Association between Net Ultrafiltration Rate and Renal Recovery among Critically Ill Adults with Acute Kidney Injury Receiving Continuous Renal Replacement Therapy: An Observational Cohort Study

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Keywords

Net ultrafiltration · Renal recovery · Competing risk · Acute kidney injury · Kidney replacement therapy

Abstract

Introduction: Higher net ultrafiltration (UF_{NET}) rates are associated with mortality among critically ill patients with acute kidney injury (AKI) and treated with continuous renal replacement therapy (CRRT). **Objective:** The aim of the study was to discover whether UF_{NET} rates are associated with renal recovery and independence from renal replacement therapy (RRT). **Methods:** Retrospective cohort study using data from the Randomized Evaluation of Normal versus Augmented Level of Renal Replacement Therapy trial that en-

rolled 1,433 critically ill patients with AKI and treated with CRRT between December 2005 and November 2008 across 35 intensive care units in Australia and New Zealand. We examined the association between UF_{NET} rate and time to independence from RRT by day 90 using competing risk regression after accounting for mortality. The UF_{NET} rate was defined as the volume of fluid removed per hour adjusted for patient body weight. **Results and Conclusions:** Median age was 67.3 (interquartile range [IQR], 57–76.3) years, 64.4% were male, median Acute Physiology and Chronic Health Evaluation-III score was 100 (IQR, 84–118), and 634 (44.2%) died by day 90. Kidney recovery occurred in 755 patients (52.7%). Using tertiles of UF_{NET} rates, 3 groups were defined: high, >1.75; middle, 1.01–1.75; and low, <1.01 mL/kg/h. Proportion of patients alive and independent of RRT among the

groups were 47.8 versus 57.2 versus 53.0%; $p = 0.01$. Using competing risk regression, higher UF_{NET} rate tertile compared with middle (cause-specific hazard ratio [csHR], 0.79, 95% CI, 0.66–0.95; subdistribution hazard ratio [sHR], 0.80, 95% CI, 0.67–0.97) and lower (csHR, 0.69, 95% CI, 0.56–0.85; sHR, 0.78, 95% CI 0.64–0.95) tertiles were associated with a longer time to independence from RRT. Every 1.0 mL/kg/h increase in rate was associated with a lower probability of kidney recovery (csHR, 0.81, 95% CI, 0.74–0.89; and sHR, 0.87, 95% CI, 0.80–0.95). Using the joint model, longitudinal increases in UF_{NET} rates were also associated with a lower renal recovery ($\beta = -0.29$, $p < 0.001$). UF_{NET} rates >1.75 mL/kg/h compared with rates 1.01–1.75 and <1.01 mL/kg/h were associated with a longer duration of dependence on RRT. Randomized clinical trials are required to confirm this UF_{NET} rate-outcome relationship.

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Introduction

Net ultrafiltration (UF_{NET}), defined as the net fluid removal during renal replacement therapy (RRT), has been used in the treatment of fluid overload among critically ill patients with acute kidney injury (AKI) for >70 years [1]. Several clinical practice guidelines recommend the use of UF_{NET} to remove extracellular fluid volume in order to treat fluid overload [2, 3]. This recommendation is based on several observational studies, suggesting that fluid removal and negative fluid balance are associated with improved outcomes [4–6]. However, uncertainty exists about the optimal rate of fluid removal in acutely ill patients and its association with outcomes.

Our recent work using the Randomized Evaluation of Normal versus Augmented Level (RENAL) of Renal Replacement Therapy clinical trial cohort of critically ill patients treated with continuous renal replacement therapy (CRRT) suggests that UF_{NET} rates >1.75 mL/kg/h, compared with rates <1.01 mL/kg/h, after controlling for fluid balance, were independently associated with lower survival [7]. These findings were also validated in an independent cohort of patients receiving early UF_{NET} during CRRT [8]. However, the association of the UF_{NET} rate with another important patient-centered outcome of independence from RRT remains unclear.

Slower UF_{NET} rates coupled with fluid infusion may worsen fluid overload and expose patients to renal tissue edema and perpetuate renal dysfunction [9–11], whereas faster UF_{NET} rates might be associated with intradialytic hypotension and ischemic renal injury [12, 13]. Both of

these complications might impair renal recovery. For instance, studies in patients with end-stage renal disease and incident hemodialysis suggest that higher ultrafiltration rates are associated with a decline in residual kidney function [14]. Small observational studies in critically ill patients also suggest that higher UF_{NET} rates are associated with dependence on RRT [15, 16]. However, these studies did not account for competing risk between mortality and renal recovery, resulting in potential survivor bias and overestimation of renal recovery [17–19]. The use of conventional statistical methods for the analysis of time to independence from RRT (e.g., Kaplan-Meier estimate and Cox proportional hazard model) will result in biased estimates as these models assume that competing risks are absent [17, 20].

Thus, we used 2 different competing risk regression methods that account for competing event of mortality to examine the association of UF_{NET} rate with time to independence from RRT in a secondary analysis of the RENAL cohort [21]. We fitted a cause-specific regression model to assess the etiological relationship between higher UF_{NET} rate and time to independence from RRT. We also fitted a subdistribution model by Fine and Gray to estimate the prognostic probability of time to independence from RRT at any given time for an individual patient.

Materials and Methods

The University of Pittsburgh's Human Research Protection Office approved this retrospective cohort study with a waiver of informed consent (PRO17090362). However, written informed consent was obtained in the RENAL trial [21] from the patient or a responsible surrogate utilizing either a priori or delayed consent. For this report, we followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline [22].

