Reduced serum albumin as a risk factor for poor prognosis in critically ill patients receiving renal replacement therapy

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Abstract

Background: Albumin is the primary body protein, which can predict the poor prognosis of several critical diseases. However, there are a few scientific studies on the relationship between albumin and the prognosis of dialysis patients. This study aims to explore the impact of hypoalbuminemia on the prognosis of critically ill patients with acute kidney injury (AKI) receiving continuous renal replacement therapy (CRRT).

Methods: This was a secondary study. Clinical, biochemical, and 28-day and 90-day mortality rates for critical patients with AKI who received CRRT between 2009 and 2016 were searched from the database to determine the effect of hypoalbuminemia on poor outcomes by univariate, multivariate, smooth curve fitting, and subgroup analysis.

Results: A total of 837 participants were enrolled in this study. Multivariate Cox proportional hazard regression analysis showed that hypoalbuminemia was associated with both 28-day and 90-day mortality risks after full adjustment for confounding variables, with an adjusted hazard ratio (95% confidence interval) of 0.63 (0.50–0.80) and 0.63 (0.51–0.78), respectively for each 1 g/dL increase of albumin. Stratified analysis showed that hypoalbuminemia was not associated with poor prognosis in oliguria.

Conclusion: Hypoalbuminemia is associated with poor prognosis in critically ill AKI patients with CRRT; therefore, measuring albumin may be helpful for predicting the prognosis. However, in those with oliguria, this conclusion is not valid.

Keywords: Albumin, Acute kidney injury, Continuous renal replacement therapy, Mortality, Subgroup

Introduction

Acute kidney injury (AKI) is a health challenge worldwide [1]. More than 13 million individuals get affected by AKI annually, which occurs in more than 60% of intensive care unit (ICU) patients [2]. Approximately 5% of ICU patients require continuous renal replacement therapy (CRRT) [3]. When the internal environment of patients with AKI is unstable, CRRT can easily control the imbalance. Therefore, CRRT is the most commonly used clinical renal replacement therapy [4, 5]. The mortality of patients with AKI is quite high, particularly in those with severe AKI who require dialysis; the mortality can exceed 50% [3]. Some clinical indicators, such as platelet, bilirubin, phosphate, Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, have reportedly been related to the prognosis of critically ill patients with AKI [6–9].

Albumin is an important protein in the human body, which mainly exists in the blood, cerebrospinal, and...
lymphatic fluids. Albumin can not only maintain body nutrition and osmotic pressure but also combine with many insoluble substances, regulate the fluid exchange between various body parts, and affect blood circulation to the kidneys [10, 11]. Albumin reduction can increase the rate of mortality in acute coronary syndrome, septic shock, heart failure, and other diseases [12–14]. The albumin decrease is caused by the body in the inflammatory state. When the body is damaged, inflammation will occur, resulting in the high expression of platelet-derived growth factor, interleukin-6, and nitric oxide-induced vascular endothelial growth factor, which increase capillary permeability and angiogenesis, leading to the escape of albumin from the blood vessels [15, 16]. Gradually decreasing serum albumin levels possibly lead to more severe inflammation [17]. Inflammation plays an important role in the development of AKI [18]. Current studies have shown that serum albumin level is associated with an increased incidence rate of AKI and mortality in such patients [19, 20]. However, since the relationship between albumin levels and dialysis patient outcomes is controversial with only a few relevant studies [21, 22]; therefore, this study aimed to investigate the relationship between hypoalbuminemia and prognosis in patients with critical AKI under CRRT. The present study further investigated whether albumin affects mortality in specific populations with different CRRT indications.

Materials and methods

Data source
This study was a secondary analysis, with data from the ‘DATADRYAD’open database. The data packages uploaded by the researchers in the database can be downloaded and quoted for free. This study refers to the data package uploaded by Jung et al. [23, 24].

