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What Are the Long-Term Outcomes After Acute, Severe Kidney Injury and What Should We Be Doing About Them?*

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The kidney is a barometer of the severity of critical illness in an individual patient. In this context, the risk of developing clinically significant renal impairment (acute kidney injury [AKI]) is related to the patient's renal physiological reserve and the severity of the systemic illness (1).

The physiological reserve can be inferred based upon age-related loss and disease-related loss (severity and duration), most commonly hypertension and diabetes mellitus. Chronic renal impairment (or disease, chronic kidney disease [CKD]), which is synonymous with a significantly reduced renal physiological reserve, is best defined based upon a combination of a functional measure, most commonly estimated glomerular filtration rate (eGFR) and a measure of damage, most commonly urinary albumin-to-creatinine ratio (ACR) (2). Depending upon the underlying cause and the presence and severity of complications and comorbidities, CKD may progress over months to years, to end-stage renal disease (ESRD) (3). However, interventions that treat the underlying cause, and/or modify the complications/comorbidities, can slow down or even arrest this progression (4).

Although CKD predisposes to AKI, severe AKI, in the context or absence of CKD, can result in, or cause accelerated progression of, CKD (5).

The analogy of the kidney as a critical illness severity barometer is reenforced by the association of an AKI with an increase in the risk of all-cause, acute episode mortality; the magnitude of the risk being proportional to the severity of the AKI. There is a similar association between ESRD and all-cause mortality. The reasons for these associations relate to the emerging appreciation of acute and chronic, organ cross talk (6). After all, these associations persist despite the widespread availability of renal replacement therapies (RRTs). RRTs are undoubtedly effective in reversing fluid overload, clearing small molecules, and normalizing electrolytes and pH. However, considerable controversy persists regarding RRT including thresholds for/timing of initiation, optimal modality and dose, and immediate risks and benefits. There are considerable costs, both personal and financial, of both acute and chronic RRT; hence, making rational decisions based upon reliable prognostic data are highly desirable though currently elusive.

In this issue of *Critical Care Medicine*, An et al (7) published a retrospective, observational study of the long-term, renal and mortality outcomes of a cohort of 1,764 patients who received RRT during their acute critical illness between 2009 and 2013. At 3 months postinitiation of RRT, only 32% of the cohort was alive. This compares to historical rates of 40%; however, these have been improving with more recent studies that report 3-month survival rates of ~ 55% (8).

The authors identified 331 of 462 survivors with renal function data preceding their acute illness and at 3 months postinitiation of RRT. I have reproduced the renal outcome at 3-month data in **Table 1**. This demonstrates that ~ 65% of patients with baseline CKD stages 1–4 had either returned to baseline function or had suffered less than 35% reduction in eGFR. Though small in numbers, this compares with only 13% of the patients with a baseline CKD stage 5. Over a median further follow-up period of 19 months from initiation of RRT, a small but significant proportion of patients suffered further CKD progression, some to ESRD. The risk of deterioration was markedly greater that CKD three patients receiving long-term surveillance. The authors then compared these long-term outcomes of their cohort to baseline CKD matched individuals. They found that if a patient had developed an AKI requiring RRT and their renal function had deteriorated by greater than 35% (decrease in eGFR), their risk of progressing to ESRD was 250× that of matched controls. If the patient had developed an AKI requiring RRT and their renal function had not deteriorated by greater than 35% (decrease in eGFR), their risk of progressing to ESRD was 14× that of matched controls. Those patients, who had suffered a progression in their CKD at 3 months, had a 2× increased risk of all-cause mortality compared with those that had not.

*See also p. 47.

Key Words: acute kidney injury; continuous renal replacement therapy; long-term outcome; progressive chronic kidney disease

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TABLE 1. Renal Outcomes in 331 Survivors at 3 Months Following the Initiation of Renal Replacement Therapy

Premorbid Chronic Kidney Disease Stage	Return to Baseline (%)	Minor Progression (Fall in eGFR < 35%) (%)	Major Progression (Fall in eGFR > 35%) (%)	End-Stage Renal Disease (%)
1	10 (20)	20 (41)	15 (31)	4 (8)
2	31 (34)	30 (33)	19 (21)	11 (12)
3	50 (51)	18 (18)	10 (10)	21 (21)
4	31 (46)	13 (19)	5 (7)	19 (28)
5	3 (13)	0	0	21 (88)

eGFR = estimated glomerular filtration rate.

The study is limited by its retrospective design and its reliance on a single premorbid assessment of eGFR without an assessment of ACR. It may also lack generalizability because of the lack of ethnic diversity in the patient cohort and the unusually high acute mortality.

The long-term consequences of AKI have been an area of increasing interest in the last few years. The topic is large and complex and has been the subject of some excellent recent review articles (6, 9, 10). The emerging story is one of significant risks of recurrent AKI, progressive CKD, cardiovascular morbidity, and increase mortality. The study by An et al (7) adds significantly to this body of work by providing some of the most detailed long-term follow-up data available. It suggests that baseline renal function is not necessarily a useful predictor of long-term prognosis, with the probable exception of CKD stage 5. Following severe AKI, progression of CKD certainly affects a significant minority of patients. These patients may well benefit from the same interventions as other progressive CKD patients (4) thereby reducing their risk of ESRD and death.

Over recent years, there has been an emerging maturity in the critical care community that has rightly drawn our attention away from merely considering short-term survival from critical illness, to also focusing on long-term survival, and most importantly, the quality of that survival. The study by An et al (7) adds yet another reason for detailed follow up of survivors of critical illness. To date, much of the focus of critical care follow-up has concerned itself with physical and psychologic rehabilitation, together with ensuring specialist follow up of primary and secondary pathologies. I would advocate that as critical care physicians, we should be screening for and managing the common cardiac, respiratory, renal, and other chronic organ pathologies that our patients suffer from. This study makes an unambiguous case for a detailed assessment of CKD at 3 months and beyond with specialist referral for those patients who do suffer CKD progression.

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Chronic Kidney Disease After Acute Kidney Injury Requiring Continuous Renal Replacement Therapy and Its Impact on Long-Term Outcomes: A Multicenter Retrospective Cohort Study in Korea*

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Objectives: Severe acute kidney injury requiring continuous renal replacement therapy is associated with a high risk of early mortality. Our objectives were to identify a cohort of early survivors and to follow their renal progress and long-term mortality.

Design: Multicenter, observational, retrospective cohort study.

Setting: ICUs in tertiary academic hospitals in Korea.

Patients: From 2009 to 2013, we identified 1,764 severe acute kidney injury patients who were started on continuous renal replacement therapy at four hospitals. Of these, we identified 331 survivors for whom we could identify renal function at baseline and at 3 months.

Interventions: None.

