ORIGINAL RESEARCH

Hyperkalemia Is Associated With Increased Mortality Among Unselected Cardiac Intensive Care Unit Patients

Benjamin Brueske, RN; Mandeep S. Sidhu, MD; Joshua Schulman-Marcus, MD; Kianoush B. Kashani, MD, MS; Gregory W. Barsness, MD; Jacob C. Jentzer, MD

***Background*—**Hyperkalemia has been associated with increased mortality in patients with myocardial infarction, but few data exist regarding hyperkalemia in cardiac intensive care unit (CICU) patients. We hypothesize that hyperkalemia is associated with increased mortality in unselected CICU patients.

***Methods and Results*—**We retrospectively reviewed a historical cohort of 9681 CICU patients admitted from January 2007 to December 2015. Hyperkalemia was defined as admission potassium ≥5.0 mEq/L and hypokalemia as admission potassium <3.5 mEq/L. Multivariate logistic regression was used to determine predictors of in-hospital mortality. Postdischarge survival was assessed using Kaplan–Meier analysis and Cox proportional hazards models. The mean age of included patients was 67±15 years, with 36% females, and in-hospital mortality was 9%. Hyperkalemia occurred in 1187 (12.3%) and hypokalemia occurred in 719 (7.4%) patients. Both patients with hyperkalemia (unadjusted odds ratio, 2.85; 95% CI, 2.40–3.39; $P<0.001$) and patients with hypokalemia (unadjusted odds ratio, 2.31; 95% CI, 1.85–2.88; $P<0.001$) were at increased risk of unadjusted in-hospital mortality. After adjustment for illness severity and renal function, only patients with hyperkalemia demonstrated increased risk of in-hospital death (adjusted odds ratio, 1.44; 95% CI, 1.11–1.87; $P=0.006$). Among hospital survivors, only patients with hyperkalemia had lower postdischarge survival by Kaplan–Meier analysis ($P<0.001$). After adjustment for illness severity and renal function, hospital survivors with admission hyperkalemia remained at increased risk for postdischarge mortality (adjusted hazard ratio, 1.20; 95% CI, 1.08–1.34; $P<0.001$).

***Conclusions*—**Hyperkalemia on CICU admission is associated with higher in-hospital and postdischarge mortality, independent of renal function and illness severity. These findings emphasize the importance of potassium abnormalities as a risk predictor in patients admitted to the CICU. **(*J Am Heart Assoc*.2019;8:e011814. DOI: 10.1161/JAHA.118.011814.)**

Key Words: critical care • intensive care unit • potassium

Prior studies in patients with acute and chronic cardiovascular disease have demonstrated a U-shaped association between admission potassium levels and mortality in hospitalized patients with heart failure (HF) or myocardial infarction,[1,2] as well as among general intensive care unit patients.[3,4] Among patients with acute myocardial infarction, studies have consistently identified hyperkalemia as a predictor of higher mortality; there is less agreement regarding the relationship between hypokalemia and death.[2] While many prior studies in acutely ill cardiac patients have focused on a specific primary admission diagnosis, contemporary cardiac intensive care unit (CICU) patients often present with undifferentiated and/or mixed disease states. Due to the changing characteristics of the CICU population, there is a need to reevaluate previously published information regarding risk predictors in the modern CICU.[5,6]

To our knowledge, the relationship between potassium levels and outcomes has not been previously examined among unselected CICU patients. This study sought to determine the association of abnormal admission potassium levels with short- and long-term mortality among unselected CICU patients and whether this association was affected by

From the Division of Cardiology, Department of Medicine, Albany Medical Center, Albany, NY (B.B., M.S.S., J.S.-M.); Division of Nephrology & Hypertension, Department of Internal Medicine (K.B.K.), Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine (K.B.K., J.C.J.), and Department of Cardiovascular Medicine (G.W.B., J.C.J.), Mayo Clinic, Rochester, MN.

Accompanying Figures S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011814

Correspondence to: Jacob C. Jentzer, MD, FACC, Department of Cardiovascular Medicine and Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: jentzer.jacob@mayo.edu

Received December 17, 2018; accepted March 4, 2019.

Clinical Perspective

What Is New?

- Hyperkalemia is a known risk factor for mortality among critically ill patients and cardiac patients. This is the first study investigating the generalizability of this knowledge to the new and emerging cardiac intensive care unit population.
- Hyperkalemia had a correlation with in-hospital and post-discharge mortality that remained after adjustment for illness severity and could be used in risk stratification among patients both in-hospital and after discharge in cardiac intensive care unit patients.

What Are the Clinical Implications?

- Assessment of admission potassium in the cardiac intensive care unit can provide valuable information to guide triage of patients, resource allocation, and identification of high-risk patients.
- The results of this study, coupled with further research regarding the generalizability of known risk indicators among critically ill patients admitted to the cardiac intensive care unit, can provide evidence to guide the use of modern risk scores in this unique population.

the discharge diagnosis. We hypothesized that abnormal potassium levels, particularly hyperkalemia, would be associated with higher in-hospital mortality among CICU patients.

Methods

The authors declare that all supporting data are available within the article and its online supplementary files, and additional data, analytic methods, and study materials will not be made available to other researchers.

Participants

This study was approved by the Mayo Clinic Institutional Review Board and was exempt from informed consent because of the minimal risk posed to enrolled patients. This is a historical cohort analysis using an institutional database of adult patients (≥18 years old) admitted to the CICU at Mayo Clinic Hospital between January 1, 2007, and December 31, 2015, as previously described.[5] The CICU at Mayo Clinic serves critically ill medical patients with acute and chronic cardiovascular disease and does not routinely admit patients after cardiac surgery. Patients were identified from archived electronic health records.[7] Patients who were readmitted to the CICU had only their first admission included in the analysis. We excluded patients who remained hospitalized on December 31, 2015, and those without admission potassium values. In compliance with Minnesota state law statute 144.295, patients who did not provide Minnesota Research Authorization were also excluded from the study.

Definitions

The admission potassium level was defined as the potassium value closest to CICU admission, either before or after the time of CICU admission. The highest and lowest potassium values during the CICU stay were also recorded. Serum potassium levels were the default, but plasma or whole blood potassium values were substituted if serum potassium was not available. For the primary analysis, patients were grouped based on admission potassium level as follows: normokalemia (admission potassium 3.5–4.9 mEq/L), hypokalemia (admission potassium <3.5 mEq/L), and hyperkalemia (admission potassium ≥5.0 mEq/L).[8] For the secondary analysis, patients were classified based on the highest and lowest potassium levels during the CICU stay into hypokalemia (lowest potassium <3.5 mEq/L), hyperkalemia (highest potassium ≥5.0 mEq/L), and normokalemia (lowest potassium ≥3.5 mEq/L and highest potassium <5.0 mEq/L) groups. Discharge diagnoses were determined using the review of hospital *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes. Among patients who had not previously undergone dialysis, acute kidney injury (AKI) in the CICU was defined using Kidney Disease: Improving Global Outcomes stages based on serum creatinine, as an increase in serum creatinine ≥0.3 mg/dL or by 50% in the CICU from either the baseline creatinine or the hospital admission creatinine (whichever was lower).[9] Severe AKI was defined as Kidney Disease: Improving Global Outcomes stage 2 or 3 AKI (ie, doubling of serum creatinine or increase in serum creatinine to ≥4.0 mg/dL or new dialysis initiation in the CICU); when AKI patients did not meet criteria for severe AKI, they were considered to have mild to moderate AKI.[9] Baseline creatinine was considered to be the latest creatinine within 1 year before the index hospital admission.

