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Published in:
Nephrology Dialysis Transplantation

DOI:
[10.1093/ndt/gfaa032](https://doi.org/10.1093/ndt/gfaa032)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Naorungroj, T., Serpa Neto, A., Zwakman-Hessels, L., Yanase, F., Eastwood, G., Murugan, R., Kellum, J. A., & Bellomo, R. (2021). Early net ultrafiltration rate and mortality in critically ill patients receiving continuous renal replacement therapy. *Nephrology Dialysis Transplantation*, 36(6), 1112-1119. <https://doi.org/10.1093/ndt/gfaa032>

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Early net ultrafiltration rate and mortality in critically ill patients receiving continuous renal replacement therapy

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ABSTRACT

Background. In patients treated with continuous renal replacement therapy (CRRT), early net ultrafiltration (NUF) rates may be associated with differential outcomes. We tested whether higher early NUF rates are associated with increased mortality in CRRT patients.

Methods. We performed a retrospective, observational study of all patients treated with CRRT within 14 days of intensive care unit admission. We defined the early (first 48 h) NUF rate as the volume of fluid removed per hour adjusted for patient body weight and analysed as a categorical variable (>1.75 , 1.01 – 1.75 and <1.01 mL/kg/h). The primary outcome was 28-day mortality. To deal with competing risk, we also compared different time epochs.

Results. We studied 347 patients {median age 64 [interquartile range (IQR) 53–71] years and Acute Physiology and Chronic Health Evaluation III score 73 [IQR 54–90]}. Compared with NUF rates <1.01 mL/kg/h, NUF rates >1.75 mL/kg/h were associated with greater mortality rates in each epoch: Days 0–5, adjusted hazard ratio (aHR) 1.27 [95% confidence interval (CI) 1.21–1.33]; Days 6–10, aHR 1.62 (95% CI 1.55–1.68); Days 11–15, aHR 1.87 (95% CI 1.79–1.94); Days 16–26, aHR 1.92 (95% CI 1.84–2.01) and Days 27–28, aHR 4.18 (95% CI 3.98–4.40). For every 0.5 mL/kg/h NUF rate increase, mortality similarly increased during these epochs.

Conclusion. Compared with early NUF rates <1.01 mL/kg/h, NUF rates >1.75 mL/kg/h are associated with increased mortality. These observations provide the rationale for clinical trials to confirm or refute these findings.

Keywords: continuous renal replacement therapy, CRRT, mortality, net ultrafiltration

INTRODUCTION

Research in the field of continuous renal replacement therapy (CRRT) in critically ill patients has focused on intensity, timing of initiation, membrane characteristics, modality and technique of solute clearance [1–5]. In contrast, limited systematic research has focused on RRT-dependent fluid management, in particular net ultrafiltration (NUF) rate. This is unfortunate because either too high or too low NUF rates plausibly could affect outcome [6, 7]. Moreover, because of a lack of data, no guidelines exist for desirable NUF rates in clinical practice [8].

Recently a secondary analysis of the Randomized Evaluation of Normal versus Augmented Level (RENAL) trial reported that a NUF rate >1.75 mL/kg/h was independently associated with a higher risk of 90-day mortality [7]. However, in this study the authors used cumulative daily NUF rate data to back-estimate the hourly NUF rate, because no actual hourly NUF data were available from the trial database. Moreover, such RENAL trial data were obtained >10 years ago. Thus it may not be reflected in current usual CRRT practice. Finally, the above study did not focus on the early management of NUF, a time where illness severity may be most likely to be either positively or negatively affected by NUF management.

Accordingly, we aimed to investigate whether a NUF rate >1.75 mL/kg/h delivered early (first 48 h) was associated with worse outcomes in a contemporaneous cohort of adult critically

ill patients who received CRRT and for whom hourly NUF rates were recorded and available for analysis.

MATERIALS AND METHODS

Study design

We performed a single-center, retrospective, observational study in a teaching hospital affiliated with the University of Melbourne. This study was approved by the Austin Health Human Research Ethics Committee with a waiver of informed consent (approval number LNR/19/Austin/18).

Population

We screened all critically ill patients admitted to the intensive care unit (ICU) during 2016–18 who were treated with CRRT within 14 days of ICU admission. We excluded patients who had received intermittent hemodialysis (IHD) and plasma exchange (PE). In addition, since the focus was the early NUF rate and to remove the competing effect of early mortality, we excluded patients who had died within 48 h of ICU admission.

