

# The Association of an Early Net Ultrafiltration Rate and 28-day Mortality in Patients Receiving Continuous Kidney Replacement Therapy: a Cohort Study

**Buyun Wu**

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

**Yining Shen**

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

**Yudie Peng**

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

**Changying Xing**

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

**Huijuan Mao** (✉ [maohuijuan72@hotmail.com](mailto:maohuijuan72@hotmail.com))

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

<https://orcid.org/0000-0001-7410-1486>

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## Research

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# Abstract

**Background:** An early net ultrafiltration (NUF) rate may be associated with prognosis in patients receiving continuous kidney replacement therapy (CKRT). In this study, we tested whether high or low early NUF rates in patients treated with CKRT were associated with increased mortality.

**Methods:** We conducted a retrospective, observational study among all patients in the Medical Information Mart for Intensive Care IV database who received CKRT for more than 24 hours within 14 days after intensive care unit admission. We defined the early (initial 48 hours) NUF rate as the amount of fluid removal per hour adjusted by the patients' weight and took it as a classified variable (low rate: < 1.6, moderate rate: 1.6–3.1 and high rate: > 3.1 mL/kg/h). The association between 28-day mortality and the NUF rate was analyzed by logistic regression and mediation analyses.

**Results:** A total of 911 patients were included in our study. The median NUF rate was 2.71 (interquartile range 1.90–3.86) mL/kg/h and the 28-day mortality was 40.1%. Compared with the moderate NUF rate, the low NUF rate (adjusted odds ratio 1.56, 95% CI 1.04–2.35,  $p = 0.032$ ) and high NUF rate (adjusted odds ratio 1.43, 95% CI 1.02–2.01,  $p = 0.040$ ) were associated with higher 28-day mortality. The putative effect of a low or high NUF rate on 28-day mortality was possibly direct [adjusted average direct effects (ADE) 1.03,  $p = 0.096$  for a low NUF rate; adjusted ADE 0.92,  $p = 0.064$  for a high NUF rate], and also mediated by effects of the NUF rate on fluid balance during the same period [adjusted average causal mediation effects (ACME) 0.96,  $p = 0.010$  for a low NUF rate; adjusted ACME 0.99,  $p = 0.042$  for a high NUF rate]. Moreover, we found an increase trend in the NUF rate corresponding to the lowest mortality when fluid input increased.

**Conclusion:** Compared with NUF rates between 1.6–3.1 mL/kg/h in the first 48 hours of CKRT, NUF rates > 3.1 mL/kg/h and < 1.6 mL/kg/h were associated with higher mortality.

## Introduction

Fluid overload (FO), defined as an absolute increase in total body volume or a relative increase in the percentage of extracellular volume over the isovolumic status of the patient, is a common complication of all emergencies. It occurs in more than 1/3 of critically ill patients and about 2/3 of patients with acute kidney injury (AKI) who need kidney replacement therapy [1, 2], and is associated with adverse outcomes [3, 4]. For patients with oliguric AKI in whom diuretic treatment is ineffective, international practice guidelines recommend the use of net ultrafiltration (NUF) for fluid management [5, 6]. Ultrafiltration, defined as fluid removal during kidney replacement therapy, has been used in the treatment of patients with AKI and FO. Observational studies have found that ultrafiltration was able to prevent the deterioration of FO, thereby reducing the risk of death [7].

To date, the ideal NUF rate has not been determined in clinical practice due to the lack of high-quality data [8]. The NUF rate range commonly used in clinical practice is 0–10 mL/kg/h. Previous studies indicated that a low NUF rate (< 1.01 mL/kg/h) was associated with decreased survival [7, 9, 10]. A high

NUF rate ( $> 1.75$  mL/kg/h) was also related to increased mortality [7, 11, 12]. Based on these studies, Murugan and his colleagues proposed that the relationship between the NUF rate and mortality in critically ill patients receiving continuous kidney replacement therapy (CKRT) might be "J" type and that a NUF rate of 1.01–1.75 mL/kg/h might be the optimal range [7]. However, the NUF rate was influenced by fluid input and hemodynamics [5]. Patients with higher fluid input may also need a higher NUF rate. Thus, the optimal NUF rate may vary in different conditions and need to be studied further.

Here, we analyzed the association between the early NUF rate and 28-day mortality in patients receiving CKRT, and we hypothesized that a different optimal range of the NUF rate may exist.

## Methods

### Source of data

Our study was based on a public critical care database in the United States named the Medical Information Mart for Intensive Care IV (MIMIC-IV) version 0.4 [13]. The MIMIC-IV recorded the demographic data, vital signs, medications, laboratory tests and other important data of 383,220 adult admissions to the intensive care unit (ICU) in the Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2008 to 2019. The establishment of the MIMIC-IV database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and the Institutional Review Boards.

Our study was conducted entirely on publicly available, anonymized data, thus individual patient consents were waived. Because this study was an analysis of third-party anonymous public databases, we completed the National Institutes of Health's web-based course and passed the Protecting Human Research Participants exam (no.38540012 and no.32559175) to apply for access to the database.

### Study Population

A total of 2360 patients who received CKRT were recorded in the MIMIC-IV database. Patients included in this analysis were those who: (1) started CKRT treatment within 14 days of ICU admission; and (2) had a CKRT duration time of over 24 hours. Patients who met the following criteria were excluded: (1) patients who died within 48 hours of ICU admission; (2) end-stage kidney disease patients; (3) patients who received intermittent hemodialysis or plasmapheresis; and (4) patients with incomplete important confounders data or ultrafiltration data in the first 48 hours of CKRT. Incomplete ultrafiltration data refers to any of the following: the lack of weight adjusted by the hourly NUF rate in the first 48 hours of CKRT, FO percentage (defined as a positive value of total fluid input minus total fluid output, adjusted based on the patients' weight in kilograms) before CKRT, overall FO percentage 48 hours after the start of CKRT and mean arterial pressure or Vasoactive-inotropic Score (VIS); and (5) patients with an NUF rate  $> 7.49$  mL/kg/h (Fig. 1).

### Data Extraction

Data for each patient were extracted from the MIMIC-IV database by the Structured Query Language in PostgreSQL (version 12) [14]. We extracted demographic characteristics (age, sex, race, height, weight, type of admission and type of ICU), complications (hypertension, diabetes mellitus, chronic kidney disease, chronic heart failure, cancer and Charlson Comorbidity Index Score), severity of the illness [Oxford Acute Severity of Illness Score (OASIS)] [15] on the first day of admission, sequential organ failure assessment (SOFA) score [16] before CKRT, VIS [17] before CKRT, laboratory tests, vital signs, CKRT data (including CKRT settings, ultrafiltration data, fluid balance and intervals from ICU admission to CKRT) and clinical outcomes, among others.

