“THE CLINICAL AND BIOCHEMICAL PROFILE OF LIVER INVOLVEMENT IN DENGUE INFECTED PATIENT”. A ONE YEAR CROSS SECTIONAL STUDY IN KLES DR PRABHAKAR KORE HOSPITAL & MRC, BELGAUM

REG NO. BG0112001

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"THE CLINICAL AND BIOCHEMICAL PROFILE OF LIVER INVOLVEMENT IN DENGUE INFECTED PATIENT". A ONE YEAR CROSS SECTIONAL STUDY IN KLES DR PRABHAKAR KORE HOSPITAL & MRC, BELGAUM** is a bonafide research work done by **CANDIDDATE REG NO. BG0112001**.

Dr. Rekha S. Patil **MD**
Professor and Head,
Department of Medicine,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. N. S. Mahantshetti **MD**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

LIST OF ABBREVIATIONS USED

/Cumm	-	Per cubic millimeter
°C	-	Degree centigrade
µL	-	Micro Liter
AD	-	Anno Domini
AIIMS	-	All India Institute of Medical Sciences
ALT	-	Alanine aminotransferase
APTT	-	Activated partial thromboplastin time
ARDS	-	Acute respiratory distress syndrome
AST	-	Aspartate aminotransferase
BP	-	Blood pressure
DENCO	-	Dengue control
DENV	-	Dengue virus
DF	-	Dengue fever
DFB	-	Dengue fever with unusual bleeding
DHF	-	Dengue hemorrhagic fever
DSS	-	Dengue shock syndrome
e.g.	-	For example
ECG	-	Electrocardiography
ELISA	-	Enzyme linked immunosorbant assay
GGT	-	Gamma-glutamyl transpeptidase
gm	-	Gram
HBsAg	-	Hepatitis B surface antigen
HBV	-	Hepatitis B virus
HCV	-	Hepatitis C virus

HIV	-	Human immunodeficiency virus
IFN	-	Interferon
IgM	-	Immunoglobulin M
IHR	-	International Health Regulation
ITNs	-	Insecticide-treated nets
mg/dL	-	Milligrams per decilitre
mm Hg	-	Millimeters of mercury
MRD	-	Medical Records Department
p	-	Probability
PPP	-	Public-private partnership
PT	-	Prothrombin time
RNA	-	Ribonucleic acid
RT-PCR	-	Reverse transcriptase polymerase chain reaction
SD	-	Standard deviation
SEA	-	South-East Asia
SEAR	-	South East Asia Region
TDR	-	Tropical diseases research
TNF	-	Tumor necrosis factor
USG	-	Ultrasonography
vs	-	Versus
WHA	-	World Health Assembly
WHO	-	World Health Organization
yrs	-	Years

ABSTRACT

Background and objectives

Over the last few years, atypical manifestations of dengue have been described, including elevations in aminotransferase levels, with reactive hepatitis and kidney involvement. The present study was undertaken to assess the clinical and bio-chemical profile of liver involvement in dengue infected patients.

Methodology

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients who presented with dengue fever from January 2013 to December 2013 were enrolled.

Results

Most of the patients were male 68% and male to female ratio was 2.12:1. The commonest age group was 18 to 30 years (63%) and the mean age was 30.33 ± 12.63 years. All the patients presented with fever (100%) and next common presentation was generalized body pain (93%). On clinical examination, pallor and icterus were present in 18% and 12% of the patients. Systemic examination revealed, 35% of the patients had hepatomegaly, 16% had pleural effusion and 1% had altered sensorium. Majority (82%) of the patients had raised AST levels and mean AST levels were 460.99 ± 1553.2 IU/L. Raised ALT levels were noted in 71% of the patients and mean ALT levels were 202.77 ± 568.91 IU/L. 27% of the patients had raised total bilirubin levels and mean bilirubin levels were 1.31 ± 1.61 mg/dL. In this study, majority of the patients were diagnosed to have dengue

fever (73%) while dengue haemorrhagic fever and dengue shock syndrome were noted in 14% and 13% respectively. Positive association was noted with raised ALT levels and DHF (p=0.016). Also serum bilirubin levels were raised significantly in patients with DHF (p=0.019).

Conclusion and interpretation

Liver dysfunction in the form of raised ALT and AST levels, and jaundice are common in patients with dengue infection.

Keywords

Liver dysfunction; Dengue fever; Dengue haemorrhagic fever; Dengue shock syndrome;

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INTRODUCTION

Dengue infection, an arthropod - borne viral hemorrhagic fever, continues to be a major challenge to public health in South-East Asia.[1] It is caused by one of the four serotypes of the dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4) also referred to as an arbovirus (arthropod-borne viruses) that belongs to the genus *Flavivirus* of the family *Flaviviridae*.[2] It is a disease with a wide clinical spectrum and a wide variety of presentations, ranging from asymptomatic to an undifferentiated fever (viral syndrome) to the more severe forms such as severe dengue (SD) or Dengue hemorrhagic fever (DHF).[3]

Transmission to humans occurs by the bite of the female *Aedes aegypti* mosquito infected by one of four serotypes of the virus. This mosquito, a domestic species adapted to urban conditions, is the main vector in Brazil.[4]

The period of transmission from humans to mosquitoes begins one day before the start of fever up to the sixth day of illness corresponding to the viremia phase. After a female bites an individual in the viremia phase, viral replication (extrinsic incubation) begins in the vector in from eight to twelve days. In humans, the incubation period ranges from 3 to 15 days (intrinsic incubation) with an average of 5 days.[4,5]

Estimates suggest that annually over 50 million cases of severe dengue occur in Asian countries with a case fatality rate of lesser than 5%. Of these, at least 90% are children younger than 15 years old.[6]

According to estimates of the World Health Organization (WHO), about 50 million cases of dengue fever occur annually worldwide and 2.5 billion people live in risk areas.(6) In 2005, the World Health Assembly, through WHA Resolution 58.3, in a review of the International Health Regulation (IHR), included dengue fever as an emergent public health disease, with implications for health safety due to the spread of the epidemic beyond national boundaries.[7]

The first outbreak of dengue fever in India was recorded in 1812.[8] In spite of preventive measures taken by the respective governments since then, recurrent outbreaks have occurred, and over the last 10 to 15 years DF has been the major cause of hospitalization and mortality after acute respiratory and diarrhoeal infections among children.[9] New Delhi, the capital of India located in the northern region of the country, experienced seven major outbreaks between 1967 and 2003.[10,11]

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]

Leukopenia is the most prominent hematological change, sometimes with counts of less than 2 x $10^3/\mu L$. However, there are reports of mild leukocytosis at the onset of the disease, with neutrophilia. Lymphocytosis is a common finding, with the presence of atypical lymphocytes. The hematocrit concentration should be

monitored according to the days of illness, remembering that, with the progression to DHF, there will be a 20% increase in hematocrit from the patient's baseline, associated with thrombocytopenia (< 100 x 10^9/L).[12]

Over the last few years, atypical manifestations of dengue have been described, including elevations in aminotransferase levels, with reactive hepatitis and kidney involvement. Of biochemical variables, the most frequent changes occur in liver function tests such as in serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase and alkaline phosphatase levels, and serum albumin concentrations.[12]

Hepatic manifestations can be characterized by manifestations of acute hepatitis with pain in the hypochondrium, hepatomegaly, jaundice and raised aminotransferase levels. In hepatitis the levels of these enzymes peak on the ninth day after onset of symptoms and gradually return to normal levels within 3 weeks. Histopathological findings include centrilobular necrosis, fatty alterations, hyperplasia of the Kupfer cells, acidophil bodies and monocyte alteration of the portal tracts. In most cases hepatic involvement prolongs the clinical course of this self-limiting viral infection but it does not constitute a sign of worse prognosis.[15]

The presence of jaundice in these patients is multifactorial. It can be due to hepatic aggression caused by the dengue virus and/or hypoxia and tissue ischaemia in cases of shock. Jaundice occurs in 12–62% of patients with dengue shock syndrome. Increased levels of alkaline phosphatase and bilirubin are found in a smaller proportion of cases.[15]

Although dengue virus is a non-hepatotropic virus, hepatomegaly is commonly seen in dengue along with a rise in serum aminotransferases. The degree of liver dysfunction varies from mild injury with elevation of aminotransferases to even fulminant hepatic failure. Hepatic dysfunction in dengue infection may be attributed to direct viral effect on liver cells or as a consequence of dysregulated host immune responses against the virus. Jaundice in dengue infection has been associated with fulminant liver failure and by itself is a poor prognostic factor.[16]

However, to-date, only few studies have evaluated liver profile of patients with dengue fever. Most of the available data on liver involvement in Dengue is from Children and data from adults are scarce[2]. Further no such study was undertaken in our hospital settings. Hence the present study was planned to assess the clinical and bio-chemical profile of liver involvement in dengue infected patients.

OBJECTIVES

The objectives of the present study were to assess the clinical and bio-chemical profile of liver involvement in dengue infected patients.

REVIEW OF LITERATURE

Historical Aspects

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 fever was first referred as "water poison" associated with flying insects in a Chinese medical encyclopedia in 992 from the Jin Dynasty (265-420 AD). The word "dengue" is derived from the Swahili phrase "Ka-dinga pepo", meaning "cramp-like seizure".[17] The term "Break bone fever" for dengue was proposed in Philadelphia in 1780 by Benjamin Rush.[18] *Aedes aegypti* mosquito as a vector of dengue virus was first discovered by Bancroft in 1906.[19]

The first historical account of DSS was reported by Benjamin Rush during an outbreak (1780) in Philadelphia among people living at Delaware River.[20] North America had similar outbreaks in the 18th and 19th centuries along the Atlantic coast, on the Caribbean Islands, and also in the Mississippi basin.

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).[18]

However, it was only in 1943-44 that the modern chapter of dengue research started. This was for the first time when dengue virus was cultured and later isolated from suckling mice brain.[19]

The Indian subcontinent is mainly affected by DENV2 and DENV3 serotypes. DENV1 and DENV4 were identified by studying neutralizing antibodies

in the blood of volunteers in 1973 while DENV1 and DENV2 were isolated as a consequence of the failure of viral strains to cross-protect human volunteers.[21]

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.[19]

Dengue disease severity

Dengue is regarded as one of the most important arboviral infections in the world. Dengue fever (DF), including its variants, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), is caused by four antigenically distinct but related dengue viruses (DENV-1, DENV-2, DENV-3 and DENV-4), also known as serotypes, belonging to genus *Flavivirus*, family Flaviviridae.[22]

There exists a considerable variation within each serotype in the form of phylogenetically distinct subtypes or genotypes. Currently, each serotype has subtype/genotype as follows:[22]

- DENV-1: Three
- DENV-2: Two (one is found in non-human primates)
- DENV-3: Four
- DENV-4: Four (one is found in non-human primates).

Infection with any one serotype confers lifelong immunity to that serotype but only two to three-months' immunity to other serotypes. Infection with another serotype or multiple serotypes leads to severe forms of dengue (DHF/DSS).[22]

Today, all serotypes/genotypes are circulating globally and all areas, which used to report epidemics of dengue earlier, are now hyperendemic areas including the WHO South-East Asia Region.[22]

Dengue is transmitted primarily by *Aedes* (Stegomyia) *aegypti,* and *Aedes* (Stegomyia) *albopictus* is the secondary vector. *Ae. aegypti* is a native of Africa which spread to other continents through slave trade and, subsequently, by globalization of trade and commerce. Today, it is regarded as a cosmotropical species breeding in urban areas between latitude 45oN and 35oS.[23]

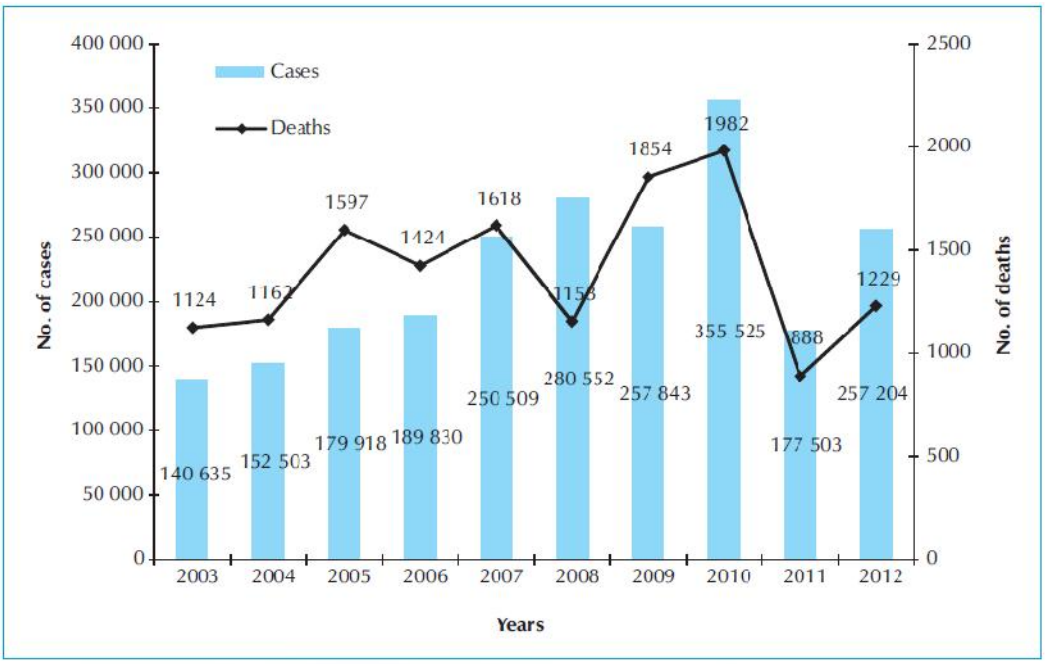
Disease burden

Global

As per the World Health Organization, dengue has shown a 30-fold increase globally over the past five decades.3 Some 50 to 100 million new infections are estimated to occur annually in more than 100 endemic countries. Every year, hundreds of thousands of severe cases arise resulting in 20 000 deaths.[24]

WHO South-East Asia Region

The WHO South-East Asia Region comprises 11 countries with a population of 1.3 billion. Bhutan and Nepal reported epidemics in 2004 only, whereas Democratic People's Republic of Korea has not yet reported any dengue outbreak. Figure 1 shows dengue cases and deaths for the years 2003 to 2012 in SEAR.[22]



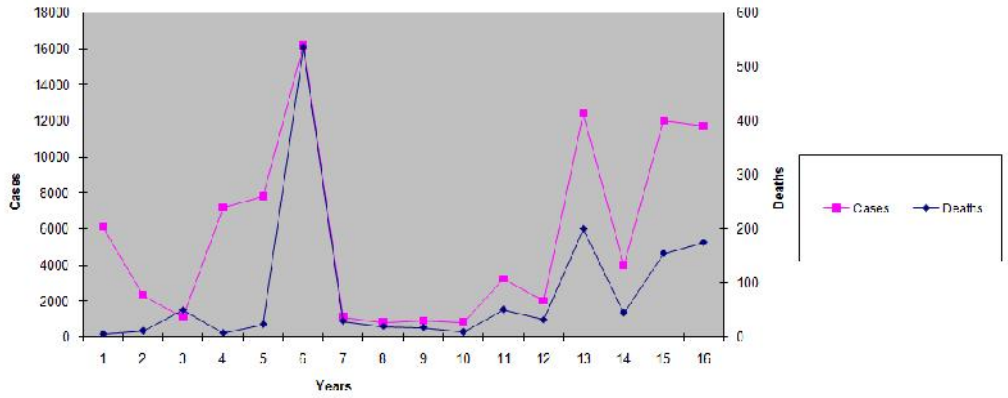
Dengue cases and deaths in the WHO South-East Asia Region[22]

From the figure, it is apparent that the South-East Asia (SEA) Region has become hyperendemic with regular reporting of dengue cases since the year 2000. The maximum number of cases (355 525) and deaths (1982) were recorded during 2010. Since then, a declining trend is being reported. Maybe it is a cyclic trend and/or non-induction of virulent serotypes/genotypes.[22]

India

The first outbreak of dengue fever in India was recorded in 1812.[8] In spite of preventive measures taken by the respective governments since then, recurrent outbreaks have occurred, and over the last 10 to 15 years DF has been the major cause of hospitalization and mortality after acute respiratory and diarrheal infections among children.[9]

New Delhi, the capital of India, located in the northern region of the country, experienced seven major outbreaks between 1967 and 2003.[9,11]



DF reported cases and deaths in India from 1991 till 2008[19]

Then in 2006 another major outbreak occurred with more than 11,000 reported cases and 165 reported fatal cases.[27]

Rapid growth of the population and sudden climatic changes contributed to the increase in cases of DF/DHF in India. During 1997 until 2004, DENV1 was seen as the causative agent of most DF/DHF cases but later in 2005, DENV3 became the leading source of dengue outbreaks. According to the WHO in 2006, the total number of reported cases reached 12,317, while in 2007 fewer cases occurred i.e.5,534 owing greatly to preventive measures taken by both the public and private sectors. In 2009, however, DF cases again reached 11,476 by November. Initial cases were reported in July 2009 with the greatest number of cases seen in October. These trends demonstrate that DENV has penetrated deep into India, with DENV2 and DENV3 predominating among different DENV serotypes.[19]

Case definition/Revised classification

Dengue is now most prevalent in tropical countries in Asia, Latin America and the Caribbean. Early detection of dengue cases and their treatment is essential to prevent deaths.[22] The first ever attempt for classification and management of DF/DHF was developed on the basis of 123 Thai children admitted to the Children's Hospital in Bangkok. Subsequently, researchers' recommendations evolved into WHO guidelines in 1974, which were updated in 1986, 1994 and in 1997.[25] These guidelines were adopted by the WHO South-East Asia Region[26] and the Region of the Americas.6 However, these guidelines were not validated.