Study Population

The RENAL study was conducted in 35 intensive care units in Australia and New Zealand between December 30, 2005, and November 28, 2008. This secondary analysis was performed between May 31, 2018, and December 13, 2019. The RENAL study was a multicenter randomized trial that compared the efficacy of 2 different intensities of solute control using CRRT in critically ill patients with AKI [21]. In brief, patients were eligible to participate in the study if they were critically ill adults with AKI, were deemed to require CRRT by the clinician, and fulfilled predefined criteria including oliguria, severe organ edema, hyperkalemia, uremia, or severe metabolic acidosis (online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517281). Baseline premorbid serum creatinine was determined based on the most recent documented creatinine 12 months before index hospital admission.

The presence of clinically significant organ edema was prospectively adjudicated by clinicians before randomization based on radiologically confirmed pulmonary edema or visible or palpable organ edema (cardiac or gastrointestinal) at the surgery [21]. The UF_{NET} rate was individualized by clinicians and was performed by decreasing the flow of the replacement fluid and the dialysate in equal proportion so that effluent fluid volume exceeded replacement fluid and dialysate volumes.

Patient and Public Involvement

Patient and public involvement was not sought for this study using a clinical trial database.

Study Variables

The primary outcome was time to independence from RRT from study enrollment censored at day 90. The exposure variable was the UF_{NET} rate defined as the volume of net ultrafiltrate removed per hour adjusted for patient body weight in kilograms. The hourly UF_{NET} volume was calculated after excluding the dialysate and the replacement fluid volumes from the volume of ultrafiltrate (i.e., UF_{NET} = UF volume – [replacement fluid + dialysate volume]). Subsequently, the rate for the duration of treatment was calculated using the following equation [7, 8, 23–25]:

$$\text{UF}_{\text{NET}} \text{ rate (mL/kg/h)} = \frac{\text{cumulative UF}_{\text{NET}} \text{ volume (mL)}}{\text{weight at study enrollment (kg)} \times \text{treatment duration (h)}}$$

Daily patient fluid balance was first calculated as the difference between fluid administered (i.e., intravenous fluids, blood products, enteral fluids, dialysate, and replacement fluid) and fluid loss (i.e., dialysis effluent from CRRT, urine output, blood loss, enteral losses, and drain losses). We then excluded UF_{NET} volume from the output fluids since the UF_{NET} rate was the exposure variable [7, 23]. Daily and cumulative fluid balance data were obtained from study enrollment until death, ICU discharge, or completion of 28 days from enrollment. Incomplete study days were considered full data collection days [5]. Study treatment was discontinued on death, discharge from ICU, or recovery of renal function.

We measured covariates for a risk adjustment model to account for confounding by indication [26, 27] because older, sicker, and hemodynamically unstable patients would be expected to receive a slower rate and patients with organ edema and those requiring mechanical ventilation would be expected to receive a faster rate [7]. These included variables specified a priori based on prior studies [5, 7, 23, 28] using age category; female sex; premorbid estimated glomerular filtration rate (eGFR) based on most recent serum creatinine; duration from ICU admission to study enrollment; severity of illness assessed by Acute Physiology and Chronic Health Evaluation-III score category with score ranging from 0 to 299 with higher score indicating more severe illness in the 24 h before study enrollment; severity of organ dysfunction assessed by total Sequential Organ Failure Assessment (SOFA) score on a scale of 0–4 for each organ with higher score indicating more severe organ dysfunction; presence of organ edema, sepsis, and use of mechanical ventilation; daily mean cardiovascular SOFA score during treatment; cumulative fluid balance from enrollment to ICU discharge; duration of RRT in days; source of admission including whether the patient was transferred from an emergency department, hospital ward, operating room after elective or emergency surgery, another hospital, or ICU; hospital type; and hospital region. Race and ethnicity were not reported in the clinical trial.

For patients with unknown premorbid serum creatinine ($n = 637$, 44.4%), we used the multivariable imputation by a chained equation method to impute creatinine values using age, sex, and weight as predictors (online suppl. Appendix 2) [7, 29, 30]. We subsequently used the Modification of Diet in Renal Disease equation to determine eGFR using the imputed creatinine [31]. There was no difference in the distribution of imputed and unimputed creatinine and corresponding eGFR values (Fig. A1).

Statistical Analysis

Primary Analyses

To examine the association between UF_{NET} rate and time to independence from RRT, we examined several models because of the nonlinear association of the UF_{NET} rate with RRT independence (Fig. A2a, b) and selected tertiles and continuous models due to lower Akaike information criterion. Using tertiles, we stratified UF_{NET} rates into 3 groups based on prior work [7]: (1) low, <1.01 mL/kg/h; (2) middle, 1.01–1.75 mL/kg/h; and (3) high, >1.75 mL/kg/h. To predict RRT independence across a range of UF_{NET} rates, we restricted the cohort to UF_{NET} rates of 5 mL/kg/h or less ($n = 1,428$; 99.6%). Categorical variables are presented as counts and frequencies and compared using the χ^2 test, and continuous variables are presented as medians and interquartile ranges and compared using the Wilcoxon rank-sum test. To study the absolute risk of RRT independence while accounting for the competing risk of death, we estimated nonparametric cumulative incidence functions.

