" TO STUDY THE SERUM CALCIUM LEVEL IN DENGUE FEVER " - A ONE YEAR CROSS SECTIONAL STUDY IN A TERTIARY CARE HOSPITAL"

BY

Dr.DINESHKUMAR PIRAJI CHAUHAN

REGISTRATION NO: BG0116005

Dissertation

Submitted to

KAHER, Belagavi, Karnataka

In partial fulfilment

of the requirements for the degree of

M .D.

IN

GENERAL MEDICINE

Under the Guidance of

DR. ARATHI DARSHAN MBBS, M.D(GENERAL MEDICINE)

PROFESSOR

DEPARTMENT OF GENERAL MEDICINE

J. N. MEDICAL COLLEGE

BELAGAVI- 590010. KARNATAKA

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Declaration by the Candidate

I herebydeclare that this dissertation entitled **"TO STUDY THE SERUM CALCIUM LEVEL IN DENGUE FEVER " - A ONE YEAR CROSS SECTIONAL STUDY IN A TERTIARY CARE HOSPITAL"** is a bonafide and genuine research work carried out by me under the guidance of Dr.Arathi Darshan, Professor, Department of General Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi-590010.

Date:

Place: Belagavi

Dr. DINESHKUMAR.P. CHAUHAN

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Certificate by the Guide

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ABSTRACT

BACKGROUND& OBJECTIVES:

Dengue is currently regarded globally as the most important mosquito-borne viral disease, contributing to significant morbidity and mortality across the globe. Association between low serum calcium levels and its positive impact on treatment outcomes has been studied by multiple researchers. But due to limited number of available, the quality of evidence available on the subject is still poor. Hence there is a strong need for further studies on the subject, specially on Indian population. The current study was conducted in this background, with an objective to study the association between the severity of dengue infection and serum calcium levels.

MATERIALS AND METHODS:

The current study was a cross sectional study,conducted in the department of general medicine, DR. Prabhakar Kore hospital, KLE University, Belgaum. A total 100 dengue cases receiving treatment from the study setting between January 2017 to December 2017, selected by universal sampling were included in the final analysis.

The study included all the proved cases of dengue fever admitted in the study setting. The study has excluded patients with hypertension, diabetes mellitus, cardiac disease and those on antihypertensive and antiarrhythmic medication.Patients those who are on calcium supplement or any other drugs which affect calcium homeostasis were also excluded.

All the relevant parameters were documented in a structured study proforma. Confirmation of diagnosis

was done with one of the following laboratory tests: IgM antibody, IgG antibody or serum dengue NS1 Antigen detection..The prevalence of myocarditis is diagnosed either by the presence of changes in the 12 lead ECG (ST Segment, T Inversion or right bundle branch block).Hypocalcaemia was defined as the presence of serum calcium < 8.5 mg/dl.

RESULTS

A total of 100 subjects were included in the final analysis. The mean age of the study population was 26.64 ± 10.65 with the ranged between 18 to 70 years.Among the study population, 10 (10%) participants were aged between 18 to 19 years, 53 (53%) were aged between 20 to 29 years, 18 (18%) were aged between 30 to 39 years, 13 (13%) were aged between 40 to 49 years, 3 (3%) were aged between 50 to 59 years and 3 (3%) were aged 60 and above years.Among the study population, 74 (74%) participants were males, and the remaining 26 (26%) were females.The mean Hemoglobin of study population was 14.32 ± 2.33 with the ranged between 9 to 20 g/dl.The mean Total count of the study population was 264.38 ± 1924.42 with the ranged from 0.40 to 17300 cells / µL. The mean platelet of the study population was 62686.87 ± 8647.45 with the ranged between 5000 to 253000 cells/µL.Among the Ns1 antigen was positive in 28% and negative in 72%, 68% were IgM Antibody positive, 71% of patients were IgG antibody positive and 50 (50%) participants had both Dengue IgM + IgG antibody Positive. Among the study population, 72 (72%) participants had Dengue fever. The number of Dengue Hemorrhagic fever and Dengue shock syndrome were 23(23%) and 5(5%) respectively.

The median serum calcium of the study population was 8.40 (8.20 to 8.60) mg/dl. Among the participants with NS1 antigen positive and Dengue IgG antibody positive had no statistically significant association with median calcium values. Among the people with Dengue IgM antibody positive, the median serum calcium was 8.0 (IQR 7 to 8.60) mg/dl, and it was 8.60 (IQR 8.45 to 9) mg/dl in people with Dengue IgM antibody negative (P Value 0.04).Among the people with Dengue IgM + IgG antibody positive, the median serum calcium was 8.20 mg/dl (IQR 8.20 to 8.60), and it was 8.50 mg/dl (IQR 8.40 to 8.68) in people with Dengue IgM + IgG antibody negative (P Value 0.022).

None of the subjects in dengue fever and DHF groups had serum calcium level below 7 mg/dl, but 20% of the subjects in DSS had serum calcium less than 7 mg/dl. A higher proportion of subjects in dengue shock syndrome and DHF had lower levels of serum calcium, as compared to dengue fever. The proportion of participants with cardiac and neurological complications increased with increasing severity ranging from dengue fever to dengue hemorrhagic fever and dengue shock syndrome

CONCLUSIONS:

The current study has documented a strong association between the dengue severity, IgM antibody positive status and lower serum calcium levels. There is a need to conduct large scale prospective studies to further assess the independent risk factors for hypocalcemia among dengue cases and its impact on treatment outcomes and mortality.

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Glossary	Abbreviations
ATPase	Adenosine triphosphatase
C	Capsid
Ca2+	Calcium ions
CAML	calcium modulating cyclophilin-binding ligand
Cdna	complementary Deoxyribonucleic acid
CF	Cytotoxic factor
CNS	Central nervous system
DF	Dengue fever
DF+WS	Dengue Fever with Warning Signs
DHF	Dengue Hemorrhagic Fever
DV, DENV	Dengue Virus
EDTA	Ethylenediaminetetraacetic acid
IgG	Immunoglobulin G
IgM	Immunoglobulin M
M phi	Macrophage
NS1 antigen	Non-structural protein 1 antigen
NVBDCP	National Vector Borne Disease Control Program
RNA	Ribonucleic acid
SD	Severe Dengue
SF	Suppressor cytokine
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
TS2	Suppressor T
USD	United States Dollar
WHO	World Health Organization

INTRODUCTION

Dengue is a mosquito-borne disease caused by four serotypes of the most prevalent arthropod-borne virus affecting humans**.** Dengue is currently regarded globally as the most important mosquito-borne viral disease. Dengue is widespread throughout the tropics, with risk factors influenced by local spatial variations of rainfall, temperature, relative humidity, the degree of urbanization and quality of vector control services in urban areas.[1]

Today, the disease is endemic in more than 100 countries in WHO's African, Americas, Eastern Mediterranean, South-East Asia and Western Pacific regions; the Americas, South-East Asia and Western Pacific regions are the most seriously affected. Transmission of dengue is now present in every World Health Organization (WHO) region of the world,and more than 125 countries are known to be dengue endemic.[2] Estimates of the global incidence of dengue infections per year have ranged between 50 million and 200 million.[3, 4]It is currently regarded as the most important arboviral disease internationally as over 50% of the world's population live in areas where they are at risk of the disease, and approximately 50% live in dengue-endemic countries.[4, 5]

The epidemiology of dengue in India was first reported in Madras (now Chennai) in 1780, and the first outbreak occurred in Calcutta (now Kolkata) in 1963; subsequent outbreaks have been reported in different parts of India. Since the 1990s, epidemics of dengue have become more frequent in many parts of Indiaespecially in urban zones, and have quickly spread to new regions, such as Orissa, Arunachal Pradesh and Mizoram, where dengue was historically non-existent. Over the period of 10 years

(1998–2009), 82,327 dengue cases (incidence: 6.34 per million population) were reported. During a more recent period (2010–2014), 213,607 cases (incidence: 34.81 per million population) of dengue fever were observed. Thus, the number of dengue cases during the past 5 years has increased markedly, by a factor of 2.6. Dengue incidence has sharply increased from 1998 to 2001 from 0.72 to 3.21 per million population. Before 2009 dengue incidence exceeded 10 per million population. Since 2010, dengue incidence of greater than 15 per million population has been reported annually.[6, 7]

The burden of dengue is large and growing. More than half of the global population lives in areas with risk of dengue transmission. Uncertainty in burden estimates, however, challenges policy makers' ability to set priorities, allocate resources, and plan for interventions.[8, 9]

Hypocalcemia is seen in cases with severe dengue Fever and has been purported to be associated with increased mortality. In vitro studies on animals and human tissue link calcium with the infectivity of the dengue virus and the immune response to dengue. Intracellular calcium derangements have been linked with myocarditis,and dengue-related cardiac dysfunction.[10] Calcium also plays a role in platelet aggregation.[11]Cabrera J I et al[12], conducted a comparative study between 2003 to 2005 in Tampico and showed that there was improvement around 36% of dengue patients when oral calcium was administered. Constantine G R et al[13], sign his study showed that calcium was significantly associated with dengue fever. Dahanayakaet al[14], also showed that serum hypocalcaemia was significantly associated with mean platelet count, mean albumin level and Albumin level.

Need for the study

The main cause of hypocalcemia in dengue fever is likely to be multifactorial. There is a paucity of clinical evidence on the role of calcium disequilibrium in dengue fever, the clinical effects of hypocalcemia in dengue fever and on the interactions between blood calcium ions and the immune pathogenesis of the disease. Even though there are several studies evaluating the therapeutic use of calcium in dengue fever, they have been underpowered and poorly designed to make any firm recommendations. Hence this study was conducted with the aim to study the association between the severity of dengue infection and serum calcium levels.

AIMS AND OBJECTIVES:

To Study the association between the severity of dengue infection and serum calcium levels.

REVIEW OF LITERATURE

Dengue disease is a mosquito-borne viral infection transmitted between humans by *Aedes* spp. that are distributed mainly in the tropical and subtropical region. The distribution of dengue disease is influenced by local variation, such as geography, rainfall, temperature, and rapid urbanization or migration. The epidemic of mosquito-borne infection significantly led to an increased number of cases and hyperendemicity which induce a more severe form of dengue. The rapid global spreading of dengue disease created public health burdens that are presently unfulfilled by the absence of specific therapy, a simple diagnosis tool for the early phase, and effective and efficient vector control system.[15]

Mortality rate

Dengue is the most important acute systemic arthropod-borne viral infection in humans.[16] This disease is becoming a global public health concern, spreading from tropical regions to most subtropical regions of the world, causing human suffering and massive socioeconomic losses.[16-18] It is estimated globally that 50 to 100 million dengue cases occur each year across approximately half of the world's population, especially in areas with co-circulation of multiple virus serotypes, known as hyperendemic regions in Southeast Asia and Pacific.[2, 19] It is also estimated that dengue is responsible for 20 000 deaths annually.[19, 20]

Epidemiological report of dengue in India

Over the period 1998–2009, 82 327 dengue cases (incidence: 6.34 per million population) were reported. During a more recent period (2010–2014), 213 607 cases (incidence: 34.81 per million population) of dengue fever were observed. Thus, the

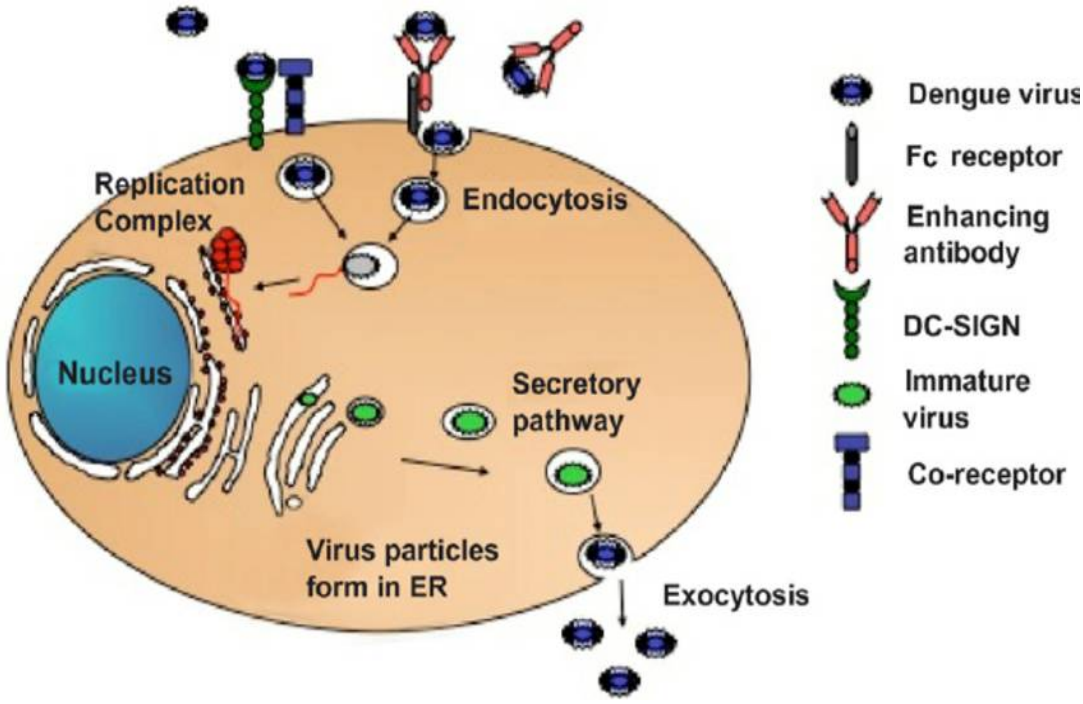
number of dengue cases during the past 5 years has increased markedly, by a factor of 2.6, with respect to the 1998–2009 period. The 1996 dengue epidemic that occurred around Delhi and in Lucknow, Uttar Pradesh, subsequently spread all over the country, causing 16000 cases and 545 deaths. The dengue incidence sharply increased from 1998 to 2001 from 0.72 to 3.21 per million population. the dengue incidence exceeded 10 per million population. Since 2010, a dengue incidence of greater than 15 per million population has been reported annually.[6]A recent review has reported that India alone contributes to 34% (about 33 million infections) of the total global threat of dengue leading to hyper-endemicity, prevailing mostly in urban areas.[21] India reported an annual average of 20,474 dengue cases and 132 deaths by the disease in 2006–2012.[22] Indian Health Ministry reported more than 138 Indian people killed by the dengue virus during the first 10 months of 2013, with more than 55,000cases recorded across the country. According to the National Vector Borne Disease Control Program [NVBDCP] data, the worst affected areas in India in 2015 were Delhi, Punjab, Haryana, Gujrat, Karnataka and Kerala with a range of about 4000–15,000 cases and 9–60 deaths.[22]However, the widespread problem of underreporting of dengue cases from India has come into focus very From 2010 onward, the states of Assam, Bihar, Jharkhand, Orissa and Uttarakhand and some union territories including Andaman and Nicobar Islands, Dadra and Nagar Haveli, and Daman and Diu have become endemic for dengue. India experienced the highest dengue incidence in 2012 (about 41 per million population), 2013 (61 per million population) and 2014 (32 per million population). From 1998 to 2014, the highest dengue incidence was reported in Pondicherry (372.92), followed by Dadra Nagar Haveli (176.31) and Delhi (102.15). Similarly, high dengue incidence, ranging

between 21 and 50 per million, was reported for the states of Punjab, Gujarat, Karnataka, Kerala, Tamil Nadu and Orissa.

