Predictive Value of Ionized Calcium in Critically Ill Patients: An Analysis of a Large Clinical Database MIMIC II

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Abstract

Background and Objective: ionized calcium (iCa) has been investigated for its association with mortality in intensive care unit (ICU) patients in many studies. However, these studies are small in sample size and the results are conflicting. The present study aimed to establish the association of iCa with mortality by using a large clinical database.

Methods: Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) database was used for analysis. Patients older than 15 years were eligible, and patients without iCa measured during their ICU stay were excluded. Demographic data and clinical characteristics were extracted and compared between survivors and non-survivors. iCa measure on ICU admission was defined as Ca₀. Caₘₐₓ was the maximum iCa during ICU stay; Caₘᵢₙ was the minimum value of iCa during the ICU stay; Caₘₑₐₜ was the arithmetic mean iCa during ICU stay.

Main results: A total of 15409 ICU admissions satisfied our inclusion criteria and were included in our analysis. The prevalence of hypocalcemia on ICU entry was 62.06%. Ca₀ was significantly lower in non-survivors than in survivors (1.11±0.14 vs. 1.13±0.10 mmol/l, p<0.001). In multivariate analysis, moderate hypocalcemia in Ca₀ was significantly associated with increased risk of death (OR: 1.943; 95% CI: 1.340–2.817), and mild hypercalcemia was associated with lower mortality (OR: 0.400–0.767). While moderate and mild hypocalcemia in Caₘₑₐₜ is associated with increased risk of death (OR: 1.153, 95% CI: 1.006–1.322 and OR: 2.520, 95% CI: 1.485–4.278), hypercalcemia in Caₘₑₐₜ is not significantly associated with ICU mortality.

Conclusion: The relationship between Ca₀ and clinical outcome follows an “U” shaped curve with the nadir at the normal range, extending slightly to hypercalcemia. Mild hypercalcemia in Ca₀ is protective, whereas moderate and mild hypocalcemia in Caₘₑₐₜ is associated with increased risk of death.

Introduction

Derangement in ionized calcium (iCa) is common in both surgical and medical patient requiring intensive care unit (ICU) admission. ICU patients are critically ill and multiple mechanisms underline the pathophysiological pathways of calcium derangement. Hypocalcemia is thought to be caused by the following mechanisms: i) increased fecal and/or urinary excretory Ca²⁺ losses in the presence of fixed dietary Ca²⁺ intake; ii) catecholamine-mediated translocation of plasma Ca²⁺ into tissues; and iii) reduced dietary Ca²⁺, often in association with vitamin D deficiency.[1] In critically ill patients, heart failure and hyperadrenergic states are the most commonly seen disorders that have been proven to be associated with calcium derangements.[2,3]

Laboratory measurement of ionized calcium is readily available in most modern ICUs and thus the determination of its clinical significance has both prognostic and therapeutic values. For instance, if iCa is associated with clinical outcome, will therapeutic interventions aiming to restore calcium homeostasis be beneficial for ICU patients? Many preliminary investigations have been conducted to examine the prognostic value of iCa in critically ill patients. However, these studies are relatively small in sample size and their results were conflicting.[4–6] In the present study, we aimed to determine the association of iCa and clinical outcome by using a large clinical database named Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II).[7] We hypothesized that derangement in iCa was associated with altered ICU mortality.

Method

The Database

The MIMIC II (version 2.6) clinical database consisted of more than 30,000 ICU patients (medical, surgical, coronary care and neonatal) admitted to Beth Israel Deaconess Medical Center (Boston, MA) from 2001 to 2008. The establishment of the
Camean remaining in the model. The significance level for selection and backward elimination technique, with Ca0 and Camax was not statistically different between survivors and non-survivors (1.11 vs 1.14 mmol/L, p = 0.10 mmol/l, p = 0.002). As expected, SOFA and SAPS-1 scores were both significantly higher in non-survivors than in survivors (59.7% vs 55.7%, p < 0.001), coagulopathy (9.26% vs 6.19%, p < 0.001), and renal failure (8.11% vs 5.63%, p = 0.002). Furthermore, “mild” hypocalcemia was defined as mild, moderate and severe as 0.9–1.15, 0.8–0.9 and <0.8 mmol/L, respectively. Hypercalcemia was divided into mild, moderate and severe as 1.25–1.35, 1.35–1.45 and >1.45 mmol/L, respectively.[11,12] Potential multicollinearity between covariates in the model were quantified by using variance inflation factor (VIF) which provided an index that measures how much the variance of an estimated regression coefficient is increased because of collinearity.[13] As a common rule of thumb, a VIF >5 was considered for the existence of multicollinearity. Furthermore, iCa was categorized into intervals and incorporated into regression models as design variable. Design variable, also known as dummy variable, is one that takes the value of 0 or 1 to indicate the presence or absence of some categorical effect that is expected to shift the outcome. It is frequent used for categorical variables with more than two categories. Normal range between 1.15 and 1.25 mmol/l was used as reference and ORs were reported for other intervals. Receiver operating characteristic curve (ROC) was depicted to show the diagnostic performance of fitted logistic regression models.

