Original Paper

A Prospective Observational Study on the Predictive Value of Serum Cystatin C for Successful Weaning from Continuous Renal Replacement Therapy

Chang Seong Kim Eun Hui Bae Seong Kwon Ma Soo Wan Kim

Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea

Key Words

Renal replacement therapy • Cystatin C • Weaning • Intensive care unit

Abstract

Background/Aims: There is a paucity of literature that investigates a biomarker associated with successful renal recovery following continuous renal replacement therapy (CRRT). Our study aimed to identify potential renal biomarkers or clinical indicators that could predict the successful weaning from CRRT. **Methods:** We conducted a prospective, observational study of 110 patients who had received CRRT and were weaned after renal recovery. Patients were considered to have successfully weaned from CRRT once there was no need for renal replacement therapy (RRT) for at least 14 days. For patients who had to restart dialysis within 14 days were considered unsuccessful. **Results:** Of the 110 patients evaluated, 89 (80.9%) were successfully weaned from CRRT. These patients had lower serum cystatin C (CysC) levels and higher urine output than the group that restarted RRT at the time of CRRT cessation. However, the levels of serum creatinine and neutrophil gelatinase-associated lipocalin were not significantly lower in the successful group compared to the restart-RRT group. A multivariable logistic regression showed that serum CysC was an independent predictor for the successful weaning from CRRT. Furthermore, in a multivariable Cox proportional hazards analysis, the group that was successfully weaned from CRRT had a lower in-hospital mortality compared to the restarted RRT group. **Conclusion:** Serum CysC, at the time of CRRT cessation, is an independent predictor of the successful weaning from CRRT in critically ill patients with acute kidney injury.

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Introduction

Acute kidney injury (AKI) is a common complication in patients admitted to the intensive care unit (ICU). A recent multinational, cross-sectional study showed that AKI occurs in more than half of ICU patients, and is associated with worsening renal function and increased mortality [1]. Because of the increasing incidence of AKI, the use of renal replacement therapy (RRT) in intensive care settings is rising [1, 2]. Much of the available data, largely derived from observational studies and a few randomized controlled trials, have focused on the optimal timing for starting RRT in ICU patients with AKI, although there are discordant results on whether early or delayed RRT initiation improves survival or kidney recovery [3-5]. Recently, a large multi-center, randomized controlled pilot trial was conducted comparing the effect of standard versus accelerated initiation of RRT in AKI (STARRT-AKI) [6]. Main, ongoing studies may offer the optimal timing of RRT initiation in patients with severe AKI. However, compared to the evidence on the timing of RRT initiation, there is a lack of data on the optimal timing for discontinuing RRT. Although a few observational studies found that urine output, at the time of continuous RRT (CRRT) cessation, was predictive for restarting RRT, the predictive ability of urine output was negatively modified by diuretics that were used to increase urine output and facilitate CRRT cessation [7-10]. Therefore, KDIGO guidelines have recommended further research programs to determine the clinical parameters or biomarkers that indicate renal recovery and to predict successful discontinuation of RRT in AKI patients [11].

Serum cystatin C (CysC) has been proposed as a better surrogate marker than serum creatinine for the glomerular filtration rate. It may also be a better biomarker to prediction all-cause AKI based on its half-life, which is shorter than that of serum creatinine [12, 13]. Moreover, neutrophil gelatinase-associated lipocalin (NGAL) has been shown to be an early biomarker for predicting AKI before serum creatinine increases [14]. However, to date, data is lacking regarding the biomarkers or clinical factors that could guide clinical decisions on the optimal time to discontinue CRRT or to predict the successful weaning from CRRT in AKI patients [2, 10, 15]. The aim of our study was to identify the level of serum CysC or serum NGAL, at the time of CRRT cessation, that is associated with successful weaning from CRRT. Additionally, we evaluated the predictive value of these two biomarkers in an attempt to find the optimal strategy for discontinuing CRRT.