Lifecycle

The below figure shows multiple ways in which the virus can attach to the cell, followed by endocytosis, membrane fusion and nucleocapsid release. The plus strand RNA is the template for polyprotein synthesis and via a replicative dsRNA, forms the template for further RNA synthesis in the cytoplasm. The NS2B-NS3 function in polyprotein processing and RNA replication is critical to viral the viral life cycle.[23]

Figure 1 :Overview of the Dengue virus life cycle[24]



Pathophysiology

During the feeding of mosquitoes on humans, DENV is presumably injected into the bloodstream, with spillover in the epidermis and dermis, resulting in infection of immature Langerhans cells [25, 26], and keratinocytes.[25] Infected cells then migrate from the site of infection to lymph nodes, where monocytes and macrophages are recruited, which become targets of infection. Consequently, infection is amplified and the virus is disseminated through the lymphatic system. As a result of this primary viremia, several cells of the mononuclear lineage, including blood-derived monocytes [27], myeloid DC[28], [29, 30] and splenic and liver macrophages[31, 32]are infected. DENV has also been shown to have tropism for circulating mononuclear cells in blood and for cells residing in the spleen, lymph nodes, and bone marrow of infected AG129 mice. Leukocytes also have been shown to be infected with DENV in experimentally infected nonhumans primates. It should be noted that during secondary infections with heterologous DENV, high concentrations of DENV-specific immunoglobulin G (IgG) will complex newly produced virus that adheres to and is taken up by mononuclear cells. Following infection, mononuclear cells predominantly die by apoptosis.[33] while abortively infected,or bystander DC are stimulated to produce the bulk of mediators that are involved in inflammatory[34] and hemostatic[35]responses of the host. In this regard, factors that influence the number of target cells infected, and consequently the levels of viremia, may determine the ratio of different proinflammatory and anti-inflammatory cytokines, chemokines, and other mediators, as well as the way in which the inflammatory response affects the hemostatic system.[27] Bone marrow stromal cells have also been shown to be susceptible to infection with DENV.[36]

Hypocalcaemia in dengue

Several causes for low blood calcium levels have been suggested, including reduced $Na^{+}K$ adenosine triphosphatase (ATPase) activity, reduced Ca2+ATPase activity, acquired parathyroid hormone deficiency, renal one alpha-hydroxylase insufficiency, reduced dietary vitamin D intake, and reduced dietary calcium intake.[37] Low blood calcium levels have been demonstrated in dengue infection, and maybe present in over 80% of patients.[38] It is often under recognized but can present with tetany.[39] There is little information on the other effects of hypocalcaemia; There is some evidence that hypocalcaemia may be more pronounced in more severe forms of dengue,[40] although lower calcium levels have not shown an association with mortality.[38]

Role of calcium in the immune pathogenesis of dengue

Depletion of Mg2+ and Ca2+ has been shown to enhance binding of dengue virus to monocytes, macrophages and cells of T cell and B cell lineages.[41] Ca2+ has been shown to be essential for the cytotoxic activity of the dengue type 2 virus (DV) induced macrophage cytotoxin (CF2); cell death has been shown to be associated with increased intracellular Ca2+.[42, 43] Ca2+ appears to play a role in the induction of dengue-specific T helper cells. Dengue antigen has been shown to increase the influx of Ca2+ into T cells. The proliferation of dengue-specific T helper cells appears to be dependent on Ca2+ and is inhibited in the absence of Ca2+ and by calcium channel antagonist drugs.[44] In another *in vitro* study, production of DV induced suppressor cytokine (SF) by cultured spleen cells was inhibited when the medium was depleted of calcium; production was restored by addition of calcium to the medium. Both the

production of SF and transmission of the suppressor signal via syngeneic macrophage (M phi) to recruit the second

subpopulation of suppressor T (TS2) cell were inhibited in a dose-dependent manner by the calcium channel antagonists verapamil and nifedipine.[45]There is some evidence that the production of nitrite in response to dengue virus infection is also calcium-dependent and can be inhibited by calcium channel blocking drugs.[46, 47] Thus, calcium appears to play a role in the immune response in dengue, although the interactions are complex, and the precise clinical implications of these interactions are yet not clearly defined.

Role of calcium in the treatment of dengue

Calcium is needed for platelet aggregation, although its precise role is not known.[48, 49] In a case series of just five patients suffering from dengue fever, the administration of oral calcium carbonate and vitamin D3 were reported to result in improvement in clinical condition and platelet counts. Platelet counts and clinical features improve spontaneously in dengue; thus these findings are insufficient to conclude that improvement was a result of the intervention.[50] Calcium plays a key role in the functioning of myocardial tissue. Cardiac involvement in dengue myocarditis and dengue-related cardiac dysfunction is also seen. There is a paucity of clinical evidence on the role of calcium disequilibrium in dengue, the clinical effects of hypocalcaemia in dengue and on the interactions between blood calcium ions and the immune pathogenesis of the disease. Although hypocalcaemia has been observed in dengue, there is no evidence currently that this hypocalcaemia has significant clinical implications.

Relevant Articles

Dahanayaka NJ et al[14] (2017), Patients with hypocalcaemia had significantly lower platelet count and serum albumin levels. All five patients with platelet count. Three of them had TSFA and hypocalcaemia on admission. Two more patients developed TSFA after admission,and they too developed hypocalcaemia before or at the time of the first detection of TSFA. None of the patients with norm calcium level developed TSFA. Positive and negative predictive values of hypocalcaemia predicting TSFA was 29% and 100% respectively with a positive likelihood ratio of 2.17 (95% CI 1.84-2.551). Mean SIC (lowest) among patients with TSFA was 0.97 (SD 0.1) mmol/l compared to 1.12 (SD 0.14) mmol/l among those without TSFA (p=0.035).

ThanujReddy et al[51] (2017), conducted a cross-sectional study to was done to determine hypocalcemia marker for severity for patients with dengue fever. This study was conducted at RLJ hospital in Kolar, Karnataka. All probable cases of dengue were diagnosed and classified according to World Health Organization criteria. The mean age was 40.8 years, and the majority were males (n = 79, 52.6%). Mean serum Ca2+ was significantly lower in patients with severe dengue (4.16mg/dl) than in those with dengue fever without warning signs and with warning signs (4.66mg/dl,4.36mg/dl) (p <0.001). Serum Ca2+ levels significantly correlated with dengue severity. Hypocalcaemia is significantly prevalent in patients with severe form than in patients of Dengue with and without warning signs severe form than in patients of Dengue with and without warning signs.

Maheshwari M et al[52] (2017), conducted an observational study to determine the Electrolyte Profile of dengue-infected patients from a tertiary care center in Rajasthan.

In this study, 60 clinically diagnosed and serologically confirmed age and sex-matcheddengue-infected cases were diagnosed. Serum electrolytes [sodium, potassium & calcium] were measured using semi-auto analyzer. The mean age of the study group was 32 years. 65% of the patients were males, and 35% were females. On analysis, it was found that the amount of calcium decreased significantly ($p < 0.03$) in the study group as compared to control group while the value of sodium ($p < 0.6$) and potassium ($p < 0.5$) reduced non-significantly. Hence timely diagnosis and supportive therapy of these electrolyte disturbances can reduce associated morbidity and mortality in dengue patients.

Jayachandran J et al [53](2017), conducted a cross-sectional study to evaluate the correlation between the severity of dengue and the serum-free calcium. This study was done in a tertiary care hospital in Bangalore. The patients with dengue fever were diagnosed using NS1 antigen and/or IgM antibody tests and were classified according to WHO criteria. The association between severity of dengue and serum-free calcium was studied. The sample size was 145. The mean age was 36.7years, and 91(62.7%) were males. 57(39.3%), 82(56.6%) and 6(4.1%) patients were classified as Dengue Fever(DF), Dengue Fever with Warning Signs(DF+WS) and Severe Dengue(SD) respectively. The mean Serum free calcium in the study was 3.82±0.52 mg/dl. The mean serum calcium (mg/dl) in each class were as follows - Severe Dengue (3.07±0.19), Dengue Fever with Warning signs (3.70±0.52) and Dengue Fever (4.07±0.40). The presence of hypocalcemia significantly correlated with the severity of dengue. It was concluded that the serum-free calcium levels significantly correlated with the severity of dengue fever. Serum-free calcium can be used as a predictor of severity in dengue fever.

Narasimhan D et al.[54](2017),conducted a Retrospective analysis of the biochemical profile of dengue infection in a tertiary care hospital between January 2011and December 2012. Results concluded that Analysis of aspartate aminotransferase results showed that 19.1% had two-fold rise, 13.3% had a three-fold rise, and 19.6% had more than a threefold rise. Analysis of alanine aminotransferase showed that 35.7% had normal values, 14.95% had a two-fold rise, 11.1% had a three-fold rise, and 11.5% had more than a threefold rise. Serum proteins were normal in 35.7% and low in 19.6%. Analysis of serum albumin showed low values in 10.6% Serum sodium levels were low in 11.1% of patients. Albuminuria was positive in 53% of patients. Serum ionized calcium levels were low in 26.8% of patients. The study concluded that biochemical abnormalities noted in this study included elevated liver enzymes, low sodium and ionized calcium levels, hypoalbuminemia and increased urine albumin excretion.

Reddy AA et al[55](2016), conducted a study to determine if Serum sodium can be a prognostic marker in dengue fever cases admitted to PICU in Navodaya hospital, Raichur, India. The study was carried out in a 5 bedded (high dependency unit) PICU of Navodaya Medical College and Hospital, Raichur, Karnataka, India. The study was performed over a period of 12 months from August 2015 - August 2016. The study group included individuals from the age group of 1 month to 18 years, who were diagnosed with dengue fever. Results: Out of the total 99 cases, 36 cases had no variation in serum sodium levels, 33 cases were mild hyponatremia, 12 cases were moderate hyponatremic, and 18 cases were severely hyponatremic. Out of the 36 cases with normal serum sodium levels, only 1 case progressed to bleeding complications. Out of the 33 cases with mild serum sodium levels, 2 cases progressed

to complications out of which 1 case having bleeding manifestations and 1 case having both bleeding and central nervous system (CNS) complications. Conclusions: Hyponatremia is the most common electrolyte disturbance in dengue fever as well as dengue-associated complications. The lower the serum sodium levels the higher is the incidence of complications associated with dengue fever. The incidence of CNS and bleeding complications is more as compared to the RS and hepatobiliary complications. The incidence of RS and hepatobiliary complications is high with moderate and severe hyponatremia. Thus, serum sodium plays a most important role in the prognosis of dengue fever and associated complications.

Murugan MR et al[56](2016), is endemic in all WHO regions, except Europe. Currently, there are means to diagnose DENV infection, but none for early prediction of severity of the disease. Cases of non-severe dengue may later develop into severe dengue, without any warning signs. Hypocalcemia has been demonstrated, in certain cases of malaria, severe meningococcal infections and other severe acute illnesses, to be associated with poor prognosis. We evaluated the association between serum corrected calcium level and severity of Dengue based on WHO 2009 classification. Methodology: Observational Prospective Study. A probable case of dengue was diagnosed and classified according to World Health Organization criteria and confirmed by either IgM antibody or NS1 antigen detection. Patients were divided into Severe Dengue Fever and Dengue Fever as per WHO 2009 classification. The Mean Corrected Calcium was compared between the 2 groups. Socio-demographic details were collected using an interviewer-administered questionnaire. Results: The sample size was 68. The mean age of patients was 32 years, 60% of which were males. 31 patients (46%) were diagnosed with severe dengue fever. The Mean

Corrected Calcium was found to be significantly lower in Severe Dengue Fever patients (7.83 mg/ dL) when compared to Dengue Fever patients (8.48 mg/dL).

Adhikari M et al[57](2015), conducted a prospective follow up study to determine the prevalence of hypocalcaemia and its potential value as a biochemical marker in patients with severe dengue infection. The study was conducted in a tertiary care centre in Sri Lanka throughout a one year period. World health organization 2009 criteria were used to diagnose the patients with severe dengue infection. All the patients with severe dengue infection were analyzed with serum ionized calcium during the first 24 hours of onset of the severe dengue clinical criteria. From the total population of 61 with severe dengue infection, 42(68.8%) were males, and 19(31.2%) were females. Mean age of the population was 28.8 years. Among the 61 patients, 52(85%) showed hypocalcaemia during the first 24 hours of onset of severe dengue infection. Mean ionized calcium level of the population was 0.96 mmol/L, range being 0.53-1.48 mmol/L. Serum ionized calcium level was significantly reduced in the majority of patients with severe dengue infection within the first 24 hours of the onset of severe dengue clinical criteria. Value of serum ionized calcium as a biochemical marker to detect severe dengue infection early should be further explored with large-scale studies.

Shivanthan MC at al[11](2015) Dengue is endemic in the tropics, and complications involving organ systems are seen with varying incidence. The manifestations of cardiac involvement include clinical, electrocardiographic, echocardiographic, cardiac enzyme and histopathologic abnormalities. Echocardiography appears to be a useful tool for detecting myocardial involvement and should be performed in patients with

electrocardiographic abnormalities or hemodynamic instability. Treatment is largely supportive, though there are some anecdotal reports of improvements with specific agents. Knowledge of cardiac manifestations in dengue is limited, and further studies are needed to establish the exact pathophysiology and role of specific agents in the prevention and treatment of cardiac complications in dengue.

Habbu P P et al[58](2015) ,conducted an observational study to determine biochemical parameters of dengue fever in an area of Solapur, Maharashtra over the period of 6 months from June to November 2014.Through convenient sampling of 70 individuals, each was taken up for the study as Healthy controls and Dengue subjects. Hb, SGOT and SGPT, creatinine and calcium estimations were done of Healthy control and Dengue patients. It was found that in dengue patients the Hb values were 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 were 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. The creatinine values were almost the same in control and patients ranging from 0.5- 2.8 mg/dl. Calcium level decreased in DF range from 5.5-10 mg/dl and 8-11 mg/dl among the controls. The study concluded that estimating the levels of serum transaminases in dengue fever may help in early detection of liver cell damage. The level of the calcium and creatinine should also be assessed in severe cases of Dengue infection. Timely diagnosis and supportive therapy reduce the morbidity and mortality from DHF.