During 2009, Dr Alex Kroger, Scientist, Tropical Diseases Research, WHO headquarters[28] presented a paper entitled "Reclassifying dengue" before a meeting of the WHO Advisory Committee on Dengue and Other Flavivirus Vaccines in 2009.[28] He gave details of the difficulties faced by clinicians in some situations in classifying their patients as per existing WHO guidelines.[25] These conditions included the following:[22]

- Dengue with haemorrhagic manifestations but without vascular leakage;
- Dengue with shock syndrome (up to 18%) but without fulfilling the four criteria;
- Organ failure reported in severe disease that does not meet WHO criteria.

He further presented the details of DENCO (dengue control), a multicentre prospective clinical study conducted during 2004–2008.[28] On the basis of this study, a revised classification system on 'severity score' on the basis of interventions was presented. This was proposed in order to make it possible to distinguish between

'severe' and 'non-severe (mild/moderate)' dengue with a sensitivity and specificity of around 95%. To determine which case might progress from mild/moderate dengue to severe dengue, the following 'warning signs' were identified as predictors of progression:

- Abdominal pain/tenderness
- Mucosal bleeding
- Rash
- Lethargy
- Low albumin
- Low platelets
- Increased haematocrit.

Dr Kroger added: "It is planned to validate the study of revised classification in clinical practice and surveillance involving 18 countries, further analyse the predictive value of 'warning signs' and the signs and symptoms of probable dengue."[28]

With this background, and on the recommendation of an expert group, WHO adopted the revised classification in 2009 based on the level of severity, i.e. dengue with warning signs and severe dengue.[29]

The validation studies carried out in 18 countries concluded that the applicability of the DF/DHF/DSS classification was limited even when strict DHF criteria were not applied (13.7% dengue cases could not be classified using the DF/DHF/DSS classification by experienced reviewers, compared with only 1.6% with the revised classification). Therefore, it was concluded that the revised dengue

classification carried a high potential of facilitating dengue case management and surveillance. However, the need for the validation of "warning signs" and "probable dengue" required further research.[22]

Subsequently, WHO-TDR took the further initiative of reviewing the development, evidence base and application of the revised dengue case classification. This document established that the revision meant a major change not only for the health care professionals, but also for surveillance officers and researchers. An analysis has shown that the revised dengue case classification is better able to standardize clinical management, raise awareness about unnecessary interventions, and match patients' categories with specific treatment.[22]

In yet another initiative, WHO-TDR has brought out a *Handbook for clinical management of dengue*11 for reorientation of clinicians/health care professionals for the clinical management of dengue cases as per the revised classification. The subject of WHO revised classification 2009 is being hotly debated.[22]

Kalayanarooj in Thailand[30] carried out a prospective study of suspected dengue patients admitted in the Dengue Unit of the Queen Sirikit National Institute of Child Health (also the WHO Collaborating Centre for Case Management of Dengue/DHF/DSS) between June and August 2009. The final diagnosis was based on the current WHO classification together with laboratory confirmation. The TDR classification was applied later by the author using the data from the study case-report form of each patient. A statistical analysis comparing the clinical and laboratory data between each group of patients was done using software SPSS version 14. As a conclusion, the author recommended continued use of the current

WHO classification because, in her opinion, the newly suggested TDR classification creates about twice the workload on health-care workers. In addition, the TDR classification needs dengue confirmatory tests. More than 90% of the DHF defined by the WHO case definition is dengue-confirmed.

However, the current WHO classification needs to be modified to be simple and more user friendly. The suggested modification is to address plasma leakage as a major criterion. Positive tourniquet test or bleeding symptoms can be combined as minor criteria. Unusual dengue is proposed to be added to the current WHO classification to cover those patients who do not fit in the current WHO classification.[22]

Hadinegoro[31] found difficulties in the application of revised classification in Indonesia and suggested that elements from the revised classification (2009) should be incorporated into the 1997 guidelines,4 which remain relevant for use. He further suggested multicentre, i.e. prospective studies using standardized protocols, in Asia and Latin America in a full range of patients' age groups.

The WHO-TDR Expert Meeting on Effective, Affordable and Evidence-based Dengue Early Warning and Response System held on 28–30 June 2012 Freiburg, Germany, recommended separate guidelines for dengue case management of children and adults. Sri Lanka has already developed national guidelines for management of DF and DHF separately for children and adults.[22]

In view of the aforesaid, WHO's Regional Office for South-East Asia adopted an attitude of 'wait and see' until validation of the revised classification. Furthermore, in view of the experience gained over a decade, the expert group of

WHO-SEAR did not follow the results of the DENCO clinical study,[28] but further expanded the existing guidelines by incorporating the range and frequencies of constitutional symptoms under each category of DF, DHF and DSS. The existing DHF grades 1–4 have been re-categorized as DHF without shock and DHF with shock.[22]

Abdominal pain/tenderness has been identified as an important predictor of progression of DF to DHF (alarm signal).[22]

Khanna et al.,[32] in a Delhi (India) hospital, analysed 100 patients presenting acute fever with abdominal pain. A probable diagnosis of DF was made, based on the presence of acute febrile illness with two or more of the following manifestations: headache, retro-orbital pain, myalgia, arthalgia, rash, haemorrhagic manifestations and leucopaenia. The diagnosis was confirmed by enzyme immunoassay-based serology. DHF was diagnosed based on WHO criteria.[25] Out of the 100 DF patients with abdominal pain, 55 patients' diagnosis was attributed to DF. The remaining 45 cases had other causes of fever with abdominal pain related to other causes.

In another study from Sri Lanka by Weerakoon et al.,[33] 14 cases of acute fever with abdominal pain of DHF/DSS were analysed during the dengue epidemic in 2009. All patients had secondary infection, probably DENV-1 (isolated elsewhere during the same period). The findings included severe thrombocytopenia, mean platelet count 18×109/l, range 12–48; high liver enzyme mean ALT 374 U/l, range 82–2692; ascities in all cases (100%); acute hepatitis in 11 cases (79%); acalculitis

cholecyslitis in 5 cases (42%); renal involvement in 3 cases (25%); normal serum amylase level (100%); normal-looking pancreas (100%).

Abdominal pain in dengue infection warrants investigation to find a specific cause.

Epidemiological change: Affected age group of DHF cases

Sedhain et al.[34] reported the first-ever large outbreak in central Nepal (virgin soil) during 2010. A total of 414 dengue-confirmed cases following application of WHO guidelines5 were included in the study. Out of 414 cases, 329 were of DF and 85 of DHF including 2 cases of DSS. DHF was more common in the elderly population than DF (mean age of 31.59 vs 35.42). These findings are contrary to the known fact that DHF is basically the disease of children >15 years.

Validation of WHO probable case definition[29]

Nujum et al.[35] conducted a study to check the performance of "probable dengue" case definition as per WHO headquarters guidelines.8 The study was carried out in Thiruvananthapuram district of Kerala, India. It included 254 patients with acute febrile illness of 2–7 days without a definite diagnosis for the community and primary and secondary case settings. The performance was assessed using RT-PCR as gold standard in the case of fever <5 days and IgM antibody detection for fever >5 days. WHO case definition had a very high negative predictive value of 97.4% (90.2, 99.6). The sensitivity and specificity were 71.4% (35.9, 91.8) and 30.7% (25.3, 36.7), respectively. The diagnostic odds ratio of the WHO classification was 1:1 which could be increased to 13.6 if any five items listed in the case definition were used.

Host genetics and DHF

Guha-Sapir and Schimmer20 have discussed various factors involved in the pathogenesis of DF. High viremia, virulence of virus, age and racial and ethnic resistance to DHF are some of the important factors. Host genetics in dengue viral infection is considered to be an important area of research to understand the end-stage complications of DHF. Aggressive studies are required in different ethnic groups in different countries on a large number of patients during the acute phase of DHF.[22]

It is noteworthy that human populations have undergone migrations for millennia globally. For example, in India, Kondrashin and Rashid23 identified 19 ethnic tribes (about 54 million population as per 1981 census) speaking over 100 languages/dialects representing ethnic diversity with different gene pools.[22]

Dudly Stamp[36] gave historical accounts of earlier migrations into India. According to him, Dravidians came from the south, Ahom from the east, Mongols from the north, Aryans from Central Asia and invaders and Moghuls from the west during the twelfth to fifteenth centuries, and finally, the British, the French and the Portuguese from Europe. The mixing of these diverse groups of populations is bound to generate 'gene pools' of great diversity. A study of the genetic make-up of these gene pools and their interaction with viral genome may provide useful information on the clinical manifestations and severity of DHF.

Vector control

In the absence of antiviral drugs and vaccines, vector control is the only option against dengue. *Ae. aegypti*, the primary vector of dengue, is a 'hygrophilic species' i.e. humidity loving.[22]

Therefore, it has adapted to breeding in water-storage containers in domestic habitation and is governed by 'microclimatic conditions' and, to a lesser extent, by macrolevel climatic environment. Thus, to a large extent, this species can breed and transmit the virus comfortably under extreme macrolevel environmental conditions. During the rainy season, when temperatures come down and humidity increases, the species invades peridomestic areas and breeds profusely in any natural or manmade container holding rainwater, building up a very high density.[22]

A study by Sharma et al.[37] in the National Capital Territory of Delhi (India), which experiences extreme weather conditions, recorded round-the-year breeding of *Ae. Aegypti* in 1998.25 The container indices varied from 83 in the winter, 1147 in the rainy season and 51 in the summer. It also recorded the corresponding incidence of DF cases which were hospital-based and serologically confirmed. The monthly distribution of 332 cases was 2, 6, 19, 79, 203 and 33 corresponding to the months from July to December, respectively. The transmission continued even in the severe winter month of December.

In contrast to this, Bohra and Andriansolo[38] reported the occurrence of outbreaks of DF/DHF in 1985 and 1990 during the months of March–April (spring season) in an arid zone of Jalore, Rajasthan (India).

This highlights the need for the study of the co-relation of microclimatic conditions to determine the threshold levels of *Ae. aegypti* breeding and transmission of DF/DHF.[22]

Globally, vector control has been executed using chemicals, bio-control agents and personal protection measures including insecticide-treated nets (ITNs) but without much success. A successful vector control programme requires intersectoral coordination, and active individual and community participation.[22]

A recent meta-analysis study[39] concluded that dengue vector control is effective in reducing vector population when interventions use a community-based integrated approach tailored to local eco-epidemiological and sociocultural settings and combined with educational programmes to increase the knowledge and understanding of best practices.

Recently, a WHO-sponsored research project entitled "Eco Bio-social Research on Dengue in Asia"[40] concluded that variable influence on vector breeding is complex and public health response should go beyond larviciding/spraying of insecticides. The study emphasized the need to develop close interaction between political leaders, religious leaders, all sectors of economics and municipal authorities, which is critical for the success of dengue vector control.

Clinical features

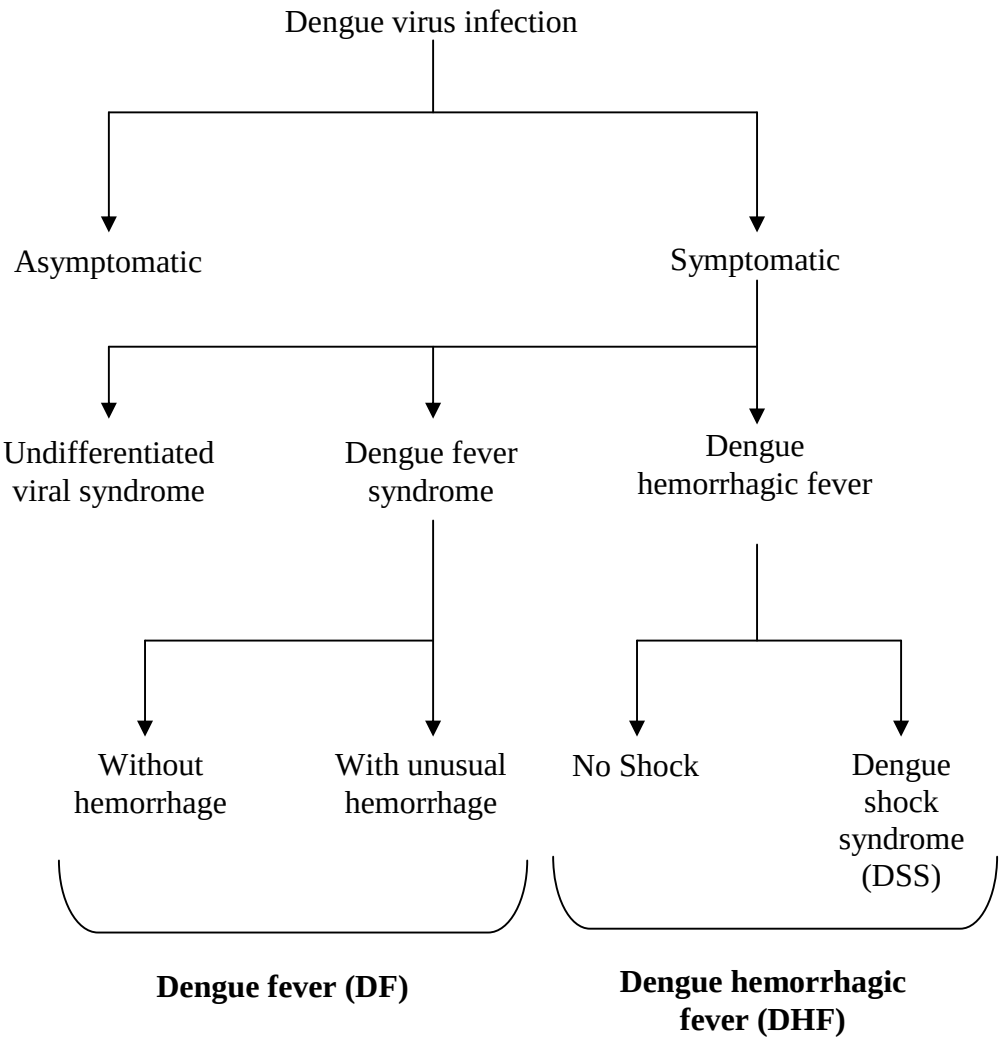
The dengue virus infection may be manifested as asymptomatic to symptomatic disease as classical dengue fever, dengue hemorrhagic fever and dengue shock syndrome.

