

# Acute Kidney Injuries of otherwise normal kidneys have different characteristics in different stages of COVID-19

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## Research Article

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# 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<sup>th</sup> day. Electrolytes, acid-base status and changes in the inflammatory markers were compared.

## Results

Patients who developed AKI after the 7<sup>th</sup> 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% for those who developed AKI after 7<sup>th</sup> day. Patients who died had lower serum albumin levels than those who survived ( $p=0.000$ ). 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 a worse prognosis and is more related to electrolyte abnormalities.

## 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<sup>th</sup> 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 etiologies and timing. This study aims to analyze the etiologies and prognosis 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 in our country 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<sup>2</sup> was already shown to be related to mortality [4], these patients were also excluded. (Figure-1).

### Evaluation of COVID -19 patients

History, physical examinations, clinical features, laboratory tests, radiologic investigations, microbiological tests and in-hospital clinical progress of the patients were retrospectively investigated. The following data were used from each category:

-History: Age, co-morbidities (diabetes, hypertension, malignancy, ischemic heart disease/heart failure), use of drugs or contrast agents.

-Physical examination: State of consciousness, blood pressure, volume status

-Laboratory tests: Urine analysis, complete blood count (CBC), serum urea, serum creatinine, urea-to-creatinine ratio, baseline GFR, uric acid, electrolytes (sodium, potassium, chloride, phosphorus, calcium, magnesium), albumin, transaminases, blood gas analysis (pH, pO<sub>2</sub>, pCO<sub>2</sub>, HCO<sub>3</sub>), CRP, pro-calcitonin, D-dimer, ferritin, lactate dehydrogenase (LDH), creatine kinase (CK), oxygen saturation.

-Radiologic Investigations: Chest computed tomography (CT), renal ultrasonography, abdominal CT (when needed).

-Microbiological tests: Blood culture and urine culture studies (when needed)

-Clinical progress: Antimicrobial treatment, anti-inflammatory treatment, the day of AKI, criteria to diagnose AKI, AKI stage, AKI duration, COVID-19 severity, duration of hospital stay, admission to ICU, renal replacement therapy (RRT) requirement and type, in-hospital mortality.

## 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<sub>75</sub> 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.

State of consciousness was evaluated by Glasgow Coma Scale and a drop of more than 2 points was a reason to call intensive care unit (ICU) team to evaluate the patient for a possible ICU admission. Mean arterial pressure was calculated as:  $[(\text{systolic blood pressure}) + (2 \times \text{diastolic blood pressure}) / 3]$ .

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-quantitatively 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), hypocalcemia (<8.4 mg/dL), hypercalcemia (>10.2 mg/dL), hypophosphatemia (<2.5 mg/dL), hyperphosphatemia (>4.5 mg/dL), hypomagnesemia (<1.6 mg/dL), hypermagnesemia (2.6 mg/dL), acidosis (pH<7.35) and alkalosis (pH>7.45) were all described according to the reference range of respective laboratory measurements. Calcium levels were corrected according to serum albumin levels.

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 1<sup>st</sup> week.

Etiologic evaluation of AKI were carried out according to following criteria:

- Transient pre-renal AKI was defined when creatinine levels could be reversed to baseline levels with relevant fluid resuscitation in 24 to 72 hours.

- AKI was attributed to rhabdomyolysis in patients with at least five times elevated CK (i.e, >950 U/L) above upper normal limit with concomitant increase in LDH and transaminases.

- Hypoxemia related kidney damage was noted in patients who had disrupted gas exchange. Such disruption was documented with partial oxygen pressure lower than 60 mmHg despite the use of high flow oxygen therapy or mechanical ventilation (either non-invasive or invasive) or when respiratory acidosis developed with increasing levels of CO<sub>2</sub> retention.

- Inflammation mediated AKI is considered in patients who have increasing levels of ferritin reaching to 5 times above the normal upper level (>750 ng/mL) or increasing levels of D-dimer that reached at least ten times of the upper normal limit (>5 mg/L).

- Secondary bacterial infections were diagnosed by blood cultures or urine cultures.

- AKI was attributed to drug toxicity if AKI developed after the patient was exposed to nephrotoxic drugs or agents.

### **Inflammation mediated injury assumption**

It's known from before that immune system dysregulation, complement system activation and hyper-coagulopathy were all linked with each other [7]. We have observed a similar phenomenon in our etiologic analysis. 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 were associated with the hyper-inflammation state of COVID-19 [8].

### **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)

- Critical (acute respiratory distress syndrome, shock) [9].