Baton S et al[59](2014), conducted a prospective cross-sectional pilot study to determine whether serum calcium is significantly decreased in patients with dengue shock

syndrome. All patients aged 0–14 years admitted for fever and confirmed by dengue serology were enrolled. A serum calcium level was taken on admission. Upon discharge, patients were grouped into dengue fever, and dengue shock syndrome and the serum calcium taken on admission was tabulated alongside the diagnosis. Serum calcium was found to be significantly decreased in patients with dengue shock syndrome compared to patients with dengue fever. Gender and nutritional status do not affect calcium levels in these patients. This may imply calcium replacement as part of the management of dengue shock syndrome. A rough estimate of the serum calcium level and its probable effect on shock could alter the management of patients with dengue.

Constantine GRet al[13](2014), Dengue fever is a major cause of morbidity and mortality in tropical regions. Serum-free calcium (Ca2+) is known to be important in cardiac and circulatory function. We evaluated the association between serum Ca2+ level and severity of dengue. A cross-sectional study was carried out at a tertiary care private hospital in Sri Lanka. A probable case of dengue was diagnosed and classified according to World Health Organization criteria and confirmed by either IgM antibody, PCR, or NS1 antigen detection. The sample size was 135. The mean age was 26.1 years, and the majority were males (n = 80, 59.3%). Dengue was diagnosed in 71 patients (52.6%). Mean serum Ca2+ level of the study population was 1.05 mmol/L (range 0.77-1.24). Mean serum Ca2+ was significantly higher in patients with dengue fever (DF) (1.09 mmol/L) than in those with DF (1.02 mmol/L) ($p < 0.05$). Prevalence of hypocalcaemia in DHF and DF patients was 86.9% (n = 60) and 29.7% (n = 11), respectively ($p < 0.05$). Serum Ca2+ levels significantly correlated with

dengue severity. Serum Ca2+ levels were significantly lower and hypocalcaemia was more prevalent in patients with DHF than in patients with DF.

Shivanthan M et al[10](2014), Dengue is potentially fatal unless managed appropriately. Evidence with regards to the role of calcium homeostasis in dengue is limited. Low blood calcium levels have been demonstrated in dengue infection and hypocalcemia maybe more pronounced in more severe forms. The cause of hypocalcemia is likely to be multifactorial. Calcium has been also implicated in the immune pathogenesis of dengue; however, the precise clinical implications of these interactions are yet not clearly defined. Derangements of calcium homeostasis are likely to be associated with myocardial dysfunction and cardiac arrhythmias observed in dengue as suggested by in vitro studies. Calcium also plays a role in platelet aggregation. Studies evaluating the therapeutic use of calcium in dengue have been underpowered and poorly designed to make any firm recommendation and concluded that Calcium plays a key role in the functioning of myocardial tissue. Cardiac involvement in dengue has been documented in many studies.

Li J et al[60] (2012), Dengue virus (DENV) capsid (C) proteins are the major structural component of virus particles. This study aimed to identify the host interacting partners of DENV C protein that could contribute to viral pathogenesis. DENV C protein was screened against human liver cDNA yeast two-hybrid library. DENV production was significantly attenuated in CAML knock-down cells at 36h post-infection. CAML did not influence DENV entry, genome uncoating, viral transcription, viral translation and virus secretion. Our study pinpointed that CAML influenced the process of apoptosis by altering mitochondrial membrane potential and caspase-3 activation from 36h post-

infection. Over-expression of CAML protected Huh7 cells from apoptosis and knock down of CAML favoured apoptosis following infection with DENV. We also showed that CAML expression was up-regulated during DENV infection. Increased CAML levels protected DENV-infected cells from undergoing apoptosis by preventing mitochondrial damage and caspase-3 activation which in turn favoured DENV production from 36h post-infection. Overall, this study demonstrated that DENV manipulated the levels of CAML to subvert the apoptotic process which in turn favoured efficient virus production.

Salgado DM et al[61](2010), Dengue fever is one of the most significant re-emerging tropical diseases; despite our expanding knowledge of the disease, viral tropism is still not known to target heart tissues or muscle. A prospective paediatric clinical cohort of 102 dengue hemorrhagic fever patients from Colombia, South America, was followed for 1 year. Eleven children with dengue hemorrhagic fever presented with symptoms of myocarditis. Widespread viral infection of the heart, myocardial endothelium, and cardiomyocytes, accompanied by inflammation was observed in 1 fatal case. Immunofluorescence confocal microscopy showed that myotubes were infected by dengue virus and had increased expression of the inflammatory genes and protein IP-10. The infected myotubes also had increases in intracellular Ca2+ concentration. Vigorous infection of heart tissues in vivo and striated skeletal cells in vitro are demonstrated. Derangements of Ca2+ storage in the infected cells may directly contribute to the presentation of myocarditis in paediatric patients.

Sanchez E et al[50](2009), A dengue epidemic is one of the most important public health problems in the tropical and subtropical areas of the World. In 2005, 7,062

dengue cases were reported in Tamaulipas on Mexico's eastern coast, including 1,832 (26%) cases classified as Dengue Hemorrhagic Fever (DHF). Dengue fever (DF) is characterized by fever, intense headache, myalgias, arthralgias, rash, nausea and vomiting. A proportion of infected persons may develop DHF characterized by prominent hemorrhagic manifestations associated with thrombocytopenia. An immune mechanism of thrombocytopenia due to increased platelet destruction appears to be operative in patients with DHF. Extracellular calcium plays a key role in platelet aggregation and for the regulation of the immune response in persons infected with Dengue Virus (DV), and dihydroxy-vitamin D has recently been found to alter IL-12 expression and dendritic cell maturation. We report the cases of five patients who received oral calcium carbonate plus Vitamin D3, who improved the overall clinical condition and reduced the duration of signs and symptoms of DF.

Cabrera J I et al[12](2008), Global climate change is one of the instigating and contributing factors for epidemic outbreaks of infectious diseases in human populations. In the years 2003 to 2005 the city of Tampico, in the northern state of Tamaulipas, Mexico, Extracellular calcium (Ca2+ o) plays a key role in blood clotting; its chelation in vitro with ethylenediamine tetraacetic acid (EDTA) or citrate prevents clotting, while exogenous re-calcification of plasma leads to shortening of clotting time. In vivo, Ca2+ is essential for platelet function and for the regulation of the immune response. In this work we report a significant increase ($p<0.05$) in the number of blood platelets of patients with clinical signs and symptoms of DF following oral administration of calcium carbonate (CAL, 1.2 to 1.8 g/day; n=10) when compared with a control group (CTL, n=10): 89 (46-132) versus 206 (155-257). Data expressed as mean value (95% confidence interval, C.I.) for x1000 cells/mm3.

CAL also improved the overall clinical condition and reduced by 36 % the duration of signs and symptoms of DF: 6.7-11.3 days, versus 11.5-16.6 days (95 % C.I., $p<0.05$) when compared with CTL patients.

Dhawan R et al [42](1997), conducted an in vivo study on the obligatory role ofcalcium ions (Ca2+) in the cytotoxic activity of the dengue type 2 virus (DV)-induced macrophage (M phi) cytotoxin (CF2). The findings show that CF2 prepared in Ca (2+)-free medium had no cytotoxic activity on normal mouse spleen cells suspended in Ca (2+)-free medium but killed the cells suspended in the medium with Ca2+. Substitution with calcium chloride restored the cytotoxic activity of CF2 the optimal dose is 10(-4) M concentration. CF2 induced an influx of Ca2+, as assayed by uptake of radiolabeled calcium chloride (45Ca), in the susceptible target cells, viz. M phi and T lymphocytes. The cytotoxic activity of CF2, as well as the CF2-induced influx of 45Ca, was inhibited by treatment of the target cell with the calcium channel blocking drugs verapamil and nifedipine. Thus, the presence of Ca2+ is obligatory for the cytotoxic activity of CF2, and cell death is associated with increased intracellular Ca2+.

M Khannaet al[43](1995),conducted an in vivo study to investigate the role of calcium ions (Ca2+) in the cytotoxic activity of the cytotoxic factor (CF) produced by T lymphocytes of the dengue type 2 virus (DV)-infected mouse spleen. It was observed that CF prepared in Ca2(+)-free medium had no cytotoxic activity on normal mouse spleen cells suspended in Ca2(+)-free medium but had activity on cells suspended in a medium having Ca2+. The cytotoxic activity of CF was restored by substitution with calcium chloride, the optimal dose is 10(-7) M. CF induced influx of Ca2+ as measured by uptake of radiolabeled calcium chloride (45Ca), in the susceptible target

cells, macrophages (M phi) and T lymphocytes, but had no effect on CF-resistant B lymphocytes. Calcium channel blocking drugs, like verapamil, nifedipine and diltiazem, inhibited the cytotoxic activity of CF and also the CF-induced influx of 45Ca in M phi and T cells. Thus, the presence of Ca2+ is obligatory for the cytotoxic activity of CF,and the cell death was associated with increased intracellular Ca2+.

Khare M et al [45](1995), conducted a study to investigate the role of calcium in the production of dengue type 2 virus (DV) induced suppressor cytokine (SF) and in transmission of the suppressor signal via syngeneic macrophage (M phi) to recruit the second subpopulation of suppressor T(TS2) cell. Effect of calcium channel blocking drugs, Verapamil and Nifedipine, on the production and activity of SF was investigated. The production of SF was inhibited in a dose-dependent manner by the calcium channel blockers. The suppressor activity of SF was also inhibited by calcium channel blocking drugs. SF could not be produced when spleen cells were cultured in a calcium-free medium, the production being restored on substitution with calcium chloride. Treatment of M phi with the calcium channel blockers inhibited the transmission of the suppressor signal from TS1 to TS2 cells in a dose-dependent manner. The influx of calcium during transmission of the suppressor signal was studied by measuring the 45Ca uptake. Calcium channel blocking drugs inhibited the 45Ca uptake by T lymphocytes. Thus, the presence of calcium is obligatory for the production and suppressor activity of SF, and it plays a critical role in the transmission of the suppressor signal.

Shivanthanetal [10](2014), demonstrated that – Hypocalcaemiais seen incases with severe dengue fever and has been purported to be associated with increased mortality. Nonetheless,there isa paucityof clinical evidenceon the roleof calcium disequilibrium in dengue fever, the clinical effects of hypocalcaemiain dengue fever and onthe interactions between blood calcium ions and the immunepathogenesis of the disease. Although hypocalcemia hasbeen observed in dengue fever, there is no evidence currently that hypocalcaemia has significant clinical implications. There is little evidence on the role, if any of calcium replacement in patients with dengue fever who are hypocalcemia. The potential role ofcalciumas therapy to modulatethe immunesystem,in either hypocalcemia ornorm calcemic patients with dengue fever areunknown.

Constantine et al[13] (2014) Suggested that –Serum calcium level was significantly lower in patients with DHF than in those with DF. A vast majority of deaths in dengue infections occur due to severe plasma leakage that occurs in DHF/DSS. The measurement of serum calcium is currently nota routine practice in patients with dengue fever. Further studies are required to determine whether the presence of hypocalcemia at the onset of the illness can be utilized as a prognostic indicator to predict disease severity.A Pilot study conducted in Mexico, on a limited number of patients with dengue infection demonstrated that, oral calcium and vitamin D3 supplementation improved the overall clinical condition and reduced the duration of illness.In a similar study, oral calcium supplementation significantly increased the number of platelets in patients of dengue infection.

Khwaja Nazim Uddin et al[40](2008), suggested that within the several biochemical derangements found in this study the detection of hypocalcemia demands special consideration. Interestingly a significant number of patients in this series had hypocalcemia and some of them were symptomatic. Hypocalcemia was correlated with conventional severity parameter, mean calcium level was lowest in DHF III Patients.

Kapoor et al[62](2012),suggested that –They reported 84 cases during A one year period, of which a significant number of patients in this series had hypocalcemia's of them had been diagnosed with hypocalcemia tetany, serum samples for calcium and routine investigations were taken. ECG was suggestive of prolongation of QTc interval.

Study site: This study was conducted in the department of general medicine, Dr. Prabhakar Kore hospital, KLE University, Belgaum.

Study population: All the proved cases of dengue fever admitted in general medicine department at DR.Prabhakar Kore hospital, KLE University were considered as the study population.

Study design: The current study was a Cross-sectional study

Sample size: All the eligible subjects presenting during the study period who satisfied the inclusion and exclusion criteria were included in the study by universal sampling. A total of 100 subjects were available for final analysis.

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration: The data collection for the study was done between January 2017 to December 2017 for a period of 1 year.

Inclusion Criteria:

1. All proved cases of dengue fever admitted in KLE'S Dr.Prabhakar kore hospital and MRC Belgaum

Exclusion criteria:

1. Patients with hypertension, diabetes mellitus, cardiac disease and those on antihypertensive and antiarrhythmic medication.
2. Patients those who are on calcium supplement or any other drugs which affect calcium homeostasis were excluded.

Ethical considerations: Study was approved by the institutional human ethics committee. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and voluntary nature of

participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology:

Patients fulfilling the inclusion and exclusion criteria were taken in to study after obtaining written informed consent. Demographic data, history, clinical examination and details of investigations. A probable case of dengue was diagnosed according to the WHO criteria:

Acute febrile illness with two or more of the following:

- A headache,
- Retro-orbital pain,
- Myalgia,
- Arthralgia,
- Rash,
- Hemorrhagic manifestation,
- Leucopenia (WBC<5000 cells/mm),
- Thrombocytopenia –platelet< 150,000 cells/mm,
- Rising hematocrit (5-10%)

Dengue Haemorrhagic Fever:

- All of the following:
- Hemorrhagic manifestation, shown by any of the following: positive tourniquet test, petechiae, ecchymosis or purpura, or bleeding from mucosa, gastrointestinal tract, injection site.

- Platelet count < 100,000 cells/mm
- Rising hematocrit > 20% from baseline

Dengue Shock Syndrome:

- Criteria for dengue hemorrhagic fever as above with signs of shock including:
- Tachycardia, cool extremities, delayed capillary refill, weak pulse, lethargy
- Pulse pressure <20 mph with increased diastolic pressure.
- Hypotension by age, defined as systolic pressure < 80 mmHg to 90 mmHg.

Confirmation of diagnosis was done with one of the following laboratory tests:IgM antibody, IgG antibody or serum dengue NS1 Antigen detection.The prevalence of myocarditis was diagnosed either by the presence of changes in the 12 lead ECG (ST Segment, T Inversion or right bundle branch block).Hypocalcaemia was defined as the presence of serum calcium < 8.5 mg/dl.

Follow up: The study was a cross sectional study, hence no follow up was done.

Investigations:

- CBC
- NS1 Antigen
- Dengue IgM antibody
- Dengue IgG antibody
- Serum calcium
- ECG

Statistical methods:

Serum calcium was considered as the primary outcome variable. NS1 antigen, Dengue IgM antibody and IgG antibody were considered as a Primary explanatory variable.

Descriptive analysis was carried out by the mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram and pie diagram.

