Predictors of withdrawal from renal replacement therapy among patients with acute kidney injury requiring renal replacement therapy

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Abstract

Background Although recovery of renal function after an episode of acute kidney injury (AKI) is an important clinical measure of morbidity, predictors of withdrawal from renal replacement therapy (RRT) among AKI patients remain unclear.

Methods In this single-center retrospective cohort study, we examined the clinical records of AKI patients requiring RRT who were hospitalized in the ICU or general wards at our hospital from January 2010 to December 2013. A priori-determined covariates of age, sex, cardiovascular disease, chronic kidney disease (CKD), mean arterial pressure (MAP), sepsis, nephrotoxic agents, and hypoalbuminemia were assessed in Cox hazard models to estimate hazard ratio (HR).

Results A total of 334 patients were enrolled (median age, 68 years; interquartile range [IQR], 57–77 years; male, 71.6%). During follow-up 157 (47.0%) patients achieved RRT withdrawal. Multivariable Cox regression analysis revealed that CKD, MAP between 95 and 105 mmHg and MAP $\geq$ 105 mmHg, compared with MAP between 65 and 75 mmHg, ventilator use and hypoalbuminemia, were significantly associated with RRT withdrawal.

Conclusion Among patients with AKI requiring RRT, CKD, ventilator use, hypoalbuminemia, and high MAP were associated with RRT withdrawal. Furthermore, keeping a higher MAP at RRT initiation can potentially lead to dependence on RRT.

Keywords Acute kidney injury (AKI) · Renal replacement therapy (RRT) · AKI requiring RRT · Predictors · Discontinuation · Withdrawal

Introduction

The mortality of patients with severe acute kidney injury (AKI) is 60.3%, despite advances in renal replacement therapies (RRT) and critical care medicine [1]. According to the Kidney Disease: Improving Global Outcome (KDIGO) guideline, AKI requiring RRT is equivalent to AKI stage 3 (severe AKI) [2], and mortality associated with severe

AKI is one of the highest observed outcomes. Studies from administrative databases provide evidence that the incidence of AKI and AKI requiring RRT have significantly increased [3, 4], and crude case-fatality has increased likely due to the increasing age and comorbidity burden of patients [4]. Moreover, even if patients could survive severe AKI, 24.6% of patients still receive RRT on day 60 from AKI onset [5] and the independent rate from RRT decreases to 25.8% at 1 year [6].

Apart from mortality, renal outcomes after AKI are crucial. Surveys show that the growth in incident end-stage renal disease (ESRD) outpaced the growth in prevalent chronic kidney disease (CKD), demonstrating that the increasing number of ESRD is not simply due to an increasing number of CKD [7]. An episode of AKI can deteriorate renal function over time after hospital discharge, and especially AKI requiring RRT significantly increases the risk of chronic dialysis [8], which negatively impacts quality of life and poses a huge financial burden.

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Despite the devastating consequence of AKI, factors associated with withdrawal from RRT among AKI patients have remained unclear. Previous studies primarily focused on risk factors associated with development of AKI, whereas predictors of RRT withdrawal among patients with AKI requiring RRT are largely unknown. To make our study closer to clinical practice and identify modifiable determinants, we considered the target range of MAP at RRT initiation, which was different from the previous studies [9–11]. Therefore, we conducted a study to determine predictors of withdrawal from RRT among patients with AKI requiring RRT.

Materials and methods

Study participants and study base

We retrospectively examined the clinical records of AKI patients requiring RRT in the Tokyo Metropolitan Boku-toh Hospital, an urban teaching hospital and a tertiary care center, from January 2010 to December 2013. To assemble our study population from medical records, we took the following steps: (1) we created a roster of information on every RRT performed in either ICU or dialysis room during this period and identified each individual; (2) for patients with multiple admissions during this period, only the first hospitalization was analyzed; (3) to confirm whether or not the patients on the list previously experienced RRT before this study period, we looked at their medical records one by one; (4) we excluded patients on maintenance RRT including hemodialysis, hemofiltration or peritoneal dialysis; (5) we evaluated whether each RRT was performed for AKI among the patients and included the patients with AKI requiring RRT, based on the definition of AKI in the KDIGO criteria [2]. After establishing the study base, for each patient, demographics, clinical information, medical record reviews, laboratory measures, and detailed information about RRT were ascertained from a common comprehensive electronic medical record.

Outcome

Primary outcome was withdrawal from RRT at the end of follow-up, defined as being free from RRT and never resuming after stopping therapy during hospitalization. This outcome was chosen because it is clinically meaningful and has been associated with morbidity and health care costs. In our hospital, each physician decided to discontinue of RRT when intrinsic renal function had adequately recovered [2], without pre-specified criteria. Follow-up was continued until they died, were discharged alive or were lost to follow-up due to transfer to other hospitals. Evaluating the descriptions in the medical records in detail enabled us to accurately

verify each patient's condition. For patients under severe and end-of-the life conditions, we distinguished them from those who were able to discontinue RRT because of renal recovery.