Patients were admitted to intensive care unit, if arterial partial oxygen pressure was persistently below 50 mmHg despite the use of venturi mask, when there was accumulation of CO<sub>2</sub> rising above 55 mmHg,

when the patient had loss of consciousness or when the patient was consistently hypotensive despite fluid resuscitation.

## **Acquisition of Data**

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.

## **Statistical Analysis**

Data were expressed as means  $\pm$  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. The mean age of COVID-19 patients hospitalized in our center was  $55 \pm 15$  years, 582 (55,2%) of them were males while 474 (44,8%) of them were females.

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<sup>2</sup> were included in the final analysis (Figure-1). Patients who were included in our study were older than other patients in the general COVID-19 cohort ( $62,4 \pm 14,2$  years) 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 starting from the second week of admission. For patients who developed AKI later than hospital admission date, AKI developed on the  $6,7^{\text{th}} \pm 5,4^{\text{th}}$  day of the admission. Initial laboratory values on hospital admission day and in-hospital prognostic indices of all 89 patients can be found in the supplementary document.

### **Etiologic evaluation**

#### **Patients who had AKI on admission**

Twenty-nine patients had AKI on admission.

Twelve (41,3%) of these patients had transient pre-renal AKIs as their kidney functions were rescued by relevant fluid resuscitation. Two (6,8%) of the patients had rhabdomyolysis related AKI. Both of these patients also had increasing levels of either ferritin ( $>750$  ng/mL) or D-dimer ( $>5$  mg/L). Six patients

(20,6%) had respiratory disruptions (persistent hypoxemia or hypercapnia). These patients were considered to have hypoxemic kidney injury. Four of these patients also had high levels of ferritin (>750 ng/mL) or D-dimer (>5 mg/L) levels. A total of eight patients (27,5%) had hyperferritinemia and/or high D-dimer levels without rhabdomyolysis. AKIs in these patients were attributed to hyper-inflammation. Direct SARS-CoV-2 renal involvement was only suspected in a 77 years old male patient (3,4%) who had shown new developed proteinuria concomitant with AKI despite normal levels of inflammatory and coagulation markers. COVID severity of the patients who had AKI on admission was mainly moderate and just 7 of them (24%) had severe or critical disease.

### **Patients who had AKI in the 1<sup>st</sup> week.**

Thirty-three patients experienced AKI during the 1<sup>st</sup> week.

10 (30,3%) patients had transient pre-renal AKI, which was cured by relevant fluid therapy. Rhabdomyolysis was noted in four patients (12,1%). All of these four patients also had concomitant hyperferritinemia (>750 ng/mL). A total of 13 patients (39,3%) had high ferritin or D-dimer levels without rhabdomyolysis. The kidney injury was attributed to hyper-inflammation in these patients. Three patients (9%) either had hypoxemia or increasing levels of CO<sub>2</sub>. AKI was attributed to hypoxemia in these patients. AKI in three patients (9%) of this group was related to drug toxicity (contrast agents in two patients and non-steroid anti-inflammatory drug in one patient). When COVID severity of the patients was evaluated, 14 of these 33 patients (42%) were classified as severe or critical.

### **Patients who had AKI after 1<sup>st</sup> week:**

Twenty-seven patients had AKI after the 1<sup>st</sup> week of their admission.

One patient (3,7%) had transient pre-renal AKI. Six patients (22,2%) had rhabdomyolysis. All of the patients who had rhabdomyolysis also had either high D-dimer or ferritin levels. Two patients (7,4%) had severely disrupted gas exchange without concomitant high ferritin or D-dimer levels. AKIs in these patients were attributed to hypoxemia. Sixteen patients (59,2%) had very high levels of either ferritin (>750 ng/mL) or D-dimer (>5 mg/L). AKIs in these patients were associated with hyper-inflammation. Two patients (7,4%) had contrast agent induced AKI. Clinical evaluation pointed out to severe or critical illness in 22 of these 27 patients (81%).

### **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+ semiquantitatively. Proteinuria was going along with hematuria in 7 patients while two patients had isolated proteinuria.

### **Imaging studies**

Chest CT to investigate pulmonary involvement was performed in all patients. COVID pneumonia was detected in a total of 82 patients (92,1%).

Kidney imaging (urinary ultrasonography or abdominal CT) was available in 14 patients. Eight of them were reported to be completely normal. Three patients had nephro-urolithiasis, one patient had pelvic ectasia, one had prostatic hypertrophy and one had the findings of cystic kidney diseases. Imaging studies neither yielded obstruction findings nor could explain the AKI etiology.

