"CLINICAL, HEMATOLOGICAL, BIOCHEMICAL AND RADIOLOGICAL PREDICTORS OF SEVERITY AND OUTCOME IN DENGUE INFECTION"

By

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Dissertation submitted to B.L.D.E (Deemed to be University) Vijayapura.

In partial fulfillment of the requirements for the award of the degree of

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In

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LIST OF ABBREVIATIONS USED

Sl no.	Abbreviation	Full form
1	ALP	Alkaline phosphatase
2	ALT	Alanine transaminase
3	APTT	Activated partial thromboplastin time
4	AST	Aspartate transaminase
5	ATT	Anti tubercular therapy
6	AUC	Area under the curve
7	BIL	Bilirubin
8	CI	Confidence interval
9	CPK-MB	Creatine phosphokinase-muscle/brain
10	DF	Dengue fever without warning signs
11	DFWS	Dengue fever with warning signs
12	ELISA	Enzyme linked immunosorbent assay
13	FFP	Fresh frozen plasma
14	GB	Gall bladder
15	IgG	Immunoglobulin G
16	IgM	Immunoglobulin M
17	IU/L	International units per litre
18	mm^3	Cubic millimeter
19	n	Number of cases
20	NPV	Negative predictive value
21	NS1	Nonstructural protein 1

22	PCV	Packed cell volume
23	PLC	Platelet count
24	PLT	platelets
25	PPV	Standard Deviation
26	PT	Prothrombin time
27	ROC	Receiver operating characteristic
28	SD	Severe dengue
29	Sec	Seconds
30	SGOT	Serum glutamic oxaloacetic transaminase
31	SGPT	Serum glutamic pyruvic transaminase
32	SPC	Specificity
33	SPSS	Statistical Package for statistical sciences
34	STD	Standard deviation
35	TLC	Total leukocyte count
36	USG	Ultrasonography
37	WHO	World Health Organization

ABSTRACT

BACKGROUND

Dengue infection, the most prevalent arthropod-borne viral illness in humans, is caused by dengue virus and is one of the most important tropical infectious diseases of the world. Several outbreaks of dengue infection have been reported from India. There are very few studies in children regarding predictors of severity and outcome in dengue infection. This study was undertaken to see if we can predict the severity and outcome of dengue infection based on clinical and laboratory parameters at time of admission.

Objectives of the study:

- To document the clinical profile of patients with Dengue.
- To assess the association of AST, ALT and ultrasound with severity of dengue infection.
- To assess the association of CPK-MB with myocarditis in dengue infection.

Methodology

Hospital based prospective observational analytical study was performed on 65 patients proven to be dengue positive [NS1 or IgM or IgG positive (card test or ELISA)] admitted in pediatric ward and pediatric intensive care unit in Shri B.M.Patil Medical College, Hospital and Research Centre.. For these patients, specific investigations like complete hemogram which includes even platelet count and hematocrit, liver function tests (bilirubin, serum protein, AST, ALT, ALP), coagulation profile(PT,APTT), CPK-MB, chest x ray, ultrasound abdomen and pelvis were done after admission.

In these patients we tried to predict the severity and outcome of dengue infection by assessing clinical, hematological, biochemical & radiological parameters.

Results:

Among the 65 cases of dengue infection proven through rapid card test NS1, IgM, IgG positive or ELISA IgM positive ,25.4% , 40% & 34.6% cases belong to 0-5yrs, 6-10yrs & 11-14yrs respectively. 63% were males and 37% were females. According to 2009 WHO classification 38.5% had dengue fever without warning signs (DF), 47.7% had dengue fever with waning signs (DFWS) and 13.8% had severe dengue(SD). Most common symptoms that they present with in decreasing order are fever, vomiting, abdominal pain, myalgia, headache, loose stools, arthralgia, cough, cold, rashes, nausea etc & warning signs in decreasing order are abdominal pain, hepatomegaly , abdomen tenderness , raised hematocrit with reduced platelet count etc. TLC <4000 cells/mm3 was seen in 27 cases (41.5%), PCV $\geq$ 35% in 41 cases , PLT < 50,000/mm3 in 17 cases , PLT: 50,000 – 1 lakh/ mm3 in 11 cases, PLT > 1 - 1.5 lakhs/ mm3 in 17 cases, PT > 13.5 sec. in 54 cases and APTT > 34 sec. in 47 cases, AST > 41U/L in 56 cases, ALT > 41U/L in 30 cases, CPK-MB > 26 U/L in 54 cases & albumin < 3.5g/dl in 34 cases.   Chest   X-ray   finding   was   mainly consolidation and is seen in 44.4% of severe dengue cases and 6.5% of DFWS cases. Pleural effusion constituted about 0%, 25.8% & 33.3% in DF, DFWS & SD respectively which shows statistical significant difference with p=0.014 stating it is specific for DFWS & SD. Prolonged duration of stay is specific for severe dengue. Out of 65 cases 2 cases of SD (22.2%) expired. In ROC the composite index (AST^2/ALT) was the most accurate (AUC 0.813; 95% CI 0.615 – 1.000) when optimal cut off is $\geq$ 400.4 with highest sensitivity (88.9%) and specificity (76.8%) stating that it may be used as a marker for identification of severe dengue based on admission AST and ALT.

Conclusion:

PCV $\geq$ 35.95%, TLC< 6200/mm^3, deranged coagulation profile, AST $\geq$ 156U/L, ALT $\geq$ 44U/L ,the composite index AST^2/ALT (AUC 0.813; 95% CI 0.615 − 1.000) optimal cut off $\geq$400.4 with a sensitivity of 88.9% and specificity of 76.8% and presence of polyserositis on USG/X-ray are predictive of Severe Dengue and should alert the clinician for more vigilant monitoring. Early prediction and anticipation of Severe Dengue and its prompt management can reduce the mortality associated with the disease and for proper counseling of the patients and their relatives**.**

KEYWORDS:

Dengue fever without warning signs, dengue fever with warning signs, severe dengue, AST, ALT, Composite Index, predictors.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

Dengue infection, the most prevalent arthropod-borne viral illness in humans is caused by dengue virus which belongs to flaviviridae family and is one of the most important tropical infectious diseases of the world. Several outbreaks of dengue infection have been reported from India. In the past 50 years, the prevalence of dengue fever has increased 30 fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural setting [1].

The 2009 World Health Organization (WHO) criteria classify[2] dengue according to levels of severity: dengue without warning signs; dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing hematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding or organ failure).

An estimated 50-100 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries. Case fatality rates vary from 1% to 5%, but can be < 1% with appropriate treatment[1].In its most severe form, it manifests itself clinically as dengue with warning signs and severe dengue. Unusual clinical manifestations of dengue fever have become more common in the last few years. Although the liver is not a major target organ, hepatic dysfunction is a well recognized feature, often characterized by acute hepatitis, with pain in the right hypochondrium, hepatomegaly, jaundice and raised aminotransferase levels[3-11]. The degree of liver dysfunction varies from mild injury with elevation of transaminase activity to severe injury with liver cell failure. The severity of liver dysfunction varies according to the type of clinical presentation of dengue fever, and is more common in children with severe dengue fever. Liver dysfunction as a result of dengue infection

can be a direct viral effect on liver cells or an adverse consequence of dysregulated host immune response against the virus [5-11].

Abdominal ultrasound can detect gall bladder thickening, ascites in addition to hepatomegaly, pleural effusion which usually occurs in severe dengue.

Heart involvement in the form of myocarditis can occur in severe dengue which can be assessed by measuring enzymes like creatine phosphokinase-MB (CPK-MB) and echocardiography.

Since our hospital (Shri. B. M. Patil medical college and hospital) is a tertiary care hospital, we do see a lot of children with dengue infection including those with atypical manifestations and at present there are very few studies done in children to predict the severity and outcome of dengue infection. Hence the present study is intended to predict the severity and outcome of dengue infection based on clinical parameters, liver enzymes like AST, ALT, CPK-MB, and abdominal ultrasound.

AIMS AND OBJECTIVES OF THE STUDY

1. To document the clinical profile of patients with Dengue.

2. To assess the association of AST, ALT and ultrasound with severity of dengue infection.

3. To assess the association of CPK-MB with myocarditis in dengue infection.

REVIEW OF LITERATURE

HISTORICAL ASPECT:

Dengue fever is an ancient disease. The term dengue is derived from a Swahili phrase "ka dinga pepo" (sudden cramp-like seizure plague). The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from the Jin Dynasty (265–420 AD) which referred to a "water poison" associated with flying insects[12].

The first recognized Dengue epidemics occurred almost simultaneously in Asia, Africa, and North America in the 1780s, shortly after the identification and naming of the disease in 1779. The first confirmed case report dates from 1789 and is by Benjamin Rush, who coined the term "breakbone fever" because of the symptoms of myalgia and arthralgia[12].

The vast expansion of shipping and the development of port cities in the 18th and 19th centuries, the mosquito vector, *Aedes aegypti* and the dengue viruses spread to new geographic areas causing major epidemics. The ecological disruption occurred in the Southeast Asia and pacific theatres during and following World War II, created ideal conditions for viral transmission and an increase of mosquito borne disease and it was in the setting that a global pandemic of dengue began.

In the year 1907, Ashburn and colleagues discovered dengue virus to be the causative agent for this disease[13]. Serotype 1 and 2 of dengue viruses were identified during the second world war. Serotype 3 and 4 dengue viruses were identified in a Manila epidemic of 1956[14]. In 1944 Dengue virus was first isolated in Japan in 1943, by inoculation of serum of patients in suckling mice. In 1944, the virus was isolated from the sera of US soldiers at many parts of the world including

Calcutta. The severe form of dengue, called DHF epidemic occurred first time in Manila, Philippines in 1953 to 1954[15].

In Asia, epidemic dengue has expanded geographically from Southeast Asian countries west to India, Srilanka, Maldives and Pakistan and east to China[16]. By the 1980s, the American region was experiencing major epidemics of dengue in countries that had been free of the disease for 35 to 130 years. Before 1980, little was known about the distribution of dengue virus in Africa. Since then, however, major epidemics caused by all four serotypes have occurred in both East and West Africa[17]. In 1997, dengue viruses and Aedes aegypti mosquitoes had a worldwide distribution in tropical and subtropical countries of the world.

Since then geographical distribution of dengue fever has become worldwide, involving nearly all tropical and subtropical countries. It has many names like dandy fever, denguero, denge, dunga, breakbone fever, bouguet, seven day fever, chapenonad, tok-kive-ana and coup-d-bare[18].

EPIDEMIOLOGY[19]

By the end of 2016, a total of 291,964 outbreak-associated dengue cases had been reported in the literature, mainly from China (27.9%), Singapore (27.0%) and Malaysia (15.1%). The majority (72.4%) of dengue patients were reported in the Western Pacific region, followed by the American region (19.4%), Southeast Asia Region (4.8%), Eastern Mediterranean region (1.5%), European region (1.5%) and African region (0.3%).

Outbreaks occurring before 2010 (America > Western Pacific > South East Asia > Eastern Mediterranean > Europe > Africa) accounted for 28.6% of the total number of cases, the majority of which were reported in Cuba (28.1%), Singapore

(19.3%) and Puerto Rico (13.4%), while patients in outbreaks after 2010 (Western Pacific > Americas > South East Asia > Europe > Eastern Mediterranean > Africa) were mainly from China (36.8%), Singapore (30.1%), and Malaysia (20.9%). 50.0% outbreaks occurred in urban areas (21/42), 28.6% in rural areas (12/42) and 21.4% in both urban and rural areas (9/42). It is important to note that nearly all rural outbreaks occurred after 2000[20]. It is consistent with the view that dengue once confined to urban areas has penetrated into the rural setup[21]. The improved road systems, better socio-economic situations and established agricultural settlements in rural areas may increase the Aedes albopictus population, and thus spread of rural dengue fever among the rural communities[22].

Among countries worldwide, the highest numbers of outbreak (58/262) are observed in India, followed by China (38/262) and Brazil (24/262) from 1990 to 2015. All the outbreaks occurred in tropical (77/262) and subtropical (174/262) regions, except for one outbreak, which occurred in Nîmes, 2015, and was considered the first considerable dengue outbreak in mainland France[23].

Among the six WHO regions, the largest number of outbreaks occurred in the Southeast Asia region (82/262), followed by the Western Pacific region (72/262) and the American region (65/262), accounting for more than 83.6% of outbreaks overall. The European region (6/262) was least affected by dengue outbreaks, with only 4 outbreaks reported in France (three in overseas departments and regions of France and one in mainland France) and 2 outbreaks reported in Portugal. However, the Western Pacific Region had most dengue outbreaks reported after 2010 (Western Pacific: 33/112 > Southeast Asia: 27/112 > Americas: 24/112 > Eastern Mediterranean: 13/112 > Africa: 11/112 > Europe: 4/112)[19].
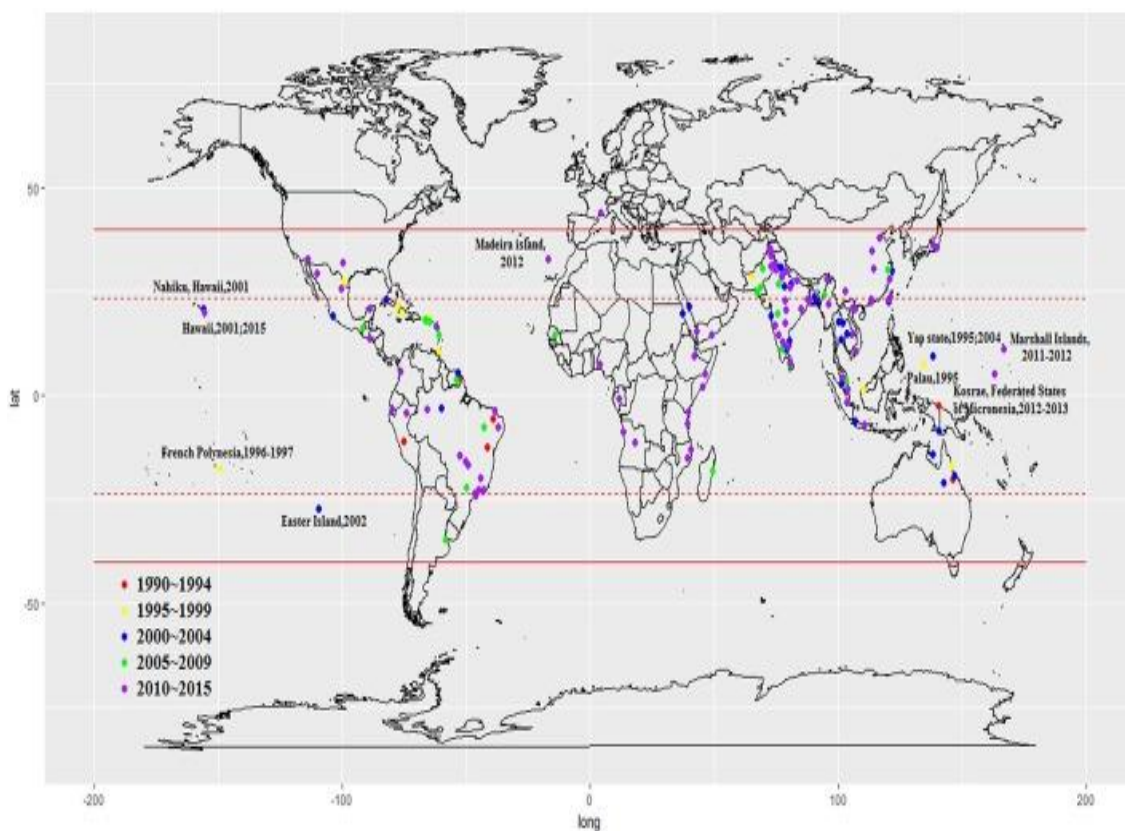
Global dengue outbreaks distribution from 1990–2015[19]

DENGUE IN INDIA

Dengue viruses have been persisting in India year after year since 1956. In Tamil nadu, the first major outbreak of dengue was noticed in Vellore, South Arcot district in 1961 and the viral etiology was established later by the isolation of dengue virus[13]. The first virologically proved epidemic of DF in India occurred in Calcutta and eastern coast of India in 1963 – 1964[24,25]. Then, the dengue infection spread northwards and reached Delhi in 1967[26]. Subsequently, the whole country was involved with wide spread epidemics followed by endemic or hyper endemic prevalence of all four serotypes of dengue virus.

