Association Of Potassium Concentration And Variability With Mortality Among Patients Requiring Continuous Renal Replacement Therapy In Intensive Care Units: A Hospital-Based Retrospective Cohort Study

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Research Article

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Abstract

Background: Serum potassium between 3.5 to 5.0 mmol/L is known to be a safe range for patients. The optimal serum potassium level for critically-ill patients with acute kidney injury undergoing continuous renal replacement therapy (CRRT) remains uncertain. This retrospective analysis investigated the association between ICU mortality and potassium concentrations and variability.

Methods: ICU patients aged 20 or older, with a minimum of two serum potassium values during received CRRT, treated in ICU in a tertiary hospital in central Taiwan between 1 January 2010 and 30 April 2021 were eligible for inclusion. Patients were categorized into groups of mean potassium: <3.0, 3.0 to <3.5, 3.5 to <4.0, 4.0 to <4.5, 4.5 to <5.0, and ³5.0 mmol/L; potassium variability was divided by quartiles of the average real variation. We analyzed the association between potassium concentration and variability with mortality and performed Cox's proportional hazard models.

Results: We studied 1991 CRRT patients with 9891 serum potassium values within 24 hours after receiving CRRT. There was a J-shaped association between serum potassium and mortality, with the lowest mortality observed in patients with mean potassium concentrations between 3.0 and 4.0 mmol/L. The risk of in-hospital death was also significantly increased in those with the highest variability [HR and 95% CI=1.31(1.03-1.65) for in-hospital mortality; 1.39(1.06-1.82) for 28-day mortality and 1.43(1.11-1.83) for 90-day mortality, respectively].

Conclusions: Patients receiving CRRT may benefit from a lower and tighter serum potassium control. During CRRT, progressively increased mortality was noted in patients with higher potassium variability. Thus, careful and timely correction of dyskalemia among these patients is particularly important.

Background

There has been an increased incidence of acute kidney injury (AKI) in recent decades, which is now emerging as a global concern for the health care system. In intensive care unit (ICU) settings, AKI affects up to 60% of patients admitted to ICU and may be associated with complications such as fluid overload, refractory hyperkalemia, and metabolic derangement [1]. In addition, AKI is associated with adverse outcomes, including increased length of stay in ICU and hospital, higher mortality, subsequent development of chronic kidney disease (CKD), etc. In ICU patients, according to EPI-AKI reports [2], up to 23.5% of patients with AKI and 13.5% of all ICU patients need renal replacement therapy (RRT).

Continuous renal replacement therapy (CRRT) is a modality of RRT that has the advantages of gentle and accurate removal of fluid overload and stable acid-base and electrolyte correction. Therefore, CRRT is the most common technique for hemodynamically unstable patients with AKI in ICU [2]. Despite significant advances in the management of critically ill patients with AKI, mortality remains high, reported to be in the range of 28%-90% [3–7]. Several predictors to predict mortality in AKI with initiation CRRT in the ICU have been proposed, including demographic characteristics and variables that define the severity of illness.

Potassium ([K+]) is an important body electrolyte that plays a crucial role in maintaining normal cell function through the kidneys [8–9]. Therefore, [K+] homeostasis is critical, as a tilt in this balance can lead to differential disease progression and further life-threatening consequences [9], especially in critically ill patients [10]. To date, the association of [K+] levels and its variability and clinical outcome has been largely emphasized in patients with advanced CKD and peritoneal dialysis patients [11–12]. A large-scale study of the German Clinical Trials Register found that increased serum [K+] levels and their variability during hospitalization are also associated with increased in-hospital mortality in ICU patients [13]. Intensive care patients are often diverse, and target [K+] ranges may vary depending on the patient's condition. To the best of our knowledge, lack of studies establishing the association of serum [K+] levels and their variability with mortality in patients with CRRT.

Apart from these purposes, we hypothesized that the [K+] level could be used for clinical management and prognostic factors for patient outcomes. Therefore, we conducted this study to assess the association between [K+] levels and [K+] variability within 24 hours after initiation of CRRT and mortality in CRRT patients.

Materials And Methods

Study populations

We conducted a retrospective observational cohort study at Changhua Christian Hospital (CCH), a tertiary medical center with 130 ICU beds in 5 separate wards in central Taiwan. A total of 3303 consecutive ICU patients who received CRRT between 1 January 2010 and 30 April 2021 were screened based on data from Changhua Christian Hospital Clinical Research Database (CCHRD), which is the integration of all electronic medical record systems, including the CRRT database, inpatient care, prescriptions, laboratory data, clinical visit records, and death records.

To assess the role of CRRT-acquired potassium variability, we studied the ICU patients receiving CRRT for more than 24 hours. Patients aged 20 or older with a minimum of two serum potassium values during received CRRT treated in one of the Medical Intensive Care Unit and Surgery Intensive Care Medicine were eligible for inclusion. We excluded the patients with pre-existing ESRD and incomplete biochemical data. Finally, 1991 patients enrolled for analysis (Fig. 1).

Potassium measurements and other confounders

The exposure of interest was the patient's 24 hours mean [K+] value after receiving CRRT. Patients were categorized into groups of mean [K+] level: <3.0, 3.0 to < 3.5, 3.5 to < 4.0, 4.0 to < 4.5, 4.5 to < 5.0 and ≥5.0 mmol/L. [K+] variability was measured using the average real variability (ARV) of each patient's serum potassium measurements, a novel measure proposed by Mena et al. [14] to represent short-term, inter-testing variability in potassium in CRRT patients. ARV

considers the order of measurements and quantifies the difference between two adjacent readings, which corrects the limitation of standard deviation (SD) and only accounts for the dispersion of values around the mean [15–16]. ARV is calculated using the following formula:

$\mathrm{ARV} = \frac{1}{\sum w_i} \sum_{i=1}^{n-1} w_i \times \left| K_{i+1} - K_i \right|$ where n is the number of serum potassium reports, i ranges from 1 to n-1, and w_i is the time interval between K_i and K_{i+1}.

[K+] variability was divided by quartiles, and high variability was defined as values in the highest quartile. Finally, we computed the risk matrix using mean [K+] level categories combined with [K+] variability quantile and analyzed in-hospital mortality risk.

