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

Chitchai Rattananukrom
Khon Kaen University Faculty of Medicine

Pantipa Tonsawan
Khon Kaen University Faculty of Medicine

Anupol Panitchote (✉ panupo@kku.ac.th)
Khon Kaen University Faculty of Medicine

Research article

Keywords: acute kidney injury, renal replacement therapy, mortality, vasopressors, lactate, intensive care unit

Posted Date: October 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-76983/v1

License: ☒️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

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

**Methods:** This is a retrospective cohort study from prospectively collected data over a year (2014-2015). AKI patients requiring RRT were included. We collected demographic and laboratory data of AKI patients requiring RRT within 24 hours before 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] 49.7-67.8) and 72.1% (95%CI 63.3-79.9). On multivariable analysis, clinical predictors for 28-day mortality were baseline serum creatinine (hazard ratio [HR] 0.57, 95% CI 0.36-0.90), SOFA score before initiation of RRT (HR 1.08, 95%CI 1.01-1.15), presence of vasopressors before initiation of RRT (HR 3.04, 95%CI 1.12-8.25), serum lactate > 4 mmol/L before initiation of RRT effect <10 days of survival time (HR 2.49, 95%CI 1.17-5.26), and serum lactate > 4 mmol/L before initiation of RRT effect ≥10 days of survival time (HR 1.31, 95%CI 0.47-3.60).

**Conclusion:** A lower baseline serum creatinine was associated with the mortality in AKI patients requiring RRT. SOFA score, presence of vasopressors, and a higher serum lactate before initiation of RRT are useful clinical predictors for the 28-day mortality.

Introduction

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 [1]. 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 [2]. Incidence of AKI is up to 20% of hospitalized patients [3] and 30–60% of critically ill patients [4–6].

Patients with AKI has a high mortality rate ranging 25–60% [3, 4, 6] and there is a stepwise increase of mortality with increase of AKI severity, particularly stage II and III AKI [7, 8]. These rates remained virtually unchanged despite the optimization of care [9]. 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 [10]. Timing and intensity of renal replacement therapy (RRT) do not have a beneficial effect on mortality [11–14].
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 [15]. Because RRT is costly and consumes healthcare resources [16], 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 (ICU) or a cardiac ICU 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/1.73m² or on chronic dialysis) [17] 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 [18]. Demographic data were recorded including; age, sex, body mass index, ICU diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) 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 [19, 20]. 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 [21]. Sepsis and septic shock are defined according to the 2012
surviving sepsis campaign [22]. 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 Fischer’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 [23, 24]. The imputation processes included variables that were incorporated into both regression models and also included outcomes variables [25]. The number of imputed datasets was based on a quadratic function of the fraction of missing information [26]. 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 is $> 0.05$, 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. 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 0–10.8) and median time from AKI onset to RRT initiation was 1 day (IQR 0–1.8). Among 122 patients, 72 patients (59%, 95% confidence interval [CI] 49.7–67.8) did not survived by day 28 and 88 patients (72.1%, 95%CI 63.3–79.9) by day 90 after AKI diagnosis.

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 Table 2).
Table 1  
Baseline characteristics of patients with renal replacement therapy by mortality at day 28

| Characteristic                                      | Survivors (50) | Non-survivors (72) | P     | 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/m²                     | 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 (3–7)        | 5 (3–6.25)         | 0.29  | 5 (4.1)        |
| ICU type, n (%)                                      | 43 (86)        | 65 (90.3)          | 0.47  | 0 (0)          |
| Medical ICU                                         | 7 (14)         | 7 (9.7)            |       |                |
| Cardiac ICU                                         |                |                    |       |                |
| Time to RRT, median (IQR), days                     | 1.0 (0–7.5)    | 2.5 (0–11)         | 0.38  | 0 (0)          |
| Hospital admission to RRT                           | 0 (0–1.00)     | 0 (0–1.25)         | 0.46  |                |
| ICU admission to RRT                                | 1 (0–2)        | 0 (0–1)            | 0.09  |                |
| AKI to RRT                                          |                |                    |       |                |
| Mode of RRT                                         | 37 (74)        | 68 (94.4)          | 0.001* | 0 (0)        |
| CRRT                                                | 13 (26)        | 4 (5.6)            |       |                |
| Intermittent hemodialysis                           |                |                    |       |                |
| Etiology of AKI                                      | 31 (62)        | 66 (91.7)          | < 0.001* | 0 (0)     |
| Septic AKI                                          | 19 (38)        | 6 (8.3)            |       |                |
| Non-septic AKI                                       |                |                    |       |                |
| Known baseline SCr, n (%)                           | 22 (44)        | 43 (59.7)          | 0.09  |                |
| Baseline SCr, median (IQR), mg/dL                   | 1.38 (0.90–2.18) | 0.9 (0.65–1.3) | 0.01* | 57 (46.7)     |

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.