All the Groups of age, Hemoglobin, Total count, Platelet and serum calcium were checked for a normal distribution within each category of NS1 antigen, Dengue IgM antibody and IgG antibody by using visual inspection of histograms and normality Q-Q plots. Shapiro-Wilk test was also conducted to assess normal distribution.Shapiro Wilk test p-value of >0.05 was considered as a normal distribution.

For non-normally distributed serum calcium, Medians and Interquartile range (IQR) were compared between study groups (NS1 antigen, Dengue IgM antibody and IgG antibody) using Mann Whitney u test

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[63]

RESULTS

A total of 100 subjects were included in the final analysis

Table 1: Descriptive analysis of age in the study population (N=100)

Parameter	Mean ± SD	Median	Min	Max	95% C.I	
					Lower	Upper
Age	26.64 ± 10.65	26.50	18	70	27.52	31.75

The mean age of the study population was 26.64 ± 10.65 with the ranged between 18 to 70 years. (Table 1)

Table 2: Descriptive analysis of age group in the study population (N=100)

Age group	Frequency	Percentages
18 to 19	10	10%
20 to 29	53	53%
30 to 39	18	18%
40 to 49	13	13%
50 to 59	3	3%
60 and above	3	3%

Among the study population, 10 (10%) participants were aged between 18 to 19 years, 53 (53%) were aged between 20 to 29 years, 18 (18%) were aged between 30 to 39 years, 13 (13%) were aged between 40 to 49 years, 3 (3%) were aged between 50 to 59 years and 3 (3%) were aged 60 and above years. (Table 2& Figure 2)

Figure 2: Bar chart of the age group in the study population(N=100)

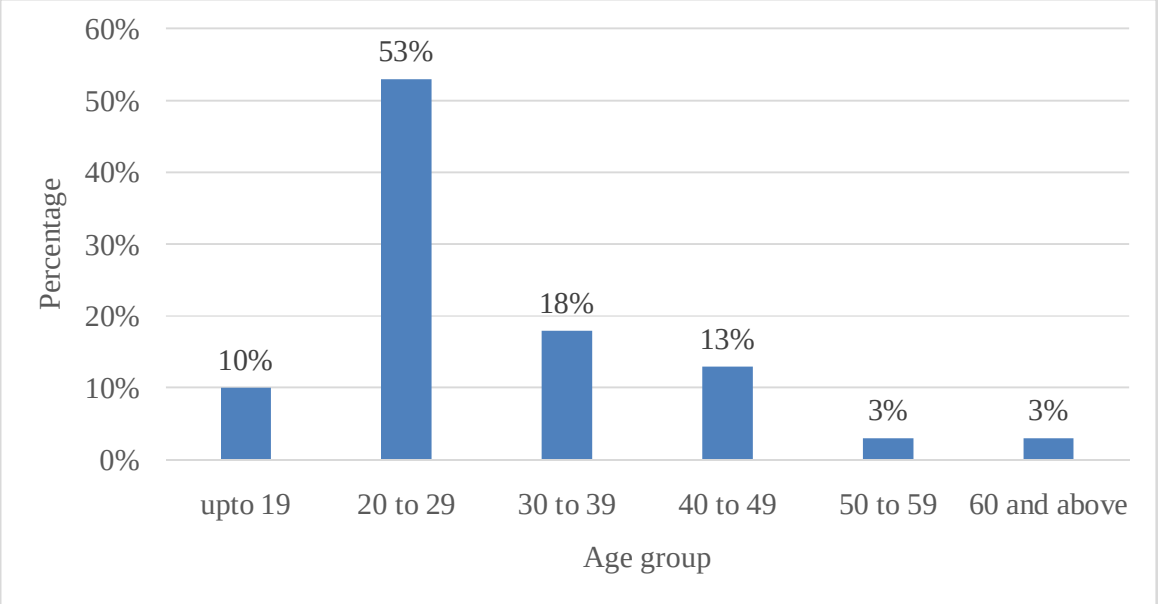


Table3:Descriptive analysis of gender in the study population (N=100)

Gender	Frequency	Percentages
Male	74	74%
Female	26	26%

Among the study population, 74 (74%) participants were males, and the remaining 26 (26%) were females. (Table 3 & figure 3)

Figure 3:Pie chart of gender in the study population (N=100)

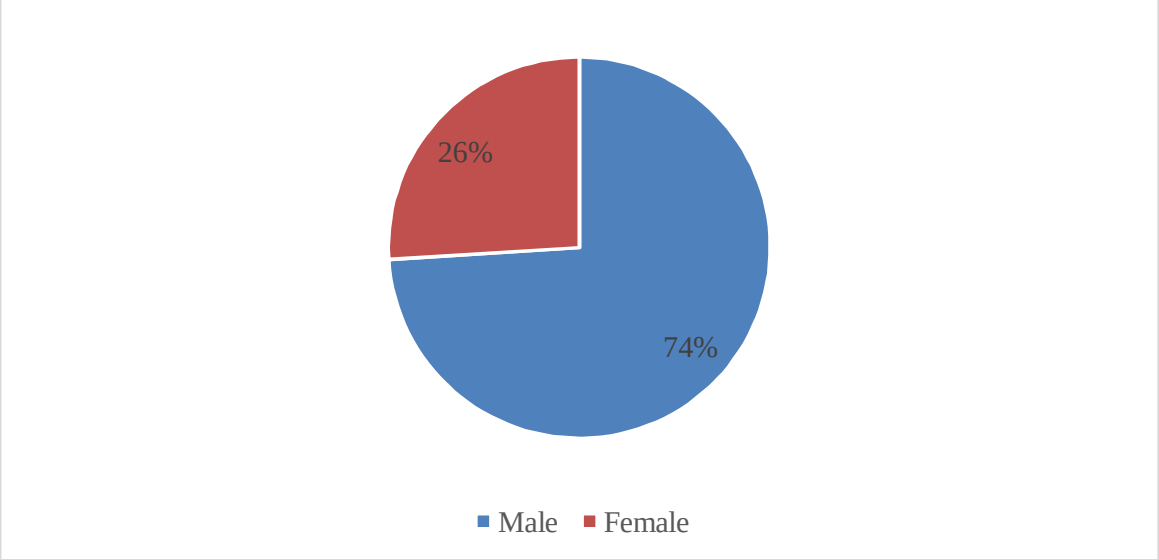


Table 4: Descriptive analysis of haemoglobin in the study population (N=100)

Parameter	Mean ± SD	Median	Min	Max	95% C.I	
					Lower	Upper
Hemoglobin (g/dl)	14.32 ± 2.33	14.3	9.0	20.0	13.85	14.78

The mean Hemoglobin of study population was 14.32 ± 2.33 with the ranged between 9 to 20 g/dl. (Table 4)

Table 5: Descriptive analysis of total count in the study population (N=100)

Parameter	Mean ± SD	Median	Min	Max	95% C.I	
					Lower	Upper
Total count (cells/µL)	264.38 ± 1924.42	4.3	0.4	17300	119.44	648.20

The mean Total count of the study population was 264.38 ± 1924.42 with the ranged from 0.40 to 17300 cells / µL.(Table 5)

Table 6: Descriptive analysis of platelet in the study population (N=100)

Parameter	Mean ± SD	Median	Min	Max	95% C.I	
					Lower	Upper
Platelet	62686.87 ± 8647.45	42000	5000	253000	50989.84	74383.90

The mean platelet of the study population was 62686.87 ± 8647.45 with the ranged between 5000 to 253000 cells/µL. (Table 6)

Table 7: Descriptive analysis of Ns1 antigen in the study population (N=100)

Ns1 antigen	Frequency	Percentages
Positive	28	28%
Negative	72	72%

Among the sample size, i.e.,100 patients Ns1 antigen was positive in 28% and negative in 72% of patients respectively. (Table 7 & Figure 4)

Figure 4: Pie chart of Ns1 antigen in the study population (N=100)

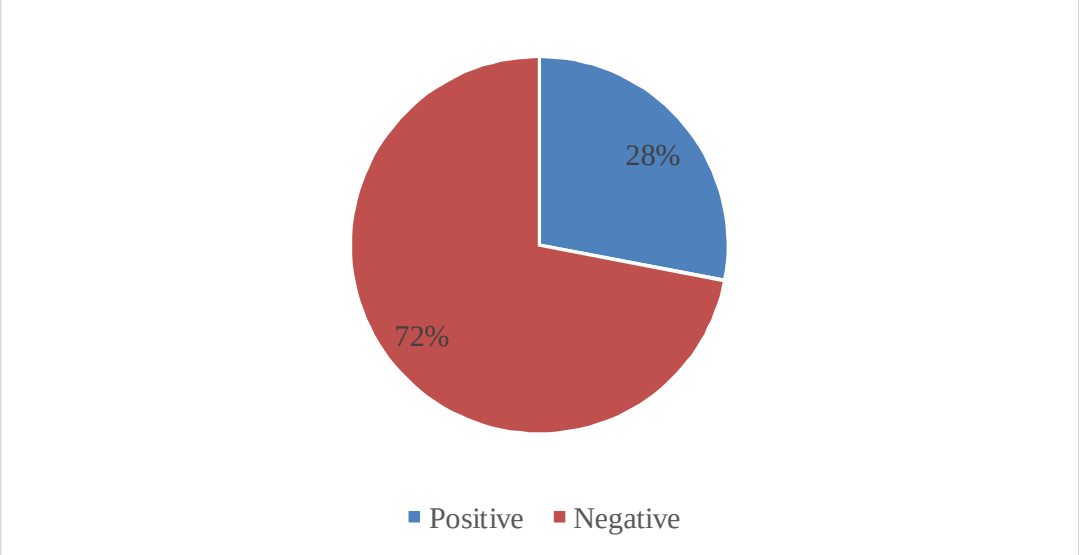


Table 8: Descriptive analysis of dengue IgM antibody in the study population (N=100)

Dengue IgM antibody	Frequency	Percentages
Positive	68	68%
Negative	32	32%

Among the study population, 68% were IgM Antibody positive and 32% were IgM Antibody negative. (Table 8 & figure 5)

Figure 5: Pie chart of Dengue IgM antibody in the study population (N=100)

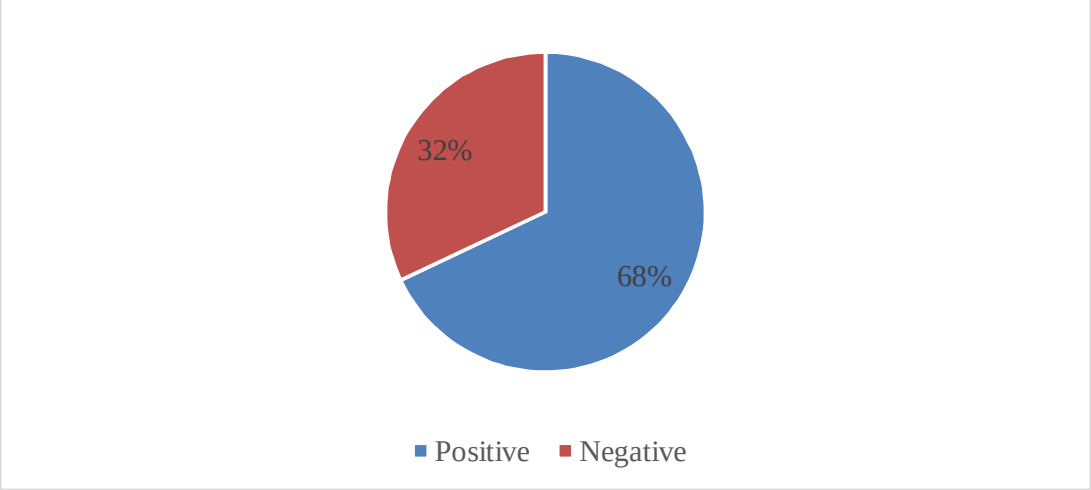


Table 9: Descriptive analysis of dengue IgG antibody in the study population (N=100)

IgG antibody	Frequency	Percentages
Positive	71	71%
Negative	29	29%

Among the study population, 71% of patients were IgG antibody positive and 29% were IgG antibody Negative status. (Table 9 & Figure 6)

Figure 6: Pie chart of Dengue IgG antibody in the study population (N=100)

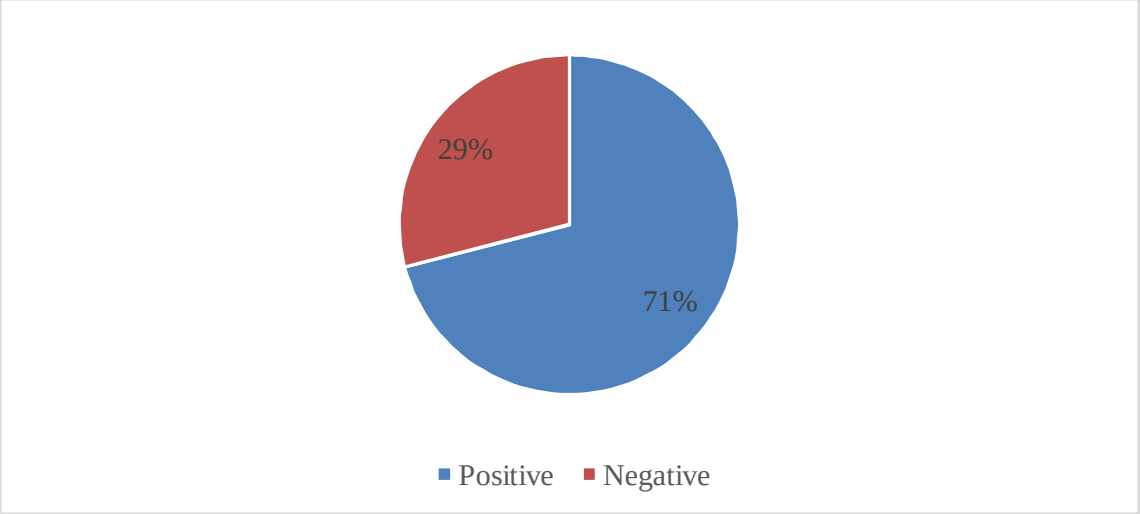


Table 10: Descriptive analysis of Dengue IgM + IgG antibody in the study population (N=100)

Dengue IgM +IgG antibody	Frequency	Percentage
Positive	50	50%
Negative	50	50%

Out of 100 participants, 50 (50%) participants had both Dengue IgM + IgG antibody Positive. (Table 10 & Figure 7)

Figure 7: Pie chart of dengue IgM + IgG antibody in the study population (N=100)