Clinical evaluation

To determine covariates, we systematically performed a literature review, focusing on the association between AKI requiring RRT and outcome. This was because we hypothesized determinants and confounders of mortality, among patients with AKI requiring RRT, might share the causal diagram with RRT withdrawal from the perspective of etiological model. In addition, among the covariates from the previous studies [12–21], we considered the retrospective feasibility of collecting their information, and finally determined covariates.

The demographic information was extracted from the electrical medical chart review on admission. Regarding physiological data, we retrieved information on blood pressure measured at the beginning of RRT, and if not available, we used the measurements at least 10 min before RRT initiation. Mean arterial pressure (MAP) was calculated by $(\text{systolic blood pressure} + 2 \times \text{diastolic blood pressure})/3$. Chronic medical conditions included cardiovascular disease (CVD), cerebrovascular accident (CVA), CKD, diabetes mellitus (DM), hypertension, arteriosclerosis obliterans (ASO), chronic obstructive pulmonary disease (COPD), liver disease, and malignancies. The information on comorbidities was referred to medical records and any referral letters from other facilities. If the patient had been admitted before, we attempted to extract and verify the information on comorbidities. Between admission and the initiation of RRT during the corresponding hospitalizations, if the patient was eligible, we retrieved information on the following variables: administration of vasopressors, mechanical ventilation, surgery, sepsis, infection, nephrotoxic agents, and diuretics. The information on administrations of angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blockers (ARB) or β -blockers was collected under the same approach. CVD included a history of myocardial infarction, angina pectoris, and heart failure. CVA contained a history of brain hemorrhage, brain infarction, subarachnoid hemorrhage, and transient ischemic attack. CKD was defined by the description of medical history on the medical charts or detected if the laboratory data before admission were available. Surgery was defined as experience of any surgeries before RRT initiation during the hospitalization. Sepsis, the most common cause of AKI in critical illness and septic AKI is associated with poor prognosis [22, 23], was defined according to the consensus guideline before RRT initiation [24]. We collected information about the use of diuretics [25, 26] for proxy of fluid overload [27]. Nephrotoxic agents

included non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and contrast medium. The laboratory data were obtained from the latest information on samples prior to RRT initiation at the same days. Anemia was defined as hemoglobin level below 10.0 g/dL based on the reference range of starting erythropoiesis-stimulating agent according to the KDIGO guideline for anemia [28]. Hypoalbuminemia was defined as level of serum albumin below 2.5 g/dL based on previous studies [29, 30]. Hyponatremia was defined as level of sodium below 135 mEq/L based on reference range at our hospital. To reduce the misclassification and measurement error when retrieving the medical information, we reviewed data by three independent board-certified nephrologists.

Statistical analysis

To evaluate normal distribution, we conducted the Shapiro–Wilk test at the 0.05 level of significance. Based on the result of the test, continuous variables are expressed as mean $\pm$ standard deviation (SD) for variables whose underlying distributions were regarded as normal or median (interquartile range [IQR], 25th and 75th percentiles) values for not as normal. Categorical variables are expressed in frequency and percentage. To reflect clinical practice based on the recommendation of AKI guideline [2], MAP was categorized into <65 mmHg, ≥ 65 and <75 mmHg, ≥ 75 and <85 mmHg, ≥ 85 and <95 mmHg, ≥ 95 mmHg and <105 mmHg, and ≥ 105 mmHg for reference on MAP between 65 and 75 mmHg. Difference in distributions of each continuous variable was analyzed using Student's *t* test for variables underlying normal distribution and Wilcoxon rank-sum test for non-normal. Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate. To deal with missing values in our analyses, we conducted complete case analyses. To account for varying length of follow-up, survival analysis methods should be used. Cox regression analyses were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs). First, we performed univariate Cox regression analysis for each of the covariates. Next, we accounted for several known risk factors of AKI in our model, based on prior studies (age [12, 14, 18] and sex [21], CVD [14, 15], CKD, MAP [31], sepsis [22, 23], nephrotoxic agents, and hypoalbuminemia [29, 30]). Moreover, we included anemia as a significant predictor resulting from the univariate analysis. Finally, among the nonsignificant predictors in the univariate analysis, ventilator use was subsequently added to the model because it showed a significant association in the multivariable Cox regression model. Subgroup analyses were performed because different mechanisms according to different demographics, physiologic conditions, and comorbidities have been suggested to explain the effect of baseline MAP on RRT withdrawal; age,