### **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. Hyponatremia and hypernatremia 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. Calcium disturbances were observed less frequently. Hypocalcemia was seen in 16 patients (17,9%) and hypercalcemia was detected in 3 patients (3,3%). Among patients for whom phosphorus levels were evaluated (79 patients); 22 had hypophosphatemia (27,8%) and 20 patients (25,3) had hyperphosphatemia. In patients who had their magnesium levels checked (83 patients) 6 (6,7%) had hypomagnesemia and 21(25,3%) had hypermagnesemia. 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 [10]. 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 between the groups formed according to the AKI timing**

Patients of the three groups (AKI on admission, AKI in the 1<sup>st</sup> week, AKI after the 1<sup>st</sup> 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 7<sup>th</sup> day. Patients who develop later AKIs had lower serum albumin levels as well as lower arterial O<sub>2</sub> 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 (table-2). AKI related prognostic indices of the patients can be found in 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 not different between the groups (Table-4). RRT had to be performed in 6 patients who developed AKI later (2 among the 1<sup>st</sup> week AKIs and 4 among the AKIs developed after the 1<sup>st</sup> week) but none of the patients who had AKI on admission needed RRT. Anti IL-6 receptor antibody tocilizumab use was significantly more frequent for patients who developed AKI after 7<sup>th</sup> day. Pulmonary involvement (i.e. COVID pneumonia) was similar between the groups and there was not a statistically significant difference for secondary bacterial infections (Table-2).

### **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-5).

AKI had 24,7% mortality in our patients who had eGFRs above 60 ml/min/1,73 m<sup>2</sup>. 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-5).

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-5.

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

Different studies reported variable AKI incidences in COVID-19 [11-14]. In the consensus report of Acute Disease Quality Initiative, AKI incidence was reported to be around 20% for hospitalized patients [15]. 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 [16]. In a meta-analysis, it was found that 52% of patients who developed AKI had died [17]. Another study showed that, chronic kidney disease and male sex were independent predictors of AKI severity [18]. However, AKI studies in patients with normal kidney functions are scarce. In this study, we exclusively focused on the prognosis of AKI by excluding patients whose eGFRs were below 60 ml/min/1.73 m<sup>2</sup>.

Consequences of all AKIs 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 were still 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 that were responsive to fluid therapy (41%). This decreased to 30% for first week AKIs and to 3% after the 1<sup>st</sup> week. It may not possible to differentiate between pure coagulopathy and cytokine release as both pathologies may be intertwined with each other [19, 20]. 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 COVID-19 was more common in patients who developed AKI later.

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 [21, 22, 23]. 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 [24]. 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 [25]. We didn't perform kidney biopsies, as it was neither clinically indicated nor would change treatment modalities in the vast majority of our patients. Clinical findings, laboratory values and response to the planned interventions guided us to reach the possible etiologies.

12 of our patients had rhabdomyolysis. Exact mechanism of rhabdomyolysis in COVID-19 is not very clear. While one theory is direct viral invasion of muscles that results in rhabdomyolysis, the other

postulates that cytokine storm causes muscular injury [26]. Concomitant increase in ferritin or D-dimer levels in our patients underlines the latter.

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 develops 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.

Hyponatremia, or hypochloremia were common electrolyte abnormalities in COVID-19 patients who had AKIs, but they were not related to mortality. 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 related to poor prognosis. Hyperphosphatemia mainly develops as a consequence GFR loss in patients who have AKI. 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 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 over 60 ml/min/1.73 m<sup>2</sup>. Due to reasons stated above, kidney biopsies, which might have given more information about etiologies, were not performed.

## **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**

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None

## Declaration of Interest

The authors declare that there is no conflict of interest.

## Ethics Approval

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).

## Availability of data

All data generated or analyzed during this study are anonymized and can be made available upon request.

## 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.

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## Tables

Table-1: Characteristics and initial laboratory values of patients in three groups according to the timing of AKI.

