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Original Article

ORIGINAL ARTICLE

Achievement of fluid removal targets during intermittent renal replacement therapy in the intensive care unit

Michel Gouin[1,*], Rose Joyal[1,*], Mathilde Lamothe[1], Yi Hui Luo[1], Xin Yi Fan[1], Karel Huard[2], Jean-Maxime Côté[3,4], Javier A. Neyra[5], Ron Wald[6] and William Beaubien-Souligny[3,4]

[1]Faculté de Médecine, Université de Montréal, Montreal, Quebec, Canada, [2]Department of Medicine, McGill University, Montreal, Quebec, Canada, [3]Service of Nephrology, Department of Medicine, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada, [4]Centre de recherche du CHUM (CR CHUM), Montreal, Quebec, Canada, [5]Department of Medicine, Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL, USA and [6]Division of Nephrology, St. Michael's Hospital, University of Toronto, Li Ka Shing Knowledge Institute, Toronto, ON, Canada

*These authors contributed equally to this work: Michel Gouin, Rose Joyal.
Correspondence to: William Beaubien-Souligny; E-mail: William.beaubien-souligny@umontreal.ca

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ABSTRACT

Background. In patients with acute kidney injury (AKI), fluid balance management often relies on the prescription and achievement of fluid removal using intermittent renal replacement therapy (IRRT). This study aimed to describe characteristics associated with the failure to achieve target fluid removal (FATFR).

Methods. This is a retrospective cohort study including IRRT sessions of conventional duration (<5 hours) performed for AKI in the intensive care unit (ICU) from 2017 to 2022 at a tertiary academic center. FATFR-50% was defined as fluid removal of <50% of the prescribed target. Characteristics of patients and sessions, as well as outcomes at 90 days were collected. The causes of FATFR were manually adjudicated.

Results. A total of 291 patients and 1280 IRRT sessions in the ICU were included. FATFR-50% occurred in 7.3% of sessions and 19.2% of patients had at least one session with FATFR-50% during the first week of IRRT. Sessions with FATFR-50% were characterized by a higher occurrence of intradialytic hypotension (24.2% vs 60.2%, $P < .001$) and a higher planned fluid removal (6.19 vs 5.27 m/kg/h, $P = .02$). Multiple episodes of FATFR-50% were associated with a positive cumulative fluid balance (β 3876 (CI 2053–5899) $P < .001$). At 90-day follow-up, FATFR-50% during the first week after IRRT initiation was independently associated with fewer ICU- and hospital-free days, as well as with a higher risk of mortality (odds ratio 2.01 CI 1.04–3.89, $P = .04$).

Conclusions. FATFR occurs in about one out of five critically ill patients within the first week of IRRT and is associated with adverse clinical outcomes.

Keywords: acute kidney injury, fluid overload, intermittent hemodialysis, renal replacement therapy, ultrafiltration

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KEY LEARNING POINTS

What was known:

- Intermittent renal replacement therapy (IRRT) is used in critically ill patients with acute kidney injury (AKI) for fluid balance control. However, the ability to achieved the desired ultrafiltration can be limited.

This study adds:

- Failure to achieve target fluid removal (FATFR) occurs in about one-fifth of sessions during the week after initiation of IRRT in the ICU. FATFR is attributed to patient- and technique-related factors. The occurrence of FATFR is associated with fluid accumulation and adverse outcomes including 90-day mortality.

Potential impact:

- FATFR may represent an indicator that can be reliably measured and may be partially amendable to quality improvement efforts aiming to improve the care of critically ill patients with AKI.

INTRODUCTION

Among critically ill patients initiating renal replacement therapy (RRT) for acute kidney injury (AKI), fluid accumulation is associated with higher mortality and a lower likelihood of kidney recovery [1–3]. Moreover, the duration of persistent fluid accumulation following the initiation of RRT has been linked to unfavorable outcomes [2]. Fluid accumulation may represent a modifiable mediator of adverse outcomes due to the congestion of vital organs [2, 4–12]. Hence, proactively managing or promptly reversing fluid accumulation could prevent the development of complications and improve patient outcomes.

Intermittent RRT (IRRT) is an essential modality to support critically ill patients with AKI. While the use of continuous RRT (CRRT) may enable a more precise fluid balance control, it is be more costly and may delay physical rehabilitation. Therefore, most ICUs rely on a combination of CRRT and IRRT, although IRRT may be the sole modality available in some centers. Although preventive measures may mitigate the risk of hemodynamic instability on IRRT [13], intradialytic hypotension and other factors likely affect the achievement of fluid management goals. However, the frequency with which prescribed fluid removal is achieved with IRRT and its association with clinical outcomes has seldom been reported.

In this work, we aimed to report the incidence of failure to achieve target fluid removal (FATFR) and the clinical factors associated with it including patient characteristics, acute illness severity, and factors related to RRT prescription or the delivery of fluid removal. Secondarily, we aimed to determine whether FATFR is associated with fluid accumulation during the first week following IRRT initiation, and clinical outcomes including mortality and intensive care unit (ICU) and hospital length of stay. Finally, we aimed to investigate the root causes of FATFR through the analysis of nursing notes.

