"CORRELATION OF CLINICAL PROFILE WITH DIFFERENT SEROLOGICAL DIAGNOSTIC PARAMETERS IN DENGUE FEVER – ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

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ENDORSEMENT

This is to certify that the dissertation entitled **"CORRELATION OF CLINICAL PROFILE WITH DIFFERENT SEROLOGICAL DIAGNOSTIC PARAMETERS IN DENGUE FEVER – ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"** is a bonafide research work done by **CANDIDATE REG NO. BG0113009**

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LIST OF ABBREVIATIONS USED

/Cumm	-	Per cubic millimeter
°C	-	Degree centigrade
AD	-	Anno Domini
ADE	-	Antibody-dependent enhancement
AIIMS	-	All India Institute of Medical Sciences
ALP	-	Alkaline phosphatase
ALT	-	Alanine transaminase
AMAF	-	American African
ANOVA	-	Analysis of variance
APTT	-	Activated partial thromboplastin time
AST	-	Aspartate amino transferase
Bicarb.	-	Bicarbonate
bili.	-	Bilirubin
BUN	-	Blood urea nitrogen
C	-	Core protein
CBC	-	Complete blood count
CI	-	Confidence interval
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
DBP	-	Diastolic blood pressure
DCs	-	Dendritic cells
DEN 3	-	Dengue Type 3
DENV	-	Dengue virus
DF	-	Dengue fever

DHF	-	Dengue hemorrhagic fever
DIC	-	Disseminated intravascular coagulation
DSS	-	Dengue shock syndrome
DV	-	Dengue virus
E	-	Envelope protein
e.g.	-	For example
ELISA	-	Enzyme-linked immunosorbent assay
etc.	-	Etcetera
gm%	-	Gram percentage
Hb	-	Haemoglobin
HIV	-	Human immunodeficiency virus
HR	-	Heart rate
hrs	-	Hours
i.e,	-	That is,
IFN	-	Interferon
IgA	-	Immunoglobulin A
IgE	-	Immunoglobulin E
IgG	-	Immunoglobulin G
IgM	-	Immunoglobulin M
IL	-	Interleukin
iNK	-	Invariant natural killer
IU/L	-	International units per liter
L	-	Liter
LFT	-	Liver function tests
M	-	Membrane associated protein

mAb	-	Monoclonal antibody
meq/L	-	Milliequivalent per liter
mg/dL	-	Milligram per deciliter
mm Hg	-	Millimeters of mercury
mm^3	-	Cubic millimeter
mmol/L	-	Millimole per liter
n	-	Total number
NAAT	-	Nucleic acid amplification test
nm	-	Nanometer
NS	-	Non-structural protein
p	-	Probability
PAHO	-	Pan American Health Organization
PC	-	Platelet count
PCR	-	Polymerase chain reaction
pH	-	Power of hydrogen
PRNT	-	Plaque reduction neutralization test
PT	-	Prothrombin time
RDTs	-	Rapid Diagnostic Tests
RNA	-	Ribonucleic acid
RR	-	Respiratory rate
SBP	-	Systolic blood pressure
SD	-	Standard deviation
SEA	-	Southeast Asia
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamic pyruvic transaminase

sNS1	-	Secreted non-structural protein of virus type 1
TC	-	Total count
TGF	-	Transforming growth factor
TNF	-	Tumour necrosis factor
US	-	United States
USA	-	United States of America
WHO	-	World Health Organization
WWII	-	World War II
µL	-	Microliter

ABSTRACT

Background and objectives

There is wide variation in the clinical profile of dengue fever we hypothesized that, clinical profile may also vary in different serological tests which used for the detection of dengue infection and attempted to evaluate and correlate the clinical profile in different serological diagnostic parameters.

Methodology

This one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 180 dengue fever patients confirmed through dengue serology with either NS1 antigen or IgM and/or IgG antibody from January 2014 to December 2014 were studied.

Results

Majority of the patients (72.22%) were males and male to female ratio was 2.6:1. The commonest age group was 18 to 30 years (50.56%) and mean age was 32.96 ± 12.79 years. Mean day of presentation to the hospital was 5.92±2.04 days. All the patients presented with fever (100%). 34.44% of the patients were IgM and IgG positive, 33.89% IgG positive, 26.11% NS1 positive and 5.56% of the patients were IgM positive. With regard to clinical features, arthralgia, rash and melaena significantly varied in different dengue serological tests ($p<0.050$). Significant difference was noted pertaining to platelet count ($p=0.010$) as IgM and IgG positive had significantly higher number of patients with severe thrombocytopenia (<20,000 /cumm) ($p=0.010$). The mean platelet count differed

significantly in dengue serological tests. Positive association was noted between rash and platelet count ($p<0.050$). With regard to renal profile, significant difference was noted in serum creatinine levels ($p=0.029$). Significantly higher number of patients with IgG positive had low bicarbonate levels and mean bicarbonate levels also differed significantly with dengue serology ($p<0.050$).

Conclusion and interpretation

There is wide variation in clinical profile of dengue fever within the different serological tests.

Keywords

Dengue fever; Dengue serology; Immunoglobulin G; Immunoglobulim M; Non structural protein 1;

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INTRODUCTION

Dengue made its debut as early as 1780, when Benjamin Rush described the condition as “break bone fever”. This hitherto unfamiliar infection has now grown to demand the attention of all public health care providers. A mosquito borne fast emerging viral infection manifesting in four serotypes capable of causing dengue fever (DF) poses an increasingly perilous situation due to lack of antiviral drugs or vaccine.[1]

Dengue fever is the most important arthropod-borne viral infection of humans. Worldwide, an estimated 2.5 billion people are at risk of infection, approximately 975 million of whom live in urban areas of tropical and sub-tropical countries like Southeast Asia, the Pacific and the Americas.[2] The rural areas are also being increasingly affected in regions of Africa and the eastern Mediterranean. It is estimated that more than 50 million infections occur each year, of which 500,000 hospitalizations are of dengue haemorrhagic fever with the case fatality rate exceeding 5% in some areas.[1-4]

India is one of the seven identified countries in the South-East Asia region regularly reporting incidence of DF outbreaks and may soon transform into a major niche for dengue infection in the near future. The first confirmed report of dengue infection in India dates back to 1940s, and since then more and more new states have been reporting the disease which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality, in both urban and rural environments.[5] Several fatal cases have been reported in India.[6-9] Until mid-1990s, dengue was reported from only three of the four South Indian states, namely, Andhra Pradesh,

Karnataka and Tamil Nadu. All the four serotypes of the virus have been in circulation and documented.[10]

Dengue is transmitted by several species of mosquito within the genus *Aedes*, principally *Aedes aegypti*. The virus has four different types; infection with a given type usually confers lifelong immunity to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications.[11]

After an incubation period of 3–10 days, the illness starts with acute onset of high fever, which is typically accompanied by headache, myalgia, arthralgia, and occasionally a characteristic maculopapular skin rash. Most infected people have few if any symptoms, and most of those who do have symptoms recover spontaneously. In a small proportion of cases, the disease progresses to a more severe life threatening forms which is characterized by hemorrhage, thrombocytopenia, and leakage of blood plasma, or to dengue shock syndrome.[11]

Diagnosis of dengue fever is a very important step in the management. The diagnosis of dengue fever is carried out based on clinical, epidemiological and laboratory data. Among laboratory tests, both non-specific [blood count, platelet count, tourniquet test, prothrombin time (PT), activated partial thromboplastin time (APTT), liver function tests and serum albumin concentration] and specific tests (viral isolation tests and serology for antibody examination) are used.[12,13]

In general practice, the widely used tests are serological tests. The two main tests are dengue IgM and dengue IgG. The general criteria for diagnosis of dengue infection are positive dengue IgM or IgG. Focusing on these tests, accuracy is

dependent on the timing of their sample collection.[14,15] Normally, IgM/IgG ELISA are useful to confirm the physician's clinical diagnosis because the severe cases need to be cured as soon as possible. Therefore, early laboratory diagnosis (within 1–2 days of illness) will be more important.

Since the simple serological tests might not provide a very early diagnosis, other alternatives might be selected. Early diagnostic approaches, including virus isolation and molecular tests such as reverse transcription PCR, are still expensive and need expertise to perform.[14] Recently, an up-to-date test for early diagnosis of dengue infection is dengue NS1 antigen detection. These diagnostic test kits, especially the immunochromatographic strip kits, can help early diagnosis and shorten the turnaround time.[15] Evaluation of the NS1 assay indicated moderately high sensitivity and very high specificity to dengue infection. The combination of NS1 and IgM assay would further enhance the sensitivity of the tests. However, early dengue diagnosis still remains a problem, as all these assays have their own pitfalls.[14]

To date various studies have assessed the clinical profile of dengue fever based on the diagnosis determined by either IgM with IgG or NS1 or using all the three tests. There is wide variation in clinical profile based on the test used for the detection of dengue infection. Also there is scanty data on correlation of clinical profile with different serological diagnostic parameters in dengue fever patients. Hence the present study was an attempt to evaluate and correlate the clinical profile of patients with dengue fever under different serological diagnostic parameters.

OBJECTIVES

The objective of this research was to study and correlate the clinical profile with different serological diagnostic parameters in dengue fever patients.

REVIEW OF LITERATURE

Historical perspectives

The term “Dengue” was coined in the English medical literature from the West Indies during the 1827–1828 Caribbean epidemic that presented as exanthema with arthralgia. Dengue is a Spanish synonym for the Swahili “Ki denga Pepo” (a sudden cramp like seizure caused by an evil spirit).[17]

Dengue has been present for centuries. The first recorded symptoms was noted in a Chinese medical encyclopedia in 992 AD, however originally it was published by the Chin Dynasty centuries earlier 265–420 AD, prior to being formally edited.[18] Epidemics that resembled dengue, occurred as early as 1635 and 1699 in the West Indies and Central America respectively, they had same disease course.[18]

A major epidemic occurred in Philadelphia in 1780 and since then epidemics became common in the USA which continued into the early 20th century, the last outbreak occurred in New Orleans in 1945.[18]

The viral etiology and the transmission by mosquitoes were only finally determined in the 20th century. The origin of the primary mosquito vector, *Aedes. aegypti*, is debated to be from either Africa or Asia. Regardless, by 1800 it was widespread throughout urban tropical coastal cities of the world due to the use of shipping vessels with commercial expansion. These shipping vessels allowed transportation of breeding sites for the vector along with humans to complete the

transmission cycle, allowing for slow but evident introduction of the virus and the mosquito to coastal destinations around the world.[18,19]

Expansion of the disease heightened during World War II (WWII), when troops began to disperse inland and utilize modern transportation within and between countries; thus epidemic dengue became more far-reaching. By the end of the war, transportation and rapid urbanization led to increased transmission of dengue and hyperendemicity (multiple serotypes present) in most South East Asian countries, with subsequent emergence of the severe forms of dengue.[18]

Following WWII, dengue epidemics appeared to be under control in Central and South America. Due to collaborative efforts with the yellow fever disease control campaign initiated by the Pan American Health Organization (PAHO), to eliminate Aedes aegypti which effectively restricted the transmission of dengue throughout the American continent.[18]

The first case of dengue hemorrhagic fever in Southeast Asia was noted in Manila between in 1953 to 1954 and outbreaks have since then been reported throughout Southeast Asia.[20]

The first major epidemic of the dengue fever occurred in 1953-1954 in Philippines followed by a quick global spread of epidemics of dengue fever which was occurring in the adjoining countries but it was absent in India for unknown reasons though all the risk factors were present.[18]

In 1970s, dengue epidemics in America was short lived and the control campaign was discontinued in the 1970s which led to increase incidence in the 1980s.[21]

Global dengue incidence has increased precipitously over the last five decades and severity of dengue cases have also expanded. Prior to 1970, only nine countries had experienced severe dengue cases, a number which has since quadrupled.[18]

Current situation of dengue

Global

Up to 3.6 billion people are estimated to now live in tropical and subtropical areas where the dengue viruses have the potential to be transmitted. Global estimates vary, but regularly approximate 50 million to 200 million dengue infections, 500,000 episodes of severe dengue and over 20,000 dengue related deaths occur annually.[22,23]

Figure 1 shows the geographic distribution of dengue cases reported in 2011.

Figure 1. Countries or areas of the world where dengue was reported in 2011, as per data collected by the World Health Organization.[18,24]

The incidence of dengue has grown dramatically around the world in recent decades. The actual numbers of dengue cases are under reported. One recent estimate indicates 390 million dengue infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease).[25] Another study, of the prevalence of dengue, estimates that 3900 million people, in 128 countries, are at risk of infection with dengue viruses.[26]

Member States in 3 WHO regions regularly report the annual number of cases. In 2010, nearly 2.4 million cases were reported. Although the full global burden of the disease is uncertain, the initiation of activities to record all dengue cases partly explains the sharp increase in the number of cases reported in recent years. Other features of the disease include its epidemiological patterns, including hyper-endemicity of multiple dengue virus serotypes in many countries and the alarming impact on both human health and the global and national economies.[27]

Before 1970, only 9 countries had experienced severe dengue epidemics. The disease however now is endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. The America, South-East Asia and Western Pacific regions are the most seriously affected. Dengue also continues to affect several South American countries, notably Costa Rica, Honduras and Mexico.[27]

Cases across the Americas, South-East Asia and Western Pacific exceeded 1.2 million in 2008 and over 3 million in 2013 (based on official data submitted by Member States). Recently the number of reported cases has continued to increase. In

2013, 2.35 million cases of dengue were reported in the Americas alone, of which 37,687 cases were of severe dengue.[27]

Not only is the number of cases increasing as the disease spreads to new areas, but explosive outbreaks are occurring. The threat of a possible outbreak of dengue fever now exists in Europe the local transmission of dengue was reported for the first time in France and Croatia in 2010 and imported cases were detected in 3 other European countries. Whereas in 2012, an outbreak of dengue occurred in the Madeira islands of Portugal which resulted in over 2000 cases and imported cases were detected in 10 other countries in Europe.[27]

In 2013, cases have occurred in Florida (United States of America) and Yunnan province of China. In Asia, Singapore has reported an increase in cases after a lapse of several years and outbreaks have also been reported in Laos. In 2014, trends indicate increases in the number of cases in the People's Republic of China, the Cook Islands, Fiji, Malaysia and Vanuatu, affecting the Pacific Island countries after a lapse of over 10 years. Dengue was also reported in Japan after a lapse of over 70 years. In 2015 an increase in the number of cases was reported in Brazil and several neighbouring countries. The Pacific island countries of Fiji, Tonga and French Polynesia have continued to record cases.[27]

An estimated 500,000 people with severe dengue require hospitalization each year. About 2.5% of those affected die.[27]

<u>WHO Southeast Asia (SEA) region</u>

It is evident that dengue is now a worldwide concern; however, almost 75% of the global population exposed to dengue live in Asia-Pacific.[28,29] 1.3 billion of

these at-risk individuals live in ten dengue endemic countries in SEA, and dengue is a leading cause of hospitalization and death in this region.[19]

The rates of disease reported in each of the SEA countries varies as they include either laboratory confirmed, probable, or suspected cases.[30]

However, it is clearly evident from data collated by WHO that, in SEA, an overall expansion of dengue has occurred over the last decade.[29]

WHO in 2010 reported, 187,333 dengue cases from the region.[31] Eight SEA countries are now also classified as hyperendemic were all four serotypes of dengue virus are present.[29] Severe dengue is endemic in most SEA countries, with rates of severe dengue being 18 times higher in this region compared with the Americas.[18,29]

Epidemics of dengue fever in India

The epidemiology of dengue fevers in the Indian subcontinent has been very complex and it has substantially changed over the past six decades in terms of prevalent strains, affected geographical locations and severity of disease.[32]

In India, way back in 1946 the existence of dengue fever was reported. In 1963-1964, an initial epidemic of dengue fever was reported on the Eastern Coast of India,[33] it spread northwards and reached Delhi in 1967[31] and Kanpur in 1968.[35,36] Simultaneously it also involved the southern part of the country and gradually the whole country was involved with wide spread epidemics followed by endemic/hyperendemic prevalence of all the four serotypes of dengue virus.[33]

Epidemiological studies where dengue virus was identified[33]

Year	Region	Type of dengue virus
1964	Vellore, Tamil Nadu	DV-2
1966	Vellore, Tamil Nadu	DV-3
1968	Vellore, Tamil Nadu	DV- 1,2,3 & 4
1968	Kanpur, Uttar Pradesh	DV-4
1969	Kanpur, Uttar Pradesh	DV-4 and DV-2
1970	Hardoi, Uttar Pradesh	DV-2
1983	Kolkata, West Bengal	DV-3
1985	Jalore town, South-West Rajasthan	DV-3
1988	Delhi	DV-2
1990	Calcutta, West Bengal	DV-3
1988	Rural and urban areas of Gujarat	DV-2
1993	Mangalore, Karnataka	DV-2
1996	Ludhiana, Punjab	DV- 1,2,3 & 4
1996	Lucknow	DV-2
1996	Delhi	DV-2
1996	Delhi	DV-2
1997	Delhi	DV-1
1996	Delhi	DV-2 (Genotype IV)
1997	Delhi	DV-1
1996	Rural areas of Haryana	DV-2
2001	Dharmapuri district, Tamil Nadu	DV-2
NA	Andaman and Nicobar Islands	DV-2
2001	Gwalior, Madhya Pradesh	DV-2
2001	Chennai, Tamil Nadu	DV-3
2003	Northern India (Delhi & Gwalior)	DV-3
2005	Kolkata, West Bengal	DV-3
2003	Kanyakumari district, Tamil Nadu	DV-3
2003-04	Delhi	DV-3 (subtype III)
2003-05	Delhi	DV-1,2,3 & 4
2006	Delhi	DV-3
2006	Delhi	DV-1 & 3
2001-07	North India (Delhi and Gwalior region)	DV-1 (Genotype III)
2006	Delhi	DV-1,3 & 4
2008	Delhi region	DV-1,2 & 3
1956-2005	Entire country	DV-2
2002-06	Delhi	DV-1, 2, 3 & 4
2003	Delhi	DV-3 (Genotype III)
2008	Ernakulam, Kerala	DV-2 & 3
2007	Rural areas of Madurai, Tamil Nadu	DV-3 (Genotype III)
2007	Andhra Pradesh	DV-1 & 4 (Genotype I)
2003-08	Different parts of the country	DV-3 (Genotype III)
2007-09	Delhi	DV 1, 2, 3 & 4
2009-10	Pune, Maharashtra	DV-4 (Genotype I)

The history of dengue outbreaks in India has been recently reviewed. More recent and systematic data are now available because of the National Vector Borne Disease Control Programme. The data on the web site of the National Vector Borne Disease Control Programme and earlier publications by National Institute of Virology show that dengue has been endemic in 16 states since the beginning: Andhra Pradesh, Goa, Gujarat, Haryana, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh, West Bengal, Chandigarh, Delhi and Puduchery. During 2010–2012, dengue encroached into the remaining states. Figure shows the distribution of dengue cases among the states of India in 2013.[37,38]

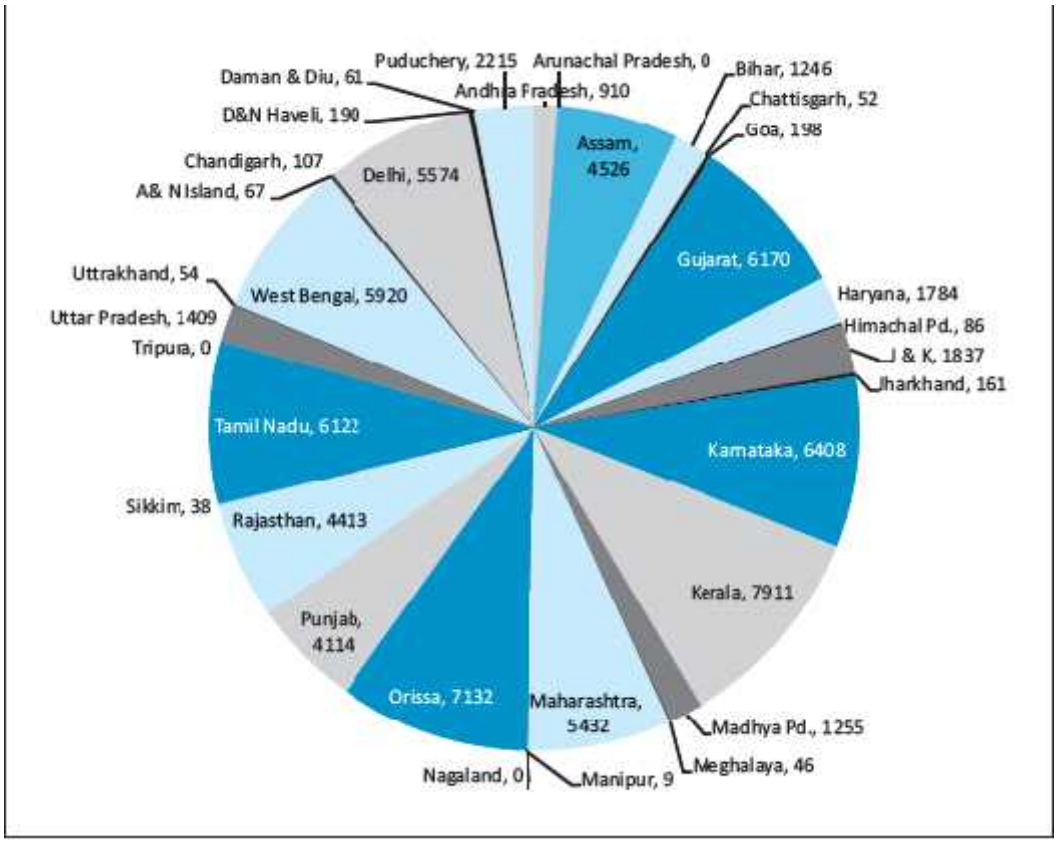


Figure 2. Distribution of dengue cases in Indian states in 2013[38]

Although the number of dengue cases has shown a steady rise with every passing year, the mortality has reduced.