Study population
Initially, a total of 2391 patients with AKI were enrolled in the study, all of whom received CRRT from January 2009 to September 2016 in the ICU of Yonsei University Health System Severance Hospital and the National Health Insurance Service Medical Center Ilsan Hospital. All participants met the Acute Kidney Injury Network criteria [25]. After analyzing the data of all participants, 281 with stage 1 AKI and 298 with stage 2 AKI were excluded. Also, the following populations were excluded: (1) minor patients (n = 42); (2) those with chronic kidney disease (CKD) or dialysis or CRRT history (n = 585); (3) those who were pregnant or lactating (n = 12); (4) those with retrorenal obstruction (n = 263); (5) those with renal transplantation history (n = 64); and (6) those with albumin deficiency (n = 9). Finally, 837 patients were included in this study.

In the study published in the original data [23], Jung et al. showed that the study followed the declaration of Helsinki and was approved by the Yonsei University health system, Severance Hospital, and Institutional Review Committee. Owing to the de-identified data, the patient’s written consent requirement was abandoned.

Data collection
This study collected demographic and clinical data of patients before CRRT, including age, sex, body mass index (BMI), comorbidities, and CRRT causes. The main causes of AKI, including sepsis, nephrotoxin, ischemia, surgery and so on, were also listed in this paper. The laboratory indices recorded at 0 h of CRRT in the ICU were C-reactive protein (CRP), glomerular filtration rate (GFR), hemoglobin (Hb), white blood cell (WBC), serum creatinine (CR), blood urea nitrogen (BUN), albumin (Alb), bicarbonate (HCO3−), potassium (K+), and phosphate. Also, scores on the severity of the patient’s disease were collected, such as the Charlson comorbidity index (CCI), SOFA score, and APACHE II score.

CRRT protocol
Clinically, doctors would decide whether to initiate CRRT according to the degree of renal function damage in critically ill patients. Patients with uremia, persistent oliguria, volume overload, and decompensated metabolic acidosis should start CRRT as soon as possible. The femoral, internal jugular, and subclavian veins were selected as the central venous catheterization sites of CRRT. The multiFiltrate (Fresenius Medical Care, Bad Homburg, Germany) or the Prismaflex (Baxter International Inc. Lundia AB, Sweden) machine was used for all patients. The initial CRRT blood flow velocity was 100 mL/min, which was increased to 150 mL/min. The total outflow of CRRT in all patients was targeted to deliver ≥35 mL/kg/h.

Statistical analysis
Continuous variables following normal distribution were expressed as the mean ± standard deviation, and skew variables were expressed as the median (quartile 1–quartile 3). Categorical variables were reported as the frequency or percentage. Box chart was used to show the relationship between serum albumin and different survival status, and analysis of variance was used to evaluate the difference between the survival and death groups. A univariate Cox proportional hazards model was established to analyze the risk relationship between albumin and 28-day and 90-day mortality in critically ill patients. Then, the multivariate Cox regression model was used to determine the independent effect of albumin on short-term and medium-term prognosis in critically ill patients. To ensure the robustness of the analysis results,
this study not only gives the results of unadjusted, slight adjustment, and comprehensive adjustment analyses, but also converts albumin into classified variables for analysis according to the quartile method, and calculates the $p$-value of the trend to observe the possibility of nonlinearity. According to the indication of CRRT and the etiology of AKI, subgroup analysis was performed to further determine the relationship between albumin and short-term and medium-term prognosis. In order to explore whether there is a nonlinear relationship between albumin and prognosis, after adjusting all covariates, the correlation fitting curve between albumin and 28 and 90 day mortality was drawn by using the restrictive cubic spline function following on Cox proportional hazards models. In this study, $P < 0.05$ was considered a significant difference.

In the present study, the variable CCI was transformed into continuous variable processing, and all data were processed using EmpowerStats (www.empowerstats.com, X&Y solutions, inc. Boston, Massachusetts) and statistical packages R (http://www.R-project.org; The R Foundation; version 3.4.3).