All statistical analyses were performed using the software STATA 11.2 (College Station, Texas 77845 USA). Two-tailed p<0.05 was considered to be statistically significant.

Results

A total of 15409 ICU admissions satisfied our inclusion criteria and were included in our analysis. Nine thousand five hundred and sixty-three (62.1%) patients had hypocalcemia on ICU admission, in which there were 105 patients with severe hypocalcemia, 265 with moderate hypocalcemia and 9193 with mild hypocalcemia. One thousand two hundred and seven (7.8%) patients had hypercalcemia on admission, including 865, 226 and 116 patients in respective mild, moderate and severe hypercalcemia groups. There were 13754 survivors and 1655 non-survivors during ICU stay, with the ICU mortality rate of 10.7% (Table 1). Non-survivors were significantly older than survivors (69.0 ±16.2 vs 64.0±19.9 years, p<0.001), and there were more male patients in survivors than that in non-survivors (59.7% vs 55.7%, p = 0.002). As expected, SOFA and SAPS-1 scores were both significantly higher in non-survivors than in survivors (10.1±4.6 vs 7.2±3.7, p<0.001; 19.7±5.6 vs 15.6±4.9, p<0.001). Comorbidities were significantly different between survivors and non-survivors. There were more patients with congestive heart failure (27.77% vs 19.88%, p<0.001), renal failure (8.11% vs 5.63%, p<0.001), coagulopathy (9.26% vs 6.19%, p<0.001), and weight loss (4.05% vs 3.11%, p = 0.039) in non-survivors than in survivors. On the contrary, there were less patients with uncomplicated diabetes (17.60% vs 20.13%, p=0.015) and obesity (0.85% vs 2.05%, p<0.001) in non-survivors than in survivors. Patients admitted to CCU (22.30% vs 14.68%, p<0.001) and MICU (48.28% vs 29.66%, p<0.001) were more likely to die, whereas patients in CSRU (24.17% vs 50.31%, p<0.001) were less likely to die. Ca0 was significantly lower in non-survivors than in survivors (1.11±0.14 vs 1.13±0.10 mmol/l, p<0.001). Camean was also significantly lower in non-survivors than in survivors (1.11±0.15 vs 1.14±0.19 mmol/l, p<0.001). Camax was not statistically different between survivors and non-survivors.

Table 2 displays the main effect model built by using stepwise forward selection and backward elimination technique for Ca0 and
## Table 1. Characteristics between intensive care unit survivors and non-survivors.

