Net ultrafiltration intensity and mortality in critically ill patients with fluid overload

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Abstract

Background: Although net ultrafiltration (UFNET) is frequently used for treatment of fluid overload in critically ill patients with acute kidney injury, the optimal intensity of UFNET is unclear. Among critically ill patients with fluid overload receiving renal replacement therapy (RRT), we examined the association between UFNET intensity and risk-adjusted 1-year mortality.

Methods: We selected patients with fluid overload ≥ 5% of body weight prior to initiation of RRT from a large academic medical center ICU dataset. UFNET intensity was calculated as the net volume of fluid ultrafiltered per day from initiation of either continuous or intermittent RRT until the end of ICU stay adjusted for patient hospital admission body weight. We stratified UFNET as low (≤ 20 ml/kg/day), moderate (> 20 to ≤ 25 ml/kg/day) or high (> 25 ml/kg/day) intensity. We adjusted for age, sex, body mass index, race, surgery, baseline estimated glomerular filtration rate, oliguria, first RRT modality, pre-RRT fluid balance, duration of RRT, time to RRT initiation from ICU admission, APACHE III score, mechanical ventilation use, suspected sepsis, mean arterial pressure on day 1 of RRT, cumulative fluid balance during RRT and cumulative vasopressor dose during RRT. We fitted logistic regression for 1-year mortality, Gray’s survival model and propensity matching to account for indication bias.

Results: Of 1075 patients, the distribution of high, moderate and low-intensity UFNET groups was 40.4%, 15.2% and 44.2% and 1-year mortality was 59.4% vs 60.2% vs 69.7%, respectively (p = 0.003). Using logistic regression, high-intensity compared with low-intensity UFNET was associated with lower mortality (adjusted odds ratio 0.61, 95% CI 0.41–0.93, p = 0.02). Using Gray’s model, high UFNET was associated with decreased mortality up to 39 days after ICU admission (adjusted hazard ratio range 0.50–0.73). After combining low and moderate-intensity UFNET groups (n = 258) and propensity matching with the high-intensity group (n = 258), UFNET intensity > 25 ml/kg/day compared with ≤ 25 ml/kg/day was associated with lower mortality (57% vs 67.8%, p = 0.01). Findings were robust to several sensitivity analyses.

Conclusions: Among critically ill patients with ≥ 5% fluid overload and receiving RRT, UFNET intensity > 25 ml/kg/day compared with ≤ 20 ml/kg/day was associated with lower 1-year risk-adjusted mortality. Whether tolerating intensive UFNET is just a marker for recovery or a mediator requires further research.

Keywords: Net ultrafiltration, Intensity, Fluid overload, Renal replacement therapy, Dialysis, Mortality

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Background
Fluid overload (FO) is a common complication of acute illness affecting more than a third of critically ill patients and approximately two-thirds of patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) [1, 2]. Several studies have documented that FO is independently associated with more than 50% mortality among patients receiving RRT [3, 4]. Observational studies suggest that fluid removal using net ultrafiltration (UFNET) may be associated with improved outcomes [2], and clinical and consensus guidelines recommend UFNET for the treatment of FO in patients with oliguric AKI who are resistant to diuretic therapy [5, 6]. However, the optimal intensity of UFNET (i.e., rate and volume of net fluid removal) in critically ill patients remains uncertain more than 70 years after the first clinical use of ultrafiltration [7].

Less intensive UFNET, characterized by a slower rate or smaller volume of fluid removed, may be associated with prolonged exposure to tissue and organ edema and increased morbidity and mortality [8, 9]. More intensive UFNET with a faster rate or larger volume of fluid removal, however, may be associated with increased hemodynamic and cardiovascular stress [10], leading to ischemic organ injury and mortality in critically ill patients [11]. Indeed, three observational studies in outpatients with end-stage renal disease suggest that UFNET intensity > 10 ml/kg/h is associated with increased overall [12–14] and cardiovascular [12] mortality.

Understanding the relationship between UFNET intensity and outcome in critically ill patients is essential for two important reasons. First, if more intensive UFNET is associated with lower mortality, then clinical trials could be designed to reduce the risk of death. Second, understanding the intensity–outcome relationship will aid in standardizing UFNET intensity and implementing quality measures [15, 16].

In this observational study involving a large heterogeneous cohort of critically ill patients with ≥ 5% FO and receiving RRT, we examined the association between UFNET intensity and its association with risk-adjusted 1-year mortality. Because the magnitude of FO is independently associated with mortality, we hypothesized that intensive UFNET would be associated with lower mortality. However, our null hypothesis was that there is no difference in mortality for an intensive UFNET group compared with a less intensive UFNET group.