Investigated confounders were including age, gender, BMI, APACHE II evaluated at ICU admission, diagnostic criteria for AKI, the timing of initiated CRRT, vital sign within 24 hours after CRRT initiation, urine output, medication use, and multiple organ support before CRRT, serum biochemical data (albumin, hemoglobin, WBC count, platelet count, pH, sodium, lactate, calcium, base excess, O_2 saturation, creatinine), and coexisting comorbidity disease. Diagnosis of AKI is based on KDIGO-defined serum creatinine elevation, defined using creatinine criteria, comparing baseline serum creatinine levels on admission to serum creatinine levels before initiation of CRRT. All confounders were taken from CCHRD.

Endpoint

The death records of the patients were reviewed, and the primary endpoint was in-hospital mortality after receiving CRRT. The secondary endpoint was the 28- and 90-day mortality after receiving CRRT. Follow-up for mortality analyses started at CRRT initiation, and patients were censored at the end of the respective follow-up periods (discharge, 28-day or 90-day) or the last date of available follow-up, whichever occurred first.

Statistical analysis

Categorical and continuous variables are expressed as numbers (proportions) and the median and interquartile range (IQR). The chi-square test was used to compare categorical variables, and the Kruskal-Wallis H test was used to compare continuous variables. Mortality rates (per 100 patient-days) during the follow-up period according to [K+] level and its variability within 24 hours after receiving CRRT were presented in Fig. 2. Restricted cubic splines provide a data visualization method to present the hazard ratio of mortality on mean [K+] level and its variability. Survival analyses were performed to assess the association of [K+] levels and its variability with mortality, using the categories of [K+] 3.0 to < 3.5 mmol/L and variability 0.35 to < 0.50 mmol/L as the reference group. Crude and multivariate Cox's proportional hazard models were constructed to estimate mortality rates during the follow-up period according to [K+] level and variability categories. The study aimed to assess the association of [K+] levels and its variability with survival outcomes to help clinicians manage potassium levels to prevent death. Thus, the risk matrix provides an easy-to-understand method to visualize the results of the additive effects of mean [K+] levels, variability, and mortality associations.

All descriptions statistical analyses were performed using SAS, and a visualization plot was performed R software (version 4.1.0; The Comprehensive R Archive Network: http://cran.r-project.org). All two-sided P values less than 0.05 were considered statistically significant.

Results

Baseline Characteristics of Study Cohort

We studied 1991 CRRT patients, including 1346 (67.6%) in-hospital deaths. These patients had 9891 serum [K+] values within 24 hours after receiving CRRT, with a median [K+] concentration per patient was 3.6 mmol/L, median [K+] variability was 0.5 mmol/L, and a median number of [K+] measurements was 5. The median age of CRRT patients was 70 years; 1267(63.6%) were men, 1561 (78.4%) were treated in the medical ICU. There were 575 (28.9%) in oliguria, 452 (22.7%) in anuria, 501 (25.2%) in AKI achieves KDIGO-defined serum creatinine elevation, and 463 (23.3%) in others.

Table 1 shows the baseline characteristics of CRRT patients stratified by [K+] levels. Patients in the higher mean [K+] group had more elevated [K+] variability, WBC count, platelet count, pH, and creatinine, and had a higher prevalence of CKD and insulin use. Older age and the highest prevalence of DM were observed in patients with mean [K+] level at 4.0 to < 4.5 mmol/L; patients with mean [K+] levels of 3.0 to < 4.0 mmol/L were more likely to use ECMO; patients with mean [K+] levels at 4.5 to < 5.0 mmol/L had the lowest urine output. The lowest prevalence of death was observed in patients with mean [K+] levels between 3.0 to < 3.5 mmol/L.

Table 1
Baseline characteristics of CRRT patients according to categories of serum potassium