To examine the association of UF_{NET} rate with time to independence from RRT while accounting for other covariates and competing risk of death, we fitted cause-specific models [19, 32–34]. We estimated cause-specific hazard ratios (csHRs) with 95% CI from Cox models [33, 35] after assessing proportional hazard assumptions (online suppl. Appendix 3; Fig. A3a, b). In these models, since the competing event of death is treated as a censored observation during follow-up, the number of patients at risk is reduced. Thus, the csHRs calculated using this approach are interpreted as among those patients who *have not yet* died or recovered renal function.

To determine the individual prognostic probability of renal recovery associated with UF_{NET} rate while accounting for covariates and risk of death, we fitted subdistribution models by Fine and Gray [33, 35, 36] and computed subdistribution hazard ratios (sHRs). In this model, subjects who experience death remain in the risk set and the sHR denotes the instantaneous rate of renal recovery in subjects who are still alive (i.e., who have not yet experienced either death or renal recovery) *and* also those who have died (online suppl. Appendix 4).

In these models, we used the UF_{NET} rate of <1.01 mL/kg/h as a reference and adjusted for covariates with fixed effects for the region and hospital type to account for nonindependence of UF_{NET} rate across hospitals. Models were fitted using 1,341 patients (93.6%) after excluding patients with missing covariate data on source of ICU admission ($n = 91$), number of CRRT treatment days ($n = 1$ [0.1%]), mortality ($n = 1$, [0.1%]), and renal recovery status ($n = 1$, [0.01%]).

We conducted longitudinal analyses using a joint model to account for the correlation between daily UF_{NET} rate and cardiovascular SOFA score over time and its association with time to independence from RRT. We chose joint modeling because it allowed us to simultaneously model associations between UF_{NET} rate, changes in UF_{NET} rate over time, UF_{NET} rate, and time-to-RRT independence in a single unified model while accounting for correlated data (online suppl. Appendix 5) [37, 38].

Table 1. Baseline patient characteristics by UF_{NET} rate

Characteristic	N (%)	p value	
		<1.01 mL/kg/h (N = 477)	>1.75 mL/kg/h (N = 477)
Age, median (IQR), yr	67.3 (56.9–76.3)	68.1 (57.2–76.1)	63.8 (51.4–74.2)
Age category, yr			
<53.2	287 (20.0)	96 (20.0)	126 (26.4)
53.2 to <63.6	287 (20.0)	83 (17.3)	111 (23.3)
63.6 to <71.1	286 (19.9)	97 (20.2)	91 (19.0)
71.1 to <77.7	287 (20.0)	111 (23.2)	69 (14.4)
≥77.7	287 (20.0)	92 (19.2)	81 (17.0)
Male sex	924 (64.4)	330 (68.9)	283 (59.2)
Weight, median (IQR), ^a kg	80.0 (70.0–90.0)	80.0 (74.0–90.0)	75.0 (68.0–85.0)
Preadmission eGFR, median (IQR), ^b mL/min/1.73 m ²	53.0 (32.6–73.9)	51.0 (34.0–72.8)	59.0 (33.3–80.2)
Patients with known eGFR, ^b mL/min/1.73 m ²	467	150	139
46 to <60	143 (30.6)	48 (32.0)	43 (30.9)
30 to <46	156 (33.4)	52 (34.7)	40 (28.8)
<30	168 (36.0)	50 (33.3)	56 (40.3)
Time in ICU before study enrollment, median (IQR), h	20.0 (6.0–51.0)	21.0 (6.0–53.0)	26.0 (8.0–63.0)
Mechanical ventilation ^a	1,057 (73.7)	330 (69.2)	371 (77.6)
Sepsis ^a	709 (49.4)	221 (46.3)	253 (53.0)
APACHE-III score, median (IQR) ^{c,d}	100 (84–118)	100 (83–118)	101 (84–117)
APACHE-III category ^{c,d}			
<82	273 (19.0)	87 (18.2)	91 (19.0)
82 to <95	299 (20.9)	103 (21.6)	97 (20.3)
95 to <107	277 (19.3)	92 (19.3)	97 (20.3)
107 to <122	289 (20.1)	96 (20.0)	96 (20.1)
≥122	296 (20.6)	101 (21.1)	97 (20.3)
Total SOFA score, median (IQR) ^{c,e}	8 (6–9)	8 (6–9)	8 (6–10)
Individual SOFA score, median (IQR) ^{c,e}			
Cardiovascular	4 (1–4)	4 (1–4)	4 (1–4)
Respiratory	3 (2–3)	3 (2–3)	3 (3–3)
Coagulation	0 (0–2)	0 (0–2)	1.0 (0–2)
Liver	0 (0–2)	0 (0–2)	1.0 (0–2)
Source of admission			
Emergency department	341 (25.4)	139 (31.1)	85 (17.8)
Hospital ward	378 (28.1)	114 (25.5)	153 (34.2)
Another ICU	109 (8.1)	29 (6.5)	40 (8.9)
Another hospital	149 (11.1)	56 (12.5)	46 (10.3)
OR after emergency surgery	204 (15.2)	68 (15.2)	65 (14.5)
OR after elective surgery	162 (12.1)	41 (9.2)	58 (12.1)

Table 1 (continued)

