ORIGINAL ARTICLE

Serum Calcium Levels as a Marker of Dengue Severity: A Clinical Observational Study

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Abstract

Background: Dengue fever continues to pose a major global health challenge. Electrolyte disturbances, particularly hypocalcemia, are frequently observed in dengue but are underutilized for prognostication.

Objective: To evaluate the relationship between corrected serum calcium levels and dengue severity.

Materials and methods: A prospective observational study of 210 adult patients with confirmed dengue was conducted at Shiv Ram Hospital. Serum calcium was measured within 24 hours of admission and corrected for albumin. Severity was classified per World Health Organization (WHO) 2009 criteria. Correlation analyses and multivariate logistic regression were used to assess associations with clinical and laboratory parameters.

Results: Mean corrected serum calcium declined with increasing severity (group A: 8.39 ± 0.59 mg/dL, group B: 8.05 ± 0.62 mg/dL, group C: 7.61 ± 0.67 mg/dL; $p < 0.001$). Hypocalcemia (<8.5 mg/dL) was observed in 91.3% of severe cases. Calcium levels negatively correlated with hematocrit, platelet count, and hospitalization duration ($p < 0.01$). Hypocalcemia independently predicted severe dengue (aOR: 3.94; 95% CI: 1.98–7.84; $p < 0.001$).

Conclusion: Hypocalcemia is a frequent and significant predictor of severe dengue. Serum calcium offers a simple, cost-effective tool for early triage and management in dengue-endemic regions.

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Introduction

Dengue fever, a mosquito-borne viral illness caused by the dengue virus (DENV), affects nearly 390 million individuals annually, with approximately 96 million symptomatic cases.[1] India remains hyperendemic, witnessing escalating outbreaks that strain public health systems.[2] Clinical manifestations range from mild febrile illness to life-threatening complications, including plasma leakage, hemorrhage, and multiorgan dysfunction. The 2009 World Health Organization (WHO) classification framework, although helpful, depends on the appearance of warning signs that may not always be timely or specific.[3] Hence, identifying simple, accessible, and early biomarkers of severity remains a pressing priority.

Electrolyte imbalances are common in dengue, with hypocalcemia being frequently reported in both adult and pediatric populations.[4] Calcium is integral to cellular signaling, vascular integrity, platelet aggregation, and cardiac contractility, all of which are crucial in dengue pathophysiology.[5] Infection-induced capillary leakage, proinflammatory cytokines [interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)], and hypoalbuminemia are known to disrupt calcium homeostasis.[6,7] Moreover, reduced total and ionized calcium levels have been implicated in shock, bleeding tendencies, and poor outcomes in various infectious diseases.[8]

This study investigates whether corrected serum calcium levels, obtained early during hospitalization, can serve as a reliable and cost-effective marker of dengue severity. It aims to correlate calcium levels with clinical severity, laboratory abnormalities, and patient outcomes in a representative Indian population.

Materials and Methods

Study Design and Setting

This was a prospective observational study conducted between July 2023 and October 2024 at a tertiary care center catering to both rural and semi-urban populations.

Inclusion and Exclusion Criteria

Adults aged 18 years and older with confirmed dengue infection based on NS1 antigen and/or IgM ELISA were included. Patients with chronic kidney disease, parathyroid disorders, malignancies, or on calcium supplementation were excluded.

Data Collection

Demographic details, comorbidities, clinical symptoms, and laboratory parameters were recorded on predesigned case report forms. Blood samples collected within 24 hours of admission were tested for total serum calcium, albumin, hematocrit, platelet count, liver function, and renal function. Corrected calcium was calculated using Payne's formula. A random subset ($n = 38$) underwent ionized calcium estimation using ion-selective electrode technology.

Clinical severity was categorized based on WHO 2009 classification:

Group A: Dengue without warning signs.

Group B: Dengue with warning signs.

Group C: Severe dengue (plasma leakage, bleeding, or organ failure).

Hypocalcemia was defined as corrected calcium <8.5 mg/dL.