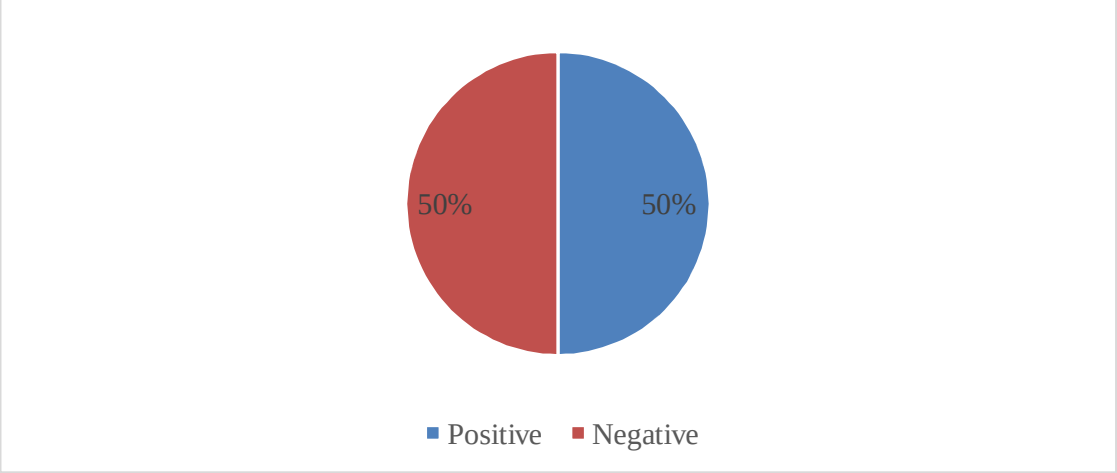


Table 11: Descriptive analysis of serum calcium in the study population (N=100)

Parameter	Median	Interquartile range
Serum calcium (mg/dl)	8.40	(8.20 to 8.60)

The median serum calcium of the study population was 8.40 (8.20 to 8.60) mg/dl. (Table 11)

Table 12: Comparison of median value between serum calcium and NS1 antigen test (N=100)

Ns1 antigen	Serum calcium Median (IQR)	Mann Whitney U test (P value)
Positive	8.45 (8.32 to 8.60)	0.294
Negative	8.40(8.20 to 8.60)	

Among the people with NS1 antigen positive, the median serum calcium was 8.45 mg/dl (IQR 8.32 to 8.60), and it was 8.40 mg/dl (IQR 8.20 to 8.60) in people with NS1 antigen negative. The difference between the serum calcium and NS1 antigen groups was statistically not significant (P Value 0.294).(Table 12 & Figure 8)

Figure 8: Comparison of the bar chart of median value between serum calcium and NS1 antigen test (N=100)

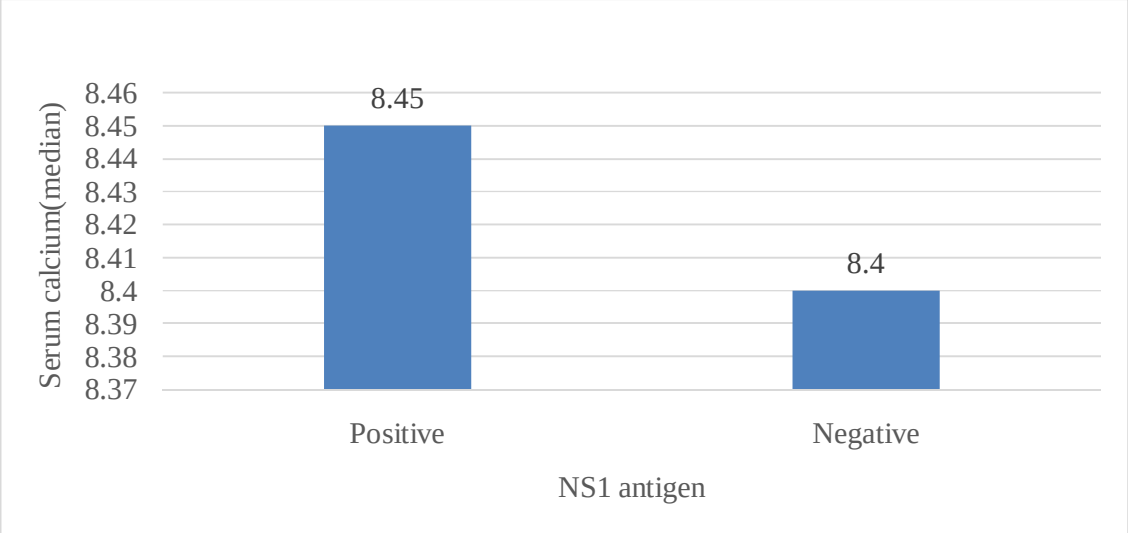


Table 13: Comparison of median value between serum calcium and Dengue IgM antibody (N=100)

Dengue IgM antibody	Serum calcium Median (IQR)	Mann Whitney U test (P value)
Positive	8.00(7.00 to 8.60)	0.042
Negative	8.60(8.45 to 9.00)	

Among the people with Dengue IgM antibody positive, the median serum calcium was 8.0 (IQR 7 to 8.60), and it was 8.60 (IQR 8.45 to 9) in people with Dengue IgM antibody Negative. The difference between the serum calcium and Dengue IgM antibody groups was statistically significant (P Value 0.04). (Table 13& Figure 9)

Figure 9: Comparison of the bar chart of median value between serum calcium and Dengue IgM antibody test (N=100)

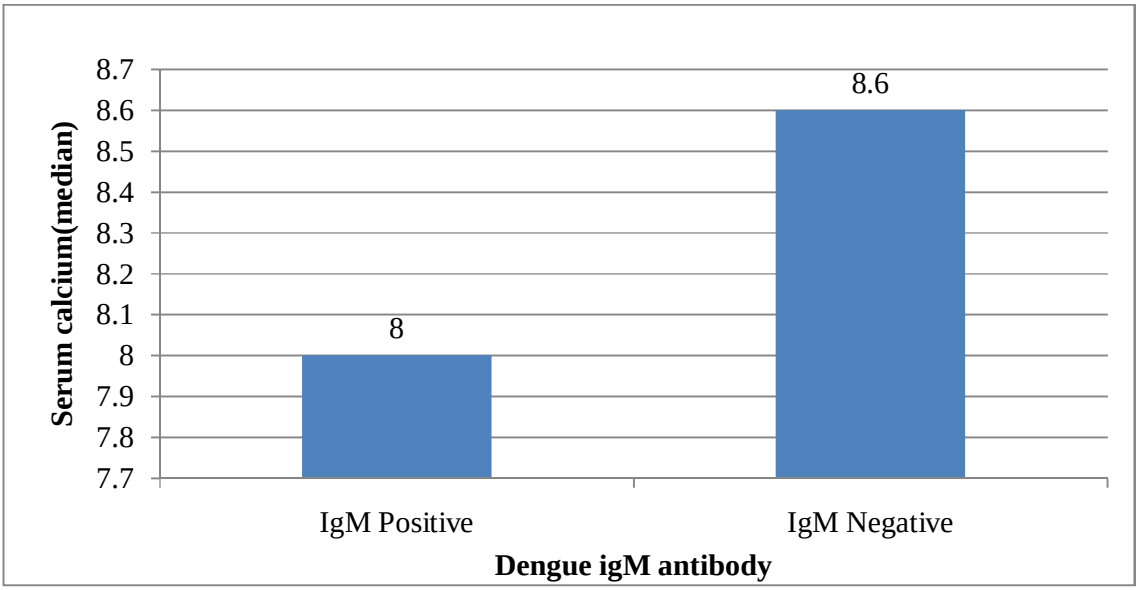


Table 14: Comparison of median value between serum calcium and Dengue IgG antibody test (N=100)

Dengue IgG antibody	Serum calcium Median (IQR)	Mann Whitney U test (P value)
Positive	8.40(8.20 to 8.60)	0.642
Negative	8.50(8.40 to 8.68)	

Among the people with Dengue IgG antibody positive, the median serum calcium was 8.40 mg/dl(IQR 8.20 to 8.60), and it was 8.50 mg/dl (IQR 8.40 to 8.68) in people with Dengue IgG antibody negative. The difference between the serum calcium and Dengue IgG antibody groups was statistically not significant (P Value 0.642). (Table 14& Figure 10)

Figure 10: Comparison of the bar chart of median value between serum calcium and Dengue IgG antibody test (N=100)

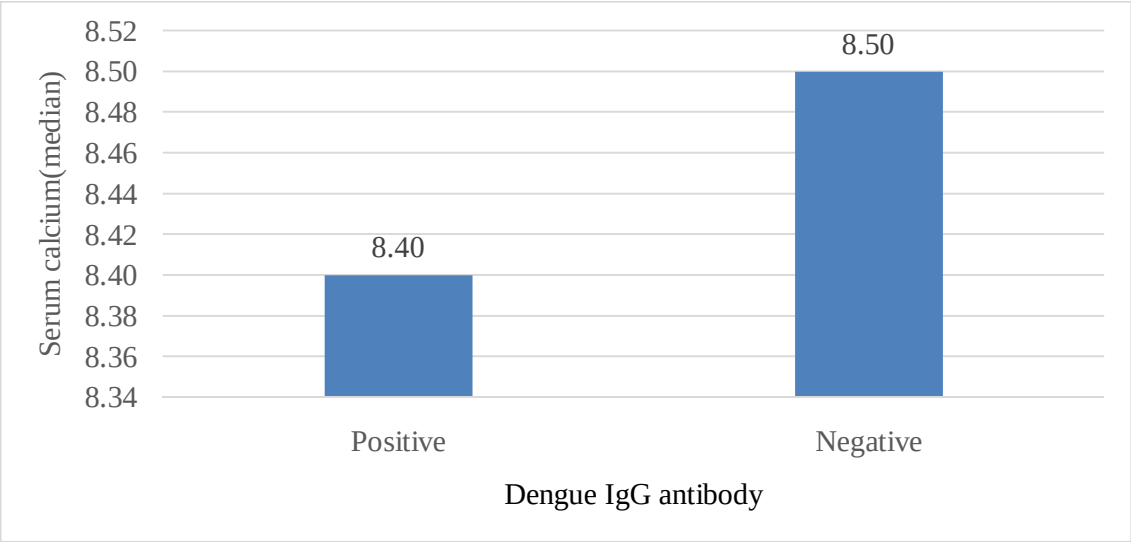


Table 15: Comparison of median value between serum calcium and Dengue IgM + IgG antibody test (N=100)

Dengue IgM+IgG antibody	Serum calcium Median (IQR)	Mann Whitney U test (P value)
Positive	8.20(8.20 to 8.60)	0.022
Negative	8.50(8.40 to 8.68)	

Among the people with Dengue IgM+IgG antibody positive, the median serum calcium was 8.20 mg/dl (IQR 8.20 to 8.60), and it was 8.50 mg/dl (IQR 8.40 to 8.68) in people with Dengue IgM+IgGantibody negative. The difference between the serum calcium and Dengue IgM +IgG antibody groups was statistically significant (P Value 0.022). (Table 15& Figure 11)

Figure 11: Comparison of the bar chart of median value between serum calcium and Dengue IgM +IgG antibody test (N=100)

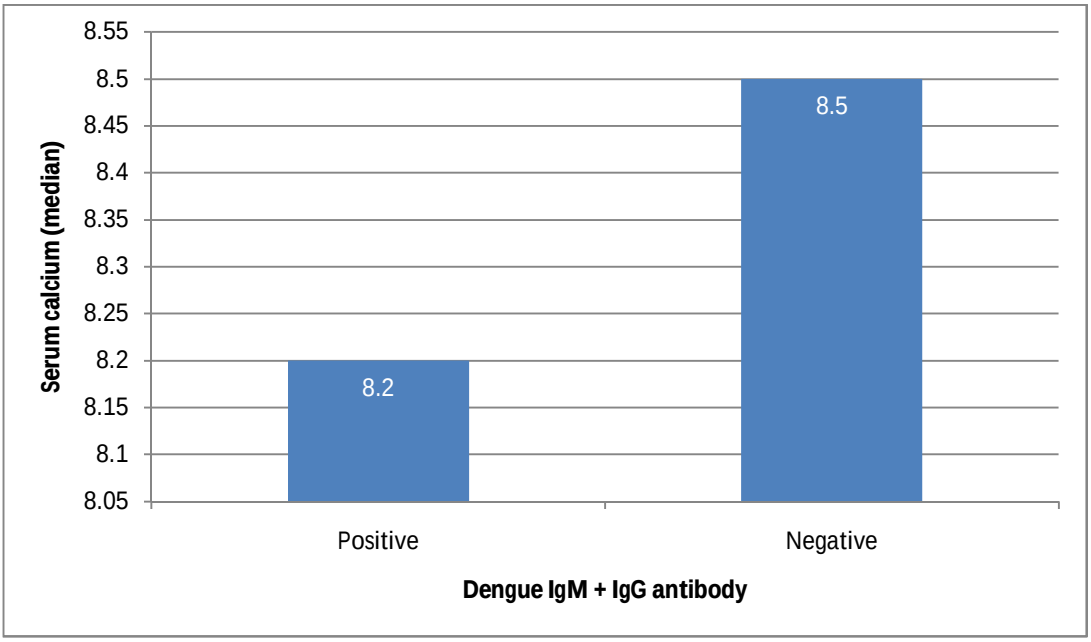


Table 16: Descriptive analysis of Dengue fever in the study population (N=100)

Diagnosis	Frequency	Percentage
Dengue fever	72	72%
Dengue Hemorrhagic fever	23	23%
Dengue shock syndrome	05	5%

Among the study population, 72 (72%) participants had Dengue fever. The number of Dengue Hemorrhagic fever and Dengue shock syndrome were 23(23%) and 5(5%) respectively. (Table 16 & figure 12)

Figure 12: Pie chart of diagnosis in the study population (N=100)

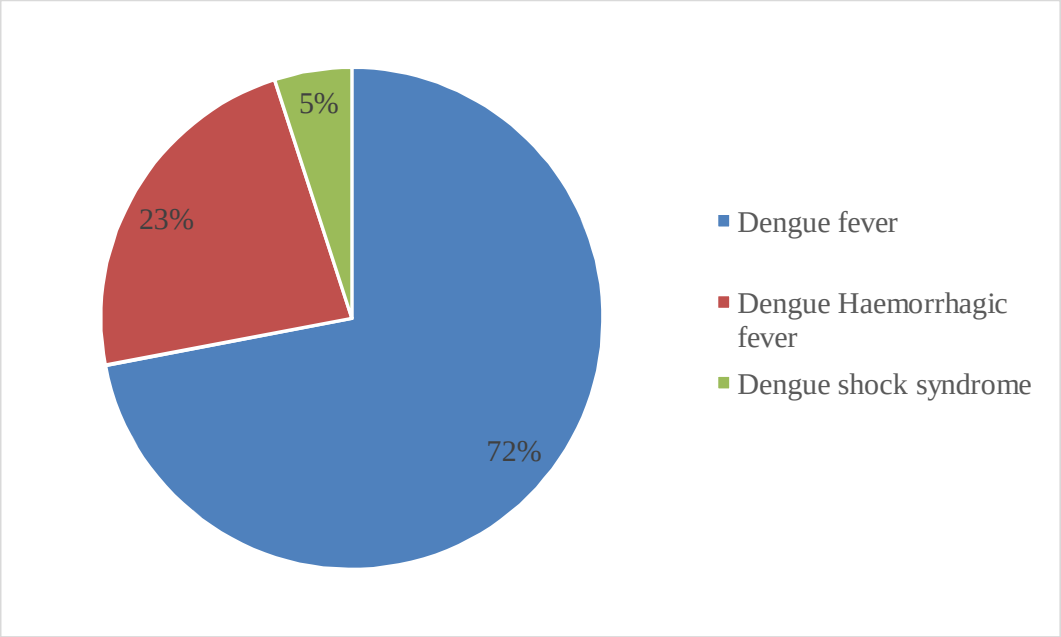


Table 17: Comparison of serum calcium level with diagnosis (N=100)

