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Development and Validation of a Novel Laboratory-Specific Correction Equation for Total Serum Calcium and Its Association With Mortality Among Hemodialysis Patients

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Abstract

Conventional albumin-corrected calcium is inaccurate in predicting ionized calcium, and hidden hypercalcemia, characterized as high ionized calcium with normal total calcium, is associated with higher mortality in hemodialysis patients. By using a national cohort of hemodialysis patients in the Unites States, a novel laboratory-specific prediction equation composed of total calcium, albumin, and phosphorus was derived from 242 patients in the South Atlantic division (adjusted R^2 = 0.80 versus 0.71 for the conventional equation) and then validated among 566 patients in the other divisions (adjusted R^2 = 0.79 versus 0.68 for the conventional equation). Compared with the conventional equation, the novel equation showed a greater correlation with intact parathyroid hormone. Its relative performance against the conventional equation was consistent across subgroups based on medications related to calcium metabolism. The novel equation also had a

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higher sensitivity (57% versus 34%) and an equivalent specificity (99% versus 100%) against ionized hypercalcemia at a cut-off value of 10.2 mg/dL. Sensitivity and specificity at 9.4 mg/dL was 94% and 76% (versus 87% and 82% for the conventional equation), respectively. A survival analysis in 87,779 incident hemodialysis patients showed that among patients who were categorized as having a high-normal calcium status (ie, >9.4 to 10.2 mg/dL) by the conventional equation, there appeared a trend toward higher adjusted mortality risk across higher calcium status defined according to the novel equation. Meanwhile, the mortality risk was consistent across calcium strata defined according to the conventional equation within the categories defined by the novel equation. In conclusion, in comparison to the conventional equation, a novel laboratory-specific correction equation derived for correction of total calcium performs significantly better in ascertaining hidden hypercalcemia in hemodialysis patients, and aids in identifying patients at higher risk for mortality.

Keywords

DISORDERS OF CALCIUM/PHOSPHATE METABOLISM; EPIDEMIOLOGY; STATISTICAL METHODS

Introduction

Hypercalcemia is associated with higher mortality in patients with end-stage renal disease (ESRD).[1–5] The risk of vascular calcification is increased in patients with higher extracellular calcium levels, and hypercalcemia along with hyperphosphatemia may contribute to the development of cardiovascular disease in this population.[6–8]

Because serum calcium is bound to serum albumin, total serum calcium is often corrected in clinical practice as follows: Corrected total calcium (*mg/dL*) = serum total calcium (*mg/dL*) + 0.8 × [4.0 − serum albumin (*g/dL*)] [*if serum albumin* < 4.0 *g/dL*].[9,10] This equation was first published anonymously in 1977 as a crude simplification of seven correction factors that had appeared in the literature up to that point, rather than being derived from a specific cohort.[11–13] However, the proportion of ionized calcium changes depending upon acid-base balance and serum organic and inorganic anions, including phosphorus and sulfate, and hence, neither uncorrected nor conventional corrected total calcium adequately predict ionized calcium concentrations among patients with advanced chronic kidney disease.[13–17] The current clinical practice guidelines for patients with ESRD suggest maintaining albumin-corrected total calcium concentrations within the normal or low-normal range, but also support measurement of ionized calcium as the preferred method to evaluate calcium status.[9,10]

Given that measuring ionized calcium incurs additional time, effort, and costs, several hemodialysis population-specific correction equations for total calcium have been suggested.[13–16] Notably, although data suggest the contribution of total calcium concentrations to the discrepancy between ionized calcium and total calcium, these equations do not include a factor for total calcium.[13–17] In addition, there has not been prior study of how these corrected equations for total calcium predict patient mortality.

Although the prevalence of high albumin-corrected total calcium (>10.2 mg/dL) has been shown to be 4% to 5% in the 2010s,[18,19] we recently reported that the majority of incident hemodialysis patients with high ionized calcium were incorrectly categorized as normocalcemic by either uncorrected or albumin-corrected total serum calcium and were thus considered to have "hidden hypercalcemia."[20] Furthermore, patients with hidden hypercalcemia demonstrated a higher mortality risk, indicating a need for a more accurate evaluation of calcium status. The goal of the current study was to develop and validate a novel laboratory-specific correction equation for total serum calcium in the ESRD population. We also hypothesized that hemodialysis patients identified as having higher calcium status by using the newly developed equation are at higher risk of mortality compared with patients identified as normocalcemic.

Materials and Methods

The parent study was approved by the Institutional Review Boards of the Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California Irvine Medical Center, and the University of Washington as exempt from informed consent.[21–25]

We extracted, refined, and examined electronic data from all incident dialysis patients who were aged ≥18 years and received conventional hemodialysis treatment in a total of 1737 facilities operated by a large dialysis organization in the US from January 1, 2007, to December 31, 2011.[21] Information on death, race/ethnicity, primary insurance, access type, ICD-9 codes, and medication were obtained from the electronic database of the dialysis provider. Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the central laboratory in Deland, Florida, typically within 24 hours. All laboratory values were measured by automated and standardized methods. Specifically, serum ionized calcium and albumin were measured by using ion-selective electrode and bromocresol green (BCG) methods. Most laboratory values other than ionized calcium were measured monthly, while serum ferritin and intact parathyroid hormone (PTH) were measured at least quarterly, and hemoglobin was measured weekly to biweekly in most patients.

