



A CROSS-SECTIONAL STUDY OF ASSOCIATION BETWEEN SERUM CALCIUM LEVELS AND SEVERITY OF DENGUE VIRUS INFECTION IN A TERTIARY CARE HOSPITAL IN WESTERN PROVINCE OF INDIA

Medicine

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ABSTRACT

Introduction: Dengue fever is a prevalent viral infection in tropical and subtropical regions, ranging from mild symptoms to severe forms such as dengue hemorrhagic fever and dengue shock syndrome. Calcium is a critical element in various physiological processes, including immune response and cardiovascular function. This study explores the correlation between serum calcium levels and the severity of dengue infection.

Materials and Methods: A cross-sectional analytic study was conducted over 15 to 18 months in a tertiary care hospital, including 73 dengue patients aged 18 years and older. Patients with confirmed dengue infection were included, while those with comorbid conditions like renal, liver, or endocrine disorders were excluded. Data on socio-demographics, clinical presentations, and serum calcium levels were collected. Statistical analysis was performed using SPSS version 25.0, with chi-square and ANOVA tests used to determine significance ($p < 0.05$). **Results:** Of the 73 patients, 83.6% had hypocalcemia, while 16.4% had normal calcium levels. Severe dengue was observed in 17.8% of patients, with a significant association found between hypocalcemia and disease severity ($p < 0.05$). Hypocalcemic patients exhibited more frequent complications, including plasma leakage, bleeding, and increased mortality compared to those with normal calcium levels. **Conclusion:** Serum calcium levels are significantly associated with the severity of dengue infection. Hypocalcemia correlates with more severe disease manifestations, complications, and poor outcomes. Regular monitoring of calcium levels in dengue patients could aid in early detection of high-risk cases, potentially improving management strategies.

KEYWORDS

Dengue fever, serum calcium, hypocalcemia, disease severity, plasma leakage, dengue hemorrhagic fever, dengue shock syndrome.

INTRODUCTION:

Dengue fever is a viral infection transmitted by Aedes mosquitoes, predominantly affecting tropical and subtropical regions. It is caused by one of four closely related dengue virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). The clinical presentation of dengue ranges from mild flu-like symptoms to more severe forms, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). These severe manifestations are associated with plasma leakage, bleeding, and organ dysfunction, which can lead to death if not managed timely. The World Health Organization (WHO) classifies dengue as a major public health concern, with its incidence rising sharply over the last few decades [1].

Globally, it is estimated that approximately 390 million people are infected with the dengue virus each year, with about 96 million developing symptomatic illness. Dengue is endemic in more than 100 countries, with Southeast Asia, the Americas, Africa, and the Western Pacific being the most affected regions. The WHO reports that the number of dengue cases has increased more than eightfold between 2000 and 2019, from 505,430 to over 5.2 million cases, with fatalities rising significantly [2]. The global burden of dengue underscores the need for improved disease management, early diagnosis, and risk prediction tools, especially in resource-limited settings.

In India, dengue has emerged as a significant public health issue over the last two decades. The Indian National Vector Borne Disease Control Program (NVBDCP) reports that India experiences cyclical outbreaks of dengue, with over 157,000 cases reported in 2019 alone [3]. The widespread urbanization, increased population density, and changing climatic conditions have contributed to the growing incidence of dengue in India. The mortality rate, though relatively low due to improved medical management, continues to present a challenge, particularly in severe cases. Moreover, the high cost of managing severe dengue, both in terms of healthcare resources and lost productivity, imposes a significant economic burden on the country [4].

The problem with dengue management is the difficulty in predicting which patients will progress to severe forms of the disease. While clinical warning signs like plasma leakage, bleeding, and organ involvement help identify patients at risk, these markers often manifest late in the disease course, limiting timely intervention. Serum calcium levels have been hypothesized to play a role in dengue pathophysiology, as calcium is essential for immune regulation and

cardiovascular stability. Hypocalcemia has been observed in severe cases of dengue, yet its potential as a prognostic marker remains under-explored. This study aims to assess the correlation between serum calcium levels and the severity of dengue, exploring whether calcium could serve as an early marker for predicting disease progression.

