Time and the etiology of Acute Kidney Injury define prognosis in the course of COVID-19

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Abstract

Aim Kidneys are among the affected organs in COVID-19 and there may be different etiologies resulting in acute kidney injury (AKI) in different stages of the disease. This study aimed to analyze AKI among hospitalized COVID-19 patients in relation to the time and etiologies of AKI.

Methods 1056 patients who were hospitalized with COVID-19 diagnosis in our institution were retrospectively evaluated and 383 of them met the inclusion criteria. Eighty-nine patients who developed AKI 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 7^{th} day. Initial lymphocyte counts, creatinine levels, electrolytes, acid-base status and changes in the inflammatory markers were compared between the groups. A comparison between patients who survived and who died was also performed.

Results AKI had 24% mortality in COVID-19 patients who had eGFRs of over 60 ml/min/1,73 m^2. Patients who developed AKI later had higher peak CRP and D-dimer levels with lower nadir lymphocyte counts (p=0,000, 0,004 and 0,003 respectively). Mortality of patients who had AKI on hospital admission (13%) was similar to the overall COVID-19 mortality for inpatients, however it was 44% for those who developed AKI after 7^{th} day. Early AKI was related to pre-renal causes and had a milder course. However, later AKIs were more related to immunologic response and had significantly higher mortality.

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.

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the pathogen of Coronavirus Disease 19 (COVID-19), is mainly a respiratory virus. The clinical course of 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]. Although the lungs are the most common involved organs, other systems might also be affected and kidneys are among them [2]. 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 [3,4].

Kidney involvement in COVID-19 can be manifested as acute kidney injury (AKI). Based on previous observations, we hypothesized that all AKIs seen in COVID-19 are not uniform and we aimed to analyze

the etiologies and prognosis of AKI among hospitalized COVID-19 patients in relation to the time of AKI during different phases of the disease.

Materials And Methods

Setting

Patients who were admitted to the designated COVID wards in Cerrahpasa Medical Faculty, a university hospital as a tertiary healthcare center, between 15th March and 1st July were retrospectively analyzed. This period has been the first wave of the pandemic in our country and there was a tendency to admit symptomatic patients immediately.

We have only included patients who were confirmed by real-time polymerase chain reaction (RT-PCR) test in our study. Kidney transplant patients as well as those who were younger than 18 years old were excluded from the study. Additionally, as eGFR below 60 mL/min/1,73 m^2 was already shown to be related to mortality [5], these patients were also excluded. (Figure-1).

Evaluation of COVID -19 patients with AKI

History, physical examinations, clinical features, laboratory tests, radiologic investigations, microbiological tests and in-hospital clinical progress of the patients were retrospectively analyzed. 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 eGFR (calculated by using CKD-EPI formula with baseline creatinine) uric acid, electrolytes (sodium, potassium, chloride, phosphorus, calcium, magnesium), albumin, transaminases, blood gas analysis (pH, pO_2, pCO_2, HCO_3), 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: Hemo-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 the last 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. [6].

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 [7,8].

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.

State of consciousness was evaluated by Glasgow Coma Scale and a drop of more than 2 points was a reason to call ICU team to evaluate the patient for a possible ICU admission. Mean arterial pressure was calculated as [(systolic blood pressure) + (2 x 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 semiquantitavely 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), hyperkelamia (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 assessments. Calcium levels were corrected according to serum albumin levels.

In order to make comparisons between etiologies and outcomes of AKIs that were developed in different periods of the disease, we defined three groups regarding the time of development of AKI; those seen on admission, those developed in the 1st week and those developed after the 1st week.

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

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

- Patients with at least five times elevated creatine kinase (i.e, >950 U/L) above upper normal limit with concomitant increase in lactate dehydrogenase and transaminases were accepted as AKI due to rhabdomyolysis.

- 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_2 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 reaches at least ten times of the upper normal limit (>5 mg/L).

-AKI was attributed to bacterial secondary infections in patients for whom a bacterial sepsis could be documented by hemocultures or urine cultures.

-Obstruction findings either clinically or from renal imaging studies were used for post-renal AKI.