After the occurrence of first epidemic in 1961, Vellore experienced outbreaks in the year 1964, 1966 and 1968. The virological investigations carried out during that period proved the presence of dengue 2 in 1964 outbreak. Dengue 3 virus was isolated in 1966 outbreak[27] and all four types of dengue virus in 1968 outbreak[28]. The epidemic at Vishakapatnam in 1964 was due to dengue 2 virus.

The epidemic of dengue in Nagpur in 1965 documented the presence of dengue 4 virus in that region[29]. In the same year, another outbreak was observed in Madras which was caused by dengue 3 viruses[30]. Later, outbreaks of dengue occurred in Jabalpur (MP) by dengue virus 3 in 1966[29]in Asansol in 1967 by dengue 2 and 4, in Delhi in 1967 by dengue 2[26], in Kanpur in 1968 and 1969 by dengue 4 and dengue 2[31], in Ajmeer in 1969 by dengue 1 and dengue 3[32], in Gwalior in 1970 by dengue 3, in Bangalore in 1971 by dengue 1 and dengue 2 ; in Jaipur in 1971 and 1973 by dengue 1 and 2 , in Jammu in 1974 by dengue 2 and in Trichur in 1974 by dengue 2[33].

Dengue 3 has been isolated during the epidemic at Calcutta in 1983. An epidemic of dengue at Rajasthan in 1985 was due to dengue 3 virus . Dengue 2 was isolated during the epidemics of dengue in urban and rural areas of Gujarat state during 1988 and 1989. Outbreaks occurred at Gwalior in 2003 and 2004 by dengue 3[33].

Padbiri et al (1995)[34] reported dengue in Mangalore, Karnataka in 1993. In Punjab, there was an outbreak of dengue in 1996. The outbreak of dengue in Delhi in 1996 was due to dengue 2[35]. Hence, the presence of all four types of dengue virus and occurrence of the disease all over the India were well documented.

DENGUE VIRUS

The etiologic agent of "break-bone fever" was found to be dengue virus (DENV). DENV is a flavivirus of the family Flaviviridae. Other flaviviruses in the same genus include Japanese encephalitis, yellow fever, West Nile, and tickborne encephalitis viruses. Dengue viruses are single-stranded positive-sense RNA viruses[36]. The DENV genome is 11kb in length and encodes three structural and seven nonstructural proteins[36]. DENV has four different serotypes: DENV1, DENV2, DENV3, and DENV4. Infection with one serotype provides lifelong immunity to the infecting serotype only but has been associated with increased risk of severe dengue illness upon secondary infection with a different serotype[37]. It is debatable if one serotype is more infectious or causes a more severe infection compared to another. Some studies have suggested there are differences in the pathophysiology of the different dengue serotypes, but currently no one serotype is considered more dangerous than another[38].

Globally all the four serotypes have been found to infect the high risk areas, DEN 2 and DEN 3 being most common. In India DEN 1 and DEN 2 are the most common serotypes isolated. The infecting severity determines the severity of the disease. DEN 2 causing the most severe form of the infection and increased mortality[39].

DENGUE VECTOR[40]

The female Aedes aegypti mosquito, the most important vector for transmission of DENV, is known to be a nervous feeder and will disrupt a feeding at the slightest movement and return later to continue feeding on the same individual or a different individual. Due to this type of feeding, the female Aedes aegypti can infect

numerous individuals in a single blood meal spreading the virus to each person it feeds on. Furthermore, Aedes aegypti are indoor mosquitoes, in that they prefer to feed inside a residence, making control efforts more cumbersome due to the inability to effectively reach breeding sites with spraying of insecticides.

DENGUE ILLNESS

Dengue viruses are transmitted through the bite of an infected mosquito, usually *Aedes aegypti* or *Aedes albopictus*[41]. Once a susceptible host is infected, symptoms of dengue infection may occur and usually appear after an incubation period typically between 4 and 7 days, with a range from 3 to 14 days[40].

Dengue illness can range from an uncomplicated febrile illness, as seen in most dengue fever (DF) cases, to a more severe illness with bleeding tendency, thrombocytopenia, and plasma leakage as seen in dengue hemorrhagic fever (DHF). DF and DHF are emerging infectious diseases that are endemic in tropical and subtropical areas[42].

Patients with confirmed dengue are classified as having DF if fever and any two of the following are present: headache, myalgia, arthralgia, rash, hemorrhagic manifestations, and leukopenia[23]. Patients are classified as having DHF according to World Health Organization (WHO) guidelines based on the presence of all four of the following four signs: fever, thrombocytopenia (platelet count <100,000/μL), bleeding tendency (positive tourniquet test or spontaneous bleeding), and evidence of plasma leakage (evidence of pleural effusion, ascites 3 or ≥20% hemoconcentration)[43]; however, these findings may not appear until patients are already critically ill.

DHF is categorized by severity into four grades[43]. A diagnosis of DHF grades 3 and 4, termed dengue shock syndrome (DSS), includes all DHF criteria with the

addition of circulatory failure. There is not a reliable definition of what constitutes a severe dengue illness and much controversy surrounds the WHO definition of DHF. This classification system is often impractical in the clinical setting, which leads to inconsistency of scientific data, such as under- or over reporting of severe dengue cases. Studies have shown that the WHO classification of DHF doesn't account for all severe dengue illnesses[44].

Setiati et al found that a modified classification system using only hemo concentration with either thrombocytopenia or hemorrhagic tendency was in better agreement with the treating physician's diagnosis of DHF than the WHO criteria. Harris et al found that strict adherence to the WHO classification of DHF excluded severe dengue patients that had shock, defined as hypotension for age or narrow pulse pressure with clinical signs of shock, but lacked thrombocytopenia or hemoconcentration, so they set up another category in their study "dengue with signs associated with shock", which included 3% of 1,027 patients[45].

The term 'hemorrhagic' in DHF can lead to the false assumption that suspected dengue cases must have hemorrhage before being classified as 4 severe; however,

1) dengue can be severe even without significant hemorrhage,

2) hemorrhage is not the sole criterion for DHF, and

3) dengue can be severe without meeting all the criteria for DHF.

For example, Murgue et al found that when dengue cases were classified according to severity score (developed after close examination of clinical and laboratory data), the 50 most-severe cases were characterized by hemorrhage, decreased platelet count, and associated hepatic disorders, of which 17 were DF cases as classified by WHO criteria. Specifically, the most severe DF cases were

characterized by severe hemorrhage, miscellaneous (cardiac, renal, pulmonary) manifestations, and elevated serum transaminase levels[46]. These studies demonstrate the failure of the WHO classification system to account for disease severity in all dengue cases. Recently, Srikiatkhachorn et al studied a cohort of Thai children (the same cohort of patients presented in this study) and used the need for clinical intervention (fluid intervention or blood transfusion) as an indicator of disease severity; 15% of DF cases met the criteria for a severe dengue illness and 42% of physician-diagnosed DHF cases did not meet the criteria for a severe dengue illness[44].

A prospective observational study conducted by Kalayanarooj et al, (1997)[47] in Bangladesh in 1994 revealed that 18 % of the dengue fever patients had anorexia, 61 % had nausea, 66 % had vomiting, 28 % had abdominal pain and 80 % had headache. A comparative analysis of clinical symptoms between DF patients and patients with OFI showed that DF patients were more likely to report anorexia, nausea and vomiting than patients with OFI. However, the history of headache, abdominal pain and bleeding were not significantly different between these groups. Among the study groups the male: female ratio for dengue and OFI patients were 1:1.12 and 1:1.45 respectively. The mean ages for DF and OFI patients were 8.01($\pm$3.15) and 6.2 ($\pm$3.0) years respectively.

Mohan et al (2000)[48] prospectively studied during the acute attack in Delhi during 1999 and found hepatic function of 61 children diagnosed to have dengue infection aged 2 months to 12 years comprising 37 cases of dengue fever, 16 with DHF and 8 with DSS. Hepatomegaly (74 %), epitaxis (26 %), Jaundice (25 %) and petechial rashes (18 %) were the common clinical manifestation of DF.

A prospective study conducted by Endy et al (2002)[49] with primary school children in Thailand from 1998 to 2000 and found that head ache (64 %) was the most common presenting symptoms in children with acute dengue virus infection followed by cough (43 %), rhinorrhea (35 %) lethargy (32 %), anorexia (25 %), muscular pain (23 %), vomiting (20 %) and nausea (19 %). Other symptoms include rash (5 %), abdominal pain (17 %), diarrhea (4 %), joint pain (15 %) and bleeding (2 %). Headache, although the most common symptom reported for acute dengue infection was less frequently in dengue affected children than children with OFI. Similarly, rhinitis, cough and diarrhea were more in children with OFI than children with dengue infection.

Kalayanarooj et al (2002)[50] recorded the following clinical symptoms in patients with DF admitted in the hospital during the period 1995-1999 in Thailand. Abdominal pain was the most common complaint (30.1 %) in DF patients. Myalgia was seen in 12.9 % of the patients. Maculopapular rash during the febrile phase was found in 11.6 % of the DF patients. Typical convalescence rash was found in 19.4 % of the patients. Hepatomegaly was seen in 80.4 % of the patients. The mean age for DF cases was observed as 7.9 years. The age group 5-9 years was the most affected group by dengue fever. No gender difference was observed in DF patients.

Narayanan M et al (2002)[51] made a study to identify symptoms, signs and laboratory values of dengue fever during an outbreak of dengue at Chennai in 2001 and reported that children who developed complications had more fever, body pain and bleeding than children with dengue and did not have complications. The mean age of their study population was 6.07 (with shock) and 6.96 (without shock).

Kabilan et al (2003)[52], in their study on dengue disease spectrum among infants in the year 2001 dengue epidemic in Chennai found fever, hepatomegaly and rash in 100 %, 93.1 % and 55.2 % of the infants respectively. Oedema of the lower extremity, retro orbital puffiness and vomiting were seen in 17.2 %, 27.6 % and 24.1 % of the infants respectively. The age group of the study population was 1 to 11 months (mean age 7 months).

Mendez and Gonzalez (2003)[53] conducted a cross – sectional study in children under 13 years in Colima by during the period 1992-2002 (10 years) showed that the most important clinical features were fever and hemorrhagic manifestation (100 %), vomiting (60 %), abdominal pain (37 %), head ache (50 %), osteomyatea (40.8 %) and macular rash (29 %).

Wichmann et al (2004)[54] found that out of 347 patients with serological confirmed dengue infection during an epidemic in 2001 in Thailand, 26 % had cough,15 % had headache, 8 % had myalgia, 40 % had hepatomegaly, 21 % had petechiae, 57 % had nausea and 59 % had vomiting. All patients were presented with fever (100 %). Forty percent of patients had hepatomegaly. The total number of patients included in their study was 347 of which 287 were children and 60 were adults. The male: female ratio was 1.08:1 and the median age was 10 (4 months to 66 years).

IraShah and Kathira (2005)[55] undertook a prospective study in Mumbai, India in 2003 to determine the clinical features of dengue. The mean age of presentation was 4.9 years. Fever (100 %), hepatomegaly (47.1 %), vomiting (50 %), bleeding (38

%), tenderness (38.2 %), and erythematous rash (14.7 %) were seen in the patients. Thrombocytopenia was the predominant clinical features observed.

In a study by Betty Chacko and Gayathri Subramanian (2007)[56] of 73 cases aged between 0-14 years, sex ratio was 1.52:1(M: 44, F: 29), mean age of the study population was 7.87 years with 16 (21.92%) infants. The youngest patient was 1 month old. DF was diagnosed in 24(32.88%), DHF in 15 (20.55%) and DSS in 34 (46.57%) patients. The most common presentation was fever in 69(94.52%). Bleeding manifestations were seen in 11(15.07%) and it was significantly commoner in patients without DSS (p¼0.0404). Average haematocrit was 37.68%. In those with DSS, it was significantly more (p¼00.01352). Only 21(28.77%) patients had haematocrit levels of 40% or more of which 13(61.9%) had DSS. It was also found that 14/21(66.67%), (six children without and eight with DSS) were of the age >10 years with a haematocrit >40%. A haematocrit of 35% or more, leucopenia, platelet count of <1 lakh/mm3, deranged International normalized ratio (INR), SGPT levels > or equal to 40IU, serum sodium < or equal to 130meq/l and bicarbonate levels of <18mmol/l were all significantly associated with DSS. USG abdomen was performed in 44 (60.27%) patients of which 15 (34.1%) were normal. Patients without DSS had normal USG (p¼0.0021). Occurrence of pleural effusion was significantly higher in patients with DSS (p50.0001). The presence of any other factor on ultrasonogram of the chest or abdomen was not significantly associated with DSS. Duration of hospital stay averaged 6.19 days with a maximum stay of 20 days and a minimum of 3 days. There was no significant difference in number of patients needing blood component therapy between the two groups. Fresh frozen plasma transfusions were given to 14.7% of patients with DSS and 12.8% of those without DSS. Similarly platelet

transfusions were also given in a similar proportion of patients with and without DSS (2.9% and 5.1%, respectively). The case fatality rate was 2.74%.

Banerjee et al (2008)[57] studied 50 cases of fever clinically suspected to be dengue in Pune, India. The commonest clinical feature was fever with rash (85 %). Retro orbital and headache were reported by 63 % of the patients. Myalgia was seen in 81 % of the patients. Hepatomegaly was seen in 15 % of the patients. Conjunctival congestion was observed in 37 % of the patients. The frequencies of clinical symptoms were comparatively higher in IgM positive patients than IgM negative patients.

Kumar et al (2008)[58] conducted a study with 27 dengue positive children in Lucknow, India in 2006. Clinical features of dengue IgM positive cases included bleeding (57 %), convulsion (50 %), rash (14.3 %), swelling (28.6 %), headache (21.4 %) and vomiting (35.7 %). No one was found to have diarrhea and there was no significant differences in clinical feature among dengue IgM positive and negative cases. Hepatomegaly was observed in 64.3 % of the patients.

The 2009 World Health Organization (WHO) [2] criteria classify dengue according to levels of severity: dengue without warning signs; dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing hematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure).

Dengue case classification by severity

Dengue ± warning signs   **Severe dengue**

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

Criteria for dengue ± warning signs

Probable dengue
Live in/travel to dengue endemic area. Fever and 2 of the following criteria:
• Nausea, vomiting
• Rash
• Aches and pains
• Tourniquet test positive
• Leucopenia
• Any warning sign
Laboratory confirmed dengue
(important when no sign of plasma leakage)

Warning signs*
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy; restlessness
• Liver enlargement >2cm
• *Laboratory:* Increase in HCT concurrent with rapid decrease in platelet count

Requiring strict observation and medical intervention

Criteria for severe dengue

1. **Severe plasma leakage** leading to:
• Shock (DSS)
• Fluid accumulation with respiratory distress

2. **Severe bleeding** as evaluated by clinician

3. **Severe organ involvement**
• Liver: AST or ALT>=1000
• CNS: Impaired consciousness
• Heart and other organs

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; DSS = dengue shock syndrome; HCT = haematocrit

WHO Dengue case classification by severity [2]

Chau et al (2010)[59] conducted a prospective descriptive study in Vietnam in 2007 and observed clinical symptoms such as fever (83 %), diarrhea (43 %), running nose (37 %), cough (56 %), vomiting (57 %), jaundice (1 %) and petechial rash (34 %). Infants with dengue did not present specific clinical signs compared to patients with OFI. Common features of upper respiratory tract viral infection including

running nose and cough were observed with similar frequencies in both groups, however diarrhea, vomiting and petechial rash occurred more frequently in dengue patients than in infants with OFI. The age of study population ranged between 2 and 18 months (median − 7 months) and the male to female ratio was 173:126.

Anker and Arima (2011)[60] in their regional analysis of male, female difference in the number of reported incident of dengue fever cases in 6 Asian countries explained that in Philippines, there was a significant excess of male cases among those ≥ 15 years of age and among infants. A high proportion of male cases were also recorded in Singapore, Srilanka, Malaysia and Cambodia.