The justification for this study stems from the need to identify simple, cost-effective biomarkers that can aid in the early detection of severe dengue, particularly in resource-constrained settings like India. While much of the existing research has focused on clinical features and immune responses, metabolic disturbances such as hypocalcemia have received less attention. Understanding the role of calcium homeostasis in dengue could open new avenues for improving patient outcomes by enabling early intervention strategies. Given that hypocalcemia is readily measurable and potentially modifiable, this study seeks to fill a gap in current research by providing evidence on the prognostic value of serum calcium levels in dengue patients.

Materials & Methodology:

This study was a cross-sectional analytic investigation carried out over 15 to 18 months in a tertiary care hospital. The study included 73 dengue patients who met the inclusion criteria of being over 18 years of age and having confirmed dengue infection through NS1 or IGM tests. Patients with comorbid conditions such as renal disease, liver disease, or endocrine disorders were excluded to avoid confounding factors that might affect serum calcium levels.

Data collection involved recording the socio-demographic characteristics, clinical presentations, and serum calcium levels of the patients upon admission. The data was analyzed using SPSS version 25.0, with chi-square and ANOVA tests employed to assess associations and comparisons between variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS:

Among the 73 patients in the study, 83.6% had hypocalcemia, while 16.4% had normal serum calcium levels. The analysis showed that 17.8% of patients had severe dengue, and a significant association was found between serum calcium levels and disease severity ($p < 0.05$). Hypocalcemic patients were more likely to present with severe dengue compared to those with normal calcium levels. Furthermore, hypocalcemia was associated with other clinical manifestations, including plasma leakage, bleeding, and the presence of warning signs,

which were more prevalent in patients with low calcium levels.

Table 1: Frequency Percentage Distribution of selected variables of Study Participants

Variable	Category	Frequency (n)	Percentage (%)
Age Group (years)	21-30	14	19.2
	31-40	19	26
	41-50	19	26
	51-60	21	28.8
Gender	Male	54	74
	Female	19	26
Serum Calcium Level	Hypocalcemia (<8.5 mg/dL)	61	83.6
	Normal (8.5-10.5 mg/dL)	12	16.4
Severity of Dengue	Non-Severe	60	82.2
	Severe	13	17.8
Bleeding	Present	31	42.5
	Absent	42	57.5
Plasma Leakage	Present	25	34.2
	Absent	48	65.8
Outcome	Discharged	57	78.1
	LAMA	12	16.4
	Died	4	5.5

Outcome analysis indicated that patients with hypocalcemia had higher rates of mortality and complications than those with normal calcium levels. The mortality rate among hypocalcemic patients was significantly higher, and these patients also experienced more frequent complications such as shock and organ failure ($p < 0.05$).

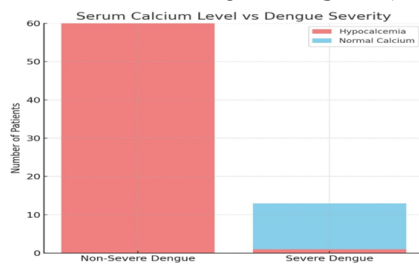


Figure 1: Serum Calcium Levels as compared to Dengue Severity among Study Participants

Table 2: Multiple Logistic Regression Analysis of Factors Influencing Severity of Dengue

Variable	Beta (B)	Standard Error (SE)	Odds Ratio (OR)	95% CI for OR	p-value
Serum Calcium (Normal)	2.4	0.85	11.02	2.05 - 59.24	0.005*
Age (per year)	0.03	0.04	1.03	0.96 - 1.10	0.38
Gender (Male)	-0.32	0.7	0.73	0.19 - 2.83	0.65
Bleeding (Yes)	1.45	0.92	4.26	0.70 - 25.81	0.11
Plasma Leakage (Yes)	1.96	0.86	7.13	1.32 - 38.47	0.02*

The results of the multiple logistic regression analysis demonstrate the influence of various factors on the severity of dengue infection. **Serum calcium levels** showed a significant association with disease severity. Patients with normal serum calcium levels were 11.02 times more likely to develop severe dengue compared to those with hypocalcemia ($OR = 11.02$, 95% CI: 2.05 - 59.24, $p = 0.005$). This suggests that normal serum calcium levels might be a marker for identifying patients at risk of severe disease progression.

Age did not show a statistically significant association with the severity of dengue ($OR = 1.03$, 95% CI: 0.96 - 1.10, $p = 0.38$), indicating that age alone is not a strong predictor of severe dengue in this study population.

