Title:

Low-dose Continuous Kidney Replacement Therapy and Mortality in Critically Ill Patients with Acute Kidney Injury: A Retrospective Cohort Study

Running title: Mortality and Low-dose CKRT

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ABSTRACT

Rationale & Objective: Continuous kidney replacement therapy (CKRT) is preferred when available for hemodynamically unstable acute kidney injury (AKI) patients in the intensive care unit (ICU). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a delivered CKRT dose of 20–25 mL/kg/h, however in Japan, doses are typically below this recommendation due to government health insurance system restrictions. This study investigated the association between mortality and dose of CKRT.

Study Design: Single-center retrospective cohort study.

Setting & Participants: Critically ill patients with AKI treated with CKRT at a tertiary Japanese university hospital between January 1, 2012, and December 31, 2021.

Exposure: Delivered CKRT doses below or above the median.

Outcome: 90-day mortality after CKRT initiation.

Analytical Approach: Multivariable Cox regression analysis and Kaplan–Meier analysis.

Results: The study population consisted of 494 patients. The median age was 72 years, and 309 patients (62.6%) were men. Acute tubular injury was the leading cause of AKI, accounting for 81.8%. The median delivered CKRT dose was 13.2 mL/kg/h. 456 (92.3%) study participants received delivered CKRT doses below 20 mL/kg/h, and 204 (41.3%) died within 90 days after CKRT initiation. Multivariable Cox regression analysis revealed increased mortality in the below-median group (hazard ratio: 1.73, 95% confidence interval: 1.19–2.51, P = 0.004). Additionally, a significant, inverse, non-linear association between 90-day mortality and delivered CKRT dose was observed using delivered CKRT dose as a continuous variable.

Limitations: Single-center, retrospective, observational study.

Conclusions: A lower delivered CKRT dose was independently associated with higher 90-day mortality among critically ill patients who mostly received dosing below current KDIGO

recommendations.

Index Words: Continuous kidney replacement therapy, acute kidney injury, delivered continuous kidney replacement therapy dose, The Kidney Disease: Improving Global Outcomes guidelines recommendation, mortality.

Plain Language Summary

Title: Low doses of Continuous Kidney Replacement Therapy in Patients with Acute Kidney Injury Are Associated with Higher Mortality

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend delivering a continuous kidney replacement therapy (CKRT) dose of 20–25 mL/kg/h. However, it is not clear if it is safe to use delivered CKRT doses below this recommendation. In this study, where over 90% of patients received CKRT with a delivered dose below the KDIGO recommendation, we divided the patients into two groups based on the median delivered CKRT dose. Our findings show that a delivered CKRT dose below the median was associated with increased risk of death within 90 days. These findings show that a lower delivered CKRT dose was independently associated with higher 90-day mortality among critically ill patients who mostly received dosing below current KDIGO recommendations.

INTRODUCTION

Continuous kidney replacement therapy (CKRT) is an important intervention for hemodynamically unstable patients with acute kidney injury (AKI) in the intensive care unit (ICU). The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend delivering an effluent volume (CKRT dose) of 20 to 25 mL/kg/h for CKRT in AKI.[1] This recommendation is based on the results of two randomized controlled trials (RCTs): the "Acute Renal Failure Trial Network (ATN)" study and the "Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy" study.[2,3]

The ATN study compared mortality within 60 days between a CKRT dose of 20 and 35 mL/kg/h, while the RENAL study compared mortality within 90 days between 25 and 40 mL/kg/h.[2,3] Both studies demonstrated no statistically significant difference in mortality between the groups. Though notably the delivered dose was lower than the prescribed dose in both the ATN and RENAL studies,[4] the KDIGO guidelines suggest prescribing a CKRT dose of 25 to 30 mL/kg/h to achieve a delivered dose of 20 to 25 mL/kg/h.[1] Thus, the prescribed dose occasionally may not be delivered because of CKRT treatment interruption, known as "CKRT down-time." CKRT down-time is caused by various factors, such as dysfunctional vascular access, mobilization from the ICU for imaging studies or surgery, and intended/unintended filter changes to manage clotting.[5] A previous study conducted in the U.S. found that 20.7% of patients who underwent CKRT had delivered CKRT doses below 20 mL/kg/h.[6]

