Late initiation of CVVH therapy is associated with a lower survival rate in surgical critically ill patients with postoperative acute kidney injury.

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***Running title*: CVVH in surgical critically ill patients.**

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Abstract

Purpose

There was controversy about the appropriate timing for renal replacement therapy (RRT) in patients with acute kidney injury (AKI). We were interested in the appropriate timing for initiation of continuous RRT in surgical critically ill patients with postoperative acute kidney injury.

Patients and methods: Seventy-three surgical critically ill patients with postoperative AKI and received CRRT were enrolled. Indications for CRRT were (1) AKI with hyperkalemia (2) metabolic acidosis (3) pulmonary edema refractory to diuretics (4) oligouria with progressive azotemia; especially in unstable hemodynamics.

Using RIFLE classification, patients received CRRT in the "Risk" stage were defined as early group, whereas those in the "Injury/ Failure" stage were labeled as late group. We use CVVH as CRRT in this series.

Result: There were 20 patients in the early group and 53 patients in the late group. The mean ages were 61.5 ± 21.8 years versus 60.8 ± 17.5 years. The mortality rate was 50% versus 84.9 %. There were no significant differences in demographic characteristics or type of surgery or physiological scores.

Conclusions: Our data show that late initiation of CRRT is associated with a lower survival rate in surgical critically ill patients with postoperative AKI; however, further studies are required.

Key words: surgical critically ill, CVVH, Acute kidney injury

Introduction

Acute kidney injury (AKI) is often-encountered in critically ill patients and may occur in up to 30% of such patients[1, 2]. It is also an independent risk factor for mortality in critically ill patients [3-5]. In addition, the development of postoperative AKI is common in severely burned patients [6-7], and there is a higher risk of developing AKI among critically ill patients who have undergone major surgeries [8]. The use of renal replacement therapy (RRT) is thought to support renal function, maintain solute clearance and fluid balance, and allow for the recovery of renal function [9-10] . AKI remains a major cause of mortality and morbidity in surgically critically ill patients despite the progress and application of RRT [11]. In addition to the conventional classification criteria for kidney injury, the RIFLE (Risk, Injury, Failure, Loss, End stage) criteria have been suggested and used in the ICU setting to stratify and identify patients with AKI who may be in need of RRT [12-13]. As a result, the use of RIFLE criteria for categorizing early kidney injury has been adopted and evolved to the AKIN (Acute Kidney Injury Network) staging system[14-19].

Recently, continuous renal replacement therapy (CRRT) has been the preferred mode of RRT for AKI in intensive care units through much of the developed countries [1, 20, 26]. There were discussions of timing; dose or intensity; and modalities of CRRT in the management of critically ill patients [21, 30]. Yet, there were observational studies shows that late initiation of RRT is associated with an increased risk of mortality and morbidity [23-25]. However, to what extent these results are related to the timing of the initiation remain undetermined [26]. Therefore, in the current series, we are interested in the appropriate timing for the initiation of RRT in non-traumatic surgical critically ill patients; we use RIFLE criteria for stratification in our retrospective study.

Materials and methods

This investigation is a retrospective study and review of the medical records of consecutive surgical critically ill patients receiving CRRT in our intensive care unit from January 2008 to March 2010. Patients with previous end stage renal disease (ESRD) or chronic renal failure (CRF) were excluded from this study; surgical critically ill patients who did not receive operative procedures were also excluded (e.g., severe acute pancreatitis, non-operative trauma).

Patients were admitted from emergent department and received standard operating procedures. e.g.: early goal direct therapy (EDGT) resuscitation and adequate management of shock status, appropriate ventilator support, tight blood sugar control, precaution and prevention of ventilator associated pneumonia.

There was no definitive cutoff point for the timing of initiation of CRRT among our intensivists and nephrologists during this study period. However, patients received CRRT based on the following indications after the consultation of nephrologists in our hospital: (1) acute renal failure with hyperkalemia (serum K $\geqq$ 6.0 meq/L), (2) metabolic acidosis (serum HCO_3^- $\leqq$ 12 meq/L), (3) pulmonary edema refractory to diuretics, or (4) oligouria with progressive azotemia, especially in patients with unstable hemodynamics.

