Original Article

Clinical Predictors of Mortality of Patients with Acute Kidney Injury Requiring Renal Replacement Therapy

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Objective: Acute kidney injury (AKI) is frequently encountered around 40% in critically ill patients and associate with a high mortality. The objective was to assess the clinical predictors for 28-day mortality in AKI patients requiring renal replacement therapy (RRT).

Materials and Methods: This is a retrospective cohort study from prospectively collected data. AKI patients requiring RRT were included. We collected demographic and laboratory data within 24 hours before the initiation of RRT. We excluded patients with pre-existing chronic kidney disease stage 5 and AKI patients requiring peritoneal dialysis. We compared clinical characteristics and analyzed the predictors of mortality of survivors and non-survivors according to 28-day mortality.

Results: We included 122 AKI patients requiring RRT. Mortality rate at day 28 and 90 after AKI diagnosis were 59% (95% confidence interval [CI] 49.7 to 67.8) and 72.1% (95% CI 63.3 to 79.9). On multivariable analysis, clinical predictors for 28-day mortality were serum creatinine before RRT (hazard ratio [HR] 0.84, 95% CI 0.74 to 0.95), SOFA score before initiation of RRT (HR 1.10, 95% CI 1.03 to 1.18), presence of vasopressors before initiation of RRT (HR 2.80, 95% CI 1.03 to 7.64), serum lactate >4 mmol/L before initiation of RRT affected the first 10 days of survival time (HR 2.17, 95% CI 1.03 to 4.57). However, serum lactate >4 mmol/L before initiation of RRT did not affect the after 10 days of survival time (HR 0.99, 95% CI 0.37 to 2.66).

Conclusion: AKI patients with shock and multiorgan failure had a lower chance of survival. In addition, a lower serum creatinine that represents a high fluid overload can predict death as well.

Keywords: Acute kidney injury; Lactate; Mortality; Renal replacement therapy; Vasopressors

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Acute kidney injury (AKI) is a syndrome characterized by an abrupt deterioration of renal function resulting in a sharp increase in serum creatinine (SCr) and/or decrease in urine output. Advanced severity of AKI leads to the accumulation of nitrogenous metabolites and water electrolyte imbalances, which harmfully affects distant organ functions such as lungs, heart, and brain(1). Incidence of AKI is up to 20% of hospitalized patients(2) and 30 to 60% of critically ill patients(3-5).

Patients with AKI has a high mortality rate ranging 25 to 60%(2,3,5) and there is a stepwise increase of mortality with increase of AKI severity, particularly stage 2 and 3 AKI(6,7). These rates remained virtually unchanged despite the optimization of care(8). In the literature, risk factors associated with death of critically ill patients with AKI include old age, prolonged hospitalization, a higher severity of illness, presence of comorbidities, oliguria, hypovolemia, metabolic acidosis, sepsis, multiple trauma, use of vasoactive drugs and respiratory failure(9). Timing and intensity of renal replacement therapy (RRT) do not have a beneficial effect on mortality(10-13).

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Although various modalities of RRT are generally safe, there are some potential adverse events associated with RRT such as hypotension, bleeding, allergic reactions, and complications of vascular access. Because RRT is costly and consumes healthcare resources, patient selection for RRT is a crucial step. Predictive factors and a model for death should be investigated. However, clinical predictors for death in AKI patients requiring RRT are not fully elucidated. The aim of this study is to determine clinical predictors associated with mortality in AKI patients requiring RRT in intensive care units.

Materials and Methods

We conducted a retrospective study from prospectively collected data submitted to the epidemiological study of organ failure and support in the intensive care unit of Srinagarind Hospital, Khon Kaen University, Thailand. from June 1, 2014 to May 31, 2015. Our hospital is a tertiary academic referral center. We included all adult (>18 years old) patients admitted to the medical intensive care unit (MICU) or a cardiac ICU (CCU) with diagnosis of AKI requiring RRT. We excluded patients with pre-existing chronic kidney disease stage 5 (defined as an estimated glomerular filtration rate [GFR] <15 mL/min/1.73 m^2 or on chronic dialysis) and AKI patients requiring peritoneal dialysis. We compared clinical characteristics and analyzed the predictors of mortality of survivors and non-survivors based on 28-day mortality.

This study was approved by the Khon Kaen University Ethics Committee for Human Research (Approval Number: HE581457). Informed consent was waived by the Institutional Review Board because this study is the retrospective study of the data analysis using information contained in medical charts and records, which were completely anonymized.