In Japan, the CKRT dose differs from other countries due to restrictions imposed by the Japanese government health insurance system, aimed at reducing healthcare costs for the aging society.[7] This system covers a fixed range of 15 to 20 L of dialysate plus replacement fluid per day, irrespective of the patients' body weight.[8] In other words, a standard practice in Japan is to prescribe a fixed dialysate plus replacement fluid rate of either 700 mL/h (16.8

L/day) or 800 mL/h (19.2 L/day) regardless of the patients' body weight. As a result, a typical CKRT dose range in Japan is 10 to 15 mL/kg/h, and the CKRT dose is mainly affected by the patients' body weight.[7,8] Therefore, most hospitals in Japan do not follow the KDIGO recommendation in terms of the CKRT dose. In countries following the KDIGO recommendation, CKRT doses below 20 mL/kg/h have been regarded as undertreatment and assumed to result in worse outcomes, although there is no evidence to support this assumption.[9,10] However, the CKRT dose in Japan is usually below 20 mL/kg/h, although there is also no evidence to support the effectiveness of this approach.[8] In this study, we investigated the association between mortality and delivered CKRT dose among patients treated with dosing mostly below the KDIGO recommendation.

METHODS

Study Design, Population, and CKRT

This single-center retrospective cohort study evaluated consecutive Japanese adult patients (aged ≥ 20 years) who underwent CKRT in the medical and surgical ICU at Nara Medical University Hospital between January 1, 2012, and December 31, 2021. The following patients were excluded from the study: those with end-stage kidney disease (ESKD), those who died within 24 hours after ICU admission, those who underwent CKRT for non-renal indications, and those who received CKRT for more than 28 days. The information of the CKRT machines and solution used during the study periods was presented in **Table S1**. The study protocol was approved by the Ethics Committee of Nara Medical University Hospital (Approval No. 3288), and the requirement for informed consent was waived because of the retrospective design.

Data Collection and Measurements

Baseline patient and CKRT information collected at the time of CKRT initiation included age, sex, body mass index (BMI), body weight, mean arterial pressure (MAP), urine

output, Acute Physiology and Chronic Health Evaluation (APACHE) II score,[11] comorbidities such as hypertension or diabetes mellitus, baseline serum creatinine, cause of AKI, presence of sepsis, modality of CKRT, dialysis catheter site, type of anticoagulation, use of mechanical ventilation, vasopressor requirement, and laboratory data. The mean delivered CKRT dose, mean prescribed CKRT dose, and ratio of delivered CKRT dose to prescribed CKRT dose were calculated from the data of electronic medical record (EMR), and included as baseline information. Hourly CKRT status parameters such as blood flow rate, dialysate flow rate, replacement fluid flow rate, and fluid removal rate, as well as the time of CKRT interruption and restart, implementation of filter change, daily patient body weight, and hourly vasopressor flow rate, were recorded in the EMR. The CKRT dose (mL/kg/h) was defined as the sum of the replacement fluid rate (mL/h), fluid removal rate (mL/h), and dialysate fluid rate (mL/h), divided by the patient's body weight (kg). To calculate the delivered CKRT dose, we collected data regarding the daily actual total use of replacement fluid and dialysate fluid, as well as the daily total fluid removal and daily actual CKRT running time from the EMR. Laboratory data were available regarding hemoglobin, C-reactive protein (CRP), serum albumin, blood urea nitrogen (BUN), serum creatinine, serum potassium, and pH and bicarbonate from arterial blood gas analysis. The APACHE II score was calculated within the first 24 h of ICU admission.

Exposures, Major Confounders, and Outcomes

The exposure variable in this study was the delivered CKRT dose, which was used to categorize patients into two groups according to whether the delivered CKRT dose was above or below the median. Analyses were performed with adjustment for potential confounding variables, including age, sex, MAP at the time of CKRT initiation, BMI, urine output on the day of CKRT initiation, APACHE II score, presence of sepsis, mechanical ventilation use at the time of CKRT initiation, and laboratory data including hemoglobin, serum albumin, BUN,

serum creatinine, and CRP; these variables have been associated with mortality in critically ill patients.[11-20] The primary outcome of interest was all-cause mortality within 90 days after CKRT initiation; secondary outcomes included norepinephrine-equivalent total and mean pressor requirement while receiving CKRT, CKRT duration, length of ICU stay, and length of hospital stay. Vasopressor dose was standardized to norepinephrine equivalents using conversion formulas from a previous study (**Table S2**).[21]

Statistical Analysis

Patient and CKRT characteristics are shown as medians (interquartile ranges) for continuous variables and numbers (percentages) for categorical variables. The Mann–Whitney U test and Pearson's chi-squared test were used for comparisons of continuous and categorical variables, respectively. The correlation between the prescribed dialysate plus replacement fluid rate and the patients' body weight was assessed using Pearson correlation coefficient.