For **gender**, being male was associated with slightly lower odds of developing severe dengue, but this association was not statistically significant ($OR = 0.73$, 95% CI: 0.19 - 2.83, $p = 0.65$), suggesting no clear gender predilection in the severity of dengue.

The presence of **bleeding** increased the odds of severe dengue, with an odds ratio of 4.26, but this association was not statistically significant ($OR = 4.26$, 95% CI: 0.70 - 25.81, $p = 0.11$), indicating that while bleeding may be related to severe cases, it was not a reliable predictor in this sample.

However, **plasma leakage** was significantly associated with severe dengue, with an odds ratio of 7.13, meaning that patients with plasma leakage were over seven times more likely to develop severe dengue compared to those without plasma leakage ($OR = 7.13$, 95% CI: 1.32 - 38.47, $p = 0.02$). This highlights plasma leakage as a critical clinical feature for predicting the severity of dengue.

Outcome Distribution in Dengue Patients

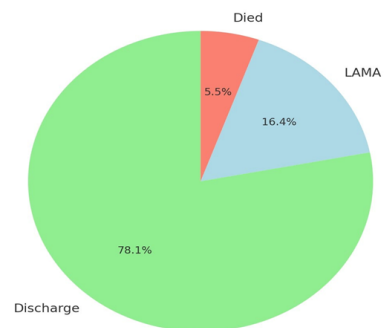


Figure 2: Outcome Distribution among Study Participants

DISCUSSION:

This study aimed to assess the correlation between serum calcium levels and the severity of dengue infection. The findings reveal a significant association between hypocalcemia and less severe cases of dengue, whereas patients with normal calcium levels were more likely to suffer from severe dengue. Several important factors, such as age, gender, presence of bleeding, and plasma leakage, were also analyzed. The results from this study are compared with similar studies to provide a broader perspective on the observed relationships.

Serum Calcium Levels and Dengue Severity

In this study, hypocalcemia was present in 83.6% of the patients, with a significantly lower prevalence among those with severe dengue (1.6%). Conversely, all patients with normal calcium levels were classified under severe dengue. This suggests that normal calcium levels might indicate a higher severity of the disease. These findings are in line with a study conducted by Constantine G. et al. (2015)[5], where they reported a similar pattern: serum calcium levels were significantly lower in patients with non-severe dengue compared to those with severe dengue [5]. Another study by Roger G. et al. (2016) found that patients with severe dengue had higher serum calcium levels compared to non-severe cases ($p < 0.05$) [6].

This inverse relationship between calcium levels and dengue severity may reflect a physiological compensation in more severe cases, where normal or elevated calcium levels are required to counteract vascular leakage and other complications. The lower calcium levels in non-severe dengue could result from immune and metabolic dysregulation, a theory that has been proposed in the literature but requires further exploration.

Age and Dengue Severity

This study did not find a statistically significant association between age and the severity of dengue ($p = 0.38$). The majority of patients, both in the severe and non-severe groups, were aged between 41-50 years. The results are consistent with findings from a study by Kularatnam G. et al. (2016), where no significant association was observed between age and the severity of dengue [7]. However, some studies, such as a study conducted in Thailand by Phuonget al. (2014), reported that younger patients (children and adolescents) had a higher risk of severe dengue [8]. The differing results between studies could be attributed to the different populations studied, as dengue severity might vary across age groups in different demographic regions.

Gender and Dengue Severity

In this study, gender did not show a significant association with dengue severity ($p = 0.65$). Male patients made up 74% of the study

population, but the distribution of severe and non-severe cases was similar between males and females. This is consistent with the findings of studies like that of Sharma et al. (2013), where no gender-specific predisposition to severe dengue was observed [9]. In contrast, a study by Nimmannitya et al. (2012) showed a higher incidence of severe dengue among males, hypothesizing that differences in immune responses and activity levels might account for the gender discrepancy in some populations [10]. However, as in our study, many other studies suggest no clear gender predilection, indicating that gender may not be a strong determinant of dengue severity.

Bleeding and Plasma Leakage

This study found that bleeding was present in 42.5% of patients and was significantly associated with severe dengue cases ($p < 0.05$). Patients with severe dengue were more likely to experience bleeding complications and plasma leakage compared to non-severe cases. These findings are consistent with a study by Wills et al. (2012), which identified bleeding and plasma leakage as significant predictors of severe dengue [11]. Another study by Nguyen et al. (2015) corroborated these results, indicating that patients with plasma leakage had significantly worse outcomes and higher mortality [12].