For repeated measurement data, we evaluated the maximum and minimum values at the same time. We did not attempt to estimate the sample size of the study, and all eligible patients in the database were included to maximize the statistical power of the predictive model. As missing data may deviate the analysis, we used the multiple interpolations to deal with the missing data of body mass index (BMI), which demonstrated a missing ratio of 18.9% (172/911).

## Definitions

Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in the total SOFA score  $\geq 2$  points consequent to the infection [18]. VIS can be used to objectively quantify the degree of hemodynamic support and reflects the dosage of vasoactive drugs [17]. The definition of baseline serum creatinine was defined by the following rules: (i) if the lowest creatinine value during this admission was normal ( $< 1.1$  mg/dL), then we used the value; (ii) if the patient was diagnosed with chronic kidney disease, we used the lowest creatinine value during ICU stay, although in some cases it was rather high; and (iii) otherwise, we estimated the baseline serum creatinine using serum creatinine calculated from the simplified modification of diet in renal disease equation set to 75 mL/min per 1.73 m<sup>2</sup>.

## Exposures

The primary exposure was the NUF rate during the first 48 hours of CKRT, defined as the volume of NUF removed per hour, adjusted by the patients' weight in kilograms. The NUF rate was calculated using the following equation: NUF rate (in milliliters per kilogram per hour) = cumulative NUF volume at the end of 48 hours (in milliliters) / [weight at the beginning of CKRT (in kilograms)  $\times$  treatment duration in the first 48 hours (in hours)] [11].

## Primary Endpoint

The primary outcome was 28-day mortality. Patients discharged from the hospital alive before 28 days were considered alive at Day 28.

## Statistical Analyses

First, we confirmed that the relationship between the NUF rate and 28-day mortality was non-linear. According to the multivariate generalized additive linear model, we found that the minimum 28-day mortality was 31%. By adding 5% (taking as an acceptable boundary value) on this basis, we arrived at a mortality rate of 36% as a cutoff value, which corresponded to an NUF rate of 1.6 and 3.1 mL/kg/h. Then, we stratified the NUF rate into three groups: low (< 1.6 mL/kg/h), moderate (1.6-3.1 mL/kg/h) and high (> 3.1 mL/kg/h) (Fig. 2).

Categorical variables were presented as numbers and percentages and compared by  $\chi^2$  tests. Continuous variables were presented as medians and interquartile ranges and compared using the Wilcoxon rank-sum test.

We used Kaplan–Meier survival plots with the log-rank test to compare mortality over the first 28 days among the groups (Additional file 1: Figure S1). We applied univariate and multivariate logistic regression models with the NUF rate in the first 48 hours as a categorical variable to evaluate the relationship between the NUF rate and 28-day mortality. The confounding factors taken into account in this model included age, gender, BMI, ICU type (cardiovascular ICU or other), baseline serum creatinine, Charlson Comorbidity Index Score, OASIS on the first day of admission, sepsis on the first day of admission, need of mechanical ventilation on the first day of admission, time from ICU admission to the initiation of CKRT in minutes, mean arterial pressure before CKRT, VIS before CKRT, SOFA score before CKRT, FO percent before CKRT and cumulative FO percent in the first 48 hours of CKRT.

We assessed the robustness of the findings through multiple sensitivity analyses. First, a logistic regression model was used to evaluate the relationship between the NUF rate in the first 48 hours of CKRT and hospital mortality. Second, using a different mortality rate (34%) as the cutoff value, we evaluated the relationship between the NUF rate in the first 48 hours of CKRT and 28-day mortality. Third, as the potential impact of the NUF rate categories on the primary outcome of 28-day mortality violated the proportional hazards assumption, we applied a Gray piecewise-constant time-varying coefficients model, which considered the above-mentioned confounders. We estimated risk-adjusted hazard ratios with 95% confidence interval (CI) at five time-intervals and four nodes. The number of time intervals were selected based on prior work [9, 11, 12], and the duration of each time interval was selected by the model to ensure approximately equal distribution of deaths within each time interval. Fourth, using subgroup analysis, the patients were divided into two subgroups based on the presence or absence of FO, and logistic regression was used to evaluate the relationship between the NUF rate and 28-day mortality.

In order to explore why our ultrafiltration range was different from that of others, we divided the fluid input of the first 48 hours of CKRT into three groups according to the tertiles and divided the NUF rate into nine groups according to the eighth percentile. Then, we calculated the 28-day mortality of the three groups with different input in different NUF rate ranges.

We applied a multivariable mediation model [19-21] to investigate whether the association of the NUF rate with mortality was modulated by its effect with cumulative FO percent in the first 48 hours of CKRT

as a mediator. The following estimates were described: (1) the total effect (estimate of the total putative effect of the NUF rate on 28-day mortality); (2) the average causal mediation effect (ACME), a variable that explains how much of the putative effect of the NUF rate on mortality was explained by the possible effect of the mediator; and (3) the average direct effect (ADE), a variable that explains how much of the putative effect of the NUF rate on mortality is still explained by the rate after considering the effect of any given mediator.

All hypothesis tests were 2-tailed with a  $p$  value of  $< 0.05$  considered statistically significant. All analyses were performed using R software, version 4.0.3 [22].

## Results

### Study population

Following the inclusion and exclusion criteria, we included 911 patients from the MIMIC-IV database (Fig. 1). Among these, 165 (18.1%) had an NUF rate of  $< 1.6$  mL/kg/h, 369 (40.5%) had an NUF rate of 1.6–3.1 mL/kg/h and 377 (41.4%) had an NUF rate of  $> 3.1$  mL/kg/h (Table 1).

