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Association of serum total and ionized calcium with all-cause mortality incritically ill patients with acute kidney injury

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ABSTRACT

Background: There have been no epidemiological studies exploring the prognostic ability of serum total and ionized calcium (tCa and iCa) in critically ill patients with acute kidney injury (AKI). We assessed the association of admission tCa and iCa concentrations with all-cause mortality in these patients.

Methods: We extracted clinical data from the MIMIC-III V1.4 database. Only the data for the first intensive care unit (ICU) admission of each patient were used and baseline data were extracted within 24 h after ICU admission. Cox proportional hazards models and subgroup analyses were used to determine the relationship between tCa and iCa concentrations and 30, 90 and 365-day all-cause mortality in critically ill patients with AKI. A total of 10,207 eligible patients were studied. In multivariate analysis, adjusted for age, ethnicity and gender, both low-tCa (< 7.9 mg/dl) and low-iCa (< 1.06 mmol/l) concentrations were significant predictors of risk of all-cause mortality. Furthermore, after adjusting for more confounding factors, low-iCa concentrations remained a significant predictor of all-cause mortality at 30 days, 90 days, 365 days (HR, 95% CI: 1.19, 1.06–1.33; 1.15, 1.05–1.27; 1.10, 1.01–1.20).

Conclusions: Low-iCa concentrations were independent predictors of all-cause mortality in critically ill patients with AKI.

1. Introduction

Acute kidney injury (AKI) is a common dangerous syndrome, defined as abrupt and often reversible decline in glomerular filtration [1], with an especially high incidence in the intensive care unit (ICU) [2]. The mortality of critically ill patients with AKI increases to as much as 60–70% [3,4]. Evidence suggests that patients do not directly die from AKI; however, because of its severe complications, common causes of death include hyperkalemia, severe acidosis and sepsis [5,6]. Given the high incidence of AKI and poor prognosis in ICU patients, researchers have been looking for a simple and reliable clinical predictor of mortality in AKI. Unfortunately, most of them are unsuccessful [7,8].

The stabilization of ionized calcium (iCa) in the blood is important for many basic physiological regulatory mechanisms [9]. Abnormal calcium metabolism causes severe cardiovascular complications and organ dysfunctions, including heart failure and renal failure [10–12]. The possible mechanism of renal failure is that hpercalcemia causes renal vasoconstriction and reduced renal blood flow, inducing renal ischemia and tubular injury [12]. Most previous studies focused on the iCa, and several studies found an independent, U-shaped association between iCa and mortality in critical illness [13,14]. Moreover, the findings indicated that disorders in iCa were likely to represent the degree of physiologic derangements, reflecting illness severity [13]. Currently, the role of total calcium (tCa) has been received substantial attention. Dickerson et al. [15] reported that there was a close relationship between iCa and tCa. Recently, several retrospective studies demonstrated that the association between initial tCa concentration and mortality in critical illness [16] and both hyper- and hypo-tCa were associated with increased risk of hospital-acquired AKI [17].

2. Methods

2.1. Data source

The Multiparameter Intelligent Monitoring in Intensive Care III ver 1.4 (MIMIC-III v1.4) is a large, single-center, publicly available critical care database. It includes > 40,000 ICU admissions hospitalized at the Beth Israel Deaconess Medical Center (Boston, USA) from 2001 to 2012 [18]. To apply for access to the database, we passed the Protecting Human Research Participants exam (No. 6182750). The project was

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Table 1
Characteristics of the study patients according to serum ionized calcium levels.