Data collection and definition

AKI was defined according to the Kidney Disease Improving Global Outcomes 2012 guidelines, using SCr and urine output criteria[14]. We divided etiologies of AKI in to 4 groups: (1) prerenal AKI is renal hypoperfusion that causes renal dysfunction from any causes; (2) intrinsic renal AKI is an abnormal renal pathology such as glomerulus, renal tubule, renal interstitium, or renovascular cause renal dysfunction; (3) sepsis-induced AKI is a patient who has sepsis or septic shock cause renal dysfunction; (4) postrenal AKI is a condition of AKI due to obstructive uropathy.

Demographic data were recorded including; age, sex, body mass index, ICU diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHEII) score at ICU admission, Sequential Organ Failure Assessment (SOFA) score at ICU admission, Charlson comorbidity index and baseline SCr. Modes of RRT including intermittent hemodialysis and continuous renal replacement therapy (CRRT) were collected. Timing of RRT initiation since hospital admission, ICU admission and AKI diagnosis were also recorded. Clinical characteristics within 24 hours before initiation of RRT were recorded including presence of acute respiratory failure, shock requiring vasopressor, pulmonary edema, acute coronary syndrome, SOFA score, urine volume and cumulative fluid balance. The worst laboratory parameters were collected within 24 hours before initiation of RRT including blood urea nitrogen (BUN), SCr, serum bicarbonate, arterial blood gas, base excess, serum albumin and serum lactate.

Acute respiratory failure is defined as a patient who requires invasive mechanical ventilation or non-invasive ventilation for ≥24 hours[15,16]. Shock is defined as a patient having mean arterial pressure <65 mmHg along with tissue hypoperfusion including cold clammy skin, mottled skin, altered mental status or decrease of urine output[17]. Sepsis and septic shock are defined according to the 2012 surviving sepsis campaign[18]. The primary outcome of interest is the mortality at day 28 after diagnosis of AKI.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) or median (interquartile range [IQR]) as appropriate. Categorical variables were expressed as counts and percentages (%). Study population was divided into two groups (survivors and non-survivors at day 28 after diagnosis of AKI). Two sample t-test and Wilcoxon rank-sum were used to compare continuous variables as appropriate between survivors and non-survivors. Chi-square test and Fisher's exact test were used to compare categorical variables as appropriate between two groups.

Multiple imputation

There were five predictors that had missing values more than 10%, which could produce biased estimates and lead to invalid conclusions if the complete case analysis were performed. Therefore, missing data was handled using multiple imputation by chained equations and analyzed 50 imputed data sets in order to complete Cox proportional hazard regression models[19]. The imputation processes included variables that were incorporated into both regression models and also included outcomes variables. The variables included mortality at day 28 and day 90, survival time at day 28 and day 90, mode of RRT, etiologies of AKI, severity of illness, and clinical and laboratory results before RRT (acute respiratory failure, shock, vasopressor, PaO_2/FiO_2 ratio, pH, base excess, albumin, cumulative fluid, urine output).

The number of imputed datasets was based on a quadratic function of the fraction of missing information[20]. Calculations of missing values were done in R version 4.0.0 using automatic predictor selection tool of the mice 3.8.0 package.

Derivation of the survival model

A Cox proportional hazards (PH) model and an extended Cox model were used to examine the association between clinical predictors and survival time at day 28 after diagnosis of AKI. The PH assumption was tested using Schoenfeld residuals. The lactate variable violated the PH assumption; hence, the extended Cox model with Heaviside functions were applied. To build multivariable regression model, univariable regression was first performed. The variables significant at p<0.2 by univariable analysis were identified as potential predictor variables and entered into a multivariable regression model.

Variable selection techniques included two steps. The first step involved performing backward and forward stepwise model selection based on the Akaike information criterion separately on each imputed dataset, followed by the construction of a new supermodel that contained all variables that were present in at least a half of the initial models. Second, a special procedure for backward elimination was applied to all variables present in the supermodel. The pooled likelihood ratio p-value was calculated. If the largest p-value >0.05, the corresponding variable was removed, and the procedure was repeated on the smaller model. The procedure stops if all $p \leq 0.05$. The model estimates and standard errors were combined into a single set of results using Rubin's rules. The model performance was evaluated using Harrell's discrimination index (or C-statistics). All the statistical analyses were performed using R software version 4.0.0. The level of statistical significance was set at $p<0.05$ (two tailed).