Collected Data

Laboratory results, patient demographics, and discharge diagnoses were collected. The Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation (APACHE)-III scores along with APACHE predicted mortality were automatically generated using electronic medical record data during the first 24 hours of CICU admission; missing variables were imputed as normal as the default.[10–12] The mean value of all daily Sequential Organ Failure Assessment scores during the first week in the CICU was calculated; for patients remaining in the CICU for

<1 week, this was calculated as the mean of all daily Sequential Organ Failure Assessment values for those days the patient was in the CICU. Baseline comorbid conditions and the Charlson Comorbidity Index were electronically derived.[13] Length of stay in the CICU and hospital, hospital disposition, and all-cause in-hospital mortality were identified via review of electronic medical records or notification of patient death.[5,14] Follow-up was performed via electronic chart review on February 1, 2018.

Statistical Analysis

The primary study end point was all-cause in-hospital mortality, and the secondary study end points were all-cause CICU mortality and all-cause postdischarge mortality. Groups were compared using ANOVA for continuous variables and chi-square tests for categorical variables. Cochran-Armitage trend tests were used to determine trends in categorical variables across groups. Predictors of in-hospital mortality were identified using univariate logistic regression, which was followed by multivariate logistic regression using backward stepwise variable selection ($P<0.25$ to enter the model, $P>0.1$ to leave the model). A continuous propensity score (range, 0–1) was developed using multivariate logistic regression to predict hyperkalemia on admission; multivariate logistic regression to predict in-hospital mortality was repeated using this propensity score. Postdischarge survival between groups was assessed using Kaplan–Meier analysis, with groups compared using the log-rank test. Predictors of in-hospital mortality were included in a Cox proportional hazards model to determine predictors of postdischarge survival among hospital survivors. $P<0.05$ was considered statistically significant. Analyses were performed using JMP 13.0 Pro (SAS Institute, Cary, NC). Jacob C. Jentzer had full access to all data in this study and takes responsibility for data integrity and statistical analysis.

Results

We screened 12 904 CICU admissions and excluded 2900 patients who met the initial exclusion criteria for the study cohort, including 1877 readmissions, 755 patients with no Minnesota Research Authorization, and 268 patients admitted outside of the study period. Of the remaining 10 004 potentially eligible patients, we excluded an additional 323 (3.2%) who did not have an available admission potassium level measurement, yielding a final study population of 9681 patients (Figure S1). The mean age of included patients was 67±15 years, with 3629 (36%) females. Baseline characteristics of the study population grouped by admission serum potassium level are listed in Table 1. The mean admission potassium level was 4.3±0.6, and the median admission potassium level was 4.2 (interquartile range, 3.9, 4.6). Hyperkalemia was present on admission in 1187 (12.3%), and hypokalemia was present on admission in 719 (7.4%). Admission potassium level was <3.0 mEq/L in 121 (1.2%) patients and ≥6 mEq/L in 175 (1.8%) patients. Patients with hypokalemia or hyperkalemia differed from patients with normokalemia regarding illness severity, renal function, diagnoses, and comorbidities (Table 1). Patients with either hypokalemia or hyperkalemia had higher illness severity including higher rates of AKI in the CICU. Patients with hyperkalemia had worse renal function on admission and more frequently had a prior history of chronic kidney disease (CKD) or diabetes mellitus.

In-hospital mortality occurred in 866 (8.9%) patients, including 542 (5.6%) CICU deaths. Admission potassium level was positively associated with in-hospital mortality (unadjusted odds ratio [OR], 1.46 per 1 mEq/L increase; 95% CI, 1.32–1.61; $P<0.001$). Compared with normokalemic patients, both hyperkalemic (unadjusted OR, 2.85; 95% CI, 2.40–3.39; $P<0.001$) and hypokalemic patients (unadjusted OR, 2.31; 95% CI, 1.85–2.88; $P<0.001$) were at increased risk of in-hospital mortality (Table 2). When separated on the basis of presence or absence of HF and the presence or absence of acute coronary syndrome (ACS), patients with hyperkalemia or hypokalemia continued to demonstrate an increased risk of in-hospital mortality compared with patients with normokalemia (Table 2). More than 20% of the patients with an admission potassium level <3.0 mEq/L died in the hospital, as did >25% of the patients with an admission potassium level ≥6.0 mEq/L.

A U-shaped relationship was observed between admission potassium level and both CICU and in-hospital mortality (Figure 1). This U-shaped relationship was also present in patients with and without ACS (Figure 2A) and in patients with and without HF (Figure 2B). The admission potassium level associated with the lowest in-hospital mortality in the overall population was 4.0 to 4.4 mEq/L (Figure 1). The admission potassium level associated with the lowest in-hospital mortality for patients with and without ACS (Figure 2A) and patients without HF (Figure 2B) was 4.0 to 4.4 mEq/L, but the admission potassium level associated with the lowest in-hospital mortality for patients with a diagnosis of HF was 3.5 to 3.9 mEq/L (Figure 2B).

AKI in the CICU was present in 39.0% of the 8900 patients with available data to determine the presence of AKI, including 12.6% with severe AKI. There was a graded relationship between AKI severity in the CICU and increasing prevalence of both hypokalemia and hyperkalemia (both $P<0.001$). A U-shaped relationship between admission potassium level and in-hospital mortality was seen for patients with and without AKI in the CICU, although this relationship was

Table 1. Baseline Characteristics, Discharge Diagnoses, and Provided Therapies for Patients With Normokalemia (Admission Potassium Level 3.5–4.9 mEq/L), Hypokalemia (Admission Potassium Level <3.5 mEq/L) and Hyperkalemia (Admission Potassium Level ≥5.0 mEq/L)

