



## Study of Serum Calcium Levels as Early Prognostic Indicator and Its Association with Severity and Outcome of Dengue Fever

J A Deva <sup>1</sup>, Premkumar G <sup>2</sup>, J. Aarthi <sup>3</sup>, Gautam Sarkar <sup>4</sup>

<sup>1</sup>Post graduate, Department of General Medicine, AVMC&H, Pondicherry

<sup>2</sup>Professor, Department of General Medicine, AVMC&H, Pondicherry

<sup>3</sup>Assistant Professor, Department of General Medicine, AVMC&H, Pondicherry

<sup>4</sup>Professor, Department of Biochemistry, AVMC&H, Pondicherry

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### KEYWORDS

Dengue fever, serum calcium, prognostic indicator, severity, hypocalcemia, dengue outcome.

### ABSTRACT:

**Background:** Dengue fever is a significant vector-borne disease caused by the Dengue virus, transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. It presents with a wide clinical spectrum, from mild fever to severe manifestations like Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Early identification of severe cases is crucial for better management and reducing complications. Serum calcium plays a vital role in vascular integrity and coagulation, and its depletion has been associated with severe dengue cases.

**Aim:** To evaluate serum calcium levels as an early prognostic indicator in predicting the severity and outcome of dengue fever.

**Materials and Methods:** An observational cross-sectional study was conducted on 130 dengue-NS1Ag, IgM positive patients at Aarupadai Veedu Medical College. Patients aged 18–70 years were included. Serum calcium levels corrected for albumin were measured during different phases of dengue fever—febrile, critical, and convalescent. Categorised them as MILD/SEVERE DENGUE based on WHO CRITERIA of 1997. Statistical analysis was performed using SPSS version 28, with significance set at  $p < 0.05$ .

**Results:** The mean age of patients was 32.27 years, with a marginal female predominance (51.5%). Among the study population, 65.4% exhibited warning signs, including plasma leakage (54.2%) and abdominal pain with vomiting (45.8%). Blood transfusion was required in 47.7% of cases. Mild dengue was observed in 87.7%, while severe dengue occurred in 12.3% of patients. Serum calcium levels significantly decreased in the critical phase ( $8.51 \pm 0.61$  mg/dL) compared to the febrile phase ( $8.62 \pm 0.57$  mg/dL,  $p < 0.05$ ) and remained lower in the convalescent phase ( $8.52 \pm 0.63$  mg/dL,  $p < 0.05$ ). Patients with severe dengue had significantly lower calcium levels than those with mild dengue ( $p < 0.05$ ).

**Conclusion:** The study establishes a strong correlation between declining serum calcium levels and dengue severity. Serum calcium monitoring may serve as an early prognostic marker, allowing timely intervention to prevent complications. Further research is required to explore the role of calcium supplementation in dengue management.



## INTRODUCTION:

Dengue is a transmittable vector borne disease caused by member of flavi virus- Dengue virus. "They are grouped into four genetically and antigenically related viruses that are known as serotypes.<sup>1-4</sup> They are transmitted to humans by the vector mosquito *Aedes aegypti* or *Aedes albopictus*. Dengue has caused significant morbidity and mortality in our country and has been implicated as a major a public health problem.

In order to improve and guide better clinical practices, dengue illness is clinically classified into Dengue fever, Dengue haemorrhagic fever I, Dengue haemorrhagic fever II, Dengue haemorrhagic fever III, Dengue haemorrhagic fever IV. The natural history of Dengue illness progresses through three separate phases the acute febrile phase, the critical phase with plasma leakage and the convalescent or reabsorption phase.

A predicted 50 million dengue infections occur international annually and "about 2.5 billion human beings, i.e., -5<sup>th</sup> of world wide's population in tropical and subtropical nations are at hazard. The mentioned case fatality charge in India is 3-5%.<sup>5,6</sup> Dengue infection threatens approximately two-fifths of the world's population (those living in tropical and subtropical countries), or up to 2.5 billion people.<sup>7</sup> An estimated 50 million infections occur each year worldwide, with 0.5 million of these cases requiring hospitalisation for dengue haemorrhagic fever. Approximately 90% of these cases involve children under the age of five.<sup>7</sup> However, epidemiology is changing both regionally and globally. Adults are more likely than children to contract classic dengue fever.<sup>6</sup>

The infection is now endemic in over 100 countries, primarily in South East Asia, the Western Pacific, and the Americas.<sup>7-10</sup> Severe manifestations, such as dengue haemorrhagic fever and dengue shock syndrome, as well as other unusual manifestations, are becoming more common in previously unreported cases.

