RESEARCH ARTICLE

Predictive accuracy of serum total calcium for both critically high and critically low ionized calcium in critical illness

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Background: The accuracy of total calcium and its corrected value for predicting critically high and critically low ionized calcium in critical illness is controversial. The aim of this study was to investigate whether the concentration of total serum calcium, either corrected for albumin or not, could predict critically high or low values in critical illness.

Methods: This report describes a retrospective study using the Medical Information Mart for Intensive Care (MIMIC) III database. Test panels that contained serum albumin, total calcium, and ionized calcium (named ATI panels) with order time intervals of less than one hour were extracted. The predictive accuracy of total calcium, either corrected for albumin or not, was assessed using receiver operating characteristic (ROC) curve analysis.

Results: A total of 12 118 ATIs with 103 critically low and 92 critically high ionized calcium results were extracted. The areas under ROC curves (AUCs) of corrected and uncorrected total calcium for predicting critically low ionized calcium were 0.69 (95% CI: 0.61-0.76) and 0.70 (95% CI: 0.63-0.78), respectively. For predicting critically high ionized calcium, the AUCs were 0.98 (95% CI: 0.97-1.00) and 0.97 (95% CI: 0.95-1.00), respectively. With positive predictive values (PPVs) of 0.05 and 0.10, the sensitivities (both corrected and uncorrected) were approximately 0.50 for predicting critically low ionized calcium and 0.95 for predicting critically high ionized calcium.

Conclusions: Total calcium, either corrected for albumin or not, is not a reliable test to predict critically low ionized calcium in critical illness. Total calcium's predictive accuracy for critically high ionized calcium is high.

KEYWORDS

Calcium, critical illness, critical value, sensitivity, specificity

1 | INTRODUCTION

Critical value reporting is one of the most important issues in post-analytical phase for clinical laboratories.¹ It can be life-threatening if a critical value is missed or delayed. For serum or plasma calcium tests, critical value reporting is more complex than other laboratory tests. In plasma or serum, calcium exists in three physiochemical states: protein-bound calcium (approximately 40%), free (ionized) calcium (approximately 50%), and calcium complexes with small anions (approximately 10%).² The actual percentage of calcium in

each state is strongly affected by many factors, such as serum total protein, albumin, and pH.^{2,3} Among these three states, only ionized calcium is physiologically relevant, and critically high or low ionized calcium is life-threatening.^{2,4} Indeed, previous studies concluded that extremely low or high ionized calcium is independently associated with hospital mortality in adult patients admitted to the intensive care unit (ICU).^{5,6}

Therefore, to detect hypercalcemia or hypocalcemia, direct measurement of ionized calcium is recommended.^{2,7} However, the International Federation of Clinical Chemistry and Laboratory

Medicine's (IFCC)-recommended assay for ionized calcium is ion-selective electrodes (ISE),⁸ which is usually performed on blood gas analyzers^{2,3} and the majority of commercial vendors do not offer an ionized calcium assay based on large chemistry analyzers.^{3,9} By contrast, total calcium is usually measured on large chemistry analyzers along with other blood chemistry tests. Consequently, ionized calcium is less frequently measured than total calcium in clinical practice,⁷ and total calcium is usually used as an alternative test to detect hypercalcemia or hypocalcemia. Considering that total calcium is affected by serum protein and pH, many methods have been proposed to correct total calcium.¹⁰

Several studies have investigated the accuracy of total calcium and its corrected value for predicting hypocalcemia or hypercalcemia,^{10,11} but the sample sizes of these studies were small, and the results were heterogeneous. To the best of our knowledge, no study has investigated whether the accuracy of total calcium for predicting critically high or low calcium is acceptable in critical illness. Therefore, we investigated whether the concentration of total serum calcium, either corrected for albumin or not, could predict critically high or low values in critically ill patients.

2 | MATERIALS AND METHODS

2.1 | Study subjects

Similar to a previous study,¹² this report describes a retrospective study using the Medical Information Mart for Intensive Care (MIMIC) III database (version 1.4).^{13,14} MIMIC III is a large, publically accessible clinical database established by Beth Israel Deaconess Medical Center. There are 46 520 critically ill patients (including 38 645 adults and 7875 neonates) with 58 976 admissions in this database. The laboratory test results of patients are recorded in a table named LABEVENTS.

The establishment of MIMIC III was approved by the Institutional Review Board (IRB) of the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA). After completing a required training course (certification number: 1678079), one author (Z-D Hu) was approved to obtain the data for research aims. All data were extracted using the structured query language (SQL) with the pgAdmin platform. Informed consent was waived because this was a database-based retrospective study.

The inclusion criteria of this study were (i) test panel that contained albumin (*itemid* = 50862), total calcium (*itemid* = 50893), and ionized calcium tests (*itemid* = 50808) (named an ATI panel) during the ICU admission; and (ii) the time intervals (defined as *charttime* in MIMIC III database) between these three tests were less than 1 hour. If an ionized calcium had more than one matched albumin or total calcium, only the panel with smallest time intervals was used for analysis. We corrected total calcium using the method proposed by Payne et al.¹⁵ Similar to previous studies,^{1,9} the thresholds for defining critically low and high ionized calcium were 0.79 mmol/L and 1.58 mmol/L.

