



Impact of Early Initiation of Continuous Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury

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Abstract

Background: Although continuous renal replacement therapy (CRRT) has become the most commonly used modality for critically ill patients with acute kidney injury (AKI), the optimal timing of initiation remains controversial. CRRT is usually initiated when conventional indications of AKI arise; however, preemptive therapy may be beneficial. We evaluated the prevalence of preemptive and conventional CRRT initiation in critically ill patients and compared the associated 90-day mortality and renal recovery.

Methods: This retrospective study was performed in 2 tertiary centers between 2014 and 2017. Patients were divided into preemptive and conventional groups according to CRRT indications at the time of initiation. The primary clinical outcomes were 90-day mortality and renal recovery. Renal recovery was defined as a creatinine clearance of ≥ 15 mL/min and no need for renal replacement therapy for an additional 90 days.

Results: Patients with preemptive initiation showed higher diastolic blood pressure, higher bicarbonate level, lower blood urea nitrogen, and lower initial 6-h urine output at the time of initiation. More required simultaneous extracorporeal membrane oxygenation. This group showed a significantly lower 90-day mortality and higher renal recovery rate. In multivariate analysis, late initiation of CRRT remained an independent risk factor for increased 90-day mortality and lack of renal recovery in survivors.

Conclusion: Our study demonstrated that early preemptive CRRT initiation is associated with significantly lower 90-day mortality and higher renal recovery. Additional large-scale randomized controlled trials are needed to determine the optimal timing of therapy.

Keywords

Acute Kidney Injury, Continuous Renal Replacement Therapy, Intensive Care Unit, Timing, Mortality

Introduction

Acute kidney injury (AKI) is frequently encountered in critically ill patients, and the in-hospital mortality rate of those who require dialysis is high [1]. Although

continuous renal replacement therapy (CRRT) is a cornerstone of treatment for AKI and has been widely used for more than a decade, the optimal timing of CRRT initiation remains controversial [2,3].

Traditionally, CRRT has been initiated only when life-threatening AKI complications, including refractory hyperkalemia, severe acidosis, fluid overload unresponsive to medical management, and overt uremic symptoms and signs such as bleeding, pericarditis, and encephalopathy, arise [4]. However, as several recent studies demonstrated a possible survival benefit of earlier initiation, preemptive CRRT has become increasingly common [5-7]. The theoretical advantage of early CRRT initiation is more efficient control of volume overload, uremic toxins, and acid-base abnormalities. However, earlier CRRT initiation also carries the inherent risks of blood stream infection, hemodynamic instability, and complications related to blood dialyzer interactions in patients who might recover from AKI with only supportive treatment. A recent extensive systematic review concluded that early CRRT initiation had no impact on patient survival or intensive care unit (ICU) length of stay [8]. However, heterogeneity of patient populations, particularly for differences in how early and late initiation was defined, or differences in study quality, might be responsible for this discrepancy.

This retrospective study investigated the clinical practice patterns of CRRT with regard to timing in 2 large tertiary hospitals in Korea. We compared the clinical characteristics and outcomes of patients who commenced CRRT without conventional indications to those with one or more conventional indications.

Materials and Methods

Ethics Statement:

The Institutional Review Board of Korea University Anam Hospital and Guro Hospital, Seoul, Korea approved the study (IRB No. 2017AN0310, 2017GR0019). Informed consent was waived because this was a non-interventional retrospective study and the subjects were deidentified.

Patients and Study Design:

This was a retrospective, two-center cohort study conducted in the adult ICUs of Korea University Anam Hospital and Guro Hospital. We enrolled patients who were admitted to the ICU and had acute CRRT for at least 48 h due to AKI between January 2014 and December 2017. The patient exclusion criteria were

end-stage renal disease (ESRD) with maintenance hemodialysis, peritoneal dialysis, or a previous history of kidney transplantation.