The relationship between serum calcium levels and dengue fever was analysed by various studies across the world and observed that calcium level is reduced in severe form of dengue infection. In in-vitro studies, the presence of calcium ion is obligatory for the cytotoxic

activity of the dengue virus and the cell death is associated with increased concentration of intracellular calcium ion. Therefore, it's postulated that hypocalcaemia in dengue fever could be due to the influx of calcium ions and calcium replacement could enhance the dengue virus activity by increasing the concentration of intracellular calcium ions.

## METHODOLOGY:

This Observational cross-sectional study conducted at Department of General Medicine, AVMC, Puducherry enrolled 130 patients whose Age  $\geq 18$  years to 70 years, both sex, Dengue positive patients (NS1Ag, IgM positive) by rapid card test in study period from July 2023 to November 2024 after obtaining informed written consent. The patients with pre-existing hepatic or renal dysfunction and endocrine disorders causing hypocalcemia like Hypoparathyroidism, Pseudohypoparathyroidism has been excluded. Ethical approval (IHEC No: AV/IHEC/2023/049) was obtained. Using data collection proforma demographic details, Patient ID, food habits, BMI, Clinical History like fever onset date, pre-existing disease history( DM,HTN, CARDIAC DISEASES), personal history (smoking and alcohol), Clinical status by General Physical Examination( conscious level, vitals), systemic examination ( CVS, RS, P/A, CNS), daily Haematocrit, platelet count, daily vitals, Warning signs( bleeding symptoms, Torniquet test, abdomen pain) daily, serum calcium level corrected for albumin at 3 different phases based on symptom onset ( febrile phase (1-3 days, critical phase ( 4-7 days), convalescent phase (>8 days), USG -Abdomen findings in critical and convalescent phase for plasma leakage, Daily Blood Transfusion during admission, Patient was discharged/referred/death and classified them based WHO criteria of 1997 for Dengue fever and classified them as DF,DHF I,II,III,IV and with DF, DHF I,II as MILD and DHF III& IV as SEVERE and measured the outcome variable Serum Calcium level corrected for albumin and correlated with severity of dengue fever. A total of 130 patients were selected via convenience sampling method. All the Patients data were collected in proforma and entered in excel sheet. The Categorical variables were summarized as frequency and percentage and Continuous variables summarized as mean  $\pm$  standard deviation. The Chi-square test or Fischer's



exact test was used to find the association between severity of dengue and serum calcium levels (corrected for albumin) and for continuous data unpaired t-test was used and follow-up data the paired t-test was used. For all statistical purpose a P- value less than 0.05 will be considered as statistically significant. The analysis of data was done using SPSS version 28.

## RESULTS:

Present study included total of 130 patients fulfilling inclusion criteria, with mean age of 32.27yrs. Among the 130, 48.5% were male and 51.5% were female with marginal female preponderance. Majority were local of Pondicherry 73.8% followed by 23.8% from Cuddalore. Among them 9.2% were vegetarian and 90.8% were mixed veg. The mean BMI of patients was found to be 25.2kg/m<sup>2</sup>. Among the comorbid condition, diabetes mellitus was present in 13.8%, hypertension in 15.4% and CAD in 8.5% of the patients. The warning signs of dengue fever were present in 65.4% of the patients. The various warning signs included with presence of 54.2% with plasma leakage, 45.8% with abdominal pain and vomiting, 31.7% with malena, 14.5% with gum bleeding, 14.1% with hypotension and 12.9% with prevaginal bleeding in females. Blood transfusion was given in 47.7% of the cases. Majority presented with mild dengue severity in 87.7% and 12.3% with severe dengue. Among the outcome 5.4% of the cases were referred to higher centres and 94.6% were discharged. Paired test showing the changes in mean level of plasma calcium. There is significant decrease in calcium level in critical phase (8.51±0.61) compared to febrile phase in patients (8.62±0.57) i.e (p<0.05) Similarly there is significant lower mean calcium levels in convalescent phase (8.52±0.63) compared to febrile phase (8.62±0.57) i.e (p<0.05). There is no significant difference noted in critical phase and convalescent phase, however the mean was slightly higher in convalescent phase compared to critical phase of dengue. There is significant association of decrease in calcium level with severity of dengue. The mean level of calcium in febrile phase, critical phase and convalescent phase were significantly lower in severe dengue compared to mild dengue (p<0.05).