2.2 | Statistical analysis

All statistical analyses were performed in SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). The normality of the distribution of data was tested by the Shapiro-Wilk test. Normally distributed data are expressed as the mean and standard deviation, and skewed data are expressed as median and interquartile range.¹⁶ The correlation between total and ionized calcium was analyzed using Spearman's approach. Receiver operating characteristic (ROC) curve analysis was used to estimate the predictive accuracy of total calcium for critically high and low ionized value. The positive predictive value (PPV) of total calcium, either corrected or uncorrected, was prespecified at 0.05 or 0.10. In other words, to avoid missing one case of critical hypercalcemia or hypocalcemia, twenty or ten critical value calls were acceptable. *P* values less than .05 were considered to be statistically significant.

3 | RESULTS

3.1 | Summary of tests results

Figure 1 is a flowchart of data extraction. In the end, 12 118 ATI panels with 4699 patients were included. Table 1 summarizes the included ATI panels. Age, total calcium, ionized calcium, and albumin were not normally distributed and thus are expressed as median and interquartile range. A majority of cases were transferred from the Emergency Department (ED). A total of 103 (0.85%) cases of critically low ionized calcium and 92 (0.76%) of critically high calcium were observed. Total calcium was positively correlated with ionized calcium, with a coefficient of 0.51 (Figure 2, *P* < .001).

3.2 | Accuracy of corrected and uncorrected total calcium for predicting critically high and low ionized calcium values

Figure 3 is a ROC curve depicting the predictive value of corrected and uncorrected total calcium for critically high and low ionized

FIGURE 1 Flowchart of the data extraction procedure

TABLE 1 Characteristics of the subjects

Parameter	Result (n = 12 118)
Gender	
Male	7146
Female	4972
Age (years)	61 (49–73)
Age < 18 y (%)	23 (0.19%)
Admission type	
Newborn	6
Urgent	462
Elective	1360
Emergency	10 290
Albumin (g/L)	26 (22–31)
Total calcium (mmol/L)	2.08 (1.95–2.25)
Ionized calcium (mmol/L)	1.14 (1.08–1.20)
Critically high ionized calcium (%)	92 (0.76%)
Critically low ionized calcium (%)	103 (0.85%)

The gender distribution and average age were calculated per test panel (ionized calcium, total calcium and albumin, and designated ATI).

FIGURE 2 Scatter plot of total calcium and ionized calcium

calcium values. The AUCs of corrected and uncorrected total calcium for predicting a critically low value were 0.69 (95% CI: 0.61–0.76, $P < .001$) and 0.70 (95% CI: 0.63–0.78, $P < .001$), respectively ($P = .78$ for AUC comparison). The AUCs of corrected and uncorrected total calcium for predicting a critically high value were 0.97 (95% CI: 0.95–1.00, $P < .001$) and 0.98 (95% CI: 0.97–1.00, $P < .001$), respectively ($P = .48$ for AUC comparison).

Next, we fixed the PPV at 0.05 or 0.10 and calculated the corresponding thresholds, sensitivities, and specificities. As the critically low and high values of total calcium in many laboratories are fixed at 1.50 mmol/L and 3.25 mmol/L,¹⁷ we also calculated the sensitivity, specificity, PPV, and negative predictive value (NPV) of total calcium at these thresholds. The results are summarized in Table 2.

4 | DISCUSSION

In this study, we found that the incidence rates of critically low and high values for ionized calcium were 0.85% and 0.76%, respectively. These results indicate that the incidence rate of critically high and low ionized calcium is high in critical ill patients.¹⁸ Our findings are supported by a previous study, which reported that the incidence rates of moderate hypocalcemia (ionized calcium less than 0.9 mmol/L) and hypercalcemia (ionized calcium more than 1.35 mmol/L) were 10.8% and 6.7%, respectively.⁵ The increased rate of abnormal ionized calcium in critical illness may be due to the following:^{6,18,19} (i) increased urine or fecal calcium excretion; (ii) decreased intake of dietary calcium and vitamin D, a promoter of calcium absorption in the intestine; (iii) underlying diseases or comorbidities affecting calcium homeostasis, such as sepsis and renal failure; and (iv) medication side effects, such as parathyroid surgery, catecholamine administration, and transfusion of citrated blood.