	Presented with AKI (n=29)	AKI in the 1st week (n=33)	AKI after 7 days (n=27)	p
Age	61,6 ± 14,2	62,5 ± 12,9	63,1 ± 16,2	0,926
Baseline eGFR (ml/min/1,73 m <sup>2</sup> )	79,6 ± 16,38	82,11 ± 14,53	86,55 ± 16,43	0,258
MAP (mmHg)	89,9 ± 17,2	88,9 ± 13,1	87,4 ± 10,1	0,801
Hemoglobin (g/dL)	12,3 ± 1,9	12,5 ± 1,5	11,9 ± 1,9	0,474
Lymphocytes (per µL)	1317 ± 568	1509 ± 798	1044 ± 437	0,022*
CRP (mg/L)	81,9 ± 76,1	68,5 ± 79,1	98,4 ± 77,6	0,336
Prokalsitonin (ng/mL)	0,27 ± 0,38	0,4 ± 1,1	0,4 ± 0,8	0,683
CK (IU/L)	383 ± 955	282 ± 663	149 ± 111	0,442
LDH (IU/L)	400 ± 194	408 ± 480	441 ± 213	0,889
Ferritin (ng/mL)	615 ± 599	474 ± 524	840 ± 599	0,055
D-dimer (mg/L)	1,5 ± 2,5	1,6 ± 2,4	2,5 ± 3,9	0,346
Uric acid (mg/dL)	6,9 ± 2,6	5,5 ± 1,5	4,6 ± 1,6	0,000**
Sodium (mmol/L)	136,59 ± 5,4	138,67 ± 4,9	141,67 ± 5,89	0,03*
Chloride (mmol/L)	97,01 ± 5,40	98,16 ± 4,88	99,54 ± 4,51	0,168
Potassium (mmol/L)	4,31 ± 0,55	4,45 ± 0,63	4,57 ± 0,67	0,291
Calcium (mg/dL)	8,44 ± 0,44	8,52 ± 0,59	8,42 ± 0,66	0,775
Phosphorus (mg/dL)	n=24 3,47 ± 0,69	n=29 3,56 ± 1,03	n=26 3,38 ± 1,56	0,853
Magnesium (mg/dL)	n=26 2,05 ± 0,18	n=31 2,20 ± 0,35	n=26 2,11 ± 0,37	0,201
HCO <sup>3</sup> (mmol/L)	n=20 24,23 ± 3,14	n=22 24,28 ± 3,61	n=23 24,65 ± 8,23	0,963
Albumin (g / dL)	3,61 ± 0,37	3,51 ± 0,50	3,04 ± 0,42	0,000*

eGFR: estimated glomerular filtration rate, MAP: mean arterial pressure, CK: creatine kinase, LDH: lactate dehydrogenase, AKI: Acute kidney injury

\*Post-hoc analysis reveals that the significance is because of the levels in patients who had AKI after the 1<sup>st</sup> week.

\*\* Significance is mainly because of higher levels in patients who were presented with AKI.

Table-2: 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	0,123
DM (n)	4	10	9	0,189
HT (n)	9	11	11	0,729
Malignancy (n)	3	4	6	0,398
IHD/HF (n)	8	7	5	0,702
AKI stage 1 (n, (%))	26 (89,2)	26 (78,7)	16 (59,2)	0,058
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)	0,000*
Lung Involvement (n, (%))	28 (96)	29 (87)	25 (92)	0,446
Secondary bacterial infections (n, (%))	6 (20)	8 (24)	12 (44)	0,108
Duration of hospital stay (days)	11,3 ± 6,4	11,8 ± 7,9	17,3 ± 6,5	0,003*
ICU requirement (n, (%))	5 (17)	9 (27)	17 (62)	0,001*
pH	n=20 7,41 ± 0,7	n=22 7,38 ± 0,98	n=23 7,35 ± 0,12	0,114
sPO <sub>2</sub>	93,24 ± 2,7	93,04 ± 3,85	87,33 ± 7,5	0,000*
Arterial PO <sub>2</sub> (mmHg)	N=15 65,02 ± 9,53	N=15 67,49 ± 14,18	N=21 56,95 ± 10,95	0,025*
In hospital death (n, (%))	4 (13,7)	5 (15)	12 (44)	0,009*
Death on (day)	11,75 ± 7,4	10,8 ± 6,3	17,3 ± 8,0	0,21

DM: diabetes mellitus, HT: hypertension, IHD/HF: ischemic heart disease and heart failure  
ICU: Intensive Care Unit , AKI: Acute kidney injury

\*Significance mainly results from patients who developed AKI after 7<sup>th</sup> day.