Methods
Data source and study population
We conducted a retrospective study using a large tertiary care academic medical center ICU database: the High-Density Intensive Care dataset, details of which have been published elsewhere (Additional file 1: S1) [1, 17, 18]. The study population included adults admitted to medical, cardiac, abdominal transplant, cardiothoracic, surgical, neurovascular, neurotrauma and trauma ICUs during July 2000 through October 2008. We included patients with AKI receiving RRT who had a cumulative fluid balance ≥ 5% prior to RRT initiation (Additional file 1: Figure S1). We extracted the daily fluid balance before and for the duration of RRT (Additional file 1: S2), hourly mean arterial pressure (MAP) and vasopressor type and dose (Additional file 1: S3) during RRT. The University of Pittsburgh’s institutional review board approved the study.

Determination of UFNET intensity
For patients receiving continuous renal replacement therapy (CRRT), we first extracted data on the total duration (in hours) of any form of CRRT (i.e., continuous venovenous hemodiafiltration (CVVHDF), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) and slow continuous ultrafiltration (SCUF)). We then determined the UF volume produced and the amount of substitution fluids given each hour for patients receiving CVVHDF and CVVH. The UFNET each hour was calculated as the difference between the UF volume and the volume of substitution fluids given [19]. For patients receiving CVVHD and SCUF, UFNET corresponded to the UF volume removed. We then calculated the total number of days of CRRT for each patient based on the hourly duration of CRRT and the total UFNET.

For patients receiving intermittent hemodialysis (IHD), we extracted the total number of IHD sessions and the UF volume removed per session from the time of ICU admission to the end of ICU stay. We excluded patients if they received IHD prior to ICU admission. UFNET corresponded to the volume ultrafiltered during each session. We then expressed the total number of IHD sessions as the number of days for each patient. Subsequently, we estimated the UFNET intensity using the equation:

\[
UFNET\text{intensity}(ml/kg/day) = \frac{\text{Total UFNET volume (ml)}}{\text{Hospital admission weight (kg) } \times \text{RRT duration (days)}}.
\]

For instance, if an 80-kg patient is on CVVH with an UF rate of 2000 ml/h and substitution fluid of 1500 ml/h, the total UFNET produced is 500 ml/h (2000 – 1500 = 500 ml) or 500 × 24 = 12,000 ml/day. The total UFNET produced for 5 days is 12,000 × 5 = 60,000 ml. Thus, the total UFNET intensity is [60,000 / (80 × 5)] = 150 ml/kg/day. During CVVHD and IHD, the UF volume is equivalent to UFNET.
Outcomes
The primary outcome was 1-year mortality from the index ICU admission and mortality data were obtained from the Social Security Death Master File [20]. We chose 1-year mortality because our prior work showed that a positive fluid balance was associated with risk of death at 1 year and use of renal replacement therapy was associated with lower risk of death in patients with a positive fluid balance [1]. Secondary outcomes included hospital length of stay, hospital mortality and renal recovery. Renal recovery was defined as alive and independent from RRT at 1 year. Dialysis dependence was associated with lower risk of death in patients with a positive fluid balance [1]. Secondary outcomes in- cluded hospital length of stay, hospital mortality and renal recovery. Renal recovery was defined as alive and independent from RRT at 1 year. Dialysis dependence data were obtained from the US Renal Data System [21].

Statistical analysis
We stratified UF_{NET} intensity into three groups because of the nonlinear (i.e., J-shaped) association between UF_{NET} intensity and hospital mortality (Additional file 1: Figure S2). We defined UF_{NET} ≤ 20 ml/kg/day as “low” intensity, UF_{NET} > 20 to ≤ 25 ml/kg/day as “moderate” intensity and UF_{NET} > 25 ml/kg/day as “high” intensity. Categorical variables were compared using the chi- squared test, and continuous variables using one-way analysis of variance and the Kruskal–Wallis test. We assessed time-to-mortality censored at 1 year using Kaplan–Meier failure plots.

We used three methods to examine the association between UF_{NET} intensity and mortality. First, we fitted logistic regression and estimated risk-adjusted odds ratios (AORs) for high and moderate intensity, compared with low intensity UF_{NET} (reference), on 1-year mortality. Sec- ond, we fitted Gray’s survival model [22, 23] to estimate risk-adjusted hazard ratios (AHRs) for time to mortality using four time nodes and five intervals (Additional file 1: S4). We adjusted for differences in age, sex, race, body mass index, history of liver disease and sequela from liver disease, admission for liver transplantation, admission for surgery, baseline glomerular filtration rate, Acute Physio- logic and Chronic Health Evaluation (APACHE) III score, presence of sepsis, use of mechanical ventilation, percentage of FO before initiation of RRT, oliguria before initiation of RRT, time to initiation of RRT from ICU admission, MAP on first day of RRT initiation, cumulative vasopressor dose and cumulative fluid balance during RRT, first RRT modality and duration of RRT.