- AKI was attributed to drug toxicity if AKI developed after the patient was exposed to a nephrotoxic drugs or agents such as non-steroid anti-inflammatory drugs, antibiotics or radio-contrast agents

Inflammation mediated injury assumption

It's known from before that immune system dis-regulation, complement system activation and hyper-coagulopathy were all linked with each other [9]. 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 hyper-ferritinemia were accepted to be related to the hyper-inflammation state of COVID-19 [10].

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) [11].

Patients were admitted to intensive care unit, if partial oxygen pressure was persistently below 50 mmHg despite the use of venturi mask, when there was an accumulation of CO_2 rising above 55 mmHg, the patient has loss of consciousness or the patient is consistently hypotensive despite fluid resuscitation.

Acquisition of Data

Hospital electronic health records (ISHOP-Istanbul University-Cerrahpasa Hospital Automation program) and patient files were used to collect the data of the patients. In-hospital stay length and duration of AKI and their relations with outcomes and other recorded variables were analyzed. Hospital admission day was accepted as admission date to the COVID ward.

The study was approved by institutional ethics committee of Cerrahpasa Medical Faculty (nr. 22/05/2020-63863) and ministry of health COVID-19 research committee (nr. 2020-05-08T17_38_07). Patient data was anonymized before the analysis.

Statistical Analysis

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. The mean age of COVID-19 patients in our hospital cohort was 55 ± 15 years old, 582 (55,2%) of them were males while 474 (44,8%) of them were females.

427 patients were confirmed by RT-PCR. Mortality of admitted COVID-19 patients in with a confirmed RT-PCR was previously found to be 12% in our center [12]. 104 of them experienced AKI (24,3%). There were 44 patients who had eGFR under 60 ml/min/1.73 m2. While15 of them had AKI (34%), 8 of them died (53,3%).

As can be seen in figure-1, 89 patients who developed AKI with an eGFR of over 60 ml/min/1.73 m2 were included in the final analysis. Patients who were included in our study were older than other patients in the general COVID-19 cohort (62,4 ± 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 6,7 ± 5,4 days.

Initial laboratory values on hospital admission day were shown in table-1 and in-hospital prognostic indices of all 89 patients who were included in the study can be found in table-2.

Etiologic evaluation

Patients who had AKI on admission

Twenty-nine patients had AKI on admission.

- Kidney functions in the 12 (41,3%) of on-admission AKIs were rescued by fluid resuscitation and were accepted to have transient pre-renal AKI due to hypovolemia.

- Two (6,8%) of the patients had high creatine kinase (CK) levels with concomitant high LDH and transaminase levels and accepted to have 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 documented gas exchange disruptions (persistent hypoxemia or hypercapnia). These patients were considered to have hypoxemic kidney injury. 4 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%) who had hyperferritinemia and/or high D-dimer levels without rhabdomyolysis. Thus, they were noted to have hyper-inflammation related AKI.

-Direct SARS-CoV-2 renal involvement was suspected only in a one 77 years old male patient (3,4%) who had shown new developed proteinuria concomitant with AKI despite normal levels of CK levels or inflammatory and coagulation markers.

COVID severity of the patients with AKI on admission was mainly moderate and just 7 of them (24%) had severe or critical disease.

Patients who had AKI in the 1st week.

Thirty-three patients experienced AKI during the 1st 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%) who had high creatine kinase (CK) levels with concomitant high LDH and transaminase levels. 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 rhabdamyolysis and accepted to have hyper-inflammation mediated kidney injury.

- Three patients (9%) either had hypoxemia or increasing levels of CO_2 retention. These were accepted to have hypoxemia related AKI.

- AKI in three patients (9%) of this group was thought to be 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 1st week:

Twenty-seven patients had AKI after the 1st week of their admission.

- AKI in one patient (3,7%) could be cured by relevant fluid therapy and accepted to have transient pre-renal AKI.

- Six patients had very high levels of CK (22,2%) with concomitant high LDH and transaminase levels and noted to have rhabdomyolysis. All of these patients 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. AKI 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). These patients were accepted as hyper-inflammation induced AKI.

- 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+ semiquantitavely. 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%). (28 of the on admission AKIs, 29 of the 1st week AKIs and 25 of the AKIs after 1st week).

Kidney imaging (urinary ultrasonography or abdominal CT) was available in a total of 14 patients. Eight of them were reported to be completely normal. Three patients had one sided nephro-urolithiasis, one patient had one sided pelvic ectasia, one had prostatic hypertrophy and one had the findings of cystic kidney diseases. None of the imaging studies yielded obstruction findings. Pathologies revealed by imaging studies could explain hematuria in some patients but none could be attributed to their AKIs.