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)	1st week AKI (n=33)	AKI after 7th day (n=27)	p
Peak creatinin (mg/dL)	1,62 ± 0,53	1,69 ± 0,78	1,88 ± 0,87	0,405
AKI duration (days)	4,0 ± 3,7	3,03 ± 4,66	3,19 ± 3,3	0,602
Nadir lymphocytes (per µL)	967 ± 574	1100±692	585±343	0,003*
Peak CRP (mg/L)	125 ± 83	145 ± 122	246 ± 86	0,000*
Peak procalcitonin (ng/mL)	0,57 ± 0,87	3,36 ± 8,37	3,86 ± 6,34	0,100
Peak CK (IU/l)	445 ± 974	387 ± 696	611 ± 641	0,545
Peak LDH (IU/L)	533 ± 314	679 ± 794	888 ± 510	0,087
Peak ferritin (ng/mL)	754 ± 596	806 ± 659	1546 ± 1406	0,004*
Peak D-dimer (mg/L)	7,1 ± 16,3	8,03 ± 10,65	15,39 ± 14,53	0,058
Pro-BNP (pg/mL)	N=10 9029 ± 12542	N=19 4691 ± 10770	N=20 7050 ± 10870	0,593
Uric acid (mg/dL) (on the AKI day)	7,03 ± 2,7	5,81 ± 2,14	5,13 ± 2,0	0,01**
Urine density	N=15 1009,8 ± 6,6	N=9 1012 ± 7,9	N=11 1010 ± 6,9	0,668
Urea (mg/dL) (on the AKI day)	56,72 ± 34,89	51,76 ± 17,22	63,89 ± 36,23	0,303
Peak urea (mg/dL)	72,14 ± 46,23	72,27 ± 46,04	97,52 ± 70,78	0,140
Creatinine (mg/dL) (on the AKI day)	1,48 ± 0,35	1,43 ± 0,32	1,54 ± 0,47	0,565
Urea/creatinine (on AKI day)	37,08 ± 17,19	37,5 ± 14,64	41,83 ± 20,78	0,534
Urea/creatinine (peak levels)	N/A	42,25 ± 15,4	51,00 ± 28,69	0,207
Hematuria (n, (%))	N=15 7, (46)	N=9 5, (55)	N=11 9, (81)	0,186
Proteinuria (n, (%))	N=15 3, (20)	N=9 1, (11)	N=11 5, (45)	0,173
Leucocyturia (n, (%))	N=15 3, (20)	N=9 0	N=11 0	0,112

Hyponatremia (n; (%))	16 (29)	14 (42)	20 (74)	0,048*
Hypernatremia (n; (%))	4 (13)	6 (18)	12 (44)	0,016*
Hypochloremia (n; (%))	20 (68)	19 (57)	26 (96)	0,03*
Hyperchloremia (n; (%))	3 (10)	5 (15)	10 (37)	0,03*
Hypokalemia (n; (%))	3 (10)	4 (12)	9 (33)	0,044*
Hyperkalemia (n; (%))	4 (13)	16 (48)	15 (55)	0,02*
Hypocalcemia (n; (%))	6 (20)	7 (21)	3 (11)	0,179
Hypercalcemia (n ;(%))	1 (3)	1 (3)	1 (3)	0,989
Hypophosphatemia (n; (%))	N=24 5 (20)	N=29 6 (20)	N=26 11 (42)	0,133
Hyperphosphatemia (n; (%))	N=24 4 (16)	N=29 8 (27)	N=26 8 (30)	0,487
Hypomagnezemia (n; (%))	N=26 0	N=31 4 (12)	N=26 2 (7)	0,172
Hypermagnezemia (n; (%))	N=26 4 (15)	N=31 5 (16)	N=26 12 (57)	0,013*
Acidosis	N=20 3 (15)	N=22 8 (36)	N=23 12 (52)	0,039*
Alkalosis	N=20 13 (65)	N=22 9 (40)	N=23 16 (69)	0,116

AKI: Acute kidney injury

N indicates the number of patients who had available laboratory measurements.

\*Post-hoc analysis reveals that the significant difference was because of the values of AKIs after 7<sup>th</sup> day.

\*\*Significance is because of the values in patients who had AKI on admission.

Table 4: Different treatment modalities and renal replacement therapy requirement.

	AKI on presentation (n=29)	AKI in the first week (n=33)	AKI after 7 days (n=27)	p
Antiviral Treatment				NS
Hq	2	3	-	
Hq+favipiravir	4	1	4	
Hq+oseltamivir	12	10	2	
Hq+oseltamivir+favipiravir	9	16	18	
Hq+osemtamivir+favipiravir+lopinavir	2	3	3	
Anticoagulant use	20	21	22	0,376
Steroids use	5	1	5	0,131
Tocilizumab	5	6	13	0,014
RRT requirement	0	2	4	0,224

AKI: acute kidney injury Hq: hydroxychloroquine, RRT: renal replacement therapy, NS: not studied

Table-5: Comparison of survivors and non-survivors. Laboratory values are initial values on hospital admission date.