Third, in order to account for indication bias, we con- ducted a propensity score-matched analysis. Since the mortality associated with moderate (≥ 20 to ≤ 25 ml/kg/day) vs high (≥ 25 ml/kg/day) or moderate (≥ 20 to ≤ 25 ml/kg/day) vs low (≤ 20 ml/kg/day) intensity UF_{NET} was not different (Table 1), we combined the moderate and low-intensity groups into a single low-intensity group (reference). We then matched the low-intensity UF_{NET} (≤ 25 ml/kg/day) with the high-intensity UF_{NET} (> 25 ml/kg/day) using propensity scores on a 1:1 basis without replacement, creating 258 matched pairs (Additional file 1: S5).

We performed five sensitivity analyses and two sub- group analyses. First, we restricted the UF_{NET} intensity only up to 72 h from initiation of RRT. Second, we used an alternative definition of UF_{NET} intensity moving the threshold down as follows: low, < 15 ml/kg/day; moderate, 15–20 ml/kg/day; and high, > 20 ml/kg/day. Third, we moved the threshold up: low, < 25 ml/kg/day; moderate, 25–30 ml/kg/day; and high, > 30 ml/kg/day. Fourth, we divided the cohort into tertiles: low, ≤ 16.7 ml/kg/ day; moderate, 16.7 to ≤ 27.7 ml/kg/day; and high, > 27.7 ml/kg/day. Fifth, we performed quantitative bias analysis to assess the magnitude of a hypothetical unmeasured confounder that would be necessary to account for the association between UF_{NET} intensity and risk-adjusted mortality (Additional file 1: S6) [24, 25].

Sixth, we restricted our analyses only to the subgroup of patients with > 20% FO. Seventh, we confined our analysis of UF_{NET} intensity to the hour (i.e., ml/kg/h) instead of the day among the subgroup of patients who only received CRRT as follows: low, < 0.5 ml/kg/h; moderate, 0.5–1.0 ml/kg/h; and high, > 1 ml/kg/h. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA), Gray’s model used R 3.2.1, and quanti- tative bias analysis was performed using STATA 15 (STATCorp., TX, USA). All hypotheses tests were two-sided with a significance level of \( p < 0.05 \).

Results
Study population and patient characteristics
Of 45,568 patients, we excluded patients with no available baseline weight (\( n = 2214 \)), ICU duration ≤ 48 h (\( n = 18,032 \)), death within 72 h of ICU admission (\( n = 663 \)), chronic dialysis (\( n = 2386 \)), admission for or with history of renal transplantation (\( n = 1232 \)), serum creatinine ≥ 3.5 mg/dl within 1 year of hospitalization (\( n = 147 \)) and missing data on fluid balance (\( n = 2810 \)). Of 18,084 patients in whom cumulative fluid balance data were available, we excluded those with cumulative fluid balance < 5% of body weight (\( n = 9900 \)). Of patients with cumulative balance ≥ 5% of body weight (\( n = 8184 \)), we excluded those who did not receive RRT (\( n = 7023 \)) and patients without data on UF_{NET} (\( n = 86 \)) (Additional file 1: Figure S1).

