor for COVID-19.[14] In a meta-analysis, it was found that 52% of patients who developed AKI had died.[15] Another study showed that chronic kidney disease and male sex were independent predictors of AKI severity.[16] However, AKI studies solely analyzing patients with normal kidney functions are scarce. In this study, we focused on the prognosis of AKI in otherwise normal kidneys by excluding patients whose eGFRs were below 60 mL/min/1.73 m^2. Overall mortality was calculated as 24.7% in this group.

Consequences of all AKIs in COVID-19 might not be the same. As COVID-19 is a febrile illness and patients are experiencing gastrointestinal disturbances, pre-renal AKI is somewhat expected upon admission and should be transient. There may still be AKIs related to other etiologies on admission, and this may be because of differences in the severity of the disease or relatively late referrals of some patients. On admission, AKIs were mainly transient AKIs (41%) that were responsive to fluid therapy in 48 hours. This decreased to 30% for first week AKIs and to 3% for AKIs after the first week. It may not be possible to differentiate between coagulopathy and cytokine release as both pathologies may be intertwined with each other.[17,18] When high levels of ferritin (>750 ng/mL) and D-dimer (>5 mg/L) were taken together, inflammation-mediated injury was around 27.5% on admission AKIs. This increased to 39.3% for first week AKIs, and it was 59.2% for patients who experienced AKI starting from the second week. Severe or critical COVID-19 was more common in patients who developed AKI later. The mortality of patients who experienced AKI in the early period was 13.7%, and this increased to 44% for

Table 2. Characteristics and Initial Laboratory Values of Patients in 3 Groups According to the Timing of AKI

	Presented with AKI (n = 29)	AKI in the First Week (n = 33)	AKI After 7 Days (n = 27)	*P*
Age	61.6 ± 14.2	62.5 ± 12.9	63.1 ± 16.2	.926
Baseline eGFR (mL/min/1.73 m^2)	79.6 ± 16.38	82.11 ± 14.53	86.55 ± 16.43	.258
Urea-to-creatinine ratio	37.08 ± 17.19	58.42 ± 32.68	59.25 ± 24.11	.000**
MAP (mmHg)	89.9 ± 17.2	88.9 ± 13.1	87.4 ± 10.1	.801
Hemoglobin (g/dL)	12.3 ± 1.9	12.5 ± 1.5	11.9 ± 1.9	.474
Lymphocytes (per µL)	1317 ± 568	1509 ± 798	1044 ± 437	.022*
CRP (mg/L)	81.9 ± 76.1	68.5 ± 79.1	98.4 ± 77.6	0.336
Procalsitonin (ng/mL)	0.27 ± 0.38	0.4 ± 1.1	0.4 ± 0.8	.683
CK (IU/L)	383 ± 955	282 ± 663	149 ± 111	.442
LDH (IU/L)	400 ± 194	408 ± 480	441 ± 213	.889
Ferritin (ng/mL)	615 ± 599	474 ± 524	840 ± 599	.055
D-dimer (mg/L)	1.5 ± 2.5	1.6 ± 2.4	2.5 ± 3.9	.346
Uric acid (mg/dL)	6.9 ± 2.6	5.5 ±1.5	4.6 ± 1.6	.000**
Sodium (mmol/L)	136.59 ± 5.4	138.67 ± 4.9	141.67 ± 5.89	.03*
Chloride (mmol/L)	97.01 ± 5.40	98.16 ± 4.88	99.54 ± 4.51	.168
Potassium (mmol/L)	4.31 ± 0.55	4.45 ± 0.63	4.57 ± 0.67	.291
Phosphorus (mg/dL)	N = 24	N = 29	N = 26	.853
	3.47 ± 0.69	3.56 ± 1.03	3.38 ± 1.56	
HCO_3 (mmol/L)	N = 20	N = 22	N = 23	.963
	24.23 ± 3.14	24.28 ± 3.61	24.65 ± 8.23	
Albumin (g/dL)	3.61 ± 0.37	3.51 ± 0.50	3.04 ± 0.42	.000*

eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; CK, creatine kinase; LDH, lactate dehydrogenase; AKI, acute kidney injury; HCO_3, bicarbonate.
N in the boxes indicates the number of available measurements, when they are not available for all patients.
*Post hoc analysis reveals that the significance is because of the levels in patients who had AKI after the first week.
**Significance is mainly because of the levels in patients who were presented with AKI.

patients who had AKI after the seventh day. Kaplan–Meier estimation of survival did not reveal any difference between 3 groups. This is most probably because of longer hospital stay of patients who experienced AKI later in the disease course. Increasing creatinine and ferritin levels were related to poor prognosis. In a multi-center study of the Turkish Society of Nephrology, mortality of COVID-19 patients who experienced AKI was found as 38.9%.[19] Although that study found similar mortality between CKD and non-CKD patients, there were still increasing rates of mortality with further AKI stages, pointing out to increasing levels of creatinine as a poor prognostic factor.