Characteristics	Total (n = 10,207)	Ionized calcium levels (mmol/L)			
		< 1.06 (n = 3128)	≥1.06, < 1.14 (n = 3433)	≥1.14 (n = 3646)	P value
Age, years	63.9 ± 17.3	61.1 ± 18.4	64.3 ± 17.5	66.0 ± 15.8	< 0.001
Gender, n (%)					0.006
Female	4211 (41.3)	1360 (43.5)	1363 (39.7)	1488 (40.8)	
Male	5996 (58.7)	1768 (56.5)	2070 (60.3)	2158 (59.2)	
Ethnicity, n (%)					< 0.001
White	7203 (70.6)	2117 (67.7)	2453 (71.5)	2633 (72.2)	
Black	2264 (22.2)	776 (24.8)	756 (22.0)	732 (20.1)	
Other	740 (7.2)	235 (7.5)	224 (6.5)	281 (7.7)	
ICU LOS, day	6.5 ± 7.8	7.5 ± 8.7	6.1 ± 7.3	5.9 ± 7.5	< 0.001
iCa, mmol/l	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.0	1.2 ± 0.1	< 0.001
tCa, mg/dl	8.3 ± 1.2	7.8 ± 1.2	8.3 ± 0.9	8.7 ± 1.2	< 0.001
SBP, mmHg	118.0 ± 16.7	116.9 ± 17.2	118.6 ± 16.5	118.4 ± 16.3	< 0.001
DBP, mmHg	60.0 ± 10.3	60.8 ± 10.8	60.0 ± 10.3	59.2 ± 9.8	< 0.001
MBP, mmHg	78.2 ± 10.9	78.5 ± 11.4	78.4 ± 10.9	77.8 ± 10.5	0.029
Heart rate, beats/min	88.3 ± 16.4	91.5 ± 17.5	87.3 ± 16.0	86.5 ± 15.4	< 0.001
Respiratory rate, beats/min	19.0 ± 4.3	19.4 ± 4.5	18.8 ± 4.1	18.7 ± 4.1	< 0.001
Temperature, ℃	36.9 ± 0.7	36.9 ± 0.8	36.9 ± 0.7	36.9 ± 0.7	0.014
SPO_2, %	97.4 ± 2.8	97.3 ± 3.7	97.5 ± 2.3	97.4 ± 2.4	0.137
Comorbidities, n (%)					
Coronary artery disease	2643 (25.9)	520 (16.6)	896 (26.1)	1227 (33.7)	< 0.001
Congestive heart failure	1438 (14.1)	326 (10.4)	518 (15.1)	594 (16.3)	< 0.001
Atrial fibrillation	2910 (28.5)	718 (23.0)	1021 (29.7)	1171 (32.1)	< 0.001
Stroke	1025 (10.0)	279 (8.9)	368 (10.7)	378 (10.4)	0.038
Renal disease	1254 (12.3)	331 (10.6)	440 (12.8)	483 (13.2)	0.002
Liver disease	753 (7.4)	342 (10.9)	222 (6.5)	189 (5.2)	< 0.001
Diabetes uncomplicated	2373(23.2)	847 (27.1)	608 (17.7)	918 (25.2)	< 0.001
Pneumonia	2762 (27.1)	885 (28.3)	923 (26.9)	954 (26.2)	0.140
COPD	196 (1.9)	43 (1.4)	68 (2.0)	85 (2.3)	0.016
Malignancy	1911 (18.7)	605 (19.3)	660 (19.2)	646 (17.7)	0.151
Respiratory failure	4286 (42.0)	1498 (47.9)	1388 (40.4)	1400 (38.4)	< 0.001
ARDS	193 (1.9)	68 (2.2)	57 (1.7)	68 (1.9)	0.309
Laboratory parameters					
Bicarbonate, mg/dl	20.8 ± 5.0	19.3 ± 5.1	21.3 ± 4.7	21.6 ± 5.0	< 0.001
Creatinine, mEq/l	1.4 ± 1.5	1.6 ± 1.8	1.3 ± 1.3	1.4 ± 1.4	< 0.001
Chloride, mmol/l	102.5 ± 6.4	102.1 ± 7.6	102.5 ± 5.7	102.9 ± 5.9	0.003
Glucose, mg/dl	146.1 ± 44.7	149.3 ± 48.9	145.7 ± 42.0	143.7 ± 43.2	< 0.001
Hematocrit, %	28.6 ± 6.2	27.7 ± 6.3	28.9 ± 6.0	29.1 ± 6.2	< 0.001
Platelet, 10^9 /l	185.7 ± 106.9	170.6 ± 110.3	190.8 ± 102.2	193.7 ± 106.8	< 0.001
Sodium, mmol/l	135.9 ± 5.1	135.4 ± 5.9	135.9 ± 4.7	136.3 ± 4.7	< 0.001
BUN, mg/dl	25.8 ± 20.9	27.7 ± 23.9	24.6 ± 19.3	25.3 ± 19.5	0.002
WBC, 10^9 /l	10.9 ± 8.1	10.8 ± 9.2	10.7 ± 5.8	11.2 ± 8.8	0.028
Anion gap, mmol/l	13.1 ± 3.6	13.7 ± 4.1	12.8 ± 3.3	12.8 ± 3.3	< 0.001
Scoring systems					
SOFA	5.6 ± 3.6	6.4 ± 4.0	5.3 ± 3.4	5.3 ± 3.2	< 0.001
SAPSII	40.7 ± 15.3	43.1 ± 16.2	39.5 ± 14.9	39.8 ± 14.7	< 0.001
AKI stage, n (%)					< 0.001
Stage 1	2119 (20.8)	583 (18.6)	756 (22.0)	780 (21.4)	
Stage 2	1834 (18.0)	626 (20.0)	612 (17.8)	596 (16.3)	
Stage 3	6254 (61.3)	1919 (61.3)	2065 (60.2)	2270 (62.3)	
30-day mortality, n (%)	1938 (19.0)	766 (24.5)	590 (17.2)	582 (16.0)	< 0.001
90-day mortality, n (%)	2554 (25.0)	948 (30.3)	781 (22.7)	825 (22.6)	< 0.001
365-day mortality, n (%)	3309 (32.4)	1167 (37.3)	1062 (30.9)	1080 (29.6)	< 0.001

ICU: intensive care unit; LOS: length of stay; tCa: total calcium; iCa: ionized calcium; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; WBC: white blood cell; BUN: blood urea nitrogen; SOFA: sequential organ failure assessment; SAPSII: simplified acute physiology score II; AKI: acute kidney injury.

approved by the institutional review boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) and was given a waiver of informed consent.

2.2. Population selection criteria

Adult patients (≥18 y) with AKI who had been hospitalized in the ICU for more than two days were included. Patients were excluded with the following criteria: 1) no serum tCa and iCa measured during the ICU stay; and 2) missing > 5% individual data. AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) classification [19].

