Original Paper

Predictive Factors for Successful Discontinuation of Continuous Renal Replacement Therapy: A Retrospective Single-Center Observational Study

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Introduction. Determining the optimal timing for discontinuing continuous renal replacement therapy (CRRT) in intensive care units (ICUs) remains a significant clinical challenge. This study aimed to identify the clinical and laboratory determinants of successful CRRT discontinuation in critically ill patients with acute kidney injury (AKI).
Methods. This retrospective, single-center observational study was conducted in Gülhane Training and Research Hospital, Ankara, Türkiye. A total of 396 patients who received CRRT between January 2019 and March 2023 were screened. After excluding patients with prior renal replacement therapy (RRT) (n = 66) and end-stage kidney disease (n = 250), 80 patients were included in the final analysis. Successful discontinuation was defined as independence from any RRT for at least seven consecutive days following CRRT cessation. Clinical variables were compared between the successful and unsuccessful groups.
Results. The mean age of the patients was 71.16 ± 14.96 years. In univariate analysis, successful discontinuation was significantly associated with higher 24-h urine output during CRRT [385 (0–3880) mL vs. 100 (0–1850) mL; P = .010], a stable or decreasing lactate trend in the first four hours (69% vs. 40%; P = .033), and a lower requirement for invasive mechanical ventilation (36.4% vs. 58.3%; P = .050). Receiver operating characteristic (ROC) curve analysis identified 24-h urine output as a significant predictor of success (Area under the curve (AUC) = 0.666; 95% Confidence interval (CI): 0.546–0.786; P = .011) with a threshold of 365 cc/24h (sensitivity: 52.3%, specificity: 80.6%). In the final logistic regression model, urine output in the last 24 hours remained an independent predictor of weaning success (Odds ratio (OR) = 1.001; 95% CI: 1.000–1.002; P = .009).
Conclusion. The 24-h urine output preceding CRRT termination and the trend of lactate levels during the 4-hour period post-initiation are important predictive values for the success of CRRT discontinuation.

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INTRODUCTION

Acute kidney injury (AKI) is a common complication associated with high mortality in intensive care unit (ICU) patients.[1] The incidence of AKI in the ICU is reported to be between 27-67%.[2,3] Approximately 23.5% of patients who develop AKI require renal replacement therapy (RRT).[2] Continuous renal replacement therapy

(CRRT) is often preferred in critically ill patients due to its advantages such as better hemodynamic stabilization, improved cytokine and solute removal, and a higher likelihood of renal recovery compared to other RRT modalities.[4] CRRT is applied in about 70% of patients requiring RRT globally, surpassing other modalities such as intermittent hemodialysis, continuous low-flow hemodialysis, and peritoneal dialysis.[2] However, the concept of CRRT trauma has emerged recently, referring to CRRT-related side effects such as catheter-related complications,[5] bleeding due to continuous anticoagulant use, and immobilization.[4] Therefore, the discontinuation of CRRT is a significant issue and is subject to ongoing debate. Despite numerous studies focusing on the timing and dosage of CRRT,[6-8] there are very few studies addressing the successful discontinuation of CRRT.[2] Some studies have explored the relationship between successful CRRT discontinuation and factors such as urine volume, Sequential Organ Failure Assessment (SOFA) score, age (> 65), and CRRT duration.[9-11] The AKI guideline published by The Kidney Disease Improving Global Outcomes (KDIGO) organization in 2012 recommends discontinuing RRT treatment "when it is no longer necessary, when adequate renal recovery is achieved, or when RRT treatment is deemed no longer beneficial".[12] However, this recommendation, based on expert opinion, has not significantly improved clinicians' success in discontinuing CRRT treatment.[10] Given the frequent use of CRRT in ICU patients with AKI and the side effects associated with prolonged CRRT, the timing of its discontinuation is a critical issue. Given the lack of evidence and guidelines, this retrospective study aimed to identify predictive factors for successful CRRT discontinuation.