Materials and Methods

Study design and patient population

This was prospective study of patients with AKI, who required CRRT in the ICU, between July 2013 and September 2015. Amongst these patients, inclusion criteria included patients who were weaned from CRRT after renal recovery. Weaning from CRRT was not based on standardized criteria, but was decided based on improvements in fluid overload, electrolytes, acid-base status, hemodynamic stability and an increase in urine output in ICU patients. Patients were excluded if they had hemodialysis or peritoneal dialysis treatment before admission to the ICU, were < 18 years old or possibly pregnant women, required intermittent or continuous hemodialysis after cessation of CRRT due to poor renal function, died during CRRT or within 12 h after discontinuation CRRT, or had a do-not-resuscitate order. A total of 112 patients were enrolled at CRRT cessation for determining the successful weaning from CRRT, although two patients were excluded since there was no available data. This left 110 patients for the final analysis. All patients were followed until discharge or in-hospital mortality (Fig. 1).

This study was approved by the institutional review board of Chonnam National University Hospital (CNUH-2013-078), and was performed in accordance with the tenets of the Declaration of Helsinki of 1975, as revised in 2000. Written informed consent was obtained from all patients or family members before enrollment.

Data collection and definitions

Demographic and laboratory data were collected from the medical records, including age, sex, body mass index, previous history of hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, and smoking, reasons for ICU admission (sepsis/septic shock, cardiogenic shock, and post-surgery), and setting of CRRT upon initiation. Additionally, the use of diuretics, vasopressors and mechanical ventilator, levels of serum blood urea nitrogen, creatinine, NGAL, serum CysC, and urine output were collected at the time of CRRT cessation. The Simplified Acute Physiology Score (SAPS) III was calculated

to provide the risk of mortality without having to specify a primary diagnosis [16]. The levels of serum CysC and serum NGAL were assayed using methods that are traceable to International Federation of Clinical Chemistry and an enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN, USA).

Patients were considered to have successfully weaned from CRRT once there was no need for renal replacement therapy for at least 14 days after cessation of CRRT. Patients who had to restart dialysis within 14 days were considered unsuccessful, in accordance with previous studies [15, 17, 18].

Statistical analysis

Demographic and biochemical data are expressed as a mean $\pm$ standard deviation or median with interquartile ranges (25th and 75th percentiles) for parametric variables and nonparametric continuous variables, respectively. Categorical variables are presented as the number and percentage of patients. The two groups were separated based on patients who did not require RRT for at least 14 days after CRRT cessation (successfully weaned group) and patients who had to restart RRT due to insufficient renal recovery (restarted RRT group). We compared the variables between the 2 groups using the Student's *t*-test and Mann-Whitney test, or Pearson chi-square and Fisher exact test, as appropriate. We assessed the area under curves (AUC) for the receiver operating characteristic (ROC), and used the Euclidean distance and Youden index to find the optimal cut-off value for weaning patients from CRRT. A multivariable logistic regression was used to evaluate the association of biomarkers and clinical variables with successful weaning from CRRT. All independent variables in the multivariable logistic regression were tested for multi-collinearity; if the variance inflation factor exceeded 10, the variable was considered to be collinear. The Box-Tidwell test was conducted to identify the assumption for log-linearity in continuous variables. The variables for multivariable adjustment were selected on the basis of factors known to be associated with successful weaning of CRRT and the results of the statistically significant univariable analysis ($p < 0.1$). Moreover, a Cox proportional hazards analysis was performed to investigate the independent association between successful weaning from CRRT and the risk of in-hospital mortality in patients that discontinued CRRT. All statistical tests were two-tailed and a *P*-value of < 0.05 was considered statistically significant. Analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 21.0 (IBM Corp, Armonk, NY).

Fig. 1. Flowchart of the study population. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ICU, Intensive care unit; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; DNR, do not resuscitation.

