The effect of resolution time of acute kidney injury on clinical outcomes

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ABSTRACT

Acute kidney injury (AKI) is a frequent and complex disease. It is not clearly defined whether its duration is related to adverse outcomes. We determined the effect of AKI resolution time on patient's clinical outcomes. A prospective cohort of hospitalized patients with AKI by AKI network (AKIN) creatinine criteria was included. Variables for prognosis and follow-up were analyzed. One hundred and thirteen patients were included in the study. Seventy-seven (68.1%) were males, mean age 55 years (range, 16–76 years), and 48 (42.5%) were diabetic. The most common cause of AKI was sepsis (31%). AKI resolution time ≤2 days and >2 days was seen in 47 (41.6%) and 66 (58.4%) of the cases, respectively. AKI resolution time >2 days was common in older patients (66.24 ± 17.6 year vs. 47.16 ± 12.32 year, P = 0.004), with the use of mechanical ventilation (27% vs. 4%, P = 0.02) and vasopressors (41% vs. 11%, $P \leq 0.01$); it was associated with increased mortality (47% vs. 4%, $P \leq 0.01$), and a discharge estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (52% vs. 2%, P = 0.01), than in patients with resolution time ≤2 days. Survival rate was significantly worse in patients with a resolution time >2 days. By multivariate logistic step-wise regression analysis, AKI >2days, vasopressor use, and AKIN stage 2–3 were independently associated with higher mortality. AKI >2 days and vasopressor utilization were independently associated to an eGFR <60 ml/min/1.73 m^2 at the time of discharge. We conclude that AKI resolution time >2 days is linked to adverse clinical outcomes.

Key words: Acute kidney injury, mortality, prognosis, resolution time, sepsis

Introduction

Acute kidney injury (AKI) is the real epidemic of nephrology[1] and its frequency is on the rise.[2] It is present in up to 5% of hospital admissions and in 5% to 20% of hospitalized patients.[3,4] It has been reported that close to 25% of patients in Intensive Care Units (ICU) develop this complication,[3] and half of them would require renal replacement therapy.[5] The risk of developing AKI during hospitalization is high,[4] and mortality can reach between 50% and 70%.[6-8] In addition, AKI is associated with increased hospitalization expenditures, poor quality of life, and higher hospital complications.[9-13]

AKI has been traditionally diagnosed by the sudden rise of serum creatinine (SCr) and reduction of urinary output by risk, injury, failure, loss, and end-stage renal disease (RIFLE)[14] and AKI network (AKIN)[15] classifications, and more recently by kidney disease improving global outcomes (KDIGO) guidelines.[16] These classification systems do not assign a value to the time of AKI resolution. In the present study, we evaluate the effect of AKI resolution time on patient's clinical outcomes.

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Materials and Methods

From January 2009 to January 2010, a prospective cohort study was conducted in hospitalized patients diagnosed with AKI by the AKIN SCr criteria.[11] Patients older than 16 years of age, with serial SCr, who met the AKIN criteria, were included in the analysis. Baseline SCr was considered when the patient had a SCr of at least 3 months before hospitalization; in those cases without a baseline SCr, it was estimated using the Modification of Diet in Renal Disease, assuming a baseline estimated glomerular filtration rate (eGFR) of 75 ml/min/1.73 m^2, as suggested by KDIGO guidelines.[12] The peak SCr during hospitalization was chosen to classify AKIN stage. A prolonged resolution time was defined as >2 days for SCr to return to baseline value.[9] An eGFR <60 ml/min/1.73 m^2 at the time of discharge was considered abnormally low. Patients with baseline chronic kidney disease (eGFR <60 ml/min/1.73 m^2) and without serial SCr readings, and those with a history of end-stage renal disease or kidney transplantation were excluded from the analysis. Only the first episode of AKI was recorded. Resolution of AKI was defined as an eGFR ≥60 ml/min/1.73 m^2 on follow-up.

Demographic information, laboratory results, as well as clinical evolution data were obtained from medical records. Demographic information is presented as simple relative frequencies. Pearson's Chi-square or Fisher's exact tests were used when appropriate to compare frequencies for nominal qualitative variables between two groups or to evaluate the homogeneity in the distribution of variables in three or more groups. Student's *t*-test was used to compare continuous variables between two groups: To compare three or more groups, analysis of variance was used.