Variable	Normokalemia (n=7775)	Hypokalemia (n=719)	Hyperkalemia (n=1187)	*P* Value
Demographics				
Age, y	67.2±15.2	66.7±15.3	69.7±14.4	<0.0001
Female	37.1%	46.0%	35.4%	<0.0001
White race	92.6%	90.1%	92.1%	0.0530
Body mass index	29.5±6.8	29.0±7.0	30.4±8.1	<0.0001
Comorbidities				
Charlson comorbidity index	2.2±2.5	2.2±2.5	3.4±2.9	<0.0001
History of myocardial infarction	19.8%	16.2%	23.1%	0.0011
History of heart failure	18.8%	18.4%	27.3%	<0.0001
History of stroke	11.8%	13.7%	14.6%	0.0131
History of chronic kidney disease	18.4%	17.6%	36.5%	<0.0001
History of diabetes mellitus	26.7%	25.6%	42.9%	<0.0001
History of cancer	20.9%	20.5%	24.8%	0.0080
History of lung disease	18.7%	17.9%	25.8%	<0.0001
Prior dialysis	4.4%	4.3%	16.0%	<0.0001
Discharge diagnoses				
Cardiogenic shock	6.9%	15.0%	14.9%	<0.0001
Acute coronary syndrome	44.4%	40.2%	34.6%	<0.0001
Coronary artery disease	62.0%	59.2%	54.1%	<0.0001
Atrial fibrillation	30.3%	36.3%	40.3%	<0.0001
Ventricular fibrillation	4.6%	13.8%	3.7%	<0.0001
Ventricular tachycardia	13.5%	15.9%	11.3%	0.0156
Heart failure	36.9%	43.4%	51.9%	<0.0001
Cardiac arrest	6.8%	18.4%	10.3%	<0.0001
ESRD	2.8%	2.9%	8.8%	<0.0001
Sepsis during hospitalization	15.1%	27.0%	24.9%	<0.0001
AKI in CICU	53.2%	34.7%	61.8%	<0.0001
Severe AKI in CICU	20.4%	10.4%	24.4%	<0.0001
Inpatient procedure				
Inpatient coronary angiogram	54.4%	53.3%	40.8%	<0.0001
Inpatient PCI	35.9%	31.7%	27.2%	<0.0001
Invasive ventilation	33.0%	13.8%	23.2%	<0.0001
Noninvasive ventilation	18.1%	13.8%	22.8%	<0.0001
Vasoactive drugs	22.3%	39.9%	34.6%	<0.0001
>1 vasoactive drug	10.2%	21.8%	17.6%	<0.0001
Use of inotropes	8.7%	14.7%	11.3%	<0.0001
Use of vasopressors	18.3%	35.3%	31.8%	<0.0001
Dialysis in CICU	4.1%	6.4%	9.5%	<0.0001
IABP in CICU	8.4%	13.6%	8.4%	<0.0001
PAC in CICU	7.2%	9.6%	7.6%	0.0651
Transfusion in CICU	10.8%	19.9%	15.9%	<0.0001

Continued

Table 1. Continued

Variable	Normokalemia (n=7775)	Hypokalemia (n=719)	Hyperkalemia (n=1187)	*P* Value
Severity of illness scores				
APACHE-III score	58.9±23.6	69.4±28.8	75.5±27.3	<0.0001
Day 1 SOFA score	3.3±3.0	4.9±3.7	5.3±3.7	<0.0001
Mean week 1 SOFA	2.8±2.5	3.9±3.0	4.4±3.2	<0.0001
Length of stay				
CICU LOS	2.5±4.8	3.1±4.1	2.8±3.8	0.0003
Hospital LOS	7.9±13.5	10.1±14.6	8.6±10.8	<0.0001
Admission laboratory values				
Admission potassium level	4.2±0.4	3.2±0.3	5.5±0.5	<0.0001
Admission sodium level	138.1±4.1	137.9±5.3	136.1±5.4	<0.0001
Admission bicarbonate	24.1±4.1	23.8±5.5	22.7±5.3	<0.0001
Admission creatinine level	1.25±0.90	1.21±1.06	2.24±1.92	<0.0001
Admission BUN level	24.5±16.6	24.3±18.3	41.9±24.8	<0.0001
Admission glucose level	145.7±65.8	178.7±94.5	165.6±87.7	<0.0001

Data represented as % or mean±standard deviation. *P* value is for chi-squared test (categorical variables) or analysis of variance (continuous variables) between groups. AKI indicates acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; BUN, blood urea nitrogen; CICU, cardiac intensive care unit; ESRD, end-stage renal disease; IABP, intra-aortic balloon pump; LOS, length of stay; PAC, pulmonary artery catheter; PCI, percutaneous coronary intervention; SOFA, Sequential Organ Failure Assessment.

present only for patients without severe AKI (Figure 2C). Patients with either mild or no AKI had an increased risk of in-hospital mortality in the presence of either hypokalemia or hyperkalemia, but this relationship was not seen for patients with severe AKI (Table 2). Patients with and without CKD similarly displayed a U-shaped relationship between admission potassium level and in-hospital mortality (Figure 2D). Among patients with or without CKD, those with hypokalemia or hyperkalemia were at increased risk of in-hospital mortality (Table 2).

Table 2. Unadjusted Odds Ratio (95% CI) Values for Hospital Mortality Using Logistic Regression for Hypokalemia and Hyperkalemia (Relative to Normokalemia) in Various Patient Subgroups

Group	Hypokalemia	Hyperkalemia
Overall population	2.85 (2.40–3.39)*	2.31 (1.9–2.88)*
Patients with ACS	3.22 (2.29–4.51)*	3.02 (2.24–4.07)*
Patients without ACS	1.81 (1.35–2.44)*	2.65 (2.14–3.27)*
Patients with HF	1.52 (1.08–2.14)*	2.10 (1.66–2.67)*
Patients without HF	3.15 (2.35–4.24)*	3.49 (2.71–4.49)*
Patients with CKD	1.81 (1.11–2.96)*	1.86 (1.38–2.51)*
Patients without CKD	2.50 (1.95–3.22)*	3.23 (2.61–3.99)*
Patients without AKI	2.37 (1.49–3.77)*	3.57 (2.46–5.18)*
Patients with AKI	1.49 (1.10–2.01)*	1.87 (1.48–2.35)*
Patients with mild AKI	1.93 (1.30–2.88)*	2.38 (1.75–3.24)*
Patients with severe AKI	0.95 (0.60–1.52)	1.22 (0.86–1.73)

ACS indicates acute coronary syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; HF, heart failure.
*$P<0.05$.

After adjustment for demographics, admission renal function, CICU therapies and illness severity using multivariate regression (Table 3), admission hyperkalemia was associated with an increased risk of in-hospital mortality compared with normokalemia (adjusted OR, 1.44; 95% CI, 1.11–1.87; $P=0.006$); hypokalemia was not associated with in-hospital mortality ($P>0.1$). After adjusting this multivariate regression model using the propensity score for predicting admission hyperkalemia, the presence of admission hyperkalemia remained associated with higher in-hospital mortality compared with normokalemia (adjusted OR, 1.43; 95% CI, 1.11–1.86; $P=0.006$).