	The levels of serum [K+] within 24 hours after initial CRRT						*P* value
	< 3.0	3.0 to < 3.5	3.5 to < 4.0	4.0 to < 4.5	4.5 to < 5.0	≥5.0	
Sample size	86	477	663	394	217	154	
Gender, Male	50 (58.1%)	286 (60%)	427 (64.4%)	251 (63.7%)	147 (67.7%)	106 (68.8%)	0.189
Age	66 (56–78)	69 (56–80)	70 (59–80)	73 (62–81)	71 (60–80)	70 (58–82)	0.007
BMI	23.1 (20.3–26.6)	24.4 (21.5–28)	24.6 (21.4–27.5)	24.2 (20.9–28.2)	25 (21.8–27.8)	24 (22.1–28.9)	0.261
APACHE II at admission	29 (23–37)	28 (22–35)	29 (22–35)	29 (22–35)	30 (24–36)	30 (23–38)	0.071
ICU type							
Medicine ICU	54 (62.8%)	355 (74.4%)	531 (80.1%)	319 (81%)	175 (80.6%)	127 (82.5%)	0.001
Surgery ICU	32 (37.2%)	122 (25.6%)	132 (19.9%)	75 (19%)	42 (19.4%)	27 (17.5%)	
The average level of serum [K+] within 24 hours after initial CRRT	2.9 (2.7–2.9)	3.3 (3.2–3.4)	3.7 (3.6–3.9)	4.2 (4.1–4.4)	4.7 (4.6–4.9)	5.4 (5.2–5.7)	< 0.001
The variability of serum [K+] within 24 hours after initial CRRT	0.51 (0.36–0.71)	0.40 (0.26–0.58)	0.46 (0.33–0.66)	0.55 (0.39–0.78)	0.64 (0.46–0.91)	0.78 (0.58–1.11)	< 0.001
Q1: <0.35	20 (23.3%)	190 (39.8%)	193 (29.1%)	74 (18.8%)	30 (13.8%)	13 (8.4%)	< 0.001
Q2: 0.35 to < 0.50	22 (25.6%)	116 (24.3%)	178 (26.8%)	100 (25.4%)	35 (16.1%)	15 (9.7%)	
Q3: 0.50 to < 0.78	35 (40.7%)	144 (30.2%)	249 (37.6%)	175 (44.4%)	107 (49.3%)	72 (46.8%)	
Q4: ≥0.78	9 (10.5%)	27 (5.7%)	43 (6.5%)	45 (11.4%)	45 (20.7%)	54 (35.1%)	
Diagnostic criteria for AKI							
Oliguria	19 (22.1%)	146 (30.6%)	201 (30.3%)	114 (28.9%)	65 (30%)	30 (19.5%)	< 0.001
Anuria	11 (12.8%)	93 (19.5%)	155 (23.4%)	104 (26.4%)	49 (22.6%)	40 (26%)	
AKI achieves KDIGO-defined serum Creatinine elevation	22 (25.6%)	107 (22.4%)	152 (22.9%)	109 (27.7%)	59 (27.2%)	52 (33.8%)	
Others	34 (39.5%)	131 (27.5%)	155 (23.4%)	67 (17%)	44 (20.3%)	32 (20.8%)	
Timing of initiated CRRT*							
Early Strategy	56 (65.1%)	279 (58.5%)	412 (62.1%)	225 (57.1%)	124 (57.1%)	85 (55.2%)	0.323
Delayed Strategy	30 (34.9%)	198 (41.5%)	251 (37.9%)	169 (42.9%)	93 (42.9%)	69 (44.8%)	
Vital Sign							
Systolic BP (mmHg)	110 (104–123)	109 (102–122)	110 (101–120)	111 (102–120)	110 (101–125)	110 (99–121)	0.851
Diastolic BP (mmHg)	58 (52–66)	59 (52–66)	59 (52–68)	57 (51–65)	58 (52–67)	59 (51–67)	0.564
Pulse rate (bpm)	107 (88–122)	105 (88–117)	103 (88–117)	100 (85–115)	105 (90–117)	101 (87–114)	0.158
Body Temperature (degree Celsius)	36.2 (35.5–37.2)	36.2 (35.4–36.9)	36.2 (35.4–36.8)	36.1 (35.4–36.8)	36.2 (35.6–36.9)	36.2 (35.7–36.9)	0.556
Respiratory rate (/min)	20 (17–24)	20 (17–23)	20 (17–23)	20 (17–22)	21 (18–23)	21 (18–25)	0.009
SPO2	98 (95–99)	97 (95–99)	97 (95–99)	97 (95–99)	97 (95–99)	96 (94–98)	0.118
Multiple organ support before CRRT— no. (%)							
Invasive mechanical ventilation	77 (89.5%)	423 (88.7%)	578 (87.2%)	333 (84.5%)	187 (86.2%)	127 (82.5%)	0.270
Extracorporeal Membrane Oxygenation (ECMO)	10 (11.6%)	73 (15.3%)	92 (13.9%)	30 (7.6%)	12 (5.5%)	4 (2.6%)	< 0.001
Vasopressors support with norepinephrine or epinephrine	70 (81.4%)	400 (83.9%)	547 (82.5%)	332 (84.3%)	184 (84.8%)	129 (83.8%)	0.942

*Early-strategy group was defined by the renal-replacement therapy was initiated within 24 hours after admins hospital documentation of failure-stage acute kidney injury.

	The levels of serum [K+] within 24 hours after initial CRRT						*P* value
	< 3.0	3.0 to < 3.5	3.5 to < 4.0	4.0 to < 4.5	4.5 to < 5.0	≥5.0	
Medication use before CRRT — no. (%)							
Sedative	54 (62.8%)	358 (75.1%)	482 (72.7%)	284 (72.1%)	146 (67.3%)	111 (72.1%)	0.136
Corticosteroids	49 (57%)	264 (55.3%)	372 (56.1%)	225 (57.1%)	129 (59.4%)	94 (61%)	0.807
Loop diuretic	86(100%)	477(100%)	663(100%)	394(100%)	217(100%)	154(100%)	–
Parental nutrition	79 (91.9%)	401 (84.1%)	537 (81.0%)	330 (83.8%)	178 (82.0%)	144 (93.5%)	0.002
Furosemide	47 (54.7%)	237 (49.7%)	307 (46.3%)	206 (52.3%)	105 (48.4%)	83 (53.9%)	0.292
Antibiotics	84 (97.7%)	459 (96.2%)	619 (93.4%)	369 (93.7%)	210 (96.8%)	146 (94.8%)	0.113
Insulin use within 24 hours after initial CRRT	36 (41.9%)	254 (53.2%)	355 (53.5%)	230 (58.4%)	130 (59.9%)	108 (70.1%)	< 0.001
Urine Output before CRRT — ml/24 hr	25 (6–52)	16 (4–35)	10 (2–29)	10 (3–29)	6 (0–22)	14 (2–42)	< 0.001
Coexisting conditions — no. (%)							
Hypertension	20 (23.3%)	170 (35.6%)	260 (39.2%)	152 (38.6%)	81 (37.3%)	59 (38.3%)	0.101
Diabetes Mellitus	24 (27.9%)	149 (31.2%)	248 (37.4%)	162 (41.1%)	79 (36.4%)	53 (34.4%)	0.030
Hyperlipidemia	10 (11.6%)	67 (14%)	122 (18.4%)	71 (18%)	37 (17.1%)	31 (20.1%)	0.221
Coronary artery disease	12 (14%)	100 (21%)	171 (25.8%)	107 (27.2%)	52 (24%)	33 (21.4%)	0.050
Congestive heart failure	4 (4.7%)	51 (10.7%)	145 (21.9%)	95 (24.1%)	40 (18.4%)	26 (16.9%)	< 0.001
Chronic pulmonary disease	8 (9.3%)	80 (16.8%)	132 (19.9%)	72 (18.3%)	52 (24%)	29 (18.8%)	0.056
Chronic Renal Disease	24 (27.9%)	145 (30.4%)	247 (37.3%)	162 (41.1%)	91 (41.9%)	64 (41.6%)	0.002
Malignancy	14 (16.3%)	87 (18.2%)	91 (13.7%)	73 (18.5%)	35 (16.1%)	32 (20.8%)	0.163
Laboratory data before CRRT							
Albumin, mg/dL	1.9 (1.5–2.4)	2.1 (1.7–2.6)	2.3 (1.9–2.8)	2.3 (1.8–2.9)	2.2 (1.7–2.8)	2.2 (1.7–2.6)	< 0.001
Hemoglobin, g/dL	9 (9–11)	10 (9–11)	10 (9–12)	9 (8–11)	10 (8–11)	10 (8–11)	0.022
WBC count, 1000/uL	9 (5–13)	11 (7–18)	12 (7–17)	12 (8–18)	13 (9–21)	13 (8–20)	< 0.001
Platelet count, 1000/uL	74 (33–121)	95 (58–170)	109 (58–181)	111 (64 –183)	136 (72–208)	141 (79–228)	< 0.001
pH	7.3 (7.2–7.4)	7.3 (7.3–7.4)	7.3 (7.3–7.4)	7.3 (7.2–7.4)	7.3 (7.2–7.4)	7.3 (7.2–7.4)	0.003
Sodium, mmol/L	139 (133–145)	139 (134–143)	138 (134–142)	138 (134–142)	137 (134–141)	137 (133–142)	0.103
Lactate, mmol/L	5.1(1.6–9)	4(1.9–8.5)	4.1(1.7–8.7)	3.6(1.8–8.5)	3.5(2.1–8.1)	5.4(1.6–9.7)	0.737
Calcium, mg/dL	7 (7–8)	8 (7–8)	8 (7–8)	8 (7–9)	8 (7–8)	8 (7–9)	< 0.001
Base Excess, mmol/L	-9 (-13– -6)	-8 (-11– -5)	-7 (-11– -4)	-8 (-11– -4)	-8 (-11– -5)	-8 (-12– -4)	0.235
O2 Saturation, %	99 (97–100)	98 (96–100)	98 (96–100)	98 (96–100)	98 (96–100)	98 (95–100)	0.220
Creatinine, mg/dL	2.0 (1.0–3.1)	1.9 (1.2–3.3)	2.5 (1.4–4.3)	2.4 (1.3–5.2)	2.8 (1.4–5.1)	2.7 (1.3–4.9)	< 0.001
Outcome							
In-hospital mortality	59 (68.6%)	302 (63.3%)	435 (65.6%)	276 (70.1%)	160 (73.7%)	114 (74.0%)	0.024
28-day mortality	52 (60.5%)	246 (51.6%)	353 (53.2%)	234 (59.4%)	137 (63.1%)	107 (69.5%)	< 0.001