	Survivors (n=67)	Non-survivors (n=22)	p
Age	60,3 ± 14,3	68,9 ± 12,0	0,03
<u>Co-morbidities (n)</u>	37	18	0,011
Diabetes (n)	17	6	0,779
Hypertension (n)	23	8	0,795
Malignancy (n)	3	10	0,000
IHD/HF (n)	16	4	0,772
eGFR (ml/min/1,73 m <sup>2</sup> )	83,60 ± 16,49	81,22 ± 15,07	0,551
Peak creatinine (mg/dL)	1,49 ± 0,49	2,45 ± 0,89	0,000
AKI developed on (days)	5,81 ± 4,87	8,50 ± 5,85	0,070
AKI duration (days)	2,67 ± 3,48	5,59 ± 4,57	0,002
MAP (mmHg)	89,4 ± 13,7	86,7 ± 13,7	0,430
Hemoglobin (g/dL)	12,7 ± 1,5	10,8 ± 1,9	0,000
Lymphocytes (per µL)	1470 ± 661	804 ± 260	0,000
CRP (mg/L)	65,6 ± 66,2	131,8 ± 90,0	0,000
Prokalsitonin (ng/mL)	0,30 ± 0,93	0,62 ± 0,68	0,139
CK (IU/L)	295 ± 767	209 ± 254	0,618
LDH (IU/L)	351 ± 184	613 ± 545	0,001
Ferritin (ng/mL)	504 ± 469	1069 ± 737	0,000
D-dimer (mg/L)	1,0 ± 0,96	4,73 ± 4,96	0,000
Uric acid (mg/dL)	5,93 ± 2,16	4,88 ± 2,16	0,056
Duration of hospital stay (days)	13,0 ± 7,4	14,5 ± 7,4	0,419
Pro-BNP (pg/mL)	N= 31 2271 ± 6478	N=18 13889 ± 13471	0,000
Urea (mg/dL)	51,15 ± 24,11	75,05 ± 39,07	0,001
Peak urea (mg/dL)	59,15 ± 31,34	143,05 ± 64,93	0,000
Creatinine (mg/dL) (on AKI day)	1,43 ± 0,34	1,62 ± 0,45	0,045
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	0,000
Sodium (mmol/L)	138,28 ± 4,74	140,77 ± 7,88	0,077
Chloride (mmol/L)	98,48 ± 4,71	97,36 ± 5,82	0,365