Electrolyte and acid/base disturbances

Hypochloremia and hyponatremia were the most common electrolyte abnormalities in our cohort with 65 of the 89 patients (73%) experiencing hypochloremia and 50 (56,1%) of the patients having 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. Calcium disturbances was seen less frequent, hypocalcemia in 16 patients (17,9%) and hypercalcemia just 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 depending on the institutional availabilities and 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 [13]. These can be found in supplementary document-2. 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 denoted by the timing of AKI

Patients of the three groups (on admission AKI, 1st week AKI, after the 1st week AKI) 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. While CRP and D-dimer levels on admission didn't differ between the groups, patients who were presented with lower lymphocyte counts tend to develop AKI later in the disease course. 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-3.

In hospital stay length, 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 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-4). AKI related prognostic indices of patients can also be found in table-4.

While there were no significant differences between the initial values of the three groups, comparison of changes in the inflammatory markers 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-5). 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. These included both abnormally low and abnormally high levels of sodium, chlorine and potassium (Table-5). Among absolute electrolyte levels on the day of AKI, sodium levels tend to be higher in patients who developed AKI later (Table-3).

Treatment modalities were not different between the groups (Table-6). CRRT had to be performed in 6 patients who developed AKI later (2 among the 1st week AKI and 4 for AKIs developed after the 1st week) but none of the patients who had AKI on admission needed RRT. Anti IL-6 receptor antibody tocilizumab was used in patients who had high inflammatory response and its use was significantly more frequent for patients who developed AKI after 7th day. Pulmonary involvement (i.e. COVID pneumonia) was not

different between the groups and there was not a statistically significant difference for secondary bacterial infections (Table-4).

Comparison between survivors and non-survivors

Survivors and non-survivors among patients who developed AKI were also compared. In-hospital stay length was not different for survivors and non-survivors. Those who died were older than those who didn't. Patients who survived had similar diabetes or hypertension rates as patients who didn't, while concomitant malignancies were more frequent in patients who died (Table-7).

AKI had 24,7% mortality in our patients who had eGFRs above 60 ml/min/1,73 m^2 according to the baseline creatinine values. Baseline eGFRs were similar for survivors and non-survivors. AKI developed later in non-survivors and it lasted longer. Non-survivors had significantly higher initial CRP, LDH, ferritin and D-dimer levels while significantly lower hemoglobin and lymphocyte counts. (Table-7).

Patients who died had lower serum albumin levels than those who survived. Blood pH, oxygen saturation and arterial oxygen pressure levels were also calculated lower in patients who died. 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) was more common in patients who died.

Among electrolyte disturbances hyponatremia and hypochloremia were not different 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. Both hyperphosphatemia (p=0,002, OR:3,3 ; 95%CI:1,6 – 6,9) and hypophosphatemia (p=0,000, OR:3,9; 95% CI: 2,0-7,9) were found to be significantly different between survivors and non-survivors. Hypomagnesemia was not different between survivors and non-survivors, however hypermagnesemia was more common in patients who died (p=0,000 , OR:7,3 ; 95% CI:3,2 – 16,5)

Patients who couldn't survive had more acidotic blood pH (p=0,000; OR:7,0 95%CI: 3,0 – 16,4) and they also had more secondary bacterial infections (OR: 3,5 ; 95%CI: 1,9 – 6,4) than patients who survived. However, ferritin levels 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 which was checked both on the day of AKI and on the day of peak creatinine levels, were higher in non-surviving patients (p=0,02 and p=0,000 respectively).

Discussion

We previously found that reduced eGFR was related to mortality in COVID-19 patients [12]. And, in this current study with an extended cohort, we exclusively focused on the prognosis of AKI by excluding patients who had eGFR below 60 ml/min/1,73 m^2. Patients who already had decreased kidney functions

might be more prone to kidney injuries and have worse outcomes. We wanted to eliminate the effects of this tendency in order to have an idea for the exact prognosis of AKI.