MATERIALS AND METHODS

This retrospective, single-center, observational study was conducted in a 36-bed adult medical ICU of Gülhane Training and Research Hospital, Ankara, Turkey. Approval for the study was obtained from the local ethics committee (Approval No. 2022/23). A total of 396 patients aged 18 and above, who underwent CRRT between January 1, 2019, and March 1, 2023, were screened for eligibility. To ensure a focused analysis on weaning from CRRT, 316 patients were excluded from the study. Specifically, 66 patients were excluded because they had received RRT within thirty days prior to their ICU admission, and 250 patients were excluded due to having end-stage kidney disease and being on a routine dialysis program. Ultimately, the final analyzed sample size consisted of 80 patients (Figure 1). This final cohort was divided into successful and unsuccessful discontinuation groups for further statistical comparison. Only patients who underwent continuous veno-venous hemodialysis (CVVHD) or continuous veno-venous hemodiafiltration (CVVHDF) with bicarbonate-based solutions (FRENSENIUS multiBIC®) via the FRENSENIUS multifiltrate® device (Frensenius Medical Care, Germany) were included. If a patient received CRRT repeatedly during the ICU stay, only the first CRRT session was considered.

Baseline characteristics including age, sex, comorbidities, Charlson comorbidity index score, Acute Physiology And Chronic Health Evaluation (APACHE-II) score and SOFA score at 24 hours of admission, as well as indications, anticoagulation methods, modalities, and duration (in hours) of the CRRT session were recorded. Additionally, arterial blood pressure, inotropic and/or vasopressor treatment, mechanical ventilation requirement, total urine output, and diuretic use during the CRRT session were noted.Bicarbonate, pH, lactate, creatinine, and urea levels at CRRT initiation, as well as urine output in the 24 hours preceding CRRT initiation, were also documented. Furthermore, repeated lactate level measurements in the early period of CRRT (0th, 1st, and 4th hours) were recorded to assess the lactate trend. Reasons for CRRT discontinuation were documented as well. Successful discontinuation was defined as "no requirement for RRT within the first seven days after CRRT termination". The decision to reinitiate RRT is determined by the patient's primary physician. Consequently, patients were categorized into successful and unsuccessful discontinuation groups.

Statistical Analysis

Parametric continuous variables were presented as mean (standard deviation), and non-normally distributed continuous variables were presented as median (minimum–maximum).

Kolmogorov–Smirnov test, skewness and kurtosis coefficients, and histogram graphs were used to differentiate parametric and nonparametric variables from continuous variables. Receiver

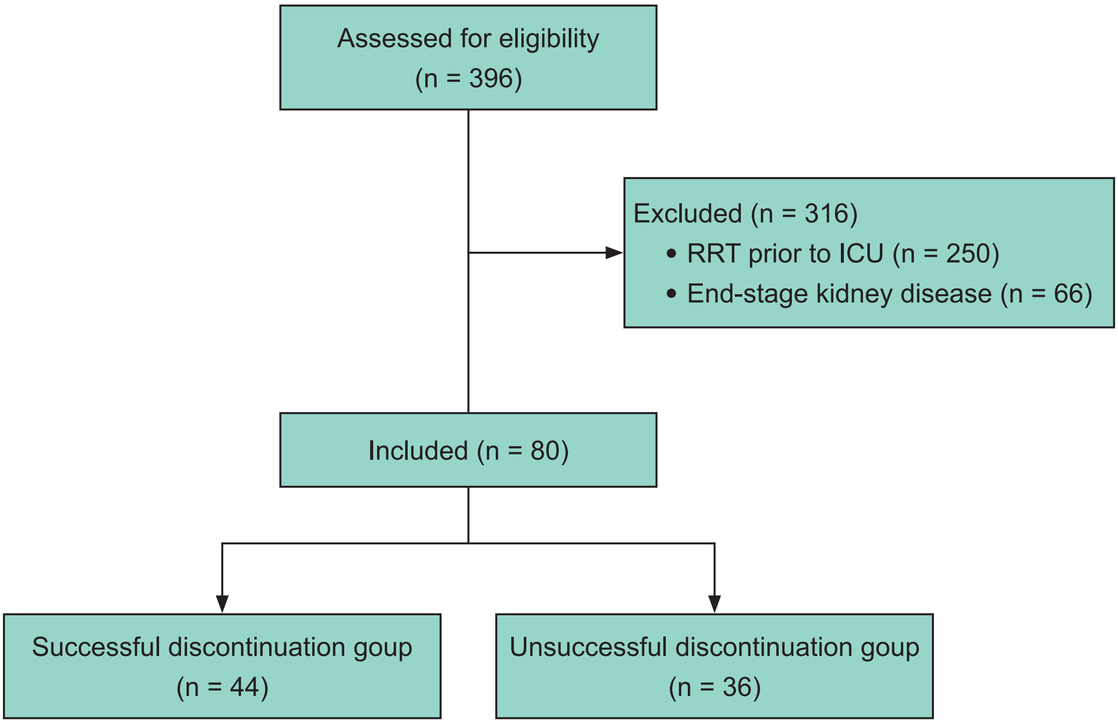

Figure 1. Flowchart of patient recruitment and selection process. This diagram illustrates the screening of 396 adult patients receiving CRRT between January 2019 and March 2023 at our 36-bed medical ICU. A total of 316 patients were excluded: 66 patients received RRT within thirty days prior to ICU admission, and 250 were end-stage kidney disease patients on a routine dialysis program. The final analysis was conducted on a cohort of 80 patients.

