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

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Abstract

Introduction 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.

Materials & 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. As immunologic response is generally accepted to start with the second week of COVID-19 course, 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 and inflammatory markers as well as changes in these parameters were compared between the groups.

Results AKI was seen in 23% of the patients and 23% of those who developed AKI died. 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). Additionally, patients who died had higher initial inflammatory marker levels and lower lymphocyte counts than those who survived. Mortality of patients who had AKI on hospital admission (13%) was similar to the overall COVID-19 mortality for inpatients, however it was as high as 44% for those who developed AKI after 7^{th} day.

Conclusion Early AKI was more related to pre-renal causes and had a milder course. However, later AKIs were more related to immunologic response and had significantly higher mortality. Findings of this study suggest that AKI in COVID-19 is not of one kind. When developed, AKI should be evaluated in conjunction with the disease stage and possible etiologies.

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 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.

A total of 1056 patients were admitted in this specified period. 77 Patients who were younger than 18 years old and 7 kidney transplant patients were excluded from the study. 427 of the remaining patients were confirmed by real time polymerase chain reaction (RT-PCR) test. Patients among confirmed cases with baseline estimated glomerular filtration rate (eGFR) over 60 mL/min/1,73 m^2 who experienced AKI were included in the analysis (Figure-1). As eGFR below 60 mL/min/1,73 m^2 was already shown to be related to mortality [5], we didn't include these patients in our study.

Definitions related to AKI

We observed the progression of creatinine values in all patients who were admitted with COVID-19 diagnosis. 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 [6].

In patients with an increase in creatinine levels, we directly applied KDIGO criteria. In patients in whom creatinine levels decreased following hospital admission, KDIGO criteria were applied after backwards calculation of their baseline creatinine levels 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. 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.

Pre-renal AKI was defined as AKIs that were responsive to relevant fluid resuscitation. AKI was attributed to drug toxicity when stopping the offending drug cured it. AKIs in patients with at least five times elevated creatinine kinase above upper normal limit were noted as rhabdomyolysis related AKIs. AKIs in patients either with persistent hypoxemia, increased D-dimer levels or cytokine release syndrome were accepted to be related to the hyper-inflammation state of COVID-19.

Clinical picture of COVID-19 patients were classified according to a scale that involved 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) categories [9].

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 addition to the demographic data, daily checked creatinine levels, complete blood counts, inflammatory markers and D-dimer levels were recorded. eGFR of the patients were calculated by using CKD-EPI formula [10].

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

The mean age of COVID-19 patients in our hospital cohort was 55 ± 15 years old, 538 (55%) of them were males while 441 (45%) of them were females.

383 of the 427 confirmed cases had a baseline eGFR of higher than 60 ml/min/1,73 m^2. Eighty-nine of these 383 patients (23%) experienced AKI according to the KDIGO criteria. Patients who developed AKI were older than other patients in the cohort (62,4 ± 14,2 years) and there was a male predominance. 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 and in-hospital prognostic indices of all 89 patients who were included in the study can be found in supplementary document-1.

Twenty-nine patients had AKI on admission. Kidney functions in the 15 of on-admission AKIs were rescued by fluid resuscitation and were accepted to have pre-renal AKI (51%). Two (6%) of the patients had high creatine kinase (CK) levels (5243 and 1045 IU/L), thus accepted to have rhabdomyolysis related AKI. Six patients (20%) were hypoxemic while remaining six patients (20%) had either coagulopathy or the features of cytokine release syndrome. COVID severity of the patients with AKI on admission was mainly moderate and just 7 of them (24%) had severe or critical disease.

Among patients who experienced AKI during the 1st week (n:33), eight patients had pre-renal AKI which was cured by relevant fluid therapy (24%). Seven patients (21%) had hypoxemia concomitant with the AKI diagnosis. Twelve patients either had coagulopathy or the features of cytokine release (36%). AKI in three patients (9%) was thought to be related to drug toxicity and was cured by stopping the offending agents.

