Associations Between Predialysis Creatinine, SOFA Score, and Mortality in Acute Kidney Injury Patients Requiring Dialysis

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Abstract

Background: Creatinine is widely used to estimate renal function, but this is not practical in critical illness. Low creatinine has been associated with mortality in many clinical settings. However, the associations between predialysis creatinine level, Sepsis-related Organ Failure Assessment (SOFA) score, and mortality in acute kidney injury patients receiving dialysis therapy (AKI-D) has not been fully addressed.

Methods: We extracted data for AKI-D patients in the eICU (n = 1,992) and MIMIC (n = 1,001) databases. We conducted a retrospective observational cohort study using the eICU dataset. The study cohort was divided into the high-creatine group and the low-creatinine group by the median value (4 mg/dL). The baseline patient information included demographic data, laboratory parameters, medications, and comorbid conditions. The independent association of creatinine level with mortality was examined using multivariate logistic regression analysis. We also carried out a sensitivity analysis using the MIMIC dataset.

Results: In all 1,992 eICU participants, the *30-day* intensive care unit mortality rate was 32.2%. The crude overall mortality rate in the low-creatinine group (43.7%) was significantly higher than that in the high-creatinine group (20.6%; $P < 0.001$). In the fully adjusted models, the high-creatinine group was associated with a lower risk of all-cause mortality (odds ratio, 0.56; 95% confidence interval, 0.42–0.75; $P < 0.001$) compared with the low-creatinine group. The nonrenal SOFA score was higher in the low-creatinine group. The results were consistent when the MIMIC dataset was used as an external validation dataset.

Conclusions: AKI-D patients with a low predialysis creatinine value had a significantly higher risk of mortality that might be associated with more organ dysfunctions. Moreover, SOFA and nonrenal SOFA scores did not sufficiently reflect the severity of illness without considering the impact of the creatinine value in AKI-D patients.

Introduction

Acute kidney injury (AKI) is a common and significant problem in the intensive care unit (ICU), and about 25% of patients with AKI require renal replacement therapy (RRT) [1,2]. However, a high mortality rate of 30%–50% is noted [3,4]. Although many severity of illness scoring systems have been developed for mortality prediction, they either performed well in a single-center study without external validation or had limited results during external validation [5-8]. In terms of the Sepsis-related Organ Failure Assessment (SOFA) score, it doesn't have good discrimination in this patient group [5,9].

Creatinine is a metabolite of creatine and creatine phosphate, which are in the highest concentration in skeletal muscle, and is mainly eliminated via the kidney [10,11]. Therefore, serum creatinine is used to not only estimate renal function but also to reflect muscle mass. Low serum creatinine is also a marker of malnutrition [11]. However, it is also related to sex, age, diet, and fluid status [12,13]. Because creatinine is

affected by many factors, it usually overestimates renal function in critically ill patients [14]. Studies have shown that low creatinine was associated with high mortality in the ICU and an increased mechanical ventilation use rate and was also a risk marker of mortality in hemodialysis (HD) patients [11,12,15]. Only a few studies with small sample sizes have addressed mortality and the creatinine level in patients with AKI [5,8,13,16].

For this reason, we conducted this retrospective study using two public datasets to explore the associations between predialysis creatinine, SOFA, and mortality among patients with AKI who were receiving dialysis (AKI-D) in the ICU.

Methods

Participants and Measurements

This retrospective, observational cohort study was performed using two publicly available ICU datasets, the MIMIC-III [29] and the eICU [30] Collaborative Research Database (eICU-CRD). The MIMIC-III database was released in 2016 by the Massachusetts Institute of Technology Laboratory for Computational Physiology (MIT-LCP) and contained data from a single tertiary care hospital (Beth Israel Deaconess Medical Center). The eICU-CRD is a multicenter critical care database containing data from rural/nonacademic hospitals across the US and was made available in 2018 by Philips Healthcare with the help of researchers from MIT-LCP. There is no overlap in the patients included in these two databases.

We included adult patients 18 years of age or older who received RRT (either intermittent HD or continuous RRT [CRRT]) in the ICU for AKI. The AKI in this study was defined according to the Kidney Disease Improving Global Outcomes clinical practice guidelines [31] and diagnosis codes.. We only used the creatinine criteria because of unreliable urine data in the retrospective databases. For patients who did not have more than one creatinine value to make a comparison, but who had RRT records, we included patients who were diagnosed as having AKI based on their ICD-9 diagnosis codes (Table S1). If a patient had been admitted to the ICU multiple times in one hospitalization course, data from the ICU admission that included the initial dialysis treatment was extracted for the study. Patients with a history of end-stage kidney disease who underwent chronic peritoneal dialysis or HD (Table S1) were excluded from the study. We also excluded patients who had chronic kidney disease (CKD) stage 4 and 5 based on ICD-9 codes (Table S1), because we were interested in patients who did not have advanced CKD at baseline. Patients with a history of any organ transplant were also excluded as they may have other confounding risk variables that affect mortality. We excluded patients who did not have complete records of vital signs and creatinine data one day before RRT start.