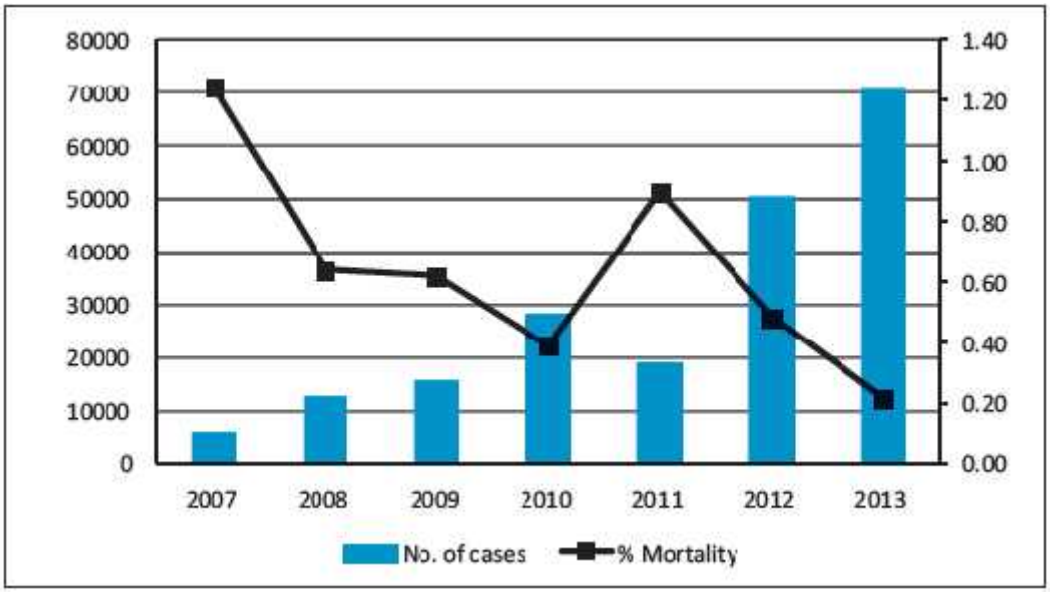


Figure 3. Total dengue cases (left axis) and percentage mortality (right axis) in India, 2007–2013[38]

The overall mortality rate of 1.2% in 2007 dropped to 0.25% in 2013. This reduction is probably the result of the cumulative effects of better patient management, increased diagnostic capabilities and better reporting. Compared with the rest of South-East Asia, the number of dengue shock syndrome (DSS) cases in India remains low.[37]

During 2003–2005 All India Institute of Medical Sciences, New Delhi reported 44.56% positivity in 1820 samples. The maximum number of cases belonged to the 21–30 years age group and the peak was in October. Co-circulation of all four serotypes was observed in 2003 and emergence of DENV-3 as the dominant serotype in 2005.[39]

Another study from a tertiary care hospital in Delhi covering 7 years (2002–2008), reported 30.15% positivity in 7846 samples and circulation of all four serotypes in 2003 followed by DENV-3 in 2004–2006, DENV- 2 in 2007 and DENV-1 in 2008.[40]

A longitudinal study for a period of 6 years (2005–2010) in Pune city involving 24 private and government clinics/hospitals[41] on 5106 testing samples observed a positivity of 48.45%. The 21–30 years age group was most affected by dengue throughout the 6 years.

Dengue fever in Karnataka

Until mid-1990s, dengue was reported from only three of the four South Indian states, namely, Andhra Pradesh, Karnataka and Tamil Nadu. A recent study from Mangalore reported that, of the total 466 cases, admitted to the hospital between 2002 and 2008, 391 (83.9%) had dengue fever, 41 (8.8%) had dengue hemorrhagic fever, and 34 (7.3%) had dengue shock syndrome. The year 2007 had the highest number of reported cases, 219 (47%). Most of dengue cases occurred during the month of September, 89 (19.1%). Davangere (41.2%), Shimoga (23%), and Udupi (7.5%) were the districts from where the cases were reported predominantly.[42]

Etiology

Arboviruses (Arthropod borne viruses) are viruses of vertebrates, biologically transmitted by hematophagous insect vector. Taxonomically, Arboviruses belong to families as diverse as Togaviridae, Bunyaviridae, Reoviridae, Arenaviridae and Rhabdoviridae.

lphavirus : Arbovirus Group A

Flavivirus : Arbovirus Group B. The name being derived from flavi meaning yellow

Rubivirus : Rubella virus. It is antigenically and epidemiologically unrelated to arboviruses.

Dengue viruses like other flavi viruses have a single stranded RNA genome surrounded by an icosahedral nucleocapsid and covered by lipid envelope. The virion is around 50 nm in diameter. The flavivirus genome is approximately 11 kb in length.[28] The genome is composed of three structural protein genes encoding the nucleocapsid or core protein (C), a membrane associated protein (M), envelope protein (E) and seven non structural protein genes.

The isolation and detection of dengue virus dates back to World War II and further characterization led to postulation of dengue virus as an agent involved in various past outbreaks which were exhibiting dengue-like symptoms. *Aedes aegypti* mosquito as a vector of dengue virus was first discovered by Bancroft in 1906.[43]

Dengue viruses for the first time were adapted to laboratory animals in the 1940's (Dengue type 1 and 2) and 1950's (Dengue type 3 and 4).[17]

In 1943, the dengue virus was isolated in Japan by inoculation of serum of patients into suckling mice and in India it was done at Kolkata in 1944 from serum samples of US soldiers.[33]

Dengue virus has four serotypes, namely DENV1, DENV2, DENV3 and DENV4. All four virus serotypes cause similar illness, but severe and fatal

hemorrhagic disease is more often associated with DENV2 and DENV3 infections. DENV2 (genotype IV) and DENV3 (genotype III) are the most commonly isolated genotypes.[43]

DV-1 was isolated in 1956 at Vellore. All the Indian DV-1 isolates belong to the American African (AMAF) genotype. The Indian DV-1 isolates are distributed into four lineages, India I, II, III. Of these, India III is the oldest and extinct lineage; the Afro-India is a transient lineage while India I is imported from Singapore and India II, evolving *in situ*, are the circulating lineages.[44] The American genotype of DV-2 which circulated predominantly in India during the pre-1971 period, was subsequently replaced by the Cosmopolitan genotype. Post-1971 Indian isolates formed a separate subclade within the Cosmopolitan genotype. DV-2 strains were isolated in India over a time span of more than 50 years (1956-2011). The re-emergence of an epidemic strain of DV type-3 in Delhi in 2003 and its persistence in subsequent years marked a changing trend in DV circulation in this part of India. Occasional reports of circulation of DV-4 are also seen, though it is not the predominant type in India.[33]

Transmission and vector

The *Aedes aegypti* mosquito is the primary vector of dengue. The virus is transmitted to humans through the bites of infected female mosquitoes. After virus incubation for 4–10 days, an infected mosquito is capable of transmitting the virus for the rest of its life.[27]

Infected humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. Patients who are already infected

with the dengue virus can transmit the infection (for 4–5 days; maximum 12) via *Aedes* mosquitoes after their first symptoms appear.[27]

The *Aedes aegypti* mosquito lives in urban habitats and breeds mostly in man-made containers. Unlike other mosquitoes *Ae. aegypti* is a day-time feeder; its peak biting periods are early in the morning and in the evening before dusk. Female *Ae. aegypti* bites multiple people during each feeding period.[27]

Aedes albopictus, a secondary dengue vector in Asia, has spread to North America and Europe largely due to the international trade in used tyres (a breeding habitat) and other goods (e.g. lucky bamboo). *Ae. albopictus* is highly adaptive and, therefore, can survive in cooler temperate regions of Europe. Its spread is due to its tolerance to temperatures below freezing, hibernation, and ability to shelter in microhabitats.[27]

Natural History

An incubation period of 5-8 days followed by the onset of a high-peak fever, headache, malaise and myalgia with a rash developing after 3-4 days is common. Generally, most dengue infections are classified as simple dengue fever. The affected patients usually present with high fever (almost all cases) and present a positive tourniquet test. The fever usually lasts 4-7 days due to the nature of viral infection. Most patients experience a complete recovery without complications; however, a number of atypical forms of clinical manifestation can be seen. These atypical infections can manifest without fever or clinically serious symptoms, and gastrointestinal and respiratory symptoms can be detected.[16]

Focusing on the serious form of dengue, the forms with overt bleeding (dengue hemorrhagic fever) and shock (dengue shock syndrome) are classified as dengue with high severity. In the simple form of dengue infection, a petechia is the only sign of infection, seen after application of the tourniquet test.[16]

However, if severe infection occurs, high morbidity and mortality can be expected if appropriate treatment is not administered. An important step in the management of dengue is monitoring severe forms of infection. It is observed that platelet count progressively decreases from simple dengue to dengue shock syndrome.[16]

Clinical presentation

Following an incubation period, the illness begins abruptly, going through three phases: febrile, critical and recovery.[45]

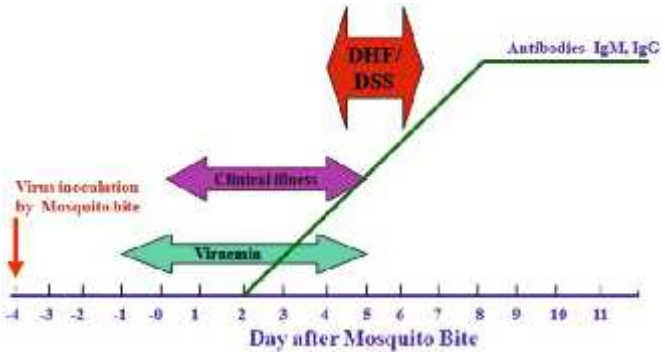


Figure 4. Sequence of events during dengue virus infection following the bite of infected mosquito[45]

DF is observed more frequently in adults and adolescents, and can present with either mild fever only or a more incapacitating disease. This latter presentation is characterised by the sudden onset of high fever, severe headache, retro-orbital

pain, myalgia, arthralgia and rash, symptoms occurring predominantly in the early febrile stage.[45]

In the critical phase, the skin is flushed with the appearance of a petechial rash. This usually occurs around the time of defervescence, typically on days 3–7, and is associated with capillary leakage and haemorrhage.[45]

Severe dengue usually affects children younger than 15 years, although it can occur in adults. DHF is characterised by a transient increase in vascular permeability resulting in plasma leakage, with high fever, bleeding, thrombocytopenia and haemoconcentration, which can lead to shock (termed dengue shock syndrome (DSS). However, it can be difficult to differentiate DHF from DF and other viral diseases, e.g. typhoid fever, particularly during the acute phase of the illness.[45]

Secondary dengue infection is considered to be the principal risk factor for DHF, but the interaction of virus, host and epidemiological risk factors are determinants of the occurrence of DHF epidemics.[45] A study by Siquira JB et al.[46] reported significant risk of dengue infection with older age ($P < 0.01$), low education (odds ratio [OR] = 3.45, 95% confidence interval [CI] = 1.82-6.55), and low income (OR = 1.32, 95% CI = 1.02-1.71) in multivariate analysis.

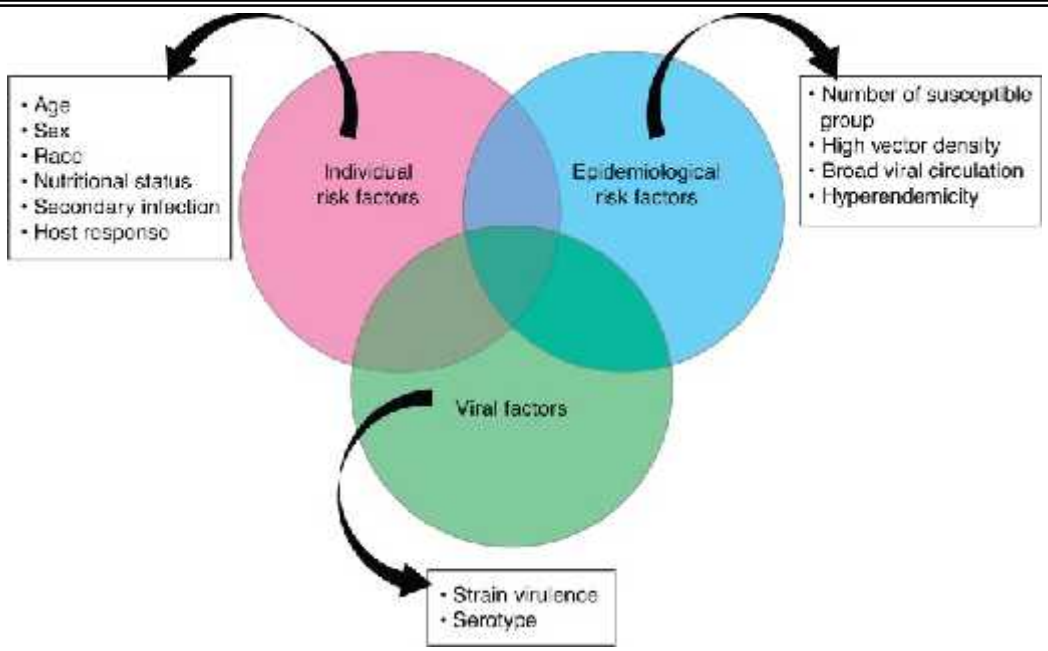


Figure 5. Risk factors for dengue haemorrhagic fever[1]

Dengue fever

The symptoms usually start with a sudden onset of high fever lasting for 4-8 days. Intense headache, retro-orbital pain, fatigue, muscle and joint pain, loss of appetite, unpleasant metallic taste in mouth, vomiting, diarrhea, and abdominal pain are the other symptoms. Manifestations of the skin commonly occur as rashes on the face, extremities and spreads to the trunk. The other features, which could be present are minor epistaxis or bleeding gums, heavy menstrual periods, petechiae, and gastrointestinal bleeding. Several individuals with DF have been reported with a positive tourniquet test.

Dengue haemorrhagic fever

It is characterized by pyrexia, hemorrhagic phenomena, hepatomegaly and features of circulatory failure.

The clinical progression of DHF is alienated into three stages namely febrile, leakage and convalescent stages. The febrile stage begins with rapid onset fever. The pyrexia is intermittent, high grade (usually >39°C), and associated with chills and rigors. Bleeding manifestations and rashes appear in the initial febrile stage. The fever persists for 2-7 days and then falls to usual or subnormal levels when the patient recuperates or progresses to plasma leakage stage. Patients remain ill, despite normalization of temperature.

In severe cases with high plasma leakage, frank shock is apparent with low pulse pressure cyanosis, hepatomegaly, pleural effusions, pericardial effusion, ascites melaena and gastrointestinal bleeding followed by epistaxis. During convalescence period, decreased heart rate and confluent petechial rashes, erythema and pallor are seen. The threatening stage in DHF is signs of circulatory failure and hemorrhagic tendencies. Hematological investigations usually show platelet count, ≤100,000/mm^3 as an evidence of a vascular leak syndrome. WHO definition for DHF is recent fever lasting for 2-7 days, occasionally biphasic, hemorrhagic tendencies evidenced by at least one of the A positive tourniquet test; Petechiae or purpura; Mucosal bleeding; Hematemesis, melena; and Platelet count ≤100 000/mm^3.

Objective indication of plasma leakage initiated by increased vascular permeability is demonstrated by at least one of the following: Elevated hematocrit, pleural or other effusion.

Dengue shock syndrome

Is defined as DHF associated with a weak rapid pulse, narrow pulse pressure, which is <20 mmHg, cold, clammy skin, restlessness, circumoral cyanosis and high

mortality. Patients with DSS die due to progressively worsening shock and multi-organ failure and disseminated intravascular coagulation. The phase of shock is transient, and the patient promptly recuperates with right supportive therapy.[47,48]

Classification

The 1997 guidelines classified dengue into DF, DHF (Grades 1 and 2) and DSS (DHF Grades 3 and 4).[49] The case diagnosis for DF emphasized the need for laboratory confirmation and the suggested DF classifications are shown below together with those for DHF and DSS.

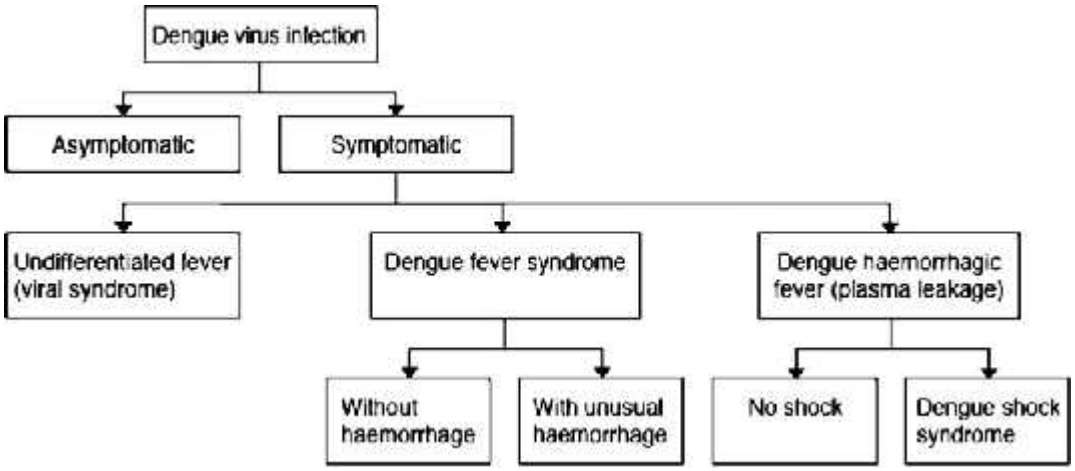


Figure 6. The 1997 WHO classification of dengue virus infection[50]

The 2009 Dengue Case Classification

The 2009 WHO criteria classify dengue according to levels of severity: dengue without warning signs; dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure).[51] Patients

who recover following defervescence are considered to have non-severe dengue, but those who deteriorate tend to manifest warning signs. These individuals are likely to recover with intravenous rehydration. However, further deterioration is classified as severe dengue, though recovery is possible if appropriate and timely treatment is given.[51]

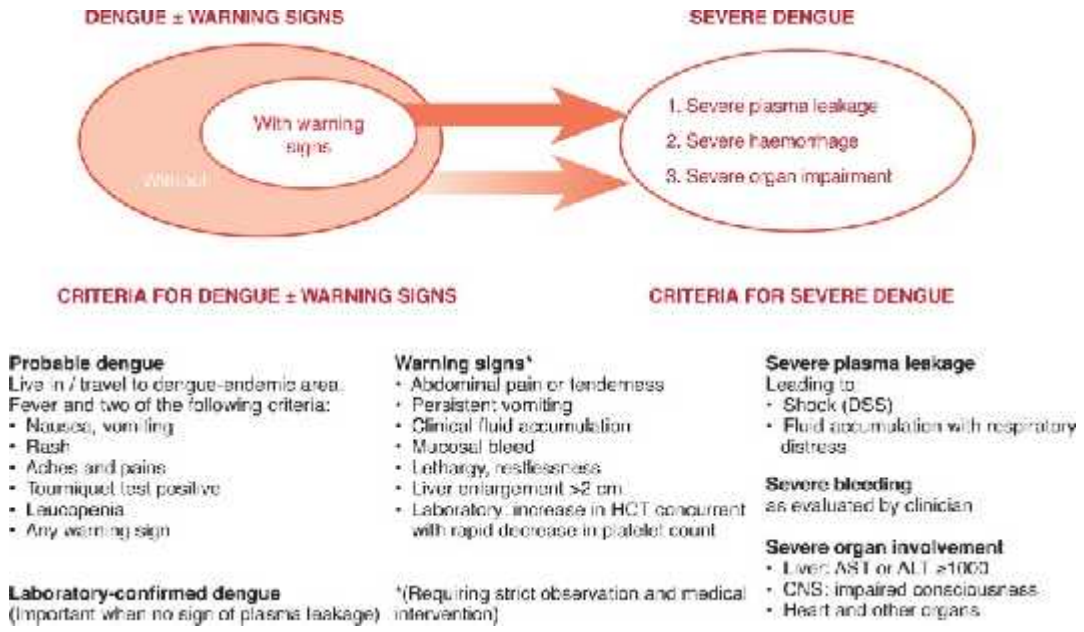


Figure 7. The 2009 revised dengue case classification[51]

The 1997 WHO case classification system for dengue was revised because of differences across the broad geographical areas and the age groups affected by dengue. However, the current 2009 WHO classification has yet to be definitively proved to be effective. The question remains, therefore, whether this latest classification requires further modification.[51] A solution may be to incorporate elements from the 2009 classification of severe dengue into the 1997 guidelines,[49] much of which remains relevant for use.

Pathogenesis

Understanding the factors that are involved in the pathogenesis of DHF continues to be one of the most active areas of dengue research. It has been established that DHF is caused by a "Cytokine Tsunami" but despite extensive studies for over four decades, its genesis is still not fully understood. The mechanisms that have been considered to cause DHF include antibody-dependent enhancement (ADE), T cell response, and a shift from Th-1 to Th-2 response. The combined effect of all of these is cytokine tsunami resulting in movement of body fluids in extravascular space. Various cytokines have been implicated in the immuno-pathogenesis of DF/DHF as summarized below.[33]

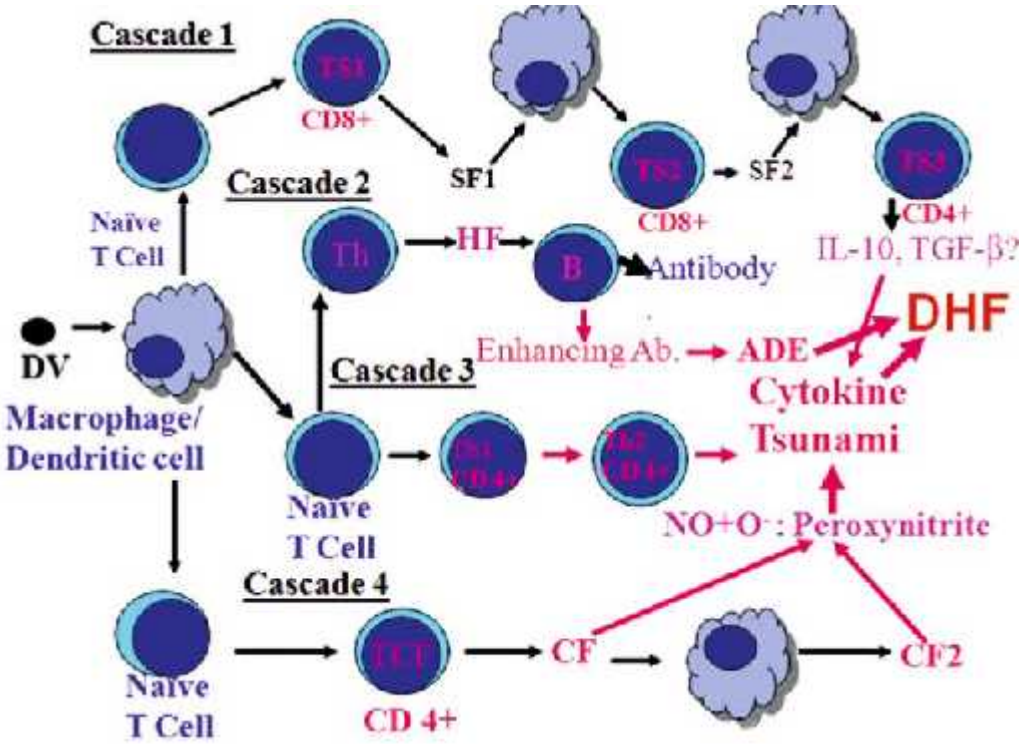


Figure 8. Immunopathogenesis of DHF via induction of four cascades of T cells as dissected out by U C Chaturvedi and colleagues[45]

Cytokine	Levels in DF	Levels in DHF	References
IL-1β	-	-	173
IL-2	↑↑	↑	139
IL-4	↓	↑↑	139, 174, 175
IL-6	↑	↑↑	139, 173, 176
IL-8	↑↑	↑↑	173, 176, 177
IL-10	↓	↑↑	139, 173
IL-12	↑↑	↓	173, 178
IL-13	↓	↑↑	179
IL-18	↑	↑↑	179
TNF-α	↑↑	↑↑	139, 173, 175, 176, 180
IFN-γ	↑↑	↑	139, 174, 175, 176, 180
TGF- β	↓	↑↑	181
Human CF	↑	↑↑	136, 139

IL, interleukin; TNF, tumour necrosis factor; IFN, interferon; TGF, transforming growth factor

Figure 9. Serum cytokine levels in the pathogenesis of dengue[33]

It has been suggested that in dengue a Th1 response is linked to recovery from infection while a Th2 type response leads to severe pathology and exacerbation of the disease. The role of Th17 cells in dengue pathogenesis has been examined and warrants serious consideration by researchers. CF/CF2 induces macrophage to produce free radicals, nitrite, reactive oxygen and peroxynitrite.[33]

The free radicals, besides killing the target cells by apoptosis also directly upregulate production of pro-inflammatory cytokines; interleukin (IL-1), tumour necrosis factor (TNF)-alpha, IL-8, and hydrogen peroxide in macrophage. Oxidative

stress develops from the onset of dengue infection. Plasma protein carbonylation, protein carbonylation to protein-bound sulphydryl group ratio are reported to predict DHF/DSS.[33]

The change in relative levels of IL-12 and transforming growth factor (TGF)-beta shifts a Th1-dominant response to a Th2 biased response resulting in an exacerbation of dengue disease. The vascular permeability is increased due to combined effect cytokine tsunami, release of histamine, free radicals and the products of the complement pathway, *etc*. Thus the key player appears to be CF/CF2, but the activity is regulated by CF-autoantibodies generated in patients with dengue disease.[33]

The accompanying factors that have been discussed from time to time are dengue non-structural protein of virus type 1 (NS1)-antibodies cross-reacting with vascular endothelium (a type of autoimmune phenomenon), immune complex disease, complement and its products, memory T cells, various soluble mediators including cytokines selection of virulent strains and virus virulence, *etc*.[33]

Other mechanisms that have been suggested are that DV utilizes calcium modulating cyclophilin-binding ligand to subvert the apoptotic process which in turn favoured efficient virus production. A correlation of elevated lipopolysaccharide levels with disease severity has also been reported.[33]

Still the exact cascade of mechanisms involved in dengue disease pathogenesis remains unexplained and lot more needs to be done.