Measurements and Main Results: The 331 patients were separated into two groups based on their renal function at 3 months after the start of continuous renal replacement therapy. Those who displayed significant deterioration in renal function compared to baseline, defined as greater than or equal to 50% increase in serum creatinine or greater than or equal to 35% decrease in the estimated glomerular filtration rate, or those who continued to receive renal replacement therapy were designated as a "3-month chronic kidney disease progression" group. Those with a return to baseline, less than 50% increase in serum creatinine or less than 35% decrease in the estimated glomerular filtration rate, were designated as a "3-month chronic kidney disease nonprogression" group. The acute kidney injury patients requiring continuous renal replacement therapy showed a higher risk of progression to end-stage renal disease compared to that of stage 3 chronic kidney disease patients who did not undergo an acute kidney injury episode, even if the acute kidney injury was recovered at 3 months after continuous renal replacement therapy initiation. Furthermore, "3-month chronic kidney disease progression" was associated with a high risk of progression to end-stage renal disease and long-term mortality over a median follow-up period of 12.7 (3.8–33.2) and 20.4 (7.5–39.7) months, respectively. Older age, higher baseline serum creatinine levels, and higher blood urea nitrogen concentrations at continuous renal replacement therapy initiation, and lower 24-hour urine output after continuous renal replacement therapy initiation are associated with an increased risk of "3-month chronic kidney disease progression."

Conclusions: Renal functional assessment at 3 months after continuous renal replacement therapy initiation can be useful in predicting progression to end-stage renal disease and long-

*See also p. 136.

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term mortality. Furthermore, continuous close monitoring and management of acute kidney injury patients requiring continuous renal replacement therapy are required, even in those with recovered renal function. (*Crit Care Med* 2017; 45:47–57)
Key Words: acute kidney injury; chronic kidney disease; continuous renal replacement therapy; long-term outcomes

Although continuous renal replacement therapy (CRRT) has been considered as one useful treatment modality in the management of critically ill patients with fluid overload and metabolic imbalance who cannot tolerate the hemodynamic shifts of intermittent hemodialysis (1), mortality remains high (2–5). Thus, improved prognostic assessment is vital for guiding medical decision making and optimizing the use of limited resources. However, no widely acknowledged predictive model exists despite several attempts to identify potential risk factors for death (6, 7). In addition, most previous research has primarily focused on assessing in-hospital mortality in patients with acute kidney injury (AKI) requiring CRRT (3, 8–10), and to the best of our knowledge, only a few reports have assessed long-term outcomes following discharge (1, 11). Therefore, we are unable to predict long-term renal outcomes and the mortality risk of early survivors although this information is highly sought after by investigators.

In the present study, we primarily identified a cohort of early survivors and analyzed the effects of AKI episodes in patients requiring CRRT on long-term renal outcomes compared with a control population of patients who had normal renal function or each stage of chronic kidney disease (CKD), but did not experience an AKI episode. We then assessed whether 3-month CKD progression among AKI patients was a risk factor for long-term clinical outcomes such as progression to end-stage renal disease (ESRD) and long-term mortality. We also investigated which factors are associated with 3-month CKD progression.

MATERIALS AND METHODS

Study Population

From September 2009 to December 2013, 1,764 adult severe AKI patients started CRRT in ICUs in a multicenter cohort (Seoul National University Hospital, Seoul National University Boramae Medical Center, Seoul National University Bundang Hospital, and Yonsei University Medical Center) in Korea. The patients who survived and had laboratory results indicating renal function at 3 months after the start of CRRT were included in this study. Patients who had already received renal replacement therapy (RRT) due to ESRD and without data on baseline renal function were excluded. A total of 331 patients were enrolled in this study (**Fig. 1**). We also enrolled a control population of 11,481 patients who comprised the following two groups and did not experience an AKI episode: the KoreaN Cohort Study for Outcome in Patients With CKD, a national prospective cohort including CKD stage 1–5 nondialysis patients for which the design and methods have been previously published (12) and overall outpatients of the Nephrology clinic at Seoul National University Boramae Medical Center from 2009 to 2013. This study was approved by the Institutional Review Board (number: 26-2014-15/022). The need for informed consent from patients was waived because of the retrospective design of the study. All clinical investigations were conducted in accordance with the guidelines of the 2013 Declaration of Helsinki.

Data Collection

Patient demographics and baseline clinical characteristics at the time of hospitalization were assessed by the examination of electronic medical records. Detailed evaluations of coexisting medical conditions, ICU records, and information related to CRRT were also undertaken for all identified patients using the electronic medical record systems of the above-mentioned institutions.

Overall, comorbidities were defined by diagnosis codes based on the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision. Hypertension and diabetes were also defined as the concurrent use of antihypertensive drugs and oral hypoglycemic agents or insulin, respectively. Diabetic nephropathy was defined as severely increased albuminuria with urinary albumin excretion above 300 mg/d but without coexisting intrinsic renal disease in diabetic patients. Congestive heart failure or myocardial infarction was defined by echocardiography or coronary angiography. A cerebrovascular accident was defined as an ischemic stroke or a documented transient ischemic attack, with the exception of an intracerebral hemorrhage. Peripheral vascular disease included only lesions diagnosed by peripheral angiography that required revascularization. The Charlson Comorbidity Index (CCI) was calculated as described elsewhere (13, 14).

As indicators of illness severity, the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were calculated at the time of CRRT initiation (9). The decision to administer

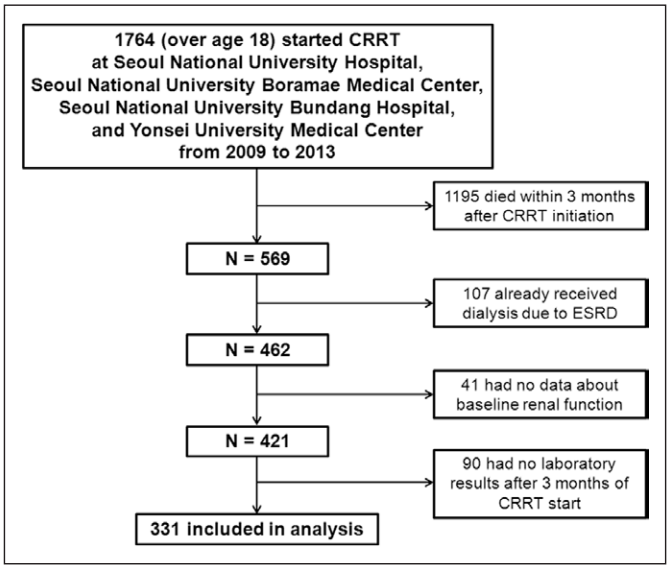

Figure 1. Flow diagram for patient enrollment. CRRT = continuous renal replacement therapy, ESRD = end-stage renal disease.

vasopressors or to initiate mechanical ventilation was made by the attending physicians and the intensivists in ICUs according to the hemodynamic status of each patient.

