Acute kidney injury in hospitalized COVID-19 patients

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Abstract
Background Acute kidney injury (AKI) in COVID-19 patients is associated with poor prognosis. However, the incidence, risk factors and potential outcomes of AKI in hospitalized patients are not well studied.

Materials and methods This is a retrospective cohort study conducted in two major university hospitals. Electronic health records of the patients, 18 years or older, hospitalized between 13 April and 1 June 2020 with confirmed COVID-19 were reviewed. We described the incidence and the risk factors for AKI development in COVID-19 patients. Furthermore, we investigated the effects of AKI on the length of hospital and intensive care unit (ICU) stay, the admission rates to ICU, the percentage of patients with cytokine storm and in-hospital mortality rate.

Results Among 770 hospitalized patients included in this study, 92 (11.9%) patients developed AKI. The length of hospital-stayed days (16 vs 9.9, \(p < 0.001\)) and days spent in the hospital until ICU admission (3.5 vs 2.5, \(p = 0.003\)) were higher in the AKI group compared to patients without AKI. In addition, ICU admission rates were also significantly higher in patients with AKI (63% vs. 20.7%, \(p < 0.001\)). The percentage of patients with AKI who developed cytokine storm was significantly higher than patients without AKI (25.9% vs. 14%, \(p = 0.009\)). Furthermore, the in-hospital mortality rate was significantly higher in patients with AKI (47.2% vs. 4.7%, \(p < 0.001\)).

Conclusions AKI is common in hospitalized COVID-19 patients. Furthermore, we show that AKI increases the admission rates to ICU and in-hospital mortality. Our findings suggest that AKI should be effectively managed to prevent the adverse outcomes in COVID-19 patients.

Keywords COVID-19 · Acute kidney injury · Hospital stay · Mortality

Introduction
Coronavirus disease 2019 (COVID-19), a viral illness affecting multiple organs including the kidneys, has led to high morbidity and mortality [1, 2]. Several reports indicate that the presence of acute kidney injury (AKI) in COVID-19 patients contributes to the poor prognosis [3, 4]. The incidence of AKI in patients hospitalized for COVID-19 varies widely, with some studies reporting an incidence ranging from 0.5% to as high as 46% [3, 5, 6]. Kidney involvement in COVID-19 has been associated with the invasion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the kidney tissue via the angiotensin-converting-enzyme 2 (ACE2) expressed in renal proximal tubular cells, glomerular visceral and parietal epithelium, and the cytoplasm of the distal tubules and collecting ducts [7–9].

Acute tubular necrosis (ATN) and endothelial injury caused by severe inflammation and hemodynamic
instability have also contributed to the kidney damage in COVID-19 patients [7, 10]. The characteristics and outcomes of AKI in patients with COVID-19 have not been well established. Thus far, there has been a limited number of studies investigating the incidence and severity of AKI, the epidemiology of AKI, especially recovery from AKI in hospitalized COVID-19 patients. In this multi-center study, we delineate the incidence and risk factors of AKI in COVID-19 patients. We also investigate the relationship between AKI development and length of hospital stay, days from first symptom to hospitalization, days spent in intensive care unit (ICU), days from hospitalization to ICU, the admission rates to ICU, the percentage of patients with cytokine storm and in-hospital mortality rate.

Materials and methods

This was a multi-center retrospective cohort study conducted in Istanbul, the largest cosmopolitan city in Turkey. The patient data were obtained from the electronic health records (EHRs) of two major university hospitals, Koc University Hospital and Istanbul University, Faculty of Medicine Hospital.

Inclusion criteria

All patients included in this study were at least 18 years old and were hospitalized for COVID-19 infection in one of the two above-mentioned university hospitals from April 13, 2020 until June 1, 2020 with follow-up data. COVID-19 infection was defined by a positive RT-PCR assay of a specimen collected via nasopharyngeal sampling. COVID-19 infection was also diagnosed based on clinical presentation, radiographic lung abnormalities with chest computed tomography in patients with negative PCR results according to the Turkish Ministry of Health ‘Covid-19 Diagnosis and Treatment Guideline’ [11]. All included patients received the same treatment protocol. The treatment protocol consisted of hydroxychloroquine, favipiravir and acetaminophen according to the Ministry of Health ‘Covid-19 Diagnosis and Treatment Guideline’ [11]. Patients were hospitalized based on their clinical, laboratory and imaging findings (hypoxia, hemodynamic instability, more than 30% lung involvement in computed tomography) and hospital bed availability.