* P < 0.05 when compared with survivors
| Characteristic | Survivors (50) | Non-survivors (72) | P     | Missing, n (%) |
|---------------|---------------|-------------------|------|---------------|
| eGFR, mean±SD, mL/min per 1.73 m² | 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 I       | 3 (13)        | 9 (20.5)          |      |               |
| Stage II      | 5 (21.7)      | 10 (22.7)         |      |               |
| Stage III     | 7 (30.4)      | 12 (27.3)         |      |               |
| Stage IV      | 6 (26.1)      | 4 (9.1)           |      |               |

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.

* P < 0.05 when compared with survivors
Table 2
Clinical and laboratory investigations 24 hours before renal replacement therapy

| Characteristic                                      | Survivors (50) | Non-survivors (72) | P      | Missing, n (%) |
|----------------------------------------------------|----------------|--------------------|--------|----------------|
| SOFA, median (IQR), points                         | 11 (8.5–13)    | 13 (10–17)         | 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 (60–982)   | 108 (9–495)        | 0.03*  | 17 (13.9)      |
| Cumulative fluid balance, median (IQR), mL         | 1643 (362–3714) | 3677 (1576–7133)  | 0.01*  | 19 (15.6)      |
| Arterial pH, median (IQR)                          | 7.34 (7.29–7.42) | 7.34 (7.21–7.43)  | 0.45   | 28 (23)        |
| Base excess, mean±SD                               | -8.2 (7.5)     | -9.8 (9.1)         | 0.40   | 29 (23.8)      |
| \(\text{PaO}_2/\text{FiO}_2\), median (IQR)        | 298 (198–433)  | 183 (120–351)      | 0.01*  | 28 (23)        |
| BUN, median (IQR), mg/dL                           | 79.7 (53.2–101.5) | 78.3 (43.8–110.9) | 0.92   | 4 (3.3)        |
| Serum creatinine, median (IQR), mg/dL              | 4.8 (3.4–7.6)  | 3.3 (2.4–4.9)      | < 0.001* | 4 (3.3)        |
| Serum bicarbonate, median (IQR), mEq/L             | 14.4 (11.8–17.7) | 13.6 (10.1–18.9)  | 0.58   | 4 (3.3)        |
| Serum potassium, median (IQR), mEq/L               | 4.5 (3.8–5.2)  | 4.9 (4.0–5.8)      | 0.27   | 4 (3.3)        |
| Serum albumin, median (IQR), g/dL                  | 2.4 (2.2–3.1)  | 2.4 (2.0–2.7)      | 0.06   | 4 (3.3)        |
| Serum lactate, median (IQR), mmol/L                | 3.5 (2.1–7.6)  | 8.4 (4.1–15.1)     | 0.01*  | 40 (32.8)      |

BUN = blood urea nitrogen; IQR = interquartile range; SD = standard deviation; SOFA = sequential organ failure assessment.

* P < 0.05 when compared with survivors
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 severity of illness at the day of ICU admission (mean SOFA score 13.7 vs 10.3, \( P < 0.001 \); mean APACHE II score 33.1 vs 25.8, \( P < 0.001 \)) and lower baseline SCr (0.90 [0.65–1.30] vs 1.38 [0.90–2.18], \( P = 0.01 \)). 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 [10–17] vs 11 [8.5–13], \( P = 0.002 \)), a significantly lower \( \text{PaO}_2/\text{FiO}_2 \) (183 [120–351] vs 298 [198–433], \( P = 0.01 \)), 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 [4.1–15.1] vs 3.5 [2.1–7.6], \( P = 0.01 \)). In addition, the non-survivors had a significantly lower SCr before RRT (3.3 [2.4–4.9] vs 4.8 [3.4–7.6], \( P < 0.001 \)), a significantly lower 24-hours urine volume before RRT (108 [9–495] vs 280 [60–982], \( P = 0.03 \)) and a significantly higher cumulative fluid balance (3677 [1576–7133] vs 1643 [362–3714], \( P = 0.01 \)).

