

# Prognosis of Patients with Acute Kidney Injury due to Type 1 Cardiorenal Syndrome Receiving Continuous Renal Replacement Therapy

Yusuke Watanabe<sup>a,b</sup> Tsutomu Inoue<sup>a</sup> Shintaro Nakano<sup>c</sup> Hirokazu Okada<sup>a</sup>

<sup>a</sup>Department of Nephrology, Saitama Medical University, Saitama, Japan; <sup>b</sup>Division of Dialysis Center and Department of Nephrology, Saitama Medical University International Medical Center, Saitama, Japan;

<sup>c</sup>Department of Cardiology, Saitama Medical University International Medical Center, Saitama, Japan

## Keywords

Acute kidney injury · Continuous renal replacement therapy · Type 1 cardiorenal syndrome · Acute heart failure · Advance care planning

## Abstract

**Introduction:** The prognosis of patients with acute kidney injury (AKI) caused by type 1 cardiorenal syndrome (CRS) requiring continuous renal replacement therapy (CRRT) is unclear. We investigated the in-hospital mortality and prognostic factors in these patients. **Methods:** We retrospectively identified 154 consecutive adult patients who received CRRT for AKI caused by type 1 CRS between January 1, 2013, and December 31, 2019. We excluded patients who underwent cardiovascular surgery and those with stage 5 chronic kidney disease. The primary outcome was in-hospital mortality. Cox proportional hazards analysis was performed to analyze independent predictors of in-hospital mortality. **Results:** The median age of patients at admission was 74.0 years (interquartile range: 63.0–80.0); 70.8% were male. The in-hospital mortality rate was 68.2%. Age  $\geq 80$  years (hazard ratio [HR], 1.87; 95% confidence interval [CI], 1.21–2.87;  $p = 0.004$ ), previous hospitalization for acute heart failure (HR, 1.67; 95% CI, 1.13–2.46;  $p = 0.01$ ), vasopressor or inotrope use (HR, 5.88; 95% CI, 1.43–24.1;  $p = 0.014$ ), and mechanical ventilation at CRRT initiation (HR,

2.24; 95% CI, 1.46–3.45;  $p < 0.001$ ) were associated with in-hospital mortality. **Conclusion:** In our single-center study, the use of CRRT for AKI due to type 1 CRS was associated with high in-hospital mortality.

© 2023 The Author(s).

Published by S. Karger AG, Basel

## Introduction

Japan has the highest proportion of the elderly population worldwide. In 2019, 8.9% of the total Japanese population was aged  $\geq 80$  years, and the proportion of the elderly is expected to rise [1]. Although heart failure (HF) can occur at any age, it is particularly prevalent among the elderly [2]. There is a concern that the number of patients with HF may increase as the population ages. A report estimated that the incidence of left ventricular dysfunction may increase to 1.32 million patients by 2035, with rapid acceleration occurring by 2020 [3]. Therefore, Japan faces an upcoming HF pandemic [4].

Acute HF (AHF) frequently complicates acute kidney injury (AKI), a condition known as type 1 cardiorenal syndrome (CRS) [5]. Hemodynamically unstable type 1 CRS patients with diuretic resistance often receive continuous renal replacement therapy (CRRT) [6]. However, little is known about these patients' outcomes [7]. This is

the first study to evaluate in-hospital mortality and short-term prognostic factors for patients requiring CRRT for AKI due to type 1 CRS.

## Materials and Methods

### Study Population

This retrospective cohort study was conducted at a tertiary referral academic hospital (Saitama Medical University International Medical Center, Japan). Patients who received CRRT for AKI caused by type 1 CRS between January 1, 2013, and December 31, 2019, were identified using electronic medical records. We collected serum creatinine (sCr) data acquired at the patients' last visit to their primary care doctors within 3 months before admission. Patients with unavailable information, stage 5 chronic kidney disease before hospitalization, cardiac surgery-associated AKI and septic AKI, and renal replacement therapy before admission were excluded. AKI was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) recommendations [8, 9].

In patients with AKI who were resistant to diuretics, CRRT was initiated based on a consensus between a cardiologist and a nephrologist (particularly for pulmonary edema due to volume overload, azotemia, hyperkalemia, and severe acidosis) [8, 9]. We do not use the severity of the KDIGO AKI stage as a criterion for CRRT induction in the treatment of type 1 CRS.

This study was approved by the Medical Ethical Review Board of the Saitama Medical University International Medical Center (reference number 19-292), and the requirement for informed consent was waived due to the retrospective nature of the study. All procedures were in accordance with the Ethical Standards of the Helsinki Declaration of 1975, as revised in 2000.