Table 1  
Baseline characteristics of each NUF rate group at ICU admission before CKRT

	NUF rate < 1.6 mL/kg/h (n = 165)	NUF rate 1.6–3.1 mL/kg/h (n = 369)	NUF rate > 3.1 mL/kg/h (n = 377)	p value
Age (year)	64.0(53.0, 73.0)	62.0 (51.0, 73.0)	64.0 (52.0, 74.0)	0.265
Male gender (%)	108 (65.5)	231 (62.6)	208 (55.2)	0.034
White Ethnicity (%)	97 (58.8)	237 (64.2)	252 (66.8)	0.321
Weight (kg)	100(86, 120)	99(85, 116)	83(70, 97)	< 0.001
BMI (kg/m <sup>2</sup> )	34.7 (29.3,40.0)	33.8(29.3,40.8)	29.9(26.1, 35.1)	< 0.001
Surgical admission (%)	72 (43.6)	151 (40.9)	149 (39.5)	0.668
Cardiovascular ICU (%)	67 (40.6)	121 (32.8)	98 (26.0)	0.003
Comorbidity				
Hypertension (%)	97 (58.8)	217 (58.8)	197 (52.3)	0.146
Diabetes (%)	33 (20.0)	67 (18.2)	53 (14.1)	0.155
Chronic kidney disease (%)	63 (38.2)	138 (37.4)	171 (45.4)	0.065
Chronic heart failure (%)	80 (48.5)	143 (38.8)	139 (36.9)	0.035
Cancer (%)	17 (10.3)	34 (9.2)	38 (10.1)	0.894
Charlson Comorbidity Index Score	4 (2, 5)	3(2, 5)	3 (2, 5)	0.154
OASIS day1	46(40, 51)	45 (38, 51)	46 (38, 52)	0.736
Sepsis (%)	118 (71.5)	242 (65.6)	251 (66.6)	0.389
Ventilation (%)	125 (75.8)	267 (72.4)	281 (74.5)	0.661
Baseline serum creatinine (mg/dl)	1.0 (0.8, 1.1)	0.9 (0.7, 1.1)	0.9 (0.6, 1.1)	0.249
Data before CKRT				

*Abbreviations: BMI* body mass index, *BUN* blood urea nitrogen, *CKRT* continuous renal replacement therapy, *FiO<sub>2</sub>* fraction of inspired oxygen, *FO* fluid overload, *ICU* intensive care unit, *NUF* net ultrafiltration, *OASIS* Oxford Acute Severity of Illness Score, *PaO<sub>2</sub>* partial pressure of oxygen, *PCO<sub>2</sub>* partial pressure of carbon dioxide, *SOFA* sequential organ failure assessment, *VIS* Vasoactive-inotropic Score

	NUF rate < 1.6 mL/kg/h (n = 165)	NUF rate 1.6–3.1 mL/kg/h (n = 369)	NUF rate > 3.1 mL/kg/h (n = 377)	p value
Mean Heart rate (beats/minute)	93 (81, 108)	91 (80, 103)	89 (80, 102)	0.266
Mean arterial pressure (mmHg)	71.0 (64.0, 79.0)	72.0 (66.0, 79.0)	72.0 (66.0, 81.0)	0.151
VIS	1.00 (0.00, 2.68)	0.80 (0.00, 2.35)	0.80 (0.00, 2.18)	0.465
Vasopressor (%)	111 (67.3)	247 (66.9)	247 (65.5)	0.889
Inotropics (%)	24 (14.5)	32 (8.7)	30 (8.0)	0.044
SOFA score	13 (11, 15)	13 (11, 15)	12 (10, 14)	0.002
Urine output in 6 hours (mL)	75 (17, 256)	80 (24, 220)	69 (22, 200)	0.579
Oliguria (%)	85 (55.6)	198 (56.1)	215 (61.1)	0.321
Fluid overload (%)	46 (27.9)	115 (31.2)	167 (44.3)	< 0.001
FO percent before CKRT (%)	5.2(2.0, 10.3)	5.7(2.1, 12.1)	8.6 (2.9, 15.0)	< 0.001
Interval from admission to CKRT (day)	2.0(0.8,4.6)	1.9 (0.8, 3.9)	2.1(0.9, 4.4)	0.147
Laboratory data before CKRT				
Minimum pH	7.27 (7.15, 7.35)	7.27 (7.19, 7.33)	7.27 (7.19, 7.34)	0.694
Minimum PaO <sub>2</sub> /FiO <sub>2</sub>	145(81, 206)	163 (101, 222)	158 (100, 235)	0.155
Maximum PCO <sub>2</sub> (mmHg)	45(39, 51)	44 (38, 52)	42(36, 49)	0.013
Minimum bicarbonate(mmol/L)	17(14, 22)	18 (14, 20)	17 (13, 21)	0.703
Maximum potassium (mmol/L)	5.0 (4.3, 5.6)	5.0 (4.4, 5.7)	4.8 (4.2, 5.5)	0.018
Maximum BUN (mg/dl)	59.0 (36.0, 94.0)	64.0 (42.8, 94.0)	67.0 (44.0, 97.0)	0.304

*Abbreviations: BMI* body mass index, *BUN* blood urea nitrogen, *CKRT* continuous renal replacement therapy, *FiO<sub>2</sub>* fraction of inspired oxygen, *FO* fluid overload, *ICU* intensive care unit, *NUF* net ultrafiltration, *OASIS* Oxford Acute Severity of Illness Score, *PaO<sub>2</sub>* partial pressure of oxygen, *PCO<sub>2</sub>* partial pressure of carbon dioxide, *SOFA* sequential organ failure assessment, *VIS* Vasoactive-inotropic Score

	NUF rate < 1.6 mL/kg/h (n = 165)	NUF rate 1.6–3.1 mL/kg/h (n = 369)	NUF rate > 3.1 mL/kg/h (n = 377)	<i>p</i> value
Maximum creatinine (mg/dl)	3.8 (2.8, 5.2)	4.1 (2.8, 5.3)	3.9 (2.9, 5.0)	0.356
Minimum albumin (g/dl)	2.6 (2.2, 3.2)	2.9 (2.4, 3.4)	2.9 (2.3, 3.4)	0.179
<i>Abbreviations: BMI</i> body mass index, <i>BUN</i> blood urea nitrogen, <i>CKRT</i> continuous renal replacement therapy, <i>FiO<sub>2</sub></i> fraction of inspired oxygen, <i>FO</i> fluid overload, <i>ICU</i> intensive care unit, <i>NUF</i> net ultrafiltration, <i>OASIS</i> Oxford Acute Severity of Illness Score, <i>PaO<sub>2</sub></i> partial pressure of oxygen, <i>PCO<sub>2</sub></i> partial pressure of carbon dioxide, <i>SOFA</i> sequential organ failure assessment, <i>VIS</i> Vasoactive-inotropic Score				

Table 1 shows the baseline characteristics of the study patients according to NUF rate category. The group with an NUF rate < 1.6 mL/kg/h was mostly male, heavier, had higher BMI, more were from the cardiovascular ICU, more were complicated by chronic heart failure, there was more usage of inotropic drugs and higher SOFA scores. There were no differences in disease severity scores such as the Carlson score, OASIS on the first day of ICU admission, baseline creatinine level, urine volume 6 hours before CKRT, VIS before CKRT or other key baseline characteristics (such as the presence of sepsis or oliguria or the need for vasopressor or mechanical ventilation). In the group with an NUF rate < 1.6 mL/kg/h, the positive value of FO before CKRT was smaller and less complicated with FO. The group with an NUF rate of 1.6–3.1 mL/kg/h was more likely to have higher maximum serum potassium.