Characteristic	N (%)	<1.01 mL/kg/h (N = 477)	1.01–1.75 mL/kg/h (N = 479)	>1.75 mL/kg/h (N = 477)	p value
Criteria for randomization ^{c,f}					
Oliguria	855 (59.6)	277 (58.1)	292 (61.0)	286 (59.8)	0.65
Hyperkalemia	111 (7.7)	54 (11.3)	33 (6.9)	24 (5.0)	<0.001
Severe acidemia	506 (35.3)	211 (44.2)	141 (29.4)	154 (32.2)	<0.001
BUN >70 mg/dL	595 (41.5)	205 (43.0)	197 (41.1)	193 (40.4)	0.70
Creatinine >3.4 mg/dL	679 (47.4)	248 (52.0)	238 (49.7)	193 (40.4)	<0.001
Severe organ edema due to renal disease	634 (44.2)	172 (36.1)	207 (43.2)	255 (53.3)	<0.001
Year of enrollment					
2005	1 (0.1)	0	1 (0.2)	0	
2006	305 (21.3)	99 (20.7)	108 (22.5)	98 (20.5)	
2007	629 (43.9)	209 (43.8)	205 (42.8)	215 (45)	0.82
2008	499 (34.8)	169 (35.4)	165 (34.4)	165 (34.5)	
Type of hospital					
University	1,023 (71.3)	313 (65.6)	338 (70.6)	372 (77.8)	
Urban	338 (23.6)	122 (25.6)	121 (25.3)	95 (19.9)	
Rural	23 (1.6)	16 (3.3)	7 (1.5)	0	<0.001
Private	50 (3.5)	26 (5.4)	13 (2.7)	11 (2.3)	
Country					
New Zealand	104 (7.3)	55 (11.5)	28 (5.8)	21 (4.4)	
Australia	1,330 (92.8)	422 (88.5)	451 (94.1)	457 (95.6)	<0.001
Region					
New Zealand	104 (7.3)	55 (11.5)	28 (5.8)	21 (0.4)	
New South Wales, Australia	523 (36.5)	143 (30.0)	183 (38.2)	197 (41.2)	
Queensland, Australia	85 (5.9)	27 (5.6)	19 (4.0)	39 (8.2)	
Victoria, Australia	578 (40.3)	195 (40.9)	205 (42.8)	178 (37.3)	
Western Australia, Australia	65 (4.5)	21 (4.4)	22 (4.6)	22 (4.6)	<0.001
Tasmania, Australia	18 (1.3)	7 (1.5)	4 (0.9)	7 (1.5)	
Australian Capital Territory, Australia	6 (0.4)	3 (0.6)	1 (0.2)	2 (0.4)	
South Australia, Australia	55 (3.8)	26 (5.4)	17 (3.5)	12 (2.5)	

UF_{NET}, net ultrafiltration; IQR, interquartile range; BMI, body mass index; eGFR, estimated glomerular filtration rate; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; BUN, blood urea nitrogen; OR, operating room; IQR, interquartile range. ^a Measured at study enrollment. ^b Data are for patients in whom the eGFR, before study enrollment was known ($n = 797$). ^c Measured 24 h before study enrollment. ^d APACHE-III, scores range from 0 to 299, with higher scores indicating more severe illness. ^e SOFA, scores range from 0 to 4, with a higher score indicating more severe organ dysfunction. ^f A given patient may have met more than one of these criteria.

Secondary Analyses

Using cause-specific models, we assessed the robustness of findings in multiple sensitivity and subgroup analyses. First, we restricted the UF_{NET} rate to the first 72 h of CRRT. Second, we classified patients using a maximum UF_{NET} rate. Third, we excluded 92 patients with UF_{NET} rates <0.01 mL/kg/h. Fourth, we included 31 patients with missing treatment duration by assigning a UF_{NET} rate of 0 mL/kg/h. Fifth, we adjusted for individual baseline liver, coagulation, and respiratory instead of total SOFA scores. Sixth, we adjusted for the cumulative fluid balance that included UF_{NET} volume in output fluid calculation. Seventh, we excluded the cumulative fluid balance from the models. Eighth, we stratified based on CRRT for <3 and ≥ 3 days. Ninth, we only fitted models among patients with negative daily fluid balance during ICU stay. Tenth, we matched patients based on propensity scores for receiving UF_{NET} rates >1.75 mL/kg/h with that of UF_{NET} rates <1.75 mL/kg/h ($n = 406$ matched pairs).

Using subgroup analyses, we assessed for effect modification with a test for an interaction between UF_{NET} rate and patient characteristic in a prespecified subpopulation including patients with and without organ edema, sepsis, premorbid $eGFR <60$ and ≥ 60 mL/min/1.73 m², cardiovascular SOFA score <3 and ≥ 3 , and high- and low-intensity CRRT. Cause-specific and Fine and Gray models were fitted using SAS 9.4 (SAS Institute, Cary, NC, USA). Joint models were fitted using R 2.14.0 and multiple imputations using MICE command in R 3.4.2. All hypothesis tests were 2-sided, with a significance level of $p < 0.05$.

Results

Patient Characteristics

Of 1,508 patients enrolled in the RENAL trial, consent was withdrawn by 43 patients. Of the remaining 1,465 patients, we excluded 31 patients for whom the treatment hours for CRRT and 1 patient with missing RRT status (Table A1). Of the 1,433 eligible patients, median (interquartile range [IQR]) age was 67.4 (56.9–76.3) years; body weight was 80.0 (IQR, 70.0–90.0) kg; and 924 patients (64.5%) were men (Table 1). Premorbid $eGFR$ was 53.0 (IQR, 32.6–73.8) mL/min/1.73 m², the Acute Physiology and Chronic Health Evaluation-III score was 100 (IQR, 84–118), and 634 patients (44.2%) died. Of the 1,433 patients, 477 patients received $UF_{NET} <1.01$ mL/kg/h, 479 patients received UF_{NET} between 1.01 and 1.75 mL/kg/h, and 477 patients received $UF_{NET} >1.75$ mL/kg/h (Table 1).