Dengue fever

The illness is characterized by an incubation period of three to ten days. The onset is sudden with chills and high fever, intense headache, muscle pain, joint or bony pain (Break bone fever), retro orbital pain and photophobia. Other common symptoms include weakness, abdominal pain, sore throat and general depression. Fever is usually between 39°C and 40°C, followed by a remission of a few hours to two days (biphasic fever or saddle back fever).Arthritis and marked prostration are characteristic of dengue fever.

The skin eruptions in 80% of cases appear during the remission or during second febrile phase, which lasts for one to two days. The rash may be diffuse flushing, mottling or fleeting pinpoint eruptions or the rash may be maculopapular or scarlatiniform.

Spectrum of clinical features of dengue virus infection[29]



Dengue fever with unusual bleeding (DFB)

Some patients with dengue fever have evidence of mucosal or cutaneous bleeding without other evidence of DHF/DSS like hemoconcentration or fluid leak; such patients are classified as dengue fever with unusual bleeding (DFB).[41]

Dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS)

DHF/DSS is a severe form of dengue fever, caused by infection with more than one dengue virus and may be fatal in 40-50% of untreated patients. The disease is confined usually to children less than 15 years of age, but due to change in epidemiological trend the disease may occur in adult population.

After an incubation period of four to six days the patient develops clinical features of dengue fever. There may be varying degree of tender hepatomegaly or less commonly splenomegaly. All patients have some degree of hemorrhagic phenomenon like positive tourniquet test, petechial spots, bruising at venepuncture site, bleeding from gums, epistaxis, hematemesis or melena, muscle hematoma, hematuria and rarely intracranial hemorrhage may occur.

Fever may subside after two to seven days. At this stage patient may develop varying degrees of peripheral circulatory failure. With progressive peripheral circulatory failure, patient may have sweating, restlessness, cold extremities .The pulse pressure gets narrow, blood pressure starts falling and ultimately leads to unrecordable blood pressure and irreversible shock

Several studies[8,29,41-50] have reported different clinical features and complications of dengue fever. Thrombocytopenia is a very important indicator of prognosis in DHF as was shown by the study conducted in Philippines by Chua MN, et al.[51] in 1992.

Sharma S et al.[42] from AIIMS, New Delhi studied 98 adult patients diagnosed to have dengue hemorrhagic fever (DHF) (n=75) and dengue shock syndrome (DS) (n=23) during an epidemic of dengue fever in the middle of August

1996. Fever (100%), body aches (45.9%), abdominal pain (38.7%), purpura (33.6%), epistaxis (32.6%), melena (26.5%), hematemesis (22.4%) and ecchymoses (20%) were commonly present symptoms. ELISA IgM antibodies for serodiagnosis of dengue virus infection was positive in 23 of the 27 patients tested. At the time of admission, 94 patients had a platelet count below 100,000/mm3. Four patients with hemorrhagic manifestations had an initial platelet count of >100,000/mm3. Severe thrombocytopenia (platelet count <20,000 /mm^3) was present in 43.8% of the patients. The ultrasound tests showed pleural effusion in 10 out of the 12 patients and ascites in 5 patients tested when they were not clinically evident.

Wali JP et al.[43] studied 17 consecutive patients of DHF/DSS in New Delhi to assess cardiac function by radionuclide ventriculography, echocardiography and electrocardiography (ECG) during the epidemic of Dengue virus type-2 (DENV-2) in Delhi, India (1996). Fourteen patients were seropositive for Dengue infection. In radionuclide ventriculography study, the mean left-ventricular ejection fraction was 41.69 (5.04% (range 33-49%) and 7 patients had an ejection fraction less than 40%, global hypokinesia was detected in 12 (70.59%) patients. In echocardiography, the mean ejection fraction was 47.06 (3.8%). Eight patients had Dengue Shock Syndrome and the mean ejection fraction was 39.63%. Authors concluded that, acute reversible cardiac insult may be noticed in DHF and DSS could be responsible for hypotension/shock.

Kuo CH et al.[44] studied the impact of dengue on liver function by biochemical tests on 125 male and 145 female patients diagnosed with this disease during an outbreak that extended from November 1987 to December 1988 in Taiwan. Abnormal levels of aspartate aminotransferase (AST), alanine

aminotransferase (ALT), bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase (GGT) were observed in 93.3%, 82.2%, 7.2%, 16.3% and 83.0% of the patients, respectively. Study concluded that, dengue fever might cause hepatic injury and transaminase elevation similar to that in patients with conventional viral hepatitis. In epidemic or endemic areas, dengue fever infection should be considered in the differential diagnosis of hepatitis.

In a study by Shivbalan S et al.[46] during 2004 on the predictors of spontaneous bleeding in dengue, a platelet count of less than 50,000 was found to be significantly associated with increased risk of bleeding. The other associated predictors of bleeding in the study conducted were prolonged PT, raised AST/ALT and hemoconcentration.

In a study by Venkat Sai PM et al.[48] on the role of USG in dengue fever, 100% of the patients showed gall bladder thickening and pericholecystic fluid, 21% had hepatomegaly, 6.25% had splenomegaly and minimal right pleural effusion. In a follow up USG on the 5th day in the same patients, 53% had ascites. Study concluded that, in an epidemic of dengue, ultrasound features of thickened gall bladder wall, pleural effusion and ascites should strongly favour the diagnosis of dengue fever.

Recently, Kumar A et al.[49] in his record-based study conducted in a coastal district of Karnataka to study the clinical manifestations, trend and outcome of all confirmed dengue cases admitted in a tertiary care hospital assessed the laboratory confirmed cases from 2002 to 2008 from Medical Records Department (MRD). 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, 22 (33.3%) had ARDS and 20 (30.3%) had pleural effusion.

More recently Karoli R et al.[50] in their cross-sectional study at Lucknow during the monsoon and post-monsoon seasons in the year 2010 on 356 patients with suspected dengue fever found 138 (39%) had serologically confirmed dengue infection. Out of this Ninety-six (70%) patients had classical dengue fever while 42 (30%) had dengue hemorrhagic fever. The most common symptoms were headache (105, 76%), abdominal pain (87, 63%), vomiting (80, 58%), rash (36, 26%) and cutaneous hypersensitivity (22, 16%). Hemorrhagic manifestations were present in 55 (40%) patients. Notably, 14% of patients had neurological involvement and 4% had acute hepatic failure. Study concluded that dengue infection had varied and multi-systemic manifestations that can go unrecognized.

Atypical Manifestations of dengue fever

As the spread of dengue and dengue haemorrhagic fever is increasing, atypical manifestations are also on the rise, although they may be under reported because of lack of awareness. The endothelium is the target of the immunopathological mechanisms in dengue and DHF. The hallmark is vascular permeability and coagulation disorders. These mechanisms can explain varied systemic involvement.[16]

There should be a high index of suspicion of the various atypical clinical presentations involving various organs / systems which include;[17]

- Neurological manifestations - Encephalopathy, acute motor weakness, seizures, neuritis, Guillain Barre syndrome, hypokalemic paralysis, acute viral myositis, acute encephalitis;
- Hepatic involvement - Acute liver failure, hepatic encephalopathy, hepatomegaly, jaundice and petechial rashes;
- Myositis - Acute myositis, pure motor quadriplegia;
- Cardiac involvement - Acute reversible cardiac insult, sinoatrial block and atrioventricular dissociation;
- Lupus erythematosus (systemic) - Abnormal immune response leading to systemic lupus erythematosus;
- Occlar complications & uveitis - Unilateral blurring of inferior visual field;
- Renal complications - Renal dysfunction, acute kidney injury;
- Gastrointestinal Complications- such as Lower gastrointestinal bleeding and acute inflammatory colitis;
- Cutaneous manifestations - Maculopapular/morbilliform eruption followed by ecchymotic, petechial, and macular/scarlatiniform eruption, confluent erythema, morbilliform eruptions, and hemorrhagic lesions;

Involvement of liver in dengue infections

DF usually starts with a high fever and is often accompanied by a rash, headache and abdominal pains lasting 2–7 days. Frank haemorrhage is uncommon during DF but gastrointestinal bleeding, gingival bleeding and petechiae have been reported in some patients. DHF can occur in primary infections but is more common in secondary infections and also starts with a high fever that is not significantly different from that observed in DF patients. Haemorrhagic phenomenon may be

minimal, but around the time of defervescence, patients develop the hallmark of DHF, namely, significant plasma leakage, which in DSS is further characterized by tachycardia and hypotension. If the plasma leakage is severe and remains untreated, patients may develop shock, which can be fatal.[52]

While the main manifestations of severe dengue disease are primarily haemorrhagic in nature, a significant body of work has been accumulated which implicates the liver as a critical part of the disease pathology.[52]

Hepatomegaly

Perhaps the most obvious sign of the involvement of the liver in dengue infections is the high proportion of dengue cases with liver enlargement. In one of the earliest large-scale series of clinical investigations into dengue, Halstead and colleagues observed that the frequency of liver enlargement was similar in both primary and secondary dengue infections, and the authors proposed that a moderate liver enlargement may be a part of the "normal" pathological response to dengue infection.[52]

More recent studies have been somewhat divided, with some reports suggesting that hepatomegaly is present at between 50–100% of cases[53-55] while others document a significantly lower rate of hepatomegaly.[48,56-58] In addition, some studies support a higher rate of hepatomegaly in DHF/ DSS cases as opposed to DF cases although this may not reach statistical significance. On balance, the studies tend to support a high level of hepatomegaly in dengue cases, with perhaps a slightly higher rate in the more severe cases, although this may depend somewhat upon the exact case definitions used.[52]

Clinical evidence of liver involvement in dengue infections includes the presence of hepatomegaly and increased serum liver enzymes. Hepatomegaly is frequent and is commoner in patients with DHF than in those with DF. Several studies document raised serum transaminase levels in dengue infection. Transaminase levels are also higher in DHF/DSS than in DF and tend to return to normal 14—21 d after infection.[52]

Kuo et al.[44] (1992) evaluated 270 dengue patients and found abnormal aspartate transaminase (AST) and alanine aminotransaminase (ALT) levels in 93.3 and 82.2%, respectively. Most had mild to moderate increases, while levels more than 10 times the normal upper limit were seen in 11.2 and 7.4% of patients.

Nimmannitya[59] (1987), investigating 145 dengue patients, found ALT levels to be normal, slightly elevated or significantly elevated in 74, 18 and 8% of patients, respectively. No mention of AST levels were found in this report.

Wahid et al.[60] (2000) studied 50 serologically confirmed cases of dengue (25 cases each of DF and DHF), and found serum AST and ALT levels to be significantly higher in patients with DHF.

In addition, Mohan et al.[45] (2000), who evaluated children with dengue (37 cases of DF, 16 with DHF and 8 with DSS), found abnormal transaminases in 96%, with higher levels in DHF/DSS.

Of 1585 dengue patients (65% with primary dengue, 91% with DF) studied by Souza et al.[61] (2004), during a dengue epidemic in Rio de Janeiro, Brazil, alterations in AST and ALT were seen in 63.4 and 45% of patients, with 3.8% having transaminase levels >10 times the upper limit of normal. Fulminant hepatic

failure complicating severe DHF/DSS has also been documented, and is associated with a poor prognosis.[62]

Nimmannitya et al.[59] (1987) have reported 18 DHF cases with jaundice and encephalopathy, of whom 10 died. Varying abnormalities in liver enzymes appear to be present in most patients with symptomatic dengue infections, but they tend to recover soon. There does not appear to be chronic liver damage as with the hepatitis B and C viruses. In a subgroup of predominantly DHF/DSS patients, severe liver dysfunction occurs and is a marker of poor prognosis. During some dengue epidemics, greater degrees of liver damage are seen. Although this may be a consequence of different dengue serotypes having varying tissue trophism, this has not been widely studied.[62]

Liver enzymes

Upon injury to the liver, the enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are released into the bloodstream, and as a consequence these enzymes are believed to be sensitive indicators of liver damage. Perhaps, unsurprisingly, these enzymes are frequently elevated in dengue patients, as has been shown in numerous studies.[44,58,63-65]

In one large series of patients examined for both AST and ALT levels, Kuo and colleagues evaluated 240 dengue patients from the 1987–1988 outbreak in Taiwan.[44] Elevated levels of AST and ALT were found in 93.3% and 82.2% of cases respectively. While the majority of patients had only mildly or moderately elevated levels of these transaminases, some 10% (11% and 7% for AST and ALT respectively) of patients had levels elevated by 10-fold or greater.

Somewhat lower levels of liver enzyme disorder were noted by de Souza and colleagues[65] in their study of 1585 dengue patients, and they observed alterations of AST and ALT levels in 63% and 45% of patients respectively.

Interestingly, however, the authors noted that the average levels of AST and ALT were significantly higher in DHF patients than in DF patients, an observation supported by other studies.[45,60]

Several authors have noted that the levels of serum AST are greater than serum ALT,[45,5864] which is in contrast to the normal finding with viral hepatitis.[66] Some evidence has suggested that there is a greater degree of involvement of the liver in infections with DENV-3 and DENV-4.[52]

Overall, the studies are consistent with elevated levels of liver enzymes being a common characteristic of dengue disease, and as such possibly represent a discriminating factor in differentiating dengue from other febrile diseases, but is of less use in differentiating DF from DHF.[52]

While both hepatomegaly and alterations in liver enzymes point to the involvement of the liver in the disease, they are unable to distinguish between the result of a bystander or secondary effect. As such, a number of studies have sought to provide direct evidence for the involvement of the liver in the disease process.