Table 2 shows the baseline characteristics of the three groups after the beginning of CKRT and clinical outcomes. The group with a high NUF rate was more likely to require citrate anticoagulation and had more negative fluid balance. There was no significant difference among the three groups in terms of CKRT mode, duration of CKRT and lengths of hospital and ICU stay after the start of CKRT. The group with a moderate NUF rate had lower 28-day mortality, hospital mortality and ICU mortality and was more likely to be independent of CKRT.

Table 2  
Characteristics of the therapy and clinical outcomes

	NUF rate < 1.6 mL/kg/h (n = 165)	NUF rate 1.6–3.1 mL/kg/h (n = 369)	NUF rate > 3.1 mL/kg/h (n = 377)	<i>p</i> value
CKRT mode (%)				0.588
CVVH	15 (9.1)	30 (8.1)	22 (5.8)	
CVVHD	2 (1.2)	5 (1.4)	3 (0.8)	
CVVHDF	147 (89.1)	329 (89.2)	350 (92.8)	
SCUF	1 (0.6)	5 (1.4)	2 (0.5)	
Dose of CKRT (mL/kg/h)	25.1 (20.5, 28.4)	24.7 (20.9, 28.1)	26.6 (22.9, 30.0)	< 0.001
Anticoagulation (%)				< 0.001
Citrate + heparin	6 (3.6)	5 (1.4)	13 (3.4)	
Citrate	59 (35.8)	216 (58.5)	293 (77.7)	
Heparin	29 (17.6)	29 (7.9)	14 (3.7)	
None	71 (43.0)	119 (32.2)	57 (15.1)	
Duration of CKRT (hour)	137.9 (80.0, 224.0)	129.4 (70.0, 266.1)	120.0 (71.0, 212.0)	0.301
FO percent in first 24h of CKRT (%)	0.0 (−2.0, 2.6)	−1.2 (−2.7, 0.6)	−2.1 (−3.9, 0.3)	< 0.001
FO percent in second 24h of CKRT (%)	−0.5 (−2.0, 1.4)	−1.8 (−3.2, −0.4)	−2.8 (−4.8, −1.0)	< 0.001
FO percent in first 48h of CKRT (%)	−0.6 (−3.3, 3.7)	−2.8 (−5.2, −0.2)	−4.8 (−8.1, −1.3)	< 0.001
FO percent in total CKRT (%)	−3.9 (−9.3, 3.6)	−7.7 (−13.6, −2.7)	−9.2 (−15.9, −3.1)	< 0.001
NUF data in first 48h of CKRT				
Median mean NUF (mL/h)	113 (72, 146)	226 (181, 285)	350 (297, 414)	< 0.001
Median prescribed NUF (mL/h)	230 (150, 350)	350 (260, 425)	410 (350, 500)	< 0.001

*Abbreviations:* CKRT continuous renal replacement therapy, CVVH continuous veno-venous hemofiltration, CVVHD continuous veno-venous hemodialysis, CVVHDF continuous veno-venous hemodiafiltration, FO fluid overload, ICU intensive care unit, NUF net ultrafiltration, SCUF slow continuous ultrafiltration

	NUF rate < 1.6 mL/kg/h (n = 165)	NUF rate 1.6–3.1 mL/kg/h (n = 369)	NUF rate > 3.1 mL/kg/h (n = 377)	<i>p</i> value
NUF rate (mL/kg/h)	1.11 (0.75, 1.35)	2.33 (1.97, 2.67)	4.02 (3.53, 4.79)	< 0.001
Outcomes				
28-day mortality after CKRT (%)	83 (50.3)	132 (35.8)	150 (39.8)	0.007
In-hospital mortality (%)	88 (53.3)	149 (40.4)	167 (44.3)	0.021
ICU mortality (%)	79 (47.9)	130 (35.2)	141 (37.4)	0.018
Length of hospital stay after CKRT (day)	13.0 (5.3, 23.8)	15.9 (9.3, 25.0)	14.7 (7.7, 26.8)	0.084
Length of ICU stay after CKRT (day)	8.9 (5.0, 15.8)	10.0 (5.4, 16.7)	9.0 (5.2, 15.9)	0.430
Length of hospital stay (day)	16.2 (8.9, 28.2)	19.7 (12.0, 29.0)	17.8 (11.7, 30.0)	0.178
Length of ICU stay (day)	12.3 (7.7, 20.3)	13.2 (8.0, 20.6)	13.0 (8.0, 20.3)	0.774
Length of hospital stay in survivors (day)	26.8(20.0, 40.3)	23.0(16.0, 33.3)	24.0 (16.2, 39.2)	0.164
Length of ICU stay in survivors (day)	16.2 (9.9, 26.9)	13.8 (9.0, 21.4)	13.2 (8.7, 22.8)	0.127
Independent from CKRT (%)	91 (55.2)	262 (71.0)	262 (69.5)	0.001
<i>Abbreviations:</i> CKRT continuous renal replacement therapy, CVVH continuous veno-venous hemofiltration, CVVHD continuous veno-venous hemodialysis, CVVHDF continuous veno-venous hemodiafiltration, FO fluid overload, ICU intensive care unit, NUF net ultrafiltration, SCUF slow continuous ultrafiltration				

### Associations between the NUF rate and primary outcome

Compared with the moderate the NUF rate group, the low NUF rate group was significantly associated with a higher risk of 28-day mortality [adjusted odds ratio (OR) = 1.56, 95% CI: 1.04–2.35; *p* = 0.032], and the high NUF rate group was also associated with a higher risk of 28-day mortality (adjusted OR = 1.43, 95% CI: 1.02–2.01; *p* = 0.040) (Table 3).

