Tohoku J. Exp. Med., 2014, **233**, 233-241

Classical Indications Are Useful for Initiating Continuous Renal Replacement Therapy in Critically Ill Patients

Jeonghwan Lee,[1] Jang-Hee Cho,[2] Byung Ha Chung,[3] Jung Tak Park,[4] Jung Pyo Lee,[5] Jae Hyun Chang,[6] Dong Ki Kim[7] and Sejoong Kim[8]

[1]Department of Internal Medicine, Hallym University Hangang Sacred Heart Hospital, Seoul, Korea
[2]Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, Korea
[3]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[4]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
[5]Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, Korea
[6]Department of Internal Medicine, Gachon University of Medicine and Science, Incheon, Korea
[7]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea
[8]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Korea

The optimal timing for initiating continuous renal replacement therapy (CRRT) remains controversial, and it is not obvious which parameters should be considered during this process. We investigated the predictive value of physiological parameters among critically ill patients receiving CRRT due to acute kidney injury (AKI). A total of 496 patients who started CRRT were prospectively enrolled. The following physiological parameters were significantly associated with mortality even after multivariate adjustments: level of pH [hazard ratio (95% CI): 7.15 < pH ≤ 7.20, 1.971 (1.319-2.946); pH ≤ 7.15, 2.315 (1.586-3.380); reference > 7.25, *P*-for-trend < 0.001]; bicarbonate level (HCO_3^-) [≤ 14 mmol/L, 2.010 (1.542-2.620); reference > 18 mmol/L, *P*-for-trend < 0.001]; phosphorus level [> 7 mmol/L, 1.736 (1.313-2.296); reference ≤ 5 mmol/L, *P*-for-trend < 0.001]; and urine output < 0.3 ml/kg/hr [1.509 (1.191-1.912); reference > 0.3 ml/kg/hour]. Weight gain over 2 kg was associated with mortality exclusively according to univariate analysis [1.516 (1.215-1.892)]. The diagnostic value of the composite of these factors (pH, bicarbonate level, phosphorus level, urine output, weight gain, and potassium levels) [area under the curve (AUC) 0.701, 95% CI 0.644-0.759] was comparable to or higher than the blood urea nitrogen level (AUC 0.571, 95% CI 0.511-0.630), serum creatinine level (AUC 0.462, 95% CI 0.399-0.525), eGFR (AUC 0.541, 95% CI 0.478-0.605), and AKI Network stage (AUC 0.627, 95% CI 0.561-0.692). In conclusion, the physiological parameters are useful in predicting post-AKI mortality and should be considered when initiating CRRT in critically ill patients with AKI.

Keywords: acute kidney injury; continuous renal replacement therapy; indication; mortality; renal replacement therapy
Tohoku J. Exp. Med., 2014 August, **233** (4), 233-241.

Introduction

Acute kidney injury (AKI), which is a common and serious health problems in patients with various critical illness, is characterized by a sudden decrease of kidney function that results in the accumulation of urea and other waste products, the retention of sodium and water, and the development of physiological imbalances such as metabolic acidosis and hyperkalemia (Tolwani 2012). AKI develops in approximately 10% to 67% of critically ill patients being treated in intensive care units (Hoste and De Waele 2008; Palevsky et al. 2008; Lameire et al. 2013). Additionally, renal replacement therapy (RRT) is required in 5% to 30% of patients with AKI (Lameire et al. 2005, 2006; Uchino et al. 2005), which is an independent risk factor for future renal insufficiency and mortality in critically ill patients (Coca et al. 2009; Wald et al. 2009). The mortality rate of critically ill patients with AKI who require RRT can be as high as 50-80% (Metcalfe et al. 2002; Mehta et al. 2004; Uchino et al. 2005). To improve clinical outcomes and prevent complications of this devastating condition, the administration of RRT in the right clinical situations and at the right time is crucial in clinical practice.

Many of recent investigations have suggested that ini-

Received April 18, 2014; revised and accepted June 24, 2014. Published online July 29, 2014; doi: 10.1620/tjem.233.233.
Correspondence: Sejoong Kim, M.D., Ph.D., Division of Nephrology, Department of Internal Medicine, Seoul National University Bundang Hospital, 166 Gumi-ro, Bundang-gu, Seongnam 463-707, Republic of Korea.
e-mail: sejoong2@snu.ac.kr

tiating RRT earlier may benefit patients with AKI (Liu et al. 2006; Bagshaw et al. 2009; Karvellas et al. 2011). However, optimal timing for RRT initiation in AKI remains a matter of debate. Presently, there is no universally accepted consensus regarding when to initiate RRT in critically ill patients with AKI. Hyperkalemia, severe metabolic acidosis, volume overload, oliguria, overt uremic symptoms, and medication intoxication are all traditionally considered to be classic indications for RRT (Bellomo et al. 2001; Mehta 2001; Palevsky 2005). Guidelines recommend that RRT should be initiated in patients who present life-threatening changes in fluid, electrolytes, and acid-base balance (Khwaja 2012). Although a fair number of clinicians have decided to start RRT according to the stage of AKI, the levels of blood urea nitrogen or serum creatinine, or the estimated glomerular filtration rate (eGFR) in clinical practice, there is no agreed-upon cut-off level or laboratory value that can be used to make this choice. Clinical studies have reported controversial results concerning whether initiating RRT early based on the levels of blood urea nitrogen and serum creatinine or on the stage of AKI is beneficial (Ostermann et al. 2012; Jamale et al. 2013).

It is important to find suitable indications for initiating RRT in critically ill patients with AKI. We aimed to investigate the predictive value of parameters considered while deciding when to initiate RRT.