MATERIALS AND METHODS

Study design and population

This single-center retrospective cohort study was conducted at the Centre Hospitalier de l'Université de Montréal (CHUM), a quaternary care academic center in Canada. Our cohort included adults who received at least one IRRT session in the ICU from January 2017 to May 2022 for AKI, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria [14]. Only sessions performed in the ICU were considered up to 90 days after IRRT initiation. Patients who received any RRT outside the ICU in the preceding 90 days or for whom RRT was initiated for the urgent treatment of intoxication were excluded. The conduct of this study was approved by the ethics committee of the CHUM (2023–10 835).

Description of usual care

The CHUM offers IRRT of conventional duration (up to 4–5 hours) but does not offer prolonged IRRT (>5 hours) outside of special indications such as intoxications. IRRT modalities include standard hemodialysis and online hemodiafiltration [15] using the Cordiax 5008s machine (Fresenius, Germany) equipped with a blood volume monitor that estimates relative blood volume during treatment. IRRT sessions are monitored by dialysis nurses who can stop IRRT session, in agreement with the ICU physicians and the consulting nephrologist: for example, in cases of decrease in relative blood volume, hypotension episodes, or other intolerances to the IRRT that are deemed unmanageable. Vital signs and notes are collected in a dialysis-specific electronic medical record (Renal Insight, Constellation Kidney Group).

Data collection

Patient electronic medical records were reviewed to collect demographic data, date of admission and discharge to hospital and ICU, and relevant clinical information. Baseline health status as defined by the Charlson Comorbidity Index [16] was assessed from scanned hospitalization and outpatient clinic medical notes. Information about disease severity at IRRT initiation, including sequential organ failure assessment (SOFA) score [17], use of mechanical ventilation or vasopressors, 24 h urine output before the initiation of IRRT, and patient outcomes, as well as characteristics of dialysis sessions, including prescribed and achieved net ultrafiltration (UF), machine parameters, and patient vital signs during dialysis, and interventions such as medication given were extracted from scanned medical records, ICU charts, nursing notes, and the dialysis-specific medical record. Discharged patients were followed at the hospital's outpatient nephrology clinic for up to 90 days post-dialysis. Post-discharge medical notes were available in the electronic medical records and were used for the assessment of outcomes in the post-discharge period of the follow-up.

Outcome definitions

The primary outcome was FATFR, which was defined, for each RRT session, as the proportion of achieved over prescribed fluid

removal volume inferior to 50% (FATFR-50%). An alternate definition corresponding to 75% of target is also presented throughout the manuscript (FATFR-75%). When fluid removal was prescribed as an interval (i.e. 2 to 3 l), the lower bound was considered as the prescribed fluid removal volume. We estimated the planned net ultrafiltration rate by dividing the prescribed fluid removal (liters) by admission body weight (kilograms), and by the planned session duration (hours). Patients were divided into two groups based on the occurrence of one or more FATFR episodes during the first week after the initiation of IRRT.

Secondary outcomes included average daily fluid balance for the 7 days after RRT initiation; intradialytic hypotension as defined by the nadir systolic blood pressure of 90 mmHg with corrective interventions such as the initiation/increase in dose of vasopressor agent or fluids [18]; kidney recovery defined as a period of ≥2 weeks during which any type of RRT was not provided (with the kidney recovery date being the last date of IRRT preceding this period); and vasopressor support, ICU, and hospital-free days. The mean UF gap in the first week of IRRT was calculated as the mean of the differences in ml between planned and achieved UF of all sessions performing in the ICU during this period.

Root-cause analysis of FATFR

Nurses' notes associated with all sessions with FATFR were reviewed by two investigators (R.J., M.G.) to adjudicate the root causes of FATFR based on the following pre-specified categories: hypotension, intolerance to fluid removal other than hypotension (i.e. new onset of arrhythmia or tachycardia, patient symptoms, etc.), technical factors leading to a shortening of the session (filter thrombosis, catheter dysfunction, etc.), and decrease in relative blood volume. In case of uncertainty, a third investigator (W.B.S.) was consulted for adjudication.

Statistical analysis

The incidence of FATFR is presented as a percentage of all sessions as well as the percentage of patients who had at least one FATFR episode during the first week after IRRT initiation. To assess the association between sessions' characteristics and FATFR, a generalized estimating equation (GEE) method was used to account for the presence of repeated sessions in the same patient.

The association between cumulative fluid balance during the first 7 days after IRRT initiation was assessed using GEEs with FATFR as a binary factor. The association between FATFR and 90-day mortality was evaluated using multivariable logistic regression with adjustment for Charlson comorbidity score, SOFA score at IRRT initiation, and age. The association with ICU-free and hospital-free days was evaluated using multivariable linear regression with the same adjustment variables. The adjustment variables were chosen *a priori* based on clinical significance.

As sensitivity analyses, we investigated whether the planned UF rate was predictive of FATFR through receiving operating characteristics analysis with the associated *C*-statistic as well as a general additive model presented graphically as a spline (four knots). We produced additional models using the proportion of session with FATFR during the first week after IRRT initiation as the exposure variable. Finally, we excluded patients who died during the first week from the model to assess whether the association with 90-day mortality remained consistent. *P* values <.05 were considered significant. Statistical analysis was performed in R and SPSS.