The direct histological investigations of specimens from the livers of fatal cases of dengue infection were microvesicular steatosis and small foci of hepatocellular necrosis in addition to the presence of councilman bodies, Kupffer cell hyperplasia and mononuclear cell infiltrates at the portal tract.[52] In this respect, the liver damage seen in fatal dengue cases is significantly less severe than that seen

in fatal cases of yellow fever virus infection. While relatively uncommon, cases of fulminant hepatitis have also been documented.[52]

Several studies have used an immunohistochemical approach to detect the presence of dengue antigens in liver specimens. These studies have predominantly used antibodies directed against dengue E protein, although one recent study used an antibody directed against dengue NS3 protein, which gives a greater degree of certainty that infected cells are undergoing viral replication and do not reflect the presence of endocytosed or phagocytosed virus particles without viral replication. The majority of the studies detect, to a greater or lesser extent, the presence of dengue antigen in hepatocytes, the major cell type composing the liver. Interestingly, while some studies have suggested that 80–90% of hepatocytes show immunoreactivity, other studies fail to detect dengue antigen in hepatocytes at all. Whether this extreme difference is due to methodological or samplepreparation differences, or truly reflects a different tissue tropism of some dengue virus lineages remains unclear at this point.[52] While some studies have detected the presence of dengue antigen in Kupffer cells, the study by Balsitis and colleagues[67] did not detect the presence of immunoreactive NS3 in these cells, suggesting thereby that Kupffer cells do not support replication of the dengue virus, and immunoreactivity to dengue structural proteins noted by others may reflect phagocytosed virus. This would be consistent with the studies by Marianneau and colleagues who showed that dengue was efficiently taken up by isolated primary human Kupffer cells, but that the infection was non-productive.[52]

Histological changes reported in the liver in dengue include: microvesicular steatosis, hepatocellular necrosis, Kupffer cell hyperplasia and destruction,

Councilman bodies and cellular infiltrates at the portal tract. Most reports are based on small numbers of samples obtained from fatal cases. The presence of thrombocytopenia and coagulative dysfunction makes it difficult to obtain samples from others. As such, one is unsure of the degree of changes present in those with milder disease. Steatosis occurs frequently in hepatitis of viral origin and no special significance can be attributed to this process in dengue infections. Hepatocellular necrosis in dengue generally affects the midzonal area and sometimes the centrolobular area. Reasons for this pattern may be that hepatocytes in this zone are more sensitive to anoxia or the products of an immune response (e.g. cytokines and chemokines) or that the dengue virus preferentially infects cells in this zone. In fact, dengue viral RNA and protein have been detected in midzonal hepatocytes, mostly around necrotic foci. Councilman (acidophilic) bodies correspond to hepatocytes showing the characteristic morphology of apoptosis. Inflammatory mononuclear cell infiltrates (of varying intensity) are seen in most specimens studied so far.[62]

Some investigators suggest that liver damage may be potentiated by the intake of drugs (such as acetaminophen and anti-emetics) during the early phase of the illness, but others do not see this. The course appears not to be influenced by concomitant hepatitis virus infection. Although hepatitis B virus (HBV) is hyperendemic in parts of South America and in the Far East, no evidence exists that HBV infection acts as a co-factor for hepatic damage in dengue infections. In dengue infections, elevations in serum AST appear to be greater than ALT levels. This differs from the pattern in viral hepatitis, in which ALT levels are usually higher than or equal to AST levels, but it is similar to that seen with alcoholic hepatitis. The exact significance of this pattern seen in dengue is uncertain. It has

been suggested that it may be due to excess release of AST from damaged myocytes during dengue infections, but this has not been formally tested. Simultaneous measurement of muscle isoforms of lactate dehydrogenase and creatinine kinase may help further clarify this observation. The elevated AST levels tend to return to normal more rapidly than ALT levels. This is possibly because AST (12.5—22 h) has a shorter half-life than ALT (32—43 h).[62]

Overall, clinical and experimental observations suggest that liver involvement occurs during dengue infections. Clinical evidence includes hepatomegaly and increased serum liver enzymes, with liver involvement being more pronounced in the more severe forms of infection. Dengue viral antigens have been found within hepatocytes, and the virus appears to be able to replicate in both hepatocytes and Kupffer cells, and dysregulated host immune responses may play an important causative role in liver damage. Modulating these immune responses may have a therapeutic potential. There are limitations in the investigation of liver involvement in dengue infection. Immunopathological lesions in the liver are difficult to study in patients with thrombocytopenia and coagulative dysfunction; present knowledge is based mainly on post-mortem specimens and animal models.

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was one year cross-sectional study.

Study period and duration

This study was conducted for the period of one year from January 2013 to December 2013.

Place

The present study was done in the 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 during the study period were enrolled.

Sample size

A total of 100 patients with dengue fever were studied.

Sampling procedure

Due to scarcity of literature on the involvement of hepatic dysfunction in patients with dengue fever, all the patients fulfilling the inclusion criteria during the study period were included in the study.

Selection criteria

Inclusion

- Patients with age group more than 18 yrs.
- Patients with signs and symptoms of dengue infection like fever, headache, arthralgia, myalgia, retro-orbital pain, nausea, vomiting, prostration, leukopenia, blood hemoconcentration and low platelet count.
- Serologically positive for anti-dengue IgM antibodies.

Exclusion

- Patients on hepatotoxic drugs
- Alcoholics
- Hepatitis B and Hepatitis C infections.
- Other concurrent liver dysfunction.

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 briefed about the nature of study and a written informed consent was obtained (Annexure I).

Method of collection of data

Demographic data such as age and sex were noted. Patients were interviewed and presenting complaints were noted. These patients underwent general physical examination and systemic examination and the findings were noted on a predesigned and pretested proforma (Annexure II).

Investigations

The selected patients underwent the following investigations.

- Complete blood count
- Platelet count
- DENGUE IgM
- Liver function tests (transaminases, bilirubin, albumin, PT)
- USG Abdomen
- IgM HCV, HBsAg, ELISA for HIV

Outcome variables

Severity of dengue fever

Patients who were seropositive for Dengue were classified on the basis of WHO Criteria[68,69] as follows:

- Dengue Fever (DF)
- Dengue Hemorrhagic Fever (DHF)

  Four cardinal features of DHF as defined by WHO are as follows:

  1. Fever or history of fever lasting 2–7 days, occasionally biphasic
  2. A hemorrhagic tendency shown by at least one of the following: a positive tourniquet test; petechiae, ecchymoses or purpura; bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations; or hematemesis or melena
  3. Thrombocytopenia [≤ 100,000 cells/mm^3 (100×10^9/L)]
  4. Evidence of plasma leakage owing to increased vascular permeability shown by: an increase in hematocrit ≥20% above the average for age, sex and population; a decrease in the hematocrit after intervention ≥ 20% of baseline; signs of plasma leakage such as pleural effusion, ascites or hypoproteinaemia.

- Dengue Shock Syndrome (DSS) - For a case of DSS, all four criteria for DHF must be met, in addition to evidence of circulatory failure manifested by:
  - Rapid and weak pulse *and* narrow pulse pressure (<20 mmHg or 2.7 kPa) *manifested by* Hypotension for age a*nd* Cold, clammy skin and restlessness or lethargy.

Liver involvement

Patients with raised AST (> 40 IU/L) and ALT (> 50 IU/L) levels and raised total bilirubin levels (>1.00 mg/dL) were regarded having liver involvement.

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 and Fisher's exact test. The continuous data was expressed as mean ± standard deviation (SD). A probability value ('p' value) of less than or equal to 0.05 at 95% CI was considered as statistically significant.

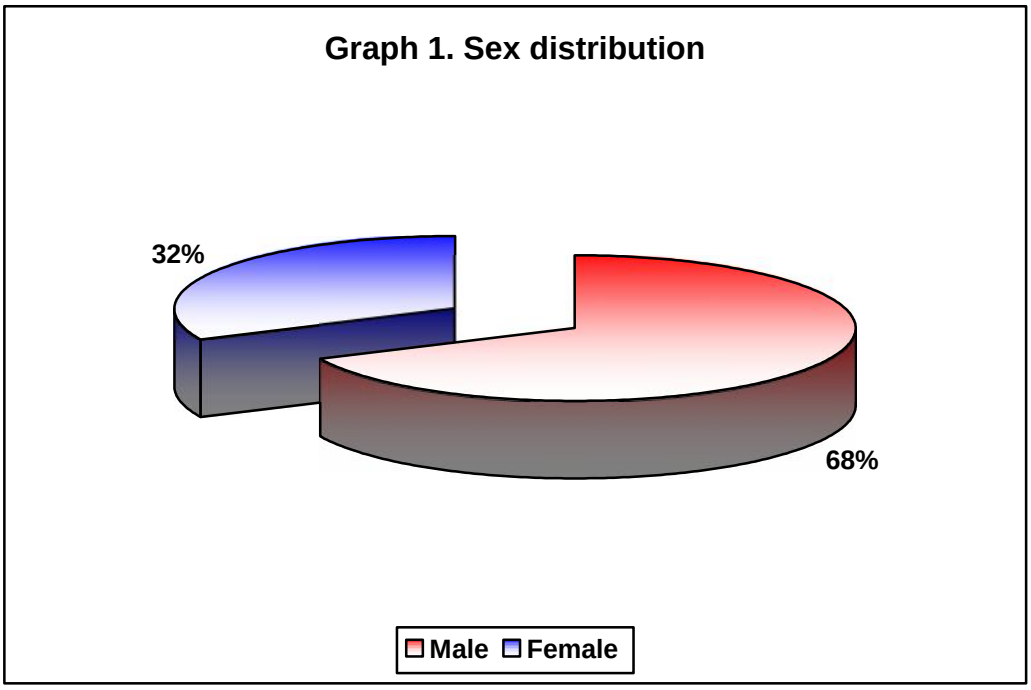
RESULTS

This one year cross-sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients who presented with dengue fever from January 2013 to December 2013 were enrolled.

Data obtained was analysed and the final results and observations were tabulated as below.

Table 1. Sex distribution

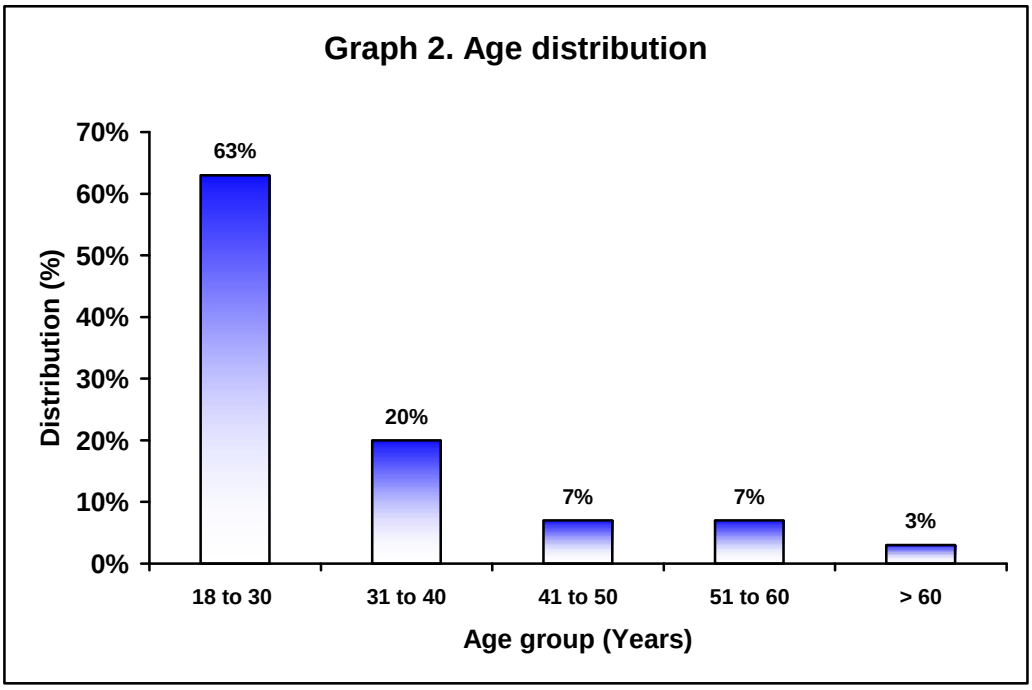
Sex	Distribution (n=100)	
	Number	**Percentage**
Male	68	68.00
Female	32	32.00
Total	**100**	**100.00**



In the present study 68% of the patients were males and 32% were females. The male to female ratio was 2.12:1.

Table 2. Age distribution

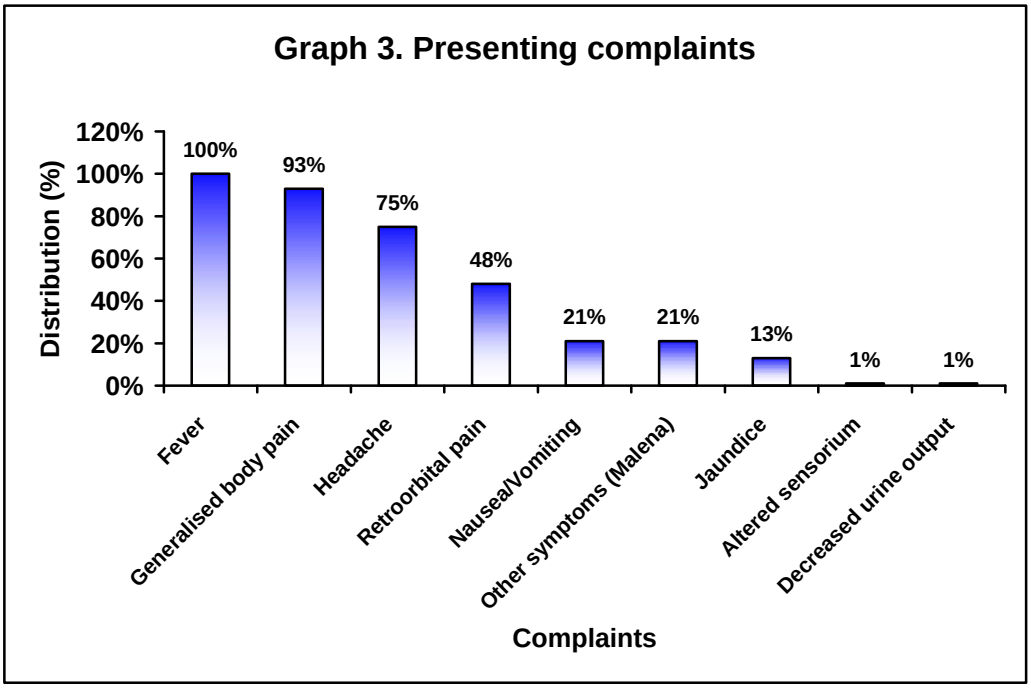
Age group (Years)	Distribution (n=100)	
	Number	**Percentage**
18 to 30	63	63.00
31 to 40	20	20.00
41 to 50	7	7.00
51 to 60	7	7.00
> 60	3	3.00
Total	**100**	**100.00**



In the present study the commonest age group was 18 to 30 years (63%) followed by 31 to 40 years (20%). The mean age was 30.33 ± 12.63 years.

Table 3. Presenting complaints

Complaints	Distribution (n=100)	
	Number	Percentage
Fever	100	100.00
Generalised body pain	93	93.00
Headache	75	75.00
Retroorbital pain	48	48.00
Nausea / Vomiting	21	21.00
Malena	21	21.00
Jaundice	13	13.00
Altered sensorium	1	1.00
Decreased urine output	1	1.00



In this study all the patients presented with fever (100%). The next common presentation was generalized body pain (93%) followed by headache (75%), Retroorbital pain (48%), nausea and vomiting (21%), malena (21%). The other symptoms are as shown in table 3 and graph 3.

Table 4. History of other comorbid conditions

History	Distribution (n=100)	
	Number	**Percentage**
Hypertension	6	6.00
Diabetes mellitus	1	1.00

In the present study 6% of the patients gave history of hypertension and 1% had diabetes mellitus.

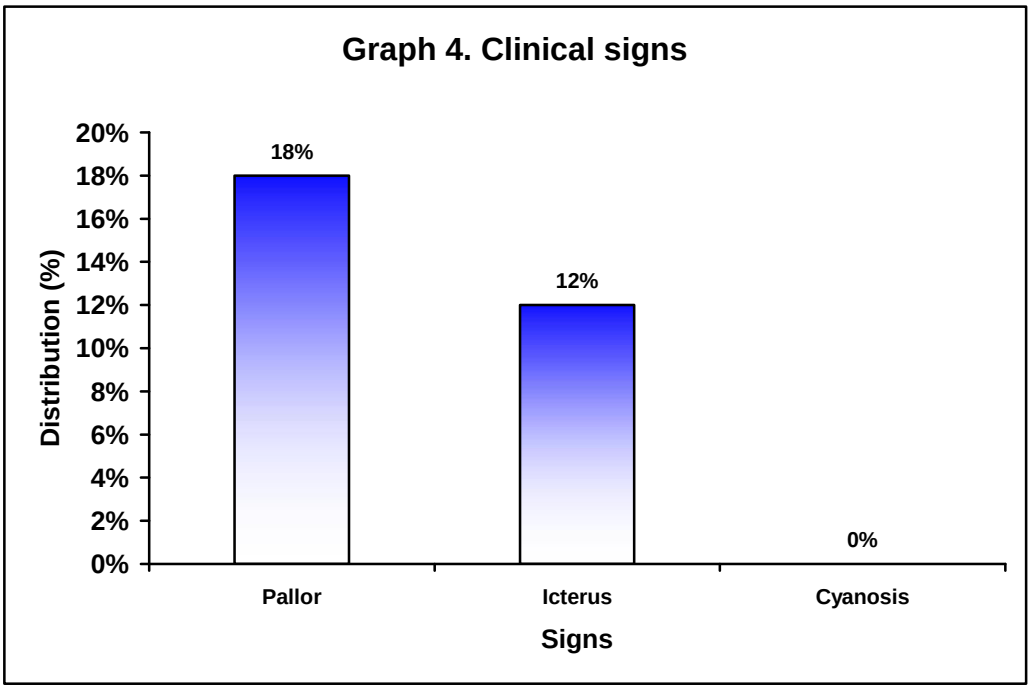
Table 5. Clinical examination findings - Vitals

Variables	Distribution (n=100)	
	Mean	**SD**
Pulse (Per minute)	67.78	9.31
Respirator rate (per minute)	13.02	2.11
Systolic BP (mm Hg)	105.50	10.92
Diastolic BP (per minute)	69.74	6.96

The mean pulse rate, respiratory rate, systolic blood pressure, diastolic blood pressure of the study population are as shown in table 5.