Results

Baseline characteristics of the patients

The demographic and clinical characteristics of the patients in the two groups are shown in Table 1. Of the 110 patients evaluated, 89 (80.9%) were successfully weaned from CRRT, while 21 (19.1%) had to restart RRT within 14 days of cessation. The restarted RRT group had a higher prevalence of hypertension and a higher daily dose of furosemide, during the 24 h before cessation of CRRT, compared to patients in the weaned group, although the differences were not significant.

Biomarkers and urine output at cessation of CRRT were also compared between the groups (Table 1). Serum CysC levels were significantly lower and urine output was significantly higher in the successfully weaned group compared with the restarted RRT group (CysC: 1.70 ± 0.68 mg/L vs. 2.47 ± 0.93 mg/L, $p < 0.001$; urine output: 1.33 [0.67, 2.56] mL/h/kg vs. 0.78 [0.27, 1.42] mL/h/kg, $p = 0.016$, Fig. 2). However, serum creatinine and NGAL levels were

Table 1. Baseline demographic, clinical characteristics and outcomes of the patients. ^a At initiation of CRRT. ^b 24h before CRRT cessation. Abbreviations: RRT, renal replacement therapy; BP, blood pressure; BMI, body mass index; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; SAPS, Simplified Acute Physiology Score; CRRT, continuous renal replacement therapy; IQR, interquartile range; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CysC, cystatin C; NGAL, neutrophil gelatinase-associated lipocalin; U/O, urine output