## DISCUSSION:

Dengue fever is a mosquito-borne viral infection that poses a significant global health burden, especially in tropical and subtropical regions. “The disease spectrum ranges from mild febrile illness to severe manifestations, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Severe cases are often characterized by plasma leakage, multi-organ dysfunction, and coagulopathy, leading to increased morbidity and mortality. Early identification of patients at risk for severe dengue is critical for timely intervention and improved clinical outcomes.

Calcium plays an essential role in various physiological processes, including vascular integrity, neuromuscular function, and coagulation pathways. Emerging evidence suggests that serum calcium levels may serve as an early prognostic biomarker in critically ill patients, including those with dengue fever. Hypocalcemia, or reduced serum calcium levels, has been associated with increased disease severity, possibly due to endothelial dysfunction, cytokine-mediated inflammation, and capillary leakage observed in severe dengue cases.

This study aimed to assess the association between serum calcium levels and the severity of dengue fever across different phases of the disease—febrile, critical, and convalescent. The findings indicate a significant decrease in calcium levels during the critical phase compared to the febrile phase, with levels remaining low in the convalescent phase. Furthermore, patients with severe dengue exhibited significantly lower calcium levels than those with mild disease, highlighting the potential role of calcium as a prognostic marker.

Present study included total of 130 patients fulfilling inclusion criteria, with mean age of 32.27yrs. Among the 130, 48.5% were male and 51.5% were female with marginal female preponderance. Among the comorbid condition, diabetes mellitus was present in 13.8%, hypertension in 15.4% and CAD in 8.5% of the patients.

In similar, study by Uddin K et al., among the patients, 52 were men (approximately 62%) and 32 were women (about 38%).<sup>38</sup>



The warning signs of dengue fever were present in 65.4% of the patients. The various warning signs included with presence of 54.2% with plasma leakage, 45.8% with abdominal pain and vomiting, 31.7% with melena, 14.5% with gum bleeding, 14.1% with hypotension and 12.9% with prevaginal bleeding in females. Blood transfusion was given in 47.7% of the cases

In similar study by Manjunath VG et al., 16% had dengue without warning signs, 54.7% had dengue with warning signs, and 29.3% had severe dengue.<sup>41</sup> in Chatterjee R et al., study most common symptoms included fever (98%), rash with myalgia (86%), vomiting (72%), and abdominal pain (60%). Other symptoms were itching (38%), melena (31%), breathlessness (22%), CNS involvement (16%), and epistaxis (12%).<sup>44</sup>

Majority presented with mild dengue severity in 87.7% and 12.3% with severe dengue. Paired test showing the changes in mean level of plasma calcium. There is significant decrease in calcium level in critical phase ( $8.51 \pm 0.61$ ) compared to febrile phase in patients ( $8.62 \pm 0.57$ ). ( $p < 0.05$ ) Similarly there is significant lower mean calcium levels in convalescent phase ( $8.52 \pm 0.63$ ) compared to febrile phase ( $8.62 \pm 0.57$ ). ( $p < 0.05$ ) There is no significant difference noted in critical phase and convalescent phase, however the mean was slightly higher in convalescent phase compared to critical phase of dengue. There is significantly association of reduction in calcium level with severity of dengue. The mean level of calcium in febrile phase, critical phase and convalescent phase were significantly lower in severe dengue compared to mild dengue according to severity of dengue. ( $p < 0.05$ ).

