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The incidence of acute kidney injury and its association with mortality in patients diagnosed with COVID-19 followed up in intensive care unit

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Abstract

Introduction: The kidneys are some of the most frequently affected organs during coronavirus disease 2019 (COVID-19). This multicenter study evaluated the incidence of and risk factors for acute kidney injury (AKI) in COVID-19 patients followed up in intensive care unit (ICU) and its association with mortality.

Methods: Three hundred twenty-eight patients diagnosed with COVID-19 and hospitalized in ICU were included. Risk factors associated with AKI and mortality were evaluated.

Results: Eighty-eight patients (27.9%) were diagnosed with AKI. AKI was significantly associated with older age, higher baseline creatinine level, lower albumin level, and coexistence of cardiovascular disease and chronic obstructive pulmonary disease. Mortality in the entire study group was significantly associated with AKI, older age, requirement of invasive mechanical ventilation, higher neutrophil level, lower lymphocyte, and albumin levels.

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Conclusion: AKI is frequently seen during the course of COVID-19 and is associated with high mortality. Identifying AKI-related risk factors appears essential in the management of COVID-19 patients.

KEYWORDS

acute kidney injury, COVID-19, intensive care unit, mortality

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first identified in China in December 2019 and was declared a pandemic in March 2020. As of July 2021, there had been over 187 million confirmed cases, with over 4 million deaths [1]. Although most prominent finding of the disease is diffuse alveolar hemorrhage, COVID-19 is a multisystem infectious disease with a wide spectrum of symptoms and signs, caused by severe acute respiratory distress syndrome coronavirus 2. One of the most frequently affected organs after the lungs is the kidney. Histological findings of renal damage frequently reported in autopsy series and in recent molecular studies suggest that the virus may have kidney tropism, possibly via angiotensin converting enzyme 2 [2]. Renal involvement in COVID-19 varies from mild histological changes to advanced acute kidney injury (AKI). AKI is a major cause of mortality and morbidity in hospitalized patients [3]. The reported incidence of AKI among hospitalized patients is 0.2%–11.6%, but this rises to 22.7% in patients with severe sepsis and to 52.8% in patients with septic shock [3–5]. Although negligible rates were cited in the first reports, it is now clear that AKI rates in the course of COVID-19 cannot be ignored [6]. While over 20% of hospitalized patients have been reported to develop AKI, this rate increases to 50% in intensive care units (ICUs) [7]. AKI seems to be associated with more severe infection and high mortality in COVID-19 patients [8].

The aim of this study was to investigate the incidence, characteristics, predictors, and prognosis of AKI among COVID-19 patients followed up in secondary and tertiary ICUs.

2 | MATERIALS AND METHODS

Electronic medical records of 439 laboratory-confirmed (real-time polymerase chain reaction–positive) COVID-19 patients hospitalized between March 2020 and December 2020 in ICU were reviewed in this retrospective, multicenter study performed in the Turkish province of Tekirdag. The following exclusion criteria were used; age of <18 years old, patients with ESRD and renal transplantation, length of hospital stay <48 h, patients with incomplete data, and patients with declining serum creatinine value after admission. After excluding 111 patients according to these criteria, 328 patients were enrolled in the study. The patients were divided into two groups: AKI and non-AKI. Kidney Disease Improving Global Outcome criteria were used for AKI definition based on serum creatinine values. AKI was defined as an increase in serum creatinine by 0.3 mg/dl within 48 h or a 50% increase in serum creatinine from the baseline within 7 days. [9]. The baseline serum creatinine level was defined as the value determined on admission or the lowest value observed during hospitalization before the diagnosis of AKI. HD requirements and serum creatinine levels at discharge were noted. Complete blood count and serum biochemistry, demographic data, duration of hospitalization, comorbidities, and medications (antivirals, antibiotics, corticosteroid, and anticoagulants) were also recorded. The local ethical committee approved the study and confirmed that the protocol was compatible with the second Declaration of Helsinki.