**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 and Fig. 1. On multivariable analysis, non-survivors at day 28 showed significant association with a lower baseline SCr (hazard ratio [HR] 0.57, 95%CI 0.36–0.90, \( P = 0.02 \)), a higher SOFA score before RRT (HR 1.08, 95%CI 1.01-1.15, \( P = 0.03 \)), a higher rate of shock requiring vasopressor (HR 3.04, 95%CI 1.12-8.25, \( P = 0.03 \)), and serum lactate > 4 mmol/L for survival time < 10 days (HR 2.49, 95%CI 1.17-5.26, \( P = 0.02 \)). For the measure of discrimination, the Harrell C-statistics for the reduced model was 0.76 (95%CI 0.70-0.82).

**Table 3** Factors associated with non-survivors in patients with renal replacement therapy
| Variable                                                                 | Univariable analysis\(^a\) | Multivariable analysis\(^b\) |
|-------------------------------------------------------------------------|-----------------------------|------------------------------|
|                                                                         | HR  | 95% CI    | P   | HR  | 95% CI    | P   |
| Baseline serum creatinine, mg/dL\(^c\)                                 | 0.52 | 0.32 - 0.87 | 0.01 | 0.57 | 0.36 - 0.90 | 0.02 |
| Time from AKI to RRT, days\(^c\)                                       | 0.93 | 0.83 - 1.03 | 0.15 | Not included |
| Mode of RRT                                                             |     |             |     | Not included |
| Intermittent hemodialysis                                               | 1.00 | Reference   |     | Not included |
| Continuous renal replacement therapy                                    | 4.25 | 1.55 - 11.69 | 0.005 | Not included |
| Etiology of AKI                                                         |     |             |     | Not included |
| Septic AKI                                                              | 4.09 | 1.77 - 9.45 | < 0.001 | Not included |
| Clinical and laboratory before RRT 24 hours                             |     |             |     | Not included |
| SOFA score, points\(^c\)                                               | 1.14 | 1.08 - 1.22 | < 0.001 | 1.08 | 1.01 - 1.15 | 0.03 |
| Acute respiratory failure                                               | 4.50 | 1.41 - 14.30 | 0.01 | Not included |
| Shock                                                                   | 4.90 | 1.97 - 12.18 | < 0.001 | Not included |
| Vasopressor                                                             | 5.55 | 2.23 - 13.80 | < 0.001 | 3.04 | 1.12 - 8.25 | 0.03 |
| Urine output (per 100 mL)                                               | 0.96 | 0.92 - 1.00 | 0.06 | Not included |
| Cumulative fluid balance (per 1 L)                                     | 1.03 | 0.99 - 1.06 | 0.12 | Not included |
| PaO\(_2\)/FiO\(_2\) (per 10 mm Hg)                                      | 0.97 | 0.95 - 0.99 | 0.002 | Not included |
| Serum creatinine, mg/dL\(^c\)                                          | 0.81 | 0.72 - 0.91 | < 0.001 | Not included |
| Serum albumin, g/dL\(^c\)                                              | 0.58 | 0.38 - 0.89 | 0.01 | Not included |
| Serum lactate > 4 mmol/L (< 10 days survival time)                      | 2.97 | 1.51 - 5.85 | 0.002 | 2.49 | 1.17 - 5.26 | 0.02 |
| Serum lactate > 4 mmol/L (≥ 10 days survival time) | 2.11 | 0.66 | - | 6.72 | 0.21 | 1.31 | 0.47 | - | 3.60 | 0.60 |

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 = 0.76 (95%CI 0.70-0.82).

\(^a\) analysis from non-imputed data

\(^b\) Pool analysis after multivariable extended Cox regression of 50 imputed data set

\(^c\) per 1-point increase

**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 baseline SCr before hospitalization was strongly associated with mortality. Moreover, a higher 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 50–80% [8, 12, 27, 28]. 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 [4]. 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 baseline SCr before admission 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 [4]. Moreover, a lower SCr was associated with death of not only AKI patients but also of general hospitalized patients [29]. SCr is one of the surrogates for muscle mass; hence, low Scr reflects poor nutritional status [30]. Cr 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 [31]. SCr at the time of RRT can also predict mortality [32], possibly reflecting hemodilution due to fluid overload.
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 [32].

In addition, model for predicting mortality at the day of dialysis had more predictive power than the day of AKI diagnosis [32]. 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 [33–35]. Moreover, indicators of hemodynamic failure were retained in the final multivariable model. Renal replacement therapy may lead to intradialytic hypotension [36–38] 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 [39], external validation is low [40]. Hence, implication of clinical predictive models need to be developed in a larger population.