Data collection

We extracted and validated data from the ICU electronic database and scanned medical records. The current practice on dose of CRRT at the Austin Hospital is standardized and prescription follows the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [9] and the protocol in the RENAL trial [2], with an effluent volume between 20 and 25 mL/kg/h. However, either fluid removal rate or ultrafiltration rate is individualized according to baseline clinical characteristics of patients and the rate was adjusted by the medical team in charge of patient care. We focused our data collection on the CRRT hourly NUF rate as recorded in the electronic fluid chart during the early (first 48 h) period of treatment. We calculated the hourly NUF rate as the difference between hourly fluid removal from the CRRT machine and hourly replacement fluid, infused pre- and/or post-filter in continuous veno-venous haemofiltration or continuous veno-venous haemodiafiltration. For continuous veno-venous haemodialysis, the hourly NUF rate was equal to the delivered ultrafiltration rate (effluent flow rate minus dialysate flow rate) for that hour. The hourly NUF rate was recorded with a positive sign (+) if fluid removal was greater than the hourly replacement fluid and with a negative sign (–) if hourly fluid removal was less than the hourly replacement fluid. In this study we focused on analysis of NUF in the first 48 h of CRRT treatment because we reasoned that the early period of CRRT is likely most important and influential to patient outcomes. Moreover, observing NUF during the entire period of treatment generates a problem with the competing risk of mortality. Although statistical techniques can be applied to deal with such competing risk, they are imperfect. In particular, they cannot account for major time-variant confounders, which are so common in critically ill patients.

Exposure

The primary exposure was a NUF rate in the first 48 h of CRRT, calculated as [7]:

$$\text{NUF rate} = \frac{\text{Cum}_{\text{NUF}}}{\text{Weight}_{\text{beginning}} \times \text{Duration}_{\text{treat}}}$$

where Cum_{NUF} is the cumulative NUF volume in milliliters at the end of 48 h, $\text{Weight}_{\text{beginning}}$ is the weight in kilograms at the beginning of CRRT and $\text{Duration}_{\text{treat}}$ is the duration of CRRT in hours in the first 48 h.

Study outcome

The primary outcome was 28-day mortality (with patients discharged from the hospital alive before 28 days being considered alive at Day 28).

Statistical analyses

First, we confirmed that the association of NUF rate and 28-day mortality was non-linear and that tertiles resulted in the lowest Akaike information criterion (428.6) (Supplementary data, Figure S1). Thus, according to a previous publication [7], we stratified the NUF rate into three groups: low (<1.01 mL/kg/h), middle (1.01 – 1.75 mL/kg/h) and high (>1.75 mL/kg/h). We reported categorical variables as numbers and percentages and compared them using the chi-square test. We reported continuous variables as median (quartiles 25%–75%) and compared them using the Wilcoxon rank sum test.

As the potential impact of NUF rate categories on the primary outcome of 28-day mortality violated the proportional hazards assumption (Supplementary data, Figure S2), we applied a Gray piecewise-constant time-varying coefficients model, which considered confounders based on clinical experience and previous studies [6, 7, 10, 11]. These included age, gender, baseline estimated glomerular filtration rate (eGFR), time from ICU admission until start of CRRT, severity of illness assessed by the Acute Physiology and Chronic Health Evaluation III (APACHE III) score, presence of fluid overload as documented in the scanned and electronic medical record before CRRT initiation, sepsis, need for mechanical ventilation, cumulative fluid balance in the first 48 h, need for vasopressor at CRRT initiation, mean arterial pressure (MAP) at CRRT initiation, dose of norepinephrine at CRRT initiation, duration of CRRT in days and source of admission. For these variables, only one patient had a missing baseline eGFR and creatinine, thus complete case analysis was carried out excluding this case. We used Kaplan–Meier survival plots with the log-rank test to compare mortality over the first 28 days among the groups.

To further validate the findings, we conducted a sensitivity analysis applying univariable and multivariable logistic regression models with NUF rate as a categorical and continuous variable.

As a subgroup analysis, the effect of NUF rate in specific subgroups was assessed as an interaction in the Gray model for the 28-day mortality. The following subgroups were assessed: patients with or without sepsis, patients receiving or not receiving vasopressors and baseline $\text{eGFR} < 60$ mL/min/1.73 m² or ≥ 60 mL/min/1.73 m².