Statistical analysis was performed using SPSS version 25 software. Compatibility with normal distribution of parametric variables was evaluated using the Kolmogorov–Smirnov test. The *t* test was applied in the comparison of normally distributed data, and the Mann–Whitney *U* test for non-normally distributed data. Demographic variables were presented using descriptive statistics and frequencies. The chi-square test was used to analyze the relationships between AKI and categorical variables (demographic parameters, comorbidities, and medications). Pearson correlation analysis was employed for determining correlations. Binary logistic regression was used to analyze the factors associated with AKI and mortality. Invasive mechanical ventilation (IMV) requirement was not included in the regression analysis for AKI because some patients needed IMV after developing AKI. The variables included in the regression analysis for AKI were age, comorbidities, BP, baseline serum creatinine, ferritin, albumin, neutrophil, lymphocyte, and monocyte levels. The variables included in the regression analysis for mortality were age, gender, comorbidities, BP, IMV requirement, development of AKI and albumin, ferritin, lymphocyte, neutrophil, monocyte, and Hb levels. Variables found to be associated with AKI and

mortality in univariate analysis, and those predicted to be associated with AKI and mortality were included in the multivariate analysis; 95% CI was employed and is shown when appropriate. p values < 0.05 were regarded as statistically significant.

3 | RESULTS

Three hundred twenty-eight ICU patients diagnosed with COVID 19 were enrolled. The patients' median age was 63 (19–95) years, and 54.9% were male. The median length of hospital stay was 9 (3–124) days. While no comorbidity was documented in 46.9% of the patients, cardiovascular disease (CVD) was present in 36.6%, DM in 18.6%, chronic obstructive pulmonary disease (COPD) in 11.9%, and malignancy in 5.2%. Sixty-four patients needed IMV support (19.5%). Sixty-five patients (19.8%) died during hospital follow-up. Eighty-eight patients (27.9%) were diagnosed with AKI, and 16 of them (18.1%) required HD. Patients with AKI were older than those in the non-AKI group. The percentages of CVD, DM, and COPD were higher in AKI group. Whereas favipiravir use was more common in the non-AKI group, hydroxychloroquine use was higher in non-AKI group. There was no difference between the AKI and non-AKI groups in terms of the time between symptom onset and hospital admission (2 [1–112] vs. 1 [1–112] days; $p = 0.455$). APACHE II score and the percentage of patients needed IMV were higher in the AKI group. The AKI group was also hospitalized longer than the non-AKI group. Death occurred in 22 patients (9.2%) in the non-AKI group, compared to 43 (48.9%) in the AKI group (Table 1). Death occurred in 9 of 16 patients (56.3%) who underwent HD.

Serum creatinine, glucose, lactate dehydrogenase, uric acid, potassium, ferritin, neutrophil, monocyte and prothrombin levels, and neutrophil-to-lymphocyte ratio were significantly higher in AKI group, while serum albumin, alanine aminotransferase, sodium, and Hb levels were significantly higher in the non-AKI group on admission (Table 2).

Logistic regression analysis revealed that higher baseline serum creatinine was the strongest risk factor for AKI (OR = 164.9, $p < 0.001$). Older age, lower albumin level, and coexistence of CVD and COPD were also associated with AKI (Table 3).

Logistic regression analysis for the entire study group revealed that mortality was significantly associated with AKI (OR = 4.98, $p = 0.001$). IMV requirement was strongly associated with mortality (OR = 70.43,

TABLE 1 Characteristics of the study population

Characteristics	All ($n = 328$)	AKI ($n = 88$)	No-AKI ($n = 240$)	p value
Age (year)	63 (19–95)	72 (20–95)	60 (19–92)	<0.001
Male n, (%)	180 (54.9)	50 (56.8)	130 (54.2)	0.669
Comorbid diseases, n (%)				
CVD	120 (36.6)	43 (48.9)	77 (32.1)	0.005
DM	61 (18.6)	24 (27.3)	37 (15.4)	0.014
COPD	39 (11.9)	21 (23.9)	18 (7.5)	0.004
Malignancy	17 (5.2)	7 (8.0)	10 (4.2)	0.170
Drugs, n (%)				
Favipiravir	166 (50.6)	59 (67.0)	107 (44.8)	<0.001
Hydroxychloroquine	156 (47.6)	24 (27.3)	132 (55.0)	<0.001
Oseltamivir	31 (10.2)	4 (4.5)	27 (11.3)	0.066
Corticosteroid	55 (16.8)	18 (20.5)	37 (15.4)	0.279
Antibiotic	198 (60.4)	60 (68.2)	138 (57.5)	0.080
Anticoagulant	113 (34.5)	37 (42.5)	76 (32.1)	0.080
IMV, n (%)	64 (19.5)	40 (45.5)	24 (10.0)	<0.001
Length of hospital stay (day)	9 (3–124)	12 (3–124)	8 (3–48)	0.006
SBP (mm Hg)	120 (90–220)	120 (90–180)	130 (100–220)	0.120
DBP (mm Hg)	76 (59–120)	75 (59–100)	76 (62–120)	0.980
APACHE II score	8 (4–46)	6 (4–46)	5 (4–40)	0.023
Exitus, n (%)	65 (19.8)	43 (48.9)	22 (9.2)	<0.001