Previously, AKI incidence has been reported to be between 0,5% to 13% [14-17]. AKI incidence may be higher in severe COVID-19 cases [18] and in the study of Hirsch et al who found an AKI incidence of 36%, the temporal association between initiation of mechanical ventilation and AKI was underlined [19]. However, time elapsed from disease onset to mechanical ventilation was not made clear in that study. AKI has been proposed as a poor prognostic factor for COVID-19 [20]. In a recent meta-analysis, it was found that 52% of patients who developed AKI had died [21]. Another study showed that, chronic kidney disease and male sex were independent predictors of AKI severity [22]. However, as seen in our cohort, consequences of all AKIs in COVID-19 may not be the same. There may be different etiologies resulting in AKI in different phases of the disease.

To our knowledge, this is the first study, comparing AKIs in different phases of the disease. 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. 41% of our patients who had AKI upon admission responded to fluid therapy. 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 to our center. On admission AKIs were mainly transient pre-renal AKIs that were related to fluid disturbances (41%). This decreased to 30% for first week AKIs and to 3% for AKIs starting from the second week. It may not possible to differentiate between pure coagulopathy and cytokine release as both pathologies may be intertwined with each other [23, 24]. When they are taken into account together; inflammation-mediated injury was around 27,5% for on admission AKIs. This increased to 39,3% for first week AKIs and it was as high as 59,2% for patients who experienced AKI starting from the second week.

Patients who have severe or critical clinical picture tend to develop AKI later, and generally with the start of second week. Although stage 1 AKI was predominant among patients who developed AKI, the rate of stage 1 AKI decreased gradually for AKIs seen later in the disease course (89,6% upon admission, 78,7% for first week AKIs and 59,2% for AKIs that develop after the first week). Patients who needed RRT also increased for AKIs that develop after the first week.

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 proximal tubular injury as well as podocytopathies [25, 26]. In a recent report, Kudose et al. performed kidney biopsies in COVID-19 patients, 88% of which was done to investigate AKIs. Podocytopathies and

tubulo-interstitial diseases were main findings while immune mediated glomerular diseases were also found in some of the patients [27]. That study didn't detect virus particles in the kidney. Such a result suggests that direct viral infection may be rare and cytokine mediated effects were more likely in the course of COVID-19. 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 [28]. We could attribute AKI to direct virulence of SARS-CoV-2 in just one patient as others already had high levels of inflammatory markers or coagulopathy. Rhabdomyolysis was seen in 2, 4 and 6 of the patients of on-admission AKI, first week AKI and after the first week AKI groups respectively. Exact mechanism of rhabdomyolysis in COVID-19 is not very clear yet. While one theory is direct viral invasion of muscles that results in rhabdomyolysis, the other postulates that cytokine storm causes muscular injury [29].

Differences in outcomes of the patients may be attributed to different etiologies that caused AKI in different stages of the disease. We didn't perform kidney biopsies as it was neither clinically indicated nor would change treatment modalities in the vast majority of our patients. Experimental biopsies could have been done in selected patients but the clinical picture of the patients was not suitable for such an approach. Besides, we wouldn't find it in line with the merits of medical ethics. Clinical findings and progress, laboratory values and response to the planned interventions guided us to reach the possible etiologies.

The composition of our cohort, which includes patients with baseline eGFRs over 60 ml/min/1,73 m^2 gives the opportunity to define the prognostic value of AKI in patients without previous renal failure. Although AKI had an overall mortality rate of 24%, the prognosis was different in relation with the time of AKI. Mortality rate was 13% for patients who had AKI on admission, 18% for those who developed AKI in the first week and 44% for those who developed AKI starting from the second week. There were not statistically significant differences between initial CRP, D-dimer or ferritin levels of the three groups. However, initial lymphocyte levels were lower for patients who developed AKI later. Higher uric acid for patients who had AKI on admission may be related to the initial eGFR loss of these patients.

Surviving patients had higher lymphocytes, higher hemoglobin levels, lower CRP, lower D-dimer, lower ferritin and lower LDH levels initially. Similar results were found previously for general COVID-19 patients [30]. When changes in the inflammatory markers during the disease course were compared, 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 variable, ferritin levels, as a marker of inflammatory response in patients with or without secondary bacterial infections didn't differ. Mortality of AKI, which is seen on admission, was comparable

to the mortality of general COVID-19 patients who were followed as inpatients in our institution, which was found to be around 12% [12]. However, mortality reaches as high as 44% in patients who develop AKI later. Higher immune response may explain worse prognosis for late AKIs.