To evaluate the association between mortality and delivered CKRT dose, we performed univariable and multivariable Cox regression analyses to calculate hazard ratios (HRs), as well as the Kaplan–Meier method and the log-rank test. The dependent variable in the Cox regression analysis was all-cause death within 90 days after CKRT initiation. Fourteen independent variables were included in the multivariable Cox regression analysis: CKRT dose above versus below the median, age, sex, MAP at the time of CKRT initiation, BMI, urine output on the day of CKRT initiation, APACHE II score, presence of sepsis, mechanical ventilation use at the time of CKRT initiation, as well as the levels of hemoglobin, serum albumin, BUN, serum creatinine, and CRP. We also conducted a multivariable Cox regression analysis using the delivered CKRT dose as a continuous variable instead of CKRT dose above versus below the median. The relationship between adjusted HRs for 90-day mortality and delivered CKRT dose was presented via a restricted cubic spline curve with 3 knots. Secondary outcomes were assessed by both unadjusted (Mann–Whitney U test) and

adjusted (Analysis of Covariance) analyses. A subgroup analysis was performed to evaluate whether the observed association interacted with relevant variables such as age, sex, BMI, APACHE II score, and presence of sepsis.

Two sensitivity analyses were conducted to determine study robustness. The first sensitivity analysis included multivariable Cox regression and subgroup analysis, like the primary analysis. It focused on patients' prescribed dialysate and replacement fluid rates, not on delivered CKRT dose, with categories of ≥800 mL/h or <800 mL/h. The second sensitivity analysis was a multivariable Cox regression analysis, categorizing the delivered CKRT dose into four groups: <10, 10–14.9, 15–19.9, and ≥20 mL/kg/h.

All statistical tests were considered to be significant at two-sided $P < 0.05$. Missing data for multivariable Cox regression analysis was handled by the complete case analysis since, out of fourteen independent variables, serum albumin was the only one with missing values (3 out of 494 patients, 0.6%). All analyses were performed using R statistical software version 4.1.3 (R Foundation for Statistical Computing).

RESULTS

Patient Flow

In total, 603 patients received CKRT between January 1, 2012, and December 31, 2021; after the exclusion of 109 patients based on the predefined criteria, 494 patients were included in the analysis (**Figure 1**). These 494 patients were classified into two groups (below-median and above-median; n = 247 per group) based on the median delivered CKRT dose of 13.2 mL/kg/h.

Baseline Patient and CKRT Characteristics

Tables 1 and **2** show the baseline patient and CKRT characteristics, respectively. The median patient age was 72 years, and 62.6% of patients were men. Acute tubular injury was the leading cause of AKI (81.8%). Nafamostat mesylate was the most commonly used

anticoagulant. The median delivered CKRT dose was 13.2 mL/kg/h, and 456 (92.3%) patients received delivered CKRT doses below 20 mL/kg/h in the entire crude cohort. **Figure S1** shows a histogram of the mean prescribed dialysate plus replacement fluid rate. Most patients had a mean prescribed dialysate plus replacement fluid rate of either 700 or 800 mL/h. **Figure S2** shows the correlation between the mean prescribed dialysate plus replacement fluid rate and patients' body weight. The Pearson correlation coefficient indicated statistically significant but little correlation between the mean prescribed dialysate plus replacement fluid rate and patients' body weight (correlation coefficient 0.12, P = 0.007). Patients in the below-median group were younger (68 versus 76 years), more frequently men (74.9% versus 50.2%), had a higher BMI (24.8 versus 19.8 kg/m^2), were less anemic (hemoglobin level of 10.7 versus 9.8 g/dL), had a higher serum creatinine level (2.7 versus 2.3 mg/dL), were less septic (42.1 versus 52.2%), and less mechanical ventilation use (66.0 versus 74.5%) at the time of CKRT initiation. The median delivered CKRT doses were 11.3 mL/kg/h in the below-median group and 16.2 mL/kg/h in the above-median group. MAP at the time of CKRT initiation, urine output on the day of CKRT initiation, APACHE II score, serum albumin, BUN, and CRP did not significantly differ between the groups. Nearly all patients underwent post-dilution continuous venovenous hemodiafiltration, with the exception of one patient in the below-median group and two patients in the above-median group who underwent continuous venovenous hemodialysis. Among the fourteen independent variables used for multivariable Cox regression analysis, missing data were identified only in the variable of serum albumin, accounting for 3 out of 494 patients (0.6%); one patient in the below-median group and two patients in the above-median group. The remaining thirteen independent variables did not exhibit any missing data.