Methods

Patients and Data Collection

This study is derived from the prospective observational cohort of critically ill patients with AKI requiring continuous renal replacement therapy (CRRT), and the institutional review board of Seoul National University Hospital approved this investigation (no. 1404-028-568). All adult patients (aged > 20 years) in intensive care units who needed clinically for CRRT due to complications of AKI were included in this cohort study, and a total of 496 patients who started CRRT at Seoul National University Hospital, Seoul, Korea from May 2010 to April 2013 were enrolled. Initially, 602 patients who started CRRT were screened, and 83 patients were excluded from analysis because they refused to participate this cohort study. Of the 519 patients who provided informed consent, 23 patients with any unrecorded or missed demographic, laboratory, or survival data were excluded for the final analysis. The initiation of CRRT was chosen according to the clinical judgement of internists, intensivists, or nephrologists in intensive care units. Basic concept for CRRT indications applied in Seoul National University Hospital is as follows: AKI and complications associated with decreased renal function such as 1) decreased urine output (< 0.5 ml/kg/hr) combined with signs of volume overload, including pulmonary edema and/or pleural or pericardial effusion 2) persistent or refractory electrolyte imbalance (e.g. hyperkalemia) or metabolic acidosis. All of the CRRT cases were managed by a nephrologist after consultation within 12 hours after CRRT initiation. At the time of CRRT initiation, the demographic data and clinical and laboratory parameters were collected, and the data at the time of hospital admission and intensive care unit admission were retrieved from electronic medical records after the patients were enrolled in the study. The etiology of AKI was classified as septic, ischemic, nephrotoxic, and post-operative AKI, as well as other. The data regarding comorbidities were gathered to calculate the Charlson Comorbidity Index (CCI) (Charlson et al. 1987). To assess the severity of illness, the Acute Physiology and Chronic Health Evaluation (APACHE) II scores and the Sequential Organ Failure Assessment (SOFA) scores were calculated at the time of dialysis initiation (Knaus et al. 1985; Vincent et al. 1996). The baseline serum creatinine level was defined as the level before the development of kidney failure accompanied by critical illness, which was the primary cause of intensive care unit admission. Systemic inflammatory response syndrome (SIRS) was defined as follows (with two or more of criteria being met): 1) body temperature lower than 36°C or higher than 38°C, 2) heart rate over 90 beats per minute, 3) high respiratory rate with more than 20 breaths per minute or an arterial partial pressure of carbon dioxide below 32 mmHg, and 4) leukocyte levels below 4,000 cells/mm^3 or above 12,000 cells/mm^3 (Muckart and Bhagwanjee 1997).

Decision Factors for CRRT Initiation

We compared the hazard of in-hospital mortality using kidney function parameters and conventional parameters of CRRT initiation. The kidney function parameters included blood urea nitrogen, serum creatinine, increase (value or percentage) in serum creatinine, or eGFR calculated using the MDRD equations (Levey et al. 2006). We identified the conventional parameters of dialysis initiation as body weight gain during the time of intensive care unit admission and CRRT start, amount of urine output, potassium levels, phosphorus levels, pH, and bicarbonate levels.

Statistical Analysis

All of the calculations and statistical analyses were performed using the IBM SPSS version 21.0 software program. Continuous variables were expressed as the mean and standard deviation, and categorical variables were described numerically with a percentage. All of the variables were tested for normal distribution using the Kolmogorov-Smirnov test. The hazard ratios (HRs) and 95% confidence interval (CI) of CRRT initiation parameters for in-hospital mortality were calculated using the univariate and multivariate Cox proportional hazard models, comparing kidney function parameters and conventional parameters of dialysis initiation. The continuous variables were converted to categorized variables to evaluate the hazard of in-hospital mortality. Initially, the continuous variables were divided into quartile ranges, and the hazard ratios were compared. Subsequently, theses continuous variables were divided into two to four categorical ranges according to clinical decisions to describe the increasing hazard ratios. The covariates included in the multivariate analysis were age, sex, CCI, presence of SIRS, APACHE II scores, and SOFA scores. After confirming that all of these covariates were significantly associated with the hazard of in-hospital mortality, the covariates were selected for inclusion in the multivariate analysis. The model fit was evaluated using a goodness-of-fit test. The discrimination power of parameters for predicting in-hospital mortality was assessed by calculating the receiver operating characteristic (ROC) curve and the area under the curve (AUC). To evaluate the superiority of the conventional dialysis initiation parameters, the composite scores of these parameters were calculated from the sum of the parameters as follows: pH (0, > 7.25; 1, 7.2-7.25; 2, 7.15-7.2; 3, ≤ 7.15), bicarbonate levels (0, > 18 mmol/L; 1, 14-18 mmol/L; 2, ≤ 14 mmol/L), phosphorus levels (0, ≤ 5 mg/dL; 1, 5-7 mg/dL; 2, > 7

mg/dL), potassium levels (0, ≤ 5.5 mmol/L; 1, > 5.5 mmol/L), weight gain from the time of admission to the intensive care units to the time of CRRT initiation (0, ≤ 2 kg; 1, > 2 kg), and urine output (0, > 0.3 ml/kg/hour; 1, ≤ 0.3 ml/kg/hour).

Results

Patient Characteristics

The clinical and laboratory characteristics of the 496 patients enrolled in the present study are listed in Table 1. The mean age of the patients was 63.4 ± 14.3 years old. The patients were predominantly male (60.1%). The etiology of the AKI was septic (47.6%), ischemic (18.8%), post-operative (8.9%), and nephrotoxic (5.8%) AKI. The patients who reported a history of hypertension comprised 47.0% of the total study enrollment; the patients who reported a history of diabetes comprised 34.5%; and those who reported a history of malignancy comprised 35.9%. The mean CCI was 3.32 ± 2.30. The proportion of patients with SIRS was 72.8% and that of patients with sepsis was 52.2%. The baseline creatinine level was 1.52 ± 1.37 mg/dL and eGFR was 65.3 ± 39.2 ml/min/1.73 m^2.