*Early-strategy group was defined by the renal-replacement therapy was initiated within 24 hours after admins hospital documentation of failure-stage acute kidney injury.

	The levels of serum [K+] within 24 hours after initial CRRT						*P* value
	< 3.0	3.0 to < 3.5	3.5 to < 4.0	4.0 to < 4.5	4.5 to < 5.0	≥5.0	
90-day mortality	59 (68.6%)	295 (61.8%)	431 (65%)	276 (70.1%)	158 (72.8%)	112 (72.7%)	0.014

*Early-strategy group was defined by the renal-replacement therapy was initiated within 24 hours after admins hospital documentation of failure-stage acute kidney injury.

Association of Mean [K+] Levels after CRRT Initiation With Mortality

As shown in Fig. 2A, the lowest incidence of death (in-hospital, 28-day and 90-day) was observed in patients with [K+] levels of 3.0 to < 3.5 mmol/L (23.9, 29.4, and 15.9 incidences of death per 100 patient-days, respectively) and the highest in that of [K+] level ≥5.0 mmol/L (42.4, 63.6 and 27.4 incidences of death per 100 patient-days, respectively). Mortality rates were slightly higher for [K+] levels of < 3.0 mmol/L (30.4, 38.8, and 20.9 incidences of death per 100 patient-days, respectively), compared with those with levels between 3.0 to < 3.5 mmol/L.

In the unadjusted model, serum [K+] levels of 4.0 to < 4.5, 4.5 to < 5.0, and ≥5.0 mmol/L were associated with an increased risk of mortality; serum [K+] levels of < 3.0 mmol/L were marginally increased mortality in Table 2. After adjustments, the risk of in-hospital death was also significant in those with [K+] of 4.0 to < 4.5, 4.5 to < 5.0, and ≥5.0 mmol/L [Hazard ratio (HR) and 95% confidence interval (CI) = 1.59 (1.31−1.94), 1.85(1.44−2.36) and 1.72(1.30−2.27), respectively]. The risk of 28-day and 90-day mortality was also significant in those with [K+] of 4.0 to < 4.5, 4.5 to < 5.0, and ≥5.0 mmol/L [HR and 95% CI = 1.65(1.32−2.07), 2.00(1.52−2.64) and 2.10(1.54−2.86) for 28-day mortality; HR and 95% CI = 1.66(1.35−2.04), 2.06(1.60−2.66) and 1.96(1.45−2.64) for 90-day mortality, respectively]. In contrast, patients with [K+] levels of < 3.0 mmol/L showed an increased tendency of mortality, although not statistically significant (Table 2). As shown in Figs. 3A, 3C, 3E, restricted cubic spline modeling associated with mortality and mean serum [K+] as continuous variables were J-shaped. All mortality risks were lowest at serum [K+] values of approximately 3.0 to < 3.5 mmol/L, increased steadily with serum [K+], and increased slightly at [K+] levels < 3.0 mmol/L, which was consistent with the results of the multivariate Cox model.

Table 2
Crude and adjusted hazard ratio for in-hospital, 28-day, 90-day mortality