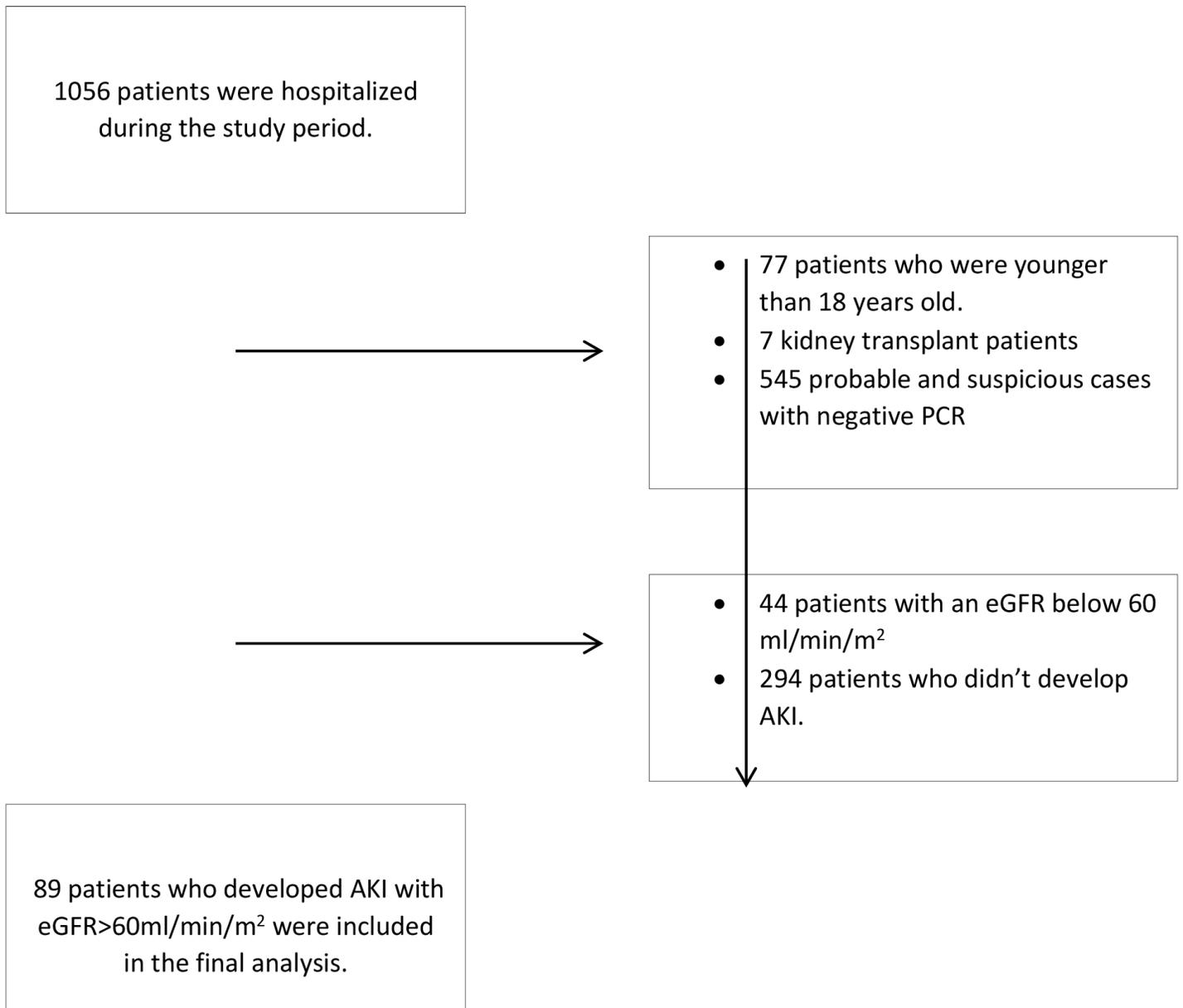
Potassium (mmol/L)	4,42±0,58	4,52±0,73	0,491
Calcium (mg/dL)	8,61 ± 0,47	8,02 ± 0,61	0,000
Phosphorus (mg/dL)	N=58 3,44 ± 0,81	N=21 3,57 ± 1,79	0,664
Magnesium (mg/dL)	N=62 2,11 ±0,23	N=21 2,19 ± 0,49	0,331
Albumin (g/dL)	3,59 ± 0,39	2,83 ± 0,34	0,000
HCO <sub>3</sub> (mmol/L)	N=43 25,0 ± 3,1	n=22 23,1 ± 8,4	0,195
pH	7,42 ± 0,6	7,30 ± 0,13	0,000
SPO <sub>2</sub>	93,79 ± 2,7	84,01 ± 5,79	0,000
Arterial PO <sub>2</sub> (mmhg)	N=31 68, 82 ± 11,26	N=20 52,51 ± 6,56	0,000
Hematuria (n, (%))	N=24 10 (41)	N=11 11 (100)	0,001 [OR:2,4 ; 95% CI: 1,4 - 3,8]
Proteinuria (n, (%))	N=24 3 (12,5)	N=11 6 (54)	0,015 [OR: 4,3 95% CI: 1,3 - 14,3]
Leucocyturia (n, (%))	N=24 2 (9)	N=11 1 (9)	1,00
Hyponatremia (n, (%))	35 (52)	15 (68)	0,223
Hypernatremia (n, (%))	7 (10)	15 (68)	0,000 [OR: 6,5 ; 95%CI: 3 - 13,9]
Hypokloremia (n, (%))	46 (68)	19 (86)	0,165
Hyperkloremia (n, (%))	8 (11)	10 (54)	0,002 [OR: 3,8 ; 95%CI: 1,7 - 8,4]
Hypokalemia (n, (%))	8 (11)	8 (36)	0,21
Hyperkalemia (n, (%))	25 (37)	10 (45)	0,616
Hypokalsemia (n, (%))	12 (18)	4 (18)	1,000
Hyperkalsemia (n, (%))	1 (1)	2 (9)	0,150
Hypophosphatemia (n, (%))	N=58 9 (15)	N=21 13 (61)	0,000 [OR: 3,9 ; 95%CI: 2,0 - 7,9]
Hyperphosphatemia (n, (%))	N= 58 9 (15)	N=21 11 (52)	0,002

			[OR: 3,3 ; 95% CI: 1,6 - 6,9]
Hypomagnezemia (n, (%))	N= 62 3 (4)	N=21 3 (16)	0,167
Hypermagnezemia (n, (%))	N=62 6 (9)	N=21 15 (71)	0,000 [OR: 7,3 ; 95% CI: 3,2 - 16,5]
Acidosis	N=43 5 (11)	N=22 18 (81)	0,000 [OR: 7,0 ; 95% CI: 3,0 - 16,4]
Secondary bacterial infections (n; (%))	12 (17)	14 (63)	0,000 [OR: 3,5 ; 95% CI: 1,9 - 6,4]

