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Published in:
Blood purification

DOI:
[10.1159/000503771](https://doi.org/10.1159/000503771)

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:
2020

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

Citation for published version (APA):

Naorungroj, T., Neto, A. S., Zwakman-Hessels, L., Yanase, F., Eastwood, G., & Bellomo, R. (2020). Hourly Fluid Balance in Patients Receiving Continuous Renal Replacement Therapy. *Blood purification*, 49(1-2), 93-101. <https://doi.org/10.1159/000503771>

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Hourly Fluid Balance in Patients Receiving Continuous Renal Replacement Therapy

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Keywords

Continuous renal replacement therapy · Fluid overload · Hourly fluid balance · Mortality · Vasopressors

Abstract

Introduction: Little is known about early (first 48 h) hourly and cumulative fluid balance (FB) during continuous renal replacement therapy (CRRT). **Objectives:** To study the characteristics and outcome associations of early hourly and cumulative FB. **Methods:** We studied FB in CRRT patients (2016–2018). **Results:** Among 350 patients, mean hourly FB became negative after 20 CRRT hours, but within 6 CRRT hours in patients with baseline fluid overload. A negative early FB was never achieved in patients receiving vasopressor therapy ($p < 0.001$). Mortality was 31%. The percentage of hourly negative FB was independently associated with decreased ICU mortality. A time-weighted hourly FB between 18.5 and -33 mL/h was also significantly and independently associated with decreased mortality. **Conclusions:** In CRRT patients, an early FB conservative approach is possible, modulated by patient characteristics, and associated with a low mortality. Moreover, avoidance of an early positive FB is associated with decreased mortality.

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Introduction

Fluid overload is relatively common in adult critically ill patients [1, 2], and a positive fluid balance (FB) is strongly associated with poor clinical outcomes [3–8]. In patients receiving continuous renal replacement therapy (CRRT), both excessive fluid administration and inadequate fluid elimination contribute to clinically important fluid overload [4]. Therefore, optimization of FB and volume control is considered a cornerstone in patient care [9, 10].

A negative FB is associated with improved clinical outcomes in a variety of settings [6, 11]. Data from the RENAL study (“The Randomized Evaluation of Normal vs. Augmented Level” study) [12] found that a negative FB in patients on CRRT was an independent predictor of reduced mortality [13]. However, whether this association represents a marker of illness severity or contributes to morbidity and mortality or a combination of both remains unclear. In this setting, understanding the early management of FB and obtaining data on how such FB might change on an hourly basis would provide more information about early volume control and subsequent outcomes.

Early FB management with attention to hourly fluid removal during CRRT targeting a negative FB [14, 15] can

potentially influence the course of a patient's illness. However, during CRRT, little is known about how early hourly fluid balance (FB^{HO}) is managed and how often, when, and under what clinical circumstances, an early (first 48 h) negative FB^{HO} is or is not achieved. Accordingly, we aimed to test the primary hypothesis that early FB^{HO} would be affected by baseline patient characteristics and the secondary hypothesis that early FB^{HO} management would be independently associated with clinical outcomes.

Methods

Study Design and Population

We performed a retrospective, observational study in a tertiary ICU affiliated to 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).

Populations

We investigated all critically ill patients admitted to the ICU between 2016 and 2018 who received CRRT within 14 day of ICU admission. We excluded patients who had received intermittent hemodialysis during ICU admission or plasma exchange at any time.

Data Collection

We calculated FB^{HO} as the difference between total fluid input (intravenous fluid + blood products + enteral fluid) and total fluid output (urine output + net ultrafiltration rate + blood losses + enteral losses + drain losses) for each hour. Net ultrafiltration rate was equal to CRRT effluent minus the sum of replacement fluid and dialysate fluid. The current practice on dose of CRRT prescription in our hospital follows the KDIGO guidelines [16] and the protocol of the RENAL study [12] with an effluent volume of 20–25 mL/kg/h. However, fluid removal rate and ultrafiltration rates are individualized and modulated by attending medical treatment team.