Of 1075 patients, the distribution of low, moderate and high-intensity UF_{NET} groups was 44.2%, 15.2% and 40.4%, respectively. Minor differences were noted among male sex, race and body mass index between the groups (Table 1). There was a higher prevalence of liver disease (34.5%), sequel from liver disease (28.8%) and liver transplantation (21.5%) among those with low-intensity UF_{NET}. There was a higher prevalence of oliguria in those who received moderate and high-intensity UF_{NET}.
|                                | ≤ 20 ml/kg/day (n = 475) | > 20 to ≤ 25 ml/kg/day (n = 166) | > 25 ml/kg/day (n = 434) | p value |
|--------------------------------|--------------------------|---------------------------------|--------------------------|---------|
| Age (years), median (IQR)      | 61 (52–69)               | 59 (51–71)                       | 58 (48–70)               | 0.16    |
| Male sex                       | 301 (63.4)               | 114 (68.7)                       | 218 (50.2)               | < 0.001 |
| Race                           |                          |                                 |                          |         |
| Caucasian                      | 380 (80)                 | 136 (81.9)                       | 335 (77.2)               | 0.018   |
| African-American               | 24 (5.1)                 | 6 (3.6)                          | 43 (9.9)                 |         |
| Other                          | 71 (14.9)                | 24 (14.5)                        | 56 (12.9)                |         |
| BMI (kg/m²), median (IQR)      | 28.3 (24.2–34.3)         | 27.7 (24.2–31.7)                 | 25.1 (21.9–29.3)         | < 0.001 |
| Comorbid condition             |                          |                                 |                          |         |
| Hypertension                   | 169 (35.6)               | 72 (43.4)                        | 161 (37.1)               | 0.19    |
| Diabetes                       | 121 (25.5)               | 34 (20.5)                        | 97 (22.4)                | 0.33    |
| Cardiac disease                | 84 (17.7)                | 36 (21.7)                        | 99 (22.8)                | 0.14    |
| Heart failure                  | 70 (14.7)                | 30 (18.1)                        | 86 (19.8)                | 0.12    |
| Vascular disease               | 41 (8.6)                 | 16 (9.6)                         | 43 (9.9)                 | 0.79    |
| Liver disease                  | 164 (34.5)               | 47 (28.3)                        | 107 (24.7)               | 0.005   |
| Sequela from liver disease     | 137 (28.8)               | 43 (25.9)                        | 95 (21.9)                | 0.056   |
| Malignancy                     | 23 (4.8)                 | 4 (2.4)                          | 14 (3.2)                 | 0.26    |
| Liver transplantation          | 43 (9.1)                 | 13 (7.8)                         | 42 (9.7)                 | 0.77    |
| Multiple comorbidity           | 298 (62.7)               | 93 (56)                          | 252 (58.1)               | 0.19    |
| Surgical admission             | 321 (67.6)               | 122 (73.5)                       | 301 (69.4)               | 0.72    |
| Medical admission              | 131 (27.6)               | 37 (22.3)                        | 112 (25.8)               | 0.72    |
| Admission for liver transplantation | 102 (21.5)       | 31 (18.7)                        | 53 (12.2)                | 0.001   |
| Baseline serum creatinine (mg/dl), median (IQR) | 1.029 (0.81–1.27) | 1.035 (0.83–1.3) | 1.032 (0.8–1.3) | 0.89    |
| Baseline eGFR (ml/min/1.73 m²)  |                          |                                 |                          |         |
| > 90                           | 107 (22.5)               | 27 (16.3)                        | 91 (20.9)                | 0.54    |
| 60–90                          | 235 (49.5)               | 97 (58.4)                        | 212 (48.9)               |         |
| 30–60                          | 89 (18.7)                | 30 (18.1)                        | 92 (21.2)                |         |
| 15–30                          | 34 (7.2)                 | 8 (4.8)                          | 31 (7.1)                 |         |
| < 15                           | 10 (2.1)                 | 4 (2.4)                          | 8 (1.8)                  |         |
| APACHE III score, median (IQR) | 95 (70–118)              | 91 (71–116)                      | 91 (69–112)              | 0.27    |
| Sepsis†                        | 128 (26.9)               | 39 (23.5)                        | 138 (31.8)               | 0.08    |
| Mechanical ventilation†        | 353 (74.3)               | 129 (77.7)                       | 329 (75.8)               | 0.66    |
| Vasopressor†                   | 261 (54.9)               | 87 (52.4)                        | 218 (50.2)               | 0.36    |
| Oliguria before initiation of RRT‡ |                       |                                 |                          |         |
| Stage 2                        | 50 (10.5)                | 9 (5.4)                          | 21 (4.8)                 | 0.017   |
| Stage 3                        | 406 (85.5)               | 154 (92.8)                       | 402 (92.6)               |         |
| MAP during RRT (mmHg), mean (SD) |                          |                                 |                          |         |
| All patients                   | 75.1 (0.58)              | 77.5 (1.19)                      | 79.4 (0.62)              | < 0.001 |
| CRRT only (n = 386)            | 72.7 (0.70)              | 72.4 (1.89)                      | 77.5 (1.01)              | < 0.001 |
| IHD only (n = 210)             | 85 (1.84)                | 84.1 (2.85)                      | 82.1 (1.27)              | 0.77    |
| CRRT and IHD (n = 487)         | 74.5 (0.91)              | 79.1 (1.66)                      | 79.7 (0.98)              | 0.002   |
| Vasopressor dose (NE), median (IQR) |                       |                                 |                          |         |
| All patients                   | 0.11 (0.04–0.25)         | 0.09 (0.03–0.21)                 | 0.09 (0.04–0.25)         | 0.25    |
| Patients on CRRT only          | 0.14 (0.05–0.30)         | 0.13 (0.03–0.25)                 | 0.10 (0.03–0.28)         | 0.31    |
Patients in the low-intensity Up\textsuperscript{NET} group had lower MAP compared with the moderate and high-intensity Up\textsuperscript{NET} groups (Table 1 and Additional file 1: Table S1).