	In-hospital mortality				28-day mortality				90-day mortality			
	cHR (95% CI)	P value	aHR (95% CI)[a]	P value	cHR (95% CI)	P value	aHR (95% CI)[b]	P value	cHR (95% CI)	P value	aHR (95% CI)[c]	P value
Serum [K+] level												
< 3.0	1.28 (0.97–1.70)	0.082	1.24 (0.88–1.75)	0.228	1.28 (0.95–1.73)	0.104	1.10 (0.74–1.63)	0.630	1.23 (0.93–1.63)	0.142	0.99 (0.68–1.44)	0.968
3.0 to < 3.5	Reference		Reference		Reference		Reference		Reference		Reference	
3.5 to < 4.0	1.10 (0.95–1.27)	0.200	1.17 (0.97–1.39)	0.094	1.06 (0.90–1.25)	0.477	1.15 (0.93–1.41)	0.194	1.08 (0.93–1.26)	0.289	1.15 (0.95–1.39)	0.150
4.0 to < 4.5	1.32 (1.12–1.56)	0.001	1.59 (1.31–1.94)	< 0.001	1.29 (1.08–1.54)	0.006	1.65 (1.32–2.07)	< 0.001	1.30 (1.10–1.53)	0.002	1.66 (1.35–2.04)	< 0.001
4.5 to < 5.0	1.46 (1.20–1.76)	< 0.001	1.85 (1.44–2.36)	< 0.001	1.47 (1.20–1.82)	< 0.001	2.00 (1.52–2.64)	< 0.001	1.43 (1.18–1.73)	< 0.001	2.06 (1.60–2.66)	< 0.001
≥5.0	1.77 (1.42–2.19)	< 0.001	1.72 (1.30–2.27)	< 0.001	1.90 (1.51–2.38)	< 0.001	2.10 (1.54–2.86)	< 0.001	1.66 (1.33–2.06)	< 0.001	1.96 (1.45–2.64)	< 0.001
Serum [K+] variability												
Q1: <0.35	1.09 (0.93–1.27)	0.273	1.12 (0.93–1.35)	0.2421	1.09 (0.92–1.30)	0.299	1.10 (0.89–1.36)	0.381	1.05 (0.90–1.23)	0.539	1.07 (0.88–1.30)	0.490
Q2: 0.35 to < 0.50	Reference		Reference		Reference		Reference		Reference		Reference	
Q3: 0.50 to < 0.78	1.14 (0.99–1.32)	0.067	1.06 (0.89–1.26)	0.500	1.14 (0.97–1.33)	0.101	1.04 (0.86–1.27)	0.688	1.11 (0.96–1.28)	0.149	1.04 (0.87–1.24)	0.677
Q4: ≥0.78	1.62 (1.34–1.96)	< 0.001	1.31 (1.03–1.65)	0.027	1.71 (1.40–2.10)	< 0.001	1.39 (1.06–1.82)	0.018	1.61 (1.33–1.95)	< 0.001	1.43 (1.11–1.83)	0.005

Abbreviations: CI = confidence interval; cHR = crude hazard ratio; aHR = adjusted hazard ratio; aHR was calculated from multivariate Cox proportional regression model with a stepwise elimination procedure and variables with a p-value < 0.05 in a univariate model were included in a multivariate model. Model 0: age, BMI, APACHE II at admission, strategy time, creatinine, O2 saturation, base excess, platelet count, albumin, lactate, calcium, sodium, hemoglobin, diabetes mellitus, hypertension, hyperlipidemia, chronic renal disease, malignancy, vasopressor, corticosteroids, parental nutrition, antibiotics, invasive mechanical ventilation, SPO2, respiratory rate, pulse rate, systolic BP, diastolic BP and body temperature³36.2 were commonly used confounders in mortality models. [a] adjusted for variables in model 0 plus chronic pulmonary disease and insulin use. [b] adjusted for variables in model 0 plus furosemide. [c] adjusted for variables in model 0 plus chronic pulmonary disease, furosemide and insulin use.

Association of Potassium Variability after CRRT Initiation with Mortality

Figure 2B shows no tendency in mortality in patients with [K+] variability < 0.78 mmol/L (Q1 to Q3). In contrast, patients with [K+] variability greater than 0.78 mmol/L (Q4) had the highest mortality rates (41.4, 59.3, and 30.9 incidences of death per 100 patient-days, respectively). In the unadjusted model, the highest [K+] variability (Q4) was associated with increased mortality risk. After adjustments, the risk of in-hospital death was also significant in those with the highest [K+] variability [HR and 95% CI = 1.31(1.03–1.65) for in-hospital mortality; 1.39(1.06–1.82) for 28-day mortality and 1.43(1.11–1.83) for 90-day mortality, respectively]. As shown in Figs. 3B, 3D, and 3F, the risk of death was less pronounced when the [K+] variability was < 0.78 mmol/L, while the mortality risk increased steadily when the variability was greater than 0.78 mmol/L, which is also consistent with the results of Table 2.

In-hospital Mortality Risk matrix of mean [K+] Levels and its variability

Figure 4 is an in-hospital mortality risk matrix that combines mean [K+] level categories with [K+] variability quantiles. Patients with a higher category of mean [K+] levels and concomitant larger [K+] variability exhibited a higher risk of death (Fig. 4). In general, in patients with serum [K+] levels < 4.0 mmol/L, changes in [K+] did not increase the risk of death, except for serum [K+] levels < 3.0 mmol/L combined with [K+] variability less than 0.35, and serum [K+] levels at 3.5 to < 4.0 mmol/L combined with [K+] variability more than 0.78. Patients with serum [K+] levels ≥4.0 mmol/L, regardless of the change in [K+] value, have a higher risk of death.

Other significant factors affecting in-hospital mortality

The association between other factors and in-hospital mortality is reported in Fig. 5. A significantly higher risk of in-hospital mortality was associated with vasopressor use [HR and 95% CI = 1.25 (1.01–1.56)], higher lactate [HR and 95% CI = 1.05 (1.03–1.06)], higher respiratory rate [HR and 95% CI = 1.03 (1.01–1.05)], higher pulse rate [HR and 95% CI = 1.01 (1.00–1.01)], higher APACHE II score [HR and 95% CI = 1.02 (1.02–1.03)], older age [HR and 95% CI = 1.01 (1.01–1.02)], and delayed strategy of CRRT initiation [HR and 95% CI = 1.57 (1.36–1.82)]. Lower risk of in-hospital mortality was associated with higher creatinine [HR and 95% CI = 0.96 (0.93–0.98)], higher O2 saturation [HR and 95% CI = 0.98 (0.97–0.99)], higher base excess [HR and 95% CI = 0.98 (0.97–1.00)], higher platelet count [HR and 95% CI = 0.99 (0.98–1.00)], higher albumin [HR and 95% CI = 0.82 (0.74–0.90)], pre-existing of diabetes mellitus [HR and 95% CI = 0.82 (0.71–0.94)], and higher of systolic BP [HR and 95% CI = 0.99 (0.99–1.00)]. Body temperature over 36.2 marginally protective against death [HR and 95% CI = 0.87 (0.75–1.01)].

Discussion

Our study observed a strong correlation between serum [K+] level and ICU mortality with a J-shaped association, and mean [K+] level between 3.0 to 4.0 mmol/L showed the lowest mortality rate. In-hospital and ICU mortality were significantly higher with hyperkalemic (mean serum [K+] ≥ 4.0 mmol/L) patients but increased insignificantly with hypokalemic (mean serum [K+] < 3.0 mmol/L) patients. Furthermore, higher [K+] variability within the first 24 hours after initiation of CRRT indicated increased mortality. In addition, we found that delayed strategy (CRRT initiated > 24 hours after renal failure) would increase mortality risk.