The variables collected consisted of demographics, medical history, mechanical ventilation usage, AKI stage, vital signs, laboratory test results, dialysis modality (intermittent HD or CRRT), and medications (diuretics and vasopressors, see Table S2). The time window of mechanical ventilation, vital signs, laboratory tests, and medications were recorded one day before RRT initiation. Past medical history was

extracted from database records using ICD-9 codes (Table S1). Relevant past medical history included in the study were diabetes mellitus (DM), CKD, hypertension (HTN), congestive heart failure (CHF), liver cirrhosis (LC), and cancer. Vital signs in this study included the mean values of the following variables: shock index (SI), Glasgow Coma Scale (GCS), mean arterial pressure (MAP), respiratory rate (RR), and heart rate (HR). The mean SI was calculated by the formula: SI = mean HR/mean systolic blood pressure. For laboratory tests, we used the mean value of all variables recorded one day before the date of the first dialysis therapy because some laboratory data values would have been influenced by dialysis. We excluded the variables with >25% missing values, except for albumin level, because we thought that albumin was an important factor for mortality prediction. Table S3 reveals the percentages of missing data in the laboratory tests. Multiple imputation by chained equations (MICE) with five imputed datasets was used to impute the missing values of the laboratory tests and vital signs and the results were pooled using the MICE package [32].

We modified the codes from https://github.com/nus-mornin-lab/oxygenation_kc and https://github.com/MIT-LCP/mimic-code/tree/master/concepts/severityscores to calculate the SOFA score using variables collected one day before RRT start in the eICU and MIMIC datasets based on methods used in the original study [33]. For patients with missing variables, the

The primary aims of the investigation were to assess whether the predialysis creatinine level was associated with 30-day mortality independent of other risk factors and to explore the association between the predialysis creatinine level and the SOFA score.

Statistical Analyses

The study cohort was stratified into two groups according to the median creatinine value. Categorical variables were presented as counts, proportions, and frequencies; continuous variables were expressed as mean with standard deviation. Numeric variables of clinical characteristics between the two groups were compared using the Student's *t* test. The chi-square test was used to compare the differences of the categorical variables. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the analyses of predictors of mortality. The comparison of survival status between the two groups was done using the Kaplan–Meier curve with significance levels determined by the log rank test. We implemented four models for the adjustments of the covariates: model 1, adjusted for age, sex, and ethnicity; model 2, adjusted for all variables in model 1 plus DM, HTN, CKD, malignancy, and LC; model 3, adjusted for all variables in model 2 plus GCS, HR, MAP, RR, SI, ICU days before dialysis, CRRT, diuretics, vasopressors, and mechanical ventilation; model 4, adjusted for all variables in model 3 plus laboratory parameters. We used the *Kruskal*–Wallis test to compare the SOFA score difference between the groups.

Each analysis was repeated using the MIMIC dataset to explore the heterogeneity using sensitivity analysis. Analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing).

Results

Baseline Characteristics of the Study Cohort

The cohort from the eICU database included 8,201 patients who required dialysis therapy. Of those patients, 1,992 patients met the inclusion and exclusion criteria for the study. The cohort from the MIMIC database included 3,357 patients who required dialysis therapy. Of those patients, 1,093 patients met the criteria for inclusion in the study (Figure 1).

The median creatinine level among all 1,992 eICU participants was 3.96 mg/dL. Their mean age was 62.8 ± 14.7 years, and 1,167 (58.6%) patients were men. The overall mortality rate was 32.2%. The cohort was divided into low- and high-creatinine groups according to the median creatinine value (4 mg/dL); the patient characteristics are presented in Table 1. The high-creatinine group had a lower mean age and a greater proportion of patients who were men and patients who were black than the low-creatinine group. The high-creatinine group had higher mean levels of blood urea nitrogen, hemoglobin, albumin, anion gap, platelet count, and potassium than the low-creatinine group. Comorbid conditions of malignancy and LC were more common in the low-creatinine group, whereas the prevalence of DM, HTN, and CKD was higher in the high-creatinine group. The high-creatinine group had a lower proportion of prescriptions for diuretics, vasopressors, CRRT, and mechanical ventilation than the low-creatinine group. In terms of vital signs, the low-creatinine group had lower mean values for GCS and MAP but higher mean values for RR and HR.