RESULTS

Incidence of failure to achieve target fluid removal

Our cohort comprised 291 patients who received 1280 sessions of IRRT in the ICU (Figure S1). An episode of FATFR-75% or FATFR-50% occurred in 208/1280 (16.3%) and 93/1280 (7.3%) of sessions, respectively. Within the first week after IRRT initiation 94/291 (32.3%) patients had at least one session of FATFR-75%, and 56/291 (19.2%) of FATFR-50%. The proportions of repeated FATFR-75% and FATFR-50% within the first week were 20.2% and 10.7%, respectively.

Hemodialysis sessions characteristics

Session-related characteristics in relationship with the occurrence of FATFR are presented in Table 1. Sessions with FATFR had a higher planned net ultrafiltration rate but a lower achieved net UF rate at the end of the session and a lower actual mean UF. While the prescribed length of the session did not differ, the actual duration of sessions with FATFR was significantly shorter than for sessions in which FATFR-50% did not occur, with a greater proportion being of an actual duration of <3 hours.

Pre-dialysis systolic and diastolic arterial blood pressures were lower before sessions during which FATFR-50% or FATFR-75% occurred. Sessions with FATFR were more often complicated by intradialytic hypotension or required intensification (new initiation or escalation) of vasopressors.

While sessions in which FATFR occurred had a higher median planned UF rate per body weight, the ability of the planned UF rate to predict the occurrence of FATFR was low [FATFR-50%: *C*-statistic 0.55 (CI:0.50; 0.60), FAFTR-75%: C-statistic 0.60 (CI:0.57–0.65)]. While FATFR was more likely to occur at prescribed UF rates >10–13 ml/kg/h, there was no clear UFR threshold that was associated with FATFR (Fig. 1). However, only 10.2% of sessions had a prescribed UF rate of >10 ml/kg/h (Figure S2 of the Supplementary Material).

Patient characteristics

Patients were assigned to two groups based on the occurrence of at least one episode of FATFR in the ICU during the 7 days following IRRT initiation. Patients' characteristics are presented in Table 2. The proportion of females was higher in the FATFR groups. The proportion of patients receiving CRRT before IRRT initiation, the SOFA score, as well as Charlson's comorbidity score were not different. At the time of IRRT initiation, mechanical ventilation was more common (50.5% vs 35.7%, $P = .02$) and 24 h urine output was lower in patients who experienced FATFR-75% [median 112 (IQR 10; 815) vs 360 (IQR 58; 1353) ml $P = .002$].

Patient outcomes

In the week following IRRT initiation, patients with at least one episode of FATFR had a higher mean daily fluid balance as well as a higher mean UF gap for the delivered RRT sessions. In terms of cumulative fluid balance during the first week, the occurrence of multiple episodes (≥2) of FATFR was associated with a more positive cumulative fluid balance as shown in Fig. 2.

Associations between FATFR and patients' outcomes are presented in Table 3. Mortality at 90 days was similar between patients with and without FATFR-75% (33.3% vs 25.2%, $P = .28$), but higher in patients with FATFR-50% (33.9% vs 18.7%, $P = .01$). After multivariable adjustment, the occurrence of at least one

Table 1: Session-level characteristics associated with the failure to achieve at least 50% of target fluid removal (FATFR-50%).

Characteristics	Achievement of ≥50% of target fluid removal			Achievement of ≥75% of target fluid removal		
	Success (*N* = 1187)	Failure (*N* = 93)	*P* value	Success (*N* = 1072)	Failure (*N* = 208)	*P* value
Net fluid removal						
Prescribed net UF (l)	1.58 ± 1.05	1.69 ± 0.77	.19	1.52 ± 1.06	1.91 ± 0.83	<.001
Planned mean UF rate (ml/kg/h)	5.27 ± 3.70	6.19 ± 3.61	.02	5.1 (2.2; 7.7)	6.3 (4.1; 8.5)	<.001
Achieved net UF (l)	1.53 ± 1.02	0.38 ± 0.38	<.001	1.55 ± 1.05	0.90 ± 0.68	<.001
Achieved mean UF rate (ml/kg/h)	5.00 ± 3.49	1.65 ± 183	<.001	5.05 ± 3.59	3.22 ± 2.49	<.001
Gap between prescribed and achieved UF	0 (0; 0.10)	1.20 (0.90; 1.50)	<.001	0 (0; 0)	0.93 (0.60; 1.21)	<.001
% of target achieved	100 (90; 100)	20 (0; 40)	<.001	100% (100; 100)	50.0% (26.7%; 65.0%)	<.001
Vital signs at initiation and organ support before session						
Initial systolic BP (mmHg)	134 ± 26	125 ± 23	<.001	134 ± 25	130 ± 25	.03
Initial diastolic BP (mmHg)	63 ± 13	60 ± 15	<.001	64 ± 13	61 ± 14	.01
Mechanical ventilation	393 (33.1%)	33 (35.5%)	.59	350/1067 (32.8%)	77/207 (37.2%)	.23
Vasopressor support (any)	192 (16.2%)	22 (23.7%)	.06	178/1067 (16.7%)	43/207 (20.8%)	.006
Intradialytic events						
Nadir systolic BP	106 ± 25	88 ± 24	<.001	106 ± 25	93 ± 24	<.001
Nadir diastolic BP	50 ± 14	42 ± 13	<.001	51 ± 14	45 ± 12	<.001
Intradialytic hypotension[a]	290 (24.4%)	56 (60.2%)	<.001	240/1068 (22.5%)	106/207 (51.2%)	.006
Intensification of vasopressor support	281 (23.7%)	39 (41.9%)	<.001	249/1072 (23.2%)	70/208 (33.7%)	.005
Sessions duration						
Prescribed duration of <3 hours	54 (4.5%)	4 (4.3%)	.91	51/1072 (4.8%)	7/208 (3.4%)	.36
Actual duration of <3 hours	105 (8.8%)	31 (33.3%)	<.001	98/1068 (9.2%)	46/207 (22.2%)	<.001
Prescribed duration of the session (min)	240 (240; 240)	240 (240; 240)	.65	240 (240; 240)	240 (240; 240)	.91
Actual duration of the session (min)	241 (218; 247)	238 (150; 244)	<.001	241 (217; 246)	240 (187; 247)	<.001