There is a lack of evidence that the mean [K+] level and [K+] variability are associated with mortality in AKI patients requiring CRRT in ICU. Serum [K+] level 3.5 to 5.0 mmol/L is currently accepted as a safe range for critically ill patients.[17] In a retrospective study conducted by Hessels et al. in 2015 [17], a U-shaped association between [K+] and in-hospital mortality for all ICU patients had been reported, and serum [K+] levels between 3.5 and 5.0 mmol/L were associated with the lowest mortality. However, the optimal range of serum [K+] levels for specific patient groups in ICU remains inconclusive. This issue has been studied in several cohorts, such as 3.5 to 4.5 mmol/L [18] and even 4.5 to 5.5 mmol/L [19] in acute myocardial infarction and > 3.5 to 4.0 mmol/L in patients with atrial fibrillation [13]. However, in the acute stage of ARDS patients with positive fluid balance, relative hyperkalemia (up to 5.9 mmol/L) is associated with a reduced risk of death [20]. Compared to previous reports, our study observed a tighter [K+] level (3.0–4.0 mmol/L) in AKI patients supported with CRRT in ICU. The possible explanation was that those patients requiring CRRT were often hemodynamically unstable and needed intravenous inotropic agents. These inotropic agents, such as norepinephrine, epinephrine, vasopressin, or dopamine, were commonly known as arrhythmogenic [21]. Both lower and higher serum values have electrophysiological effects of promoting cardiac arrhythmias or myocardial ischemia [22–23]. Those patients with CRRT in ICU are assumed to be more vulnerable to cardiovascular events and may require a stricter control of serum [K+] level. Thus, [K+] level of 3.5 to 5.0 mmol/L should not be regarded as a normal range in this critical population. To go a step further, the [K+] monitoring and correction protocol for CRRT in each institute may need revision to achieve a better clinical outcome.

The variability or fluctuations of serum [K+] level recently emerged as a new focus on investigating its relationship with mortality in the hospital setting. In a monocentric and retrospective observational study by G. Lombardi et al. in Rome, 64,057 hospitalized patients were analyzed. High [K+] variability was reported to be an independent risk factor of in-hospital mortality, even within the normal [K+] range [24]. However, according to this large-scale cohort study, the data was insufficient to address the relationship in specific medical conditions. Some previous studies were designed to investigate the association in critically-ill patients. Using a computerized regulation protocol designed for surgical ICU [25] to minimize the time in hypo- and hyperkalemia, Hessels et al. reported a low mortality rate with the lower [K+] variability [17]. In the Soroka Acute Myocardial Infarction II (SAMI-II) Project, [K+] variability was associated with increased risk of mortality in patients with acute myocardial infarction (AMI) [26]. Thongprayoon et al. reported hypokalemia (≤ 3.4 mmol/L) and hyperkalemia (≥ 4.5 mmol/L) before CRRT and hyperkalemia (≥ 4.5 mmol/L) during CRRT predicted higher 90-day mortality [27]. Nevertheless, studies evaluating the prognostic value of [K+] fluctuations in patients with CRRT settings are scarce. As far as we know, our study was the first study to describe this issue. Although a direct causal relationship cannot be demonstrated in our study design, there are several possible explanations of the relationship between [K+] variability and mortality in our study. First, fluctuation in cell membrane resting electrical conditions could increase cellular instability and increase the risk of arrhythmogenic deaths. Another potential explanation is that higher [K+] variability may be a surrogate marker of baseline characteristics or disease processes with a poorer prognosis. Interestingly, very low [K+] variability was associated with an increased mortality rate in both hypo- and hyperkalemia (Fig. 4). This phenomenon reminded clinicians to correct dyskinesia more intensively to a normokalemic status.

In line with previous studies, we observed lower mortality in patients with higher serum albumin levels [28] and pre-existing diabetes mellitus [29]. On the contrary, the delayed strategy of CRRT was associated with increased risk, similar to the result in the ELAIN randomized clinical trial [30]. In addition, vasopressors therapy and the presence of malignancy were also risk factors for mortality, and the association has been reported in previous studies [31–32]. It's noteworthy that our study was observed marginally lower mortality with higher body temperature. Hypothermia was reported to have negative clinical consequences [33–34]. In ICU patients, hypothermia risk is increased by sedation, immobility, paralytic drugs, sepsis, underlying endocrine disorders, and higher CRRT dose. However, the patients' body temperature could partially be manipulated via extracorporeal blood circulation and warming system in CRRT. Whether the body temperature is a maker or indicator for ICU mortality and the optimal body temperature range during CRRT could not be explained clearly in our study and warranted further investigation.

There are some limitations to be considered in our study. First, this was a retrospective observational study, and therefore, a causal relationship between serum [K+] level or variability and mortality could not be concluded. Second, we pooled all adult patients in medical and surgical ICUs together. However, different [K+] target ranges may depend on individual conditions. Third, some possible residual confounders may not be considered despite the adjusted analysis. Furthermore, we did not record the exact causes of death to better address the mechanistic linkage in our findings. Finally, we conducted this study

using a large-scale electronic database from a single center with a primarily Taiwanese patient population. This design might limit the generalizability of our results to other patient populations.

Conclusion

Our findings indicate that adult AKI patients with CRRT in ICU may benefit from a more stringent [K+] control target between 3.0 and 4.0 mmol/L within 24 hours after initiation of CRRT. A negative correlation was observed between mortality and [K+] variability, but the causal relationship is not clear yet. Dealing with dyskalemia, a prompt but careful correction with minimal [K+] fluctuation is suggestive. Further large randomized controlled trials are needed to confirm our findings and may change CRRT protocol and routine in the future.

Abbreviations

CI
confidence interval
cHR
crude hazard ratio
aHR
adjusted hazard ratio
aHR was calculated from multivariate Cox proportional regression model with a stepwise elimination procedure and variables with a p-value < 0.05 in a univariate model were included in a multivariate model.