Because there were not evident indications for initiation of CRRT, attending physicians make their own judgments with complex thought processes individually under each various situation.

In the current series, we use continuous veno-venous hemofiltration (CVVH) in our CRRT instead of intermittent hemodialysis (IHD). All CVVHs were performed with blood flow rates ranging from 100 ml/min to 150 ml/min, pre-dilution methods, initial doses of about 20 ml/kg/h of bicarbonate buffered replacement fluid that was subsequently increased to about 35 ml/kg/h, and a dialysis membrane composed of

polyethersulfone (DF-080, HF 400, Informed SA, Geneva, Switzerland).

Criteria for determining the timing for the discontinuation of CRRT therapy include the following: (1) recovery to normal laboratory renal function (BUN, serum creatinine) or normal urine output, (2) stable hemodynamics without inotropics, allowing for a shift to intermittent hemodialysis or regular hemodialysis, and (3) deterioration of condition and mortality.

Retrospectively, we reviewed chart records using RIFLE classification (GFR criteria and urine output criteria) for re-stratification of stage in our patients who received CRRTs [12-13]; we defined the start of CRRT in the "Risk" stage (RIFLE-R) as early initiation, whereas as the start of CRRT in the "Injury" or "Failure" stage (RIFLE-IF) was defined as late initiation. The application of CRRT can be available within 2 hours at our institution.

The demographic data, comorbidities, indication and type of surgery, blood urea nitrogen (BUN), serum creatinine (sCr), admission hemodynamics and coagulation status, lactate, base deficit, total length of stay, and RIFLE stage were collected for analysis.

Evaluations of preoperative and operative status of severity were with physiological severity scores which include: Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score. In addition, we also use the physiological and operative severity scores for the enumeration of mortality and morbidity (POSSUM) scoring system, the POSSUM includes physiological score (P-POSSUM) and operative severity score (O-POSSUM)

Chronic kidney disease was defined as a serum creatinine of 1.5 mg/dl or greater documented prior to this episode, and these patients were excluded.

Patients with episodes of PaO_2 / FiO_2 less than 300 were considered to have acute lung injury, whereas patients with values less than 200 were considered to have

episodes of acute respiratory distress syndrome (ARDS) [27].

Statistical analysis

The Mann-Whitney U test was performed for continuous variables. The chi-square test or Fisher exact test was used for categorical comparison of the data. Survival analysis was evaluated with the Kaplan-Meier method and the log rank test. The Cox proportional hazards model was used to study the prognostic impact of the different variables on survival. All reported p values were based on two-sided tests with statistical significance at 0.05. Analysis was performed on a personal computer with the SPSS statistical software package, version 15.0 (SPSS, Inc., Chicago, Illinois).

Results

From January 2008 to March 2010, there were 123 consecutive surgical critically ill patients receiving continuous renal replacement therapy in our intensive care unit. Twenty-eight patients with previous ESRD or CRF were excluded, and another 12 nonoperative surgical critically patients (e.g.: nonoperative trauma, severe acute pancreatitis.) were also excluded.

Therefore, a total 73 surgical critically ill patients who received postoperative CRRT were enrolled in the current study; all these patients were vasopressor dependent at the initiation of CRRT (Fig.1).

According to the re-stratification of the patients with RIFLE criteria (Table 1), there were 20 patients who received CVVH in the “Risk” (RIFLE-R) stage due to oliguria, refractory to diuretics who were labeled as the early group; another 53 patients received CVVH in the “Injury/ Failure” stage (RIFLE-IF) due to anuria refractory to diuretics; or clinical presentation of metabolic acidosis, hyperkalemia,

fluid overload or azotemia were labeled as the late group.