Cumulative FO before RRT initiation was lowest in the low-intensity group, compared with the moderate and high-intensity Up\textsuperscript{NET} groups (15.6% vs 17.3% vs 21% of body weight, respectively, \(p < 0.001\); Table 2). Following initiation of RRT, the median cumulative FB for the low, medium and high-intensity Up\textsuperscript{NET} groups was 13.5 vs 22 vs 19 l, \(p < 0.001\); Table 2). During RRT, the MAP was lower and the cumulative vasopressor dose was higher in the low-intensity Up\textsuperscript{NET} group compared with the moderate and high-intensity Up\textsuperscript{NET} groups (Table 2 and Additional file 1: Table S1).

The median duration of RRT for the low, moderate and high-intensity Up\textsuperscript{NET} groups was 4.7 vs 8.7 vs 7 days, respectively (\(p < 0.001\)). The median duration of CRRT was 3.9 vs 5.8 vs 5.9 days (\(p < 0.001\)) and the median Up\textsuperscript{NET} volume was 3.4 vs 11.6 vs 16.2 l (\(p < 0.001\)). The median duration of IHD was 2 vs 7 vs 4 days (\(p = 0.004\)) and the median Up\textsuperscript{NET} volume was 5.5 vs 12.6 vs 9.2 l (\(p < 0.001\)). The median duration of RRT for patients who received both CRRT and IHD was 14.7 vs 15.2 vs 10.7 days (\(p < 0.001\)) and the median Up\textsuperscript{NET} volume was 19.5 vs 27.9 vs 26.6 l (\(p < 0.001\)). The median hospital length of stay was 32 vs 37.5 vs 37 days (\(p < 0.001\)) (Table 2). This shorter length of stay among patients with low-intensity Up\textsuperscript{NET} was primarily due to higher mortality in this group. However, there was no difference in renal recovery at 1 year (25.1% vs 28.9% vs 31.8%, \(p = 0.078\)) as well as within the subgroup of survivors at 1 year (82.6% vs 72.7% vs 78.4%, \(p = 0.25\)) between the three groups.

### Association between Up\textsuperscript{NET} intensity and mortality

The crude hospital and 1-year mortality was higher among the low-intensity group compared with the moderate and high-intensity Up\textsuperscript{NET} groups: 69.7% vs 60.2% vs 59.4% (\(p = 0.003\)), respectively (Table 2, Fig. 1a). Using logistic regression, high-intensity compared with low-intensity Up\textsuperscript{NET} was associated with lower 1-year mortality (AOR 0.61, 95% CI 0.41–0.93, \(p = 0.02\), C-statistic 0.811; Table 3 and Additional file 1: Table S2). This association persisted using Up\textsuperscript{NET} as a continuous variable (AOR 0.98, 95% CI 0.97–0.99, \(p = 0.005\); Additional file 1: Table S3). Compared with Up\textsuperscript{NET} of 0–5 ml/kg/day, increasing Up\textsuperscript{NET} intensity was associated with a trend toward lower odds of death (C-statistic – 0.813; Fig. 1b), whereas moderate-intensity compared with low-intensity Up\textsuperscript{NET} was not associated with mortality (AOR 0.81, 95% CI 0.48–1.35, \(p = 0.41\); Additional file 1: Table S2).

Using Gray’s model, high-intensity compared with low-intensity Up\textsuperscript{NET} had variable association with mortality. Early on after ICU admission, high-intensity Up\textsuperscript{NET} was associated with lowest risk of death that was subsequently attenuated over time, but nevertheless persisted up to 39 days after ICU admission (AHR range 0.50–0.73, \(p < 0.001\); Table 4 and Additional file 1: Figure S3A). Subsequently, between 39 and 365 days, high-intensity Up\textsuperscript{NET} was not associated with mortality (AHR range 0.76–1.02). High-intensity compared with moderate-intensity Up\textsuperscript{NET} was only associated with lower risk of death up to 15 days (AHR 0.53, 95% CI 0.33–0.86; Additional file 1: Table S5 and Figure S3C).

After propensity matching, 258 matched pairs were created wherein patients with Up\textsuperscript{NET} intensity ≤ 25 ml/kg/ day had similar baseline characteristics compared with Up\textsuperscript{NET} intensity > 25 ml/kg/day, except for cumulative vasopressor dose (Additional file 1: Table S4). Patients with Up\textsuperscript{NET} intensity > 25 ml/kg/day had lower 1-year mortality (57% vs 67.8%, \(p = 0.01\); Fig. 2), which persisted after adjusting for vasopressor dose (AOR 0.63, 95% CI 0.44–0.90, \(p = 0.011\)).