Nephrotoxic drugs or agents should not be underestimated in AKIs that develop during the disease course. Drugs that resulted in AKI were non-steroidal anti-inflammatory drugs, antibiotics (e.g. aminoglycosides) and contrast agents that were used for computer tomography scans.

Hyponatremia, as the most common electrolyte abnormality in hospital admissions [31], was observed in a high amount of our patients. Similarly hypochloremia was also quite often. Hyponatremia or hypochloremia were not related to mortality in our cohort. These abnormalities are more commonly seen early in the disease course and they are more responsible to relevant fluid therapies. Hypernatremia tended to develop later, mostly because of hypertonic enteral feeding formulas, saline fluid administrations or steroid use [32]. Use of saline fluids in patients with reduced oral intake may also explain hyperchloremia seen in these group. Also, hypernatremia and hyperchloremia were related to mortality in our cohort.

Both hyperpohospatemia and hypophosphatemia were also related to poor prognosis. Hyperphosphatemia develops mainly as a result of accumulation with a drop in GFR. For hypophosphatemia; tubular injury, anti-acid drugs, malnutrition, respiratory alkalosis or CRRTs may be responsible factors. Hypophosphatemia, as a poor prognostic factor, might have resulted in impaired myocardial functions and decreased diaphragmatic contractility [33].

Our findings showed that urea-to-creatinine ratio was higher in patients who died. Critically ill patients may have higher serum urea levels that point out to higher catabolic state and these patients also have relatively lower creatinine levels, which is indicative of reduced muscle mass. Increasing levels of urea-to-creatinine ratio might be a marker of poor prognosis. There have been similar findings in a previous study that studied hospitalized patients who had infectious diseases [34].

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^2. Due to reasons stated above, kidney biopsies which might have given more information about etiologies were not performed.

Conclusions

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. Although hyponatremia and

hypochloremia were the most common electrolyte disturbances, hypernatremia and hyperchloremia were found as poor prognostic factors.

Declarations

Funding

None

Conflicts of Interest

The authors declare that there is no conflict of interest. The results presented in this paper have not been published previously in whole or part.

Ethics Approval

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

Availability of data

All data generated or analyzed during this study are anonymized and included

as a supplementary material.

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 study population.

Age	62,4 ± 14,2
Sex (Male/Female)	67 / 22
Mean arterial pressure (mmHg)	88,7 ± 13,7
Hemoglobin (g/dl)	12,3 ± 1,9
eGFR (ml/min/1,73m^2)	82,6 ± 15,8
CRP (mg/L)	82,0 ± 77,8
Lactate Dehydrogenase (IU/L)	416 ± 331
D-dimer (mg/L)	1,9 ± 3,0
Lymphocytes (per µL)	1305 ± 654
Creatine kinase (IU/L)	274 ± 680
Ferritin (ng/mL)	629 ± 584
Uric acid (mg/dL)	5,6 ± 2,2
Albumin (gr/dL)	3,4 ± 0,5
Pro-BNP (pg/mL)	6539 ± 11069

Table 2. Hospital stay length and prognostic indices of the study population

Hospital Stay (days)	13,3 ± 7,4
AKI developed on (days) (excluding the AKIs seen on admission day)	6,7 ± 5,4
AKI Stage 1 (n ,(%))	68 (76,4)
AKI Stage 2 (n ,(%))	13 (14,6)
AKI Stage 3 (n ,(%))	8 (8, 9)
Severe or critical clinical picture (n, (%))	43 (48,3)
ICU requirement (n, (%))	31 (34,8)
Death (n, (%))	22 (24,7)

ICU: Intensive Care Unit, AKI: Acute kidney injury

Table-3: 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^2)	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^3 (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 1st week.

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

Table-4: 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	n=22	n=23	0,114
	7,41 ± 0,7	7,38 ± 0,98	7,35 ± 0,12	
sPO_2	93,24 ± 2,7	93,04 ± 3,85	87,33 ± 7,5	0,000*
Arterial PO_2 (mmHg)	N=15	N=15	N=21	0,025*
	65,02 ± 9,53	67,49 ± 14,18	56,95 ± 10,95	
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^{th} day.