Average ages of patients were 61.5 ± 21.8 years in the early group and 60.8 ± 17.5 years in the late group. The overall mortality rate in these patients was 75.3% (55/73). The overall mortality rate was 50% (10/20) in the early group and 84.9 % (45/53) in the late group. The causes of mortality were septic shock with MOF (8 in early group and 36 in late group), the other 5 patients in the late group were liver cirrhosis with hepatorenal failure". There were another six patients (2 in early group and 4 in late group) survived 30 days and died in home care within 90 days. The average duration of use of CRRT was 3.1 ± 2.1 days in the early group and 4.1 ± 3.1 days in the late group.

The type and indications for surgery are listed and for comparison; there were no differences or inequality in the distributions of type of surgeries (Table 2).

There were no significant differences in any demographic characteristics or physiological scores between the early and late groups, there were higher serum BUN and creatinine levels at the time of initiation of CRRT in the late groups (Table 3)

There were no significances between the early and late groups in comparisons of preexisting comorbidity, shock, or coagulation status during admission. Yet, there were significantly higher 30- and 90-day mortality rates in the late group. (Table 4)

When logistic regression analysis was used for comparison of 30-day survivors and non-survivors, there were no significant differences in age, gender, preoperative preexisting diseases, APACHE II scores, SOFA scores, POSSUM scores or CRRT duration; however, early initiation of CRRT was associated with a significantly higher (5.125) odds ratio. (Table 5)

There were no significant differences in 90-day mortality rates when comparing demographics and other variables, except that late initiation of CRRT was associated with a significantly higher (2.389) hazard ratio. (Table 5)

On comparison of APACHE and POSSUM scores, there were no significant differences between these two physiological status evaluation tools (Table 3).

The members of the early group had a higher 90-day and cumulative survival rate. (Fig. 2)

In the current series, there was at least one observed episode of acute lung injury (e.g., image evidence of bilateral pulmonary infiltrates or a P/F ratio <300) in every patient in the early and late groups during their ICU courses. (Data not shown).

Discussion

AKI is a condition that is often encountered in critically ill patients [1, 2], especially in those receiving anesthesia and surgeries. It is not uncommon that critically ill patients receiving emergent surgeries frequently have post- operative kidney injuries and multiple organ failure [3-7]. Despite recent progress in the care of the critically ill, AKI still occurs in up to 30% of critically ill patients, remains one of the most complicated clinical problems in modern ICU [1-2] and is associated with increased morbidity and mortality [28-29].

The concept of renal replacement therapy (RRT) in AKI has been introduced for more than 50 years [30-31]. There were modalities of RRT that include intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). Since CRRT achieve solute clearance and fluid balance gradually and were thought to be less likely to cause abrupt changes in plasma biochemistry and permit better control of fluid balance [20]. It is considered that CRRT might be a crucial form of RRT for AKI in most ICUs; especially in vasopressor dependent patients[1, 26].

The general indications for CRRT include severe azotemia, oliguria, hyperkalemia, severe metabolic acidosis and fluid overload. However, because there was no definitive cutoff point for acute kidney injury, there might be marked

and progressive cell level damage of the kidney when these conditions are encountered [32-33]. In order to initiate CRRT more appropriate and adequate, the judgment for starting CRRT might be, at least in part, base on a more complex thought process and intangibles, which was also encountered in each judgment for initiation of CRRT in our institution. Therefore, searching for a more practical measure for early detection of AKI is essential. Recently, the RIFLE criteria have been widely adopted and used in ICU settings to stratify and identify patients with AKI and the need for CRRT [12-19].

Because there was vague distinctive point for AKI [9], there have been questions about the differences in severity between the "early" and "late" groups, and there have been concerns that such unequal severities might hamper the interpretation of the final results [22, 24].

We deemed that the start of CRRT in the "Risk" stage was considered early initiation (RIFLE-R), whereas initiation in the "Injury" or "Failure" stage (RIFLE-IF) was considered late initiation. In the current series, there were higher 30 and 90 day survival rates in the early group than in the late group (Table 4), this is in agreement with others that early and aggressive application of CRRT may be beneficial in critically ill population who develop AKI [5, 9, 24, 34].