Creatinine and All-Cause Mortality

The crude mortality rate was 20.6% (n = 204) for the high-creatinine group and 43.7% (n = 437) for the low-creatinine group ($P < 0.001$). The Kaplan–Meier analysis revealed that the patient survival was significantly better for the high-creatinine group than for the low-creatinine group ($P < 0.0001$) (Figure 2). The unadjusted and adjusted ORs are presented in Table 2. Compared with the low-creatinine group, the OR for the high-creatinine group was 0.33 (95% CI: 0.27 to 0.41) for all-cause mortality in the unadjusted model. In the fully adjusted model (model 4), the risk of mortality in the high-creatinine group was 44% lower (OR, 0.56; 95% CI: 0.42 to 0.75). Although CKD was significantly associated with mortality in the unadjusted analysis, it was no longer significant in the fully adjusted model.

Interactions

Figure 3 shows that there was a significant interaction between creatinine and age. That is, the OR was 0.46 for 30-day mortality in subjects aged ≥65 in the high-creatinine group, whereas the OR was 0.77 in subjects with a younger age (P for the interaction 0.04). We also noted a significant interaction ($P = 0.02$) between creatinine and albumin with regard to 30-day mortality. In patients with CKD, high creatinine was associated with an OR of 1.34 (P for the interaction 0.03).

Creatinine and SOFA score

Figure 4 shows that the SOFA and nonrenal SOFA scores were higher in the low-creatinine group. The median (range) values of the SOFA and nonrenal SOFA scores were 12 (3–21) and 10 (3–18), respectively, in the low-creatinine group and 11 (6–22) and 7 (3–18), respectively, in the high-creatinine group.

Sensitivity analysis

Table S4 reveals the distribution between the eICU and MIMIC datasets. The mortality rate, comorbidity, and many other variables were significantly different. The results of external validity using the MIMIC dataset were consistent with those using the eICU dataset. The low-creatinine group had a higher mortality risk (Table S5), worse survival (Figure S1), and higher nonrenal SOFA score (Figure S2).

Discussion

In this study of patients with AKI-D, we identified that a low creatinine level was independently associated with all-cause mortality. A high creatinine (≥4 mg/dL) was associated with a 44% lower risk of mortality in these patients. The association between high creatinine and lower 30-day mortality was constant in the ICU. Moreover, most of the subgroup analyses further confirmed our results. The SOFA and nonrenal SOFA scores in the low-creatinine group were higher than those in the high-creatinine group, indicating that AKI-D patients with low predialysis creatinine values have more organ dysfunctions.

A low creatinine level can relate to an increase in excretion or a decrease in generation. Real kidney function improvement was uncommon in critically ill patients [17], whereas those patients usually have more complicated underlying problems that affect creatinine generation, such as sepsis [18], fluid accumulation [13], poor nutrition status and low muscle mass [11,19], liver failure, and older age [19]. The relationship between low creatinine at the start of RRT and mortality in AKI-D patients was demonstrated in previous reports [5,8]. Our results showed that the low-creatinine group had a higher mean age, a lower mean albumin value, and a higher proportion of patients with LC, as well as increased mortality. In addition, in the interaction analysis, we found that lower creatinine increased the mortality risk in all subgroups, except for the CKD subgroup. The high creatinine group seemed to have better survival in the older age (≥65 years) and high albumin (≥3.5 g/dL) subgroups. Implicitly, nutritional status is not the only reason for the relation of mortality to low creatinine, as oliguria and fluid accumulation may also be reasons [8,13]. Oliguric AKI was an independent factor for mortality and would lead to low creatinine caused by fluid overload (FO) [20,21]. FO can result in tissue edema and organ dysfunctions and increased risk of mortality [13,20,22,23]. The possible reason that the effect of lower creatinine was not prominent in CKD patients may be that elevated levels of creatinine were associated with increased risk of myocardial infarction, cancer, and infection [24-26].

In addition to causing organ dysfunctions, oliguria and FO are also the results of organ failure. In other words, there may be other causes than oliguria and FO in relation to low creatinine associated with high mortality. The hypothetical reason is that the more severely and rapidly critical illnesses develop, the

lower the predialysis creatinine is in AKI-D patients. Creatinine needs time to achieve a steady state in AKI patients [27]. However, for severe and critically ill patients, there would not be enough time for the creatinine to reach a steady state when RRT starts. In our study, the low-creatinine group had higher SOFA and nonrenal SOFA scores. Compared with the high-creatinine group, the nonrenal SOFA score was more representative than the SOFA score in the low-creatinine group. Therefore, AKI patients with low predialysis creatinine but who require dialysis therapy implicitly have more organ dysfunctions. Because it does not consider the effect of creatinine, the SOFA score does not perform well for mortality prediction in AKI-D patients [5,9]. The nonrenal SOFA score is slightly better at mortality prediction than the SOFA score, but it still does not take into account the effect of a low creatinine level. The impact of creatinine should be considered in scoring systems used for AKI-D patients, as with the Acute Physiology And Chronic Health Evaluation (APACHE) score [28], the HEpatic failure, LactatE, NorepInephrine, medical Condition, and Creatinine (HELENICC) score [8], and the ATN score [5].