AKI: Acute Kidney Injury, eGFR: estimated glomerular filtration rate, MAP: mean arterial pressure, CK: creatine kinase, LDH: lactate dehydrogenase, OR: odds ratio, CI: Confidence Interval

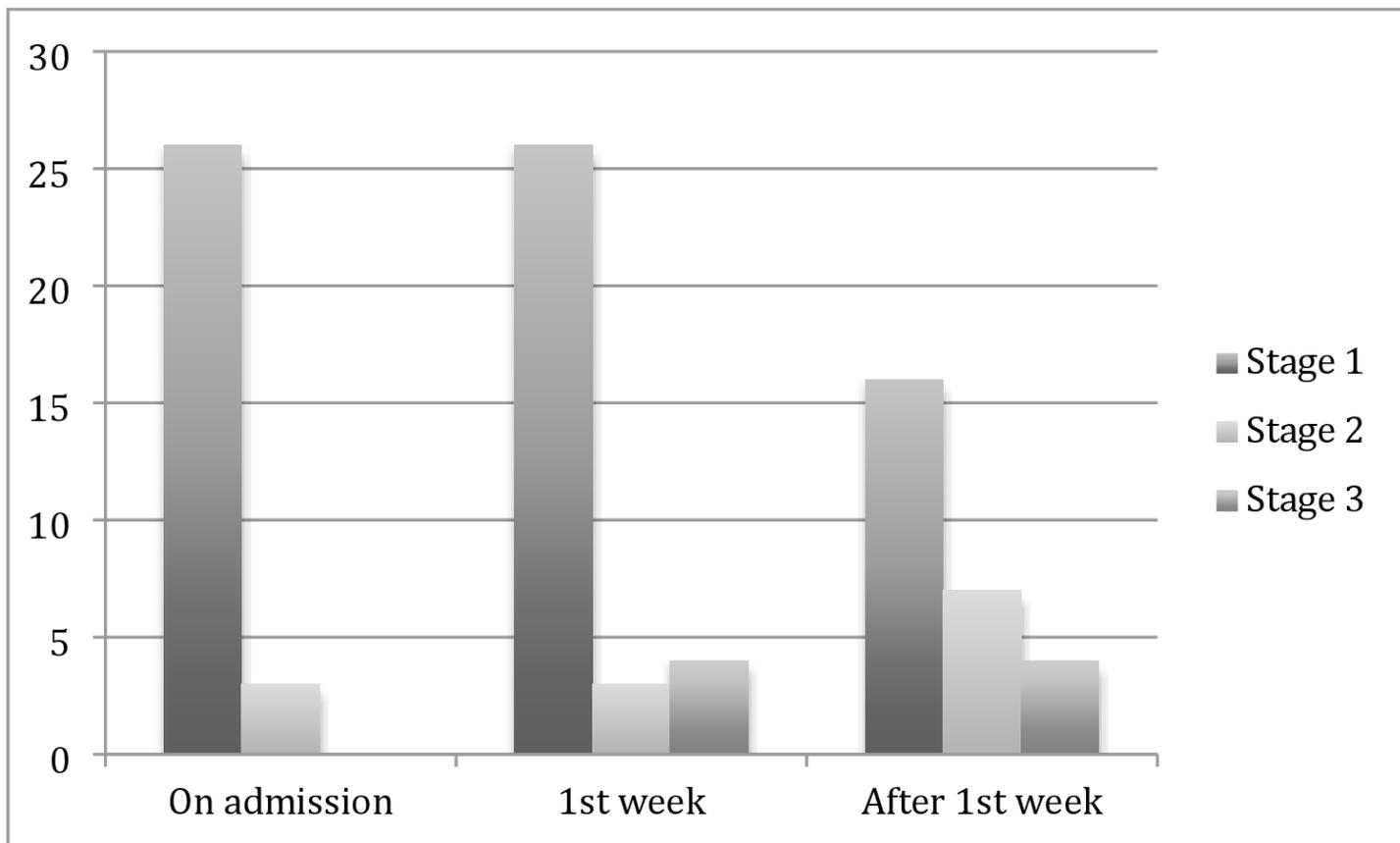
N indicates the number of patients with available laboratory measurements.

## Figures



**Figure 1**

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



**Figure 2**

Stages of Acute Kidney Injury in relation to the time elapsed after hospital admission

## Supplementary Files

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