One probable explanation for the higher survival rate in the early group might be that early CRRT may eliminate fluid overload early in the critically ill. In the current series, at least one episode of acute lung injury (PaO_2 / FiO_2 less than 300) was noted in every patient in both groups during their early admissions, indicating that there might be lung insults resulting from AKI-induced volume overload. Furthermore, the overall mortality rate in these patients was 75.3% (55/73) in our series. This is similar to others series[35]. Concerning the fact that volume overload induced increases in hydrostatic pressure may result in acute lung injury and organ

dysfunction. Therefore, early removal of the overloaded volume might avoid progressive kidney failure and remote organ function deterioration [32]. However, this might not be extrapolated robustly to other causes of acute lung injuries.

As for the dose or intensity of CRRT, two large multicenter RCT trials [21, 28] have shown that a dose increased to 25ml/kg/hr is not beneficial. In the current series, we started from 20 ml/kg/hr initially and increased to 35 ml/kg/hr according to previous suggestion[36].

It has been proposed that early treatment of CRRT may lead to inclusion of patients whose renal function might subsequently improve with fair outcome irrespective of treatment[20]. Such predisposition may lead to inadequate conclusion because of unequal disparity between sorting early and late groups. In addition, because there was multiple-factorial concern and complicated organ interactions as well as dynamic changes associated with physiologic homeostasis and alterations in critically ill patients. It is difficult to clearly identify a single accountable related factor or elucidate the exact relationships between organs.

Therefore, we use the physiological and operative severity scores for the enumeration of mortality and morbidity (POSSUM) scoring system for evaluating physiological status. The POSSUM includes evaluation of physiological severity, operative severities, operational procedures, total blood loss, degree and extent of peritoneal soiling, mode of surgery… etc; which is thought to be reliable for evaluation of patients and operative severity and for surgical audit [37-38]. Therefore, we use these scores; as well as conventional APACHEII and SOFA scores for incorporated evaluations of the preoperative and postoperative conditions of our surgical patients.

There were no statistical differences in these scoring systems or other variables between two groups (Table 4). Therefore, it is assumed that there might

be equivalent physiological and operational severities/morbidities (Table 2, 4). On the other hand, it has been suggested that there were no CRRT related variables (mode, filter material, drug for anticoagulation and prescribed dose) that predicted hospital mortality [39]. Given that these surgical critically ill patients received equivalent intensive care services in our institution; and an 84.9 % mortality rate in the late group, it seems that the timing of initiation of CRRT played an important role in the subsequent mortalities.

There were higher serum BUN and creatinine level in the late group; this can be expected as this is what has already defined the group. Yet, there were reports that increased serum creatinine level before RRT is associated with improved survival[40]; possibily because that higher serum creatinine level are associated with greater muscle mass and better premorbid condition[41]. Because that male were thought to be with higher underlying muscle mass, this condition might impact and bias AKI stratification. In the current series, there was no difference in the distribution of gender among early and late groups (Table 4), indicating that higher serum creatinine level might be the anticipated consequence of grouping.

Despite the more frequent use and the physiologic advantages of CRRT, there still were disagreements among studies. Vinsonneau et al showed that there is no survival advantage to CRRT over intermittent hemodialysis[42]. Furthermore, it has been reported that AKI related mortality was decreased by intermittent H/D and that surgical critically ill patients who need RRT should be considered preferentially for H/D[11]. There have also been studies that failed to demonstrate evidence of a survival advantage for patients who receive CRRT [43-44]. Though there were still divergences, it is suggested that CRRT be considered appropriate for vasopressor-dependent AKI in intensive care unit[1].

There were complications associated with CRRT [39] (e.g: hypotension,

bleeding and arrhythmias). There have also been concerns about catheter related sepsis, prolonged anticoagulation status and removal of nutrients and electrolytes [45], as well as risks for requiring permanent dialysis [46] and limitation for early mobilization, suggesting that adequate application and careful consideration are required for CRRT initiation.