It may be difficult to find the exact etiology of AKI in the course of COVID-19. Kidney biopsies may give some clues. Direct virulence of SARS-CoV-2 may be responsible for kidney involvement with acute tubular injury and podocytopathies.[20-22] In a report of kidney biopsies in COVID-19 patients, podocytopathies and interstitial diseases were the main findings while immune-mediated glomerular diseases were also found.[23] That study did not detect virus particles in the kidney. Another study of kidney biopsies on a series of 10 patients found acute tubular necrosis as the leading pathology of AKI. Myoglobin casts as well as thrombotic microangiopathy were also reported.[24] We did not perform kidney biopsies, as it was neither clinically indicated nor would change treatment modalities in the vast majority of our patients. It is known from before that immune system dysregulation, complement system activation, and hyper-coagulopathy were all linked with each other.[25] It may not be always possible to define which has started before and caused the others. That is why AKIs in patients either with increasing D-dimer levels or cytokine release syndrome that manifests with increasing levels of ferritin might be associated with the hyper-inflammation state of COVID-19.[26]

Patients who develop AKI later had higher peak CRP, D-dimer, and ferritin levels. Such a higher inflammatory response may point out that later AKI is more immune-mediated. Although secondary bacterial infections could be a confounding factor, ferritin levels, as a marker of inflammatory response in patients with or without secondary bacterial infections did not differ.

Drug-induced nephrotoxicity should not be overlooked in AKIs that develop later. Drugs that resulted in AKI in our patients were

Table 3. Comparison of Changes in the Inflammatory Markers, Lymphocyte Counts, Electrolyte Abnormalities, and Acid/Base Disturbances During the Course of the Disease

	AKI on Presentation (n = 29)	First Week AKI (n = 33)	AKI After Seventh Day (n = 27)	*P*
Peak creatinin (mg/dL)	1.62 ± 0.53	1.69 ± 0.78	1.88 ± 0.87	.405
AKI duration (days)	4.0 ± 3.7	3.03 ± 4.66	3.19 ± 3.3	.602
Nadir lymphocytes (per μL)	967 ± 574	1100 ± 692	585 ± 343	.003*
Peak CRP (mg/L)	125 ± 83	145 ± 122	246 ± 86	.000*
Peak procalcitonin (ng/mL)	0.57 ± 0.87	3.36 ± 8,37	3.86 ± 6.34	.100
Peak CK (IU/L)	445 ± 974	387 ± 696	611 ± 641	.545
Peak LDH (IU/L)	533 ± 314	679 ± 794	888 ± 510	.087
Peak ferritin (ng/mL)	754 ± 596	806 ± 659	1546 ± 1406	.004*
Peak D-dimer (mg/L)	7.1 ± 16.3	8.03 ± 10.65	15.39 ± 14.53	.058
Pro-BNP (pg/mL)	N = 10	N = 19	N = 20	.593
	9029 ± 12 542	4691 ± 10 770	7050 ± 10 870	
Uric acid (mg/dL) (on the AKI day)	7.03 ± 2.7	5.81 ± 2.14	5.13 ± 2.0	.01**
Urea (mg/dL) (on the AKI day)	56.72 ± 34.89	51.76 ± 17.22	63.89 ± 36.23	.303
Peak urea (mg/dL)	72.14 ± 46.23	72.27 ± 46.04	97.52 ± 70.78	.140
Creatinine (mg/dL) (on the AKI day)	1.48 ± 0.35	1.43 ± 0.32	1.54 ± 0.47	.565
Urea/creatinine ratio (on AKI day)	37.08 ± 17.19	37.5 ± 14.64	41.83 ± 20.78	.534
Urea/creatinine ratio (peak level)	N/A	42.25 ± 15.4	51.00 ± 28.69	.207
Hematuria (n, %)	N = 15	N = 9	N = 11	.186
	7 (46)	5 (55)	9 (81)	
Proteinuria (n, %)	N = 15	N = 9	N = 11	.173
	3 (20)	1 (11)	5 (45)	
Hyponatremia (n, %)	16 (29)	14 (42)	20 (74)	.048*
Hypernatremia (n, %)	4 (13)	6 (18)	12 (44)	.016*
Hypochloremia (n, %)	20 (68)	19 (57)	26 (96)	.03*
Hyperchloremia (n, %)	3 (10)	5 (15)	10 (37)	.03*
Hypokalemia (n, %)	3 (10)	4 (12)	9 (33)	.044*
Hyperkalemia (n, %)	4 (13)	16 (48)	15 (55)	.02*
Hypophosphatemia (n, %)	N = 24	N = 29	N = 26	.133
	5 (20)	6 (20)	11 (42)	
Hyperphosphatemia (n, %)	N = 24	N = 29	N = 26	.487
	4 (16)	8 (27)	8 (30)	
Acidosis	N = 20	N = 22	N = 23	.039*
	3 (15)	8 (36)	12 (52)	
Alkalosis	N = 20	N = 22	N = 23	.116
	13 (65)	9 (40)	16 (69)	