operating characteristic (ROC) analyses were performed to assess the discriminative ability of urine output amount for successful CRRT discontinuation. Area under the curve (AUC) and statistical significances were presented. In the univariate analysis comparing successful and unsuccessful groups, logistic regression analysis was performed for variables showing significant differences between groups in terms of predicting successful discontinuation. *P*-values < .05 were considered statistically significant.

RESULTS

A total of 80 patients were included in our study (Figure 1). The mean age of the patients was 71.16 ± 14.96 years. Forty-one (51.2%) of the patients were female. The most common comorbid disease was hypertension (HTN), affecting 57 patients (71.3%). This was followed by chronic heart disease in 34 patients (42.5%), diabetes mellitus (DM) in 31 patients (38.8%) and malignancy in 14 patients (17.5%). Thirty-seven patients (46.3%) required invasive mechanical ventilation (IMV), and 33 patients (41.3%) received vasopressor and/or inotropic therapy during the CRRT session. The most common reasons for initiation of CRRT were hypervolemia and uremia in 46 patients (57.5%), followed by deep metabolic acidosis in 35 patients (43.8%), resistant hyperkalemia in 16 patients (20%), and intoxication in 2 patients (2.5%). While CVVHD was used in 47 patients (58.8%), CVVHDF was preferred in 33 patients (41.3%). The mean duration of the CRRT session was 21.91 ± 12.01 hours.

Demographic data, comorbid conditions and baseline data of the patients are summarized in Table 1. When the patients were compared in terms of CRRT success, the amount of urine output during CRRT [385 (0-3880) mL vs 100 (0-1850) mL] was significantly higher in the successful discontinuation group (*P* = .01). Anticoagulation with heparin [41 (93.2%) vs 22 (61.1%), *P* < .001] and a decreasing or stable trend of lactate level in the first four hours of CRRT [20 (69%) vs 10 (40%)] were significantly more frequent in the successful group. IMV requirement [16(36.4%) vs 21(58.3%)] was significantly less frequent in the successful termination group (*P* = .05). A comparison of the successful and unsuccessful discontinuation groups is presented in Table 2.

Table 1. Baseline characteristics of the patients

Characteristic	Total (n = 80)
Age, year	71.16 ± 14.96
Female sex, n (%)	41 (51.2)
APACHE II score	26.20 ± 7.37
SOFA score	11.26 ± 4.54
Charlson comorbidity index	7.50 ± 2.98
Mechanical ventilation, n (%)	37 (46.3)
Vasopressor/inotropic treatment, n (%)	
NE	47 (58.8)
Dopamine	1 (1.3)
Both (NE + Dopamine)	1 (1.3)
None	31 (38.8)
Comorbidities, n (%)	
CHD	34 (42.5)
DM	31 (38.8)
HT	57 (71.3)
Malignancy	14 (17.5)
CRRT time, hour	21.92 (12.01)
CRRT modalities, n (%)	
CVVHD	47 (58.8)
CVVHDF	33 (41.2)
Anticoagulation, n (%)	
Heparin	63 (78.8)
Saline flush (No anticoagulation)	17 (21.3)
CRRT indication, n (%)	
Metabolic acidosis	35 (43.8)
Uremia	46 (57.5)
Hyperkalemia	16 (20)
Volume overload	46 (57.5)
Intoxication	2 (2.5)

Data are given as mean ± SD unless otherwise indicated. APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CHD, Chronic Hearth Disease; DM, Diabetes Mellitus; HT, Hypertension; CRRT, Continuous Renal Replacement Therapy; CVVHD, continuous Veno-Venous Hemodialysis; CVVHDF, Continuous Veno-Venous Hemodiafiltration; NE, Norepinephrine.