| Characteristics                        | Survivors (n = 13754) | Non-survivors (n = 1655) | p       |
|---------------------------------------|-----------------------|--------------------------|---------|
| Age (years)                           | 64.0 ± 19.9           | 69.0 ± 16.2              | < 0.001 |
| Sex (male, %)                         | 8205 (59.7%)          | 921 (55.7%)              | 0.002   |
| SAPS-I on admission                   | 15.6 ± 4.9            | 19.7 ± 5.6               | < 0.001 |
| SOFA on admission                     | 7.2 ± 3.7             | 10.1 ± 4.6               | < 0.001 |
| Comorbidity (n, %)                    |                       |                          |         |
| Congestive heart failure              | 2731 (19.88%)         | 459 (27.77%)             | < 0.001 |
| Paralysis                             | 198 (1.44%)           | 28 (1.69%)               | 0.420   |
| Renal failure                         | 773 (5.63%)           | 134 (8.11%)              | < 0.001 |
| Uncomplicated diabetes                | 2766 (20.13%)         | 291 (17.60%)             | 0.015   |
| Complicated diabetes                  | 738 (5.37%)           | 87 (5.26%)               | 0.853   |
| Coagulopathy                          | 815 (6.19%)           | 153 (9.26%)              | < 0.001 |
| AIDS                                  | 78 (0.57%)            | 12 (0.73%)               | 0.425   |
| Chronic pulmonary disease             | 2254 (16.41%)         | 285 (17.24%)             | 0.387   |
| Obesity                               | 281 (2.05%)           | 14 (0.85%)               | < 0.001 |
| Weight loss                           | 427 (3.11%)           | 67 (4.05%)               | 0.039   |
| Types of care unit (n, %)             |                       |                          |         |
| CCU                                   | 2019 (14.68%)         | 369 (22.30%)             | < 0.001 |
| CSRU                                  | 6919 (50.31%)         | 400 (24.17%)             | < 0.001 |
| MICU                                  | 4080 (29.66%)         | 799 (48.28%)             | < 0.001 |
| SICU                                  | 736 (5.35%)           | 87 (5.26%)               | 0.872   |
| Ionized calcium (mmol/l)              |                       |                          |         |
| Ca₀                                   | 1.13 ± 0.10           | 1.11 ± 0.14              | < 0.001 |
| Caₘₐₑₐₜ                                | 1.14 ± 0.19           | 1.11 ± 0.15              | < 0.001 |
| Caₘₜₙₐₓ                                | 1.26 ± 1.86           | 1.27 ± 2.05              | 0.577   |
| Caₘₚₑₐₜ                                | 1.04 ± 0.12           | 1.00 ± 0.15              | < 0.001 |

Abbreviations: CCU, coronary care unit; CSRU, cardiac surgery care units; MICU, medical intensive care unit; SICU, surgical intensive care unit; SOFA, sequential organ failure assessment; SAPS, Simplified Acute Physiology Score.

doi:10.1371/journal.pone.0095204.t001

## Table 2. Main effect model derived using stepwise forward selection and backward elimination technique.

| Model 1 | Model 2 |
|---------|---------|
| Variable | Odds ratio | 95% CI | p   | Variable | Odds ratio | 95% CI | p   |
| Ca₀      | 0.317    | 0.187–0.540 | <0.001 | Caₘₑₐₜ | 0.288 | 0.140–0.591 | 0.001 |
| Age      | 1.008    | 1.005–1.011 | <0.001 | Age    | 1.008 | 1.005–1.011 | <0.001 |
| Sex      | 1.104    | 0.979–1.245 | 0.107 | Sex    | 1.101 | 0.977–1.243 | 0.116 |
| SAPS-I   | 1.110    | 1.093–1.127 | <0.001 | SAPS-I | 1.109 | 1.093–1.126 | <0.001 |
| SOFA     | 1.126    | 1.104–1.148 | <0.001 | SOFA   | 1.126 | 1.105–1.148 | <0.001 |
| Congestive heart failure              | 1.147    | 0.998–1.317 | 0.053 | Congestive heart failure | 1.145 | 0.997–1.315 | 0.055 |
| Paralysis                            | 1.399    | 0.914–2.142 | 0.122 | Paralysis | 1.402 | 0.916–2.145 | 0.120 |
| CSRU                                 | 0.277    | 0.236–0.325 | <0.001 | CSRU | 0.280 | 0.238–0.329 | <0.001 |
| Uncomplicated diabetes                | 0.798    | 0.683–0.933 | 0.005 | Uncomplicated diabetes | 0.799 | 0.684–0.934 | 0.005 |
| Complicated diabetes                  | 0.791    | 0.597–1.047 | 0.101 | Complicated diabetes | 0.792 | 0.598–1.049 | 0.104 |
| MICU                                 | 1.106    | 0.957–1.277 | 0.171 | MICU   | 1.111 | 0.962–1.283 | 0.153 |
| Obesity                              | 0.624    | 0.352–1.104 | 0.105 | Obesity | 0.615 | 0.347–1.091 | 0.096 |

Note: The variance inflation factor (VIF) for model 1 is 1/(1−R²) = 1/(1−0.1661) = 1.199; and for model 2 is 1/(1−R²) = 1/(1−0.1657) = 1.199.

Abbreviations: SOFA, sequential organ failure assessment; SAPS, Simplified Acute Physiology Score; CSRU, cardiac surgery care units; MICU, medical intensive care unit.

doi:10.1371/journal.pone.0095204.t002
Camean. Both models contained the same variables, including age, sex, SAPS-1, SOFA, congestive heart failure, paralysis, CSRU, uncomplicated diabetes, MICU and obesity were remained in the model. Figure 1 shows the relationship between iCa and logit transformed probability of death. The result showed that both Ca0 and Camean were non-linear in the model. We used linear spline function to explore the non-linear function. Furthermore, we divided iCa into categories and transformed it into design variable, with the normal range of 1.15–1.25 mmol/l as the reference group.