The Koc University and Istanbul University Ethical Committees approved the study protocol allowing for the analysis of individual patient data.

Exclusion criteria

We excluded all hospitalized patients tested positive for COVID-19 younger than 18 years old and who had a kidney transplantation or having estimated glomerular filtration rates (eGFRs) < 30 ml/min/1.73 m² represented advanced chronic kidney disease or known history of end-stage kidney disease (ESKD) prior to admission.

Data collection

We gathered, for each patient, the demographic findings (age, gender, body mass index), the presenting clinical symptoms (fever, coughing, sputum, dyspnea, fatigue or myalgia, nausea, diarrhea, anosmia), prior medical history and prior comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, malignancy), medications used (angiotensin-converting-enzyme inhibitor and angiotensin II receptor blocker), history of risks (travel history, contact history, smoking, alcohol), laboratory findings and data about the hospital and ICU stay from the electronic health records (EHRs) of the two university hospitals. Laboratory data consisted of complete blood count (hemoglobin, platelet, white blood cells, neutrophils, lymphocyte count, monocyte), electrolyte (sodium, potassium, chloride), kidney (blood urea nitrogen, creatinine) and liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase), glucose, lactate dehydrogenase, total protein, albumin, C-reactive protein, ferritin, triglyceride, d-dimer, troponin, pro-brain natriuretic peptide, hemostasis parameters (fibrinogen, international normalized ratio, activated partial thromboplastin time). The data involving the hospital stay and ICU stay recorded from the medical charts of the patients. We assessed in-hospital mortality defined by survival status at discharge.

Definitions of outcomes

AKI, the primary end point, was defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria: a change in the serum creatinine of 0.3 mg/dl over a 48-h period or 50% increase in baseline creatinine [12]. We used KDIGO criteria to define AKI severity as follows: Stage 1—increase in serum creatinine by 0.3 mg/dL within 48 h or a 1.5–1.9 times increase in serum creatinine from baseline within 7 days; Stage 2—2 to 2.9 times increase in serum creatinine within 7 days; Stage 3—3 times or more increase in serum creatinine within 7 days or initiation of
renal replacement therapy (RRT) [12]. The need for acute dialysis was ascertained from the medical records of the patients.

The secondary end point of the study was length of hospital and ICU stay, in-hospital mortality associated with AKI in COVID-19 patients. Lastly, we looked at the association between AKI and development of cytokine storm. We accepted cytokine storm development if the patients had hyperactive immune response based on the COVID-19-associated hyperinflammatory syndrome (cHIS) criteria [13]. AKI was diagnosed according to KDIGO criteria prior to ICU admission and cytokine storm development.

**Statistical analysis**

Statistical analysis was performed using IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp. The normality of continuous variables were investigated by Shapiro–Wilk’s test. Descriptive statistics were presented using mean and standard deviation for normally distributed variables and median [interquartile ratio (IQR)] for the non-normally distributed variables. For comparison of two normally distributed groups Student’s *t* test was used. Non-parametric statistical methods were used for values with skewed distribution. For comparison of two non-normally distributed groups Mann–Whitney *U* test was used. The *χ²* test was used for categorical variables and expressed as observation counts (and percentages). The identify effect of risk factors on outcome Logistic Regression analysis was performed. Statistical significance was accepted when the two-sided *p* value was lower than 0.05.

We performed logistic regression analysis to find association of AKI with in-hospital mortality or ICU admission in COVID-19 patients. We constructed four models for adjustments. The variables of each model were selected according to the results of univariate analysis and clinical point of view. In model 1, we adjusted for only the age variable. In model 2, we adjusted for age, hypertension history, diabetes mellitus history, coronary artery disease, congestive heart failure and malignancy. In model 3, in addition to the variables in model 2, we adjusted for hemoglobin, lymphocytes, sodium, blood urea nitrogen, glucose, gamma-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, albumin, C-reactive protein, *d*-dimer, troponin, pro-brain natriuretic peptide, international normalized ratio, activated partial thromboplastin time. In addition to the variables in model 3, we adjusted model 4 for cytokine storm.