Data are presented in *N* (%), mean ± SD, or median (IQR).
[a]Defined as a drop in systolic blood pressure below 90 mmHg with corrective intervention.
Abbreviation: BP: blood pressure.

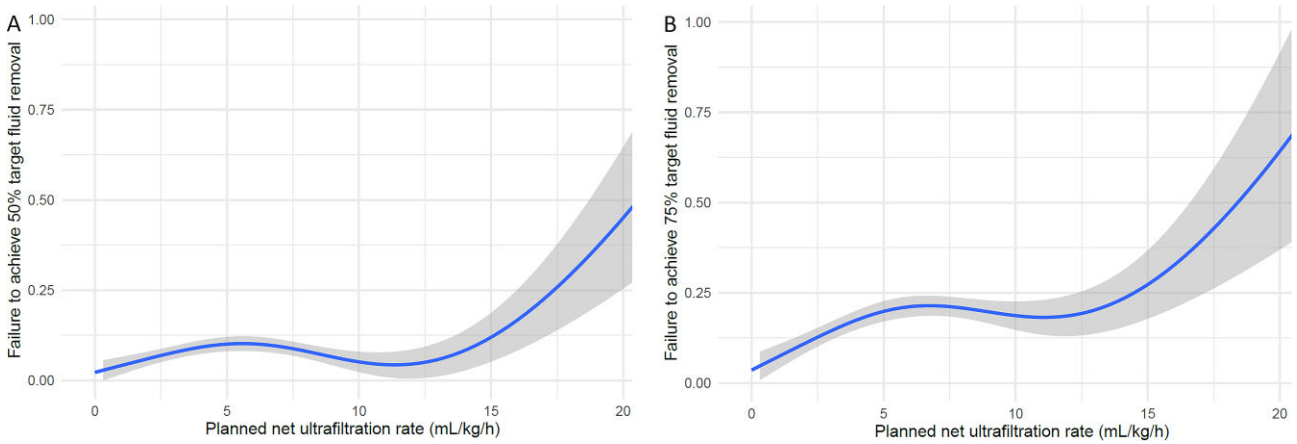

Figure 1: Estimated probability of FATFR in relationship with planned net ultrafiltration rate (Generalized additive model with four knots). (**A**) Failure to achieve 50% of target fluid removal (FATFR-50%). (**B**) Failure to achieve 75% of target fluid removal (FATFR-75%).

episode of FATFR-50% in the first week after IRRT initiation, as well as the ratio of sessions within the first week complicated by FATFR-50%, were associated with mortality (aOR 2.01 CI:1.04; 3.89, *P* = .04 and aOR 3.26 CI:1.16; 9.13 *P* = .03). The association between FATFR-50% and day 90 mortality remained consistent when excluding patients who died during the first week (aOR 2.15 CI:1.02; 4.52 *P* = .04). Patients with an episode of FATFR-50% or FATFR-75% had a lower number of ICU-free and hospital-free days. After multivariable adjustment, FATFR-50% and FATFR-75% were associated with lower ICU-free and hospital-free days (Table 3). As additional sensitivity analysis, we constructed an additional model including the difference in weight between ICU admission and IRRT initiation as well as the mean daily fluid balance available during the week before IRRT initiation, which showed similar results.

Underlying causes of FATFR

We categorized the reasons documented by nurses during 191/208 (92%) dialysis sessions with FATFR-75% and 92/93 (98.9%)

Table 2: Patient-level characteristics associated with the failure to achieve FATFR-50%.