At least 1 potassium level during the CICU stay was available for 9499 (98.1%) patients. Patient with hypokalemia (lowest potassium level <3.5 mEq/L, n=1662) during the CICU stay were at increased risk of unadjusted in-hospital mortality (17.2% versus 7.0%; unadjusted OR, 2.78; 95% CI, 2.38–3.24; $P<0.001$), as were patients with hyperkalemia (highest potassium level ≥5.0 mEq/L, n=1901) during the CICU stay (21.4% versus 5.6%; unadjusted OR, 4.60; 95% CI, 3.97–5.33; $P<0.001$). Patients with both hypokalemia and hyperkalemia

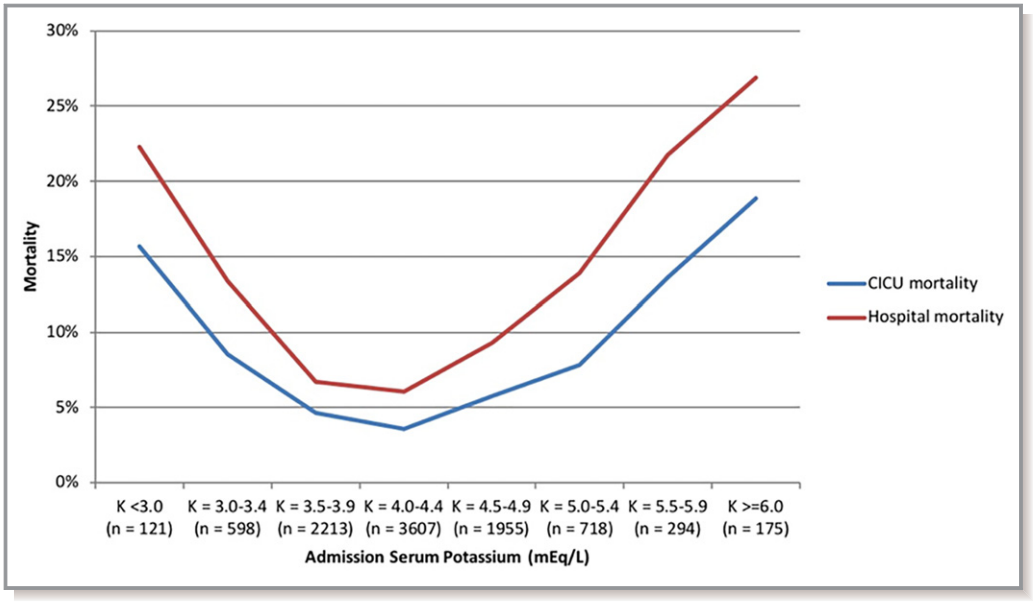


Figure 1. CICU and hospital mortality as a function of admission potassium level. CICU indicates cardiac intensive care unit.

during the CICU stay (n=333; 3.5%) had the highest CICU mortality (24.0%) and in-hospital mortality (33.0%), as shown in Figure S2. An increase in CICU and in-hospital mortality was observed as a function of the highest potassium level during the CICU stay (Figure 3A); patients with a maximum potassium level <3.5 mEq/L in CICU were at increased risk of mortality.

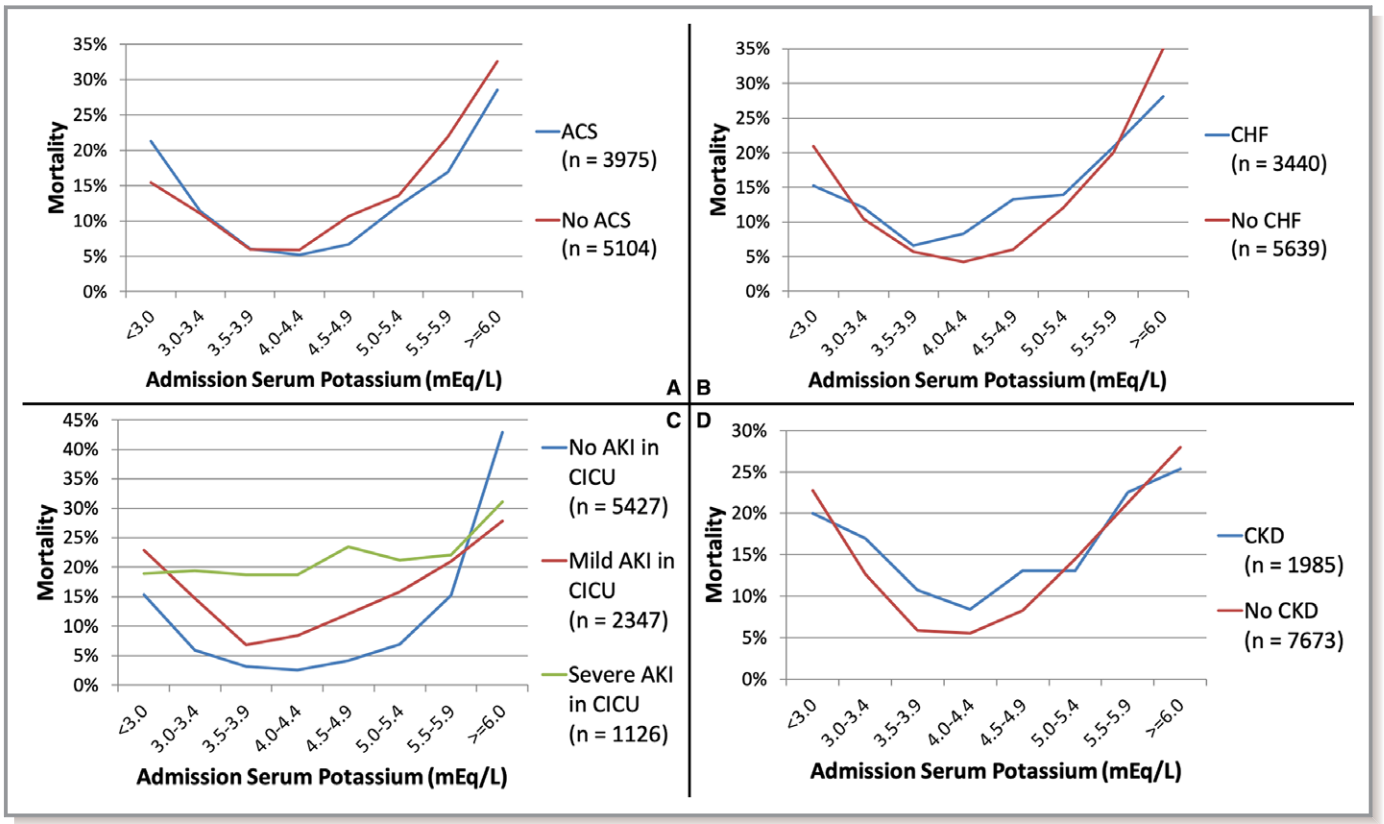


Figure 2. Hospital mortality as a function of admission potassium level in patients with and without ACS (**A**), HF (**B**), AKI (**C**), and CKD (**D**). $P<0.0001$ for all trends, except for patients with severe AKI ($P=0.59$). ACS indicates acute coronary syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; HF, heart failure.