### Sensitivity analyses

When Up\textsuperscript{NET} intensity calculation was limited within 72 h of initiation of RRT, high-intensity Up\textsuperscript{NET} was associated with lower mortality (AOR 0.56, 95% CI 0.35–0.88, \(p = 0.013\); Table 5). Using the alternative thresholds of low, moderate and high-intensity Up\textsuperscript{NET} of < 15 ml/ kg/h, 15–20 ml/kg/h and > 20 ml/kg/h, respectively, we found Up\textsuperscript{NET} intensity > 20 ml/kg/h was associated with lower mortality (AOR 0.63, 95% CI 0.41–0.97, \(p = 0.038\)). Similar results were found moving the threshold up (AOR 0.58, 95% CI 0.34–0.99, \(p = 0.04\); Table 5) and
patients who received high-intensity UFNET as among those that our results would be robust unless an unmeasured confounder was at least twice as prevalent among participants receiving CRRT, UFNET intensity > 1.0 ml/kg/h compared with UFNET intensity < 0.5 ml/kg/h was associated with lower odds of death (AOR 0.41, 95% CI 0.24–0.71, p = 0.0013).

**Discussion**

We found that UFNET intensity > 25 ml/kg/day, compared with < 20 ml/kg/day, was independently associated with lower risk-adjusted 1-year mortality in critically ill patients with FO. Using Gray's model, this survival benefit was greater early on after ICU admission and persisted up to 39 days. In the propensity-matched analysis, UFNET > 25 ml/kg/day, compared with ≤ 25 ml/kg/day,
Fig. 1  

a. Association between net ultrafiltration intensity and time to mortality. Kaplan–Meier failure plots by UF NET intensity for probability of death over 1 year from ICU admission in overall cohort (n = 1075). Red line, low-intensity UF NET (≤ 20 ml/kg/day); blue line, moderate-intensity UF NET (> 20 to ≤ 25 ml/kg/day); green line, high-intensity UF NET (> 25 ml/kg/day). Probability of death highest in low-intensity compared with moderate and high-intensity UF NET groups (log-rank p < 0.001). 

b. Association between net ultrafiltration intensity and risk-adjusted 1-year mortality. Shown are adjusted odds ratio with 95% CI for association between UF NET intensity and mortality. Increasing UF NET intensity associated with trend toward lower mortality. Odds ratios adjusted for differences in age, sex, race, BMI, history of liver disease and sequela from liver disease, admission for liver transplantation, admission for surgery, baseline glomerular filtration rate, Acute Physiology and Chronic Health Evaluation III score, presence of sepsis, use of mechanical ventilation, percentage of cumulative fluid overload before initiation of RRT, oliguria before initiation of RRT, time to initiation of RRT from ICU admission, MAP on first day of RRT initiation, cumulative vasopressor dose and cumulative fluid balance during RRT, first RRT modality and duration of RRT. 

Table 3 Association between UF NET intensity and 1-year risk-adjusted mortality

| Covariates                        | Unadjusted odds ratio (95% CI) | p value | Adjusted a odds ratio (95% CI) | p value |
|-----------------------------------|--------------------------------|---------|--------------------------------|---------|
| Moderate vs low-intensity UF NET (reference) | 0.65 (0.42–0.94) | 0.024 | 0.81 (0.48–1.35) | 0.41 |
| High vs low-intensity UF NET (reference) | 0.64 (0.49–0.85) | 0.002 | 0.61 (0.41–0.93) | 0.02 |

UF NET net ultrafiltration, CI confidence interval, FO fluid overload, RRT renal replacement therapy, ICU intensive care unit

aAdjusted for age, sex, race, body mass index, history of liver disease and sequela from liver disease, admission for liver transplantation, admission for surgery, baseline glomerular filtration rate, Acute Physiology and Chronic Health Evaluation III score, presence of sepsis, use of mechanical ventilation, percentage of FO before initiation of RRT, oliguria before initiation of RRT, time to initiation of RRT from ICU admission, mean arterial pressure on first day of RRT initiation, cumulative vasopressor dose and cumulative fluid balance during RRT, first RRT modality and duration of RRT
was also associated with lower risk of death. To our knowledge, this is the first study in the literature examining the association between UFNET intensity and long-term mortality.

Our finding is somewhat analogous to the association between intensity of solute control and mortality in critically ill patients receiving RRT in which a threshold intensity of at least 20–25 ml/kg/h of effluent dosing in CRRT or KT/V of 1.2–1.4 per session in patients receiving IHD is associated with improved survival [26, 27]. However, in contrast to studies on solute control, the optimal “dosing” for UFNET in critically ill patients with fluid overload is unclear. In our study, we first explored whether there was an association between UFNET dose and mortality, and then aimed to determine the overall “average dose” that is associated with a long-term mortality benefit. It is important to note that our finding does not suggest that UFNET should be dosed > 25 ml/kg/day throughout the duration of fluid removal. Day-to-day dosing may vary in patients depending on the severity of fluid overload, patient tolerability and hemodynamics.

