Acute Kidney Injuries in different stages of COVID-19: An analysis on patients without prior kidney disease

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Research Article

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

Posted Date: May 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-105205/v5

Abstract

Background

Kidney involvement in COVID-19 may manifest as acute kidney injury (AKI). This study aimed to analyze and compare AKIs in different stages of COVID-19.

Methods

1056 hospitalized COVID-19 patients were retrospectively evaluated and 383 of them met the inclusion criteria. Eighty-nine patients who developed AKI, but didn't have prior kidney diseases were involved in the final analysis. Patients were classified into three groups, those who had AKI on admission, those who developed AKI in the first week and those who developed AKI starting from the 7^{th} day. Electrolytes, acid-base status and changes in the inflammatory markers were compared.

Results

AKIs that were seen on hospital admission day were generally transient. Patients who developed AKI after the 7^{th} day had higher peak CRP and D-dimer levels and lower nadir lymphocyte counts (p=0.000, 0.004 and 0.003 respectively). AKI that developed later was more related to immunologic response and had significantly higher mortality, reaching as high as 44% after 7^{th} day. Hematuria and proteinuria (p=0.001; OR: 2.4; 95% CI: 1.4 – 3.8 and p=0.015; OR: 4.34; 95% CI: 1.3 – 14.3 respectively) were more common in patients who died. Hypernatremia (p=0.000, OR: 6.5; 95% CI:3.0 – 13.9) and hyperchloremia (p=0,002, OR:3,8; 95%CI: 1,7 – 8,4) were also observed more often in patients who died.

Conclusions

AKI in COVID-19 is not of one kind. When developed, AKI should be evaluated in conjunction with the disease stage and possible etiologies. AKI that develops later has worse prognosis and is more related to electrolyte abnormalities even in patients with normal kidney functions.

Introduction

The clinical course of Coronavirus Disease 19 (COVID-19) patients who needed hospital admission might 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 7^{th} 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 2nd week of 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 can 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.

Materials And Methods

Setting

Patients who were admitted to the designated COVID wards in Cerrahpasa Medical Faculty, a tertiary healthcare center, between 15th March and 1st July 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 KDIGO criteria. The first calculated creatinine level after being admitted to 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 backwards calculated using the $MDRD_{75}$ 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 three red blood cells per high power field in the urine sediment. Proteinuria was detected semi-quantitavely by a fully automated urine dipstick test. The level

of proteinuria was graded as +1, +2 or +3; indicating levels between 30-100 mg/dL, between 100-300 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 three groups on the basis of the timing of AKI; those seen on admission, those developed in the 1st week and those developed after the 1st week.

Severity of COVID-19

Clinical picture of COVID-19 patients were classified according to a scale that included 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 the day zero 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 three groups that were created according to the timing of AKI, ANOVA test was performed. Tukey HSD test was used for post-hoc analysis. All tests were applied using SPSS for Windows, version 22.0 software (SPSS Inc. Chicago, IL, USA). P values less than 0.05 were accepted as statistically significant.

Results

A total of 1056 patients were admitted in this specified period. 427 patients were confirmed by RT-PCR. 104 of the PCR confirmed COVID-19 patients experienced AKI (24,3%). 89 patients who developed AKI with an eGFR of over 60 ml/min/1.73 m^2 were included in the final analysis (Figure-1). Patients who were 62,4 ± 14,2 years old and there was a male predominance (67 males, 75%).

Twenty-nine (32%) of the patients had AKI on admission. 33 of them (37%) developed AKI during the first week of admission and 27 patients (30%) developed AKI after the 1st week. For patients who developed AKI later than 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+ semiquantitavely.

Proteinuria was going along with hematuria in 7 patients while two patients had isolated proteinuria.

Electrolyte and acid/base disturbances

Hypochloremia and hyponatremia were the most common electrolyte abnormalities. 65 of the 89 patients (73%) had hypochloremia and 50 (56.1%) of the patients had hyponatremia. Hypernatremia and hyperchloremia was 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 include different combinations of hydroxychloroquine, favipiravir and lopinavir. Anti IL-6 receptor antibody tocilizumab or steroids were used in patients who had high inflammatory response. Low-molecular-weight heparin were prescribed for all patients in line with the MoH guidelines [8]. Continuous renal replacement therapy (CRRT) in ICU setting was performed with Prismaflex® system in a citrate anti-coagulated circuit, aiming a blood flow of around 20 mL/kg/hour.