Table 3  
The association of primary outcome and NUF rate

Model	Association	NUF rate		
		1.6–3.1 mL/kg/h	< 1.6 mL/kg/h	> 3.1 mL/kg/h
<b>Model 1</b>	OR (95% CI)	1 (reference)	1.82 (1.25–2.64)	1.19 (0.88–1.60)
	<i>p</i> value	/	0.002	0.258
<b>Model 2</b>	OR (95% CI)	1 (reference)	1.79 (1.23–2.60)	1.17 (0.86–1.60)
	<i>p</i> value	/	0.002	0.312
<b>Model 3</b>	OR (95% CI)	1 (reference)	1.83 (1.25–2.69)	1.21 (0.88–1.66)
	<i>p</i> value	/	0.002	0.233
<b>Model 4</b>	OR (95% CI)	1 (reference)	1.56 (1.04–2.35)	1.43 (1.02–2.01)
	<i>p</i> value	/	0.032	0.040
<i>Abbreviations: CI</i> confidence interval, <i>NUF</i> net ultrafiltration, <i>OR</i> odds ratio				
Model 1: unadjusted model;				
Model 2: model 1 adjusted by age, gender and body mass index;				
Model 3: model 2 with the addition of ICU type (whether from Cardiovascular ICU), baseline serum creatinine, Charlson Comorbidity Index Score, Oxford Acute Severity of Illness Score on the first day of admission, sepsis and need of mechanical ventilation on the first day of admission;				
Model 4: model 3 and mean arterial pressure before CKRT, sequential organ failure assessment score before CKRT, Vasoactive-inotropic Score before CKRT, fluid overload percent before CKRT, time from ICU admission until start of CKRT in minutes and cumulative fluid overload percent in the first 48 hours of CKRT.				

In addition, we divided the fluid input during the first 48 hours of CKRT into three groups according to the quartiles and the NUF rate into nine groups according to the eighth percentile. We then calculated the 28-day mortality of the three groups with different input in different NUF range groups. The NUF rate corresponding to the lowest mortality was 1.78–2.12 mL/kg/h for a lower tertile group, 2.52–3.00 mL/kg/h for a middle tertile group and 3.00–3.43 mL/kg/h for an upper tertile group. With the increase of fluid input during the first 48 hours of CKRT, the range of ultrafiltration corresponding to the lowest 28-day mortality also increased (Table 4).

Table 4  
The lowest mortality in groups classified by tertiles of input

Eighth percentile of NUF rate (mL/kg/h)	Tertiles of input at the first 48 hours of CKRT (mL/kg)		
	1 (28.4–129.8)	2 (130.1–185.5)	3 (189.7–634.3)
<1.20	(20/45) 44.4%	(24/38) 63.1%	(9/18) 50.0%
1.20–1.78	(32/68) 47.0%	(8/20) 40.0%	(5/13) 38.5%
1.78–2.12	<b>(16/52) 30.8%</b>	(9/31) 29.0%	(7/15) 46.7%
2.12–2.52	(16/36) 44.4%	(13/41) 31.7%	(10/24) 41.7%
2.52–3.00	(15/46) 32.6%	<b>(11/41) 26.8%</b>	(7/22) 31.8%
3.00–3.43	(14/26) 53.8%	(17/36) 47.2%	<b>(9/38) 23.7%</b>
3.43–3.97	(7/18) 38.9%	(17/46) 37.0%	(23/37) 62.2%
3.97–4.76	(3/7) 42.8%	(10/34) 29.4%	(22/57) 38.6%
> 4.76	(3/6) 50.0%	(5/16) 31.2%	(33/80) 41.2%

*Abbreviations: CKRT* continuous renal replacement therapy, *NUF* net ultrafiltration

## Mediation analyses

In adjusted mediation analyses, compared with the moderate NUF rate, the putative effect of high or low NUF rates on 28-day mortality was possibly direct (adjusted ADE for a low NUF rate = 0.92, 95% CI: 0.84–1.01,  $p = 0.064$ ; adjusted ADE for a high NUF rate = 1.03, 95% CI: 1.00–1.06,  $p = 0.096$ ) and also mediated by its effect on fluid balance during the first 48 hours of CKRT (adjusted ACME for a low NUF rate = 0.96, 95% CI: 0.93–0.99;  $p = 0.010$ ; adjusted ACME for a high NUF rate = 0.99, 95% CI: 0.98–1.00,  $p = 0.042$ ) (Fig. 3).

## Sensitivity analyses

We used logistic regression to evaluate the relationship between the NUF rate during the first 48 hours after the start of CKRT and hospital mortality. After adjusting for confounders, patients with a high NUF rate independently had a higher risk of hospital mortality than those with a moderate NUF rate (adjusted OR = 1.45, 95% CI: 1.04–2.03;  $p = 0.030$ ) (Additional file 1: Table S2).

Then, by adding 3% to the lowest 28-day mortality, we arrived at a mortality rate of 34% as a cutoff value, which corresponded to an NUF rate of 1.9 and 3.0 mL/kg/h (Additional file 1: Figure S2). Next, we stratified the NUF rate into three groups: low (< 1.9 mL/kg/h), moderate (1.9–3.0 mL/kg/h) and high (> 3.0 mL/kg/h). After adjusting for confounders, an NUF rate > 3.0 mL/kg/h independently had a higher risk

of hospital mortality than an NUF rate 1.9–3.0 mL/kg/h (adjusted OR = 1.58, 95% CI: 1.10–2.26;  $p = 0.012$ ) (Additional file 1: Table S3).

The Gray model revealed that, compared with a moderate NUF rate, a low NUF rate (adjusted hazard ratio = 1.77, 95% CI: 1.20–2.61) and high NUF rate (adjusted hazard ratio = 1.25, 95% CI: 1.05–1.47) were significantly associated with a higher risk of 28-day mortality from day 5 to day 8 after the initiation of CKRT (Additional file 1: Table S4 and Figure S3). We demonstrated that the median early NUF rate was only beneficial during the first 5–8 days of CKRT initiation.

We also divided patients into two subgroups according to the presence or absence of FO, which was defined as fluid accumulation adjusted by weight before CKRT > 10% or > 5%. After adjusting for confounders, the low NUF rate group was independently associated with a higher risk of 28-day mortality than the moderate NUF rate group in the subgroup without FO percent > 10% before CKRT (adjusted OR = 1.80, 95% CI: 1.09–2.97;  $p = 0.021$ ) (Additional file 1: Table S5) or in the subgroup without FO percent > 5% (adjusted OR = 2.25, 95% CI: 1.20–4.24;  $p = 0.011$ ) (Additional file 1: Table S6).