Results

Of the 572 patients who were admitted to MICU and CCU, 332 patients (58%) developed AKI. RRT was initiated in 124 patients; however, we excluded 2 patients who received acute peritoneal dialysis. Thus, a total of 122 patients were included as AKI requiring RRT. Flow chart was shown in Figure 1. Mean patient age was 57.4±18.8 years. Among 122 patients, 108 (88.5%) were diagnosed at medical ICU and 14 (11.5%) were diagnosed at CCU. Sepsis was the most common cause of AKI (97 [79.5%]). Of 122 patients, 105 patients (86.1%) underwent CRRT and 17 patients (13.9%) underwent intermittent hemodialysis. Median time from hospital admission to RRT initiation was 2 days (IQR 0 to 10.8) and median time from AKI onset to RRT initiation was 1 day (IQR 0 to 1.8). Among 122 patients, 72 patients (59%, 95% confidence interval [CI] 49.7 to 67.8) did not survived by day 28 and 88 patients (72.1%, 95% CI 63.3 to 79.9) by day 90 after AKI diagnosis. Incident rate of death at day 28 was 1.08 patients per one person month (95% CI 0.85 to 1.36). Median survival time was 21 days (95% CI 11 to 29).

The percentages of missing data across 15 variables that were put in the full regression model varied from 0 to 46.7%. The percentages of baseline SCr and serum lactate before RRT were the two most common missing variables, 46.7% and 32.8%, respectively (Table 1 and 2).

Baseline clinical characteristics between survivors and non-survivors at day 28 after diagnosis of AKI were shown in Table 1. The non-survivors had a significantly higher

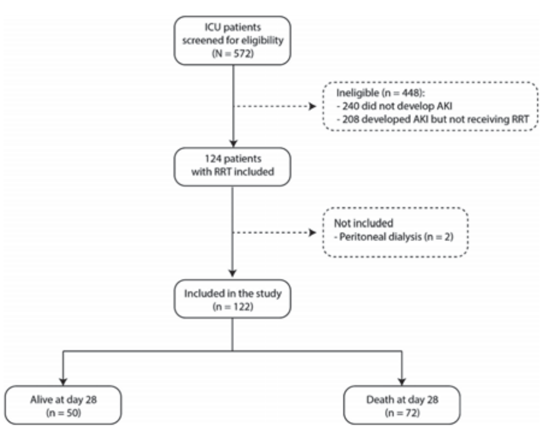

Figure 1. Flow diagram.

severity of illness at the day of ICU admission (mean SOFA score 13.7 vs. 10.3, $p<0.001$; mean APACHEII score 33.1 vs. 25.8, $p<0.001$) and lower baseline SCr (0.90 [0.65 to 1.30] vs. 1.38 [0.90 to 2.18], $p=0.01$). The non-survivors had a higher prevalence of septic AKI (66 [91.7%] vs. 31 [62%], $p<0.001$) but had a lower prevalence of renal AKI (14 [19.4%] vs. 18 [35%], $p=0.04$). In addition, the number of patients requiring CRRT was higher among non-survivors (68 [94.4%] vs. 37 [74%], $p=0.001$).

Clinical and laboratory investigations at 24 hours before RRT initiation of survivors and non-survivors at day 28 after diagnosis of AKI were shown in Table 2. Compares to the survivors, the non-survivors had a significantly higher SOFA score (13 [10 to 17] vs. 11 [8.5 to 13], $p=0.002$), a significantly lower PaO_2/FiO_2 (183 [120 to 351] vs. 298 [198 to 433], $p=0.01$), higher rate of acute respiratory failure (69 [95.8%] vs. 37 [75.5%], $p<0.001$), higher rate of shock requiring vasopressor (67 [93.1] vs. 30 [60%], $p<0.001$), and a higher serum lactate level (8.4 [4.1 to 15.1] vs. 3.5 [2.1 to 7.6], $p=0.01$). In addition, the non-survivors had a significantly lower SCr before RRT (3.3 [2.4 to 4.9] vs. 4.8 [3.4 to 7.6], $p<0.001$), a significantly lower 24-hours urine volume before RRT (108 [9 to 495] vs. 280 [60 to 982], $p=0.03$) and a significantly higher cumulative fluid balance (3,677 [1,576 to 7,133] vs. 1,643 [362 to 3,714], $p=0.01$).