Parameter	Total (n = 110)	Successfully weaned (n = 89)	Restarted RRT (n = 21)	p value
Age (year)	63.2 ± 14.6	62.6 ± 15.2	65.5 ± 12.1	0.419
Male, n (%)	69 (62.7)	55 (61.8)	14 (66.7)	0.678
Systolic BP (mmHg)	121 ± 29	120 ± 26	126 ± 37	0.421
Diastolic BP (mmHg)	64 ± 21	62 ± 17	71 ± 32	0.079
Current/former Smoker, n (%)	52 (46.3)	41 (46.1)	11 (52.4)	0.730
BMI (kg/m ²)	23.5 ± 4.4	23.3 ± 4.3	24.3 ± 4.9	0.368
Diabetes, n (%)	55 (50.0)	41 (46.1)	14 (66.7)	0.089
Hypertension, n (%)	65 (59.1)	48 (53.9)	17 (81.0)	0.027
Chronic kidney disease, n (%)	13 (11.8)	8 (9.0)	5 (23.8)	0.071
COPD, n (%)	8 (7.3)	7 (7.9)	1 (4.8)	1.000
Reason for ICU admission				
Sepsis/septic shock, n (%)	41 (37.3)	30 (33.7)	11 (52.4)	0.111
Cardiogenic shock, n (%)	23 (20.9)	20 (22.5)	3 (14.3)	0.556
Post-surgery, n (%)	13 (11.8)	11 (12.4)	2 (9.5)	1.000
Other, n (%)	41 (37.3)	35 (39.3)	6 (28.6)	0.359
SAPS III score	58.1 ± 16.2	56.9 ± 15.8	63.2 ± 17.1	0.107
SAPS III death rate, %	35.0 ± 23.5	33.0 ± 23.3	43.0 ± 23.3	0.081
Setting of CRRT				
Blood flow rate, mL/hr (IQR)	150 (150, 150)	150 (130, 150)	150 (150, 150)	0.188
Dialysate flow rate, mL/hr (IQR)	1200 (1000, 1325)	1100 (1000, 1350)	1200 (1050, 1325)	0.583
Replacement flow rate, mL/hr (IQR)	1200 (1000, 1400)	1100 (1000, 1400)	1200 (1000, 1325)	0.744
Ultrafiltration rate, mL/hr (IQR)	50 (0, 100)	50 (0, 100)	50 (0, 100)	0.897
Vasopressors/inotropes ^a				
Dopamine, n (%)	33 (30.0)	24 (27.0)	9 (42.9)	0.153
Dopamine, µg/min/kg (IQR)	0 (0, 4.2)	0 (0, 3.0)	0 (0, 5.5)	0.291
Norepinephrine, n (%)	60 (54.5)	47 (52.8)	13 (61.9)	0.451
Norepinephrine, µg/min/kg (IQR)	0.09 (0.0, 0.46)	0.07 (0, 0.46)	0.20 (0.0, 0.47)	0.489
Dobutamine, n (%)	6 (5.5)	5 (5.6)	1 (4.8)	1.000
Dobutamine, µg/min/kg (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.900
Furosemide, n (%)	74 (67.3)	56 (62.9)	18 (85.7)	0.068
Intravenous furosemide, mg/day (IQR)	40 (0, 153)	40 (0, 120)	60 (20, 230)	0.045
At CRRT cessation				
Furosemide, n (%) ^b	43 (39.1)	32 (36.0)	11 (52.4)	0.165
Intravenous furosemide, mg/day (IQR) ^b	0 (0, 40)	0 (0, 30)	20 (0, 50)	0.289
BUN (mg/dL)	22.1 ± 13.5	20.8 ± 10.3	27.3 ± 21.4	0.169
Creatinine (mg/dL)	1.3 ± 1.0	1.2 ± 0.9	1.5 ± 1.3	0.147
eGFR ^c	69.5 ± 32.4	72.1 ± 32.6	58.4 ± 29.9	0.082
Serum CysC (mg/L)	1.85 ± 0.79	1.70 ± 0.68	2.47 ± 0.93	<0.001
Serum NGAL (ng/mL)	586.7 ± 386.8	553.4 ± 390.2	728.0 ± 345.8	0.062
U/O, mL/hr/kg (IQR)	1.23 (0.61, 2.27)	1.33 (0.67, 2.56)	0.78 (0.27, 1.42)	0.016
Mechanical ventilation, n (%)	40 (36.4)	30 (33.7)	10 (47.6)	0.233
Clinical outcomes				
CRRT duration, day (IQR)	3.0 (3.0, 5.0)	3.0 (3.0, 5.0)	4.0 (3.0, 6.0)	0.136
ICU stay, day (IQR)	10.0 (6.0, 22.0)	9.0 (5.5, 18.5)	20.0 (8.5, 33.0)	0.004
Hospital stay, day (IQR)	21.0 (14.0, 38.3)	19.0 (14, 38.5)	27.0 (20.5, 39.5)	0.149
In-hospital mortality, n (%)	26 (23.6)	13 (14.6)	13 (61.9)	<0.001

not significantly lower in the successfully weaned group than in the restarted RRT group (serum creatinine: 1.2 ± 0.9 mg/dL vs. 1.5 ± 1.3 mg/dL, $p = 0.147$; NGAL: 553 ± 390 ng/mL vs. 728 ± 346 ng/mL, $p = 0.062$). There were also no significant difference in the reasons for ICU admission, SAPS III score, setting of CRRT, the use of mechanical ventilator at the time of CRRT cessation and other baseline characteristics between both groups.

Predictive factors for successful weaning from CRRT

To determine the predictive accuracy and cut-off values for biomarkers including serum CysC, serum NGAL and/or creatinine, and urine output at cessation of CRRT for successful weaning from CRRT, a ROC curve analysis was performed (Table 2). Serum CysC and urine output were significantly associated with the successful weaning from CRRT. Among them, serum CysC had the greatest AUC of 0.739 [95% confidence interval [CI], 0.624–0.853, $p = 0.001$]; sensitivity and specificity were 76.2% and 62.9%, respectively, at a cutoff of 1.85 mg/L. The AUC of urine output was 0.669 (95% CI, 0.547–0.792, $p = 0.016$) and the best cut-off value was 1.26 mL/h/kg, with a sensitivity of 59.6% and specificity of 66.7%. However, serum NGAL showed an AUC of 0.654 (95% CI, 0.539–0.768, $p = 0.029$). The ROC curves are shown in Fig. 3.