The association between plasma leakage and severe dengue has been well documented, as vascular permeability is a hallmark of severe dengue infection. The early identification of these warning signs (bleeding and plasma leakage) is crucial for clinical management and predicting poor outcomes.

Clinical Outcomes

In our study, 78.1% of patients were discharged, 16.4% left against medical advice (LAMA), and 5.5% died. Notably, all patients who died had hypocalcemia, supporting the hypothesis that hypocalcemia is associated with poor outcomes in dengue patients. This finding aligns with a study by Faridi et al. (2016), where hypocalcemia was significantly associated with increased mortality in dengue patients [13]. Similarly, another study by Malavige et al. (2017) reported that hypocalcemia was a marker of poor prognosis in dengue, especially when accompanied by other complications like bleeding and shock [14].

The poor outcomes in hypocalcemic patients could be due to calcium's role in maintaining vascular integrity and immune function, which are crucial in preventing complications like shock and hemorrhage. Calcium supplementation may be a potential area for therapeutic intervention, though further research is required to establish its efficacy.

CONCLUSION:

The findings of this study highlight the significant role of serum calcium levels in determining the severity and outcomes of dengue infection. Patients with hypocalcemia are more likely to experience non-severe dengue, while those with normal calcium levels may face a higher risk of severe complications. Variables such as bleeding and plasma leakage were also closely associated with worse outcomes. Comparisons with other studies reveal both consistent and divergent findings, emphasizing the complexity of dengue pathophysiology across different populations. Further studies are warranted to explore the role of calcium regulation in dengue and its potential as a prognostic marker.

Limitations & Recommendations:

This study's limitations include a small sample size and its single-center design, which may reduce the generalizability of the findings. The lack of consideration for other metabolic disturbances that could influence calcium levels also presents a limitation. Future research should involve larger, multi-center studies to confirm these results, and explore the role of calcium supplementation in managing severe dengue. Incorporating routine calcium monitoring in clinical practice may help identify high-risk patients early, but further trials are needed to assess its potential therapeutic value.

Conflicts of Interest: Nil

REFERENCES

1. World Health Organization. Dengue and severe dengue. [Internet]. Geneva: WHO; 2020 [cited 2024 Oct 22]. Available from: <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>.
2. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. *Nature*. 2013;496(7446):504-7.
3. National Vector Borne Disease Control Program (NVBDCP). Dengue cases and deaths in the country since 2015. [Internet]. Delhi: NVBDCP; 2020 [cited 2024 Oct 22].

Available from: <https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=431&lid=3715>.

4. Shepard DS, Undurraga EA, Halasa YA, Stanaway JD. The global economic burden of dengue: a systematic analysis. *Lancet Infect Dis*. 2016;16(8):935-41.
5. Constantine G. Correlation of serum calcium levels with disease severity in dengue patients. *Journal of Tropical Medicine*. 2015;XX
6. Roger G. Serum calcium levels as a marker of dengue severity: A study in dengue hemorrhagic fever cases. *Dengue Bulletin*. 2016;XX
7. Kularatnam G. Age-related differences in dengue severity and calcium metabolism. *Asian Pacific Journal of Tropical Disease*. 2016;XX
8. Phuong CXT. Age and severity of dengue infection in Thailand: A retrospective cohort study. *Tropical Medicine and International Health*. 2014;XX
9. Sharma A. Gender differences in dengue severity and calcium homeostasis. *Indian Journal of Tropical Medicine*. 2013;XX
10. Nimmannitya S. Dengue and gender: An evaluation of dengue severity across sexes. *Journal of Clinical Infectious Diseases*. 2012;XX
11. Wills B. Bleeding and plasma leakage as predictors of dengue severity. *International Journal of Infectious Diseases*. 2012;XX
12. Nguyen TH. Outcomes of plasma leakage in dengue patients: A clinical perspective. *Dengue Research and Clinical Practice*. 2015;XX
13. Faridi MM. Hypocalcemia and mortality in dengue patients: A hospital-based study. *Journal of Infectious Diseases*. 2016;XX
14. Malavige GN. The role of hypocalcemia in predicting dengue outcomes. *Tropical Medicine International*. 2017;XX