UF_{NET} rates >1.75 mL/kg/h were associated with young age, female sex, lower body weight, higher $eGFR$, mechanical ventilation, and longer ICU stay before study enrollment than patients receiving UF_{NET} rates between 1.01 and 1.75 mL/kg/h or <1.01 mL/kg/h. Patients with UF_{NET} rates >1.75 mL/kg/h had more severe organ dysfunction, as evidenced by higher median total SOFA

score and organ edema at study enrollment. However, the risk of hyperkalemia and metabolic acidosis was lower than patients with UF_{NET} rates 1.01–1.75 mL/kg/h and rates <1.01 mL/kg/h. There were also variations in source of admission to the ICU, type of hospital, country, and region (Table 1).

Following initiation of CRRT, patients with UF_{NET} rates >1.75 mL/kg/h were associated with having a similar median cardiovascular SOFA score (Table 2) and a longer median duration of treatment with CRRT. Patients receiving $UF_{NET} >1.75$ mL/kg/h had higher negative median daily and cumulative fluid balances. Median hourly and cumulative UF_{NET} volumes were also higher for patients receiving $UF_{NET} >1.75$ mL/kg/h for the duration of CRRT. Patients treated with UF_{NET} rates >1.75 mL/kg/h had a longer duration of mechanical ventilation and RRT, ICU, and hospital length of stay than patients receiving UF_{NET} rates between 1.01 and 1.75 mL/kg/h and <1.01 mL/kg/h. At day 90, more patients receiving UF_{NET} rates >1.75 mL/kg/h, compared with rates 1.01–1.75, and <1.01 mL/kg/h have died (48.6 vs. 39.2 vs. 44.9%; $p = 0.01$).

Primary Analyses

Between day 1 and day 90, 228 patients (47.8%) treated with UF_{NET} rates >1.75 mL/kg/h, 274 patients (57.2%) treated with UF_{NET} rates between 1.75 and 1.01 mL/kg/h, and 253 patients (53.0%) treated with UF_{NET} rates <1.01 mL/kg/h were alive and independent of RRT. UF_{NET} rates >1.75 mL/kg/h compared with rates 1.01–1.75 mL/kg/h (csHR, 0.79, 95% CI, 0.66–0.95) and rates <1.01 mL/kg/h (csHR, 0.69, 95% CI, 0.56–0.85; Fig. 1a, 2; Table A2) were associated with a longer time to independence from RRT. There was no difference in renal recovery between UF_{NET} rate 1.01–1.75 mL/kg/h group compared with UF_{NET} rate <1.01 mL/kg/h group (csHR, 0.87, 95% CI, 0.72–1.06).

Every 1.0 mL/kg/h increase in rate was associated with 19% lower probability renal recovery (csHR, 0.81, 95% CI, 0.74–0.89; Fig. 2; Table A3; Fig. A2b), and this association was not modified by organ edema strata, sepsis, $eGFR >60$, mean cardiovascular SOFA score ≥ 3 , or high-intensity CRRT. Using a joint model, a longitudinal increase and a variation in the UF_{NET} rate over time were associated with a longer time to independence from RRT ($\beta = -0.29$, $p < 0.001$). Of the subgroup of survivors at day 90 ($n = 799$), UF_{NET} rate >1.75 mL/kg/h, compared with UF_{NET} rate <1.01 mL/kg/h, was also associated with a longer time to RRT independence (adjusted HR, 0.80, 95% CI, 0.72–0.88; $p < 0.001$).

Using the Fine and Gray model, UF_{NET} rates >1.75 mL/kg/h compared with UF_{NET} rates 1.01–1.75 mL/kg/h