Statistical Analysis

Data were analyzed using SPSS v. 26. Continuous variables were expressed as mean ± SD or median [interquartile range (IQR)] and compared using ANOVA or Kruskal–Wallis tests. Categorical variables were compared using Chi-squared tests. Pearson or Spearman correlations assessed associations between calcium and clinical/laboratory parameters. A multivariate logistic regression model identified predictors of severe dengue. Model calibration was tested with the Hosmer–Lemeshow goodness-of-fit test. A p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics and Severity Distribution

Demographic Characteristics

Out of 210 patients, 120 were male (57.1%), and the mean age was 32.4 ± 11.8 years. Table 1 details demographic data across severity categories. No statistically significant

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differences were observed in age or comorbidities across groups.

Corrected Calcium and Severity Correlation

Mean corrected calcium decreased with increasing severity (group A: 8.39 ± 0.59 mg/dL, group B: 8.05 ± 0.62 mg/dL, group C: 7.61 ± 0.67 mg/dL; F = 14.25; $p < 0.001$). Hypocalcemia prevalence rose from 43.5% in group A to 91.3% in group C ($\chi^2 = 25.4$; $p < 0.001$) (Fig. 1).

Correlations and Outcomes

Calcium levels negatively correlated with hematocrit ($r = -0.42$; $p < 0.001$) and duration of hospitalization ($r = -0.45$; $p < 0.001$), while positively correlating with platelet count ($r = 0.38$; $p < 0.01$) (Fig. 2). Patients with calcium <7.5 mg/dL had significantly longer hospital stays (7.2 vs 4.8 days; $p < 0.01$) and more frequent intensive care unit (ICU) admissions (28.3 vs 9.1%; $\chi^2 = 11.8$; $p < 0.001$) (Table 2).

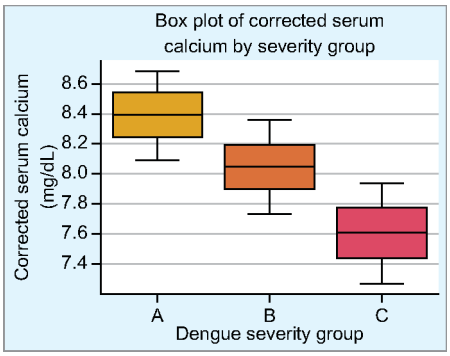


Fig. 1: Box plot of corrected serum calcium by severity group

Logistic Regression Analysis

Hypocalcemia was an independent predictor of severe dengue (aOR: 3.94; 95% CI: 1.98–7.84; $p < 0.001$). Hematocrit was also significant (aOR: 1.12; 95% CI: 1.03–1.20; $p = 0.006$). Age and albumin were not statistically significant predictors (Table 3).

The ANOVA was used for continuous variables, and the Chi-squared test was used for categorical data.

Multivariate logistic regression was performed, with Wald Chi-square values shown.

Discussion

This study underscores the clinical utility of serum calcium as a prognostic marker in dengue fever. Hypocalcemia was highly prevalent among patients with severe dengue and showed a strong inverse relationship with key severity indicators such as hematocrit, platelet count, and hospitalization duration. Importantly, hypocalcemia emerged as an independent predictor of severe dengue on multivariate regression analysis, suggesting its value in clinical triage.

Several pathophysiological mechanisms likely underpin the calcium derangements observed in dengue. Calcium is a tightly regulated ion, essential for membrane stability, vascular tone, intracellular signaling, and homeostasis. The endothelial dysfunction in dengue, driven by proinflammatory cytokines such as IL-6 and TNF-α, can significantly disturb calcium homeostasis by altering membrane calcium channels and transporter expression.[5] This may lead to increased transcellular calcium flux and extravascular loss, particularly during the critical phase marked by plasma leakage.