The clinical and laboratory characteristics of the patients at the time of CRRT initiation are summarized in Table 2. The mean time from admission to the intensive care units to the initiation of CRRT was 83.3 ± 372.2 hours. Weight gain from the time of admission to the intensive care units to CRRT initiation was 1.63 ± 3.63 kg. Urine output was 0.46 ± 0.81 ml/kg/hour. The blood urea nitrogen level was 58.6 ± 32.5 mg/dL, and the serum creatinine level was 3.62 ± 2.34 mg/dL. The potassium level was 4.4 ± 0.9 mmol/L, and the phosphorus level was 5.47 ± 2.32 mg/dL. The bilirubin level was 5.67 ± 8.54 mg/dL, and the albumin level was 2.63 ± 0.51 g/dL. The pH was 7.32 ± 0.12, and the bicarbonate level was 17.9 ± 6.0 mmol/L. The APACHE II score was 28.6 ± 7.7, and the SOFA score was 13.2 ± 3.6. The target CRRT clearance was 47.4 ± 17.3 ml/kg/hour, and the initial CRRT blood flow rate was 109.2 ± 22.6 ml/min. The actual delivered dose of CRRT during the first 24 hours was 47.0 ± 16.4 ml/kg/hour.

Comparisons of the Clinical and Laboratory Parameters of CRRT Initiation

The in-hospital mortality rate was 70.4% (349 of 496 patients), and the duration of follow-up was 26.0 ± 36.1 days. The hazard ratios of kidney function parameters are listed in Table 3. Blood urea nitrogen levels above 80 mg/dL (reference, 60 mg/dL) were associated with an increased hazard ratio of in-hospital mortality using univariate (HR 1.407, 95% CI 1.089-1.817) and multivariate (HR 1.367, 95% CI 1.054-1.773) analyses. However, increased serum creatinine levels (either differences from baseline values or an increased percent) were not associated with in-hospital

Table 1. Baseline demographics and comorbidities of enrolled critically ill patients just before the initiation of renal replacement therapy (*N* = 496).

Characteristics	All participants (*N* = 496)	Survivor (*N* = 147)	Non-survivor (*N* = 349)	*P*-value
Age (years)	63.4 ± 14.3	63.9 ± 13.7	63.2 ± 14.5	0.591
Sex (male)	298 (60.1%)	88 (59.9%)	210 (60.2%)	1.000
Weight (kg)	61.3 ± 12.9	61.0 ± 10.9	61.4 ± 13.7	0.649
Hypertension	233 (47.0%)	84 (57.1%)	149 (42.7%)	0.003
Diabetes	171 (34.5%)	65 (44.2%)	106 (30.4%)	0.003
Malignancy	178 (35.9%)	38 (25.9%)	140 (40.1%)	0.001
CCI	3.32 ± 2.30	3.59 ± 2.61	3.20 ± 2.14	0.113
SIRS	361 (72.8%)	92 (62.6%)	269 (77.1%)	0.001
Sepsis	259 (52.2%)	60 (40.8%)	199 (57.8%)	0.001
Respiratory	104 (40.2%)	15 (25.0%)	89 (44.7%)	
Gastrointestinal	87 (33.6%)	23 (38.3%)	64 (32.2%)	
Genitourinary	20 (7.7%)	13 (21.7%)	7 (3.5%)	
CNS	2 (0.8%)	0 (0%)	2 (1.0%)	
Unknown	4 (1.5%)	0 (0%)	4 (2.0%)	
Others	42 (16.2%)	9 (15.0%)	33 (16.6%)	
Causes of acute kidney injury				< 0.001
Septic	236 (47.6%)	52 (35.6%)	184 (53.6%)	
Ischemic	93 (18.8%)	26 (17.8%)	67 (19.5%)	
Post-operative	44 (8.9%)	30 (20.5%)	14 (4.1%)	
Nephrotoxic	29 (5.8%)	8 (5.5%)	21 (6.1%)	
Others	94 (19.0%)	31 (21.1%)	63 (18.1%)	

Data are presented as the mean ± standard deviation or as the number and percent.
CCI, Charlson comorbidity index; CNS, central nervous system; SIRS, systemic inflammatory response syndrome.

Table 2. Clinical and laboratory parameters at the initiation of the renal replacement therapy (N = 496).

