Predictive and prognostic value of RIFLE classification on ICU Patients with acute kidney injury treated with continuous renal replacement therapy

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Abstract: Background: The optimal timing to start continuous renal replacement therapy (CRRT) for acute kidney injury (AKI) in critically ill ICU patients has not been accurately detected. The recently proposed risk, injury, failure, loss, end-stage kidney disease (RIFLE) criteria for diagnosis of AKI may provide a method for nephrologists to decide the "optimal timing" for starting dialysis. **Objective:** our study aimed: (1) to analyze the correlation between RIFLE stages at the start of CRRT and 90-day survival rate after CRRT start, (2) to further analyze the correlation of RIFLE stage with the malignant kidney outcome in the 90-day survivors, and (3) to determine the effect of the timing of CRRT on the 90-day survival and malignant kidney outcome in 90-day survivors. **Methods:** A retrospective cohort analysis was performed on the data of 96 critically ill patients in ICU, CCU, and CICU with AKI, treated with CRRT during a 1-year period in MOH hospital, makkah, Saudi Arabia from November 2011 to November 2012. Information such as age, sex, RIFLE stage, sepsis, sepsis-related organ failure assessment (SOFA) score, and number of organ failures before CRRT, CRRT time, survival, and kidney outcome conditions at 90 days after CRRT start was collected. According to their baseline severity of AKI at the start of CRRT, the patients were assigned to three groups according to the increasing severity of RIFLE stages: RIFLE-R (risk of renal dysfunction, R), RIFLE-I (injury to the kidney, I) and RIFLE-F (failure of kidney function, F) using RIFLE criteria. The malignant kidney outcome was classified as RIFLE-L (loss of kidney function, L) or RIFLE-E (end-stage kidney disease, E) using RIFLE criteria. The correlation between RIFLE stage and 90-day survival rate was analyzed among these three RIFLE-categorized groups. Additionally, the association between RIFLE stage and the malignant kidney outcome (RIFLE-L+RIFLF-E) in the 90-day survivors was analyzed. **Results:** forty eight of the overall 96 patients survived to 90 days after the start of CRRT. There were 14, 20 and 62 patients in RIFLE-R, RIFLE-I and RIFLE-F groups respectively with corresponding 90-day survival rate of 78.5 % (11/14), 60 % (12/20) and 40.3 % (25/62) (P <0.01, compared among groups). The percentage of the malignant kidney outcome of 90-day survivors in the RIFLE-R, RIFLE-I, and RIFLE-F groups was 18.18 % (2/11), 25 % (3/12) and 56 % (14/25), respectively (P <0.01). After adjustment for other baseline risk factors, the relative risk (*RR*) for the 90-day mortality significantly increased with baseline RIFLE stage. Patients in RIFLE-F had a higher *RR* of 1.96 (95% confidence interval (*CI*): 1.06–3.62) than patients in RIFLE-I (*RR*: 1.09, 95% *CI*: 0.55–2.15) compared with patients in RIFLE-R (P for trend <0.01). Similarly, baseline RIFLE stage also significantly correlated with the odds ratio (*OR*) for the malignant kidney outcome in 90-day survivors (P <0.05). Ninety-day survivors in the RIFLE-F group had a borderline significantly highest *OR* of 6.88 (95% *CI*: 0.85–55.67). **Conclusions:** The RIFLE classification may be used to predict 90-day survival after starting CRRT and the malignant kidney outcome of 90-day survivors in the critically ill patients with AKI treated with CRRT. Early versus late initiation of dialysis prior to RIFLE-F stage may be the optimal timing.

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Keywords: RIFLE stage; CRRT; acute kidney injury; prognosis.

1. Introduction

The reported incidence of acute renal failure (ARF) in the general intensive care unit (ICU) population varies from 1% to 25% (**1, 2**). Hospital mortality from ARF ranges from 43% to 88% (**1, 3**). One of the reasons for this variability might be the absence of a generally accepted biochemical definition and classification system for ARF.