2.3. Data extraction

Similar to our previous study [20], data extraction was performed using Structured Query Language (SQL) with PostgreSQL tools (ver 9.6). Demographics, vital signs, laboratory tests, medications, and others were extracted from MIMIC-III. The laboratory parameters included iCa, tCa, bicarbonate, creatinine, chloride, glucose, hematocrit, platelet, sodium, blood urea nitrogen (BUN), white blood cell (WBC), and anion gap. Comorbidities were also extracted, including coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation (AFIB), stroke, renal disease, liver disease, pneumonia, chronic obstructive pulmonary disease (COPD), malignancy, respiratory failure and acute respiratory distress syndrome (ARDS). Furthermore, the

Table 2
HRs (95% CIs) for mortality across groups of serum calcium.

Calcium ion	Non-adjusted		Model I		Model II	
	HR (95%CIs)	*P* value	HR (95%CIs)	*P* value	HR (95%CIs)	*P* value
30-day all-cause mortality						
tCa, tertiles, mg/dl						
< 7.9	1.27 (1.14, 1.42)	< 0.0001	1.35 (1.22, 1.51)	< 0.0001	1.00 (0.89, 1.12)	NS
≥7.9, < 8.7	1.0(ref)		1.0(ref)		1.0(ref)	
≥8.7	1.06 (0.95, 1.18)	NS	1.06 (0.94, 1.18)	NS	1.01 (0.90, 1.13)	NS
iCa, tertiles, mmol/l						
< 1.06	1.51 (1.36, 1.69)	< 0.0001	1.63 (1.46, 1.81)	< 0.0001	1.19 (1.06, 1.33)	0.0023
≥1.06, < 1.14	1.0(ref)		1.0(ref)		1.0(ref)	
≥1.14	0.92 (0.82, 1.03)	NS	0.91 (0.81, 1.02)	NS	0.96 (0.85, 1.08)	NS
90-day all-cause mortality						
tCa, tertiles, mg/dl						
< 7.9	1.20 (1.09, 1.31)	0.0002	1.29 (1.18, 1.42)	< 0.0001	0.97 (0.88, 1.08)	NS
≥7.9, < 8.7	1.0(ref)		1.0(ref)		1.0(ref)	
≥8.7	1.02 (0.93, 1.12)	NS	1.01 (0.92, 1.12)	NS	0.97 (0.88, 1.07)	NS
iCa, tertiles, mmol/l						
< 1.06	1.43 (1.30, 1.57)	< 0.0001	1.56 (1.42, 1.71)	< 0.0001	1.15 (1.05, 1.27)	0.0042
≥1.06, < 1.14	1.0(ref)		1.0(ref)		1.0(ref)	
≥1.14	0.99 (0.90, 1.09)	NS	0.97 (0.88, 1.07)	NS	1.03 (0.93, 1.14)	NS
365-day all-cause mortality						
tCa, tertiles, mg/dl						
< 7.9	1.19 (1.09, 1.29)	< 0.0001	1.29 (1.19, 1.41)	< 0.0001	1.02 (0.94, 1.12)	NS
≥7.9, < 8.7	1.0(ref)		1.0(ref)		1.0(ref)	
≥8.7	1.06 (0.98, 1.15)	NS	1.05 (0.96, 1.14)	NS	1.00 (0.92, 1.09)	NS
iCa, tertiles, mmol/l						
< 1.06	1.30 (1.20, 1.41)	< 0.0001	1.44 (1.32, 1.56)	< 0.0001	1.10 (1.01, 1.20)	0.0284
≥1.06, < 1.14	1.0(ref)		1.0(ref)		1.0(ref)	
≥1.14	0.95 (0.87, 1.03)	NS	0.92 (0.85, 1.01)	NS	0.98 (0.90, 1.07)	NS

Models were derived from Cox proportional hazards regression models.
Non-adjusted model adjust for: none.
Adjust I model adjust for: age, ethnicity and gender.
Adjust II model adjust for: age, ethnicity, gender, renal disease, liver disease, coronary artery disease, stroke, failure of respiration, ARDS, pneumonia, heart rate, systolic blood pressure, diastolic blood pressure, respiration rate, SPO2, SOFA, SAPSII, bicarbonate, creatinine, chloride, glucose, hemoglobin, platelet, potassium, BUN, WBC.

sequential organ failure assessment (SOFA) score [21], and simplified acute physiology score II (SAPSII) [22] were calculated for each patient. The other data included age, gender, ethnicity, vital signs, ICU length of stay, AKI stage. Only the data for the first ICU admission of each patient were used and baseline data were extracted within 24 h after ICU admission. Death data were obtained from the US government's Social Security Death Index records. The endpoints of our study were 30, 90 and 365-day all-cause mortality.

2.4. Statistical analysis

Baseline characteristics of all patients were stratified by ionized calcium tertiles, and continuous variables were presented as mean ± SD or medians and interquartile range (IQR). Categorical data were summarized as number or percentage and were compared using the chi-squared test. Cox proportional hazards models were constructed on the basis of tCa and iCa group inclusion according to tertiles to examine the relationship between each endpoint and baseline covariates. The second tertile was as a reference, and the results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

We used 2 multivariate models for 30, 90 and 365-day all-cause mortality to facilitate clinical interpretation of our results. In model I, covariates were adjusted for age, ethnicity and gender. In model II, we further adjusted for age, ethnicity, gender, renal disease, liver disease, CAD, stroke, failure of respiration, ARDS, pneumonia, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiration rate, SPO2, SOFA, SAPSII, bicarbonate, creatinine, chloride, glucose, hemoglobin, platelet, potassium, BUN, WBC. Variables based on epidemiological and biological background were incorporated as potential confounders, and these confounders basing on a change in effect estimate of > 10% were used to obtain an adjusted model.