Parameters	All participants (N = 496)	Survivor (N = 147)	Non-survivor (N = 349)	P-value
Weight, ICU admission (kg)	61.5 ± 13.1	61.0 ± 11.5	61.7 ± 13.7	0.584
Time (ICU~CRRT) (hour)	83.3 ± 372.2	56.2 ± 174.1	94.8 ± 428.8	0.292
Weight, CRRT start (kg)	63.1 ± 12.9	61.9 ± 11.6	63.6 ± 13.3	0.181
Weight gain* (kg)	1.63 ± 3.63	0.94 ± 2.34	1.92 ± 4.02	0.001
Systolic BP (mmHg)	114.5 ± 26.3	120.6 ± 29.7	111.9 ± 24.2	0.002
Diastolic BP (mmHg)	65.0 ± 15.0	67.4 ± 15.2	64.0 ± 14.8	0.021
Mean BP (mmHg)	81.5 ± 17.1	85.2 ± 18.6	80.0 ± 16.2	0.002
Heart rate (/min)	104.5 ± 25.5	98.9 ± 25.6	106.9 ± 25.1	0.001
Respiratory rate (/min)	22.8 ± 7.2	20.1 ± 6.4	23.9 ± 7.3	< 0.001
Body temperature (°C)	36.4 ± 1.2	36.4 ± 1.1	36.4 ± 1.2	0.592
Urine output (ml/kg/hour)	0.46 ± 0.81	0.60 ± 0.89	0.40 ± 0.77	0.014
White blood cell (/μL)	13,279.2 ± 11,474.4	13,286.1 ± 9,941.6	13,276.3 ± 12,075.3	0.992
Hemoglobin (g/dL)	9.7 ± 2.0	9.9 ± 1.9	9.6 ± 2.0	0.05
Platelet (× 10^3/μL)	104.2 ± 77.6	116.5 ± 76.4	99.0 ± 77.7	0.022
BUN (mg/dL)	58.6 ± 32.5	53.7 ± 25.4	60.7 ± 34.9	0.013
Serum creatinine (mg/dL)	3.62 ± 2.34	4.08 ± 2.64	3.42 ± 2.17	0.008
eGFR (ml/min/1.73 m^2)	22.1 ± 14.2	19.2 ± 12.0	23.3 ± 14.9	0.003
Serum sodium (mmol/L)	136.4 ± 8.0	137.0 ± 7.2	136.2 ± 8.3	0.288
Serum potassium (mmol/L)	4.4 ± 0.9	4.2 ± 0.9	4.5 ± 0.9	0.004
Serum calcium (mg/dL)	7.94 ± 1.30	8.05 ± 1.23	7.94 ± 1.33	0.412
Serum phosphorus (mg/dL)	5.47 ± 2.32	4.64 ± 1.88	5.81 ± 2.40	< 0.001
Bilirubin (mg/dL)	5.67 ± 8.54	2.68 ± 2.97	6.93 ± 9.72	< 0.001
Albumin (g/dL)	2.63 ± 0.51	2.72 ± 0.51	2.59 ± 0.50	0.008
Prothrombin time (INR)	2.00 ± 2.33	1.49 ± 0.67	2.21 ± 2.72	< 0.001
AST (IU/L)	893.7 ± 2,367.1	494.2 ± 1,698.3	1,061.8 ± 2,581.3	0.004
ALT (IU/L)	421.6 ± 991.5	258.2 ± 797.3	490.3 ± 1,056.2	0.008
pH	7.32 ± 0.12	7.36 ± 0.10	7.30 ± 0.12	< 0.001
Bicarbonate	17.9 ± 6.0	19.9 ± 6.1	17.0 ± 5.8	< 0.001
PaO2 (mmHg)	111.5 ± 59.3	111.1 ± 50.3	111.7 ± 62.8	0.918
PaCO2 (mmHg)	35.5 ± 11.8	35.3 ± 9.3	35.5 ± 12.8	0.855
APACHE II score	28.6 ± 7.7	26.0 ± 7.3	29.7 ± 7.7	< 0.001
SOFA score	13.2 ± 3.6	11.5 ± 3.2	13.9 ± 3.5	< 0.001
Target CRRT clearance (ml/kg/hour)	47.4 ± 17.3	45.0 ± 16.6	48.4 ± 17.5	0.044
CRRT blood flow rate (ml/min)	109.2 ± 22.6	110.7 ± 23.8	108.6 ± 22.1	0.356
CRRT dialysate flow rate (ml/hour)	1,690.2 ± 711.6	1,530.1 ± 628.0	1,757.6 ± 734.5	0.001
CRRT replacement flow rate (ml/hour)	1,657.4 ± 735.9	1,492.8 ± 679.1	1,727.0 ± 748.8	0.001
CRRT delivered dose (ml/kg/hour)	47.0 ± 16.4	45.4 ± 15.4	47.7 ± 16.8	0.200

Data are presented as the mean ± standard deviation.

*Weight gain represent the difference of patients' weight from ICU admission to CRRT initiation.

BP, blood pressure; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; ICU, intensive care units.

mortality. Additionally, serum creatinine levels above 3 mg/dL and eGFR below 15 ml/min/1.73 m^2 were associated with decreased in-hospital mortality.

The HRs of conventional dialysis initiation parameters on mortality are summarized in Table 4. pH below 7.15 (reference, pH > 7.25) was associated with increased mortality (HR 2.315, 95% CI 1.586-3.380, P-for-trend < 0.001). Bicarbonate levels below 14 mmol/L (HR 2.010, 95% CI 1.542-2.620, reference bicarbonate levels > 18 mmol/L), phosphorus levels above 7.0 mg/dL (HR 1.736, 95% CI 1.313-2.296, reference phosphorus level ≤ 5.0 mg/dL), and urine output below 0.3 ml/kg/hour (HR 1.509, 95% CI 1.191-1.912, reference urine output above 0.3 ml/kg/hour) were also associated with increased in-hospital mortality. Weight gain above 2 kg from the time of admission to intensive care units to the time of CRRT initiation was

Table 3. Kidney function parameters and the hazard of mortality.

	Univariate		Multivariate	
BUN (mg/dL)		*P*-for-trend 0.009		*P*-for-trend 0.018
≤ 60 (reference)	1.0		1.0	
60-80	1.375 (1.004-1.812)	0.023	1.142 (0.861-1.515)	0.356
> 80	1.407 (1.089-1.817)	0.009	1.367 (1.054-1.773)	0.018
Serum creatinine (mg/dL)		*P*-for-trend 0.126		*P*-for-trend 0.012
≤ 3 (reference)	1.0		1.0	
3-4	0.774 (0.584-1.025)	0.074	0.655 (0.491-0.872)	0.004
4-5	0.777 (0.550-1.096)	0.151	0.676 (0.475-0.962)	0.030
> 5	0.770 (0.568-1.045)	0.094	0.630 (0.455-0.872)	0.005
Delta serum creatinine* (mg/dL)		*P*-for-trend 0.458		*P*-for-trend 0.265
≤ 1 (reference)	1.0		1.0	
1-2	0.869 (0.656-1.152)	0.330	0.772 (0.580-1.028)	0.076
2-3	1.017 (0.730-1.417)	0.919	0.668 (0.473-0.943)	0.022
> 3	1.096 (0.762-1.577)	0.622	0.839 (0.577-1.220)	0.357
Increase of serum creatinine (%)		*P*-for-trend 0.068		*P*-for-trend 0.975
≤ 50% (reference)	1.0		1.0	
50-100%	1.130 (0.773-1.651)	0.529	1.103 (0.751-1.622)	0.616
100-200%	1.194 (0.858-1.660)	0.293	1.074 (0.768-1.500)	0.677
> 200%	1.355 (0.978-1.879)	0.068	1.003 (0.714-1.410)	0.984
eGFR (ml/min/1.73 m^2)		*P*-for-trend 0.010		*P*-for-trend 0.001
> 30 (reference)	1.0		1.0	
15-30	0.912 (0.699-1.189)	0.495	0.785 (0.597-1.032)	0.083
10-15	0.807 (0.585-1.112)	0.190	0.592 (0.422-0.830)	0.002
≤ 10	0.626 (0.431-0.910)	0.014	0.548 (0.374-0.804)	0.002

Covariates included in multivariate analysis are age, sex, CCI, presence of SIRS, APACHE II scores, and SOFA scores.
*Delta serum creatinine is the difference of serum creatinine levels from baseline to the initiation of renal replacement therapy.
BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

associated with mortality according to univariate analysis (HR 1.516, 95% CI 1.215-1.892), but not according to multivariate analysis (HR 1.161, 95% CI 0.915-1.473). Potassium levels above 5.5 mmol/L were not associated with increased in-hospital mortality.