Enrolled patients were treated by a specialized CRRT team composed of one specialized nephrologist, one intensivist, 3 ICU residents, and two CRRT-specialized nurses. The nephrologist decided whether to initiate CRRT based on patient hemodynamic status, declining urine output, uremia, and electrolyte and acid-base imbalances, and additionally determined dialysate composition, dose of CRRT, and net ultrafiltration rate during CRRT [9]. The mode of CRRT was continuous veno-venous hemodiafiltration with the Prismaflex machine (Gambro Americas, Lakewood, CO, USA) or Fresenius system (Fresenius Medical Care North America, Waltham, MA, USA). All patients were treated with a blood flow rate of 100-150 mL/min, with predilution at a rate of approximately 25-35 mL/kg/h. Heparin was used for anticoagulation unless contraindicated. The CRRT intensity was calculated from a total effluent rate (the sum of the dialysate, replacement fluid rate, and ultrafiltration rate) and expressed in units of mL/kg/h. The body weight used for this calculation was obtained at the initiation of CRRT.

Patients who underwent CRRT were categorized into two groups based on the timing of CRRT initiation: the preemptive group (CRRT initiated without conventional indications) and the conventional group (CRRT initiated in the presence of at least one conventional indication). We considered the following factors to be conventional indications for CRRT [10-12]: hyperkalemia (serum potassium ≥ 6 mEq/L), severe metabolic acidosis (pH ≤ 7.2), oliguria or anuria (urine output < 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h), diuretic-resistant volume overload, and elevated blood urea nitrogen (BUN ≥ 100 mg/dL).

Data Collection:

Demographics, CRRT data (time of onset, duration, reason for initiation, and delivered dose), comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE II) score during the first 24 h of admission, and blood tests at the initiation of CRRT were retrospectively extracted from a standardized

database. Patient outcomes were also obtained by reviewing the hospital electronic database. The primary clinical outcome was the mortality rate within 90 days after CRRT initiation. The secondary clinical outcome was renal recovery defined as the absence of dialysis dependence at the time of hospital discharge.

Statistical Analyses:

Statistical analyses were conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as the mean \pm standard deviation unless otherwise specified. Categorical variables were expressed as a percentage. Comparisons between the two groups were performed using Student's t-test or the Mann-Whitney U test for numerical data, and the chi-square test or Fisher's exact test for categorical data.

To identify predictors of renal recovery after AKI, we initially conducted univariate analysis, and variables that were statistically significant ($p < 0.05$) in univariate analysis were included in multivariate analysis with backward selection based on the

likelihood ratio. Data are presented as odds ratio (OR) with 95% confidence interval (CI). A two-tailed p -value < 0.05 was considered statistically significant. We also performed Cox regression analysis to analyze independent predictors of the 90-day in-hospital mortality rate. Variables showing $p < 0.05$ in univariate Cox regression analysis were entered into multivariate analysis followed by stepwise variable selection. Cumulative 90-day mortality rates were calculated according to the Kaplan-Meier method. Subgroup analyses were performed according to early or late initiation of CRRT.

Results

Of 1,151 patients who received CRRT, 582 were eligible for the analysis (**Fig-1**). A total of 239 patients (41.1%) had at least one conventional indication at the initiation of CRRT and were classified into the conventional group. A total of 343 patients (58.9%) who commenced CRRT without conventional indications were classified into the preemptive group. However, the timing of CRRT initiation after ICU admission was comparable between the two groups.