Subgroup analyses were performed to access the association between the serum total and ionized calcium and 30-day all-cause mortality, including CHF, AFIB, CAD, stroke, malignancy, liver disease, renal disease, respiratory failure, pneumonia, COPD, ARDS, sodium, potassium, chloride, WBC, platelet, hematocrit, creatinine, BUN, anion gap, bicarbonate, glucose, SBP, DBP, mean blood pressure (MBP), heart rate, respiratory rate, temperature, SPO2, SOFA score, and SAPSII score. The data were analyzed using the EmpowerStats ver 2.17.8 (http://www.empowerstats.com/cn/, X&Y solutions, Inc., Boston, MA) and R software vers 3.42. A $P < .05$ was considered statistically significant and all probability values were 2-sided.

3. Results

3.1. Subject characteristics

A total of 10,207 eligible patients were enrolled in our study. Characteristics of these patients stratified by iCa tertiles were displayed in Table 1. A total of 3128 patients were in the low-iCa group (< 1.06 mmol/l), 3433 patients were in the mid-iCa group (1.06–1.14 mmol/l), and 3646 patients were in the high-iCa group (≥1.14 mmol/l). There were 5996 men and 4211 women with a mean age of 63.9 ± 17.3 years. Patients with high-iCa concentrations were more likely to be elderly with a history of CAD, CHF, AFIB, renal disease and COPD. Participants with low-iCa concentrations had faster heart and respiratory rates, higher glucose, BUN, anion gap, SOFA scores, SAPSII scores, mortality, as well as higher comorbidities of liver disease and respiratory failure.

Table 3
Subgroup analysis of the associations between ionized calcium and 30-day all-cause mortality.

	No. of patients	Ionized calcium levels (mmol/l)			*P* for interaction
		< 1.06	≥1.06, < 1.14	≥1.14	
CHF					0.0184
No	8769	1.68 (1.50, 1.89)	1.0(ref)	0.91 (0.80, 1.03)	
Yes	1438	1.15 (0.84, 1.56)	1.0(ref)	0.94 (0.71, 1.25)	
AFIB					NS
No	7297	1.59 (1.39, 1.81)	1.0(ref)	0.94 (0.81, 1.08)	
Yes	2910	1.72 (1.43, 2.07)	1.0(ref)	0.86 (0.71, 1.04)	
CAD					< 0.0001
No	7564	1.45 (1.29, 1.64)	1.0(ref)	1.04 (0.91, 1.18)	
Yes	2643	2.23 (1.75, 2.84)	1.0(ref)	0.72 (0.56, 0.93)	
Stroke					NS
No	9182	1.69 (1.50, 1.90)	1.0(ref)	0.91 (0.80, 1.03)	
Yes	1025	1.38 (1.04, 1.82)	1.0(ref)	0.90 (0.68, 1.19)	
Malignancy					0.0005
No	8296	1.70 (1.50, 1.92)	1.0(ref)	0.85 (0.74, 0.97)	
Yes	1911	1.39 (1.10, 1.76)	1.0(ref)	1.16 (0.92, 1.47)	
Liver disease					NS
No	9454	1.56 (1.39, 1.75)	1.0(ref)	0.88 (0.78, 0.99)	
Yes	753	1.87 (1.35, 2.60)	1.0(ref)	1.43 (0.98, 2.09)	
Renal disease					0.0195
No	8953	1.70 (1.51, 1.91)	1.0(ref)	0.89 (0.79, 1.02)	
Yes	1254	1.22 (0.91, 1.64)	1.0(ref)	0.98 (0.74, 1.29)	
Respiratory failure					0.0001
No	5921	1.83 (1.54, 2.17)	1.0(ref)	0.84 (0.70, 1.02)	
Yes	4286	1.38 (1.20, 1.58)	1.0(ref)	1.00 (0.87, 1.16)	
Pneumonia					< 0.0001
No	7445	2.02 (1.77, 2.31)	1.0(ref)	0.82 (0.71, 0.95)	
Yes	2762	1.00 (0.83, 1.21)	1.0(ref)	1.08 (0.91, 1.29)	
COPD					NS
No	10,011	1.64 (1.47, 1.83)	1.0(ref)	0.90 (0.80, 1.01)	
Yes	196	0.91 (0.40, 2.11)	1.0(ref)	1.15 (0.58, 2.26)	
ARDS					NS
No	10,014	1.62 (1.45, 1.80)	1.0(ref)	0.90 (0.80, 1.01)	
Yes	193	2.11 (1.02, 4.38)	1.0(ref)	1.31 (0.60, 2.84)	
Sodium, mmol/l					NS
< 136	4417	1.59 (1.35, 1.88)	1.0(ref)	0.88 (0.74, 1.06)	
≥136	5788	1.66 (1.44, 1.91)	1.0(ref)	0.93 (0.80, 1.08)	
Potassium, mmol/l					NS
< 3.7	5065	1.68 (1.43, 1.96)	1.0(ref)	0.90 (0.75, 1.07)	
≥3.7	5140	1.63 (1.40, 1.89)	1.0(ref)	0.91 (0.78, 1.06)	
Chloride, mmol/l					NS
< 99	4743	1.53 (1.31, 1.77)	1.0(ref)	0.95 (0.81, 1.12)	
≥99	5461	1.73 (1.48, 2.02)	1.0(ref)	0.87 (0.74, 1.03)	
WBC, 10^9 /l					NS
< 9.8	5079	1.96 (1.66, 2.31)	1.0(ref)	0.99 (0.83, 1.19)	
≥9.8	5116	1.39 (1.20, 1.60)	1.0(ref)	0.84 (0.72, 0.97)	
Platelet, 10^9/l					0.0178
< 171	5064	1.83 (1.58, 2.13)	1.0(ref)	0.85 (0.72, 1.01)	
≥171	5130	1.33 (1.13, 1.57)	1.0(ref)	0.97 (0.83, 1.13)	
Hematocrit, %					0.0004
< 28.2	5091	1.86 (1.59, 2.18)	1.0(ref)	0.80 (0.67, 0.96)	
≥28.2	5111	1.45 (1.24, 1.69)	1.0(ref)	1.00 (0.86, 1.16)	
Creatinine, mEq/l					NS
< 1.0	5036	1.68 (1.40, 2.02)	1.0(ref)	0.91 (0.75, 1.11)	
≥1.0	5169	1.51 (1.32, 1.72)	1.0(ref)	0.90 (0.78, 1.04)	
BUN, mg/dl					NS
< 19	4966	1.78 (1.46, 2.16)	1.0(ref)	0.94 (0.76, 1.16)	
≥19	5238	1.50 (1.31, 1.70)	1.0(ref)	0.89 (0.78, 1.02)	
Anion gap, mmol/l					NS
< 13	4876	1.59 (1.31, 1.93)	1.0(ref)	0.83 (0.68, 1.01)	
≥13	5208	1.50 (1.32, 1.71)	1.0(ref)	0.98 (0.85, 1.13)	
Bicarbonate, mg/dl					NS
< 21	4391	1.41 (1.23, 1.61)	1.0(ref)	0.90 (0.77, 1.06)	
≥21	5810	1.48 (1.24, 1.78)	1.0(ref)	1.00 (0.85, 1.18)	
Glucose, mg/dl					NS
< 136.8	5087	1.78 (1.50, 2.12)	1.0(ref)	0.88 (0.74, 1.05)	
≥136.8	5088	1.48 (1.29, 1.71)	1.0(ref)	0.96 (0.83, 1.12)	
SBP, mmHg					0.0123
< 116	5078	1.83 (1.59, 2.10)	1.0(ref)	0.92 (0.79, 1.07)	
≥116	5079	1.30 (1.10, 1.55)	1.0(ref)	0.89 (0.75, 1.06)	
DBP, mmHg					NS
< 59	5078	1.70 (1.47, 1.96)	1.0(ref)	0.87 (0.75, 1.02)	
≥59	5078	1.54 (1.31, 1.82)	1.0(ref)	0.94 (0.79, 1.12)	