Table 3 shows the different adjusted odds ratios of iCa in different intervals. For Ca0<1.15, the odds ratios were less than 1, suggesting that the probability of ICU death decreased with increasing Ca0. The OR was 0.0006 between 1.25 and 1.35, indicating that mild hypercalcemia on ICU admission was associated with decreasing mortality. Severe hypercalcemia (>1.35 mmol/l) was associated with increased risk of death (OR: 3515.89 and 6.814 for each unit increase in iCa for the intervals 1.35–1.45 and >1.45, respectively). For Ca_mean in the range of 0.9–1.15 mmol/l, the OR was 0.016 (95% CI: 0.004–0.0581) for each unit increase in Ca_mean. Multicolinearity among covariates could be excluded in the model as reflected by a VIF of 1.204.

Table 4 shows the multivariable logistic regression model by incorporating iCa as design variable. The result showed that moderate hypocalcemia was significantly associated with increased risk of death (OR: 1.943; 95% CI: 1.340–2.817); and mild
Hypercalcemia was associated with lower mortality (OR: 0.553, 95% CI: 0.400–0.767). On the other hand, mild and severe hypocalcemia, moderate and severe hypercalcemia measured on ICU entry were not associated with altered ICU mortality. C_{mean} was also investigated for its association with mortality in the multivariate model. The results showed that both mild and moderate hypocalcemia were associated with significantly increased risk of death (OR: 1.153, 95% CI: 1.006–1.322; OR: 2.520, 95% CI: 1.485–4.278). Hypercalcemia was associated with increased risk of death, but statistical significance was not reached. Multicollinearity among covariates could be excluded in the models (VIF <5). Figure 2 displays the examination of diagnostic performance of fitted model by using ROC. The result showed that the diagnostic performances were moderately good with areas under ROC of around 0.78. A total of 139 patients had undergone RRT. Sensitivity analysis by excluding these patients did not significantly change the result (data not shown).

**Discussion**

The study shows that both C_{0} and C_{mean} are associated with altered ICU mortality in unselected critically ill patients, but in a complex form. To the best of our knowledge, this is the largest study to establish the linkage between derangement in iCa and mortality in mixed ICU patients. The finding that mild hypercalcemia provided protective effect on mortality suggests that calcium supplementation may potentially benefit critically ill patients.

One advantage of the study is the use of MIMIC II clinical database.[14] This database comprises high resolution clinical information of more than 30000 ICU admissions. The data comprising MIMIC-II was collected at the Beth Israel Deaconess Medical Center in Boston over an eight-year span from 2001 to 2008. Although there are other clinical databases available for research in critical care medicine,[15,16] MIMIC II is one of the largest clinical database that can provide high resolution clinical information. Most importantly, this database is freely available to public users. The advantage of using such existing database is that it represents the “real world” setting in which no strict study protocol has been performed in collecting data. In contrast, interventional trials have been criticized for its strict inclusion and exclusion criteria, its performance in specialized centers, and its management does not represent usual care.[17]

A recent study conducted by Steele T and colleagues failed to identify the association of hypocalcemia with mortality in a cohort of heterogeneous ICU patients (p = 0.33).[18] This study is small sample sized including only 1000 ICU admissions, which significantly compromises the statistical power of the study. Furthermore, the 28-day mortality rate is significantly lower in Steele’s study than that in our study. Most probably, the negative impact of hypocalcemia is only present in more severely ill patients. In another study by Egi M and colleagues,[12] they found that iCa on ICU admission was not significantly different between survivors and non-survivors, and only extreme hypo- or
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Table 4. Multivariable logistic regression categorizing calcium values into design variables.