In all the models, a NUF rate <1.01 mL/kg/h was used as the reference and the analysis was restricted to patients receiving a NUF rate ≤ 5 mL/kg/h (100% of the patients). A two-sided P-value <0.05 was considered to be evidence of statistical

significance for primary and secondary outcomes. All analyses were performed using R software, version 3.4.1 (R Foundation, Vienna, Austria).

RESULTS

Study population

Between 30 July 2016 and 31 December 2018, 4774 critically ill patients were admitted to the ICU and 423 were treated with CRRT. In total, 53 of these 423 patients were excluded due to the use of IHD or PE or because they had initiated CRRT later than 14 days. In addition, 19 patients who died within 48 h of ICU admission were excluded. Finally, four patients with missing values in variables of interest were excluded, leaving 347 patients to be enrolled in the study. Of these, 159 (45.8%) had a NUF rate <1.01 mL/kg/h group, 102 (29.4%) had a NUF rate of 1.01–1.75 mL/kg/h and 86 (24.8%) had a NUF rate >1.75 mL/kg/h group (Figure 1).

The characteristics of study patients according to their NUF rate category are shown in Table 1. Patients in the NUF rate group >1.75 mL/kg/h were more likely to be female, weighed less, had higher urine output in the 6 h before CRRT, had lower pre-admission and pre-CRRT creatinine levels, had different medical admission diagnoses and were less likely to have hyperkalemia. There

was no difference in disease severity score according to APACHE III or in other key baseline characteristics such as diagnosis of sepsis or septic shock, the use of vasopressors, mechanical ventilation or the presence of fluid overload. However, patients in the NUF rate group >1.75 mL/kg/h had significantly more positive fluid balance from ICU admission to starting CRRT.

Patients with a NUF rate >1.75 mL/kg/h had a longer duration of CRRT treatment and longer ICU stay and experienced a more negative fluid balance (Table 2). During CRRT treatment, the coefficient of variation (CV) of NUF and haemodynamic changes, including time-weighted average MAP, the CV of MAP and the number of episodes of hypotension, were similar between groups. Moreover, vasopressor requirements during first 48 h of CRRT treatment were not significantly different among the three groups (Table 2).

Patients receiving a NUF rate >1.75 mL/kg/h had a significantly lower median lowest potassium level and a higher rate of hypophosphatemia during the first 48 h of CRRT compared with other groups (Table 2).

Associations of NUF with clinical outcomes

Compared with NUF rates <1.01 mL/kg/h, NUF rates >1.75 mL/kg/h were significantly associated with a higher risk of 28-day mortality beginning at Day 0 and in each time epoch, with the effect persisting until Day 28 (Table 3). Moreover, every 0.5 mL/kg/h increase in the NUF rate was associated with increased mortality from Days 0 to 28 (Table 3). There was no interaction between these effects and the presence of sepsis, need for vasopressors or baseline GFR (Supplementary data, Table S1).

Sensitivity analyses

Using logistic regression, after adjustment for confounders, a NUF rate >1.75 mL/kg/h was independently associated with a higher risk of death compared with a NUF rate <1.01 mL/kg/h [adjusted OR 2.33 (95% confidence interval 1.07–5.18); $P=0.034$], with good calibration and discrimination (Supplementary data, Table S2 and Figure S3). In addition, every 0.5 mL/kg/h increase in the NUF rate was associated with a 19% increase in the odds of death [adjusted OR 1.19 (95% CI 1.00–1.41); $P=0.047$] (Supplementary data, Table S3).

DISCUSSION

We investigated the association between early hourly NUF and mortality in a contemporaneous cohort of CRRT-treated patients. We found that a NUF rate >1.75 mL/kg/h was associated with increased mortality compared with a NUF rate <1.01 mL/kg/h. This relationship persisted from Days 0 to 28 in each epoch on primary Gray modeling. In this setting, every increase in the NUF rate of 0.5 mL/kg/h was associated with significantly increased 28-day mortality. Moreover, a NUF rate >1.75 mL/kg/h was significantly associated with a prolonged duration of CRRT treatment and ICU length of stay.

The observations of this study support the findings of a secondary analysis of the RENAL trial [7]. They are also consistent with prior observational studies in chronic HD patients, which demonstrated that a high rate of fluid removal was associated

FIGURE 1: Flowchart of inclusion.