## Discussion

In this study, we investigated the relationship between NUF rate and mortality in the cohort of patients receiving CKRT. After adjusting for confounding factors, we found that the NUF rates of < 1.6 mL/kg/h and > 3.1 mL/kg/h during the first 48 hours of CKRT were associated with increased mortality compared with the NUF rate 1.6–3.1 mL/kg/h group. In addition, the optimal NUF rate range may not be in the range of 1.0–1.75 mL/kg/h [11, 12], as our results showed that 2.6 mL/kg/h correlated with the lowest risk of death, which may be due to the relatively large input in our study.

The results of this study were partly consistent with four previous studies [9–12]. Murugan and his colleagues found that in patients with volume overload > 5% and receiving renal replacement therapy, the 1-year mortality in patients with an NUF rate > 25 mL/kg/d was lower than that of < 20 mL/kg/d [9]. Shahrzad found that in patients with AKI receiving CKRT, the NUF rate  $\geq 35$  mL/kg/d was associated with a lower 30-day mortality [10]. Two other studies found that, compared with an early NUF rate of < 1.01 mL/kg/h, an NUF rate of > 1.75 mL/kg/h was associated with increased mortality [11, 12]. Our results also supported the theory that the relationship between NUF rate and mortality in critically ill patients receiving CKRT was "J" [7], indicating that higher or lower fluid removal rates were associated with increased mortality, despite our model not being completely robust because of the limited sample size. A low NUF rate was associated with prolonged exposure to tissue edema and organ dysfunction [23, 24], whereas a high rate was associated with hemodynamic stress, leading to ischemic organ injury and mortality in critically ill patients [25, 26]. Both complications could associate with decreased survival.

However, the range of the NUF rate (1.6–3.1 mL/kg/h) associated with the minimum mortality in our study was different from that in above studies. We speculate that this is because the NUF rate depends on fluid input. If the patient had a larger fluid input, the NUF rate set by the doctor may be higher. Thus,

the optimal NUF rate may be dynamic, which means it is higher when the fluid input is larger and lower when the fluid input is smaller. The optimal NUF rate still needs to be explored through further research.

Whether the putative effect of the NUF rate on mortality was direct or mediated by the fluid balance during CKRT has not been determined. Naorungroj et al first reported that an early NUF rate greater than 1.75 mL/kg/h was independently associated with increased hospital mortality and the putative effect on mortality was direct, not mediated by fluid balance, but there were only 347 patients included in this study [19]. Another recent large retrospective study, which included 1434 participants, also demonstrated that in CKRT patients, compared with a moderate NUF rate (1.01–1.75 mL/kg/h), a high NUF rate (> 1.75 mL/kg/h) had an ADE effect on 90-day mortality. In contrast to the results reported by Naorungroj et al, the effect of the NUF rate on mortality was mediated by the fluid balance during CKRT [21]. Our results were also partially consistent with these two studies [19, 21]. We showed that the putative effect of a high or low NUF rate on 28-day mortality was possibly direct and also mediated by its effect on fluid balance during the first 48 hours of CKRT. The direct or indirect effect of the NUF rate on mortality needs to be determined by further studies.

We acknowledge certain limitations in this study. The study had a single-center retrospective design, therefore, it was difficult to prove the causal relationship between a high or low NUF rate and increased risk of 28-day mortality, and the result may not be applicable to other centers. Secondly, although we used multiple risk adjustments and included many potential confounders, there may be some residual confounders that were responsible for the observed association. Despite these limitations, this survey provides insight into the NUF rate prescription and practice, which may help plan future research and quality implementation initiatives. Randomized controlled trials are required to confirm whether the high or low NUF rate increases mortality in the future.

## Conclusion

In this study, as compared with an NUF rate 1.6–3.1 mL/kg/h during the first 48 hours of CKRT, NUF rates of > 3.1 mL/kg/h and < 1.6 mL/kg/h are associated with higher mortality. Finally, the optimal NUF rate may rise when the fluid input increases.

## Abbreviations

ACME: average causal mediation effect; ADE: average direct effect; AKI: acute kidney injury; BMI: body mass index; BUN: blood urea nitrogen; CI: confidence interval; CKRT: continuous renal replacement therapy; CVVH: continuous veno-venous hemofiltration; CVVHD: continuous veno-venous hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; FiO<sub>2</sub>: fraction of inspired oxygen; FO: fluid overload; ICU: intensive care unit; MIMIC-IV: Medical Information Mart for Intensive Care IV; NUF: net ultrafiltration; OASIS: Oxford Acute Severity of Illness Score; OR: odds ratio; PaO<sub>2</sub>: partial pressure of oxygen; PCO<sub>2</sub>: partial pressure of carbon dioxide; SCUF: slow continuous ultrafiltration SOFA: sequential organ failure assessment; VIS: Vasoactive-inotropic Score.

# Declarations

## Ethics approval and consent to participate

The Institutional Review Board of the Beth Israel Deaconess Medical Center (2001–P–001699/14) and the Massachusetts Institute of Technology (No. 0403000206) approved the use of the MIMIC database.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available at <https://mimic-iv.mit.edu/>.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

MH, WB and SY designed the study. WB and SY sorted the data. WB and SY analyzed the data. SY and WB drafted the manuscript and XC and MH contributed substantially to its revision. MH takes responsibility for the paper as a whole. All authors read and approved the final manuscript.