Results
Baseline characteristics of participants
Table 1 lists the general characteristics of the included participants. The average age of the study participants was 62.57 ± 14.42 years, and 62.25% were men. The mean BMI and mean arterial pressure (MAP) were 23.90 ± 4.83 kg/m² and 76.78 ± 14.51 mmHg, respectively. Most of the critically ill patients had complications, including 406 (48.51%) patients with hypertension, 266 (31.82%) with diabetes, 112 (13.38%) with congestive heart failure, and 90 (10.78%) patients with cerebrovascular disease. Also, the prevalence of peripheral vascular disease, chronic obstructive pulmonary disease (COPD), myocardial infarction, and dementia was 29 (3.46%), 51 (6.09%), 75 (8.96%), and 26 (3.11%), respectively. Among the 837 participants, the 28-day and the 90-day mortality rate was 61.89 and 71.92%, respectively. The box chart showed that serum albumin level was correlated with different survival statuses of 28 days and 90 days, and the serum albumin level of the survival group was significantly higher than that of the death group (both $p < 0.001$) (Figs. 1 and 2).

Univariate analysis
As shown in Tables 2 and 3, Univariate analysis showed that albumin was associated with 28-day and 90-day mortality in critically ill patients. The hazard ratio (HR) and 95% confidence interval (CI) were 0.66 (0.57, 0.76) and 0.62 (0.55, 0.71), respectively. Albumin was a protective factor. Also, the univariate analysis found that

| Characteristics | Values |
|-----------------|--------|
| Age, year       | 62.57 ± 14.42 |
| SEX (male/female)| 521/316 |
| BMI, kg/m²      | 23.90 ± 4.83 |
| MAP, mmHg       | 76.78 ± 14.51 |
| Myocardial infarction, n (%) | 75 (8.96%) |
| Congestive heart failure, n (%) | 112 (13.38%) |
| Cerebrovascular disease, n (%) | 90 (10.78%) |
| Peripheral vascular disease, n (%) | 29 (3.46%) |
| Dementia, n (%) | 26 (3.11%) |
| Diabetes, n (%) | 266 (31.82%) |
| Hypertension, n (%) | 406 (48.51%) |
| COPD, n (%)     | 51 (6.09%) |
| Mechanical ventilation, n (%) | 661 (78.97%) |
| K+, mEq/L       | 4.72 ± 1.10 |
| HCO₃-, mEq/L    | 16.54 ± 5.65 |
| Phosphate, g/dL | 5.94 ± 2.53 |
| CRP, g/L        | 66.45 (18.88–164.80) |
| WBC, μL         | 11,840.00 (6565.00–18,672.50) |
| HbG/dL          | 9.66 ± 2.28 |
| Albago/dL       | 2.61 ± 0.59 |
| BUN, g/dL       | 52.00 (35.00–76.00) |
| Cr, mg/dL       | 3.02 ± 1.74 |
| GFR, mL/min     | 23.30 (15.10–35.80) |
| APACHE II score | 27.58 ± 7.89 |
| SOFA score      | 12.53 ± 3.50 |
| CCI             | 3.13 ± 2.25 |
| AKI causes      |        |
| Sepsis          | 580 (69.30%) |
| Nephrotoxin     | 26 (3.11%) |
| Ischemia        | 65 (7.77%) |
| Surgery         | 70 (8.36%) |
| Others          | 96 (11.47%) |
| CRRT causes     |        |
| Volume overload | 108 (12.90%) |
| Metabolic acidosis | 183 (21.86%) |
| Hyperkalemia    | 39 (4.66%) |
| Uremia          | 93 (11.11%) |
| Oliguria        | 219 (26.16%) |
| Other           | 195 (23.30%) |
| 28-d mortality  | 518 (61.89%) |
| 90-d mortality  | 602 (71.92%) |

Data are expressed as n (%) or the mean ± SD or median (quartile 1-quartile 3)
hypertension, APACHE II score, SOFA score, CCI, phosphate, MAP, mechanical ventilation, Hb, Cr, and GFR were associated with short-term and medium-term prognosis of critically ill AKI patients with CRRT, while BMI was only associated with 90-day mortality.