Predictors of mortality at day 28

Fifteen variables were studied by multivariable extended Cox model. Because serum lactate was a time-varying covariate; hence, the extended Cox model with Heaviside functions was used to estimate effect of time varying covariate. Predictors associated with mortality at day 28 were shown in Table 3. On multivariable analysis, non-survivors at day 28 showed significant association with a lower SCr before RRT (hazard ratio [HR] 0.84, 95% CI 0.74 to 0.95, $p=0.01$), a higher SOFA score before RRT (HR 1.10, 95% CI 1.03 to 1.18, $p=0.005$), a higher rate of shock requiring vasopressor (HR 2.80, 95% CI 1.03 to 7.64, $p=0.04$), and serum lactate >4 mmol/L before RRT that affected the first 10 days of survival time (HR 2.17, 95% CI 1.03 to 4.57, $p=0.04$). However, serum lactate >4 mmol/L did not affect survival after 10 days of survival time (HR 0.99, 95% CI 0.37 to 2.66). For the measure of discrimination, the Harrell C-statistics for the reduced model was 0.75 (95% CI 0.70 to 0.81).

Discussion

AKI requiring RRT is a common condition in medical ICU settings and remains a major cause of death. Despite therapeutic and diagnostic advances, the mortality of AKI patients has remained high in recent decades. Regarding of our results, 60% of AKI patients requiring RRT did not survive at day 28 after development of AKI and the mortality rate increased up to 75% at day 90 after development of AKI. Patients with lower SCr before RRT was strongly associated with mortality. Moreover, a higher

Table 1. Baseline characteristics of patients with renal replacement therapy by mortality at day 28

Characteristic	Survivors (50)	Non-survivors (72)	p-value	Missing, n (%)
Age, mean±SD, years	55.8 (19.9)	58.5 (18)	0.44	0 (0)
Male sex, n (%)	27 (54)	45 (62.5)	0.35	0 (0)
Body mass index, mean±SD, kg/m^2	22.7 (3.5)	22.7 (4.2)	0.98	31 (25.4)
SOFA, mean (SD), points	10.3 (3.7)	13.7 (4.5)	<0.001*	5 (4.1)
APACHE II, mean (SD), points	25.8 (8.8)	33.1 (11.4)	<0.001*	7 (5.7)
Charlson comorbidities index, median (IQR), points	4 (3 to 7)	5 (3 to 6.25)	0.29	5 (4.1)
ICU type, n (%)				
Medical ICU	43 (86)	65 (90.3)	0.47	0 (0)
Cardiac ICU	7 (14)	7 (9.7)		
Time to RRT, median (IQR), days				
Hospital admission to RRT	1.0 (0 to 7.5)	2.5 (0 to 11.0)	0.38	0 (0)
ICU admission to RRT	0 (0 to 1.00)	0 (0 to 1.25)	0.46	
AKI to RRT	1 (0 to 2)	0 (0 to 1)	0.09	
Mode of RRT				
CRRT	37 (74)	68 (94.4)	0.001*	0 (0)
Intermittent hemodialysis	13 (26)	4 (5.6)		
Etiology of AKI				
Septic AKI	31 (62)	66 (91.7)	<0.001*	0 (0)
Non-septic AKI	19 (38)	6 (8.3)		
Known baseline SCr, n (%)	22 (44)	43 (59.7)	0.09	
Baseline SCr, median (IQR), mg/dL	1.38 (0.90 to 2.18)	0.9 (0.65 to 1.3)	0.01*	57 (46.7)
eGFR, mean±SD, mL/min per 1.73 m^2	60.2 (34.3)	83.4 (39.9)	0.02*	57 (46.7)
CKD staging				
No CKD	2 (8.7)	9 (20.5)	0.36	55 (45)
Stage 1	3 (13)	9 (20.5)		
Stage 2	5 (21.7)	10 (22.7)		
Stage 3	7 (30.4)	12 (27.3)		
Stage 4	6 (26.1)	4 (9.1)		

* p<0.05 when compared with survivors

AKI = acute kidney injury; APACHE = acute physiology, age, chronic health evaluation; CKD = chronic kidney disease; CRRT = continuous renal replacement therapy; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; IQR = interquartile range; RRT = renal replacement therapy; SCr = serum creatinine; SD = standard deviation; SOFA = sequential organ failure assessment.

severity of illness score (SOFA score) before initiation of RRT was also associated with mortality. Cardiovascular failure requiring vasopressors was more important than other organ failure to predict mortality. Higher degree of tissue hypoperfusion indicated by a higher serum lactate level was a strong independent factor for mortality among AKI patients requiring RRT.