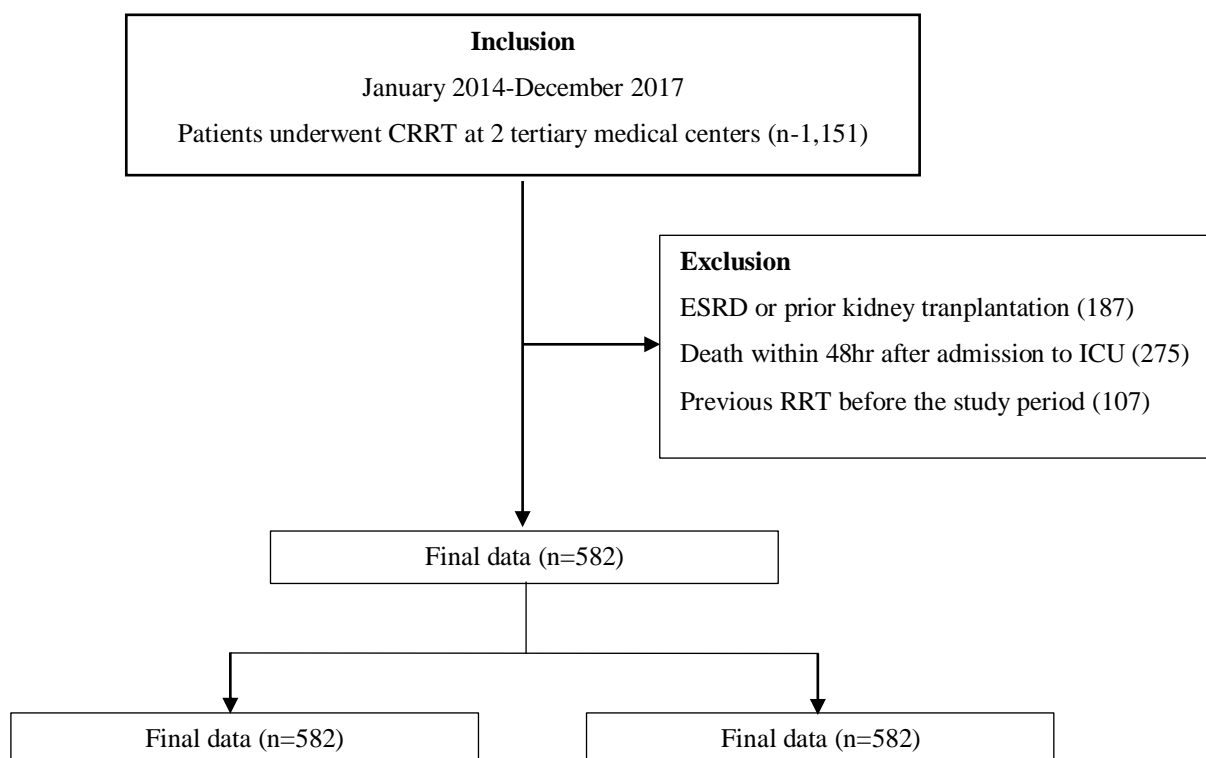


Fig-1: Patient inclusion criteria

Table-1: Baseline characteristics of patients with early (=preemptive) vs. late (=Conventional) CRRT initiation			
	Preemptive (343)	Conventional (239)	P-Value
Sex (male)	147 (43%)	120 (50%)	0.09
Age (years)	66.7	65.6	0.37
CKD (eGFR <60mU(min·1.73 m ²))	63 (19%)	143 (59%)	<0.001
HTN	188 (55%)	114 (48%)	0.05
DM	114 (33%)	79 (33%)	0.52
HF	44 (13%)	38 (16%)	0.18
CAD	57 (16%)	45 (18.9%)	0.28
COPD	17 (5%)	11 (4.6%)	0.5
Cancer	59 (17%)	52 (22%)	0.1
Liver disease	42 (12%)	55 (23%)	<0.001
Veotilator	156 (45%)	56 (23%)	0.09
ECMO	29 (8%)	3 (1%)	0.005
APACHE-II	28 [3-49]	27 [2-7]	0.28
Initial 6-h total urineoutput (ml/6 h)	385 ± 691	680 ± 919	<0.001
Initial SBP (mmHg)	110.5 ± 25	110.5 ± 23	0.97
Initial DBP (mmHg)	52.2 ± 27.0	43.2 ± 33.0	<0.001
Initial CVP (mmHg)	5.0 ± 6.7	5.0 ± 7.4	0.4
Hb (g/dL)	10.2 ± 2.1	10.0 ± 2.5	0.3
WBC (per microliter)	10924 ± 15749	6052 ± 9537	<0.001
CPR (mg/L)	123.8 ± 116.23	112.5 ± 115.7	0.28
BUN(mg/dL)	51.0 ± 25.0	70.0 ± 43.5	<0.001
Initial Cr (mg/dL)	3.3 ± 3.06	3.1 ± 3.24	0.56
Albwnin (g/dL)	2.8 ± 0.6	2.7 ± 0.6	0.4
HCO ₃ (mmol/L)	18.3 ± 4.3	13.3 ± 5.9	<0.001
CRRT start day after ICU admission	5.5 ± 13.9	4.1 ± 6.4	0.1
CRRT dose (mL(kg·h))	32.40 ± 6.55	32.39 ± 6.61	0.97
CRRT duration (days)	5.49 ± 5.6	5.42 ± 4.5	0.86
<p>Abbreviations: CRRT=contionus renal replacement therapy, CKD=chronic kidney disease, HTN=hypertension, DM=diabetes mellitus, HF=heart failure, CAD=coronary artery disease, COPD=chronic obstructive pulmonary disease, ECMO=extracorporeal membrane oxygenation, APACHE-II=acute physiology and chronic health evaluation, SBP=systolic blood pressure, DBP=diastolic blood pressure, CVP=central venous pressure, Hb=hemoglobin, WBC=white blood cell, CRP=C-reactive protein, BUN=blood urea nitrogen, Cr=creatinine, HCO₃=bicarbonate, ICU=intensive care unit</p>			