**Multivariate cox regression analysis**
To further clarify the relationship between albumin and short-term and medium-term prognosis, we established three models of unadjusted, micro adjusted, and fully adjusted in multivariate regression analysis. The results of
### Table 2 The results of univariate analysis of 28-day mortality

| Variable                  | HR (95%CI)       | p-value   |
|---------------------------|------------------|-----------|
| Age                       | 1.00 (0.99, 1.01) | 0.9847    |
| SEX                       |                  |           |
|   male                    | 1.0              |           |
|   female                  | 0.94 (0.78, 1.12) | 0.4792    |
| Myocardial infarction     | 0.99 (0.74, 1.33) | 0.9567    |
| Congestive heart failure  | 0.80 (0.61, 1.04) | 0.0947    |
| Cerebrovascular disease   | 0.90 (0.68, 1.19) | 0.4633    |
| Peripheral vascular disease | 0.76 (0.46, 1.25) | 0.2844    |
| Dementia                  | 0.71 (0.42, 1.20) | 0.1998    |
| Diabetes                  | 0.91 (0.76, 1.10) | 0.3334    |
| Hypertension              | 0.69 (0.58, 0.83) | < 0.0001  |
| COPD                      | 0.91 (0.62, 1.32) | 0.6039    |
| K+                        | 1.03 (0.95, 1.12) | 0.4208    |
| APACHE II score           | 1.03 (1.02, 1.04) | < 0.0001  |
| CCI                       | 1.10 (1.06, 1.14) | < 0.0001  |
| SOFA score                | 1.17 (1.14, 1.21) | < 0.0001  |
| CRRT causes               |                  |           |
|   Volume overload         | 1.0              |           |
|   Metabolic acidosis      | 1.45 (1.06, 1.99) | 0.0207    |
|   Hyperkalemia            | 1.66 (1.05, 2.61) | 0.0285    |
|   Uremia                  | 0.94 (0.65, 1.38) | 0.7674    |
|   Oliguria                | 1.08 (0.78, 1.47) | 0.6515    |
|   Other                   | 1.45 (1.06, 1.98) | 0.0199    |
| AKI causes                |                  |           |
|   Sepsis                  | 1.0              |           |
|   Nephrotoxin             | 1.06 (0.66, 1.70) | 0.8108    |
|   Ischemia                | 1.06 (0.76, 1.47) | 0.7251    |
|   Surgery                 | 0.81 (0.58, 1.15) | 0.2370    |
|   Others                  | 1.32 (1.00, 1.72) | 0.0464    |
| HCO3-                     | 0.99 (0.97, 1.01) | 0.3030    |
| Phosphate                 | 1.05 (1.02, 1.08) | 0.0018    |
| BMI                       | 0.98 (0.96, 1.00) | 0.0626    |
| MAP                       | 0.98 (0.98, 0.99) | < 0.0001  |
| Mechanical ventilation    | 2.12 (1.65, 2.73) | < 0.0001  |
| WBC                       | 1.00 (1.00, 1.00) | 0.1276    |
| Hb                        | 0.93 (0.90, 0.97) | 0.0004    |
| BUN                       | 1.00 (1.00, 1.00) | 0.8286    |
| Cr                        | 0.89 (0.84, 0.94) | < 0.0001  |
| Alb                       | 0.66 (0.57, 0.76) | < 0.0001  |
| CRP                       | 1.00 (1.00, 1.00) | 0.8429    |
| GFR                       | 1.00 (1.00, 1.01) | 0.0256    |