Characteristics	Achievement of ≥50% of target fluid removal in all sessions during the first 7 days			Achievement of ≥75% of target fluid removal in all sessions during the first 7 days		
	Success (*N* = 235)	Failure (*N* = 56)	*P* value	Success (*N* = 197)	Failure (*N* = 94)	*P* value
Demographic characteristics						
Age (years)	63 (53; 71)	67 (58; 72)	.18	62 (50; 72)	66 (57; 72)	.12
BMI (kg/m^2)	28.5 ± 7.0	28.8 ± 7.0	.86	28.6 ± 7.1	28.7 ± 6.8	.89
Female sex	68 (28.9%)	25 (44.6%)	.02	54 (27.4%)	39 (41.5%)	.02
Medical history						
Baseline eGFR	65 (33; 95)	85 (30; 100)	.26	65 (33; 95)	70 (33; 98)	.63
Chronic hypertension	151 (64.3%)	41 (73.2%)	.20	122 (61.9%)	70 (74.5%)	.03
Coronary artery disease	68 (28.9%)	17 (30.4%)	.83	56 (28.7%)	29 (31.2%)	.67
Diabetes	109 (46.4%)	27 (48.2%)	.81	88 (44.7%)	48 (51.1%)	.31
Heart failure	52 (22.1%)	12 (21.4%)	.91	47 (24.0%)	17 (18.3%)	.28
Peripheral artery disease	33 (14.0%)	11 (19.6%)	.29	28 (14.3%)	16 (17.4%)	.49
COPD	37 (15.7%)	13 (23.2%)	.18	30 (15.3%)	20 (21.7%)	.18
Liver disease	58 (24.7%)	16 (28.6%)	.55	51 (26.3%)	23 (24.7%)	.79
Charlson's comorbidity score	4.9 ± 2.8	4.9 ± 2.6	.82	4.9 ± 2.8	4.9 ± 2.6	.82
Index admission						
Surgical (vs. medical)	71 (30.2%)	25 (44.6%)	.04	59 (30.0%)	37 (39.4%)	.11
Admission diagnostic category						
Cardiovascular	82 (34.9%)	21 (37.5%)	.76	70 (35.6%)	33 (35.1%)	.94
GI/liver	47 (20.0%)	14 (25.0%)	.41	40 (20.3%)	21 (22.3%)	.69
Respiratory	51 (21.7%)	15 (26.8%)	.48	37 (18.8%)	29 (30.9%)	.02
Neurological	2 (0.9%)	1 (1.8%)	1.00	2 (1.0%)	1 (1.1%)	1.00
Urological	12 (5.1%)	1 (1.8%)	.33	12 (6.1%)	1 (1.1%)	.17
Other	41 (17.4%)	4 (7.1%)	.06	36 (18.3%)	9 (9.6%%)	.08
Use of CRRT before IRRT initiation	145 (61.7%)	39 (69.6%)	.27	119 (60.4%)	94 (69.1%)	.15
Characteristics at the time of IRRT initiation						
Sepsis	84 (35.7%)	20 (35.7%)	1.00	65 (33.3%)	39 (41.5%)	.16
Cardiogenic shock	66 (28.1%)	14 (25.0%)	.64	55 (28.2%)	25 (26.6%)	.81
Mechanical ventilation	89 (37.9%)	26 (46.4%)	.24	69 (35.7%)	46 (50.5%)	.02
Vasopressor support	81 (34.5%)	18 (32.1%)	.74	69 (36.5%)	30 (33.3%)	.60
Urine output in the prior 24 h (ml)	250 (36; 1137)	135 (5; 1100)	.12	360 (58; 1353)	112 (10; 815)	.002
SOFA score	5.6 ± 3.6	5.7 ± 3.7	.76	5.6 ± 3.6	5.7 ± 3.7	.76
Pre-IRRT mean daily fluid balance (ml)[a]	−31 ± 1184	−164 ± 1039	.46	−14 ± 1169	−150 ± 1125	.38
Outcomes after IRRT initiation						
Mean daily fluid balance (ml)[b]	−74 ± 967	157 ± 813	.03	-122 ± 1007	159 ± 764	0.02
Mean UF gap per session (ml)	0 (0; 67)	600 (325; 1150)	<.001	0 (0; 0)	483 (261; 981)	<0.001
ICU-free days through 90 days (days)	80 (52; 87)	67 (0; 80)	<.001	82 (52; 88)	69 (29; 80)	<0.001
Hospital-free days through 90 days (days)	59 (0; 73)	17 (0; 61)	.002	60 (0; 74)	30 (0; 64)	0.001
Death at 90 days	44 (18.7%)	19 (33.9%)	.01	39 (19.8%)	24 (25.5%)	0.27
Kidney recovery at 90 days in survivors	139 (72.8%)	37 (78.4%)	.48	113 (71.5%)	70 (78.6%)	0.27

Data are presented in *N* (%), mean ± SD, or median (IQR).

[a] Calculated from available data during the week before IRRT initiation.