The discrimination power (ROC curve and AUC) of these parameters with respect to in-hospital mortality was compared among the kidney function parameters and conventional dialysis initiation parameters (Fig. 1). When the ROC curves were analyzed for these parameters, the AUC was 0.701 (95% CI 0.644-0.759) for the composite scores of the conventional dialysis initiation parameters, 0.571 (95% CI 0.511-0.630) for the blood urea nitrogen levels, 0.462 (95% CI 0.399-0.525) for the serum creatinine levels, 0.524 (95% CI 0.460-0.589) for the difference in serum creatinine values from the baseline to the time of CRRT initiation, 0.572 (95% CI 0.508-0.636) for the increased percentage in serum creatinine, 0.541 (95% CI 0.478-0.605) for the eGFR, and AKI Network stage (AUC 0.627, 95% CI 0.561-0.692).

Discussion

Traditionally, several indications have been considered when deciding whether to administer RRT to patients with AKI, including hyperkalemia, metabolic acidosis, oliguria, and volume overload (Bellomo and Ronco 1998). However, it remains unclear when RRT should be initiated based on these physiological parameters. Recently, many clinical practitioners have begun to make this choice according to the serum creatinine levels, blood urea nitrogen levels, or stage of AKI derived from the serum creatinine or urine output data. However, uncertainty persists regarding the appropriate time to initiate RRT. We aimed to investigate and compare the predictive values of kidney function parameters and conventional physiological parameters that are considered useful when initiating RRT.

We selected blood urea nitrogen, serum creatinine and its derivatives (considering both the difference from baseline to the present time and the increase in percentage), and eGFR as parameters that describe kidney function. The blood urea nitrogen levels were significantly associated with mortality according to univariate and multivariate

Table 4. Physiological parameters and the hazard of mortality.

	Univariate		Multivariate	
pH		*P*-for-trend < 0.001		*P*-for-trend < 0.001
> 7.25 (reference)	1.0		1.0	
7.2-7.25	1.858 (1.350-2.558)	< 0.001	1.579 (1.120-2.224)	< 0.009
7.15-7.2	2.468 (1.689-3.606)	< 0.001	1.971 (1.319-2.946)	0.001
≤ 7.15	2.909 (2.055-4.119)	< 0.001	2.315 (1.586-3.380)	< 0.001
Bicarbonate (mmol/L)		*P*-for-trend < 0.001		*P*-for-trend < 0.001
> 18 (reference)	1.0		1.0	
14-18	1.534 (1.842-3.044)	0.002	1.479 (1.129-1.939)	0.005
≤ 14	2.368 (1.842-3.044)	< 0.001	2.010 (1.542-2.620)	< 0.001
Potassium (mmol/L)				
≤ 5.5 (reference)	1.0		1.0	
> 5.5	1.132 (0.827-1.550)	0.437	1.047 (0.758-1.444)	0.782
Phosphorus (mg/dL)		*P*-for-trend < 0.001		*P*-for-trend < 0.001
≤ 5.0 (reference)	1.0		1.0	
5-7	1.409 (1.100-1.804)	0.007	1.364 (1.058-1.758)	0.017
> 7.0	2.219 (1.703-2.892)	< 0.001	1.736 (1.313-2.296)	< 0.001
Urine output (ml/kg/hr)				
> 0.3 ml/kg/hr (reference)	1.0		1.0	
≤ 0.3 ml/kg/hr	1.652 (1.311-2.080)	< 0.001	1.509 (1.191-1.912)	0.001
Weight gain*		*P*-for-trend 0.010		*P*-for-trend 0.001
≤ 2 kg (reference)	1.0		1.0	
> 2 kg	1.516 (1.215-1.892)	< 0.001	1.161 (0.915-1.473)	0.218

Covariates included in multivariate analysis are age, sex, CCI, presence of SIRS, APACHE II scores, and SOFA scores.
*Wait gain is the weight gain from admission to the intensive care units to the initiation of CRRT.