The multivariable logistic regression analysis showed that serum CysC was an independent predictor for successful weaning from CRRT (odds ratio, 0.290; 95% CI, 0.119–0.709; $p = 0.007$). However, serum NGAL and urine output at cessation of CRRT were not associated with successful weaning from CRRT after adjustment for variables (Table 3).

Fig. 2. Scatter dot plots for serum CysC (A), Serum NGAL (B) and urine output (C) at CRRT cessation. The mean values with standard deviation of serum CysC in

the successfully weaned group and the restarted RRT group were 1.70 ± 0.68 mg/L and 2.47 ± 0.93 mg/L, respectively. The mean values with standard deviation of serum NGAL in the successfully weaned group and the restarted RRT group were 553.4 ± 390.2 ng/mL and 728.0 ± 345.8 ng/mL, respectively. The median values with interquartile range of urine output in the successfully weaned group and the restarted RRT group were 1.33 (0.67, 2.56) mL/h/kg and 0.78 (0.27, 1.42) mL/h/kg, respectively. CysC, Cystatin C; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy.

Table 2. AUC for biomarkers and clinical factors at cessation of CRRT for successful weaning from CRRT. ^a At the time of CRRT cessation. Abbreviations: AUC, area under the receiver operating characteristic curve; CRRT, continuous renal replacement therapy; SE, standard error; CI, confidence interval; Sen, sensitivity; Spe, specificity; CysC, cystatin C; NGAL, neutrophil gelatinase-associated lipocalin

Parameter	AUC	SE	95% CI	Sen, %	Spe, %	p value
Creatinine (mg/dL)	0.601	0.074	0.455–0.747	80.9	23.8	0.151
Serum CysC (mg/L)	0.739	0.059	0.624–0.853	76.2	62.9	0.001
Serum NGAL (ng/mL) ^a	0.654	0.058	0.539–0.768	90.5	44.9	0.029
Urine output (ml/hr/kg) ^a	0.669	0.062	0.547–0.792	59.6	66.7	0.016

Fig. 3. The area under curves for the receiver operating characteristic (AUC) for successful weaning from CRRT. Serum cystatin C (CysC) (A), serum neutrophil gelatinase-associated lipocalin (NGAL) (B), urine output (C).

Table 3. Multivariable logistic regression analysis for successful weaning from CRRT in the patients. Adjusted for older age; history of diabetes, hypertension and chronic kidney disease; SAPS III score, BUN, CysC, NGAL and urine output. ^a Reasons for ICU admission. ^b At the time of CRRT cessation. Abbreviations: CRRT, continuous renal replacement therapy; CI, confidence interval; SAPS, Simplified Acute Physiology Score; BUN, blood urea nitrogen; CysC, cystatin C; NGAL, neutrophil gelatinase-associated lipocalin

Parameter	Univariable		Multivariable	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age (> 65 years)	0.670(0.257–1.749)	0.414	1.161(0.360–3.746)	0.802
Male	0.809(0.297–2.205)	0.678		
Diabetes	0.472(0.157–1.159)	0.095	0.594(0.164–2.149)	0.427
Hypertension	0.275(0.086–0.884)	0.030	0.317(0.072–1.389)	0.128
Chronic kidney disease	0.316(0.092–1.091)	0.069	1.396(0.263–7.403)	0.695
Sepsis/septic shock ^a	0.462(0.177–1.210)	0.116		
Cardiogenic shock ^a	1.739(0.465–6.508)	0.411		
Post-surgery ^a	1.340(0.274–6.556)	0.718		
Mechanical ventilation ^b	0.559(0.214–1.465)	0.237		
Use of furosemide ^b	0.510(0.195–1.322)	0.169		
SAPS III score	0.975(0.946–1.006)	0.109	0.981(0.948–1.015)	0.274
BUN (mg/dL) ^b	0.968(0.937–1.000)	0.048	0.996(0.958–1.036)	0.836
Creatinine (mg/dL) ^b	0.745(0.491–1.131)	0.167		
Serum CysC (mg/L) ^b	0.284(0.143–0.566)	<0.001	0.290(0.119–0.709)	0.007
Serum NGAL (ng/mL) ^b	0.999(0.998–1.000)	0.066	1.000(0.998–1.002)	0.992
Urine output (ml/hr/kg) ^b	1.714(1.031–2.849)	0.038	1.476(0.942–2.314)	0.089