This study focused on the course of early FB^{HO} and its modulation in the first 48 h of CRRT treatment. For this reason and because of concern about the limited accuracy of pre-ICU FB data, we did not record FB in the period from before CRRT initiation.

A positive FB^{HO} was recorded when hourly fluid input was greater than fluid output (indicated by positive sign [+]). A negative FB^{HO} was recorded when hourly fluid input was less than fluid output (indicated by negative sign [-]). FB^{HO} was calculated each hour using the “0.00–23.59” time clock for the first 48 h. FB was assessed and described both as FB^{HO} and as mean cumulative hourly FB (CumFB^{HO}). FB^{HO} was defined as the FB at each hour in the first 48 h. CumFB^{HO} was defined the cumulative FB of each hour added to the next hour over the first 48 h.

Exposure

The primary exposure of interest was FB^{HO}, expressed as mL and assessed as the time weighted-average FB^{HO} (TwFB^{HO}). Since FB^{HO} is a dynamic process, TwFB^{HO} over the first 48 h of therapy was calculated as the area under the FB^{HO}-versus-time plot (Equation 1). This was determined by summing the mean value between consecutive time points multiplied by the period of

time between consecutive time points. Hours where data necessary to calculate the FB^{HO} were missing were not included in the time weighted-average calculation. Thus, the calculation was adjusted by the number of observations available (Equation 2).

$$AUC = \frac{1}{2} \sum_{i=0}^{n-1} (t_{i+1} - t_i) / (y_i + y_{i+1}) \quad (1)$$

Where y_1 and y_2 are measurements at time t_1 and t_2

$$TwFB^{HO} = \frac{AUC}{n_{\text{observations}}} \quad (2)$$

where AUC is the area under the curve calculated according Equation 1, and $n_{\text{observations}}$ is the number of observations available in 48 h

In addition, the following variables were tested as secondary exposures of interest:

- Time to onset of a negative FB (TNegFB), defined as the first hour in the 48-h study period when the CumFB^{HO} became negative and expressed as hours (patients who did not achieve a negative FB in the first 48 h were allocated a nominal arbitrary value of 49 h);
- Percentage of time with an hourly negative FB (%FB^{HO}), defined as the percentage of the 48-h study period that the hourly FB was negative; and
- Percentage of time under cumulative negative FB (%FB^{CUM}), defined as the percentage of the 48-h study period when the cumulative FB was negative.

Outcomes

The primary outcome was in-hospital mortality. Secondary clinical outcomes included ICU mortality, ICU, and hospital length of stay.

Statistical Analysis

In this study, we analyzed hourly FB only during first 48 h of CRRT and outcomes after such period. This is because we reasoned that early period of CRRT is likely most important for patient outcomes. In addition, obtaining data in the first 48 h allows the development of predictive models of clinical outcomes. Finally, observing FB during the entire period of treatment creates 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 with major time-variant confounders, which are so common in critically ill patients.

To understand the impact of different baseline characteristics on the dynamics of FB^{HO} in the first 48 h and considering all time points available, univariable and multivariable mixed-effect longitudinal models with patients as random effects were tested. For these models, we considered the following baseline characteristics: presence of oliguria, need of vasopressor therapy, need of mechanical ventilation, presence of fluid overload according to pre-CRRT clinical notes as diagnosed by the treating team and documented in the scanned and electronic medical record from ICU admission to the start of CRRT, severity of illness (according to Acute Physiology and Chronic Health Evaluation [APACHE] III), and body weight.

The univariable model considered FB^{HO}-related variables in the first 48 h as the dependent variable and hour, group, and an

interaction of group by hour as fixed effect. The multivariable model considered such FB^{HOU} -related variables in the first 48 h as the dependent variable and hour, presence of oliguria, need of vasopressor, need of mechanical ventilation, presence of fluid overload, APACHE III, and actual body weight as fixed effect.