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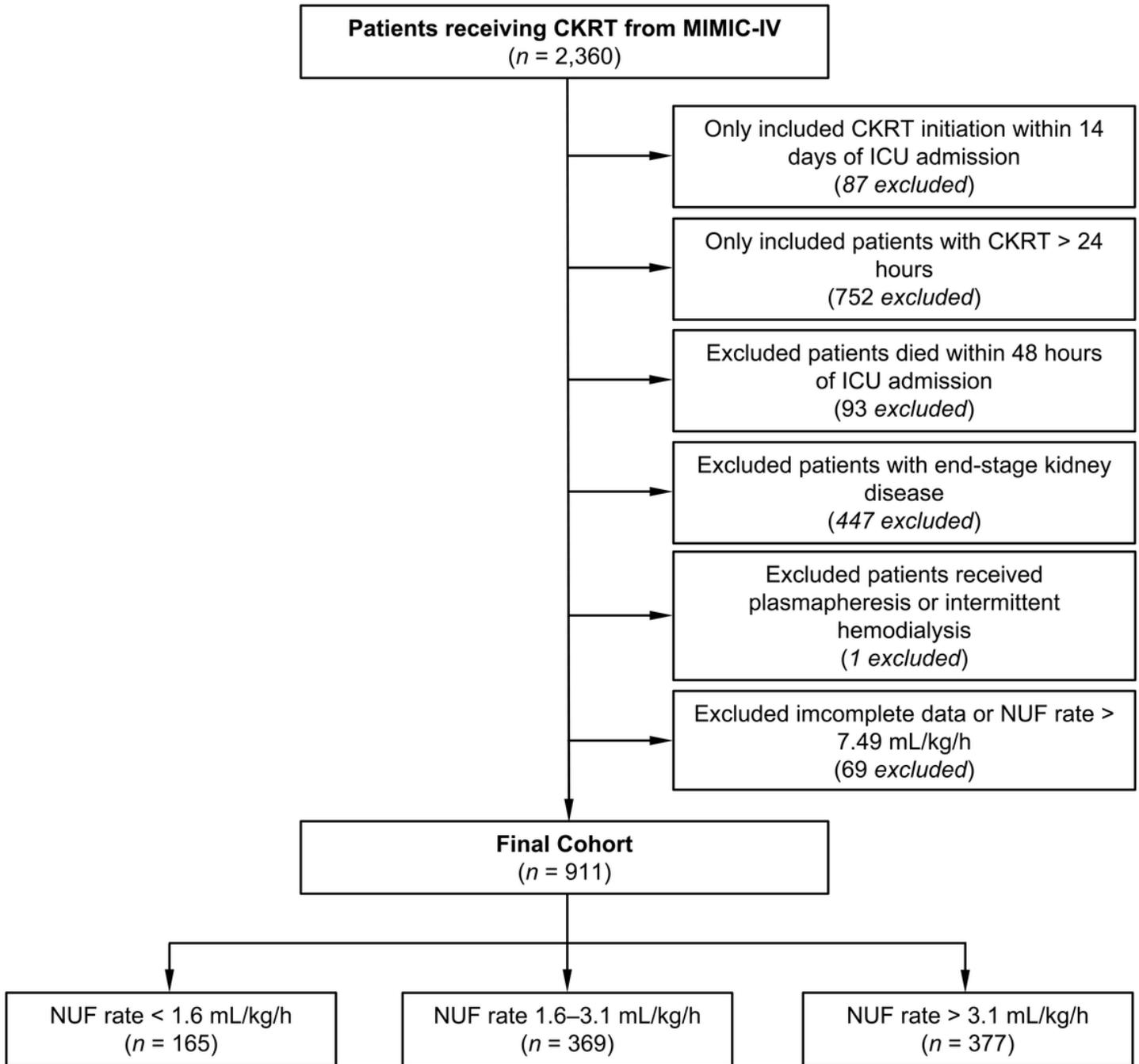
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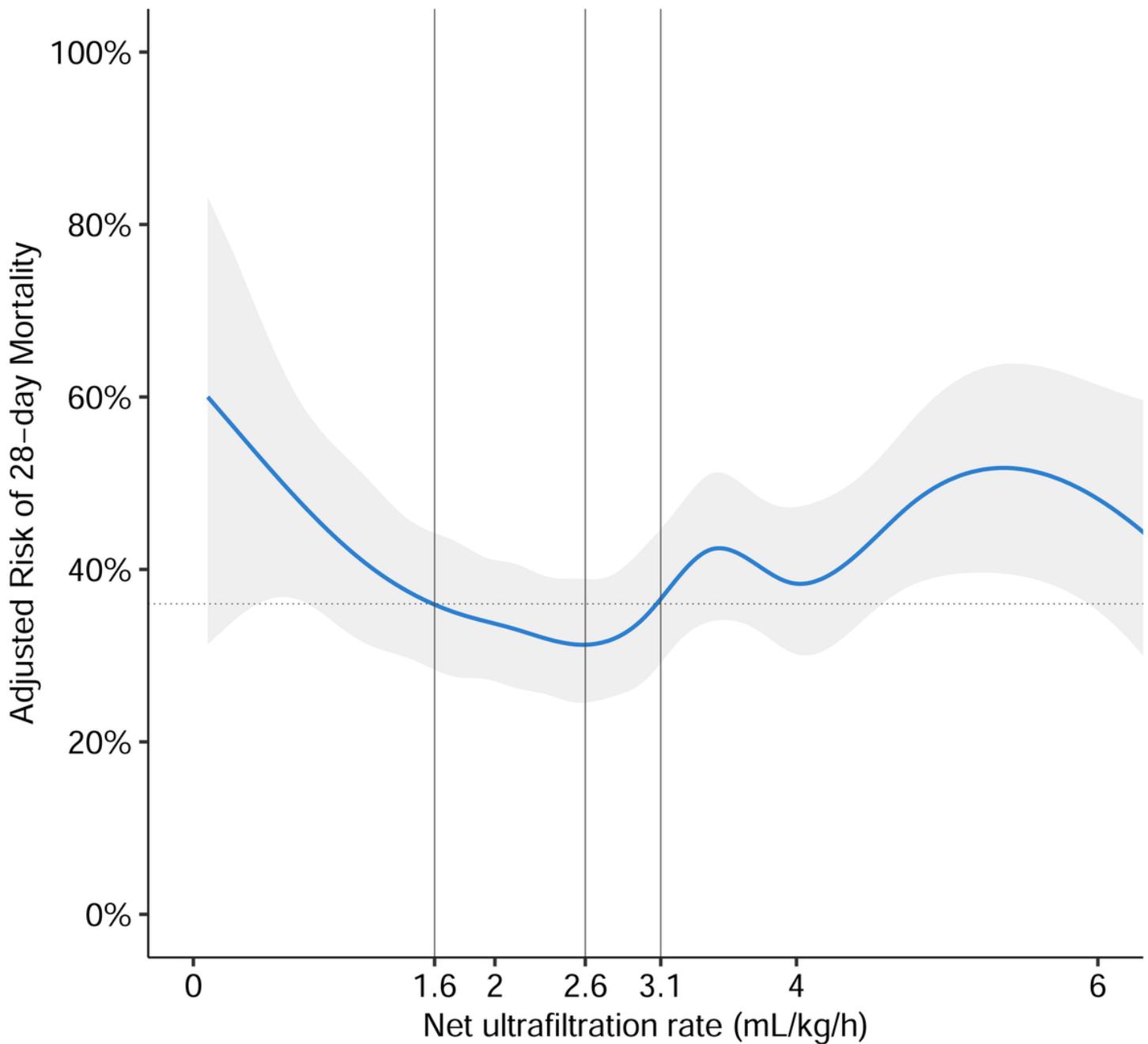
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## Figures