Patient characteristics are expressed as means ± SD, medians (IQR), or percentages, as appropriate. Differences between groups were compared by standardized differences due to the large sample size of this study.[26,27] Analyses were conducted using STATA MP version 13.1 (StataCorp, College Station, TX, USA), and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Model discrimination and calibration assessments were based on the R statistical package *rms*.

Subject selection for the derivation and validation data sets

To develop and validate a novel correction equation for total serum calcium, we identified 8015 simultaneous measurements of ionized calcium and total serum calcium among 820 ESRD patients who were treated with hemodialysis and who did not use central venous catheters as their vascular access at blood draw (Supplemental Fig. S1). We selected serum concentrations of albumin, phosphorus, and bicarbonate as candidate explanatory variables based on previous studies and their clinical accessibility in the management of hemodialysis

patients.[13–16] To ensure reliability of data, we excluded 578 measurements with missing information on these key predictors, as well as 10 measurements that were of <0.1 or >99.9 percentile of observed ionized calcium values, resulting in 10 (1.5%) fewer subjects. Compared with excluded patients in the entire cohort, included patients were more likely to be diabetic (61% versus 50%) and more likely to have a history of congestive heart failure (46% versus 29%) and higher hemoglobin levels (11.3 g/dL versus 11.0 g/dL) (standardized difference >0.2 for all; see Supplemental Table S1).

Performance of uncorrected and conventional corrected calcium

Total and ionized calcium were categorized as low, low-normal, high-normal, and high (<8.6, 8.6–9.4, >9.4–10.2, and >10.2 mg/dL and <1.16, 1.16–1.24, >1.24–1.32, and >1.32 mmol/L, respectively).[9] The kappa-statistic measure against ionized calcium was used to evaluate the inter-index agreement for these categories. For further comparison between calcium indices, uncorrected total calcium, albumin-corrected total calcium, and ionized calcium values were normalized by conversion to a z score based on the normal range in the central laboratory (not a data-derived *Z*-score) as follows:[15–17] the lower and upper limits of the normal ranges for ionized calcium (1.16 and 1.32 mmol/L) and total calcium (8.6 and 10.2 mg/dL) were treated as the 95% confidence interval (CIs) and used to calculate the mean and SD by the equation "$z\,score = \frac{measured\,value - mean}{SD} \times 1.96$," where the mean and SD were 1.24 and 0.08 mmol/L and 9.4 and 0.8 mg/dL for ionized and total calcium, respectively.

Development and validation of a novel correction equation

In the derivation data set, we used multivariable linear regression for the continuous outcome of ionized calcium. Ionized calcium values were converted to equivalent total serum calcium values based on *Z*-scores (ie, 1.16 and 1.32 mmol/L in ionized calcium to 8.6 and 10.2 mg/dL in total serum calcium, respectively) and then used as the dependent variable. We evaluated three models to develop a novel correction equation: model 1 included total calcium and albumin; model 2 included total calcium, albumin, and phosphorus; and model 3 included variables in model 2 plus bicarbonate, their squared terms, and interaction terms of albumin with total calcium, phosphorus, and bicarbonate in order to account for potential nonlinear associations and varying binding affinity of calcium to albumin depending on the concentrations of total calcium, phosphorus, and bicarbonate.[28] Internal validity was assessed in 1000 bootstrap samples by random sampling with replacement from the entire derivation data set. Final models with reduced number of predictors were obtained based on minimizing Akaike's information criterion (AIC), because it has better statistical properties in variable selection compared with *p* value–based selection.[29] Coefficients of selected variables were rounded to nearest 0.05 or 0.00 to develop correction equations, and then constants were adjusted accordingly to minimize AIC so that the new equations are simplified without loss of clinical precision. We note that for each model, the sample size in the derivation data set had >20 subjects per variable in any model (ie, 242 observations versus 11 candidate variables in model 3), which is generally considered adequate for multivariable regression analyses.[29,30] The remaining 566 patients from the other census divisions served as the validation data set.

We assessed the predictive ability (model discrimination) of uncorrected total calcium, conventional albumin-corrected calcium, and the candidate equations in both the derivation and validation data sets by adjusted R^2 along with 95% (percentile) bootstrap confidence intervals based on 1000 bootstrap samples. Adjusted R^2 was calculated using raw values without refitting in linear regression models. For model calibration, we estimated shrinkage factors for each model and examined calibration plots of predicted versus observed total corrected calcium as well as Bland-Altman plots. Model fitness was evaluated by AIC. In the validation data set, we calculated the area under the receiver operating characteristic curve, Youden index, sensitivity, and specificity against ionized hypercalcemia (>1.32 mmol/L) across observed values. Using two clinically relevant cut-off points at the median value and the upper limit of the normal reference range (ie, 9.4 mg/dL and 10.2 mg/dL, respectively), we also compared the sensitivity and specificity of these novel equations to those of uncorrected calcium and the conventional equation. Exact binomial confidence intervals are provided for the sensitivity and specificity. Additionally, nonparametric correlation with intact PTH was evaluated by using Spearman's ρ in the validation cohort. We conducted subgroup analyses based on medications including calcium salts, non-calcium containing phosphorus binders (ie, lanthanum and sevelamar), cinacalcet, and vitamin D receptor activators (VDRAs). VDRAs included calcitriol, paricalcitol, and doxercalciferol, either oral or intravenous.