In a study by K.S.Sahana et al (2015)[61] of 81 children aged between 0-15 years diagnosed with dengue , including 55(67.9 %) boys and 26(32.1 %) girls mean age of presentation was 8 y. Vomiting (60.5 %), pain abdomen (32 %), headache (30.9 %), myalgia (23.5 %) and bleeding manifestations (16 %) were the common presenting complaints. Facial puffiness (63 %), hepatomegaly (51.9 %), ascites (48.1 %), pleural effusion (39.5 %) and petechiae (14.8 %) were noted during examination. Dengue NS1 antigen, IgM, IgG were positive in 66.7%, 29.6% and 18.5% of cases respectively. Investigations showed thrombocytopenia in 82.7%, hemoconcentration in 72.8%, leucopenia in 34.5%, abnormal LFT in 33.3%. USG abdomen was suggestive of dengue in 66.7% and gall bladder wall edema was noted n 53.1%. Out of 81, two patients died with mortality rate of 2.5%. no of cases classified as dengue without warning signs(D), dengue with warning signs(DW) and severe dengue(SD) were 48.1%, 27.2% and 24.7% respectively.

In a study by Mishra S et al (2016)[62] of 97 cases, 84 were cases of non severe dengue (undifferentiated fever ,dengue fever with warning signs ,and dengue fever without warning signs) and 13 were cases of severe dengue (DHF and DSS) according to WHO guidelines. There were 75 (77.31%) males and 22(22.68%) females in our study. Both the groups of severe and non severe dengue males had high incidence. The male-to female ratio was 3.4:1. The maximum number of cases, 33(34.02%), was seen in the group above 11 years of age, out of whom male children were 25(33.33%) and female children 8(36.36%). The mean age of hospitalised patients was 8.7yrs. 63.9% of patients were admitted in the hospital for 3–6days. Seven children out of 13 severe dengue patients were admitted for more than 6 days. The mean tenure of hospitalisation was 3.8days. In severe dengue cohort the mean stay was 5.8days. The mean delay in admission after appearance of fever was 3.4days

In a study by Jain H et al (2016)[63] of 65 cases, males were 53% and females were 47% with maximum number of cases seen in the age group of 5-10 years (46%). We reported children with dengue without warning signs (23%), dengue with warning signs (64%), and severe dengue (12%) of cases. Fever was observed in all cases. Headache(64%), myalgia(63%) were most common symptoms followed by bleeding(58%) and decreased urine output (53%) each. Among the clinical findings, hepatomegaly and splenomegaly were noted in 90% and 26% of the cases, respectively. Clinical fluid accumulation in form of ascites and pleural effusion with reduced air entry were observed in 40% and 43 % of cases. Only one case had central nervous system involvement

In a study by Kumar AMK et al (2017)[64] of 48 cases of dengue, categorized according to WHO criteria into dengue fever(52%), dengue fever with warning signs(16.6%) and severe dengue(31.4%) the most common clinical symptoms at admission were fever (100%), vomiting (77%), respiratory distress (56.25%), generalised weakness (54.1%) and pain abdomen (33.3%). Less common symptoms were loose stools (6.25%), periorbital puffiness (6.25%), altered sensorium (4.1%), oliguria (2%) and bleeding manifestations (2%) and on examination signs noted were hepatomegaly (54.1%), abdominal tenderness (43.1%), polyserositis (41.6%), and bleeding manifestation in the form of mucosal and skin bleeds (35.41%), hypotension (31.25%), and meningeal signs (16.6%). Diagnosis of dengue was made by using ELISA technique, NS1, IGG and IGM, NS1 (81.2%), IGM (45.8%), IGG (33.3%) individually were found positive. NSI and IGM (35.4%), IGM and IGG (8.33%), NS1, IGM and IGG (6.25%) in combination were found positive. Treatment was initiated in these children according to WHO protocol. 8(16.6%) out of 48(100%) cases required platelet transfusion with 6.7% of DF, 26.3% of DFWS,14.3% of SD cases during the course of illness. PRBC transfused in 4.1% of these children.

In a study by Mulay S et al (2017)[65] of 88 confirmed dengue cases,56(63.6%) were males , 32(36.4%) were females and according to recent WHO classification 14(15.9%) were DF, 49(55.7%) were DFWS & 25(28.4%) were SD. Fever was present in all the cases, while other features were: vomiting (64.8%), abdominal pain (62.5%), bodyache(53.4%), shock (28.4%), headache (48.9%) and rashes (23.9%). 2 (2.27%) out of 88 patients expired who were suffering from severe dengue and all others improved.

In a study by Sujatha R et al(2017)[66] of 568 children from infancy to adolescents, diagnosed clinically with dengue fever 66(11.6%)were classified as dengue without warning signs, 308 (54.2%) were dengue with warning signs and 194 (34.2%) with severe dengue. Girls (237) accounted for 41% and the rest were boys. The proportions of symptoms like abdominal pain, vomiting, third space loss and hepatomegaly were significantly more in the SD group as compared to children diagnosed as D and DW (p < 0.01, significant). Fever was noted in 552 (97.1%) patients, maculopapular erythematous rash in 126 (22%), flushing in all the children and hepatomegaly in 192(33.8%).Other symptoms noted were abdominal pain (53.1%), vomiting (62.9%), cough (14.4%) and respiratory distress (10.9%). Bleeding manifestations were seen in 55 (9.6%) children, in the form of skin bleeds (54.5%), epistaxis (20%) GI bleed (20%) and hematuria (5.4%). Thirty six children had platelet counts less than 20,000, out of which only 11 had bleeding. Forty children, whose platelets were above 20,000, had significant bleeding. Central nervous system(CNS)involvement was seen in 5 patients in the form of drowsiness, severe headache, altered sensorium and convulsions. Hematocrit above 38 was noted in 264 out of 568 (46%) children. Thirty six children (6.3%) had platelets less than 20,000, 204 (35.9%) had between 21,000–50,000 and 236(41.5%) had between 50,000 to 100,000. Blood component therapy was used in 125 of 568 children (22%). Platelets were given to children with counts less than 20,000, and with significant mucosal bleeding. Of the125children, platelets were transfused in 80children (14% of 568) out of which 64 (32.9%) were from SD group. Fresh frozen plasma (FFP) was used in 23 children (11.8%) of severe dengue group. Four children required whole blood transfusion because of massive gastrointestinal bleed. Seven children died and all were adolescents. Five died due to refractory shock and multiorgan failure, one due to

suspected encephalitis and the other due to severe GI bleeding. Five of the seven died within six to24h of admission. Mortality rate was1.23% of the study group and 3.6% of the SD group.

In a study by Natwar Lal Sharma et al(2017)[67] of 200 cases were 113 (56.5%) were males among which 98 were suffering with non severe dengue and 15 cases were with severe dengue, 87 (43.5%) were females with 79 non severe and 8 severe dengue cases. In both severe and non-severe cases the incidence of males was higher. The male to female ratio was 1.3:1. The most common age group affected was between 8-11 years, 93 cases (46.5%), with 83 non severe and 10 severe dengue cases, with 55 males and 38 females. The mean age of hospitalized patients was 9 years. 65% of cases remained in the hospital for 3-6 days, 22.5% of cases for <3 days and 12.5% for >6 days. Out of 25 cases admitted for >6 days, 21 cases were of severe dengue and 4 cases of non-severe dengue. The mean duration of hospital stay was 4.61 days. In severe dengue cases the mean duration of stay was 4.64 days.Out of total 200 cases enrolled in the study, 8.5% were undifferentiated dengue fever, 80% were dengue fever with or without warning signs and 11.5% were of severe dengue (DHF and DSS)

In a study by Tewari et al (2018)[68] of 443 adults and 57 children between 6 months to 77 years age. NS1 was positive in 115 patients (23%). Fever (99.8%) and severe body ache (97.4%) were the commonest presentation. DF was seen in 429 (85.8 %), DFWS in 55 (11%), SD with severe bleeding in 10 (2%) and SD with severe plasma leakage in 6 cases (1.2%). Outpatient department (OPD) treatment was needed in 412 (82%) and hospitalization in 88 (18%). Intravenous fluid resuscitation was needed in 16 (3.2%) patients. Thrombocytopenia was seen in 335 (67%) patients

at presentation. Platelet transfusion was needed in 46 (9.2%). Packed red blood cell (PRBC) transfusion was given in 3 patients with DFWS and 10 of SD with severe bleeding. Death occurred in 3 patients of SD with severe plasma leak and 2 patients with SD and severe bleeding.

SERODIAGNOSIS OF DENGUE INFECTION

Serodiagnosis and seroepidemilogical survey on dengue infections have been carried out mostly by Haemagglutination Inhibition (HI) test for many years. This technique was developed for demonstrating an increase in antibody titer during infections with arboviruses[69]. Then, HI test was perfected by Clarke and Casals in 1958 and was adapted to microtitre plate by Sever in 1962. This technique is highly sensitive but it lacks specificity and requires paired samples for accurate diagnosis[70].

A study on dengue outbreak reported in Brazil in 1986 by Nogueira et al (1989)[71] revealed that 58.2 % of the patients tested by ELISA had IgM antibodies to dengue virus and they were considered as confirmed dengue patients for the further studies.

Innis et al (1989)[72] found that in Jharkand, anti dengue IgM appeared in most cases by the 3rd day of febrile illness and declined to undetectable level after 30 – 60 days. IgM capture ELISA showed 78 % sensitivity in acute serum and 97 % in paired sera. Dengue infections could be classified as primary or secondary by determining the ratio of units of dengue IgM to IgG antibody.

Chouhan et al (1990)[73] detected IgM antibodies to dengue viruses in 70 % of sera collected in Rajasthan in 1985.

Chen et al(1991)[74] carried out an investigation on the detection of IgM antibodies from cerebrospinal fluid and sera of dengue fever patients. The results showed that IgM could be detected in 14 (70 %) out of 20 suspected dengue patients. Sera IgM antibodies last up to 252 days after onset of illness.

Ram et al (1998)[75] carried out an investigation on an outbreak of dengue fever occurred in Ludhiana in 1996 and 1997. Serological examination was performed by dengue IgG and IgM blot with single serum samples of 189 patients. Of these 129 (68.25 %) samples were detected positive for anti dengue antibodies.

An outbreak of DHF/DSS occurred in 1996 in New Delhi, India was studied by Dar et al (1999)[35] and they reported that out of 270 serum samples tested by MAC – ELISA for the detection of IgM antibodies against dengue virus, 140 (51.9 %) showed anti dengue IgM antibodies. All the samples from patients with duration of fever > 5 days were tested for anti–dengue IgM antibodies. In some samples, antibodies could be detected as early as the fifth day of fever. Three of the culture positive acute phase serum samples were also positive by MAC ELISA.

A hospital based cross – sectional serodiagnostic survey under taken by Chakravarthi et al(2002)[76] during 1999-2001 in Delhi, India showed that, out of 345 patients experiencing a febrile episode, 85 cases (25 %) were confirmed as serologically positive, with 15 cases showing IgM antibodies indicating primary infection and 19 cases showing both IgM and IgG antibodies indicating secondary infection.

Narayanan et al (2002)[51] identified 89 children in a hospital in Chennai, Tamilnadu between October to December 2001 as probable dengue cases by clinical suspicion. For all cases, the rapid IgM-IgG capture ELISA was done and 59 (66.29 %) were found to be seropositive for dengue.

Ira Shah and Katira (2005)[55] reported that in Mumbai, India in 2003, out of 69 suspected dengue cases tested by ELISA for dengue IgM antibodies. 34 (49.3 %) patients had a positive dengue IgM titre. Similarly, Kalita et al., (2005) reported that in Lucknow, diagnosis of dengue was based on the results obtained by IgM ELISA.

A study in Manipal by Baruah et al (2006)[77] revealed that, out of the 100 clinically suspected cases of dengue, 44 % tested were positive for dengue IgM antibody, thus proving the current dengue infection.

Paramasivam et al (2006)[78] an outbreak of febrile illness was first time observed in the three villages of Kanyakumari district Tamilnadu, India in July 2003 and serological, virological and entomological investigations were carried out to confirm the etiology of outbreak. Of the 76 samples tested by Panbio ELISA kit for the detection of IgM antibodies, 15 (20 %) were found to be positive for dengue virus specific IgM antibodies. It was concluded in the study that based on the IgM antibody capture ELISA results it was evident that the current infection was caused by dengue virus in the affected areas. All the age groups were affected during the outbreak.

Banerjee et al(2008)[57] reported that in Pune, India, out of 50 dengue suspected patients 27(54 %) had IgM antibodies for dengue and it was stated that the serological sensitivity of ELISA (Panbio diagnostics) kit used in that study was 85.4 % - 98.9 % for the detection of primary infection and the specificity was 95.7 % -100 %.

Faridi et al (2008)[79], in their study on clinical and biochemical profile of dengue haemorrhagic fever in children in Delhi reported that IgM dengue serology was positive in 68.5 % of the cases.

Kumar et al (2008)[58] over a period of 10 weeks from July to September 2006, children admitted in hospital with acute hepatic failure in Lucknow, India were examined for the presence of IgM to dengue virus by IgM capture ELISA (Panbio, Australia). Out of 27 children, 13 (48.1 %) were positive for dengue IgM. Serum samples of 7 randomly selected IgM positive patients were subjected to real time PCR assay of which 4 were positive.

Priyadarshini et al (2010)[80] in their study conducted in Pune ,India tested sera from 372 dengue suspected cases by IgM capture ELISA and found that 195 (52.4 %) patients were positive for dengue specific IgM.

In a study by Jain H et al (2016)[63] of 65 cases of dengue infection confirmed by rapid dengue test NS 1 antigen test was positive in 80% of cases, IgM in 52% and dengue IgG was positive in 36% of cases.

HAEMATOLOGICAL INVESTIGATIONS OF DENGUE INFECTION

In Srilanka a study made by Lucas et al (2001)[81] on dengue revealed that platelet count (< 150 x 109/L) in all the patients. Fifty one patients had 100x109/L of platelet count and 13 had < 50x109/L platelet count, Hematocrit >40 % was seen in 53 patients and <40 % was observed in 6 patients.

Kalayanarooj et al(2002)[50], in their review on dengue reported that thrombocytopenia (≤100,000 cells/cu .mm) was found in 50 .2 %, 93.8 % and 92.1 % of DF, DHF and DSS patients respectively. The mean platelet count in DF, DHF and DSS patients were 123599, 63855, 53452 cells/cu.mm respectively. Leucopenia (WBC < 5,000 cells /cu.mm) was found in 77.71 %, 73.2 % and 56.1 % of DF, DHF and DSS patients with count of 4104 , 4347 and 541 cells/cu.mm in DF, DHF and DSS patients respectively.

Narayanan et al (2003)[82] in the study on clinical and laboratory parameters associated with complications reported platelet count < 50000/mm3 in 53.8 % of dengue patient with shock and 15.2 % of patients without shock .Platelet count of 50000 – 100000 was observed in 46 % of patients with shock and 50 % of patients without shock. Hematocrit >20 % was seen in 30.7 % of patient with shock and 21.7 % of patients without shock. Hemoglobin level was also found to be reduced in dengue patients.

Kabilan et al(2005)[83] investigated dengue disease spectrum among infants in 2001 dengue epidemic in Chennai, Tamilnadu and found that the mean hematocrit values were 31.1 % and 36.03 % for infants and older children. Only 15 % of the infants and 21 % of the children had hematocrit values of > 40 %. Thrombocytopenia (platelet count < 100,000/ mm3) was demonstrated for the majority of the patients irrespective of age and the mean platelet count for infants (59,900/ mm3) was significantly lesser than for older children.

In a study made in Kerala by Daniel et al (2005)[84] it was reported that 6 % of patients had >16 gm % hemoglobin. Hematocrit (<45 %) was observed in 72 %, total WBC count (< 4000 mm3) was found in 40 % of dengue patients. Platelet <100000

mm3 was found in 90 % of the patients out of which 48 % of patients had <50000 mm3 and 8.4 % had <10000 mm3 whereas Liamas et al., 2005 reported thrombocytopenia in 36.7 % of the dengue fever patients.