### Data Collection

The following clinical and demographic data were collected from individual medical records: age, sex, body weight, height, body mass index, medical history (presence or absence of previous hospitalization for AHF, diabetes mellitus, and hypertension), cause of AHF (ischemic, valvular, others [i.e., cardiomyopathy, myocarditis, and arrhythmia]), days from hospital admission to CRRT initiation, urine output before CRRT initiation, administered dose of furosemide before CRRT initiation, clinical data at CRRT initiation (systolic blood pressure [SBP], diastolic blood pressure, and heart rate [HR]), cardiovascular variables on echocardiography at CRRT initiation (left ventricular ejection fraction [LVEF], LV end-diastolic diameter, and inferior vena cava diameter), laboratory data at CRRT initiation (sCr and serum urea nitrogen [sUN]), and interventions at CRRT initiation (vasopressors or inotropes, intra-aortic balloon pumping [IABP], mechanical ventilation with intubation, and venoarterial extra-corporeal membrane oxygenation [VA-ECMO]). Vasopressors or inotropes included dopamine, dobutamine, noradrenaline, and adrenaline.

### CRRT Protocol

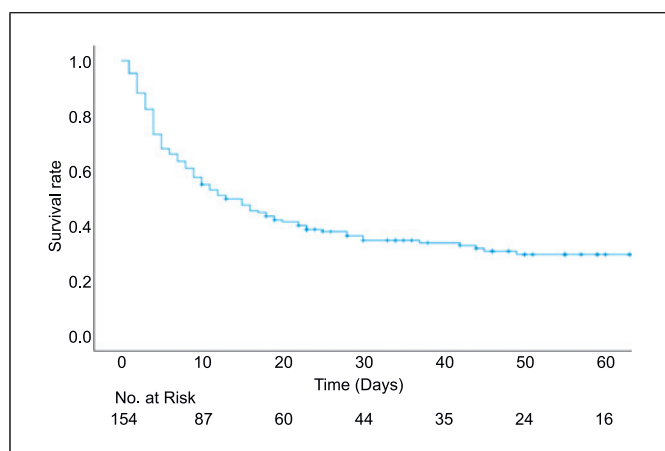
CRRT was performed using a TR 55X (Toray Medical Co., Ltd., Tokyo, Japan) device with a hemofilter through a double-lumen 12-French catheter inserted into the internal jugular or femoral

**Table 1.** Baseline characteristics of the patients included in this study

	All patients n = 154
Demographic data and medical history	
Age, years	74.0 (63.0–80.0)
Male, n (%)	109 (70.8)
BMI	23.1 (5.7)
History of hospitalization for AHF, n (%)	68 (44.2)
DM, n (%)	62 (40.3)
HT, n (%)	90 (58.4)
Cause of cardiac dysfunction	
Ischemic, n (%)	84 (54.5)
Valvular, n (%)	20 (13.0)
Others, n (%)	50 (32.5)
Urine output before CRRT, mL/kg/h	0.16 (0–0.44)
Furosemide dose before CRRT, mg/day	120 (40–240)
Days from admission to CRRT, days	4 (1–12)
Clinical data at CRRT initiation	
SBP, mm Hg	100.0 (22.1)
DBP, mm Hg	53.3 (16.0)
HR, bpm	94.1 (23.2)
Cardiovascular variables at CRRT initiation	
LVEF, %	32.5 (18.3)
LVDd, mm	52.7 (12.1)
IVC diameter, mm	17.7 (5.9)
Laboratory data at CRRT initiation	
sCr, mg/dL	2.8 (1.1)
sUN, mg/dL	58.0 (28.9)
Interventions at CRRT initiation	
Vasopressors or inotropes, n (%)	143 (92.9)
IABP, n (%)	54 (35.1)
Mechanical ventilation, n (%)	88 (57.1)
VA-ECMO, n (%)	28 (18.2)
Initial prescribed dose of CRRT, mL/kg/h	10.0 (8.0–14.4)
Duration of CRRT, days	6.0 (3.0–12.0)

Categorical variables are expressed as numbers (percentages), and continuous variables are expressed as means (standard deviations) or medians (first to third quartiles). BMI, body mass index; AHF, acute heart failure; DM, diabetes mellitus; HT, hypertension; CRRT, continuous renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; LVDd, LV end-diastolic diameter; IVC, inferior vena cava; sCr, serum creatinine; sUN, serum urea nitrogen; IABP, intra-aortic balloon pumping; VA-ECMO, venoarterial extra-corporeal membrane oxygenation.

vein. The hemofilter membrane materials used in this study were polysulfone, polyethersulfone, and cellulose triacetate membranes. CRRT involved continuous venovenous hemodialysis, hemofiltration, or hemodiafiltration. Patients were discontinued from CRRT if they recovered from AKI and were shifted to chronic maintenance dialysis if recovery was not achieved and dialysis-dependent conditions persisted.



**Fig. 1.** Survival from CRRT initiation.

### Study Outcomes

The primary outcome was in-hospital mortality. The secondary outcome was dialysis dependency at hospital discharge.