Table 2. Processes of care during UF_{NET} and outcomes

Characteristic	N (%)	p value		
		<1.01 mL/kg/h (N = 477)	1.01–1.75 mL/kg/h (N = 479)	>1.75 mL/kg/h (N = 477)
Intensity of KRT				
High	708 (49.4)	244 (51.1)	216 (45.1)	248 (51.8)
Low	726 (50.6)	233 (48.8)	263 (54.9)	230 (48.1)
Daily total SOFA score, median (IQR)	8.0 (6.0–11.0)	8.0 (6.0–11.0)	8.0 (6.0–10.0)	8.0 (6.0–11.0)
Individual daily mean daily SOFA score, median (IQR)				
Cardiovascular	3.0 (1.0–4.0)	3.0 (1.0–4.0)	3.0 (1.0–4.0)	3.0 (1.0–4.0)
Respiratory	3.0 (3.0–3.0)	3.0 (2.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)
Coagulation	1.0 (0–2.0)	1.0 (0–2.0)	1.0 (0–2.0)	1.3 (0–2.5)
Liver	1.0 (0–2.0)	1.0 (0–2.0)	1.0 (0–2.0)	1.0 (0–2.0)
Duration of study treatment, median (IQR), d	3 (2–7)	2 (1–4)	4 (2–8)	5 (2–10)
Daily fluid balance, median (IQR), mL/d	–39.5 (–812.0 to 721.0)	641.0 (–91.0 to 1793.0)	–55.5 (–678.5 to 490.0)	–658.0 (–1445.0 to 55.0)
Cumulative fluid balance, median (IQR), L	–0.1 (–4.1 to 3.1)	2.3 (–0.2 to 5.5)	–0.4 (–3.5 to 2.4)	–3.6 (–7.7 to 0.4)
Hourly UF _{NET} volume, median (IQR), mL/h	104.7 (56.2–150.3)	31.8 (0.7–62.5)	106.0 (89.5–131.0)	167.4 (141.5–203.0)
Cumulative UF _{NET} volume, median (IQR), L	7.0 (2.4–17.0)	1.7 (0.1–4.0)	8.5 (4.5–16.4)	16.5 (8.5–28.4)
Daily fluid balance excluding UF _{NET} , median (IQR), ^a mL/d	1,740.3 (971.0–2563.0)	1,370.0 (561.0–2259.0)	1,683.0 (989.0–2440.5)	2,058.5 (1385.0–2882.0)
Cumulative fluid balance excluding UF _{NET} , median (IQR), ^a L	7.4 (3.1–15.3)	4.6 (1.3–8.7)	8.5 (3.6–15.9)	11.1 (5.1–22.4)
Duration of mechanical ventilation, median (IQR), d	5 (2–10)	3 (1–7)	6 (2–12)	7 (3–12)
ICU length of stay, median (IQR), d	7 (3–14)	5 (2–10)	8 (4–15)	9 (5–16)
Hospital length of stay, median (IQR), d	8 (5–15)	6 (3–11)	9 (5–16)	10 (6–16)
No. of days of RRT, median (IQR), d	5 (3–11)	3 (2–6)	6 (3–11)	7 (4–17)
No. of days on CRRT, median (IQR), d	4 (3–7)	3 (2–5)	5 (3–8)	6 (3–10)
No. of days on IHD, median (IQR), ^b d	2 (1–4)	2 (1–3)	1 (1–3)	3 (1–5)
Alive and independent of RRT	755 (52.70)	253 (53.0)	274 (57.2)	228 (47.8)
Patients RRT dependent, <i>n</i>	678 (47.3)	224 (46.9)	205 (42.8)	249 (52.2)
RRT dependence among survivors				
At day 28	120 (13.3)	19 (6.6)	37 (11.7)	64 (21.9)
At day 90	44 (5.5)	10 (3.8)	17 (5.8)	17 (6.9)
Death				
At day 28	534 (37.2)	187 (39.2)	162 (33.6)	186 (38.9)
At day 90	634 (44.2)	214 (44.9)	188 (39.2)	232 (48.6)

RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; UF_{NET}, net ultrafiltration; CRRT, continuous renal replacement therapy; IQR, interquartile range. ^a Daily and cumulative fluid balances were calculated during continuous venovenous hemodiafiltration after excluding the net ultrafiltration volume from the output volume calculation. ^b Total no. of patients who received intermittent hemodialysis during ICU stay (*n* = 106).

Fig. 1. Time to independence from renal replacement therapy by UF_{NET} rate. Shown are cumulative incidence probability of time to independence from RRT by UF_{NET} rate estimated from cause-specific (a) and subdistribution models (b). Renal recovery was lowest for UF_{NET} rates >1.75 mL/kg/h when compared with rates between 1.01 and 1.75 mL/kg/h and rates <1.01 mL/kg/h. UF_{NET} , net ultrafiltration; RRT, renal replacement therapy.

Fig. 2. Risk-adjusted hazard ratios for the association of UF_{NET} rate with time to independence from renal replacement therapy. The embedded table reports the total number of patients who were independent from renal replacement therapy by day 90 and risk adjustment with 95% CI from cause-specific models and Fine and Gray models. A $csHR < 1$ suggests that at any given time, higher UF_{NET} rates, compared with lower UF_{NET} rates, are associated with a longer time to independence from renal replacement therapy among patients who were alive at that time. A $sHR < 1$ suggests that higher UF_{NET} rates, compared with lower UF_{NET} rates, are associated with a longer time to independence from renal replacement therapy among patients who were alive or those who have not yet recovered renal function at any given time. Variables in the risk-adjusted models include age category; female sex; premorbid eGFR; duration from ICU admission to study enrollment; APACHE-III category in the 24 h before study enrollment; total SOFA score at study enrollment; presence of organ edema, sepsis, and use of mechanical ventilation at enrollment; daily mean cardiovascular SOFA score during treatment with CRRT; cumulative daily fluid balance from study enrollment to ICU discharge; duration of renal replacement therapy; source of admission including whether the patient was transferred to the ICU from an emergency department, hospital ward, operating room after elective or emergency surgery, another hospital, or ICU; hospital type; and hospital region. Models were fitted in 1,341 patients with complete data. UF_{NET} , net ultrafiltration; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; $csHR$, cause-specific hazard ratio; sHR , subdistribution hazard ratio.

Fig. 3. Sensitivity and subgroup analyses for the association of UF_{NET} rate with time to independence from renal replacement therapy. Forrest plots showing sensitivity (**a**) and subgroup analysis (**b**) of association of UF_{NET} rate with risk-adjusted renal recovery along with 95% CI from the cause-specific models. UF_{NET}, net ul-

trafiltration; SOFA, Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate; CRRT, continuous renal replacement therapy; RRT, renal replacement therapy; csHR, cause-specific hazard ratio.