In our study only 40% of patients received intensive UFNET, whereas 44% of patients received less intensive UFNET that has implications for care. Unlike a prescription for solute clearance, the concept of a minimum or adequate “dose” for volume clearance is not usually considered in clinical practice. Although patients who received less intensive UFNET were hemodynamically unstable in our study, our findings persisted after accounting for hemodynamics, vasopressor dose and severity of illness, suggesting that less intensive UFNET per

Table 4 Association between intensity of net ultrafiltration and time to mortality from Gray’s model

| Characteristic                  | Adjusted hazard ratio (95% CI) by time intervala | p value  |
|--------------------------------|-------------------------------------------------|----------|
|                                | 5–15 days | 15–23 days | 23–39 days | 39–91 days | 91–365 days |
| High vs low UFNET              | 0.50 (0.35–0.71) | 0.62 (0.46–0.82) | 0.73 (0.55–0.97) | 0.76 (0.56–1.04) | 1.02 (0.71–1.47) | < 0.001 |
| High vs moderate UFNET         | 0.53 (0.33–0.86) | 0.69 (0.46–1.02) | 0.75 (0.52–1.09) | 0.77 (0.518–1.142) | 1.16 (0.72–1.85) | 0.039 |
| Moderate vs low UFNET          | 0.98 (0.62–1.57) | 0.87 (0.59–1.27) | 0.996 (0.69–1.43) | 1.01 (0.69–1.47) | 0.844 (0.53–1.34) | 0.91 |

*Adjusted for age, sex, race, body mass index, history of liver disease and sequelae from liver disease, admission for liver transplantation, admission for surgery, baseline glomerular filtration rate, Acute Physiology and Chronic Health Evaluation III score, presence of sepsis, use of mechanical ventilation, percentage of FO before initiation of RRT, oliguria before initiation of RRT, time to initiation of RRT from ICU admission, mean arterial pressure on first day of RRT initiation, cumulative vasopressor dose and cumulative fluid balance during RRT, first RRT modality and duration of RRT.

Fig. 2 Association between net ultrafiltration intensity and time to mortality in propensity-matched cohort. Kaplan–Meier failure plots by UFNET for probability of death over 1 year from ICU admission among patients with UFNET ≤ 25 ml/kg/day (n = 258) compared with propensity-matched patients with UFNET > 25 ml/kg/day (n = 258). Red line, UFNET ≤ 25 ml/kg/day; green line, UFNET > 25 ml/kg/day. Probability of death lower among patients who received UFNET > 25 ml/kg/day compared with UFNET ≤ 25 ml/kg/day (log-rank p < 0.001). ICU intensive care unit.
se might be associated with mortality. These findings may suggest that failure to tolerate UF\textsubscript{NET} > 25 ml/kg/day may portend a poor prognosis and, conversely, tolerating UF\textsubscript{NET} > 25 ml/kg/day may be a predictor of recovery and lower mortality in critically ill patients with fluid overload.

Our study addresses an important knowledge gap not addressed by prior studies. While numerous studies have documented an association between the severity of FO and incremental risk of death [3, 4], none examined the UF\textsubscript{NET} intensity—mortality relationship. Using the Program to Improve Care in Acute Renal Disease (PICARD) study, Bouchard et al. [4] found that patients in whom FO was corrected during RRT had lower mortality than those who remained fluid overloaded despite RRT. Using the Randomized Evaluation of Normal versus Augmented Level of Renal Replacement Therapy (RENA\textsubscript{L} RRT) cohort, Bellomo et al. [2] found that a negative fluid balance during RRT was associated with a mortality benefit. However, we asked a different question: does UF\textsubscript{NET} intensity and a threshold “dose” of UF\textsubscript{NET} matter in the treatment of FO independent of fluid balance?

There may be several biologic explanations for the association between UF\textsubscript{NET} intensity and outcome. First, intensive UF\textsubscript{NET} may reduce prolonged exposure to FO and modify host response, and could reduce the incidence of subsequent organ dysfunction [28]. Second, the salutary effects of intensive UF\textsubscript{NET} may be mediated through unknown marker clearance independent of fluid balance since the association persisted despite controlling for cumulative fluid balance. Third, clinicians who decide to initiate intensive UF\textsubscript{NET} may select for a unique group of patients to monitor and carefully titrate fluid removal. Fourth, clinicians and nurses may also have a broad variation in how they prescribe and/or practice UF\textsubscript{NET} in the real world, which may be associated with differences in outcomes [29].