The contributing factors for AKI (septic shock, cardiogenic shock, hypovolemia, drug induced, major surgery, and others) (8, 15, 16) were initially categorized by electronic medical record review and confirmed based on the clinical judgment of the researchers. In the cases that more than one factors occurred simultaneously and that were complicated, the major and most influential factor was selected based on clinical judgment of the researchers who were thoroughly blinded to the clinical outcomes. Drug-induced AKI was diagnosed if offending drugs were administered within at least 2 weeks prior to the onset of AKI and if all other causes of AKI were absent.

The decision to initiate CRRT and the CRRT settings, including target clearance, blood flow, dialysate and replacement fluid rates, and anticoagulation administration were determined through close discussion and consultation with nephrologists. The criteria for CRRT initiation included medically intractable or persistent electrolyte imbalance and/or metabolic acidosis and decreased urine output with volume overload and/or progressive azotemia. Hemodynamic instability was also an important indication. Generally, vascular access for CRRT was via a femoral venous catheter, and the predilution method of continuous venovenous hemodiafiltration was mostly performed. Blood flow was gradually increased from an initial rate of 100 to 150 mL/min according to the hemodynamic status of the patient. Although the target clearance was maintained at 35–40 mL/kg/hr in most patients, it was increased to 60 mL/kg/hr and above in patients with severe sepsis or septic shock (17), if possible. Additionally, anticoagulation was selected based on the decision of nephrologists, depending on bleeding tendency or contraindications to conventional heparin. After CRRT initiation, attending physicians and experienced nurses monitored the body weights, urine output, laboratory results, actual delivered doses, and hemodynamic statuses of the patients and discussed the results with nephrologists to maintain the adequacy of CRRT.

Baseline serum creatinine (sCr) levels, defined as the latest measurements within 6 months before hospitalization related to the AKI episode requiring CRRT, were collected. sCr levels were measured using an assay based on isotope dilution mass spectrometry (IDMS), and the estimated glomerular filtration rate (eGFR) was calculated using the following IDMS-traceable Modification of Diet in Renal Disease equation: eGFR (mL/min/1.73 m^2) = 175 × $(sCr)^{-1.154}$ × $(\text{age in years})^{-0.203}$ × (0.742 if female). According to the baseline eGFR, the patients were classified into five stages. In this study, CKD was defined as an eGFR less than 60 mL/min/1.73 m^2 (stage 3–5) lasting for at least 3 months, regardless of proteinuria or microalbuminuria, largely because data on proteinuria and other parameters suggestive of renal damage were not available for all recruited patients. The laboratory findings, including renal function measured at the time of CRRT initiation, at 24 hours, at 1 week, at 1, 2, 3, 6, 9, and 12 months after the start of CRRT, and at the last visit, were obtained from the electronic medical records.

Clinical Outcomes

First, the entire patient population was divided into three groups based on their renal function at 3 months after CRRT start: group 1, the patients whose renal function was returned to their baseline value; group 2, those who had a minor deterioration in renal function compared to baseline, defined as an increase in sCr of less than 50% or a decrease in the eGFR of less than 35%; and group 3, those who had a major deterioration in renal function compared to baseline, defined as an increase in sCr of greater than 50% or a decrease in the eGFR of greater than 35%, or those who continued to receive RRT. Group 3 was designated as "3-month CKD progression" (18), and a composite of groups 1 and 2 was designated as "3-month CKD nonprogression".

We primarily analyzed the effect of AKI episodes on long-term renal outcomes in patients requiring CRRT compared with the control patients who had normal renal function or each stage of CKD but did not experience an AKI episode. We then attempted to assess whether "3-month CKD progression" was a risk factor for long-term clinical outcomes such as progression to ESRD and long-term mortality among AKI patients who required CRRT treatment. Progression to ESRD was defined as the start of long-term RRT or eGFR less than 15 mL/min/1.73 m^2 lasting for at least 3 months. In addition, we identified factors associated with reaching "3-month CKD progression."

Statistical Analysis

Categoric variables described as frequencies and proportions were compared using chi-square tests. After a test for normality, the nonnormally distributed variables were expressed as the medians (25–75th percentiles) and were compared using the Mann-Whitney *U* or Kruskal-Wallis test. A simple logistic regression model was used to calculate unadjusted odds ratios (ORs) and 95% CIs for reaching "3-month CKD progression." Cox proportional hazard regression and Kaplan-Meier analyses were also performed to examine the effects of "3-month CKD progression" on long-term clinical outcomes such as progression to ESRD and/or mortality. We also conducted both of the above analyses to investigate the influence of AKI episodes in patients requiring CRRT on progression to ESRD and long-term mortality compared with the patients without an AKI episode. Propensity score matching (1:3) was performed to adjust for baseline characteristics between study population and control groups. Among the significant covariables identified by univariate analysis ($p < 0.1$) and the clinically important covariables, only one variable was selected after correlation analysis for avoiding multicollinearity. Final multiple logistic regression or Cox proportional hazard regression analysis was then conducted in a backward stepwise manner. A p value of less than 0.05 was considered significant. Most statistical analyses were performed with SPSS software, version 20.0 K (SPSS, Chicago, IL), and propensity score matching was performed using R version 3.2.3 (R Development Core Team, Vienna, Austria).

TABLE 1. Demographics and Baseline Clinical Characteristics at the Time of Hospitalization