Hypoalbuminemia, commonly reported in dengue due to capillary leak and hepatic dysfunction, further contributes to decreased total serum calcium levels. Although only ionized calcium reflects biologically active calcium, our study demonstrates that corrected total calcium—calculated using Payne's formula—still provides clinically significant information. This is especially relevant in low-resource settings where ionized calcium measurement is not routinely feasible.[9]

The observed negative correlation between calcium and hematocrit likely reflects the shared pathophysiological pathway of capillary leak. As plasma escapes into interstitial spaces, hemoconcentration occurs (elevated hematocrit), and simultaneously, bound calcium is lost, explaining the parallel reduction in corrected calcium levels. Similarly, the positive correlation between calcium and platelet count aligns with the role of calcium in platelet activation and clot formation. Calcium deficiency impairs platelet aggregation, increasing bleeding risk, which is a hallmark of severe dengue.[4]

Table 1: Demographic characteristics by severity group

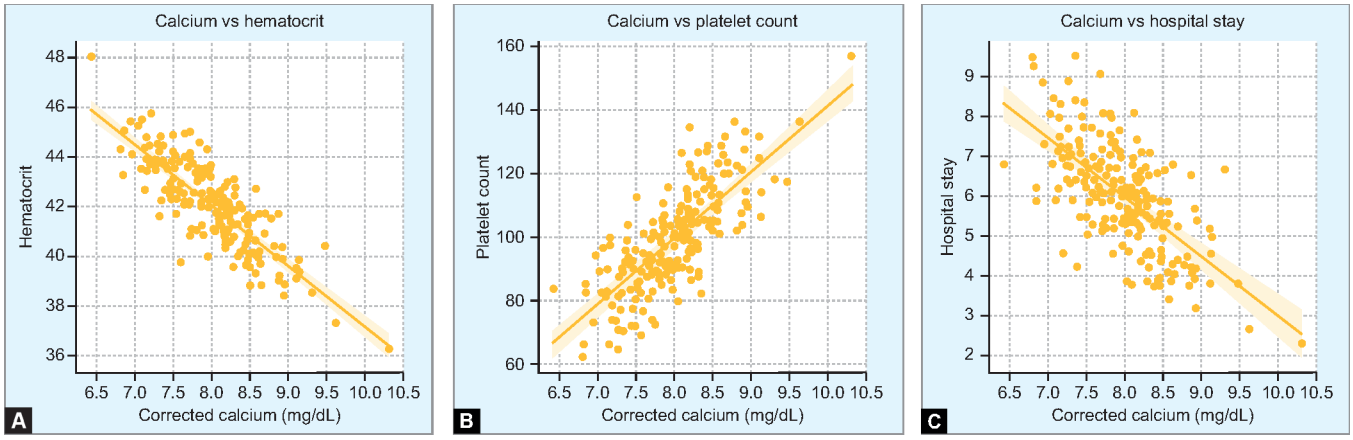
Variable	*Group A (n = 84)*	*Group B (n = 73)*	*Group C (n = 53)*	*Test statistic*	*p-value*
Age (years)	31.8 ± 12.3	33.1 ± 11.5	32.5 ± 11.2	F = 0.38	0.68
Male (%)	56.0	57.5	58.5	$X^2 = 0.12$	0.94
Diabetes (%)	16.7	16.4	17.0	$X^2 = 0.02$	0.98
Hypertension (%)	13.1	12.3	13.2	$X^2 = 0.05$	0.97

Table 2: Clinical and laboratory characteristics by severity group

Parameter	*Group A*	*Group B*	*Group C*	*Test statistic*	*p-value*
Corrected Ca (mg/dL)	8.39 ± 0.59	8.05 ± 0.62	7.61 ± 0.67	F = 14.25	<0.001
Hypocalcemia (%)	43.5	67.1	91.3	$X^2 = 25.4$	<0.001
Hematocrit (%)	38.1 ± 3.5	39.2 ± 4.1	41.7 ± 5.2	F = 5.98	0.002
Platelet count ($\times 10^9$/L)	98 ± 37	74 ± 26	48 ± 21	F = 21.67	<0.001
Hospital stay (days)	4.5 ± 1.6	5.3 ± 2.1	7.2 ± 2.8	F = 10.42	<0.001
ICU admission (%)	9.1	13.7	28.3	$X^2 = 11.8$	<0.001