Survival analyses

We then selected one novel correction equation and examined the association between its calcium status classifications with all-cause and cardiovascular mortality risk using Cox regression models. We used hemodialysis patients with a vintage of at least 6 months given that total calcium concentrations tend to be low at hemodialysis initiation, rise during the first 6 months of dialysis, and stabilize thereafter.[4] Among 90,941 patients who survived the first 6 months of dialysis and who were treated only with conventional hemodialysis during follow-up, we excluded 3162 patients with missing information on either serum total calcium, albumin, or phosphorus, with the final analytic cohort composed of 87,779 hemodialysis patients (Supplemental Fig. S2). To minimize measurement variability, all repeated measures for each patient during months 4–6 were averaged and served as the baseline values. A associations with all-cause and cardiovascular mortality were examined with adjustment for age, sex, race/ethnicity, central venous catheter use as vascular access, primary insurance, body mass index (natural log-transformed values), and history of diabetes, hypertension, congestive heart failure, atherosclerotic heart disease, and other cardiovascular diseases, as well as laboratory variables (ie, single-pool Kt/V, hemoglobin, serum concentrations of albumin, creatinine, and phosphorus, and natural log-transformed intact parathyroid hormone and ferritin) and the use of medications described above (i.e., calcium salts, non-calclum containing phosphorus binders, cinacalcet, and VDRAs). To account for missing laboratory variables, we created five datasets with imputed missing values using multivariate normal regression models based on all available baseline data and an indicator of death. Linearity assumption among covariates was examined by using restricted spline functions and a likelihood ratio test for goodness of fit.[31] Proportional hazards assumptions were tested using log-log against survival plots and Schoenfeld residuals.

Results

Baseline demographic, clinical, and laboratory characteristics

We identified 7427 ionized calcium measurements from 808 patients in electronic data from a large dialysis organization in the US, and then randomly selected one measurement from each patient. To develop and validate new correction equations for total serum calcium, we employed the geographic validation method rather than random splitting as per the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) statement.[32] Geographic regions were designated according to the US Census Bureau definitions. Patients from the South Atlantic division accounted for the largest proportion of subjects (ie, $n = 242$, 30%) and served as the derivation data set. All the remaining 566 patients from the other census divisions served as the validation data set.

The characteristics of 242 patients in the derivation data set from the South Atlantic division are shown in Table 1. The mean ± SD age of the cohort was 59 ± 15 years, among whom 55% were male, 30% were non-Hispanic white, 69% were non-Hispanic black, 59% were diabetic, and the median ESRD vintage was 13 months (interquartile range [IQR], 8 to 23 months). The prevalence of hypercalcemia varied among calcium indices; 4 (1.7%), 6 (2.5%), and 27 (11.2%) of patients were considered hypercalcemic according to uncorrected total calcium, conventional corrected total calcium, and ionized calcium, respectively (Supplemental Table S2). There was only fair agreement of calcium status between ionized calcium and uncorrected/corrected total calcium ($\kappa = 0.28$ and 0.26, respectively).[33] A scatter diagram of Z-scores between ionized calcium and uncorrected/corrected total calcium showed a slope of <0.6 and a negative constant in the regression line in either index (Fig. 1), suggesting potential misclassification of ionized calcium status by uncorrected/corrected total calcium.

Derivation of novel correction equations

We applied multivariable linear regression with Akaike's information criterion (AIC)-based backward selection to model 1–3 and found that the coefficient of total calcium was 1.34 to 1.35 across models (Table 2). In addition to serum albumin, model 2 identified serum phosphorus as an independent variable, and albumin–bicarbonate product, not bicarbonate itself, was further identified in model 3. Based on these models, we developed three potential equations (EQ1–3) as follows:

$$\text{Corrected total calcium}\,(mg/dL) = 1.35 \times \text{total calcium}\,(mg/dL) - 0.7 \times \text{albumin}\,(g/dL) - 0.25 \quad \text{EQ1}$$

$$\text{Corrected total calcium}\,(mg/dL) = 1.35 \times \text{total calcium}\,(mg/dL) - 0.65 \times \text{albumin}\,(g/dL) - 0.15 \times \text{phosphorus}\,(mg/dL) + 0.3 \quad \text{EQ2}$$

$$\text{Corrected total calcium}\,(mg/dL) = 1.35 \times \text{total calcium}\,(mg/dL) - 0.55 \times \text{albumin}\,(g/dL) - 0.15 \times \text{phosphorus}\,(mg/dL) - 0.005 \times \text{albumin}\,(g/dL) \times \text{bicarbonate}(mmol/L) + 0.4$$

EQ3

The predictive performance was not adequate for either uncorrected or conventional corrected total calcium (adjusted R^2 of 0.65 and 0.71, respectively), and the above three models provided substantially improved adjusted R^2 ranging from 0.77 to 0.81 (Table 3).