The already high mortality becomes even higher in patients requiring renal replacement therapy (RRT) (**4**). The acute dialysis quality initiative (ADQI) group has suggested using acute kidney injury (AKI) as the preferred nomenclature to replace ARF with the consideration that the spectrum of AKI is broader with different degrees of severity(**5**) .The most recent proposal for a uniform definition of AKI made by ADQI group (**5**) includes criteria for three

categories of injury (risk of acute renal failure (R), injury to the kidney (I) and failure of kidney function (F) with increasing severity) and two classes of kidney outcome (loss of kidney function (L) and end-stage kidney disease (E)) (RIFLE, Table 1).

Therefore, we conducted this retrospective cohort study using originally gathered data of critically ill patients with AKI received CRRT in the intensive care units (ICU,CCU,CICU) during a 1-year period. The aims of this study were: **(1)** to analyze the correlation between RIFLE classification at the start of CRRT and 90-day survival rate after CRRT start, **2)** to further analyze the correlation of RIFLE classification with the malignant kidney outcome of the 90-day survivors, and **(3)** to determine the influence of the timing of CRRT start guided by RIFLE classification on the 90-day survival rate and the kidney outcome.

Table 1 – Proposed classification for acute kidney injury – RIFLE

RIFLE classification	GFR criterion	Urine output criterion
Risk	SCr increase x 1.5 or GFR reduced > 25%	diuresis < 0.5mL/Kg/h in 6h
Injury	SCr increase x 2 or TFG reduction > 50%	diuresis < 0.5mL/Kg/h in 12h
Failure	SCr increase x 3 or GFR reduction > 75% or SCr > 4mg/dL	diuresis < 0.3mL/Kg/h in 24h ou anuria for 12h
Loss	completely loss renal function > 4 weeks	
End-stage kidney disease	RRT needed > 3 months	

RIFLE - Risk Injury Failure Loss End; GFR - glomerular filtration rate; SCr – serum creatinine; RRT – renal replacement therapy.
Adapted from: Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Iniciative (ADQI) Group. Crit Care. 2004;8(4):R204-12.

2. Methods

Study population

All AKI patients treated with CRRT between November, 2011 and November, 2012 in ICU,CCU, and CICU of MOH hospital, makkah, Saudi Arabia were screened. AKI was diagnosed according to RIFLE criteria (**Table 1**). Patients were excluded if they were younger than 18 years, had pre-admission RRT, and were treated with CRRT for non- renal indications.

CRRT was ordered by the attending physicians (ICU and nephrology) based on the presence of AKI and hemodynamic instability or severity of illness. Different CRRT modalities (CVVH, CVVHD, OR CVVHDF) were in use during the study period. Bicarbonate-buffered solution was used with a replacement fluid amount of 20–45 ml /kg/h. The filters in use were HF 600 (Baxter, USA) with pre-dilution. Unfractionated heparin was used as an anticoagulant in the treatment modalities. The post-filter APTT was monitored every 6 hours and maintained between 40–60, or 60-80 seconds by regulating the dosage of unfractional heparin.

SOFA score	0	1	2	3	4
Respiration PaO_2/FIO_2	>400	≤400	≤300	≤200	≤100
Coagulation Platelets $10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Liver Bilirubin (mg/dL)	<1.2	1.2-1.9	2-5.9	6-11.9	>12
Cardiovascular Hypotension	No hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2-1.9	2-3.4	3.5–4.9 or <500	>5.0 or <200

Data collection

All the data were collected at ICU entry during treatment and recorded on specially designed case report forms in a standardized manner. The case report forms included patients′ laboratory data, orders, CRRT registry forms, nursing notes, and the ICU flow sheets. When reviewing a patient′s file, we looked at previous health status, organ function at the start of CRRT, and the relevant physiological and pharmacological data needed for the RIFLE classification. The indications for CRRT were documented and specific data regarding the CRRT

including CRRT time in the ICU was recorded in detail. The case report forms also contained the following information: gender, age, pre-existing diseases(DM,hypertension), main diagnosis including sepsis, baseline pre-admission serum blood urea nitrogen and serum creatinine (Cr), urine output, sepsis-related organ failure assessment, (SOFA) score (**10**) , number of organ failures at the start of CRRT. Moreover, we gathered information on the causes of death for the patients who died within 90 days of CRRT start and the kidney outcome of 90-day survivors after CRRT starts.