We acknowledge a number of limitations of the current study, which are in part due to the retrospective cohort study. Since half of the study population did not have a baseline SCr, we addressed this problem using multiple imputation instead of complete case analysis. However, a large epidemiological study of AKI had missing baseline SCr of one-third [4]. We explored both of baseline characteristics and laboratory data before initiation of RRT to build an exhaustive model. A future study needs to be conducted in a larger population.

**Conclusions**

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

**Abbreviations**

AKI
Acute kidney injury; APACHE:Acute Physiology and Chronic Health Evaluation; CI:confidence interval; CRRT:continuous renal replacement therapy; GFR:glomerular filtration rate; HR:hazard ratio; ICU:intensive care units; IQR:interquartile range; PH:proportional hazards; RRT:renal replacement therapy; SCr:serum creatinine; SOFA:Sequential Organ Failure Assessment.

**Declarations**

Ethics approval and consent to participate
This study was approved by the Khon Kaen University Ethics Committee for Human Research (Approval Number: HE581457) and granted a waiver of informed consent.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

All authors report no competing interests relevant to this article.

**Funding**

This study received funding from the Faculty of Medicine, Khon Kaen University (IN59123).

**Authors’ contributions**

CR designed the study, participated in data collection and cleaning, performed the analysis, wrote the first draft of the manuscript, and critically revised the manuscripts. PT designed the study, interpreted the data, and critically revised the manuscript. AP is designed the study, participated in data collection and cleaning, performed the analysis, developed the predictive model, and critically revised the manuscripts. AP is also the guarantor, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. All authors read and approved of the final manuscript.

**Acknowledgements**

We would like to acknowledge Professor Yukifumi Nawa, for editing the manuscript via Publication Clinic Khon Kaen University, Thailand.

**Authors’ information**

1 Department of Medicine, Faculty of Medicine, Khon Kaen University, Thailand. 2 Division of Nephrology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Thailand. 3 Division of Critical Care Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Thailand

**References**

1. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019;394(10212):1949-64.
2. Lee SA, Cozzi M, Bush EL, Rabb H. Distant Organ Dysfunction in Acute Kidney Injury: A Review. Am J Kidney Dis. 2018;72(6):846-56.

3. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482-93.

4. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23.

5. Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int. 2012;81(9):819-25.

6. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimitsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E et al. Acute renal failure in critically ill patients: a multinational, multicenter study. Jama. 2005;294(7):813-8.

7. Xu X, Nie S, Liu Z, Chen C, Xu G, Zha Y, Qian J, Liu B, Han S, Xu A et al. Epidemiology and Clinical Correlates of AKI in Chinese Hospitalized Adults. Clin J Am Soc Nephrol. 2015;10(9):1510-8.

8. Panitchote A, Mehkri O, Hastings A, Hanane T, Demirjian S, Torbic H, Mireles-Cabodevilla E, Krishnan S, Duggal A. Factors associated with acute kidney injury in acute respiratory distress syndrome. Ann Intensive Care. 2019;9(1):74.

9. Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract. 2013;2013:479730.

10. Piccinni P, Cruz DN, Gramaticopolo S, Garzotto F, Dal Santo M, Aneloni G, Rocco M, Alessandri E, Giunta F, Michetti V et al. Prospective multicenter study on epidemiology of acute kidney injury in the ICU: a critical care nephrology Italian collaborative effort (NEFROINT). Minerva Anestesiol. 2011;77(11):1072-83.

11. Barbar SD, Clere-Jehl R, Bourredjem A, Hemu R, Montini F, Bruyère R, Lebert C, Bohé J, Badie J, Eraldi JP et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med. 2018;379(15):1431-42.

12. Gaudry S, Hajage D, Schortgen F, Martin-Lefèvre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016;375(2):122-33.

13. Fayad AI, Buamscha DG, Ciapponi A. Timing of renal replacement therapy initiation for acute kidney injury. Cochrane Database Syst Rev. 2018;12(12):Cd010612.

14. Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. Cochrane Database Syst Rev. 2016;10(10):Cd010613.

15. Shingarev R, Wille K, Tolwani A. Management of complications in renal replacement therapy. Semin Dial. 2011;24(2):164-8.

16. Silver SA, Chertow GM. The Economic Consequences of Acute Kidney Injury. Nephron. 2017;137(4):297-301.
Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713-35.

17. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1-138.