### Statistical Analyses

The baseline characteristics of the study participants were analyzed using descriptive statistics. Continuous variables are expressed as either means  $\pm$  standard deviations or medians (interquartile ranges [IQRs]) and were compared using the unpaired *t* test or Mann-Whitney U test, respectively. The Shapiro-Wilk test was used to test for normality of distribution. Categorical variables are expressed as percentages and compared using the  $\chi^2$  test or Fisher's exact test. Curves for patient survival were estimated for each category using the Kaplan-Meier method. The log-rank test was used to analyze the differences between the curves. Cox regression analysis was used to evaluate independent predictors of in-hospital mortality after simultaneously controlling for potential confounders. The variables (including age, vasopressors or inotropic use, mechanical ventilation, VA-ECMO, and IABP) were selected based on the previous literature [10] and factors (including previous hospitalization for AHF) identified by univariate regression. Multicollinearity was analyzed by Spearman's rank correlation coefficient to assess correlations between covariates. Statistical analyses were performed using IBM SPSS software, version 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at a two-sided *p* value  $<0.05$ .

## Results

### Clinical Characteristics

In total, 154 consecutive adult patients who received CRRT for AKI caused by type 1 CRS between January 1, 2013, and December 31, 2019, were included in this study. Baseline clinical characteristics are described in Table 1. The median age at admission was 74.0 years

(IQR: 63.0–80.0). A history of hospitalization for AHF was present in 68 patients (44.2%).

### Clinical Outcomes

Figure 1 shows the survival rate from the time of CRRT initiation. Of the 154 adult patients who received CRRT for AKI caused by type 1 CRS, 105 died in the hospital (in-hospital mortality: 68.2%). The nonsurvivors did not recover their renal function and remained on CRRT until death or until CRRT was terminated for palliative care. No patients experienced severe complications from CRRT that would have influenced in-hospital mortality. Of the 49 patients who survived, six (12.2%) were dialysis-dependent at discharge. We captured the clinical course of all patients until discharge.

### In-Hospital Survivors versus Nonsurvivors

We compared the clinical variables between in-hospital survivors and nonsurvivors (Table 2). No significant difference in age at admission was identified; however, the survivors tended to be younger than the nonsurvivors (median [IQR]: 71.0 [58.0–78.5] vs. 75.0 [66.0–82.0],  $p = 0.17$ ). Survivors had significantly less history of hospitalization for AHF than nonsurvivors ( $p = 0.003$ ). There was a significant difference in the proportion of AHF-causing diseases, with a lower proportion of ischemic heart disease and a higher proportion of nonischemic heart disease in the survivors ( $p = 0.03$ ).

Survivors showed significantly higher SBP ( $p < 0.001$ ), LVEF ( $p = 0.007$ ), and sCr and sUN values ( $p < 0.001$  and  $p = 0.03$ , respectively) and significantly lower requirements of vasopressors or inotropes ( $p < 0.001$ ), IABP ( $p = 0.009$ ), mechanical ventilation ( $p < 0.001$ ), and VA-ECMO ( $p = 0.008$ ) at CRRT initiation.

### Patients Aged $<80$ versus $\geq 80$ years

To assess the influence of age, we compared clinical variables between patients aged  $<80$  years and those aged  $\geq 80$  years at admission, which is the top 25% of the IQR of the patients' age distribution (Table 3). Patients aged  $\geq 80$  years had a significantly lower body mass index ( $p = 0.01$ ) and a significantly higher prevalence of hypertension ( $p = 0.04$ ) than those aged  $<80$  years. There was no significant age difference in the proportion of AHF-causing diseases ( $p = 0.15$ ), although the proportion of ischemic heart disease tended to be higher in patients aged  $\geq 80$  years. Patients aged  $\geq 80$  years had a significantly higher LVEF ( $p = 0.008$ ), a significantly smaller LV end-diastolic diameter ( $p = 0.008$ ), and a significantly higher sUN at CRRT initiation ( $p = 0.01$ ), with significantly lower mechanical ventilation ( $p = 0.02$ ) and VA-ECMO ( $p = 0.001$ ) rates.