Limitations of this study

We recognize the limitations of this study, including its retrospective nature, small sample size and the probable bias in case selection, which may restrict our analytical conclusions. In addition, only RIFLE classifications were retrospectively used in this study, and it is apparent that further data are needed to postulate our classification and the initiation of CRRT in "R-risk" stage as early and in the "I/F" stage as late. Another limitation was the lack of data for detailed clinical parameters for this study in which the physiological statuses of the patients were evaluated with scores. Furthermore, there were shortcomings for this current observational study to deduce that early initiation of CRRT is beneficial in these surgical critical ill patients by its retrospective nature. i.e.: early treatment may include patients that renal function might improve subsequently and were thought to be with fair outcome irrespective of treatment [26]. Such bias may lead to an inadequate conclusion. Therefore, our results might not be suitable to be robustly extrapolated to patients with AKI elsewhere. Further multi-center randomized studies are warranted with predefined enrollment criteria for a better understanding of this issue.

Summary

We present our experiences from a single center in the management of surgical critically ill patients who developed acute kidney injuries after surgery; we found that late application of CRRT for postoperative acute kidney injuries was associated with a lower survival rate.

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Legends

Fig. 1 Surgical critical ill patients receiving CRRT

Fig. 2 The comparison of Cumulative survival between early and late CRRT group.

Table 1: RIFLE classification

Table 2: Indications for operation

Table 3: Comparison of laboratory data and clinical scores.

Table 4: Comparison of demographics and preexisting diseases.