Table 3. Predictors of Hospital Mortality on Multivariate Logistic Regression and Predictors of Postdischarge Mortality on Cox Proportional Hazards Analysis (Among 8815 Hospital Survivors)

	Logistic Regression		Cox Proportional Hazards	
Variable	OR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.02 (1.02–1.03)*	<0.0001*	1.04 (1.03–1.04)*	<0.0001*
Female sex	1.12 (0.91–1.37)	0.2863	1.03 (0.96–1.11)	0.3958
Mean week 1 SOFA	1.59 (1.52–1.67)*	<0.0001*	1.14 (1.11–1.16)*	<0.0001*
Admission blood urea nitrogen	1.01 (1.01–1.02)*	<0.0001*	1.01 (1.01–1.01)*	<0.0001*
Admission creatinine	0.77 (0.63–0.93)*	0.0072*	0.92 (0.85–1.00)*	0.0463*
Chronic kidney disease	0.61 (0.46–0.82)*	0.0010*	1.01 (0.91–1.11)	0.9204
Diabetes mellitus	0.74 (0.58–0.93)*	0.0110*	0.99 (0.91–1.07)	0.7802
Charlson comorbidity index	1.11 (1.07–1.16)*	<0.0001*	1.15 (1.13–1.17)*	<0.0001*
Cardiac arrest	5.18 (4.00–6.71)*	<0.0001*	0.82 (0.69–0.97)*	0.0239*
End-stage renal disease	0.95 (0.46–1.96)	0.8893	0.85 (0.61–1.17)	0.3168
AKI in CICU	1.17 (0.92–1.48)	0.2020	1.21 (1.11–1.32)*	<0.0001*
Dialysis in CICU	2.00 (1.56–2.96)*	0.0005*	2.16 (1.81–2.57)*	<0.0001*
Invasive ventilator	0.74 (0.56–0.97)*	0.0303*	0.93 (0.82–1.06)	0.2575
Vasoactive drugs				
One vs none	1.12 (0.85–1.47)	0.4235	1.00 (0.89–1.11)	0.9762
>1 vs none	1.70 (1.29–2.25)*	0.0002*	0.95 (0.83–1.10)	0.5023
>1 vs one	1.52 (1.14–2.03)*	0.0043*	0.95 (0.82–1.11)	0.5348
Potassium group				
Low vs normal	1.06 (0.77–1.48)	0.7149	0.96 (0.83–1.10)	0.5184
High vs normal	1.44 (1.11–1.87)*	0.0058*	1.20 (1.08–1.34)*	0.0007*
High vs low	1.36 (0.92–2.00)	0.1239	1.26 (1.07–1.49)*	0.0065*

Unit odds ratio (OR) values are shown for logistic regression and hazard ratio (HR) values are shown for Cox proportional-hazards analysis, with 95% CI. AKI indicates acute kidney injury; CICU, cardiac intensive care unit; SOFA, Sequential Organ Failure Assessment.
*Significant OR and HR values (P<0.05).

The highest potassium level during the CICU stay was a predictor of in-hospital mortality (unadjusted OR, 2.71 per 1 mEq/L increase; 95% CI, 2.46–2.98; P<0.001), with an optimal cutoff of 4.9 mEq/L by receiver operating characteristic analysis. An increase in CICU and in-hospital mortality was observed as a function of the lowest potassium level during the CICU stay (Figure 3B); patients with a minimum potassium level ≥5.0 mEq/L in CICU were at increased risk of mortality. The lowest potassium level during the CICU stay was a predictor of in-hospital mortality (unadjusted OR, 0.70 per 1 mEq/L decrease; 95% CI, 0.61–0.80; P<0.001), with an optimal cutoff of 3.5 mEq/L by receiver operating characteristic analysis. In addition, the potassium range (maximum potassium level−minimum potassium level) during the CICU stay was higher among patients who died in the hospital (1.2 versus 0.6 mEq/L; P<0.001), and the potassium range was positively associated with in-hospital mortality (unadjusted OR, 2.53 per 1 mEq/L; 95% CI, 2.32–2.75; P<0.001).

Of 8815 hospital survivors, a total of 5266 (59.7%) died during a mean follow-up of 3.4±2.9 years; 1235 (14.0%) patients had a follow-up duration of <1 year. Among hospital survivors, patients with admission hyperkalemia had lower postdischarge survival than patients with hypokalemia or normokalemia on Kaplan–Meier analysis (Figure 4; P<0.001); patients with hypokalemia and normokalemia had similar postdischarge survival (P>0.1). Using Cox proportional hazards analysis adjusting for demographics, renal function, CICU therapies, and illness severity (Table 3), patients with admission hyperkalemia were at increased risk of postdischarge mortality compared with either normokalemia (adjusted HR, 1.20; 95% CI, 1.08–1.34; P<0.001) or hypokalemia (adjusted OR, 1.26; 95% CI, 1.07–1.49; P=0.006); hypokalemia was not associated with higher postdischarge mortality. Admission hyperkalemia remained a significant predictor of postdischarge survival (P<0.05) after inclusion of the propensity score in the Cox proportional hazards model.

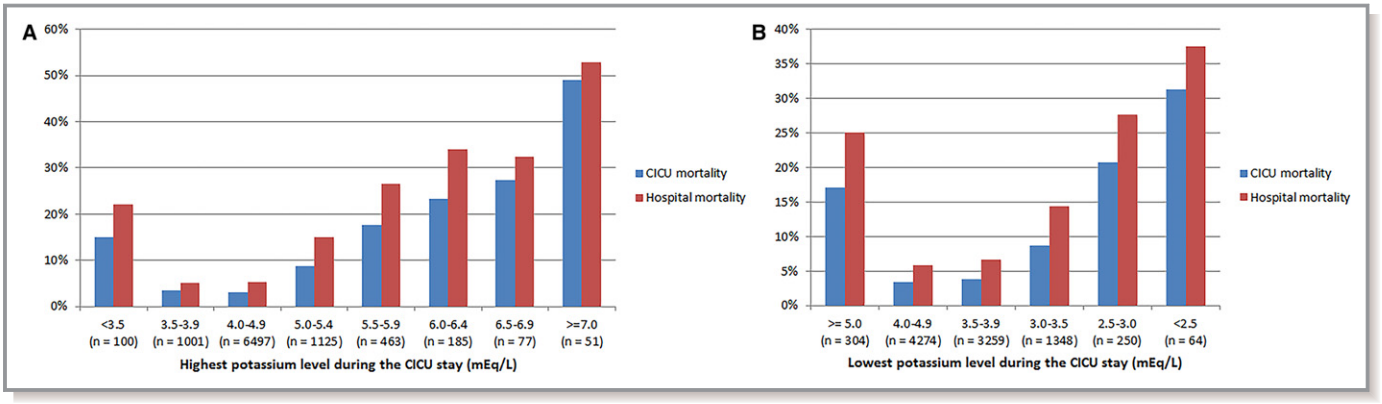


Figure 3. CICU and hospital mortality as a function of the highest (**A**) and lowest (**B**) potassium level during the CICU stay for the overall population. *P*<0.001 for trends. CICU indicates cardiac intensive care unit.

Discussion

This is the first study to evaluate the association between mortality and hyperkalemia in a large cohort of unselected contemporary CICU patients. We observed a U-shaped relationship between admission potassium level and unadjusted in-hospital mortality that was present in the general CICU population, including patients with or without a discharge diagnosis of ACS or HF, patients with or without a history of CKD and patients with or without AKI. Patients with either hypokalemia or hyperkalemia were found to be more critically ill, with a higher prevalence of critical care diagnoses and greater use of CICU therapies reflecting cardiopulmonary instability. After adjustment for illness severity and other factors, hyperkalemia (admission potassium ≥5.0 mEq/L) remained associated with higher in-hospital mortality; this relationship was not observed with hypokalemia. Hospital survivors with hyperkalemia on CICU admission demonstrated lower adjusted postdischarge survival compared with those with either hypokalemia or normokalemia. Importantly, our results suggest that in this population, even mild hyperkalemia during the CICU stay is associated with increased mortality, while patients with more severe hyperkalemia had markedly higher in-hospital mortality rates. Given the higher illness severity among CICU patients with abnormal potassium levels, we hypothesize that hyperkalemia acts as a risk marker in a manner complementary to current risk stratification methods.