Ali N et al (2007)[85] performed a retrospective observational study of dengue fever, including 210 patients (male:female ratio 1.6:1, ages 6-74 y, mean 29.7 y) attending the Aga Khan University Hospital, Karachi from January 2001 to December 2006. All included patients proved dengue IgM antibody positive. Of these, 19 (9%) showed increased haemoglobin/haematocrit levels on admission which remained elevated in 4 (2.1%) at the time of discharge. 56 patients (26.6%) had leucopenia and neutropenia and 77.1% (161) had thrombocytopenia at the time of admission; 2.5% (5) and 16.7% (35) had deranged PT and APTT, respectively. Atypical lymphocytes were seen in 109 patients (52%). Platelet transfusion was given in 45 (22.1%) cases. The majority of patients were discharged without any adverse sequelae. The fatality rate was 3.3% (n=7) and these patients died of dengue shock syndrome, while 196 (93.3%) recovered completely. Haematological parameters are an important clue and should be tested when a patient presents with symptoms suggestive of dengue fever.(ank)

Faridi et al (2008)[79] found that in New Delhi, India all the dengue confirmed patients had a platelet count of less than 1, 00,000 mm 3 and only one child had a platelet count of less than 20,000 mm3 .The haematocrit 20 – 40 % was seen in all the patients. The total leucocytes count (< 4000/mm3) was seen in 5.8 % of the patients.

Kumar et al (2008)[58] studied prevalence of dengue infection in north Indian children with acute hepatic failure and found that none of the patients had thrombocytopenia or anaemia.

Khan et al (2010)[86] found that in Pakistan from 2003 – 2007, 14.8 % of dengue patients had hemoglobin level less than 10 mg /dl. Total leukocyte count was decreased in 40.3 % of the patients. In the differential leukocyte, 32.5 % had monocytosis, 31.8 % had neutropenia, 24 % had lymphocytosis and 79.4 % had thrombocytopenia.

In Pakistan Arshad et al (2011)[87] found thrombocytopenia and leucopenia were the most common haematological abnormalities in dengue patients. Platelet count below 50x103 /µL was seen in 78 % of the patients studied. Forty nine percent (49 %) had total WBC count below 4x103 /µL. The mean hemoglobin and hematocrit levels were normal in majority of the patients.

Jain et al (2011)[88], in their prospective clinical study of dengue fever reported that anemia was commonly seen in males (66 %) and females (34 %). Leucopenia was found in 31 % of the patients and thrombocytopenia (Platelet count less than 150.000/mm3) was found in 92 % of the total cases.

In a study by Jain H et al(2016)[63] of 65 cases evidence of raised hematocrit (>35%) was observed in 84% of cases, thrombocytopenia (<1-lakh) was observed in 80% of cases with 10% of patients having platelet count <20,000/ mm and most of the cases had platelet count between 50,000 and 1-lakh . Leucopenia (<5000) was observed in 44% of cases.

In a study by Pothapregada S et al(2016)[89] of 261 confirmed cases of dengue fever non-severe and severe dengue infection was seen in 60.9% and 39.1%, respectively. The mean age (standard deviation) of the presentation was 6.9 + 3.3 years and male: female ratio was 1.2:1. The most common clinical manifestations were fever (94.6%), conjunctival congestion (89.6%), myalgia (81.9%), coryza (79.7%), headache (75.1%), palmar erythema (62.8%), and retro-orbital pain (51.3%). The common early warning signs at the time of admission were persistent vomiting (75.1%), liver enlargement (59.8%), cold and clammy extremities (45.2%), pain abdomen (31.0%), hypotension (29.5%), restlessness (26.4%), giddiness (23.0%), bleeding (19.9%), and oliguria (18.4%). The common manifestation of severe dengue infection was shock (39.1%), bleeding (19.9%), and multi-organ dysfunction (2.3%). Platelet count did not always correlate well with the severity of bleeding.The hematological parameters showed anemia (29.5%), leukopenia (19.1%) and thrombocytopenia in 215 (82.4%) cases. Hemoconcentration was in 46.4% of cases, and the mean hematocrit was 38.9 (4.4). Seven children (2.7%) had platelet count <10,000/mm 3 , five children (1.9%) were between 10,000 and 20,000/mm 3 , 31 children (11.9%) were between 20,000 and 50,000/mm 3 , 58 (22.2%) children had platelet count between 50,000 and 100,000/mm 3 , 114 (43.7%) children had platelet count between 1 and 1.5 lakh/mm 3 and 46 children (17.6%) were >1.5 lakh/mm 3). Severe thrombocytopenia (platelet count <50,000/mm 3) was seen in 43 (16.5%) cases and among them 36 (83.7%) cases had severe dengue infection. All children who had platelet count <20,000/mm 3 had severe dengue infection. Disordered coagulation (prolongation of the prothrombin and/or activated partial thromboplastin time) was seen in 13 children (5.0%). Altered liver enzymes were seen in 29 cases (11.1%).

BIO CHEMICAL MARKERS OF DENGUE INFECTION:

LIVER ENZYMES:

Dengue virus may provoke varying degrees of damage to the hepatic parenchyma, ranging from mild increase in aminotransferases to increase up to 30 times the reference values. Therefore, the use of liver test, to evaluate the degree of liver damage is of great importance.

Kuo et al(1992)[90] in his study of liver biochemical tests and dengue fever reported that approximately 90% of the patients in his study had abnormal AST levels, while abnormal levels of ALT, bilirubin, alkaline phosphatase and gamma glutamyl transferase (GGT) were found in 80%, 7%, 16% and 83%, respectively, of patients with classic dengue.

A prospective observational study conducted by Kalayanarooj et al (1999)[91] in Thailand in 1994 -1997 showed that plasma AST and ALT levels were significantly higher in children with dengue virus infection than in children with OFI. The levels of AST and ALT in dengue patients were 61.65 IU/L and 33.71 IU/L respectively. In patients with OFI, they were 38 IU/l and 21.72 IU/L. The percentage of AST > 40 U in DF and OFI patients were 90.9 % and 57.1 % respectively. The percentage of AST > 60 U in DF and OFI patients were 63.07 % and 15.1 % respectively. The percentage of ALT > 40 U in DF and OFI patients was 53.98 % and 12.69 % respectively. In percentage of ALT > 60U in DF and OFI patients was 28.98 % and 5.10 % respectively.

Mohan et al (2000)[48] found during dengue epidemic in Delhi in 1999, children with dengue infection showed 80 − 87 % of elevation in the level of AST,

ALT and ALP. During the second week of hospitalization the proportion of cases with raised level of AST, ALT and ALP were higher and these levels gradually declined over the next 2 - 3 weeks.

Cam et al (2001)[92] conducted a prospective case control study of dengue children with DHF in Vietnam in 1999 showed a significant increase in the level of AST (2751 U/L), ALT (984U/L) and ALP (279 U/L) in patients with dengue encephalopathy as compared to dengue patients without encephalopathy. The AST, ALT and ALP level in dengue patients without encephalopathy were 234 ± 485, 81 ± 152 and 161 ± 59 respectively.

Kalayanarooj et al (2002)[50] made a retrospective review of 5,332 patients with DF and DHF between 1995 -1999 in Bangkok, Thailand. They reported that the mean AST level in DF, DHF and DSS patients was 109, 192 and 423 U/L respectively. Almost 95 % of dengue patients had elevation of AST. Most of them had mild elevation of AST (78.5 % of DF, 70.6 % of DHF and 58.7 % of DSS patients). Elevation of AST >200U was found in 9.6 % of DF, 25.3 % of DHF and 39.2 % of DSS patients. The mean ALT level in DF, DHF and DSS patients was 53U, 88U and 159 U respectively .About 55.3 % patients had mild elevation of ALT (31 % of DF, 48.4 % of DSS). Elevation of ALT > 200 was found in 3.9 % of DF 8.8 % of DHF and 16.3 % of DSS patients.

Daniel et al (2005)[84] in the study on a major epidemic of dengue in Kerala in 2003 recorded elevated AST in 83.9 % of the patients. Among those patients with a normal AST, no mortality was observed. It was found that bilirubin was above 2 mg % in 9.7 % of the patients.

Ira Shah and Katrira (2005)[55] found that in Mumbai in 2004 elevated level of AST was seen in 73.5 % patients and ALT in 67.6 % patients. The mean levels of AST and ALT were 319.9 (IU/L) and 211 (IU/L) respectively.

A study on profile of liver involvement in dengue virus infection by Itha et al (2005)[4] during an outbreak of dengue in Lucknow in 2003 revealed ALT and AST elevation in 96 % (each) of study population and 5 fold elevated levels were found to be more frequent in severe disease of the patients.

In a study done by Chhina RS et al (2008)[3] in Punjab deranged total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin and prothrombin time index (PTI) [international normalized ratio (INR)] was present in 19.5% , 97.7% , 93.9% , 32.6% , 29.1% and 15.5% patients respectively.

Prakash et al (2010)[5], studied six hundred and ninety nine patients with dengue fever in Karachi in 2010, out of which 13%(94) patients had DHF or DSS. Liver functions tests showed median ALT of 88.50 IU/L; IQR 43.25-188 IU/L, median AST of 174 IU/L; IQR 87-371.5 IU/L and median total bilirubin of 0.8 mg/dl; IQR 0.6-1.3 mg/dl. Seventy one percent (496) had mild to moderate hepatitis and 15% (103) had severe hepatitis.

Mahmuduzzaman et al (2011)[93] conducted a cross sectional prospective hospital based observational study in Dhaka, Bangladesh in dengue patients and found that the mean levels of AST and ALT were 84.5 ± 42.4 IU/L and 59.9 ± 31.1 IU/L respectively in classic DF patients and they were significantly lower than the mean

levels of aminotransferases in DHF patients. The rise of AST is for greater than ALT in both DF and DHF patients.

In a study by Kulothungan R et al (2015)[94] of 103 children of dengue fever based on the NS1 antigen positivity 48% (50) of children had warning signs at the time of admission. Thirty-seven children (35%) with warning signs progressed to severe dengue. Children with dengue fever with warning signs had higher serum levels of AST, ALT, CPK and LDH than in children with dengue fever.70% (35) of children with dengue with warning signs had marked increase in CPK levels, which is significant (p value<0.001) in comparison to children with dengue fever. Amongst the 50 children with dengue with warning signs, 20 (40%) had significant elevation of AST (p value of < 0.005), in comparison to children with dengue fever (Table 3).Serum ALT is drastically raised in children (22%) with dengue fever with warning signs(p value<0.001) in contrast to children with dengue fever.

Sani SS et al (2017)[95] reviewed 365 cases, of which twenty-two (6%) patients had severe dengue. AST and ALT were found to be good at identification of severe dengue. The AST2/ALT composite index was the most accurate (AUC 0.83; 95% CI 0.73 - 0.93). Optimal cut off was 402 with a sensitivity of 59.1% (95% CI: 36.4 - 79.3%) and specificity of 92.4% (95% CI: 89.1 - 95.0%). Modified cutoff of 653 had a sensitivity of 40.9% (95% CI: 20.7 - 63.7%) and specificity of 97.4% (95% CI: 95.1 - 98.8%). Our analyses also suggested that several underlying biological processes represented by biomarkers tested were unrelated despite occurring in the same disease entity. Also, markers of plasma leakage were discordant and AST was likely hepatic in origin. The composite index AST2/ALT may be used as a marker for identification of severe dengue based on admission AST and ALT, with two choices of cut off

values, 402 and 653. AST is most likely of liver origin and CK does not provide additional value.

SERUM PROTEINS (ALBUMIN)

Kalayanarooj et al (2002)[50] in their retrospective study with 5332 patients in Thailand during 1995 -1999 found that the mean albumin level in DF, DHF and DSS patients before plasma leakage was 4.5, 4.5 and 4.3 gm % respectively. The mean albumin level of DHF and DSS patients after plasma leakage was 4.1 and 3.6 gm % respectively.

Brito CA et al (2007)[96] in their study of 14 patients diagnosed with dengue hemorrhagic fever at two private hospitals in Recife, Brazil, between January and May 2002 were followed up with daily hematocrit and serum albumin assays. Eight (57%) of the cases presented hemoconcentration of 20% or more. Hypoalbuminemia was detected in ten patients (71%). Serum albumin assays increased the detection of permeability abnormalities in six cases (43%) in which the hemoconcentration was less than 20% and the symptoms were compatible with an exacerbated immune response. Thus, the use serum albumin quantification increased the sensitivity of dengue hemorrhagic fever detection.

Villar-Centeno et al (2008)[97] in their comparative study of biomarkers between patient with dengue and OFI patients in Colombia indicated that there was no significant difference in the albumin level between these two groups. The mean value of albumin was 4.11 g/dl in DF patients and 4.21 g/dl in patients with OFI. However, there was a significant difference in albumin level between the patients with OFI and DHF and also patients with DF and DHF.

Kumar et al (2008)[58] in their study in Lucknow, India with 27 children, found that the mean level of protein, albumin and globulin in dengue IgM positive patients were 66.3, 31.4 and 0.7 g/L respectively.

Kalayanarooj (2011)[98], in his study conducted in Thailand in 2000 reported that the mean minimum serum albumin in non-dengue and dengue confirmed patients were 4.53 and 3.93 gm% respectively.

CPK-MB

Dengue is a disease whose clinical manifestations range from asymptomatic infections to a severe disease. There have been some previous reports of myocardial involvement in dengue, but this association has not been completely established.

In a retrospective study by Gupta VK et al (2010) [99] of 28 patients of DHF none of the patients had clinical features of overt myocarditis. 4 patients had sinus bradycardia and sinus tachycardia was present in 6 cases. There were no other ECG abnormalities. Out of 28 patients of DHF, 20 patients (71%) had significantly raised cardiac enzymes CPK-MB, LDH and SGOT. 12 patients tested positive for serum Troponin-T. 4 patients (14%) had grade 1 diastolic dysfunction in 2D-Echo, and 1 patient (3.5%) had mild pericardial effusion. It was concluded that significant number (71%) of patients of dengue developed asymptomatic involvement of heart as evidenced by raised cardiac enzymes (CPK-MB, S. trop.T, LDH and SGOT). Myocardial involvement was subclinical as 2D-Echo was normal in 23 patients (82%). Possible cause of raised cardiac enzymes in these patients is subclinical myocarditis.

In a study done by Miranda CH et al (2013) [100] of 81 patients from January to July of 2011, patients hospitalized with dengue having abnormal biomarkers underwent echocardiography and when any abnormality was detected, they underwent cardiac magnetic resonance imaging. Of the 10 patients who underwent echocardiography, depressed left ventricular ejection fraction (LVEF) was identified in 1, left ventricular segmental abnormalities with preserved LVEF in 2, and an important pericardial effusion with tamponade in another. Cardiac involvement was confirmed by CMR in these 4 patients. Dengue viruses were shown to cause cardiac disease with clinical manifestations ranging from mild elevation of biomarkers to myocarditis and/or pericarditis.

Salas IY et al (2017)[101] in their study by of 54 serologically confirmed dengue patients and 10 healthy controls to determine the serum activity of CK and CK-MB a blood sample was taken to measure the activity of CK and CK-MB. The median age of dengue cases was 18 years and the median age of healthy controls was 28.5 years. Half of dengue patients (50.9 %) had elevated levels of CK-MB, in contrast with the healthy controls in which none presented increase of this enzyme. No patient presented myocarditis; however, elevated CK-MB was observed in 33.3 %, 44.4 % and 40 % of cases with bradycardia, tachycardia and hypotension respectively. In 29.6 % of the dengue patients, high level of CK was detected, in contrast to 10 % in the control group. Activity of CK elevated was observed in dengue patients with symptoms such as vomiting, hematemesis and abdominal pain, 87.5 %, 60 % and 50 %, respectively. In this study, no patient with dengue infection had heart disease or myositis; however, the finding of a higher frequency of elevated level CK and CK-MB in the dengue patients compared to the control group suggests the involvement of the striated muscle and of the cardiac muscle in this group. For this reason, the

monitoring of these enzymes should be considered as part of the monitoring of patients with dengue.

IMAGING FINDINGS (CHEST X-RAY & ULTRASOUND)

Setiawan MW et al (1998)[102] in a prospective study of 73 cases, the relationship between the clinical severity of dengue haemorrhagic fever (DHF) and the sonographic findings was examined. The cases were classified as mild (grades I-II) and75 as severe (grades III--IV). Ultrasonography in the mild group revealed pleural effusions in 30%, ascites in 34%, gallbladder wall thickening in 32%, hepatomegaly in 49%, splenomegaly in 16%, and pancreatic enlargement in 14%. In the severe group, pleural effusions, ascites and gallbladder wall thickening were found in 95%, pararenal and perirenal fluid collections in 77%, hepatic and splenic subcapsular fluid collections in 9%, pericardial effusion in 8%, hepatomegaly in 56%, splenomegaly in 16%, and pancreatic gland enlargement in 44%. They concluded ultrasound may be useful for early prediction of the severity of DHF in children.