[b] Calculated from available data during the week after IRRT initiation.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate based on the CKD-EPI formula.

dialysis sessions with FATFR-50% to explain why the target fluid removal was not reached. As shown in Fig. 3, the most common reason was hypotension. In a significant proportion of such cases, the nadir blood pressure during the session did not reach our definition of hypotension (<90 mmHg) but the decrease in arterial pressure was judged severe enough for the nurse to stop/reduce fluid removal (FATFR-75% 24.8%, FATFR-50% 47.2%). In addition, other issues related to the tolerability of the patient to fluid removal were noted in about a quarter of sessions. These included perceived discomfort, nausea, dyspnea, sinus tachycardia, arrhythmia, and severe events such as cardiorespiratory arrest (three patients). In an important proportion of sessions, a decrease in relative blood volume was reported as a reason to reduce the UF rate. Of note, concurrent hypotension did not occur in a substantial proportion of these sessions (FATFR-75% 45.5%, FATFR 17.2%). Finally, technical difficulties such as filter thrombosis and catheter dysfunction were mentioned as contributing factors to the non-achievement of the target fluid removal in a substantial proportion of sessions. In half of these cases, the technical problem was the only reason noted by the nurse to explain FATFR (FATFR-75% 50%, FATFR-75% 50%).

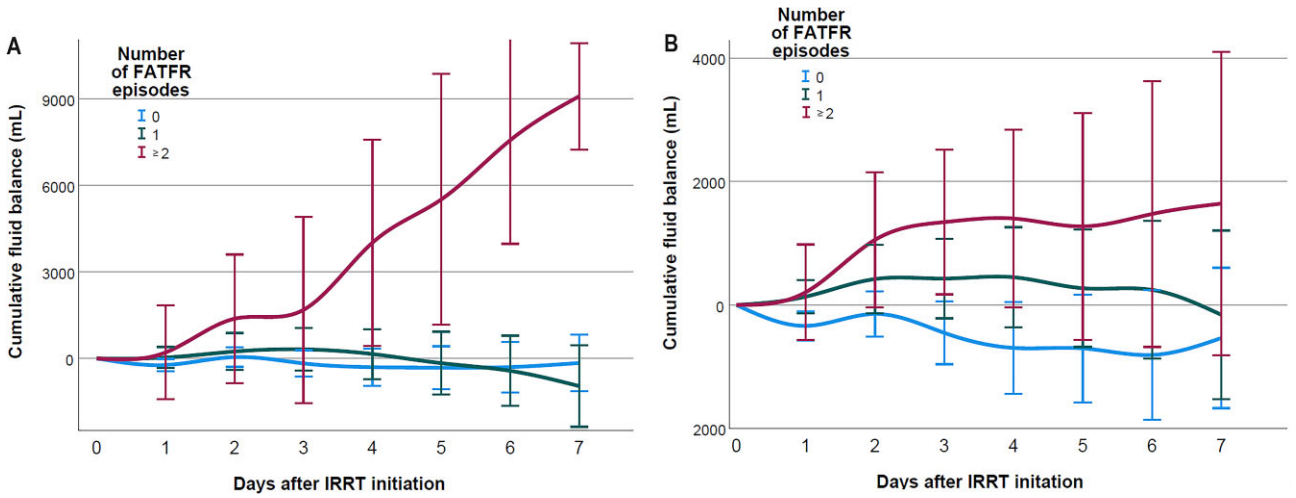

Figure 2: Cumulative fluid balance during the week following IRRT initiation in the ICU in 292 patients. The occurrence of failure to achieve (**A**) 50% or (**B**) 75% of fluid removal target (FATFR) in ≥2 sessions during the first week was associated with a greater cumulative fluid balance (FATFR-50%: $\beta = 3976$ CI:2053; 5899 $P < .001$, FATFR-75%: $\beta = 1636$ CI: 413; 2860, $P = .009$).

Table 3: Adjusted associations between FATFR during the week after IRRT initiation and 90-day outcomes.

	Model 1	Model 2
90-day mortality		
≥1 episode of FATFR-50%	OR: 2.01 CI: 1.04; 3.89 P = .04	OR: 2.13 CI: 1.08; 4.18 P = .03
Proportion of sessions with FATFR-50%	OR: 3.26 CI: 1.16; 9.13 P = .03	OR: 3.40 CI: 1.19; 9.65 P = .02
≥1 episode of FATFR-75%	OR: 1.29 CI: 0.71; 2.35 P = .40	OR: 1.30 CI: 0.71; 2.38 P = .39
Proportion of sessions with FATFR-75%	OR: 1.67 CI: 0.71; 3.94 P = .25	OR: 1.64 CI: 0.69; 3.91 P = .27
ICU-free days through day 90		
≥1 episode of FATFR-50%	β: −11.3 CI: −21.2; −1.45 P = .03	β: −11.6 CI: −21.4; −1.7 P = .02
Proportion of sessions with FATFR-50%	β: −18.7 CI: −34.7; −2.7 P = .02	β: −19.0 CI: −34.9; −3.08 P = .02
≥1 episode of FATFR-75%	β: −8.7 CI: −17.0; −0.3 P = .04	β: −8.9 CI: −17.2; −0.5 P = .04
Proportion of sessions with FATFR-75%	β: −12.6 CI: −25.3; 0.2 P = .05	β: −12.4 CI: −25.1; 0.3 P = .06
Hospital-free days through day 90		
≥1 episode of FATFR-50%	β: −14.1 CI: −23.4; −4.9, P = .003	β: −14.7 CI: −23.9; −5.5 p = 0.002
Proportion of sessions with FATFR-50%	β: −16.0 CI: −31.2; −0.9 P = .04	β: −16.3 CI: −31.4; −1.3 P = .03
≥1 episode of FATFR-75%	β: −14.1 CI: −21.9; −6.4 P < .01	β: −14.3 CI: −22.0; −6.6 P < .001
Proportion of sessions with FATFR-75%	β: −15.8 CI: −27.8; −3.8 P = .01	β: −15.9 CI: −27.5; −3.7 P = .01