Validation of the correction equations

Compared with patients in the derivation data set, 566 patients in the validation data set of non-South Atlantic divisions were more likely to be non-Hispanic white or Hispanic and less likely to be non-Hispanic black (absolute standardized difference >0.5; Table 1). All three models were very well calibrated with essentially no shrinkage; the estimated shrinkage factors were 1.001, 1.000, and 0.995, respectively. Despite the large difference in race/ethnicity, uncorrected total calcium, conventional albumin-corrected calcium, and total calcium corrected by the novel equations showed consistent performance in the validation data set (Table 3). These trends in performance across calcium indices persisted even after stratifying patients based on medications or interdialytic interval (Supplemental Table S3). The calibration plots show that the predicted corrected calcium values (both apparent and bias-corrected) for each model were close to ideal calibration (Supplemental Fig. S3). Uncorrected calcium was excluded from the following analysis given its apparent poor performance.

Bland-Altman plots showed a large systematic error indicated by a steep slope for the conventional correction equation, which was attenuated with the newly developed equations in both the derivation and validation data sets (Fig. 2). The area under the receiver operating characteristic curve against ionized hypercalcemia (ionized calcium >1.32 mmol/L) in the validation data set was high irrespective of equations; 0.93, 0.94, 0.95, and 0.95 for the conventional correction equation, EQ1, EQ2, and EQ3, respectively (Fig. 3*A*). At 10.2 mg/dL, however, the conventional equation had the lowest Youden index, a performance measure of diagnosing ionized hypercalcemia (Fig. 3*B*). Youden index was higher at a cut-off value of 9.4 mg/dL than at 10.2 mg/dL and was comparable across those equations. For detecting high ionized calcium concentrations (>1.32 mmol/L) at a cut-off value of 10.2 mg/dL, the sensitivities were particularly poor at only 34% for the conventional equation and were not high for the novel equations (ie, 50%, 57%, and 59% for EQ1, EQ2, and EQ3, respectively), whereas the specificities were high (99% to 100%) for all methods (Fig. 3*C, D*; Table 4). The specificities declined to 75% to 82% when a lower cut-off value of 9.4 mg/dL was used, but the sensitivities improved ranging from 87% to 94% with the highest values in EQ2 and EQ3.

Overall, EQ2 showed consistently better performance than EQ1 and comparable performance to EQ3. Hence, we adopted EQ2 as the primary novel correction equation and

further evaluated the correlation with intact PTH and mortality predictability in comparison to the conventional correction equation.

Correlation with intact parathyroid hormone

Given that ionized calcium concentration is one of the major regulators in PTH secretion, we evaluated the nonparametric correlation (ie, Spearman's ρ) between intact PTH and each calcium index. Among 564 of 566 patients in the validation cohort, we identified data on intact PTH that were obtained on the same day or the closest day within 3 months before ionized calcium measurement. Intact PTH concentrations were measured on the same day of ionized calcium measurement in 490 patients (87%) and within 28 days in 530 patients (94%). The median PTH concentration was 230 (IQR, 141–378) pg/mL. Overall, Spearman's ρ was −0.05, −0.17, −0.22, and −0.25 for uncorrected total calcium, the conventional equation, EQ2, and ionized calcium, respectively (Table 5). When compared with the conventional equation, EQ2 consistently showed a stronger correlation with intact PTH, which was closer to ionized calcium, across subgroups of calcium metabolism-related medications including calcium salts, non-calcium containing phosphorus binders (ie, lanthanum and sevelamar), and VDRAs with an exception for cinacalcet users where neither calcium index had a significant correlation with intact PTH.

Association with mortality

To examine the mortality risk associated with discordance between the conventional correction equation and EQ2, we used 87,779 incident hemodialysis patients, whose mean age was 62 ± 15 years, among whom 56% were male, 52% were white, 33% were black, and 62% were diabetic (Supplemental Table S4). Total calcium corrected by the conventional equation and EQ2 were 9.1 ± 0.5 and 9.1 ± 0.7 mg/dL, respectively. During the total follow-up period of 13,178 patient-years, 21,896 patients died with a crude mortality rate of 16.6 per 100 patient-years. Death resulting from cardiovascular disease was observed in 7987 patients with a crude rate of 6.1 per 100 patient-years. We conducted multivariable Cox regression analyses after categorizing patients according to calcium status (ie, low, low-normal, high-normal, and high) defined by those two equations (Fig. 4*A*). There was an incremental risk of all-cause death associated with higher calcium status defined by EQ2 yet within the same category of the conventional equation when EQ2 showed ≥8.6 mg/dL (p_{trend} = 0.008, Fig. 4*B*). For example, among 22,474 patients who were categorized as having a high-normal calcium status by the conventional equation, 2888 (13%), 16,857 (75%), and 2706 (12%) patients were categorized as having low-normal, high-normal, and high calcium by EQ2. When compared with 36,637 patients who were categorized as low-normal calcium status by both equations, their adjusted hazard ratios (95% CI) for all-cause mortality were 0.99 (0.92–1.06), 1.06 (1.03–1.10), and 1.18 (1.10–1.28), respectively. Conversely, mortality risk was consistent across calcium strata defined according to the conventional equation within the categories defined by EQ2 (p_{trend} = 0.622). Consistent findings were observed for cardiovascular mortality with accentuating the risk associated with higher calcium status, especially when identified by EQ2 (Fig. 4*C*).