Table 3: Logistic regression predicting severe dengue

Variable	*aOR*	*95% CI*	*Wald X^2*	*p-value*
Hypocalcemia	3.94	1.98–7.84	14.7	<0.001
Hematocrit	1.12	1.03–1.20	7.5	0.006
Age	1.01	0.98–1.05	1.37	0.24
Albumin	0.86	0.65–1.12	1.12	0.29



Figs 2A to C: Correlation plots of corrected serum calcium

Another critical observation is the association between hypocalcemia and hospitalization metrics. Patients with corrected calcium <7.5 mg/dL had significantly longer hospital stays and were more likely to require ICU admission. This supports the concept that hypocalcemia is not just a surrogate for severity but may also directly contribute to disease complications through its effect on cardiovascular stability, neuromuscular function, and coagulation.

The logistic regression analysis reinforces hypocalcemia as an independent risk factor for severe dengue, with an adjusted odds ratio of 3.94. Even after controlling for albumin, hematocrit, and age, calcium levels remained significantly associated with severity. This suggests that calcium levels offer additive predictive value beyond routine markers. Moreover, while hematocrit and platelet count are already used in clinical practice for dengue monitoring, calcium is rarely considered in prognostication algorithms. Our findings argue for its inclusion as a routine part of dengue evaluation.

This study underscores the clinical utility of serum calcium as a prognostic marker in dengue fever. Hypocalcemia was highly prevalent among patients with severe dengue and showed a strong inverse relationship with key severity indicators such as hematocrit, platelet count, and hospitalization duration. These findings are consistent with prior studies, including an Indian observational study that demonstrated a significant decline in calcium levels with increasing dengue severity.[9] Similar trends have been documented in Sri Lanka by Constantine et al.[10] and by Remya et al.,[11] supporting the broader applicability of calcium monitoring across populations. Our findings regarding predictors of ICU admission are consistent with previous studies on dengue severity.[12] Other tropical infections such as malaria, leptospirosis, and sepsis have also demonstrated hypocalcemia as a marker of poor prognosis, reinforcing its generalizable pathophysiological significance.[13]

Clinically, the ability to use corrected calcium as a triage tool is especially valuable in primary and secondary healthcare settings where rapid decision-making is critical and access to advanced diagnostics is limited. Serum calcium testing is widely available, inexpensive, and already integrated into basic metabolic panels. Its application could therefore be immediate and impactful, helping to prioritize patients for observation, intravenous fluids, and escalation of care.

However, it is also important to contextualize these findings. While hypocalcemia is clearly associated with severe dengue, whether calcium supplementation could modify outcomes remains an open question. Randomized trials are needed to determine whether correcting hypocalcemia therapeutically would reduce complications or shorten hospital stays. Additionally, serial measurements of calcium during the disease course may provide further insights into its dynamic role and prognostic trajectory.

A major limitation of our study is the single-center design, which may restrict generalizability. Ionized calcium was only measured in a subset of patients, limiting comprehensive comparison. Furthermore, our study did not include pediatric patients or track calcium values longitudinally. Despite these limitations, the consistency of our results with existing literature and the strength of statistical associations underscore the robustness of our findings.

Conclusion

This study establishes that corrected serum calcium levels measured at admission are strongly and independently associated with dengue severity. Hypocalcemia was significantly more prevalent in patients with severe dengue, and it correlated with key clinical outcomes such as hospitalization duration, hematocrit levels, and ICU admission rates. The findings suggest that serum calcium, a widely available and inexpensive test, can serve as an early biomarker to identify high-risk patients and guide triage in resource-limited settings. Incorporating calcium assessment into initial clinical evaluation protocols could enhance risk stratification and prompt timely interventions. Given the simplicity and accessibility of this tool, it holds substantial potential for public health impact in dengue-endemic regions, and its clinical application should be further validated through larger multicenter studies.

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