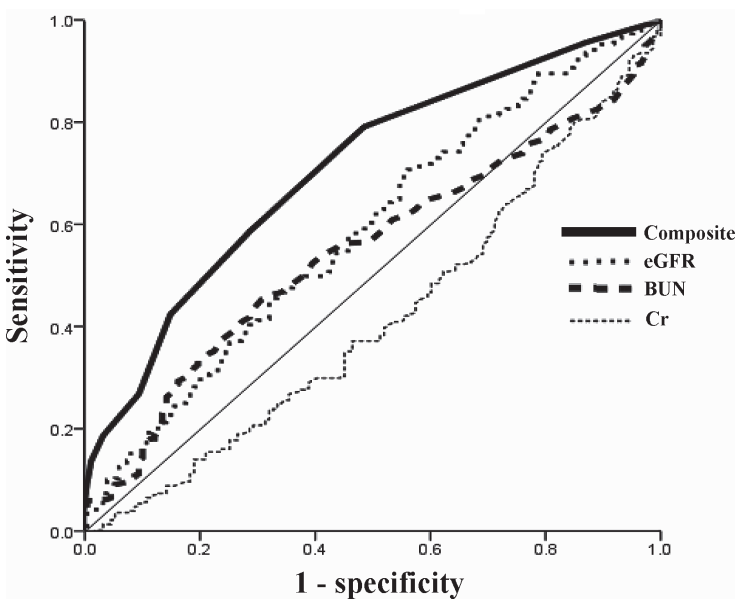

Fig. 1. Receiver operating characteristic (ROC) curves and area under the curve (AUC) for mortality.
Composite, sum of the parameters as follows: pH (0, > 7.25; 1, 7.2-7.25; 2, 7.15-7.2; 3, ≤ 7.15), bicarbonate levels (0, > 18 mmol/L; 1, 14-18 mmol/L; 2, ≤ 14 mmol/L), phosphorus levels (0, ≤ 5 mg/dL; 1, 5-7 mg/dL; 2, > 7 mg/dL), potassium levels (0, ≤ 5.5 mmol/L; 1, > 5.5 mmol/L), weight gain from the time of admission to the intensive care units to the time of CRRT initiation (0, ≤ 2 kg; 1, > 2 kg), and urine output (0, > 0.3 ml/kg/hour; 1, ≤ 0.3 ml/kg/hour). BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate.

analyses. Blood urea nitrogen is the representative indicator for uremic products, which are increased during decreased kidney function, and has been used as an important parameter during the initiation of RRT. Although several researchers have reported that blood urea nitrogen levels are unrelated to mortality in AKI (Bagshaw et al. 2009; Jamale et al. 2013), the majority of studies consistently found that increased blood urea nitrogen levels were significantly associated with mortality in critically ill patients with AKI (Gettings et al. 1999; Liu et al. 2006; Wu et al. 2007; Ostermann and Chang 2009; Carl et al. 2010). In our study, the strength of the risk associated with blood urea nitrogen did not surpass the expected findings. On the contrary, serum creatinine levels and eGFR were negatively associated with mortality, and the associations were even stronger after multivariate analysis was performed. The serum creatinine level is a useful parameter for assessing renal function in patients with stable kidney function or chronic kidney disease and serves as an important variable in various equations used to estimate GFR (Levey et al. 1999, 2006, 2009). However, in patients with rapidly deteriorating kidney function or critically ill patients with severe catabolism, decreased serum creatinine levels can indicate a loss of muscle mass or debilitating clinical conditions. Several similar reports have indicated that decreased serum creatinine levels are associated with increased mortality after AKI (Bagshaw et al. 2009, 2012; Ostermann and Chang 2009; Jamale et al. 2013). Interestingly, several studies have recently reported that in patients with advanced chronic kidney disease, the early initiation of RRT based on eGFR was unable to improve patient survival (Cooper et al. 2010; Chang et al. 2012), and even led to worse survival and clinical outcomes (Crews et al. 2014). Considering these findings, clinicians should not initiate RRT based solely on serum creatinine levels and eGFR.

Reflecting on the fact that traditional indications for RRT include metabolic acidosis, hyperkalemia and other electrolyte imbalances, oliguria, and volume overload, we selected the pH, bicarbonate level, potassium level, phosphorus level, urine output, and weight gain as physiological parameters. Although the serum bicarbonate level and pH are useful indicators of metabolic acidosis, there is little evidence that these parameters increase the risk of mortality after AKI. Ostermann and Chang (2009) reported that a pH below 7.2 was significantly associated with a poor prognosis after AKI. In our study, a pH below 7.25 and a serum bicarbonate level below 18 mmol/L were incrementally associated with mortality, and a pH below 7.15 and a serum bicarbonate level below 14 mmol/L were more strongly associated with the risk compared to other parameters. Contrary to expectations, the serum potassium levels were not associated with mortality at any level. On the other hand, serum phosphorus levels were positively associated with mortality. There are several explanations regarding why serum potassium and phosphorus might play such different roles in the risk of mortality after AKI. Hyperkalemia can be more easily treated using medical therapy, including cation exchange resin (e.g., ion polystyrene sulfonate) medications or enema, intravenous insulin injection, and other medications. The risk of hyperkalemia is well known among intensive care unit staff, and hyperkalemia is generally treated more rapidly compared to other electrolyte imbalances. On the other hands, hyperphosphatemia, which is usually treated aggressively in patients with advanced chronic kidney disease, is often overlooked among clinicians who care critically ill patients in intensive care units. Although we collected laboratory data before CRRT initiation and did not continue to gather and adjust information concerning the medical treatment of electrolyte imbalance upon final analysis, it is evident that the risk of hyperkalemia is not significant and that the risk of hyperphosphatemia is higher than expected. Oliguria, fluid balance, and volume overload are known risk factors of mortality and indications for RRT in AKI (Sugahara and Suzuki 2004; Bagshaw et al. 2012). In our study, we found a significant association between decreased urine output (urine output below 0.3 ml/kg/hr; HR, 1.509; 95% CI, 1.191-1.912) and the risk of mortality after AKI. Weight gain was also associated with a significant risk according to the univariate analysis; however, this risk was not observed in the multivariate analysis. Pulmonary edema is an indicator of volume overload; however, the measurement itself is inevitably semi-quantitative. Weight gain was selected in our study as a parameter of volume overload, and its effect on the risk of mortality was not significant, which was likely due to the relative inaccuracy of the measurement compared to urine output.

The stage of AKI, for example, according to the Risk Injury Failure Loss End-stage kidney disease (RIFLE) or Acute Kidney Injury Network (AKIN) criteria, is broadly used to classify the severity of illness and to predict prognosis (Bellomo et al. 2004; Mehta et al. 2007; Valette and du Cheyron 2013). Shiao et al. (2009) reported that the RIFLE criteria were useful in predicting post-AKI mortality; however, Chou et al. (2011) stated that the RIFLE criteria were not associated with the mortality of critically ill patients with AKI. In our study, we noted that the AKIN stage (stage 2: HR, 0.819; 95% CI, 0.527-1.273; stage 3: HR, 1.277; 95% CI, 0.945-1.725; reference, stage 0 or 1) was not associated with the risk of mortality after AKI. The RIFLE or AKIN stage of AKI is based on increased levels of serum creatinine and decreased urine output. The absence of an effect of the AKIN stage on mortality in our study results from the negative or the insignificant effect of the serum creatinine and its derivatives (difference or change in percentage) on mortality. At minimum, in critically ill patients with AKI who receive RRT, serum creatinine indices or the stage of AKI derived from serum creatinine levels should be carefully applied to the prognostic assessment or decision concerning whether to initiate RRT.