Demographics and Baseline Clinical Characteristics	Total, *n* = 331	3-Mo CKD Progression, *n* = 125 (37.8%)	3-Mo CKD Nonprogression, *n* = 206 (62.2%)	*p*
Male gender	198 (59.8)	78 (62.4)	120 (58.3)	0.456
Age (yr)	67.3 (56.0–75.0)	70.0 (61.0–76.0)	66.7 (54.0–75.0)	0.055
Weight (kg)	60.4 (55.0–70.3)	61.1 (53.7–71.8)	60.4 (55.6–70.0)	0.854
Body mass index (kg/m^2)	23.4 (20.9–26.1)	23.1 (20.5–26.1)	23.6 (21.2–26.1)	0.272
Serum creatinine (mg/dL)	1.2 (0.9–2.0)	1.2 (0.9–2.5)	1.2 (0.9–1.9)	0.530
Modification of Diet in Renal Disease-glomerular filtration rate (mL/min/1.73 m^2)	52.9 (27.1–78.4)	50.0 (20.6–78.2)	53.6 (31.4–78.7)	0.048
Chronic kidney disease[a]				< 0.001
Stage 1	49 (14.8)	19 (15.2)	30 (14.6)	
Stage 2	91 (27.5)	30 (24.0)	61 (29.6)	
Stage 3	99 (29.9)	31 (24.8)	68 (33.0)	
Stage 4	68 (20.5)	24 (19.2)	44 (21.4)	
Stage 5	24 (7.3)	21 (16.8)	3 (1.4)	
Hypertension	177 (53.5)	64 (51.2)	113 (54.9)	0.518
Diabetes mellitus	160 (48.3)	61 (48.8)	99 (48.1)	0.896
Diabetic nephropathy	73 (22.1)	37 (29.6)	36 (17.5)	0.010
Myocardial infarction	47 (14.2)	25 (20.0)	22 (10.7)	0.019
Ischemic heart disease	63 (19.0)	32 (28.2)	31 (17.4)	0.028
Congestive heart failure	85 (25.7)	31 (24.8)	54 (26.2)	0.775
Cerebrovascular attack	50 (15.1)	23 (18.4)	27 (13.1)	0.192
Malignancy	83 (25.1)	24 (19.2)	59 (28.6)	0.055
Charlson Comorbidity Index	6.0 (3.0–7.0)	5.0 (3.0–8.0)	6.0 (3.0–7.0)	0.888
Contributing factors for acute kidney injury				0.020
Septic shock	114 (34.5)	32 (25.6)	82 (40.0)	
Cardiogenic shock	80 (24.2)	38 (30.4)	42 (20.5)	
Hypovolemia	59 (17.9)	23 (18.4)	36 (17.6)	
Major surgery	54 (16.4)	26 (20.8)	28 (13.7)	
Drug induced	23 (7.0)	6 (4.8)	17 (8.3)	
Location before ICU				0.574
General ward	111 (33.5)	39 (31.2)	72 (35.0)	
Emergency department	128 (38.7)	48 (38.4)	80 (38.8)	
Emergent operation	52 (15.7)	24 (19.2)	28 (13.6)	
Elective operation	26 (7.9)	9 (7.2)	17 (8.3)	
Others	14 (4.2)	5 (4.0)	9 (4.3)	
Renal outcomes during follow-up period[b]				< 0.001
Group 1	125 (37.8)	0	125 (60.7)	
Group 2	81 (24.4)	0	81 (39.3)	
Group 3	125 (37.8)	125 (100.0)	0	

CKD = chronic kidney disease.

[a]According to the baseline estimated glomerular filtration rate (eGFR), the patients were classified into five stages: stage 1, an eGFR of at least 90 mL/min/1.73 m^2; stage 2, an eGFR of 60–89 mL/min/1.73 m^2; stage 3, an eGFR of 30–59 mL/min/1.73 m^2; stage 4, an eGFR of 15–29 mL/min/1.73 m^2; and stage 5, an eGFR of < 15 mL/min/1.73 m^2.

[b]The renal outcomes stratified based on the patients' renal function at 3 mo after continuous renal replacement therapy (RRT) start: group 1, the patients whose renal function was returned to their baseline value; group 2, those who had a minor deterioration in renal function compared to baseline, defined as an increase in serum creatinine (sCr) of < 50% or a decrease in the eGFR of < 35%; and group 3, those who had a major deterioration in renal function compared to baseline, defined as an increase in sCr of > 50% or a decrease in the eGFR of > 35%, or those who continued to receive RRT.

Data are presented as the median (25–75th percentiles) or as an *n* (%).

TABLE 2. Clinical Parameters at the Time of or 24 Hours After Continuous Renal Replacement Therapy Initiation

Clinical Parameters	Total, *n* = 331	3-Mo CKD Progression, *n* = 125 (37.8%)	3-Mo CKD Nonprogression, *n* = 206 (62.2%)	*p*
Time from ICU admission to CRRT start	13.0 (1.9–43.9)	17.3 (2.2–56.2)	12.1 (1.9–36.8)	0.118
Systolic blood pressure (mm Hg)	117.0 (104.0–134.0)	122.0 (106.5–140.5)	113.5 (101.8–129.3)	0.006
Mean blood pressure (mm Hg)	82.0 (72.0–94.0)	86.3 (73.5–95.0)	80.8 (71.0–91.5)	0.085
Vasopressor	171 (51.7)	56 (56.6)	115 (68.0)	0.059
Mechanical ventilation	202 (61.0)	78 (62.4)	124 (60.2)	0.690
Acute Physiology and Chronic Health Evaluation II score	24.0 (19.0–29.0)	24.0 (19.0–28.0)	25.0 (19.0–30.0)	0.681
Sequential Organ Failure Assessment score	11.0 (8.0–13.0)	11.0 (9.0–13.0)	11.0 (8.0–13.0)	0.541
Glasgow Coma Scale	11.0 (4.0–14.3)	11.0 (4.0–14.0)	11.0 (4.0–15.0)	0.653
Kidney Disease: Improving Global Outcomes acute kidney injury criteria				0.723
1	26 (7.9)	8 (6.4)	18 (8.7)	
2	56 (16.9)	20 (16.0)	36 (17.5)	
3	249 (75.2)	97 (77.6)	152 (73.8)	
Weight (kg)	62.2 (56.1–71.5)	64.0 (55.9–72.1)	61.8 (56.3–71.5)	0.973
24-hr urine output before CRRT (mL/kg/hr)	0.36 (0.09–0.90)	0.35 (0.04–0.83)	0.38 (0.13–0.95)	0.274
2-hr urine output before CRRT (mL/kg/hr)	0.25 (0.04–0.58)	0.22 (0.02–0.58)	0.27 (0.06–0.61)	0.323
Laboratory findings at CRRT initiation				
Hemoglobin (g/dL)	9.5 (8.5–10.7)	9.5 (8.4–10.5)	9.5 (8.7–10.8)	0.121
Hematocrit (%)	28.9 (25.9–32.1)	28.5 (24.8–31.3)	29.2 (26.2–33.3)	0.015
Sodium (mEq/L)	137.0 (133.0–141.0)	137.0 (133.0–141.0)	137.0 (133.0–142.0)	0.869
Potassium (mEq/L)	4.1 (3.7–4.8)	4.1 (3.7–4.7)	4.1 (3.7–4.9)	0.406
Calcium (mEq/L)	7.8 (7.1–8.6)	7.9 (7.3–8.7)	7.7 (7.1–8.5)	0.087
Phosphorus (mEq/L)	4.6 (3.5–6.0)	4.7 (3.6–6.0)	4.6 (3.4–6.0)	0.722
Total bilirubin (mg/dL)	1.3 (0.7–2.7)	1.1 (0.6–2.6)	1.4 (0.7–2.9)	0.211
Albumin (mg/dL)	2.9 (2.6–3.3)	3.0 (2.7–3.3)	2.9 (2.5–3.3)	0.394
Blood urea nitrogen (mg/dL)	45.1 (31.4–64.5)	49.0 (37.0–73.0)	41.0 (29.1–56.5)	< 0.001
Serum creatinine (mg/dL)	2.8 (2.0–4.0)	3.3 (2.4–4.7)	2.5 (1.8–3.6)	< 0.001
Prothrombin time (international normalized ratio)	1.4 (1.2–1.7)	1.4 (1.2–1.6)	1.4 (1.2–1.7)	0.216
pH	7.38 (7.31–7.43)	7.36 (7.29–7.42)	7.40 (7.33–7.44)	0.009
CRRT setting				
Target clearance (mL/kg/hr)	40.0 (35.0–40.0)	40.0 (34.1–40.0)	40.0 (35.0–41.0)	0.232
Blood flow rate (mL/min)	100.0 (100.0–120.0)	100.0 (100.0–120.0)	100.0 (100.0–120.0)	0.974
Dialysate (mL/hr)	1,200 (1,000–1,500)	1,200 (1,000–1,500)	1,200 (1,000–1,500)	0.252
Replacement (mL/hr)	1,200 (1,000–1,500)	1,175 (1,000–1,400)	1,200 (1,000–1,500)	0.476
Anticoagulation	179 (54.2)	64 (51.2)	115 (56.1)	0.386
At 24 hr after CRRT initiation				
Systolic blood pressure (mm Hg)	122.0 (108.0–140.0)	129.0 (110.0–146.5)	119.0 (106.0–135.3)	0.001
Mean blood pressure (mm Hg)	84.0 (72.0–93.0)	85.0 (73.8–94.0)	83.5 (70.3–92.0)	0.191
24-hr urine output (mL/kg/hr)	0.16 (0.03–0.54)	0.09 (0.02–0.32)	0.24 (0.05–0.65)	< 0.001