Note: Data are expressed as "mean ± SD" or median (min–max). p value < 0.05 is considered to be significant.
Abbreviations: AKI, Acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease (including hypertension, coronary artery disease, heart failure, and peripheral artery disease); DBP, diastolic blood pressure; IMV, invasive mechanical ventilation; SBP, systolic blood pressure.

TABLE 2 Baseline laboratory findings of the study population

Parameter	All ($n = 328$)	AKI ($n = 88$)	Non-AKI ($n = 240$)	p value
Creatinine[a] (mg/dl)	1.01 (0.4–9.04)	1.53 (0.40–9.04)	0.93 (0.4–2.15)	<0.001
Creatinine[b] (mg/dl)	0.93 (0.45–9.13)	2.18 (0.45–9.13)	0.85 (0.46–1.80)	<0.001
Glucose (g/dl)	123 (65–623)	147 (65–623)	120 (70–518)	<0.001
AST (IU/L)	30 (10–278)	39 (10–113)	29 (11–278)	0.188
ALT (IU/L)	23 (8–221)	19 (8–169)	25 (9–221)	0.028
LDH (IU/L)	312 (43–4859)	396 (116–4859)	396 (43–1001)	0.017
Uric acid (mg/dl)	5.3 (1.4–12.3)	6.6 (1.7–12.3)	5.4 (1.4–10.6)	<0.001
Sodium (mEq/L)	138 (116–149)	137 (118–149)	139 (116–146)	0.021
Potassium (mEq/L)	4.10 (3.0–6.0)	4.35 (3.0–6.0)	4.02 (3.0–5.2)	0.002
Albumin (g/dl)	3.7 (1.2–4.9)	3.4 (1.6–4.7)	3.8 (1.2–4.9)	<0.001
Ferritin (ng/ml)	317 (14–9090)	607 (17–1776)	605 (14–9090)	0.012
Hb (g/dl)	12.7 ± 2.1	11.9 ± 2.3	12.9 ± 2.0	<0.001
Leucocyte (10^3/μl)	7.34 (1.00–42.46)	10.08 (2.19–42.46)	6.89 (1.00–32.20)	<0.001
Neutrophil (10^3/μl)	5.3 (0.15–30.1	7.5 (1.5–22.5)	4.8 (0.2–30.1)	<0.001
Lymphocyte (10^3/μl)	1.21 (0.01–15.2)	1.05 (0.04–7.53)	1.27 (0.01–15.20)	0.074
NLR	4.74 (0.21–236.26)	7.80 (1.06–236.26)	3.69 (0.21–0.53)	<0.001
Monocyte (10^3/μl)	0.55 (0.001–23.4)	0.67 (0.01–23.4)	0.50 (0.01–4.12)	<0.001
Platelet (10^3/μl)	231 (18–754)	232 (18–633)	232 (23–754)	0.298
MPV (fl)	9.2 (6.5–12.8)	9.3 (6.7–12.8)	9.1 (6.5–12.7)	0.063
D-dimer (mg/L)	0.68 (0.01–89.7)	2.02 (0.08–89.7)	2.01 (0.01–43.4)	0.268
INR	1.1 (0.7–9)	1.25 (0.90–2.20)	1.10 (0.70–9.0)	0.005
PT (s)	13.2 (10.1–132)	14.6 (10.1–24.7)	12.9 (10.5–132)	0.003
aPTT (s)	25.3 (13.6–263)	27.6 (13.6–36)	25.3 (14.7–263)	0.572

Note: Data are expressed as "mean ± SD" or median (min–max). p value < 0.05 is considered to be significant.
Abbreviations: AKI, Acute kidney injury; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; INR, international normalization rate; LDH, lactate dehydrogenase; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time.
[a]Baseline serum creatinine.
[b]Serum creatinine at discharge.