Primary Outcome

Within 90 days after CKRT initiation, a total of 204 (41.3%) out of 494 patients died

in the entire cohort: 102 (41.3%) out of 247 patients in both the below-median and the above-median groups each. The 90-day survival curves according to Kaplan–Meier analysis are shown in **Figure 2A**. There was no statistically significant difference in the 90-day survival rate between the two groups (log-rank test, P = 0.9). In the univariable Cox regression analysis, there was no statistically significant difference in the 90-day mortality between the groups. The HR for 90-day mortality in the below-median group was 1.00 [95% confidence interval (CI): 0.76–1.32, P = 0.9]. However, in the multivariable Cox regression analysis using predefined fourteen variables, a statistically significant increase in 90-day mortality was observed in the below-median group. The adjusted HR for 90-day mortality in the below-median group was 1.73 [95% CI: 1.19–2.51, P = 0.004]. The parameter estimates for each independent variable of the multivariable Cox regression analysis were presented in **Table S3**. **Figure 2B** shows the survival curves generated from the multivariable Cox regression analysis. We next conducted a multivariable Cox regression analysis using delivered CKRT dose as a continuous variable. We included the same variables used in the above analysis, except for the delivered CKRT dose, which was changed from a categorical variable to a continuous variable. **Figure 3** displays the restricted cubic spline curve with 3 knots, illustrating the relationship between adjusted HRs for 90-day mortality and delivered CKRT doses. Delivered CKRT dose displayed a significant, inverse, non-linear relationship with adjusted HRs for 90-day mortality (P = 0.02, P for non-linearity = 0.02).

Secondary Outcomes

The secondary outcomes are summarized in **Table 3**. There were no statistically significant differences observed between the below-median and above-median groups regarding norepinephrine-equivalent total pressor dose, norepinephrine-equivalent mean pressor rate, delivered CKRT duration, length of ICU stay, and length of hospital stay in both unadjusted and adjusted analyses.

Subgroup Analyses

In the subgroup analyses, presented in **Figure 4**, there were no statistically significant interactions observed in the subgroups.

Sensitivity Analyses

As the first sensitivity analysis, we performed a multivariable Cox regression analysis to assess the impact of prescribed dialysate plus replacement fluid rate (≥800 or <800 mL/h) on outcomes. This analysis aimed to assess the influence of fluid rate choice on outcomes, independently of body weight. Baseline patient and CKRT characteristics between these two groups were presented in **Tables S4** and **S5**, respectively. **Table S6** shows the results of the multivariable Cox regression analysis, showing no statistically significant difference between the groups. Subgroup analysis was depicted in **Figure S3**, indicating no statistically significant interactions among subgroups.

As the second sensitivity analysis, we performed a multivariable Cox regression analysis by categorizing delivered CKRT doses into four groups: <10, 10–14.9, 15–19.9, and ≥20 mL/kg/h. Baseline patient and CKRT characteristics for these groups were presented in **Tables S7** and **S8**, respectively. The results of the multivariable Cox regression analysis are summarized in **Table S9**. Among the four delivered CKRT dose groups, with the 15–19.9 mL/kg/h group as the reference, a statistically significant increase in 90-day mortality was observed in the 10–14.9 mL/kg/h group. The adjusted hazard ratio for 90-day mortality in the 10–14.9 mL/kg/h group was 1.53 [95% CI: 1.03–2.27, P = 0.04].

DISCUSSION

In this single-center retrospective study, we investigated the association between mortality and delivered CKRT dose using a unique Japanese cohort, in which more than 90% of patients received CKRT with a delivered dose below the KDIGO recommendation. Our results showed that treatment with a delivered CKRT dose below the median was

independently associated with increased mortality compared to treatment with a delivered CKRT dose above the median but mostly below the KDIGO recommendation.