Table 1. Baseline characteristics according to the NUF rate at ICU admission and before CRRT

Characteristics	NUF rate category			P-value
	<1.01 mL/kg/h (n = 159)	1.01–1.75 mL/kg/h (n = 102)	>1.75 mL/kg/h (n = 86)	
Age (years)	64.0 (54.5–71.0)	65.0 (54.2–71.7)	61.5 (50.2–70.7)	0.302
Male gender, n (%)	117 (73.6)	65 (63.7)	35 (40.7)	<0.001
Weight (kg)	86.0 (72.0–100.0)	86.5 (75.0–100.0)	70.5 (63.3–88.7)	<0.001
BMI (kg/m ²)	29.0 (24.6–33.9)	29.5 (26.3–35.3)	27.3 (23.8–32.2)	0.114
APACHE III score	71.0 (53.5–87.0)	80.0 (53.0–93.7)	71.0 (56.2–89.5)	0.250
Pre-admission renal function				
Creatinine (µmol/L)	119.0 (82.0–194.0)	114.5 (77.5–180.0)	92.5 (68.2–129.5)	0.006
eGFR (mL/min/1.73 m ²)	53.0 (25.5–79.0)	55.0 (31.0–86.2)	60.5 (45.0–90.7)	0.140
Comorbidities, n (%)				
Hypertension	82 (51.6)	48 (47.1)	35 (40.7)	0.264
Diabetes mellitus	58 (36.5)	37 (36.3)	29 (33.7)	0.903
Coronary artery disease	47 (29.6)	35 (34.3)	22 (25.6)	0.423
Atrial fibrillation	24 (15.1)	16 (15.7)	5 (5.8)	0.074
End-stage renal disease	15 (9.4)	8 (7.8)	7 (8.1)	0.889
Chronic liver disease	25 (15.7)	20 (19.6)	18 (20.9)	0.542
Cancer	26 (16.4)	19 (18.6)	17 (19.8)	0.779
Immunosuppression, n (%)	33 (20.8)	20 (19.6)	22 (25.6)	0.574
Source of ICU admission, n (%)				0.207
Emergency department	34 (21.4)	25 (24.5)	12 (14.0)	
Hospital ward	49 (30.8)	24 (23.5)	34 (39.5)	
Transfer from another ICU	11 (6.9)	6 (5.9)	9 (10.5)	
Transfer from another hospital	13 (8.2)	14 (13.7)	12 (14.0)	
OR after emergency surgery	13 (8.2)	7 (6.9)	7 (8.1)	
OR after elective surgery	37 (23.3)	23 (22.5)	10 (11.6)	
Other	2 (1.3)	3 (2.9)	2 (2.3)	
ICU admission diagnosis, n (%)				
Non-surgical admission				0.004
Cardiovascular	21 (19.3)	18 (25.4)	11 (15.9)	
Genitourinary	29 (26.6)	11 (15.5)	6 (8.7)	
Respiratory	11 (10.1)	13 (18.3)	15 (21.7)	
Gastrointestinal	31 (28.4)	21 (29.6)	33 (47.8)	
Liver failure	14 (8.8)	13 (12.7)	18 (20.9)	
Other	17 (15.6)	8 (11.3)	4 (5.8)	
Surgical admission				0.253
Cardiovascular	31 (62.0)	15 (48.4)	6 (35.3)	
Cardiac surgery	22 (13.8)	12 (11.8)	5 (5.9)	
Gastrointestinal	14 (28.0)	13 (41.9)	7 (41.2)	
Liver transplantation	9 (5.7)	9 (8.8)	4 (4.7)	
Other	5 (10.0)	3 (9.7)	4 (23.5)	
Before CRRT initiation, n (%)				
Mechanical ventilation	100 (62.9)	70 (68.6)	63 (73.3)	0.239
Need of vasopressor	109 (68.6)	61 (59.8)	47 (54.7)	0.079
Sepsis or septic shock	43 (27.0)	23 (22.5)	30 (34.9)	0.165
Other type of shock	9 (5.7)	9 (8.8)	7 (8.1)	0.583
Cardiac arrest	6 (3.8)	13 (12.7)	8 (9.3)	0.025
Fluid overload	10 (6.3)	12 (11.8)	12 (14.0)	0.114
Oliguria	99 (62.3)	67 (65.7)	48 (55.8)	0.374
Laboratory before CRRT				
Creatinine (µmol/L)	350.0 (204.5–501.5)	319.0 (231.5–433.7)	250.5 (162.7–335.0)	0.001
Creatinine >300 µmol/L, n (%)	89 (56.0)	54 (52.9)	32 (37.2)	0.016
Urea (mmol/L)	21.0 (13.2–28.4)	21.0 (12.9–29.9)	17.6 (9.6–28.2)	0.203
Urea >25 mmol/L, n (%)	52 (32.7)	38 (37.3)	25 (29.1)	0.488
pH	7.35 (7.27–7.39)	7.35 (7.27–7.41)	7.33 (7.25–7.39)	0.743
pH <7.20, n (%)	19 (12.8)	9 (9.5)	7 (8.6)	0.548
Potassium (mmol/L)	4.5 (4.0–5.2)	4.5 (3.9–5.2)	4.3 (3.9–4.8)	0.108
Potassium >5.5 mmol/L, n (%)	28 (17.6)	15 (14.7)	4 (4.7)	0.017
Bicarbonate (mmol/L)	19.0 (15.7–23.0)	20.0 (17.0–23.9)	19.0 (16.0–23.0)	0.211
Base excess (mmol/L)	−5.0 (−10.0 to −2.0)	−4.0 (−8.0 to −0.8)	−5.2 (−9.0 to −1.9)	0.225
Lactate (mmol/L)	2.1 (1.2–4.2)	1.9 (1.4–3.4)	2.0 (1.3–4.6)	0.805
PaO ₂ /FiO ₂	287.9 (210.9–381.5)	275.0 (200.0–352.7)	282.5 (222.5–420.0)	0.469
Vital signs before CRRT				
MAP (mmHg)	74.0 (67.5–80.0)	75.0 (70.0–86.0)	75.5 (67.0–85.0)	0.268