Diagnosis

In management of any disorder in medicine, diagnosis is a very important step. Without diagnosis, specific management cannot be carried out, offering no hope for success in treatment. To diagnose dengue infection, one first has to understand the nature of dengue infection. Important characteristics include: it is a viral infection, and hence the duration of illness is usually within 1 week; it is an arboviral mosquito-borne infection, hence, a history of mosquito exposure or living in an endemic area should be investigated; and that it is an acute febrile illness, hence the main clinical presentation should be high fever, and dengue has to be included in the differential diagnosis of all cases with acute febrile illness.[14]

To make a diagnosis for dengue infection, general concepts in medical practice can be applied. First, it has to start with taking a full history. Useful information that leads to suspicion of dengue infection include: history of acute febrile illness within 1 week and without relief by acetaminophen; history of living or traveling to endemic area of dengue (tropical countries, especially in south and southeast Asia); and history of bleeding complications such as petechiae, epistaxis and passing melena, among others. With the described clinical history, the physician can summarize that the patient has the problem of acute febrile illness that could be a case of dengue infection.[14]

Second, it is necessary to search for more evidence by physical examination. The general physical examination might be of little help in diagnosis of dengue infection. The clinical symptoms of dengue disease vary case by case. In nonsevere forms, the symptoms can be mild and the patients can recover spontaneously without

need of any medication from the physician. However, in severe forms, the more serious symptoms can be seen. These symptoms include bleeding diathesis, shock and many complications (e.g., pleural effusion and neurological impairment, among others). Potential useful findings or signs are usually the clues of bleeding, which can be seen in case of dengue hemorrhagic fever. These signs include petechiae and tender hepatomegaly, among others. A widely used physical examination tool for screening for dengue infection in endemic areas is the tourniquet test.[14] This test can be easily performed using a simple tourniquet or blood pressure cuff.

It is reported that about four-fifths of patients with dengue infection can be detected by applying a tourniquet test.[52] The tourniquet test can help presumptively diagnose cases of dengue infections, however, false positives can be seen in cases of other tropical hemorrhagic fevers, as well as in physically fragile capillaries in females.[53] Cao et al.[54] concluded that "A positive test should prompt close observation or early hospital referral, but a negative test does not exclude dengue infection".

The general clinical symptoms of dengue diseases are very similar to those of other febrile illnesses that are caused by other viruses, although thrombocytopenia and atypical lymphocytosis might guide the physicians to diagnose dengue infection. The most reliable evidence for diagnosis of dengue infection can be derived from laboratory investigation. With the use of laboratory techniques, the final definitive diagnosis of dengue infection can be made. In general, there are two groups of widely used laboratory diagnosis for dengue infection. The first group of tests help in making a primary presumptive diagnosis of dengue infection. The most important test is complete blood count, with use of complete blood count, atypical

lymphocytosis and thrombocytopenia can be seen. Nevertheless, the data from routine complete blood count are sometimes useful in prediction of severity of disease. Hematocrit and platelet count can help predict severe bleeding episodes, but not shock, in patients. The second group is the test for confirmation of dengue infection. This is very important in providing epidemiological data for planning dengue management at the community scale. Also, it can be used as evidence to rule out other similar conditions that can mimic dengue infection.[14]

Some laboratory tests can be used to support physician diagnoses (such as serological test, reverse transcription PCR, dengue NS1 antigen, among others.). However, in general practice, the widely used tests are serological tests. The two main tests are dengue IgM and dengue IgG. Focusing on these tests, accuracy is dependent on the timing of their sample collection. In serological tests, according to the already mentioned immunopathogenesis, IgM could be raised during days 3–5 of illness whereas the IgG is delayed during days 5–10 of illness. Normally, IgM/IgG ELISA are useful to confirm the physician's clinical diagnosis because the severe cases need to be cured as soon as possible. Therefore, early laboratory diagnosis (within 1–2 days of illness) will be more important.[14]

Early diagnostic approaches, including virus isolation and molecular tests such as reverse transcription PCR, are still expensive and need expertise to perform.[14] Recently, an up-to-date test for early diagnosis of dengue infection is dengue NS1 antigen detection. There are both ELISA and immunochromatographic test (rapid test) formats available on the market. These diagnostic test kits, especially the immunochromatographic strip kits, can help early diagnosis and shorten the turnaround time.[16,55]

Low et al.[56] recently reported that use of both the WHO 1997[48] and 2009 classification schematics[50] in the diagnosis of dengue and concluded that "older adults who present with fever and leukopenia should be tested for dengue, even in the absence of other symptoms".

Laboratory tests

The characteristics of an 'ideal' dengue diagnostic test depend on the purpose for which the test will be used. The optimal window for diagnosing a dengue infection is roughly from the onset of fever to 10 days post-infection; however, as not all patients are diagnosed within this period, an ideal diagnostic test should be sensitive regardless of the stage of infection.[57]

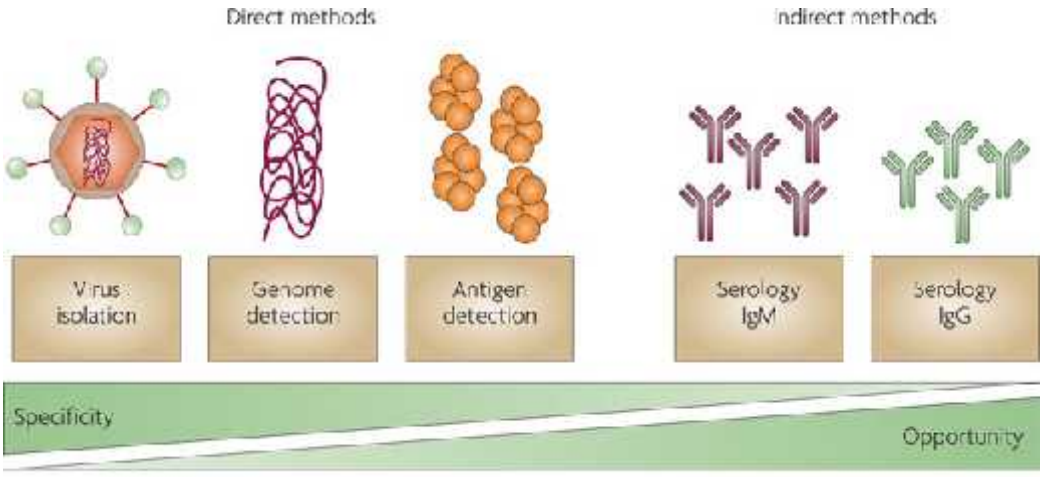


Figure 10. Comparative merits of direct and indirect laboratory methods for the diagnosis of dengue infections[58]

Current laboratory methods for dengue diagnosis

Antigen detection

NS1-based assays

A simplified method of diagnosis of dengue infection during the acute stage compared to viral isolation or nucleic acid detection is the detection of viral antigens in the bloodstream.[58]

New developments in enzyme-linked immunosorbent assay (ELISA) and rapid immunochromographic assays that target non-structural protein 1 (NS1) have shown that high concentrations of this antigen can be detected in patients dengue infections up to 9 days after the onset of illness. NS1 is synthesized by all flaviviruses and is secreted from infected mammalian cells. The presence of secreted NS1 (NS1) in the bloodstream stimulates a strong humoral response. Many studies have investigated the utility of NS1 detection as a diagnostic tool during the acute phase of a dengue infection. A serotype specific monoclonal antibody (mAb) based NS1 antigen-capture ELISA has recently been developed and shows good serotype specificity.[58]

Serological methods

The acquired immune response to dengue virus infection consists of the production of immunoglobulins (IgM, IgG and IgA) that are mainly specific for the virus envelope (E) protein.[58]

IgM-based assays

The detection of dengue-specific IgM is a useful diagnostic and surveillance tool. IgM is initially detectable between 3 to 5 days post onset of fever in ~50% of hospitalized patients and has a sensitivity and specificity of ~90% and 98%, respectively, when assays are undertaken five days or more after the onset of fever. Dengue-specific IgM is expressed earlier than dengue-specific IgG.[58]

The sensitivity and specificity of IgM-based assays is strongly influenced by the quality of the antigen used and can vary greatly between commercially available products. ELISA-based IgM assays have become an invaluable tool for the surveillance of dengue.[58]

IgG-based assays

Dengue-specific IgG-based assays can be used for the detection of past dengue infections and current infections.[58]

The most important development in dengue diagnostics in recent years is the advent of the specific detection of dengue virus NS1 antigen. Dengue RDTs (Rapid Diagnostic Tests) that detect NS1 antigen employ a number of serotype-specific anti-NS1 monoclonal antibodies to capture and detect soluble NS1 antigen in serum, plasma, or blood. The first commercial assays for dengue NS1 antigen detection used the ELISA format[59,60] and demonstrated excellent sensitivity and specificity in the early phase of infection that diminished with falling viraemia levels. The major commercial diagnostics manufacturers, Panbio, Biorad, and SD, have all developed RDT-based NS1 antigen tests, and have equivalent ELISA-based assays.[60]

To take advantage of the entire temporal spectrum of patient presentation during the acute phase of dengue infection (usually from 1 to 7 days after onset of fever), NS1 antigen and IgM antibody results have been combined in a Boolean manner using AND/OR operators. NS1 antigen is present in the serum in the early phase of infection; however, patients that present late in the course of infection may have undetectable levels of NS1 antigen. Dengue IgM antibodies are usually present following 2–5 days of infection, and, by combining the results of dengue NS1 antigen and IgM antibody testing, accurate diagnosis during acute presentation is possible. This approach was initially described by combining the results of the Panbio NS1 antigen and IgM antibody ELISAs.[60]

Other Laboratory Tests

The following laboratory tests should also be performed:

- Complete blood count (CBC)
- Liver function tests
- Renal function test

Characteristic findings in dengue fever are thrombocytopenia (platelet count < 100 x 10^9/L), leukopenia, and mild-to-moderate elevation of aspartate aminotransferase and alanine aminotransferase values. Jaundice and acute liver failure are uncommon. Liver enzyme levels begin to rise during the early stage and peak during the second week.[61]

Chest radiography should be performed to look for pleural effusion and bronchopneumonia. Head computed tomography without contrast may be indicated

in patients with altered level of consciousness, to detect intracranial bleeding or cerebral edema from dengue hemorrhagic fever.

Complete Blood Cell Count

Thrombocytopenia has been demonstrated in up to 50% of dengue fever cases. Platelet counts less than 1,00,000 cells/μL are seen in dengue fever and occur before defervescence and the onset of shock. The platelet count should be monitored at least every 24 hours to facilitate early recognition of dengue hemorrhagic fever.[62]

Electrolyte abnormalities and Liver Enzymes

Hyponatremia is the most common electrolyte abnormality in patients with dengue hemorrhagic fever or dengue shock syndrome. Metabolic acidosis is observed in those with shock and must be corrected rapidly. Elevated blood urea nitrogen (BUN) levels are observed in those with shock. Acute kidney injury is uncommon.[63,64]

Transaminase levels may be mildly elevated or may be into the several thousands in patients with dengue hemorrhagic fever who have acute hepatitis.

Ultrasonography

Ultrasonography is a timely, cost-effective, and easily used modality in the evaluation of potential dengue fever. Positive and reliable ultrasonographic findings include fluid in the chest and abdominal cavities, pericardial effusion and a thickened gallbladder wall. Thickening of the gallbladder wall may precede clinically significant vascular permeability.[65]

Overall, dengue infection will still be an important public health problem worldwide in the future. Due to the changes in climate and global warming, dengue infection will appear more worldwide. The diagnosis of dengue infection will still be the most important issue determining success in clinical management of dengue cases. New diagnostic tools will be continuously developed, corresponding with the expanding importance of the disease.

METHODOLOGY

The present study was conducted in Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum In patients with dengue fever from January 2014 to December 2014.

Study design and duration

The study design was one year cross-sectional study.

Study period

The present study was conducted from January 2014 to December 2014.

Place

This study was done in Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients with dengue fever admitted in the wards of Medicine Department were included in the study.

Sample size

A total of 180 dengue fever patients were studied.

Sampling procedure

Based on average 80% of the past three year hospital admission satisfying selection criteria the sample size was calculated as below.

Admission during 2011	194
Admission in 2012	228
Admissions in 2013	256
Total	678
Average admission during three years	226
80% of the average	180.8 ≈ 180

Selection criteria

Inclusion

- Patients with confirmed dengue infection with either one of the following
    - Isolated NS1 positive (IgM and IgG negative)
    - Isolated IgM positive (NS1 and IgG negative)
    - Isolated IgG positive (NS1 and IgM negative)
    - Both IgM and IgG positive (NS1 negative)
- Patient age more than 18 years with confirmed dengue infection.

Exclusion

- Patients with other co infections, mixed infections and known case of liver disease.

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

Patients fulfilling the selection criteria were explained about the nature of study and a written informed consent and enrolled (Annexure I).

Method of collection of data

Demographic data such as age and sex were obtained through an interview and the presenting complaints like fever, arthralgia, retro-orbital pain, melaena and rash were noted. Further these patients underwent general physical examination and vitals including heart rate, blood pressure were documented. The systemic examination was done and the findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The data regarding the following investigations of the selected patients from case records done for diagnosis and management of dengue fever was documented in predesigned proforma (Annexure II).

- Dengue serology
- Complete blood count
- Platelet count
- Total bilirubin

- Direct bilirubin
- SGOT and SGPT
- Alkaline phosphatase
- Blood urea nitrogen
- Serum creatinine
- Serum sodium
- Serum potassium
- Serum chloride
- Serum bicarbonate

Outcome variables

Dengue serology

The cases were isolated according to the positive dengue serology and were divided into four cohorts that is,

- NS1 positive
- IgM positive
- IgG positive
- Both IgM and IgG positive

Clinical profile

The patients were evaluated for clinical profile based on symptoms at presentations (fever, arthralgia, retro-orbital pain, melaena and rash), General physical examination findings (heart rate and blood pressure) and systemic

examination findings (cardiovascular, respiratory, central nervous system and per abdomen).

Haematological profile

Based on the case sheet the haematological profile was assessed and abnormalities like anaemia, leucopenia and thrombocytopenia were looked for based on haemoglobin levels, total count and platelet count.

Liver profile

The liver profile was assessed by evaluating bilirubin, SGOT and SGPT, alkaline phosphatase levels.

Renal profile

The assessment of renal profile was based on blood urea nitrogen and serum creatinine levels.

Serum electrolytes

The electrolyte imbalance was determined by assessing serum sodium, serum potassium, serum chloride and serum bicarbonate levels.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test or Fisher's exact test. The continuous data was expressed as mean ± standard deviation (SD). In case of more

than three means one way ANOVA test was used for the comparison. A probability value (‘p’ value) of less than or equal to 0.05 at 95% CI was considered as statistically significant.

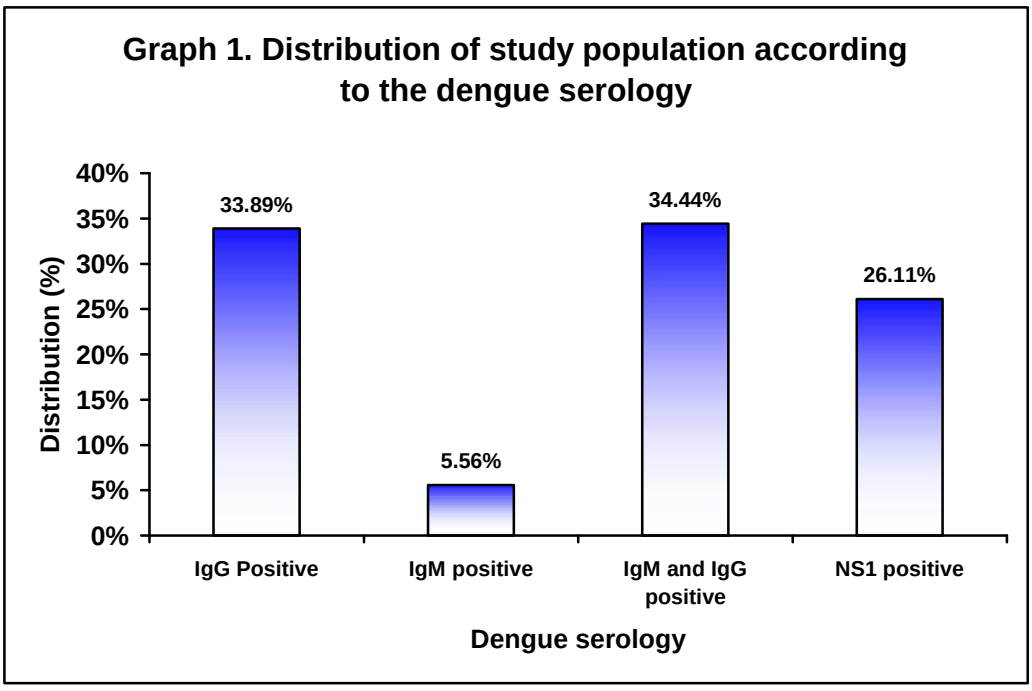
RESULTS

This one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 180 dengue fever patients were studied from January 2014 to December 2014 were studied.

The data obtained was analysed, the observations were tabulated and interpreted as below.

Table 1. Distribution of study population according to the dengue serology

Dengue serology	Distribution (n=180)	
	Number	**Percentage**
IgG Positive	61	33.89
IgM positive	10	5.56
IgM and IgG positive	62	34.44
NS1 positive	47	26.11
Total	**180**	**100.00**



In the present study dengue serology revealed 34.44% of the patients both IgM and IgG positive, 33.89% IgG positive, 26.11% with NS1 positive and 5.56% of the patients with IgM positive.

Table 2. Mean day of presentation to the hospital according to the dengue serology

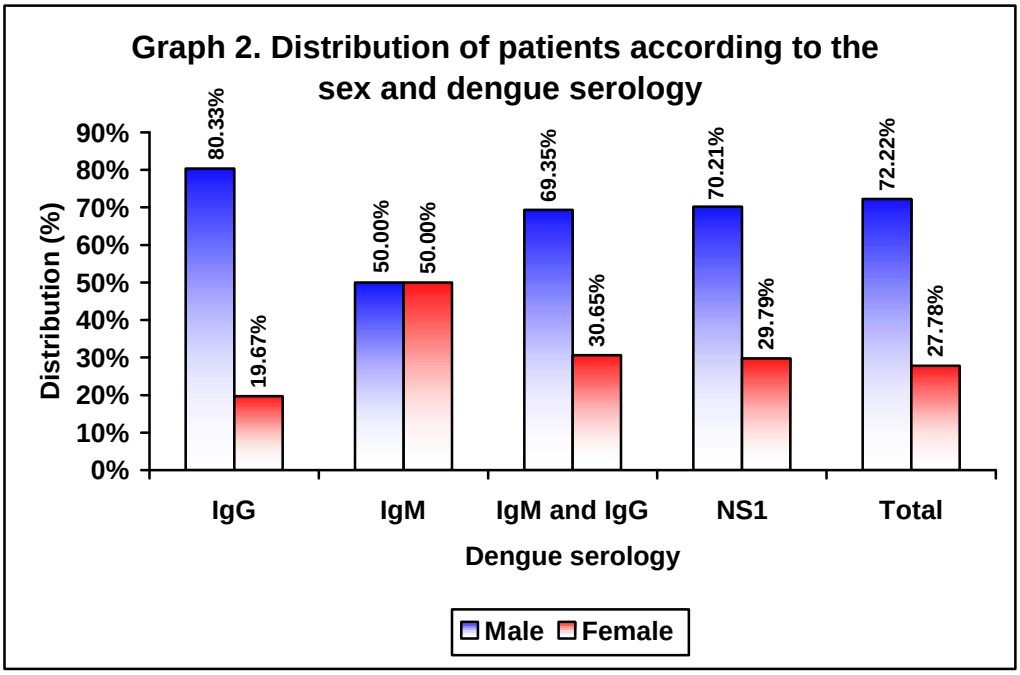
Dengue serology	Mean days (n=180)	
	Mean	**SD**
IgG Positive	8.03	1.18
IgM positive	6.20	1.69
IgM and IgG positive	6.69	1.72
NS1 positive	3.91	1.21
Overall	**5.92**	**2.04**

In this study the mean day of presentation to the hospital was 5.92 ± 2.04 days. The mean day of presentation in patients with NS1 positive was early (3.91 ±1.21 days) compared to IgM positive (6.20 ± 1.69 days), both IgM and IgG positive (6.69 ± 1.72 days) and IgG positive (8.03 ± 1.18 days).

