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Research Article

New Population- and Laboratory-Specific Albumin-Adjusted Calcium Equation: Derivation and Internal Validation

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ABSTRACT

Background: Albumin-adjusted calcium equations are influenced by both analytical methods and population characteristics. Existing albumin-adjusted calcium equations, such as the Payne formula, were derived using older assays and often overcorrect or undercorrect in modern laboratory settings. This study aimed to derive and internally validate a new locally appropriate correction equation.
Methods: A total of 3585 calcium–albumin pairs were analyzed. Serum calcium and albumin values were divided into derivation and validation groups. Linear regression, shrinkage assessment, and Bland–Altman analysis were performed. A Payne-format corrected calcium equation was derived.
Results: The regression model produced the equation Ca = 5.6812 + 0.8443×Albumin. The new Adjusted calcium formula was: Adjusted Ca = Measured Ca + 0.8443× (4 – Albumin). Shrinkage between derivation and validation groups was low (0.0228) which indicates good internal validity. Comparison with the traditional formula showed systematic differences.
Conclusion: The derived formula demonstrates higher internal validity and better agreement than the historical Payne equation. Laboratories should consider population-specific and laboratory specific equations for improved clinical accuracy.

Keywords*: Albumin-Adjusted Calcium, Internal validation, Regression analysis, Hypoalbuminemia, Calcium status classification.*

INTRODUCTION

Calcium is the fifth most abundant element in the body with >99% residing in the skeleton as hydroxyapatite, a complex calcium phosphate molecule. This mineral supplies the strength to bones that support locomotion, but it also serves as a reservoir to maintain serum calcium concentrations(1). Its metabolism is regulated by 3 major transport systems: intestinal absorption, renal reabsorption, and bone turnover(1). Serum calcium concentration is maintained within a very narrow range. Approximately 45% of the plasma calcium is bound to plasma proteins, notably albumin. Approximately 15% is bound to small anions such as phosphate and citrate(2). Most laboratories report total serum calcium concentration, which usually ranges between 8.6 – 10.3mg/dl(3). If there is a reduction in the serum albumin, the portion of the calcium bound to protein will fall. This will reduce the total serum calcium. This reduction in the portion of calcium bound to protein will occur even if the ionized calcium (the physiologically important portion) is normal or elevated(4). A significant portion of calcium circulates bound to albumin, low serum albumin levels may result in a low serum total calcium despite normal ionized calcium levels(4). Each 1 g/dL reduction in the serum albumin concentration will lower the total calcium concentration by approximately 0.8 mg/dL (0.2 mmol/L) without affecting the ionized calcium concentration and, therefore, without producing any symptoms or signs of hypocalcemia(4). One commonly used equation which continues to be widely mentioned in text books and hence familiar to clinical people is Adjusted calcium (CaAd) (mmol/L) = Measured Total Ca (CaT) (mmol/L) + 0.02 (40- [albumin] (g/L) or CaAd (mg/dL) = CaT (mg/dL) + 0.8 * (4.0 - Serum Albumin [g/dL]). This equation was derived using cresophthaleincomplexone and bromocresol green (BCG) methods for measuring serum total calcium and serum albumin respectively(5). Albumin-adjusted calcium equations are derived from regression between measured calcium and albumin concentrations. Changes in analytical methods, particularly calcium assays, alter the regression slope and intercept, which may invalidate older equations. Therefore, laboratory-specific equations may provide more accurate interpretation. The aim of the study is to derive an albumin-adjusted calcium equation specific to our population and to our laboratory's total calcium and albumin methodologies.

MATERIALS AND METHODS

Present study was conducted in tertiary care hospital over a period of 6 months from June 2025 to December 2025. The study included patients from 18 – 80 years of age and included both inpatients and outpatients coming to tertiary care hospital. The study excluded patients with renal impairment, liver impairment, patients from endocrinology, oncology, intensive care units. Total of 3585 calcium–albumin pairs were analyzed.

Serum calcium was measured by Arsenazo dye III method and serum albumin was measured by Bromocresol green method on Beckman coulter AU5800. Quality control(QC) for serum total calcium and albumin was maintained using a Westgard multirule QC approach, with two levels of control materials analyzed in every run.

Serum calcium and albumin measurements were randomly divided into derivation(n = 1792) and validation sets(n = 1793). Linear regression was performed with calcium as the dependent variable and albumin as the predictor(6). The resulting regression equation was used to construct a Payne-style correction formula. The derived regression equation was subsequently evaluated in the validation set by estimating the degree of shrinkage in its predictive performance(7). This involved applying the equation developed from the derivation set to the validation set to generate predicted calcium values for each participant. These predicted values were then regressed against the actual measured calcium in the validation group to obtain the adjusted r^2. The adjusted r^2 from the validation group was compared with that of the derivation group, and the difference represented the shrinkage, indicating how much predictive strength is lost when the model is used in a new sample. A minimal shrinkage value suggests good internal validity(7). To further examine internal validity, a bootstrapping procedure was performed as recommended by James et al(7).