| Variables                  | Odds ratio | 95% CI   | p     | Variables                  | Odds ratio | 95% CI   | p     |
|----------------------------|------------|----------|-------|----------------------------|------------|----------|-------|
| Referent group with Ca0 1.15–1.25 | 1          |          |       | Referent group with Cmean 1.15–1.25 | 1          |          |       |
| Severe hypocalcemia (<0.8) | 1.712      | 0.971–3.019 | 0.063 | Severe hypocalcemia (<0.8) | 1.332      | 0.478–3.716 | 0.583 |
| Moderate hypocalcemia (0.8–0.9) | 1.943      | 1.340–2.817 | <0.001 | Moderate hypocalcemia (0.8–0.9) | 2.520      | 1.485–4.278 | 0.001 |
| Mild hypocalcemia (0.9–1.15) | 1.014      | 0.888–1.159 | 0.832 | Mild hypocalcemia (0.9–1.15) | 1.153      | 1.006–1.322 | 0.041 |
| Mild hypercalcemia (1.25–1.35) | 0.553      | 0.400–0.767 | <0.001 | Mild hypercalcemia (1.25–1.35) | 0.872      | 0.597–1.274 | 0.48  |
| Moderate hypercalcemia (1.35–1.45) | 0.976      | 0.588–1.619 | 0.924 | Moderate hypercalcemia (1.35–1.45) | 1.439      | 0.782–2.647 | 0.243 |
| Severe hypercalcemia (>1.45) | 1.407      | 0.760–2.605 | 0.277 | Severe hypercalcemia (>1.45) | 1.975      | 0.888–4.390 | 0.095 |
| Age                        | 1.008      | 1.005–1.011 | <0.001 | Age                        | 1.008      | 1.005–1.011 | <0.001 |
| Sex                        | 1.100      | 0.975–1.241 | 0.121 | Sex                        | 1.109      | 0.983–1.251 | 0.094 |
| SAPS-1                     | 1.110      | 1.094–1.127 | <0.001 | SAPS-1                     | 1.110      | 1.093–1.127 | <0.001 |
| SOFA                       | 1.126      | 1.105–1.148 | <0.001 | SOFA                       | 1.126      | 1.104–1.148 | <0.001 |
| Congestive heart failure   | 1.145      | 0.997–1.316 | 0.055 | Congestive heart failure   | 1.143      | 0.996–1.313 | 0.058 |
| Paralysis                  | 1.384      | 0.903–2.120 | 0.135 | Paralysis                  | 1.380      | 0.901–2.115 | 0.139 |
| Uncomplicated diabetes     | 0.796      | 0.681–0.930 | 0.004 | Uncomplicated diabetes     | 0.802      | 0.687–0.938 | 0.006 |
| Complicated diabetes       | 0.789      | 0.596–1.045 | 0.098 | Complicated diabetes       | 0.795      | 0.600–1.053 | 0.109 |
| Obesity                    | 0.614      | 0.345–1.091 | 0.096 | Obesity                    | 0.622      | 0.351–1.102 | 0.104 |
| MICU                       | 1.106      | 0.958–1.278 | 0.17  | MICU                       | 1.104      | 0.956–1.276 | 0.178 |
| CSRU                       | 0.276      | 0.235–0.324 | <0.001 | CSRU                       | 0.279      | 0.237–0.327 | <0.001 |

Note: *model 1 contains initial calcium (Ca0) and the variance inflation factor (VIF) was 1.201; *model 2 contains mean calcium (Cmean) and the VIF was 1.199.

Abbreviations: SOFA, sequential organ failure assessment; SAPS, Simplified Acute Physiology Score; CSRU, cardiac surgery care units; MICU, medical intensive care unit.

doi:10.1371/journal.pone.0095204.t004

Hypercalcemia was independent predictors of mortality. This is in contrast to our findings that both severe hypocalcemia and hypercalcemia are not independent predictors of outcome. However, Egi’s study found that incident (occurring once during ICU stay) hypocalcemia and hypercalcemia were significantly associated with worse clinical outcome. It is probably that there is no consensus on the management of iCa derangement in ICU and the protocol may vary across institutions. In Egi’s study, intravenous calcium supplementation is given only for severe hypocalcemia associated with bleeding; but the protocol is not explicitly reported in the MIMIC II database. Calcium supplementation has been investigated in both animal and clinical studies for its effect on mortality, showing that calcium supplementation will have negative impact on clinical outcomes.[19] Since there is not specific calcium management protocol in these studies, such confounding effect cannot be excluded. Consistently with our study, Choi YC and colleagues [20] identified a strong association between initial hypocalcemia and mortality in 253 consecutive trauma patients, and this association remained after adjustment of important confounders. Also, another two studies, one conducted in emergency department and the other in ICU, consistently reported a strong association between on-admission hypocalcemia and mortality.[21,22] In the later study, Hastbacka J and colleagues excluded patients who had received calcium supplementation to exclude the impact of the intervention on serum iCa.