In concordance to present study Baton SM et al., serum calcium levels are notably lower in patients with dengue shock syndrome compared to those with dengue fever. These calcium levels are not influenced by the patient's gender or nutritional status. Patients with dengue shock syndrome experience a significant drop in serum calcium, suggesting that calcium supplementation could be considered in the treatment of this condition.<sup>40</sup>

In line with present study, Manjunath VG et al., documented the mean calcium level in cases without

warning signs was 1.0950 mmol/l, with warning signs was 1.1088 mmol/l, and in severe cases was 1.0559 mmol/l, with severe cases having significantly lower calcium compared to those with warning signs ( $p = 0.04$ ). Hypocalcemia occurred in 56% of dengue cases compared to 14% of controls. All seven children with severe dengue who died had hypocalcemia. In conclusion, hypocalcemia is prevalent in dengue fever and lower ionic calcium levels are linked with more severe dengue, potentially serving as a prognostic indicator of poor outcomes.<sup>41</sup>

Singh A et al., demonstrates a clear link between hypocalcemia and the severity of dengue infection in children, suggesting that ionic calcium can be used as an early biochemical marker to identify severe dengue.<sup>42</sup>

The results suggest that routine monitoring of serum calcium levels in dengue patients could aid in early risk stratification and clinical decision-making. Identifying hypocalcemia early in the disease course may prompt more aggressive supportive management, including calcium supplementation if necessary. Further large-scale studies are needed to validate these findings and determine whether calcium correction could improve patient outcomes. Integrating calcium level assessment into dengue management protocols may contribute to better clinical prognosis and reduce complications associated with severe disease.

## Recommendations

Based on the findings of this study on serum calcium levels as an early prognostic indicator in dengue fever, the following recommendations are proposed:

- 1. Routine Monitoring of Serum Calcium Levels:**
  - Serum calcium levels should be routinely assessed in all dengue patients, especially during the febrile and critical phases, to identify early signs of severity and potential complications.



## 2. Early Identification of High-Risk Patients:

- Patients with significantly lower calcium levels should be closely monitored for worsening symptoms, as hypocalcemia is associated with increased disease severity.
- Special attention should be given to patients with comorbidities such as diabetes mellitus, hypertension, and coronary artery disease, as they may be at higher risk of complications.

## 3. Timely Interventions and Management:

- Early correction of hypocalcemia through appropriate calcium supplementation could be considered in patients with severe dengue to support recovery.
- Patients showing warning signs such as plasma leakage, bleeding tendencies, or hypotension should be prioritized for intensive care to prevent progression to severe dengue.

## 4. Public Health Strategies:

- Public awareness campaigns should emphasize early recognition of dengue warning signs and the importance of seeking timely medical attention.
- Preventive measures such as vector control, environmental sanitation, and community education should be strengthened to reduce the incidence of dengue.

## 5. Further Research and Policy Implementation:

- Larger multicentre studies should be conducted to validate the role of serum calcium as a prognostic marker

and its potential therapeutic implications.

- Clinical guidelines should incorporate serum calcium evaluation as part of the routine dengue management protocol for better patient stratification and improved outcomes.

By implementing these recommendations, the early detection and management of severe dengue cases can be improved, ultimately reducing morbidity and mortality associated with the disease.

## CONCLUSION

This study highlights the significance of serum calcium levels as an early prognostic indicator in dengue fever and its association with disease severity and outcomes. Among the 130 patients analyzed, a marginal female preponderance was observed, with a mean age of 32.27 years. The presence of warning signs in 65.4% of patients underscores the need for close monitoring in high-risk cases. The study also found a significant association between lower serum calcium levels and increased severity of dengue fever.

A notable decline in calcium levels was observed during the critical phase ( $8.51 \pm 0.61$  mg/dL) compared to the febrile phase ( $8.62 \pm 0.57$  mg/dL), with persistently lower levels in the convalescent phase ( $8.52 \pm 0.63$  mg/dL), suggesting a prolonged impact of dengue infection on calcium homeostasis. Patients with severe dengue consistently exhibited lower calcium levels in all phases compared to those with mild dengue ( $p < 0.05$ ), reinforcing the correlation between hypocalcemia and disease severity.

The findings suggest that serum calcium levels could serve as a valuable biomarker for assessing disease progression in dengue fever. Early identification of hypocalcemia may help predict the likelihood of severe complications, enabling timely interventions and improved patient outcomes. Further large-scale studies are warranted to validate these findings and explore the potential benefits of calcium supplementation in dengue management.



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