Continued

Table 1. Continued

Characteristics	NUF rate category			P-value
	<1.01 mL/kg/h (n = 159)	1.01–1.75 mL/kg/h (n = 102)	>1.75 mL/kg/h (n = 86)	
Heart rate (bpm)	90.0 (75.0–101.0)	87.0 (75.0–95.0)	85.0 (75.0–102.0)	0.723
Urine output 6 h before CRRT				
In mL	150 (25–434)	107 (30–256)	212 (66–479)	<0.001
In mL/kg	1.75 (0.30–5.17)	1.08 (0.34–3.21)	2.93 (0.88–5.64)	0.723
In mL/kg/h	0.29 (0.05–0.86)	0.18 (0.05–0.53)	0.48 (0.14–0.94)	<0.001
Beginning of therapy				
Start from ICU admission (days)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.244
Start from ICU admission (h)	9.0 (3.1–33.2)	13.4 (3.1–40.9)	19.0 (3.8–47.5)	0.293
Fluid balance before CRRT (mL)	215 (–272–1189)	310 (–32–2095)	682 (–28–2908)	0.038

Data are median (quartiles 25%–75%) unless stated otherwise.

BMI, body mass index; OR, operating room; PaO₂, partial pressure of oxygen; FiO₂, fraction of inspired oxygen.

with increased cardiovascular mortality [12, 13]. Higher NUF rates may exceed vascular refilling capacity and thus cause haemodynamic instability [14]. Such instability may cause reduced blood flow to vital organs and induce myocardial stunning [15–18] and subclinical myocardial ischaemia [18]. However, our findings do not support a significant association between a higher NUF rate and greater haemodynamic instability. Moreover, higher rates of NUF may be associated with electrolyte and acid–base disturbance, such as hypophosphataemia, with its attendant risks [7, 19–22]. In keeping with this, our findings suggest that both hypokalemia and hypophosphataemia were greater with the highest NUF rates. Finally, high NUF rates may also increase convective removal of some antibiotics and adversely affect their levels [23–25].

Our findings imply that early NUF is a modifiable risk factor for mortality in patients treated with CRRT. Moreover, they imply that there is a continuous increase in risk as NUF increases, even after adjustment for multiple confounders. Finally, by identifying a potential maximum limit for the NUF rate, we identify a target for further studies.

This is the first study to provided direct data on hourly NUF rates in patients receiving CRRT. Moreover, the study cohort is large and contemporaneous and includes patients treated in a tertiary hospital in a resource-rich country. The study ICU was a leading site in the RENAL trial 10 years earlier. Thus this confirmation, a decade later, of RENAL trial-derived findings associating NUF with worse outcomes [7] suggests that these observations are robust and persistent. Finally, the finding, both in primary Gray and multivariable logistic regression models, that higher NUF rates are associated with higher mortality provide further confidence of their robustness.

