IONIZED CALCIUM OUTPERFORMS CORRECTED CALCIUM FOR HYPERCALCEMIA ASSESSMENT IN MULTIPLE MYELOMA

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INTRODUCTION

Hypercalcemia is one of the four original CRAB criteria, defined as a serum calcium level >1 mg/dL above the upper limit of normal or >11 mg/dL. In patients with multiple myeloma (MM), disease-related protein abnormalities may impair the accuracy of total serum calcium for detecting hypercalcemia. Although current guidelines recommend corrected calcium for the diagnosis of hypercalcemia, ionized calcium represents the biologically active fraction. However, it has not been validated in MM and may have superior diagnostic utility in this clinical context.

AIM

To **evaluate the diagnostic performance**, **validity,** and **concordance** of **ionized calcium compared** with **serum calcium** for **detecting hypercalcemia** in patients with **multiple myeloma.**

METHOD

-Retrospective, observational, single-center study was conducted at a tertiary care hospital in Mexico.

-Adults with confirmed between January 2013 and April 2026 who had simultaneous corrected and ionized calcium measurements.

-Hypercalcemia was defined as corrected calcium >11 mg/dL and ionized calcium >5.2 mg/dL.

-Diagnostic performance was assessed using sensitivity, specificity, predictive values, and ROC analysis. Correlation was evaluated with Spearman rho, and agreement between two quantitative measurement techniques was evaluated with Bland–Altman analysis and the intraclass correlation coefficient (ICC).

-Calcium values were normalized to their respective upper limits of normal. The effects of hypoalbuminemia and paraproteinemia were analyzed using stratified Bland–Altman analysis and linear regression.

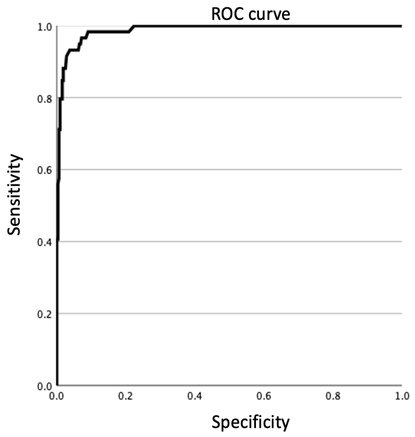
CONCLUSIONS

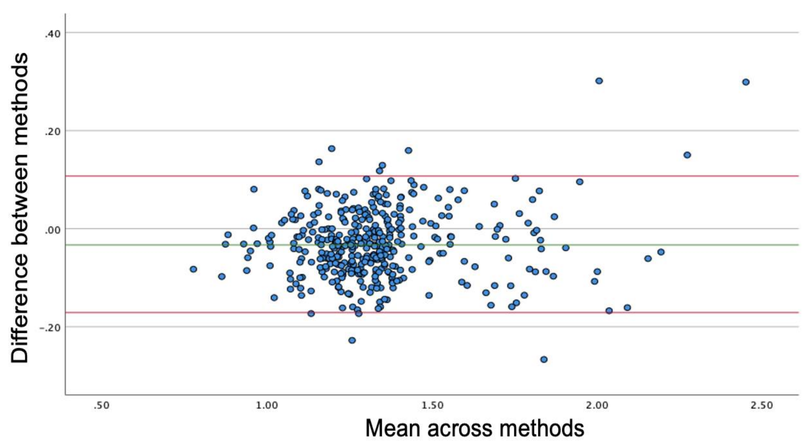
In patients with multiple myeloma**, ionized calcium demonstrated excellent diagnostic performance for the detection of hypercalcemia**, with **high sensitivity, specificity**, and discriminative ability. **Ionized calcium** showed a **strong correlation** and **good agreement with Corrected calcium.** Bland–Altman analysis demonstrated moderate individual variability between the two methods. Albumin significantly influenced the discrepancy between both methods, whereas paraproteinemia mainly affected variability.

RESULTS

105 patients with **380 simultaneous** measurements were include**. Median age was 62 years** (range, 34–86), and **56% were male**. **Hypoalbuminemia was present in 56.1%** of measurements and **paraproteinemia in 44.7%.** Heavy-chain involvement was present in 70% (n = 266) of measurements, of which 52.9% (n = 201) were IgG-related. Light-chain involvement was present in 99.5% (n = 378), and 52.9% (n = 201) had kappa light-chain involvement. **Hypercalcemia was identified in 15.5% (n = 59) of measurements using corrected calcium and in 18.4% (n = 70) using ionized calcium.** Ionized calcium demonstrated 93.2% sensitivity, 95.3% specificity, 78.6% positive predictive value, and 98.7% negative predictive value. ROC analysis showed excellent discriminative performance (AUC, 0.988; 95% CI, 0.978–0.997; p < 0.001), with an optimal cutoff of 5.15 mg/dL. Corrected and ionized calcium showed strong correlation (Spearman rho = 0.797; p < 0.001) and good agreement (ICC = 0.877; 95% CI, 0.802–0.918).

Bland–Altman analysis demonstrated a **mean bias of −0.0317** (limits of agreement, −0.1709 to 0.1075), **showing a slight tendency of corrected calcium to underestimate ionized calcium**. The **ICC showed good agreement between corrected calcium and ionized calcium** (ICC = 0.877; 95% CI, 0.802–0.918; p < 0.001). Stratified analysis demonstrated that patients with hypoalbuminemia had a mean bias of −0.0093 (limits of agreement, −0.1474 to 0.1288). Patients with elevated paraprotein levels had a mean bias of −0.0140 (limits of agreement, −0.1702 to 0.1422). In multiple linear regression analysis, **hypoalbuminemia was significantly associated with the difference between corrected and ionized calcium measurements** (β = −0.430, p < 0.001), whereas paraproteinemia was not (β = 0.036; p = 0.478).





TAKE-HOME MESSAGE

Ionized calcium may therefore represent a more accurate method for evaluating calcium status in this population.

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REFERENCES

1. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. JAMA. 2022;327(5):464-477.
2. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2024;99(9):1802-1824.
3. Kenny CM, Murphy CE, Boyce DS, Ashley DM, Jahanmir J. Things we do for no reason: calculating a “corrected calcium” level. J Hosp Med. 2021;16(7):E1-E2.
4. Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J. 1973;4:643-646.