Hypocalcemia is prevalent in ICU patients, as reported in our study and has never been reported in the literature. In previous mentioned study by Egi M and colleagues, incident mild hypocalcemia (the same reference range) was associated with increased risk of death. Another two small studies failed to identify statistically significant association between hypercalcemia and D-parathyroid-calcium axis and critical illness has shown to be associated with dysfunction of this axis. Proposed mechanisms include impairment of parathyroid hormone by pro-inflammatory cytokines, catecholamine excess in ICU patients, end organ resistance to parathyroid hormone, inhibition of parathyroid hormone secretion and cellular redistribution of Ca2+.[24,25] A recent study conducted by Nair P and colleagues [26] showed that vitamin D insufficiency or deficiency were prevalent among ICU patients (78%) and the level did not recover during treatment. This prevalent hypovitaminosis D explains the high incidence of hypocalcemia as reported in our study and many others. Although hypovitaminosis D was not reported to be associated with higher mortality in Nair’s study, it was associated with worse disease severity and fewer hospital-free days. Probably, that study was under-powered to detect a difference of mortality due to limited sample size (100 subjects).

Hypercalcemia was investigated in our study and the result showed that mild hypercalcemia was associated with reduction in mortality risk, and the relationship was only valid for Ca0 rather than Cmean. One plausible explanation is that Cmean can be influenced by calcium supplementation during ICU stay. If hypocalcemia is a marker of disease severity, elevation of iCa by supplementation may not necessarily translate to clinical benefit. The protective effect of mild hypercalcemia is a unique finding in our study and a plausible explanation is that Camean can be used as a marker of disease severity and fewer hospital-free days. Probably, that study was under-powered to detect a difference of mortality due to limited sample size (100 subjects).

PLOS ONE | www.plosone.org  6  April 2014 | Volume 9 | Issue 4 | e95204
mortality. [27,28] Severe hypercalcemia is thought to be associated with increased mortality risk. Great majority of patients with severe hypercalcemia is attributable to either primary hyperparathyroidism or malignancy. [29] These comorbidities per se are associated with increased mortality. On the other hand, severe hypercalcemia is a well-known risk factor for acute kidney injury (AKI) in critically ill patients, and the occurrence of AKI has been associated with increased mortality. [30,31] However, severe hypercalcemia in neither \( \text{Ca}_0 \) nor \( \text{Ca}_{\text{mean}} \) was associated with increased mortality risk in the present study. Actually, severe hypercalcemia is rarely seen in ICU patients, accounting for only 0.75% in our study. The limited sample size may significantly compromise the statistical power. As shown in table 4, severe hypercalcemia is associated with 1.4-fold increase in the risk of death, but statistical significance is not reached. This is most probably attributable to the limited sample size in severe hypercalcemia group. However, based on current evidence, the clinical significance of hypercalcemia cannot be determined and further investigations are needed.

There are several limitations need to be acknowledged. First, the study is retrospective in nature and bears potential limitations of such design. For instance, patients without iCa measured during ICU stay were excluded from the analysis, this may cause bias that the included cohort cannot represent the whole study population. However, included and excluded cohorts are similar in many clinical characteristics (data not shown), making our cohort representative of the target population. Second, ICU patients were heterogeneous including medical, surgical and cardiac surgical patients, whether narrowing study population will improve the prognostic value of iCa for mortality requires further investigations. Third, although every effort has been made to adjust for the confounding factors by using multivariate analysis, other unknown factors may still exist to confound the prognostic value of iCa. This may partly explain the disparity of the results between our study and others'. Finally, we used ICU mortality instead of the more commonly used ones such as 28-day and 90-day mortality as the study endpoint. This is because data are not directly available in the MIMIC-2 database after ICU discharge. Therefore, if we use 28-day or 90-day mortality, many patients discharged from ICU or hospital before the certain time period will be regarded as censored, and this will result in too many censored data.

**Conclusion**

In aggregate, by the analysis of a large clinical database, our study shows that both hypocalcemia and hypercalcemia is associated with altered mortality, but in a complex form.

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**Figure 2. Receiver operating characteristic curve (ROC) shows that the areas under ROC are approximately 0.78 for the four fitted models.**

![Figure 2](https://example.com/fig2.png)

**doi:10.1371/journal.pone.0095204.g002**
Interestingly, mild hypercalcemia on ICU admission is found to be protective and is associated with reduction in mortality risk.

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