In our study, the predictive value of the physiological parameters was generally superior to that of the kidney

function parameters. In clinical practice, clinicians decide whether to initiate RRT while taking into consideration various clinical, physiological and laboratory findings that can serve as effective indicators for RRT. Therefore, we combined the physiological parameters included in our study with the composite score to predict the post-AKI mortality and compared the ROC curves and AUC for mortality. The composite scores of the physiological parameters were significantly higher than all of the kidney function parameters.

The optimal timing to initiate RRT is critical in the management of critically ill patients with AKI. Various clinical, physiological, and laboratory parameters have been deemed important while deciding when to initiate RRT. Our study confirms that the classical physiological parameters, including pH, serum bicarbonate levels, phosphorus levels, and urine output at the start of RRT, are significantly associated with prognosis after AKI and that composite scores that include these physiological parameters are superior to blood urea nitrogen, serum creatinine, eGFR, and the stage of AKI derived from serum creatinine levels. Moreover, our data suggest cut-off levels for these physiological parameters, which can be used in clinical practice as reference values for initiating RRT. Additional randomized clinical trials are needed to validate the predictive values and cut-off levels of classical physiological parameters in critically ill patients with AKI.

Acknowledgments

This work was supported by a grant from the National Research Foundation of Korea (No. 2013R1A1A1012689). We gratefully acknowledge the dedication of clinical research coordinators and medical staff members of the participating centers. The authors would like to thank the generosity of the study participants.

Conflict of Interest

The authors declare no conflict of interest.

References

Bagshaw, S.M., Uchino, S., Bellomo, R., Morimatsu, H., Morgera, S., Schetz, M., Tan, I., Bouman, C., Macedo, E., Gibney, N., Tolwani, A., Oudemans-van Straaten, H.M., Ronco, C. & Kellum, J.A. (2009) Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. *J. Crit. Care*, **24**, 129-140.

Bagshaw, S.M., Wald, R., Barton, J., Burns, K.E., Friedrich, J.O., House, A.A., James, M.T., Levin, A., Moist, L., Pannu, N., Stollery, D.E. & Walsh, M.W. (2012) Clinical factors associated with initiation of renal replacement therapy in critically ill patients with acute kidney injury-a prospective multicenter observational study. *J. Crit. Care*, **27**, 268-275.

Bellomo, R., Kellum, J. & Ronco, C. (2001) Acute renal failure: time for consensus. *Intensive Care Med.*, **27**, 1685-1688.

Bellomo, R. & Ronco, C. (1998) Indications and criteria for initiating renal replacement therapy in the intensive care unit. *Kidney Int. Suppl.*, **66**, S106-109.

Bellomo, R., Ronco, C., Kellum, J.A., Mehta, R.L. & Palevsky, P. (2004) 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*, **8**, R204-212.

Carl, D.E., Grossman, C., Behnke, M., Sessler, C.N. & Gehr, T.W. (2010) Effect of timing of dialysis on mortality in critically ill, septic patients with acute renal failure. *Hemodial. Int.*, **14**, 11-17.

Chang, J.H., Rim, M.Y., Sung, J., Ko, K.P., Kim, D.K., Jung, J.Y., Lee, H.H., Chung, W. & Kim, S. (2012) Early start of dialysis has no survival benefit in end-stage renal disease patients. *J. Korean Med. Sci.*, **27**, 1177-1181.

Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.*, **40**, 373-383.

Chou, Y.H., Huang, T.M., Wu, V.C., Wang, C.Y., Shiao, C.C., Lai, C.F., Tsai, H.B., Chao, C.T., Young, G.H., Wang, W.J., Kao, T.W., Lin, S.L., Han, Y.Y., Chou, A., Lin, T.H., et al. (2011) Impact of timing of renal replacement therapy initiation on outcome of septic acute kidney injury. *Crit. Care*, **15**, R134.

Coca, S.G., Yusuf, B., Shlipak, M.G., Garg, A.X. & Parikh, C.R. (2009) Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am. J. Kidney Dis.*, **53**, 961-973.

Cooper, B.A., Branley, P., Bulfone, L., Collins, J.F., Craig, J.C., Fraenkel, M.B., Harris, A., Johnson, D.W., Kesselhut, J., Li, J.J., Luxton, G., Pilmore, A., Tiller, D.J., Harris, D.C. & Pollock, C.A. (2010) A randomized, controlled trial of early versus late initiation of dialysis. *N. Engl. J. Med.*, **363**, 609-619.

Crews, D.C., Scialla, J.J., Liu, J., Guo, H., Bandeen-Roche, K., Ephraim, P.L., Jaar, B.G., Sozio, S.M., Miskulin, D.C., Tangri, N., Shafi, T., Meyer, K.B., Wu, A.W., Powe, N.R. & Boulware, L.E. (2014) Predialysis health, dialysis timing, and outcomes among older United States adults. *J. Am. Soc. Nephrol.*, **25**, 370-379.

Gettings, L.G., Reynolds, H.N. & Scalea, T. (1999) Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. *Intensive Care Med.*, **25**, 805-813.

Hoste, E.A. & De Waele, J.J. (2008) Acute kidney injury in the intensive care unit: it's the gene, stupid! *Crit. Care Med.*, **36**, 3266-3267.

Jamale, T.E., Hase, N.K., Kulkarni, M., Pradeep, K.J., Keskar, V., Jawale, S. & Mahajan, D. (2013) Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. *Am. J. Kidney Dis.*, **62**, 1116-1121.

Karvellas, C.J., Farhat, M.R., Sajjad, I., Mogensen, S.S., Leung, A.A., Wald, R. & Bagshaw, S.M. (2011) A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit. Care*, **15**, R72.

