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Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy

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Abstract *Objective:* The aim of this study was to identify risk factors for redialysis in postoperative patients with acute renal failure (ARF) who had previously been weaned from acute dialysis. Although recovery of renal function is anticipated in patients with ARF, no data have been reported on successful weaning from acute dialysis. *Design and setting:* Retrospective observational case-control study in a 64-bed surgical ICU. *Patients and methods:* Success in discontinuing dialysis was defined

as cessation from dialysis for at least 30 days. A total of 304 postoperative patients who underwent acute renal replacement therapy in a surgical ICU between July 2002 and April 2005 were included. SOFA score biochemical data and renal function parameters were assessed on the day after the last session of renal replacement therapy, designated as day 0 (D0). *Results:* We could wean 94 patients (30.9%) from acute dialysis for more than 5 days, and 64 of these (21.1%) were successfully weaned for at least 30 days. The independent predictors for resuming dialysis within 30 days were: (a) longer duration of dialysis (OR 1.06), (b) higher SOFA score on D0 (OR 1.44), (c) oliguria (urine output < 100cc/8 h; OR 4.17) on D1, and (d) age over 65 years (OR 6.35). The area under the ROC curve was 0.880. Two-way analysis of variance with repeated measurements over time showed a larger decline in SOFA score and an increase in urine output in patients with successful cessation of dialysis. Kaplan–Meier analysis showed a significant differ-

ence in early resumption of dialysis between patients with or without oliguria at D0. **Conclusions:** More than two-thirds of patients weaned from postoperative acute dialysis for more than 5 days were free of dialysis

for at least 30 days. Less urine output, longer duration of dialysis, age over 65 years, and higher disease severity score are predictive of a patient's redialysis after initial weaning from acute dialysis.

Keywords Acute renal failure · Renal replacement therapy · Redialysis · Sequential Organ Failure Assessment · Urine output · Dialysis duration

Introduction

Although recovery of renal function is usually expected in patients undergoing acute dialysis, data are limited regarding successful weaning from acute dialysis [1–3]. Physicians often confront the decision of continuing or withdrawing dialysis. Perioperative ischemic reperfusion injury may result in acute renal failure (ARF), from which patients can generally recover [4]. However, there remain a large number of patients whose kidneys fail to recover from ARF, and therefore long-term dialysis is required [5, 6]. Clinically many indicators of renal recovery from ARF have been proposed. For example, a nonoliguric state is usually considered an indicator of mild kidney injury and a good prognostic indicator in ARF [7] and may lead to withholding renal replacement therapy (RRT) in anticipation of recovery. Older age is a risk factor for renal failure in critically ill patients undergoing acute dialysis [3]. Shorter periods of dialysis have also been reported to predict independence from dialysis in ARF [8]. Nevertheless, the factors associated with the inability to withdraw acute RRT have not been elucidated. There is also a paucity of data on the course in patients weaned from acute RRT and subsequently relapsing and requiring RRT again.

The aim of the current study was to determine the indicators that predict the resumption of dialysis in patients with postoperative ARF who were initially weaned from acute RRT. We underscore the point that there is likely an under-appreciation of the severity of renal injury at time of cessation of dialysis and also highlight the need for more standardized criteria for withdrawing dialysis.

Patients and methods

Patients

This retrospective observational case-control study was conducted in the 64-bed surgical ICU of a tertiary hospital, where 304 patients underwent acute RRT following major surgical procedures between July 2002 and January 2005. Surgical procedures were considered major if the length of the patient's hospital stay in a given diagnosis-related group exceeded 2 days [9, 10]. Exclusion criteria were: (a) patients who resumed dialysis within 5 days (fewer than three sessions during an alternative-day protocol of

RRT) after attempting dialysis cessation ($n=42$) or not weaned at all ($n=104$), (b) patients who underwent renal transplantation ($n=5$), (c) patients who were terminally ill and had stopped dialysis because of a do-not-resuscitate order ($n=45$), (d) patients who only underwent acute RRT for less than 3 days ($n=25$), and (e) patients who resumed dialysis because of reoperation ($n=9$). A successful weaning was defined as the cessation of dialysis for at least 30 days.