Associations of 90-mortality are assessed using multivariable logistic regression and presented as OR. Associations of ICU/hospital-free days are assessed using multivariable linear regression and presented as linear regression coefficients (β). In model 1, all analyses are adjusted for the following: age, Charlson's comorbidity score, and SOFA score at IRRT initiation. In model 2, difference in weight between admission and IRRT initiation, mean daily fluid balance in the week before were added as adjustment variables to model 1.

DISCUSSION

In this work, we report the common occurrence of FATFR in a cohort of ICU patients undergoing IRRT. We have highlighted patient- and session-related factors associated with FATFR, as well as the associations with fluid management parameters and relevant clinical outcomes. FATFR occurring during the first week after IRRT initiation is associated with greater fluid accumulation, fewer ICU and hospital-free days, and a higher risk of 90-day mortality (FATFR-50% only).

The ability to achieve target fluid removal is affected by the tolerance of the patient to the planned fluid removal rate during the duration of the session, as well as the occurrence of technical or organizational factors that could lead to shortening the duration of the session. We observed that hypotension during the IRRT session was much more common in sessions where FATFR occurred and the most common contributing factor cited by nursing staff. Of note, the decision to resume fluid removal after a hypotensive episode is based on the judgment of the clinical team and may influence the magnitude of the gap between prescribed and achieved fluid removal. We also observed that nurses frequently reported that the decrease in relative blood volume is a factor that contributed to the reduction of the fluid removal rate. Relative blood volume monitoring is a technology integrated into the hemodialysis machine used by the nursing staff to anticipate hypotensive episodes and potentially prevent them by stopping or reducing the rate of fluid removal. While the evidence for the use of this technology is mixed in outpatient dialysis [19, 20], relative blood volume was shown to be a poor predictor of intradialytic hypotension in critically ill patients [21, 22]. The use of this technology can therefore result in FATFR, although it is unclear whether this practice prevents hypotension.

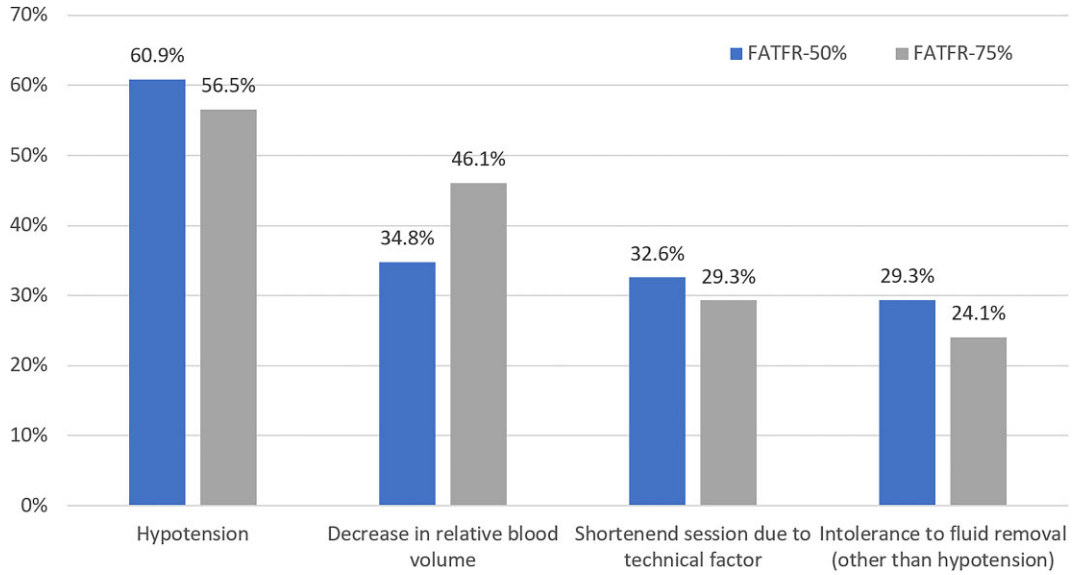

Figure 3: Underlying causes of FATFR according to nursing documentation. Note: multiple factors can be present in each session.

We observed that the planned mean fluid removal rate was higher in sessions with FATFR. Patients with important daily fluid intake and oliguria may be more at risk for FATFR during IRRT sessions since they inherently have greater ultrafiltration (UF) requirements to avoid fluid accumulation. While a slightly higher median planned net UF rate normalized for body weight was observed in the session in which FATFR occurred, we did not observe a threshold at which FATFR becomes very likely. Nevertheless, although the prescription of high UF rate was rare in this cohort, we observed that the risk of FATFR tended to increase >10–13 ml/kg/h. This threshold has been associated with worse outcomes in outpatient maintenance hemodialysis sessions [23]. Acutely ill patients may be even more sensitive to such UF rates supporting the current practice of prescribing conservative fluid removal rates in most patients.