Organ function failure was defined when the SOFA score of an organ was equivalent to or greater than 3 points according to SOFA criteria (**10).**

Patients were divided to three groups **I**, **II**, and **III** according to RIFLE stage at the start of dialysis (RIFLE-R, RIFLE-I and RIFLE-F).

Group assignment was decided by glomerular filtration rate (GFR) or serum Cr at the start of CRRT (**Table 1**).

In the RIFLE system, RIFLE-L (loss of renal function) and RIFLE-E (end-stage renal disease) are two categories of kidney outcome for AKI patients (**Table 1**).

In this study RIFLE-L and RIFLE-E were defined as the malignant kidney outcome. The proportion of the malignant kidney outcome (RIFLE-L + RIFLE-E) in 90-day survivors was determined among the three RIFLE categorized groups.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as number and percent. A $\chi 2$ test was used to analyze categorical variables; analysis of variance (ANOVA) and F test were used to analyze continuous variables. The 90-day cumulative survival was calculated according to the Kaplan-Meier method. The Log-rank test was used to compare the 90-day survival rate among the three RIFLE-categorized groups (**Figure**). The correlation of baseline RIFLE classification with the 90-day survival was analyzed using Cox regressions after adjustment for baseline age, sex, sepsis, SOFA score, and number of organ failures (Table 3). In addition, the incidence of malignant kidney outcome of 90-day survivors among RIFLE-categorized groups was compared using $\chi 2$ test with linear trend test. Adjusted odds ratio (*OR*) of the malignant kidney outcome was calculated by logistic regression with adjustment for baseline age, sex, sepsis, SOFA score, and number of organ failure (**Table 4**). All analyses were performed using the SPSS 11.5 package (SPSS for Windows, version 19, SPSS Inc, Chicago, USA). *P* values less than 0.05 were considered statistically significant.

3. Results

Demographics and medical characteristics

The present study included 96 critically ill patients with AKI, treated with CRRT, started at different RIFLE stages, 33% were females, 67%males. The average age of all patients was (57.0±13.4) years.95% of all patients had SOFA score ≥6.75% required mechanical ventilation.50% required inotropic support.

Table 2 presents the clinical features of the overall study population according to RIFLE classification. At the start of CRRT, 14, 20, and 62 patients met the criteria for RIFLE-R, RIFLE-I, and RIFLE-F respectively. All those 34 patients at RIFLE-R or RIFLE-I stage were complicated with sepsis, hemodynamic instability, or multiple organ dysfunction syndrome (MODS).

Table (2) characteristics of patients according to RIFLE stage

	All patients N =96	Group I RIFLE-R,N =14	Group II RIFLE-I,N= 20	Group III RIFLE-F,N= 62	*P* value
Age(years)					
<65	68%	88%	64%	65%	NS
≥65	32%	12%	36%	35%	
SEX					
FEMALE	33%	69%	27%	26%	<0.01
MALES	67%	31%	73	74%	
SEPSIS					0.05
YES	50%	31%	36%	59%	
NO	50%	69%	64%	41%	
SOFA score					NS
<6	5%	0%	0%	7%	
6-11	60%	75%	64%	54%	
≥12	35%	25%	36%	39%	
NO of organ failure					NS
0-1	28	19	27	31	
≥2	72	81	73	69	
CRRT time (hours)	53±26	43±19	51±21	55±28	NS

CRRT was ordered for them to eliminate inflammatory mediators and cytokines in the body so as to protect the vital organ function,. The other 62 patients at RIFLE-F stage at the start of CRRT had conventional indications dialysis, such as high BUN, high serum creatinine, or pulmonary edema

By 90 days after the start of CRRT, all-cause mortality was 48/96 (50.0%). The causes of death within 90 days were multiple organ dysfunctions, cardiovascular events
, stroke, and unidentified causes.