In univariate analysis, the variables showing a significant difference between the successful and unsuccessful discontinuation groups—IMV requirement, the amount of urine output in the last 24 hours before CRRT discontinuation, and the need for vasopressor and/or inotropic treatment during CRRT—were included in the backward logistic regression analysis. The overall model was statistically significant (Omnibus test, $P < .05$) and demonstrated acceptable goodness of fit (Hosmer–Lemeshow $\chi^2 = 11.238$, df = 6, $P = .081$). The explanatory power of the model was modest, with a Nagelkerke R^2 of 0.20, and the classification accuracy was 76.3%. Of these variables, only the amount of urine output in the last 24 hours before CRRT discontinuation maintained its significance up to the third and final step (B = 0.001, SE = 0.000, Wald = 6.892, $P = .009$). The odds ratio (OR) for successful discontinuation increases as the amount of urine output in the last 24 hours before CRRT discontinuation increases (OR = 1.001, 95% Confidence interval (CI), 1.000-1.002). The lactate trend in the first 4 hours after the start of CRRT, which showed significant differences between groups in the univariate analysis, was not included in the multivariate analysis due to missing data.

To further evaluate the predictive value of urine output at the time of CRRT discontinuation, a ROC curve analysis was performed. A urine output threshold of 365 mL within the 24 hours preceding discontinuation predicted successful weaning with a sensitivity of 52.3% and specificity of 80.6%. The AUC was 0.666 (95% CI: 0.546–0.786, $P = .011$), indicating modest discriminative ability (Figure 2). Given the moderate sensitivity and AUC, these findings should be interpreted with caution. Moreover, no time-to-event analysis was performed, which may limit the ability to fully capture the dynamics of renal recovery over time.

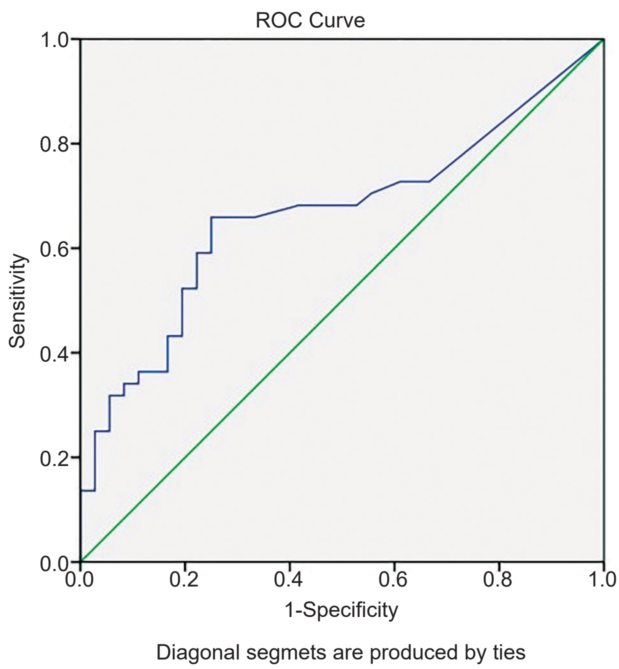

Figure 2. Receiver Operating Characteristic (ROC) curve analysis of 24-hour urine output preceding CRRT discontinuation for predicting weaning success. A threshold of 365 cc/24h predicted successful discontinuation with a sensitivity of 52.3% and a specificity of 80.6% (AUC = 0.666; 95% CI: 0.546–0.786; $P = 0.011$).