Comparisons of clinical outcomes

In-hospital clinical outcomes are listed in Table 1. The successfully weaned group showed a significantly lower rate of in-hospital mortality and shorter length of ICU stay than the restarted RRT group (in-hospital mortality: 14.6% vs. 61.9%, $p < 0.001$; ICU stay: 9.0 [5.5, 18.5] day vs. 20.0 [8.5, 33.0] day, $p = 0.004$, respectively). However, there were no significant differences in the duration of CRRT or the length of hospital stay between the groups. Furthermore, in a multivariable Cox proportional hazards analysis, successfully weaned patients were associated with lower in-hospital mortality, even after adjusting for confounding variables (hazard ratio, 0.283; 95% CI, 0.114–0.701; $p = 0.006$) (Table 4).

Table 4. Prognostic values of successful weaning from CRRT for in-hospital mortality after cessation of CRRT (Cox proportional hazards model). ^a Model 1, adjusted for age and sex. ^b Model 2, adjusted for Model 1 plus hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, heart failure, cerebral vascular disease, use of mechanical ventilation at the time of CRRT cessation, urine output and SAPS III score. Abbreviations: CRRT, continuous renal replacement therapy; RRT, renal replacement therapy

Variable	Unadjusted	P value	Model 1 ^a	P value	Model 2 ^b	P value
Restarted RRT group	Reference		Reference		Reference	
Successfully weaned group	0.232(0.103–0.522)	<0.001	0.240(0.106–0.542)	0.001	0.283(0.114–0.701)	0.006

Discussion

In this prospective observational study, serum CysC levels, at the time of CRRT cessation, was a good predictor for critically ill patients to successfully discontinue CRRT. Moreover, lower serum CysC was independently associated with successful weaning from CRRT after adjusting for other variables. Importantly, patients with successful weaning from CRRT had a significantly lower in-hospital mortality rate than those who had to restart RRT.

CysC is regularly produced by nucleated cells, freely filtered by the glomerulus, mostly reabsorbed at the proximal tubule via megalin-mediated endocytosis, and finally catabolized [19]. Moreover, the serum CysC level is less dependent on age, sex, race, and muscle mass compared to serum creatinine. Therefore, serum CysC could be an optimal marker, not only for the diagnosis of chronic kidney disease, but also for predicting AKI [12]. Zhang et al. [20] performed a retrospective study, and showed that higher serum CysC is associated with poor renal recovery and a longer dependence on CRRT in critically ill patients. This suggests that the diagnostic performance of CysC in predicting renal recovery is clinically useful. However, it has been unclear whether serum CysC at cessation is an optimal indicator for successful weaning from CRRT, since prior studies focused on CysC levels at the time of CRRT initiation but not at its cessation [20]. Concerning this, our study found that serum CysC, at the time of CRRT cessation, was significantly predictive in the successfully weaned group during follow-up, with an AUC value of 0.739. Similarly, a recent study also found that serum CysC, measured when RRT was discontinued, showed the largest AUC value for predicting 60-day renal recovery. In this study, recovery was defined as a serum creatinine level not exceeding 0.5 mg/dL above the baseline value, in patients with AKI who required RRT in the ICU [10]. These results could be supported by the evidence that levels of CysC are less likely to be influenced by continuous venovenous hemodiafiltration or hemofiltration, compared with serum NGAL or creatinine [21–23]. In a previous study, the corrected sieving coefficient for CysC was 0.52 and the CysC clearance was 17 ml/min during continuous venovenous hemodiafiltration, while the sieving coefficient and clearance of creatinine were 0.90 and 30.1 ml/min, respectively [21]. Moreover, the quantity of CysC removed was less than 30% of its production, and no significant changes in serum concentration between the afferent and efferent blood line were observed. However, NGAL could be adsorbed by the polysulfone membranes and ultra-filtrated during hemofiltration [22]. Therefore, serum CysC level may be used to predict renal outcomes during CRRT and to monitor residual renal function.