The 90-day survival rates for RIFLE-R, RIFLE-I, and RIFLE-F group were 78.5% (11/14), 60% (12/20) and 40.3% (25/62). When the Kaplan-Meier plot was stratified according to RIFLE classification (Figure), the differences among the survival curve of the three groups were significant (*P* <0.01). Further multivariate analysis was performed after the adjustment of other baseline risk factors including sex, age, sepsis, SOFA score, and the number of organ failures. This analysis revealed that the relative risk (*RR*) for the 90-day mortality significantly increased with the increment of baseline RIFLE stage (*P* for trend <0.01, Table 3). When compared with patients in RIFLE-R, patients in RIFLE-F had the higher *RR* of 1.96 (95% confidence interval (*CI*) 1.06–3.62), but not in RIFLE-I (*RR*: 1.09, 95% *CI*: 0.55–2.15).

Table (3) RR for 90 days mortality among all groups:

RIFLE	Case (n)	Percent (%)	RR (95% CI)	RR* (95% CI)
GROUP I (RIFLE –R)	14	21.5%	1.00	1.00
GROUP II (RIFLE –I)	20	40%	1.09	1.09
GROUP III (RIFLE –F)	62	59.7%	1.65	1.96
P for trend		0.004	0.034	0.008

*Adjusted for age (≥ 65 years vs. <65 years), sex (male vs. female), SOFA score, sepsis (yes vs. no) and number of organ failure (≥2 vs. 0–1).

18 of the 48, 90-day survivors had malignant kidney outcome (RIFLE-L or RIFLE-E). In the 90-day survivors, the percentages of the malignant kidney outcome in the RIFLE-R, RIFLE-I, and RIFLE-F groups were 18.18% (2/11), 25% (3/12), and 56% (14/25). The percentage of malignant kidney outcome significantly increased with the increment of the severity of RIFLE stage (*P* for trend <0.01, **Table 4**). After the adjustment for other baseline risk factors including sex, age, sepsis, SOFA score, number of organ failure, multivariable-adjusted logistic regression showed that the 90-day survivors in RIFLE-F group had a borderline significantly higher OR of 6.88 (95% CI: 0.85–55.67) compared with in those in RIFLE-R (**Table 4).** The baseline RIFLE severity had a significant correlation with the increased OR for the malignant kidney outcome (*P* for trend <0.05).

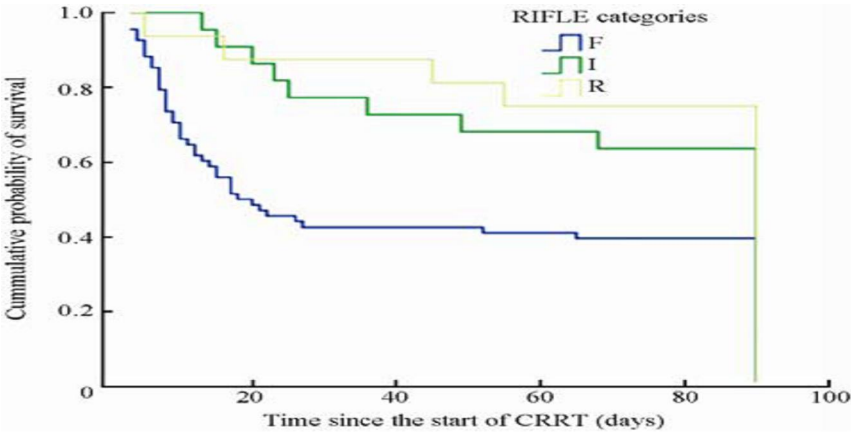

Figure. 90-day survival rate according to the baseline RIFLE classification. *P* <0.01 compared among the three groups.0