### Table 3 The results of univariate analysis of 90-day mortaity

| Variable                  | HR (95%CI)       | p-value   |
|---------------------------|------------------|-----------|
| Age                       | 1.00 (1.00, 1.01) | 0.4307    |
| SEX                       |                  |           |
|   male                    | 1.0              |           |
|   female                  | 0.96 (0.82, 1.14) | 0.6630    |
| Myocardial infarction     | 0.93 (0.70, 1.24) | 0.6179    |
| Congestive heart failure  | 0.90 (0.71, 1.14) | 0.3679    |
| Cerebrovascular disease   | 1.02 (0.79, 1.33) | 0.8560    |
| Peripheral vascular disease | 0.94 (0.60, 1.47) | 0.7887    |
| Dementia                  | 0.87 (0.53, 1.40) | 0.5580    |
| Diabetes                  | 0.87 (0.73, 1.04) | 0.1202    |
| Hypertension              | 0.72 (0.61, 0.84) | < 0.0001  |
| COPD                      | 0.94 (0.67, 1.32) | 0.7179    |
| K+                        | 1.07 (0.99, 1.15) | 0.0922    |
| APACHE II score           | 1.03 (1.02, 1.04) | < 0.0001  |
| CCI                       | 1.07 (1.04, 1.11) | < 0.0001  |
| SOFA score                | 1.13 (1.10, 1.15) | < 0.0001  |
| CRRT causes               |                  |           |
|   Volume overload         | 1.0              |           |
|   Metabolic acidosis      | 1.41 (1.05, 1.87) | 0.0205    |
|   Hyperkalemia            | 1.78 (1.18, 2.70) | 0.0063    |
|   Uremia                  | 1.08 (0.77, 1.52) | 0.6628    |
|   Oliguria                | 1.14 (0.86, 1.52) | 0.3584    |
|   Other                   | 1.32 (0.99, 1.75) | 0.0596    |
| AKI causes                |                  |           |
|   Sepsis                  | 1.0              |           |
|   Nephrotoxin             | 0.96 (0.60, 1.54) | 0.8664    |
|   Ischemia                | 1.01 (0.75, 1.37) | 0.9277    |
|   Surgery                 | 0.67 (0.49, 0.93) | 0.0151    |
|   Others                  | 0.90 (0.70, 1.17) | 0.4399    |
| HCO3-                     | 0.99 (0.98, 1.01) | 0.4557    |
| Phosphate                 | 1.04 (1.01, 1.08) | 0.0054    |
| BMI                       | 0.98 (0.96, 1.00) | 0.0163    |
| MAP                       | 0.98 (0.98, 0.99) | < 0.0001  |
| Mechanical ventilation    | 1.97 (1.58, 2.46) | < 0.0001  |
| WBC                       | 1.00 (1.00, 1.00) | 0.2207    |
| Hb                        | 0.93 (0.90, 0.97) | 0.0002    |
| BUN                       | 1.00 (1.00, 1.00) | 0.5005    |
| Cr                        | 0.89 (0.84, 0.93) | < 0.0001  |
| Alb                       | 0.62 (0.55, 0.71) | < 0.0001  |
| CRP                       | 1.00 (1.00, 1.00) | 0.8145    |
| GFR                       | 1.01 (1.00, 1.01) | 0.0003    |
the unadjusted model (model 1) showed that albumin was negatively correlated with 28-day and 90-day mortality. In model 2 (adjusted for age and sex only), the risks of 28-day and 90-day mortality decreased by 34 and 38%, respectively for every 1 g/dL increase in albumin. After adjusting all the covariates (model 3), the HR (95% CI) of 28-day and 90-day mortality was 0.63 (95% CI 0.50–0.80, \( p = 0.0001 \)) and 0.63 (95% CI 0.51–0.78, \( p < 0.0001 \)), respectively for each 1 g/dL increase of albumin. To explore the nonlinearity of albumin regarding 28-day and 90-day mortality of critically ill AKI patients with CRRT, we also converted albumin into categorical variables (quartile) and found that P for the trend of albumin with 28-day and 90-day mortality of the patients was less than 0.01 (Table 4).