Declarations

Authors' contributions

Conception and design: I.C.M, Acquisition of data: I.C.M, P.R.L, and C.T.K, Interpretation of data: I.C.M, P.R.L, S.H.W, H.H.H, P.S.H, and C.T.K. Statistical analysis: P.R.L and C.T.K. Drafting of the manuscript: I.C.M and C.T.K. Final revision of manuscript: I.C.M, P.R.L, S.H.W, H.H.H, P.S.H, and C.T.K. Study supervision: C.T.K. All authors read and approved the final manuscript

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Availability of data materials

The dataset of the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Institutional Review Board of CCH granted the waiver for informed consent and approved the study (IRB No: 211214).

Consent for publication

Not applicable.

Competing interests

The author reports no conflicts of interest in this work.

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Figures

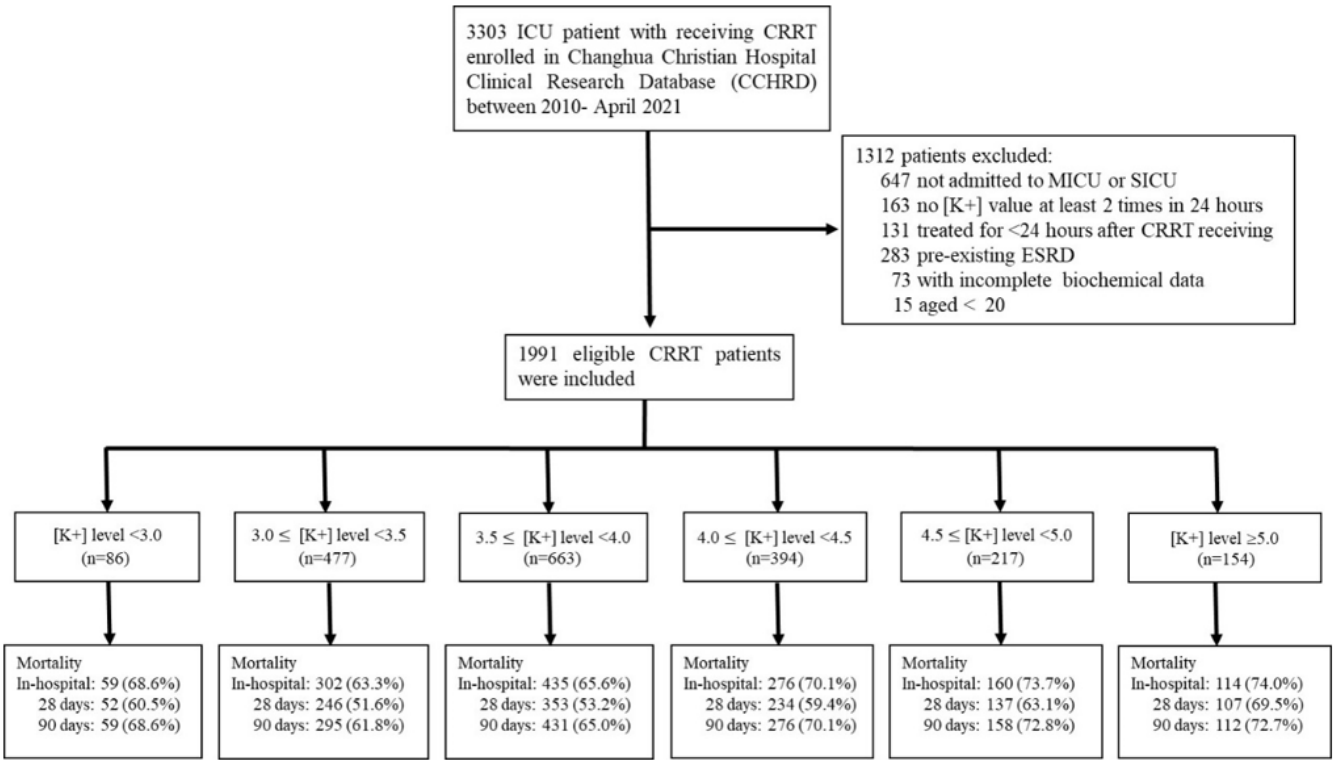

Figure 1

Flowchart of the study population

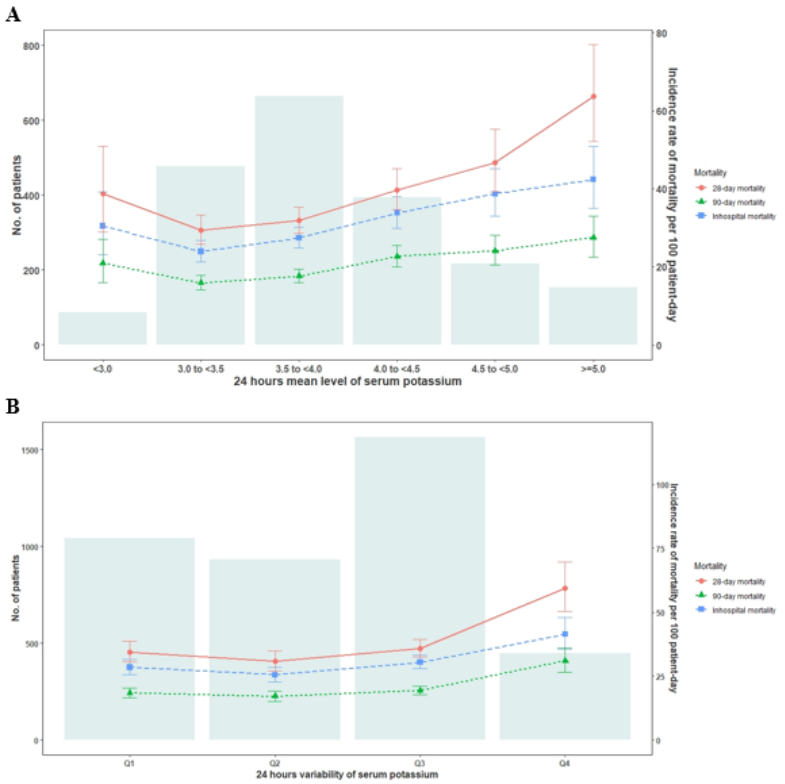

Figure 2

The distribution of serum [K+] level and serum [K+] variability within 24 hours after initial CRRT and corresponding mortality rate. (**A**) serum [K+] level within 24 hours after initial CRRT; (**B**) serum [K+] variability within 24 hours after initial CRRT