Strengths and Limitations

Our study has several advantages. The first is that the eICU and MIMIC datasets are from distinct regions and hospitals across the US. Also, our findings were consistent in these two datasets. However, there were several limitations to our study. First, as previously mentioned , some data were missing and the urine output might not be reliable in the retrospective databases. Second, other potential confounding data, like FO and body mass, were not available in these datasets. Third, the association between CKD and predialysis creatinine in AKI-D patients needs further study. Fourth, the underlying mechanism of the creatinine impact on mortality remains unknown, and further studies are warranted.

Conclusion

The low-creatinine group had a significantly higher risk of mortality compared with that of the high-creatinine group. The higher mortality risk of low creatinine was consistent across patient subgroups, except for CKD. Moreover, we should be more cautious regarding AKI-D patients with lower creatinine because implicitly they had more organ dysfunctions. The mechanism of how creatinine impacts mortality remains unclear and needs further studies for clarification.

Declarations

AUTHORS' CONTRIBUTIONS

H.H.C contributed to the design of the study and collected the data. C.L.W analyzed and interpreted the data. H.H.C and P.F.C drafted the manuscript. P.F.C reviewed the manuscript. All authors read, commented, and approved the final manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The data in the Medical Information Mart for Intensive Care (MIMIC) and eICU Collaborative Research Database (eICU-CRD) has been previously de-identified anonymised databases with pre-existing institutional review board (IRB) approval.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data underlying this article are available at https://eicu-crd.mit.edu/ and https://mimic.mit.edu/.

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Tables

Table 1. Baseline characteristics of the study population as a whole and divided according to the median creatinine level

Variables	Total	Cr < 4 mg/dL	Cr ≥ 4 mg/dL	*P* value
Number of patients	1,992	1,001	991	
Demographics				
Age, years	62.8 ± 14.7	64.0 ± 14.4	61.6 ± 14.9	<0.001
Sex, % male	1167 (58.6%)	516 (51.5%)	651 (65.7%)	<0.001
Black race, %	268 (13.5%)	95 (9.5%)	173 (17.5%)	<0.001
Comorbidity, %				
Diabetes mellitus	260 (13.1%)	105 (10.5%)	155 (15.6%)	0.001
Hypertension	235 (11.8%)	98 (9.8%)	137 (13.8%)	0.007
CHF	308 (15.5%)	165 (16.5%)	143 (14.4%)	0.23
CKD	292 (14.7%)	120 (12.0%)	172 (17.4%)	0.001
Malignancy	100 (5.0%)	68 (6.8%)	32 (3.2%)	<0.001
Liver Cirrhosis	114 (5.7%)	75 (7.5%)	39 (3.9%)	0.001
Medication, %				
Diuretics	243 (12.2%)	150 (15.0%)	93 (9.4%)	<0.001
Vasopressors	764 (38.4%)	503 (50.2%)	261 (26.3%)	<0.001
Laboratory data				
BUN (mg/dL)	63.9 ± 37.6	48.8 ± 29.4	79.1 ± 38.9	<0.001
FiO_2 (%)	51.0 ± 26.8	55.2 ± 25.8	46.8 ± 27.2	<0.001
Hgb (mg/dL)	9.8 ± 2.1	9.7 ± 2.2	9.9 ± 2.1	0.007
O_2 Sat (%)	95.2 ± 5.8	94.9 ± 5.9	95.4 ± 5.7	0.03
WBC count ($\times 10^3/\mu L$)	15.8 ± 23.4	17.0 ± 31.6	14.6 ± 9.8	0.02
Albumin (g/dL)	2.7 ± 0.7	2.6 ± 0.7	2.8 ± 0.7	<0.001
HCO3 (mmol/L)	20.4 ± 5.9	21.2 ± 5.8	19.5 ± 5.9	<0.001
Anion gap (mmol/L)	14.9 ± 6.5	13.4 ± 5.8	16.6 ± 6.8	<0.001
Calcium (mg/dL)	8.1 ± 1.1	8.1 ± 1.0	8.1 ± 1.1	0.18
Glucose (mg/dL)	150.2 ± 72.3	149.6 ± 59.1	150.8 ± 83.6	0.71
Platelet ($\times 10^3/\mu L$)	182.9 ± 110.9	159.1±103.6	206.9 ± 113.0	<0.001
Potassium (mmol/L)	4.7 ± 1.1	4.5 ± 1.0	5.0 ± 1.1	<0.001