(*continued on next page*)

Table 3 (*continued*)

	No. of patients	Ionized calcium levels (mmol/l)			*P* for interaction
		< 1.06	≥1.06, < 1.14	≥1.14	
MBP, mmHg					0.0407
< 77	5088	1.81 (1.58, 2.08)	1.0(ref)	0.84 (0.73, 0.98)	
≥77	5089	1.38 (1.16, 1.64)	1.0(ref)	0.99 (0.83, 1.18)	
Heart rate, beats/min					NS
< 87	5088	1.58 (1.34, 1.87)	1.0(ref)	0.94 (0.80, 1.11)	
≥87	5089	1.58 (1.37, 1.82)	1.0(ref)	0.88 (0.75, 1.03)	
Respiratory rate, beats/min					NS
< 18	5082	1.62 (1.34, 1.96)	1.0(ref)	0.86 (0.71, 1.05)	
≥18	5088	1.55 (1.36, 1.76)	1.0(ref)	0.94 (0.82, 1.09)	
Temperature,° C					NS
< 36.9	4974	1.65 (1.43, 1.90)	1.0(ref)	0.86 (0.74, 1.00)	
≥36.9	4978	1.50 (1.27, 1.78)	1.0(ref)	0.97 (0.81, 1.16)	
SPO2, %					NS
< 97.9	5082	1.78 (1.54, 2.05)	1.0(ref)	0.97 (0.83, 1.13)	
≥97.9	5088	1.46 (1.23, 1.72)	1.0(ref)	0.81 (0.68, 0.97)	
SOFA score					NS
< 5	4455	1.29 (1.03, 1.61)	1.0(ref)	0.92 (0.75, 1.14)	
≥5	5752	1.58 (1.39, 1.79)	1.0(ref)	0.90 (0.78, 1.03)	
SAPSII score					NS
< 39	4990	1.41 (1.10, 1.81)	1.0(ref)	0.97 (0.76, 1.23)	
≥39	5217	1.43 (1.27, 1.61)	1.0(ref)	0.90 (0.79, 1.03)	

CHF: congestive heart failure; AFIB: atrial fibrillation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; SOFA: sequential organ failure assessment; SAPSII: simplified acute physiology score II.