Table 3. Distribution of patients according to the sex and dengue serology

Sex	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Male	49	80.33	5	50.00	43	69.35	33	70.21	130	72.22
Female	12	19.67	5	50.00	19	30.65	14	29.79	50	27.78
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.182

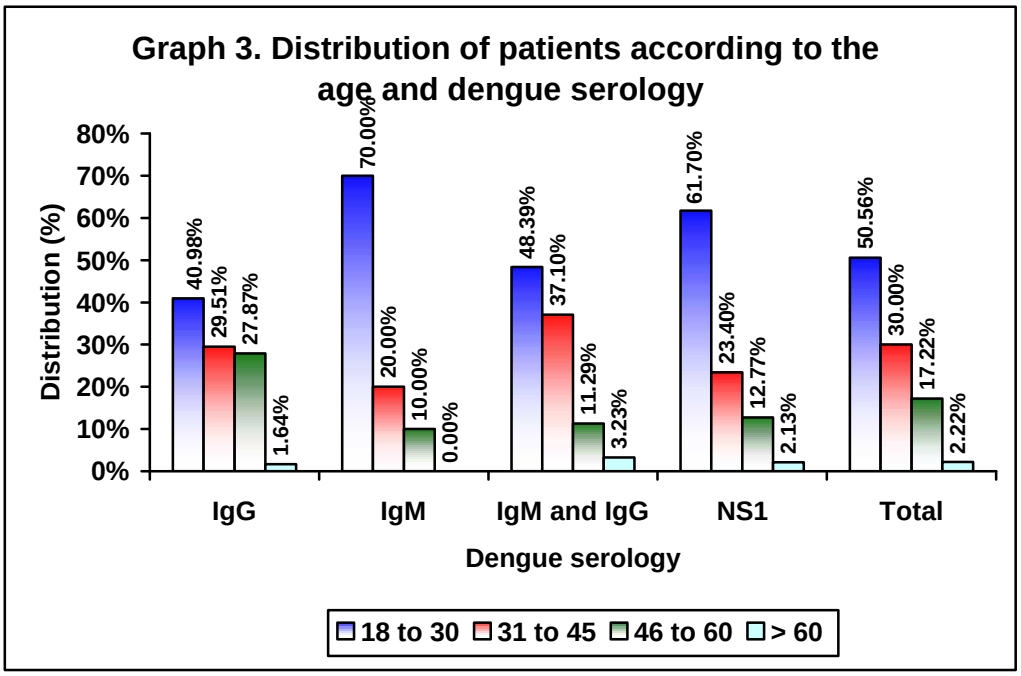


In the present study 72.22% of the patients were males. Male to female ratio was 2.6:1. Most of the males were IgG positive (80.33%) while most of the female were diagnosed IgM positive (50%). However the difference was statistically not significant (p=0.182).

Table 4. Distribution of patients according to the age and dengue serology

Age group (Years)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
18 to 30	25	40.98	7	70.00	30	48.39	29	61.70	91	50.56
31 to 45	18	29.51	2	20.00	23	37.10	11	23.40	54	30.00
46 to 60	17	27.87	1	10.00	7	11.29	6	12.77	31	17.22
> 60	1	1.64	0	0.00	2	3.23	1	2.13	4	2.22
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

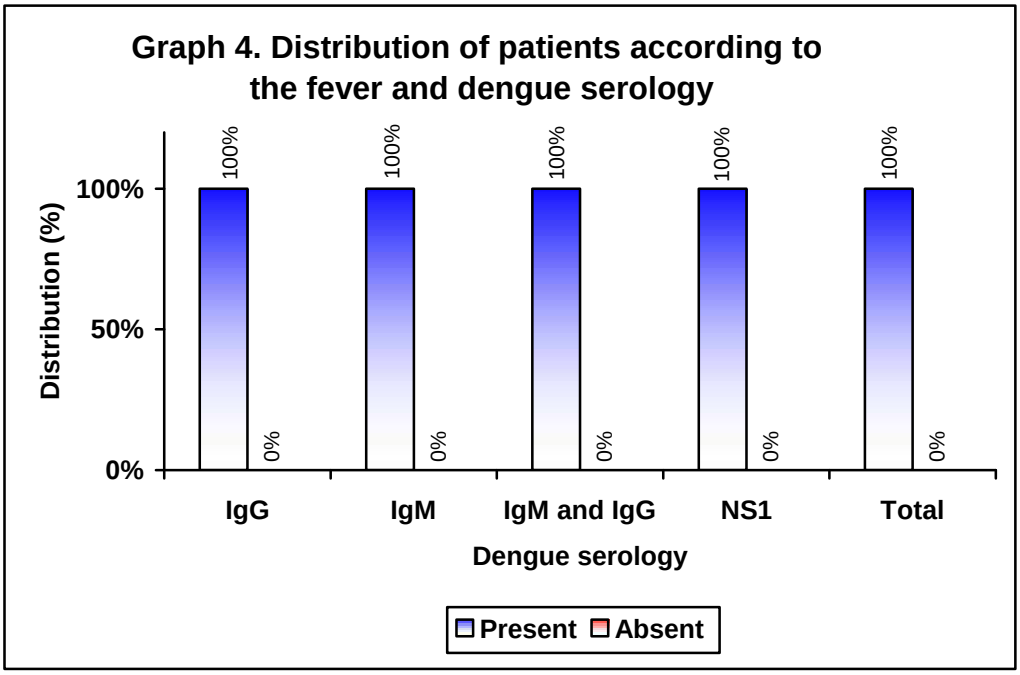
p = 0.220



In this study most of the patients were aged between 18 to 30 years (50.56%) and majority of the patients were diagnosed to have IgM positive (70%) and least in IgG positive (40.98%). However, the dengue serology was comparable in all the age groups (p=0.220).

Table 5. Distribution of patients according to the fever and dengue serology

Fever	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Present	61	100.00	10	100.00	62	100.00	47	100.00	180	100.00
Absent	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

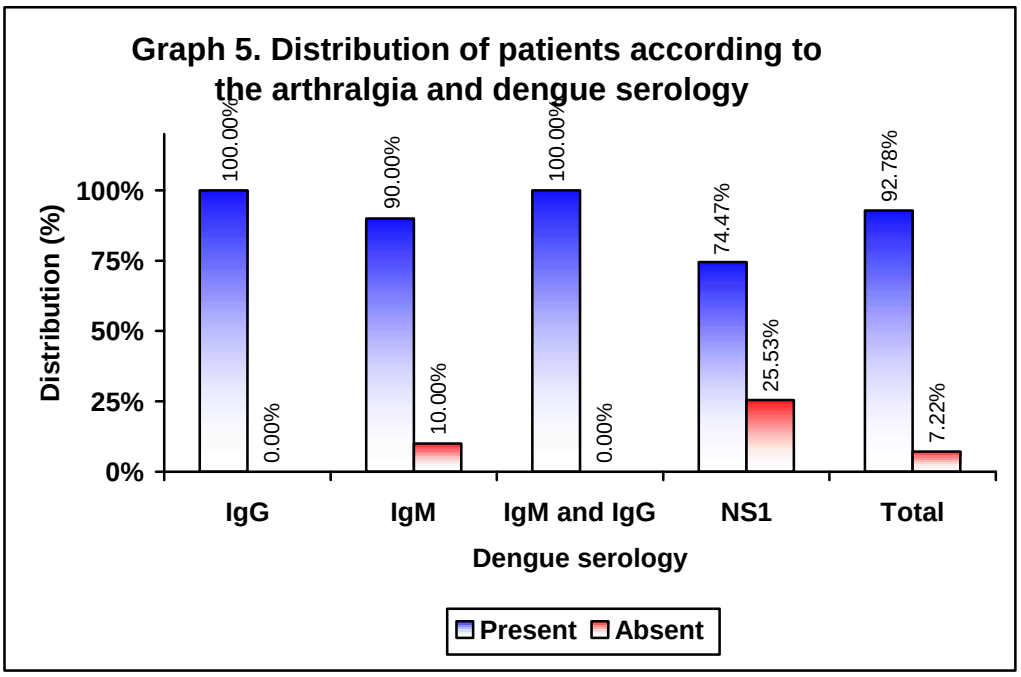


In the present study all the patients presented with fever (100%).

Table 6. Distribution of patients according to the arthralgia and dengue serology

Arthralgia	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Present	61	100.00	9	90.00	62	100.00	35	74.47	167	92.78
Absent	0	0.00	1	10.00	0	0.00	12	25.53	13	7.22
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p<0.001

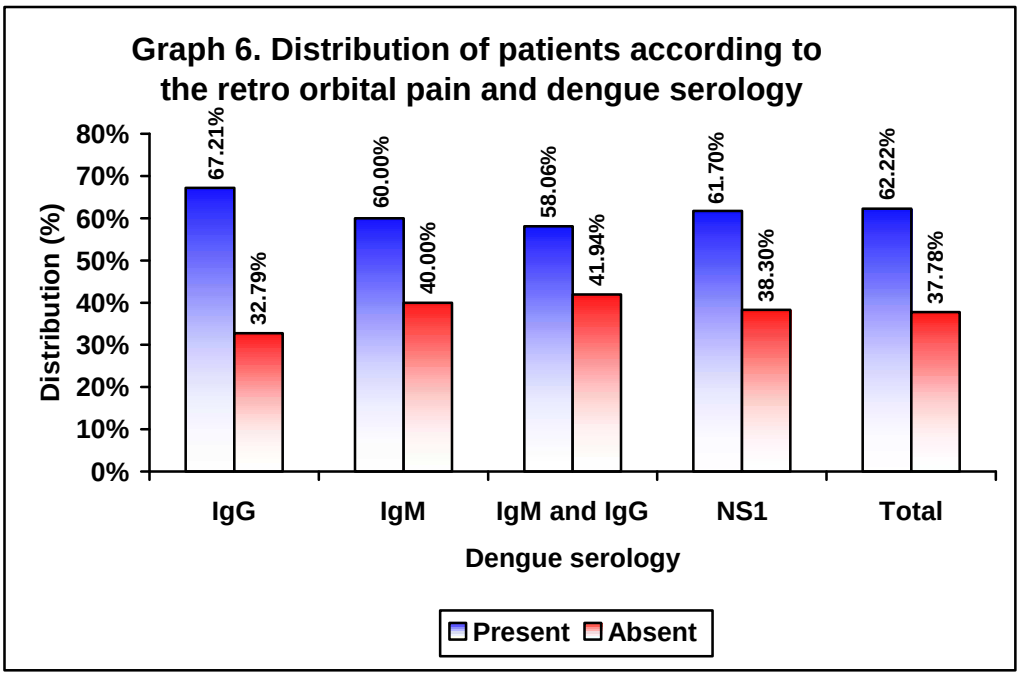


In this study arthralgia was present in 167 patients (92.78%). Of these, significantly higher number of patients were IgG positive (100%) and both IgM & IgG positive (100%) compared to IgM positive (90%) and NS1 positive (74.47%) (p<0.001).

Table 7. Distribution of patients according to the retro orbital pain and dengue serology

Retro orbital pain	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Present	41	67.21	6	60.00	36	58.06	29	61.70	112	62.22
Absent	20	32.79	4	40.00	26	41.94	18	38.30	68	37.78
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.766

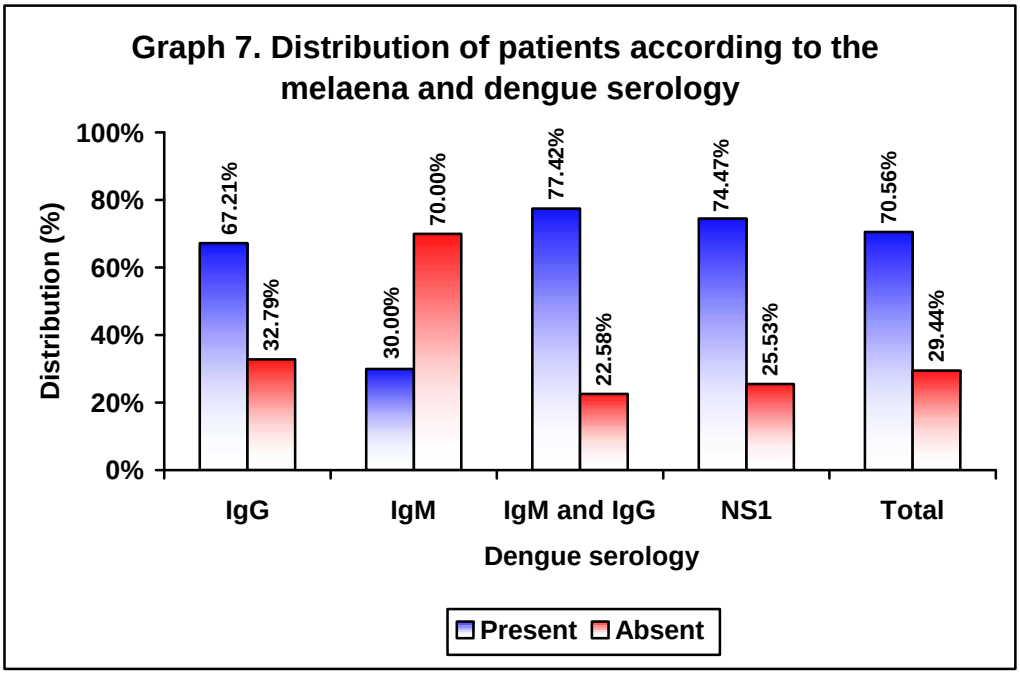


In the present study retro-orbital pain was reported by 112 (62.22%) patients. However, the frequency of patients with retro-orbital pain was high among the patients with IgG positive (67.21%) compared to NS1 positive (61.7%), IgM positive (60%) and both IgM and IgG positive (58.06%) but the difference was statistically not significant (p=0.766).

Table 8. Distribution of patients according to the melaena and dengue serology

Melaena	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Present	41	67.21	3	30.00	48	77.42	35	74.47	127	70.56
Absent	20	32.79	7	70.00	14	22.58	12	25.53	53	29.44
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.025

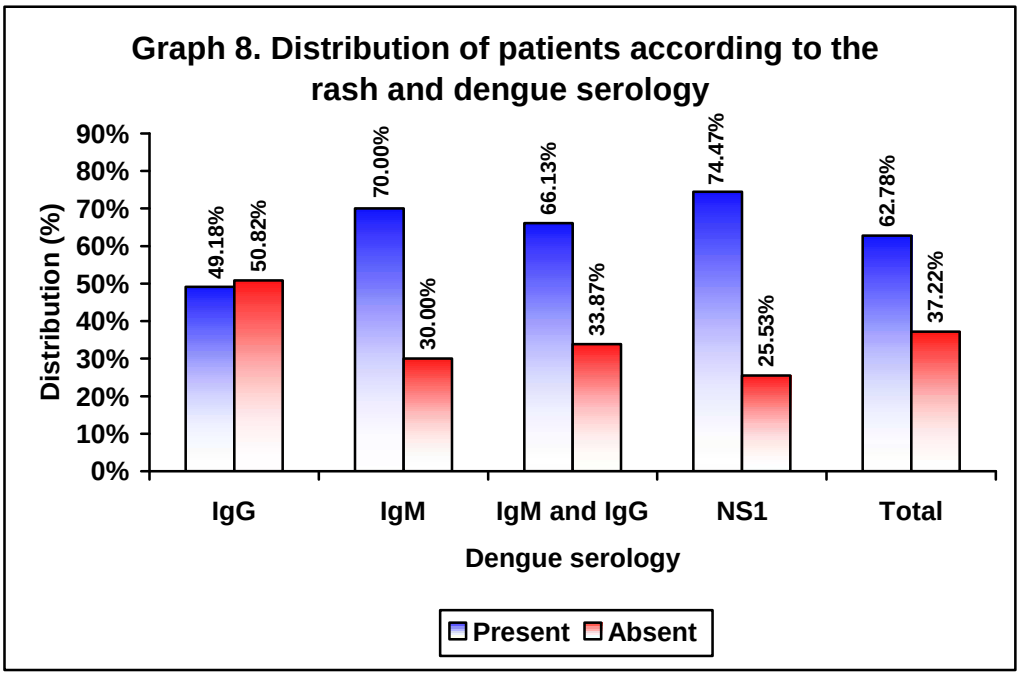


In this study 127 (70.56%) patients presented with melaena and of these maximum patients were IgM & IgG positive (77.42%) and NS1 positive (74.47%) compared to IgG positive (67.21%) and IgM positive (30%). This difference was statistically significant (p=0.025)

Table 9. Distribution of patients according to the rash and dengue serology

Rash	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Present	30	49.18	7	70.00	41	66.13	35	74.47	113	62.78
Absent	31	50.82	3	30.00	21	33.87	12	25.53	67	37.22
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.045

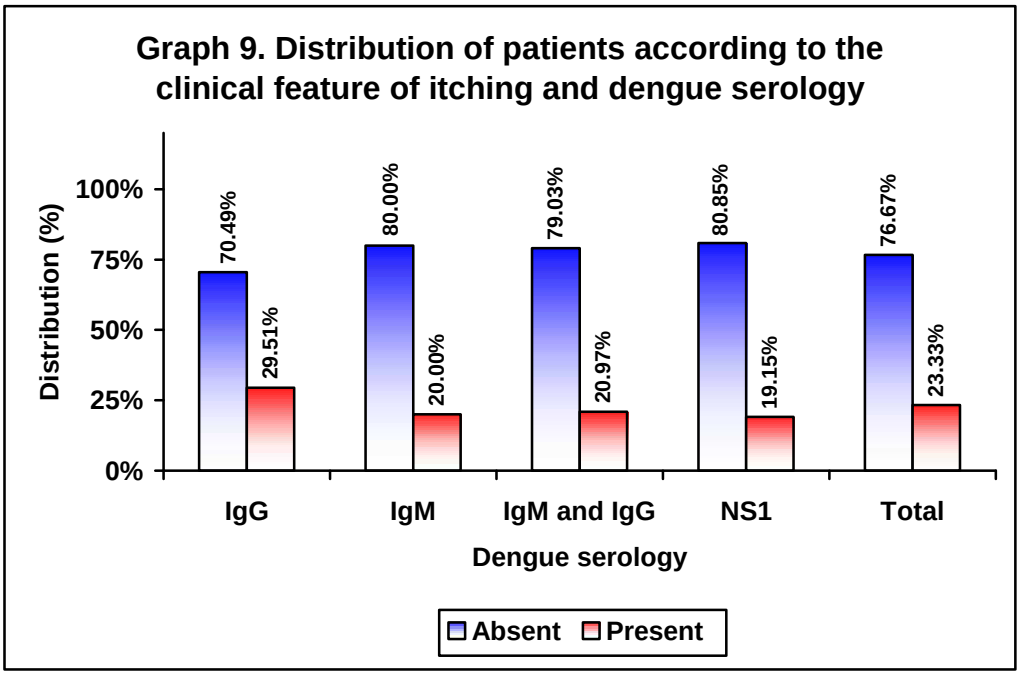


In the present study 113 (62.78%) patients presented with rash. Further, maximum patients with NS1 positive (74.47%), IgM positive (70%) and both IgM and IgG positive (66.13%) had rash compared to IgG positive (49.18%). This difference was statistically significant (p=0.045).

Table 10. Distribution of patients according to the clinical feature of itching and dengue serology

Itching	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Present	18	29.51	2	20.00	13	20.97	9	19.15	42	23.33
Absent	43	70.49	8	80.00	49	79.03	38	80.85	138	76.67
Total	**61**	**100.00**	**10**	**100.00**	**62**	**100.00**	**47**	**100.00**	**180**	**100.00**

p = 0.596

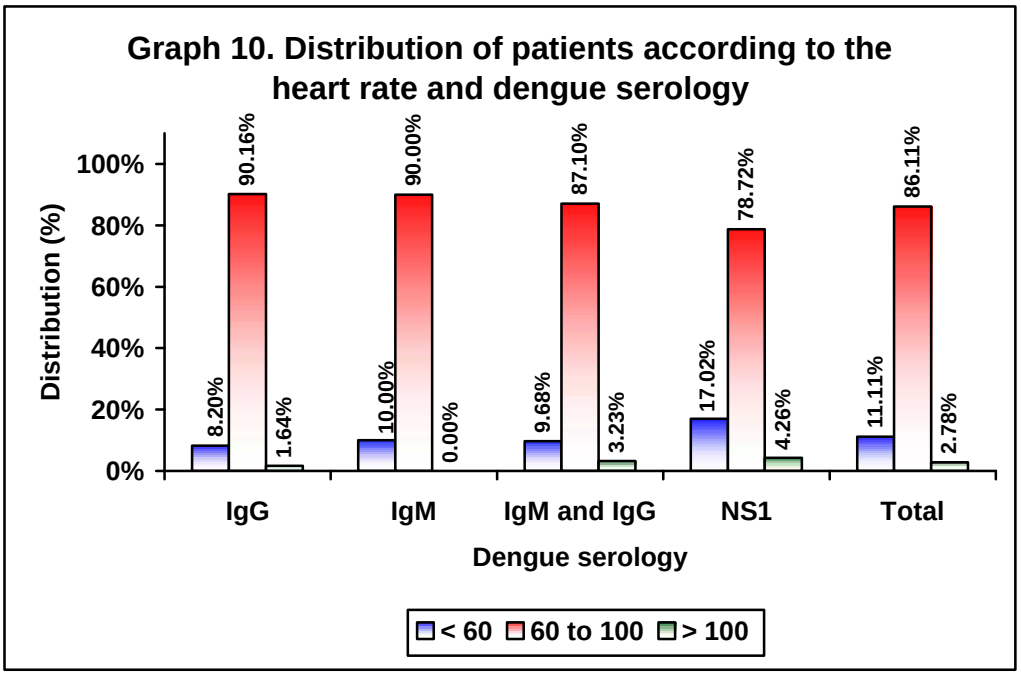


In the present study clinical presentation of Itching was present in 29.51% of the patients with IgG positive, 20.97% with both IgM and IgG positive, 20% with IgM positive and 19.15% with NS1 positive. However this difference was statistically not significant (p=0.596).