Three patients (9%) had high CK values (1214, 1198 and 3690IU/L) pointing out to rhabdomyolysis as the etiology. When COVID severity of the patients was evaluated, 14 of these 33 patients (42%) were classified as severe or critical.

Among patients who had AKI with the start of 2nd week (n:27), 18 patients were in the hyper-inflammation state (66%). Three patients (11%) had pre-renal AKI, five patients (18%) had drug toxicity and one patient (3%) had rhabdomyolysis (CK: 1977 IU/L). Clinical evaluation pointed out to severe or critical illness in 22 of these 27 patients (81%).

Patients of three groups 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-1. 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. 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 (figure-2). AKI related prognostic indices of patients in three groups can be found in table-2.

Table-1: Characteristics and initial laboratory values of patients of three groups.

	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**

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 between AKI in the 1^{st} week and AKI after 7^{th} day.

** 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	16	18	21	0,123
DM				
HT	4	10	9	0,189
Malignancy	9	11	11	0,729
IHD/HF	3	4	6	0,398
	8	7	5	0,702
AKI stage 1	26	26	16	0,058
AKI stage 2	3	3	7	
AKI stage 3	0	4	4	
Severe or critical COVID-19 (n, (%))	7 (24)	14 (41)	22 (81)	0,000
Duration of hospital stay (days)	11,38 ± 6,41	11,85 ± 7,9	17,33 ± 6,58	0,003*
ICU requirement (n, (%))	5 (17)	9 (27)	17 (62)	0,001*
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 7th day.

Although there is no specific validated treatment for COVID-19 yet, some antiviral therapies were applied depending on the institutional availabilities. These can be found in supplementary document-2. Hemodialysis as renal replacement therapy (RRT) had to be performed in 6 patients who developed AKI later 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.

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-3). Although it couldn't reach the statistical significance, peak ferritin levels were also higher for patients who developed AKI later.

Table-3: Comparison of changes in the inflammatory markers and lymphocyte counts 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

AKI: Acute kidney injury

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

Survivors and non-survivors among patients who developed AKI were also compared. In-hospital stay length was not different for survivors (12,9 ± 7,48) and non-survivors (14,5 ± 7,6) (p=0,397). Those who died were older (68,14 ± 11,81) than those who didn't (60,6 ± 14,5) (p=0,03). Patients who survived had similar diabetes or hypertension rates as patients who didn't, while concomitant malignancies were more frequent in patients who died.

AKI had 23% mortality in our patients who had eGFRs above 60 ml/min/1,73 m^2 according to the baseline creatinine values. Baseline creatinine levels 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 4).

Table-4: Comparison of survivors and non-survivors. Laboratory values are initial values on hospital admission date.

	Survivors (n=68)	Non-survivors (n=21)	p
Age	60,6 ± 14,5	68,1 ± 11,8	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)	82,86 ± 16,15	82,03 ± 14,95	0,835
Peak creatinine (mg/dL)	1,48 ± 0,49	2,51 ± 0,87	0,000
AKI developed on (days)	5,93 ± 5,17	8,94 ± 5,71	0,053
AKI duration (days)	2,66 ± 3,45	5,76 ± 4,61	0,001
MAP (mmHg)	89,0 ± 14,1	88,0 ± 12,6	0,784
Hemoglobin (g/dL)	12,7 ± 1,5	10,8 ± 1,9	0,000
Lymphocytes (per µL)	1455 ± 667	819 ± 258	0,000
CRP (mg/L)	67,9 ± 68,5	127,3 ± 89,8	0,002
Prokalsitonin (ng/mL)	0,30 ± 0,92	0,63 ± 0,70	0,132
CK (IU/L)	292 ± 762	213 ± 260	0,651
LDH (IU/L)	357 ± 189	608 ± 558	0,002
Ferritin (ng/mL)	515 ± 475	1059 ± 757	0,000
D-dimer (mg/L)	1,04 ± 1,01	4,7± 5,09	0,000
Uric acid (mg/dL)	5,9 ± 2,1	4,8 ± 2,1	0,056
Duration of hospital stay (days)	12,9 ± 7,4	14,5 ± 7,6	0,397

AKI: Acute Kidney Injury, eGFR: estimated glomerular filtration rate, MAP: mean arterial pressure, CK: creatine kinase, LDH: lactate dehidrogenase

Discussion

We previously found that reduced eGFR was related to mortality in COVID-19 patients [11]. 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.