3.2. Association between serum tCa and iCa concentrations and clinical endpoints

In multivariate analysis, we analyzed tCa and iCa concentrations, also stratified by tertiles, to determine whether tCa and iCa were independently-associated with all-cause mortality (Table 2). In model I, adjusted for age, ethnicity and gender, compared with the referent group (tCa: 7.9–8.7 mg/dl, iCa: 1.06–1.14 mmol/l), both low-tCa (< 7.9 mg/dl) and low-iCa (< 1.06 mmol/l) concentrations were significant predictors of risk of 30-day, 90-day and 365-day all-cause mortality. The HRs (95% CIs) for tCa were 1.35 (1.22, 1.51), 1.29 (1.18, 1.42), 1.29 (1.19, 1.41) and for iCa were 1.63 (1.46, 1.81), 1.56 (1.42, 1.71), 1.44 (1.32, 1.56). In model II, after adjusting for age, ethnicity, gender, renal disease, liver disease, CAD, stroke, failure of respiration, ARDS, pneumonia, heart rate, SBP, DBP, respiration rate, SPO2, SOFA, SAPSII, bicarbonate, creatinine, chloride, glucose, hemoglobin, platelet, potassium, BUN, and WBC, low-iCa concentrations remained a significant predictor of all-cause mortality at 30 days, 90 days, 365 days (HR, 95% CI: 1.19, 1.06–1.33; 1.15, 1.05–1.27; 1.10, 1.01–1.20).

3.3. Subgroup analyses

We performed subgroup analyses to assess the association between the serum iCa concentrations and 30-day all-cause mortality (Table 3). There was no interaction in most strata (P = .0532–0.6288). Only patients with CAD showed a decreased risk with a high-iCa (HR 0.72, 95% CI 0.56–0.93).

4. Discussion

We evaluated 10,207 patients to measure the association of admission serum total and ionized calcium with all-cause mortality in critically ill patients with AKI. In multivariate analysis, adjusted for age, ethnicity and gender, low-tCa (< 7.9 mg/dl) and low-iCa (< 1.06 mmol/l) concentrations were significant predictors of risk of 30-day, 90-day and 365-day all-cause mortality. Furthermore, after adjusting for more confounding factors, only low-iCa concentrations were independent predictors of all-cause mortality.

AKI is a common, dangerous, costly and severe syndrome encompassing various etiologies [1] including specific kidney diseases, non-specific conditions and extrarenal pathologies. The common specific etiologies include acute glomerular renal diseases, ischemia injury and acute postrenal obstructive nephropathy [19]. Patients with AKI often fail to restore renal function and require long-term dialysis. Long-term mortality may be increased, especially in those with persistent renal insufficiency [23,24]. In fact, as a syndrome, it includes patients whose have no actual damage to the kidney but are functionally impaired with respect to physiological needs. This means that AKI includes reversible injury and these patients may benefit from early intervention. Thus, finding an ideal biomarker for the prognosis of acute kidney injury is significant.

Previous studies have reported that hypercalcemia leads to arteriosclerosis [25,26], and is associated with an increased risk of heart failure in patients with type 2 diabetes [27]. Currently, calcium alone is not only consistently associated with cardiovascular outcomes, and much attention has been focused on the association between the incidence of AKI and calcium metabolism disorders [17]. There are several possible explanations for this association. Calcium plays a vital role in almost all biological processes, including enzyme activity and contraction of vascular smooth muscle [10,28,29]. Several studies indicated that hypocalcemia was associated with poor left ventricular ejection fraction [30–32], liquid capacity overload [33]; hypercalcinemia led to calcium salt deposition in renal tubules and/or interstitial tissue, resulting in renal dysfunction [12,34]. All these may be causes of AKI. The findings of our study demonstrated that low-iCa concentrations on admission were independently associated with an increase in all-cause mortality. These may be related to the evolution of critical illness. Due to the skeletal resistance to parathyroid hormone, hypocalcemia usually occurs in the early stages of the process, and later release of calcium from necrotic muscle can cause hypercalcemia [35]. In subgroup analysis, there was no interaction in most strata. This suggests that the heterogeneity of clinical factors among those effects and the iCa was relatively small.

The major strength of our study was that it was, to the best of our knowledge, the first to investigate the association between serum total and ionized calcium and all-cause mortality of AKI. Moreover, we selected 30, 90 and 365-day all-cause mortality as adverse outcomes.

This study had several limitations. First, we measured tCa and iCa in

patients only upon admission to the ICU and did not assess changes during the ICU stay. Single serum calcium measurements did not reflect the time course of changes in calcium, and these may possibly influence the summary results. Second, we did not know the calcium concentrations of patients before admitting to the ICU, and whether they were treated with calcium, possibly affecting calcium values. Third, several important clinical indicators, such as serum albumin, are seriously missing, which may affect the result analysis. Fourth, although every effort had been made to adjust for confounding factors using multivariate analysis, there remained other unknown factors that confused the prognostic value of tCa and iCa. Finally, as a single-center retrospective study, selection bias was inevitable; therefore, multicenter registry, prospective studies are needed to confirm these findings.

5. Conclusions

Low-iCa concentrations were independent predictors of all-cause mortality in critically ill patients with AKI. Further studies, especially large prospective studies, are needed to confirm this relationship and validate its clinical significance.