CKD = chronic kidney disease, CRRT = continuous renal replacement therapy.
Data are presented as the median (25–75th percentiles) or as an *n* (%).

RESULTS

Baseline Clinical Characteristics and Clinical Parameters Related to CRRT

As shown in Figure 1, 1,195 patients (68%) had died after 3 months of CRRT initiation, and final analysis included 72% of eligible patients of survivors at 3 months. The baseline clinical characteristics and clinical parameters related to CRRT are listed in **Tables 1** and **2**. At baseline, 140 patients (42.4%) had normal renal function, and 191 (57.7%) were CKD patients. After classification of the entire patient cohort into three groups, 125 (37.8%), 81 (24.4%), and 125 (37.8%) patients were categorized into groups 1, 2, and 3, respectively.

Sequential Changes of Renal Function in the Entire Patient Cohort

We represented consecutive renal function with the number of patients at each time point classified by baseline CKD stage 1–5 (**Fig. 2**). The patients who started permanent RRT after the discontinuation of CRRT gradually increased over time; these patients were mostly included in group 3. Although these patients were excluded, the sCr and eGFR values assessed at 1, 3, 6, and 12 months after the start of CRRT significantly differed among the three groups, regardless of baseline CKD stage.

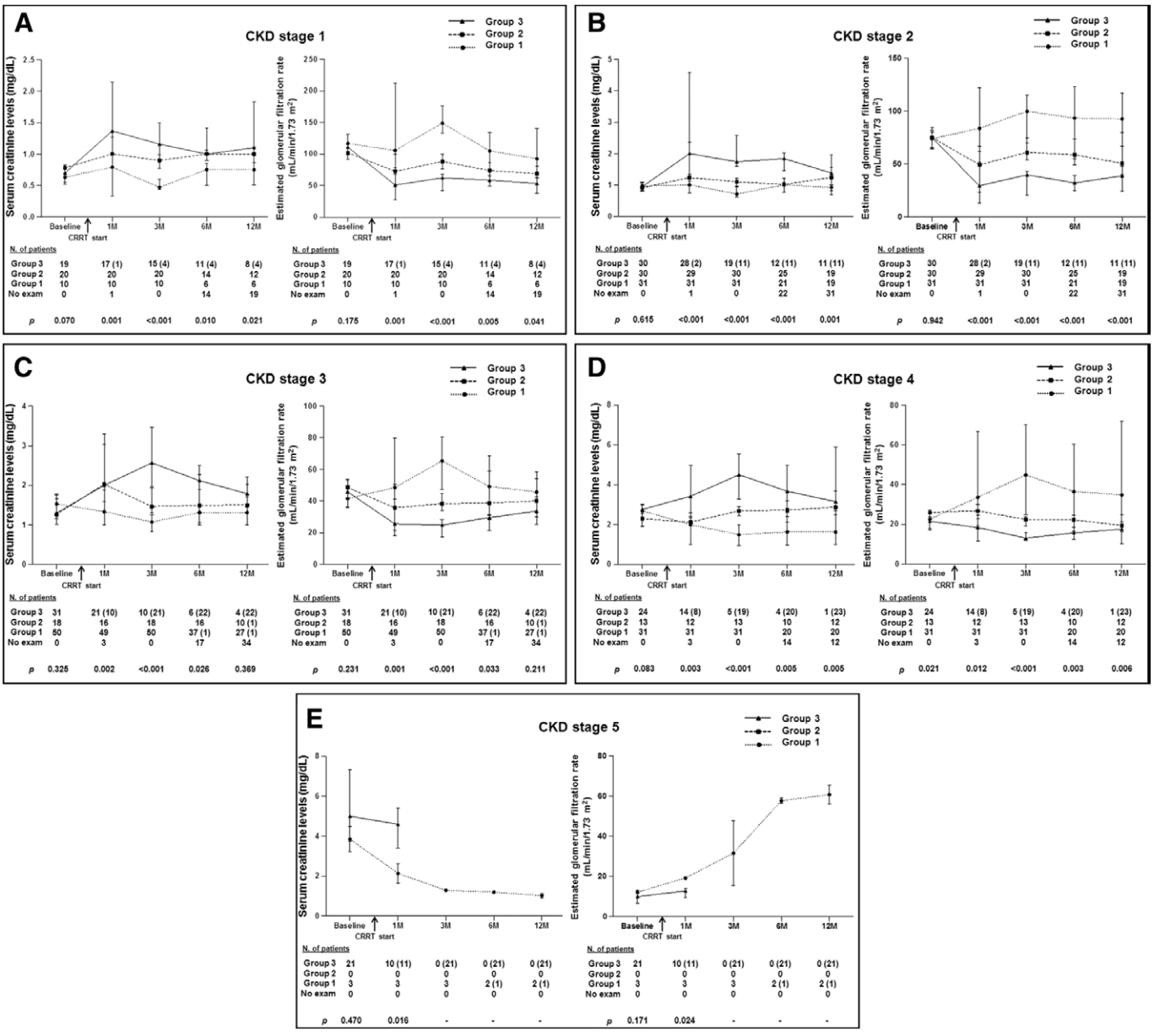

Figure 2. Sequential changes of renal function in the entire patient cohort. The patients who started permanent renal replacement therapy (RRT) after the discontinuation of continuous RRT (CRRT) gradually increased over time; these patients were mostly included in group 3. Although these patients were excluded, the serum creatinine (sCr) and estimated glomerular filtration rate (eGFR) values assessed at 1, 3, 6, and 12 mo after the start of CRRT significantly differed among the three groups, regardless of baseline chronic kidney disease (CKD) stage. *Numbers in parenthesis refer to the number of patients who started permanent RRT. The sCr and eGFR value of these patients were excluded from the graph presentation.