**Table 2.** Baseline characteristics of the patients stratified by survival

	Survivors <i>n</i> = 49	Nonsurvivors <i>n</i> = 105	<i>p</i> value
Demographic data and medical history			
Age, years	71.0 (58.0–78.5)	75.0 (66.0–82.0)	0.17
Male, <i>n</i> (%)	37 (75.5)	72 (68.6)	0.38
BMI	23.7 (7.3)	22.8 (4.8)	0.47
History of hospitalization for AHF, <i>n</i> (%)	13 (26.5)	55 (52.4)	0.003*
DM, <i>n</i> (%)	22 (44.9)	40 (38.1)	0.42
HT, <i>n</i> (%)	31 (63.3)	59 (56.2)	0.41
Cause of cardiac dysfunction			
Ischemic, <i>n</i> (%)	20 (40.8)	64 (61.0)	0.03*
Nonischemic, <i>n</i> (%)	29 (59.2)	41 (39.0)	
Urine output before CRRT, mL/kg/h	0.16 (0–0.54)	0.16 (0–0.42)	0.58
Furosemide dose before CRRT, mg/day	120 (40–240)	120 (40–240)	0.73
Days from admission to CRRT, days	4 (1.3–8.8)	5.5 (1–18.5)	0.62
Clinical data at CRRT initiation			
SBP, mm Hg	108.7 (22.2)	96.1 (21.0)	<0.001*
DBP, mm Hg	56.9 (17.7)	51.7 (15.0)	0.07
HR, bpm	90.9 (24.8)	95.6 (22.4)	0.26
Cardiovascular variables at CRRT initiation			
LVEF, %	38.8 (20.5)	29.5 (16.5)	0.007*
LVDd, mm	53.1 (11.9)	52.5 (12.2)	0.78
IVC diameter, mm	17.4 (6.1)	17.9 (5.8)	0.65
Laboratory data at CRRT initiation			
sCr, mg/dL	3.2 (1.0)	2.6 (1.1)	<0.001*
sUN, mg/dL	65.8 (29.9)	54.4 (27.8)	0.03*
Interventions at CRRT initiation			
Vasopressors or inotropes, <i>n</i> (%)	40 (81.6)	103 (98.1)	<0.001*
IABP, <i>n</i> (%)	10 (20.4)	44 (41.9)	0.009*
Mechanical ventilation, <i>n</i> (%)	17 (34.7)	71 (67.6)	<0.001*
VA-ECMO, <i>n</i> (%)	3 (6.1)	25 (23.8)	0.008*
Initial prescribed dose of CRRT, mL/kg/h	9.5 (7.4–11.5)	10.0 (8.2–14.3)	0.48
Duration of CRRT, days	7.8 (8.7)	10.8 (11.5)	0.08

BMI, body mass index; AHF, acute heart failure; DM, diabetes mellitus; HT, hypertension; CRRT, continuous renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; LVDd, LV end-diastolic diameter; IVC, inferior vena cava; sCr, serum creatinine; sUN, serum urea nitrogen; IABP, intra-aortic balloon pumping; VA-ECMO, venoarterial extracorporeal membrane oxygenation. \**p* < 0.05.

### Clinical Outcomes Stratified by sCr and Urine Volume Criteria

All patients in this study received CRRT and were classified as KDIGO AKI stage 3 by definition. For reference, we analyzed the number of patients and outcomes by KDIGO AKI stages at CRRT initiation, which were evaluated using sCr and urine volume criteria. A number (%) of patients in stages 1, 2, and 3 were 74 (48.1%), 49 (31.8%), and 31 (20.1%), respectively. Mortality rates at stages 1, 2, and 3 were 68.9%, 75.5%, and 54.8%, respectively, with no significant difference among the three groups (*p* = 0.16).

### Predictors of In-Hospital Mortality

Figure 2a–f shows the Kaplan-Meier survival curves depicting the period between CRRT initiation and death. Short-term survival was worse in patients with a history of hospitalization for AHF (*p* = 0.019) (Fig. 2a). Similarly, patients aged ≥80 years had significantly lower short-term survival rates (*p* = 0.038) (Fig. 2b). Significantly lower short-term survival rates were observed in patients treated with vasopressors or inotropes (*p* = 0.002) (Fig. 2c), IABP (*p* = 0.021) (Fig. 2d), mechanical ventilation (*p* < 0.001) (Fig. 2e), and VA-ECMO (*p* = 0.047) (Fig. 2f) than in those without these interventions.

**Table 3.** Baseline characteristics of the patients stratified by age

	Age <80 years <i>n</i> = 109	Age ≥80 years <i>n</i> = 45	<i>p</i> value
Demographic data and medical history			
Age, years	69.0 (58.0–74.3)	84.5 (82.0–87.0)	<0.001*
Male, <i>n</i> (%)	80 (73.4)	29 (64.4)	0.27
BMI	23.8 (6.0)	21.4 (4.6)	0.01*
History of hospitalization for AHF, <i>n</i> (%)	49 (45.0)	19 (42.2)	0.76
DM, <i>n</i> (%)	45 (41.3)	17 (37.5)	0.69
HT, <i>n</i> (%)	58 (53.2)	32 (71.1)	0.04*
Cause of cardiac dysfunction			
Ischemic, <i>n</i> (%)	55 (50.5)	29 (64.4)	0.16
Nonischemic, <i>n</i> (%)	54 (49.5)	16 (35.6)	
Urine output before CRRT, mL/kg/h	0.14 (0–0.61)	0.17 (0–0.38)	0.48
Furosemide dose before CRRT, mg/day	120 (40–240)	120 (40–240)	0.74
Days from admission to CRRT, days	4 (1–13)	6 (1–17)	0.9
Clinical data at CRRT initiation			
SBP, mm Hg	98.9 (21.6)	102.8 (23.3)	0.33
DBP, mm Hg	54.6 (15.5)	50.3 (17.1)	0.15
HR, bpm	93.0 (21.9)	96.7 (26.1)	0.4
Cardiovascular variables at CRRT initiation			
LVEF, %	29.7 (16.7)	39.3 (20.4)	0.008*
LVDd, mm	54.3 (12.4)	48.9 (10.4)	0.008*
IVC diameter, mm	18.0 (6.5)	17.1 (4.0)	0.34
Laboratory data at CRRT initiation			
sCr, mg/dL	2.8 (1.2)	2.8 (0.9)	0.72
sUN, mg/dL	54.0 (26.2)	67.9 (32.8)	0.01*
Interventions at CRRT initiation			
Vasopressors or inotropes, <i>n</i> (%)	103 (94.5)	40 (88.9)	0.21
IABP, <i>n</i> (%)	43 (39.4)	11 (24.4)	0.08
Mechanical ventilation, <i>n</i> (%)	69 (63.3)	19 (42.2)	0.02*
VA-ECMO, <i>n</i> (%)	27 (24.8)	1 (2.2)	0.001*
Initial prescribed dose of CRRT, mL/kg/h	9.4 (7.3–14.0)	10.5 (8.5–12.5)	0.26
Duration of CRRT, days	7.0 (3.0–13.0)	5.0 (3.0–9.0)	0.48
Hospital survivors, <i>n</i> (%)	38 (34.8)	11 (24.4)	0.2