A new albumin-adjusted calcium equation was formulated by modifying the regression formula obtained from the derivation group, specifically by adjusting the y-intercept based on the difference between the intercept value and the mean serum total calcium of the study population. After deriving this updated equation, its clinical applicability was evaluated by comparing calcium status classifications within a subgroup of hypoalbuminemic patients (serum albumin < 3.5 gm/dl). In this subgroup, albumin-adjusted calcium values were calculated using both the existing correction formula and the newly developed equation. The differences between the two adjusted calcium values were examined using a Bland–Altman plot. The calcium status classification (hypocalcemia, normocalcemia, hypercalcemia) was further quantified using the weighted kappa statistic(7). In addition, the Wilcoxon signed-rank test was applied to compare calcium status outcomes before and after implementing the newly derived equation(7).

RESULTS

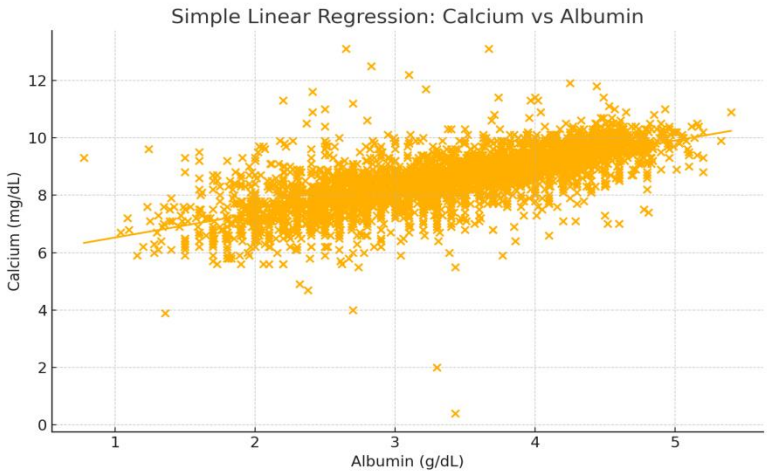
The present study analyzed a total of 3,585 participants, who were randomly allocated into a derivation set (n = 1,792) and a validation set (n = 1,793). Table 1 outlines the biochemical characteristics of both groups. The mean serum calcium and albumin concentrations in the derivation group were 8.50 mg/dL and 3.33 g/dL, respectively.

Table 1. Mean ± SD of Calcium and Albumin

Group	n	Calcium Mean	Calcium SD	Albumin Mean	Albumin SD
Derivation	1792	8.50	0.995	3.33	0.837
Validation	1793	8.47	1.048	3.31	0.841

The relationship between total calcium and serum albumin is given by linear regression formula Calcium = 5.6812 + 0.8443 × Albumin. The corrected calcium equation became Adjusted Ca(mg/dl) =Measured total Ca(mg/dl)+ 0.8443(4 – Albumin(gm/dl)). The shrinkage between validation and derivation group is 0.0228. This minimal shrinkage demonstrates excellent internal validity.

Figure 1. Simple linear regression of total calcium against albumin



To examine the clinical impact of this new equation, albumin-adjusted calcium values were compared with those obtained using the traditional Payne-type formula in 1,991 hypoalbuminemic patients (albumin < 3.5 g/dL). Bland–Altman analysis revealed a mean difference of –0.0576 mg/dL, indicating that the existing equation consistently produced slightly lower adjusted calcium values. The 95% limits ranged from –0.1024 to –0.0127 mg/dL, confirming a systematic negative bias. Weighted kappa analysis demonstrated excellent agreement between the two equations (κ = 0.93), reflecting consistent classification patterns despite the numerical differences in adjusted calcium values. A Wilcoxon signed-rank test confirmed that the difference between adjusted calcium values produced by the two formulas was highly statistically significant ($p < 0.0001$).

Among the 1,991 hypoalbuminemic patients, hypocalcemia classifications decreased from 566 to 510 using the new equation, while normocalcemia increased from 1,336 to 1,380 and hypercalcemia from 89 to 101. Overall, 68 patients were reclassified: 56 shifted from hypocalcemia to normocalcemia and 12 from normocalcemia to hypercalcemia.

Figure 2. Bland–Altman plot comparing the difference between albumin-adjusted calcium concentration derived using the classical Payne equation and the newly derived equation.