The study thus included 94 postoperative patients (68 men, 26 women; mean age 58.8 ± 20.0 years) who were weaned from acute dialysis for more than 5 days and compared the patients ($n=64$) who were successfully weaned from RRT for at least 30 days to those who were not ($n=40$). The mean duration of RRT was 15.6 ± 14.7 days. Most patients (54.3%) received intermittent hemodialysis at cessation. Cardiovascular surgery was performed in 50 patients (53.2%), thoracic surgery in 5 (5.3%), neurological surgery in 4 (4.3%), and abdominal surgery in 35 (37.2%). Approval for this study was obtained from the Institutional Review Board of National Taiwan University Hospital, Taipei, Taiwan (no. 31MD03).

Clinical assessments

Disease severity was assessed using the Sequential Organ Failure Assessment (SOFA) score [11]. Day 0 (D0) was defined as the day after the last session of acute dialysis. Day 1 was the day of the last session. The SOFA score and renal function parameters [i. e., amount of urine, blood urea nitrogen (BUN), and serum creatinine (sCr)] were assessed on the day of intensive care unit admission, on the day of initial postoperative dialysis, and on D0. Older age was defined as that over 65 years [12, 13], chronic kidney disease (CKD) as sCr of 1.5 mg/dl or greater before hospital admission [14], oliguria as a urine amount less than 100 ml in 8 h [15] on D1. A daily diet of 1.0–1.2 g protein/kg was prescribed for patients. To estimate the response to diuretics we calculated the total daily dose of loop diuretic (in furosemide equivalents) divided by the total urine output in milliliters (index of diuretic responsiveness). For the calculation of diuretics and urine output 1 mg bumetanide was considered to be equivalent to 40 mg furosemide [16].

Organ failure was classified according to the following findings: respiratory failure, a partial pressure of arterial blood gas oxygen/fraction of inspired oxygen ratio ($\text{PaO}_2/\text{FIO}_2$) higher than 200; coagulopathy, platelets

less than $50 \times 10^3/\text{mm}^3$, hepatic failure, total bilirubin above 6.0 mg/dl; central nervous system dysfunction; Glasgow Coma Score greater than 9 [17]; cardiac failure, low cardiac output with a central venous pressure more than 12 mmHg, and a dopamine equivalent greater than $5 \mu\text{g}/\text{kg}$ per minute [18]. Sepsis was defined as persistence or progression of the signs and symptoms of the systemic inflammatory response syndrome with a documented or presumed persistence of infection [19].

Early redialysis, defined as relapsed need for RRT within 30 days after D0, was considered the primary outcome variable. Hospital mortality and hospital redialysis were considered as the secondary outcomes.

Interventions of acute RRT

The indications for dialysis were: (a) azotemia (BUN > 80 mg/dl and sCr > 2 mg/dl) with uremic symptoms ($n = 40$), (b) fluid overload with a central venous pressure level higher than 12 mmHg or pulmonary edema with a $\text{PaO}_2/\text{FIO}_2$ greater than 300 ($n = 32$), (c) hyperkalemia (serum $\text{K}^+ > 5.5$ mmol/l) despite medical treatment ($n = 9$), (d) oliguria (urine < 100 ml/8 h) with or without use of diuretics ($n = 31$), and (e) acidosis (pH < 7.2 in arterial blood gas; $n = 4$). There were no generally accepted criteria for terminating RRT in ARF. In our groups to fulfill the following criteria was considered mandatory criteria for patients to be weaned off dialysis: (a) serum K^+ greater than 5.5 mmol/l, (b) arterial blood gas pH higher than 7.33 or HCO_3^- above 23 mEq/l, (c) sCr less than 5 mg/dl, (d) a trend of decreasing sCr, and (e) urine output more than 100cc/8 h without the use of diuretics or more than 150 cc/8 h with diuretics and a trend of increasing urine output on the dialysis day with an evaluation by the attending physician. The diuretics group was defined as patients who received more than 20 mg loop diuretics (furosemide) daily at least 2 days before cessation of dialysis.

