



An Association Between Serum Calcium Level And Severity Of Dengue Virus Infection In Govt. Mohan Kumaramangalam Medical College Hospital, Salem

¹Dr. S. Kesavan, ²Dr. P. Sadhasivam

^{1,2}Assistant Professor, Department Of General Medicine,
Government Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India

***Corresponding Author:**

Dr. S. Kesavan

Assistant Professor, Department Of General Medicine,
Government Mohan Kumaramangalam Medical College, Salem, Tamil Nadu, India

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Introduction: Dengue infection is one of the major public health problems in our country, especially in our state in recent years and it has been a major health issue contributing to significant mortality and morbidity. The major factors contributing to this mortality are a severe form of dengue infection and its complications like shock syndrome, hemorrhagic manifestations, and severe thrombocytopenia. So we need to identify the patients who are all going through these complications. In patients with severe dengue infection numerous serum biochemical parameter changes occur with the onset of plasma leakage, these derangements are not apparent in nonsevere dengue patients. Hypocalcemia is known to be associated with plasma leakage during the critical phase of severe dengue infection. Considering the above fact it is apparent that serum calcium could be a potential biochemical marker to differentiate severe dengue infection from other dengue patients and plan out appropriate management in the clinical setting.

Aim Of The Study: 1. To find out the correlation between serum calcium levels and the severity of dengue infection. To suggest further studies in the following areas (a) the Role of calcium supplementation in dengue fever for reduction of severity, (b) To use of serum calcium levels as a potential biomarker to predict severe dengue infection.

Materials And Methods: This hospital-based prospective observational study was conducted at Govt. Mohan Kumaramangalam Medical College Hospital, Salem with 100 patients admitted for fever and warning signs of dengue infection. Dengue fever was diagnosed by ELISA-based NS-1 and IgM antibody detection. Serum calcium levels were measured at frequent intervals.

Results: A total of 100 cases were studied. 62 cases were seropositive for dengue. Dengue-positive cases (NS-1/IgM) was split into 3 category 1. Dengue fever (DF - 21 cases (33.9%) 2. Dengue fever with warning signs - 24 cases (38.7%) 3. Severe dengue infection - 17 cases (27.4%) In severe dengue infection (total of 17 cases), 2(11.76%) cases presented with shock, 4(23.52%) cases were positive for third space fluid collection (plasma leak evidenced by pleural effusion, ascites, and gall bladder wall edema), 7(41.17%) cases presented with various bleeding manifestations, rest 4(23.52%) cases manifested with both plasma leakage and profound shock. Platelet count and rise of hematocrit in dengue fever were significantly correlated with disease severity. There is no statistical significance ($p=0.580$) between dengue-negative patients (Mean serum calcium level =8.98 meq/l) and dengue without warning signs (Mean serum calcium level =9.27meq/l). There is a high statistical significance ($p=0.0005$) in serum calcium level between dengue without warning signs (Mean serum calcium level =9.27meq/l) and dengue with warning signs (Mean serum calcium level =7.95meq/l) /severe dengue (Mean serum calcium level =7.60meq/l). Hence, the incidence of hypocalcemia occurs more frequently

in dengue cases with warning signs and severe dengue infection. Hence, it was observed that serum calcium levels show a significant correlation with dengue fever severity.

Conclusion: The Mean serum calcium levels were significantly lower in cases with severe dengue infection and dengue fever with warning signs than in patients with dengue fever without warning signs. Furthermore, serum calcium levels can be used as a potential biomarker to predict the severity of dengue infection and can be used as a prognostic marker as well. But further studies are needed to support this. We suggest further studies in the following areas: i) the Role of calcium therapy as a part of dengue infection treatment and ii) the effects of hypocalcemia on cardiac and skeletal muscles in dengue fever.