Table 11. Distribution of patients according to the heart rate and dengue serology

Heart rate (/Minute)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
< 60	5	8.20	1	10.00	6	9.68	8	17.02	20	11.11
60 to 100	55	90.16	9	90.00	54	87.10	37	78.72	155	86.11
> 100	1	1.64	0	0.00	2	3.23	2	4.26	5	2.78
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.741

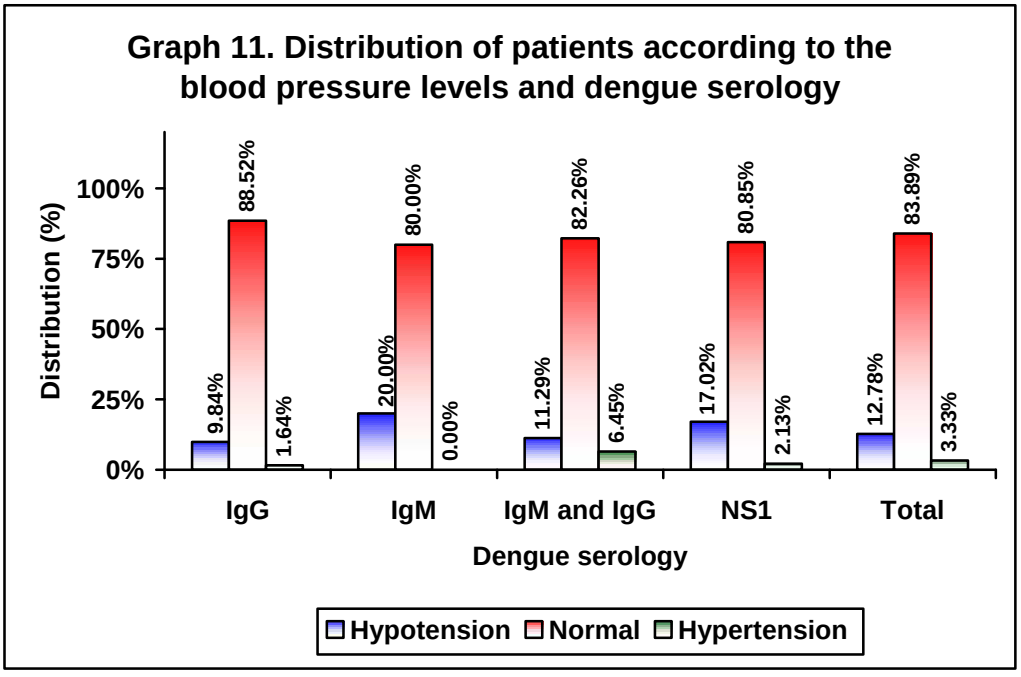


In this study heart rate of < 60 /minute was noted in 17.02% patients with NS1 positive while in patients with IgM positive, both IgM and IgG positive, and IgG positive, heart rate was < 60 / minute in 10%, 9.68% and 8.2% of the patients respectively but the difference was statistically not significant (p=0.741)

Table 12. Distribution of patients according to the blood pressure levels and dengue serology

Blood pressure	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Hypotension	6	9.84	2	20.00	7	11.29	8	17.02	23	12.78
Normal	54	88.52	8	80.00	51	82.26	38	80.85	151	83.89
Hypertension	1	1.64	0	0.00	4	6.45	1	2.13	6	3.33
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.619

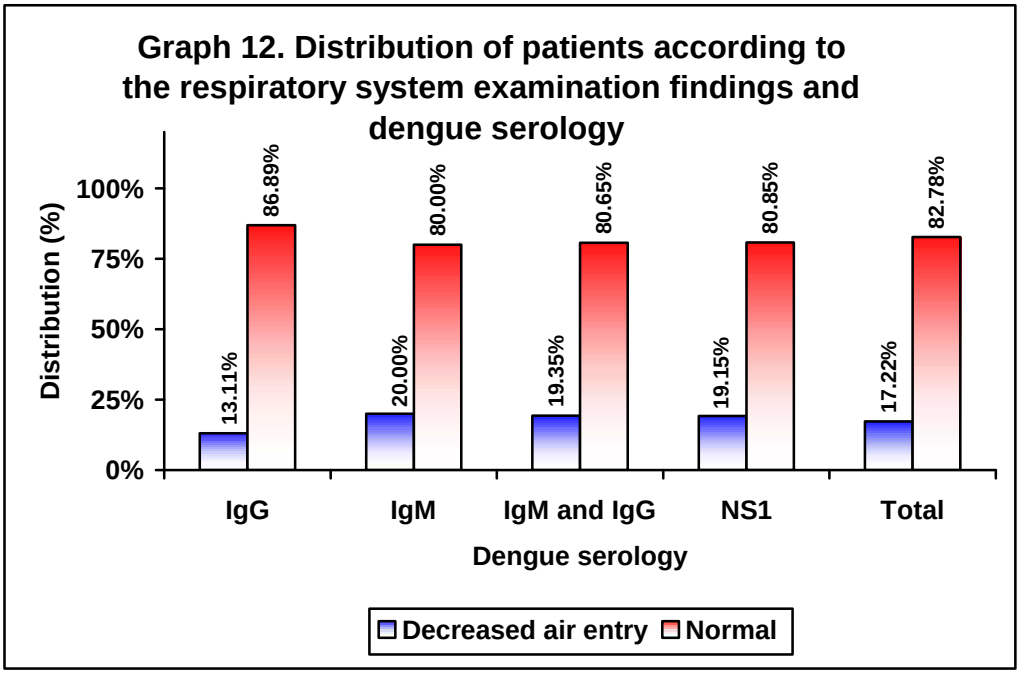


In the present study hypotension was present in maximum patients with IgM positive (20%) followed by NS1 positive (17.02%),both IgM and IgG positive (11.29%) and IgG positive (9.84%) but the difference was statistically not significant (p=0.619)

Table 13. Distribution of patients according to the respiratory system examination findings and dengue serology

Findings	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Decreased air entry	8	13.11	2	20.00	12	19.35	9	19.15	31	17.22
Normal	53	86.89	8	80.00	50	80.65	38	80.85	149	82.78
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.741

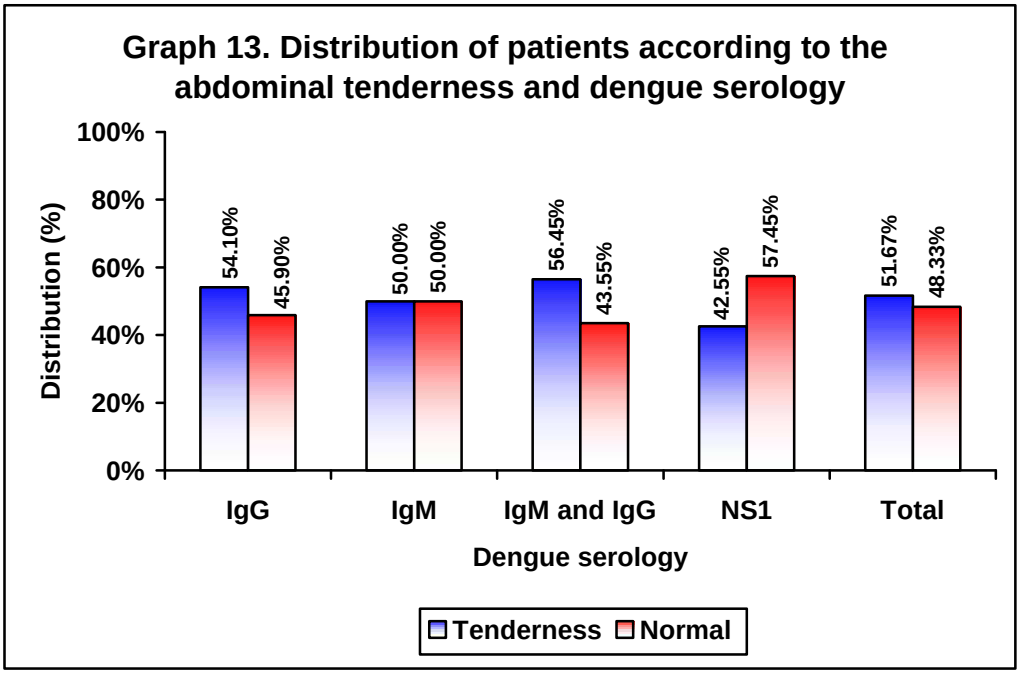


In the present study 20%, 19.35% and 19.15% of the patients had decreased air entry who were IgM positive, both IgM and IgG positive, and NS1 positive respectively. In those with IgG positive 13.11% of the patients had similar findings but this difference was statistically not significant (p=0.741).

Table 14. Distribution of patients according to the abdominal tenderness and dengue serology

Findings	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Tenderness	33	54.10	5	50.00	35	56.45	20	42.55	93	51.67
Normal	28	45.90	5	50.00	27	43.55	27	57.45	87	48.33
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

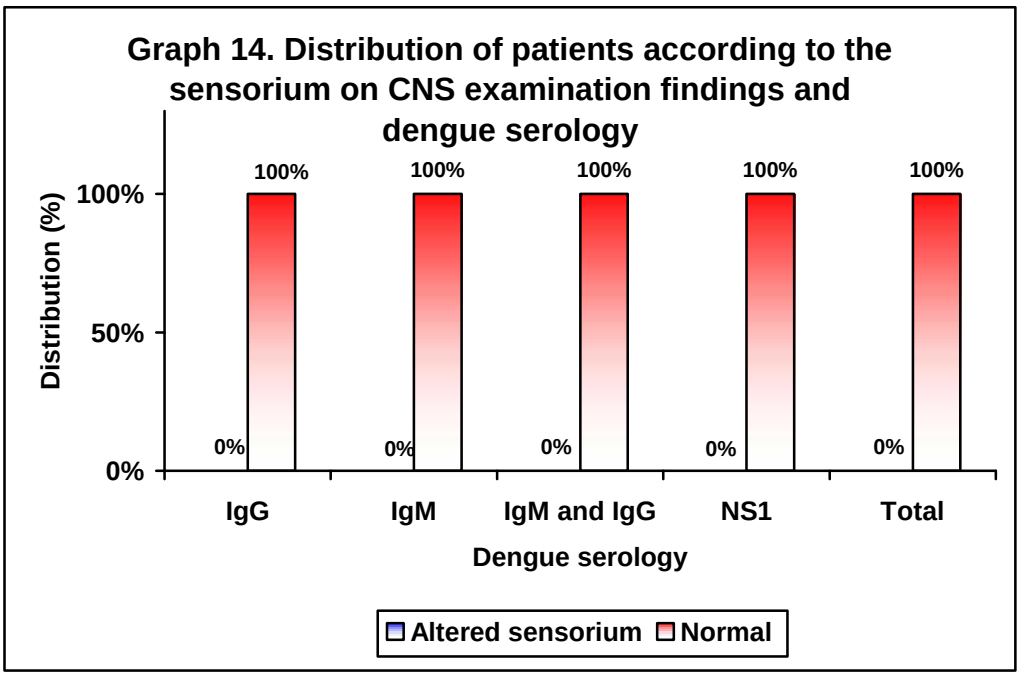
p = 0.513



In this study abdominal tenderness was observed in 51.67% of the patients. However the presence of tenderness was comparable in all the dengue serologies (p=0.513).

Table 15. Distribution of patients according to the sensorium on CNS examination findings and dengue serology

Findings	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Altered sensorium	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Normal	61	100.00	10	100.00	62	100.00	47	100.00	180	100.00
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

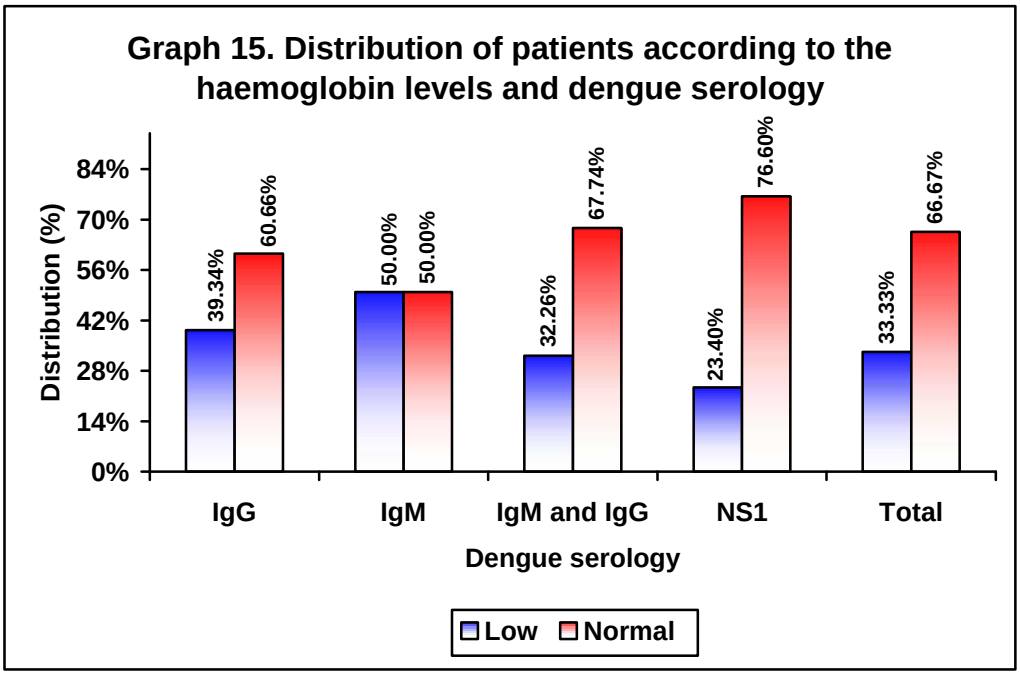


In the present study none of the patient presented with altered sensorium.

Table 16. Distribution of patients according to the haemoglobin levels and dengue serology

Haemoglobin levels (gm%)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Low	24	39.34	5	50.00	20	32.26	11	23.40	60	33.33
Normal	37	60.66	5	50.00	42	67.74	36	76.60	120	66.67
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p =0.215

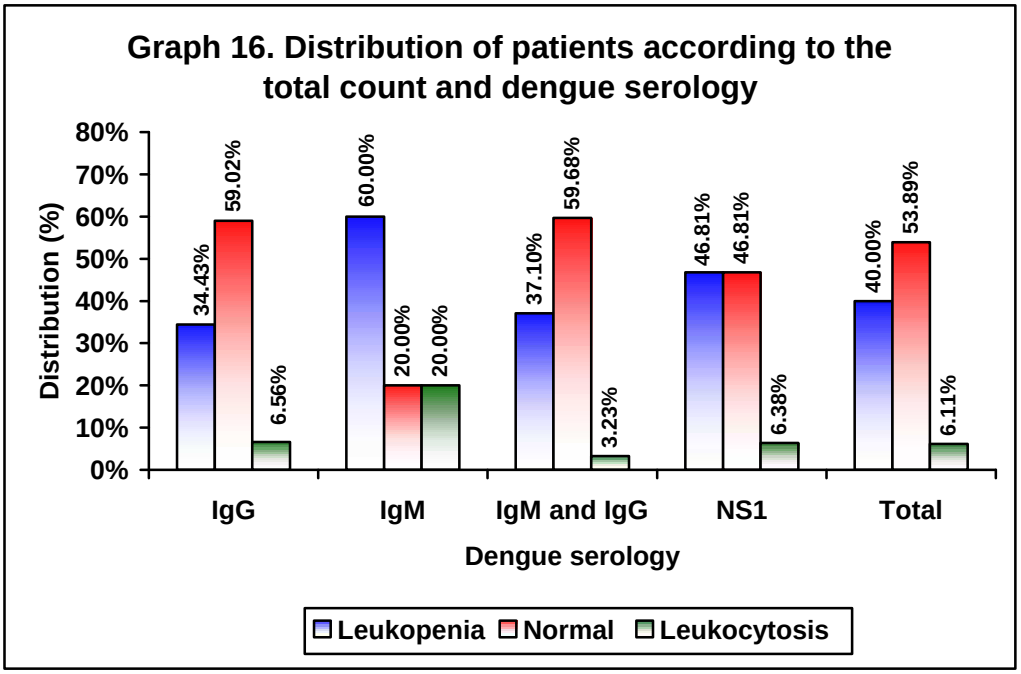


In this study haemoglobin levels were low among 50% of the patients with IgM positive while 23.4% of the patients with NS1 positive, 32.26% with both IgM and IgG positive, and 39.34% of the patients with IgG positive had low haemoglobin levels. This difference was statistically not significant (p=0.215).

Table 17. Distribution of patients according to the total count and dengue serology

Total count (/Cumm)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Leukopenia	21	34.43	6	60.00	23	37.10	22	46.81	72	40.00
Normal	36	59.02	2	20.00	37	59.68	22	46.81	97	53.89
Leukocytosis	4	6.56	2	20.00	2	3.23	3	6.38	11	6.11
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.129

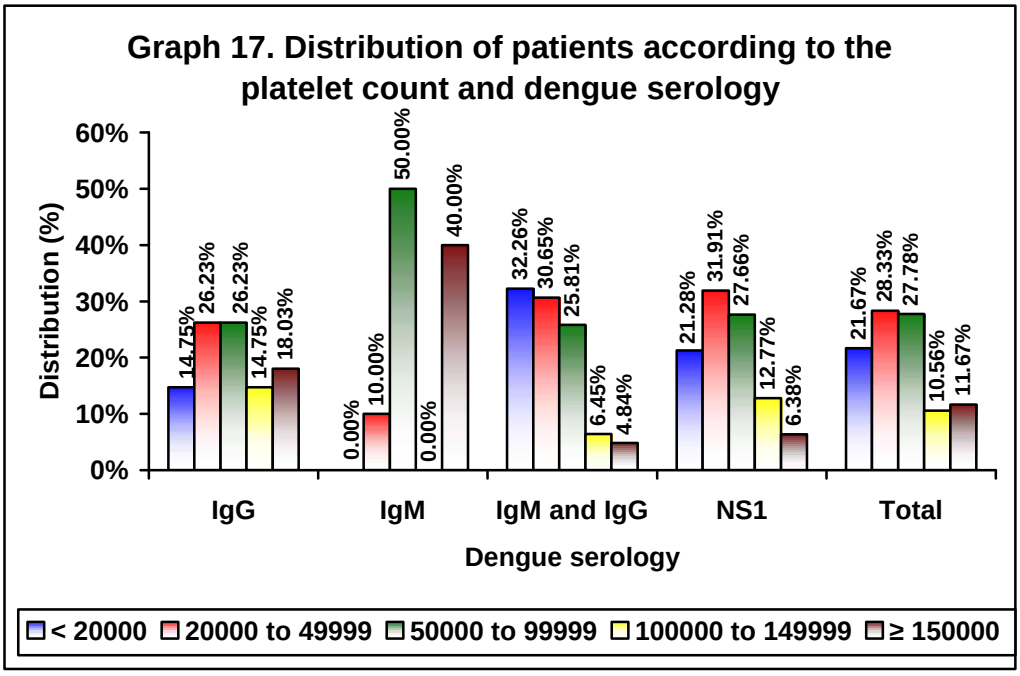


In the present study leucopenia was in 72 (40%). Further IgM positive had 60% patients with leukopenia followed by NS1 positive (46.81%), both IgM & IgG positive (37.10%) and IgG positive (34.43%). However this difference was statistically not significant (p=0.129).

Table 18. Distribution of patients according to the platelet count and dengue serology

Platelet count (/Cumm)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
< 20000	9	14.75	0	0.00	20	32.26	10	21.28	39	21.67
20000 to 49999	16	26.23	1	10.00	19	30.65	15	31.91	51	28.33
50000 to 99999	16	26.23	5	50.00	16	25.81	13	27.66	50	27.78
100000 to 149999	9	14.75	0	0.00	4	6.45	6	12.77	19	10.56
≥ 150000	11	18.03	4	40.00	3	4.84	3	6.38	21	11.67
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.010



In this study 32.26% of the patients with both IgM and IgG positive had platelet count of <20000/cumm compared to 21.18% of the patients with NS1 positive and 14.75% with IgG positive and no patients of IgM positive had platelet count < 20000/cumm. Further, platelet count of 20000 to 49999/cumm was in 51 patients (28.33%). Among them significantly higher number of patients were NS1 positive (31.91%), IgM and IgG positive (30.65%) and IgG positive (26.23%) compared to only 10% in IgM positive (p=0.010).

Table 19. Association of rash with platelet count

Platelet count (/Cumm)	Rash			
	Present		Absent	
	No	%	No	%
< 20000	25	64.10	14	35.90
20000 to 49999	7	36.84	12	63.16
50000 to 99999	5	23.81	16	76.19
100000 to 149999	28	54.90	23	45.10
≥ 150000	19	38.00	31	62.00
Total	**84**	**46.67**	**96**	**53.33**

p=0.012

In the present study significantly higher number of patients with platelet count of <20000 /cumm had rash (64.10%; p=0.012).

Table 20. Association of Melaena with platelet count

Platelet count (/Cumm)	Melaena			
	Present		Absent	
	No	%	No	%
< 20000	11	28.21	28	71.79
20000 to 49999	7	36.84	12	63.16
50000 to 99999	23	60.53	15	39.47
100000 to 149999	6	17.65	28	82.35
≥ 150000	18	36.00	32	64.00
Total	**65**	**36.11**	**115**	**63.89**

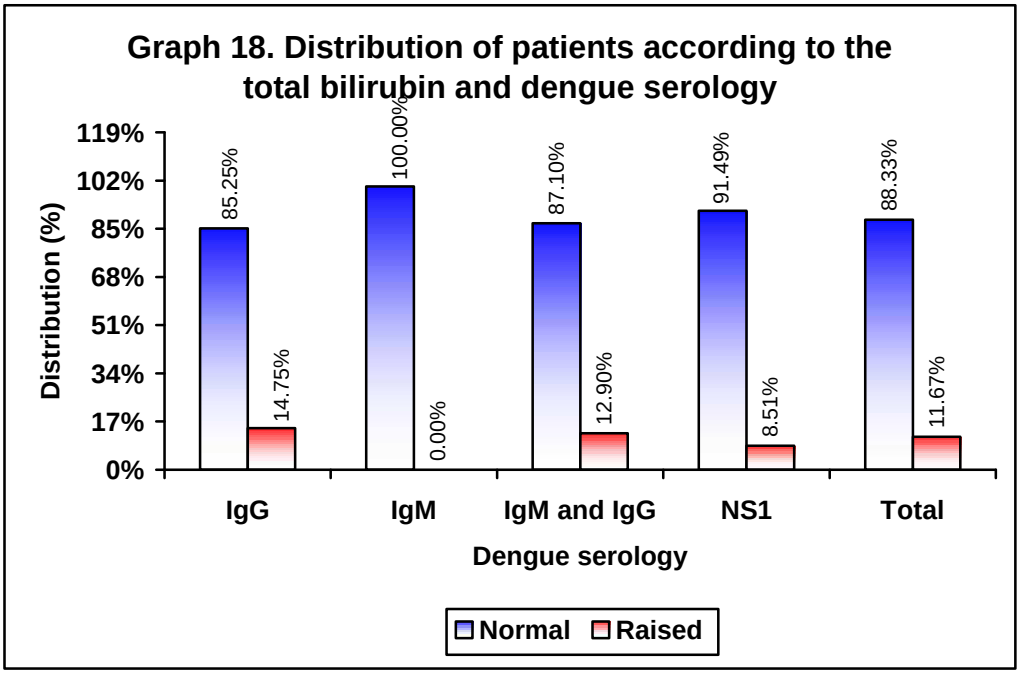
p=0.516

In the present study no association was found between platelet count and melaena (p=0.516).

Table 21. Distribution of patients according to the total bilirubin and dengue serology

Total bilirubin (mg/dL)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	52	85.25	10	100.00	54	87.10	43	91.49	159	88.33
Raised	9	14.75	0	0.00	8	12.90	4	8.51	21	11.67
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.604

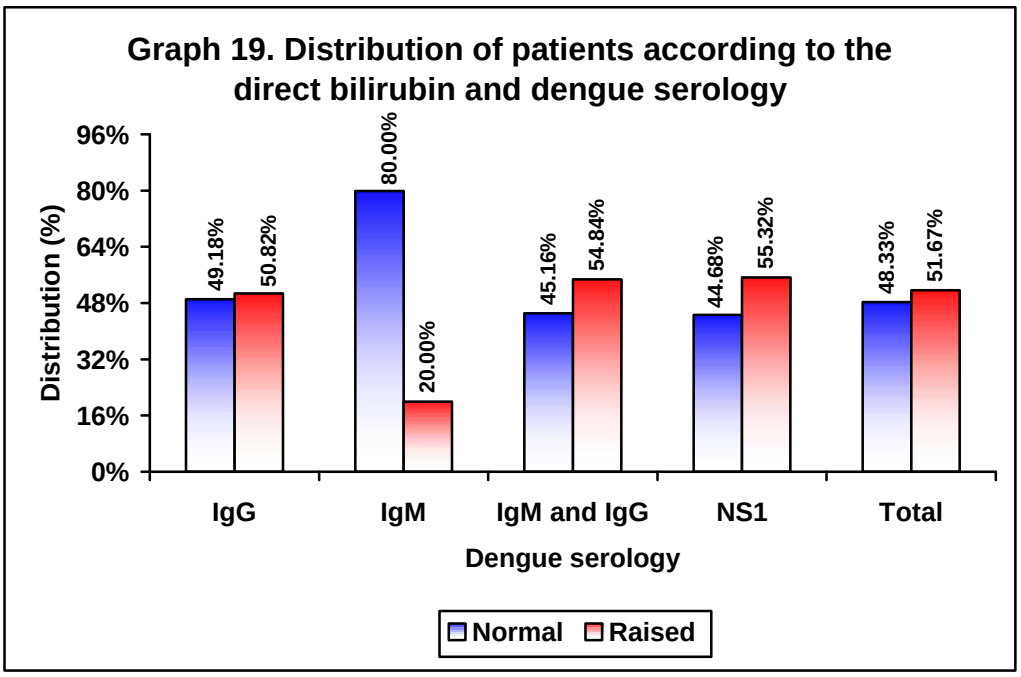


In the present study 8.51% of the patients with NS1 positive had raised bilirubin levels compared to 12.9% with both IgM and IgG positive, and 14.75% with IgG positive. However in patients with IgM positive, none of the patient were found to have raised total bilirubin levels (p=0.604).