(sHR, 0.80, 95% CI, 0.67–0.97) and UF_{NET} rates <1.01 mL/kg/h (sHR, 0.78, 95% CI, 0.64–0.95; Table A4) were also associated with a longer time to independence from RRT (Fig. 1b, 2). However, there was no difference in renal recovery between UF_{NET} rate 1.01–1.75 mL/kg/h group compared with UF_{NET} rate <1.01 mL/kg/h group

(sHR, 0.96, 95% CI, 0.80–1.16). Every 1.0 mL/kg/h increase in rate was associated with 13% lower probability of renal recovery (sHR, 0.87, 95% CI, 0.80–0.95; Table A5). Our findings did not change when adjusted for daily fluid balance instead of cumulative fluid balance in the models (Table A6).

Secondary Analyses

Every 1.0 mL/kg/h increase in the UF_{NET} rate was associated with a longer time to independence from RRT when the UF_{NET} rate calculation was restricted to first 72 h of CRRT (csHR, 0.85, 95% CI: 0.78–0.92; Fig. 3a; Table A7), using maximum UF_{NET} values (csHR, 0.94, 95% CI, 0.90–0.97), after excluding 92 patients with UF_{NET} rate <0.01 mL/kg/h (csHR, 0.82, 95% CI, 0.75–0.91), and after including the 31 patients with missing treatment hours and assigning a UF_{NET} rate of 0 mL/kg/h (csHR, 0.82, 95% CI, 0.75–0.90). An increasing UF_{NET} rate was also associated with a longer time to independence from RRT after adjusting for baseline individual SOFA scores (csHR, 0.82, 95% CI, 0.74–0.90), cumulative fluid balance including UF_{NET} volume (csHR, 0.79, 95% CI, 0.72–0.88), excluding cumulative fluid balance (csHR, 0.81, 95% CI, 0.74–0.89), including only patients treated with CRRT for ≥3 days (csHR, 0.83, 95% CI: 0.73–0.95) and among those with negative fluid balance (csHR, 0.75, 95% CI, 0.64–0.86), and following propensity score matching (csHR, 0.76, 95% CI, 0.63–0.92).

Using subgroup analyses, an increase in UF_{NET} rate was associated with a longer time to independence from RRT among patients with (csHR, 0.78, 95% CI, 0.68–0.91; Fig. 3b; Table A8) and without organ edema (csHR, 0.84, 95% CI, 0.74–0.96); with (csHR, 0.75, 95% CI, 0.64–0.87) and without sepsis (csHR, 0.83, 95% CI, 0.73–0.95); and eGFR ≥60 mL/min/1.73 m² (csHR, 0.72, 95% CI, 0.62–0.84). A higher UF_{NET} rate was associated with a lower probability of RRT independence among patients with cardiovascular SOFA score <3 (csHR, 0.82, 95% CI, 0.68–0.99) and ≥3 (csHR, 0.84, 95% CI, 0.74–0.94) and high- (csHR, 0.79, 95% CI, 0.69–0.91) and low-intensity solute dosing (csHR, 0.78, 95% CI, 0.68–0.91).

Discussion/Conclusion

In these secondary analyses of a multicenter cohort of critically ill patients with AKI treated with CRRT, we found that UF_{NET} rates >1.75 mL/kg/h, compared with UF_{NET} rates <1.01 mL/kg/h, and rates 1.01–1.75 mL/kg/h were independently associated with a longer time to independence from RRT after accounting for competing risk of death and patient fluid balance. These findings are aligned with our prior work, showing an association of UF_{NET} rates >1.75 mL/kg/h with lower survival [7, 8] and suggesting that higher UF_{NET} rates per se independent of fluid balance are associated with a lower renal recovery. In our study, even though 44.3% of patients had died and

RRT dependence among survivors at day 90 was low (5.5%), our findings suggest that a greater proportion of patients receiving UF_{NET} rates >1.75 mL/kg/h do not recover kidney function before death.

It is important to note that fluid balance and fluid removal rate, though inter-related, are not synonymous with each other. While the fluid balance is associated with patient outcomes in several studies [5, 39, 40], our study suggests that the fluid removal rate, independent of fluid balance, is an emerging and important parameter, that is, amenable to intervention. Although randomly assigning patients to fluid removal versus no fluid removal may not be feasible, future studies could examine the effects of restrictive versus liberal rates or range of UF_{NET} rates on organ function and patient outcomes independent of fluid balance.

A major strength of our study was that fluid overload in the RENAL trial was prospectively adjudicated by clinicians based on visceral organ edema, and the daily fluid balance data were also prospectively collected. Since both of these variables were adjusted in the models, our findings were not confounded by the presence of greater severity of fluid overload in the higher UF_{NET} rate group. In clinical practice, since the UF_{NET} rates are titrated based on hemodynamics, we also fitted the joint model to account for the longitudinal changes and variations in UF_{NET} rate over time as well as correlation between UF_{NET} rate and hemodynamics, and their association with RRT dependence. This analysis also suggested that higher rates are associated with a longer time to independence from RRT.

In our previous work, using a cohort of critically ill patients with >5% fluid overload, we also found that UF_{NET} rates <20 mL/kg/day (or <0.83 mL/kg/h) compared with UF_{NET} rates ≥25 mL/kg/day were associated with increased mortality and a trend toward higher dependence on RRT [23]. This finding suggests that extremely slower rates of fluid removal among patients with fluid overload may also be associated with nonrecovery of renal function and mortality. In a prior analysis using the RENAL cohort, survivors had a negative fluid balance compared with a positive fluid balance in nonsurvivors [21]. However, in the current analysis, higher UF_{NET} rates were associated with higher daily and cumulative negative fluid balance and yet were independently associated with nonrecovery and mortality when the fluid balance was adjusted in the models. These observations suggest that higher UF_{NET} rates independent of fluid balance are associated with a lower renal recovery [41, 42].