sex, DM, hypertension, CKD, sepsis, nephrotoxic agents, hypoalbuminemia, and vasopressor use. We estimated the effect of MAP on RRT withdrawal by change in quartiles for simplicity. To examine the effect of multiplicative interaction, we performed log-likelihood ratio tests comparing models with and without the interaction term. We also performed subgroup analyses to explore whether RRT withdrawal was associated with underlying severity of the conditions among patients, which is simply implied in the admission status, either ICU or general ward. In sensitivity analysis, we restricted analyses to survivors to account for the competing risk of death. All analyses were performed using the Statistical Package for Social Science (SPSS®) for Windows, version 23.0 (IBM, Chicago, IL, USA) or SAS for windows, version 9.4 (SAS Institute, Cary, NC). Two-sided *p* values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 334 patients were included in the analysis. Baseline characteristics are shown in Table 1. According to the descriptions of medical records, we were able to categorize the indications for RRT into oliguria, azotemia with increase of BUN and/or serum Cr, fluid overload, acidosis, and hyperkalemia, although physicians at our hospital did not follow any pre-specified criteria of each category (i.e., oliguria on medical records did not necessarily match the criteria of urinary volume of less than 0.5 mL/kg for 6 h in KDIGO guideline [2]). Based on a definition of community-acquired AKI [32, 33], the number of patients with AKI requiring RRT within 48 h after admissions was 230 (68.9%). Missing rates of information on covariates were 0.9% of CVD, 0.6% of CVA, CKD, DM, hypertension, ASD, hepatic failure, malignancy, 0.3% of COPD, 4.5% of ACE inhibitor or ARB use, and 4.2% of β -blocker use. The median age was 68 years (IQR 57–77 years), and 71.6% were men. Regarding medical history, 36.3% had CVD, 39.8% had CKD, and 36.7% had DM. The median MAP was 78.7 mmHg (IQR 65.3–96.3 mmHg). Vasopressors were used in 167 (50.0%) patients. Nearly half of the patients were diagnosed with sepsis, 156 (46.7%), at initiation of RRT. Nephrotoxic agents before RRT initiation were used 57.2% of patients. Patients admitted to ICU were the majority of our study population (77.8%). As expected, ICU patients were significantly under severer condition (e.g., lower median MAP, more use of ventilator, sepsis, etc.) compared with those who were in general ward, while those in general ward had more comorbidities such as CKD, hypertension, and malignancy.

Table 1 Baseline characteristics of the study population

	Total <i>N</i> = 334	ICU <i>N</i> = 260 (77.8%)	General ward <i>N</i> = 74 (22.2%)	<i>P</i> value
Age	68 [57–77]	68 [57–77]	69 [60–77]	0.369
Male	239 (71.6)	185 (71.2)	54 (73.0)	0.760
RRT indication				0.098
Oliguria	188 (56.3)	152 (58.5)	36 (48.7)	
Azotemia	83 (24.9)	61 (23.5)	22 (29.7)	
Fluid overload	51 (15.3)	35 (13.5)	16 (21.6)	
Acidosis	6 (1.8)	6 (2.3)	0 (0.0)	
Hyperkalemia	6 (1.8)	6 (2.3)	0 (0.0)	
MAP (mmHg)	78.7 [65.3–96.3]	75.8 [63.0–89.8]	92.1 [81.0–107.3]	<0.0001
MAP < 65	79 (23.7)	73 (28.1)	6 (8.1)	<0.0001
65 ≤ MAP < 75	58 (17.4)	51 (19.6)	7 (9.5)	
75 ≤ MAP < 85	67 (20.1)	55 (21.2)	12 (16.2)	
85 ≤ MAP < 95	37 (11.1)	23 (8.9)	14 (18.9)	
95 ≤ MAP < 105	34 (10.2)	20 (7.7)	14 (18.9)	
105 ≤ MAP	59 (17.7)	38 (14.6)	21 (28.4)	
Vasopressor administration	167 (50.0)	157 (60.4)	10 (13.5)	<0.0001
Ventilator use	196 (58.7)	185 (71.2)	11 (14.9)	<0.0001
Surgery	71 (21.3)	68 (26.2)	3 (4.1)	<0.0001
Sepsis	156 (46.7)	133 (51.2)	23 (31.2)	0.002
Nephrotoxic agent use	191 (57.2)	175 (67.3)	16 (21.6)	<0.0001
Diuretics	133 (39.8)	95 (36.5)	38 (51.4)	0.022
Continuous RRT	146 (43.7)	146 (56.2)	0 (0.0)	<0.0001
Comorbidities				
CVD	120 (36.3)	102 (39.7)	18 (24.3)	0.015
CVA	52 (15.7)	39 (15.1)	13 (17.6)	0.609
CKD	130 (39.2)	79 (30.6)	51 (68.9)	<0.0001
DM	123 (37.0)	91 (35.3)	32 (43.2)	0.211
Hypertension	208 (62.7)	146 (56.6)	62 (83.8)	<0.0001
ASO	21 (6.3)	19 (7.4)	2 (2.7)	0.146
COPD	19 (5.7)	15 (5.8)	4 (5.4)	0.900
Hepatic failure	69 (20.8)	56 (21.7)	13 (17.6)	0.439
Malignancy	59 (17.8)	38 (14.7)	21 (28.4)	0.007
ACEi/ARB use	113 (35.4)	74 (30.2)	39 (52.7)	0.0004
Beta blocker use	42 (13.1)	34 (13.8)	8 (10.8)	0.501
Laboratory				
WBC ($\times 10^3/\text{mm}^3$)	10.6 [7.2–15.4]	11.4 [7.6–16.4]	8.8 [5.7–12.2]	0.001
Hb (g/dL)	9.7 [8.2–12.2]	10.2 [8.6–12.7]	8.6 [7.3–10.3]	<0.0001
Ht (%)	29.1 [24.7–36.5]	30.2 [25.8–37.4]	25.6 [21.8–30.6]	<0.0001
Anemia	175 (52.4)	124 (47.7)	51 (68.9)	<0.0001
Plt ($\times 10^4/\text{mm}^3$)	13.3 [7.3–20.6]	12.2 [6.1–19.2]	16.3 [12.4–24.2]	0.0002
TP (g/dL)	5.6 [4.8–6.3]	5.6 [4.7–6.3]	5.5 [5.0–6.3]	0.704
Alb (g/dL)	2.6 ± 0.7	2.7 ± 0.8	2.5 ± 0.6	0.017
Hypoalbuminemia	141 (42.2)	106 (40.8)	35 (47.3)	0.316
BUN (mg/dL)	68.0 [41.0–106.0]	59.0 [33.5–89.0]	105.5 [78.0–125.0]	<0.0001
Cr (mg/dL)	4.3 [2.5–7.1]	3.7 [2.1–5.5]	7.9 [6.2–10.4]	<0.0001
Na (mEq/L)	136.5 ± 7.5	136.7 ± 7.8	135.6 ± 6.0	0.246
Hyponatremia	130 (38.9)	97 (37.3)	33 (44.6)	0.257
K (mEq/L)	4.9 [4.1–5.8]	5.0 [4.2–6.0]	4.7 [4.0–5.7]	0.047
Cl (mEq/L)	103 [98–107]	103 [98–107]	103 [98–107]	0.943
T-Bil (mg/dL)	0.7 [0.4–1.5]	0.9 [0.4–1.9]	0.4 [0.3–0.6]	<0.0001
CRP (mg/dL)	7.6 [1.6–18.2]	8.7 [2.3–19.3]	4.3 [0.9–13.5]	0.010