Serum calcium(mg/dl)	**Diagnosis**		
	Dengue Fever (N=72)	**Dengue Hemorrhagic Fever(N=23)**	**Dengue Shock syndrome(N=5)**
Upto 7.0	0 (0%)	0 (0%)	1(20%)
7.1-7.5	0 (0%)	0 (0%)	2(40%)
7.6-8.0	1 (1.4%)	5 (21.7%)	1(20%)
8.1-8.5	38 (52.8%)	16 (69.6%)	1(20%)
8.6-9.0	31 (43.1%)	2 (8.7%)	0 (0%)
9.1 and above	2 (2.8%)	0 (0%)	0 (0%)

Among the people with diagnosis of Dengue fever, 1 (1.4%) participants had serum calcium level in between 7.6 to 8 mg/dl, 38 (52.8%) had 8.1 to 8.5 mg/dl, 31 (43.1%) had 8.6 to 9 mg/dl and 2 (2.8%) had 9.1 mg/dl and above.Among the people with a diagnosis of Dengue Hemorrhagic fever, 5 (21.7%) participants had serum calcium level in between7.6 to 8 mg/dl, 16 (69.6%) had 8.1 to 8.5 mg/dl, and 2 (8.7%) had 8.6 to 9 mg/dl.Among the people with Dengue Shock syndrome, 1 (20%) participants had serum calcium upto 7 mg/dl,2 (40%) had 7.1 to 7.5 mg/dl serum calcium.1 (20%) had 7.6 to 8 mg/dl serum calcium level, 1 (20%) had 8.1 to 8.5 mg/dl serum calcium level. (Table 17)

Table 18: Comparison between diagnosis and complications (N=10)

Diagnosis	Complications	
	Cardiac(N=7)	Neurological(N=3)
Dengue fever	1 (14.3%)	0 (0%)
Dengue Hemorrhagic fever	4(57.1%)	1(33.3%)
Dengue shock syndrome	2(28.6%)	2(66.7%)

Among the people with cardiac complications, 1 (14.3%) participants had Dengue fever, 4 (57.1%) had Dengue Hemorrhagic fever,and2 (28.6%) participants had Dengue shock syndrome.Among the people with Neurological complications, 1 (33.3%) participants had Dengue Hemorrhagic fever,and2(66.7%) participants had Dengue shock syndrome. (Table 18)

Table 19: Co-relation between serum calcium level and ECG findings in the study group

No. Of the patients with a cardiac complication	Calcium level (mg/dl)	ECG Finding
01	**7.0**	Atrial fibrillation,ventricular tachycardia
02	**7.1-7.5**	Sinus bradycardia, Non-specific ST, T wave changes
04	**7.6-8.2**	Sinus bradycardia, Non-specific ST, T wave changes

A cardiac complication that includes arrhythmias, cardiogenic shock and ECG changes (Sinus bradycardia, Non-specific ST, T changes, Tachyarrhythmia – Atrial fibrillation, ventricular tachycardia)

A neurological complication that includes Dengue encephalopathy, Dengue encephalitis and Dengue transient muscle dysfunction.

DISCUSSION

Dengue fever is the most prevalent mosquito-borne viral infection in the world. Each year, there are ~50 million dengue infections, and~500,000 individuals are hospitalized with Dengue, mainly in Southeast Asia, the Pacific, and the Americas. The average total economic burden faced by dengue epidemic in India in 2006 was estimated to be 27.4 million United States Dollar (USD).[64]In the last decade, dengue has assumed pan-India proportions. Outbreaks and deaths have been reported from northern states of Haryana, Punjab and Uttar Pradesh; southern states of Andhra Pradesh, Tamil Nadu and Karnataka; western states of Gujarat and Rajasthan; and the eastern state of West Bengal. In fact, the case fatality rate has been above 1% over the last 10 years[65]Dengue fever is potentially fatal unless managed appropriately. No specific treatment is available, and the mainstay of treatment is fluid management with careful monitoring, organ support, and correction of metabolic derangement. Evidence with regards to the role of calcium homeostasis in dengue fever is limited. Low blood calcium levels have been demonstrated in dengue infection and hypocalcemia may be more pronounced in more severe forms. Calcium has been also implicated in the immune pathogenesis of dengue fever; however, the precise clinical implications of these interactions are yet not clearly defined.

The current study was conducted with 100 subjects of dengue fever and aimed to study the association between the severity of dengue infection and serum calcium levels

Age and Gender:

In the current study, the mean age of the study population was 26.64 years, and all the participants were aged between 18 to 70 years. Majority of the study participants were males (74%), and 26% of them were females.

Similarfindings were reported by Constantine GR et al.[13] where 135 subjects were recruited with the mean age of 26.1 years, and most of the participants were males (59.3%).

Adhikari M et al.[57] conducted a prospective study in 2015 with61 patients and with similar study settings. The mean age of the study population was 28.8 years, and the proportion of male participantswas 68.8%.

Murugan M R et al.[56]recruited 68 participants in their study.The mean age reported was 32 years which is slightly higher than the current study finding. The majority of the participants were males (60%) in their study. This finding was similar to our study.

Recently, Jayachandran J et al.[53] conducteda study in 2017, to assess the correlation between the severity of dengue fever and serum-free calcium. In their study, 145 participants were recruited. But the mean age was 36.7 years which is slightly higher than the current study finding. Similar to our study, there was a male preponderance (62.7%).

Table 20: Study comparison of the basic demographic characteristics

	Current study	Constantine GR et al[13] (2014)	Adikari, M., et al[57] (2015)	Murugan M R et al [56] (2016)	Jayachandra J et al[53] (2017)
Mean Age	26.4 years	26.1 Years	28.8 years	32 years	36.7 years
Gender(Male predominance)	74%	59.3%	68.8%	60%	62.7%
serum calcium level	Mean-8.4 mg/dl	Mean-4.2 mg/dl (Free calcium)	Mean-3.84 mg/dl (Free calcium)	-	Mean-3.82±0.52 mg/dl(free calcium)

Biomarkers of Dengue fever:

In the current study, out of 100 participants, 28% were Ns1 antigen positive, 68% IgM antibody positive, 71% IgG antibody positive and both IgM + IgG antibodypositivity were seen in 50% participants.

Constantine G R et al.[13] have shown the slightly higher proportion of Ns1 antigen positive cases (48.1%)than current study but IgM positivity was seen in only 28.9% cases which are lower than the current study.

Similar to our study,Murugan M R et al.[56] also used Dengue NS1 antigen or Dengue IgM ELISA for diagnosis and confirmation of dengue fever.

Contrary to our study, a study byJayachandran J et al.[53]reported, 131 (90.3%) patients had NS1 antigen positivity, and only 16.6% patients had IgM positivity.

Dengue fever:

In the current study, the majority of the participants were diagnosed with dengue fever. That accounted for 72% of cases, 23% participantshad Dengue Hemorrhagic fever, and only 5% had Dengue shock syndrome.

Contrary to our study, Constantine GR et al.[13]reported52.6% of the study participants had DHF. But Dengue shock syndrome was not reported in any patient.

Murugan M R et al.[56] reported46% of patients had Severe Dengue (n=31), and the remaining patients had Dengue fever(n=37, 54%).

A study done by Jayachandra J et al.[53] have reported a largerproportion of Dengue Fever with Warning Signs (DF+WS) (56.6%) than dengue fever(39.3%). Only 4.1% of patients were classified as Severe Dengue.

Table 21:Study comparison of the characteristics of dengue fever

Diagnosis	Current study	Constantine G. R et al.[13] (2014)	Murugan, M. R et al.[56] (2016)	Jayachandra, J et al.[53] (2017)
Dengue Fever	72%	48%	54%	39.3%
Dengue Hemorrhagic fever	23%	52%	46%	56.6%
Dengue shock syndrome	5%	0	0	41.1%

Serum Calcium level:

In our study, the median serum calcium of the study population was 8.40 (8.20 to 8.60) mg/dl.Constantine G.R et al.[13] have reported the meanserum free calcium levels as 4.2mg/dl. Adhikari M et al.[57] have conducted a prospective study with 61 patients. Mean free calcium level of the population was 3.84 mg/dl, the range being 2.12-5.92 mg/dl. Jayachandran J et al.[53] have shown the mean Serum free calcium in the study was 3.82±0.52 mg/dl.

Serum calcium level and co-relation with the severity of dengue fever:

In the current study, in patients with dengue fever median serum calcium of 8.50 (IQR 8.30 to 8.60) mg/dl was noted.It was 8.40 (IQR 8.10 to 8.50) mg/dl and 7.50 (IQR 6.10 to 8.10) mg/dl among participants with dengue hemorrhagic fever and dengue shock syndrome respectively. The difference in the serum calcium across diagnosis combination was statistically significant (P Value <0.001).

The mean serum free calcium in patients with dengue fever was 4.36 mg/dl and was significantly lower in patients with dengue hemorrhagic fever where mean serum calcium was 4.08 mg/dl.The mean serum free calcium levels in the different stages of DHF were: DHF I – 4.304 mg/dl, DHF II – 4.088 mg/dl, and DHF III – 4.132 mg/dl.

A study done by Murugan M R et al.[56] have reported findings similar to our study. They show that the mean Corrected Calcium in Dengue Haemorrhagic Fever (7.83 +/- 0.4 mg/dL) was significantly lower than Dengue fever (8.48 +/- 0.4mg/dL) [p value 0.001].

Adhikari M et al.[57]demonstrated that among a study population of 61 patients, 52 (85%) patients showed hypocalcemia, i.e., serum ionized calcium level was below 4.44 mg/dl. Mean free calcium level of the study population was 3.84 mg/dl, the range being 2.12-5.92 mg/dl.

Study findings of Jayachandra J et al.[53]were similar to our study, Where the mean serum calcium (mg/dl)was comparatively lower in Severe Dengue fever when compared toDengue Fever with Warning signsand Dengue Fever. Similar to our study, they also support the fact that the presence of hypocalcemia significantly correlated with the severity of Dengue Fever.

Similar to our study findings,Thanuj Reddy V et al.[51] havereported that the mean free serum Calcium was significantly lower in patients with severe dengue (4.16mg/dl) than in those with dengue feverwith warning signs (4.36mg/dl)($p < 0.001$).

Dengue Fever with complications:

In our study, one patient of Dengue fever had cardiac complications. Brady-arrhythmias with ECG changes like Sinus bradycardia, Non-specific ST, T changes were noted. None of them had neurological complications.

Among 23 participants with Dengue Hemorrhagic fever, 4 (17.39%) had cardiac complications that included Brady-arrhythmias, cardiogenic shock with ECG changes like Sinus bradycardia, Non-specific ST, T changes. One Patient(4.34%) of DHF had a neurological complication that included Dengue encephalopathy.

Among 5 patients with dengue shock syndrome, 2(40%) patients had cardiac complications that included, cardiogenic shock and Tachyarrhythmias with ECG changes (Tachyarrhythmia –Atrial fibrillation,ventricular tachycardia) and 2(40%) patients had neurological complications that included Dengue encephalopathy.

In a study by Constantine G R et al.[13] evidence of myocarditis (ECG and/or 2D echo) was seen in 16 patients, of which 14 (87.5%) were in the DHF group and 2 were in the DF group (12.5%) ($p < 0.05$).

Salgado DMet al.[66] reported 79 DHF patients. 11 patients presented with clinical myocarditis, one of whom had a fatal outcome on the 7th day of the illness.Electrocardiogram did, in 9 of the 11 myocarditis patients, showed sinus bradycardia while 2 patients had tachycardia

CONCLUSIONS:

- The current study analyzed 100 Dengue Fever patients with an average age of 26.64 ± 10.65 years, with the majority of subjects aged between 20 to 29 years. There was a higher male preponderance. Three-fourths of the study population were males.
- The proportion of subjects with IgM antibody positivity, IgG antibody positivity and combined Dengue IgM + IgG antibody positivity was 68%, 71% and 50% respectively.
- Among the participants with NS1 antigen positive and Dengue IgG antibody positive had no statistically significant association with median calcium values.
- The median serum calcium was significantly lower among patients with Dengue IgM antibody positivity, as compared to Dengue IgM antibody negative population (P Value <0.001).
- The median serum calcium was significantly lower among people with both Dengue IgM and IgG antibody positivity, as compared to single antigen positive or both antigen negative group (P Value <0.001).
- Among the study population, 72 (72%) participants had Dengue fever. The number of cases with Dengue Hemorrhagic Fever and Dengue shock syndrome was 23(23%) and 5(5%) respectively.
- The average calcium level showed a declining trend with increasing severity of dengue infection from dengue fever to dengue hemorrhagic fever and dengue shock syndrome (P Value <0.001).
- None of the subjects in dengue fever and DHF groups had serum calcium level below 7 mg/dl, but 20% of the subjects in DSS had serum calcium less than 7

mg/dl. A higherproportion of subjects in dengue shock syndrome and DHF had lower levels of serum calcium, as compared to dengue fever.

- The proportion of participants with cardiac and neurological complications increased with increasing severity ranging from dengue fever to dengue hemorrhagic fever and dengue shock syndrome

RECOMMENDATIONS:

- There is a need to conduct large-scale prospective studies to identify independent predictors of lower serum calcium levels among patients with Dengue Fever.
- There is also a need to understand the association between low serum calcium level and the occurrence of various complications and the final treatment outcomes.
- The effect of interventions to correct the serum calcium levels on the treatment outcomes also need to be studied by appropriate randomized controlled trials.

LIMITATIONS:

- The sample size of the study was limited conduct regression analysis to identify independent predictors of lower serum calcium level among the study population
- The generalizability of study findings is limited, as the study was done on a small sample of the population attending a tertiary hospital.

SUMMARY:

A cross-sectional hospital-based study was conducted on 100 dengue fever patients to assess the impact of dengue fever and serum calcium levels in a tertiary care teaching hospital. In the current study, the average age was26.64 ± 10.65 years, with the majority of subjects aged between 20 to 29 years, with 74% male preponderance. The factors which have shown a statistically significant association with lower serum calcium levels were Dengue IgM antibody positivity, combined Dengue IgM and IgG antibody positivity and severity of dengue fever. The proportion of subjects with various cardiac and neurological complications was higher in severe degrees of dengue fever. The study has highlighted the association between calcium level and severity of dengue fever.