AKI, acute kidney injury.
N indicates the number of measurements when they are not available for all patients.
*Post hoc analysis reveals that the significant difference was because of the values of AKIs after seventh day.
**Significance is because of the values in patients who had AKI on admission.

Table 4. Comparison Between Survivors and Non-survivors

	Survivors (n = 67)	Non-survivors (n = 22)	*P*
Age	60.3 ± 14.3	68.9 ± 12.0	.03
Co-morbidities (n)	37	18	.011
Diabetes (n)	17	6	.779
Hypertension (n)	23	8	.795
Malignancy (n)	3	10	.000
IHD/HF (n)	16	4	.772
eGFR (mL/min/1.73 m^2)	83.60 ± 16.49	81.22 ± 15.07	.551
Peak creatinine (mg/dL)	1.49 ± 0.49	2.45 ± 0.89	.000
AKI developed on (days)	5.81 ± 4.87	8.50 ± 5.85	.070
AKI duration (days)	2.67 ± 3.48	5.59 ± 4.57	.002
MAP (mmHg)	89.4 ± 13.7	86.7 ± 13.7	.430
Hemoglobin (g/dL)	12.7 ± 1.5	10.8 ± 1.9	.000
Lymphocytes (per µL)	1470 ± 661	804 ± 260	.000
CRP (mg/L)	65.6 ± 66.2	131.8 ± 90.0	.000
Prokalsitonin (ng/mL)	0.30 ± 0.93	0.62 ± 0.68	.139
CK (IU/L)	295 ± 767	209 ± 254	.618
LDH (IU/L)	351 ± 184	613 ± 545	.001
Ferritin (ng/mL)	504 ± 469	1069 ± 737	.000
D-dimer (mg/L)	1.0 ± 0.96	4.73 ± 4.96	.000
Uric acid (mg/dL)	5.93 ± 2.16	4.88 ± 2.16	.056
Length of hospital stay (days)	13.0 ± 7.4	14.5 ± 7.4	.419
Pro-BNP (pg/mL)	N = 31	N = 18	.000
	2271 ± 6478	13 889 ± 13 471	
Urea (mg/dL)	51.15 ± 24.11	75.05 ± 39.07	.001
Peak urea (mg/dL)	59.15 ± 31.34	143.05 ± 64.93	.000
Creatinine (mg/dL) (on AKI day)	1.43 ± 0.34	1.62 ± 0.45	.045
Urea/creatinine (on admission)	49.4 ± 24.4	55.2 ± 37.0	.40
Urea/creatinine (on AKI day)	35.5 ± 13.2	48.34 ± 24.33	0.02
Urea/creatinine (peak levels)	39.01 ± 13.85	62.38 ± 30.76	.000
Sodium (mmol/L)	138.28 ± 4.74	140.77 ± 7.88	.077
Chloride (mmol/L)	98.48 ± 4.71	97.36 ± 5.82	.365
Potassium (mmol/L)	4.42 ± 0.58	4.52 ± 0.73	.491
Phosphorus (mg/dL)	N = 58	N = 21	.664
	3.44 ± 0.81	3.57 ± 1.79	
Albumin (g/dL)	3.59 ± 0.39	2.83 ± 0.34	.000
pH	7.42 ± 0.6	7.30 ± 0.13	.000

(*Continued*)

Table 4. Comparison Between Survivors and Non-survivors (*Continued*)