18. Lewandowski K, Metz J, Deutschmann C, Preiss H, Kuhlen R, Artigas A, Falke KJ. Incidence, severity, and mortality of acute respiratory failure in Berlin, Germany. Am J Respir Crit Care Med. 1995;151(4):1121-5.

19. Luhr OR, Antonsen K, Karlsson M, Aardal S, Thorsteinsson A, Frostell CG, Bonde J. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. Am J Respir Crit Care Med. 1999;159(6):1849-61.

20. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726-34.

21. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637.

22. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011;45(3):1-67.

23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.

24. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol. 2006;59(10):1092-101.

25. von Hippel PT. How many imputations do you need? A two-stage calculation using a quadratic rule. Sociological Methods & Research. 2018:0049124117747303.

26. Srisawat N, Kulvichit W, Mahamitra N, Hurst C, Praditponsilpa K, Lumlertgul N, Chuasuwan A, Trongtrakul K, Tasnarong A, Champunot R et al. The epidemiology and characteristics of acute kidney injury in the Southeast Asia intensive care unit: a prospective multicentre study. Nephrol Dial Transplant. 2019.

27. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, Boanta A, Gerß J, Meersch M. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. Jama. 2016;315(20):2190-9.

28. Thongprayoon C, Cheungpasitporn W, Kittanamongkolchai W, Harrison AM, Kashani K. Prognostic Importance of Low Admission Serum Creatinine Concentration for Mortality in Hospitalized Patients. Am J Med. 2017;130(5):545-54.e1.

29. Liu KD, Thompson BT, Ancukiewicz M, Steingrub JS, Douglas IS, Matthay MA, Wright P, Peterson MW, Rock P, Hyzy RC et al. Acute kidney injury in patients with acute lung injury: impact of fluid
accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med. 2011;39(12):2665-71.

32. Chertow GM, Soroko SH, Paganini EP, Cho KC, Himmelfarb J, Ikizler TA, Mehta RL. Mortality after acute renal failure: models for prognostic stratification and risk adjustment. Kidney Int. 2006;70(6):1120-6.

33. Barton IK, Hilton PJ, Taub NA, Warburton FG, Swan AV, Dwight J, Mason JC. Acute renal failure treated by haemofiltration: factors affecting outcome. Q J Med. 1993;86(2):81-90.

34. Siddiqui AH, Valecha G, Modi J, Saqib A, Weerasinghe C, Siddiqui F, El Sayegh S. Predictors of 15-Day Survival for the Intensive Care Unit Patient on Continuous Renal Replacement Therapy: A Retrospective Analysis. Cureus. 2020;12(5):e8175.

35. Douma CE, Redekop WK, van der Meulen JH, van Olden RW, Haeck J, Struijk DG, Krediet RT. Predicting mortality in intensive care patients with acute renal failure treated with dialysis. J Am Soc Nephrol. 1997;8(1):111-7.

36. Bitker L, Bayle F, Yonis H, Gobert F, Leray V, Taponnier R, Debord S, Stoian-Cividjian A, Guérin C, Richard JC. Prevalence and risk factors of hypotension associated with preload-dependence during intermittent hemodialysis in critically ill patients. Crit Care. 2016;20:44.

37. Massicotte-Azarniouch D, Amin SO, Hesketh C, Clark EG. Renal Replacement Therapy: Timing of Initiation and Intradialytic Hypotension. Am J Respir Crit Care Med. 2017;196(1):102-4.

38. Sigwalt F, Bouteleux A, Dambricourt F, Asselborn T, Moriceau F, Rimmelé T. Clinical Complications of Continuous Renal Replacement Therapy. Contrib Nephrol. 2018;194:109-17.

39. Demirjian S, Chertow GM, Zhang JH, O’Connor TZ, Vitale J, Paganini EP, Palevsky PM. Model to predict mortality in critically ill adults with acute kidney injury. Clin J Am Soc Nephrol. 2011;6(9):2114-20.

40. Ohnuma T, Uchino S. Prediction Models and Their External Validation Studies for Mortality of Patients with Acute Kidney Injury: A Systematic Review. PLoS One. 2017;12(1):e0169341.

Figures
Figure 1

Forest plot showing the results of multivariable extended Cox regression for clinical predictors associated with 28-day mortality after acute kidney injury. The x-axis represents the adjusted hazard ratio (HRadj) on a log scale with the reference line (solid vertical line), adjusted hazard ratio (square), and 95% confidence interval (whisker).