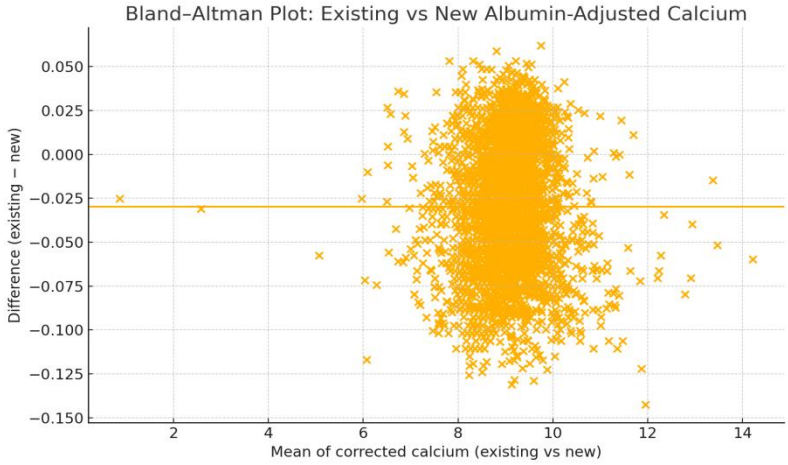


Table 2. Calcium Status Classification in 1,991 Hypoalbuminemic Patients

Existing ↓ / New →	Hypocalcemia < 8.6 mg/dL	Normocalcemia 8.6–10.3 mg/dL	Hypercalcemia > 10.3 mg/dL
Hypocalcemia (n = 566)	510	56	0
Normocalcemia (n = 1336)	0	1324	12
Hypercalcemia (n = 89)	0	0	89

Hypoalbuminemia defined as serum albumin < 3.5 g/dL.
Existing equation vs Newly derived equation comparison.

DISCUSSION

In the present study, we derived a calcium-adjustment (CaAd) equation based on our local laboratory dataset, which differs from those reported previously. This difference reinforces that variations in calcium–protein binding, particularly to albumin, contribute to measurable differences in total serum calcium levels(8). Albumin, being the primary calcium-binding protein, causes total serum calcium to fall in hypoalbuminemia without altering ionized calcium levels, a concept supported by clinical reviews of hypocalcemia and pseudohypocalcemia(1). The difference between equations can be due to racial or ethnic differences across populations, as well as variations in dietary patterns. Ashby et al. demonstrated that even within a single laboratory, a change in analytical methodology altered the regression coefficient describing calcium–albumin binding(9). Likewise, Barth et al. reported inter-laboratory variability in this relationship, despite the use of comparable assay platforms(10).These differences have been attributed mainly to modifications in the formulation of the bromocresol green (BCG) reagent used for albumin estimation, particularly its variable reactivity with serum globulins(10). In our study, albumin measurement was performed using the BCG method, consistent with previously published adjustment equations that were also developed using BCG-based assays(9)(10)(11)(12).

From a clinical standpoint, deriving laboratory-specific and population specific minimizes the risk of misdiagnosing hypo- or hypercalcemia, which is important because untreated calcium abnormalities can lead to severe neuromuscular manifestations, cardiac arrhythmias, seizures, and laryngospasm(1). Moreover, improper correction may lead to unnecessary treatments or missed diagnoses, especially in critically ill patients where albumin varies widely.

In addition, modern understanding of calcium physiology—including the interplay between PTH, vitamin D, and renal handling—underscores the need for precise biochemical interpretation. Population-level variations in calcium intake, protein status, chronic illness prevalence, and analytical platforms further justify the development of laboratory-specific correction models(14).

Previous research consistently highlights the limitations of universal calcium correction formulas. The Payne equation, though historically influential, overestimates calcium in hypoalbuminemic patients and underestimates it in hyperalbuminemia due to its fixed correction factor. The regression slope of 0.8443 derived in this study differs meaningfully from Payne's 0.8, reflecting assay-specific and population-specific factors. Similar findings have been reported in multiple institutional studies, including those from tertiary centres examining adjusted calcium accuracy across various albumin methodologies(13).

The Bland–Altman analysis in this study provides an important clinical insight that although the two formulas follow a similar mean trend, systematic bias exists, with the classical formula consistently producing higher corrected calcium values across the measurement range. This shows similarity with the earlier validation papers indicating that incorrect use of universal correction formulas may lead to incorrect classification of calcium disorders.

Overall, the derived equation displayed strong internal validity and improved agreement compared with the classical formula. Laboratories using modern assays should consider validating or replacing older correction equations to enhance diagnostic accuracy.

CONCLUSION

This study provides a population-specific albumin-adjusted calcium formula based on regression analysis and internal validation. The newly developed equation offers improved performance over the classical Payne formula and reduces the risk of misclassification. Adoption of updated correction formulas tailored to laboratory methods and to the local population is recommended to improve clinical decision-making.

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