Table 22. Distribution of patients according to the direct bilirubin and dengue serology

Direct bilirubin (mg/dL)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	30	49.18	8	80.00	28	45.16	21	44.68	87	48.33
Raised	31	50.82	2	20.00	34	54.84	26	55.32	93	51.67
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.217

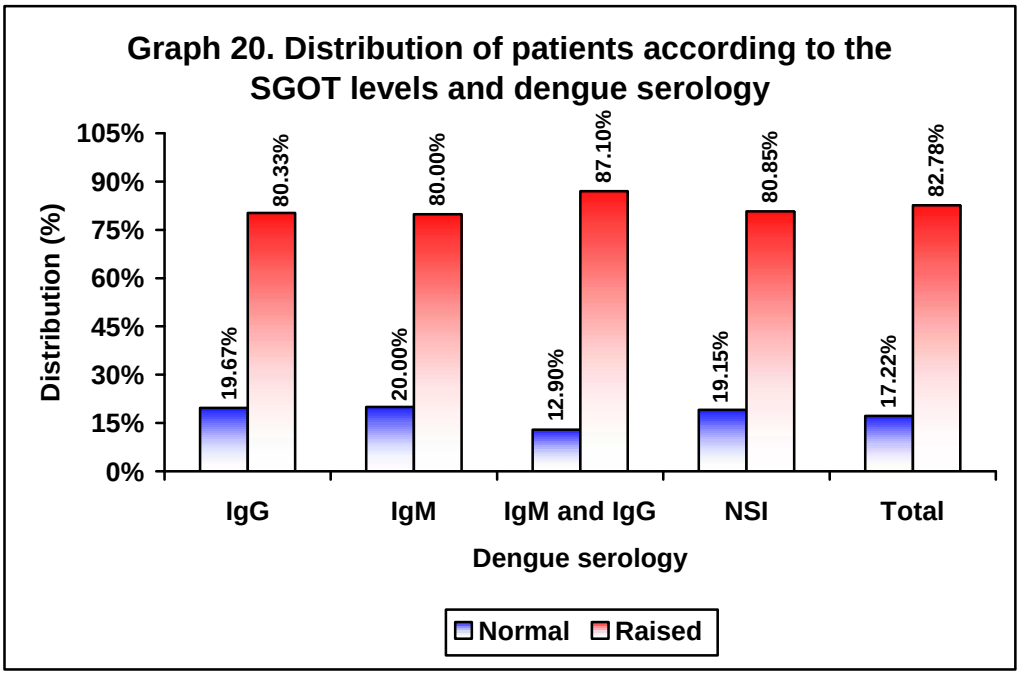


In this study maximum patients with NS1 positive had raised direct bilirubin (55.32%) followed by both IgM and IgG positive (54.84%), IgG positive (50.82%) and IgM positive (20%). However this difference was statistically not significant (p=0.217).

Table 23. Distribution of patients according to the SGOT levels and dengue serology

SGOT levels (IU/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	12	19.67	2	20.00	8	12.90	9	19.15	31	17.22
Raised	49	80.33	8	80.00	54	87.10	38	80.85	149	82.78
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.712

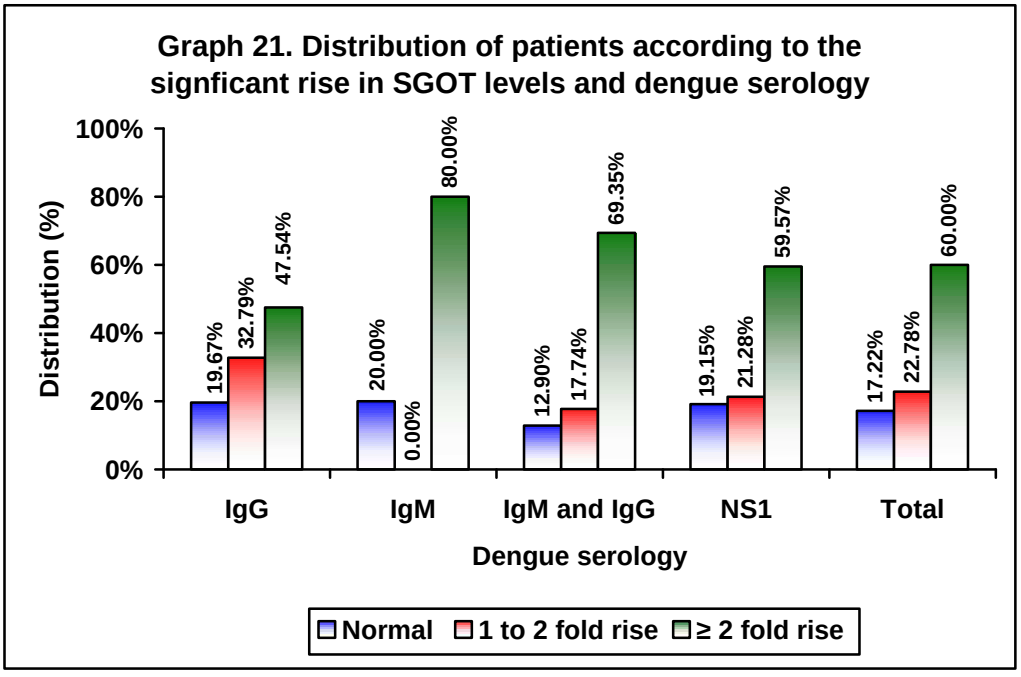


In this study SGOT levels were raised in 87.10% of the patients with IgM and IgG positive compared to 80.85% of the patients with NS1 positive, 80.33% with IgG positive, and 80% of the patients with IgM positive. However, this difference was statistically not significant (p=0.712).

Table 24. Distribution of patients according to the significant rise in SGOT levels and dengue serology

SGOT levels (IU/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	12	19.67	2	20.00	8	12.90	9	19.15	31	17.22
1 to 2 fold rise	20	32.79	0	0.00	11	17.74	10	21.28	41	22.78
≥ 2 fold rise	29	47.54	8	80.00	43	69.35	28	59.57	108	60.00
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.177

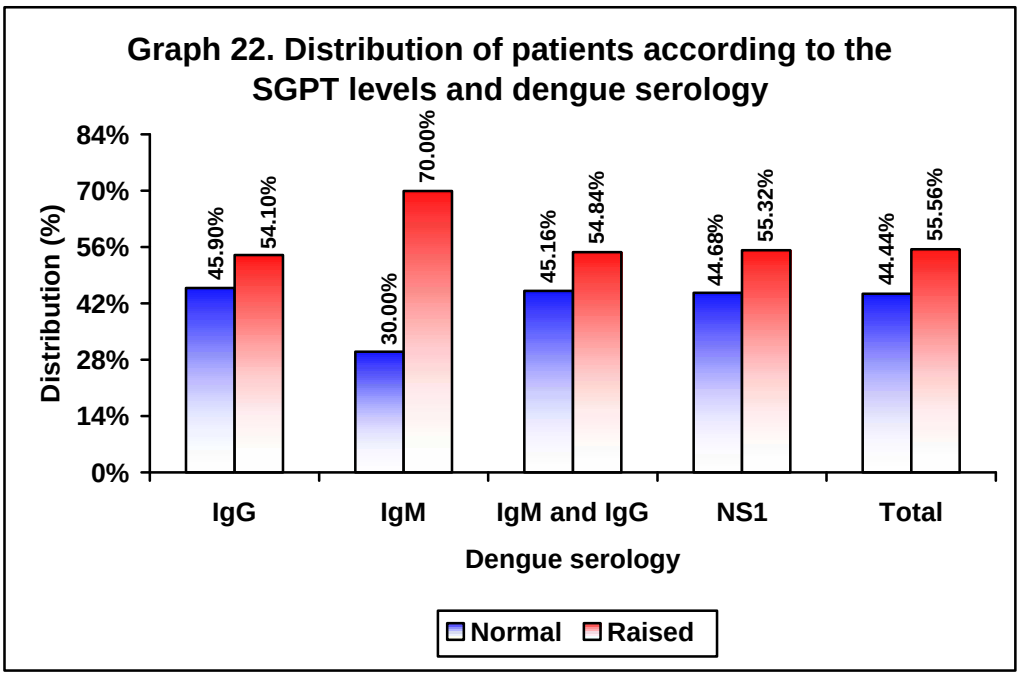


In this study maximum patients had ≥ 2 fold rise in SGOT (60%). The ≥ 2 fold rise in SGOT was present in maximum patients with IgM positive (80%) followed by both IgM and IgG positive (69.35%), NS1 positive (59.57%) and IgG positive (47.54%) the difference was statistically not significant (p=0.177).

Table 25. Distribution of patients according to the SGPT levels and dengue serology

SGPT levels (IU/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	28	45.90	3	30.00	28	45.16	21	44.68	80	44.44
Raised	33	54.10	7	70.00	34	54.84	26	55.32	100	55.56
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.855

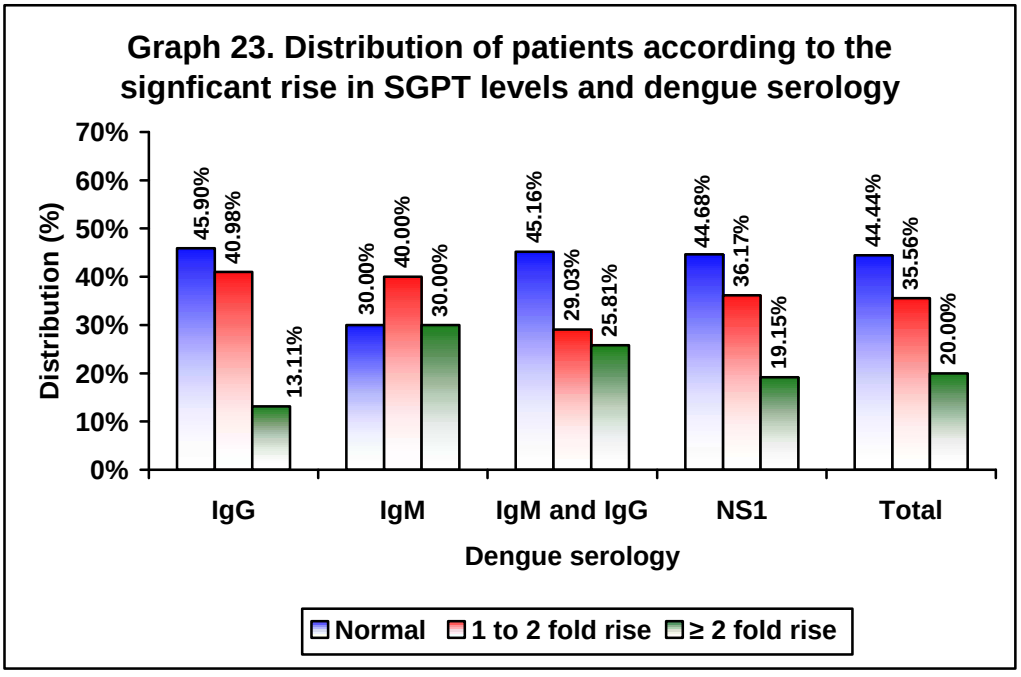


In this study SGPT levels were raised in 70% of the IgM positive patients compared to 55.32% of the NS1 positive , 54.10% with IgG positive, and 54.84% of the patients with both IgM and IgG positive dengue serology (p=0.855).

Table 26. Distribution of patients according to the signficant rise in SGPT levels and dengue serology

SGPT levels (IU/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	28	45.90	3	30.00	28	45.16	21	44.68	80	44.44
1 to 2 fold rise	25	40.98	4	40.00	18	29.03	17	36.17	64	35.56
≥ 2 fold rise	8	13.11	3	30.00	16	25.81	9	19.15	36	20.00
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.533

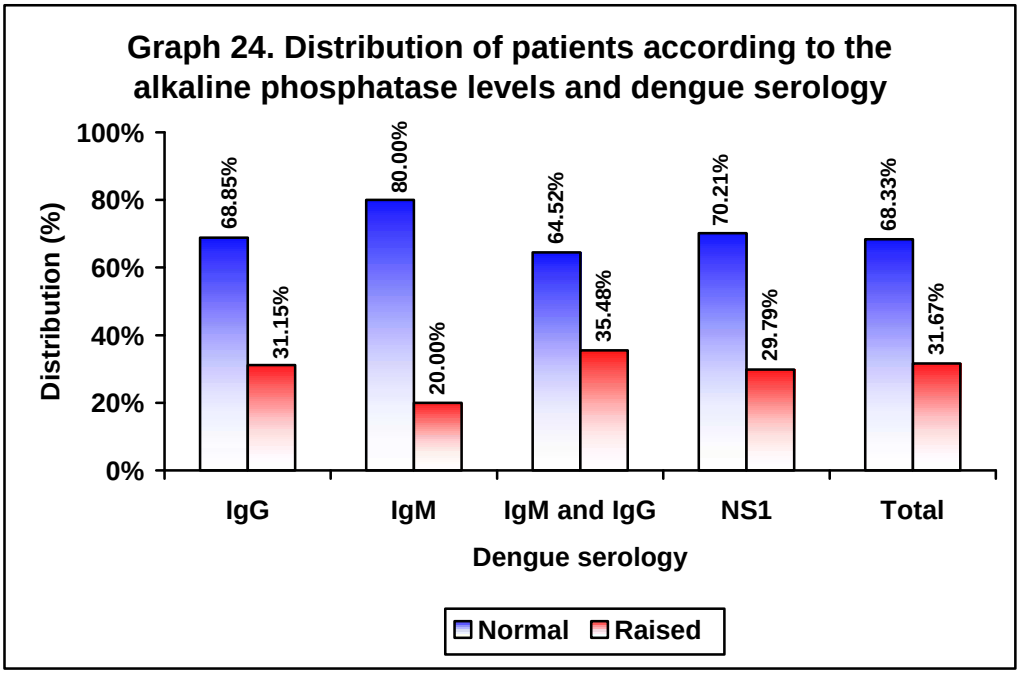


In this study maximum patients had 1 to 2 fold rise in SGPT (35.56%). And this was comparable in patients with different dengue serological tests (p=0.533).

Table 27. Distribution of patients according to the alkaline phosphatase levels and dengue serology

Alkaline phosphatase levels	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	42	68.85	8	80.00	40	64.52	33	70.21	123	68.33
Raised	19	31.15	2	20.00	22	35.48	14	29.79	57	31.67
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.806

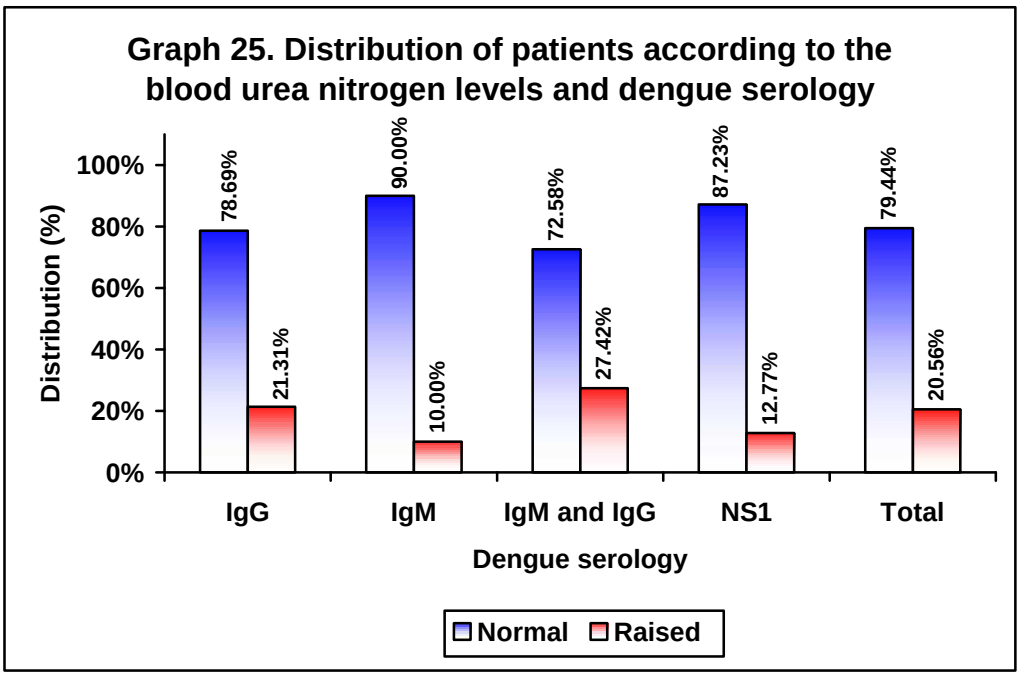


In the present study 35.48% of the patients with both IgM and IgG positive had raised alkaline phosphatase levels compared to 31.15% with IgG positive, 29.79% with NS1 positive and 20% with IgM positive. However this difference was statistically not significant (p=0.806).

Table 28. Distribution of patients according to the blood urea nitrogen levels and dengue serology

Blood urea nitrogen (mg/dL)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	48	78.69	9	90.00	45	72.58	41	87.23	143	79.44
Raised	13	21.31	1	10.00	17	27.42	6	12.77	37	20.56
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.262

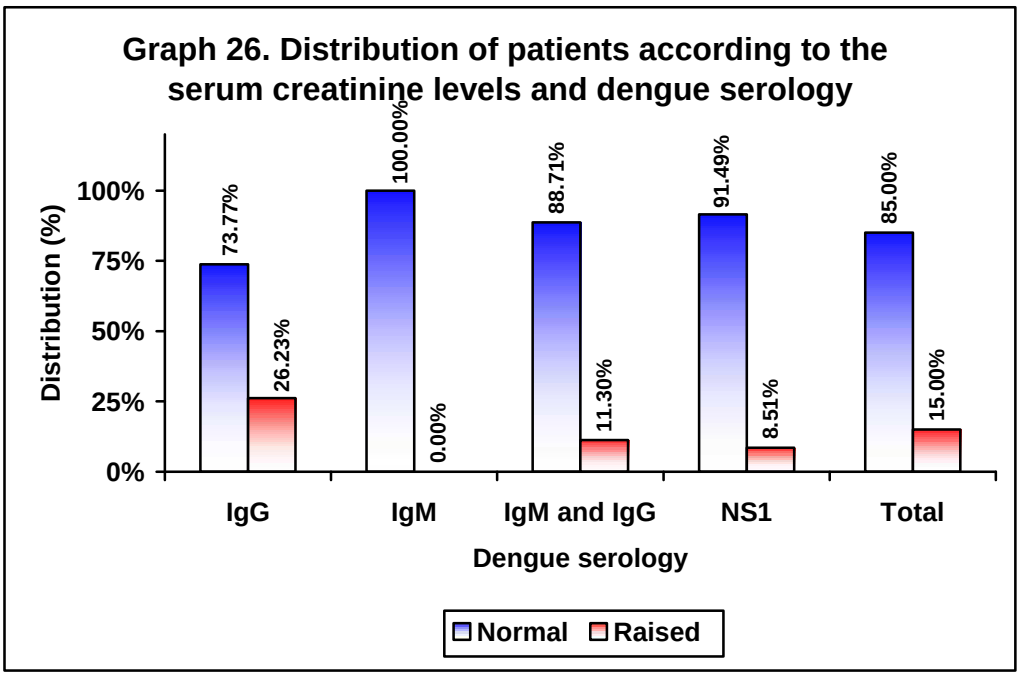


In this study 27.42% of the patients with both IgM and IgG positive patients had raised blood urea nitrogen levels compared to 21.31% with IgG patients, 12.77% with NS1 positive and 10% with IgM positive but the difference was statistically not significant (p=0.262).

Table 29. Distribution of patients according to the serum creatinine levels and dengue serology

Serum creatinine (mg/dL)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	45	73.77	10	100.00	55	88.71	43	91.49	153	85.00
Raised	16	26.23	0	0.00	7	11.29	4	8.51	27	15.00
Total	**61**	**100**	**10**	**100**	**62**	**100.00**	**47**	**100**	**180**	**100**

p = 0.029

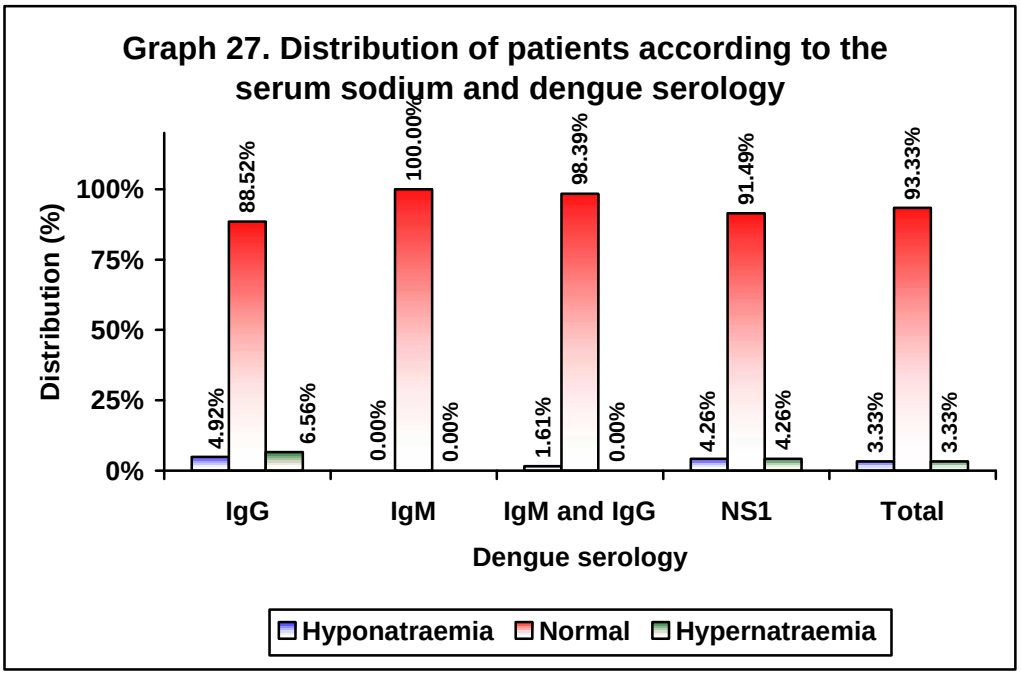


In this study serum creatinine levels were raised in 26.23% of the patients with IgG positive compared to 8.51% of the patients with NS1 positive and 11.29% with both IgM and IgG positive, while none of the patient with IgM positive had raised serum creatinine levels (p=0.029).