Values are given as median [interquartile range], *n* (%) and mean ± SD

MAP mean arterial pressure, RRT renal replacement therapy, CVD cardiovascular disease, CVA cerebrovascular accidents, CKD chronic kidney disease

Table 1 (continued)

ney disease, *DM* diabetes mellitus, *ASO* arteriosclerosis obliterans, *COPD* chronic obstructive pulmonary disease, *ACEi* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blocker, *WBC* white blood cell, *Hb* hemoglobin, *Ht* hematocrit, *anemia* defined as $Hb < 10.0$ g/dL, *Plt* platelet, *TP* total protein, *Alb* albumin, *hypoalbuminemia* defined as $Alb < 2.5$ g/dL, *BUN* blood urea nitrogen, *Cr* serum creatinine, *Na* sodium, *hyponatremia* defined as $Na < 135$ mEq/L, *K* potassium, *Cl* chloride, *T-Bil* total bilirubin, *CRP* C-reactive protein

Association between covariates and RRT withdrawal

Table 2 shows the characteristics of the study population by status of RRT withdrawal. Median follow-up period was 6 days (IQR 2–23 days) and, of the overall population, 47.0% patients withdrew from RRT. In-hospital mortality between patients who were able to withdraw from RRT and those who were not were 15.9% and 70.1%, respectively. There was no significant difference in the history of CVD, CKD, DM, hypertension, and MAP at RRT initiation between the two groups, whereas use of ventilator and sepsis on RRT initiation were significantly different. Notably, the mortality in patients who did not withdraw from RRT was significantly higher than that in patients who withdrew. Apparently, the patients who were not able to withdraw from RRT seemed to have more severe conditions.

When predictors of RRT withdrawal were assessed in univariate Cox models (Table 3), significant factors were CKD (HR 0.58, 95% CI 0.42–0.81, $P = 0.001$), nephrotoxic agents (HR 1.38, 95% CI 1.00–1.90, $P = 0.048$), and anemia (HR 0.60, 95% CI 0.44–0.83, $P = 0.002$).

Table 4 shows the results of multivariable Cox analysis. Model 1 adjusted for age and sex. Model 2 adjusted for predefined covariates (i.e., age and sex, MAP at RRT initiation, history of CVD and CKD, sepsis and use of nephrotoxic agents), anemia, and hypoalbuminemia. Finally, model 3 further adjusted for ventilator use, in addition to the covariates for model 2. In the final model (model 3), CKD (HR 0.63, 95% CI 0.41–0.96, $P = 0.030$), MAP between 95 and 105 mmHg (HR 0.42, 95% CI 0.21–0.85, $P = 0.015$) and ≥ 105 mmHg (HR 0.55, 95% CI 0.31–0.96, $P = 0.036$), compared with MAP between 65 and 75 mmHg on the RRT initiation, hypoalbuminemia (HR 0.70, HR 0.49–0.99, $P = 0.042$), and ventilator use before RRT initiation (HR 0.65, 95% CI 0.44–0.97, $P = 0.035$) remained significant.