Table 6. Clinical signs

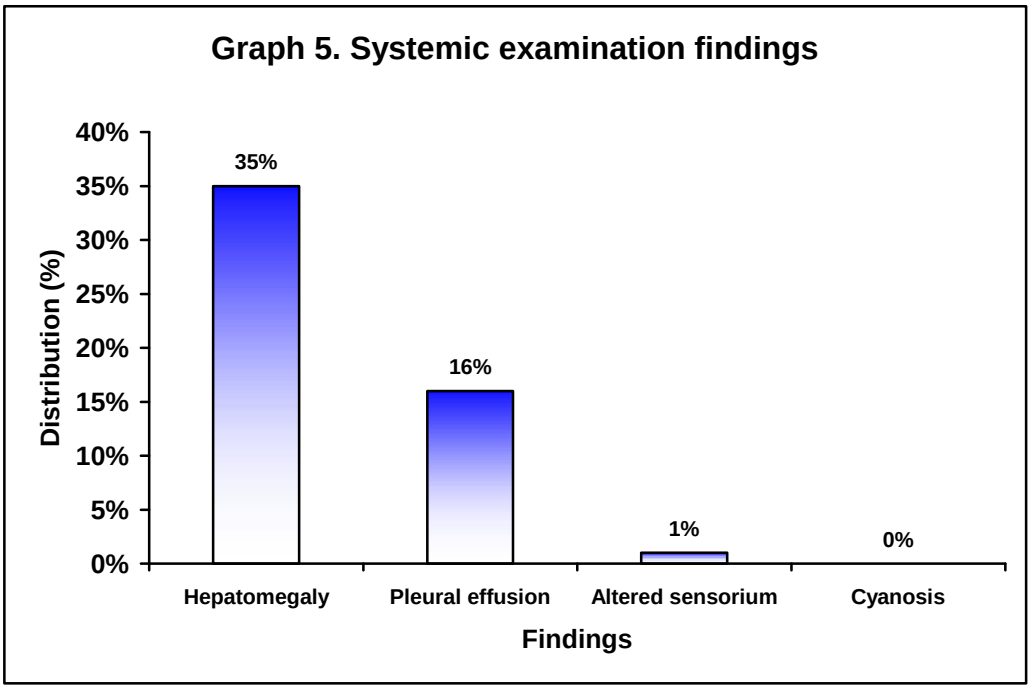
Signs	Distribution (n=100)	
	Number	Percentage
Pallor	18	18.00
Icterus	12	12.00
Cyanosis	0	0.00



In this study on clinical examination, pallor and icterus were present in 18% and 12% of the patients.

Table 7. Systemic examination findings

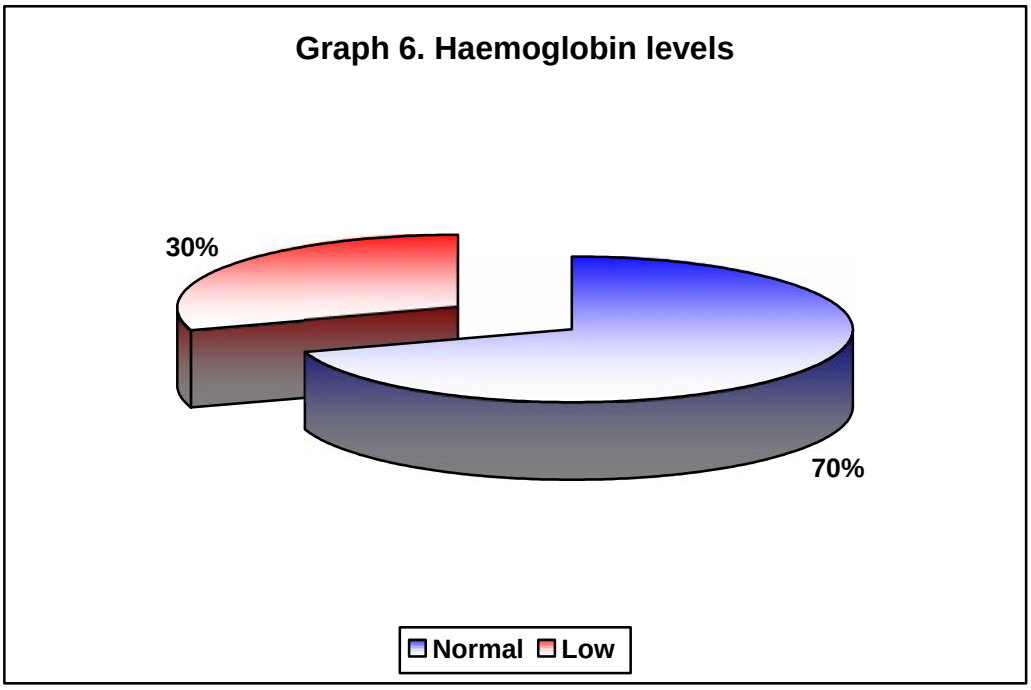
Findings	Distribution (n=100)	
	Number	Percentage
Hepatomegaly	35	35.00
Pleural effusion	16	16.00
Altered sensorium	1	1.00
Cyanosis	0	0.00



In the present study on systemic examination, 35% of the patients had hepatomegaly, 16% had pleural effusion and 1% had altered sensorium.

Table 8. Haemoglobin levels

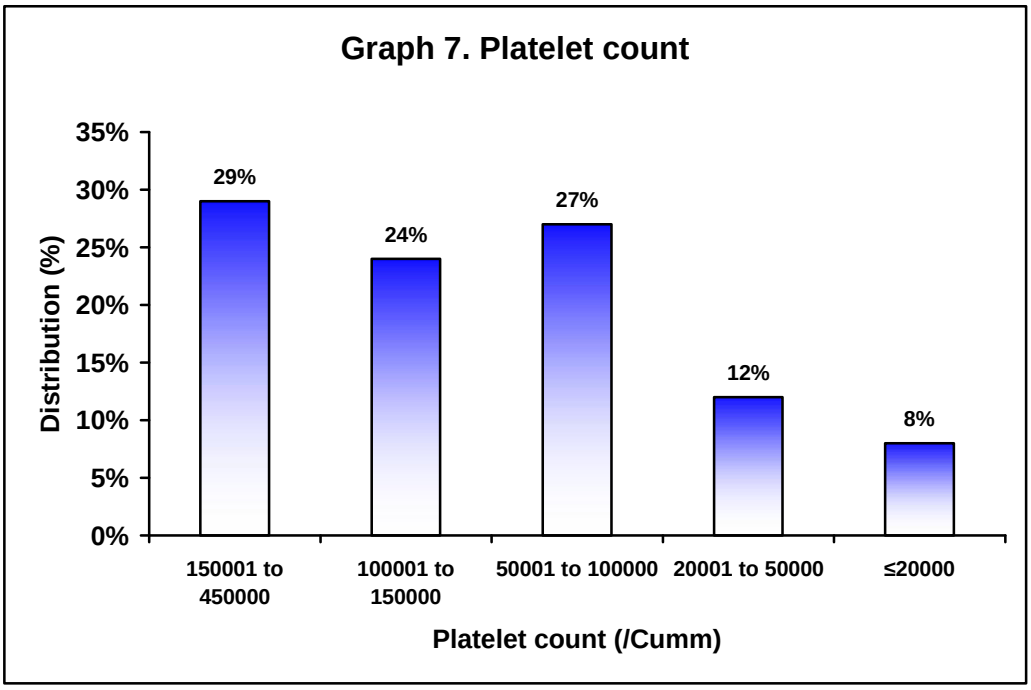
Haemoglobin	Distribution (n=100)	
	Number	Percentage
Normal (≥12.5 gm%)	70	70.00
Low (<12.5 gm%)	30	30.00
Total	**100**	**100.00**



In the present study haemoglobin levels were < 12.5 gm% in 30% of the patients. The mean haemoglobin levels were 13.57 ± 2.79 gm%.

Table 9. Platelet count

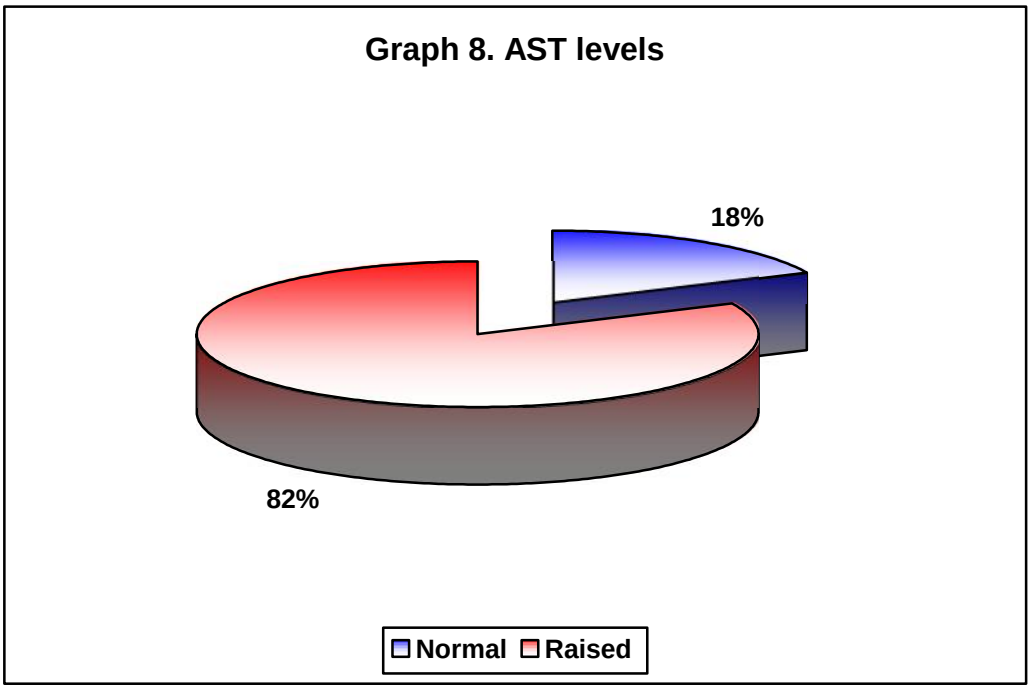
Platelet count (/Cumm)	Distribution (n=100)	
	Number	**Percentage**
150001-450000	29	29.00
100001-150000	24	24.00
50001-100000	27	27.00
20001-50000	12	12.00
≤20000	8	8.00
Total	**100**	**100.00**



In this study most of the patients (29%) had platelet count between 150001 to 450000 /cumm. The mean platelet count was found to be 64427 ± 56848 /cumm.

Table 10. AST levels

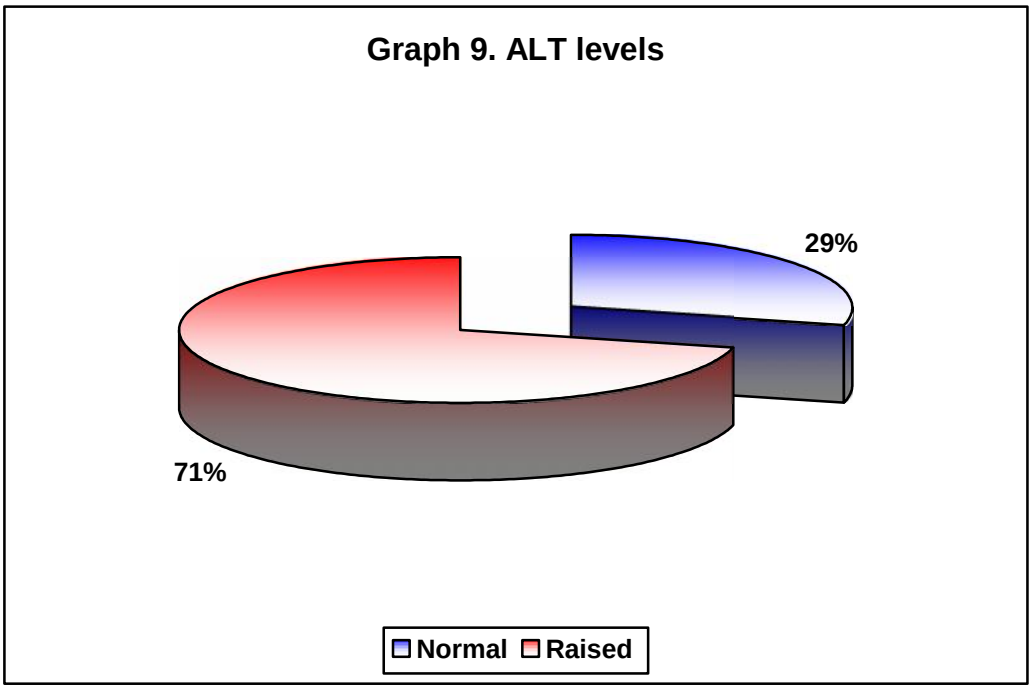
AST (IU/L)	Distribution (n=100)	
	Number	**Percentage**
Normal (≤ 40)	18	18.00
Raised (>40)	82	82.00
Total	**100**	**100.00**



In the present study 82% of the patients had raised AST levels. The mean AST levels were 460.99 ± 1553.2 IU/L.

Table 11. ALT levels

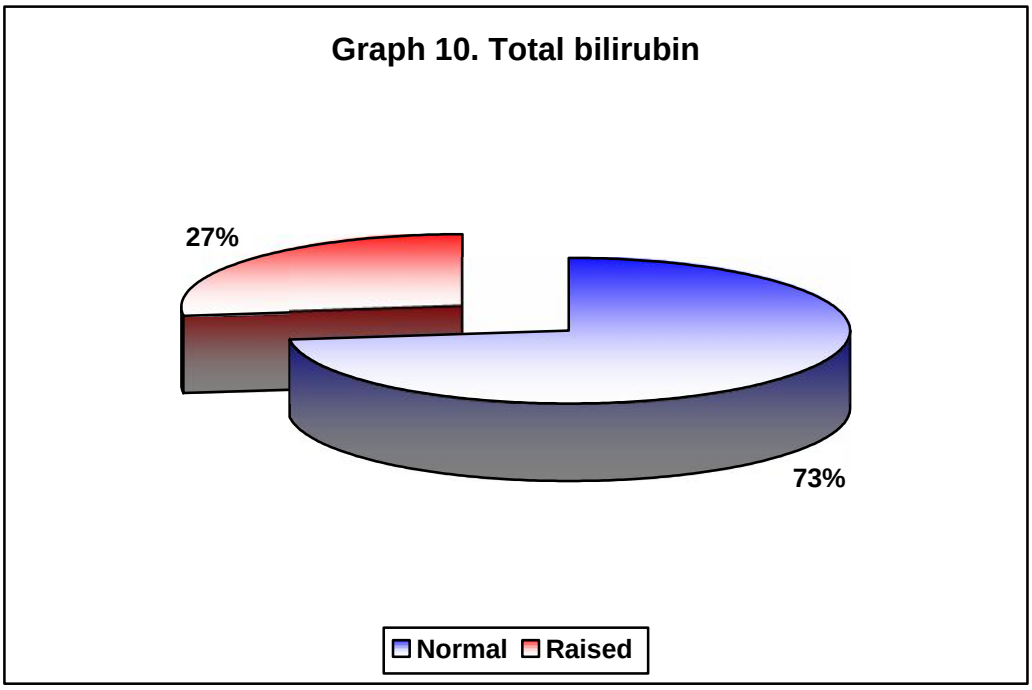
ALT (IU/L)	Distribution (n=100)	
	Number	**Percentage**
Normal (≤ 40)	29	29.00
Raised (>40)	71	71.00
Total	**100**	**100.00**



In the present study 71% of the patients had raised ALT levels. The mean ALT levels were 202.77 ± 568.91 IU/L.