Table 30. Distribution of patients according to the serum sodium and dengue serology

Serum sodium (meq/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Hyponatremia	3	4.92	0	0.00	1	1.61	2	4.26	6	3.33
Normal	54	88.52	10	100.00	61	98.39	43	91.49	168	93.33
Hypernatremia	4	6.56	0	0.00	0	0.00	2	4.26	6	3.33
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.384

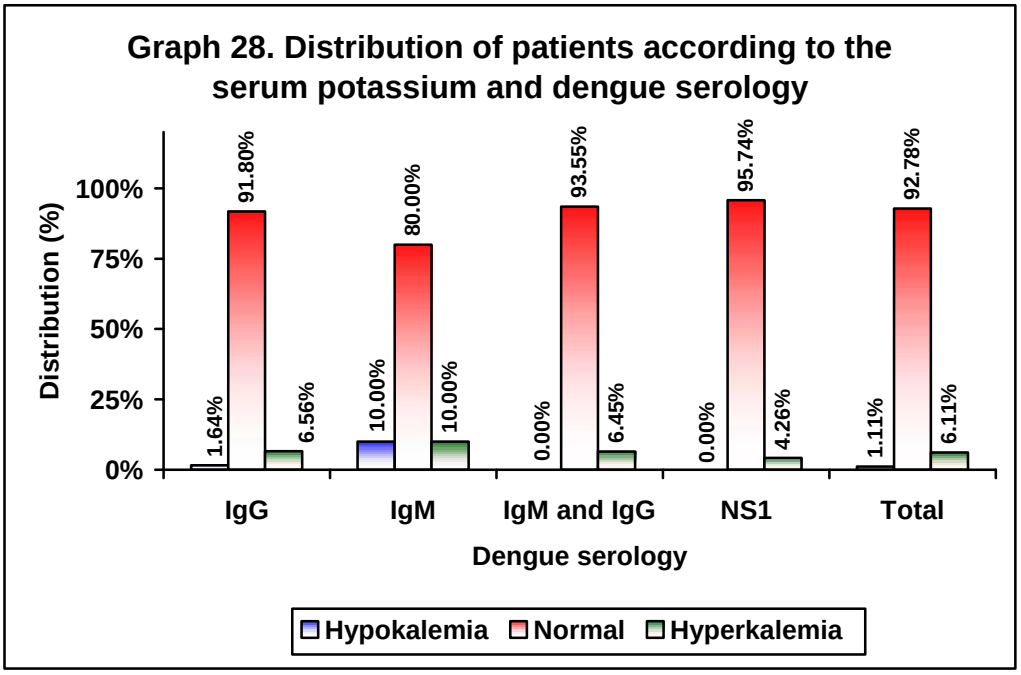


In this study hyponatremia was present in 4.92% of the patients with IgG positive compared to 4.26% of the patients with NS1 positive and 1.61% of the patients with both IgM and IgG positive. However, none of the patients with IgM positive was found to have hyponatremia (p=0.384).

Table 31. Distribution of patients according to the serum potassium and dengue serology

Serum potassium (meq/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Hypokalemia	1	1.64	1	10.00	0	0.00	0	0.00	2	1.11
Normal	56	91.80	8	80.00	58	93.55	45	95.74	167	92.78
Hyperkalemia	4	6.56	1	10.00	4	6.45	2	4.26	11	6.11
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.286

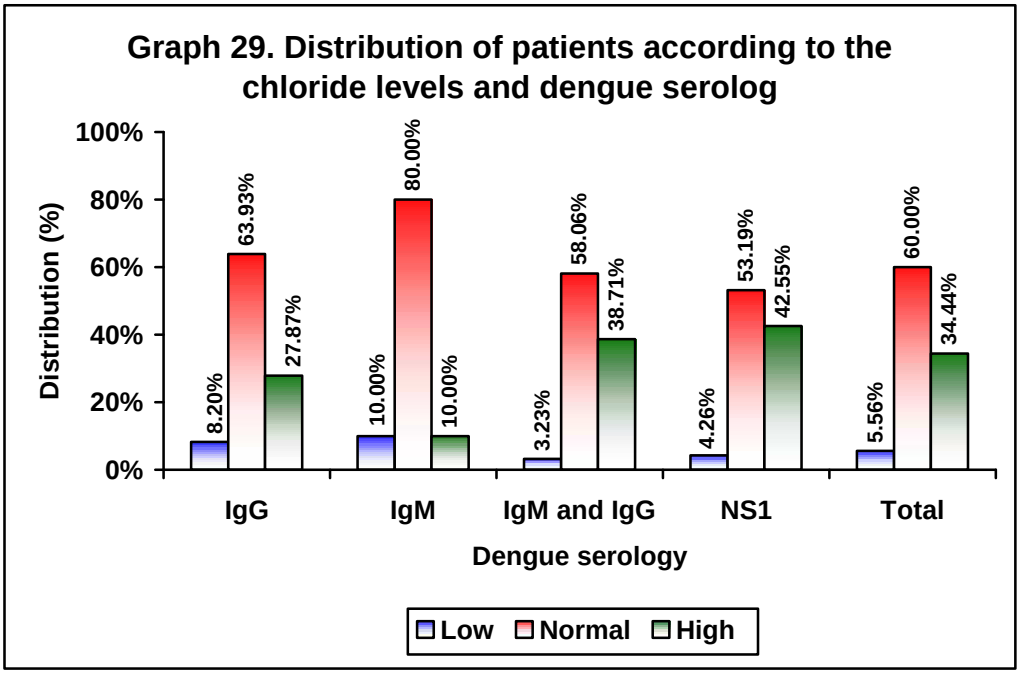


In the present study hypokalemia was present in 10% of the patients with IgM positive compared to 1.64% of the patients with IgG positive while none of the patient with both IgM and IgG positive, and NS1 positive had hypokalemia, whereas Hyperkalemia was seen in 6.11% of the patients, of them 10% of patients were IgM positive compared to IgG positive (6.56%), both IgM and IgG positive (6.45%) and NS1 positive (4.26%) only (p=0.286).

Table 32. Distribution of patients according to the chloride levels and dengue serology

Chloride (meq/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Low	5	8.20	1	10.00	2	3.23	2	4.26	10	5.56
Normal	39	63.93	8	80.00	36	58.06	25	53.19	108	60.00
High	17	27.87	1	10.00	24	38.71	20	42.55	62	34.44
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.273

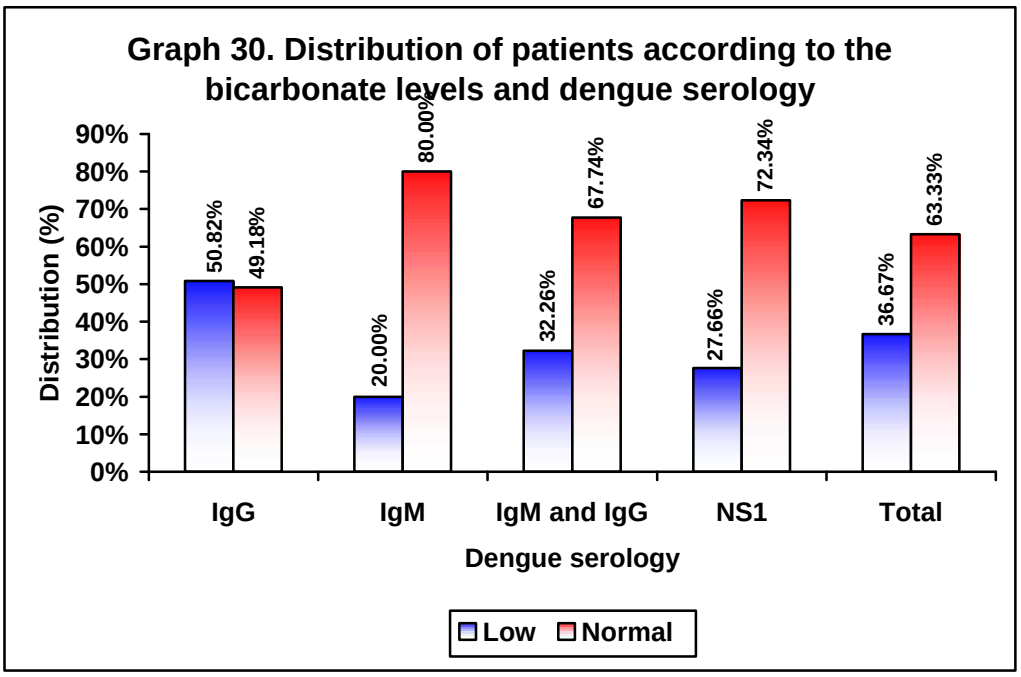


In this study chloride levels were high in 42.55% of the patients with NS1 positive and 38.71% of the patients with both IgM and IgG positive. 27.87% patients with IgG positive and 10% of the patients with IgM positive had higher chloride levels (p=0.273).

Table 33. Distribution of patients according to the bicarbonate levels and dengue serology

Bicarbonate (mmol/L)	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Low	31	50.82	2	20.00	20	32.26	13	27.66	66	36.67
Normal	30	49.18	8	80.00	42	67.74	34	72.34	114	63.33
Total	**61**	**100**	**10**	**100**	**62**	**100**	**47**	**100**	**180**	**100**

p = 0.040

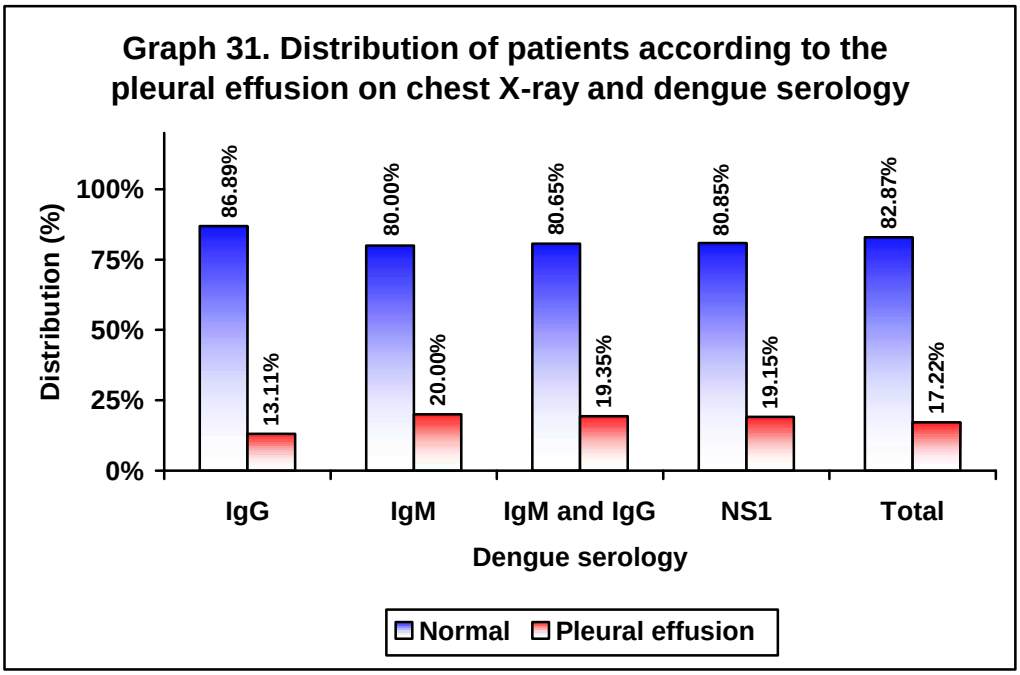


In the present study low bicarnonate levels were in 66 patients (36.67%). Among them there were significantly higher number of patients with IgG positive (50.82%) compared to both IgM and IgG positive (32.26%), NS1 positive (27.66%) and IgM positive (20%) (p=0.040).

Table 34. Distribution of patients according to the pleural effusion on chest X-ray and dengue serology

Chest X-ray findings	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	53	86.89	8	80.00	50	80.65	38	80.85	149	82.78
Pleural effusion	8	13.11	2	20.00	12	19.35	9	19.15	31	17.22
Total	**61**	**100.00**	**10**	**100.00**	**62**	**100.00**	**47**	**100.00**	**180**	**100.00**

p = 0.741

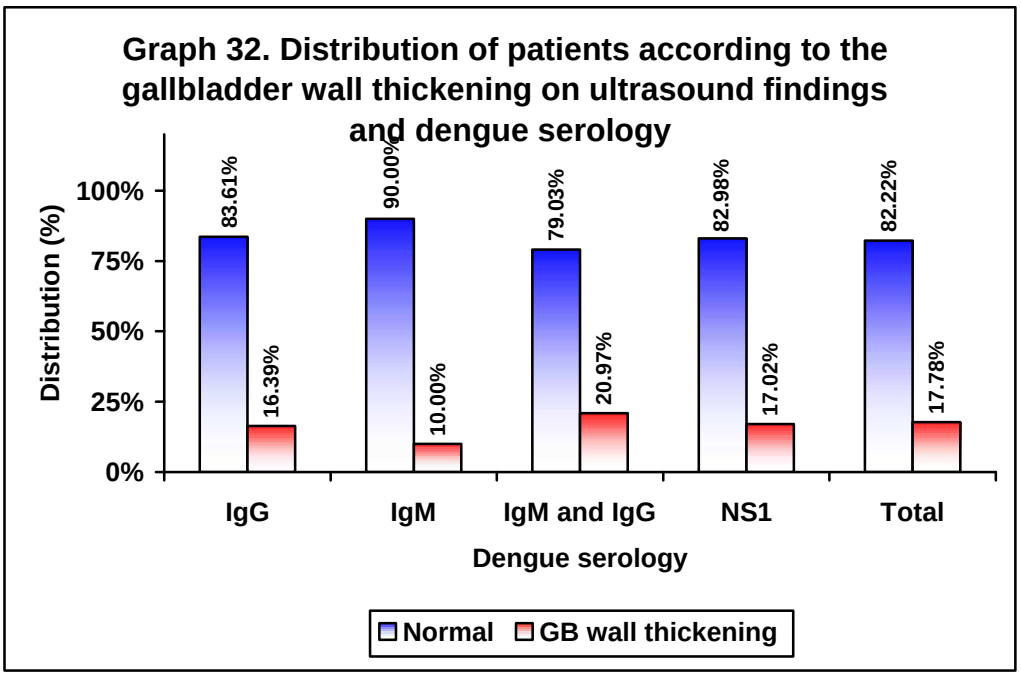


In the present study chest X-ray revealed pleural effusion in 17.22% of the patients. However the presence of pleural effusion was comparable in all the dengue serologies that is, 20% of the patients with IgM positive, 19.35% with both IgM and IgG positive, 19.15% with NS1 positive and 13.11% of the patients with IgG positive. (p=0.741).

Table 35. Distribution of patients according to the Gall bladder wall thickening on ultrasound findings and dengue serology

Ultrasound findings	Dengue serology								Total	
	IgG		IgM		IgM & IgG		NS1			
	No	%	No	%	No	%	No	%	No	%
Normal	51	83.61	9	90.00	49	79.03	39	82.98	148	82.22
GB wall thickening	10	16.39	1	10.00	13	20.97	8	17.02	32	17.78
Total	**61**	**100.00**	**10**	**100.00**	**62**	**100.00**	**47**	**100.00**	**180**	**100.00**

p = 0.874



In the present study maximum patients with thickened gall bladder wall on ultrasound findings were noted in IgM and IgG positive (20.97%) followed by NS1 positive (17.02%), IgG positive (16.39%) and IgM positive (10%). However this difference was statistically not significant (p=0.874).

Table. 36. Clinical and biochemical profile of the patients

Variables	Mean (n=192)		Median	Range	
	Mean	SD		Minimum	Maximum
Age (Years)	32.96	12.79	30.00	18.00	74.00
Heart rate (/Minute)	78.37	13.58	80.00	50.00	142.00
Systolic BP (mm Hg)	119.62	15.19	122.00	90.00	160.00
Diastolic BP (mm Hg)	77.27	8.52	80.00	60.00	100.00
Respiratory rate (/Minute)	16.95	2.26	16.00	13.00	22.00
Haemoglobin (gm%)	13.62	2.11	13.80	3.80	18.30
Total count (/Cumm)	5284.78	2796.99	4800.00	1200.00	13700.00
Platelet count (/Cumm)	70518.89	70759.04	50000.00	5000.00	395000.00
Total bilirubin (mg/dL)	1.05	1.12	0.68	0.20	9.87
Direct bilirubin (mg/dL)	0.54	0.98	0.22	0.00	8.33
AST /SGOT (IU/L)	156.04	392.39	88.00	12.00	5115.00
ALT /SGPT (IU/L)	103.66	169.88	69.50	14.00	2177.00
Alkaline phosphate (mg/dL)	136.2278	79.6857	110	47	489
Blood Urea nitrogen (mg/dL)	28.35	20.66	24.00	10.00	184.00
Creatinine (mg/dL)	1.04	0.41	0.95	0.40	4.24
Sodium (meq/L)	138.31	4.74	138.00	126.00	164.00
Potasium (meq/L)	4.27	0.50	4.26	2.98	5.84
Chloride (meq/L)	103.62	4.53	103.50	88.00	115.00
Bicarbonate (mmol/L)	25.11	3.57	25.50	14.90	33.00

The clinical, haematological, liver, renal and electrolyte profile of the patients is as depicted in Table

Table 37. Comparison of clinical, biochemical, liver and renal profile of the patients

Parameters	Dengue serology								p value
	IgG		IgM		IgM and IgG		NS1		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (Years)	35.20	13.53	26.70	9.26	33.18	12.17	31.28	12.97	0.166
HR (/Minute)	79.61	13.00	72.10	6.44	78.28	14.16	78.38	14.67	0.671
SBP (mm Hg)	120.66	13.09	110.60	12.26	122.92	16.24	116.13	15.90	**0.030**
DBP (mm Hg)	78.00	7.98	72.20	7.57	78.52	9.01	75.91	8.42	0.099
RR (/Minute)	17.05	2.31	16.40	2.50	17.07	2.16	16.81	2.36	0.802
Hb (gm%)	13.16	2.23	13.28	1.94	13.89	2.11	13.89	1.93	0.164
TC (/Cumm x 100)	5.81	2.95	5.14	3.72	5.06	2.50	4.92	2.74	0.875
PC (/Cumm x 10^6)	0.91	0.85	1.16	6.49	5.21	6.27	5.68	4.65	**0.002**
Total bili. (mg/dL)	1.08	0.91	0.64	0.31	1.02	0.95	1.15	1.61	0.601
Direct bili. (mg/dL)	0.54	0.76	0.21	0.25	0.44	0.67	0.75	1.53	0.279
SGOT (IU/L)	103.67	90.73	152.60	128.09	232.38	655.25	128.30	112.64	0.334
SGPT (IU/L)	82.84	52.13	113.40	73.02	132.48	276.42	92.11	78.63	0.412
ALP (mg/dL)	132.97	78.29	107.10	52.54	139.80	76.49	142.49	90.97	0.518
BUN (mg/dL)	31.96	29.74	24.78	8.41	28.44	15.84	24.34	11.40	0.225
Creatinine (mg/dL)	1.17	0.54	0.85	0.21	0.96	0.35	0.99	0.28	0.186
Sodium (meq/L)	138.02	5.83	138.00	4.06	138.02	3.81	139.06	4.44	0.655
Potasium (meq/L)	4.16	0.54	4.20	0.71	4.30	0.48	4.36	0.40	0.210
Chloride (meq/L)	102.53	4.77	102.20	4.16	103.97	3.88	104.83	4.86	**0.040**
Bicarb. (mmol/L)	23.72	3.64	26.44	3.34	25.42	3.59	26.24	2.99	**0.001**

Table shows comparison of clinical, haematological, liver, renal and electrolyte profile of the patients in different dengue serology. It was observed that, systolic blood pressure, platelet count, serum chloride and serum bicarbonate levels differed significantly with respect to dengue serology ($p<0.050$).

DISCUSSION

As the initial symptoms of dengue mimic those of malaria, typhoid and leptospirosis which are endemic in the country, availability of a diagnosis at an early stage of infection is of utmost importance for better patient management.

Detection of dengue by virus isolation or molecular methods (RT-PCR) are considered as confirmatory tests with high sensitivity and specificity for the diagnosis of dengue infection. However, the need for necessary infrastructure, technical expertise and high cost of the test, make these methods limited in selected advanced laboratories.

However, to date several studies[36,39,40,42] have reported the clinical profile of dengue fever using either IgM with IgG or NS1. Hence the present study was an attempt to evaluate and correlate the clinical profile and laboratory parameters of dengue fever patients with different serological diagnostic parameters.

The present one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 180 dengue fever patients confirmed through dengue serology with either NS1 antigen or IgM and/or IgG antibody were studied.

Dengue serology

In the present study out of the 180 seropositive cases, nearly one third of the patients had both IgM and IgG positive (62 patients, 34.44%) and IgG positive (61 cases, 33.89%) followed by NS1 positive (47 cases, 26.11%) while

IgM positive in (10 cases, 5.56%). In a study by Tathe SS. et al.,[65] out of 236 serum samples tested, 93 (39.41%) were positive for either one or more of the three serological markers. Of these 93 samples, 60.22% were positive for NS1 antigen with or without antibody and remaining 39.78% were positive for either IgM or IgG or both. Among the 56 NS1 positive samples, 34 (60.71%) were exclusively positive for NS1 antigen, 5 (8.93%) were also positive for IgM antibody and 17 (30.36%) were positive for all the three serological markers.

Badave GK. et al.[66] tested 327 serum samples and found a total of 126 (38.5%) specimens were positive for either one or more of the three serological markers. Of the 126 positive serum samples, 54 (42.9%) specimens were positive for NS1 only, 6 (4.7%) positive for IgM only, while 30 (23.9%) patients had only IgG positive. A combination of more than one serological marker was detected in the remaining 36 samples.

In the present study NS1 antigen test was positive in 47 cases that is, 26.11%. Several studies[65,67-69] have reported a lesser values of 16%,[67] 23.3%,[68] 30%[69] as well as higher value of even 60%[65] positivity exclusively for NS1 antigen for diagnosis of dengue.

Day of presentation to hospital

In this study the mean day of presentation to hospital was early in patients with NS1 positive (3.91 ±1.21 days) and late (8.03 ± 1.18 days) in patients with IgG positive and the overall mean day of presentation was 5.92 ± 2.04 days.

Demographic data

In the present study male preponderance was noted with 72.22% of the males. The male to female ratio was 2.6:1. Maximum males were IgG positive (80.33%) compared to females who were IgM positive (50%) but the difference was statistically not significant (p=0.182) suggesting that all the four tests were equally effective among both the genders despite of male preponderance. Several other studies[8,70] from different geographical areas and India have reported male preponderance. An Indonesian study[70] had documented a Male:Female ratio of 1.32:1 and a Indian Study by Padbidri VS et al[8] documented male:female ratio of 1.26:1. The results of this study were similar to these studies.