Death rates of dialysis patients with severe AKI and multiple organ failure is at around 50 to 80%[7,21]. Similar to those data in the literatures, our study showed mortality of 59% among AKI patients requiring RRT. A wide range of mortality in AKI could be explained by the heterogeneity of patients.

The multinational AKI-EPI study showed that older age, a higher severity of illness, a higher severity of AKI, presence of liver failure, emergency surgery and a lower SCr at ICU admission were associated with death[3]. Regarding the predictors of mortality, our study focused on AKI patients requiring RRT population because some factors may be modified to improve survival. This study showed inverse correlation between SCr before RRT and mortality. This result was in line with the AKI-EPI study in that the higher the SCr at time of ICU admission, the lower the likelihood ratio of death[3]. Moreover, a lower SCr was associated with death of not only AKI patients but also of general hospitalized patients[22]. SCr is one of the surrogates for muscle mass;

Table 2. Clinical and laboratory investigations 24 hours before renal replacement therapy

Characteristic	Survivors (50)	Non-survivors (72)	p-value	Missing, n (%)
SOFA, median (IQR), points	11 (8.5 to 13)	13 (10 to 17)	0.002*	4 (3.3)
Acute respiratory failure, n (%)	37 (75.5)	69 (95.8)	<0.001*	1 (0.8)
Shock, n (%)	32 (64)	67 (93.1)	<0.001*	0 (0)
Vasopressor, n (%)	30 (60)	67 (93.1)	<0.001*	0 (0)
Acute coronary syndrome, n (%)	6 (12)	5 (6.9)	0.36	0 (0)
Pulmonary edema, n (%)	9 (18)	13 (18.1)	0.99	0 (0)
Urine output, median (IQR), mL	280 (60 to 982)	108 (9 to 495)	0.03*	17 (13.9)
Cumulative fluid balance, median (IQR), mL	1,643 (362 to 3,714)	3,677 (1,576 to 7,133)	0.01*	19 (15.6)
Arterial pH, median (IQR)	7.34 (7.29 to 7.42)	7.34 (7.21 to 7.43)	0.45	28 (23)
Base excess, mean±SD	-8.2 (7.5)	-9.8 (9.1)	0.40	29 (23.8)
PaO_2/FiO_2, median (IQR)	298 (198 to 433)	183 (120 to 351)	0.01*	28 (23)
BUN, median (IQR), mg/dL	79.7 (53.2 to 101.5)	78.3 (43.8 to 110.9)	0.92	4 (3.3)
Serum creatinine, median (IQR), mg/dL	4.8 (3.4 to 7.6)	3.3 (2.4 to 4.9)	<0.001*	4 (3.3)
Serum bicarbonate, median (IQR), mEq/L	14.4 (11.8 to 17.7)	13.6 (10.1 to 18.9)	0.58	4 (3.3)
Serum potassium, median (IQR), mEq/L	4.5 (3.8 to 5.2)	4.9 (4.0 to 5.8)	0.27	4 (3.3)
Serum albumin, median (IQR), g/dL	2.4 (2.2 to 3.1)	2.4 (2.0 to 2.7)	0.06	4 (3.3)
Serum lactate, median (IQR), mmol/L	3.5 (2.1 to 7.6)	8.4 (4.1 to 15.1)	0.01*	40 (32.8)

* $p<0.05$ when compared with survivors
BUN = Blood urea nitrogen; IQR = Interquartile range; SD = Standard deviation; SOFA = Sequential organ failure assessment

hence, low Scr reflects poor nutritional status[23]. Creatinine is distributed in the total body water. Thus, positive fluid balance can increase total body water, which confer the diluting effect on SCr concentration resulting a falsely lowered SCr in the ICU[24]. SCr at the time of RRT can also predict mortality, possibly reflecting hemodilution due to fluid overload. Although CKD patients had a likelihood of higher SCr and lower likelihood of death in our study, the difference is not significantly.