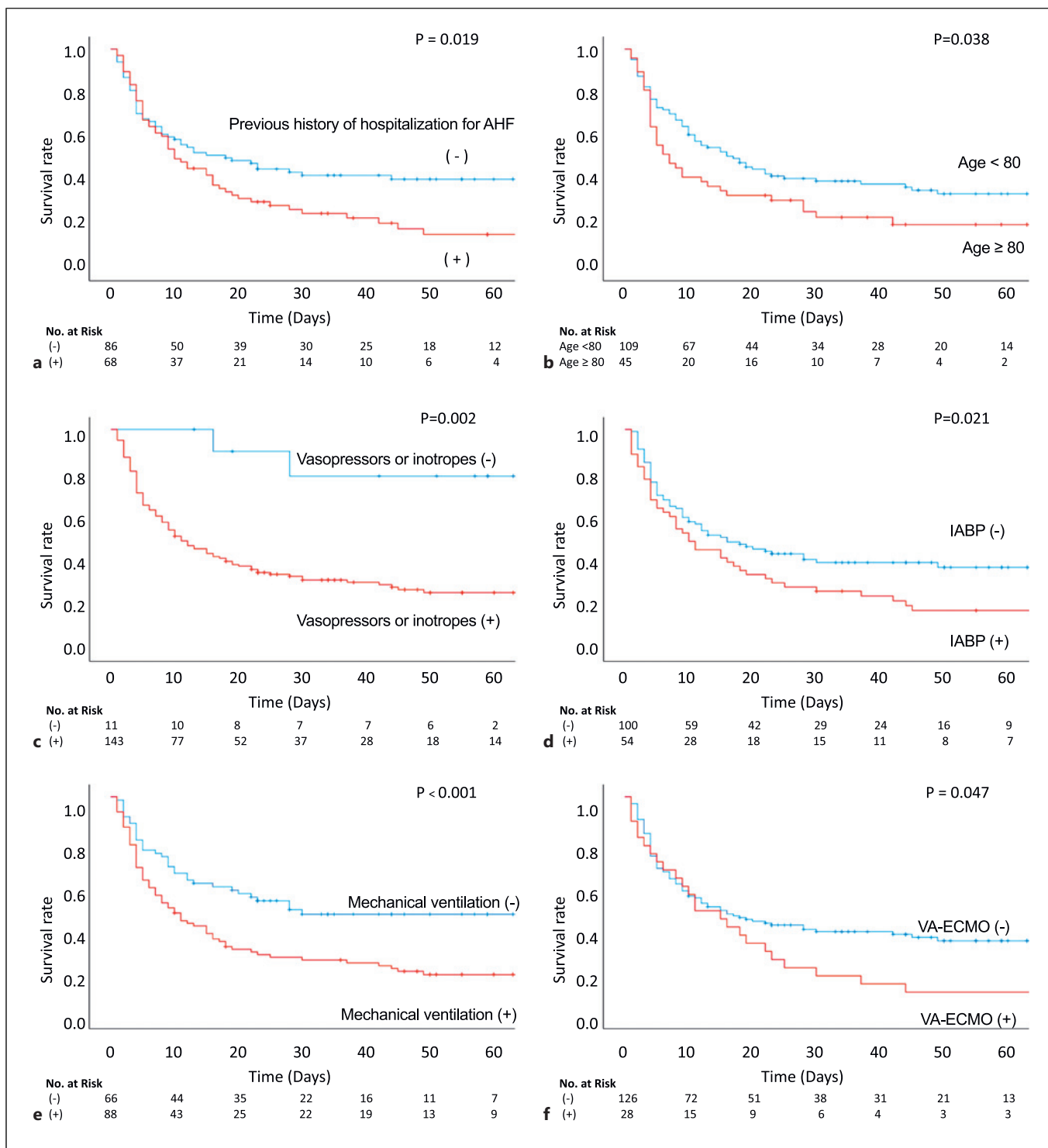
BMI, body mass index; AHF, acute heart failure; DM, diabetes mellitus; HT, hypertension; CRRT, continuous renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; LVDd, LV end-diastolic diameter; IVC, inferior vena cava; sCr, serum creatinine; sUN, serum urea nitrogen; IABP, intra-aortic balloon pumping; VA-ECMO, venoarterial extracorporeal membrane oxygenation. \**p* < 0.05.