Table 5: Regression analysis results for survival and mortality

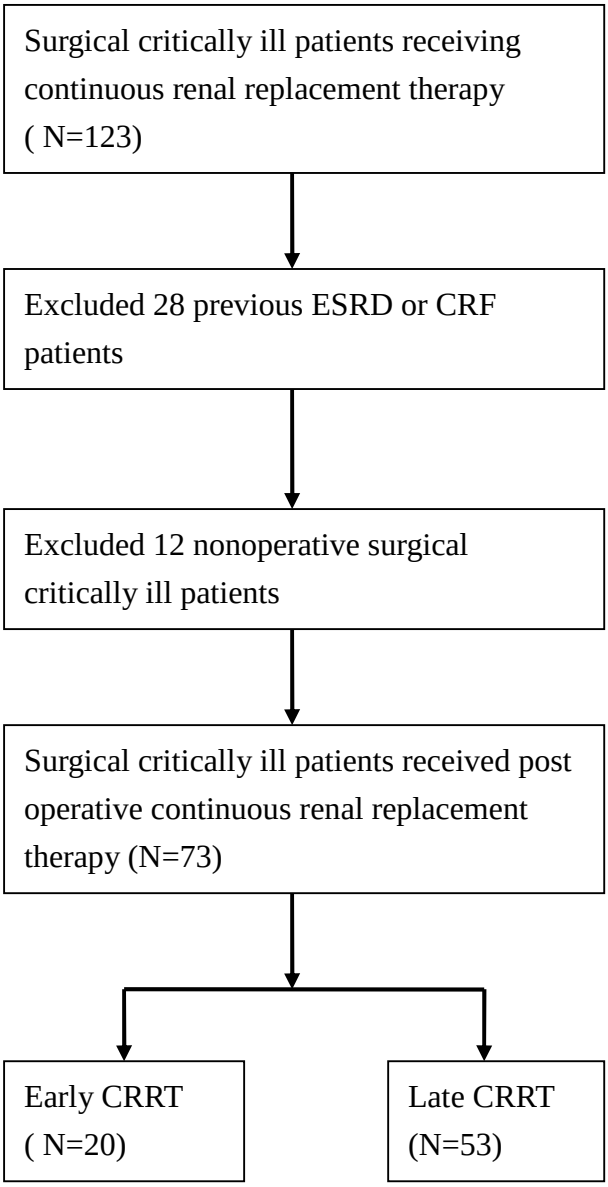

Fig. 1. Surgical critically ill patients receiving CRRT

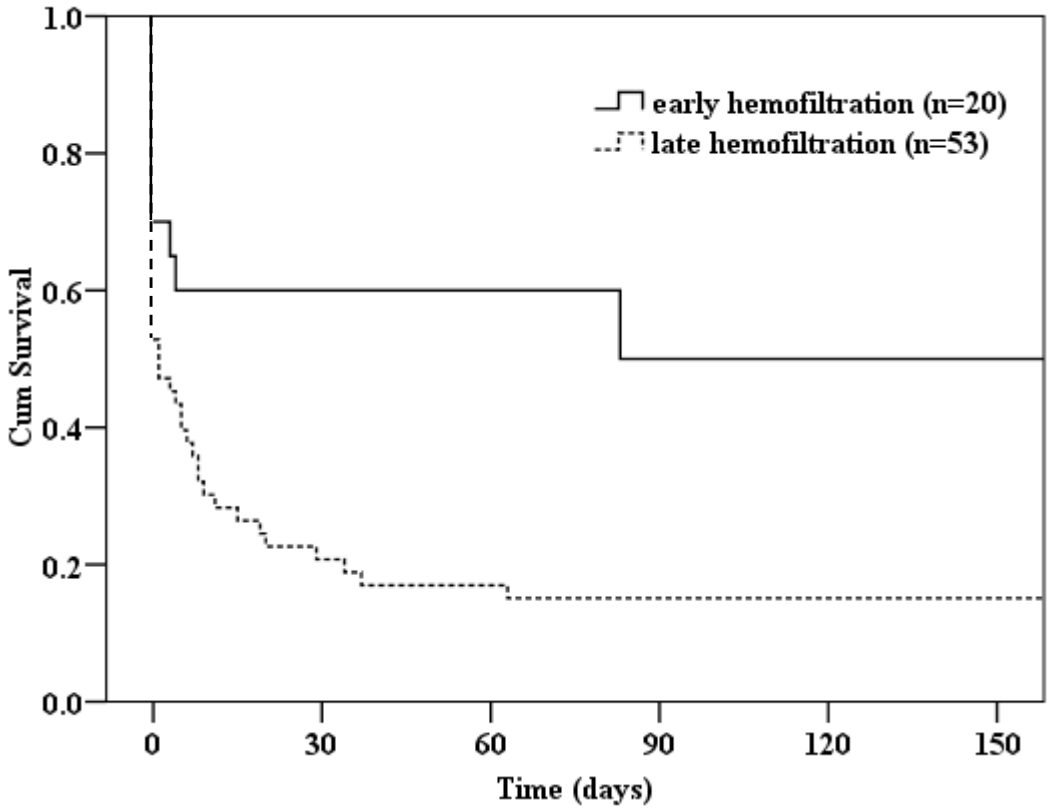

Fig. 2. Comparison of cumulative survival between the early and late CRRT groups.

Cumulative patient survival between the early and late CRRT groups (Kaplan-Meier method). Time indicates survival days from the initiation of CRRT.

Table 1. RIFLE classification

RIFLE classification for acute kidney injury [12]

	GFR criteria	Urine output criteria
Risk	Increase plasma creatinine ×1.5 or GFR decrease > 25%	< 0.5 ml/kg/hr × 6 hr
Injury	Increase plasma creatinine ×2 or GFR decrease > 50%	< 0.5 ml/kg/hr × 12 hr
Failure	Increase plasma creatinine ×3 or GFR decrease > 75%, or serum creatinine ≥ 4 mg/dl with an acute rise > 0.5 mg/dl	< 0.3 ml/kg/hr × 24 hr or anuria ×12 hr
Loss	Persistent ARF = complete loss of kidney function > 4 wks	
ESRD	End-stage renal disease (> 3 months)	

ARF: acute renal failure; GFR: glomerular filtration rate; ESRD: end stage renal disease; hr: hours.

Table 2. Type and indications for operation

Type of operation	Early CVVH (n=20)		Late CVVH (n=53)	
	N	%	N	%
Upper GI perforation, hemorrhage, obstruction	9	45.0	26	49.1
Lower GI perforation, hemorrhage, obstruction	3	15.0	7	13.2
Primary mesenteric ischemia	2	10.0	1	1.9
Hepato-biliary-pancreas infection	4	20.0	7	13.2
Extremity necrotizing fasciitis	2	10.0	5	9.4
Decompressive laparotomy for IAH	0	0.0	4	7.5
GI tract varices bleeding	0	0.0	3	5.7

The Fisher's exact test showed that the distribution of type of operation was not statistically different between early CVVH and late CVVH (p-value=0.578).