All values for *P* in comparisons and correlations were calculated and considered as significant when $P < 0.05$. The relative risk and confidence intervals (CIs) were estimated at 95% (CI 95%). Survival analysis was determined by Kaplan–Meier analysis. Multivariate stepwise logistic regression analysis was employed to evaluate the association between AKI resolution time and mortality. PASW Statistics software version 18.0 and SPSS version 15.0 (SPSS Inc., Chicago IL) were used in all the calculations.

Results

One hundred and thirteen patients were included in the analysis [Table 1]. None of the patients were on vasopressors or mechanical ventilation at baseline. About 77 (68.1%) were males, with a mean age of 55 years (range, 16–76 years); 48 (42.5%) were diabetic, 53 (46.9%) had hypertension, 2 (1.7%) had malignancies, and 11 (9.73%) had used analgesics. The most common cause for AKI was sepsis, reported in 35 (31%) of the cases. AKI severity was staged according to the AKIN classification. As expected, AKIN III was associated to prolonged hospital stay, greater use of mechanical ventilation and vasopressors, increased mortality, and a discharge eGFR <60 ml/min/1.73 m^2 [Table 2]. AKI resolution time (≤2 days or >2 days) was seen in 47 (42%) and 66 (58%) patients, respectively. In patients with a resolution time ≤2 days, 27 (67%) had AKIN I, 18 (34%) AKIN II, and 2 (10%) AKIN III. Resolution time >2 days was seen in 66 (58%) patients, 13 (33%) AKIN I, 35 (66%) AKIN II, and 18 (90%) AKIN III. A total of 33 (29%) patients died.

Table 1: Demographic and clinical characteristics of patients

Characteristic	*n*=113
Gender	
Male (%)	77 (68.1)
Age (years)	55±9.0
Diabetes (%)	48 (42.5)
Hypertension (%)	53 (46.9)
Neoplasm (%)	2 (1.76)
Use of analgesics (%)	11 (9.73)
Sepsis (%)	35 (31.0)
CHF (%)	25 (22.8)
DKA (%)	15 (12.7)
Dehydration (%)	10 (8.8)
Hypovolemic shock (%)	9 (7.9)
HHS (%)	5 (4.4)
SLE (%)	3 (2.6)
Rhabdomyolysis (%)	3 (2.6)
BPH (%)	2 (1.8)
Hypertensive emergency (%)	2 (1.8)
UTI (%)	2 (1.8)
Hepatorenal syndrome (%)	2 (1.8)

CHF: Congestive heart failure, DKA: Diabetic ketoacidosis, HHS: Hyperglycemic hyperosmolar state, SLE: Systemic lupus erythematous, BPH: Benign prostatic hyperplasia, UTI: Urinary tract infection

AKI resolution time >2 days was more commonly associated to old age (66.24 ± 17.6 year vs. 47.16 ± 12.32 year, RR 1.16 CI 95% 1.05–1.29 $P = 0.004$); to the use of mechanical ventilation (27% vs. 4%, RR 4.82 CI 95% 1.27–18.3, $P = 0.02$) and vasopressor use (41% vs. 11%, RR 3.31, CI 95% 1.44–7.62, $P \leq 0.01$); it was also associated to increased mortality (47% vs. 4%, RR 9.28, CI 95% 2.38–36.05, $P \leq 0.01$), and a discharge eGFR <60 ml/min/1.73 m^2 (54.5% vs. 2%, $P = 0.01$) than in patients with resolution time ≤2 days. Eight (12%) patients with a resolution time >2 days required dialysis [Table 3].