AKI has been proposed as a poor prognostic factor for COVID-19 [12]. In a recent meta-analysis, it was found that 52% of patients who developed AKI died [13]. Another study showed that, chronic kidney disease and male sex were independent predictors of AKI severity [14]. However, as seen in our cohort, consequences of all AKIs in COVID-19 are not the same. There may be different etiologies resulting in AKI in different phases of the disease.

Previously, AKI incidence has been reported to be between 0,5% to 13% [15-18]. AKI incidence may be higher in severe COVID-19 cases [19] 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 [20]. However, time elapsed from disease onset to mechanical ventilation was not made clear in that study. 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 responsive to relevant fluid therapies. 51% of our patients who had AKI upon admission responded to fluid therapy. There were still AKIs related to other etiologies on admission, mostly because of late referrals to our center. It may not possible to differentiate between pure coagulopathy and cytokine release as both pathologies may be intertwined with each other [21, 22]. However, 18 of the 27 patients who had AKI starting from the 2nd week of the disease had cytokine release syndrome, coagulopathy and/or persistent hypoxemia. Patients who have severe or critical clinical picture upon admission tend to develop AKI later, with the start of 2nd week. Although stage 1 AKI was predominant among patients who developed AKI, rate of stage 1 AKI decreased gradually for AKIs seen later in the disease course (89% upon admission, 59% after 7^{th} day). Patients who needed renal replacement therapy also increase for AKIs that develop after 7^{th} 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 proximal tubular injury as well as podocytopathies [23, 24]. 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 [25]. 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 [26].

Differences in outcomes of the patients may be attributed to different etiologies that caused AKI in different stages of the disease. As we didn't perform kidney biopsies on our patients, the clinical progress and response to the planned interventions guided the etiologies we defined. Missing urinary ultrasounds and missing urinalysis in most of our patients might be accepted as other limitations of our study.

On admission AKIs were mainly pre-renal AKIs that were related to fluid disturbances (51%). This decreased to 21% for 1st week AKIs and to 11% for AKIs starting from the 2nd week. Inflammation-mediated injury was around 20% for on admission AKIs and increased to around 66% for AKIs in the 2nd week.

Our findings indicate that around 23% of patients who are hospitalized with a confirmed COVID-19 diagnosis developed AKI. 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 exclusive prognostic value of AKI. Although AKI had an overall mortality rate of 23%, the prognosis was different in relation with the time of AKI. Mortality rate was 13% for patients who had AKI on admission, 15% for those who developed AKI in the first week and 44% for those who developed AKI starting from the 2nd 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 [27]. 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. 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% [11]. However, mortality reaches as high as 46% in patients who develop AKI later. Higher immune response may explain worse prognosis for late AKIs. Drug toxicity should not be underestimated in AKIs that develop during the disease course. Three patients in the first week and five patients after 7th day developed drug-related AKIs, which were rescued by stopping the offending agents. Drugs that resulted in AKI were non-steroidal anti-inflammatory drugs, antibiotics (e.g. amikacin) and contrast agents that were used for chest computer tomography scans.

Conclusions

AKI in COVID-19 is not of one kind. When developed, AKI should be evaluated in conjunction with the disease stage. Early AKI is mainly due to pre-renal causes and may be more suitable to be responsive to fluid resuscitation. However, AKI developing later is related to immunological response and has worse prognosis.

Declarations

Funding

None

Conflicts 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 COVID-19 research committee (nr. 2020-05-08T17_38_07).