The results of subgroup analyses
A subgroup analysis was performed according to the CRRT indications. In the subgroup analysis based on the reasons for using CRRT, albumin was found to have a protective effect on the prognosis of patients with volume overload and metabolic acidosis. In patients with volume overload, the HR (95% CI) of 28-day and 90-day mortality were 0.10 (95% CI 0.02–0.39, \( p < 0.001 \)) and 0.15 (95% CI 0.05–0.43, \( p < 0.001 \)), respectively for each 1 g/dL increase in albumin after adjusting for all covariates. In patients with metabolic acidosis, the risks of 28-day and 90-day mortality decreased with the increasing albumin, and the adjusted HR (95% CI) was 0.24 (95% CI 0.11–0.51, \( p < 0.001 \)) and 0.28 (95% CI 0.15–0.53, \( p < 0.001 \)), respectively (Table 5).

Curve fitting analysis
To investigate the relationship between albumin and prognosis in CRRT patients with critical AKI, we performed a fitting curve analysis. After adjusting age, sex, myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, dementia,

### Table 4 The results of multivariate Cox proportional hazards regression analysis

| Variable | 28-d mortality (HR 95%CI, \( p \)) | 90-d mortality (HR 95%CI, \( p \)) |
|----------|----------------------------------|----------------------------------|
| **Model 1** | | |
| Alb | 0.66 (0.57, 0.76) < 0.0001 | 0.62 (0.55, 0.71) < 0.0001 |
| Alb(quantile) | | |
| Q1 | 1.0 | 1.0 |
| Q2 | 0.93 (0.73, 1.18) 0.5395 | 0.84 (0.67, 1.05) 0.1222 |
| Q3 | 0.75 (0.59, 0.96) 0.0219 | 0.69 (0.55, 0.86) 0.0012 |
| Q4 | 0.56 (0.43, 0.72) < 0.0001 | 0.49 (0.38, 0.62) < 0.0001 |
| P for trend | < 0.0001 | < 0.0001 |
| **Model 2** | | |
| Alb | 0.66 (0.57, 0.76) < 0.0001 | 0.62 (0.55, 0.71) < 0.0001 |
| Alb(quantile) | | |
| Q1 | 1.0 | 1.0 |
| Q2 | 0.92 (0.73, 1.17) 0.5021 | 0.84 (0.68, 1.05) 0.1289 |
| Q3 | 0.75 (0.59, 0.96) 0.0220 | 0.69 (0.55, 0.86) 0.0012 |
| Q4 | 0.55 (0.43, 0.72) < 0.0001 | 0.49 (0.38, 0.62) < 0.0001 |
| P for trend | < 0.0001 | < 0.0001 |
| **Model 3** | | |
| Alb | 0.63 (0.50, 0.80) 0.0001 | 0.63 (0.51, 0.78) < 0.0001 |
| Alb(quantile) | | |
| Q1 | 1.0 | 1.0 |
| Q2 | 0.71 (0.50, 1.02) 0.0622 | 0.66 (0.47, 0.92) 0.0152 |
| Q3 | 0.62 (0.44, 0.88) 0.0076 | 0.63 (0.46, 0.87) 0.0054 |
| Q4 | 0.52 (0.35, 0.76) 0.0008 | 0.52 (0.37, 0.74) 0.0003 |
| P for trend | 0.0007 | 0.0006 |