Comparison according to the timing of AKI

Patients of the three groups (AKI on admission, AKI in the 1st week, AKI after the 1st week) were in similar age and had 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 three groups. CRP and D-dimer levels on admission didn't differ between the groups. Patients who had AKI on admission day had higher initial uric acid levels. All initial laboratory values of the patients can be found in table-1.

Duration of hospital stay, intensive care unit (ICU) requirement and mortality was higher when AKI developed later in the disease course, especially after 7th day. Patients who develop later AKIs 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 worse prognosis tend to increase with AKIs that occurred later. Similarly COVID-19 was more severe in patients who had later AKIs (table-2).

While there were no significant differences between the initial inflammatory markers of the three groups, comparison of changes put forth significant differences. Nadir lymphocyte counts were significantly lower while peak CRP and peak D-dimer levels were significantly higher for patients who developed AKI

later in the disease course (Table-3). Although it couldn't reach the statistical significance, peak ferritin levels were also higher for 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 for all groups. RRT had to be performed in 6 patients who developed AKI later (2 among the 1st week AKIs and 4 among the AKIs developed after the 1st 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 didn't had 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 eGFRs 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=0.001; OR: 2.4; 95% CI: 1.4 – 3.8 and p=0.015; OR: 4.34; 95% CI: 1.3 – 14.3 respectively) were 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=0.000, OR: 6.5; 95% CI: 3.0 – 13.9) and hyperchloremia (p=0.002, OR:3.8; 95%CI: 1.7 – 8.4) were more common in patients who died. Comparison of other electrolytes can be found 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 hadn't (n=24; 1120 ±691 vs n=62; 976 ± 109; p=0.548). 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=0,02 and p=0,000 respectively).

Discussion/conclusion

Different studies reported variable AKI incidences in COVID-19 [9-12]. In the consensus report of 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 of 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 pre-renal 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 1st week. It may not 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% for 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 patients who had AKI after the 7th day.

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 [19-21]. In a report of kidney biopsies in COVID-19 patients, podocytopathies and tubulo-interstitial diseases were main findings while immune mediated glomerular diseases were also found [22]. That study didn't 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 [23]. We didn't perform kidney biopsies, as it was neither clinically indicated nor would change treatment modalities in the vast majority of our patients. It's known from before that immune system dysregulation, complement system activation and hyper-coagulopathy were all linked with each other [24]. 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 [25]..

Patients who develop AKI later had higher peak CRP, D-dimer and ferritin levels. Such 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 didn't differ.

Drug induced nephrotoxicity should not be overlooked in AKIs that develop later. Drugs that resulted in AKI in our patients were 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 [26]. Mortality was increased in patients who had hypernatremia or hyperchloremia.

Both hyperpohospatemia 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 [27].

Our findings showed that high urea-to-creatinine ratio could be a marker of poor prognosis. These patients might have higher serum urea levels that point out to higher catabolic state and they may also have relatively lower creatinine levels, which is indicative of reduced muscle mass.

There are some limitations of our study. Firstly, 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 reasons stated above, kidney biopsies, which might have given more information about etiologies, were not performed.

In conclusion, AKI in COVID-19 is not of one kind. 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 later AKIs are also more prone to electrolyte abnormalities.

Declarations

Statement of Ethics

This study was approved by institutional ethics committee of Cerrahpasa Medical Faculty (nr. 22/05/2020-63863) and ministry of health (Turkey) COVID-19 research committee (nr. 2020-05-08T17_38_07).

All participants provided written informed consent for their data to be used anonymously for research purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare

Funding Sources

None.

Author Contributions

AhM conceptualized the study, collected the data, designed and performed the analysis, wrote the manuscript and submitted the work. MTD collected and interpreted the data and evaluated the results. CK collected and interpreted the data. ST and NS contributed to the analysis, interpreted the data, evaluated the results and revised the manuscript. IIB and RK interpreted the data and evaluated the results MRA evaluated the results, revised the manuscript and was supervisor of the study. All authors approved the final version for publication.

Data Availability Statement

The datasets of the current study are available from the corresponding author on reasonable request.