We performed univariable analyses for comparisons between groups according to in-hospital mortality using the chi-square test for proportions and Student *t* tests or Wilcoxon rank sum tests for continuous variables, as appropriate. To assess the association of the $TwFB^{HOU}$, $CumFB^{HOU}$, $TNegFB$, $\%FB^{HOU}$, and $\%FB^{CUM}$ with binary outcomes, we performed parsimonious logistic models with APACHE III, need of mechanical ventilation, need of vasopressor, and time from ICU admission until start of CRRT as covariates. Since multicollinearity was expected among the measurements, each one was included alone and one at a time in the models, resulting in a total of 5 models. We estimated the association between the measurements and ICU and hospital stay with generalized linear models considering Gaussian distributions according to best fit.

Additional Analyses

To assess whether the potential association between FB and in-hospital mortality was linear, we divided the $TwFB^{HOU}$ into tertiles and analyzed them as a categorical variable in the models described above. In addition, we used hazard ratios and 95% CI calculated with a Cox proportional hazard models with adjustment for the covariates described above to assess the time until in-hospital mortality. Patients were censored at day 28 with patients discharged before it being considered alive at day 28. In addition, we divided the $TNegFB$, $\%FB^{HOU}$, and $\%FB^{CUM}$ into tertiles and analyzed as a categorical variable in the models described above. Due to the exploratory nature of the study, a two-sided $p < 0.05$, without adjustment for multiple comparisons, was taken to indicate statistical significance. All analyses were performed using R software, version 3.4.1 (R Core Team, Vienna, Austria).

Results

Study Population

From July 30, 2016, to December 31, 2018, 4,774 critically ill patients were admitted to the study ICU and 423 received CRRT and thus were eligible for the study. Fifty-three patients were excluded due to the use of intermittent hemodialysis during ICU admission; the use of plasma exchange, or the start of CRRT later than 14 days. In addition, 19 patients who died within 48 h were excluded to avoid the competing effect of early mortality on early FB and the fact that CRRT could only be applied for a short time before death. Their details are shown in online supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000503771).

Thus, we included 350 patients. Of these patients, 109 (31%) died in hospital, for an overall mortality of 128 over 370 patients (34.59%; online suppl. Fig. S1). Among the total cohort, 232 (66%) patients were treated with mechan-

ical ventilation, 217 (62%) were treated with vasopressors, and 35 (10%) were diagnosed with fluid overload as documented in the clinical notes at time of CRRT initiation.

Baseline characteristics before starting CRRT are shown in Table 1. Survivors were younger; had lower APACHE III scores; were less likely to be admitted after cardiac arrest; received mechanical ventilation and vasopressor support less frequently; were less likely to be admitted from the ward, and had different and fewer medical diagnoses. At the time of CRRT start, survivors had higher pH values, a lower lactate concentration, and higher PaO_2/FiO_2 levels. Baseline characteristics and clinical outcomes according to FB are shown in online supplementary Table S2.

FB Characteristics

From the first hour of CRRT, there was a progressive change from a positive toward a less positive FB^{HOU} during the first 24 h of therapy ($-4.9 [-5.6 \text{ to } -4.1] \text{ mL/h}$; $p < 0.001$). However, this pattern delivered the first fully negative FB^{HOU} after 21 h of CRRT (Fig. 1). This, was then followed by approximately 11 h in the negative FB^{HOU} range and then by a slight tack back toward a positive FB^{HOU} in the second 24 h ($0.8 [0.3\text{--}1.4] \text{ mL/h}$; $p = 0.003$; Fig. 1). Hourly FB adjusted by body weight during the first 48 h of CRRT treatment is shown in online supplementary Figure S2.