Survival rate was significantly worse in patients with a resolution time >2 days ($P < 0.01$) [Figure 1]. By multivariate logistic step-wise regression

Table 2: Patients with acute kidney injury by acute kidney injury network stages and clinical outcomes

Clinical outcome	Total (*n*=113)	AKIN I (*n*=40)	AKIN II (*n*=53)	AKIN III (*n*=20)	*P*
Age, years	55±9.0	53±8.51	53±9.43	64±16.23	0.12
Male gender (%)	77 (68)	27 (67)	34 (64)	16 (80)	0.05
Hospital stay >7 days (%)	55 (49)	10 (25)	31 (58)	14 (70)	0.02
Mechanical ventilation (%)	20 (17)	4 (10)	6 (11)	10 (50)	0.01
Use of vasopressors (%)	32 (28)	8 (20)	8 (16)	16 (80)	0.01
Dialysis support (%)	8 (7)	0	0	8 (40)	
Death (%)	33 (29)	4 (10)	15 (28)	14 (70)	0.01
eGFR <60 ml/min/1.73 m^2 (%)	43 (38)	10 (25)	15 (28)	18 (90)	0.01
AKI resolution time ≤2 days, *n* (%)	47 (41)	27 (67)	18 (34)	2 (10)	0.001
AKI resolution time >2 days, *n* (%)	66 (59)	13 (33)	35 (66)	18 (90)	0.001

AKI: Acute kidney injury, AKIN: Acute kidney injury network, eGFR: Estimated glomerular filtration rate

Table 3: Resolution time and clinical course of acute kidney injury

Clinical outcome	≤2 days (*n*=47)	>2 days (*n*=66)	RR (CI 95%)	*P*
Age (years)	47.16±12.32	66.24±17.6	1.16 (1.05-1.29)	0.004
Mechanical ventilation, *n* (%)	2 (4)	18 (27)	4.82 (1.27-18.3)	0.02
Use of vasopressors, *n* (%)	5 (11)	27 (41)	3.31 (1.44-7.62)	<0.01
Dialysis *n* (%)	0	8 (12)		
Death, *n* (%)	2 (4)	31 (47)	9.28 (2.38-36.05)	<0.01
Discharge serum creatinine >1.5 mg/dl	1 (2)	34 (52)	9.48 (2.26-39.47)	<0.01

RR: Relative risk, CI: Confidence interval

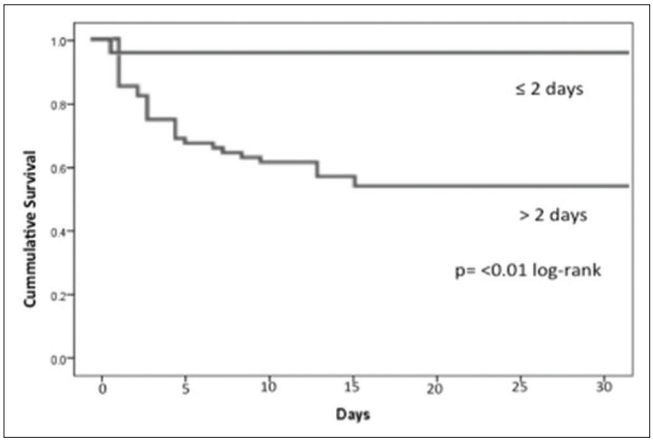

Figure 1: Thirty days survival time for acute kidney injury according to resolution time

analysis, AKI >2 days (odds ratio [OR] 8.67, 95% CI 1.09–64.48; $P < 0.05$), vasopressor use (OR 14.72, 95% CI 2.72–82.63; $P < 0.05$), mechanical ventilation (OR 18.54, 95% CI 2.21–155.09 $P < 0.05$), and AKIN stage 2–3 (OR 8.75, 95% CI 1.03–74.27; $P < 0.05$) were independently associated with higher mortality. AKI >2 days (OR 54.93, 95% CI 6.76–446.12; $P < 0.05$) and vasopressor utilization (OR 6.42, 95% CI 1.81–22.67; $P < 0.05$) were independently associated to an eGFR <60 ml/min/1.73 m^2 at the time of discharge.