Discussion

To our knowledge, this is the largest study establishing a novel correction equation for total serum calcium conducted to date. Total calcium concentrations corrected by the novel equation also showed a better correlation with intact PTH than those corrected by the conventional equation, supporting the superiority of our equation to the conventional equation. Furthermore, this is the first study to compare the mortality risk associated with corrected serum calcium levels estimated by the conventional versus novel equations in patients with chronic kidney disease. Among patients with high-normal calcium status ascertained by the conventional correction equation, there appeared a trend toward higher mortality risk across higher calcium status defined by the novel equation, especially for cardiovascular mortality. This finding suggests that use of the novel prediction equation could more accurately identify hemodialysis patients at highest risk of all-cause and cardiovascular mortality compared with the conventional equation currently used in clinical practice. Using similar methodology as we used in this study, laboratory-specific equations can be developed for implementation in heterogeneous clinical practice environments.

Previous studies explaining the discrepancy between ionized calcium and uncorrected total calcium values solely relied on non-calcium variables such as albumin, phosphorus, and bicarbonate. Thus, a key feature of our novel correction equation is its incorporation of a beta coefficient of 1.35 for total calcium.[13–16] This coefficient is partly shown as the gentle slope of the scatter diagram between *Z*-scores of ionized calcium and uncorrected total calcium (Fig. 1), which is consistent with some studies in patients with chronic kidney disease.[10,13] Indeed, a previous in vitro study demonstrated that the ratio of ultrafilterable calcium versus total calcium varies according to the total calcium value itself.[34] Data in other studies also suggested a coefficient of 1.45,[15,16] although it was not employed in their equations. Hence, the ratio between ionized versus total calcium varies as opposed to the assumption in some studies,[13,14] and it is reasonable to employ the coefficient of total calcium in the novel equation. The novel correction equation also does not require any condition for serum albumin (ie, “if albumin <4.0 g/dL”), which was also not used in the original publication of the conventional equation.[11] The squared term of albumin was also dropped in our model 3, suggesting a linear association between albumin and ionized calcium.

Estimation of corrected total calcium using the novel equation requires only two additional variables that are frequently measured in clinical practice (ie, albumin and phosphorus). In addition to serum albumin, serum phosphorus binds to ionized calcium and has been identified as a significant predictor of ionized calcium values.[15,16] Although serum bicarbonate has also been identified as a determinant of ionized calcium in the literature,[10,13] the product term between albumin and bicarbonate, not bicarbonate itself, was selected instead in EQ3, which is consistent with the observation that the affinity of albumin to free calcium varies depending on the acid-base balance of blood (ie, free calcium is more likely to bind to serum albumin in more alkaline states, leading to lower ionized calcium levels).[28] However, the performance of the novel equations did not meaningfully improve with addition of bicarbonate, which may be partly explained by the inaccuracy of serum bicarbonate in predicting acid-base balance because of the respiratory compensation for

chronic metabolic disorders and/or because of respiratory disorders such as chronic obstructive pulmonary disease. Use of blood pH may improve the performance of equations,[14–17] but this would have no practical relevance because ionized calcium is directly measurable in situations where pH can be measured.

Sensitivity for detecting high ionized calcium levels was not adequate at a cut-off value of 10.2 mg/dL (ie, the upper limit of normal range) even with the novel equation. This is not surprising because there would be residual estimation error no matter how accurate the population point estimate is; sensitivity will be 50% if the mean values of expected and observed values are the same. Therefore, lower cut-off values may be preferred for patients with low treatment-threshold probability. For example, withdrawal of calcium containing phosphorus binders or their replacement with non-calcium containing phosphorus binders is safe and low cost and thus may be warranted at >9.4 mg/dL for levels estimated with either the conventional equation or the novel equation. Also, patients with hyperphosphatemia and/or those at high risk of cardiovascular disease may require aggressive management of hypercalcemia given its association with vascular calcification.[7] On the other hand, a cut-off value of 10.2 mg/dL may be warranted for patients with a high treatment threshold, including those who would require treatment with cinacalcet or surgical intervention such as parathyroidectomy to lower serum calcium concentrations given the cost, potential adverse effects, and/or invasive nature of these treatments.

Given the comparable Youden index and net benefit between the conventional equation and the novel equation at 9.4 mg/dL, an alternative way to address the discordant calcium status may be to use the conventional equation with this lower cut-off value. This is compatible with the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines that suggested maintaining serum calcium within the lower normal range.[9] However, among patients who are categorized as high-normal calcium status according to the conventional equation, there appeared to be an incremental mortality risk associated with higher calcium levels defined by the novel equation, suggesting better stratification of all-cause and cardiovascular mortality risk attributed to calcium status by using the novel equation.