The dialysis modality was chosen according to the hemodynamics of patients. Continuous venovenous hemofiltration (CVVH) was used if the dose of inotropic equivalent [20, 21] of more than 15 points was required to maintain systolic blood pressure up to 120 mmHg. CVVH was performed with high-flux filters (Hemofilter, PAN-10, Asahi Kasei, Japan) using HF 400 (Infomed, Geneva, Switzerland) and a hemofiltration flow of 35 ml/kg per hour with a blood flow of 200 ml per minute. Replacement fluid was bicarbonate-buffered and was administered predilutionally at a dynamically adjusted rate to achieve the desired fluid therapy goals. Default composition was 142 mEq/l Na, 33 mEq/l bicarbonate, 1.4 mEq/l Mg, and 2.6 mEq/l Ca. Hemodialysis was performed using low-flux polysulfone hemofilters (KF-18C, Kawasumi Laboratories, Japan). Conventional intermittent hemodialysis was performed for 4 h except for the first and second sessions with a blood flow of 200 ml/min and a dialysate flow of

500 ml/min [21]. Hemodialysis adequacy assessment was measured: $\text{KT}/\text{V} = [(\text{in vitro urea clearance}) \times (\text{prescribed time})]/\text{predialysis total body water}$ [21, 22]. The urea distribution volume is roughly equal to the total body water. Vascular access was obtained by percutaneous placement of a double lumen catheter.

Statistical analysis

Continuous variables are expressed as the mean \pm standard deviation. The unpaired Student's *t*-test was used to analyze continuous data, and Fisher's exact test was used to analyze categorical data. Statistical analyses were performed with SPSS for Windows version 12.0 (SPSS, Chicago, Ill., USA). Significant risk factors determined by univariate analysis were included in the multivariate analysis by applying a multiple logistic regression analysis with a stepwise forward method to obtain the variables that were independently associated with the failed weaning. Calibration of the model was assessed by Cg, a goodness-of-fit statistic test described by Hosmer–Lemeshow [23], and discrimination capability was evaluated by determination of the area under the receiver operating characteristic curve [24]. Two-way analysis of variance with repeated measures over time was used to compare the changes between successful and failed weaning groups. The Kaplan–Meier (product-limit) method was used to estimate freedom from redialysis. A *p*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The ratio of diuretic use at the time of dialysis cessation was also the same between groups. However, failed weaning patients were older ($p = 0.004$), had a longer duration of dialysis ($p = 0.007$), higher SOFA score on D0 ($p < 0.001$), higher BUN on D0 ($p = 0.013$), and less urine output on D1 (598 ± 700 vs. 1435 ± 1172 ml/d, $p < 0.001$). They also had a higher rate of respiratory (40.0% vs. 17.2%, $p = 0.018$) and cardiac failure (50.0% vs. 28.1%, $p = 0.034$) at the start of dialysis than patients successfully weaned (Table 1, 2). In the redialysis group ($n = 30$) the indications for resumption of dialysis were azotemia ($n = 13$), oliguria ($n = 11$), fluid overload ($n = 4$), and electrolyte imbalance ($n = 2$). Eighteen (60%) patients resumed dialysis with inotropic agents. The mean duration from weaning to redialysis was 10.1 ± 6.1 days. Among these patients eight (26.7%) had sepsis before redialysis. Neither nephrotoxic agents nor radiocontrast materials were used after the initial cessation of dialysis, with the

Table 1 Demographic and clinical characteristics of postoperative acute dialysis patients who had successful or failed weaning from acute dialysis. To convert glomerular filtration rate in ml/min to ml/s multiple by 0.01667; creatinine in mg/dl to $\mu\text{mol/l}$ multiple by 88.4; BUN in mg/dl to mmol/l multiple by 0.357; qualitative variables compared using Fisher's exact test (*BMI*, body mass index; *BUN*, blood urea nitrogen; *CKD*, chronic kidney disease; *sCr*, serum creatinine; *eGFR*, estimated glomerular filtration rate; *ICU*, intensive care unit; *MAP*, mean arterial pressure; *SOFA*, Sequential Organ Failure Assessment)