Previous studies have reported the association between resuming dialysis and longer duration of dialysis with higher Sepsis-related Organ Failure Assessment scores during ICU

admission, patients over 65 years of age, previous CRRT cycles, serum creatinine levels, 2 h creatinine clearance, and 24 h urinary urea or creatinine at the time of RRT cessation [7-9, 15, 24, 25]. However, urine output at the time of cessation was reported as the most important predictor of the successful weaning of RRT [7-10, 26], and many studies adapted the criteria for discontinuation of RRT based on the urine output exceeding 400–500 ml/day [4, 5, 27]. Uchino et al. found that a urine output of > 400 ml/day, without diuretics at CRRT cessation, had the greatest AUC value of 0.845, but diuretics negatively affected the predictive ability of urine output [8]. Additionally, a recent study found that the 24 h urine output at the day of attempt of weaning failed to predict successful weaning from RRT [15]. In line with previous studies [8, 15, 28], our results showed that urine output at the time of CRRT cessation was not significantly associated with successful weaning, and more than 52% of patients in the restarted RRT group received furosemide. Therefore, we suppose that urine output on cessation is a necessary but not sufficient condition for successful weaning from CRRT in critically ill patients, especially with diuretics use.

Previous studies showed that daily urinary urea excretion or daily urinary creatinine were independent markers of the successful weaning from intermittent hemodialysis or RRT in ICU patients with AKI [15, 25]. However, 24 h urine collection might be time-consuming and may delay the time to predict the success of RRT weaning. Although urinary urea and creatinine are less impacted by diuretics than urinary output, muscle mass and/or degree of residual kidney function could affect its predictive ability. In this regard, a single assessment of serum CysC, at the time of CRRT cessation, might be an easier, faster way to predict the success of CRRT weaning.

This study has several limitations. First, although the study was prospective, it was an observational design without an intervention and it was a single center study. Also, the discontinuation of CRRT was not based on standardized criteria but was decided based on improvements in clinical parameters according to the physician's discretion. Additionally, although CRRT is widely used in ICU patients with AKI, most remain dialysis-dependent due to poor renal recovery and safety concerns and, therefore, weaning from CRRT could not easily be attempted. As such, there was a relatively small number of patients enrolled and higher rates of successful weaning from CRRT in enrolled patients, which limits the statistical power to detect a relevant biomarker of success. Finally, various biomarkers of kidney injury have not been evaluated as predictors for the successful weaning from CRRT in critically ill patients with AKI. Despite these limitations, our study has strengths; it included diverse groups of patients and has a pragmatic approach to the weaning from CRRT.

Conclusion

Our study showed that serum CysC, at the time of CRRT cessation, is an independent predictor of the successful weaning from CRRT in critically ill patients with AKI. Moreover, it is reasonable to successfully discontinue CRRT when serum CysC is lower than 1.85 mg/L, although adequate urine output is necessary before discontinuing CRRT. To our knowledge, our study is the first that directly determined the criteria in order to help guide physicians on when to discontinue CRRT for optimal success based on predictive biomarkers. Moreover, larger prospective randomized studies are needed to identify the role of various biomarkers and make predictive models, including serum CysC, with respect to successful weaning from CRRT in critically ill patients.

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Disclosure Statement

The authors of this manuscript state that they do not have any conflicts of interest and nothing to disclose.

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