In this study the commonest age group was 18 to 30 years comprised of nearly half of the study population (50.56%). The mean age of the study population was 32.96 ± 12.79 years and median age was 30 years with youngest patient with 18 years and oldest being 74 years. These findings were similar to the study from AIIMS by S. Sharma et al.[71] who reported the median age as 26.3 years and also similar to the Mexico study by Joel Navarette[72] that is, 26.9 years. All series indicate that the most commonly affected age group is between 20 to 40 years. The present study also confirms these findings.

In the present study, 70% of the IgM positive patients were aged between 18 to 30 years while in the same age group 61.7% were NS1 positive, 48.39% both IgM and IgG positive, and 40.98% IgG positive. However this difference was statistically not significant suggesting that equal detection rates in all the age groups (p=0.220).

Clinical presentation

In the present study fever was the universal symptom present in 100% of the cases. Similar findings were reported in other Indian studies by Sharma S. et al,[71] from AIIMS and V.S. Padabidri[8] in Mangalore who found fever in all the patients.

In the present study second most common clinical presentation was arthralgia (92.78%) followed by melaena (70.56%), rash (62.78%), retroorbital pain (62.22%) and itching (23.33%).

Several studies[9,33,42,73] have reported different clinical features and complications of dengue fever. However, there is scarcity of data on the assessment of early clinical manifestations in dengue infection. A study from Singapore by Low JGH et al.[56] reported myalgia in 69.2%, retro-orbital pain in 26% and pain abdomen in 11.6% of patients as early clinical symptoms in dengue infection.

Recently, Kumar A et al.[42] in his record-based study conducted in Karnataka to study the clinical manifestations, trend and outcome of all confirmed dengue cases. Of the 466 patients, the most common presentation was fever 462 (99.1%), followed by myalgia 301 (64.6%), vomiting 222 (47.6%), headache 222 (47.6%) and abdominal pain 175 (37.6%). The most common hemorrhagic manifestation was petechiae (67.2%). Of the 66 (14.1%) patients who developed clinical complications, 20 (30.3%) had pleural effusion.

More recently Karoli R et al.[9] in their cross-sectional study at Lucknow on 356 patients with suspected dengue fever found 138 (39%) had serologically confirmed dengue infection. The most common symptoms were headache (76%), abdominal pain (63%), vomiting (58%), rash (26%), and cutaneous hypersensitivity

(16%). The clinical profile observed in the present study was similar to several other studies.[9,42]

In the present study correlation of clinical manifestations with dengue serology was done to find out the differences in clinical patterns. Accordingly, the clinical presentation of arthralgia was highly evident in IgG positive (100%), both IgM & IgG positive (100%) and IgM positive (90%) patients compared to NS1 positive (74.47%) patients ($p<0.001$). These findings suggest that, patients with IgG positive, IgM positive and both IgM and IgG positive serological tests are more likely to have it as a clinical features than NS1 positive patients.

Also, the clinical presentation of melaena was highest in patients who were both IgM & IgG positive (77.42%), NS1 positive (74.47%) and IgG positive (67.21%) compared to IgM positive (30%), ($p=0.025$). These finding indicate that patient with both IgM & IgG positive, NS1 positive and IgG positive are at increased risk of bleeding manifestation in the form of melaena

Further, patients with rash were significantly higher number in NS1 positive (74.47%), followed by IgM positive (70%), and both IgM and IgG positive (66.13%) compared to IgG positive (49.18%) ($p=0.045$). Again these findings prompt the physician for further assessment to evaluate the risk of bleeding and treat accordingly in patients.

In this study most of the patients had retro-orbital pain (62.22%). Though maximum patients with IgG positive had retro-orbital pain (67.21%) compared to NS1 positive (61.7%), IgM positive (60%) and both IgM and IgG positive (58.06%), the features of retro-orbital pain were comparable in all the serologies ($p=0.766$).

Similarly itching was noted in 29.51% of the patients with IgG positive, 20.97% with both IgM and IgG positive, 20% with IgM positive and 19.15% with NS1 positive but this difference was statistically not significant (p=0.596). These findings suggest that, there is no significant variation in clinical manifestations of retroorbital pain and itching in different dengue serologies.

Overall, though the clinical profile of the present study is in agreement with other studies, the correlation of clinical profile in different dengue serology cannot be compared with other studies as to our knowledge none of the studies have reported correlation of clinical profile in different dengue serologies.

Vitals

In this study, few patients i.e. (11.11%) presented with bradycardia (heart rate of < 60 /minute). Among them, maximum patients i.e., 17.02% of the NS1 positive patients had bradycardia whereas, only 10% with IgM positive, 9.68% with both IgM and IgG positive, and 8.2% of the patients with IgG positive had bradycardia but statistically the same was not significant (p=0.741).

In the present study hypotension was noted in 12.78% of the patients. However, the distribution of patients with hypotension varied in different dengue serologies that is, maximum being 20% in patients with IgM positive followed by 17.02% of NS1 positive, 11.29% of both IgM and IgG positive and 9.84% of IgG positive patients, but the difference was statistically not significant (p=0.619). In Mangalore study[8] it was seen in 12% patients and in AIIMS a study by S. Sharma[71] in 23% patients. The findings of this study were similar to the study done in Mangalore by V.S. Padbidri et al.[8]

Systemic examination findings

In the present study, on examination of respiratory system for finding of pleural effusion unilateral/bilateral. 17.22% of the patients had decreased air entry suggestive of pleural effusion and abdominal examination revealed tenderness in nearly half of the study population (51.67%). However, decreased air entry was present in 20% of the patients with IgM positive, 19.35% with both IgM and IgG positive, and 19.15% with NS1 positive while very few with IgG positive had decreased air entry 13.11% ,but statistically this difference was not significant (p=0.741). The distribution pattern of abdominal tenderness in different serologies showed maximum patients with abdominal tenderness in IgG positive (54.10%) followed by both IgM and IgG positive (56.45%), IgM positive (50%) and NS1 positive (42.55%) but the difference was statistically not significant (p=0.513). These findings pertaining to respiratory system could not be compared with other studies due to lack of data in the literature. Whereas abdominal tenderness observed in the present study among 51.67% was comparable to a study by Karoli R. et al.[9] who reported in 63% of the patients.

Laboratory assessment

In this study, anaemia was evident in 33.33% of the patients. Nearly half of the patients (50%) with IgM positive were found to have low haemoglobin levels compared to 39.34% with IgG positive, 32.26% with both IgM and IgG positive, and 23.4% of the patients with NS1 positive but difference was statistically not significant (p=0.215). Hence it may be postulated that anaemia as a complications of dengue fever cannot be attributed to any specific serology.

The mean hemoglobin in our study was 13.62 ± 2.11 gm%. However, a study from AIIMS, Delhi by S. Sharma,[71] reported an average Hb concentration of 11.6 gm/dL.

Leucopenia is seen as a part of the bone marrow suppression caused by the dengue virus. In a study in Delhi by Sharma et al.[71] leucopenia was observed in 30% of the patients. Another study by V.S. Padbidri et al.[8] in Mangalore noted leucopenia in 25% of the patients. In the present study, leucopenia was observed in most of the patients (40%). The findings of our study were thus similar to the above studies.[8,71] However the leucopenia in different dengue serologies did not vary significantly that is, IgM positive (60%), NS1 positive (46.81%), both IgM and IgG positive (37.10%) and IgG positive (34.43%) (p=0.129).

Sharma S. et al[71] studied a outbreak of dengue hemorrhagic fever in Delhi, observed that out of 98 patients 94 (95.91%) had platelet count < 1,00,000/mm^3 and 43.8% had severe thrombocytopenia i.e, platelet count <20,000/mm^3.

In this study platelet count was studied in different serologies which showed that, both IgM and IgG positive had significantly higher number of patients with severe thrombocytopenia (<20,000 /cumm) that is 32.26% compared to 21.28% with NS1 positive, 14.75% with IgG positive and none of the patient with IgM positive (p=0.010).

These findings propose strong association of severe thrombocytopenia with IgM and IgG and provide clue for the vigorous management to avoid further complication of bleeding. This was evident as there was positive association between platelet count and rash (p=0.012).

However, in patients with IgM positive 40% had platelet count of >1,00,000/cumm and IgG positive 32.78% had platelet count of >1,00,000 /cumm, compared to NS1 positive and both IgM and IgG positive patients who had only 19.15% and 11.29% patients of platelet count above >1,00,000 /cumm respectively (p=0.010). These findings provide a hint that patient presenting with NS1 positive and both IgM and IgG positive are more likely to develop severe thrombocytopenia compared to other two serologies. These findings indicate the role of different serological tests in determining thrombocytopenia and risk of bleeding which will help the treating physician in early identification, confirmation and initiation of treatment so as to avoid the further consequences and complications of the dengue fever. Similar findings have been reported in other studies.

A study by Kulkarni RD et al[69] from Karnataka, tried to evaluate the association of platelet counts against NS1 and IgM/IgG in dengue infections. Of 2104 patients tested, 320 were positive for one or more dengue parameters. Of the 320, 95 were positive for NS1 only, 161 showed IgM only while 9 showed IgG only. More than one marker was detected in the remaining 55 samples. Thrombocytopenia was more consistently associated whenever NS1 was detected compared to antibody detection (p<0.001).

Dengue fever cases having NS1 positive have a higher risk to develop thrombocytopenia.[74] In the present study, a significant correlation was observed between NS1 antigen and thrombocytopenia. Various studies also concluded that the NS1 alone and with IgM correlated well with thrombocytopenia.[65,69]

Jyoti and Metri[75] studied 39 cases that were positive for NS1 alone and observed thrombocytopenia in 20 cases (51.2%). 62 samples tested positive for one or more Dengue‑specific parameters. Authors analyzed the association of thrombocytopenia with dengue parameter positivity. In a total of 62 cases, thrombocytopenia was seen in 32 cases (51.6%). Out of 46 cases that were positive for NS1, thrombocytopenia was observed in 26 cases (56.5%), whereas, when the antibodies alone were considered, thrombocytopenia was observed in 6 out of 16 cases (37.5%). Authors found that there was no significant difference (Z = 1.35, *P* = 0.179) between the above two parameters in relation to thrombocytopenia.

Liver profile

In the present study 11.67% of the patients were found to have raised total bilirubin levels. However, the raised total bilirubin levels were comparable in all the dengue serologies. Though maximum patients with raised total bilirubin were IgG positive (14.75%) compared to both IgM and IgG positive (12.90%), NS1 positive (8.51%) and IgM positive (0%) and the difference was statistically not significant (p=0.604). With regard to direct bilirubin, 48.33% of the patients were found to have raised direct bilirubin levels. The raised direct bilirubin levels for different dengue serological tests are, NS1 positive (55.32%), both IgM and IgG positive(54.84%), IgG positive (50.82%) and IgM positive (20%) which was comparable (p=0.217). The hepatic dysfunction noted in the present study as measured by bilirubin levels was comparable with a study in Taiwan by Kau CH et al.[76] on hepatic dysfunction in Dengue fever, where bilirubin was high in 7.2% of the patients.

In this study SGOT levels were raised in 82.78% of the patients and ≥ 2 fold rise was noted in 60% of the patients. Though, the ≥ 2 fold rise in SGOT was present in maximum patients with IgM positive (80%) followed by both IgM and IgG positive (69.35%), NS1 positive (59.57%) and IgG positive (47.54%) but the difference was statistically not significant (p=0.177). The SGPT levels were raised in 55.46% of the patients and 35.56% of the patients had rise between 1 to 2 fold. This 1 to 2 fold rise in SGPT levels did not vary significantly as almost equal distribution was observed between all serologies that is, IgG positive (40.98%), IgM positive (40%), NS1 positive (36.17%) and both IgM and IgG positive (29.03%) (p=0.533). These findings suggest that, though dengue fever commonly present with deranged SGOT and SGPT levels in all the four serologies, it was comparable in all four of them.

However the findings of the present study pertaining to raised SGOT and SGPT levels were consistent with a study by Sharma S et al[71] who observed elevation of SGOT in 88.4% of cases and SGPT in 76.7% of the cases. In contrast, Fu-Xi Qiu et al[77] observed mild to moderate elevation of SGOT in 29.4% of cases and overall abnormal LFT in 68 (44.2%).

In the present study raised alkaline phosphatase levels were noted among 31.67% of the patients. The raised alkaline phosphatase levels were evident in comparable subset of patients with both IgM and IgG positive (35.48%), IgG positive (31.15%), NS1 positive (29.79%) and IgM positive (20%) (p=0.806).

Renal profile

In this study nearly one fifth (20.56%) of the patients were found to have raised blood urea nitrogen levels. The rise of blood urea nitrogen was more noted in patients with both IgM and IgG positive (27.42%) compared to IgG positive (21.31%), NS1 positive (12.77%) and IgM positive (10%) but same was not true statistically (p=0.262). Further, deranged renal function was noted in 15% of the patients as measured by serum creatinine levels. The raised serum creatinine levels were noted maximum that is, 26.23% of the patients with IgG positive compared to 8.5% of the patients with NS1 positive and 11.29% with both IgM and IgG positive, while none of the patient with IgM positive had raised serum creatinine levels. This difference between all the four dengue serological tests was statistically significant (p=0.029). These findings show that patients presenting with IgG positive serology are at risk of renal failure. However, no dengue serological tests are specific in identifying renal involvement in dengue fever patients as measured by blood urea nitrogen.

Electrolytes

In this study hyponatremia was seen in small subset of the patients (3.33%). Among them, serum sodium levels were low in 4.92% of the patients with IgG positive compared to 4.26% with NS1 positive and 1.61% with both IgM and IgG positive while none of the patient with IgM positive serology was found to have hyponatremia. Hyperkalemia was seen in 6.11% of the patients, of them 10% of patients were IgM positive compared to IgG positive (6.56%), both IgM and IgG positive (6.45%) and NS1 positive (4.26%) only. Where as hypokalemia was seen in

small proportion of the patients (1.11%). Of these, 10% of the patients with IgM positive compared to 1.64% of the patients with IgG positive while none of the patient with both IgM and IgG positive, and NS1 positive had hypokalemia. These findings suggest that none of the dengue serological test was particular in identifying the patients with electrolyte imbalance as measured by serum sodium and serum potassium.

In this study serum chloride levels were raised in most of the patients (34.44%) Among these, 42.55% of the patients were NS1 positive, 38.71% both IgM and IgG positive, 27.78% IgG positive and 10% IgM positive had raised chloride levels (p=0.273). Further decreased bicarbonate levels were noted among more than one third of the study population (36.67%) of which significantly higher number of patients had IgG positive (50.82%) compared to both IgM and IgG positive (32.26%), NS1 positive (27.66%) and IgM positive (20%) (p=0.040).

Chest X-ray

In the present study presence of pleural effusion was noted on chest X-ray in 17.22% of the patients. The pleural effusion noted in 20% of the IgM positive patients, 19.35% with both IgM and IgG positive, 19.15% with NS1 positive and 13.11% of the patients with IgG positive. However, this difference was statistically not significant (p=0.741). These findings were similar to other Indian study by Sharma et al[71] in AIIMS. This can be attributed to the increased vascular permeability and plasma loss found in these cases.

Ultrasound

In this study gall bladder wall thickening was studied on ultrasound. 17.78%

of the patients had gallbladder wall thickening in dengue fever which may be due to decrease in the intravascular osmotic pressure and increase in the vascular permeability. It is a very nonspecific finding when considered in isolation ($p>0.05$). However during an epidemic of dengue fever this finding may serve as an adjunct to the other confirmatory tests in the diagnosis of dengue fever. In a study by Joshi P. et al.[78] a pseudo thickening of gallbladder wall thickening were found in most of the patients.

However, in the present study the gall bladder wall thickening on the ultrasound among different serologies that is IgM and IgG positive (20.97%), NS1 positive (17.02%), IgG positive (16.39%) and IgM positive (10%) did not differ significantly ($p=0.874$).

Overall the present study showed the usefulness of correlation of clinical profile with different serological diagnostic parameters in dengue fever patients. Understanding the clinical profile of each diagnostic dengue serology will be an excellent tool in addressing potentially fatal, epidemic prone dengue fever.

CONCLUSION

The findings of this study highlight significant variations in the clinical profile of dengue fever based on clinical features, clinical examination and laboratory parameters. Clinical features viz. arthralgia, rash and melaena, and laboratory parameters that is, platelet count, serum creatinine, bicarbonate levels showed significant variations in different dengue serological tests. While clinical features viz. fever, retroorbital pain and itching, heart rate, blood pressure, abdominal tenderness, altered sensorium and laboratory parameters viz. total count, liver and renal profile and radiological findings are similar in different dengue serological tests.

SUMMARY

Dengue fever has wide variation in clinical profile based on the test used for the detection of dengue infection. Also there is scanty data on correlation of clinical profile with different serological diagnostic parameters in dengue fever patients. Hence the present study was an attempt to evaluate and correlate the clinical profile of patients with dengue fever under different serological diagnostic parameters.

This one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 180 patients with dengue fever from January 2014 to December 2014 were studied. The important observations and implications summarized as below.

- Out of 180 patients studied, 72.22% of the patients were males and male to female ratio was 2.6:1
- Most of the patients were aged between 18 to 30 years (50.56%) and mean age was 32.96 ± 12.79 years
- Mean day of presentation to the hospital was 5.92 ± 2.04 days.
- All the patients presented with fever (100%).
- With regard to dengue serology, 34.44% of the patients were IgM and IgG positive, 33.89% IgG positive, 26.11% NS1 positive and 5.56% of the patients were IgM positive.

- Demographic features of the study population were comparable in all the dengue serologies (p>0.050).

- Clinical features viz. arthralgia, rash and melaena significantly varied in different dengue serological tests (p<0.050) while fever, retroorbital pain and itching were comparable in different dengue serological tests (p>0.050).

- Clinical examination findings that is, heart rate, blood pressure, abdominal tenderness and altered sensorium were comparable among dengue serological tests (p>0.050).

- Complete blood count revealed comparable haemoglobin levels and total count in dengue serological tests (p>0.050).

- Statistically significant difference was noted pertaining to platelet count (p=0.010) as IgM and IgG positive had significantly higher number of patients with severe thrombocytopenia (<20,000 /cumm) that is 32.26% compared to 21.28% with NS1 positive, 14.75% with IgG positive and none of the patient with IgM positive (p=0.010). Also mean platelet count differed significantly in dengue serological tests. Positive association was noted between rash and platelet count (p<0.050).

- Liver function test including total bilirubin direct bilirubin, SGOT, SGPT and alkaline phosphatase levels though deranged were comparable (p>0.050).

- With regard to renal profile, significant difference was noted in serum creatinine levels (p=0.029) while almost equal distribution of patients was noted with regard to blood urea nitrogen in different dengue serological tests.

- Significantly higher number of patients with IgG positive (50.82%) had low bicarbonate levels compared to both IgM and IgG positive (32.26%), NS1 positive (27.66%) and IgM positive (20%) and mean bicarbonate levels also differed significantly with dengue serology ($p<0.050$) but serum sodium, potassium and chloride levels were comparable ($p>0.050$).

- Radiological findings pertaining to chest X-ray and ultrasound revealed almost equal distribution of patients.

Overall the present study confirms variation in clinical profile of dengue fever within the different serological tests which is presumed to be helpful for the treating physician in case management and identification of patients who should be closely monitored.

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ANNEXURE I – CONSENT FORM

TITLE OF RESEARCH STUDY: ‘‘CORRELATION OF CLINICAL PROFILE WITH DIFFERENT SEROLOGICAL DIAGNOSTIC PARAMETERS IN DENGUE FEVER – ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY”

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Introduction and Purpose

Dengue infection has a varied clinical profile; the mainstay is correlation in different dengue infections to know how they present along with its different diagnostic parameters.

The complications of Dengue fever usually occur between 3-7 days of fever. So clinical profile is necessary to detect and prevent complications.

Procedure

If you agree to be part of the research study, you will be asked the relevant history like fever, abdominal pain, skin rash (petechaie), any bleeding manifestations, treatment history and will be subjected to detailed systemic examination and investigations which are already done as a part of diagnosis and management of Dengue fever will be documented in proforma from the case records.

Risk and Benefits:

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

A direct benefit may not be there but the result could through light for better management of dengue fever in the future.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change my 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 / compensation

In case of any injury related to the study, treatment will be made available at K.L.E.S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

There is no compensation or payment for such medical treatment by law.

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.

Questions / Contact details

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

1. Dr. *** ******,**
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2. Dr. *** *******,**
Professor & Vice Principal,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 005

3. Dr. *** *******,**
Chairman,
Jawaharlal Nehru Medical College,
Ethical Committee for Human Research,
Phone number: ****-******.
Extension: ****

CONSENT STATEMENT

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, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant :

Signature / Thumb print :

Name of the Witness :

Signature/ Thumb print :

Investigator Name :

Signature :

Date:

Place:

ANNEXURE II – PROFORMA

TITLE OF RESEARCH STUDY: ‘‘CORRELATION OF CLINICAL PROFILE WITH DIFFERENT SEROLOGICAL DIAGNOSTIC PARAMETERS IN DENGUE FEVER – ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY”

Case No :

Name :

Age / Sex :

In Patient No :

Address :

Occupation :

Dengue Diagnosis

NS1–

IgM –

IgG –

History

Fever :

Skin rash (Petechaie) :

Itching :

Retro orbital pain :

Abdominal pain :

Melaena :

Any other bleeding manifestations :

Treatment History

General Condition

Pallor :

Icterus :

Lymphadenopathy :

Cyanosis :

Clubbing :

Pedal edema :

Vitals

	At Admission						
Temperature							
Pulse							
Blood pressure							
Respiratory rate							
Petechaie							

Interpretation –

Type of fever -

Maximum variation of temp -

Total duration of fever –

Bradycardia -

Systemic Examination

Cardiovascular system :

Respiratory system :

Per abdomen :

Central nervous system :

Investigations

Haemoglobin

Total count

Differential count

Platelet count

Date					
	At admission				

Liver function test

Total bilirubin				
Direct bilirubin				
AST				
ALT				
Alkaline phosphate				

Urea

Creatinine

Electrolytes

Sodium

Potassium

Chloride

Bicarbonate

Echocardiography

Chest X Ray

Ultrasound Abdomen

Peripheral smear for Malarial parasite or Malaria card test

If necessary – Widal HIV

Weil Felix

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
/Cumm	-	Per cubic millimeter
+	-	Present
Ab	-	Abnormal
ALT	-	Alanine transaminase
AST	-	Aspartate amino transferase
BP	-	Blood Pressure
DAE	-	Decreased air entry
F	-	Female
gm	-	Grams
HbSAg	-	Hepatitis B antigen
HCV	-	Hepatitis C virus
HIV	-	Human immunodeficiency virus
IgG	-	Immunoglobulin G
IgM	-	Immunoglobulin M
IU/L	-	International units per liter
M	-	Male
meq/L	-	Milliequivalent per liter
mg/dL	-	Milligram per deciliter
mm Hg	-	Millimeters of mercury
N	-	Normal
NS1	-	Non structural protein 1
PE	-	Pleural effusion

SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamic pyruvic transaminase
Tend	-	Tenderness