Reporting the critical value of calcium is carried out in the post-analytical phase in clinical laboratories. Usually, clinical laboratories report the critical value to clinicians via telephone and/or hospital information system (HIS). For critical value reporting, there is a trade-off between the patient's safety and the clinical laboratory's workload. If the threshold of critically low calcium value is inappropriately low, some patients with critically low calcium will be missed, and their safety will be negatively affected. On the other hand, if the threshold of the critically high value is inappropriately high, the workload of the clinical laboratory will increase. Therefore, the establishment of appropriate thresholds for critical low and high calcium is a challenge for both clinicians and laboratory workers.¹ In this study, we found that, although total calcium was positively correlated with ionized calcium, the coefficient was only 0.51, indicating that total serum calcium does not well represent the level of ionized calcium. Using ROC curve analysis, we found that the AUCs of corrected and uncorrected total calcium were approximately 0.70, with no statistical significance, indicating that the predictive accuracy of total calcium is moderate and albumin correction does not improve its predictive accuracy. Furthermore, with PPVs at 0.05 and 0.10, the sensitivities for predicting critically low ionized calcium were approximately 0.50. These results can be interpreted as follows: Among 12 118 critical illness, 103 patients had critically low calcium. Approximately 1030–2060 critical value calls are needed to identify the patients with critically low calcium ($n = 103$), and using this strategy, we only identified 45–57 of them. On the other hand, the accuracy of total calcium for predicting critically high ionized calcium was high, with AUCs more than 0.95 and sensitivities more than 0.90, indicating that only small portion of critically high calcium was missed and that total calcium is a reliable predictor for critically high ionized calcium. We also found that the currently widely used threshold of total calcium to define critically low calcium is not optimal, as approximately two-thirds of patients with critically low ionized calcium will be missed at this threshold. Our results are supported by a recently published study that investigated the predictive value of total calcium for critically low ionized calcium in patients with cancer.¹¹

FIGURE 3 Receiver operating characteristic curve analyses for predicting critically high and low ionized calcium

TABLE 2 Accuracy of corrected and uncorrected total calcium for predicting critically high and low ionized calcium values ($n = 12\,118$)

	PPV at 0.05		PPV at 0.10		Conventional critical value
	Uncorrected	Corrected	Uncorrected	Corrected	
Critically low value (n = 103)					
Area under ROC curve	0.70 (0.63-0.78)	0.69 (0.61-0.76)	0.70 (0.63-0.78)	0.69 (0.61-0.76)	0.70 (0.63-0.78)
Threshold (mmol/L)	1.81	2.10	1.71	1.99	1.50
Sensitivity (95% CI)	0.55 (0.45-0.65)	0.53 (0.43-0.63)	0.49 (0.39-0.59)	0.44 (0.34-0.54)	0.35 (0.26-0.45)
Specificity (95% CI)	0.92 (0.91-0.92)	0.92 (0.91-0.92)	0.96 (0.96-0.97)	0.97 (0.96-0.97)	0.99 (0.99-0.99)
PPV (95% CI)	0.05 (0.04-0.07)	0.05 (0.04-0.07)	0.11 (0.08-0.14)	0.10 (0.08-0.13)	0.31 (0.22-0.40)
NPV (95% CI)	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
Critically high value (n = 92)					
Area under ROC curve	0.97 (0.95-1.00)	0.98 (0.97-1.00)	0.97 (0.95-1.00)	0.98 (0.97-1.00)	0.97 (0.95-1.00)
Threshold (mmol/L)	2.36	2.61	2.51	2.75	3.25
Sensitivity (95% CI)	0.98 (0.92-1.00)	0.97 (0.91-0.99)	0.97 (0.91-0.99)	0.97 (0.91-0.99)	0.40 (0.30-0.51)
Specificity (95% CI)	0.86 (0.85-0.86)	0.86 (0.85-0.86)	0.93 (0.92-0.93)	0.93 (0.93-0.94)	1.00 (1.00-1.00)
PPV (95% CI)	0.05 (0.04-0.06)	0.05 (0.04-0.06)	0.09 (0.08-0.12)	0.10 (0.08-0.12)	0.51 (0.39-0.63)
NPV (95% CI)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

In that study, the authors reported that approximately two-thirds of patients with critically low calcium would be missed if total calcium was used as a predictor. Taken together, these results indicate that the accuracy of total calcium for predicting critically low ionized calcium is low, regardless of whether it is corrected, while the accuracy of total calcium for critically high ionized calcium is high.

This study has several limitations. First, this study was based on a publicly accessible database, the representativeness of the subjects might be negatively affected by the retrospective design of this study, and the instruments used for albumin and total and ionized calcium were unavailable. Second, the subjects in this study were

critically ill patients, and the results cannot be generalized to patients not admitted to the ICU.

In conclusion, our study suggests that the predictive accuracy of total calcium, either corrected or uncorrected, for critically low ionized calcium is not reliable. Approximately half of patients with critically low ionized calcium will be missed if total calcium is used as a predictor for critically low ionized calcium. However, the predictive accuracy of total calcium for critically high ionized calcium is sufficiently high. Therefore, ionized calcium should be recommended for critically ill patients with suspected critically low calcium.

AUTHORS' CONTRIBUTIONS

Z.D. Hu and Y.Q. Han conceived and designed the study; M.Y. Wang and G.J.L. Hu provided administrative support; Z.D. Hu and Y.L. Huang contributed to collection and assembly of data; Z.D. Hu, Y.L. Huang, and Y.Q. Han analyzed and interpreted the data; all authors wrote and approved the final version of the manuscript.

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