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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Figures

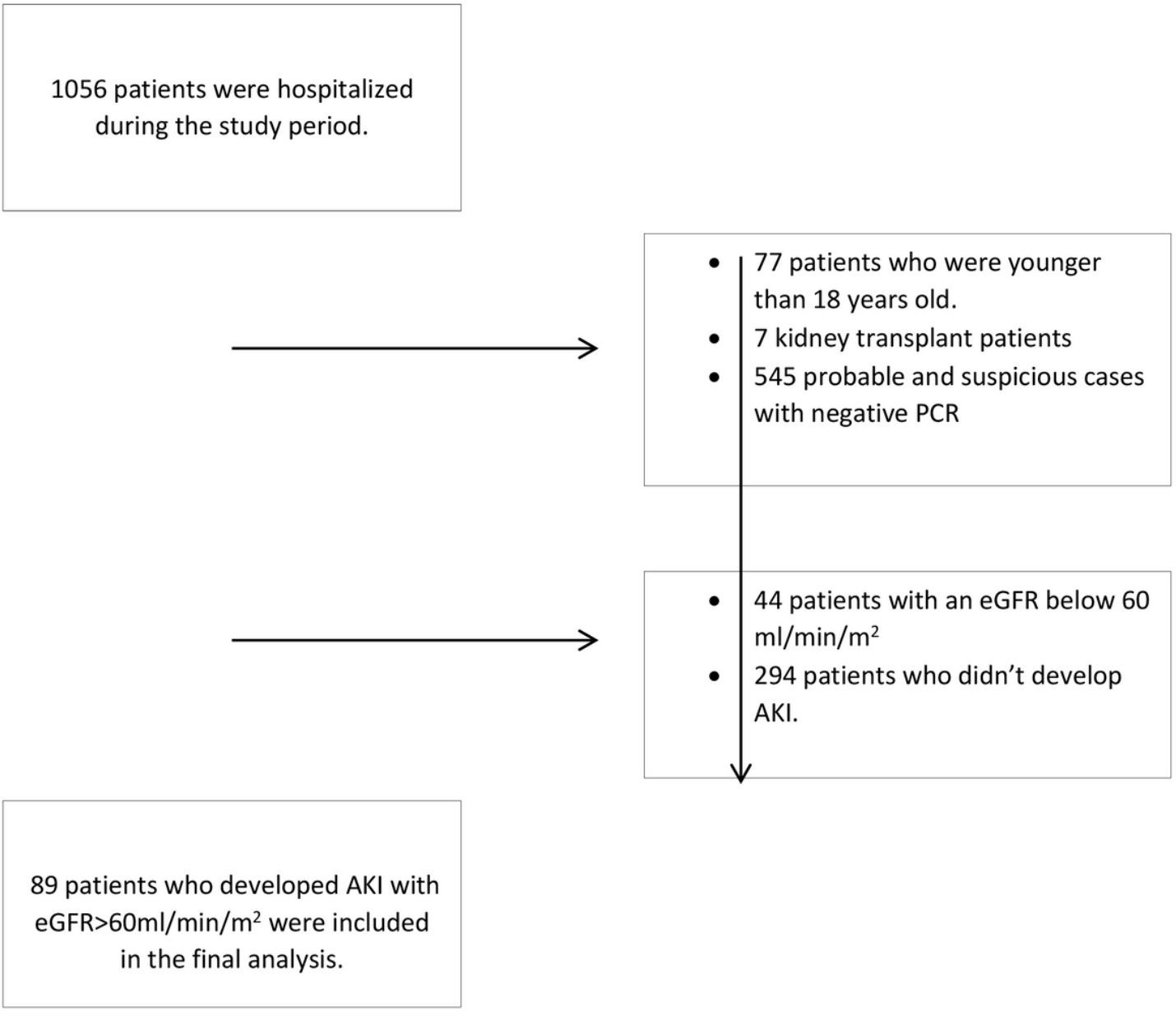
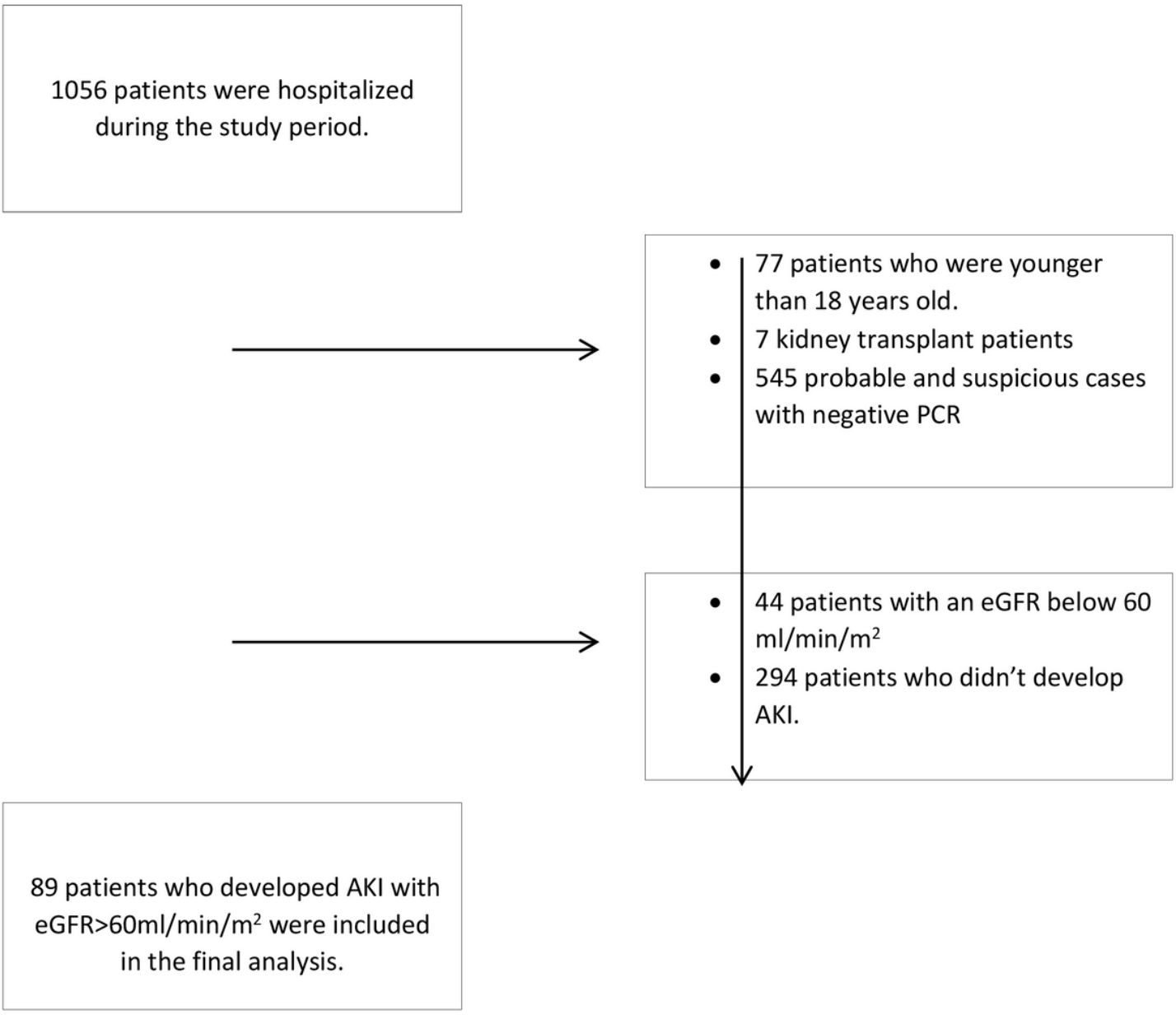