**Results**

**General characteristics of the study population**

From April 13, 2020, to June 1, 2020, 14,200 patients were admitted to Koc University Hospital and Istanbul Faculty of Medicine Hospital with a possible diagnosis of COVID-19 infection. Of these, 900 patients with COVID-19 were hospitalized due to their clinical status and all were included into the final analysis. Thirty-four dialysis patients, twenty-one kidney transplant patients and seventy-five patients with (eGFRs) < 30 ml/min/1.73 m² were excluded from the study. Tables 1, 2 shows the demographics, comorbidities, symptoms, medications and “history of risks” of 770 patients included in the study. The mean age was 58.4 years and 314 (41.8%) patients were female while 456 (59.2%) were male.

**Table 1** The demographic findings, comorbidities, symptoms, medications and ‘history of risks’ of the COVID-19 patients included in this study, stratified according to acute kidney injury (AKI) status

| Demographics                        | Total (n=770) | AKI (–) (n=678) | AKI (+) (n=92) | p value |
|-------------------------------------|---------------|-----------------|----------------|---------|
| **Demographics**                    |               |                 |                |         |
| Age, years                          | 58.4 ± 15.4   | 57.2 ± 14.8     | 67.1 ± 16.5    | <0.001c  |
| Gender, female, n (%)               | 314 (41.8)    | 275 (40.6)      | 39 (42.4)      | 0.823c  |
| Body mass index, kg/m²              | 28.1 (5.7)    | 28.1 (5.7)      | 27.9 (3.7)     | 0.491b  |
| **Comorbidities, n (%)**            |               |                 |                |         |
| Hypertension                        | 322 (42)      | 267 (39.6)      | 55 (60.4)      | <0.001c  |
| Diabetes mellitus                   | 173 (22.6)    | 144 (21.4)      | 29 (31.9)      | 0.025c  |
| Chronic obstructive pulmonary disease| 89 (11.6)    | 76 (11.3)       | 13 (14.3)      | 0.505d  |
| Coronary artery disease             | 93 (12.2)     | 69 (10.2)       | 24 (26.4)      | <0.001c  |
| Congestive heart failure            | 50 (6.5)      | 30 (4.5)        | 20 (22)        | <0.001d  |
| Malignancy                          | 58 (7.6)      | 44 (6.5)        | 14 (15.4)      | 0.005d  |

*p* values in bold indicate statistical significance

aStudent’s *t* test

bChi-square

cMann–Whitney *U* test

dYates continuity correction
body mass index of the cohort was 28.8 kg/m². Among patients with cardiovascular diseases, 322 (42%) patients had hypertension, 93 (12.2%) had coronary artery disease, and 50 (6.5%) had congestive heart failure. Diabetes mellitus was found in 173 (22.6%) patients, 89 (11.6%) had chronic obstructive pulmonary disease and 58 (7.6%) patients had malignancy. Most of the patients presented with fatigue or myalgia (80.1%), cough (76.4%), fever (69.2%) and/or dyspnea (43.1%). Angiotensin-convert-
ing-enzyme inhibitors or angiotensin II receptor blocker were used by 192 (25.3%) patients. Among patients with a “history of risks”, 10 (1.3%) patients had a recent travel history and 243 (32.8%) had a possible contact history, 94 (12.2%) patients were smokers and 12 (1.6%) patients consumed alcohol. Table 3 shows the laboratory findings of the patients included in the study.

Table 4 shows the data related to hospital, ICU stays and in-hospital mortality rates of patients included in the study. Patients were hospitalized 10.6 days on average, the mean days passed from first symptom until hospitalization was 5.1. Among the 770 patients, 198 (25.8%) were admitted to the ICU. The average days spent in the hospital until ICU admission was 2.7 days. The mean duration of ICU stay was 15 days. The number of patients who developed cytokine storm was 94 (15.6%). Within the cohort, 73 (9.7%) patients died during their hospital stay.