As a consequence of the above delay in reaching a negative FB, the $CumFB^{HOU}$ progressively increased in the first 20 h ($13.6 [11.5\text{--}15.7] \text{ mL/h}$; $p < 0.001$). In addition, as a consequence of the timing of onset of a negative FB^{HOU} , $CumFB^{HOU}$ then decreased on the second day ($-16.6 [-18.4 \text{ to } -14.8] \text{ mL/h}$; $p < 0.001$) achieving a mean negative value at 39 h (Fig. 2). Overall, the $CumFB^{HOU}$ at 48 h was $-163.0 \pm 2,770.0 \text{ mL}$ for all patients and $-332.0 \pm 2,695.0 \text{ mL}$ vs. $204.0 \pm 2,918.0 \text{ mL}$ (absolute difference -536.0 ; 95% CI $[-1,185.0 \text{ to } 113.0] \text{ mL}$; $p = 0.14$) among survivors vs. nonsurvivors, respectively.

The Impact of Baseline Clinical Characteristics

Baseline characteristics and treatment characteristics influenced FB. Patients with baseline fluid overload had a more negative FB^{HOU} , achieved a negative FB earlier, and were managed with more negative $CumFB^{HOU}$ in the first 48 h (online suppl. Fig. S3). In contrast, patients receiving vasopressor therapy at baseline never achieved a negative FB^{HOU} , and their $CumFB^{HOU}$ was always positive (online suppl. Fig. S4). A similar but less prominent pattern was seen in patients treated with mechanical ventilation (online suppl. Fig. S5).

On multivariable analysis, baseline fluid overload or heavier body weight was independently associated with a

Table 1. Clinical characteristic, CRRT timing, and clinical outcomes for in-hospital survivors and nonsurvivors

	Survivors (<i>n</i> = 241)	Nonsurvivors (<i>n</i> = 109)	<i>p</i> value
Age, years	60±15	64±12.3	0.008
Gender, male	158 (65.6)	61 (56.0)	0.110
Weight, kg	85.3±22.5	85.0±22.5	0.907
BMI, kg/m ²	30.2±7.4	29.3±6.9	0.384
APACHE III	65.7±25.4	90.5±26.0	<0.001
Renal function before admission			
Creatinine, µmol/L	191±222	166±181	0.317
Estimated glomerular filtration rate, mL/min	58.3±35.3	58.0±33.4	0.937
At admission			
Mechanical ventilation	148 (61.4)	84 (77.1)	0.006
Need of vasopressor	136 (56.4)	81 (74.3)	0.002
Sepsis or septic shock	62 (25.7)	36 (33.0)	0.200
Other type of shock	12 (5.0)	13 (11.9)	0.035
Cardiac arrest	10 (4.1)	17 (15.6)	<0.001
Fluid overload	23 (9.5)	12 (11.0)	0.817
Oliguria	142 (58.9)	73 (67.0)	0.189
Co-morbidities			
Hypertension	107 (44.4)	61 (56.0)	0.059
Diabetes mellitus	79 (32.8)	46 (42.2)	0.113
Coronary artery disease	68 (28.2)	37 (33.9)	0.338
Atrial fibrillation	26 (10.8)	21 (19.3)	0.047
End-stage renal disease	23 (9.5)	7 (6.4)	0.447
Chronic liver disease	36 (14.9)	26 (23.9)	0.061
Cancer	42 (17.4)	21 (19.3)	0.791
Immunosuppression	56 (23.2)	18 (16.5)	0.199
Source of admission			0.001
Emergency department	53 (22.0)	21 (19.3)	
Hospital ward	62 (25.7)	46 (42.2)	
Transfer from another ICU	16 (6.6)	10 (9.2)	
Transfer from another hospital	32 (13.3)	7 (6.4)	
OR after emergency surgery	18 (7.5)	9 (8.3)	
OR after elective surgery	58 (24.1)	11 (10.1)	
Other	2 (0.8)	5 (4.6)	
Admission diagnosis			
Nonsurgical reasons	165 (68.5)	88 (80.7)	<0.001
Cardiovascular	27/165 (16.4)	24/88 (27.3)	
Genitourinary	45/165 (27.3)	4/88 (4.5)	
Respiratory	22/165 (13.3)	17/88 (19.3)	
Gastrointestinal	47/165 (28.5)	38/88 (43.2)	
Liver failure	34/47 (72.3)	11/38 (28.9)	
Other	24/165 (14.5)	5/88 (5.7)	
Surgical	76 (31.5)	21 (19.3)	0.094
Cardiovascular	37 (48.7)	15 (71.4)	
Cardiac surgery	28/37 (75.7)	11/15 (73.3)	
Gastrointestinal	30 (39.5)	3 (14.3)	
Liver transplantation	21/30 (70.0)	0/3 (0.0)	
Other	9 (11.8)	3 (14.3)	
Laboratory tests before start of CRRT			
Creatinine, µmol/L	392±294	313±171	0.010
Creatinine >300	129 (53.5)	49 (45.0)	0.171
Urea, mmol/L	22.5±13.9	20.8±10.3	0.248
Urea >25	81 (33.6)	37 (33.9)	1.000
pH	7.34±0.10	7.30±0.12	0.003
pH <7.20	20 (9.0)	16 (15.2)	0.140