Model 1 adjust for: none
Model 2 adjust for: age, sex
Model 3 adjust for: age, sex, myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, dementia, diabetes, hypertension, COPD, CRP, GFR, K+, HCO3–, phosphate, BMI, MAP, WBC, Hb, BUN, Cr, mechanical ventilation, CCI, APACHE II score, SOFA score, CRRT causes, AKI causes
Q1:0.00–2.10, Q2:2.20–2.50, Q3:2.60–2.90, Q4:3.00–5.90
Table 5 The results of subgroup analysis based on continuous renal replacement therapy (CRRT) causes

| Variable | 28-d mortality (HR 95%CI, p) | 90-d mortality (HR 95%CI, p) |
|----------|------------------------------|-----------------------------|
| Volume overload |                              |                             |
| Model 1  |                             |                             |
| Alb      | 0.48 (0.31, 0.76) 0.0018     | 0.45 (0.28, 0.71) 0.0006     |
| Model 2  |                             |                             |
| Alb      | 0.47 (0.29, 0.75) 0.0016     | 0.45 (0.28, 0.71) 0.0006     |
| Model 3  |                             |                             |
| Alb      | 0.10 (0.02, 0.39) 0.0009     | 0.15 (0.05, 0.43) 0.0005     |
| Metabolic acidosis |                         |                             |
| Model 1  |                             |                             |
| Alb      | 0.59 (0.44, 0.80) 0.0006     | 0.61 (0.47, 0.80) 0.0003     |
| Model 2  |                             |                             |
| Alb      | 0.62 (0.46, 0.84) 0.0017     | 0.63 (0.49, 0.83) 0.0008     |
| Model 3  |                             |                             |
| Alb      | 0.24 (0.11, 0.51) 0.0002     | 0.28 (0.15, 0.53) 0.0001     |
| Oliguria |                              |                             |
| Model 1  |                             |                             |
| Alb      | 0.78 (0.60, 1.03) 0.0785     | 0.76 (0.59, 0.96) 0.0227     |
| Model 2  |                             |                             |
| Alb      | 0.79 (0.61, 1.04) 0.0974     | 0.76 (0.60, 0.97) 0.0290     |
| Model 3  |                             |                             |
| Alb      | 1.02 (0.60, 1.73) 0.9304     | 0.89 (0.56, 1.41) 0.6301     |
| Hyperkalemia |                           |                             |
| Model 1  |                             |                             |
| Alb      | 0.66 (0.37, 1.20) 0.1734     | 0.66 (0.39, 1.12) 0.1208     |
| Model 2  |                             |                             |
| Alb      | 0.70 (0.39, 1.28) 0.2514     | 0.71 (0.41, 1.22) 0.2104     |
| Model 3  |                             |                             |
| Alb      | ---a                        | ---a                        |
| Uremia   |                              |                             |
| Model 1  |                             |                             |
| Alb      | 0.54 (0.30, 0.95) 0.0316     | 0.33 (0.19, 0.58) 0.0001     |
| Model 2  |                             |                             |
| Alb      | 0.49 (0.27, 0.91) 0.0244     | 0.33 (0.19, 0.59) 0.0001     |
| Model 3  |                             |                             |
| Alb      | ---a                        | ---a                        |
| Other    |                              |                             |
| Model 1  |                             |                             |
| Alb      | 0.73 (0.54, 0.98) 0.0386     | 0.66 (0.50, 0.87) 0.0032     |
| Model 2  |                             |                             |
| Alb      | 0.74 (0.55, 1.00) 0.0467     | 0.65 (0.49, 0.87) 0.0037     |
| Model 3  |                             |                             |
| Alb      | 0.44 (0.25, 0.79) 0.0058     | 0.43 (0.25, 0.74) 0.0022     |

Model 1 adjust for: none
Model 2 adjust for: age; sex
Model 3 adjust for: age, sex, myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, dementia, diabetes, hypertension, COPD, CRP, GFR, K+, HCO3-, phosphate, BMI, MAP, WBC, HB, BUN, Cr, mechanical ventilation, CCI, APACHE II score, SOFA score, AKI causes
*a: The model failed because of the small sample size
Thus, inflammation plays an important role in the occurrence and development of AKI [31]. AKI can lead to long-term effects of renal fibrosis and chronic inflammation and further progress to CKD [32, 33]. Also, albumin has a large number of reduced sulfhydryl groups; therefore, it has an antioxidant effect, which in excess can lead to kidney damage. Therefore, patients with reduced albumin are prone to AKI and CKD; thus, kidney function cannot recover in a short period and will increase the risk of death [30, 34].