Table-5: 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	N=9	N=11	0,173

	3, (20)	1 ,(11)	5, (45)	
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	N=22	N=23	0,039*
	3 (15)	8 (36)	12 (52)	
Alkalosis	N=20	N=22	N=23	0,116
	13 (65)	9 (40)	16 (69)	

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 7th day.

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

Table 6: 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		16	18	
Hq+osemtamivir+favipiravir+lopinavir	9 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-7: 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
Co-morbidities (n)	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^2)	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	39,01 ± 13,85	62,38 ± 30,76	0,000

(peak levels)			
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_3 (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_2	93,79 ± 2,7	84,01 ± 5,79	0,000
Arterial PO_2 (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

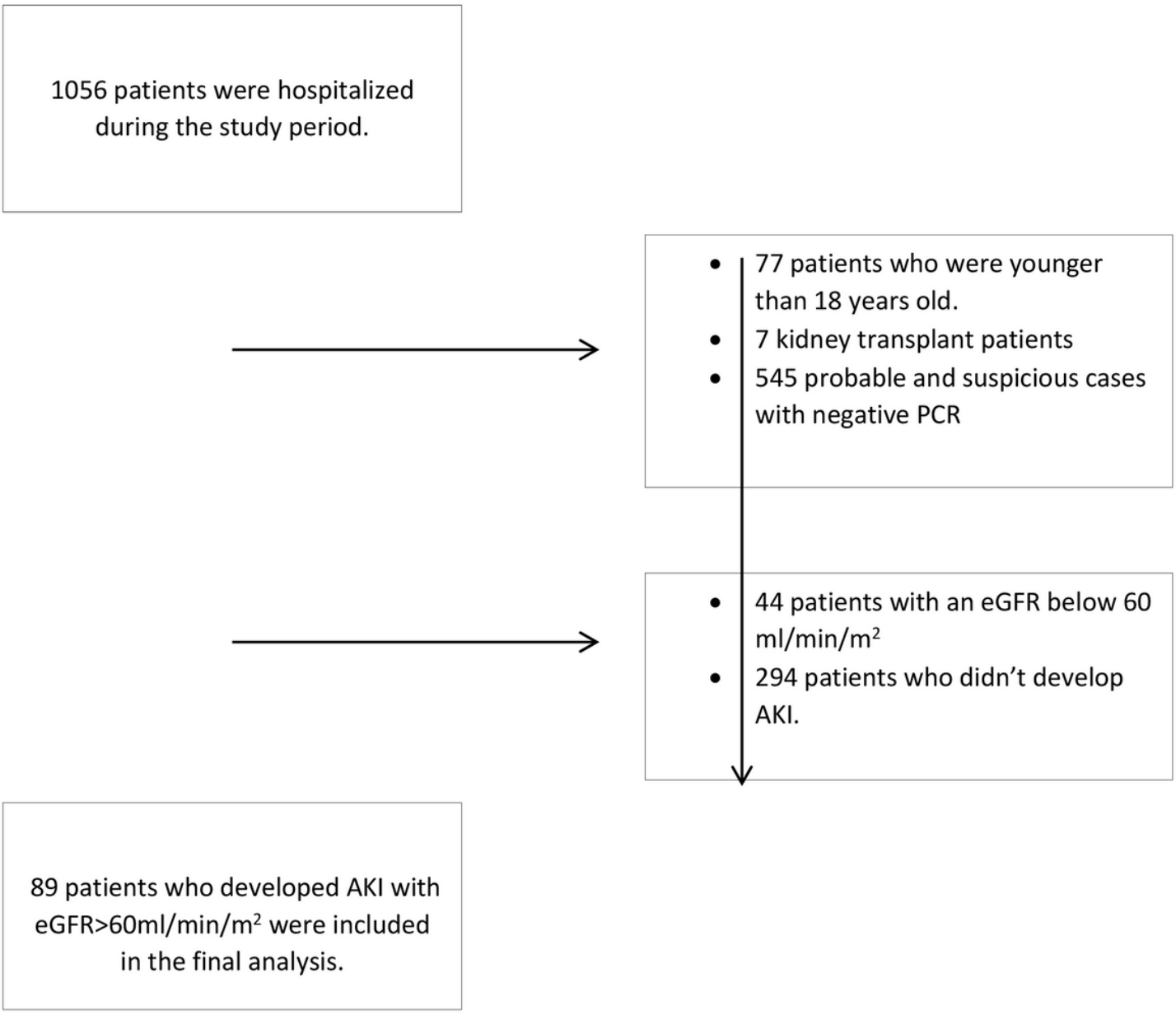

Figure 1

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

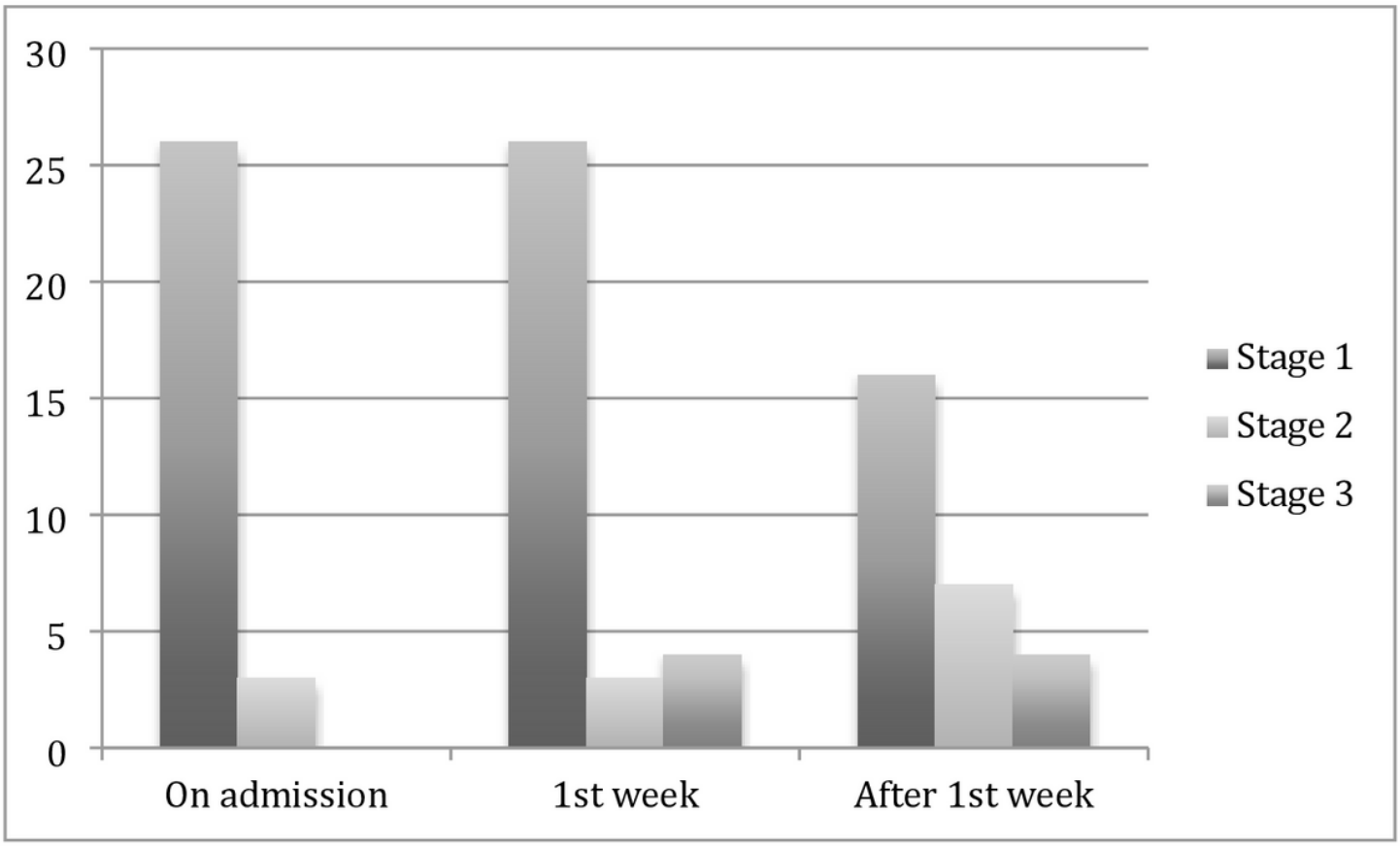

Figure 2

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

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