Sodium (mmol/L)	137.6 ± 6.4	139.0 ± 6.1	136.2 ± 6.4	<0.001
GCS score	11.2 ± 3.8	10.3 ± 3.9	12.1 ± 3.7	<0.001
HR (beats per minute)	89.4 ± 18.5	91.4 ± 18.9	87.5 ± 17.8	<0.001
MAP (mmHg)	77.0 ± 15.9	75.2 ± 13.5	78.9 ± 17.9	<0.001
RR (breaths per minute)	21.0 ± 5.6	21.7 ± 5.6	20.4 ± 5.5	<0.001
SI	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	<0.001
Days of ICU stay before RRT initiation	2.4 ± 3.9	3.1 ± 4.6	1.6 ± 3.0	<0.001
CRRT, %	514 (25.8%)	365 (36.5%)	149 (15.0%)	<0.001
MV, %	1489 (74.7%)	858 (85.7%)	631 (63.7%)	<0.001
Death, %	641 (32.2%)	437 (43.7%)	204 (20.6%)	<0.001

Data are presented as mean ± standard deviation for continuous variables and number (%) for categorical variables.

Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; BUN, blood urea nitrogen; FiO_2, fraction of inspired oxygen; Hgb, hemoglobin; WBC, white blood cell; GCS, Glasgow Coma Scale; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; SI, shock index; ICU, intensive care unit; RRT, renal replacement therapy; CRRT, continuous renal replacement therapy; MV, mechanical ventilation.

Table 2. Risk of mortality in high predialysis creatinine patients compared with low predialysis creatinine patients

Significant variables	Unadjusted OR (95% CI)	Model 1	Model 2	Model 3	Model 4
Creatinine ≥ 4 mg/dL	0.33 (0.27–0.41)	0.35 (0.28–0.42)	0.37 (0.30–0.45)	0.62 (0.48–0.79)	0.56 (0.42–0.75)
Age	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.02 (1.02–1.03)	1.04 (1.03–1.05)	1.04 (1.03–1.05)
Liver cirrhosis	2.78 (1.90–4.08)		2.96 (1.97–4.46)	2.52 (1.59–4.03)	2.16 (1.33–3.52)
Vasopressor	3.98 (3.27–4.85)			1.64 (1.28–2.10)	1.55 (1.20–2.02)
Glasgow Coma Scale	0.82 (0.80–0.84)			0.87 (0.84–0.90)	0.88 (0.85–0.92)
Mean arterial pressure	0.96 (0.95–0.97)			0.99 (0.98–1.00)	0.99 (0.98–1.00)
Shock index	12.11 (7.98–18.55)			5.32 (1.82–15.88)	2.94 (0.96–9.14)
CRRT	3.46 (2.80–4.27)			1.64 (1.27–2.11)	1.45 (1.11–1.89)
Respiratory rate	1.09 (1.07–1.11)			1.06 (1.04–1.08)	1.04 (1.02–1.07)
Albumin	0.65 (0.56–0.74)				0.84 (0.70–1.02)
Anion gap	1.04 (1.02–1.05)				1.05 (1.03–1.08)
Calcium	0.84 (0.76–0.91)				1.12 (0.98–1.27)
Platelet	1.00 (0.99–1.00)				1.00 (1.00–1.00)
FiO_2	1.03 (1.02–1.03)				1.01 (1.01–1.02)

The referent group for all models is creatinine below the median of 4 mg/dL. The variables for adjustments in models 1-4 are described.

Model 1: creatinine, age, sex, and ethnicity. Model 2: model 1 plus diabetes mellitus, hypertension, chronic kidney disease, malignancy, and liver cirrhosis. Model 3: model 2 plus Glasgow Coma Scale, heart rate, mean arterial pressure, respiratory rate, shock index, days in the ICU before dialysis, CRRT, diuretics, vasopressors, and mechanical ventilation. Model 4: model 3 plus blood urea nitrogen, FiO_2, hemoglobin, white blood cell count, albumin, HCO_3, anion gap, calcium, glucose, platelet, potassium, and sodium.

Abbreviations: OR, odds ration; 95% CI, 95% confidence interval; ICU, intensive care unit; CRRT, continuous renal replacement therapy.