We acknowledge that the large size of the dialysis organization may have limited optimal processing needed for measurements of ionized calcium. For optimal measurement of ionized calcium, arterial blood samples should be collected and processed anaerobically with complete filling of the sampling tube kept on ice and should be immediately assayed without being exposed to ambient environment to avoid change in pH owing to loss of carbon dioxide.[35,36] We selected samples collected for simultaneous serum bicarbonate measurement from patients who did not use central venous catheter, and there are no significant differences in pH and bicarbonate concentrations between blood samples obtained from arteriovenous fistula versus femoral artery in hemodialysis patients.[37] However, the use of the administrative data did not allow us to identify which samples were processed appropriately. We Ionized calcium data were not used if indicated as post-dialysis measurements, but we cannot deny the possibility that some samples were collected after dialysis treatment for unexpected reasons. Other factors that may affect the association between total and ionized calcium include fasting versus non-fasting status and circadian

rhythm.[38] Nevertheless, the stronger correlation with intact PTH and the superior predictability for cardiovascular mortality of our equation versus the conventional equation was consistent with the physiological actions of ionized calcium (ie, inhibition of PTH secretion and induction of arterial calcification), supporting the need for developing a new strategy to estimate ionized calcium status more accurately.

Another limitation of this study is that the novel equation may not be extrapolated to measurements derived from other laboratories. A previous study demonstrated that total calcium corrected by the conventional equation substantially differed depending on albumin assays (ie, bromocresol green [BCG] versus bromocresol purple [BCP]).[39] The BCG method measures α- and β-globulin fractions, whereas the BCP method is more specific to albumin and provides lower values than the BCG method. It should be noted that calcium also binds to globulins, and both the conventional and the novel equation use albumin measured with the BCG method. Furthermore, the normal reference range may differ even with the same assay, which may explain the reason why previous studies failed to validate the published correction equations.[40] Together with the inaccuracy of the conventional correction equation in hemodialysis patients, the variations in reference ranges among laboratories might have resulted in inconsistent and underestimated associations of calcium with clinical outcomes among previous studies in this population. Therefore, a laboratory-specific equation to correct total calcium values should be established in institutions with different assays and reference ranges from our study. Globulins may need to be accounted for in laboratories using the BCP method.

In conclusion, a novel correction equation for total serum calcium was derived and validated in a national cohort of hemodialysis patients in the United States. This novel equation appeared to have superior stratification of mortality risk in a hemodialysis population compared with the conventional correction equation currently used in clinical practice. Given the differences in assays and reference ranges among associated variables such as serum albumin, a laboratory-specific correction equation should be established and tested for improvement in clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' roles: Study design: YO, RM, MBR, DVN, and KKZ. Study conduct: YO, RM, MBR, VR, DVN, and ES. Data collection: RM and KKZ. Data analysis: YO, YC, and ES. Data interpretation: YO, RM, MBR, ES, CMR, WL, DVN, CPK, and KKZ. Drafting manuscript: YO. Revising manuscript content: RM, MBR, ES, CMR, WL,

CPK, and KKZ. Approving final version of manuscript: YO, RM, MBR, ES, YC, DVN, CMR, WL, CPK, and KKZ. KKZ takes responsibility for the integrity of the data analysis.

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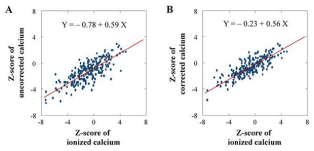

Fig. 1.

Scatter plots between ionized calcium concentrations and (*A*) uncorrected total calcium and (*B*) conventional albumin-corrected total calcium among 242 patients in the derivation data set. All values are expressed as *Z*-scores (see Materials and Methods for detail).

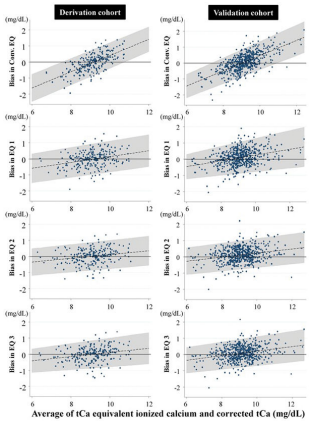

Fig. 2.

Bland-Altman plots of total calcium corrected by the conventional equation (EQ), EQ1, EQ2, and EQ3 in the derivation data set of 242 patients (the left panels) and the validation data set of 566 patients (the right panels). The *y* axis denotes the bias in each equation calculated by (total calcium-equivalent ionized calcium value) – (total calcium value corrected by a given equation). Conv. = conventional; tCa = total calcium.

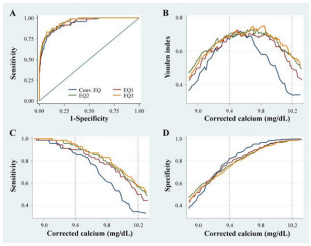

Fig. 3.