### Incidence and characteristics of acute kidney injury

Among the 770 hospitalized patients included in this study, 92 (11.9%) patients developed AKI according to the KDIGO criteria. Patients with AKI were significantly older compared to those without AKI (median age 67.1 years vs. 57.2 years, \( p < 0.001 \)). The proportion of comorbid conditions including hypertension (60.4% vs. 39.6%, \( p < 0.001 \)), diabetes mellitus (31.9% vs. 21.4%, \( p = 0.025 \)), coronary artery disease (26.4% vs. 10.2%, \( p < 0.001 \)), congestive heart failure (22% vs. 4.5%, \( p < 0.001 \)) and malignancy (15.4% vs. 6.5%, \( p = 0.005 \)) were higher in AKI patients. Furthermore, the AKI cohort developed fever less commonly (55.4% vs. 71.1%, \( p = 0.002 \)) whereas dyspnea was significantly more common (68.5% vs. 39.6%, \( p < 0.001 \)) (Table 2).

Patients with AKI had significantly higher levels of glucose, gamma-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, C-reactive protein, \( \beta \)-dimer, troponin, international normalized ratio and activated partial thromboplastin time compared to patients without AKI. Moreover, the levels of albumin and hemoglobin were significantly lower in patients who developed AKI (Table 3).
Association of AKI with ICU admission and in-hospital mortality

The length of hospitalized days (16 vs. 9.9, \(p < 0.001\)) and days spent in the hospital until ICU admission (3.5 vs. 2.5, \(p = 0.003\)) were higher in the AKI group. In addition, ICU admission rates were also significantly higher in patients with AKI (63% vs. 20.7%, \(p < 0.001\)) (Table 4). The percentage of patients with AKI who developed cytokine storm was significantly higher than patients without AKI (25.9% vs. 14%, \(p = 0.009\)). Furthermore, the in-hospital mortality rate was significantly higher in patients with AKI (47.2% vs. 4.7%, \(p < 0.001\)).

In the multivariable logistic regression analysis, the unadjusted model [odds ratio (OR) 7.531; 95% CI 4.69, 12.08; \(p < 0.001\)], model 1 (age adjusted) (OR 6.386; 95% CI 3.94, 10.36; \(p < 0.001\)), model 2 (Model 1 + hypertension, diabetes mellitus, coronary artery disease, congestive
Adjusted for Model 4 5.793 3.136–10.70
Adjusted for Model 3 6.462 3.495–11.95
Adjusted for Model 2 6.132 3.73–10.07
Adjusted for Model 1 6.386 3.94–10.36
Unadjusted 7.531 4.69–12.08

*p values in bold indicate statistical significance
In-hospital mortality or intensive care unit admission were set as dependent variable in logistic regression
In unadjusted model, we used acute kidney injury for independent value
Model 1: age
Model 2: model 1 + hypertension history, diabetes mellitus history, coronary artery disease, congestive heart failure, malignancy
Model 3: model 2 + hemoglobin, blood urea nitrogen, glucose, gamma-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, albumin, C-reactive protein, dimer, troponine, Pro-Brain natriuretic peptide, international normalized ratio, activated partial thromboplastin time
Model 4: model 3 + cytokine storm

heart failure, malignancy) (OR 6.132; 95% CI 3.73, 10.07; *p* < 0.001), model 3 (Model 2 + hemoglobin, blood urea nitrogen, gamma-glutamyl transferase, lactate dehydrogenase, albumin, C-reactive protein, dimer, troponine, Pro-Brain natriuretic peptide, international normalized ratio, activated partial thromboplastin time) (OR 6.462; 95% CI 3.495, 11.95; *p* < 0.001) and model 4 (Model 3 + cytokine storm) (OR 5.793; 95% CI 3.136, 10.70; *p* < 0.001) showed the association of AKI with in-hospital mortality or intensive care unit admission in COVID-19 patients (Table 5).

Discussion

In this multi-center study involving 770 patients, we delineated the incidence, clinical parameters, laboratory findings of AKI development in COVID-19 patients. We showed that AKI is common in hospitalized COVID-19 patients and is associated with increased hospital and ICU stay, ICU admission rate and in-hospital mortality.