Most previous studies have compared mortality between the KDIGO-recommended CKRT doses (20–25 mL/kg/h) and higher CKRT doses; they have not shown a survival benefit associated with the receipt of higher CKRT doses.[2,3] Since the publication of the ATN and RENAL studies, it has been speculated that the relationship between CKRT dose and survival plateaus between 20 and 40 mL/kg/h.[9,10] CKRT doses below 20 mL/kg/h have been regarded as undertreatment in countries following the KDIGO recommendation, whereas under the Japanese healthcare system, the CKRT dose is typically below 20 mL/kg/h.[8-10] This discrepancy arises from the different approach in determining the CKRT dose; the target CKRT dose of 20 to 25 mL/kg/h and patients' body weight determine the daily amount of dialysate plus replacement fluid in countries following the KDIGO recommendation, whereas in Japan, a fixed daily amount of dialysate plus replacement fluid of 15 to 20 L, along with patients' body weight, determines the CKRT dose. Consequently, this fixed low daily amount of dialysate plus replacement fluid in Japan ultimately results in a low CKRT dose compared to the KDIGO recommendation.

Two retrospective observational studies were conducted in Japan to assess the relationship between a low CKRT dose and mortality; both studies suggested that a low CKRT dose did not increase mortality.[22,23] These two studies generated a hypothesis that the "floor" CKRT dose may be lower than 20 mL/kg/h. These data and this hypothesis have become increasingly significant in light of the coronavirus disease 2019 pandemic, as hospitals have strived to conserve valuable CKRT resources to treat as many patients as possible safely and effectively.[4] Also, CKRT may have unintended detrimental consequences, such as phosphorus depletion and amino acid depletion.[24] Therefore, determining the floor CKRT dose may be important in anticipating potential supply shortages caused by pandemic

or disaster as well as in mitigating the unintended detrimental consequences caused by CKRT. Our study assesses the relationship between mortality in AKI patients and a delivered CKRT dose below the KDIGO recommendation. It demonstrates that a delivered CKRT dose below the median is independently associated with worse outcomes. The results of this study suggest that there is a possible threshold below which mortality increases below the KDIGO-recommended dose range of 20–25 mL/kg/h. Our findings could be valuable for the future prospective studies to confirm if such a threshold exists and, if so, to determine the threshold dose.

This study had several limitations. First, the observational nature of the study potentially allowed unknown confounding factors, thereby preventing assessment of causality. Second, the median delivered CKRT dose of 13.2 mL/kg/h in our study considerably deviated from the KDIGO recommendation, and more than 90% of the study patients underwent CKRT with a delivered dose below 20 mL/kg/h. Therefore, our study is not essentially capable of comparing the current KDIGO-recommended delivered CKRT dose with a dose below it, even though our results generate a hypothesis that the "floor" CKRT dose may be lower than 20 mL/kg/h. The ideal approach for comparison of survival between CKRT doses would be an RCT. However, the performance of an RCT comparing the KDIGO-recommended CKRT dose and lower CKRT dose in countries that adhere to the KDIGO recommendation would be challenging because lower than the KDIGO-recommended CKRT dose is regarded as undertreatment. Third, our findings may have limited generalizability because of the single-center study design and the practice patterns that are uncommon outside of Japan. For example, the use of Nafamostat mesylate as an anticoagulant for CKRT and delivery of >95% of prescribed dose are uncommon in western countries. Nafamostat mesylate, a synthetic serine protease inhibitor commonly used in Japan and South Korea,[25] has a short half-life and low molecular weight, making it suitable for elimination through

dialysis.[26] This property can extend filter life without increasing bleeding risk.[27,28] The high prescribed dose delivery may be attributed to widespread anticoagulation use at CKRT initiation and a low filtration fraction, which may have reduced filter clotting risk. Therefore, it is theoretically possible that our findings may not apply to centers which utilize different anticoagulants or having higher amounts of CKRT down-time. Finally, some data regarding baseline patient characteristics were missing because of the retrospective study design; however, the impact of missing data on the multivariable Cox regression analysis in our study may be minimal, given the low percentage of missing data (0.6% in the variable of serum albumin).

In conclusion, our results in this single-center retrospective study suggest that among critically ill patients who mostly received dosing below current KDIGO recommendations, lower delivered CKRT dosing was independently associated with higher 90-day mortality. Given the inherent limitations in our study design, our findings await confirmation in future prospective studies.