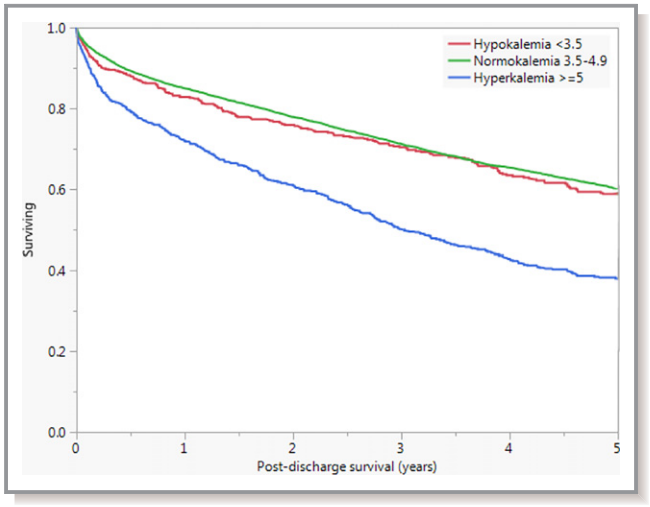


Figure 4. Kaplan–Meier survival curves for hospital survivors as a function of admission potassium levels. *P*<0.001 for comparison between patients with hyperkalemia and other groups; *P*>0.1 for comparison between hypokalemia and normokalemia.

Prior studies have demonstrated a U-shaped relationship between potassium level and mortality in a variety of patient populations.[1–3,15–18] Colombo et al[2] performed a meta-analysis of 12 studies examining the relationship between serum potassium levels and mortality in 60 547 patients with acute myocardial infarction, demonstrating higher short- and long-term mortality in patients with serum potassium <3.5 or ≥4.5 mEq/L. Similarly, patients with hypokalemia in our study had higher unadjusted in-hospital mortality, although we did not find an association between hypokalemia and adjusted in-hospital mortality or postdischarge mortality. Younis et al[1] noted an independent association between admission potassium levels >5.5 mEq/L and long-term mortality in 4031 patients hospitalized with HF. These data support an association between hyperkalemia (admission serum potassium ≥5 mEq/L) with higher adjusted in-hospital and postdischarge mortality in a broad spectrum of acutely ill cardiac patients. We also observed a positive association between potassium variability (based on the maximum and minimum potassium levels) and in-hospital mortality.

Hypokalemia was associated with higher rates of ventricular arrhythmias in the meta-analysis by Colombo et al.[2] In our study, patients with hypokalemia more frequently had discharge diagnoses of arrhythmias, including AF, VT, and VF. The Colombo et al[2] systematic review suggested an optimal serum potassium level of 3.5 to 4.4 mEq/L, reflecting disagreement amongst included studies. In our study, the lowest in-hospital mortality was observed in patients with

admission potassium 4 to 4.4 mEq/L, except in those with HF, in whom the lowest death rate was observed in patients with admission potassium levels between 3.5 and 3.9 mEq/L. While we found lower mortality in the majority of patients at an admission serum potassium level ≥4.0 mEq/L, these data do not allow specific recommendations to be made regarding target levels for potassium repletion.

Abnormal potassium levels (specifically <3.5 and >5.4 mEq/L) are included in the APACHE illness severity score for predicting in-hospital mortality among intensive care unit patients.[4] However, while the APACHE score defines hyperkalemia as a potassium level >5.4 mEq/L, a study of 39 705 critically ill patients by McMahon et al[18] observed higher 30-day mortality among patients with serum potassium levels >4.5 mEq/L at the time of critical care initiation. We noted significantly higher mortality among patients with serum potassium levels between 5.0 and 5.4 mEq/L, emphasizing the mortality hazard associated with mild hyperkalemia.[18] McMahon et al[18] found that potassium supplementation leading to hyperkalemia did not increase mortality, implying that hyperkalemia is likely indicative of underlying pathophysiology rather than being causally associated with mortality.

Although the association between hyperkalemia and adverse outcomes in this population may be explained by direct harmful effects of elevated potassium levels, we hypothesize that elevated potassium levels more likely serve as a marker to identify high-risk patients with higher illness severity or more severe comorbidities. Potassium is essential for normal cardiac myocyte function including impulse conduction and coordinated myocardial contraction.[19] As such, disturbances in potassium levels can predispose patients to arrhythmia, which may account for the increased mortality rate and more frequent arrhythmia diagnoses seen in our patients with hypokalemia and hyperkalemia.[19,20] However, we observed an increase in mortality at mildly elevated potassium levels below those usually associated with direct cardiac toxicity, indicating that arrhythmia alone is not the primary reason for the increase in mortality seen in our population.[21] Our patients with hypokalemia and hyperkalemia had higher illness severity; patients with hyperkalemia also had worse renal function. This implies that potassium abnormalities identify sicker patients with increased risk of mortality, and the effects of hypokalemia on mortality appeared to be mediated primarily by illness severity. Hyperkalemia remained associated with higher short- and long-term mortality after adjustment for illness severity and markers of renal function, implying that hyperkalemia may identify patients with more dangerous forms of renal dysfunction. Our observed relationships between AKI severity and the mortality effects of hyperkalemia may suggest that renal tubular potassium-handling abnormalities leading to hyperkalemia could be more important as a determinant of outcomes than the effect of reduced clearance alone or could modify the effects of reduced clearance on outcomes; this would explain why patients with severe AKI (and therefore severely reduced clearance) did not demonstrate an association between admission potassium levels and in-hospital mortality. Hyperkalemia may modify the safety or efficacy of standard guideline-directed medical therapies for patients with HF or ACS such as angiotensin-converting enzyme inhibitors, potentially contributing further to adverse outcomes.[22–24]

As with all retrospective cohort studies, our study has several limitations, including the inability to establish a causal relationship between abnormal admission potassium and mortality and the potential for unmeasured residual confounding factors. This tertiary referral hospital CICU population may differ significantly from other populations, although the prevalence of ACS and HF diagnoses are similar to recent CICU studies.[25] To facilitate early risk stratification, we focused on admission potassium levels, which included laboratory values from either before or after CICU admission, potentially contributing to data variability. The potassium levels we analyzed included serum, plasma, and whole blood values, which have different reference ranges and analytic techniques, and we were unable to determine which patients had potassium levels measured by which assay or the reasons that a different assay may have been used in each patient. While it remains possible that these differences in analytical technique could have influenced the observed relationship between potassium levels and mortality, the differences between the different potassium levels are relatively modest and unlikely to impact the results meaningfully. Furthermore, the rate and magnitude of change in potassium levels over time could have influenced the effects on outcomes, but we did not have preadmission potassium levels for comparison, nor did we have the time of the peak and nadir potassium levels to determine the rate of increase in its level. The secondary analysis evaluating maximum and minimum potassium levels during the CICU stay could potentially be confounded by mixing patients with low admission potassium levels and a normal maximum potassium level with patients whose potassium levels were normal at all times or mixing patients with high admission potassium levels and normal minimum potassium levels with patients whose potassium levels were normal at all times. Based on available data, we cannot determine the ways in which admission potassium levels could have influenced patient care. We specifically were not able to obtain data on medications administered while in the hospital, including potassium supplementation, guideline-directed medical therapy, or treatments administered for hypokalemia. We do not have specific data on adverse events directly related to high or low potassium levels, including treatment-emergent arrhythmias. The *ICD-9* discharge diagnoses we obtained reflect all diagnoses from the

hospitalization, including both acute and chronic conditions. Furthermore, despite careful multivariate adjustment, unmeasured confounding could remain to explain the observed associations between hyperkalemia and mortality.