Several studies have shown that the decrease in serum albumin can predict the poor prognosis of the disease. A study by Olivia et al. in 486 severely burned patients demonstrated that albumin was a good predictor of burn mortality, with a reported area under the curve of 0.869, and that the death risk increased by more than 80% when albumin level was below 2 g/dL [35]. In Reza Behrouz’s study, hypoalbuminemia was found to be independently associated with in-hospital mortality in patients with aneurysms subarachnoid hemorrhage, with an adjusted odds ratio (95% CI) of 4.26 (95% CI: 1.09–16.68, $p = 0.04$) [36]. This study shows that albumin levels are associated with prognosis in critical patients with AKI under CRRT, which is consistent with the results of previous studies by Moon et al. [22]. However, more confounding variables were adjusted in this study to make the results more reliable. Simultaneously, the sensitivity analysis was also performed in the multivariate Cox regression analysis, and the nonlinear relationship between albumin and prognosis was observed to
ensure the robustness of the results. Subgroup analysis based on CRRT indications demonstrated that some results were not significant or missing; however, the general trend was consistent. The subgroup possibly included fewer samples, which reduced the ability of the statistical system. Additionally, we observed that albumin was not associated with the risk of death in patients with oliguria. It is well-established that when renal function is impaired, the number of perirenal capillaries is reduced, and renal blood flow is greatly decreased, leading to reduced urine volume in patients [37]. Oliguria is a risk factor for poor prognosis in dialysis patients [21]. In patients with severe oliguria or anuria, the effect of decreased albumin on prognosis may be ignored. However, more research is needed to confirm the results.

There were some limitations in this study: 1) Our data were from Dryad’s open database, and knowing whether patients received albumin infusion before CRRT was infeasible, which could affect albumin levels; thus, skewing the results; 2) Due to the limitations of the database, we could not know whether patients classified according to the etiology of AKI were mutually exclusive. So, the findings of this study needed to be further confirmed by large prospective studies.

Conclusions
In this study, we investigated the predictive value of hypoproteinemia in critical CRRT patients with poor prognoses. We also observed that albumin was not associated with prognosis in patients with oliguria.

Abbreviations
AKI: Acute kidney injury; CRRT: Receiving renal replacement therapy; CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit; IL: Interleukin; NO: Nitric oxide; VEGF: Vascular endothelial growth factor; AKIN: Acute Kidney Injury Network; BMI: Body mass index; CRP: C-Reactive protein; GFR: Glomerular filtration rate; HB: Hemoglobin; WBC: White blood cell; CR: Serum creatinine; BUN: Blood urea nitrogen; Alb: Albumin; HCO3-: Bicarbonate; K+: Potassium; CCI: Charlson comorbidity index; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; SD: Standard deviation; COPD: Chronic obstructive pulmonary disease

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Authors’ contributions
L.J.Z was involved in the study’s formulation, design, data acquisition and analysis, and the drafting of the manuscript. W.M.J. and L.L.P help with data analysis. J.Y.P funded and oversaw the study. The final manuscript was read and approved by all authors.

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Availability of data and materials
The data are obtained from the ‘DataDryad’ database (www.datadryad.org).

Declarations
Ethics approval and consent to participate
Because the data that were de-identified, the patient’s written consent requirement was abandoned. The ethics committee of Yonsei University health system, Severance Hospital and Institutional Review approved the previous study. Therefore, it is also applicable to this study.

Consent for publication
Not applicable.
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