Supplementary Material

Figure S1: Histogram of the mean prescribed dialysate plus replacement fluid rate.
Figure S2: Scatter plots of Pearson correlation coefficient between the mean prescribed dialysate plus replacement fluid rate and patients' body weight.
Figure S3: Subgroup analyses comparing prescribed dialysate plus replacement fluid rates of ≥800 mL/h versus <800 mL/h.
Table S1: CKRT machines and solution used during the study periods.
Table S2: Vasopressor standardization to norepinephrine equivalents.
Table S3: Parameter estimates for each independent variable of multivariable Cox regression analysis for the primary analysis.
Table S4: Baseline patient characteristics comparing prescribed dialysate plus replacement fluid rates of ≥800 mL/h versus <800 mL/h.
Table S5: Baseline CKRT characteristics comparing prescribed dialysate plus replacement fluid rates of ≥800 mL/h versus <800 mL/h.
Table S6: Parameter estimates for each independent variable of multivariable Cox regression analysis comparing prescribed dialysate plus replacement fluid rates of ≥800 mL/h versus <800 mL/h.
Table S7: Baseline patient characteristics based on categorizing delivered CKRT doses into

four groups.
Table S8: Baseline CKRT characteristics based on categorizing delivered CKRT doses into four groups.
Table S9: Parameter estimates for each independent variable of multivariable Cox regression analysis comparing among four categories of delivered CKRT dose.

Article Information

Authors' Contributions: Conceptualization: KO; Data curation: KO; Statistical analysis: KO; Methodology: KO; Supervision/mentorship: HF, MK, and KT. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.
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TABLES

Table 1. Baseline patient characteristics

Characteristics	Overall (n = 494)	Below median (n = 247)	Above median (n = 247)	P
Age (years)	72 [62, 81]	68 [58, 77]	76 [67, 83]	<0.001
Sex (Male, n (%))	309 (62.6)	185 (74.9)	124 (50.2)	<0.001
Body mass index (kg/m^2)	22.1 [19.5, 25.2]	24.8 [22.6, 27.8]	19.8 [17.5, 21.6]	<0.001
Body weight (kg)	56.5 [48.0, 67.0]	66.0 [59.6, 75.4]	48.3 [42.0, 53.9]	<0.001
Mean arterial pressure (mmHg)	76 [64, 90]	76 [64, 91]	77 [63, 88]	0.5
Urine output (mL/day)	322 [107, 729]	332 [110, 790]	307 [100, 643]	0.2
APACHE II score	25 [19, 30]	24 [19, 30]	26 [20, 31]	0.2
Hypertension, n (%)	253 (51.2)	130 (52.6)	123 (49.8)	0.5
Diabetes mellitus, n (%)	135 (27.3)	76 (30.8)	59 (23.9)	0.09
Baseline serum creatinine (mg/dL)	0.9 [0.7, 1.3]	0.9 [0.7, 1.3]	0.9 [0.7, 1.3]	0.2
Cause of AKI, n (%)				0.7
Acute tubular injury	404 (81.8)	199 (80.6)	205 (83.0)	
Nephrotoxic agent	29 (5.9)	17 (6.9)	12 (4.9)	
Cardiorenal	9 (1.8)	5 (2.0)	4 (1.6)	
Hepatorenal	10 (2.0)	7 (2.8)	3 (1.2)	
Other	15 (3.0)	6 (2.4)	9 (3.6)	
Unknown	27 (5.5)	13 (5.3)	14 (5.7)	
Sepsis, n (%)	233 (47.2)	104 (42.1)	129 (52.2)	0.02
Hemoglobin (g/dL)	10.1 [8.6, 12.2]	10.7 [9.0, 12.9]	9.8 [8.5, 11.4]	<0.001
C-reactive protein (mg/dL)	10.0 [2.7, 19.8]	11.2 [3.2, 23.1]	9.2 [2.7, 18.2]	0.1
Serum albumin (g/dL)	2.7 [2.3, 3.2]	2.7 [2.3, 3.2]	2.7 [2.3, 3.1]	0.7
Blood urea nitrogen (mg/dL)	49 [30, 73]	49 [29, 67]	51 [32, 78]	0.1
Serum creatinine (mg/dL)	2.5 [1.7, 3.7]	2.7 [1.9, 4.0]	2.3 [1.5, 3.5]	0.02
Serum potassium (mEq/L)	4.4 [3.8, 5.2]	4.5 [3.8, 5.2]	4.4 [3.8, 5.2]	0.9
pH on ABG	7.35 [7.27, 7.41]	7.35 [7.28, 7.41]	7.34 [7.26, 7.41]	0.9
Bicarbonate on ABG (mEq/L)	19.0 [15.7, 22.7]	18.7 [15.6, 21.8]	19.3 [15.7, 23.0]	0.2
Mechanical ventilation, n (%)	347 (70.2)	163 (66.0)	184 (74.5)	0.04
Vasopressor, n (%)	358 (72.5)	172 (69.6)	186 (75.3)	0.2