Multivariable logistic regression models were used to examine the effects of independent variables on in-hospital mortality. A combination of a priori variables based on the previous literature (including age, vasopressor or inotrope use, mechanical ventilation, VA-ECMO, and IABP) and variables that were identified in this study (including previous hospitalization for AHF) was used [10, 11]. LVEF and SBP at CRRT initiation were also candidates for independent variables; however, they were not analyzed due to their significant correlation with vasopressor or inotrope use and concerns about multicollinearity. Multivariate Cox proportional hazards analysis revealed that in-hospital mortality was

significantly associated with previous hospitalization for AHF (HR, 1.67; 95% CI, 1.13–2.46; *p* = 0.01), age ≥80 years (HR, 1.87; 95% confidence interval [CI], 1.21–2.87; *p* = 0.004), vasopressor or inotrope use (HR, 5.88; 95% CI, 1.43–24.1; *p* = 0.014), and mechanical ventilation support (HR, 2.24; 95% CI, 1.46–3.45; *p* < 0.001) at CRRT initiation (Table 4).

## Discussion

We found that CRRT for AKI due to type 1 CRS was associated with high in-hospital mortality. CRRT has



**Fig. 2.** Kaplan-Meier survival curves depicting the period between CRRT initiation and death. **a** Association between the presence or the absence of a previous history of hospitalization for AHF. **b** Association between age ≥80 years and death. **c** Association between vasopressor or inotrope use and

death. **d** Association between IABP use and death. **e** Association between mechanical ventilation and death. **f** Association between VA-ECMO use and death. AHF, acute heart failure; IABP, intra-aortic balloon pumping; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

**Table 4.** Cox's proportional hazard analysis for in-hospital mortality

Variable	n (%)	HR	95% CI	p value
Age, years				
<80	109 (70.8)	Ref	Ref	Ref
≥80	45 (29.2)	1.87	1.21~2.87	0.004
History of hospitalization for AHF				
(-)	86 (55.8)	Ref	Ref	Ref
(+)	68 (44.2)	1.67	1.13~2.46	0.01
Vasopressors or inotropes				
(-)	11 (7.1)	Ref	Ref	Ref
(+)	143 (92.9)	5.88	1.43~24.1	0.014
Mechanical ventilation				
(-)	66 (42.9)	Ref	Ref	Ref
(+)	88 (57.1)	2.24	1.46~3.45	<0.001

AHF, acute heart failure; CI, confidence interval; Ref, reference. \* $p < 0.05$ .

limited clinical utility in patients with hemodynamically unstable type 1 CRS. Fewer survivors had previous hospitalizations for AHF. At CRRT initiation, survivors had a higher SBP and LVEF, and fewer required vasopressors or inotropes, IABP, mechanical ventilation, or VA-ECMO support. Multivariate Cox proportional hazards analysis showed that previous hospitalization for AHF, age  $\geq 80$  years, vasopressor or inotrope use, and mechanical ventilation at CRRT initiation were strong predictors of death, suggesting that these parameters may be useful for identifying patients at high risk of death at CRRT initiation.

The number of patients with HF was reported to be increasing in countries with an aging population, including Japan [3]. HF often worsens with repetitive acute exacerbations, and AHF is often associated with renal impairment. Type 1 CRS occurs in up to 40% of patients admitted with AHF [5, 12]. The pathogenesis of type 1 CRS is complex, although important mechanisms include renal hypoperfusion and passive venous congestion [13]. Excess fluid in patients with AHF can be removed by ultrafiltration. However, its superiority over diuretics for fluid management remains controversial [6, 14–18]. In contrast, in the case of diuretic resistance, renal replacement therapy may be required to remove excess solutes and fluid. The incidence of dialysis-requiring AKI in HF hospitalizations in the USA doubled between 2002 and 2013 and was associated with high in-hospital mortality [19].

For hemodynamically unstable AKI caused by type 1 CRS, CRRT is often selected instead of intermittent hemodialysis [6, 7, 20]. According to a large nationwide database study in Japan, nonsurgical cardiovascular

disease (including type 1 CRS) is a major cause of AKI requiring CRRT [20]. However, there have been insufficient reports on the prognosis of patients who underwent CRRT for type 1 CRS [7]. One cohort study [10] showed that rescue therapy using CRRT in refractory type 1 CRS was associated with high in-hospital mortality, especially when vasopressors or inotropes were used and when patients' age exceeded 70 years. In their cohort, only patients with acute decompensation of chronic HF were included. All patients had been admitted at least twice for AHF in the 12 months before the observed admission. Additionally, survivors had poor long-term prognoses [10]. In our patients, age  $>80$  years was associated with a poor short-term prognosis. However, some elderly patients recovered from AKI, withdrew from CRRT, survived, and were discharged. The short-term prognosis of elderly patients with type 1 CRS is not uniformly poor; therefore, prognosis should be predicted for individual patients, accounting not only for older age but also for other predictive factors identified in this study.