Our results showed that a higher severity of organ failure before initiation of RRT, which was indicated by SOFA score, was significantly associated with death. This result was in accordance with the study of Chertow, et al in that extrarenal organ failures, presence of sepsis or septic shock, and older age at the day of dialysis were associated with high mortality[25].

In addition, model for predicting mortality at the day of dialysis had more predictive power than the day of AKI diagnosis[25]. We also found that vasopressor requirement and a higher serum lactate, especially more than 4 mmol/L, are associated with higher likelihood of death. These findings were in line with several studies[26]. Moreover, indicators of hemodynamic failure were retained in the final multivariable model. Renal replacement therapy may lead to intradialytic hypotension[27] that aggravated hemodynamic disturbances. Several kidney-specific severity scores were developed using demographic data, comorbidity, organ failure, laboratory data, and treatments. However, they were developed for a decade. Although predictive risk model for 60-day mortality of Demirjian, et al, is high accuracy[28], external validation is low[29]. Hence, implication of clinical predictive models needs to be developed in a larger population.

We acknowledge several limitations of the current study, which are in part due to the retrospective cohort study. Since one third of the study population did not have serum lactate before RRT, we addressed this problem using multiple imputation instead of complete case analysis. Moreover, we have a small study population and we conducted in a single site. A future study needs to be conducted in a larger population.

Conclusion

In conclusion, the mortality rate among AKI patients requiring RRT is high. Based on our findings, a higher SOFA score, requirement of vasopressors, higher serum lactate before initiation of RRT and a lower SCr should be considered for the clinical predictors of the mortality of AKI patients requiring RRT.

What is already known on this topic?

Patients with AKI requiring RRT have high mortality. Several severity scores were developed for a decade. This study would like to explore the predictors of worse outcomes to add on or discover new predictors of mortality.

What this study adds?

Our study showed patients with high severity of illness, shock, and higher serum lactate can predict death at

Table 3. Factors associated with non-survivors in patients with renal replacement therapy

Variable	Univariable analysis+			Multivariable analysis++		
	HR	95% CI	p-value	HR	95% CI	p-value
Baseline serum creatinine, mg/dL*	0.52	0.32 to 0.87	0.01		Not included	
Time from AKI to RRT, days*	0.93	0.83 to 1.03	0.15		Not included	
Mode of RRT						
Intermittent hemodialysis	1.00	Reference			Not included	
Continuous renal replacement therapy	4.25	1.55 to 11.69	0.005		Not included	
Etiology of AKI						
Septic AKI	4.09	1.77 to 9.45	<0.001		Not included	
Clinical and laboratory before RRT 24 hours						
SOFA score, points*	1.14	1.08 to 1.22	<0.001	1.10	1.03 to 1.18	0.005
Acute respiratory failure	4.50	1.41 to 14.30	0.01		Not included	
Shock	4.90	1.97 to 12.18	<0.001		Not included	
Vasopressor	5.55	2.23 to 13.80	<0.001	2.80	1.03 to 7.64	0.04
Urine output (per 100 mL)	0.96	0.92 to 1.00	0.06		Not included	
Cumulative fluid balance (per 1 L)	1.03	0.99 to 1.06	0.12		Not included	
PaO_2/FiO_2 (per 10 mmHg)	0.97	0.95 to 0.99	0.002		Not included	
Serum creatinine, mg/dL*	0.81	0.72 to 0.91	<0.001	0.84	0.74 to 0.95	0.01
Serum albumin, g/dL*	0.58	0.38 to 0.89	0.01		Not included	
Serum lactate >4 mmol/L (<10 days survival time)	2.97	1.51 to 5.85	0.002	2.17	1.03 to 4.57	0.04
Serum lactate >4 mmol/L (≥10 days survival time)	2.11	0.66 to 6.72	0.21	0.99	0.37 to 2.66	0.99

AKI = acute kidney injury; CI = confidence interval; HR = hazard ratio; RRT = renal replacement therapy; SOFA = sequential organ failure assessment.

Harrell C-statistics for multivariable analysis = 0.75 (95% CI = 0.70 to 0.81).

"Not included" means variables could not be retained in the final model, + analysis from non-imputed data, ++ Pool analysis after multivariable extended Cox regression of 50 imputed data set, * per 1-point increase

day 28 after AKI diagnosis especially the first 10 days. In addition, lower serum creatinine before RRT was a good predictor for mortality, which may associate with fluid overload.

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Potential conflicts of interest

The authors declare no conflict of interest.

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