Note: Data are shown as median [interquartile range] or number (percentage). The number of missing values is as follows: Baseline serum creatinine, 35.2%; Serum albumin, 0.6%; all others have no missing values.

Abbreviations: APACHE, acute physiology and chronic health evaluation; AKI, acute kidney injury; ABG, arterial blood gas.

Table 2. Baseline CKRT characteristics

Characteristics	Overall (n = 494)	Below median (n = 247)	Above median (n = 247)	P
CKRT modality (CVVHDF, n (%))	491 (99.4)	246 (99.6)	245 (99.2)	0.6
Catheter placement, n (%)				0.4
Right internal jugular vein	196 (39.7)	101 (40.9)	95 (38.5)	
Right femoral vein	196 (39.7)	100 (40.5)	96 (38.9)	
Left femoral vein	76 (15.4)	32 (13.0)	44 (17.8)	
Left internal jugular vein	14 (2.8)	6 (2.4)	8 (3.2)	
Right subclavian vein	1 (0.2)	1 (0.4)	0 (0.0)	
Left subclavian vein	1 (0.2)	0 (0.0)	1 (0.4)	
ECMO circuit	10 (2.0)	7 (2.8)	3 (1.2)	
Anticoagulation, n (%)				0.2
Nafamostat Mesylate	444 (89.9)	217 (87.9)	227 (91.9)	
Heparin	20 (4.0)	15 (6.1)	5 (2.0)	
Heparin + Nafamostat Mesylate	17 (3.4)	8 (3.2)	9 (3.6)	
Argatroban Hydrate	1 (0.2)	1 (0.4)	0 (0.0)	
None	12 (2.4)	6 (2.4)	6 (2.4)	
Prescribed dialysate + replacement fluid rate ≥800 ml/h, n (%)	256 (51.8)	106 (42.9)	150 (60.7)	<0.001
Net ultrafiltration intensity (mL/kg/h)[a]	0.15 [0.00, 0.80]	0.11 [0.00, 0.67]	0.23 [0.00, 0.99]	0.3
Net ultrafiltration rate (mL/day)	190.2 [0.0, 1131.0]	171.7 [0.0, 1066.7]	218.3 [0.0, 1194.3]	0.9
Prescribed CKRT dose (mL/kg/h)	13.9 [11.8, 16.5]	11.8 [10.6, 12.8]	16.4 [15.0, 18.6]	<0.001
Delivered CKRT dose (mL/kg/h)	13.2 [11.3, 16.2]	11.3 [9.9, 12.2]	16.2 [14.5, 18.3]	<0.001
CKRT dose delivered (%)	99.0 [95.7, 100]	98.4 [92.8, 100]	99.4 [96.9, 100]	<0.001
CKRT dose range, n (%)				<0.001
<10 mL/kg/h	67 (13.6)	67 (27.1)	0 (0.0)	
10–14.9 mL/kg/h	266 (53.8)	180 (72.9)	86 (34.8)	
15–19.9 mL/kg/h	123 (24.9)	0 (0.0)	123 (49.8)	
20–25 mL/kg/h	30 (6.1)	0 (0.0)	30 (12.1)	
>25 mL/kg/h	8 (1.6)	0 (0.0)	8 (3.2)	
Filtration fraction (%)[b]	10.2 [7.8, 12.0]	10.2 [7.9, 12.1]	10.0 [7.7, 11.9]	0.9

Note: Data are shown as median [interquartile range] or number (percentage). There are no missing values for any variables.

[a]Net UF intensity was calculated as the net UF rate in mL/h divided by patients' body weight (kg).