Finally, findings from subgroup analyses of MAP at RRT initiation were similar to those of the main analyses (Fig. 1). Both CKD (P for interaction = 0.006) and nephrotoxic agents (P for interaction = 0.001) revealed statistical evidence of multiplicative interactions with MAP. Under existence of CKD or nephrotoxic agents, the point estimates of MAP were different between the two groups within categories. Investigating the effect of hemodynamic instability on outcome, we did not confirm a significant difference in MAP between vasopressor users and non-users (P for interaction = 0.094). Moreover, although the ICU patients tended to suffer from lower MAP and administered more vasopressor

compared to those who were in general ward (Table 1), the effect estimates of MAP on RRT withdrawal in ICU were similar to those of entire cohort (Table 5). Sepsis in ICU patients revealed significant effect on RRT withdrawal, while CKD did in general ward patients. Each MAP category in general ward did not show any significant effects. However, due to the small number of events among patients in general ward compared with that of determinants in the model, we should pay attention to interpreting the results. Indeed, the effects of MAP from patients between ICU and general ward were similar and there was no interaction between MAP and admitted ward (Fig. 1). Findings from sensitivity analysis accounting for the competing risk of death were also similar to main analyses (Table 6).

Discussion

In this retrospective cohort study of AKI patients requiring RRT, we found that CKD, ventilator use, hypoalbuminemia, and MAP at RRT initiation were significantly associated with RRT withdrawal after accounting for potential confounders. Particularly, we observed that $MAP \geq 95$ mmHg was rather associated with a lower chance of RRT withdrawal, which may indicate a potential targetable intervention to improve the outcome of AKI requiring RRT. Our novelty of findings is shedding light on the insight on target range of MAP at RRT initiation.

We found that CKD was associated with lower chance of RRT withdrawal. Our results were consistent with the previous studies showing the worse outcome following AKI among patients with CKD. One study reports that among patients with AKI treated with dialysis, the incidence of ESRD after 90 days from AKI is 3% among patients with previous normal renal function, whereas that of 16% among patients with CKD [34]. Similarly, one RCT suggests that pre-existing CKD is an independent predictor of renal recovery [35]; furthermore, another study shows patients with both AKI and pre-existing or concurrent CKD showed a multiplicative effect on risk for the development of ESRD [36].

The other negatively significant factors of RRT withdrawal were ventilator use and hypoalbuminemia. Although our findings confirmed the previous literature reporting of a higher mortality among AKI patients on ventilator [14, 15] requiring RRT, the underlying mechanisms are not fully understood. Indeed, it is possible that ventilator use could

Table 2 Comparison between patients with and without withdrawal of RRT

	Withdrawal <i>N</i> = 157 (47.0%)	Non-withdrawal <i>N</i> = 177 (53.0%)	<i>P</i> value
Age	67 [55–77]	69 [58–77]	0.240
Male	105 (66.9)	134 (75.7)	0.074
MAP (mmHg)	79.0 [68.2–96.0]	77.0 [62.8–97.7]	0.192
MAP < 65	28 (17.8)	51 (28.8)	0.095
65 ≤ MAP < 75	28 (17.8)	30 (16.9)	
75 ≤ MAP < 85	40 (25.5)	27 (15.3)	
85 ≤ MAP < 95	19 (12.1)	18 (10.2)	
95 ≤ MAP < 105	14 (8.9)	20 (11.3)	
105 ≤ MAP	28 (17.8)	31 (17.5)	
Vasopressor administration	70 (44.6)	97 (54.8)	0.062
Ventilator use	80 (51.0)	116 (65.5)	0.007
Surgery	34 (21.7)	37 (20.9)	0.867
Sepsis	61 (38.9)	95 (53.7)	0.007
Nephrotoxic agent use	92 (58.6)	99 (55.9)	0.623
Diuretics	67 (42.7)	66 (37.3)	0.315
Continuous RRT	61 (38.9)	85 (48.0)	0.092
Comorbidities			
CVD	54 (34.6)	66 (37.7)	0.558
CVA	21 (13.4)	31 (17.7)	0.278
CKD	56 (35.7)	74 (42.3)	0.217
DM	51 (32.5)	72 (41.1)	0.103
Hypertension	97 (61.8)	111 (63.4)	0.757
ASO	12 (7.6)	9 (5.1)	0.350
COPD	4 (2.5)	15 (8.5)	0.019
Hepatic failure	32 (20.4)	37 (21.1)	0.865
Malignancy	21 (13.4)	38 (21.7)	0.047
ACEi/ARB use	50 (32.5)	63 (38.2)	0.286
Beta blocker use	20 (12.9)	22 (13.3)	0.909
Laboratory			
WBC ($\times 10^3/\text{mm}^3$)	11.7 [7.9–17.1]	10.0 [6.6–14.2]	0.003
Hb (g/dL)	10.1 [8.6–12.5]	9.3 [7.9–11.7]	0.005
Ht (%)	30.0 [26.2–37.3]	27.9 [23.3–35.6]	0.006
Anemia	75 (42.9)	100 (57.1)	0.111
Plt ($\times 10^4/\text{mm}^3$)	13.6 [8.9–20.9]	13.0 [6.1–20.2]	0.150
TP (g/dL)	5.7 [5.0–6.5]	5.5 [4.6–6.1]	0.039
Alb (g/dL)	2.7 ± 0.8	2.6 ± 0.7	0.890
Hypoalbuminemia	61 (43.3)	80 (56.7)	0.241
BUN (mg/dL)	67.0 [40.0–103.5]	69.0 [42.0–108.5]	0.527
Cr (mg/dL)	4.2 [2.6–6.6]	4.4 [2.3–7.6]	0.236
Na (mEq/L)	135.3 ± 7.1	137.6 ± 7.7	0.050
Hyponatremia	68 (43.3)	62 (35.0)	0.121
K (mEq/L)	4.9 [4.1–5.8]	4.9 [4.1–5.9]	0.805
Cl (mEq/L)	103 [97–107]	103 [98–108]	0.224
T-Bil (mg/dL)	0.7 [0.4–1.3]	0.6 [0.3–1.9]	0.390
CRP (mg/dL)	8.8 [1.7–20.1]	7.0 [1.4–17.1]	0.464
Outcome			
In-hospital mortality	25 (15.9)	124 (70.1)	< 0.0001
Days of RRT withdrawal	4 [2–9]	11 [2–36]	< 0.0001