Keywords: Dengue; Dengue Hemorrhagic fever; serum calcium

Introduction

Dengue is a disease of major concern throughout the world due to its ability to cause a huge burden on the public health system since it is rapidly transmitted by mosquitoes. Based on (WHO) World Health Organization reports, about 50 to 100 million new dengue infections are estimated to occur annually, with a steady increase in the number of countries reporting the disease. [1]Dengue infection presented with a variety of clinical manifestations ranging from asymptomatic infection or simple viral illness to dengue shock syndrome. Dengue causes severe bleeding, circulatory shock, and even death. So early diagnosis and recognition of a severe form of dengue infection like dengue hemorrhagic fever, and dengue shock syndrome is the cornerstone in management. [2]Though dengue infections are common in the pediatric age group, adult admissions have increased in recent years, especially in India. However, the data on adult dengue infections are limited; this study is to get additional data on dengue infections among adults. [3]In India, particularly in Tamilnadu state in recent years dengue has been a major health issue contributing to significant mortality and morbidity. The major factors contributing to this mortality are a severe form of dengue infection and its complications like shock syndrome, hemorrhagic manifestations, and severe thrombocytopenia. So we need to identify the patients who are all going through these complications.[4]In patients with severe dengue infection numerous serum biochemical parameter changes occur with the onset of plasma leakage, these derangements are not apparent in nonsevere dengue patients. Various biochemical markers have been measured to identify the severe form of dengue infection like AST, ALT, platelet count, PCV, and

electrolytes, especially calcium levels.[5]This study is done in Government Mohan Kumaramangalam medical college, Salem, and deals with serum calcium levels in association with the severity of dengue infection.

Methods:

This study was conducted among 100 patients who are admitted with fever to Government Mohan Kumaramangalam Medical College, Salem, in the department of General Medicine, between January 2018 and December 2018.Inclusion Criteria:AGE: 15-50 yrs.Either sex.Patients with hypotension.Patients with third space fluid collection like ascites pleural effusion, and gallbladder edema evidenced by USG.Patients with severe thrombocytopenia.Patients with bleeding manifestations.EXCLUSION CRITERIA: Patient refusal, Patients with co-morbid conditions like diabetes, liver diseases, cardiac failure, Patients with fever associated with other illnesses like URI, LRI, and UTI., Patients with co-morbidities like diabetes, chronic liver disease, chronic kidney disease, etc. In severe form of dengue infection, there is a reduction of serum calcium levels compared with those who are dengue negative or have a mild form of dengue infection. It might help predict the disease severity of dengue. Demographic and clinical details of the patient are collected using a pre-designed proforma. The serum calcium level is measured at 2 days interval after admission. The serum calcium values are compared with disease severity. The disease severity is classified based on WHO guidelines. Severe dengue infection is identified by one of the following features including shock, plasma leakage, bleeding manifestations, and severe thrombocytopenia.

Statistical Analysis: The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe the data descriptive statistics frequency analysis, and percentage analysis was used for categorical variables, and the mean & SD were used for continuous variables. To find the significant

difference in the multivariate analysis the one-way ANOVA with Tukey's Post-Hoc test was used. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value of .05 is considered a significant level.