Conclusions

Our study demonstrated a U-shaped relationship between admission serum potassium levels and unadjusted mortality in unselected CICU patients, including relevant subgroups with ACS, HF, AKI, and CKD. After adjustment for illness severity and comorbidities (including renal function), hyperkalemia was associated with higher in-hospital and postdischarge mortality, whereas hypokalemia was not. Elevated admission potassium levels only slightly above the upper limit of normal were associated with higher short- and long-term mortality, emphasizing the importance of mild hyperkalemia as a predictor of adverse outcomes. This demonstrates that admission potassium levels may be a marker for illness severity that can help clinicians in prognostication and risk assessment in the CICU. The inconsistencies within the current literature regarding optimal potassium levels in acutely ill cardiac patients emphasize the need for future prospective studies examining electrolyte repletion protocol goals and optimal treatment of hyperkalemia in this population. Further study is needed to determine how abnormal potassium levels influence patient care and clinical outcomes in CICU patients, and how current risk indicators among general intensive care unit patients may or may not apply to the evolving CICU population.

Disclosures

None.

References

1. Younis A, Goldenberg I, Goldkorn R, Younis A, Peled Y, Tzur B, Klempfner R. Elevated admission potassium levels and 1-year and 10-year mortality among patients with heart failure. *Am J Med Sci*. 2017;354:268–277.
2. Colombo MG, Kirchberger I, Amann U, Dinser L, Meisinger C. Association of serum potassium concentration with mortality and ventricular arrhythmias in patients with acute myocardial infarction: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2018;25:576–595.
3. Hessels L, Hoekstra M, Mijzen LJ, Vogelzang M, Dieperink W, Lansink AO, Nijsten MW. The relationship between serum potassium, potassium variability and in-hospital mortality in critically ill patients and a before-after analysis on the impact of computer-assisted potassium control. *Crit Care*. 2015;19:9.
4. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818–829.
5. Jentzer JC, Bennett C, Wiley BM, Murphree DH, Keegan MT, Gajic O, Wright RS, Barsness GW. Predictive value of the sequential organ failure assessment score for mortality in a contemporary cardiac intensive care unit population. *J Am Heart Assoc*. 2018;7:e008169. DOI: 10.1161/JAHA.117.008169.
6. Goldfarb M, van Diepen S, Liszkowski M, Jentzer JC, Pedraza I, Cercek B. Noncardiovascular disease and critical care delivery in a contemporary cardiac and medical intensive care unit. *J Intensive Care Med*. 2017 Jan 1:885066617741873. Available at: https://journals.sagepub.com/doi/10.1177/0885066617741873. Accessed March 20, 2019.
7. Herasevich V, Pickering BW, Dong Y, Peters SG, Gajic O. Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. *Mayo Clin Proc*. 2010;85:247–254.
8. National Cancer Institute (US). *Common Terminology Criteria for Adverse Events (CTCAE)*. Rev. ed. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2009.
9. Group KDIGOKAKIW. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
10. Aakre C, Franco PM, Ferreyra M, Kitson J, Li M, Herasevich V. Prospective validation of a near real-time EHR-integrated automated SOFA score calculator. *Int J Med Inform*. 2017;103:1–6.
11. Chandra S, Kashyap R, Trillo-Alvarez CA, Tsapenko M, Yilmaz M, Hanson AC, Pickering BW, Gajic O, Herasevich V. Mapping physicians' admission diagnoses to structured concepts towards fully automatic calculation of acute physiology and chronic health evaluation score. *BMJ Open*. 2011;1:e000216.
12. Keegan MT, Gajic O, Afessa B. Comparison of APACHE III, APACHE IV, SAPS 3, and MPM0III and influence of resuscitation status on model performance. *Chest*. 2012;142:851–858.
13. Singh B, Singh A, Ahmed A, Wilson GA, Pickering BW, Herasevich V, Gajic O, Li G. Derivation and validation of automated electronic search strategies to extract Charlson comorbidities from electronic medical records. *Mayo Clin Proc*. 2012;87:817–824.
14. Rocca WA, Yawn BP, St. Sauver JL, Grossardt BR, Melton LJ. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clin Proc*. 2012;87:1202–1213.
15. Grodzinsky A, Goyal A, Gosch K, McCullough PA, Fonarow GC, Mebazaa A, Masoudi FA, Spertus JA, Palmer BF, Kosiborod M. Prevalence and prognosis of hyperkalemia in patients with acute myocardial infarction. *Am J Med*. 2016;129:858–865.
16. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J*. 2017;38:2890–2896.
17. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol*. 2017;46:213–221.
18. McMahon GM, Mendu ML, Gibbons FK, Christopher KB. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med*. 2012;38:1834–1842.
19. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev*. 2005;85:1205–1253.
20. Sarwar CM, Papadimitriou L, Pitt B, Piña I, Zannad F, Anker SD, Gheorghiade M, Butler J. Hyperkalemia in heart failure. *J Am Coll Cardiol*. 2016;68:1575–1589.
21. Part 10.1: life-threatening electrolyte abnormalities. *Circulation*. 2005;112:IV-121–IV-125.
22. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161.
23. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
24. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd N, Bakris G, Pitt B, Zannad F. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail*. 2014;7:51–58.
25. Katz JN, Shah BR, Volz EM, Horton JR, Shaw LK, Newby LK, Granger CB, Mark DB, Califf RM, Becker RC. Evolution of the coronary care unit: clinical characteristics and temporal trends in healthcare delivery and outcomes. *Crit Care Med*. 2010;38:375–381.

SUPPLEMENTAL MATERIAL

Figure S1. STROBE flowchart of study population, demonstrating inclusion and exclusion criteria and study groups.