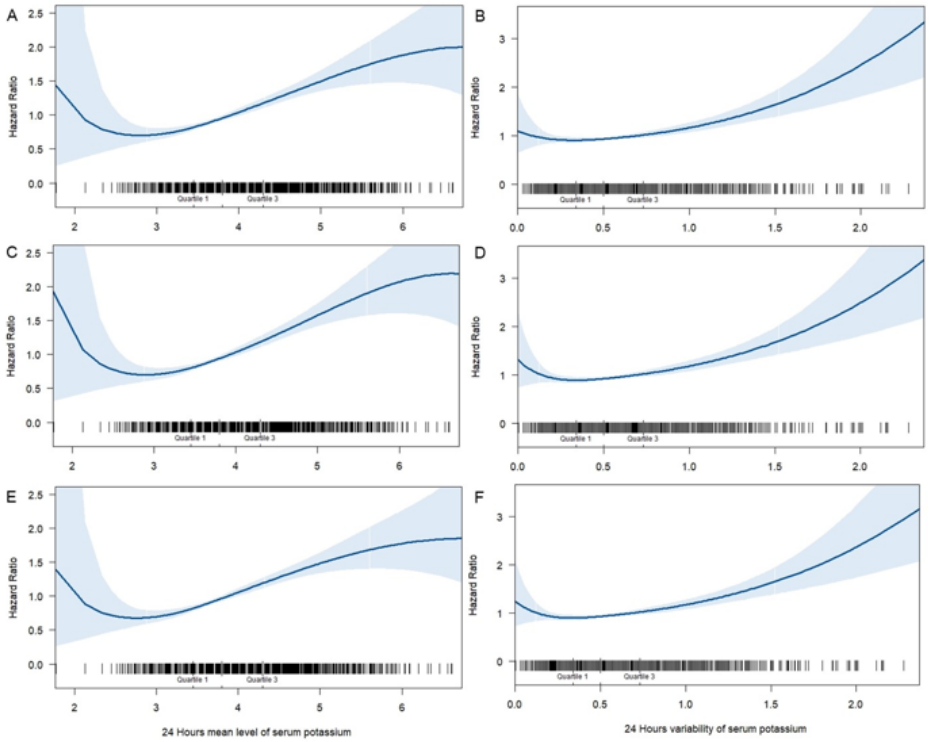

Figure 3

The restricted cubic spline plots depicting the association between serum [K+] level, variability and mortality risk. (**A**) In-hospital mortality on serum [K+] level; (**B**) In-hospital mortality on serum [K+] variability; (**C**) 28-day mortality on serum [K+] level; (**D**) 28-day mortality on serum [K+] variability; (**E**) 90-day mortality

on serum [K+] level; (**F**) 90-day mortality on serum [K+] variability.

		Serum potassium level					
		<3.0	3.0 to <3.5	3.5 to <4.0	4.0 to <4.5	4.5 to <5.0	>=5.0
Serum potassium variability	Q1: <0.35	**2.11**	1.12	1.22	**1.79**	**2.47**	**2.15**
	Q2: 0.35 to <0.50	1.05	1 (reference)	1.08	**1.90**	**2.01**	**5.71**
	Q3: 0.50 to <0.78	0.93	1.28	1.34	**1.65**	**2.31**	**2.08**
	Q4: >=0.78	0.97	0.93	**2.26**	**2.47**	**2.66**	**2.39**

Figure 4

Risk matrices showing the adjusted HRs for in-hospital mortality by using serum potassium level categories and variability in quartiles. The color of the reference cells is white. For HR <1.0 were represented as blue, while for HR >1.0 was pink. We color the cells from light to dark (away from 1.0). The numbers in bold indicate they are significant (P<0.05).

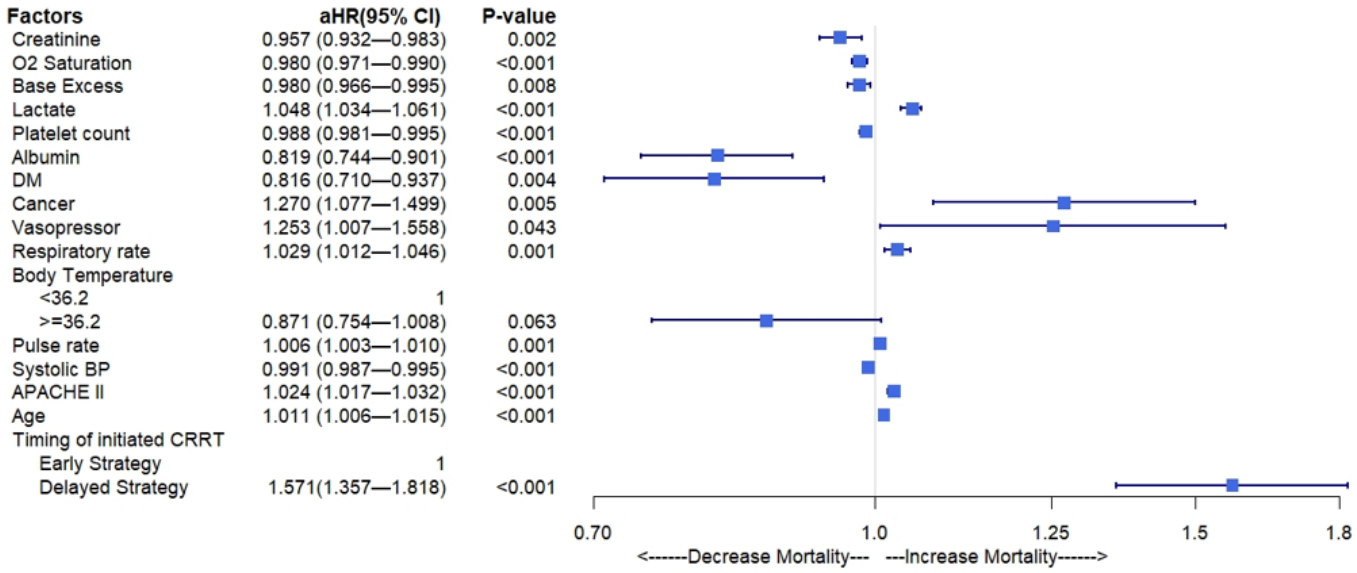

Figure 5

Other significant factor associated with mortality