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Tables

Due to technical limitations, the tables are only available as a download in the supplementary files section.

Figures

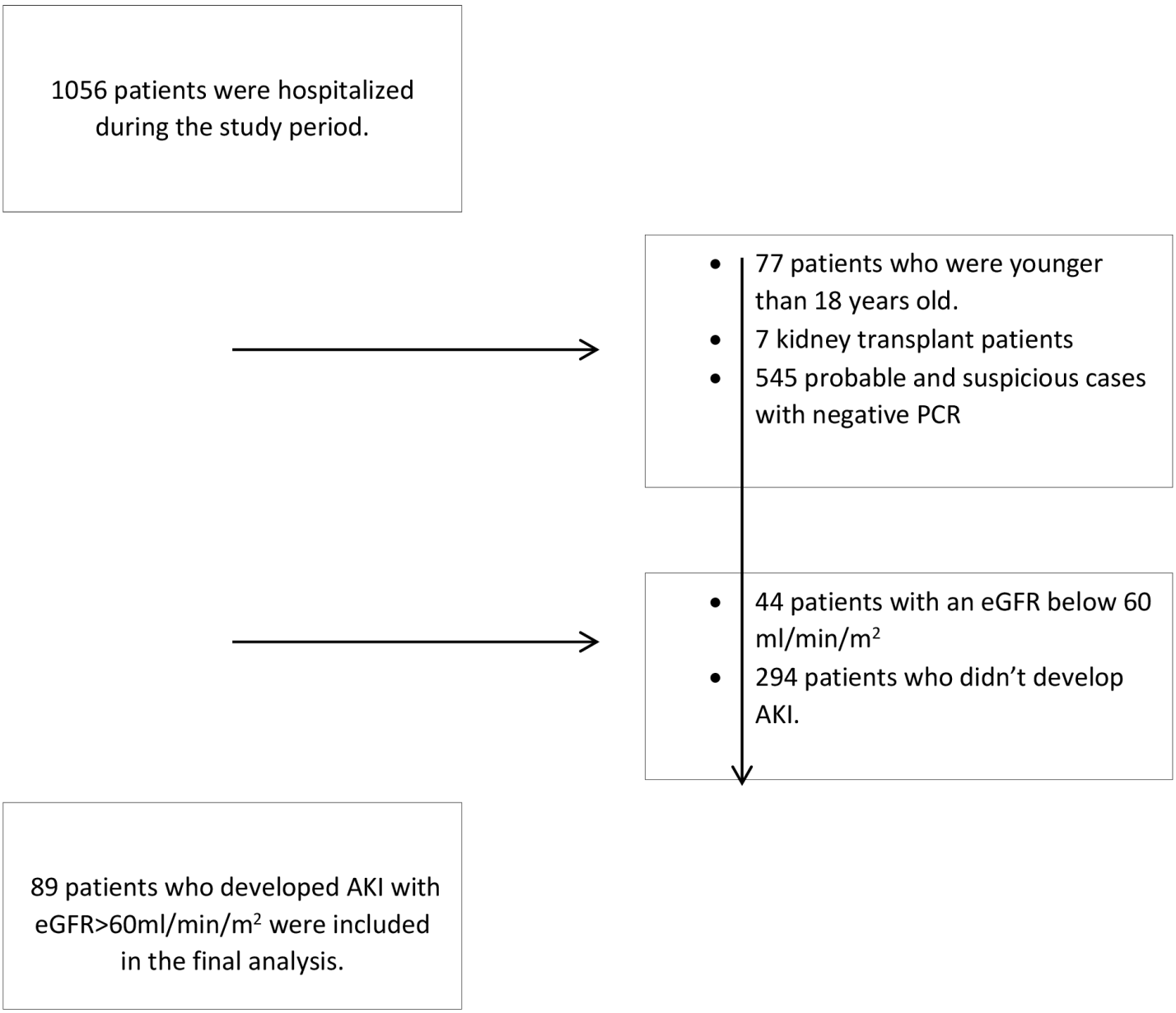

Figure 1

Flow chart of inclusion and exclusion criteria of the patients. PCR: polymerase chain reaction, eGFR: estimated glomerular filtration rate.

Supplementary Files

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- Tables.pdf