Khwaja, A. (2012) KDIGO Clinical Practice Guidelines for Acute Kidney Injury. *Nephron. Clin. Pract.*, **120**, 179-184.

Knaus, W.A., Draper, E.A., Wagner, D.P. & Zimmerman, J.E. (1985) APACHE II: a severity of disease classification system. *Crit. Care Med.*, **13**, 818-829.

Lameire, N., Van Biesen, W. & Vanholder, R. (2005) Acute renal failure. *Lancet*, **365**, 417-430.

Lameire, N., Van Biesen, W. & Vanholder, R. (2006) The changing epidemiology of acute renal failure. *Nat. Clin. Pract. Nephrol.*, **2**, 364-377.

Lameire, N.H., Bagga, A., Cruz, D., De Maeseneer, J., Endre, Z., Kellum, J.A., Liu, K.D., Mehta, R.L., Pannu, N., Van Biesen, W. & Vanholder, R. (2013) Acute kidney injury: an increasing global concern. *Lancet*, **382**, 170-179.

Levey, A.S., Bosch, J.P., Lewis, J.B., Greene, T., Rogers, N. & Roth, D. (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction

equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med.*, **130**, 461-470.

Levey, A.S., Coresh, J., Greene, T., Stevens, L.A., Zhang, Y.L., Hendriksen, S., Kusek, J.W. & Van Lente, F. (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann. Intern. Med.*, **145**, 247-254.

Levey, A.S., Stevens, L.A., Schmid, C.H., Zhang, Y.L., Castro, A.F. 3rd., Feldman, H.I., Kusek, J.W., Eggers, P., Van Lente, F., Greene, T. & Coresh, J. (2009) A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.*, **150**, 604-612.

Liu, K.D., Himmelfarb, J., Paganini, E., Ikizler, T.A., Soroko, S.H., Mehta, R.L. & Chertow, G.M. (2006) Timing of initiation of dialysis in critically ill patients with acute kidney injury. *Clin. J. Am. Soc. Nephrol.*, **1**, 915-919.

Mehta, R.L. (2001) Indications for dialysis in the ICU: renal replacement vs. renal support. *Blood Purif.*, **19**, 227-232.

Mehta, R.L., Kellum, J.A., Shah, S.V., Molitoris, B.A., Ronco, C., Warnock, D.G. & Levin, A. (2007) Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit. Care*, **11**, R31.

Mehta, R.L., Pascual, M.T., Soroko, S., Savage, B.R., Himmelfarb, J., Ikizler, T.A., Paganini, E.P. & Chertow, G.M. (2004) Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int.*, **66**, 1613-1621.

Metcalfe, W., Simpson, M., Khan, I.H., Prescott, G.J., Simpson, K., Smith, W.C. & MacLeod, A.M. (2002) Acute renal failure requiring renal replacement therapy: incidence and outcome. *QJM*, **95**, 579-583.

Muckart, D.J. & Bhagwanjee, S. (1997) American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit. Care Med.*, **25**, 1789-1795.

Ostermann, M. & Chang, R.W. (2009) Correlation between parameters at initiation of renal replacement therapy and outcome in patients with acute kidney injury. *Crit. Care*, **13**, R175.

Ostermann, M., Dickie, H. & Barrett, N.A. (2012) Renal replacement therapy in critically ill patients with acute kidney injury: when to start. *Nephrol. Dial. Transplant.*, **27**, 2242-2248.

Palevsky, P.M. (2005) Renal replacement therapy I: indications and timing. *Crit. Care Clin.*, **21**, 347-356.

Palevsky, P.M., Zhang, J.H., O'Connor, T.Z., Chertow, G.M., Crowley, S.T., Choudhury, D., Finkel, K., Kellum, J.A., Paganini, E., Schein, R.M., Smith, M.W., Swanson, K.M., Thompson, B.T., Vijayan, A., Watnick, S., et al. (2008) Intensity of renal support in critically ill patients with acute kidney injury. *N. Engl. J. Med.*, **359**, 7-20.

Shiao, C.C., Wu, V.C., Li, W.Y., Lin, Y.F., Hu, F.C., Young, G.H., Kuo, C.C., Kao, T.W., Huang, D.M., Chen, Y.M., Tsai, P.R., Lin, S.L., Chou, N.K., Lin, T.H., Yeh, Y.C., et al. (2009) Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery. *Crit. Care*, **13**, R171.

Sugahara, S. & Suzuki, H. (2004) Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. *Hemodial. Int.*, **8**, 320-325.

Tolwani, A. (2012) Continuous renal-replacement therapy for acute kidney injury. *N. Engl. J. Med.*, **367**, 2505-2514.

Uchino, S., Kellum, J.A., Bellomo, R., Doig, G.S., Morimatsu, H., Morgera, S., Schetz, M., Tan, I., Bouman, C., Macedo, E., Gibney, N., Tolwani, A. & Ronco, C. (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*, **294**, 813-818.

Valette, X. & du Cheyron, D. (2013) A critical appraisal of the accuracy of the RIFLE and AKIN classifications in defining "acute kidney insufficiency" in critically ill patients. *J. Crit. Care*, **28**, 116-125.

Vincent, J.L., Moreno, R., Takala, J., Willatts, S., De Mendonca, A., Bruining, H., Reinhart, C.K., Suter, P.M. & Thijs, L.G. (1996) 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.*, **22**, 707-710.

Wald, R., Quinn, R.R., Luo, J., Li, P., Scales, D.C., Mamdani, M.M. & Ray, J.G. (2009) Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA*, **302**, 1179-1185.

Wu, V.C., Ko, W.J., Chang, H.W., Chen, Y.S., Chen, Y.W., Chen, Y.M., Hu, F.C., Lin, Y.H., Tsai, P.R. & Wu, K.D. (2007) Early renal replacement therapy in patients with postoperative acute liver failure associated with acute renal failure: effect on postoperative outcomes. *J. Am. Coll. Surg.*, **205**, 266-276.