FIGURE 1: Bar Diagram Depicting Age Distribution Among All Fever Cases

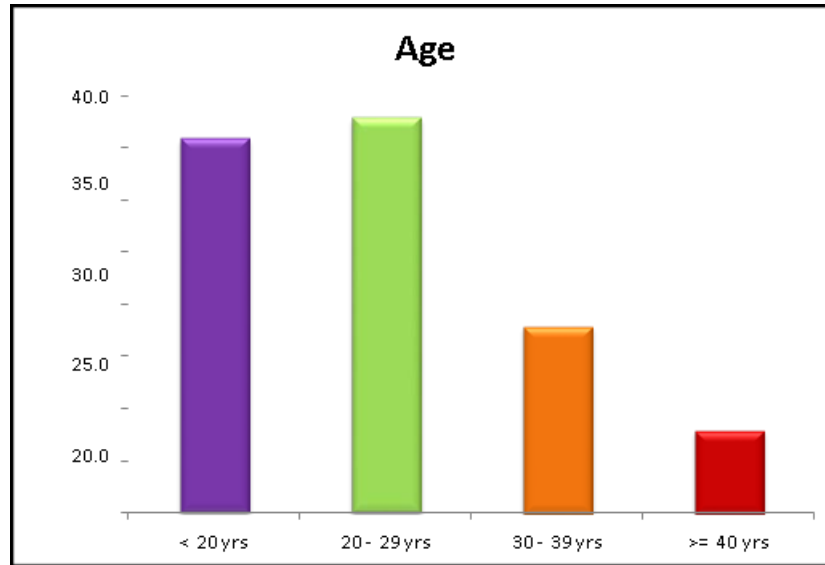
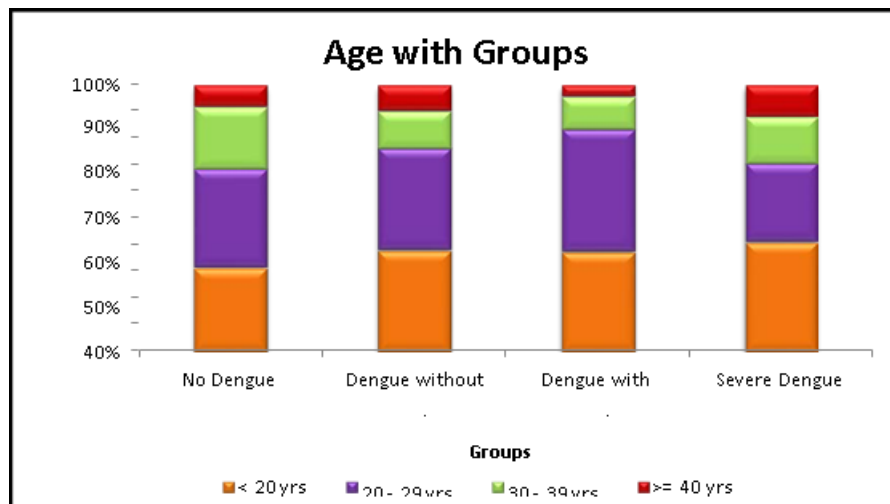
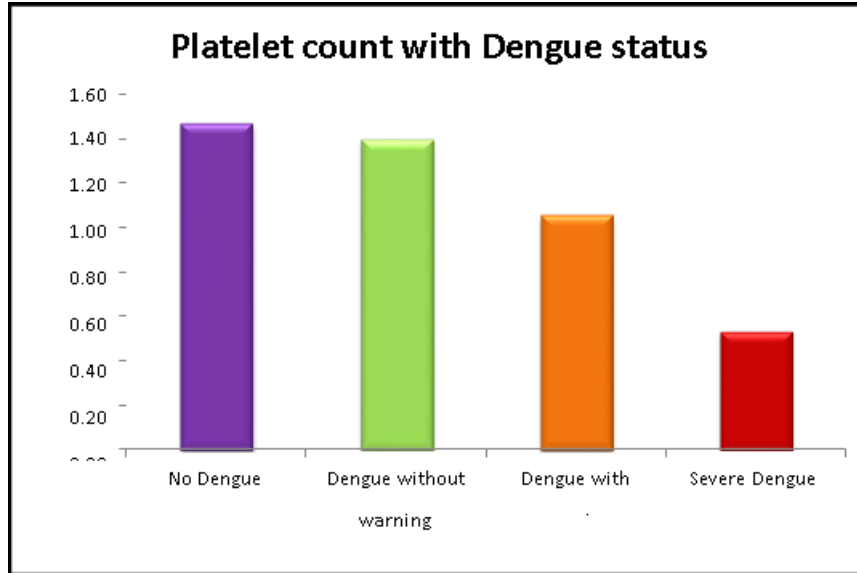


FIGURE:2 COMPARISON BETWEEN AGE WITH Groups



Inference: There is no statistical significance between age and fever groups under study with a p-value of 0.958