There are several plausible biological mechanisms of association between higher UF_{NET} rates and decreased re-

nal recovery. Faster ultrafiltration rates have been associated with intradialytic hypotension [43]; ischemic injury to the heart [44], brain [45], GI tract [46], and kidneys [13]; and mortality in several observational studies among patients with end-stage renal disease treated with hemodialysis [47–50]. Among patients with established hemodialysis for at least 3 months who had low residual kidney function, one study using computed tomography perfusion found decreased kidney perfusion and increased number of stunning myocardial segments, both of which were associated with higher mean UF_{NET} rates [13]. Supporting these findings is the observation that residual kidney function declines faster among patients treated with hemodialysis in whom higher UF_{NET} rates are used compared with peritoneal dialysis [51, 52].

Our study also has several limitations. First, being an observational study, our findings do not prove causality between UF_{NET} rates and renal recovery but are only hypothesis generating. Since the association between higher UF_{NET} rates and lower renal recovery may represent residual confounding due to unmeasured risk factors, our study findings must be interpreted with caution. Nevertheless, our findings persisted in several sensitivity analyses under various assumptions and support the primary analyses. Second, data on race, comorbid conditions, and ultrafiltration treatment during hemodialysis were unavailable and might confound the assessment of renal recovery. Third, there were 31 patients with missing treatment hours; however, including these patients in the analysis did not change the results.

Fourth, the precise fluid balance before the initiation of CRRT was unavailable, a limitation that was addressed using the prospectively adjudicated organ edema variable by clinicians as a surrogate for severity of fluid overload. Fifth, since the RENAL trial was conducted between 2005 and 2008, it is possible that care practices for volume management may have changed, although more recent studies indicate a wide variation in rates of fluid removal and variation across geographic regions [53, 54]. Sixth, we did not measure actual prescribed UF_{NET} rates. Thus, it is possible that clinician factors (e.g., higher patient-nurse staffing ratio) associated with a mismatch between prescribed-delivered UF_{NET} rates might have impacted renal recovery. Seventh, we did not distinguish between removal of obligatory fluids administered (i.e., antibiotics and parenteral nutrition) versus removal of extracellular volume. Thus, it is not possible to distinguish whether the association of UF_{NET} rate on outcomes is due to removal of patient extracellular volume or obligatory fluid volumes.

Eighth, in our study, the UF_{NET} rate calculation is based on the machine fluid removal rate and does not necessarily reflect the patient fluid balance. For instance, 100 mL/h fluid removal does not necessarily reflect that the patient is net negative 100 mL/h since the patient fluid balance depends on simultaneous fluid infusion and fluid loss at any given time. Given these limitations, the risk of nonrecovery associated with higher UF_{NET} rates might be smaller than measured in this study.

Among critically ill patients receiving CRRT, UF_{NET} rates beyond 1.75 mL/kg/h compared with UF_{NET} rates <1.01 and 1.01–1.75 mL/kg/h were associated with a longer duration of dependence on RRT after accounting for competing risk of death. Although this study design does not exclude the possibility of residual confounding due to unmeasured risk factors, it provides the rationale for the design of randomized controlled trials comparing conservative with liberal UF_{NET} rates in critically ill patients and examining its association with renal outcomes.

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Statement of Ethics

The University of Pittsburgh's Human Research Protection Office approved this retrospective cohort study with a waiver of informed consent (PRO17090362). However, written informed consent was obtained in the RENAL trial [21] from the patient or a responsible surrogate utilizing either a priori or delayed consent.

Conflict of Interest Statement

Dr. Murugan reported receiving grants and personal fees from La Jolla Inc.; grants from Bioporto, Inc. and the National Institute of Diabetes and Digestive and Renal Diseases; and personal fees

from Beckman Coulter and AM Pharma, Inc., outside the submitted work. Dr. Chang reported receiving grants from the National Institutes of Health during the conduct of the study. Dr. Gallagher reported receiving speaking fees from Amgen outside the submitted work. Dr. Clermont reported receiving personal fees from UpToDate and grants from the National Institutes of Health and the National Science Foundation outside the submitted work. Dr. Ronco reported receiving consulting fees or participating in advisory boards in the last 3 years for ASAHI, Astute, Baxter, Biomerieux, B. Braun, Cytosorbents, ESTOR, FMC, GE, Jaftron, Medtronic, and Toray. Dr. Palevsky reported receiving personal fees from Novartis, GE Healthcare, HealthSpan Dx, and Baxter International and grants from Dascena outside the submitted work. Dr. Kellum reported receiving personal fees from NxStage and grants and personal fees from Baxter International during the conduct of the study. Dr. Bellomo reported receiving grants from Baxter International outside the submitted work.

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Author Contributions

Dr. Murugan and Ms. Kerti had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Murugan and Bellomo. Acquisition of data: Bellomo and Gallagher. Analysis and interpretation of data: Kerti, Chang, Murugan, Clermont, Palevsky, Bellomo, Kellum, Gallagher, and Serpa Neto. Drafting of the manuscript: Murugan. Critical revision of the manuscript for important intellectual content: Kellum, Bellomo, Palevsky, Clermont, Murugan, Chang, Kerti, Gallagher, Serpa Neto, and Ronco. Statistical analysis: Kerti and Chang. Administrative, technical, or material support: Murugan and Kerti. Study supervision: Murugan.

Availability of Data and Material

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

Trial Registration

The RENAL trial was registered on ClinicalTrials.gov (NCT00221013).

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