	Successful (<i>n</i> = 64)	Failed (<i>n</i> = 30)	<i>p</i>
Gender male	43 (67.2%)	25 (83.3%)	0.139
Age (years)	55.6 \pm 17.1	66.2 \pm 14.4	0.004
Older age (> 65 years)	21 (32.8%)	17 (56.7%)	0.025
BMI	23.9 \pm 3.8	23.1 \pm 3.4	0.310
At Hospital admission			
BUN (mg/dl)	39.7 \pm 34.9	42.5 \pm 40.1	0.728
sCr (mg/dl)	2.4 \pm 2.3	2.1 \pm 1.2	0.463
CKD ^a	27 (42.4%)	17 (56.7%)	0.268
At dialysis initiation			
BUN (mg/dl)	58.3 \pm 37.2	75.6 \pm 45.1	0.053
sCr (mg/dl)	3.4 \pm 2.0	3.4 \pm 1.5	0.982
MAP (mmHg)	85.1 \pm 18.6	80.3 \pm 14.2	0.175
SOFA score	9.5 \pm 3.3	10.5 \pm 3.0	0.169
Comorbid disease			
Diabetes mellitus	18 (28.1%)	9 (30.0%)	1.000
Hypertension	30 (47.6%)	12 (40.1%)	0.513
Immunocompromised	6 (9.4%)	2 (6.7%)	1.000
Indication for hemodialysis			
Azotemia	29 (45.3%)	11 (36.7%)	0.505
Fluid overload	20 (31.3%)	12 (40.0%)	0.485
Severe acidosis	3 (4.7%)	1 (3.3%)	1.000
Electrolyte imbalance	5 (7.8%)	4 (13.3%)	0.460
Oliguria	22 (34.4%)	9 (30.0%)	0.815
Emergency operation	16 (25.4%)	13 (43.3%)	0.097
Surgery			0.596
Abdominal	26 (40.6%)	9 (30.0%)	
Chest	4 (6.3%)	1 (3.3%)	
Cardiovascular	31 (48.4%)	19 (63.3%)	
Neurology	3 (4.7%)	1 (3.3%)	
Organ failure at initiation of dialysis			
Central nervous system	9 (14.1%)	8 (26.7%)	0.158
Coagulopathy	4 (6.3%)	1 (3.3%)	1.000
Respiratory	11 (17.2%)	12 (40.0%)	0.018
Heart	18 (28.1%)	15 (50.0%)	0.034
Liver	10 (15.6%)	2 (6.7%)	0.326

^a Defined as sCr \geq 1.5 mg/dl before hospital admission [14]

Table 2 Clinical characteristics in patients who had successful or failed weaning from acute dialysis at the last session of acute dialysis. Day 0 (D0) was defined as the day after the last session of acute dialysis; D1 is the second day after the last session of acute dialysis. To convert creatinine in mg/dl to $\mu\text{mol/l}$ multiple by 88.4; BUN in mg/dl to mmol/l multiple by 0.357 (*BUN*, blood urine nitrogen; *FE*, furosemide dose equivalent [16]; *sCr*, serum creatinine; *SOFA*, Sequential Organ Failure Assessment; *CVVH*, continuous venous-venous hemofiltration; *IHD*, intermittent hemodialysis; *TPN*, total parenteral nutrition)