TABLE 3 Logistic regression for acute kidney injury

	Univariate			Multivariate		
Covariates	β	OR [95% CI]	p	β	OR [95% CI]	p
Age	0.06	1.05 [1.03, 1.06]	<0.001	0.05	1.05 [1.03, 1.07]	<0.001
CVD + COPD	2.44	11.5 [2.40, 55.32]	0.002	2.20	9.03 [1.59, 51.16]	0.012
SBP	0.02	1.02 [1.01, 1.04]	0.005	0.06	1.06 [0.98, 1.15]	0.134
Creatinine[a]	4.93	138.58 [42.34, 453.58]	<0.001	5.11	164.9 [43.40, 626.61]	<0.001
Albumin	−1.36	0.26 [0.16, 0.42]	<0.001	−0.744	0.48 [0.23, 0.97]	0.040
Neutrophil	0.16	1.17 [1.10, 1.25]	<0.001	0.06	1.06 [0.91, 1.23]	0.438
Monocyte	0.98	2.68 [1.63, 4.39]	<0.001	0.78	2.17 [0.57, 8.28]	0.256
Ferritin	0.01	0.99 [0.98, 1.00]	0.031	0.01	0.98 [0.97, 0.99]	0.120

Note: p value < 0.05 is considered to be significant.
Abbreviations: CVD, cardiovascular disease (including hypertension, coronary artery disease, heart failure, peripheral artery disease); COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure.
[a]Baseline creatinine.

TABLE 4 Logistic regression for mortality

	Univariate			Multivariate		
Covariates	***β***	**OR [95% CI]**	***p***	***β***	**OR [95% CI]**	***p***
Age	0.05	1.05 [1.03, 1.07]	<0.001	0.05	1.05 [1.01, 1.09]	0.014
IMV	4.43	83.67 [36.14, 193.71]	<0.001	4.26	70.43 [24.31, 204.03]	<0.001
AKI	2.20	8.98 [4.92, 16.42]	<0.001	1.61	4.98 [1.86, 13.34]	0.001
Lymphocyte	0.18	1.20 [1.13, 1.28]	<0.001	−0.42	0.66 [0.44, 0.98]	0.039
Neutrophil	0.23	1.26 [1.17, 1.35]	<0.001	0.18	1.20 [1.10, 1.31]	<0.001
Monocyte	1.16	3.20 [1.89, 5.42]	<0.001	0.35	1.42 [0.69, 2.94]	0.342
Hb	−0.26	0.77 [0.67, 0.88]	<0.001	−0.13	0.88 [0.71, 1.09]	0.242
Albumin	−1.51	0.22 [0.13, 0.37]	<0.001	−0.84	0.43 [0.23, 0.81]	0.008

Note: p value < 0.05 is considered to be significant.
Abbreviations: AKI, Acute kidney injury; IMV, invasive mechanical ventilation.

$p < 0.001$). Older age, higher neutrophil level, lower lymphocyte, and albumin levels were also associated with a higher mortality rate (Table 4).

4 | DISCUSSION

The results of this study demonstrate that AKI is common among patients with COVID-19 (26.8%) and seems to be a strong predictor of mortality.

AKI is known to increase morbidity and mortality, particularly in hospitalized patients. AKI-related mortality rates are 20% in hospitalized patients, rising to approximately 50% for those in ICU [3, 5, 10]. The factors involved in the etiopathogenesis occupy a broad clinical spectrum and are generally interrelated. As indirect factors such as the cytokine storm, coagulopathy, sepsis, hemodynamic instability, and drug toxicity seen in the course of COVID-19 constitute a risk in terms of AKI development, it has been speculated that the virus exhibits renal tropism [11, 12]. Our understanding of the adverse effect of AKI development on the course of COVID-19 and associated mortality has become clearer than in the 1st months of the pandemic for reasons such as the increasing spread of the disease, the variation in its course in different populations, new mutations altering its course, and the rapid growth in literature on the subject from across the world. Low AKI rates were of 1.6%–7% reported in studies from China performed in the early months of the pandemic [6, 13, 14]. However, subsequently reported rates were much higher. Two separate multicenter studies from the United States that examined the data for 9657 and 5700 patients reported incidences of AKI of 38.4% and 24.2%, while mortality rates in cases developing AKI were 51.8% and 66.4%, respectively [15, 16]. A large meta-analysis including 40 studies involving 24 527 patients diagnosed with COVID-19 reported a 10% incidence of AKI and a mortality rate of 63.1%, significantly higher than the 12.9% mortality rate in the group not developing AKI [8]. AKI was reported as an independent risk factor for mortality [8, 17–20].