Table 1. (continued)

	Survivors (<i>n</i> = 241)	Nonsurvivors (<i>n</i> = 109)	<i>p</i> value
Potassium, mmol/L	4.5±0.9	4.6±0.9	0.482
Potassium >5.5	31 (12.9)	17 (15.6)	0.603
Bicarbonate, mmol/L	19.6±5.9	18.8±(5.6)	0.267
Base excess, mmol/L	-5.2±6.4	-6.6±6.9)	0.080
Lactate, mmol/L	3.2±3.3	4.7±4.5	0.001
PaO ₂ /FiO ₂	319±127	269±122	0.001
Vital signs before start of CRRT			
Mean arterial pressure, mm Hg	81±17	72±11	<0.001
Heart rate, bpm	88±19	90±18	0.330
CRRT characteristics			
Start from ICU admission, days	1.2±2.1	1.3±2.1	0.762
Start from ICU admission, h	31.9±49.3	34.4±51.0	0.666
Start within first 24 h	156/241 (64.7)	62/109 (56.9)	0.199
Hours of treatment per day, h/day	15.6±7.1	17.2±7.0	<0.001
Duration, days	4.7±5.3	5.6±5.1	0.151
Duration, h	112.5±126.6	133.0±123.3	0.158
Clinical outcomes			
ICU mortality	0 (0.0)	97 (89.0)	<0.001
ICU length of stay, days	11.1±11.2	8.9±10.2	0.083
Hospital length of stay, days	33.9±28.0	14.5±13.8	<0.001

Data are presented at mean ± SD or *n*/total (%).

APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy; ICU, intensive care unit; OR, operating room; BMI, body mass index.

Fig. 1. Hourly FB expressed in mL per hour in the first 48 h. Circles are the mean and error bars the 95% CI. FB, fluid balance.

Fig. 2. Cumulative hourly FB expressed in mL per hour in the first 48 h. Circles are the mean and error bars the 95% CI. FB, fluid balance.

negative CumFB^{HO} in the first 48 h. In contrast, the presence of oliguria, vasopressor therapy, and a higher APACHE III score were associated with a positive CumFB^{HO} in the first 48 h (Fig. 3).

Primary Outcome

Table 2 compares all FB-related variables according to in-hospital survival. Overall, %FB^{HO} spent in negative FB was higher (52.2 ± 18.1 vs. 47.0 ± 20.9 ; 5.2 [0.6–9.8]; $p = 0.026$) in survivors compared to nonsurvivors (online suppl. Fig. S6). There was also an interaction between group and time to negative CumFB^{HO} such that survivors achieved a mean CumFB^{HO} in the negative range earlier than nonsurvivors (online suppl. Fig. S7). Finally, despite a univariable association between a greater %FB^{HO}, after multivariable adjustments, no FB variables remained associated with survival (online suppl. Table S3).