	Successful (<i>n</i> = 64)	Failed (<i>n</i> = 30)	<i>p</i>
At the time of dialysis cessation (D1)			
BUN (mg/dl)	60.5 \pm 30.9	79.5 \pm 32.1	0.013
BUN > 80 mg/dl	16 (25%)	14 (48%)	0.036
sCr (mg/dl)	3.0 \pm 1.7	3.5 \pm 1.4	0.134
SOFA score	6.7 \pm 2.6	10.2 \pm 3.9	< 0.001
Urine output (ml/d)	1435 \pm 1172	598 \pm 700	< 0.001
Oliguria ^a	51 (79.7%)	12 (40%)	< 0.001
Dialysis duration (days)	12.8 \pm 14.9	22.3 \pm 17.1	0.007
Vasopressors	41 (64.1%)	22 (73.3%)	0.482
IHD/CVVH	36/28	15/15	0.659
KT/V of IHD ^b	1.10 \pm 0.22	1.22 \pm 0.30	0.121
TPN	39 (60.9%)	18 (60%)	1.000
Ventilator	51 (79.7%)	27 (90.0%)	0.255
Diuretics	23 (35.9%)	11 (36.7%)	1.000
FE on D1 (mg/ml)	0.22 \pm 1.38	0.62 \pm 2.50	0.405
Postdialysis cessation			
Urine output on D0 (ml/d)	1893 \pm 967	928 \pm 915	< 0.001
Urine output on D1 (ml/d)	2048 \pm 849	1256 \pm 1149	< 0.001
FE on D0 (mg/ml)	0.23 \pm 1.46	0.17 \pm 0.30	0.823
Clinical outcome			
Hospital survival	51 (79.7%)	12 (40.0%)	< 0.001

^a Urine output < 100 ml/8 h; ^b Average prescribed: $\text{KT/V} = [(\text{in vitro urea clearance}) \times (\text{prescribed time})] / \text{predialysis total body water}$ [22]. The urea distribution volume is roughly equal to the total body water

exception of five patients (16.7%) who were administered vancomycin for the treatment of sepsis.

Factors related to weaning failure

The independent predictors for resuming dialysis were as follows: longer duration of dialysis ($p=0.005$), higher SOFA score on D0 ($p=0.003$), oliguria (urine $< 100\text{cc}/8\text{ h}$, $p=0.039$) on D1, and age over 65 years ($p=0.008$; Table 3). The multivariate logistic regression equation was: log odds of failed weaning from acute dialysis = $1.848 \times \text{older age} + 0.361 \times \text{SOFA score on D0} + 1.429 \times \text{oliguria on D1} + 0.056 \times \text{dialysis duration} + 4.188$. This model had a good calibration, as estimated by the Hosmer–Lemeshow goodness-of-fit ($C_g=2.657$, $p=0.954$), and good discriminative power (area under the receiver operating characteristic curve 0.880 ± 0.036 , $p < 0.0001$; Fig. 1).

The two-way analysis of variance with repeated measurements over time revealed significantly less decline in SOFA scores (group \times time interaction, $p=0.006$) and

less increase in urine output (group \times time interaction, $p=0.001$) but no significant difference in BUN (between groups, $p=0.096$) in the patients who failed weaning. There were no differences in diuretic use (25.8% vs. 41.3%, $p=0.174$) and the index of diuretic responsiveness on D1 (0.51 ± 2.0 , vs. 0.65 ± 0.12 , $p=0.088$) between oliguria and nonoliguric groups. Kaplan–Meier analysis showed a significant difference in returning to dialysis between patients with or without oliguria on D1 (log rank, $p < 0.001$; Fig. 2).

Outcome

In the redialysis group 15 patients died in hospital while on dialysis (41.1 ± 39.2 days), 12 were discharged from the hospital without dialysis (with a mean redialysis period of 20.5 ± 12.3 days), and 3 died during the same admission without dialysis. In 64 patients who were successfully weaned from dialysis for more than 30 days 13 died during the same hospital stay (60.8 ± 29.5 days from D0). Fifty-one patients survived to discharge; however,

Table 3 Relative risks and 95% confidence intervals (CI) of independent factors for resuming dialysis by a multivariate logistic regression analysis

Variable	Odds ratio	95% CI	<i>p</i> (adjusted)
Dialysis duration (per day)	1.06	1.02 1.10	0.005
SOFA (D0, per score)	1.44	1.13 1.83	0.003
Oliguria (D1, yes vs. no)	4.17	1.07 16.13	0.039
Older age (yes vs. no)	6.35	1.61 24.99	0.008