Table 12. Total bilirubin

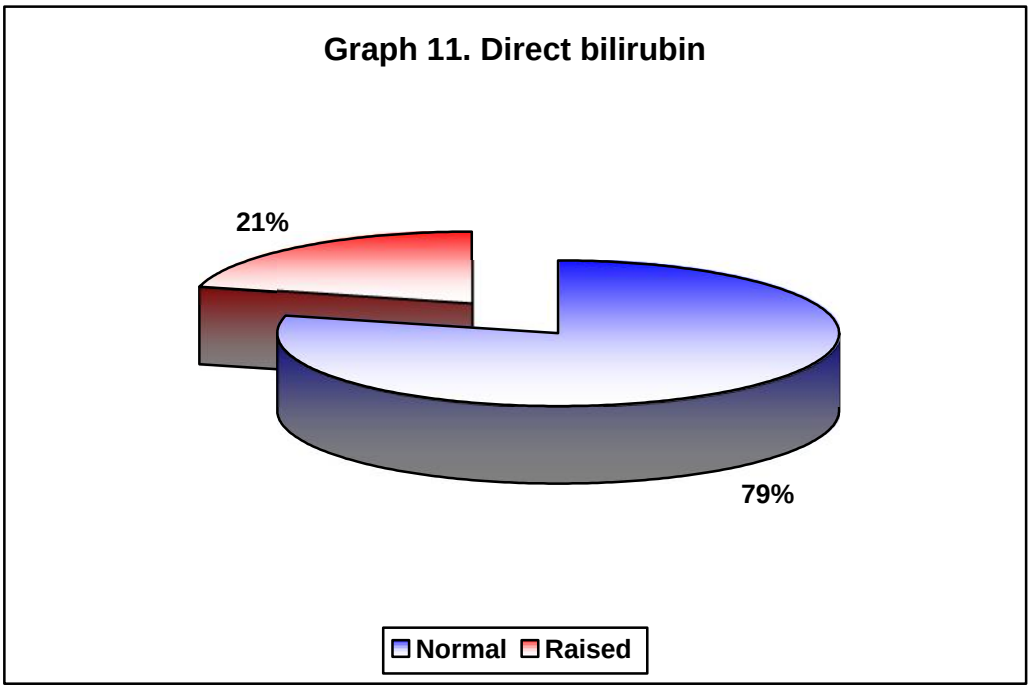
Total bilirubin (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
Normal (≤ 1)	73	73.00
Raised (>50)	27	27.00
Total	**100**	**100.00**



In this study 27% of the patients had raised total bilirubin levels. The mean bilirubin levels were noted as 1.31 ± 1.61 mg/dL.

Table 13. Direct bilirubin

Direct bilirubin (mg/dL)	Distribution (n=100)	
	Number	**Percentage**
Normal (≤ 0.8)	79	79.00
Raised (>0.8)	21	21.00
Total	**100**	**100.00**



In the present study 21% of the patients had raised direct bilirubin levels. The mean direct bilirubin levels were found to be 0.77 ± 1.36 mg/dL.

Table 14. Total protein

Total protein (g/dL)	Distribution (n=100)	
	Number	**Percentage**
≤ 6	22	22.00
>6	78	78.00
Total	**100**	**100.00**

In this study the total protein levels were found to be ≤ 6 g/dL in 22% of the patients and the mean total protein levels were 6.56 ± 0.95 g/dL.

Table 15. Albumin

Albumin (g/dL)	Distribution (n=100)	
	Number	**Percentage**
Normal (≤ 3.5)	54	54.00
Low (>3.5)	46	46.00
Total	**100**	**100.00**

In the present study the albumin levels low in 46% of the patients. The mean albumin levels were 3.33 ± 0.64 g/dL.

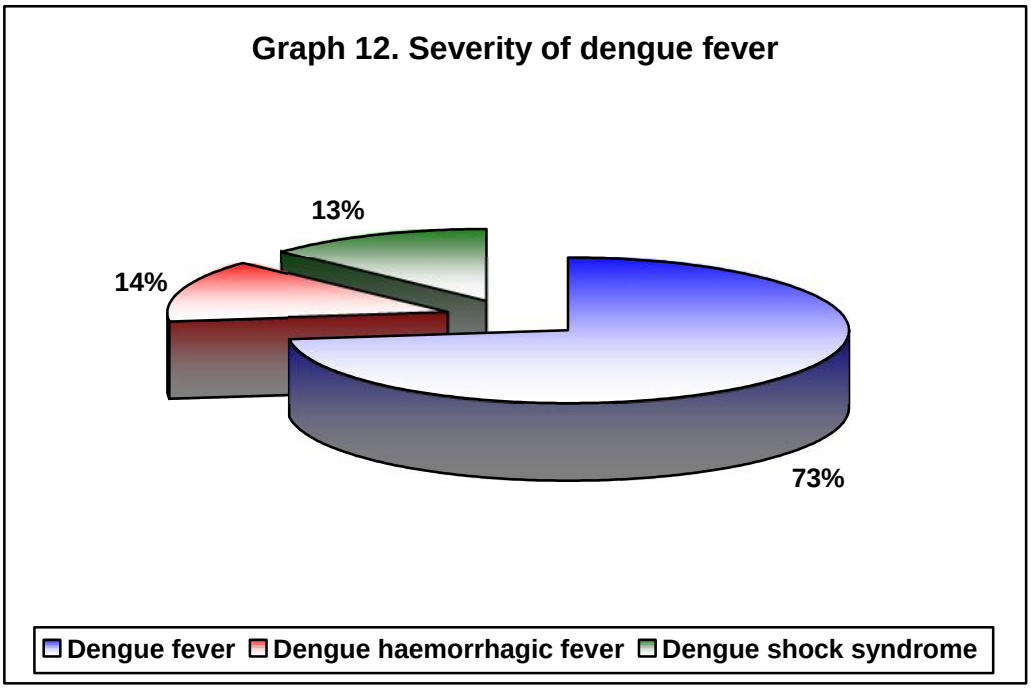
Table 16. USG findings

Findings	Distribution (n=100)	
	Number	**Percentage**
Thickened gall bladder wall	35	35.00
Normal	65	65.00
Total	**100**	**100.00**

In this study, on USG, thickened gall bladder wall was noted in 35% of the patients.

Table 17. Severity of dengue fever

Severity	Distribution (n=100)	
	Number	**Percentage**
Dengue fever	73	73.00
Dengue haemorrhagic fever	14	14.00
Dengue shock syndrome	13	13.00
Total	**100**	**100.00**



In this study, majority of the patients were diagnosed to have dengue fever (73%) while dengue haemorrhagic fever and dengue shock syndrome were noted in 14% and 13% respectively.

Table 18. Association of AST with severity of dengue

Dengue severity	AST levels (IU/L)				Total	
	≤ 40		> 40			
	No	%	No	%	No	%
Dengue fever	15	20.55	58	79.45	73	100.00
Dengue haemorrhagic fever	1	7.14	13	92.86	14	100.00
Dengue shock syndrome	2	15.38	11	84.62	13	100.00
Total	**18**	**18.00**	**82**	**82.00**	**100**	**100.00**

p = 0.586

In the present study of the maximum (92.86%) patients with DHF had raised AST levels. However no statistically significant association was found between AST and severity of dengue (p=0.586).

Table 19. Association of ALTwith severity of dengue

Dengue severity	ALT levels (IU/L)				Total	
	≤ 50		> 50			
	No	%	No	%	No	%
Dengue fever	24	32.88	49	67.12	73	100.00
Dengue haemorrhagic fever	0	0.00	14	100.00	14	100.00
Dengue shock syndrome	5	38.46	8	61.54	13	100.00
Total	**29**	**29.00**	**71**	**71.00**	**100**	**100.00**

p = 0.016

In this study all the patients with DHF (100%) had raised ALT levels and positive association was noted between ALT levels and dengue severity (p=0.016)

Table 20. Association of direct bilirubin with severity of dengue

Dengue severity	Serum Bilirubin (mg/dL)				Total	
	≤ 1		> 1			
	No	**%**	**No**	**%**	**No**	**%**
Dengue fever	58	79.45	15	20.55	73	100.00
Dengue haemorrhagic fever	6	42.86	8	57.14	14	100.00
Dengue shock syndrome	9	69.23	4	30.77	13	100.00
Total	**73**	**73.00**	**27**	**27.00**	**100**	**100.00**

p = 0.019

In the present study serum bilirubin levels were raised in 57.14% of the patients with DHF compared to 20.55% with dengue fever and 30.77% with DSS. This difference was statistically significant (p=0.019).

DISCUSSION

Dengue is one of the most important arboviral infections of humans.1 The disease is caused by four antigenically distinct but related dengue viruses (DENV 1–4) and is transmitted primarily by Aedes aegypti mosquito. The spectrum of Dengue infection has been conventionally divided into Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Unusual manifestations involving liver and central nervous system in dengue infection have been reported. Hepatic dysfunction is a well-recognized feature of dengue infections, often demonstrated by hepatomegaly and mild-to moderate increases in transaminase levels although jaundice and acute liver failure are generally less common. The incidence of hepatic dysfunction is more in DHF than in DF. However, there are few case reports of fulminant hepatic failure in DHF.[69] This study was aimed to assess the clinical and bio-chemical profile of liver involvement in dengue infected patients.

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 2013 to December 2013. A total of 100 patients presenting with dengue fever were studied.

In the present study males (68%) outnumbered females (32%) with male to female ratio of 2.12:1. These findings were comparable with a study done by Agarwal et al[70] in which male to female ratio was 1.9:1. Another study conducted by Sharma et al[42] showed that male to female ratio was 3:1.

In this study most of the patients were aged between 18 to 30 years (63%) followed by 31 to 40 years (20%) and the mean age was 30.33 ± 12.63 years suggesting most commonly affected age group is between 18 to 40 years. These findings were similar to a study from AIIMS by S. Sharma et al.[42] who reported the median age as 26.3 years and also similar to the Mexico study by Navarette J[72] that is, 26.9 years. All series indicate that the most commonly affected age group is between 20 to 40 years.

In this study fever was present in all the cases (100%). Majority of the patients had generalized body pain (93%) followed by headache (75%). The other common clinical presentations were retroorbital pain (48%), nausea and vomiting (21%), malena (21%). On clinical examination, 18% of the patients had pallor and 12% had icterus. In other Indian studies from AIIMS by S. Sharma et al,[42] fever was found in 100%, abdominal pain in 38%, skin rashes in 36.5%, bleeding tendency in 70%. In the Chennai study by Narayanan M,[73] fever was found in 98%, headache in 28%, abdominal pain in 20%, bleeding tendency in 21%. In the Mangalore study by Padabidri VS[74] fever was found in 100%, myalgia in 76% and headache in 48% of patients. Recently, Kumar A et al.[49] in his record-based study conducted in a coastal district of Karnataka to assess the clinical manifestations, trend and outcome of all confirmed dengue cases admitted in a tertiary care hospital assessed the laboratory confirmed cases from 2002 to 2008 from Medical Records Department (MRD). 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%). Another study[74] from Mumbai, to study the clinical profile of dengue fever reported fever as the major presenting complaint in all these cases

(100%). The other common presenting symptoms were icterus in 25.8%, myalgia in 25.0%, and headache in 13.9%. Overall there is wide variation in the clinical presentation of dengue fever. However the findings of our study were similar to the other Indian studies.[42,49,73,74]

Clinical evidence of liver involvement in dengue infections includes the presence of hepatomegaly. In the present study systemic examination revealed 35% of the patients with hepatomegaly. More recent studies have been somewhat divided, with some reports suggesting that hepatomegaly is present at between 50–100% of cases[53-55] while others document a significantly lower rate of hepatomegaly.[48,56-58] In a study from India, 79% of the patients had hepatomegaly.[76] Indian studies from Chennai by Manjit Narayanan[73] showed hepatomegaly in 60% and a study in Delhi by B. K. Triparhi[83] in 23% of the cases.

In the present study signs of anaemia were noted in 30% of the patients (haemoglobin levels were < 12.5 gm%). However, the mean haemoglobin levels were normal (13.57 ± 2.79 gm%). In contrast, a study from AIIMS, New Delhi by Sharma S,[42] reported an average haemoglobin concentration of 11.6 gm/dL.

In this study as high as 82% of the patients had raised AST levels with mean AST levels of 460.99 ± 1553.2 IU/L while 71% of the patients had raised ALT levels and mean ALT levels were 202.77 ± 568.91 IU/L. Hepatic involvement in dengue infections is often demonstrated by hepatomegaly and mild-to- moderate increases in transaminase levels. Clinical evidence included hepatomegaly and increased serum liver enzymes, with liver involvement being more pronounced in the more severe forms of infection. In dengue infections, elevations in serum AST

appear to be greater than ALT levels. The same was true in this study. This differs from the pattern in viral hepatitis, in which ALT levels are usually higher than or equal to AST levels. The causes from these indications are still uncertain. It has been suggested that it may be due to excess release of AST from damaged myocytes during dengue infections. The elevated AST levels tend to return to normal more rapidly than ALT levels. This is possibly because AST (12.5—22 h) has a shorter half-life than ALT (32—43 h).[69] In a study[69] from Nepal, liver enzyme AST was increased with the value more than 50 IU/ml in 78.4% and 96.5% of cases of DF and DHF respectively. Similarly, ALT value was raised in 53.8% of DF and 74.1% of DHF patients. The difference in the rise of liver enzymes in DHF and DF was statistically significant (P<0.001). Various studies in the past reported liver dysfunction to be more common in DHF than in DF patients.[76-78] The results of this study also support these findings as maximum (92.86%) patients with DHF had raised AST levels and all the patients with DHF (100%) had raised ALT levels and positive association was noted between ALT levels and dengue severity (p=0.016). However no statistically significant association was found between AST and severity of dengue (p=0.586).

Kuo et al.[44] reported that most severely ill patients had higher levels of aminotransferases whereas increases in bilirubin was unrelated to the severity of the disease. In contrast, 27% of the patients had raised total bilirubin levels in this study and mean bilirubin levels were noted as 1.31±1.61 mg/dL. The serum bilirubin levels significantly raised in 57.14% of the patients with DHF compared to 20.55% with dengue fever and 30.77% with DSS (p=0.019).

Overall the present study showed that, hepatic dysfunction in the form of raised ALT and AST levels, and jaundice is common in patients with dengue infection. However, care must be taken not to make a mistaken diagnosis of viral hepatitis.

CONCLUSION

Based on the findings of this study it may be concluded that, liver injury is nearly universal in adult patients with dengue fever. Further, the spectrum of liver involvement in dengue varies as per the severity of dengue infection.

SUMMARY

Over the last few years, atypical manifestations of dengue have been described, including elevations in aminotransferase levels, with reactive hepatitis and kidney involvement. The present study was undertaken to assess the clinical and bio-chemical profile of liver involvement in dengue infected patients.

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients who presented with dengue fever from January 2013 to December 2013 were enrolled.

Most of the patients were male 68% and male to female ratio was 2.12:1. The commonest age group was 18 to 30 years (63%) and the mean age was 30.33 ± 12.63 years. All the patients presented with fever (100%) and next common presentation was generalized body pain (93%). On clinical examination, pallor and icterus were present in 18% and 12% of the patients. Systemic examination revealed, 35% of the patients had hepatomegaly, 16% had pleural effusion and 1% had altered sensorium. Majority (82%) of the patients had raised AST levels and mean AST levels were 460.99 ± 1553.2 IU/L. Raised ALT levels were noted in 71% of the patients and mean ALT levels were 202.77 ± 568.91 IU/L. 27% of the patients had raised total bilirubin levels and mean bilirubin levels were 1.31 ± 1.61 mg/dL. In this study, majority of the patients were diagnosed to have dengue fever (73%) while dengue haemorrhagic fever and dengue shock syndrome were noted in 14% and 13% respectively. Positive association was noted with raised ALT levels and DHF

(p=0.016). Also serum bilirubin levels were raised significantly in patients with DHF (p=0.019).