Values are given as median [interquartile range], *n* (%) and mean ± SD

RRT renal replacement therapy, MAP mean arterial pressure, CVD cardiovascular disease, CVA cerebrovascular accidents, CKD chronic kidney disease, DM diabetes mellitus, ASO arteriosclerosis obliterans, COPD chronic obstructive pulmonary disease, ACEi angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blocker, WBC white blood cell, Hb hemoglobin, Ht hematocrit, anemia defined as Hb < 10.0 g/dL, Plt platelet, TP total protein, Alb albumin, hypoalbuminemia defined as Alb < 2.5 g/dL, BUN blood

Table 2 (continued)

urea nitrogen, *Cr* serum creatinine, *Na* sodium, *hyponatremia* defined as $\text{Na} < 135 \text{ mEq/L}$, *K* potassium, *Cl* chloride, *T-Bil* total bilirubin, *CRP* C-reactive protein

Table 3 Univariate analyses for RRT withdrawal in patients with AKI requiring RRT

Covariates	Crude HR	95% CI	P value
Age	1.00	0.99–1.01	0.482
Male (vs. Female)	0.82	0.59–1.15	0.254
MAP (mmHg)			0.179
MAP < 65	0.98	0.58–1.66	0.933
65 ≤ MAP < 75	1.00	Reference	
75 ≤ MAP < 85	1.17	0.72–1.90	0.527
85 ≤ MAP < 95	0.85	0.47–1.52	0.582
95 ≤ MAP < 105	0.60	0.31–1.14	0.116
105 ≤ MAP	0.66	0.39–1.11	0.117
Ventilator use	0.86	0.63–1.18	0.342
CVD	0.81	0.63–1.21	0.413
CKD	0.58	0.42–0.81	0.001
DM	0.77	0.55–1.07	0.119
ASO	1.21	0.67–2.18	0.532
Surgery	1.06	0.72–1.54	0.781
COPD	0.38	0.14–1.02	0.055
Hepatic failure	1.13	0.77–1.67	0.538
Malignancy	0.70	0.44–1.11	0.127
Sepsis	0.87	0.63–1.20	0.399
Nephrotox	1.38	1.00–1.90	0.048
Diuretics	0.90	0.65–1.23	0.505
Anemia	0.60	0.44–0.83	0.002
Hypoalbuminemia	0.76	0.55–1.05	0.101
Hyponatremia	1.20	0.87–1.65	0.259

RRT renal replacement therapy, AKI acute kidney injury, HR hazard ratio, CI confidence interval, MAP mean arterial pressure, CVD cardiovascular disease, CVA cerebrovascular accidents, CKD chronic kidney disease, DM diabetes mellitus, ASO arteriosclerosis obliterans, COPD chronic obstructive pulmonary disease, anemia defined as $\text{Hb} < 10.0 \text{ g/dL}$, hypoalbuminemia defined as $\text{Alb} < 2.5 \text{ g/dL}$, hyponatremia defined as $\text{Na} < 135 \text{ mEq/L}$

be surrogate of sicker underlying disease conditions, rather than the predictor by itself. As illustrated, future studies are needed to better understand the roles of ventilator use on AKI outcomes using sufficient information about potential mediator and confounders. On the other hand, several studies suggested serum albumin itself could protect the kidneys from toxic agents and maintain the renal perfusion [29, 30]. Therefore, hypoalbuminemia is more likely to be related to the extent of the renal dysfunction, leading to failure in RRT withdrawal.