Secondary Outcomes

On univariable analysis, %FB^{HO} was significantly associated with decreased ICU mortality, and this significant association persisted after multivariable adjust-

ments (online suppl. Table S4). However, no other FB-related variable was significantly associated with secondary outcomes in both univariable and multivariable analyses.

Sensitivity Analyses

When considering tertiles, the intermediate tertile of TwFB^{HO} was significantly associated with decreased in-hospital and ICU mortality in both univariable and multivariable analyses (online suppl. Table S5). In addition, the highest tertile of %FB^{HO} was significantly associated with decreased ICU mortality on univariable and multivariable analyses. A similar association was seen between the middle %FB^{HO} tertile and ICU length of stay (online suppl. Table S6).

Discussion

Key Findings

We assessed early hourly FB and cumulative FB management, its changes, related variables, and outcome associations in 350 patients treated with CRRT.

Fig. 3. Univariable and multivariable models with baseline characteristics predicting dynamic changes in cumulative FB in the first 48 h. Unadjusted mixed-effect longitudinal models with characteristics, hour, and the interaction of characteristics $\times$ hour as fixed effects. The multivariable model considered hour, need of vasopressor, need of mechanical ventilation, presence of fluid overload, APACHE III, and actual body weight as fixed effect. *p* values for

the group reflect the overall test for difference between groups across the 48 h. All models considered cumulative FB in the first 48 h as the dependent variable and a random effect for patients. All continuous covariates were estimated after standardization. FB, fluid balance; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 2. FB in survivors and nonsurvivors

	Survivors (<i>n</i> = 241)	Nonsurvivors (<i>n</i> = 109)	Absolute difference (95% CI)	<i>p</i> value
TwFB ^{HO} , mL/h	-6.6±66.2	5.5±70.3	-12.0 (-27.8 to 3.7)	0.133
CumFB ^{HO} , mL	88.3±1545.8	379.7±1572.3	-291.3 (-647.3 to 64.5)	0.108
TNegFB ^{HO} , h	19.5±18.5	21.7±19.3	-2.2 (-6.5 to 2.1)	0.322
%FB ^{HO} , %	52.2±18.1	47.0±20.9	5.2 (0.6 to 9.8)	0.026
%FB ^{CUM} , %	42.1±36.4	37.7±36.4	4.5 (-3.8 to 12.7)	0.288

Data are presented at mean $\pm$ SD.

FB, fluid balance; TwFB^{HO}, time-weighted average hourly FB; CumFB^{HO}, cumulative hourly FB; TNegFB^{HO}, time to onset of negative FB; %FB^{HO}, percentage of time with an hourly negative FB; %FB^{CUM}, percentage of time under cumulative negative FB.

We found that mean FB^{HO} became negative after 21 h of treatment and that mean CumFB^{HO} became negative after 39 h. However, the time-based evolution of FB^{HO} and CumFB^{HO} was more rapidly and more intensely negative in patients with baseline fluid overload. In contrast, an early negative was never achieved in patients receiving vasopressor therapy and barely achieved in patients treated with mechanical ventilation. More-

over, the presence of oliguria/anuria, lighter body weight, vasopressor therapy, and higher APACHE III scores were all independently associated with a positive CumFB^{HO}. Finally, in their aggregate, several univariable and multivariable analyses supported the view that %FB^{HO} and time-weighted FB^{HO} in the middle tertile described the FB state with the lowest ICU and in-hospital mortality risk.