On the one hand, ethical issues regarding the treatment of elderly patients with HF or AKI have been emphasized in recent years [7, 9, 21]. Whether CRRT should be performed in elderly patients with severe type 1 CRS, whose prognosis is poor, is a controversial issue. Patients with chronic HF are repeatedly hospitalized for acute exacerbations, and their condition eventually deteriorates rapidly. Therefore, it is extremely difficult to determine when end-of-life should be recognized [22].

Based on the findings reported by Prins et al. [10] and those of our study, a poor prognosis for elderly patients with a history of hospitalization for AHF may be predicted by complications of type 1 CRS requiring CRRT. In these patients, CRRT initiation should be cautiously considered if specific interventions to improve heart function are not feasible.

Recently, the importance of advance care planning (ACP) has been recognized in the palliative care of patients with HF. In 2012, the American Heart Association released a scientific statement about shared decision-making for advanced HF and recommended active ACP for patients with HF at the end-of-life stage [22]. According to this statement, consideration of CRRT should prompt physicians to formally assess prognosis and to discuss goals of care and voluntary ACP.

The optimal technical conditions and future issues of CRRT for patients with type 1 CRS are being discussed. It has been reported that the higher net ultrafiltration early after initiation of CRRT was independently associated with lower survival [23]. In type 1 CRS, starting CRRT early with a smaller ultrafiltration rate may lead to

improved outcomes. Recently, the usefulness of cytokine adsorption membranes in CRRT for septic AKI has also been reported [24]. In our study, we excluded septic AKI cases; therefore, the membrane materials used in this study were not the cytokine-adsorbing membranes. Virzi et al. [25] elucidated the involvement of inflammation in type 1 CRS, and inflammatory cytokine-adsorbing membranes may be effective in type 1 CRS, which requires further investigation.

Naturally, treatment prior to initiation of CRRT is also important to improve the prognosis of type 1 CRS. The use of diuretics and vasopressors and fluid volume management are important issues that have a significant impact on prognosis. Both hypovolemia and hypervolemia affect kidney function; as such, the fluid volume should be assessed using all available indices to maintain euvolemia. Hypotension leads to tissue hypoperfusion, which requires the use of appropriate vasopressors; diuretics should be administered in the event of fluid overload, and CRRT should be considered if the patient is unresponsive [26].

This study had some limitations. First, it was a single-center study, and its findings may not apply to patients with different risk profiles. Second, this study had a small sample size and may have been inadequately powered to detect statistically significant differences. Third, potential confounders, such as indications for CRRT and subsequent management, were not standardized due to the retrospective nature of the study. Further prospective multicenter studies are needed to validate our findings and identify other prognostic factors.

In conclusion, the use of CRRT for AKI due to type 1 CRS is associated with high in-hospital mortality. In particular, a poor prognosis was observed in patients who had a previous hospitalization for AHF, those aged  $\geq 80$  years, those who required vasopressors or inotropes, and those who required mechanical ventilation at CRRT. In patients with these poor prognostic factors, CRRT initiation should be carefully considered if other interventions to improve heart function are not feasible.

## References

- 1 Current population estimates as of October 1, 2019. The Statistics Bureau of Japan. Ministry of Internal Affairs And Communications; 2019 [cited 2021 Mar 1] Available from: <https://www.stat.go.jp/english/data/jinsui/2019np/index.html>.
- 2 Ho KK, Pinsky J.L, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol*. 1993 Oct;22(4 Suppl A):6A–13A.
- 3 Okura Y, Ramadan MM, Ohno Y, Mitsuma W, Tanaka K, Ito M, et al. Impending epidemic: future projection of heart failure in Japan to the year 2055. *Circ J*. 2008 Mar; 72(3):489–91.
- 4 Konishi M, Ishida J, Springer J, von Haehling S, Akashi YJ, Shimokawa H, et al. Heart failure epidemiology and novel treatments in Japan: facts and numbers. *ESC Heart Fail*. 2016 Sep;3(3):145–51.
- 5 Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J*. 2010 Mar;31(6):703–11.
- 6 Schaubroeck HA, Gevaert S, Bagshaw SM, Kellum JA, Hoste EA. Acute cardiorenal syndrome in acute heart failure: focus on renal replacement therapy. *Eur Heart J Acute Cardiovasc Care*. 2020 Oct;9(7):802–11.

## Acknowledgments

The authors would like to thank Eiichiro Kanda for statistical advice and the clinical engineers of the CRRT clinical practice team.