Data availability

The clinical data used to support the findings of this study were supplied by Monitoring in Intensive Care Database III version 1.4 (MIMIC-III v.1.4). Although the database is publicly and freely available, researchers must complete the National Institutes of Health's web-based course known as Protecting Human Research Participants to apply for permission to access the database.

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Competing interests

The authors declare that they have no competing interests.

References

[1] N.S. Kanagasundaram, Pathophysiology of ischaemic acute kidney injury, Ann. Clin. Biochem. 52 (2015) 193, https://doi.org/10.1177/0004563214556820 Pt 2.
[2] U. Shigehiko, J.A. Kellum, B. Rinaldo, G.S. Doig, M. Hiroshi, M. Stanislao, S. Miet, T. Ian, B. Catherine, M. Ettiene, Acute renal failure in critically ill patients: a multinational, multicenter study, JAMA J. Am. Med. Assoc. 294 (7) (2005) 813–818.
[3] J.G.M. Hofhuis, H.F. Stel, Schrijvers A.J.P. Van, J.H. Rommes, P.E. Spronk, The effect of acute kidney injury on long-term health-related quality of life: a prospective follow-up study, Crit. Care 17 (1) (2013) R17, https://doi.org/10.1186/cc12491.
[4] L.E. White, H.T. Hassoun, A. Bihorac, L.J. Moore, R.M. Sailors, B.A. Mckinley, A. Valdivia, F.A. Moore, Acute kidney injury is surprisingly common and a powerful predictor of mortality in surgical sepsis, J. Trauma Acute Care Surg. 75 (3) (2013) 432–438, https://doi.org/10.1097/TA.0b013e31829de6cd.
[5] E.M. Levy, C.M. Viscoli, R.I. Horwitz, The effect of acute renal failure on mortality. A cohort analysis, Jama 275 (19) (1996) 1489, https://doi.org/10.1001/jama.1996.03530430033035.
[6] G.M. Chertow, E.M. Levy, K.E. Hammermeister, F. Grover, J. Daley, Independent association between acute renal failure and mortality following cardiac surgery, Am. J. Med. 104 (4) (1998) 343–348, https://doi.org/10.1016/S0002-9343(98)00058-8.
[7] A.X. Garg, K. Andrea, D.I. Sessler, C. Meaghan, R. Andrea, M. Marko, C.R. Parikh, M. Richard, P.M. Jones, T. Maria, Perioperative aspirin and clonidine and risk of acute kidney injury: a randomized clinical trial, Jama 312 (21) (2014) 2254–2264, https://doi.org/10.1001/jama.2014.15284.
[8] F.P. Wilson, M. Shashaty, J. Testani, I. Aqeel, Y. Borovskiy, S.S. Ellenberg, H.I. Feldman, H. Fernandez, Y. Gitelman, J. Lin, Automated, electronic alerts for acute kidney injury: a single-blind, parallel-group, randomised controlled trial, Lancet 385 (9981) (2015) 1966–1974, https://doi.org/10.1016/S0140-6736(15)60266-5.
[9] J. Hästbacka, V. Pettilä, Prevalence and predictive value of ionized hypocalcemia among critically ill patients, Acta Anaesthesiol. Scand. 47 (10) (2010) 1264–1269.
[10] R.D. Collage, G.M. Howell, Z. Xianghong, J.L. Stripay, J.S. Lee, D.C. Angus, M.R. Rosengart, Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase kinase signaling, Crit. Care Med. 41 (11) (2013) E352–E360.
[11] N. Mikhail, A. El-Bialy, J. Grosser, Severe hypocalcemia: a rare cause of reversible heart failure, Congest. Heart Failure 7 (5) (2010) 256–263.
[12] J.M. Kruger, C.A. Osborne, R.F. Nachreiner, K.R. Refsal, Hypercalcemia and renal failure. Etiology, pathophysiology, diagnosis, and treatment, Vet. Clin. North Am. Small Anim. Pract. 26 (6) (1996) 1417–1445, https://doi.org/10.1016/S0195-5616(96)50135-X.
[13] E. Moritoki, K. Inbyung, N. Alistair, S. Edward, C.J. French, G.K. Hart, H. Colin, B. Michael, B. Rinaldo, Ionized calcium concentration and outcome in critical illness, Crit. Care Med. 39 (2) (2011) 314–321.
[14] A. Kelly, M.A. Levine, Hypocalcemia in the critically ill patient, J. Intensive Care Med. 28 (3) (2011) 166.
[15] R.N. Dickerson, N.Y. Henry, P.L. Miller, M. Gayle, R.O. Brown, Low serum total calcium concentration as a marker of low serum ionized calcium concentration in critically ill patients receiving specialized nutrition support, Nutr. Clin. Pract. 22 (3) (2007) 323.
[16] B. Wang, Y. Gong, B. Ying, B. Cheng, Association of initial serum total calcium concentration with mortality in critical illness, Biomed. Res. Int. 2018 (2018) 11):1–8.
[17] C. Thongprayoon, W. Cheungpasitporn, M.A. Mao, A. Sakhuja, S.B. Erickson, Admission calcium concentrations and risk of acute kidney injury in hospitalised patients, Int. J. Clin. Pract. 72 (Suppl. 2) (2018) e13057.