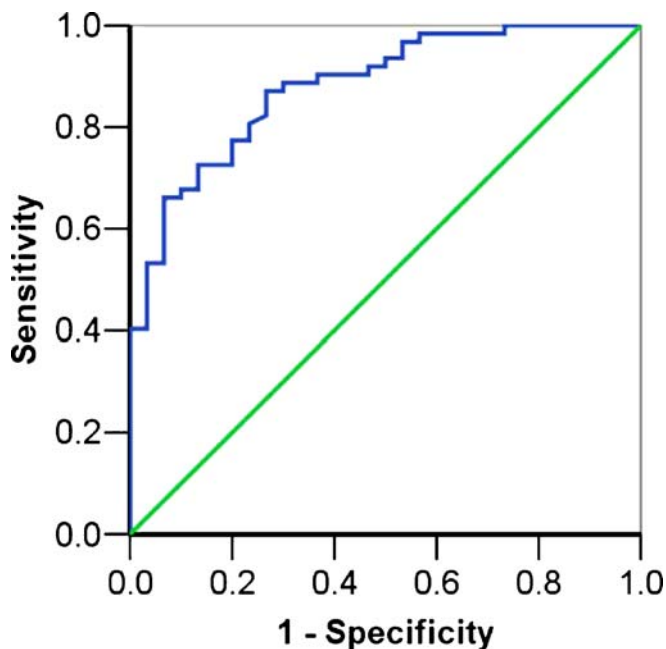


Fig. 1 Receiver operating characteristic plot of the model predicting failed cessation of dialysis. The area under the curve is 0.880 ± 0.036 ($p < 0.0001$), indicating a good capability of the model to discriminate between successful and failed weaning from dialysis

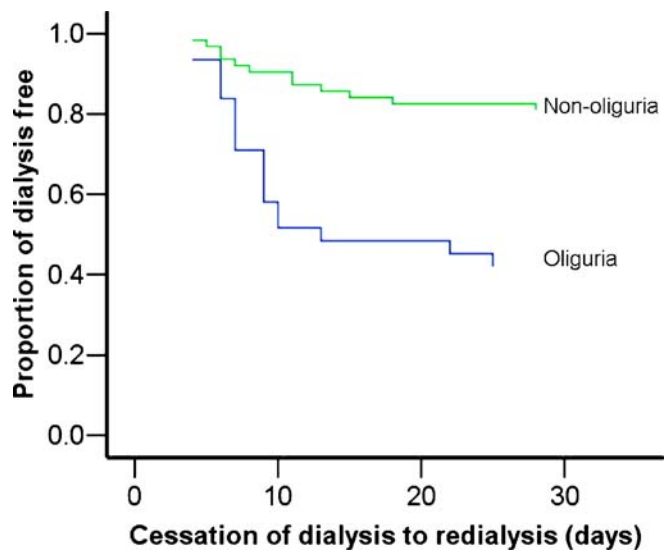


Fig. 2 Kaplan–Meier curve estimates of differences in successful weaning from postsurgical acute dialysis according to nonoliguria or oliguria on the last session of acute dialysis (day 1); $p < 0.0001$ by log-rank test

three of these patients resumed dialysis before discharge from the hospital. Successfully weaned patients had a higher rate of survival to hospital discharge than did the patients who failed weaning (79.7% vs. 40.0%, $p < 0.001$; Table 3).

Discussion

The incidence of ARF after surgery ranges from 5% to 30%, and ARF in surgical patients is associated with a mortality rate of 60–90% [25, 26]. Moreover, the survivors of postoperative ARF may develop endstage renal disease [27]. While recovery to independence from RRT occurs in approx. 38–87% at discharge from ICU [1], there have been few epidemiological studies that have specifically investigated factors predictive of renal recovery. In our study of postoperative acute dialysis more than one-third of patients resumed dialysis within 1 month after weaning for longer than 5 days.