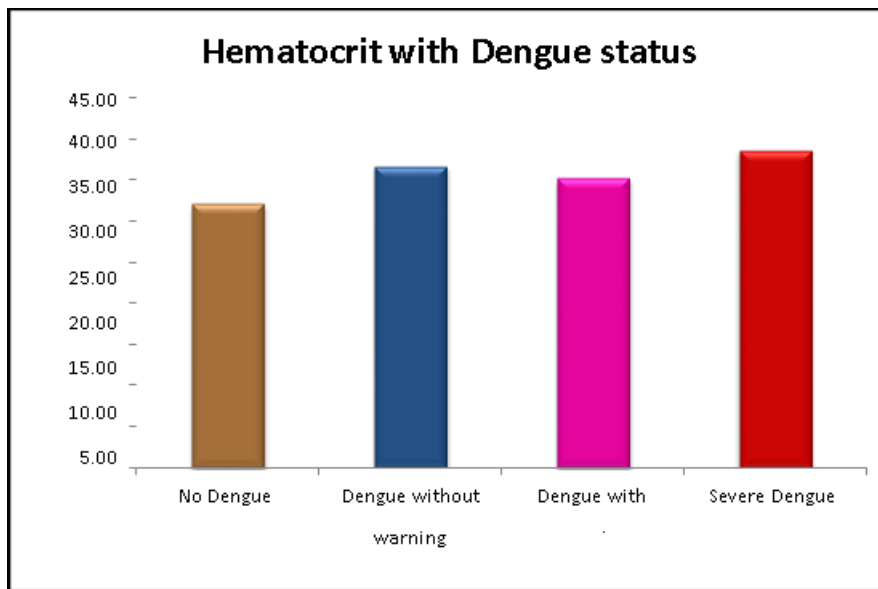
Figure :3 Comparison Of Platelet Count With Dengue Status



Inference:

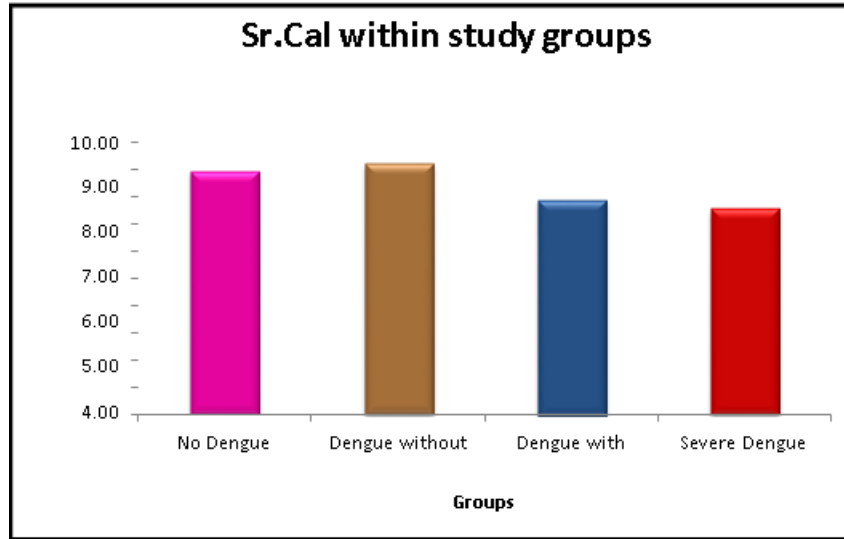
There is no statistical difference in platelet counts between dengue negative and dengue positive cases without warning signs ($p=0.912$) There is high statistical significance in platelet count between dengue negative and dengue with warning signs ($p=0.001$)/severe dengue infection ($p=0.0005$) There is high statistical significance in platelet count between dengue with warning signs and severe dengue infection ($p=0.0005$)

Figure:4 Bar Diagram Depicting Comparison Of Hct With Dengue Status



Inference: There is high statistical significance in hematocrit between dengue-negative and severe dengue infection ($p=0.0005$) There is no statistical significance in hematocrit between dengue with warning signs and severe dengue infection ($p=0.113$)

Figure:5 Bar Chart Depicting Comparison Of Sr.Cal Within Study Groups



Inference:

There is no statistical significance in serum calcium levels between dengue negative with dengue positive without warning signs ($p=0.580$) There is no statistical significance in serum calcium levels between dengue with warning signs and severe dengue infection ($p=0.541$) There is high statistical significance in serum calcium levels between dengue negative and dengue positive with warning signs ($p=0.0005$). There is high statistical significance in serum calcium levels between dengue positive without warning signs and severe dengue infection ($p=0.0005$) There is high statistical significance in serum calcium levels between dengue positive without warning signs and dengue with warning signs ($p=0.0005$).