Figures

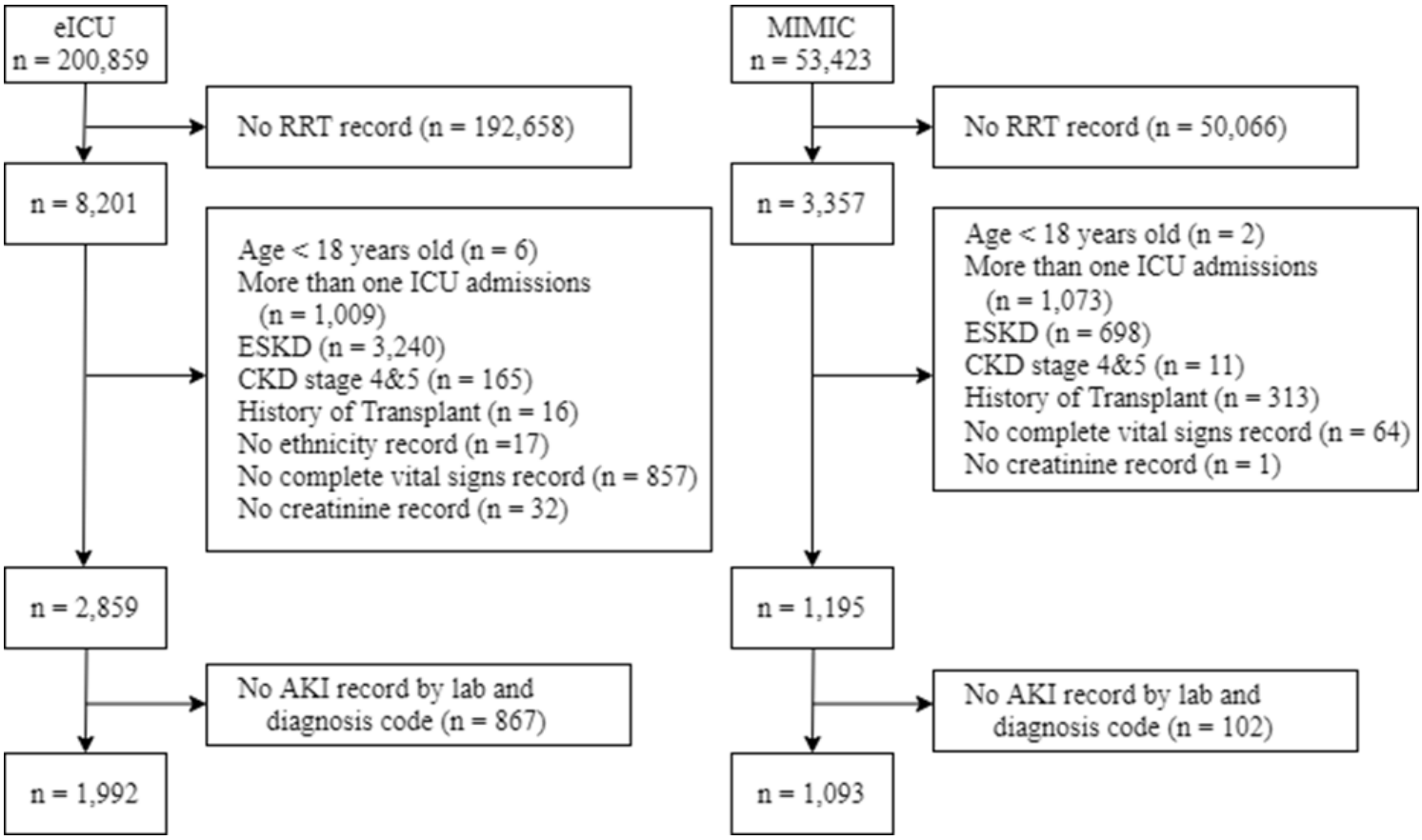

Figure 1

Participant flow diagram. n is patient unit encounter. Abbreviations: RRT, renal replacement therapy; ESKD, end-stage kidney disease; CKD, chronic kidney disease; ICU, intensive care unit; AKI, acute kidney injury.