Many sessions in which FATFR occurred had lower duration than the most commonly prescribed duration ranging from 3 to 4 hours. We found that shorter sessions were often curtailed from the initial prescription due to technical problems such as filter thrombosis in the latter portion of the dialysis session, which could be the sole cause of FATFR. As expected, nurses reported technical problems leading to a shortening of the session in about one-third of the sessions in which FATFR occurred. Filter thrombosis is a common occurrence in the ICU since anticoagulation is often withheld due to perceived risk of bleeding. Quality improvement programs have shown it is possible to optimize the filter life span in critically ill patients on CRRT [24]. Similar efforts to prevent thrombosis in IRRT could also potentially reduce the incidence of FATFR.

Patients with at least one episode of FATFR in the first week of IRRT had a lower number of ICU- and hospital-free days, and a higher mortality rate when the more severe threshold of FATFR-50% was considered. It is conceivable that the intolerance to fluid removal following the initiation of IRRT identifies patients who may be at higher risk of short-term mortality. Conversely, it is possible that greater fluid accumulation conferred by episodes of FATFR could have contributed to a protracted ICU course. However, other factors may explain this observation. For example, patients with higher urine output at IRRT initiation were less likely to experience FATFR since they have lower UF requirements but are also more likely to recover kidney function, which may explain why these patients might have had a shorter ICU/hospital stay. Of note, FATFR-75% was not associated with higher mortality rate. Although an insufficient sample size could have played a role, it is also plausible that FATFR-75% had less severe illness than patients with FATFR-50%, since they were able to tolerate a larger proportion of the prescribed UF. This is supported by the fewer occurrence of intradialytic hypotension and need for vasopressor intensification as shown in Table 3.

Our study has several strengths. First, while Neyra *et al.* [25] have shown that fluid management parameters, such as fluid overload at CRRT initiation and discrepancies in prescribed vs. achieved fluid removal, are factors associated with increased mortality in patients with AKI on CRRT, this is the first study to focus on FATFR in patients with AKI receiving specifically IRRT. Second, the study included all patients who initiated IRRT in the given observation period reducing the concern for selection bias. Third, the collection of clinical and demographic data, encompassing patient characteristics, illness severity, IRRT treatment specifics, and clinical outcomes, allowed a comprehensive description of the factors impacting fluid management. Finally, we also manually reviewed nurses' notes to accurately adjudicate the causes of FATFR, thereby enabling us to provide greater insights about the potential contributors, including technical factors, that could be amendable to improvement.

Our study has also limitations. First, even though the number of RRT sessions was substantial, the sample size was relatively small, which may have reduced our ability to detect an association with other relevant patient outcomes. Furthermore, despite adjustment for the severity of illness and comorbidities, there is a high likelihood that FATFR is not the cause of adverse clinical outcomes but is reflective of unmeasured confounding factors. It is also worth mentioning that sometimes FATFR may have been an appropriate outcome in cases where targets of fluid removal were inappropriately ambitious. Owing to the retrospective nature of this study, we could not collect information regarding the decision-making process involved in the prescription of the fluid removal target and other elements such as the decision to resume fluid removal after a hypotensive episode. Nonetheless, FATFR could be postulated as a relevant key performance

indicator of IRRT in acutely ill patients. Second, the fluid removal prescription is representative of usual care at a single center and may not be generalizable to centers that provide prolonged IRRT or other differences in practice patterns such as later transition from CRRT. Most importantly, high UF rates (>10 ml/kg/h) were rarely prescribed, which precludes the description of characteristics associated with FATFR in the context of rapid fluid removal. Third, readmissions, dialysis and death that could have occurred in other hospitals after discharge were not assessed. This could lead to an undervaluation of those outcomes in both the failure (FATFR) and the success (No-FATFR) groups. However, such cases are most likely randomly distributed among the two groups and could therefore not lead to an overestimation of the observe association between FATFR and the outcomes involved.

CONCLUSION

We propose that FATFR could be a feasible and clinically relevant indicator to consider in patients receiving IRRT in the ICU. Strategies to minimize the occurrence of FATFR include careful UF prescription that considers the likelihood of tolerance by a specific patient, strategies to avoid hypotension, and the minimization of the rate of filter thrombosis should be further studied.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

M.G. and R.J. collected data, performed data analysis, and wrote the first draft of the paper; M.L., Y.H.L., and X.Y.F. performed data collection and reviewed the paper; J.M.C., J.A.N., and R.W. contributed to interpretation of data and reviewed the paper; W.B.S. designed the study, and contributed to data analysis and writing.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

WBS has received honoraria from GSK and Bayer. RW has received honoraria from Otsuka, Baxter, Lilly and Alexion and participated to scientific advisory board for AquaPass and Eliaz Therapeutics.JAN has received consulting fees from Baxter and Spectral Medical.

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