(*A*) Receiver operating characteristic curve, (*B*) Youden index, (*C*) sensitivity, and (*D*) specificity of total calcium corrected by the conventional equation (EQ), EQ1, EQ2, and EQ3 against ionized hypercalcemia (ionized calcium >1.32 mmol/L) in the validation data set of 566 patients. Dotted vertical lines were placed at 9.4 mg/dL and 10.2 mg/dL. Sensitivity and specificity at 10.2 mg/dL against ionized hypercalcemia was 34% and 100%, 50% and 99%, 57% and 99%, and 57% and 98% for the conventional EQ, EQ1, EQ2, and EQ3, respectively. Likewise, sensitivity and specificity at 9.4 mg/dL against ionized hypercalcemia was 87% and 82%, 90% and 78%, 94% and 76%, and 94% and 74% for the conventional EQ, EQ1, EQ2, and EQ3, respectively. Conv. = conventional.

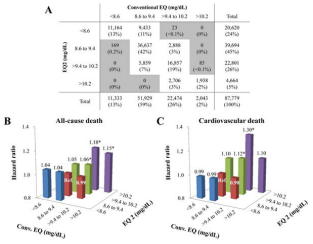

Fig. 4.

(*A*) Concordance and discordance of calcium status between the conventional equation (EQ) and EQ2 and their association with (*B*) all-cause and (*C*) cardiovascular mortality among 87,779 hemodialysis patients who survived the first 6 months of dialysis and who had data on total calcium, albumin, and phosphorus during months 4–6. Gray cells in *A* indicate groups where hazard ratios were not reported because of a limited number of patients. $^{*}p < 0.05$ (*B* and *C*).: Conv. = conventional.

Table 1

Characteristics of 242 and 566 Hemodialysis Patients From South Atlantic Division (the Derivation Data Set) and the Other Divisions (the Validation Data Set), Respectively

		Derivation cohort	Validation cohort	
Variable	**Normal range**	**30 facilities in the South Atlantic division (*n* = 242; 30%)**	**72 facilities in the other divisions (*n* = 566; 70%)**	**Std. diff.**
Age (years)		59 ± 15	61 ± 16	−0.14
Male		134 (55%)	336 (59%)	−0.08
Race				
Non-Hispanic white		72 (30%)	396 (70%)	−0.88
Non-Hispanic black		168 (69%)	93 (16%)	1.27
Hispanic		2 (1%)	77 (14%)	−0.51
Other races		7 (3%)	38 (7%)	−0.18
Diabetes		142 (59%)	352 (62%)	−0.07
ESRD vintage (month)		13 (IQR, 8 to 23)	15 (IQR, 9 to 25)	−0.09
Laboratories				
Ionized calcium (mmol/L)	(1.16 to 1.32)	1.20 ± 0.11	1.22 ± 0.11	−0.11
>1.32 mmol/L		27 (11%)	70 (12%)	−0.04
Uncorrected calcium (mg/dL)	(8.6 to 10.2)	8.9 ± 0.8	8.9 ± 0.7	0.00
>10.2 mg/dL		4 (2%)	19 (3%)	−0.11
Corrected calcium (mg/dL)	(8.6 to 10.2)	9.1 ± 0.7	9.1 ± 0.7	0.00
>10.2 mg/dL		6 (2%)	25 (4%)	−0.11
Albumin (g/dL)	(3.5 to 5.7)	3.8 ± 0.5	3.8 ± 0.5	0.00
Phosphorus (mg/dL)	(2.5 to 5.0)	5.2 ± 1.6	5.1 ± 1.6	0.05
Bicarbonate (mmol/L)	(21 to 31)	24.0 ± 3.2	23.4 ± 3.3	0.17

Values are expressed as mean ± SD, median (IQR), or *n* (percentage), appropriately. SI conversion factors: To convert total calcium to mmol/L, multiply by 0.25; phosphorus to mmol/L, multiply by 0.323; bicarbonate to mmol/L, multiply by 1.0. Standardized differences of 0.8, 0.5, and 0.2 in absolute values are considered large, medium, and small differences.

Std. diff. = standardized difference.

Table 2

Beta Coefficients (95% Confidence Intervals) for the Variables Included in Models 1–3 and the Performance of Each Model Fitted in the Derivation Data Set of 242 Patients From South Atlantic Division

	Model 1	Model 2	Model 3[a]
Total calcium (per 1 mg/dL)	1.35 (1.27 to 1.43)	1.34 (1.26 to 1.41)	1.36 (1.28 to 1.44)
Albumin (per 1 g/dL)	−0.71 (−0.87 to −0.56)	−0.65 (−0.80 to −0.51)	−0.53 (−0.71 to −0.35)
Phosphorus (per 1 mg/dL)	N/A	−0.13 (−0.17 to −0.09)	−0.14 (−0.18 to −0.10)
Albumin × bicarbonate (per 1 mg/dL × mmol/L)	N/A	N/A	−0.006 (−0.012 to −0.001)
Constant	−0.24 (−1.03 to 0.56)	0.35 (−0.36 to 1.05)	0.32 (−0.40 to 1.04)
Adjusted R^2	0.77 (0.69 to 0.85)	0.80 (0.72 to 0.86)	0.81 (0.74 to 0.87)
AIC	373	335	331

[a]Among candidate variables, bicarbonate, total calcium^2, albumin^2, phosphorus^2, bicarbonate^2, albumin × total calcium, and albumin × phosphorus were dropped by AIC-based backward elimination.