## Statement of Ethics

The study was reviewed and approved by the Medical Ethical Review Board of the Saitama Medical University International Medical Center (approval number 19-292).

The requirement for informed consent was waived due to the retrospective nature of the study.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

No fundings have been received.

## Author Contributions

Yusuke Watanabe and Hirokazu Okada were involved in the study concept, design, and data analysis and wrote the first draft of the manuscript. Tsutomu Inoue and Shintaro Nakano were involved in data analysis and critically reviewed the manuscript. Yusuke Watanabe, Tsutomu Inoue, Shintaro Nakano, and Hirokazu Okada read and approved the final manuscript.

## Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that can compromise the privacy of research participants but are available from the corresponding author H.O. (E-mail: [hirookda@saitama-med.ac.jp](mailto:hirookda@saitama-med.ac.jp)) upon reasonable request.



- 7 Jentzer JC, Bihorac A, Brusca SB, Del Rio-Pertuz G, Kashani K, Kazory A, et al. Contemporary management of severe acute kidney injury and refractory cardiorenal syndrome: JACC Council Perspectives. *J Am Coll Cardiol*. 2020 Sep;76(9):1084–101.
- 8 KDIGO working group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
- 9 Doi K, Nishida O, Shigematsu T, Sadahiro T, Itami N, Iseki K, et al. The Japanese Clinical Practice Guideline for Acute Kidney Injury 2016. *Clin Exp Nephrol*. 2018 Oct;22(5):985–1045.
- 10 Prins KW, Wille KM, Tallaj JA, Tolwani AJ. Assessing continuous renal replacement therapy as a rescue strategy in cardiorenal syndrome 1. *Clin Kidney J*. 2015 Feb;8(1):87–92.
- 11 Iwagami M, Yasunaga H, Noiri E, Horiguchi H, Fushimi K, Matsubara T, et al. Current state of continuous renal replacement therapy for acute kidney injury in Japanese intensive care units in 2011: analysis of a national administrative database. *Nephrol Dial Transplant*. 2015 Jun;30(6):988–95.
- 12 Roy AK, Mc Gorrian C, Treacy C, Kavanaugh E, Brennan A, Mahon NG, et al. A comparison of traditional and novel definitions (RIFLE, AKIN, and KDIGO) of acute kidney injury for the prediction of outcomes in acute decompensated heart failure. *Cardiorenal Med*. 2013 Apr;3(1):26–37.
- 13 Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008 Nov;52(19):1527–39.
- 14 Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the relief for acutely fluid-overloaded patients with decompensated congestive heart failure (RAPID-CHF) trial. *J Am Coll Cardiol*. 2005 Dec;46(11):2043–6.
- 15 Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007 Feb;49(6):675–83.
- 16 Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012 Dec;367(24):2296–304.
- 17 Chen HY, Chou KJ, Fang HC, Chen CL, Hsu CY, Huang WC, et al. Effect of ultrafiltration versus intravenous furosemide for decompensated heart failure in cardiorenal syndrome: a systematic review with meta-analysis of randomized controlled trials. *Nephron*. 2015;129(3):189–96.
- 18 Marenzi G, Muratori M, Cosentino ER, Rinaldi ER, Donghi V, Milazzo V, et al. Continuous ultrafiltration for congestive heart failure: the CUORE trial. *J Card Fail*. 2014 Jan;20(1):9–17.
- 19 Correa A, Patel A, Chauhan K, Shah H, Saha A, Dave M, et al. National trends and outcomes in dialysis-requiring acute kidney injury in heart failure: 2002–2013. *J Card Fail*. 2018 Jul;24(7):442–50.
- 20 Wang AY, Bellomo R. Renal replacement therapy in the ICU: intermittent hemodialysis, sustained low-efficiency dialysis or continuous renal replacement therapy? *Curr Opin Crit Care*. 2018 Dec;24(6):437–42.
- 21 Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, et al. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure – digest version. *Circ J*. 2019 Sep;83(10):2084–184.
- 22 Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation*. 2012 Apr;125(15):1928–52.
- 23 Murugan R, Kerti SJ, Chang CCH, Gallagher M, Clermont G, Palevsky PM, et al. Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: a secondary analysis of the Randomized Evaluation of Normal vs Augmented Level (RENAL) of renal replacement therapy Trial. *JAMA Netw Open*. 2019 Jun;2(6):e195418.
- 24 Doi K, Iwagami M, Yoshida E, Marshall MR. Associations of polyethylenimine-coated AN69ST membrane in continuous renal replacement therapy with the intensive care outcomes: observations from a claims database from Japan. *Blood Purif*. 2017;44(3):184–92.
- 25 Virzi GM, Breglia A, Brocca A, de Cal M, Bolin C, Vescovo G, et al. Levels of proinflammatory cytokines, oxidative stress, and tissue damage markers in patients with acute heart failure with and without cardiorenal syndrome type 1. *Cardiorenal Med*. 2018;8(4):321–31.
- 26 Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. *Nat Rev Dis Primers*. 2021 Jul;7(1):52.