	Survivors (n = 67)	Non-survivors (n = 22)	*P*
sPO_2	93.79 ± 2.7	84.01 ± 5.79	.000
Arterial PO_2 (mmHg)	N = 31	N = 20	.000
	68.82 ± 11.26	52.51 ± 6.56	
Hematuria (n, %)	N = 24	N = 11	.001
	10 (41)	11 (100)	[OR =2.4; 95% CI: 1.4-3.8]
Proteinuria (n, %)	N = 24	N = 11	.015
	3 (12,5)	6 (54)	[OR = 4.3 95% CI: 1.3-14.3]
Hyponatremia (n, %)	35 (52)	15 (68)	.223
Hypernatremia (n, %)	7 (10)	15 (68)	.000
			[OR = 6.5; 95% CI: 3-13.9]
Hypochloremia (n, %)	46 (68)	19 (86)	.165
Hyperchloremia (n, %)	8 (11)	10 (54)	.002
			[OR = 3.8; 95% CI: 1.7-8.4]
Hypokalemia (n, %)	8 (11)	8 (36)	.21
Hyperkalemia (n, %)	25 (37)	10 (45)	.616
Hypophosphatemia (n, %)	N = 58	N = 21	.000
	9 (15)	13 (61)	[OR = 3.9; 95% CI: 2.0-7.9]
Hyperphosphatemia (n, %)	N = 58	N = 21	.002
	9 (15)	11 (52)	[OR = 3.3; 95% CI: 1.6-6.9]
Acidosis	N = 43	N = 22	.000
	5 (11)	18 (81)	[OR = 7.0; 95% CI: 3.0-16.4]
Secondary bacterial infections (n, %)	12 (17)	14 (63)	.000
			[OR = 3.5; 95% CI: 1.9-6.5]

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; CK, creatine kinase; LDH, lactate dehydrogenase; OR, odds ratio.
N indicates the number of available measurements, when they are not available for all patients.

non-steroidal anti-inflammatory drugs, antibiotics (e.g., aminoglycosides), and contrast agents that were used for computer tomography scans. Apart from transient pre-renal AKIs, inflammation-related AKIs, and drug toxicities, we chose not to speculate about other etiologies as that would lead to erroneous interpretations

Hyponatremia and hypochloremia were common electrolyte abnormalities in COVID-19 patients who had AKIs, but they were at a similar rate for survivors and non-survivors. Hypernatremia tended to develop later and this might be related to hypertonic enteral feeding formulas, saline fluid administrations, or steroid use.[27] Mortality was increased in patients who had hypernatremia or hyperchloremia.

Both hyperphosphatemia and hypophosphatemia were more common in patients who died. Hyperphosphatemia mainly develops as a consequence of GFR loss in patients who have AKI. On the other hand, tubular injury, anti-acid drugs, malnutrition, respiratory alkalosis, or CRRTs may be responsible factors for the development of hypophosphatemia. Negative impact of hypophosphatemia on prognosis might be a consequence of decreased diaphragmatic contractility.[28]

Our findings showed that high urea-to-creatinine ratio might be a marker of poor prognosis. Creatinine levels were relatively higher for patients who had AKI on admission and their urea-to-creatinine ratios were lower. Higher serum urea levels may point out to higher catabolic state, and these patients may also have relatively lower creatinine levels, which are indicative of reduced muscle mass as a result of inflammatory state.

There are some limitations of our study. First, due to the retrospective nature of the study, urine analysis and urinary imaging studies were not available for all patients. Sample size is relatively small, and this is because of including only PCR-confirmed patients who have eGFRs of over 60 mL/min/1.73 m^2. Due to the reasons stated above, kidney biopsies, which might have given more information about etiologies, were not performed.

In conclusion, AKI in different stages of COVID-19 may have different clinical characteristics. When developed, AKI should be evaluated in conjunction with the disease stage. Early AKI tends to be more transient and may be more responsive to fluid resuscitation. However, AKIs that develop later are more immune-related and have worse prognosis. Patients who develop AKI

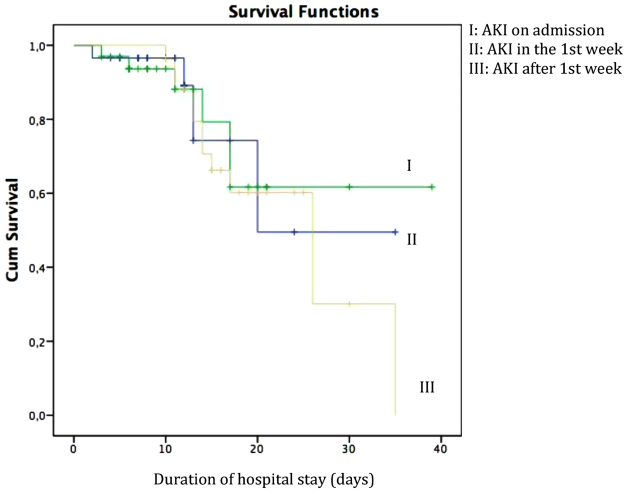

Figure 2. Kaplan–Meier curves for acute kidney injuries (AKI) grouped by timing. I, AKI on admission; II, AKI in the first week; III, AKI after seventh day.

later in the disease course are also more prone to electrolyte abnormalities.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa (Date: April 28, 2020, No: 57495).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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