Table (4) OR for malignant kidney outcome in 90 day survival patients in different groups

RIFLE	Case (n)	Percent (%)	OR (95% CI)	OR† (95% CI)
GROUP I (RIFLE –R)	11	18.18%	1.00	1.00
GROUP II (RIFLE –I)	12	25%	1.36	0.88
GROUP III (RIFLE –F)	25	56%	6.25	6.87
P for trend		0.011	0.015	0.021

†Adjusted for age (≥ 65 years vs. <65 years), sex (male vs. female), SOFA score, sepsis (yes vs. no) and number of organ failure (≥2 vs. 0–1).

4.Discussion

Indication and timing for RRT varies in different countries and institutions. Conventionally, RRT was not administered until patients met dialytic criteria of serum blood urea nitrogen ≥80 mg/dl (34.1 mmol/L) or Cr ≥6 mg/dl (530.4 μmol/L) or other indications.

In our study, critically ill patients with AKI were treated with CRRT in different RIFLE stages, all of the 62 cases in the RIFLE-F group met traditional indications for dialysis, but most of the cases of RIFLE-R or RIFLE-I did not have traditional indications for dialysis. Our primary purpose to give CRRT to patients who did not have traditional dialytic indications was to eliminate inflammatory mediators and cytokines in the patient′s body so as to reduce the inflammatory organic insult which in turn was to decrease the mortality.

It has been documented that AKI patients in need for RRT in the critical-care setting have a particularly poor prognosis (**11**, **12**). Some studies showed that "early CRRT" could improve prognosis of AKI (**13-15**).

In most studies, "early CRRT" was started at an arbitrary biochemical cut-off point. The lack of a uniform definition of "early CRRT" impaired the objective evaluation of different treatment regimens. Since the RIFLE criteria are fairly straight forward and practical to give a clear AKI classification with different severity, we hypothesized that RIFLE classification could help clinicians identify the optimal timing of RRT for critically ill patients with AKI.

To test this hypothesis, we first analyzed the correlation between RIFLE stage at the start of CRRT and 90-day survival rate after CRRT start, and then investigated the influence of timing of the start of CRRT on the kidney outcome of 90-day survivals.

Most of the studies on RIFLE criteria confirmed the correlation between RIFLE classification and prognosis (**16-19). Ostermann *et al.* (6)** performed a multi-center, retrospective study including 41 972 patients admitted to 22 ICUs. Of the 15 019 patients (35.8%) met the RIFLE criteria, 7207 (17.2%), 4613 (11%), and 3199 (7.6%)were assigned to the risk, injury, and failure group respectively with corresponding hospital mortality of 20.9%, 45.6%, and 56.8% while the hospital mortality of patients without AKI was 8.4%.

Uchino *et al.* (20) have also reported similar results. These suggest that RIFLE criteria are suitable for the definition and classification of AKI in intensive care units. The classification reflecting the severity of AKI can facilitate clinical research by allowing the comparison of data of different studies carried out by various institutions.

Only two published studies discussed the clinical significance of RIFLE classification for the special population of AKI patients in need for RRT **(7, 8).** RIFLE stage was an exclusive independent risk factor correlating to mortality **(7)**. In the other study, however, older age, number of organ dysfunctions, the presence of co morbidities, and reduced functional capacity were the main prognostic factors, but the RIFLE stage did not discriminate the prognosis **(8)**. However, there is no uniform standard to decide the optimal timing of starting RRT for AKI patients in clinic (**9**).Our present study shows RIFLE stage at the start of CRRT correlates with 90-day mortality.

The significant correlations of the RIFLE stage with the 90-day survival rate and the malignant kidney outcome in the survivors suggest starting CRRT prior to RIFLE-F
stage may be optimal for critically ill patients with AKI.