We acknowledge certain limitations. First, this is a single-centre, retrospective observational study with all the inherent limitations of such studies. However, our patients had baseline characteristics similar to those reported in other studies of CRRT in other resource-rich countries, implying a degree of external validity. Second, although we used multiple risk adjustments and included many potential confounders, there may be some residual confounders that are responsible for the observed association. However, our findings align with previous studies in both CRRT-treated and chronic HD patients [7, 12]. Third, we did not have fluid balance data before CRRT

initiation. However, the presence of fluid overload as specified by clinicians was not associated with mortality. Nonetheless, we acknowledge that the lack of detailed data on pre-CRRT fluid status is a major unmeasured confounder in this study. We further acknowledge that the number of patients with fluid overload prior to CRRT was small, making a robust statistical assessment of such fluid status impossible. Moreover, there may have been greater illness severity among patients in the highest tertile of NUF. However, several markers of illness severity suggested uncertainty around such an assessment. Fourth, we analysed only the NUF data in the first 48 h of CRRT treatment. However, the results persisted in each epoch until Day 28 after treatment. We acknowledge that the indication for starting CRRT was not available in our patients. However, such decisions are typically complex and their nuances difficult to capture in the medical records. Finally, these findings only describe an association and cannot be used to infer causality. Thus a high NUF rate may simply be yet another independent marker of illness severity in a way that is not captured by the variables inserted in our model. However, our findings provide a rationale for the continuing investigation of the role of hourly NUF in potentially affecting the outcome of CRRT patients and the necessary data to generate power estimates for future randomized interventional studies.

To conclude, in a large contemporaneous CRRT-treated cohort, a NUF rate >1.75 mL/kg/h in the first 48 h was independently associated with increased 28-day mortality compared with a NUF rate <1.01 mL/kg/h. Moreover, higher NUF rates were independently associated with a longer duration of CRRT and increased ICU length of stay. These findings were robust to sensitivity analysis and several modeling approaches and provide the rationale for further investigation of the role of NUF rates in affecting outcomes as well as informing power estimates for future interventional trials.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](https://academic.oup.com/ndt/article/36/6/1125/817462) online.

ACKNOWLEDGEMENTS

We thank Samantha J. Kerti, the biostatistician at the Biostatistics and Data Management Core of the Clinical