TABLE 3. Baseline Characteristics of the Acute Kidney Injury Patients Requiring Continuous Renal Replacement Therapy and Control Patients Without Acute Kidney Injury Episode (Before and After Propensity Scores 1:3 Matching)

Baseline Characteristics	Unmatched Cohort			Matched Cohort		
	No AKI Episode ($n = 11,481$)	AKI Requiring CRRT ($n = 319$)	p	No AKI Episode ($n = 957$)	AKI Requiring CRRT ($n = 319$)	p
Male gender	5,254 (45.8)	191 (59.9)	< 0.001	572 (59.8)	191 (59.9)	0.974
Age (yr)	61.0 (47.0–72.0)	68.0 (57.0–75.0)	< 0.001	66.0 (56.0–74.0)	68.0 (57.0–75.0)	0.099
Diabetes mellitus	2,646 (23.0)	155 (48.6)	< 0.001	481 (50.3)	155 (48.6)	0.605
Diabetic nephropathy	1,545 (13.5)	70 (21.9)	< 0.001	202 (21.1)	70 (21.9)	0.752
Hypertension	2,240 (19.5)	171 (53.6)	< 0.001	504 (52.7)	171 (53.6)	0.771
Estimated glomerular filtration rate (mL/min/1.73 m^2)	74.7 (45.1–92.3)	52.9 (27.1–78.2)	< 0.001	53.2 (29.0–76.9)	52.9 (27.1–78.2)	0.761
Chronic kidney disease			< 0.001			0.794
Stage 1	3,312 (28.8)	46 (14.4)		134 (14.0)	46 (14.4)	
Stage 2	4,008 (35.0)	89 (27.9)		263 (27.5)	89 (27.9)	
Stage 3	2,487 (21.7)	94 (29.5)		304 (31.8)	94 (29.5)	
Stage 4	1,083 (9.4)	66 (20.7)		201 (21.0)	66 (20.7)	
Stage 5	591 (5.1)	24 (7.5)		55 (5.7)	24 (7.5)	

AKI = acute kidney injury, CRRT = continuous renal replacement therapy.
Data are presented as the median (25–75th percentiles) or as an *n* (%).

Comparisons of Baseline Characteristics and ESRD Progression With the Control Group

Next, we compared the study populations with those who did not experience an AKI episode after propensity score matching (**Table 3**). "Three-month CKD progression" was an independent predictor of progression to ESRD (hazard ratio [HR], 251.12; 95% CI, 61.40–1027.04; $p < 0.001$) after adjusting for age, gender, diabetes, and hypertension (**Fig. 3**, for the risk assessment of progression to ESRD, see **Supplemental Digital Content 1**, http://links.lww.com/CCM/C44). Even the patients who recovered from an AKI episode and did not show 3-month CKD progression had a 14.1-fold higher risk for progression to ESRD compared with that of the patients in the control group with normal baseline renal function over a median follow-up period of approximately 20 (11.8–39.8) months. Furthermore, these patients exhibited a higher risk for progression to ESRD compared to that of stage 3 CKD patients who did not experience an AKI episode; however, the risk was lower than that of advanced CKD (stage 4 and 5) patients.

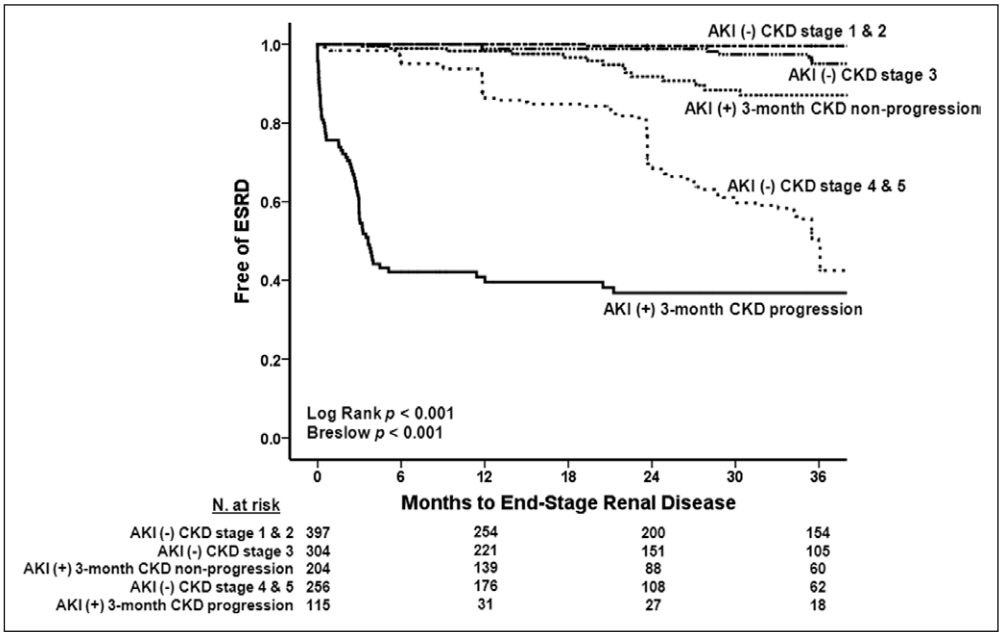

Figure 3. Comparison of progression to end-stage renal disease (ESRD) between the patients with and without acute kidney injury (AKI) episodes based on previous kidney function. "Three-month chronic kidney disease (CKD) progression" after an AKI episode was a strong predictor of progression to ESRD. Furthermore, even patients who did not experience 3-mo CKD progression after AKI were at a higher risk for progression to ESRD compared to that of stage 3 CKD patients who had not experienced an AKI episode over a median follow-up period of 20 (11.8–39.8) mo.

Three-Month CKD Progression and Clinical Outcomes

We then investigated the association between "3-month CKD progression" and the clinical outcomes. All patients could terminate CRRT during follow-up, and no significant differences were found in the CRRT duration and the length of ICU or hospital stay between the two groups (for in-hospital clinical outcomes, see **Supplemental Digital Content 2**, http://links.lww.com/CCM/C45).