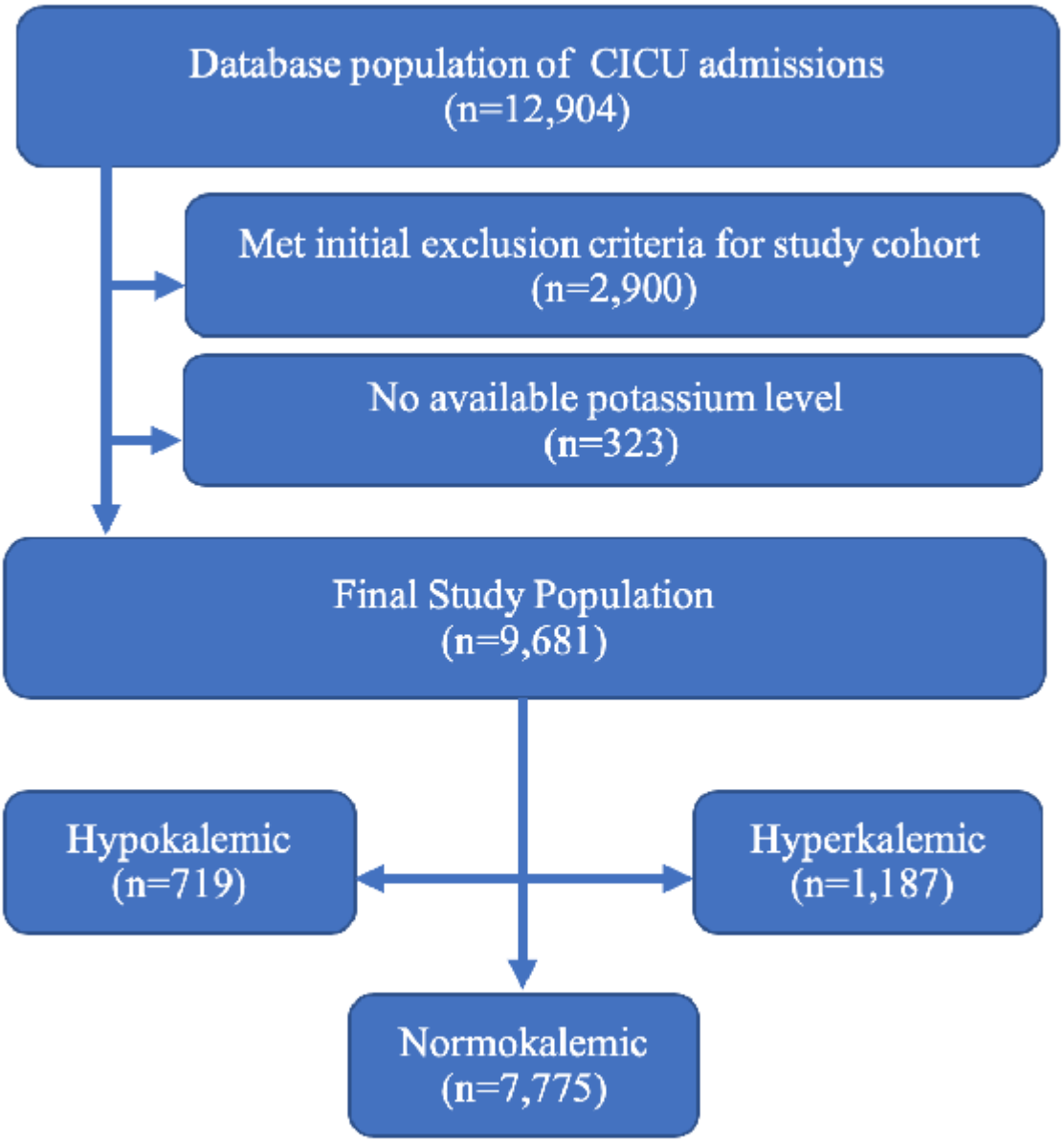
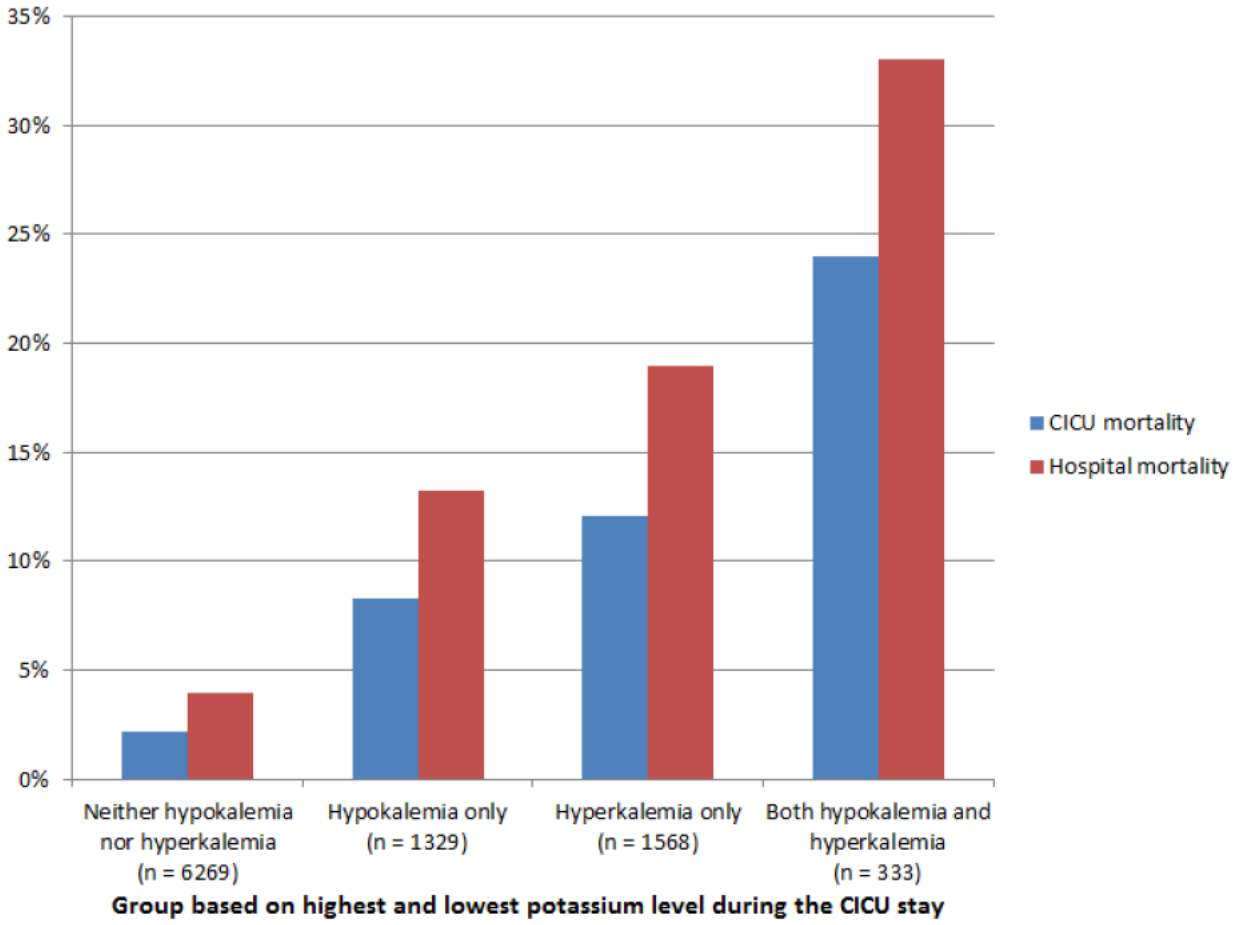


Figure S2. CICU and hospital mortality based on the presence of hyperkalemia (highest potassium level ≥5.0 mEq/L), hypokalemia (lowest potassium level <3.5 mEq/L), both or neither during the CICU stay.



P <0.001 between groups. CICU, cardiac intensive care unit.