Venkata Sai PM et al (2005)[103] had performed Ultrasound on 128 patients (2–9 years) with clinical suspicion of dengue fever. Serological tests were performed to confirm the diagnosis. 40 patients were serologically negative for dengue fever and later excluded from the study. Of the remaining 88 serologically positive cases, 32 patients underwent ultrasound on second to third day, repeated on fifth to seventh day of fever and in 56 patients ultrasound was done only on fifth to seventh day of fever. Of the 32 patients who underwent the study on second to third day of fever, all showed gall bladder wall thickening and pericholecystic fluid, 21% had hepatomegaly, 6.25% had splenomegaly and right minimal pleural effusion. Follow-up ultrasound on fifth to seventh day revealed ascites in 53% left pleural effusion in

22% and pericardial effusion in 28%. Of the 56 patients who underwent the study on fifth to seventh day of fever for the first time all had gall bladder wall thickening, 21% had hepatomegaly, 7% had splenomegaly, 96% had ascites, 87.5% had right pleural effusion, 66% had left pleural effusion and 28.5% had pericardial fluid. They concluded, in an epidemic of dengue, ultrasound features of thickened gall bladder wall, pleural effusion and ascites should strongly favour the diagnosis of dengue fever

Wang CC et al (2007)[104] retrospectively studied 363 DHF patients in southern Taiwan, and a total of 468 CXRs were obtained and reviewed. More than 50% of these showed abnormalities after the 3rd day, with infiltration only and small pleural effusion as the major findings. Progressive changes during the first week and improvements during the second week were observed in these abnormal CXRs. The CXR presentation was also significantly correlated with laboratory findings (white blood cell count, platelet levels, activated partial thromboplastin time, and alanine aminotransferase and albumin levels), as well as the clinical course (renalinsufficiency, liver function impairment, upper gastrointestinal bleeding, combination bacterial infection, and duration of admission) and outcome (mortality). They concluded that CXR may therefore be a modality for evaluating the clinical course of DHF and should be made during first week after the onset of illness.

Reddy KB et al (2013)[105] in their prospective study conducted in a tertiary pediatric centre involving 324 children with confirmed dengue fever were compared with 422 children of suspected dengue fever. Severity of illness was graded as per WHO criteria and sonography findings were correlated to the grade of illness. Results Gallbladder wall thickening was seen in 75% of the children with confirmed dengue fever. A significant difference was seen between survivors and non-survivors with

respect to pericholecystic fluid collection (P=0.002), hepatic intraparenchymal fluid (P<0.001), splenomegaly (P=0.002), splenic subcapsular fluid (P<0.001), peripancreatic fluid (P<0.001), perirenal fluid (P<0.001) and pericardial fluid (P<0.001). Other findings included ascites, pleural effusion, hepatomegaly and splenomegaly, which were present irrespective of grade of illness. They concluded Ultrasonography can be used as a useful tool in developing countries to predict the severity of dengue fever in children.

In analysis by Kulothungan R et al (2015), radiological abnormalities were detected in 30% (15) of children with dengue with warning signs and they showed significance (p value 0.003) in correlation to children with dengue fever. Ultrasound abdomen revealed abnormalities in 48% (24) of children with dengue fever with warning signs (p value <0.001) in contrast to children with dengue fever.

Pothapregada S et al (2016)[106] did a retrospective study on 254 children with dengue fever and among them non-severe dengue and severe dengue were seen in 62.6% and 37.4% respectively. Mean age of presentation was 7.0 (3.3) years. M: F ratio was 1.2:1 Ultrasound was performed on all children with dengue fever during the critical period of illness as an early sign of plasma leakage and at the time of discharge. The diagnosis was confirmed by NS1 antigen and dengue serology. Ultrasonography showed positive findings in 156 cases (61.4 %) during the critical period of illness. Ultrasound findings were analysed using logistic regression among severe and non-severe dengue and P value of <0.05 was taken as significant. The common ultrasound findings that were significantly associated with severe dengue infection on univariate analysis were gall bladder wall thickening, ascites, pleural effusion, pericardial effusion, pericholecystic fluid, hepatomegaly, splenomegaly and

mesenteric adenopathy. On multivariate analysis, gall bladder thickening and hepatomegaly were significantly associated with severe dengue infection. Gall bladder wall thickening (GBWT) with honeycombing pattern was the most specific finding in severe dengue infection in the study and significantly associated with severe thrombocytopenia (Platelet count <50,000/mm3). The clinical improvement coincided with resolving of the ultrasound findings at the time of discharge. They concluded that Ultrasound can be used as an early predictor as well as an important prognostic sign for severe dengue infection especially during an epidemic.

Renuka S Jadhav et al (2016)[107] did a study of 80 patients- 40 of Dengue fever and 40 with severe Dengue. NS1Ag, Dengue IgM, IgG test was carried out in every patient. Other investigations of complete blood count, hematocrit, Platelet count, SGPT, Prothrombin time , PTTK were done. All the patients underwent Chest radiograph, Ultrasound abdomen and chest. Maximum number of cases were seen in September and October, Radiological evidence (Ultrasonography) showed Hepatomegaly which had :Sensitivity=87.5%, Specificity=35%,OR=3.77 and Tender Hepatomegaly: with Sensitivity=80%%, Specificity=65%, OR=7.43.P value of Pleural effusion hepatomegaly, Ascites, Gall bladder changes was also significant P<0.05).Pleural effusion was seen significantly more in severe Dengue group. It is inferred that inclusion of radiological investigations in evaluating the course of dengue fever will help in detecting cases of impending shock, thereby helping in early hospitalization and management.

Malleshappa K et al (2017)[108] in their study of 120 dengue serology-positive cases in the age group of 2 months to 18 years were studied. These children were divided into two groups - mild (dengue hemorrhagic fever [DHF] I-II without

shock) and severe dengue (DHF III-IV with shock. Among the 120 cases of DF studied, chest X-ray showed pleural effusion in 42 (35%) cases and USG thorax showed pleural effusion in 66 (55%) cases, suggesting higher sensitive of USG thorax than the chest X-ray in identifying the pleural effusion. Ultrasound was performed on all patients, among the 120 cases, GBWT >3 mm was seen in 100(83.3%) cases. This thickening was seen in all 32 (100%) cases of severe dengue and 68 (77%) cases with mild dengue (p=0.89). Pericholecystic edema was seen in 98 (81.6%) out the 120 cases; all 32 (100%) cases of severe dengue and 66 (75%) with mild dengue (p=0.06). Ascites was seen in 68 (56%) out of 120 cases; however, significantly, more (p=0.0015) cases with severe dengue (32, 100%) had ascites than with mild dengue 36 (40.9%). Similarly, pleural effusion was seen in 66 (55%) out of 120 cases and it was more commonly present in severe dengue group (87.5% vs. 43.18%) than in mild group (p=0.0058).78 (65%) out of 120 cases of DF had hepatomegaly including 22 (68.25%) from severe dengue group and 56 (63.6%) from the mild group (p=1.000). Splenomegaly was found in total 36 (30%) cases; out of which 12 (37.5%) were from severe and 24 (27.7%) were from mild group (p=0.654). Perinephric edema was seen significantly more cases with severe dengue than with the mild dengue (16 vs. 2) (p<0.0001).Out of 120 cases, gallbladder wall thickness (83.3%) and pericholecystic edema (81.6%) were the most common sonographical findings. When sonographic variables of mild and severe groups compared, significant statistical difference was noted in variables such as ascites, pleural effusion, and perinephric edema with p=0.0015, p=0.0058, p<0.000, respectively. They concluded ultrasound can be used as an adjunct modality in patients with suspected DF to detect early signs suggestive of the disease and also useful tool to predict severity of the disease.

In a study by Kumar AMK et al (2017)[64]of 48 cases of dengue, ultrasound was done to see for polyserositis manifesting in the form of pleural effusion and ascites with 20% of DF, 47.4% of DFWS and 57.1% of SD cases showing polyserositis. Chest x-ray showed pleural effusion in 22.9% cases.

In a study by Mulay S et al (2017)[65] the ultrasonographic findings showed hepatomegaly in 35(39.8%) cases, gall bladder thickening in 47(53.4%) cases, splenomegaly in 18 (20.5%) cases, pleural effusion in 34(38.6%) cases while ascites was seen in 27(30.7%) cases. Overall 65 (73.8%) out of 88 cases had one of the positive finding in ultrasonography.

MATERIALS AND METHODS

Source of data:

Children with dengue infection admitted in paediatric ward and/or paediatric intensive care unit in BLDEU Shri B.M.Patil Medical College, Hospital and Research Centre, Vijayapur, fulfilling the inclusion and exclusion criteria.

Period of study – 18 months (October 2016-march 2018)

Method of collection of Data (including sampling procedures if any)

After obtaining ethical clearance from institutional ethical committee the study will be started. The written informed consent will be taken from the parents of patients fulfilling inclusion and exclusion criteria and then the patients are included in the study. In this prospective observational analytical study, a sample of 35 patients proven to be dengue positive [NS1 or IgM or IgG positive (card test or ELISA)] admitted in pediatric ward and pediatric intensive care unit in Shri B.M.Patil Medical College, Hospital and Research Centre will be included. For these patients, specific investigations like complete hemogram which includes even platelet count and hematocrit, liver function tests(bilirubin, serum protein, AST, ALT, ALP), coagulation profile(PT,APTT), CPK-MB, chest x ray, ultrasound abdomen and pelvis shall be done between day 1 and day 3 of admission. At the time of admission blood will be collected in different vacutainers for these investigations and sent to the laboratory .Following which, the results of these investigations will be analysed in order to interpret the severity of dengue infection in the subjects.

Determination of sample size (n):

With 90% proportion of hepatic derangement among patients with dengue infection [90] at 95% significance level and at ± 15% allowable error sample size is 65, with finite population correction.

Statistical formula:

$$n = \frac{Z^2 P(100 - P)}{d^2}$$

Z=level of significance

P=expected proportion/prevalence=90%

d=expected margin of error

Statistical analysis:

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value.

C= (number of rows-1)* (number of columns-1)

In cases of more than 30% cell frequency <5, Freeman-Halton Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\dfrac{s_1^2}{n_1} + \dfrac{s_2^2}{n_2}}}$$

where $\overline{x}_1$ = mean of sample 1

$\overline{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

s_1^2 = variance of sample 1 = $\dfrac{\Sigma(x_1 - \overline{x}_1)^2}{n_1}$

s_2^2 = variance of sample 2 = $\dfrac{\Sigma(x_2 - \overline{x}_2)^2}{n_2}$

The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance.

ANOVA

Source	d.f.	SS	MS	F
Treatment	$a - 1$	SS_{treat}	$\dfrac{SS_{treat}}{a-1}$	$\dfrac{MS_{treat}}{MS_{error(a)}}$
Error (a)	$N - a$	$SS_{error(a)}$	$\dfrac{SS_{error(a)}}{N-a}$	
Time	$t - 1$	SS_{time}	$\dfrac{SS_{time}}{t-1}$	$\dfrac{MS_{time}}{MS_{error(b)}}$
Treat x Time	$(a - 1)(t - 1)$	$SS_{treat\ x\ time}$	$\dfrac{SS_{treat\ x\ time}}{(a-1)(t-1)}$	$\dfrac{MS_{treat\ x\ time}}{MS_{error(b)}}$
Error (b)	$(N - a)(t - 1)$	$SS_{error(b)}$	$\dfrac{SS_{error(b)}}{(N-a)(t-1)}$	
Total	$Nt - 1$	SS_{total}		

The sources of the variation include treatment; Error (a); the effect of Time; the interaction between time and treatment; and Error (b). Error (a) is the effect of subjects within treatments and Error (b) is the individual error in the model. All these add up to the total.

Degrees of Freedom: *a*-1, the number of treatments minus 1, .. *N-a,* the total number of all experimental units minus the number of treatments, .. *t*-1, for time, .. Total *df* is the total number of subjects times the number of times minus 1. The degrees of freedom for error(b) is obtained by subtraction.

Tukey's post-hoc test was used for multiple comparison.

The formula for Tukey's test is:

$$\frac{M_1 - M_2}{\sqrt{MS_w\left(\frac{1}{n}\right)}}$$

M = treatment/group mean

n = number per treatment/group

ROC analysis for Sensitivity- specificity was done to check relative efficiency.

sensitivity or true positive rate (TPR)
   eqv. with hit rate, recall
$$TPR = TP/P = TP/(TP + FN)$$
specificity (SPC) or true negative rate
$$SPC = TN/N = TN/(FP + TN)$$
precision or positive predictive value (PPV)
$$PPV = TP/(TP + FP)$$
negative predictive value (NPV)
$$NPV = TN/(TN + FN)$$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007.

Selection criteria

Inclusion criteria:

1.   All patients aged 1month-14years with dengue NS1 positive or IgM positive or IgG positive (card test or ELISA) at Shri B.M.Patil Medical College Hospital & Research Center.

Exclusion criteria:

1.   Known case of liver disease.

2.   Known case of heart disease

3.   Patients on ATT, anticonvulsants and long term steroid therapy

4.   Patients who are on regular blood transfusions for thalassemia

5.   Denial of consent

RESULTS AND ANALYSIS

TABLE 01:

AGE WISE DISTRIBUTION AMONG TYPES OF DENGUE ILLNESS:

Age (Yrs)	Total cases		Dengue fever		Dengue fever with warning signs		Severe dengue		P value
	n	%	n	%	n	%	n	%	
0-5	16	24.6	6	24.0	6	19.4	4	44.4	0.012*
6-10	26	40.0	11	44.0	12	38.7	3	33.3	
11-14	23	35.4	8	32.0	13	41.9	2	22.2	
Total	65	100.0	25	100.0	31	100.0	9	100.0	
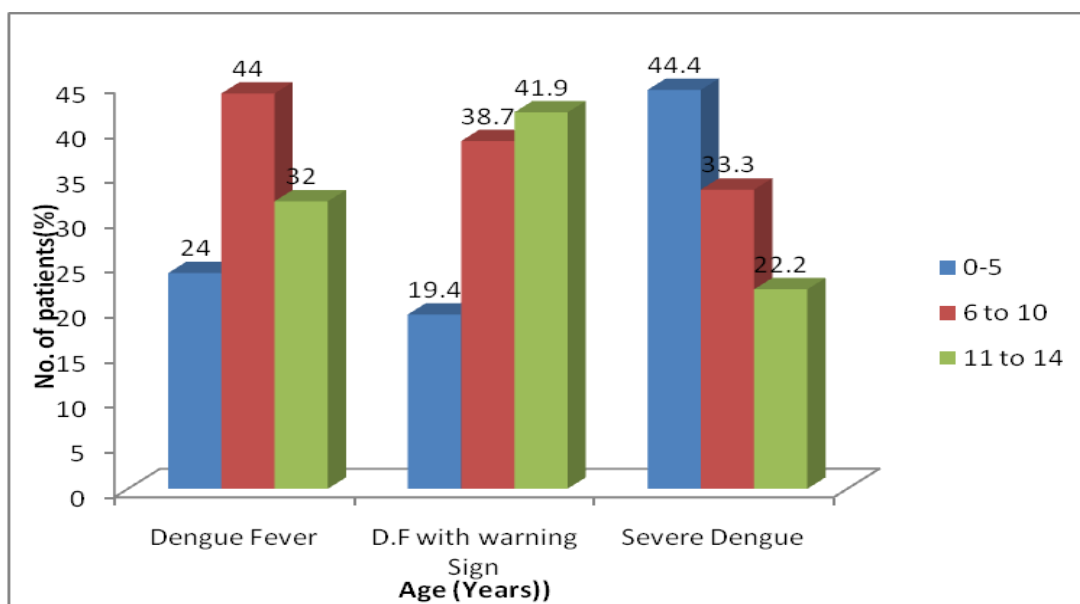
- Out of 65 cases majority of the cases were under age group 6-10 years (n=26) accounting to 40%.