Liver dysfunction in the form of raised ALT and AST levels, and jaundice are common in patients with dengue infection.

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ANNEXURE I – CONSENT FORM

"THE CLINICAL AND BIOCHEMICAL PROFILE OF LIVER INVOLVEMENT IN DENGUE INFECTED PATIENT" A ONE YEAR CROSS SECTIONAL STUDY

Objective and purpose of the study

This research is intended to study the clinical and biochemical profile of liver involvement in patients with dengue infection. The data on liver involvement in dengue is scarce. So this study intends to study the profile of liver involvement in dengue fever. The principal investigator of the study is Dr. **** **** under the guidance of Dr. **** ******

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood sample and undergo USG abdomen.

Risk and Benefits:

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

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

VOLUNTARY PARTICIPATION/ WITHDRAWAL:

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

Privacy and Confidentiality

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

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

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

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing. If you have any questions about your rights as a participant you may call

Dr. **** *****
Investigator,
PG in General Medicine,
J. N. Medical College,
Phone No.: 9964318727

Dr. ****** ****** MD
Associate professor
Department of Medicine,
J. N. Medical College,
Phone No: 08312473788,
Extn: 1371/1520

Dr. ***** ***** MD DCP DTM
Chairman,
J.N.M.C Ethical Committee for
Human Research,
Phone number: 0831-2471350.
Extn: 1527

CONSENT FORM

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

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

Participant's Name/ : ……

Signature/ Left Thumb
Impression of the participant's : ……

Name of the legally
authorized representative/ Guardian : ……

Signature/ Left Thumb
Impression. : ……

Witness's Name : ……

Signature/ Left Thumb Impression. :……

Investigators name and Signature : ……

Date and Place : …….

ANNEXURE II – PROFORMA

"THE CLINICAL AND BIOCHEMICAL PROFILE OF LIVER INVOLVEMENT IN DENGUE INFECTED PATIENT"

1. SL.NO
2 NAME:
3. AGE:
4. SEX
5. OCCUPCTION:
6. RELIGION:
7. I.P. NO./O.P. NO.:
8. ADDRESS:
9. DATE OF ADMISSION: 10.DATE OF DISCHARGE:

HISTORY:

FEVER	YES/NO
JAUNDICE	YES/NO
GENERILISED BODY PAINS	YES/NO
HEADACHE	YES/NO
NAUSEA / VOMITING	YES/NO
ALTERED SENSORIUM	YES/NO
DECREASE URINE OUTPUT	YES/NO

ANY OTHER SYMPTOM:

PAST HISTORY:

TREATMENT HISTORY:

PERSONAL HISTORY:

H/O SMOKING:	YES / NO
H/O ALCOHOL CONSUMPTION	YES/ NO
GENERAL CONDITION:	
PALLOR	YES/NO
ICTERUS	YES/NO
CYANOSIS	YES/NO

VITALS:

TEMPERATURE:

PULSE:

RESPIRATORY RATE:

BLOOD PRESSURE:

SYSTEMIC EXAMINATION:

- CVS:
- RESPIRATORY SYSTEM:
- PER ABDOMEN:
- CNS:

INVESTIGATIONS:

- CBC
- DENGUE IgM
- LIVER TRANSAMINASES
- USG ABDOMEN
- IgM HCV,
- HBsAg,
- ELISA FOR HIV

DIAGNOSIS

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
ALT	-	Alanine transaminase
AST	-	Aspartate aminotransferase
BP	-	Blood pressure
CNS	-	Central nervous system
Cumm	-	Cubic millimeter
CVS	-	Cardiovascular system
DF	-	Dengue fever
DHF	-	Dengue haemorrhagic fever
DSS	-	Dengue shock syndrome
ELISA	-	Enzyme linked immunosorban assay
F	-	Female
GBWT	-	Gall bladder wall thickening
gm	-	Grams
H	-	Hepatomegaly
HBsAg	-	Hepatitis B surface antigen
HCV	-	Hepatitis C virus
HIV	-	Human immunodeficiency virus
IgM	-	Immunoglobin M
IU/L	-	International units per liter
M	-	Male
mg/dL	-	Milligrams per deciliter

ML	-	Malena
mm Hg	-	Millimeters of mercury
N	-	Normal
Syst. exam.	-	Systemic examination
USG	-	Ultrasound

ANNEXURE III - MASTER CHART

Serial Number	In patient number	Age (Years)	Sex	Preentation										History			Habits		General physical examination							Syst. Exam.				Investigations																				
																			Vitals																																
																					BP																														
				Fever	Jaundice	Generalised body pain	Headache	Retroorbital pain	Nausea / Vomiting	Altered sensorium	Decreased urine output	Other symptoms	Diabetes mellitus	Hypertension	Hepatotoxic drugs	Alcohol	Smoking	Pulse (/Minute)	Respiratory rate (/Minute)	SBP (mm Hg)	DBP (mm Hg)	Pallor	Icterus	Cyanosis	CVS	Respiratory system	Per abdomen	CNS	Haemoglobin (gm%)	Platelet count (/Cumm)	Total count (/Cumm)	Dengue IgM	AST (IU/L)	ALT (IU/L)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	Total protein	Albumin	Serum creatinine (mg/dL)	USG abdomen	IgM anti HCV	HBsAg	ELISA for HIV	Diagnosis
1	553224	34	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	66	10	110	70	-	-	-	N	N	H	N	14.2	90000	3000	+	57	66	0.54	0.18	6.7	3.9	1.1	N	-	-	-	DF
2	550968	48	F	+	-	+	+	+	+	-	-	ML	-	+	-	-	-	74	12	144	80	-	-	-	N	N	N	N	15.3	8000	12600	+	1473	592	1.45	1.4	4.7	2	1.4	GBWT	-	-	-	DHF
3	548908	22	M	+	+	+	+	+	+	-	-	ML	-	-	-	-	-	90	16	114	80	-	+	-	N	N	N	N	16.4	6000	9800	+	8605	2769	7.46	5.28	4.9	2.8	1.1	GBWT	-	-	-	DHF
4	567465	34	F	+	+	+	+	+	+	-	-	ML	-	-	-	-	-	92	20	100	70	-	+	-	N	N	N	N	14.5	14000	11500	+	5264	1811	4.5	3.2	5.4	3	1.2	GBWT	-	-	-	DHF
5	567552	42	F	+	-	+	+	+	-	-	-	-	-	-	-	-	-	66	10	134	80	-	+	-	N	N	H	N	15.1	65000	2500	+	158	115	1.5	1.2	5.2	3.1	1	N	-	-	-	DF
6	567799	26	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	68	12	104	70	-	-	-	N	N	N	N	17.5	25000	3000	+	261	101	1.4	1.1	4.5	3	0.9	N	-	-	-	DF
7	549678	19	F	+	-	+	-	-	-	-	-	-	-	-	-	-	-	74	14	110	70	-	-	-	N	N	N	N	15.2	2E+05	5400	+	107	72	1.6	1	5	2.8	0.8	N	-	-	-	DF
8	551981	21	M	+	-	+	+	-	+	-	-	-	-	-	-	-	-	88	20	90	70	+	-	-	N	N	H	N	5.8	6000	700	+	538	174	0.79	0.71	4.7	1.7	0.83	N	-	-	-	DF
9	538370	20	M	+	-	+	+	+	-	-	-	ML	-	-	-	-	-	70	16	120	70	-	-	-	N	N	N	N	18.8	5000	5400	+	254	172	1.8	1.14	7.8	4.5	1.09	N	-	-	-	DHF
10	533663	32	M	+	+	+	+	+	+	-	-	ML	-	-	-	-	-	70	18	106	70	-	+	-	N	N	H	N	15.6	33000	7900	+	262	135	9.22	7.42	7	3.5	0.79	GBWT	-	-	-	DHF
11	519856	29	M	+	+	+	+	+	+	-	-	ML	-	-	-	-	-	84	16	110	70	-	+	-	N	N	H	N	11.9	8000	9700	+	698	395	7.38	5.83	5.2	2.2	2.18	N	-	-	-	DHF
12	519606	34	F	+	-	+	-	-	-	-	-	-	-	-	-	-	-	78	14	114	80	-	-	-	N	N	N	N	13.6	3E+05	13400	+	29	149	0.37	0.09	7.3	3.9	0.95	N	-	-	-	DF
13	548851	19	F	+	-	+	+	+	-	-	-	-	-	-	-	-	-	68	14	110	70	+	-	-	N	N	N	N	9.1	77000	2800	+	108	92	0.47	0.15	6.4	3.1	0.43	N	-	-	-	DF
14	550913	25	F	+	-	+	-	-	-	-	-	-	-	-	-	-	-	72	12	106	70	-	-	-	N	N	H	N	11.9	91000	3000	+	68	33	0.92	0.55	7	3.6	0.9	N	-	-	-	DF
15	511719	27	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	64	14	100	70	-	-	-	N	N	N	N	15.2	74000	3300	+	142	54	0.7	0.2	6.9	3.8	0.7	N	-	-	-	DF
16	532045	37	M	+	-	-	-	-	-	-	-	-	-	-	-	-	-	72	12	116	80	-	-	-	N	N	N	N	11.5	96000	12400	+	255	207	0.74	0.24	6.2	3.2	1.24	N	-	-	-	DF
17	550948	34	F	+	-	-	-	-	-	-	-	-	-	-	-	-	-	74	14	106	70	-	-	-	N	N	H	N	12.9	1E+05	6800	+	99	81	0.5	0.2	6.5	3.5	1.1	N	-	-	-	DF
18	529422	19	M	+	+	+	+	+	+	-	-	ML	-	-	-	-	-	56	12	100	70	-	-	-	N	N	N	N	18.1	10000	3600	+	525	269	2.2	1.8	7.2	3.8	1.2	GBWT	-	-	-	DHF
19	538593	38	F	+	+	+	+	+	+	+	+	-	-	-	-	-	-	88	18	90	60	+	+	-	N	CR	N	AS	11.9	13000	32000	+	10077	4486	3.2	1.96	5	1.9	3.2	GBWT	-	-	-	DSS
20	557987	47	M	+	+	+	-	-	+	-	-	-	-	+	-	-	-	60	16	130	80	+	+	-	N	N	H	N	10.4	75000	4800	+	41	83	5.77	4.98	5.1	2.1	1.35	N	-	-	-	DF
21	557937	52	M	+	+	+	+	+	-	-	-	-	+	+	-	-	-	56	15	126	70	-	+	-	N	CR	N	N	15.3	44000	2300	+	134	142	2.97	2.56	6.2	3	1.43	GBWT	-	-	-	DF
22	548467	21	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	52	14	96	60	-	-	-	N	N	N	N	16.4	32000	11300	+	128	64	0.54	0.15	6.2	3.1	0.88	GBWT	-	-	-	DF
23	546797	50	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	62	14	100	70	-	-	-	N	N	N	N	15.7	46000	8400	+	40	38	0.95	0.41	6.8	3.4	1.34	N	-	-	-	DF
24	534722	27	F	+	-	-	-	-	-	-	-	-	-	-	-	-	-	66	12	104	60	+	-	-	N	N	H	N	10.9	1E+05	2000	+	230	160	1.2	1	6.5	3	1.1	N	-	-	-	DF
25	528792	23	F	+	-	+	+	+	+	-	-	-	-	-	-	-	-	56	14	90	60	+	-	-	N	CR	N	N	6.7	21000	2100	+	30	29	0.37	0.25	5.4	2.6	1.18	N	-	-	-	DSS
26	528668	19	M	+	-	+	+	+	-	-	-	ML	-	-	-	-	-	54	14	80	50	-	-	-	N	CR	N	N	16.5	13000	6500	+	193	114	0.45	0.09	5.6	3	0.83	GBWT	-	-	-	DSS
27	532920	31	M	+	+	+	-	-	-	-	-	ML	-	-	-	-	-	58	16	90	50	-	+	-	N	CR	H	N	17.3	15000	5900	+	121	161	2.06	0.5	6.7	3.3	0.85	GBWT	-	-	-	DSS
28	532049	19	M	+	-	+	+	-	-	-	-	ML	-	-	-	-	-	58	16	90	60	-	-	-	N	CR	N	N	16	11000	2600	+	119	31	0.39	0.08	5.2	2.8	0.8	GBWT	-	-	-	DSS
29	520388	20	M	+	-	+	+	+	-	-	-	ML	-	-	-	-	-	55	14	94	60	+	-	-	N	CR	H	N	11.3	10000	7000	+	48	32	1.19	0.46	4.6	2.2	0.94	GBWT	-	-	-	DSS
30	543567	35	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	63	12	110	70	-	-	-	N	N	N	N	14.3	24000	6560	+	114	106	0.9	0.3	6.7	3.4	1.3	N	-	-	-	DF