N/A = not available; AIC = Akaike's information criterion.

Table 3

Beta Coefficient and Performance of Uncorrected Total Calcium and Corrected Calcium Using the Conventional and Novel Equations in the Derivation and Validation Data Set

	Uncorrected calcium	Conventional equation	Equation 1	Equation 2	Equation 3
Coefficient					
Total calcium (mg/dL)	1	1	1.35	1.35	1.35
Albumin (g/dL)		−0.8[a]	−0.70	−0.65	−0.55
Phosphorus (mg/dL)				−0.15	−0.15
Albumin × bicarbonate					−0.005
Constant		3.2[a]	−0.25	0.30	0.40
Derivation data set (n =242)					
Adjusted R^2 (95% CI)	0.65 (0.53–0.73)	0.71 (0.62–0.77)	0.77 (0.68–0.84)	0.80 (0.72–0.86)	0.81 (0.73–0.87)
AIC	474	433	374	337	332
Validation data set (n = 566)					
Adjusted R^2 (95% CI)	0.57 (0.50–0.63)	0.68 (0.64–0.72)	0.74 (0.68–0.79)	0.79 (0.74–0.83)	0.79 (0.75–0.83)
AIC	1211	1044	922	818	798

[a]If serum albumin <4.0 mg/dL.

AIC = Akaike's information criterion.

Table 4

Sensitivity and Specificity and Their 95% Exact Binomial Confidence Intervals for Detecting High Ionized Calcium Levels (>1.32 mmol/L) in the Validation Data Set (n = 566)

Cut-off point	Equation	Sensitivity (95% CI)	Specificity (95% CI)
>10.2 mg/dL	Conventional	0.34 (0.23, 0.47)	1.00 (0.99, 1.00)
	Equation 1	0.50 (0.38, 0.62)	0.99 (0.97, 0.99)
	Equation 2	0.57 (0.45, 0.69)	0.99 (0.97, 0.99)
	Equation 3	0.59 (0.46, 0.70)	0.99 (0.97, 0.99)
>9.4 mg/dL	Conventional	0.87 (0.77, 0.94)	0.82 (0.79, 0.86)
	Equation 1	0.90 (0.80, 0.96)	0.79 (0.75, 0.82)
	Equation 2	0.94 (0.86, 0.98)	0.76 (0.72, 0.80)
	Equation 3	0.93 (0.84, 0.98)	0.75 (0.71, 0.79)

Table 5

Nonparametric Correlation Between Each Calcium Index and Intact Parathyroid Hormone Among 564 Patients Who Had Data on Intact Parathyroid Hormone in the Validation Data Set

	Uncorrected calcium	Conventional equation	Equation 2	Ionized calcium
Overall	−0.05 (−0.13 to 0.05)	−0.17 (−0.25 to −0.08)	−0.22 (−0.30 to −0.13)	−0.25 (−0.33 to −0.16)
Calcium salts				
Yes (25%)	−0.28 (−0.43 to −0.08)	−0.31 (−0.47 to −0.12)	−0.38 (−0.53 to −0.21)	−0.35 (−0.50 to −0.18)
No (75%)	0.04 (−0.06 to 0.15)	−0.12 (−0.21 to −0.02)	−0.16 (−0.25 to −0.06)	−0.22 (−0.31 to −0.12)
Lanthanum/sevelamar				
Yes (33%)	−0.03 (−0.19 to 0.13)	−0.13 (−0.28 to 0.02)	−0.17 (−0.32 to −0.01)	−0.22 (−0.37 to −0.07)
No (67%)	−0.06 (−0.18 to 0.04)	−0.19 (−0.30 to −0.08)	−0.24 (−0.34 to −0.14)	−0.26 (−0.35 to −0.16)
Cinacalcet				
Yes (10%)	0.13 (−0.20 to 0.44)	0.08 (−0.25 to 0.38)	0.04 (−0.28 to 0.36)	0.05 (−0.27 to 0.36)
No (90%)	−0.07 (−0.16 to 0.02)	−0.20 (−0.29 to −0.11)	−0.25 (−0.34 to −0.16)	−0.29 (−0.37 to −0.20)
VDRAs				
Yes (68%)	−0.04 (−0.15 to 0.07)	−0.10 (−0.20 to 0.01)	−0.16 (−0.26 to −0.05)	−0.17 (−0.27 to −0.06)
No (32%)	−0.15 (−0.31 to 0.02)	−0.35 (−0.47 to −0.20)	−0.37 (−0.49 to −0.22)	−0.43 (−0.55 to −0.28)

Values are expressed as bias-corrected Spearman's ρ (95% bootstrap confidence intervals). VDRAs included calcitriol, paricalcitol, and doxercalciferol, either oral or intravenous.

VDRAs = vitamin D receptor activators; PTH = parathyroid hormone.