Patient Characteristics:

Table-1 shows patient characteristics. Age, sex, and mean APACHE II score during the initial 24 h of ICU admission were not different between the two groups.

However, the prevalence of chronic kidney disease (CKD) or chronic liver disease was significantly higher in the conventional group. Although patients in the preemptive group showed a significantly higher

diastolic blood pressure, higher bicarbonate level, and lower BUN at the time of CRRT initiation, leukocyte counts were significantly higher and 6-h urine output was significantly lower. A higher proportion of patients in the preemptive group were simultaneously treated

with extracorporeal membrane oxygenation (ECMO). The dose and duration of CRRT were comparable between the two groups. Comparison between age distribution and comorbidities revealed none of statistically significant correlation (appendix Table-1).

Appendix Table-1: Age and comorbidities distribution

Age (years)	CKD	DM	HTN	HF	CAD	COPD	Cancer	Liver Disease
29<	1	0	0	0	0	0	1	1
30-39	7	2	6	3	0	0	3	6
40-49	21	16	23	3	6	0	10	21
50-59	34	30	43	12	13	1	18	19
60-69	55	58	82	23	35	11	30	28
70-79	108	89	134	32	50	11	47	23
80-89	62	43	80	30	22	7	18	8
90-99	2	2	5	2	2	0	0	0

Table-2: Clinical outcomes with early vs. late CRRT initiation

	Preemptive (343)	Conventional (239)	P-value
90-day mortality	198 (57%)	160 (67%)	0.012
Renal recovery in survivors	103/145 (71%)	42/79 (53%)	0.001
Survival period (days)	58.04±94.5	42.2±87.8	0.03

Table-3: Multivariate Cox regression analysis for 90-day mortality

	Model 1 (Late CRRT only)			Model 2 (Model 1+Age, Sex, D:M, HTN, Liver Disease, ECMO)			Model 3 (Model 2+ CKD, APACHE-II)		
	Hazard Ratio	95% CI	P - value	Hazard Ratio	95% CI	P - value	Hazard Ratio	95% CI	P - value
Late Initiation	1.27	0.96-1.67	0.08	1.8	1.0-2.87	0.05	2.25	1.33-3.63	0.002
Age				1.9	1.23-2.9	0.004	2.2	1.6-3.0	<0.001
Liver disease				1.57	1.1-2.24	0.011	1.58	1.12-2.24	0.008
ECMO				1.74	1.14-2.65	0.01	1.66	1.1-2.5	0.01
CKD							1.5	1.3-1.8	0.01
APACHE-II							1.1	1.01-1.03	0.001