These also support the rationale that early CRRT can eliminate a significant amount of inflammatory mediators and cytokines which in turn restrains the cascade of inflammatory reaction and ultimately plays a protective role on kidney and other vital organs (**21, 22).**

In conclusion, the RIFLE stage may be used to predict 90-day survival rate and the malignant kidney outcome in the critically ill patients with AKI treated with CRRT.

Starting CRRT prior to RIFLE-F stage may be the optimal timing. Prospective, multi-center, randomized controlled trials are crucial to confirm its predictive value of RIFLE stage.

References

1. De Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, *et al.* Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000; 26: 915-921.
2. Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units -causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on Acute Renal Failure. Crit Care Med 1996; 24: 192-198.
3. Spiegel DM, Ullian ME, Zerbe GO, Berl T. Determinants of survival and recovery in acute renal failure patients dialyzed in intensive-care units. Am J Nephrol 1991; 11: 44 47.
4. Jochimsen F, Schafer JH, Maurer A, Distler A. Impairment of renal function in medical intensive care: predictability of acute renal failure. Crit Care Med 1990; 18: 480-485.
5. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure — definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: R204-R212.
6. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007; 35: 1837-1843.
7. Max B, Eva L, Fredrik G, Jessica F, Anders E, Claes-Roland M. Optimal follow-up time after continuous renal replacement therapy in actual renal failure patients stratified with the RIFLE criteria. Nephrol Dial Transplant 2005; 20: 354-360.
8. Maccarilello E, Soares M, Valente C, Nogueira L, Valenca R, Machado JES, *et al.* RIFLE classification in patients with acute kidney injury in need of renal replacement therapy. Intensive Care Med 2007; 33: 597-605.
9. Overberger P, Pesacreta M, Palevsky PM. Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. Clin J Am Soc Nephrol 2007; 2: 623-630.
10. Vencent JL, Moreno R, Takala J, Willatts S, De Mendonca A. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22: 707-710.
11. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002; 39: 2 Suppl 1: s76-s92.
12. Douma CE, Redekop WK, van der Meulen JH, Van Olden RW, Haeck J, Struijk DG, *et al.* Predicting mortality in intensive care patients with acute renal failure treated with dialysis. J Am Soc Nephrol 1997; 8: 111-117.
13. Demirkilic U, Kuralay E, Yenicesu M, Caglar K, Oz BS, Cingoz F, *et al.* Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg 2004; 19: 17-20.
14. Piccinni P, Dan M, Barbacini S, Carraro R, Lieta E, Marafon S, *et al.* Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 2006; 32: 80-86.
15. Elahi MM, Lim MY, Joseph RN, Dhannapuneni RR, Spvt TJ. Early hemofiltration improves survival in post-cardiotomy patients with acute renal failure. J Card Surg 2004; 19: 17-20.
16. Hoste EJA, Clermont G, Kersten A, Verkataraman R, Angus DC, Bacquer DD, *et al.* RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10: R73.
17. Lin CY, Chen YC, Tsai FC, Tian YC, Jeng CC, Fang JT, *et al.* RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation. Nephrol Dial Transplant 2006; 21: 2867-2873.
18. Jeng CC, Tsai MH, Tian YC, Lin CY, Yang C, Liu NJ, *et al.* RIFLE classification can predict short-term prognosis in critically ill cirrhotic patients. Intensive Care Med 2007; 33: 1232-1238.
19. Lopes JA, Jorge S, Resina C, Santos C, Pereira A, Neves J, *et al.* Acute renal failure in patients with sepsis. Crit Care Med 2007; 11: 411-412.
20. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006; 34: 1913-1917.
21. Bellomo R, Ronco C. Blood purification in the intensive care unit: evolving concepts. World J Surg 2001; 25: 677-683.
22. Xie HL, Ji DX, Gong DH, Liu Y, Xu B, Zhou H, *et al.* Continuous veno venous hemofiltration in treatment of acute necrotizing pancreatitis. Chin Med J 2003; 116: 549-553.