- In Dengue fever (DF) cases, out of 25 maximum cases (n=11) are from 6-10 years accounting to 44%.

- In Dengue fever with warning signs (DFWS) cases, out of 31 maximum cases (n=13) are from 10-14 years accounting to 41.9%.

- In Severe Dengue (SD) cases, out of 9 maximum cases (n=4) are from 0-5 years accounting to 44.4%.

- 'p value' = 0.012 suggests that there is statistically significant difference among age wise distribution of different types of dengue illness.

TABLE 02:

SEX DISTRIBUTION AMONG TYPES OF DENGUE ILLNESS:

Sex	Total cases		Dengue fever		Dengue fever with warning signs		Severe dengue		P value
	n	%	n	%	n	%	n	%	
Male	41	63	15	60.0	20	64.5	6	66.7	
Female	24	37	10	40.0	11	35.5	3	33.3	0.914
Total	65	100.0	25	100.0	31	100.0	9	100.0	
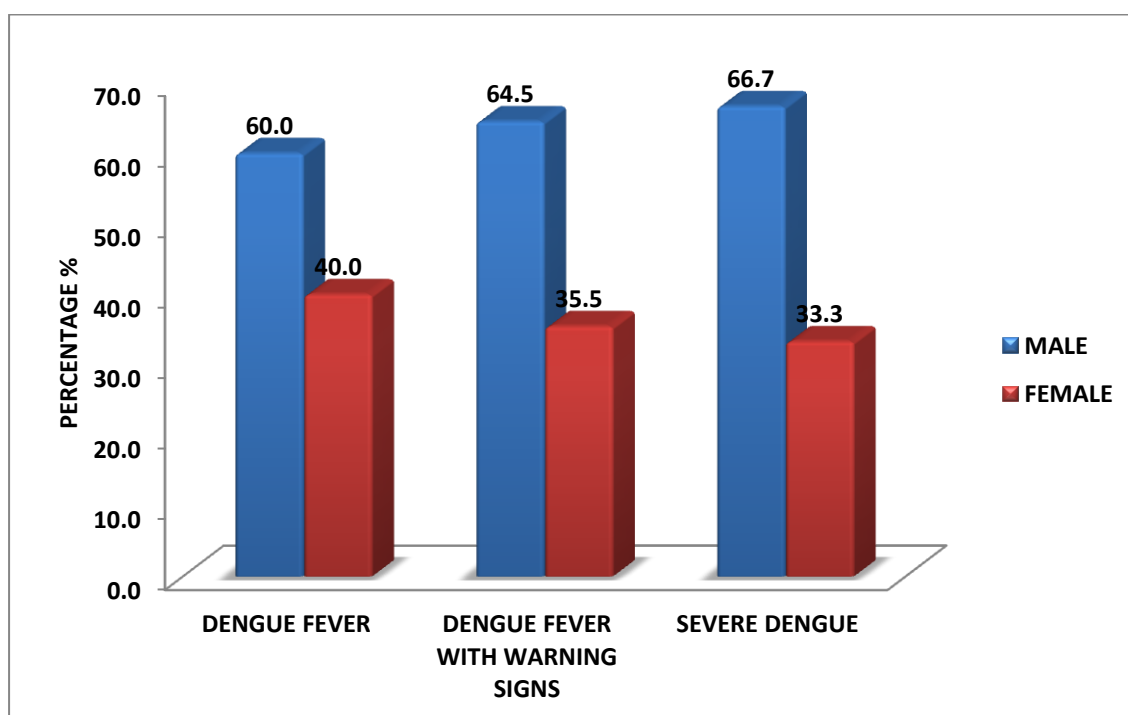
- Out of 25 cases of DF majority of patients are males (n=15) accounting to 60%.

- Out of 31 cases of DFWS majority of patients are males (n=20) accounting to 64.5%.

- Out of 9 cases of SD majority of patients are males (n=6) accounting to 66.7%.

- 'p value' = 0.914 suggests no statistical significance in gender distribution among various types of dengue illness i.e no gender is specific to any group.

TABLE 03

DISTRIBUTION OF CASES ACCORDING TO DIAGNOSIS:

Type Of Illness	No. Of Cases (n)	Percentage (%)
Dengue Fever (DF)	25	38.5
DF With Warning Signs	31	47.7
Severe Dengue	9	13.8
Total	65	100
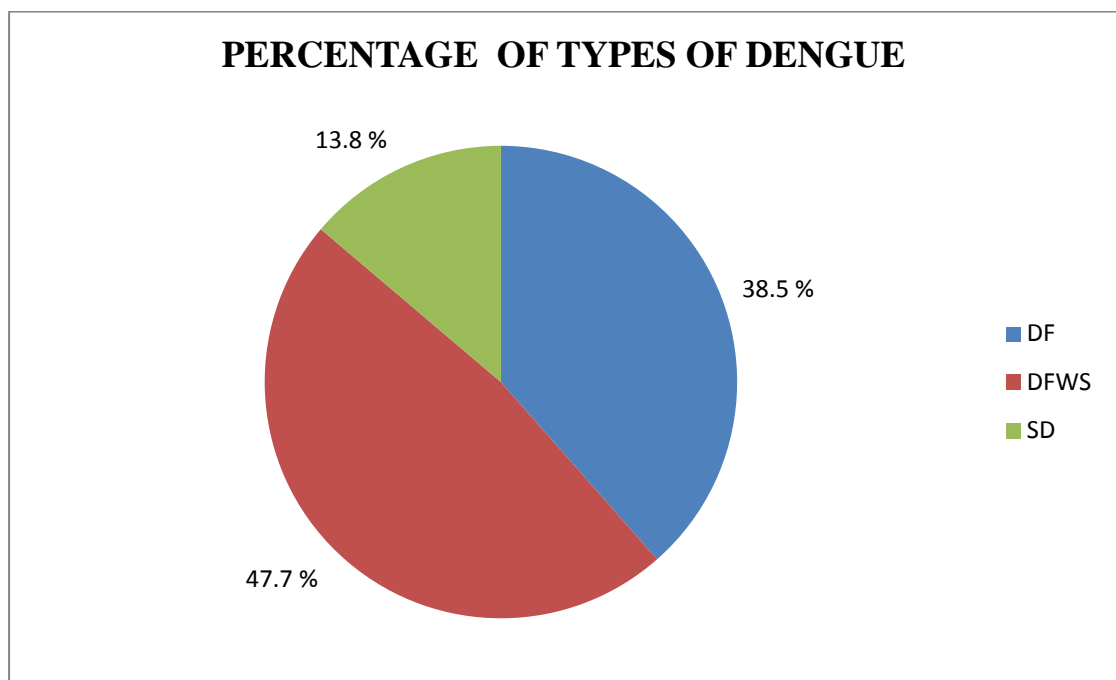
Out of 65 cases maximum cases (n=31) are of DFWS accounting to 47.7% followed by DF (n=25) accounting to 38.5% and SD (n=9) accounting to 13.8%.

TABLE 04

04A. DISTRIBUTION OF CLINICAL SYMPTOMS ACCORDING TO TYPES OF DENGUE ILLNESS:

SYMPTOMS	Total		DF		DFWS		SD	
	n	%	n	%	n	%	n	%
FEVER	65	100	25	100	31	100	9	100
VOMITING	31	47.6	8	32	19	61.29032	4	44.44
PAIN ABDOMEN	23	35.4	2	8	19	61.29032	2	22.22
HEPATOMEGALY	16	24.6	0	0	13	41.94	3	33.3
MYALGIA	9	13.85	6	24	3	9.677419	0	0
HEADACHE	7	10.77	2	8	3	9.677419	2	22.22
LOOSE STOOLS	6	9.23	2	8	2	6.451613	2	22.22
ARTHRALGIA	5	7.7	3	12	2	6.451613	0	0
COUGH	3	4.6	0	0	1	3.225806	2	22.22
COLD	3	4.6	1	4	0	0	2	22.22
NAUSEA	2	3.08	2	8	0	0	0	0
GIDDINESS	2	3.08	1	4	1	3.225806	0	0
LOSS OF APPETITE	2	3.08	1	4	1	3.225806	0	0
RASHES	2	3.08	0	0	2	6.451613	0	0
HURRIED BREATHING	2	3.08	0	0	0	0	2	22.22
ITCHING	1	1.84	1	4	0	0	0	0
IRRITABILITY	1	1.84	1	4	0	0	0	0
PERI ORBITAL PAIN	1	1.84	1	4	0	0	0	0
ICTERUS	1	1.84	0	0	1	3.225806	0	0
BLEEDING PER NOSE	1	1.84	0	0	1	3.225806	0	0
LETHARGY	1	1.84	0	0	0	0	1	11.11
DROWSINESS	1	1.84	0	0	0	0	1	11.11
EDEMA	1	1.84	0	0	0	0	1	11.11
CONVULSION	1	1.84	0	0	0	0	1	11.11

- Fever was found to be the most common symptom and is present in all cases (n=65) i.e100%.

- Vomiting is present in 8 of 25 cases of DF (32%), 19 of 31 cases in DFWS (61.2%) & 4 of 9 cases in SD (44.4%).

- Next most common is Myalgia (n=6) in DF accounting to 24% and pain abdomen(n=19) in DFWS (61.2%)

04B. DISTRIBUTION OF CASES ACCORDING TO DAY OF

PRESENTATION AFTER THE ONSET OF ILLNESS:

TYPES OF DENGUE ILLNESS	DAY OF PRESENTATION OF SYMPTOMS:				TOTAL n=65	P value
	1-2 days n	3-4 days n	5-7 days n	>7days n		
DF	2	15	7	1	25	
DFWS	2	17	9	3	31	0.872
SD	1	3	4	1	9	

This table shows distribution of cases according to the day of presentation to the hospital after the onset of fever. In present study of 65 cases there is no statistical difference between the three groups of dengue illness according to day of presentation to the hospital (p value = 0.872).

MOST COMMON SYMPTOMS IN DENGUE ILLNESS:
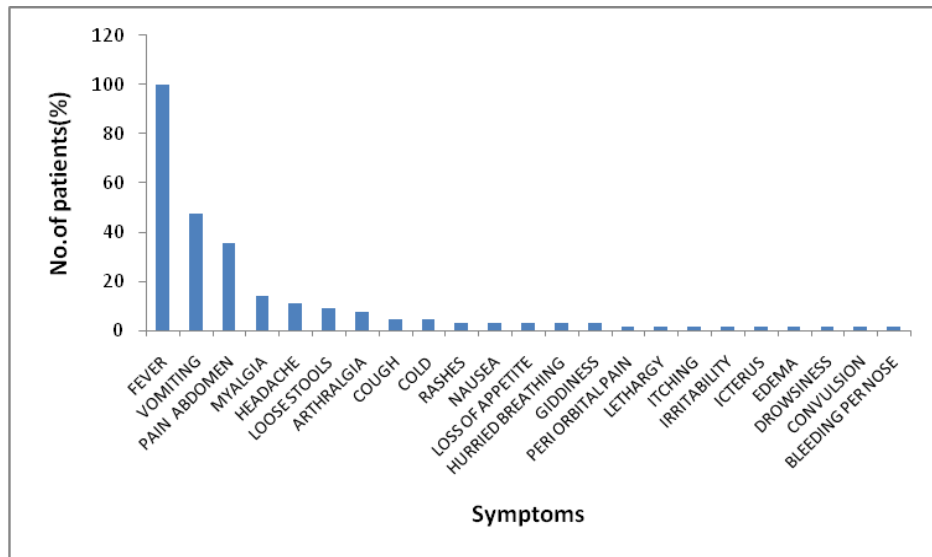
 Above figure shows the most common symptoms in dengue, in descending order it is as follows : fever, vomiting, abdominal pain, myalgia, headache, loose stools, arthralgia, cough, cold, rashes, nausea etc.

MOST COMMON WARNING SIGNS IN DENGUE ILLNESS:
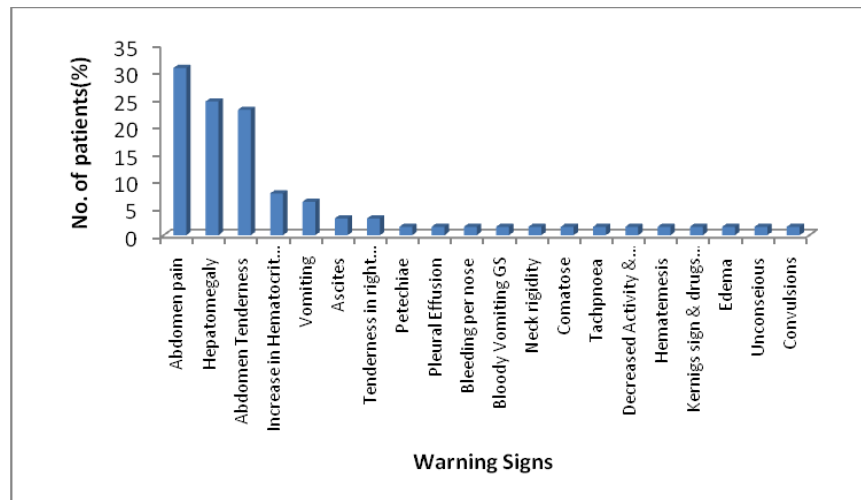
Above figure shows the most common warning signs in dengue, in descending order abdominal pain (30.7%), hepatomegaly (24.6%), abdomen tenderness (23%), raised hematocrit with reduced platelet count (6%),3% each in ascites & tender right hypochondrium.

TABLE 05

05A. DISTRIBUTION OF SEROLOGICAL TESTS

TEST	TOTAL		DF		DFWS		SD		CHI SQUARE TEST
	Positive cases	%	Positive cases	%	Positive cases	%	Positive cases	%	
CARD TEST NS1	58	89.2	25	100.0	28	90	5	56	0.001*
CARD TEST IgM	10	15.4	2	8.0	7	23	1	11	0.300
CARD TEST IgG	15	23.1	5	20.0	8	26	2	22	0.875
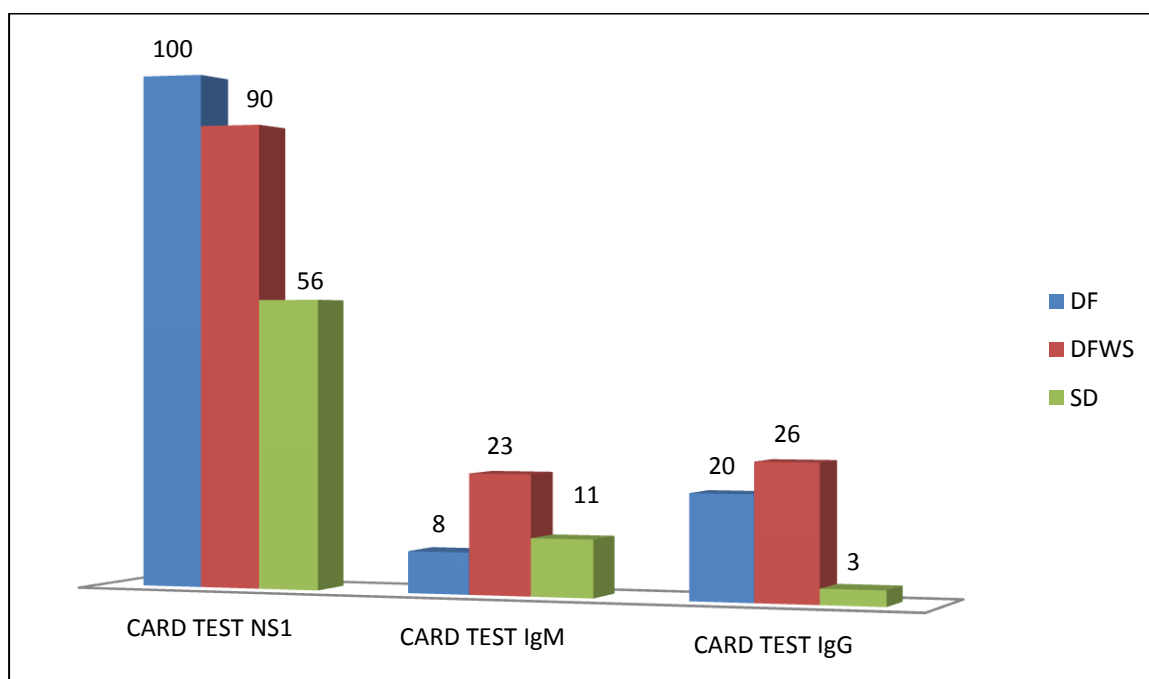
- Card test NS1 was positive in 100% cases of DF, 90% of DFWS & 56% of SD.