Table 3: Comparison of laboratory data and clinical scores

	RIFLE score							P-value
	Risk				Injury/Failure			
	N	Median	IQR		N	Median	IQR	
Age	20	62.5	42.5 -	80.5	53	61.0	47.0 -	74.5	NS
BUN (ER)	20	29.0	22.3 -	43.0	53	34.0	16.5 -	59.5	NS
Cr (ER)	20	1.6	1.2 -	2.1	53	1.9	1.1 -	3.3	NS
BUN at initiation of CRRT	20	39.0	28.5 -	54.5	53	61.0	38.0 -	91.5	0.005
Cr at initiation of CRRT	20	1.7	1.2 -	2.5	53	3.5	2.3 -	4.2	<0.001
Serum lactate at admission	13	41.7	30.5 -	66.3	29	50.5	21.2 -	88.4	NS
Base deficit at admission	16	-8.2	-10.4 -	-3.5	39	-8.3	-14.3 -	-5.8	NS
APACHE score at admission	20	22.0	17.0 -	28.8	53	25.0	16.5 -	31.5	NS
SOFA score	16	9.5	6.3 -	14.5	28	10.0	6.0 -	15.0	NS
O-POSSUM	20	18.5	12.3 -	23.8	53	20.0	14.5 -	23.0	NS
Sum of POSSUM	20	53.5	42.3 -	63.0	53	50.0	42.0 -	62.5	NS
CVVH days	20	2.0	2.0 -	3.8	53	3.0	1.5 -	6.0	NS
ICU days	20	13.0	5.3 -	33.8	53	17.0	9.0 -	25.5	NS
Total length of stay	20	45.0	15.3 -	88.8	53	23.0	17.5 -	37.5	NS

P-values were obtained with Mann-Whitney U Tests.

IQR: interquartile range. O-POSSUM: operative severity score.

A few data points are missing due to lack of clinical values.

(This table indicates that regarding RIFLE criteria, there were no differences in the R and IF group in demographics except BUN and Cr (at initiation of CRRT).

Table 4. Comparison of demographics and preexisting diseases

	RIFLE score				P-value
	Risk (n=20)		Injury/Failure (n=53)		
	N	%	N	%	
Gender (Male)	10	50.0	38	71.7	NS
DM	5	25.0	17	32.1	NS
Hypertension	9	45.0	18	34.0	NS
Cirrhosis	1	5.0	11	20.8	NS
Previous heart/lung disease	6	30.0	12	22.6	NS
Shock at admission (SBP<90)	7	35.0	9	17.0	NS
Admission coagulopathy prolonged PT/INR	13	68.4	35	71.4	NS
30 day mortality	8	40.0	41	77.4	0.002
90 day mortality	10	50.0	45	84.9	0.005

P-values were obtained with a Chi-Square Test or Fisher's Exact Test when appropriate. A few data points are missing due to the lack of clinical values. There were six patients who survived 30 days and died in home care within 90 days.

Table 5. Regression analysis results for survival and mortality

	Logistic regression analysis				Cox Proportional-Hazards regression analysis			
RIFLE score	Survival	Odds ratio	95% C.I.	P-value	Mortality	Hazard ratio	95% C.I.	P-value
Risk	12/20	5.125	1.703 - 15.425	0.004	10/20	1.000		
Injury/Failure	12/53	1.000			45/53	2.389	1.191 - 4.794	0.014

Survival: survival > 30 days

When comparing causes of mortality (or survival > 30 days), there were no significant differences between variables (Age, Gender, DM, Hypertension, Cirrhosis, Heart Lung disease, Shock, Admission coagulopathy prolonged PT/INR, APACHE score, SOFA score, P-POSSUM score, O-POSSUM score, SUM of POSSUM score, and CVVH days) in the early and late groups except whether CRRT was initiated during the Risk or Injury/Failure stage.