Table 2. Comparison of patient groups for CRRT discontinuation success

Variables	Successful discontinuation group n=44 (55%)	Unsuccessful discontinuation group n=36 (45%)	*P*
Age, year	75 (26-92)	72 (22-96)	.489$^{\gamma}$
Female sex, n (%)	23 (52.3)	18 (50)	.840$^{\alpha}$
APACHE II score	25.8 ± 8.1	26.6 ± 6.4	.612$^{\beta}$
SOFA score	10 (4-25)	12 (4-20)	.205$^{\gamma}$
Charlson comorbidity index	7 (2-13)	7 (0-15)	.834$^{\gamma}$
Mechanical ventilation, n (%)	16 (36.4)	21 (58.3)	.050$^{\alpha *}$
Vasopressor/inotropic treatment, n (%)	22 (50)	11 (30.6)	.079$^{\alpha}$
Increased vasopressor need for the first 4h of CRRT	10 (22.7)	7 (19.4)	.721$^{\alpha}$
Laboratory at CRRT starting			
Creatinine, mg/dL	3.93 (1.46-10.50)	3.88 (1.44-13.20)	.414$^{\gamma}$
Urea, mg/dL	192.5 (89-657)	212 (61-371)	.408$^{\gamma}$
pH	7.31 (6.87-7.46)	7.31 (7.11-7.43)	.992$^{\gamma}$
Lactate, mmol/L	1.6 (0.6-11.8)	1.9 (0.1-29.0)	.187$^{\gamma}$
Bicarbonate, mmol/L	18.9 (6.7-32.0)	18.7 (9.8-30.3)	.886$^{\gamma}$
Lactate trend in first 4h of CRRT¶,n (%)			
Increasing	9 (31)	15 (60)	.033$^{\alpha *}$
Stable or decreasing	20 (69)	10 (40)	
CRRT time, hour	23.2 ± 14.1	20.3 ± 8.6	.274$^{\beta}$
24-h U/O during CRRT, mL	385 (0-3880)	100 (0-1850)	.010$^{\gamma *}$
24-h U/O before CRRT, mL	315 (0-3570)	210 (0-2170)	.556 $^{\gamma}$
CRRT modalities, n (%)			
CVVHD	28 (63.6)	19 (52.8)	.326$^{\alpha}$
CVVHDF	16 (36.4)	17 (47.2)	
Anticoagulation, n (%)			
Heparin	41 (93.2)	22 (61.1)	< .001$^{\alpha *}$
Saline flush (No anticoagulation)	3 (6.8)	14 (38.9)	
Reason for CRRT discontinuation, n (%)			
Adequate renal recovery	34 (77.3)	20 (55.6)	.090$^{\alpha}$
Hemodynamic deterioration	7 (15.9)	7 (19.4)	
Circuit failure	3 (6.8)	7 (19.4)	
Cardiac Arrest	0 (0)	2 (5.6)	

Data are expressed as mean ± standard deviation (SD) or median (minimum-maximum) unless otherwise indicated. Categorical variables are presented as frequencies and percentages [n (%)].
APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CRRT, Continuous Renal Replacement Therapy; CVVHD, Continuous Veno-Venous Hemodialysis; CVVHDF, Continuous Veno-Venous Hemodiafiltration; U/O, Urine Output.
$^{\alpha}$ Chi-Square test
$^{\beta}$ Independent samples t-test
$^{\gamma}$ Mann-Whitney U test
* = *P* < .05
¶ A total of 54 patients with available lactate levels at 4th hour of CRRT included in the analysis.
The successful CRRT discontinuation was significantly associated with higher 24-hour urine output during therapy, a stable or decreasing 4-hour lactate trend, and a lower requirement for mechanical ventilation.

DISCUSSION

In our study, effective anticoagulation, the absence of lactate increase in the early phase of CRRT (first 4 hours) and no need for IMV were significantly more frequent in the group with successful discontinuation. Additionally, our study showed that a last 24-hour urine volume > 365 mL/24h before CRRT discontinuation was an independent predictor of successful CRRT discontinuation.

The decision for discontinuation, in comparison to the initiation decision of CRRT, modality, and dose determination, stands out as an area with limited research in the literature. Therefore, definitive recommendations are not yet available. Our study involves a retrospective evaluation of the discontinuation decisions made in CRRT applications conducted at our center. Similar to many other centers, at our center, the decision to discontinue of CRRT is made according to the clinician's judgement, considering hemodynamic stability, volume status, solute control, and other metabolic parameters, without following a fixed protocol.

In a retrospective multicenter study conducted by Uchino *et al.* in 23 countries and 54 centers, it was reported that a 24-hour urine output of 400 mL (sensitivity of 46.5% and specificity of 80.9%) or more before CRRT discontinuation was significant in predicting successful CRRT discontinuation.[11] Likewise, a recent systematic review and meta-analysis revealed that 24-hour urine output had a sensitivity of 66.2% (95% CI, 53.6%-76.9%) and specificity of 73.6% (95% CI, 67.5%-79.0%) in predicting successful discontinuation of CRRT.[10] In the AKIKI study, the presence of > 500 mL/24 hours spontaneous urine output in both early and late RRT groups was accepted as CRRT discontinuation criteria.[13] However, the optimal urine output amount cut-off values vary considerably in the literature.[14,15] In this study, > 365 mL/24 hours urine output was found to be an independent predictor of discontinuation success, supporting the aforementioned literature data.