- Card test IgM was positive in 8% cases of DF, 23% of DFWS & 11% of SD.

- Card test IgG was positive in 20% cases of DF, 26% of DFWS & 22% of SD.

TABLE 05B: DISTRIBUTION OF SEROLOGICAL TESTS

RAPID CARD TEST	DF no of cases	DFWS no of cases	SD no of cases	TOTAL no of cases
NS1	19	20	5	44
IgM	0	1	1	2
IgG	0	1	2	3
NS1, IgM	1	2	0	3
NS1, IgG	4	3	0	7
IgM, IgG	0	1	0	1
NS1, IgM, IgG	1	3	0	4

Out of 65 cases of dengue illness

- DF constitutes 25 cases of which 19(76%) were only NS1 positive, 1(4%) was NS1 & IgM positive, 4(16%) were NS1 & IgG positive & 1(4%) was NS1, IgM, IgG positive.

- DFWS constitutes 31 cases of which 20(64.51%) were only NS1 positive, 1(3.22%) was only IgM positive, 1(3.22%) was only IgG positive, 2(6.45%) were NS1 & IgM positive , 3(9.68%) were NS1 & IgG positive, 1(3.22%) was IgM & IgG positive & 3(9.68%) were NS1, IgM, IgG positive.

- SD constitutes 9 cases of which 5(55.56%) were only NS1 positive, 1(11.1%) was only IgM positive, 2(22.22%) were only IgG positive.

TABLE 05C & 05D: DIAGNOSTIC EFFICACY OF CARD TEST TO DETECT IGM POSITIVE COMPARED TO ELISA TEST

| DENGUE | CARD TEST IGM | ELISA | | | | p value |
| | | POSITIVE | | NEGATIVE | | |
		n	%	n	%	
DF	POSITIVE	0	0.0	1	20.0	0.198
	NEGATIVE	11	100.0	4	80.0	
	TOTAL	11	100.0	5	100.0	
DFWS	POSITIVE	1	12.5	0	0.0	0.589
	NEGATIVE	7	87.5	5	100.0	
	TOTAL	8	100.0	5	100.0	
SD	POSITIVE	0	0.0	0	0.0	1
	NEGATIVE	3	100.0	1	100.0	
	TOTAL	3	100.0	1	100.0	
OVERALL	POSITIVE	1	4.5	1	9.1	0.606
	NEGATIVE	21	95.5	10	90.9	
	TOTAL	22	100.0	11	100.0	

| | CARD TEST | | | | ELISA |
	DF	DFWS	SD	OVERALL	
Sensitivity	0.00%	12.50%	0.00%	4.55%	100.00%
Specificity	80.00%	100.00%	100.00%	90.91%	100.00%
PPV	0.00%	100.00%	-	50.00%	100.00%
NPV	26.67%	41.67%	25.00%	32.26%	100.00%
Accuracy	25.00%	46.15%	25.00%	33.33%	100.00%

In present study ELISA IgM was done in 33 cases and is compared to rapid card test IgM of the same cases. ELISA is more efficacious in detecting dengue IgM with a100% sensitivity and 100% specificity than rapid card test whose sensitivity and specificity are 4.55% and 90.91% respectively.

TABLE 06

HAEMATOLOGICAL & BIOCHEMICAL PARAMETERS:

Parameter	n(65)	Percentage
TLC<4000 cells/mm^3	27	41.5
PCV $\geq$ 35%	41	63.07
PLT < 50,000/mm^3	17	26.1
PLT: 50,000 – 1 lakh/ mm^3	11	16.9
PLT > 1 lakh/ mm^3-1.5lakhs	17	26.1
PT > 13.5 sec.	54	83
APTT > 34 sec.	47	72.3
AST> 41 U/L-100U/L	25	38.46
> 101 U/L-200U/L	15	23.07
> 200U/L	16	24.61
ALT > 41 U/L-100U/L	15	23.07
> 101 U/L-200U/L	7	10.76
> 200U/L	8	12.3
ALBUMIN < 3.5 g/dl	34	52.3
CPK-MB > 26 IU/L	54	83.07

In our study of 65 cases, TLC <4000 cells/mm^3 was seen in 27 cases (41.5%), PCV $\geq$ 35% in 41 cases , PLT < 50,000/mm^3 in 17 cases , PLT: 50,000 – 1 lakh/ mm^3 in 11 cases, PLT > 1 -1.5 lakhs/ mm^3 in 17 cases, PT > 13.5 sec. in 54 cases and APTT > 34 sec. in 47 cases, AST > 41U/L in 56 cases, ALT > 41U/L in 30 cases, CPK-MB > 26 U/L in 54 cases & albumin < 3.5g/dl in 34 cases.

TABLE 07:

07A. COMPARISON OF VARIOUS PARAMETERS BETWEEN DIFFERENT TYPES OF DENGUE:

Variable	TOTAL		DF		DFWS		SEVERE DENGUE		ANOVA test
	Mean	STD	Mean	STD	Mean	STD	Mean	STD	
Total count at admission	6578.3	3456.3	4490.40	2447.51	5700.32	3241.056	9544.44	4680.804	0.001*
Platelet at admission	108699.6	79663.5	138160.00	66021.89	110161.32	82991.560	77777.78	89977.466	0.121
PCV at admission	36.7	5.45	36.80	4.717	36.16	5.962	37.44	5.703	0.801
PT	18.03	4.23	15.5	3.5	16.0	3.4	22.6	5.8	<0.001*
APTT	50.1	20.6	47.9	14.2	51.4	22.6	51.0	25.1	0.801
AST	316.4	253.7	82.9	61.1	140.5	99.7	725.9	600.5	<0.001*
ALT	233.6	278.1	31.7	18.9	80.7	87.1	588.4	728.3	<0.001*
BIL	0.8	1.03	0.4	0.1	0.7	1.2	1.3	1.8	0.108
Albumin	3.36	0.63	3.6	0.3	3.2	0.6	3.3	1.0	0.044*
ALP	179	62.3	148.1	43.3	171.7	76.8	217.2	66.9	0.026*
CPKMB	64.5	46.03	51.3	28.7	41.4	20.8	100.8	88.6	0.001*

Note: * significant at 5% level of significance (p<0.05)

- The mean of total count at admission is 6578.3 ± 3456.3, Platelet at admission is 108699.6±79663.5, PCV at admission is 36.7±5.45, PT is 18.03±4.23, APTT is 50.1±20.6, SGOT is 316.4±253.7, SGPT is 233.6±278.1, BIL is 0.8±1.03, Albumin is 3.36±0.63, ALP is 179±62.3 and CPKMB is 64.5±46.03.

- The mean of total count at admission in DF is 4490.4 ± 2447.5, in DFWS is 5700.32 ±3241.056 and in SD is 9544.44 ± 4680.804 with statistically significant p value (0.001).

- The mean of platelet count at admission in DF is 138160 ± 66021.8, in DFWS is 110161.3 ±82991.5 and in SD is 77777.7 ±89977.4 without statistically significant p value.

- The mean PCV value at admission in DF is 36.8 ± 4.7, in DFWS is 36.16 ±5.96 and in SD is 37.4 ±5.7 without statistically significant p value.

- The mean PT value at admission in DF is 15.5 ± 3.5, in DFWS is 16 ±3.4 and in SD is 22.6 ±5.8 with statistically significant p value (<0.001).

- The mean APTT value at admission in DF is 47.9 ± 14.2, in DFWS is 51.4 ± 22.6 and in SD is 51 ± 25.1 without statistically significant p value.

- The mean AST value at admission in DF is 82.9 ± 61.1, in DFWS is 140.5 ± 99.7 and in SD is 725.9 ± 600.5 with statistically significant p value (<0.001).

- The mean ALT value at admission in DF is 31.7 ± 18.9, in DFWS is 80.7 ± 87.1 and in SD is 588.4 ± 728.3 with statistically significant p value (<0.001).

- The mean Bilirubin value at admission in DF is 0.4 ± 0.1, in DFWS is 0.7 ± 1.2 and in SD is 1.3 ± 1.8 without statistically significant p value.

- The mean Albumin value at admission in DF is 3.6 ± 0.3, in DFWS is 3.2 ± 0.6 and in SD is 3.3 ± 1 with statistically significant p value (=0.044).

- The mean ALP value at admission in DF is 148.1 ± 43.3, in DFWS is 177.7 ± 76.8 and in SD is 217.2 ± 66.9 with statistically significant p value (=0.026).

- The mean CPKMB value at admission in DF is 51.3 ± 28.7, in DFWS is 41.4 ± 20.8 and in SD is 100.8 ± 88.6 with statistically significant p value (=0.001).

07 B. 'P value' comparison of Laboratory parameters among DF, DFWS & SD.

Multiple Comparisons (Post hoc test)	P Value
Total count at admission	
Dengue Fever with Dengue fever with warning signs	0.377
Dengue Fever with Severe Dengue	0.001*
Dengue fever with warning signs with Severe Dengue	0.009*
PT	
Dengue Fever with Dengue fever with warning signs	0.590
Dengue Fever with Severe Dengue	<0.001*
Dengue fever with warning signs with Severe Dengue	<0.001*
APTT	
Dengue Fever with Dengue fever with warning signs	0.501
Dengue Fever with Severe Dengue	0.654
Dengue fever with warning signs with Severe Dengue	0.961
AST	
Dengue Fever with Dengue fever with warning signs	0.014*
Dengue Fever with Sever Dengue	<0.001*
Dengue fever with warning signs with Severe Dengue	<0.001*
ALT	
Dengue Fever with Dengue fever with warning signs	0.008*

Dengue Fever with Sever Dengue	<0.001*
Dengue fever with warning signs with Severe Dengue	<0.001*
BIL	
Dengue Fever with Dengue fever with warning signs	0.249
Dengue Fever with Severe Dengue	0.018*
Dengue fever with warning signs with Severe Dengue	0.248
Albumin	
Dengue Fever with Dengue fever with warning signs	0.003*
Dengue Fever with Sever Dengue	0.163
Dengue fever with warning signs with Severe Dengue	0.819
ALP	
Dengue Fever with Dengue fever with warning signs	0.176
Dengue Fever with Severe Dengue	0.001*
Dengue fever with warning signs with Severe Dengue	0.117
CPK-MB	
Dengue Fever with Dengue fever with warning signs	0.138
Dengue Fever with Severe Dengue	0.132
Dengue fever with warning signs with Severe Dengue	0.001*

Note: * significant at 5% level of significance ($p < 0.05$)

TABLE 08

DISTRIBUTION OF CHEST XRAY FINDINGS AMONG TYPES OF

DENGUE ILLNESS:

CXR	TOTAL		Dengue Fever		D.F With warning sign		Sever Dengue		Chi square test
	n	%	n	%	n	%	n	%	
NORMAL	59	90.7	25	100	29	93.5	5	55.6	
LUNG CONSOLIDATION	6	9.23	0	0	2	6.5	4	44.4	<0.001*
Total	65	100	25	100.0	31	100.0	9	100.0	
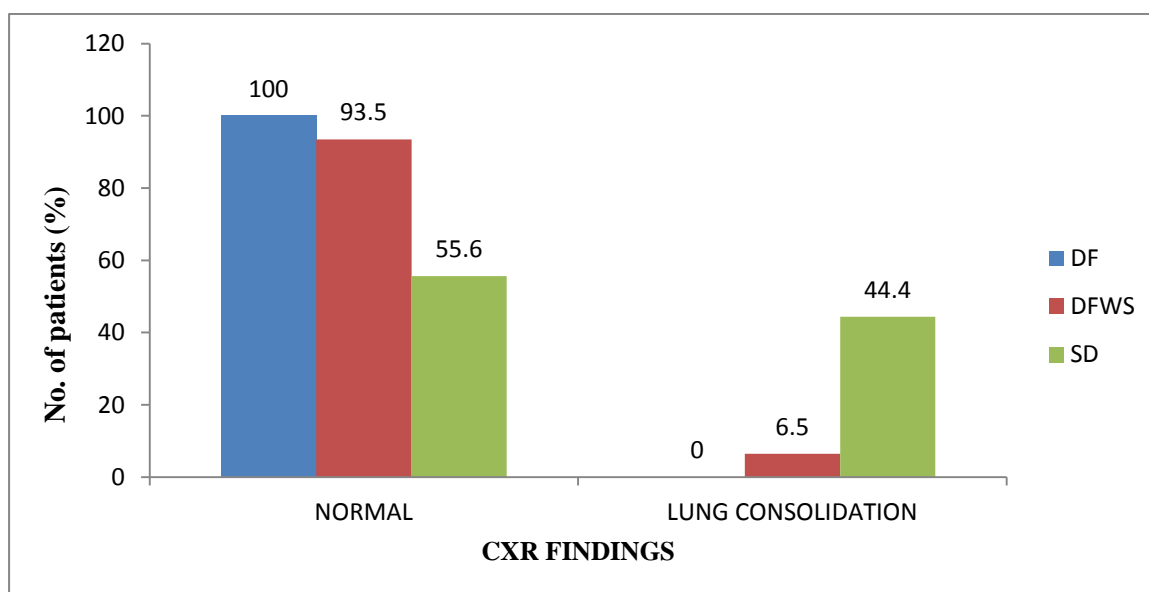
- Chest X-ray findings was mainly consolidation and is seen in 44.4% of severe dengue cases and 6.5% of DFWS cases.

- X-ray was normal in 100% cases of DF, 93.5% of DFWS and 55.6% of SD.

- Chi square test p<0.001 suggests consolidation is more common & specific in severe dengue over DFWS & DF.

TABLE 09

DISTRIBUTION OF ULTRASOUND FINDINGS AMONG TYPES OF DENGUE ILLNESS:

USG Abdomen &pelvis	Total		Dengue fever		Dengue fever with warning signs		Severe dengue		p value
	n	%	n	%	n	%	n	%	
CHOLECYSTITIS	25	38.4	5	20.0	16	51.6	4	44.4	0.049*
ASCITES	32	27.07	8	32.0	19	61.3	5	55.6	0.086
HEPATOMEGALY	6	9.23	1	4.0	5	16.1	0	0.0	0.174
SPLENOMEGALY	3	4.61	0	0.0	3	9.7	0	0.0	0.178
GB WALL EDEMA	8	12.3	3	12.0	4	12.9	1	11.1	0.988
PLEURAL EFFUSION	11	16.92	0	0.0	8	25.8	3	33.3	0.014*
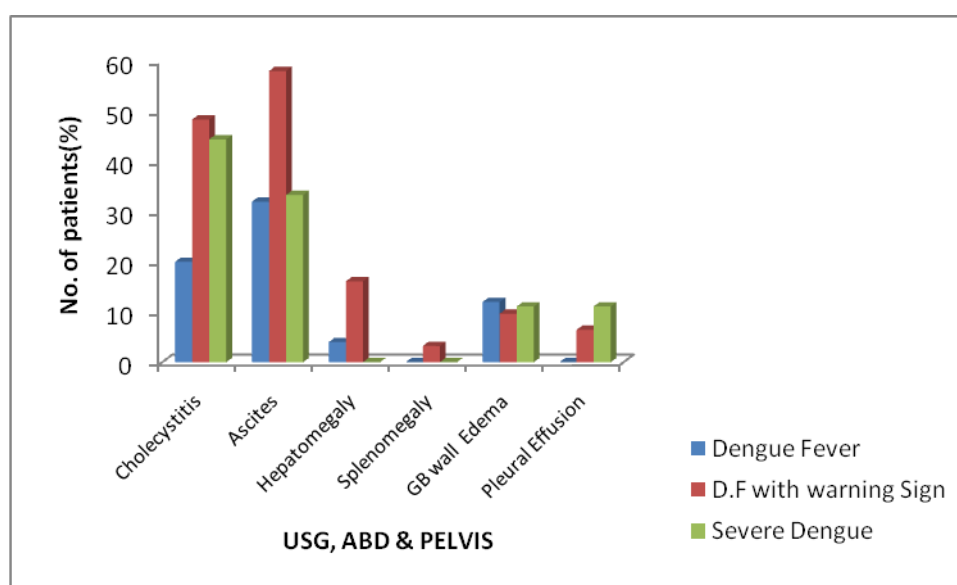
- Out of 65 cases maximum cases (n=32) showed ascites accounting to 49.2% followed by cholecystitis (n=25) accounting to 38.4% and pleural effusion (n=11) accounting to 17%.