ANNEXURE III - MASTER CHART

				Preentation										History			Habits		General physical examination							Syst. Exam.				Investigations																		
																			Vitals																														
																					BP																										
Serial Number	In patient number	Age (Years)	Sex	Fever	Jaundice	Generalised body pain	Headache	Retroorbital pain	Nausea / Vomiting	Altered sensorium	Decreased urine output	Other symptoms	Diabetes mellitus	Hypertension	Hepatotoxic drugs	Alcohol	Smoking	Pulse (/Minute)	Respiratory rate (/Minute)	SBP (mm Hg)	DBP (mm Hg)	Pallor	Icterus	Cyanosis	CVS	Respiratory system	Per abdomen	CNS	Haemoglobin (gm%)	Platelet count (/Cumm)	Total count (/Cumm)	Dengue IgM	AST (IU/L)	ALT (IU/L)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	Total protein	Albumin	Serum creatinine (mg/dL)	USG abdomen	IgM anti HCV	HBsAg	ELISA for HIV	Diagnosis
31	543599	49	M	+	+	+	-	-	+	-	-	-	-	+	-	-	-	70	14	134	80	-	-	-	N	N	H	N	14.4	49000	5900	+	61	58	2.5	1.1	7.5	3.5	0.8	N	-	-	-	DF
32	544725	26	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	54	14	90	70	-	-	-	N	N	N	N	15.1	14000	5300	+	305	255	0.6	0.2	6.1	3.5	1	GBWT	-	-	-	DSS
33	544899	21	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	64	12	106	80	-	-	-	N	N	N	N	15.3	41000	2820	+	299	191	0.9	0.3	6.7	3.8	0.9	N	-	-	-	DF
34	546031	23	F	+	-	-	-	-	-	-	-	-	-	-	-	-	-	70	14	100	70	-	-	-	N	N	H	N	11.3	2E+05	2580	+	26	18	0.8	0.2	6.9	3.9	0.6	N	-	-	-	DF
35	546053	19	M	+	-	+	+	-	-	-	-	ML	-	-	-	-	-	54	16	94	60	-	-	-	N	CR	N	N	13.4	12000	6890	+	105	107	0.9	0.5	8.5	4.1	0.9	GBWT	-	-	-	DSS
36	548479	23	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	60	14	104	60	-	-	-	N	N	N	N	14.6	24000	4620	+	17	20	0.9	0.3	7	3.4	0.8	GBWT	-	-	-	DF
37	548502	27	F	+	-	+	-	-	-	-	-	-	-	-	-	-	-	64	12	110	70	-	-	-	N	N	H	N	13.4	47000	4500	+	109	88	0.4	0.2	8.2	3.6	1.2	N	-	-	-	DF
38	550795	35	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	70	14	100	70	-	-	-	N	N	N	N	11.2	1E+05	14000	+	24	15	0.8	0.2	8.2	3.7	0.9	N	-	-	-	DF
39	550956	22	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	66	12	96	70	-	-	-	N	N	N	N	12.1	33000	3400	+	233	105	0.13	0.14	6.2	2.8	0.54	N	-	-	-	DF
40	544875	39	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	56	14	106	70	-	-	-	N	N	H	N	15.4	56000	3400	+	194	127	1.03	0.42	8	3.5	0.94	N	-	-	-	DF
41	544890	29	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	60	12	110	70	-	-	-	N	N	N	N	13	1E+05	1900	+	38	48	0.38	0.05	6.3	3.2	0.89	N	-	-	-	DF
42	551970	25	M	+	-	-	-	-	-	-	-	-	-	-	-	-	-	76	12	108	70	-	-	-	N	N	H	N	15.1	1E+05	3000	+	24	23	0.7	0.2	6.8	3.4	1.6	N	-	-	-	DF
43	551959	35	M	+	-	-	-	-	-	-	-	-	-	-	-	-	-	70	14	100	60	-	-	-	N	N	N	N	15.3	1E+05	4600	+	34	11	0.8	0.2	7	3.8	2.1	N	-	-	-	DF
44	549740	35	F	+	-	-	-	-	-	-	-	-	-	-	-	-	-	66	12	110	70	-	-	-	N	N	H	N	13.3	2E+05	2700	+	60	55	0.8	0.2	8.2	3.9	0.7	N	-	-	-	DF
45	549646	60	M	+	-	+	+	-	-	-	-	-	-	+	-	-	-	56	14	90	70	+	-	-	N	CR	N	N	9	24000	4760	+	31	20	1	0.4	6.2	3.3	0.9	GBWT	-	-	-	DSS
46	546049	51	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	76	12	124	70	-	-	-	N	N	N	N	13.8	2E+05	5050	+	58	60	0.9	0.3	8	4.2	1	N	-	-	-	DF
47	539840	28	F	+	-	+	+	+	-	-	-	-	-	-	-	-	-	64	12	106	80	+	-	-	N	N	H	N	8.2	69000	2500	+	43	28	0.32	0.11	5	2.1	0.7	GBWT	-	-	-	DF
48	538134	75	M	+	-	+	+	-	-	-	-	ML	-	+	-	-	-	60	14	100	60	+	-	-	N	CR	N	N	8.3	5000	3100	+	36	75	0.31	0.06	6.2	3.2	2.1	GBWT	-	-	-	DHF
49	538362	29	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	70	12	110	70	-	-	-	N	N	N	N	16.6	61000	10500	+	51	61	0.67	0.18	7.3	3.6	0.65	N	-	-	-	DF
50	538553	20	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	60	12	100	70	-	-	-	N	N	H	N	15.6	20000	11500	+	109	50	0.42	0.12	6.9	3.5	1	N	-	-	-	DF
51	539719	19	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	78	14	120	80	-	-	-	N	N	N	N	12.6	2E+05	7800	+	41	80	1.1	0.5	8.1	4.5	1.3	N	-	-	-	DF
52	539669	40	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	62	12	100	70	-	-	-	N	N	N	N	12.6	1E+05	4300	+	21	38	0.7	0.2	7.7	4.1	0.9	N	-	-	-	DF
53	539697	24	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	70	14	122	80	-	-	-	N	N	H	N	14.7	3E+05	9700	+	19	26	0.7	0.2	8.3	4.4	1.1	N	-	-	-	DF
54	536960	55	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	66	12	106	70	+	-	-	N	N	N	N	6.4	23000	3600	+	121	110	0.8	0.2	6.2	3.6	2	GBWT	-	-	-	DF
55	536854	65	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	60	14	110	80	-	-	-	N	N	N	N	12.5	86000	3700	+	38	21	0.6	0.2	7	4	1.2	N	-	-	-	DF
56	536481	28	M	+	-	+	+	+	+	-	-	ML	-	-	-	-	-	56	14	100	70	-	-	-	N	CR	N	N	15.9	22000	3200	+	354	134	0.35	0.13	6	3.5	1.04	GBWT	-	-	-	DHF
57	536887	19	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	54	12	90	70	-	-	-	N	CR	H	N	17.4	16000	6900	+	513	228	0.71	0.24	6.5	3.2	0.9	GBWT	-	-	-	DSS
58	536967	19	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	76	10	122	84	-	-	-	N	N	N	N	13.5	82000	2300	+	83	42	0.8	0.2	6.5	4	1.3	N	-	-	-	DF
59	536483	21	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	70	16	110	80	+	-	-	N	N	N	N	8.3	85000	2800	+	97	70	0.6	0.1	7.6	4.4	1.1	N	-	-	-	DF
60	536464	40	F	+	-	+	+	+	-	-	-	ML	-	-	-	-	-	60	12	100	60	-	-	-	N	N	H	N	14.2	15000	9000	+	249	116	0.8	0.2	6.5	3.5	2.4	N	-	-	-	DF

ANNEXURE III - MASTER CHART

				Preentation										History			Habits		General physical examination							Syst. Exam.				Investigations																					
																			Vitals																																	
																					BP																														
Serial Number	In patient number	Age (Years)	Sex	Fever	Jaundice	Generalised body pain	Headache	Retroorbital pain	Nausea / Vomiting	Altered sensorium	Decreased urine output	Other symptoms	Diabetes mellitus	Hypertension	Hepatotoxic drugs	Alcohol	Smoking	Pulse (/Minute)	Respiratory rate (/Minute)	SBP (mm Hg)	DBP (mm Hg)	Pallor	Icterus	Cyanosis	CVS	Respiratory system	Per abdomen	CNS	Haemoglobin (gm%)	Platelet count (/Cumm)	Total count (/Cumm)	Dengue IgM	AST (IU/L)	ALT (IU/L)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	Total protein	Albumin	Serum creatinine (mg/dL)	USG abdomen	IgM anti HCV	HBsAg	ELISA for HIV	Diagnosis
61	536491	36	F	+	-	+	+	+	-	-	-	-	-	-	-	-	-	78	14	110	70	+	-	-	N	N	N	N	8.5	1E+05	3700	+	87	93	0.8	0.1	7.5	4.1	1.1	N	-	-	-	DF
62	539655	26	M	+	-	+	+	+	+	-	-	-	-	-	-	-	-	60	12	100	70	-	-	-	N	N	H	N	14.8	34000	6100	+	189	100	0.39	0.16	5.7	3.1	0.79	N	-	-	-	DF
63	539634	19	M	+	-	+	+	+	+	-	-	ML	-	-	-	-	-	64	14	94	70	+	-	-	N	N	N	N	9.2	2000	6000	+	73	158	0.9	0.98	6.7	2.5	0.9	GBWT	-	-	-	DHF
64	539521	24	M	+	-	+	+	+	+	-	-	-	-	-	-	-	-	70	16	90	70	-	-	-	N	CR	H	N	17.6	52000	6000	+	414	173	0.81	0.34	6.8	3.1	1.5	GBWT	-	-	-	DSS
65	551942	20	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	86	12	104	70	-	-	-	N	N	N	N	15.8	89000	5600	+	169	102	1.1	0.29	7.8	3.7	1.23	N	-	-	-	DF
66	536011	26	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	70	12	100	60	-	-	-	N	N	H	N	15.7	3700	4400	+	140	130	0.8	0.2	6.8	3.4	0.8	N	-	-	-	DF
67	536034	28	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	80	10	110	70	+	-	-	N	N	N	N	8.6	74000	2500	+	27	25	0.9	0.3	6.4	3.3	0.8	N	-	-	-	DF
68	536768	19	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	60	10	104	60	-	-	-	N	N	H	N	12.3	70000	4000	+	76	37	0.3	0.1	7.6	4.4	1	GBWT	-	-	-	DF
69	537058	31	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	78	12	110	70	-	-	-	N	N	N	N	13.5	2E+05	11000	+	110	80	0.8	0.5	8	3.4	1.1	N	-	-	-	DF
70	537098	19	F	+	-	+	+	+	-	-	-	-	-	-	-	-	-	70	10	120	70	+	-	-	N	N	N	N	8.7	2E+05	4240	+	54	32	0.7	0.2	7.8	4.3	0.9	N	-	-	-	DF
71	537212	22	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	54	12	90	70	-	-	-	N	CR	N	N	13.3	68000	2770	+	212	125	0.5	0.3	6.7	4	1.3	GBWT	-	-	-	DSS
72	538351	40	F	+	-	+	-	-	-	-	-	-	-	-	-	-	-	80	12	110	80	+	-	-	N	N	N	N	9	1E+05	10100	+	27	25	0.8	0.2	7.7	3.8	0.8	N	-	-	-	DF
73	540159	20	M	+	-	+	+	+	+	-	-	-	-	-	-	-	-	60	14	94	70	-	-	-	N	N	H	N	14.7	28000	4600	+	617	180	0.3	0.1	6.4	3.2	0.8	N	-	-	-	DF
74	557974	42	M	+	+	+	+	+	-	-	-	-	-	-	-	-	-	70	11	100	70	-	+	-	N	N	N	N	15.2	75000	15000	+	93	79	5.4	5.1	6.2	2.2	2	GBWT	-	-	-	DF
75	560070	19	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	74	10	104	70	-	-	-	N	N	H	N	17.2	36000	3900	+	62	56	0.2	0.08	6.2	3	1.2	N	-	-	-	DF
76	559073	20	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	70	12	100	60	-	-	-	N	N	N	N	15	25000	8300	+	75	121	0.9	0.65	7	3.5	0.92	N	-	-	-	DF
77	564892	19	M	+	-	+	+	+	-	-	-	ML	-	-	-	-	-	60	10	110	70	-	-	-	N	N	H	N	15	26000	11400	+	299	155	0.3	0.1	7.6	3.3	0.8	GBWT	-	-	-	DHF
78	564215	26	F	+	+	+	+	+	+	-	-	ML	-	-	-	-	-	70	14	100	60	-	+	-	N	N	N	N	15.2	13000	11000	+	7121	1875	6.04	4.42	5.2	2.3	0.5	GBWT	-	-	-	DHF
79	564210	19	M	+	+	+	+	-	-	-	-	-	-	-	-	-	-	60	12	110	80	-	+	-	N	N	H	N	11.9	1E+05	14000	+	163	129	3.64	3.39	5.2	1.9	1.1	GBWT	-	-	-	DF
80	538404	46	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	70	14	100	80	-	-	-	N	N	N	N	12	1E+05	3900	+	287	113	1.66	0.97	6.5	2.2	1.01	N	-	-	-	DF
81	538370	20	M	+	-	+	+	+	+	-	-	ML	-	-	-	-	-	56	12	90	70	-	-	-	N	CR	H	N	18	5000	5400	+	254	172	0.83	0.14	7.8	4.5	1.09	N	-	-	-	DHF
82	537010	19	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	78	14	110	80	-	-	-	N	N	N	N	16	39000	1700	+	104	107	0.61	0.37	6.5	3	0.6	N	-	-	-	DF
83	547117	19	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	82	14	120	70	-	-	-	N	N	N	N	17	19000	2200	+	136	109	0.8	0.2	5.9	3.2	1.06	GBWT	-	-	-	DF
84	536756	31	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	70	10	110	80	-	-	-	N	N	N	N	16	51000	3800	+	98	44	0.3	0.1	6.9	4	1	N	-	-	-	DF
85	536703	20	M	+	-	+	-	-	-	-	-	-	-	-	-	-	-	84	12	120	70	-	-	-	N	N	H	N	13.5	2E+05	2400	+	134	117	0.8	0.2	6.4	4	1.3	N	-	-	-	DF
86	536726	23	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	60	14	100	60	-	-	-	N	N	N	N	14	2E+05	5300	+	32	25	0.9	0.2	6.5	3.1	1	N	-	-	-	DF
87	536854	65	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	70	12	110	70	-	-	-	N	N	N	N	12.5	86000	3700	+	58	21	0.6	0.2	7	4	1.2	N	-	-	-	DF
88	537061	58	F	+	-	+	+	+	-	-	-	-	-	-	-	-	-	76	10	100	70	-	-	-	N	N	N	N	11.2	80000	14000	+	54	31	0.76	0.19	5.1	2.6	0.9	GBWT	-	-	-	DF
89	541705	19	F	+	-	+	+	+	+	-	-	-	-	-	-	-	-	60	12	104	70	+	-	-	N	N	H	N	11	49000	6500	+	52	30	0.6	0.29	7.4	3.4	0.6	N	-	-	-	DF
90	542790	23	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	80	12	114	60	-	-	-	N	N	N	N	13.5	97000	5100	+	41	59	0.86	0.44	7.2	3.4	0.86	N	-	-	-	DF

ANNEXURE III - MASTER CHART

				Preentation										History			Habits		General physical examination							Syst. Exam.				Investigations																					
																			Vitals																																	
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Serial Number	In patient number	Age (Years)	Sex	Fever	Jaundice	Generalised body pain	Headache	Retroorbital pain	Nausea / Vomiting	Altered sensorium	Decreased urine output	Other symptoms	Diabetes mellitus	Hypertension	Hepatotoxic drugs	Alcohol	Smoking	Pulse (/Minute)	Respiratory rate (/Minute)	SBP (mm Hg)	DBP (mm Hg)	Pallor	Icterus	Cyanosis	CVS	Respiratory system	Per abdomen	CNS	Haemoglobin (gm%)	Platelet count (/Cumm)	Total count (/Cumm)	Dengue IgM	AST (IU/L)	ALT (IU/L)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	Total protein	Albumin	Serum creatinine (mg/dL)	USG abdomen	IgM anti HCV	HBsAg	ELISA for HIV	Diagnosis
91	540865	35	F	+	-	+	+	+	-	-	-	-	-	-	-	-	-	64	10	104	70	-	-	-	N	N	N	N	13.6	61000	3200	+	131	156	1.9	1.24	5.7	2.9	0.7	GBWT	-	-	-	DF
92	540447	24	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	76	14	110	70	-	-	-	N	N	N	N	15.5	70000	1700	+	83	62	0.26	0.06	6.2	3.7	0.9	N	-	-	-	DF
93	542238	29	M	+	-	+	+	+	+	-	-	ML	-	-	-	-	-	60	10	104	70	-	-	-	N	N	H	N	15	11000	2100	+	66	55	0.58	0.28	6.2	3.5	1.17	N	-	-	-	DF
94	540159	20	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	80	12	110	70	-	-	-	N	N	N	N	14.7	24000	4600	+	617	180	0.8	0.3	6.4	3.2	0.8	GBWT	-	-	-	DF
95	542368	19	F	+	-	+	+	-	-	-	-	-	-	-	-	-	-	72	10	106	70	-	-	-	N	N	N	N	12	70000	5860	+	34	25	1	0.4	7.1	3.1	0.7	N	-	-	-	DF
96	541059	21	M	+	-	+	+	+	-	-	-	ML	-	-	-	-	-	60	12	100	60	-	-	-	N	N	H	N	15	15000	5800	+	141	66	0.9	0.3	6.6	3.5	1.7	GBWT	-	-	-	DHF
97	541094	27	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	70	10	106	60	-	-	-	N	N	N	N	14.7	82000	3600	+	21	17	0.8	0.2	6.9	3.5	0.8	N	-	-	-	DF
98	542357	28	M	+	-	+	+	+	-	-	-	-	-	-	-	-	-	66	12	100	70	-	-	-	N	N	N	N	14.8	2E+05	3300	+	61	50	0.9	0.2	6.3	3.4	0.9	N	-	-	-	DF
99	541088	51	F	+	-	+	+	+	+	-	-	-	-	-	-	-	-	60	10	90	70	-	-	-	N	CR	N	N	11.9	32000	10000	+	49	47	1.48	0.5	5.5	2.4	1.5	GBWT	-	-	-	DSS
100	541008	56	M	+	-	+	+	-	-	-	-	-	-	-	-	-	-	78	14	110	80	-	-	-	N	N	N	N	15.8	1E+05	5100	+	67	103	2.05	0.59	6.4	3.7	0.65	N	-	-	-	DF