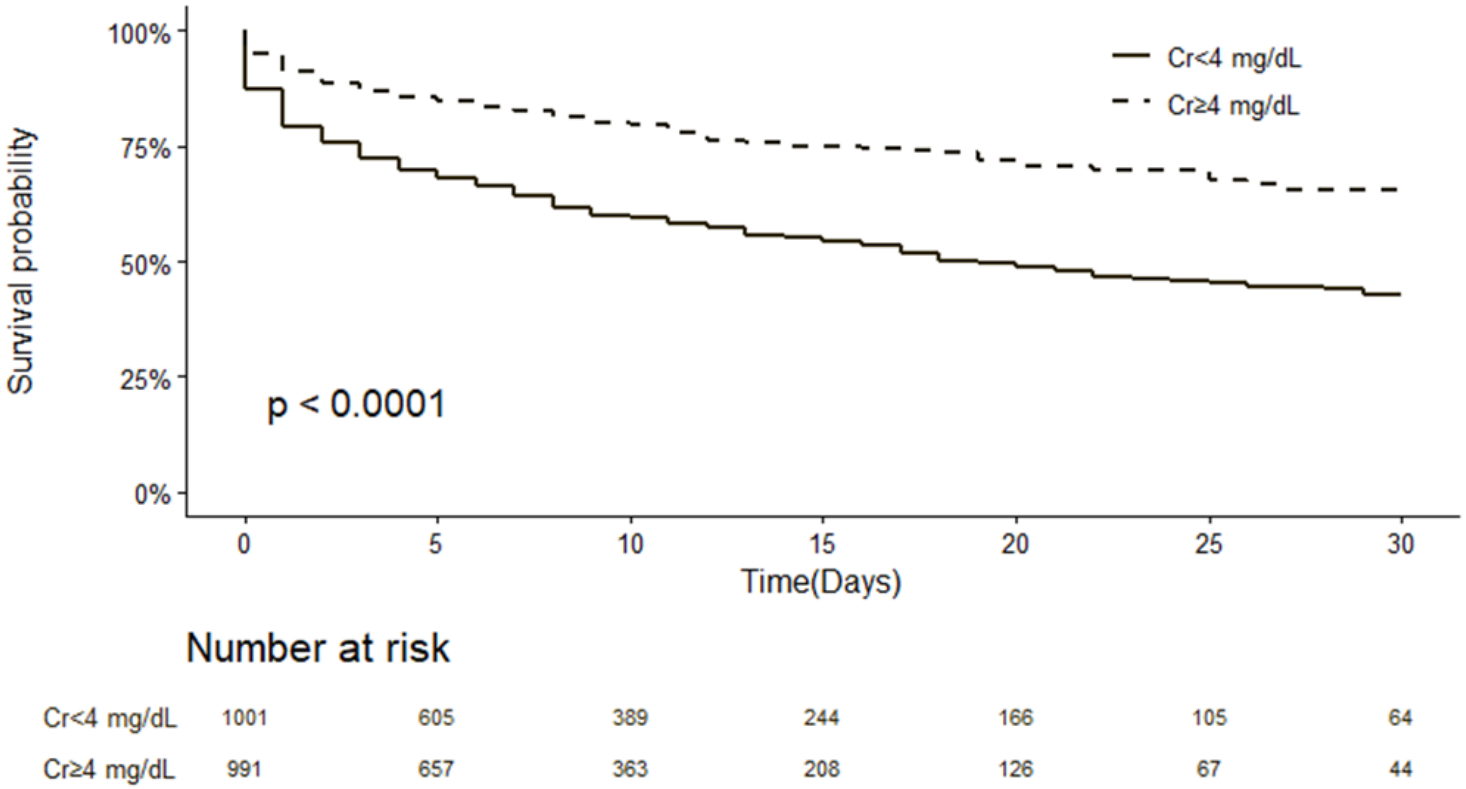

Figure 2

Kaplan–Meier curve of mortality according to creatinine category. The high creatinine (Cr ≥ 4 mg/dL) group was associated with better survival than the low creatinine (Cr < 4 mg/dL) group (log rank test, P < 0.0001).

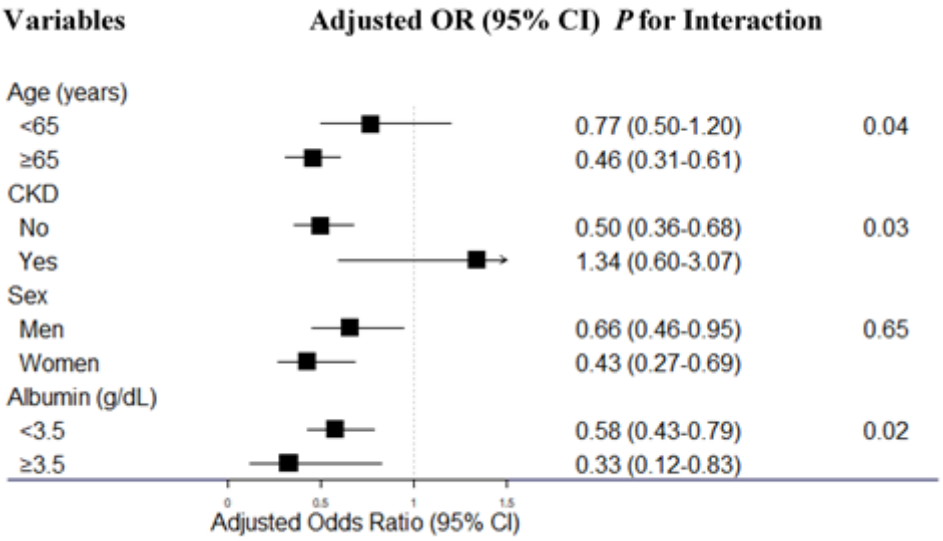

Figure 3

Subgroup analysis of associations of high creatinine (Cr ≥ 4 mg/dL) group with the mortality in patients with acute kidney injury undergoing dialysis. Abbreviations: OR, odds ratio; 95% CI, 95% confidence

interval; CKD, chronic kidney disease.