Table-4: Multivariate logistic regression for 90-day renal recovery						
	Univariate			Multivariate		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Sex (male)	0.426	0.45-0.95	<0.001	-	-	-
Age	0.518	0.981-1.006	0.12	-	-	-
CRRT dose (mL(kg.h))	0.99	0.958-1.014	0.32	-	-	-
Diabetes	0.776	0.524-1.148	0.2	-	-	-
Hypertension	0.73	0.5-1.064	0.1	-	-	-
HF	0.76	0.45-1.28	0.3	-	-	-
CAD	0.87	0.52-1.45	0.6	-	-	-
CKD	0.804	0.539-1.2	0.29	-	-	-
COPD	0.98	0.4-2.36	0.96	-	-	-
Liver Disease	0.83	0.5-1.4	0.49	-	-	-
Cancer	0.5	0.3-0.94	0.03	-	-	-
ECMO	0.4	0.1-1.38	0.15	-	-	-
Ventilator	0.34	0.21-0.61	<0.001	-	-	-
SBP (mmHg)	1.009	1.001-1.019	0.048	-	-	-
DBP (mmHg)	1.001	0.995-1.007	0.7	-	-	-
MABP	1.018	1.003-1.033	0.02	-	-	-
CVP (mmHg)	1.013	0.976-1.05	0.5	-	-	-
Hb (g/dL)	1.1	1.02-1.2	0.015	-	-	-
WBC (per μ L)	1	0.999-1.001	0.89	-	-	-
CRP (mg/dL)	1.001	0.999-1.002	0.49	-	-	-
Albumin (g/dL)	1.75	1.3-2.4	<0.001	-	-	-
APACHE-II	0.5	0.926-0.976	<0.001	0.962	0.935-0.991	0.01
Ventilator	0.34	0.21-0.61	<0.001	0.96	0.935-0.991	0.004
Early Initiation	1.9	1.28-2.9	0.002	2.099	1.084-4.063	0.028
<p>Abbreviations: CRRT=continuous renal replacement therapy, HF=heart failure, CAD=coronary artery disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, ECMO=extracorporeal membrane oxygenation, SBP=systolic blood pressure, DBP=diastolic blood pressure, MABP=mean arterial blood pressure, CVP=central venous pressure, Hb=hemoglobin, WBC=white blood cell, CRP=C-reactive protein, APACHE-II=acute physiology and chronic health evaluation</p>						

Mortality:

The 90-day crude mortality rate was 57% in the preemptive group and 67% in the conventional group ($p = 0.012$) (Table-2). Multivariate regression analysis showed that CRRT initiation after onset of any conventional indication was associated with a significantly higher risk of 90-day mortality after adjusting for multiple confounders (hazard ratio 2.25; 95% CI, 1.33-3.63, $p = 0.002$) (Table-3, Fig-2). Additional factors associated with increased 90-day mortality risk were advanced age, presence of underlying CKD, chronic liver disease, higher APACHE II score, and simultaneous use of ECMO.

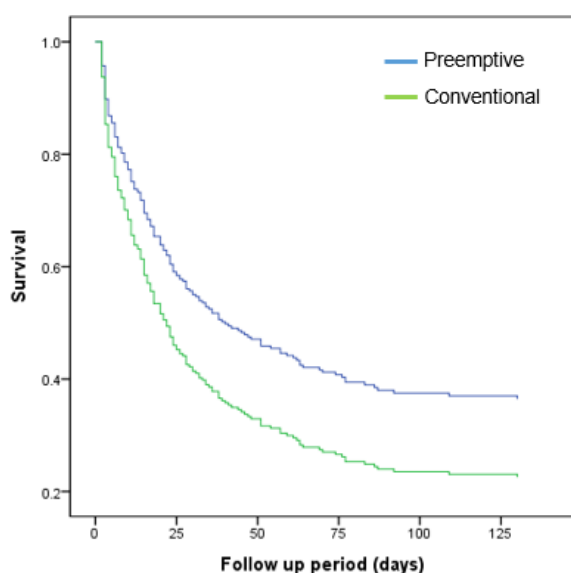


Fig-2: Kaplan-Meier plots of 90-day mortality for early vs. late CRRT initiation

Renal Recovery:

Renal recovery, defined as a creatinine clearance ≥ 15 mL/min and no renal replacement therapy for an additional 90 days, was also significantly higher in the preemptive group than in the conventional group (31% vs. 18%, $p = 0.001$) (Table-4). Preemptive CRRT initiation was still associated with a higher risk of renal recovery after adjusting for multiple factors (OR, 2.09; 95% CI 1.084-4.063, $p = 0.028$). A higher APACHE II score and need for a ventilator were also independently associated with a significantly lower risk of 90-day renal recovery.