The adverse renal effects of IMV have been known for many years. The best known adverse effect is that positive pressure ventilation decreases venous return and causes a decrease in cardiac stroke volume. Additionally, IMV has been associated with decreased glomerular filtration rate (GFR) and renal biotrauma mediated by the release of various mediators and cytokines.[16,17] While existing studies have not yet demonstrated a direct correlation between continued IMV following discontinuation of CRRT, it is plausible to consider that sustained IMV in patients who have ceased CRRT may exacerbate renal injury. This study contributes novel insights into this relationship, filling a gap in the current literature.

In clinical practice, concerns regarding an elevated risk of bleeding often lead to the preference for administering CRRT without anticoagulation. Uchino *et al.*'s research revealed that approximately one-third of CRRTs conducted worldwide were administered without anticoagulation.[18] Multiple studies have shown that anticoagulation-free CRRT can reduce the lifespan of filters and circuits, leading to more frequent premature circuit failures.[19,20] Similarly, our study found a higher frequency of anticoagulation-free CRRT in the unsuccessful group. Although not statistically significant, 19.4% (7 patients) of the unsuccessful CRRT termination group was discontinued due to circuit failure.

Lactate is a crucial indicator of tissue perfusion. Progressive elevation in lactate levels and impaired clearance has been associated with poor prognosis and increased mortality risk in various critical illnesses such as sepsis and trauma.[21,22] However, studies investigating the predictive value of initial lactate levels and changes in lactate levels for the success of the procedure in patients undergoing CRRT are limited. In a recent retrospective study of 1661 CRRT patients with AKI, higher initial lactate levels were associated with increased mortality compared to lower levels. Furthermore, patients with decreasing lactate levels within 24 hours exhibited lower mortality rates than those with increasing levels. It has been repeatedly reported that hemodynamic instability during CRRT often occurs at the beginning and early period of CRRT.[23] However, the importance of the trend rather than a single lactate level measurement is a prognostic marker that has been emphasized for many clinical conditions. Based on these data, no correlation was found between baseline lactate levels and CRRT success in our study. However, the trend of change in lactate levels in the first four hours of CRRT may be an important determinant of CRRT success. Sustaining CRRT until the targeted metabolic needs are reached requires hemodynamic stability. In our study, the high success rate of CRRT in the group of patients in whom the lactate level trend in the early period of CRRT (first four hours) did not show an increase may be a strong evidence of this.

This retrospective study was limited by the absence of standardized criteria for CRRT discontinuation decisions, which relied on the subjective judgment of the attending clinician. Consequently, discontinuation decisions lacked standardization, potentially impacting study outcomes. Additionally, inclusion of patients necessitating CRRT termination due to cardiac arrest and circuit failure during therapy, comprising 15% (n = 12) of the study cohort, presents another limitation. Cardiac arrest and circuit failure are inherent complications of CRRT, and premature discontinuation due to these events may contribute to discontinuation failure.

Furthermore, the relatively small sample size and the retrospective design may have introduced selection and information bias, as well as the influence of unmeasured confounding factors. The clinician-driven decision-making process regarding RRT reinitiation, in the absence of a standardized protocol, represents another limitation that may have affected the consistency and generalizability of the findings. Another potential limitation of our analysis is that renal function trajectory may act as a confounder that was not fully accounted for. Other factors influencing urine output—such as severity of illness, vasopressor use, acid–base status, and nutrition—were considered determinants of the outcome rather than independent confounders, and therefore were not adjusted for.

Despite these limitations, given the paucity of research on CRRT discontinuation success and the absence of definitive guidelines for such a critical scenario, we contend that our study represents a meaningful contribution to the literature.

CONCLUSION

In summary, while randomized controlled trials have established criteria to guide clinicians in determining CRRT initiation, there remains a dearth of literature assessing CRRT discontinuation decisions. The volume of 24-hour urine output before termination of CRRT and the 4-hour post-initiation lactate trend are important predictive values for the success of CRRT discontinuation. It is essential to discontinue the CRRT at the right time to avoid the potential adverse effects of unnecessary prolonged CRRT. Moreover, the lactate trend in the early phase (first four hours) of CRRT may be instructive for this purpose. Our findings were obtained with limited resources. Validation of the observed relationship across multiple centers would provide important evidence to support or refute these results

Acknowledgment

There is no funding to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

This study has local ethical approval (Approval No. 2022/23).

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