[18] A.E.W. Johnson, T.J. Pollard, L. Shen, L.H. Lehman, M. Feng, M. Ghassemi, B. Moody, P. Szolovits, L.A. Celi, R.G. Mark, MIMIC-III, a freely accessible critical care database, Sci. Data 3 (2016) 160035, , https://doi.org/10.1038/sdata.2016.35.
[19] A K, KDIGO clinical practice guidelines for acute kidney injury, Nephron Clin. Pract. 120 (4) (2012) 179–184.
[20] B. Wang, H. Lu, Y. Gong, B. Ying, B. Cheng, The association between red blood cell distribution width and mortality in critically ill patients with acute kidney injury, Biomed. Res. Int. 2018 (2018) 9658216, , https://doi.org/10.1155/2018/4387689.
[21] J.L. Vincent, R. Moreno, J. Takala, S. Willatts, M.A. De, H. Bruining, C.K. Reinhart, P.M. Suter, L.G. Thijs, The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on Sepsis-related problems of the European society of intensive care medicine, Intensive Care Med. 22 (7) (1996) 707–710, https://doi.org/10.1007/BF01709751.
[22] J.R. Le Gall, S. Lemeshow, F. Saulnier, A new simplified acute physiology score (SAPS II) based on a European/north American multicenter study, Jama 270 (24) (1993) 2957–2963, https://doi.org/10.1001/jama.1993.03510240069035.
[23] S. Helmut, F. Rainald, Five-year outcomes of severe acute kidney injury requiring renal replacement therapy, Nephrol. Dial. Transplant. 23 (7) (2008) 2235.
[24] T. Pierre-Alain, M. Pierre-Yves, R. Jacques, P. Jerome, P. Thomas, S. Patrick, Long-term prognosis after acute kidney injury requiring renal replacement therapy, Nephrol. Dial. Transplant. 24 (7) (2009) 2186–2189.
[25] G. Schlieper, V. Brandenburg, Z. Djuric, T. Damjanovic, N. Markovic, L. Schurgers, T. Kruger, R. Westenfeld, D. Ackermann, A. Haselhuhn, et al., Risk factors for cardiovascular calcifications in non-diabetic Caucasian haemodialysis patients, Kidney Blood Press. Res. 32 (3) (2009) 161–168, https://doi.org/10.1159/000221064.
[26] S. Ribeiro, A. Ramos, A. Brandão, J.R. Rebelo, A. Guerra, C. Resina, A. Vila-Lobos, F. Carvalho, F. Remédio, F. Ribeiro, Cardiac valve calcification in haemodialysis patients: role of calcium-phosphate metabolism, Nephroldialtransplant 13 (8) (1998) 2037.
[27] J. Li, N. Wu, W. Dai, L. Jiang, Y. Li, S. Li, Z. Wen, Association of serum calcium and heart failure with preserved ejection fraction in patients with type 2 diabetes, Cardiovasc. Diabetol. 15 (1) (2016) 140.
[28] K. Michaelsson, H. Melhus, E. Warensjo Lemming, A. Wolk, L. Byberg, Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study, BMJ (Clin. Res. Ed.) 346 (2013) f228.
[29] S.D. Yan, X.J. Liu, Y. Peng, T.L. Xia, W. Liu, J.Y. Tsauo, Y.N. Xu, H. Chai, F.Y. Huang, M. Chen, et al., Admission serum calcium concentrations improve the GRACE risk score prediction of hospital mortality in patients with acute coronary syndrome, Clin. Cardiol. 39 (9) (2016) 516–523, https://doi.org/10.1002/clc.22557.
[30] S. Miura, A. Yoshihisa, T. Mai, T. Shimizu, Y. Nakamura, H. Yamauchi, S. Iwaya, T. Owada, M. Miyata, S. Abe, Association of Hypocalcemia with Mortality in hospitalized patients with heart failure and chronic kidney disease, J. Card. Fail. 21 (8) (2015) 621–627, https://doi.org/10.1016/j.cardfail.2015.04.015.
[31] K. Hurley, D. Baggs, Hypocalcemic cardiac failure in the emergency department, J. Emerg. Med. 28 (2) (2005) 155–159, https://doi.org/10.1016/j.jemermed.2004.06.014.
[32] A.S. Kazmi, B.M. Wall, Reversible congestive heart failure related to profound hypocalcemia secondary to hypoparathyroidism, Am J Med Sci 333 (4) (2007) 226–229.
[33] Steven N. Levine, Christopher N. Rheams, Hypocalcemic heart failure, Am. J. Med. 78 (6) (1985) 1033–1035, https://doi.org/10.1016/0002-9343(85)90228-1.
[34] S.E. Dumas, T.M. Grandys, A.W. Stern, E.F. Garrett, M.D. Ridgway, Primary hyperparathyroidism with chronic renal failure in a Vietnamese pot-bellied pig (sus scrofa), Vet. Q. 33 (4) (2013) 195, https://doi.org/10.1080/01652176.2013.864429.
[35] S.G. Massry, Skeletal resistance to the calcaemic action of parathyroid hormone in uraemia: a mechanism for the hypocalcaemia and secondary hyperparathyroidism of chronic renal failure, Clin. Endocrinol. 5 (s1) (2010) s317–s325.