However, the factors that underlie successful weaning from acute dialysis have not yet been defined. The reason that such factors have been elusive may be because ARF patients are often labeled as dialysis-dependent and rarely regain their renal function [28]. We identified four factors that were independently associated with dialysis weaning failure. The assessment of renal function remains rudimentary as there is no method available at present to monitor real-time glomerular filtration rate. The only practical measurement is urine output [4]. Urine output is not only a simple and early prognostic index for ARF patients requiring dialysis [7, 17, 29, 30], but oliguria is also a marker for the severity of renal and multiorgan injury [8]. Although the perioperative urine output may not be predictive of postoperative renal function [31], the patients with successful weaning from acute RRT in the current study showed a significant higher urine output on the day of dialysis cessation. Those patients successfully weaned regained normal urine output more quickly, as was also reported in a retrospective cohort study of chronic kidney disease patients who required acute hemodialysis [32]. Diuretics increase urine output; however, our results showed that the effect of furosemide on a patient's renal recovery at the time dialysis was withdrawn was equivocal [16].

Although dialysis is the mainstay of supportive care in patients with severe ARF, performance of this life-sustaining treatment can have untoward effects that contribute to the prolongation of renal failure or impede the ultimate recovery of renal function [33]. Renal biopsy in patients with prolonged ARF managed by using hemodialysis demonstrates regions of fresh tubular necrosis days-to-weeks after the initial inciting insult [34]. The association of shorter dialysis duration with improved outcomes is likely a reflection of early renal recovery

and/or improved hemodynamic stability, which facilitate the successful cessation of dialysis [8].

Age and disease severity scores have been reported as risk factors for poor prognosis in ARF [7, 17, 35]. Older patients with increasing comorbidities have been proposed as being causal [2]. Although failure of a single organ does not significantly contribute to the failed cessation of RRT, a number of dysfunctional organs do, as based on SOFA scores, thereby stressing the role of associated organ failure as an important prognostic determinant in postoperative patients with regard to both mortality and morbidity [6, 17, 30].

In the current study BUN was not an independent risk factor for resumption of dialysis; however, patients who failed weaning from dialysis had higher BUN levels than patients in the successfully weaned group on D0. A higher BUN may be associated with increased protein catabolism, a subtle sign of metabolic stress (e.g., gastrointestinal bleeding, nutritional supplementation, and corticosteroid use) [7]. Despite the greater hemodynamic stability in continuous RRT-treated patients, dialysis modality does not determine the success of weaning from postoperative acute dialysis, although a trend toward complete renal recovery is observed with continuous therapy [35–37].

The main limitation in a study such as the current one is in part due to the great heterogeneity of the patient population, in particular, the causes of ARF, the severity of kidney injuries, and the accompanying chronic comorbid factors [2]. Therefore we defined early redialysis as the primary endpoint because other than the underlying patient's characteristics, the need for resumption of dialysis is always influenced by subsequent events that can result in new insults to the kidney with a long hospital stay, especially in intensive care units. Nevertheless, there were several other important limitations to this study. First, we were limited by the frequency of measurement of some physiological and laboratory variables that may be associated with redialysis. Second, data on urine output were not appropriate. Although we recorded urine output on the day of the last dialysis, dialysis modality and ultrafiltration influences the volume status and urine output and therefore likely reduced the predictive power of our model. Third, the weaning from dialysis was not based on standardized criteria and that the experience comes from a single center, although general rules were followed. Further prospective studies should be carried out to reconcile weaning early (reducing the period of dialysis) or weaning late (permitting the urine output to increase).

In conclusion, albeit retrospective, our study is the first to address a clinically relevant question of risk factors for redialysis after initially weaning from postoperative acute RRT. Our data indicate that surgical patients with ARF may remain ill with an increased risk for resuming dialysis after temporarily being taken off acute RRT. Older age, higher SOFA scores, oliguria, and a longer dialysis-

dependent period were independent predictors of early re-dialysis in postoperative ARF patients.

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