Discussion

In this retrospective analysis of 582 critically ill ICU

patients treated with CRRT, only 41% had at least one conventional indication for CRRT at the time of initiation, while 59% received preemptive treatment. Patients with delayed CRRT initiation showed significantly higher 90-day mortality rates and significantly lower renal recovery rates. These associations between delayed CRRT initiation and higher mortality and lower rates of renal recovery persisted, even after adjusting for multiple confounding factors including severity of illness and comorbid conditions, suggesting that earlier preemptive CRRT initiation may improve the patient's outcomes.

Determining the optimal timing for CRRT initiation in critically ill AKI patients has been a priority for researchers in the field of AKI. However, despite numerous observational studies and several recently published randomized trials, the optimal timing of CRRT initiation remains unclear. Many clinicians still rely on the expert recommendations released by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. While initiating CRRT early or preemptively may be theoretically beneficial due to the avoidance of life-threatening hyperkalemia, pulmonary edema, and more rapid correction of electrolyte and acid-base abnormalities, it also carries an increased risk of catheter related bacteremia, loss of water-soluble vitamins and micronutrients, and antibiotic underdosing, collectively called dialytrauma [13-15].

We retrospectively reviewed the most recent 5-year CRRT data of two tertiary teaching hospitals in Korea with specialized CRRT teams consisting of a nephrologist, nurses, and an internal medicine resident. We found that 59% of CRRT was initiated without conventional indications, suggesting that broader clinical contexts or concepts of renal support are increasingly being considered as indications for CRRT initiation. Patients in the preemptive group were more likely to be simultaneously treated with ECMO and showed significantly decreased 6-h urine outputs despite their higher mean diastolic blood pressure and bicarbonate levels. These data suggest that the decision to initiate CRRT seems to be more likely based on non-renal organ failure such as heart and lung, or ongoing diuretic-resistant oligo/anuria. Because fluid overload

at the time of CRRT initiation has been associated with increased mortality [16], an approach using broader clinical contexts for the timing of CRRT initiation seems reasonable. A meta-analysis showing reduced mortality with early CRRT initiation for volume control within 24 h after AKI in post-cardiac surgery patients supports our findings [17]. Of interest, the prevalence of CKD or chronic liver disease was significantly higher in the conventional group. However, the underlying causes for this discrepancy are not clear.

Despite several differences in the baseline characteristics of the two groups, the severity of acute illness represented by the APACHE II score at the time of ICU admission was comparable. In addition, the dose, duration, and initiation time after ICU admission were not different between the two groups. Several previous studies used the time from ICU admission to CRRT initiation or the creatinine level to define “early” and “late or delayed” CRRT [1,2,18]. Recent randomized trials have used the time after the diagnosis of KDIGO stage 2 or 3 AKI as a parameter of early vs. delayed CRRT [5,19]. However, given that critically ill AKI patients present with various degrees of severity, with non-renal organ dysfunction, or with different underlying comorbidities, these approaches are likely to be oversimplified.

Therefore, we used more comprehensive criteria to define early or delayed CRRT commencement and assessed the impact on outcomes. Despite comparable levels of acute illness severity, patients who received CRRT without conventional indications showed significantly lower 90-day mortality and better renal recovery rates. This approach, using comprehensive criteria, was initially introduced by a Finnish AKI study group that showed higher mortality in patients with one or more conventional indications for CRRT than in those without indications [20].