Relationship to Previous Studies

A few previous studies have analyzed the relationship between cumulative FB and outcomes in CRRT patients. The RENAL study [12] and Finnish Acute Kidney Injury study [8] found that a positive FB was associated with a two-fold increase in 90-day mortality. However, in both studies, mean daily FB switched from positive to negative only after >48 h of CRRT, later than in our cohort. This was despite documented fluid overload in 43.8 and 26.9% of RENAL and Finnish Acute Kidney Injury patients, respectively [8, 12, 13]. In the Program to Improve Care in Acute Renal Disease study, fluid overload at dialysis cessation was associated with greater mortality [6]. Yet, mean percentage of fluid accumulation remained >10% after 48 h of treatment. In the Dose Response Multicenter Investigation on Fluid Assessment, peak fluid overload occurred approximately 3 days after RRT initiation, implying continuing positive cumulative FB well beyond the first 48 h [17]. Thus, no previous studies have explored early FB management in CRRT, particularly on an hourly detail, described what factors modulate both hourly FB and cumulative FB or demonstrated the achievement of an overall negative cumulative FB before 48 h.

Study Implications

Our findings imply that, in CRRT patients, a mean negative FB^{HOU} can be achieved by 20 h of CRRT and a mean negative $CumFB^{HOU}$ by 39 h. Such a relatively fluid-conservative strategy was associated with a hospital mortality of 35%, one of the lowest mortality rates reported in a large cohort of such patients so far. Thus, our findings imply that this fluid-conservative approach implemented during CRRT is probably safe. However, by demonstrating that the management of FB is independently affected by vasopressor therapy, oliguria, and APACHE III, our findings also imply that, in the first 48 h, hemodynamic instability and illness severity inhibit the pursuit of an earlier and more intensive negative FB. In contrast, they imply that a residual urinary output facilitates a more negative FB and that baseline fluid overload triggers its earlier and more aggressive pursuit. Finally, the observation that highest tertile of percentage of time in a negative FB^{HOU} and intermediate tertile of $TwFB^{HOU}$ were independently associated with improved survival implies that avoidance of a positive FB, even in the early phase of CRRT may have beneficial effects.

Study Strengths and Limitations

Our study is the first to present detailed data on hourly and cumulative FB in cohort of CRRT patients and the first to demonstrate their dynamic hour-by-hour changes. It is also the first to identify factors, which independently affect early FB management. Finally, it is the first to describe that, in an ICU practicing the most negative FB strategy reported in the literature, mortality was one of the lowest reported so far for CRRT patients. Finally, even in such a fluid-conservative environment, it provides evidence that avoidance of a positive FB is linked with unfavorable outcomes.

There are some limitations of this study. It is a single center, retrospective, observational study with the inherent limitations of such studies. However, the study ICU is typical of other tertiary ICUs in Australia and New Zealand and likely other developed countries. Moreover, all the data presented were electronically recorded during therapy by the ICU electronic medical record and are numerical, verifiable, and objective. The severity scores [18] of the patients included in this study are slightly lower than in other studies [6–8]. However, early RRT initiation in the first 24 h as practiced in our ICU modifies many variables (pH, creatinine, and temperature) in a favorable direction. Thus, it creates a bias toward artificially lower scores. The association between FB and outcomes was studied in the first 48 h of CRRT patients who survived at least 48 h. Thus, these findings do not apply to patients who died before 48 h. However, we excluded very severely ill patients who would likely not survive regardless of RRT initiation, who received only 11 h of CRRT, and whose cumulative FB represented only 5.4% of the total FB. The inclusion of their FB would not materially alter our findings. Moreover, their mortality was considered in our estimate of cohort mortality rates. We reported that only 10% of patients were diagnosed fluid overload by clinicians, which was a relatively low percentage compared to previous studies. This was due a stringent approach to its definition, which required specific documentation in the electronic medical record. We also did not report FB in pre-CRRT period due to the limited robustness of such data. Nonetheless, this criterion was strong enough to influence clinicians to modulate FB management. The relationship between markers of fluid management and mortality cannot be used to make inferences on causality and, despite the use of multivariable models to adjust for key factors that might affect outcome; the presence of residual confounding cannot be excluded. Only randomized controlled trials targeting specific fluid management strategies and comparing them to usual care can provide

such inferences. However, our findings provide the necessary preliminary data for the design and powering of such studies.