During the median 19.3 (7.3–38.1) months of follow-up, increased progression to ESRD and mortality were shown in the "3-month CKD progression" group compared with the "3-month CKD nonprogression" group (**Table 4**). "Three-month CKD progression" was a significant factor for predicting progression to ESRD and long-term mortality even after adjusting for any clinical outcome-related covariables (HR, 13.39; 95% CI, 7.65–23.45; $p < 0.001$ for progression to ESRD and HR, 1.95; 95% CI, 1.20–3.19; $p = 0.008$ for long-term mortality) (**Table 5** and **Fig. 4**).

Risk Factors for 3-Month CKD Progression

To investigate the risk factors for "3-month CKD progression," we performed logistic regression analysis (for risk factors of 3-month CKD progression, see **Supplemental Digital Content 3**, http://links.lww.com/CCM/C46). Older age, higher baseline sCr levels, and higher blood urea nitrogen (BUN) levels at CRRT initiation were also significantly correlated with 3-month CKD progression. In addition, the patients who showed a urine output increase of 0.5 mL/kg/hr during the first 24 hours following the initiation of CRRT had an OR of 0.49 (95% CI, 0.33–0.72; $p < 0.001$) for 3-month CKD progression. However, gender, other comorbidities, and APACHE II or SOFA score were not related to reaching "3-month CKD progression."

DISCUSSION

This study showed not only that patients requiring CRRT who experienced an AKI episode had a greater chance of

TABLE 4. Renal Outcome and Mortality According to Three-Month Chronic Kidney Disease Progression

Clinical Outcomes	Total, $n = 331$	3-Mo CKD Progression, $n = 125$ (37.8%)	3-Mo CKD Nonprogression, $n = 206$ (62.2%)	p
Renal outcome at 3 mo				
Dependent on dialysis	79 (23.9)	79 (63.2)	0 (0.0)	< 0.001
Independent of dialysis	252 (76.1)	46 (36.8)	206 (100.0)	< 0.001
Serum creatinine (mg/dL)	1.1 (0.8–1.7)	1.8 (1.3–2.9)	1.1 (0.8–1.4)	< 0.001
eGFR (mL/min/1.73m^2)	60.3 (37.5–81.5)	34.0 (19.4–50.9)	66.1 (43.2–89.9)	< 0.001
Renal outcome at last visit				
Months from CRRT to the last visit	19.3 (7.3–38.1)	14.3 (5.0–33.9)	20.3 (9.2–41.5)	0.017
Dependent on dialysis	86 (26.0)	77 (61.6)	9 (4.4)	< 0.001
Independent of dialysis	245 (74.0)	48 (38.4)	197 (95.6)	< 0.001
Serum creatinine (mg/dL)	1.2 (0.9–1.7)	1.5 (1.2–2.1)	1.1 (0.9–1.6)	0.001
eGFR (mL/min/1.73m^2)	55.7 (34.0–79.1)	40.1 (30.1–62.2)	57.7 (37.4–82.5)	0.003
Progression to ESRD	94 (28.5)	78 (62.4)	16 (7.8)	< 0.001
Months from CRRT to ESRD progression	12.7 (3.8–33.2)	3.2 (1.1–12.3)	19.4 (9.1–41.3)	< 0.001
All-cause mortality	68 (20.5)	35 (28.0)	33 (16.0)	0.009
Months from CRRT to death	20.4 (7.5–39.7)	15.6 (5.1–34.3)	22.3 (10.9–43.1)	0.004
Cause of death				
Septic	21 (30.9)	10 (28.6)	11 (33.3)	0.828
Respiratory	7 (10.3)	4 (11.4)	3 (9.1)	
Cardiogenic	15 (22.1)	8 (22.9)	7 (21.2)	
Cancer	5 (7.3)	0 (0.0)	5 (15.2)	
Others	5 (7.3)	3 (8.6)	2 (6.1)	
Unknown	15 (22.1)	10 (28.6)	5 (15.2)	

CKD = chronic kidney disease, CRRT = continuous renal replacement therapy, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease. Data are presented as the median (25–75th percentiles) or as an n (%).

TABLE 5. The Effect of 3-Month Chronic Kidney Disease Progression on Progression to End-Stage Renal Disease or Mortality Compared With 3-Month Chronic Kidney Disease Nonprogression

Clinical Outcomes	Multivariate Analysis	
	Unadjusted	Risk Adjusted[a]
Progression to end-stage renal disease (median follow-up period of 12.7 mo)		
HR (95% CI)	13.03 (7.58–22.39)	13.39 (7.65–23.45)
p	< 0.001	< 0.001
Mortality (median follow-up period of 20.4 mo)		
HR (95% CI)	2.11 (1.31–3.39)	1.95 (1.20–3.19)
p	0.002	0.008

HR = hazard ratio.

[a]Adjusted for gender, age, baseline estimated glomerular filtration rate, baseline body mass index, and age-adjusted Charlson Comorbidity Index.

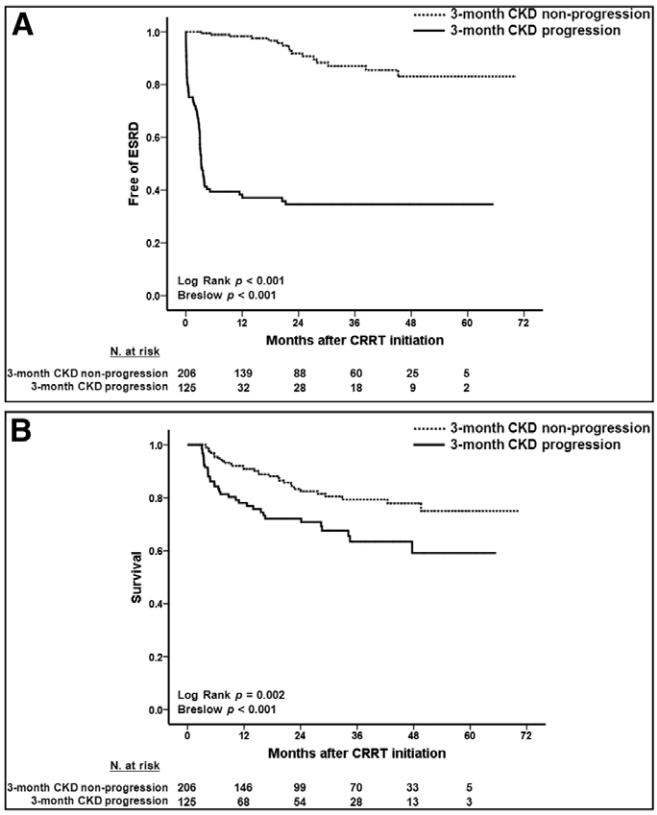

Figure 4. Kaplan-Meier curves for progression to end-stage renal disease (ESRD) (**A**) and mortality (**B**) between the "3-mo chronic kidney disease (CKD) progression" and "3-mo CKD nonprogression" groups. "Three-month CKD progression" was significantly associated with an increased risk of progression to ESRD (**A**) and mortality (**B**) over a median follow-up period of 12.7 (3.8–33.2) and 20.4 (7.5–39.7) mo, respectively. CRRT = continuous renal replacement therapy.