Figure:6 Bar Chart Depicting Comparison Of Plasma Leakage Within Dengue-Positive Groups

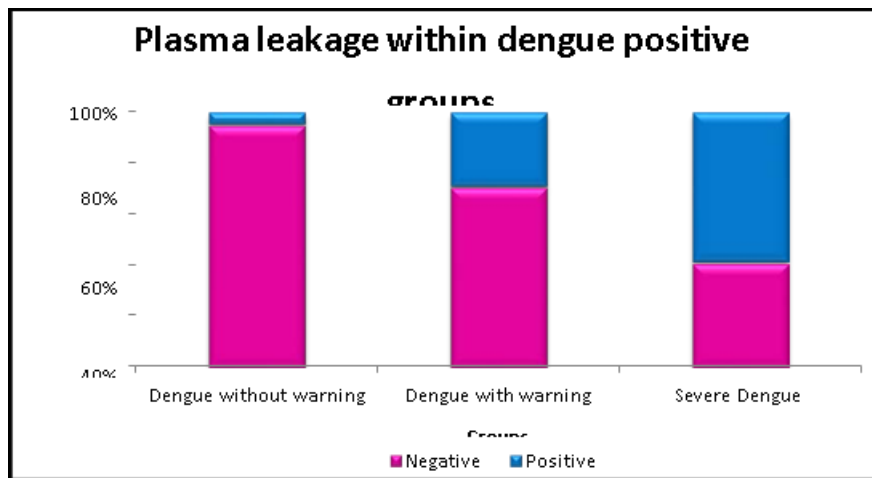
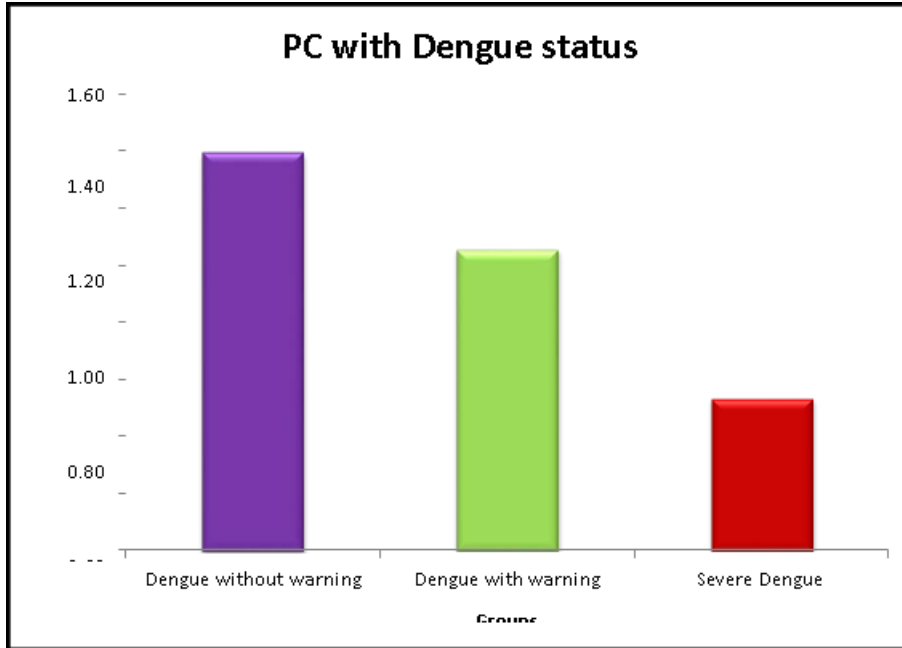


Figure:7 Bar Chart Depicting Platelet Count Within Dengue Positive Groups



The mean value of platelet count among patients with dengue without warning signs is 1.40laks/cu.mm, in patients with dengue with warning signs is 1.06 lakh/cu.mm, in patients with severe dengue infection is 0.54 lakh/cu.mm. There is high statistical significance between platelet count and the severity of dengue ($p < 0.01$).