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PROFORMA

"To study the serum calcium level in dengue fever- a one year cross-sectional study in a tertiary care hospital"

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION: YES/NO

fever
Vomiting
Abdominal pain
Headache
Retro-orbital pain
Myalgia
rash

Past history: Yes/No

Ischemic heart disease
Diabetes mellitus
Hypertension
Any other

Family history

Personal history

Treatment history

PHYSICAL EXAMINATION:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

PETECHIAE
ECCHYMOSIS
PURPURA
OTHER BLEEDING MANIFESTATION

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

P.A.:

C.N.S.:

Diagnosis:

Complications:

INVESTIGATION:

HAEMOGLOBIN
PCV
PLATELET COUNT
DENGUE NS 1 ANTIGEN
DENGUEIGM
DENGUEIGG
SERUM CALCIUM
ECG

INFORMED CONSENT

Title Of Research Study:"To study the serum calcium level in dengue fever – a one year cross-sectional study "

Principal Investigator:-
Dr. Dineshkumar Chauhan
Post Graduate Student,
Department Of General Medicine,
JNMC, Belgaum.

Guide:-
Dr. ArathiDarshan
Professor & Head of Unit,
Department of General Medicine,
JNMC, Belgaum.

Introduction and Purpose:-

•Dengue fever is endemic in over 100 countries. Infection with the dengue virus may be asymptomatic or may give rise to spectrum of clinical illness ranging from undifferentiated fever to a severe life threatening hemorrhagic / shock syndrome with multiple organ failure and fatality (1)

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness (rarely happens) at the site from where the blood is drawn.

You may not be benefitted by these investigations but you will be part of this study which is going to be useful to others in the future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study.

If you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons,

Dr.ArathiDarshan,M.D
Professor & Head of Unit,
Dept of General Medicine,
JNMC,Belgaum
984845883

.
Dr.Dineshkumar Chauhan
Investigator
PG in General Medicine,
JNMC,Belgaum.
9164026086

DR. GANGA PILLI,
Chairman,
JNMC Institutional Ethics Committee
On HumanSubjects Research,
JNMC, Belgaum
9448863866

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me and has been explained to me in my vernacular language and all my questions have been answered. I will be given a copy of this consent form.

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's name :……...

Signature / Left thumb impression :……...
of the participant

Name of the legally authorized:……...
representative / guardian

Signature / Left thumb impression:……...

Witness' name :……...

Signature / Left thumb impression:……...

Investigator's name and signature:……...

Date:

Place:

ತಿಳುವಳಿಕೆ ಒಪ್ಪಿಗೆ ಪತ್ರ

ಸಂಶೋಧನೆಯ ಶಿರ್ಷಿಕೆ : "ಟು ಸ್ಟಡಿ ದಿ ಸಿರಮ್ ಕ್ಯಾಲ್ಸಿಯಂ ಲೆವೆಲ್ಸ್ ಇನ್ ಡೆಂಗ್ಯೂ ಫೀವರ್, ಒನ್ ಇಯರ್ ಕ್ರಾಸ್ ಸೆಕ್ಷನಲ್ ಸ್ಟಡಿ"

ಮುಖ್ಯ ಸಂಶೋಧಕರು:-

ಡಾ. ದಿನೇಶ ಚೌಹಾಣ
ಸ್ನಾತಕೋತ್ತರ ವೈದ್ಯಕೀಯ ವಿದ್ಯಾರ್ಥಿ
ಜನರಲ್ ಮೆಡಿಸಿನ್ಸ್ ವಿಭಾಗ
ಜೆ.ಎನ್.ಎಮ್.ಸಿ, ಬೆಳಗಾವಿ

ಮಾರ್ಗದರ್ಶಕರು:-

ಡಾ. ಆರತಿ ದರ್ಶನ
ಪ್ರಾಧ್ಯಾಪಕರು ಮತ್ತು ಘಟಕದ ಮುಖ್ಯಸ್ಥರು
ಜನರಲ್ ಮೆಡಿಸಿನ್ಸ್ ವಿಭಾಗ
ಜೆ.ಎನ್.ಎಮ್.ಸಿ, ಬೆಳಗಾವಿ

ಸಂಶೋಧನೆಯ ಪರಿಚಯ ಮತ್ತು ಉದ್ದೇಶ :-

ಡೆಂಗ್ಯೂ ಜ್ವರವು ನೂರಕ್ಕೂ ಹೆಚ್ಚು ದೇಶಗಳಲ್ಲಿ ಕಾಣಿಸಿಕೊಂಡಿದ್ದು, ಈ ವೈರಸ್ ಅಸಾಮಾನ್ಯವಾಗಿ ಜ್ವರ ಹಾಗೂ ಇನ್ನಿತರೆ ಜ್ವರದಿಂದ ಸಂಭವಿಸುವ ಖಾಯಿಲೆಗೆ ತುತ್ತಾಗಬಹುದು. ಇದರಿಂದಾಗಿ ಮರಣವು ಸಹ ಸಂಭವಿಸುತ್ತದೆ. ಡೆಂಡ್ಯೂ ಜ್ವರದ ರೋಗ ಲಕ್ಷಣಗಳನ್ನು ಬೇಗನೆ ಪತ್ತೆ ಹಚ್ಚಿ ಅದನ್ನು ಉಪಚರಿಸುವುದರಿಂದ ವ್ಯಕ್ತಿಯನ್ನು ಸಾವಿನಂಚಿನಿಂದ ಪಾರುಮಾಡಬಹುದಾಗಿದೆ.

ವಿಧಾನ:–

ನೀವು ಈ ಸಂಶೋಧನೆಯ ಭಾಗವಾಗಲು ಒಪ್ಪಿಕೊಂಡಲ್ಲಿ ನಿಮಗೆ ಖಾಯಿಲೆಗೆ ಸಂಬಂಧಿಸಿದ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲಾಗುವುದು ಹಾಗೂ ವೈದ್ಯಕೀಯ ತಪಾಸಣೆಗೆ ಒಳಪಡಬೇಕಾಗುತ್ತದೆ. ಇದರ ಜೊತೆಗೆ ನೀವು ನಿಮ್ಮ ರಕ್ತ ಮಾದರಿಯನ್ನು ನೀಡಬೇಕಾಗುತ್ತದೆ.

ಅನುಕೂಲ ಹಾಗೂ ಅನಾನುಕೂಲತೆಗಳೂ :–

ಈ ಸಂಶೋಧನೆಯ ಸಮಯದಲ್ಲಿ ಆಗುವ ಏಕೈಕ ಅನಾನುಕೂಲತೆಯೆಂದರೆ ತಪಾಸಣಾ ಸಂದರ್ಭದಲ್ಲಿ ಆಗುವ ನೋವು. ಆದರೆ ಇದು ನಿಮಗೆ ನೋವಾಗಿ ಕಂಡರೂ ಮುಂದಿನ ಪೀಳಿಗೆಗೆ ಈ ಸಂಶೋಧನೆಯು ತೊಂಬಾ ಲಾಭದಾಯಕವಾಗಿರುತ್ತದೆ.

ಪರ್ಯಾಯಗಳು :–

ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ನೀವು ಸ್ವ ಇಚ್ಛೆಯಿಂದ ಮತ್ತು ಒಪ್ಪಿಗೆಯಿಂದ ಭಾಗವಹಿಸಬಹುದು ಅಥವಾ ನಿರಾಕರಿಸಲೂಬಹುದು. ಒಂದು ವೇಳೆ ನೀವು ಸಂಶೋಧನೆಯ ಭಾಗವಾಗಲು ಒಪ್ಪಿಕೊಂಡು ನಂತರದ ದಿನಗಳಲ್ಲಿ ಮನಸ್ಸು ಬದಲಾಯಿಸಿದರೆ ನೀವು ಇದರಿಂದ ಹೊರಬರಬಹುದು. ನಿಮ್ಮ ಈ ನಿರ್ಧಾರವು ನಿಮಗೆ ಈಗ ದೊರೆಯುತ್ತಿರುವ ವೈದ್ಯಕೀಯ ಹಾಗೂ ಇನ್ನಿತರ ಸೇವೆಗಳ ಮೇಲೆ ಯಾವುದೇ ಪ್ರಭಾವ ಬೀರುವುದಿಲ್ಲ ಹಾಗೂ ನಿಮಗೂ ಸಹ ಇತರೆ ರೋಗಿಗಳಂತೆ ನಿಮಗಿರುವ ಖಾಯಿಲೆಗನುಸಾರವಾಗಿ ಚಿಕಿತ್ಸೆ ದೊರೆಯುವುದು.

ಗೌಪ್ಯತೆ :–

ಸಂಶೋಧನೆಯ ಸಂದರ್ಭದಲ್ಲಿ ಸಂಗ್ರಹಿಸಿರುವ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಕಾನೂನಿಗನುಸಾರವಾಗಿ ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು. ಎಲ್ಲಿಯೂ ನಿಮ್ಮ ಹೆಸರು ಪ್ರಕಟವಾಗದೇ ನಿಮ್ಮನ್ನು ಗೌಪ್ಯ ಸಂಖ್ಯೆಯಿಂದ ಗುರುತಿಸಲಾಗುವುದು. ಮುಂದಿನ ದಿನಗಳಲ್ಲಿ ಈ ಸಂಶೋಧನಾ ವರದಿಯು ಪ್ರಕಟಗೊಂಡಾಗಲೂ ಸಹ ನಿಮ್ಮ ಹೆಸರನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು.

ಸಂಸ್ಥೆ ಅಥವಾ ಪ್ರಾಯೋಜಕರ ನೀತಿಗಳು :-

ಅನ್ವಯವಾಗುವುದಿಲ್ಲ.

ಪ್ರೋತ್ಸಾಹ ಧನ :-

ನಿಮಗೆ ಈ ಸಂಶೋಧನೆಯ ಭಾಗವಾಗಲು ಯಾವುದೇ ರೀತಿಯ ಹಣ, ಉಡುಗೊರೆಯನ್ನು ನೀಡಲಾಗುವುದಿಲ್ಲ.

ಫಲಿತಾಂಶ ಪ್ರಕಟಿಸಲು ಇರುವ ಅಧಿಕಾರಗಳು :-

ಈ ಸಂಶೋಧನೆಯ ಫಲಿತಾಂಶವನ್ನು ಕೆ.ಎಲ್.ಇ. ವಿಶ್ವವಿದ್ಯಾಲಯ ಬೆಳಗಾವಿ ಇವರಿಗೆ ಎಮ್.ಡಿ. ಪದವಿ ಪೂರ್ಣಗೊಳಿಸಲು, ವಿಮರ್ಶಿಸಲು ಹಾಗೂ ಪ್ರಕಟಿಸಲು ಕಳುಹಿಸಿಕೊಡಲಾಗುವುದು.

ಸಂಶೋಧನೆಯ ಸಂದರ್ಭದಲ್ಲಿ ಅಥವಾ ಮುಂದೆ ಯಾವುದಾದರೂ ಪ್ರಶ್ನೆಗಳು ಅಥವಾ ಅನುಮಾನಗಳಿದ್ದಲ್ಲಿ ಈ ಕೆಳಗಿನವರನ್ನು ಸಂಪರ್ಕಿಸಬಹುದಾಗಿದೆ.

ಡಾ. ಆರತಿ ದರ್ಶನ
ಪ್ರಾಧ್ಯಾಪಕರು ಮತ್ತು ಘಟಕದ ಮುಖ್ಯಸ್ಥರು
ಜನರಲ್ ಮೆಡಿಸಿನ್ಸ್ ವಿಭಾಗ
ಜೆ.ಎನ್.ಎಮ್.ಸಿ, ಬೆಳಗಾವಿ
944845883

ಡಾ. ದಿನೇಶ ಚೌಹಾಣ
ಸ್ನಾತಕೋತ್ತರ ವೈದ್ಯಕೀಯ ವಿದ್ಯಾರ್ಥಿ
ಜನರಲ್ ಮೆಡಿಸಿನ್ಸ್ ವಿಭಾಗ
ಜೆ.ಎನ್.ಎಮ್.ಸಿ, ಬೆಳಗಾವಿ
9164026086

ನೀವು ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಪಾಲ್ಗೊಂಡ ಮೇಲೆ ನಿಮಗೆ ನಿಮ್ಮ ಹಕ್ಕಿನ ಬಗ್ಗೆ ಯಾವುದೇ ತರಹದ ಪ್ರಶ್ನೆಗಳಿದ್ದರೆ ನೀವು ಕೆಳಗಿನವರನ್ನು ಸಂಪರ್ಕಿಸಬಹುದಾಗಿದೆ.