**Figure 1**

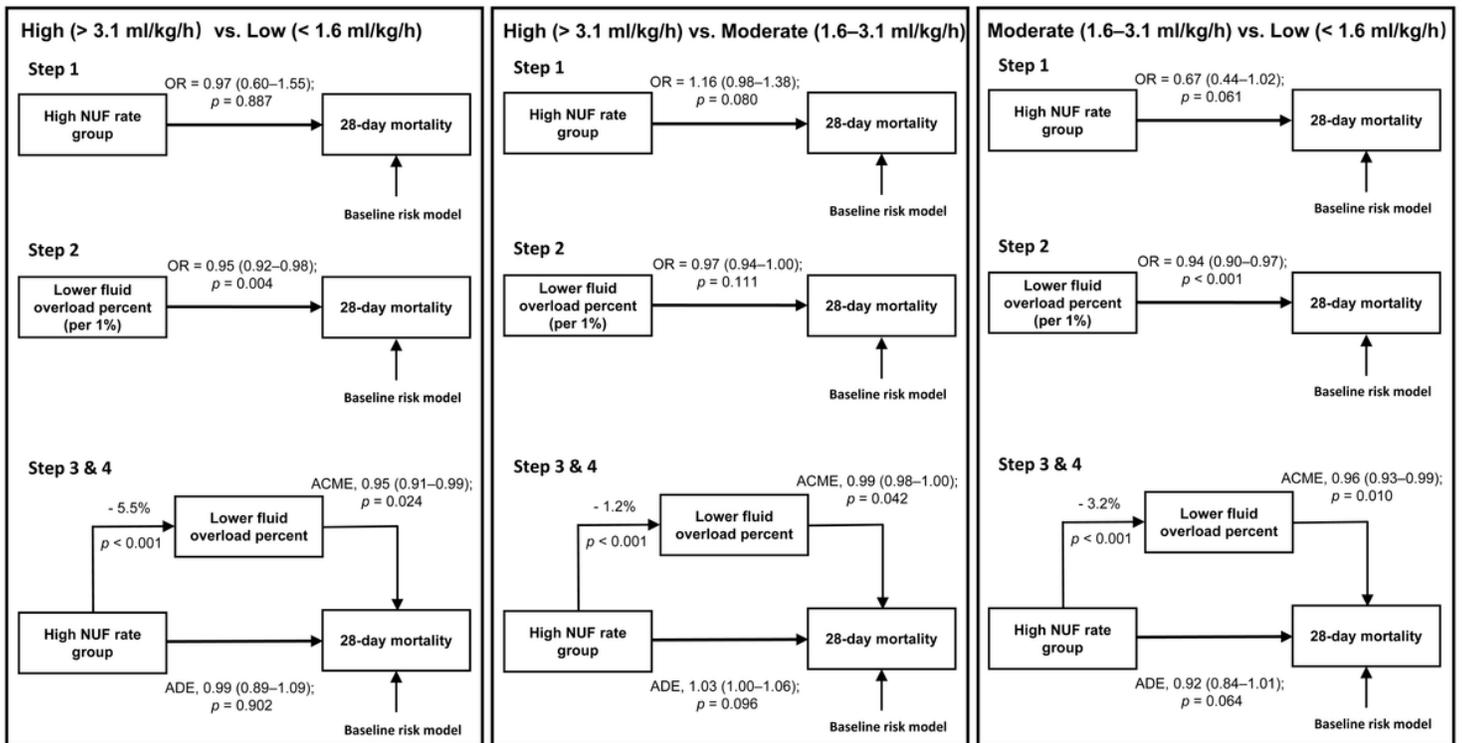
Flowchart of the study Abbreviations: CKRT continuous renal replacement therapy, ICU intensive care unit, MIMIC-IV Medical Information Mart for Intensive Care IV, NUF net ultrafiltration



**Figure 2**

The association of NUF rate and risk of 28-day mortality The association was plotted using a multivariate generalized additive linear model, which accounts for age, gender, body mass index, ICU type, baseline serum creatinine, Charlson Comorbidity Index Score, Oxford Acute Severity of Illness Score on the first day of admission, sepsis on the first day of admission, need of mechanical ventilation on the first day of admission, time from ICU admission until start of CKRT in minutes, mean arterial pressure before CKRT, Vasoactive-Inotropic Score before CKRT, sequential organ failure assessment score before CKRT, fluid

overload percent before CKRT, and cumulative fluid overload percent in the first 48 hours of CKRT. According to the multivariate generalized additive linear model, we found that the minimum 28-day mortality was 31%, which corresponded to the NUF rate of 2.6 mL/kg/h (gray solid line). By adding 5% (taking as an acceptable boundary value), we arrived at a mortality rate of 36% as a cutoff value (gray dotted lines), which corresponded to NUF rates of 1.6 and 3.1 mL/kg/h (gray solid lines). Then we stratified the NUF rate into three groups: low (< 1.6 mL/kg/h), moderate (1.6–3.1 mL/kg/h) and high (> 3.1 mL/kg/h). The blue solid line represented the relationship between the NUF rate in the first 48 hours of CKRT and 28-day mortality and the gray shadow represents the 95% confidence interval.



**Figure 3**

Mediation Pathways for the Three Comparisons Abbreviations: ACME average causal mediation effect, ADE average direct effect, NUF net ultrafiltration, OR odds ratio Baseline risk model included age, gender, body mass index, ICU type, baseline serum creatinine, Charlson Comorbidity Index Score, Oxford Acute Severity of Illness Score on the first day of admission, sepsis on the first day of admission, need of mechanical ventilation on the first day of admission, time from ICU admission until start of CKRT in minutes, mean arterial pressure before CKRT, Vasoactive-inotropic Score before CKRT, sequential organ failure assessment score before CKRT, fluid overload percent before CKRT and cumulative fluid overload percent in the first 48 hours of CKRT. Step 1: After accounting for baseline risk factors, we applied a logistic regression model with NUF rate as a categorical variable to evaluate the relationship between the NUF rate and 28-day mortality between two of each group. Step 2: After accounting for baseline risk factors, we applied a logistic regression model with FO percent in the first 48 hours of CKRT as a continuous variable to evaluate the relationship between FO percent in the first 48 hours of CKRT and 28-day mortality between two of each group. Step 3: Calculation of the influence of the NUF rate group on

the mediator. Step 4: After accounting for baseline risk factors, we applied a multivariable mediation model to investigate whether the association of NUF rate with mortality was modulated by its effect on cumulative FO percent in the first 48 hours of CKRT as a mediator.

## Supplementary Files

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