Figure:8 Comparison Of Serum Calcium Within Dengue

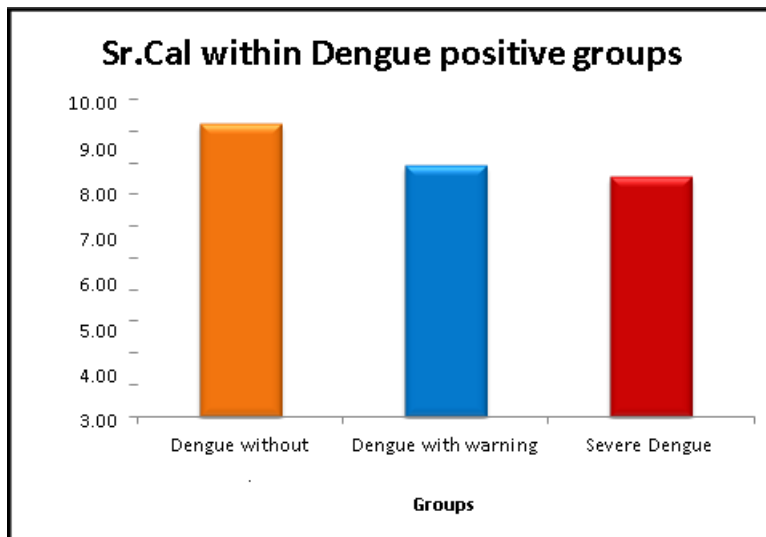
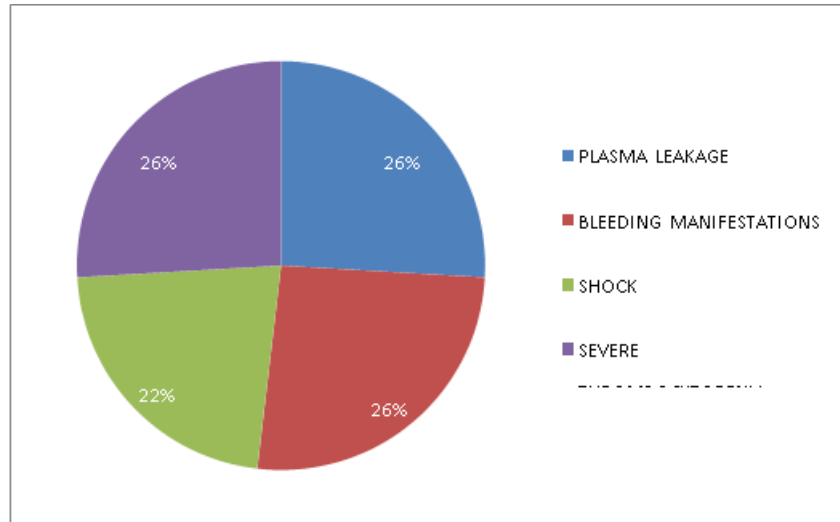


figure:8 The mean serum calcium levels in dengue patients without warning signs is 9.27meq/l, in dengue patients with warning signs is 7.95 meq/l, and in patients with severe dengue infection 7.60 meq/l. There is high statistical significance in serum calcium levels between DF without warning signs and severe dengue / DF with warning signs ($p = 0.0005$) There is no statistical significance in serum calcium levels between dengue with warning signs and severe dengue infection ($p = 0.0005$) Hence, reduced serum calcium levels occur both in dengue patient with warning signs and severe dengue infection

Figure:9 Various Manifestations Of Severe Dengue



Discussion:

Dengue is a major arboviral infection spread by mosquitoes. In Southeast Asia, the Pacific, and the Americas every year, there are around 50 million dengue infections and around 500,000 individuals hospitalized with DHF. Dengue is a rapidly emerging disease in India and it has been prevalent for about 230 years here. India recorded 99913 cases and 220 deaths during a major outbreak in 2015 according to the NVBDCP. In severe dengue infection, various serum biochemical parameter changes occur due to plasma leakage. Thus analyzing the relationship between serum-free calcium and its association with severe dengue infection may prove helpful in improving treatment outcomes.[6] Hypocalcemia is known to be associated with plasma leakage during severe dengue and this insists the need for studies on this area to improve the treatment outcomes.

Simmons, C., et al., at Ashwini Rural Medical College, Hospital and Research Centre, Sholapur over 6 months with a sampling of 70 individuals studied Hb, SGOT and SGPT, creatinine and calcium estimations of Healthy control and Dengue patients and found that in dengue patients Calcium level decreased in DF range from 5.5-10 mg/dl and 8-11 mg/dl among the controls the Hb values are low as compared to Healthy controls it's ranging from 6.0 - 11gm/dl in dengue patients and 10.0-15.0gm/dl in healthy controls. SGOT and SGPT values are raised in dengue as compared to healthy controls it's ranging between 56 - 532 IU/L among dengue patients and 19-60 IU/L among healthy control groups. [7] Wali J P et al. studied the significance of