ಡಾ. ಗಂಗಾ ಪಿಳ್ಳೆ, ಚೇರಮನ್,
ಜೆ.ಎನ್.ಎಮ್.ಸಿ ಮಾನವ
ಸಂಶೋಧನಾ ನೈತಿಕ ಸಮಿತಿ
9448863866

जानकारी हासिल होने के बाद दी गई सम्मति

संशोधन अभ्यासक्रम का नाम : "डेंग्यू के रोगियों में रक्त में कितना सिरम कॅल्शियमकी मात्रा है, इसका एक साल का सामूहिक अभ्यासक्रम।"

प्रमुख संशोधक :
डॉ. दिनेश चौहान
पोस्ट ग्रॅज्युएट छात्र
सामान्य औषधोपचार विभाग,
जे.एन.एम.सी बेळगाव

मार्गदर्शक :
डॉ. आरती दर्शन,
प्रोफेसर व विभाग प्रमुख,
सामान्य औषधोपचार विभाग,
जे.एन.एम.सी बेळगाव

❊ प्रस्तावना एवं हेतु :

डेंग्यू यह बिमारी, सौ से भी अधिक देशों में फैली हुई है। डेंग्यू के विषाणू की लागण हुई है यह समझना मुश्किल है या वैद्यकिय दृष्टिकोनसे यह बिमारी जल्दी समझने नही आती। इस रोगीमे ताप यह कम या बहुत ज्यादा दिखाई देता है, जिसकी वजहसे शरीर के अंदरुनी अवयवों में बडे पैमानेपर रक्त स्राव होता है या बदन के बहुत सारे अवयव आपना कार्य बंद करते है, जिसके कारण बडे पैमानेपर मृत्यूदर में बढोत्तरी होती है ऐसा दिखाई देता है। डेंग्यू रोग की जल्द से जल्द जानकारी होना और रोगियों के उपर योग्य उपचार करना बहुत जरुरी होता है, जिसके कारण रोगट मनोवृत्ती और मृत्युदर में कमी होने में मदत मिल सकती है।

❊ पध्दती :

यदी आप इस संशोधन अभ्यास में सम्मिलित होना चाहते हो तो, आपको आपका कौटुंबिक पूर्व इतिहास पुछा जायेगा और आपकी वैद्यकिय तपासणी और अन्य जाँच करने हेतु, लिए गये रक्त का परीक्षण करने के लिए आपका उस समय नमूने लिए जाएंगे।

✲ आपत्ती और फायदे :

आप के रक्त की जाँच करने हेतु आप के बाहों में से रक्त लिया जाएगा। और उस वक्त आपको वेदना होगी, यही आपको धोका है। जिस जगह से रक्त लिया जाएगा वहा सूजन आयेगी और वेदनाएँ होगी और वह हिस्सा रक्त रंग का (कभी होगा या न होगा) होगा। आपको इस रक्त जाँच से कोई भी फायदा नही होगा। लेकिन भविष्य में आपके द्वारा यह किये हुए अभ्यास का फायदा भविष्य में अन्य कोई व्यक्तियों को होगा।

✲ पर्याय :

इस अभ्यासक्रम में आप खुद शामिल हो सकते हो। इस अभ्यासक्रम में आप हिस्सा नही भी ले सकते है। आप इस अभ्यासक्रम में हिस्सा लिया है तो, आप इसमें से आपका नाम किसी भी समय कम कर सकते हो। आपने इस अभ्यासक्रम में हिस्सा लिया तो भी आपको इस वक्त या भविष्य में मिलनेवाली सब वैधकिय सेवा आपको यहाँसे प्राप्त होगी। अभ्यास करनेवाले डॉक्टर या इस कार्यक्रमका आयोजन करनेवाले, आपका इसमें मिलनेवाला सहयोग किसीभी वक्त बंद कर सकते है। यदी आपने इस संशोधन अभ्यासक्रम में हिस्सा नही लिया, तो भी आपको यहाँपर रोगी होने के नातेसे मिलनेवाली पूरी सुविधायें मिलेगी।

✲ गोपनियता :

इस अभ्यासक्रम में आपके द्वारा प्राप्त की हुई जानकारियाँ कायदे के दायरे के अनुसार गुप्त रखी जायेगी। इस अभ्यासक्रम के दौरान आपकी पहचान यह आपको दिए हुए कोड नंबर द्वारा की जायेगी। इस अभ्यास क्रम में मिली हुई जानकारियाँ प्रकाशित की जायेगी लेकिन आपकी पहचान इस प्रसिध्दी में गुप्त रखी जायेगी।

✲ संस्था या कार्यक्रम जाहीर करनेवालों की :

यह इस संशोधन अभ्यास को लागू नही है।

✲ कार्यक्रम में सम्मिलित होने से मिलनेवाली आर्थिक सहायता :

इस अभ्यासक्रम में हिस्सा लेने से आपको किसी भी प्रकार की आर्थिक सहायता नही मिलेगी ना ही आपको कोई वस्तु भेट दी जायेगी।

❊ निष्कर्ष प्रकाशित करनेका आधिकार :

इस संशोधक अभ्यासक्रम में निष्कर्ष के. एल ई. युनिव्हर्सिटी बेलगाम इनको जांच के लिए एवं प्रकाशन के लिए भेजे जायेंगे और यह एक एम डी. पदवी पूरी करनेका अपना यह एक हिस्सा है।

❊ यदि आपको इस संशोधन अभ्यासक्रम के बारे में इस वक्त या भविष्य में कोई प्रश्न हो तो आप निम्नलिखित व्यक्तिसे संपर्क कर सकते हों।

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❊ यदि आप को आपके कोई हक्क संबंधी शंका हो तो आप निम्नलिखित व्यक्तिसे संपर्क कर सकते है।

डॉ. गंगा पिल्ली, चेअरमन
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MASTERSHEET

1

SNO	IP	AGE	SEX	HB	TC	PLT	CALCIUM	NS1	DENGUEIGM	IGG	Diagnosis	Complication
1	4359172	18	Male	13	3.4	24000	9.3	Negative	Positive	Positive	Dengue fever	Nil
2	4355617	24	Male	12	4.5	40000	8.9	Negative	Positive	Positive	Dengue fever	Nil
3	806348	22	Female	13	2.6	117000	8.8	Negative	Positive	Positive	Dengue fever	Nil
4	804840	38	Male	16	8.0	26000	8.3	Negative	Positive	Positive	Dengue fever	Nil
5	803875	18	Female	11	3.6	56000	8.4	Negative	Positive	Positive	Dengue fever	Nil
6	4357812	26	Male	12	5.6	54000	8.0	Negative	Positive	Positive	Dengue fever	Cardiac Complication
7	837136	21	Female	16	6.1	21000	8.4	Negative	Positive	Negative	Dengue fever	Nil
8	836878	35	Female	13	4.2	13000	7.9	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
9	826398	29	Male	18	6.2	15000	8.6	Positive	Positive	Positive	Dengue fever	Nil
10	828218	25	Male	15	1.9	65000	8.9	Positive	Positive	Positive	Dengue fever	Nil
11	828732	45	Female	13	11.4	194000	4.7	Negative	Positive	Positive	Dengue shock syndrome	Cardiac Complication
12	828921	40	Male	20	3.3	5000	8.2	Negative	Positive	Positive	Dengue fever	Nil
13	824864	33	Male	17	6.9	17000	8.6	Negative	Negative	Positive	Dengue fever	Nil
14	824792	25	Male	16	5.5	11000	8.4	Positive	Positive	Positive	Dengue fever	Nil
15	836680	42	Male	15	6.8	18000	8.1	Negative	Positive	Positive	Dengue fever	Nil
16	831183	31	Male	18	4.3	45000	8.4	Negative	Positive	Positive	Dengue fever	Nil
17	830557	24	Male	18	3.1	75000	8.4	Positive	Positive	Negative	Dengue fever	Nil
18	838963	38	Male	17	5.2	15000	8.3	Positive	Negative	Negative	Dengue fever	Nil
19	839014	32	Female	14	3.2	30000	7.5	Positive	Positive	Positive	Dengue shock syndrome	Cardiac Complication
20	854854	23	Female	14	4.4	14000	7.5	Negative	Positive	Positive	Dengue shock syndrome	Neurological complication
21	808638	18	Male	13	5.1	18000	8.3	Negative	Positive	Positive	Dengue fever	Nil
22	814840	23	Male	15	4.5	25000	8.4	Negative	Negative	Positive	Dengue fever	Nil
23	823244	23	Female	9	0.4	14000	8.4	Negative	Positive	Negative	Dengue fever	Nil
24	822997	26	Male	19	6.8	21000	8.4	Positive	Negative	Negative	Dengue fever	Nil
25	822976	28	Female	13	3.5	72000	8.6	Positive	Negative	Negative	Dengue fever	Nil
26	4428329	28	Male	16	4.5	45000	8.3	Negative	Positive	Positive	Dengue fever	Nil
27	849742	18	Male	11	15.9	41000	8.9	Negative	Positive	Positive	Dengue fever	Nil
28	848142	28	Male	17	3.3	11000	7.8	Positive	Positive	Positive	Dengue Haemorrhagic fever	Nil
29	848834	30	Male	12	4.4	34000	8.2	Positive	Positive	Positive	Dengue fever	Nil

30	849873	24	Male	12	0.8	8000	8.0	Positive	Positive	Positive	Dengue Haemorrhagic fever	Nil
31	823244	22	Male	14	3.7	70000	8.4	Negative	Positive	Negative	Dengue fever	Nil
32	812263	25	Male	18	2.6	15000	8.2	Negative	Positive	Positive	Dengue fever	Nil
33	4411450	19	Male	16	4.3	34000	8.6	Negative	Positive	Positive	Dengue fever	Nil
34	809297	25	Male	18	8.7	10000	8.6	Negative	Positive	Positive	Dengue fever	Nil
35	821829	45	Male	16	6.3	43000	8.1	Negative	Positive	Positive	Dengue fever	Nil
36	823968	22	Male	17	3.2	67000	8.0	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
37	820835	29	Female	13	2.3	42000	8.3	Negative	Positive	Positive	Dengue fever	Nil
38	822983	23	Female	15	2.2	45000	8.2	Negative	Negative	Positive	Dengue fever	Nil
39	819708	27	Male	13	5.3	23000	8.1	Negative	Negative	Positive	Dengue fever	Nil
40	819800	26	Male	12	4.3	28000	9.2	Negative	Positive	Positive	Dengue fever	Nil
41	819816	30	Male	16	4.3	43000	8.5	Negative	Positive	Positive	Dengue fever	Nil
42	861255	22	Male	15	4.7	149000	8.4	Positive	Positive	Negative	Dengue fever	Nil
43	867844	24	Male	15	3.7	113000	8.1	Negative	Negative	Positive	Dengue fever	Nil
44	867868	32	Male	14	2.3	28000	8.6	Negative	Positive	Positive	Dengue fever	Nil
45	870082	45	Male	15	3.0	6000	8.9	Positive	Positive	Negative	Dengue fever	Nil
46	834503	21	Female	15	3.7	30000	8.2	Negative	Negative	Positive	Dengue fever	Nil
47	838549	25	Male	18	4.3	72000	8.0	Positive	Negative	Positive	Dengue Haemorrhagic fever	Cardiac Complication
48	849818	30	Male	13	3.0	32000	8.7	Positive	Negative	Negative	Dengue fever	Nil
49	841152	24	Male	16	4.8	136000	8.3	Negative	Negative	Positive	Dengue fever	Nil
50	841922	28	Female	14	4.7	239000	8.2	Negative	Negative	Positive	Dengue fever	Nil
51	844910	20	Male	15	4.4	14000	8.4	Positive	Positive	Positive	Dengue fever	Nil
52	845070	24	Male	13	3.5	80000	8.2	Negative	Negative	Positive	Dengue fever	Nil
53	846862	54	Male	14	3.8	131000	8.6	Negative	Negative	Positive	Dengue fever	Nil
54	854314	60	Female	13	3.8	102000	8.7	Positive	Negative	Negative	Dengue fever	Nil
55	825940	18	Male	14	2.7	71000	8.5	Positive	Positive	Negative	Dengue fever	Nil
56	826158	23	Male	16	4.5	16000	8.7	Positive	Positive	Negative	Dengue fever	Nil
57	828349	22	Male	16	3.6	16000	8.6	Positive	Negative	Negative	Dengue fever	Nil
58	828921	40	Male	20	3.3	5000	8.4	Positive	Positive	Negative	Dengue fever	Nil
59	829948	21	Male	14	2.8	10000	8.1	Positive	Negative	Negative	Dengue fever	Nil
60	831957	25	Female	13	3.1	21000	8.6	Positive	Positive	Negative	Dengue fever	Nil
61	833384	44	Male	15	5.0	187000	8.1	Negative	Negative	Positive	Dengue fever	Nil
62	891740	28	Male	14	5.2	150000	8.6	Negative	Negative	Positive	Dengue fever	Nil
63	854314	60	Female	13	3.8	102000	8.8	Positive	Negative	Negative	Dengue fever	Nil

64	781012	25	Female	11	2.5	116000	8.8	Negative	Positive	Negative	Dengue fever	Nil
65	782091	42	Male	18	3.4	19000	8.4	Positive	Positive	Negative	Dengue fever	Nil
66	784394	42	Male	17	4.9	136000	8.5	Negative	Negative	Positive	Dengue fever	Nil
67	786011	30	Male	16	3.5	109000	8.6	Positive	Positive	Negative	Dengue fever	Nil
68	790780	30	Male	13	5.5	14000	8.5	Positive	Positive	Negative	Dengue fever	Nil
69	791239	42	Male	14	17.1	134000	8.2	Negative	Positive	Positive	Dengue fever	Nil
70	712028	28	Male	16	7.3	185000	8.6	Negative	Positive	Negative	Dengue fever	Nil
71	793760	28	Male	16	5.3	15000	8.3	Negative	Negative	Positive	Dengue fever	Nil
72	794148	30	Male	14	5.5	166000	8.7	Negative	Positive	Positive	Dengue fever	Nil
73	795783	40	Male	17	7.3	30000	8.5	Negative	Positive	Positive	Dengue Haemorrhagic fever	Cardiac Complication
74	795590	22	Male	13	7.8	20000	8.4	Negative	Positive	Positive	Dengue Haemorrhagic fever	Cardiac Complication
75	796336	70	Female	16	8.2	86000	8.3	Negative	Positive	Positive	Dengue Haemorrhagic fever	Cardiac Complication
76	796560	18	Female	10	7.7	85000	8.6	Negative	Positive	Positive	Dengue fever	Nil
77	796927	31	Female	11	10.5	253000	8.6	Negative	Negative	Positive	Dengue fever	Nil
78	799417	32	Male	14	3.9	75000	8.4	Negative	Positive	Positive	Dengue Haemorrhagic fever	Neurological complication
79	799575	22	Male	9	4.1	96000	8.7	Negative	Positive	Positive	Dengue fever	Nil
80	799989	41	Male	15	7.5	237000	8.4	Negative	Negative	Positive	Dengue Haemorrhagic fever	Nil
81	801377	24	Female	14	6.7	32000	8.5	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
82	802708	43	Male	16	8.3	198000	8.4	Negative	Negative	Positive	Dengue Haemorrhagic fever	Nil
83	803923	52	Male	14	3.7	133000	8.5	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
84	803387	58	Male		2.7	42000	8.6	Negative	Negative	Positive	Dengue fever	Nil
85	807418	21	Female	12	3.8	42000	8.5	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
86	810542	21	Male	16	2.7	108000	8.6	Negative	Positive	Positive	Dengue fever	Nil
87	811624	27	Male	13	2.8	12000	8.5	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
88	811649	21	Male	11	3.3	45000	8.6	Negative	Positive	Positive	Dengue fever	Nil
89	811755	21	Female	12	2.9	10000	8.6	Negative	Positive	Positive	Dengue fever	Nil
90	811878	26	Male	13	3.2	121000	8.6	Negative	Positive	Positive	Dengue fever	Nil
91	811877	24	Male	13	3.9	68000	8.2	Negative	Positive	Negative	Dengue Haemorrhagic fever	Nil
92	4428329	25	Male	12	2.2	66000	8.3	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
93	4428911	37	Male	13	9.3	25000	8.1	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
94	4410160	37	Male	18	2.6	15000	8.2	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
95	3210907	21	Female	13	3.3	111000	8.2	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil
96	803875	18	Female	11	3.6	56000	8.4	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil

97	836878	35	Female	13	4.2	13000	7.9	Negative	Positive	Positive	Dengue shock syndrome	Neurological complication
98	826398	29	Male	18	6.2	15000	8.6	Positive	Positive	Positive	Dengue Haemorrhagic fever	Nil
99	4428329	28	Male	16	4.5	45000	8.3	Negative	Positive	Positive	Dengue shock syndrome	Nil
100	849742	18	Male	11	15.9	41000	8.9	Negative	Positive	Positive	Dengue Haemorrhagic fever	Nil