[b]Filtration fraction for post-dilution CVVHDF and CVVHD was calculated by dividing the total ultrafiltration rate by the plasma flow rate at the time of CKRT initiation, expressed as a percentage. The plasma flow rate was calculated as the blood flow rate multiplied by (1 − hematocrit).

Abbreviations: CKRT, continuous kidney replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; CVVHD, continuous venovenous hemodialysis.

Table 3. Secondary outcomes

	Unadjusted				Adjusted	
	Overall (n = 494)	**Below median (n = 247)**	**Above median (n = 247)**	**P**	**Difference (Below - Above)**	**P**
NE-equivalent total pressor dose on CKRT (mcg)	9675 [190, 28523]	11250 [720, 35385]	8500 [56, 25265]	0.2	5040.5	0.2
NE-equivalent mean pressor rate on CKRT (mcg/kg/min)	0.05 [0.00, 0.13]	0.04 [0.00, 0.12]	0.05 [0.00, 0.14]	0.5	0.017	0.2
Delivered CKRT duration (hours)	57.8 [30.8, 115.2]	58.3 [34.4, 115.1]	54.0 [27.8, 120.3]	0.7	-10.56	0.3
ICU stay (days)	8 [3, 15]	8 [3, 17]	7 [4, 14]	0.2	-5.1	0.4
Hospital stay (days)	29 [13, 56]	27 [14, 55]	30 [14, 57]	0.7	-6.9	0.3

Note: Data are shown as median [interquartile range]. Unadjusted analysis was conducted using Mann–Whitney U test. Adjusted analysis was performed via Analysis of Covariance (ANCOVA), using the same covariates as the primary analysis. These covariates include being below or above the median of delivered CKRT dose, age, sex, MAP at the time of CKRT initiation, BMI, urine output on the day of CKRT initiation, APACHE II score, presence of sepsis, mechanical ventilation use at the time of CKRT initiation, and laboratory data including hemoglobin, serum albumin, BUN, serum creatinine, and CRP. Adjusted results were presented as the difference between the below-median and above-median groups (below-median group minus above-median group).

Abbreviations: NE, norepinephrine; CKRT, continuous kidney replacement therapy; ICU, intensive care unit; MAP, mean arterial pressure; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; CRP, C-reactive protein.

FIGURE LEGENDS

Figure 1: Patient flow chart
Abbreviations: CKRT, continuous kidney replacement therapy; ESKD, end-stage kidney disease; ICU, intensive care unit.

Figure 2: Unadjusted and adjusted survival curves.
A: 90-day unadjusted survival curves for each group, generated using the Kaplan–Meier method and assessed with the log-rank test. B: 90-day adjusted survival curves for each group, generated from the multivariable Cox regression analysis. The variables for adjustment included age, sex, MAP, BMI, urine output, APACHE II score, presence of sepsis, mechanical ventilation use, hemoglobin, serum albumin, BUN, serum creatinine, and CRP.
Abbreviations: MAP, mean arterial pressure; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; CRP, C-reactive protein.

Figure 3: Association between adjusted HR for 90-day mortality and delivered CKRT dose: restricted cubic spline with 3 knots.
Solid line represents the HR, and the gray area represents the 95% CI for HRs. The reference level was set at the median of the delivered CKRT dose. A histogram of the patients is shown below the cubic spline curve. The HRs were adjusted for age, sex, MAP, BMI, urine output, APACHE II score, presence of sepsis, mechanical ventilation use, hemoglobin, serum albumin, BUN, serum creatinine, and CRP. Delivered CKRT dose displayed a significant, inverse, non-linear relationship with adjusted HRs for 90-day mortality ($P = 0.02$, P for non-linearity = 0.02).
Abbreviations: HR, hazard ratio; CKRT, continuous kidney replacement therapy; CI, confidence interval; MAP, mean arterial pressure; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; CRP, C-reactive protein.

Figure 4: Forest plot of adjusted HRs in subgroup analyses.
The positions of the squares represent adjusted HRs, and the error bars crossing the squares indicate the corresponding 95% confidence intervals. The HRs were adjusted for age, sex, MAP, BMI, urine output, APACHE II score, presence of sepsis, mechanical ventilation use, hemoglobin, serum albumin, BUN, serum creatinine, and CRP.
Abbreviations: HR, hazard ratio; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; MAP, mean arterial pressure; BUN, blood urea nitrogen; CRP, C-reactive protein.