The strengths of our study was that it was robust to three different methods of sensitivity analysis. We accounted for confounding due to severity of illness, hemodynamics, vasopressor dose and cumulative fluid balance before and during RRT. Using Gray's model, we found that high-intensity UF\textsubscript{NET} was associated with survival only up to 39 days after ICU admission. This finding is in contrast with the logistic model and propensity-matched analyses, which showed mortality benefit up to 1 year. This discordant finding is due to the differences in the models that were used. In Gray's model, the number of events...
between high-intensity and low-intensity UF<sup>NET</sup> groups was not different within the time interval of 39–365 days. Using the logistic regression model, however, a lower odds of cumulative deaths occurred by 1 year in the high->intensity UF<sup>NET</sup> group compared with the <7A3B2 thy-c<low-intensity UF<sup>NET</sup> group.

Our study is not without limitations. First, given the observational nature, it is not possible to make causal inferences between UF<sup>NET</sup> intensity and outcomes. Second, we do not know precisely whether a UF<sup>NET</sup> threshold > 25 ml/kg/day is associated with better outcomes, although our findings were robust to several sensitivity analyses. Third, our single-center study may not be generalizable to other ICU populations. Nevertheless, our study included patients typical of an academic medical center ICU population. Fourth, we were unable to distinguish whether patients received low-intensity UF<sup>NET</sup> due to low prescription, failure to remove fluid (e.g., circuit downtime, trip to operating room, etc.) or other variations in practice with respect to fluid removal. Fifth, although the sensitivity analysis indicated that any unmeasured confounder would need to be highly prevalent and have an OR < 0.7 to mask a null association, it is possible that there may be more than one residual confounder and that it may not be a binary variable.

**Conclusion**

In summary, among critically ill patients with ≥ 5% FO receiving RRT, our study found that UF<sup>NET</sup> intensity > 25 ml/kg/day is associated with lower risk-adjusted 1-year mortality compared with < 20 ml/kg/day. Whether this association between UF<sup>NET</sup> intensity > 25 ml/kg/day and lower mortality risk is just a marker for recovery or a mediator needs to be refuted or confirmed in future prospective randomized controlled trials.

**Additional file**

Additional file 1: S1. Study population. S2. Determination of cumulative fluid balance. S3. Vasopressor standardization to norepinephrine equivalents. S4. Gray’s survival model. S5. Propensity score estimation and matching. S6. Quantitative bias sensitivity analysis of potential impact of an unmeasured confounder. Figure S1. Study population and analysis cohort. Figure S2. Association between intensity of net ultrafiltration and crude hospital mortality. Figure S3. Association between net ultrafiltration intensity and time to mortality using Gray’s model. Figure S4. Quantitative bias sensitivity analysis to assess the impact of an unmeasured confounder on mortality. Table S1. Cumulative fluid balance; mean arterial pressure and vasopressor dose for entire duration of RRT. Table S2. Association between net ultrafiltration intensity and 1-year risk-adjusted mortality. Table S3. Association between net ultrafiltration intensity and 1-year risk-adjusted mortality using net ultrafiltration as a continuous variable. Table S4. Baseline characteristics by net ultrafiltration intensity after propensity matching (PDF 2022 kb)

**Abbreviations**

AHR: Adjusted hazard ratio; AKI: Acute kidney injury; AOR: Adjusted odds ratio; APACHE: Acute Physiology and Chronic Health Evaluation; CRRT: Continuous renal replacement therapy; CVVH: Continuous venovenous hemodialfiltration; CVHD: Continuous venovenous hemodiafiltration; FO: Fluid overload; IHD: Intermittent hemodialysis; MAP: Mean arterial pressure; RRT: Renal replacement therapy; SCUF: Slow continuous ultrafiltration; UF<sup>NET</sup>: Net ultrafiltration

**Availability of data and materials**

The datasets generated and/or analyzed during the current study are not publicly available as they belong to the University of Pittsburgh and University of Pittsburgh Medical Center but are available from the corresponding author on reasonable request.

**Authors’ contributions**

RM, VB, SJK and PP 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. RM and VB were responsible for study concept and design. JAK and GC were responsible for acquisition of data. SJK, C-CHC, PP, RM, VB, GC, PMP, RB and JAK analyzed and interpreted data. RM and VB drafted the manuscript. JAK, RB, PMP, GC, VB, RM, C-CHC, SJK and PP critically revised the manuscript for important intellectual content. VB and SJK performed statistical analysis. VB, RM and PP provided administrative, technical or material support. RM supervised the study. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

This project was approved by the University of Pittsburgh Institutional Review Board.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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