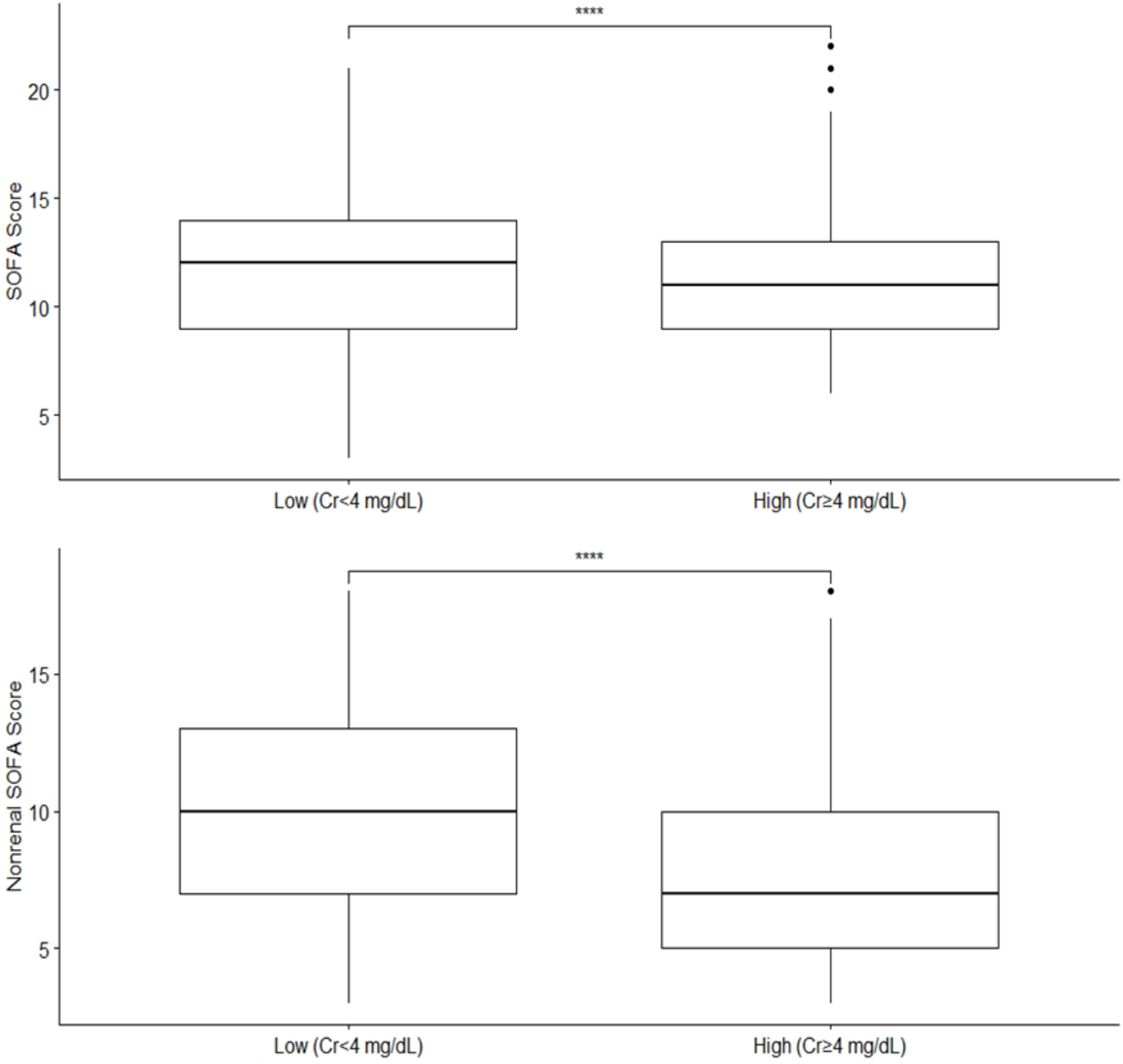

Figure 4

Sepsis-related Organ Failure Assessment (SOFA) and nonrenal SOFA scores in patients with low creatinine (Cr < 4 mg/dL) were higher than scores in patients with high creatinine (Cr ≥ 4 mg/dL). Boxplot showing the SOFA and nonrenal SOFA score between the groups. ****P value < 0.0001

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterials.docx