A novel finding of our study is a low chance of RRT withdrawal among patients with high MAP at the time of RRT initiation. In practice, we usually try to keep the $\text{MAP} \geq 65 \text{ mmHg}$ based on the AKI guideline [2]. However,

little is known about the optimal MAP target. In our study, patients with MAP of 95–105 and $\geq 105 \text{ mmHg}$ had a lower chance of RRT withdrawal, which suggests higher MAP such as 95 mmHg is not the optimal target compared to MAP 65–75 mmHg regardless of vasopressor administration. Since we can regard MAP as renal perfusion, we assume that the higher MAP prevents kidney from further damage. However, if we assume the renal autoregulation after AKI is deteriorated, higher blood pressure could easily induce more damage to glomerulus such as hypertension-induced renal damage [37], which is compatible with our observed results. There are a few reports concerning blood pressure related to mortality among AKI requiring RRT [17, 31], and instead of renal prognosis, some reports disclose better prognosis with higher MAP among AKI. Among patients with post-gastrointestinal surgery, the MAP comparing 80–95 mmHg with 65–79 mmHg is reported to have less incidence of AKI [38], and among patients with AKI requiring RRT after cardiac surgery, the lower MAP is associated with poor mortality [39]. As our results showed, the higher MAP would not be optimal rather than sole target of $\text{MAP} \geq 65 \text{ mmHg}$. This result was supported by the subgroup and sensitivity analyses. In principle, most of the patients in ICU were under severe conditions with lower MAP, likely leading to failure in RRT withdrawal. Besides, competing risk of death appeared to obscure the accurate results of RRT withdrawal. Hence, we might intuitively speculate lower MAP and competing risk of death were associated with failure in RRT withdrawal; however, we were able to disclose the robustness of our results that higher MAP would not be optimal rather than sole target of $\text{MAP} \geq 65 \text{ mmHg}$. Moreover, we reinforced our results according to evidence that the intervention in hemodynamic stability was not associated with MAP at baseline. On the other hand, some studies investigated patients with more severe conditions with higher mortality (e.g., 60.3%) [1] and, therefore, the interpretation of our results should be made with caution. Nevertheless, the nature of observational study may not allow for causality and, therefore, future studies are needed to assess whether specific MAP target interventions can improve the outcome of AKI requiring RRT.

Our study has several limitations. First, the retrospective nature of this study may potentially make it susceptible to several forms of bias. For example, a retrospective collection of medical histories from the medical charts might lead to misclassification. Second, we were unable to account for several potential confounders, such as urinary status. However, some patients were initiated RRT soon after admission into our hospital from emergency department. Therefore, we cannot sufficiently ascertain

Table 4 Multivariate analyses for RRT withdrawal in patients with AKI requiring RRT

Covariates	Model 1			Model 2			Model 3		
	Adjusted HR	95% CI	P value	Adjusted HR	95% CI	P value	Adjusted HR	95% CI	P value
Age	1.00	0.98–1.01	0.364	1.00	0.99–1.01	0.760	1.00	0.99–1.01	0.557
Male (vs female)	0.80	0.57–1.13	0.201	0.74	0.52–1.06	0.098	0.73	0.51–1.04	0.082
MAP (mmHg)						0.030			0.010
MAP < 65				1.01	0.59–1.71	0.980	1.12	0.66–1.92	0.673
65 ≤ MAP < 75				1.00	Reference		Reference	Reference	
75 ≤ MAP < 85				1.16	0.71–1.91	0.549	1.19	0.72–1.95	0.502
85 ≤ MAP < 95				0.80	0.44–1.43	0.443	0.73	0.40–1.32	0.297
95 ≤ MAP < 105				0.46	0.23–0.92	0.028	0.42	0.21–0.85	0.014
105 ≤ MAP				0.55	0.31–0.98	0.042	0.55	0.31–0.96	0.036
CVD				0.83	0.58–1.20	0.317	0.91	0.63–1.33	0.640
CKD				0.64	0.42–0.97	0.037	0.63	0.41–0.96	0.030
Sepsis				0.63	0.43–0.91	0.015	0.69	0.47–1.02	0.063
Nephrotoxic agent				1.07	0.74–1.55	0.706	1.18	0.81–1.71	0.396
Anemia				0.77	0.54–1.08	0.133	0.76	0.54–1.07	0.113
Hypoalbuminemia				0.63	0.50–0.89	0.008	0.70	0.49–0.99	0.042
Ventilator							0.65	0.44–0.97	0.035

Model 1 was adjusted for age and sex. Model 2, in addition to model 1, was adjusted for MAP at RRT initiation, the history of CVD and CKD, sepsis, the use of nephrotoxic agents, anemia, and hypoalbuminaemia. Model 3, in addition to model 2, was adjusted for ventilator use

RRT renal replacement therapy, AKI acute kidney injury, HR hazard ratio, CI confidence interval, MAP mean arterial pressure, CVD cardiovascular disease, CKD chronic kidney disease, anemia defined as Hb < 10.0 g/dL, hypoalbuminemia defined as Alb < 2.5 g/dL