Discussion

The duration of AKI has been linked to adverse clinical evolution and could provide additional information to the increase in SCr or the decrease of urinary output. Current classification systems such as RIFLE,[14] AKIN,[15] and KDIGO[16] have an implicit dose-response relationship between the AKI severity and prognosis. However, these systems do not take into account the time of recovery for AKI.[17] AKI resolution time has been associated to increased hospitalization expenditures, poor quality of life, higher hospital complications, and elevated death rate.[9,13-16] A fast resolution could suggest that the cause was not an intrinsic kidney injury since regeneration of the tubular damage as well as cellular differentiation usually take more than 48 h.[18,19]

In our study, a prolonged resolution time was associated to worse clinical outcomes such as the need for mechanical ventilation, the use of vasopressors, longer hospital stay, a discharge eGFR <60 ml/min/1.73 m^2, and higher mortality. As expected, when grouping patients by AKIN stages, an elevated mortality rate was found as AKIN stages progressed. However, in addition to AKI severity, a greater mortality rate was observed in patients with AKI >2 days.

The effect of AKI duration on long-term mortality has been examined previously. Persistent AKI is associated to increased mortality compared to patients without AKI.[20] Brown *et al*., in a postheart surgery cohort, confirmed that AKI duration in days is associated to a worse long-term survival rate.[21] Our follow-up period of 30 days, at most, does not allow us to perform long-term analysis, but it is reasonable to assume that a lengthy resolution is associated to a worse clinical course and survival rates. In addition, we found a significant correlation between age and a resolution time >2 days for AKIN AKI, similar to observations made in other studies where

age plays a key role in the clinical evolution, particularly in patients over 65 years; age is a nonmodifiable risk factor for many illnesses, among them AKI. This risk has been related to structural and functional changes in the kidney.[16] In patients over 65 who develop AKI in acute care settings, only 40% recovered after 28 days, 50% died at 60 days, and only a few survived after 1 year.[21] Even with a slight SCr increase, older patients with an acute myocardial infarction and AKI have significantly high long-term mortality.[22] When divided by AKI duration (≤2 days vs. >2 days), we found a significant difference in the eGFR at the time of discharge. Patients with a duration >2 days had a significant risk of presenting an eGFR <60 ml/min/1.73 m^2 at the time of discharge. In addition, the resolution time >2 days was significantly associated to the greater use of mechanical ventilation. The kidney and lung have direct interactions and it is frequent for both organs to fail and dramatically increase mortality.[23] Although we cannot determine causality, since no invasive measurements were made for lung hemodynamics, this link points toward the evidence of increased inflammatory trafficking and increased pulmonary vasculature permeability[24,25] as an added result of mechanical ventilation. Alkandari *et al*. demonstrated in a retrospective cohort of children that AKI is a risk factor for prolonged mechanical ventilation, as well as being linked to more hospital days and increased mortality.[26] In addition, a resolution time >2 days was associated to an increased use of vasopressors. Although we cannot establish a cause-effect relationship, the clinical impact is a worse hemodynamic scenario. In a critically ill patient, self-regulation of the kidney vasculature is diminished and varies according to the cardiac output.[23,27] The relation between hemodynamic changes and progression of AKI in sepsis is not well known. Poukkanen *et al*. demonstrated that during septic shock, a median arterial pressure >73 mmHg is linked to a lower incidence of AKI.[28] Plataki *et al*., in an observational cohort of patients with septic shock, reported that the use of phenylephrine was significantly linked to the development of AKI, unlike the use of norepinephrine and vasopressin.[29]

Our study presents several limitations. First, the low number of patients could limit AKI resolution time and outcomes. Generalization of our findings and the short follow-up time does not allow for long-term analysis of AKI evolution. Second, we did not measure urine output or urine biomarkers. We only took into account SCr AKI criteria, which could underestimate the diagnosis of AKI; finally, we did not perform kidney biopsies to demonstrate the presence of acute tubular necrosis and its severity, which could have resulted in longer duration of AKI.

Conclusion

AKI resolution time >2 days was associated to a higher mortality rate and to a discharge eGFR <60 ml/min/1.72 m^2. The duration of AKI seems to be independently linked to adverse clinical evolution, and could provide additional information to AKI severity. Further studies can approach AKI in two dimensions: The magnitude of the SCr increase and the resolution time. This data need to be validated in other AKI settings and used in future clinical studies.

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Conflicts of interest
There are no conflicts of interest.

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