Conclusion

In conclusion, in a sizeable cohort of CRRT patients, the pursuit of a fluid-conservative approach was possible and delivered a negative cumulative FB earlier than in previous studies. However, these changes were more rapid and intense in patients with baseline fluid overload but less so in patients receiving vasopressor therapy or mechanical ventilation and in the presence of oliguria. Even, in this fluid conservative setting, a higher percentage of time in negative hourly FB was associated with decreased risk of ICU mortality, and the intermediate tertile of time weighted hourly FB delivered the lowest ICU and hospital mortality rates. These observations provide useful information to guide clinicians in the prescription of fluid removal during CRRT. They also provide the basis for the design and powering of randomized controlled trials targeting volume control during CRRT.

References

- 1 Bellomo R. Issue and challenges of fluid removal in the critically ill. *Br J Anaesth*. 2014 Nov;113(5):734–5.
- 2 Rosner MH, Ostermann M, Murugan R, Prowle JR, Ronco C, Kellum JA, et al.; ADQI XII Investigators Group. Indications and management of mechanical fluid removal in critical illness. *Br J Anaesth*. 2014 Nov;113(5):764–71.
- 3 Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. *Anaesthesiol Intensive Ther*. 2014 Nov-Dec;46(5):361–80.
- 4 O'Connor ME, Prowle JR. Fluid Overload. *Crit Care Clin*. 2015 Oct;31(4):803–21.
- 5 Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. *BMC Nephrol*. 2016 Aug;17(1):109.
- 6 Bouchard J, Soroko SB, Chertow GM, Himelfarb J, Ikizler TA, Paganini EP, et al.; Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int*. 2009 Aug;76(4):422–7.
- 7 Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care*. 2008;12(3):R74.
- 8 Vaara ST, Korhonen AM, Kaukonen KM, Nilus S, Inkinen O, Hopppu S, et al.; FINNAKI Study Group. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit Care*. 2012 Oct;16(5):R197.
- 9 Finfer S, Myburgh J, Bellomo R. Author Correction: intravenous fluid therapy in critically ill adults. *Nat Rev Nephrol*. 2018 Nov;14(11):717.
- 10 Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol*. 2010 Feb;6(2):107–15.
- 11 Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al.; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006 Jun;354(24):2564–75.
- 12 Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, et al.; RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009 Oct;361(17):1627–38.
- 13 Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, et al.; RENAL Replacement Therapy Study Investigators. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. *Crit Care Med*. 2012 Jun;40(6):1753–60.
- 14 Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med*. 2013 Jun;39(6):987–97.
- 15 Ronco C, Brendolan A, Bellomo R. Online monitoring in continuous renal replacement therapies. *Kidney Int Suppl*. 1999 Nov;56(72):S8–14.
- 16 Kidney Disease Improving Global Outcomes (KDIGO) AKI Work Group. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
- 17 Garzotto F, Ostermann M, Martín-Langerwerf D, Sánchez-Sánchez M, Teng J, Robert R, et al.; DoReMIFA study group. The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients. *Crit Care*. 2016 Jun;20(1):196.
- 18 Schneider AG, Lipcsey M, Bailey M, Pilcher DV, Bellomo R. Simple translational equations to compare illness severity scores in intensive care trials. *J Crit Care*. 2013 Oct;28(5):885.e1–8.

Acknowledgment

None.

Statement of Ethics

This study was approved by the Austin Health Human Research Ethics Committee with a waiver of informed consent (approval number: LNR/19/Austin/18).

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There is no funding sources to declare.

Author Contributions

All authors have participated in the design, conduct, and analysis of the study and co-writing of the final manuscript.