experiencing worsening renal function than the patients who had normal kidney function and did not experience an AKI episode, but also that these patients were shown to have a higher risk of progression to ESRD compared to that of stage 3 CKD patients who did not experience an AKI episode, even if their renal function was recovered at 3 months following CRRT initiation. Furthermore, "3-month CKD progression" was a risk factor for progression to ESRD and long-term mortality compared with "3-month CKD nonprogression." Older age, higher baseline sCr levels, higher BUN levels at CRRT initiation, and decreased urine output at 24 hours after CRRT initiation were significant independent predictors for reaching "3-month CKD progression" among AKI patients requiring CRRT.

As shown in several reports, AKI requiring dialysis could increase the risk for progressive CKD (12, 19). Furthermore, we recognized that the chronic dialysis requirements were increased up to 23.9% at 3 months after CRRT initiation and 26.0% at 19.3 (7.3–38.1) months later, which is consistent with the results of Bagshaw et al (20), even if these patients did not require chronic dialysis at the time of the 3-month renal status check. However, Morgera et al (11) suggested that only 10% of AKI survivors continued to require dialysis during the median follow-up of 2.6 years, which is a lower percentage than our data suggest. This is likely attributable to the older age and higher APACHE II scores of patients at the time of CRRT initiation in our study, although this cannot be confirmed.

The mechanisms by which AKI induces renal fibrosis are well known from several experimental studies; a loss of renal vasculature, tubular atrophy or dilatation, and alterations in glomeruli occur after approximately 40 weeks of ischemia-reperfusion injury. These changes lead to progressive renal fibrosis and permanent renal functional loss (21–25). Additionally, AKI causes endothelial dysfunction and increases the levels of various cytokines, including tumor necrosis factor-α, interleukin-1, and interleukin-6, which are reported to injure distant organs such as the heart, lungs, and liver (26–30). Therefore, AKI may be an independent risk factor for mortality (13, 31, 32) and progression to CKD (32, 33) according to these hypotheses.

In this study, several clinical factors were found to influence "3-month CKD progression"; however, dispute remains regarding which factors are more strongly associated with progressive renal dysfunction or chronic dialysis following AKI requiring dialysis. Several previous studies (34–36) reported that higher BUN concentrations at CRRT initiation were associated with an increased risk of mortality. Augustine et al (37) showed a positive correlation between urine output on day 1 and renal recovery, indicating that urine output is an important factor for recovering renal function. Harel et al (38) reported preexisting CKD or hypertension and higher CCI scores as independent predictors of chronic dialysis in AKI survivors. Stads et al (39) demonstrated that long-term renal outcomes were associated with the degree of renal dysfunction at hospital discharge. In the future, AKI patients with an increased risk of 3-month CKD progression will require more meticulous care and urine output should be intensively monitored in the first 24 hours following CRRT initiation.

CRRT has been considered as one useful treatment modality in the management of critically ill patients with AKI (40). Currently, no widely acknowledged predictive model or report on assessing long-term outcomes after hospital discharge in AKI patients who received CRRT exists. In this study, we investigated factors that may be associated with worsening long-term renal outcomes and mortality in AKI patients requiring CRRT treatment. We did not include patients who died within 3 months after an AKI episode, to exclude the short-term effects of illness severity or hemodynamic instability. Thus, we could evaluate long-term effects on clinical outcomes instead of focusing on short-term clinical outcomes such as in-hospital mortality (8, 41). Furthermore, AKI patients experienced more serious long-term renal outcomes than did the patients who did not experience an AKI episode, even if the AKI patients had recovered after 3 months of CRRT. Taken together, these results indicate that examining renal function at 3 months following CRRT initiation and regular monitoring in survivors with a diagnosis of "3-month CKD progression" are highly recommended.

Several limitations to our study should be noted. First, the retrospective study design has inherent limitations. The potential for lead-time bias can be argued, as the presence of such a capability could encourage the earlier detection of AKI and lead to the treatment of patients who would have otherwise performed well without renal replacement. In addition, there was no established definition of baseline renal function, and a single value cannot represent the stable baseline renal function of each patient. Second, our study only examined a Korean cohort of individuals who experienced the most severe form of AKI, with hemodynamic instability and severe clinical conditions. In this regard, these findings may not be generalizable to other races or to individuals experiencing less severe yet much more common forms of AKI. However, the results of these analyses focusing on AKI patients who did not receive CRRT also indicate that renal functional assessment at 3 months following an AKI event may be useful to predict progression to ESRD, regardless of CRRT treatment (for the effect of 3-mo CKD progression on progression to ESRD or mortality in AKI patients who did not receive CRRT, see **Supplemental Digital Content 4**, http://links.lww.com/CCM/C47; and **Supplemental Digital Content 5**, http://links.lww.com/CCM/C48; legend, **Supplemental Digital Content 6**, http://links.lww.com/CCM/C49). Third, the early mortality rate was high, and those who died within 3 months following CRRT initiation were excluded from this study population; these factors might have affected the results. Additionally, our study population might not be representative of all ICU patients or AKI patients. However, the main purpose of our study was not to analyze the risk factors for mortality but rather to focus on the significance of renal functional assessment at 3 months following CRRT; therefore, only survivors after 3 months of CRRT initiation could be enrolled in this study. Fourth, we arbitrarily defined "3-month CKD progression" as a worsening renal status assessed 3 months following CRRT initiation, although we attempted to investigate whether the renal status at 3 months after CRRT initiation could be associated with long-term renal and patient outcomes. Fifth, this study was performed using a multicenter cohort; therefore, as the decisions regarding the timing of initiation and the type of CRRT are subjective and affected by both resources and the underlying disease, this study may not be completely generalizable to sites with different practice patterns or patient populations. Furthermore, completely accurate classification of the factors contributing to AKI was not feasible. Ultimately, a well-designed prospective large cohort study should be performed to overcome these limitations and to verify all of our suggestions and clinical implications regarding monitoring at 3 months after an AKI episode in a patient requiring CRRT.

In conclusion, "3-month CKD progression" is a significant, predictable risk factor for progression to ESRD and long-term mortality, suggesting that renal functional assessment at 3 months following CRRT initiation may be a useful measure to predict long-term clinical outcomes. Furthermore, continuous close monitoring and management of AKI patients requiring CRRT is required, irrespective of renal functional recovery.

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