Table 2. Characteristics of therapy and clinical outcomes

Characteristics	NUF rate category <1.01 mL/kg/h (n = 159)	1.01–1.75 mL/kg/h (n = 102)	>1.75 mL/kg/h (n = 86)	P-value
Duration of treatment				
Days	2.0 (1.0–5.0)	4.0 (2.0–7.0)	4.0 (2.0–9.0)	<0.001
Hours	56.0 (29.5–113.0)	85.5 (44.0–162.0)	96.5 (54.5–212.5)	<0.001
Fluid balance (mL)				
Day 1	533.0 (–304.5–1647.0)	–4.0 (–909.7–780.0)	–149.5 (–1249.0–627.0)	<0.001
Day 2	118.0 (–876.2–984.0)	–940.0 (–1710.5–15.2)	–1364.0 (–2244.0 to –321.0)	<0.001
Cumulative	527.0 (–824.0–2400.0)	–657.0 (–2171.7–600.0)	–1751.0 (–3477.7–376.0)	<0.001
NUF rate				
Hourly (mL/h)	42.8 (13.6–65.1)	113.3 (95.1–144.3)	175.6 (148.1–216.9)	<0.001
Cumulative (mL)	1032.0 (228.5–1808.5)	3595.5 (2463.2–4691.0)	5228.5 (3795.5–6727.7)	<0.001
CV of NUF rate	102.5 (73.3–165.6)	67.1 (51.5–80.5)	48.8 (40.6–66.2)	<0.001
Hemodynamic				
Hypotension, n (%)	93 (58.5)	56 (54.9)	44 (51.2)	0.537
Time-weighted average MAP (mmHg)	73 (67–81)	73 (69–81)	76 (69–82)	0.190
Lowest MAP in the first 48 h	62 (59–67)	63 (60–68)	63 (60–68)	0.474
Coefficient of variation of MAP (%)	9.0 (7.2–11.8)	9.4 (7.7–11.0)	9.1 (7.8–10.9)	0.830
Amplitude of MAP (mmHg)	15.0 (10.6–19.9)	16.2 (11.1–20.1)	16.2 (11.9–20.4)	0.289
Number of episodes of hypotension ^a	1 (0–4)	1 (0–2)	1 (0–3)	0.374
Percentage of measurements with hypotension	3.4 (0.0–12.3)	2.5 (0.0–6.9)	2.1 (0.0–8.0)	0.231
Need of vasopressor, n (%)	122 (76.7)	72 (70.6)	57 (66.3)	0.195
Hours with vasopressors	22 (2–29)	21 (0–32)	12 (0–32)	0.731
Total dose of norepinephrine equivalent ^b	109.0 (2.7–371.5)	77.0 (0.0–294.3)	42.0 (0.0–235.5)	0.139
Norepinephrine total dose	109.0 (2.7–357.0)	75.5 (0.0–291.0)	42.0 (0.0–235.5)	0.148
Epinephrine total dose	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.064
Vasopressin total dose	0.00 (0.00–0.08)	0.00 (0.00–0.04)	0.00 (0.00–0.00)	0.279
Phenylephrine total dose	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.207
Lowest central venous pressure (mmHg)	8 (5–10)	8 (5–11)	7 (5–10)	0.671
CV of central venous pressure (%)	20.2 (14.2–26.7)	19.9 (14.6–28.0)	20.9 (16.0–28.4)	0.607
Clinical outcomes				
Renal dependence among survivors at Day 28, n (%)	33 (21.3)	17 (17.9)	14 (18.4)	0.666
Length of stay (days)				
ICU	6.0 (3.0–11.0)	7.5 (4.0–13.0)	9.0 (6.0–14.0)	0.004
Hospital	18.0 (10.0–39.5)	21.0 (9.0–32.0)	26.0 (13.0–44.7)	0.066
Mortality, n (%)				
ICU	39 (24.5)	29 (28.4)	28 (32.6)	0.398
Hospital	41 (25.8)	33 (32.7)	34 (39.5)	0.080
28 days	41 (25.8)	33 (32.7)	34 (39.5)	0.080
Electrolytes				
Hypokalemia, n (%) ^c	29 (18.2)	19 (18.6)	23 (26.7)	0.249
Lowest potassium (mEq/L)	3.80 (3.55–4.10)	3.80 (3.60–4.00)	3.70 (3.40–3.90)	0.030
Number of episodes of hypokalemia	0 (0–0)	0 (0–0)	0 (0–1)	0.203
Percentage of measurements with hypokalemia	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–6.8)	0.274
Hypophosphatemia, n (%) ^d	22 (14.4)	13 (12.9)	23 (27.1)	0.018
Lowest phosphate (mmol/L)	1.37 (1.04–1.73)	1.34 (1.07–1.67)	1.19 (0.75–1.50)	0.006
Number of episodes of hypophosphatemia	0 (0–0)	0 (0–0)	0 (0–1)	0.011
Percentage of measurements with hypophosphatemia	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–16.7)	0.022
Lowest pH	7.32 (7.25–7.38)	7.33 (7.26–7.38)	7.31 (7.25–7.38)	0.706

Data are median (IQR) unless stated otherwise. CV defined as the standard deviation of the hourly NUF rate divided by its mean and multiplied by 100. Vasopressors defined as any need of norepinephrine, epinephrine, vasopressin, dopamine or phenylephrine.

^aDefined as MAP <65 mmHg.

^bConversion unit: norepinephrine 0.1 µg/kg/min is equal to epinephrine 0.1 µg/kg/min, vasopressin 0.04 U/min and phenylephrine 1 µg/kg/min.

^cDefined as potassium <3.5 mEq/L.

^dDefined as phosphate <0.81 mmol/L.

Research, Investigation, Systems Modelling of Acute Illness Center, for conducting data analysis.

FUNDING

This project has no funding support.