Among the 770 patients included in our study 92 patients developed AKI, with an incidence of 11.9%. The incidence of AKI varies widely in previous studies ranging from 0.5% to as high as 46% [3, 5, 6], with one study reporting 0 cases of AKI among 116 COVID-19 patients [14]. Our findings were considerably lower than the incidences of three studies (27.3%, 36.6% and 46%) from the New York area, United States [3, 6, 10]. Our incidence was higher than that reported by Guan et al. (0.5%) and was similar to a study from South Korea (9.2%) [5, 15]. It is difficult to determine the causes of these variations. One potential explanation could be related to the higher presence of comorbidities among the patient group. For example, hypertension prevalence was 68.9% and 55.7% and diabetes prevalence was 46.7% and 33% in the studies who had higher AKI incidence of 27.3% and 36.6%, respectively [3, 10]. In our study, these comorbidities prevalence were lower as hypertension was present in 42% of our cohort and diabetes was seen in 22.6%. Furthermore, differences in the age and race of the patient groups, the applied treatment protocols and the healthcare systems could all play a role in the varying incidences of AKI.

Our patients with AKI were more likely to be older, have a history of hypertension, diabetes mellitus, congestive heart failure, coronary artery disease and malignancy. However, gender, body mass index and the presence of chronic obstructive pulmonary disease had no significant difference between patients with AKI and without AKI. These findings were also similar with previous studies. Hirsch et al. have also shown age, hypertension, coronary artery disease, heart failure and diabetes mellitus as significant parameters contributing to the development of AKI [3]. In addition, they have also stated male gender, chronic obstructive pulmonary disease and asthma as other contributors of AKI development [3]. Other previous studies have also stated that AKI was more likely in patients who have an older age, those with coronary heart disease, hypertension and diabetes mellitus [6, 10]. Our findings together with previous studies shine light to the potential risks contributing to AKI development.

The current effects of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers on COVID-19 remain unclear. There is still ongoing debate on whether angiotensin-converting-enzyme inhibitors facilitate the cellular entry and intracellular replication of the virus leading to adverse outcomes [10]. In our study, we have not detected a significant effect of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blocker use on the development of AKI. Future studies are required to better understand their effects on the development of AKI in COVID-19 patients.

There were also significant differences between the laboratory findings of patients with and without AKI. Higher levels of blood urea nitrogen, glucose, gamma-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, C-reactive protein, dimer, troponin, international normalized ratio and activated partial thromboplastin time were detected in patients with AKI. These findings suggest that AKI in COVID-19 is associated with an inflammatory process and a defective procoagulant–anticoagulant balance affecting multiple organ systems [16]. In contrast, the levels of albumin, sodium, hemoglobin and lymphocyte count were significantly lower in patients who developed AKI (Table 2).
A low lymphocyte count has been a common finding associated with disease severity in COVID-19 patients [17, 18]. These findings suggest that AKI development in COVID-19 patients is associated with a severe inflammatory process and coagulative imbalance affecting multiple organs.

Furthermore, we showed that patients with AKI were more likely to develop a cytokine storm. In previous studies, the importance of AKI in the development of cytokine storm has not been fully studied. The abnormal and dysregulated production of cytokines and pro-inflammatory mediators has been associated with poorer outcomes in COVID-19 patients [19]. This uncontrolled inflammatory and immune response leading to cytokine storm contributes to the ongoing organ damage causing acute respiratory distress, pulmonary edema and multi-organ failure [16, 19]. We showed an increased incidence of cytokine storm in COVID-19 patients with AKI. These findings show the importance of close follow-up of COVID-19 patients with AKI to prevent and/or rapidly diagnose and treat any potential cytokine storm to reduce morbidity and mortality.

There were several limitations of our study. This was a retrospective cohort study, the data were collected from medical records. Patients might have had elevated baseline creatinine prior to hospitalization. Accordingly, this may have affected our incidence of AKI among COVID-19 patients. All hospitals included were from Istanbul and the study was conducted during the early stages of the pandemic; therefore, the results may not have been fully representative of the later developments as well as geographic differences in COVID-19 due to changes in patient profiles, therapeutic approaches, treatment protocols and health care capacity. Furthermore, we diagnosed AKI based on only serum creatinine values and not on urine output. This might have affected the sample size in our study. The strengths of this study include a large and diverse sample size covering multiple hospitals. During the given timeframe, all patients that met the inclusion criteria were included in this study. Furthermore, we conducted a multivariate analysis to evaluate the significance of AKI on the outcome of patients with COVID-19.

In conclusion, AKI is a common problem in COVID-19 patients. AKI development in COVID-19 patients increases ICU admission rate and in-hospital mortality. Our findings suggest that AKI should be effectively managed to prevent the adverse outcomes in COVID-19 patients.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

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