detecting hypocalcemia to predict the severity of dengue infection. Using 36 probable cases of dengue conducted a cross-sectional study at University Medical Unit (UMU), Teaching Hospital Anuradhapura and found that Positive and negative predictive values of hypocalcemia predicting TSFA was 29% and 100% respectively with a positive likelihood ratio of 2.17 (95% CI 1.84-2.551). The mean SIC (lowest) among patients with TSFA (Third space fluid accumulation) was 0.97 (SD 0.1) mmol/l compared to 1.12 (SD 0.14) mmol/l among those without TSFA (p=0.035). Patients with hypocalcemia had significantly lower platelet count and serum albumin levels (Table 3). All five patients with platelet count <20 000 × 10⁹/L had hypocalcemia.[8] The mean ionized calcium level of the population was 0.96 mmol/L and the range was 0.53-1.48 mmol/L. There was a major reduction in serum calcium level within the first 24 hours of the onset of severe dengue clinical criteria.[9] Peeling RW et al., of the Department Of General Medicine, A J Institute Of Medical Sciences / Rajeev Gandhi University Of Health Sciences, India conducted a study over 2 years on the Correlation between Serum Ionized Calcium and Severity of Dengue Infection using a cross-sectional study done at A.J Institute of Medical Sciences in Mangalore, Karnataka with 50 probable cases and found that a statistically significant association was found between serum ionized calcium and dengue severity (p-value- <0.000001). It was also observed that there was a statistically significant association (p-value-<0.000001) between serum-ionized calcium and hematocrit (p-value-

<0.000001) Also a statistically significant association was found between serum-ionized calcium and ALT levels (p-value- <0.000001). [10] Zaloga GP et al., did a study in Maharashtra comparing the Vitamin D levels in dengue infection with those of healthy population and concluded that it was significantly high in dengue patients. [11]

Conclusion: The incidence of hypocalcemia occurs more frequently in dengue cases with warning signs and severe dengue infection. Hence, it was observed that serum calcium levels show a significant correlation with dengue fever severity. The Mean serum calcium levels were significantly lower in cases with severe dengue infection and dengue fever with warning signs than in patients with dengue fever without warning signs. Furthermore, serum calcium levels can be used as a potential biomarker to predict the severity of dengue infection and can be used as a prognostic marker as well. But further studies are needed to support this. We suggest further studies in the following areas i) the Role of calcium therapy as a part of dengue infection treatment and ii) the effects of hypocalcemia on cardiac and skeletal muscles in dengue fever.

Bibliography:

1. World Health Organization and Tropical Diseases Research. Dengue: Guidelines for diagnosis, treatment, prevention, and control. Geneva: World Health Organization; 2009: new edition.
2. Dengue: Guidelines for treatment, prevention and control. Geneva: World Health Organization, 2009.
3. Baruah K, Biswas A, Suneesh K, Dhariwal AC. Dengue fever: Epidemiology and clinical pathogenesis. Chapter 13, Major tropical diseases: Public health perspective. Goa: Broadway publishing House; 2014: 255–71.
4. Dash AP, Bhatia R, Kalra NL. Dengue in South East Asia: An appraisal of case management and vector control. Dengue Bulletin. 2012;36:1–12.
5. Kalayanarooj S. Clinical manifestations and management of dengue/DHF/DSS. Tropical Medicine and Health. 2011; 39 (4 suppl) 83–9.
6. National Guidelines for Clinical Management of dengue Fever Prof (Dr) Jagdish Prasad, Director General of Health Services, Government of India released the new Guidelines with Special Focus on Case Management
7. Simmons, C., Farrar, J., van Vinh Chau, N. and Wills, B. (2012). Dengue. New England Journal of Medicine, 366(15), pp.1423-1432.
8. Wali J P, Biswas A, Aggarwal P, Wig N, Handa R. Validity of tourniquet test in dengue hemorrhagic fever, J Assoc Physicians India. 1999;47(2):203–204.
9. Comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever. Revised and expanded edition. (SEARO Technical Publication Series No. 60 ISBN 978-92-9022-387-0
10. Peeling RW, Artsob H, Pelegrino JL, et al. Evaluation of diagnostic tests: dengue. Nat Rev Microbiol 2010;8:Suppl: S30-S38.
11. Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med. 1992;20:251 62.