However, it is still possible that some patients in the preemptive group might have survived or achieved renal recovery without CRRT. This is supported by data from the Artificial Kidney Initiation in Kidney Injury trial, in which the 49% of patients randomized to a delayed arm did not receive CRRT support and showed the lowest mortality [19]. In addition, a

significantly higher number of patients with underlying CKD or chronic liver disease, which are well-known modifiers of AKI outcomes, may have contributed to the poor outcomes in the conventional group. However, this survival benefit persisted after adjusting for multiple factors in our study, including the severity of acute illness and underlying comorbidities. In addition, the fact that the decision for CRRT was made exclusively by two nephrologists on the specialized team in each hospital suggests that injudicious use or provision of unnecessary CRRT in less severely ill patients is unlikely. Advanced age, presence of CKD, chronic liver disease, higher initial APACHE II score, and simultaneous application of ECMO were also found to be independently associated with increased 90-day mortality.

While many previous studies focused on mortality, our study also assessed the impact of CRRT timing on renal recovery in survivors. We observed that renal recovery, defined as an absence of dialysis dependence at the time of hospital discharge, was significantly higher in the preemptive group than in the conventional group (71% vs. 53%). In multivariate analysis, the OR of preemptive CRRT for renal recovery was 1.9. The APACHE II score and need for a mechanical ventilator were independently associated with non-recovery of renal function. Zarbock et al. demonstrated that initiation of CRRT within 8 h of a KDIGO stage two AKI diagnosis increased the likelihood of not only short-term renal function recovery but also 1-year long-term mortality [5,21]. However, given that a recent meta-analysis showed no difference in renal function recovery between early and late initiation of CRRT in critically ill patients [22–26], the impact of early initiation on outcomes is still controversial.

Despite the theoretical advantages, several potential untoward effects of preemptive or earlier CRRT initiation exist. Patients inherently carry an increased risk of catheter-related infection and subsequent bacteremia, hypothermia, loss of water-soluble vitamins and trace elements, hypophosphatemia, and antibiotic underdosing, collectively called dialytrauma, that could potentially contribute to a poor outcome. Use of K or P supplemented dialysate and/or

replacement solution may correct the hypokalemia or hypophosphatemia and understanding the pharmacokinetics/pharmacodynamics of antibiotics might have prevented antibiotic underdosing in our study. Our finding that preemptive CRRT initiation without conventional indications for dialysis was associated with better survival and renal recovery may suggest that it is unlikely to exert harmful effects on patients. However, an understanding of this underrecognized condition, with potential harmful effects on patient outcomes, is still important.

Despite some interesting findings, our study has several limitations that need to be considered while interpreting the data. First, this was a retrospective study with confounding factors that were not measured. Moreover, sampling bias for patients who died within 48 h prior to CRRT initiation might have influenced the outcome. Second, imprecise initiation criteria in the preemptive group may also have affected the outcome. If a patient exhibits hypotension with anuria due to septic shock, the patient is considered to be a conventional indication group because of hemodynamic instability and anuria. We also tried to apply the propensity match score analysis between the two groups, but it was unavailable. They could not be established with propensity match score analysis because the characteristics of the two groups are not comparable. Lastly, there is a limit to the situation in which patients and collaborators are forced to initiate CRRT before devastating clinical condition with the conventional indication of CRRT. If the special team was strongly requested to apply CRRT, we have a discussion about the patient and try to find the best way to support, also deliver the effectiveness of early initiation has not been proven. Despite the similarity of disease severity and hemodynamic instability between the two groups in our study, it seems that there might be an effect of the clinician on intervention to early initiation. Despite these limitations, the impact of early initiation is evident. Patients should be assessed according to their individual circumstances.

In conclusion, our study demonstrated that more than 50% of critically ill AKI patients requiring dialysis underwent preemptive CRRT. Preemptive initiation was associated with a reduced risk of 90-day mortality

and better renal recovery compared to initiation of CRRT using conventional indications. However, additional well-designed, large-scale randomized controlled studies are needed to confirm these findings and determine the proper timing of CRRT initiation.

Acknowledgments

None

Competing Interests

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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