Fig. 1 Forest plot demonstrates consistent associations of mean arterial pressure (MAP) at renal replacement therapy (RRT) initiation with RRT withdrawal. Hazard ratio (HR) estimates are adjusted for age, sex, cardiovascular disease (CVD), chronic kidney disease (CKD), sepsis, nephrotoxic agents, anemia, hypoalbuminemia, ventilator use. CI confidence interval, nephrotoxic nephrotoxic agents, ICU intensive care unit

their urine volume and were not able to include urine volume into our analysis. Third, this study was conducted in a single center, which may limit the generalizability of our findings. Although we accounted for the major

confounders of MAP and RRT withdrawal, external validity of the results may be limited due to the relatively small study population conducted in a single center. Future replication studies in a larger population are warranted to

Table 5 Subgroup analysis applied our final model in ICU and general ward patients

Covariates	ICU			General ward		
	Adjusted HR	95% CI	P value	Adjusted HR	95% CI	P value
Age	1.00	0.98–1.01	0.424	1.01	0.97–1.04	0.805
Male (vs female)	0.59	0.39–0.87	0.008	1.12	0.40–3.09	0.833
MAP (mmHg)			0.058			0.024
MAP < 65	0.86	0.48–1.53	0.614	7.21	1.16–44.74	0.034
65 ≤ MAP < 75	1.00	Reference		1.00	Reference	
75 ≤ MAP < 85	1.07	0.63–1.83	0.796	3.43	0.62–18.90	0.156
85 ≤ MAP < 95	0.92	0.47–1.80	0.804	0.83	0.15–4.64	0.827
95 ≤ MAP < 105	0.41	0.18–0.92	0.030	0.93	0.16–5.26	0.934
105 ≤ MAP	0.49	0.26–0.92	0.028	0.98	0.19–5.21	0.983
CVD	0.81	0.52–1.26	0.351	0.73	0.27–1.95	0.533
CKD	0.66	0.38–1.13	0.131	0.42	0.18–0.98	0.045
Sepsis	0.64	0.41–0.98	0.040	1.39	0.48–4.04	0.545
Nephrotoxic agent	0.92	0.61–1.41	0.716	1.69	0.65–4.39	0.286
Anemia	0.88	0.59–1.32	0.544	0.72	0.28–1.83	0.489
Hypoalbuminemia	0.64	0.43–0.96	0.032	1.09	0.44–2.69	0.856
Ventilator	0.63	0.41–0.96	0.033	0.18	0.03–0.99	0.049

HR hazard ratio, CI confidence interval, MAP mean arterial pressure, CVD cardiovascular disease, CKD chronic kidney disease, anemia defined as Hb < 10.0 g/dL, hypoalbuminemia defined as Alb < 2.5 g/dL

Table 6 Restricted analyses to survivors applied our final model

Covariates	Survival		
	Adjusted HR	95% CI	P value
Age	1.01	0.99–1.02	0.167
Male (vs female)	1.15	0.75–1.75	0.523
MAP (mmHg)			0.050
MAP < 65	1.13	0.60–2.12	0.706
65 ≤ MAP < 75	1.00	Reference	
75 ≤ MAP < 85	0.77	0.43–1.39	0.391
85 ≤ MAP < 95	0.65	0.33–1.27	0.208
95 ≤ MAP < 105	0.41	0.20–0.85	0.016
105 ≤ MAP	0.47	0.25–0.88	0.017
CVD	1.05	0.67–1.63	0.845
CKD	0.46	0.27–0.76	0.003
Sepsis	0.86	0.56–1.32	0.493
Nephrotoxic agent	1.35	0.91–1.99	0.134
Anemia	0.71	0.47–1.06	0.093
Hypoalbuminemia	0.87	0.59–1.30	0.497
Ventilator	0.77	0.50–1.19	0.238

HR hazard ratio, CI confidence interval, MAP mean arterial pressure, CVD cardiovascular disease, CKD chronic kidney disease, anemia defined as Hb < 10.0 g/dL, hypoalbuminemia defined as Alb < 2.5 g/dL

explore the generalizability of our findings. Finally, we were only able to assess the short-term kidney outcomes. Although several studies suggest that renal recovery

can occur long after hospital discharge (e.g., 90 days–6 months [40, 41]), the majority of renal recovery would be observed within a short period [42].

In conclusion, CKD, ventilator use, hypoalbuminemia, and MAP were significantly associated with RRT withdrawal among individuals with AKI requiring RRT. Considering that MAP is potentially modifiable through medications, whether interventions of target BP strategy could improve the outcome of AKI requiring RRT may deserve future investigation.

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Author contributions KI designed this study, obtained the fund support, analyzed the data, wrote the manuscript, and submitted the manuscript. JI advised the study design, reviewed the analyses and the manuscript. SI supervised the study. All the authors discussed and reviewed the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval We collected the clinical data according to the Guidelines for Epidemiological Studies from The Ministry of Health, Labour and Welfare, Japan. The institutional review board and the Committee of Ethics of Tokyo Metropolitan Bokutoh Hospital approved the study protocol (# 5 in 2014).

Informed consent The IRB and ethics committee that granted approval waived the need to obtain informed consent for this study.

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