Figure 1

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



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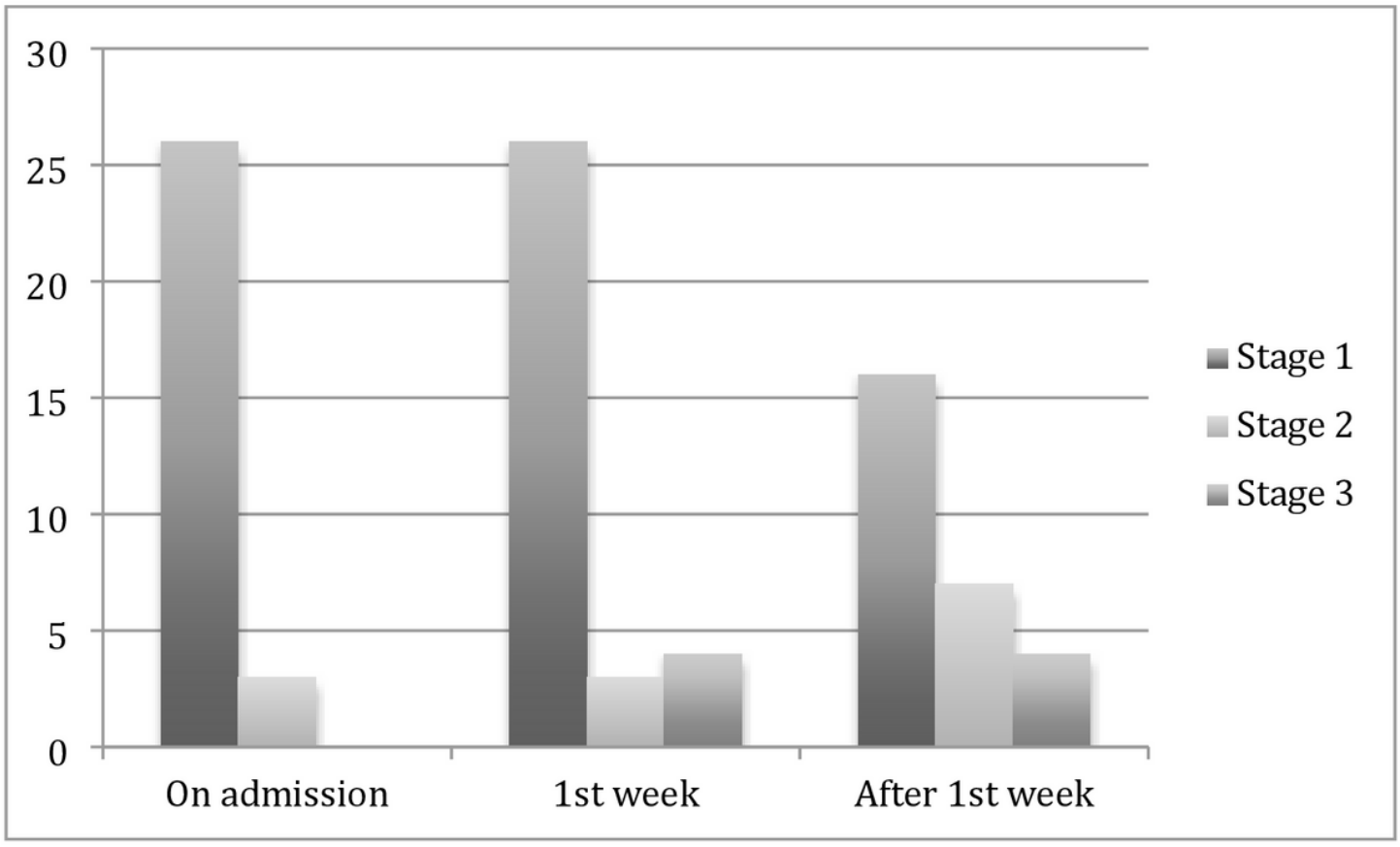
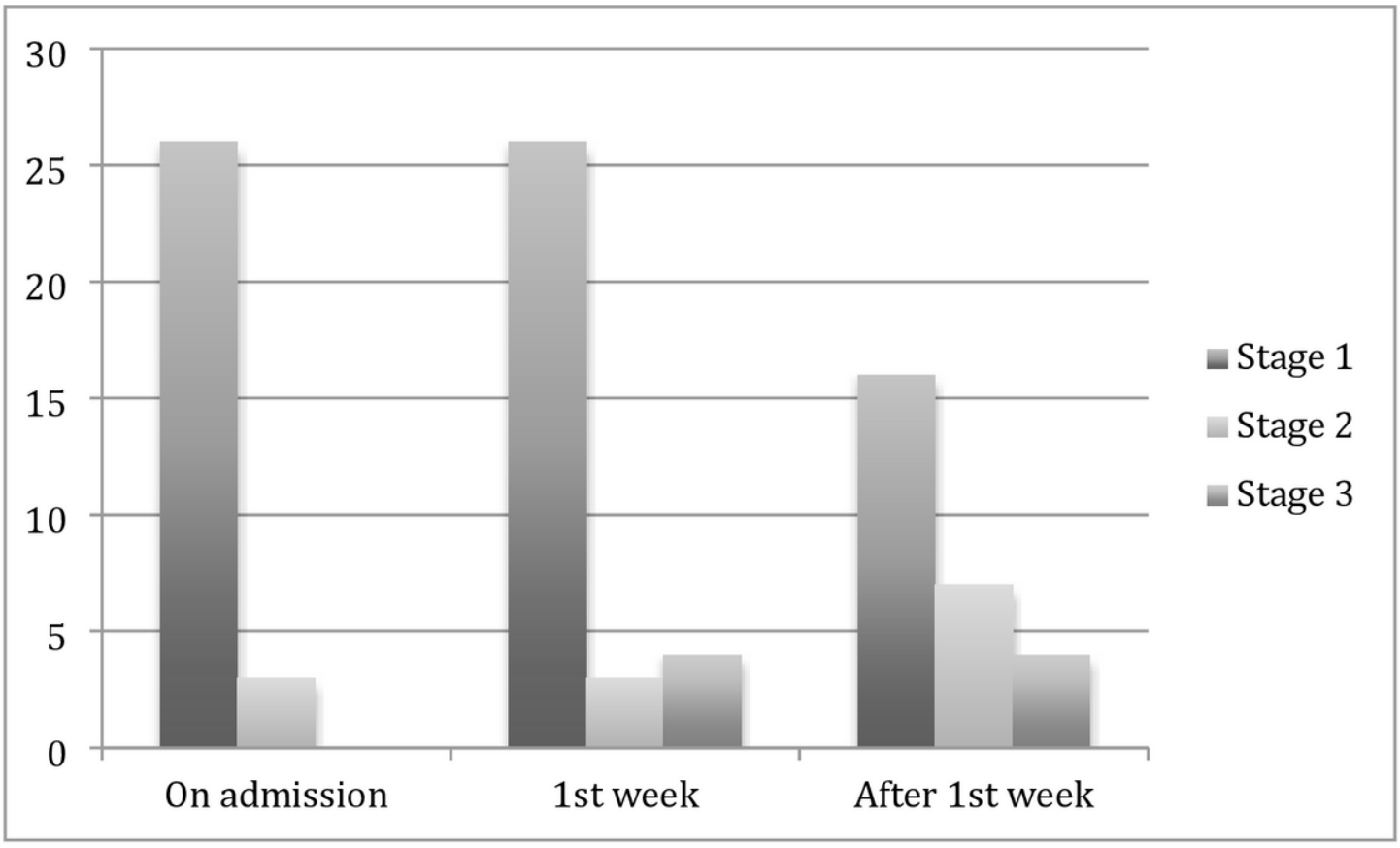


Figure 2

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



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

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