AUTHORS' CONTRIBUTIONS

T.N., G.E and R.B. were responsible for the research idea and study design, T.N., A.S.N. and L.Z.H. were responsible for data acquisition. All authors were responsible for data analysis and interpretation. A.S.N. was responsible for statistical analysis. A.S.N., R.M., J.A.K. and R.B. were responsible for

Table 3. Association of NUF rate and survival within each time interval from the primary Gray model

NUF rate (mL/kg/h)	Model	Hazard ratio (95% CI)					P-value
		0–5 days	6–10 days	11–15 days	16–26 days	27–28 days	
No. of patients at risk		347	320	293	274	253	
>1.75 versus <1.01	Unadjusted ^a	0.77 (0.74–0.81)	1.15 (1.12–1.19)	1.49 (1.44–1.54)	1.83 (1.77–1.90)	4.32 (4.15–4.50)	0.004
	Adjusted ^b	1.27 (1.21–1.33)	1.62 (1.55–1.68)	1.87 (1.79–1.94)	1.92 (1.84–2.01)	4.18 (3.98–4.40)	0.031
	No. of deaths, n/N (%)	34/86 (39.5) versus 41/159 (25.8)	30/82 (36.6) versus 26/144 (18.0)	23/75 (30.7) versus 18/136 (13.2)	36/274 (13.1) versus 8/126 (6.3)	15/253 (5.9) versus 2/120 (1.7)	
>1.75 versus 1.01–1.75	Unadjusted ^a	0.83 (0.80–0.87)	0.85 (0.82–0.88)	1.28 (1.23–1.32)	1.15 (1.11–1.20)	2.23 (2.14–2.32)	0.235
	Adjusted ^b	1.13 (1.08–1.20)	1.05 (1.00–1.09)	1.68 (1.61–1.74)	1.32 (1.27–1.38)	2.27 (2.17–2.38)	0.303
	No. of deaths, n/N (%)	34/86 (39.5) versus 33/101 (32.7)	30/82 (36.6) versus 26/94 (27.6)	23/75 (30.7) versus 14/82 (17.1)	36/274 (13.1) versus 12/80 (15.0)	15/253 (5.9) versus 4/72 (5.5)	
1.01–1.75 versus <1.01	Unadjusted ^a	0.76 (0.74–0.79)	1.68 (1.62–1.73)	0.91 (0.87–0.94)	1.68 (1.62–1.74)	1.89 (1.81–1.98)	0.053
	Adjusted ^b	0.96 (0.92–1.00)	1.92 (1.85–1.98)	0.83 (0.80–0.86)	1.55 (1.49–1.61)	1.84 (1.76–1.93)	0.061
	No. of deaths, n/N (%)	33/101 (32.7) versus 41/159 (25.8)	26/94 (27.6) versus 26/144 (18.0)	14/82 (17.1) versus 18/136 (13.2)	12/80 (15.0) versus 8/126 (6.3)	4/72 (5.5) versus 2/120 (1.7)	
Per 0.50 increase	Unadjusted ^a	0.89 (0.88–0.90)	1.01 (1.00–1.01)	1.01 (1.01–1.02)	1.10 (1.09–1.11)	1.30 (1.29–1.31)	0.006
	Adjusted ^b	1.04 (1.03–1.05)	1.12 (1.11–1.13)	1.06 (1.05–1.07)	1.12 (1.11–1.13)	1.33 (1.31–1.34)	0.043

^aUnadjusted hazard ratios estimated from the Gray model for association of the NUF rate with mortality for each time interval are shown. Models included five intervals and four nodes, with the default timing of nodes chosen by the statistical program based on the number of events within each interval. A hazard ratio <1 suggests that the NUF rate is associated with lower mortality and a hazard ratio >1 suggests that the NUF rate is associated with higher mortality within each time interval. P-values reported are for the ranges of hazard ratios across time intervals from the model.

^bAdjusted hazard ratios estimated from the Gray model for association of NUF rate with mortality for each time interval are shown. Adjusted by age, gender, baseline eGFR, time from ICU admission until start of CRRT, APACHE III score, presence of fluid overload, sepsis, need of mechanical ventilation, cumulative fluid balance in the first 48 h, need for vasopressor, MAP and dose of norepinephrine at CRRT beginning, duration of CRRT in days and source of admission.

supervision or mentorship. All authors participated in co-writing of the final manuscript.

CONFLICT OF INTEREST STATEMENT

R.M. reported receiving grants and personal fees from La Jolla Pharmaceuticals, grants from Bioporto and the National Institute of Diabetes and Digestive and Kidney Diseases and personal fees from Beckman Coulter and AM Pharma outside the submitted work. J.A.K. reported receiving personal fees from NxStage and grants and personal fees from Baxter International outside the submitted work. R.B. reported receiving grants from Baxter International outside the submitted work. T.N., A.S.N., F.Y., L.Z.-H. and G.E. declare that they have no relevant financial interests.

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Received: 9.10.2019; Editorial decision: 15.1.2020