In our study, the incidence of AKI was 26.8%, with mortality rates of 48.9% in the AKI group and 9.2% in the non-AKI group, and AKI was found to increase the risk of mortality by 4.98 times. Our findings are consistent with the literature in terms of the association between AKI and mortality in the course of COVID-19. The rate of renal replacement requirement in the present study was 18.1%, close to the figure of approximately 20% reported in the majority of studies [7, 21]. Increased mortality has been reported in the presence of HD requirements in COVID-19 patients developing AKI. However, no such relationship was determined in our study.

In addition to AKI, advanced age, need for IMV, higher neutrophil, lower lymphocyte, and albumin levels were identified as independent risk factors for mortality in our study. Consistent with our results, older age and need for IMV have been reported as independent risk factors for mortality in the majority of previous publications [19, 22–26]. Reported findings on the relationship between hematological indices and COVID-associated mortality are inconsistent. Although anemia, leukocytosis, lymphopenia, neutrophilia, and monocytosis are frequently reported in the course of COVID-19, some of these publications have defined them as independent risk factors in terms of disease severity [27–30]. We found that higher neutrophil and lower lymphocyte counts were independent risk factors for mortality in COVID-19 patients. Several studies reported that hypoalbuminemia was an independent risk factor for mortality in COVID-19 patients, consistent with our findings [31, 32]. The correlation between changes in both hematological

indices and albumin levels and mortality was thought to be related to the severity of inflammation. Hypoalbuminemia has also been interpreted as an indicator of poor nutrition status in patients with severe COVID-19 [33].

The majority of reports in the literature indicate that hypertension, DM, chronic respiratory diseases, CVDs, and immunosuppression increased mortality during the course of COVID-19, although some studies have also determined no association [7, 34–36]. Comorbidities were not identified as risk factors for mortality in our study, possibly due to the small number of patients or due to different thresholds for hospitalization.

The aforementioned comorbidities are known to increase the risk of AKI in the general population and also the most frequently reported comorbidities in hospitalized COVID-19 patients. It has also been reported that the presence of more than one comorbidity increases mortality even more. [7, 16, 17]. In our study, CVD, DM, and COPD were more common in AKI group. However, only the coexistence of CVD and COPD was identified as an independent risk factor for AKI.

Other risk factors for AKI development were older age and higher serum creatinine on admission in the recent study, which were emerged as a risk factor in terms of development of AKI in general and in the course of COVID-19 [7, 18, 20, 37–39]. Since the baseline creatinine value of all patients was not known, creatinine values at admission were taken into account for the evaluation of AKI, as we explained in Section 2. Therefore, there is a possibility that some patients may have an underlying CKD or may have developed AKI prior to hospital admission.

The number of patients needed IMV was higher in AKI group in our study. IMV was reported as an independent risk factor for AKI in COVID-19 patients, previously [18, 20]. In our study, IMV requirement was not included in the regression analysis for AKI because some patients needed IMV after developing AKI.

Similar to other infectious processes, systemic inflammation in the course of COVID-19 increases the disposition to AKI, while the severity of inflammation copresent with AKI development also increases. In our study, patients with AKI had higher neutrophil and monocyte counts but lower albumin and Hb levels, which had been reported in the literature before and were interpreted in favor of increased inflammation during the COVID-19 course [37, 39]. While lower albumin level was an independent risk factor for AKI, no such relationship was not found for hematological indices in the present study. Hypoalbuminemia may be associated with the inflammation cascade, or it may have developed due to renal loss during AKI.

Retrospective design, limited information about home medication of the patients, inability to use the urine output criterion for AKI diagnosis, and lack of follow-up data after discharge from the hospital were the limitations of our study.

In conclusion, in contrast to early reports during the pandemic, AKI frequently accompanies COVID-19, and this is supported by the results of the present study. Also consistent with the majority of the literature, AKI significantly increased mortality during the course of COVID-19. Therefore, it is essential that risk factors be identified and the requisite precautionary measures be taken. We think that our study will make a useful contribution to the literature from that perspective.

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The ethical committee of Tekirdag Namik Kemal University approved the study and confirmed that the protocol was compatible with the second Declaration of Helsinki (approval date: February 10, 2021).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

INFORMED CONSENT

Informed consent was obtained from the participants.

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