- Ascites constituted about 32%, 61.3% & 55.6% in DF, DFWS & SD respectively.

- Cholecystitis constituted about 20%, 51.6% & 44.4% in DF.DFWS & SD respectively which shows statistical significant difference with p=0.049 stating it is more specific for DFWS & SD.

- Pleural effusion constituted about 0%, 25.8% & 33.3% in DF.DFWS & SD respectively which shows statistical significant difference with p=0.014 stating it is specific for DFWS & SD.

TABLE10:

ROC ANALYSIS OF SELECTED PARAMETERS TO DETECT SEVERE DENGUE

TABLE 10A:

Test Variables	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
PCV	0.528	0.105	0.79	0.322	0.734
AST	0.824	0.102	0.002*	0.625	1.000
ALT	0.824	0.081	0.002*	0.665	0.984
BIL	0.81	0.082	0.003*	0.649	0.97
ALP	0.756	0.107	0.014*	0.545	0.967
PT	0.890	0.047	<0.001*	0.798	0.983
APTT	0.495	0.128	0.697	0.208	0.710
CPK-MB	0.691	0.114	0.067	0.467	0.916
AST^2/ALT	0.813	0.101	0.003*	0.615	1.000

Note: * significant at 5% level of significance (p<0.05)

TABLE 10B:

	Positive if Greater Than or Equal To	Sensitivity	Specificity
PCV	35.95	44.4%	41.1%
AST	156.0	77.8%	76.8%
ALT	44.00	66.7%	62.5%
BIL	0.45	88.9%	53.6%
ALP	191.5	77.8%	75.0%
PT	17.35	77.8%	75.0%
APTT	45.85	55.6%	50.0%
CPK-MB	45.5	66.7%	66.1%
AST^2/ALT	400.4	88.9%	76.8%

Diagonal segments are produced by ties.
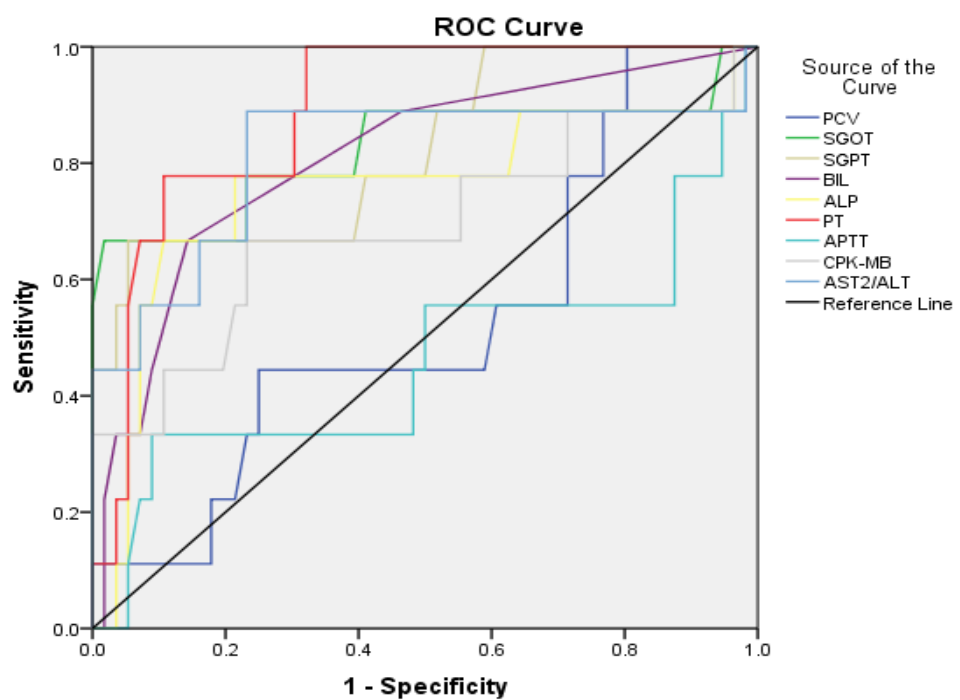
TABLE 10C:

Test Variables	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
TOTAL COUNT	0.163	0.060	0.001*	0.044	0.281
PLATELET	0.739	0.102	0.022	0.540	0.939
ALBUMIN	0.643	0.123	0.171	0.402	0.884

Note: * significant at 5% level of significance (p<0.05)

TABLE 10D:

	Positive if Less Than or Equal To	Sensitivity	Specificity
TOTAL COUNT	6220	33.3%	25.0%
PLATELET	80500	66.7%	66.1%
ALBUMIN	3.25	66.7%	66.1%
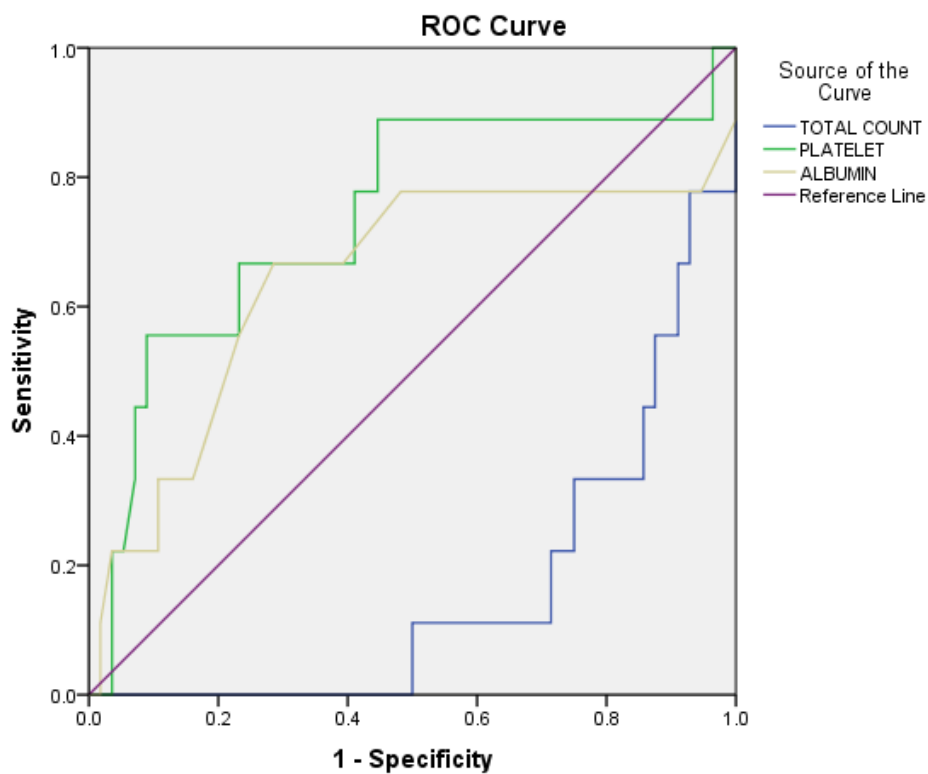
Diagonal segments are produced by ties.

TABLE 11:

BLOOD COMPONENT USAGE IN MANAGEMENT.

Blood	DF		DFWS		SD		Pooled Chi square test
	No. of cases	%	No. of cases	%	No. of cases	%	
FFP	0	0	2	6.5	1	11.1	P=0.0067*
PLATELET	0	0	6	19.4	3	33.3	
WHOLE BLOOD	0	0	1	3.2	2	22.2	

- FFP was administered to 2 (6.5%) of 31 DFWS cases , 1(11.1%) out of 9 cases of SD and none of the cases with DF received FFP.

- Platelets was administered to 6(19.4%) of 31 DFWS cases , 3(33.3%) out of 9 cases of SD and none of the cases with DF received platelets.

- Whole blood was administered to 1(3.2%) of 31 DFWS cases , 2(22.2%) out of 9 cases of SD and none of the cases with DF received whole blood.

- There is a statistically significant difference in transfusion of blood components between different types of dengue with p value of 0.0067.

TABLE 12:

DISTRIBUTION OF CASES ACCORDING TO DURATION OF STAY:

Variable	Dengue Fever		Dengue Fever with warning signs		Sever Dengue		ANOVA test
	Mean	STD	Mean	STD	Mean	STD	
Duration of Stay	4.92	1.470	6.00	1.732	7.78	3.701	0.002*
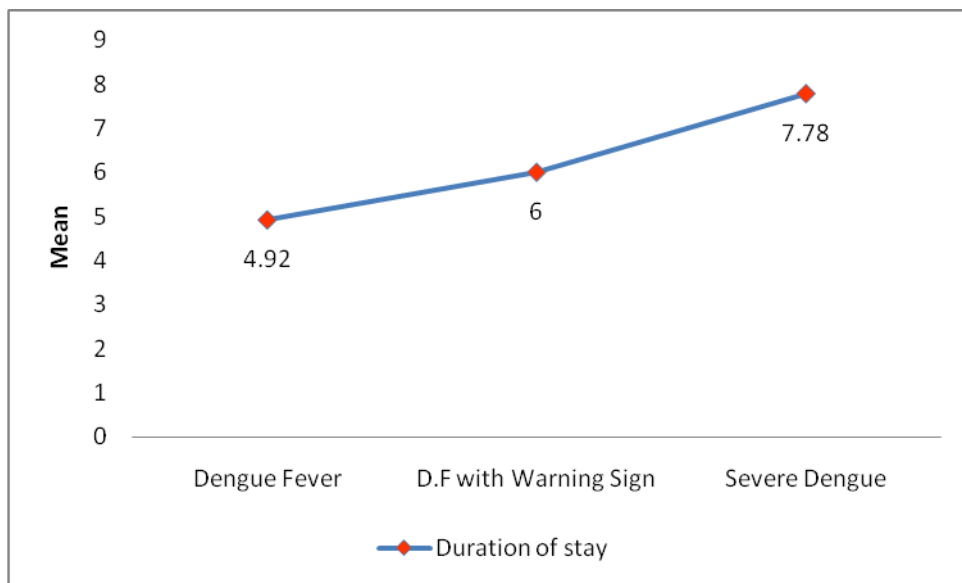
ANOVA test shows 'p value' of 0.002 suggesting it is statistically significant and states that prolonged duration of stay is specific for severe dengue.

TABLE 13:

DISTRIBUTION OF CASES ACCORDING TO OUTCOME:

Outcome	Dengue Fever		D.F With warning sign		Severe Dengue		Chi square test
	No of cases	%	No of cases	%	No of cases	%	
IMPROVED	25	100.0	31	100.0	7	77.8	0.001*
EXPIRED	0	0	00	0	2	22.2	
Total	25	100.0	31	100.0	9	100	
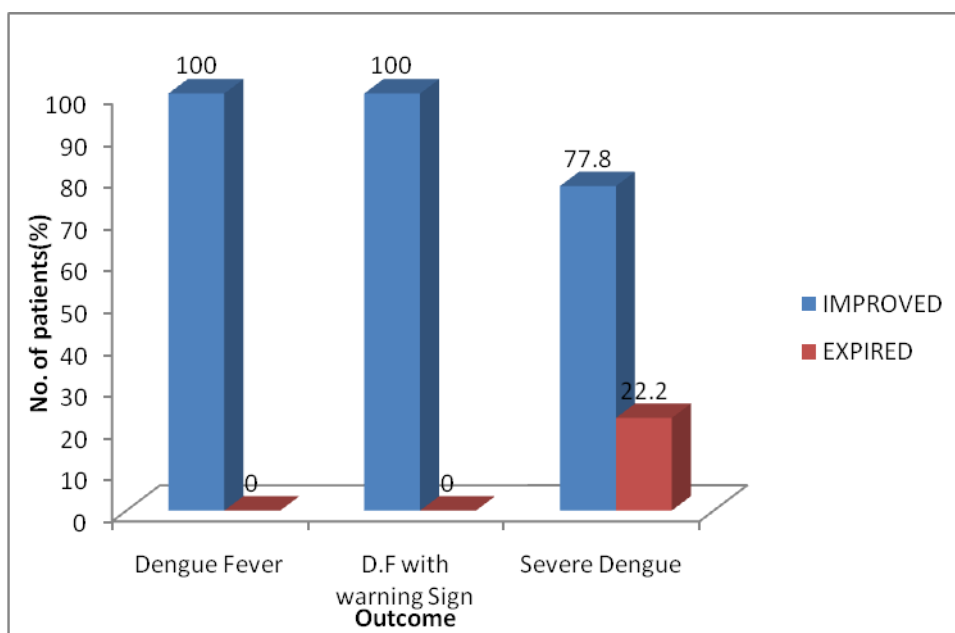
Out of 65 cases 2 cases of SD (22.2%) expired with chi square test of 'p value =0.001' stating it is specific for SD.

DISCUSSION

A total of 65 proven cases of dengue enrolled during the study period from November 2016 to September 2018 were studied & classified based on 2009 WHO classification into dengue fever without warning signs (DF), dengue fever with warning signs (DFWS) and severe dengue (SD). The cases are proven to be dengue positive by card test (NS1, IgM & IgG) or ELISA IgM.

The levels of haematological, biochemical parameters were evaluated in each case to assess the severity of Dengue infection. Imaging findings involving Chest x-ray and Ultrasound abdomen and pelvis were assessed in each case.

AGE:

Age group and mean age of patients at presentation in this study were comparable to studies by **K.S.Sahana et al[61] & Chacko B et al[56].**

STUDY SERIES	AGE IN YEARS	MEAN AGE
Present study	0-14	7.6
K.S.Sahana et al [51]	0-15	8
Chacko B et al[45]	0-14	7.87

The mean age of presentation of children with Dengue fever without warning signs ,with warning signs and severe dengue in the present study were 8.91 yrs, 9 yrs and 4.88 yrs respectively with p value of 0.012 suggesting there is age wise significant difference.

GENDER:

Gender distribution in present study was comparable to studies by **Mulay S et al[65]**, **Chacko B et al[56] & Jain H et al[63].**

STUDY SERIES	MALE (no of cases)	FEMALE (no of cases)	M:F
Present Study	41	24	1.70:1
Mulay S et al[4]	56	32	1.75:1
Chacko B et al[45]	44	29	1.52:1
Jain H et al[2]	35	30	1.16:1

INCIDENCE:

Incidence in our study was comparable to studies by **Mulay S et al [65] & Jain H et al** [63] where there is predominance of DFWS and opposed to study by **Kumar AMK et al[64]** where there is predominance of DF cases.

STUDY	DENGUE FEVER WITHOUT WARNING SIGNS	DENGUE FEVER WITH WARNING SIGNS	SEVERE DENGUE
Present study	38.5%	47.7%	13.8%
Jain H et al[2]	23%	64.6%	12.3%
Mulay S et al[4]	15.9%	55.7%	28.4%
Kumar AMK et al	52%	16.6%	31.4%

CLINICAL FEATURES:

Dengue virus infections may be classified into dengue fever without warning signs, dengue fever with warning signs and severe dengue based on symptoms and signs in 2009 WHO classification. Infants and young children usually develop an undifferentiated febrile disease that can be accompanied by a maculopapular rash. Older children and adults may develop either a mild febrile syndrome or the classical dengue fever, characterized by fever, headache, myalgia, arthralgia and rash.

Most of the cases (n=40) in present study came to the hospital with in first 4 days of onset of illness accounting to 61.5%. Maximum cases of DF, DFWS presented during 3-4 days of onset of illness where as SD presented during 5-7 days. This is comparable to study by **Mishra S et al** [62].

In our study most common symptom was found to be fever which is noted in all cases(100%) followed by vomitings(47.6%), pain abdomen (35.4%) which was considered as a warning sign only when it was persistent(30.77%), hepatomegaly (24.6%), myalgia (13.85%), headache (10.7%), loose stools (9.23%), arthralgia (7.7%), cough & cold (4.6% each), hurried breathing (3.08%) and other fewer symptoms like nausea, giddiness, rashes, icterus, convulsions. This was comparable to studies by **Narayanan et al**[51] **& Mulay S et al**[65] where fever and vomiting are the most common symptoms with variations in other symptoms and opposed to study by **Jain H et al**[63] where most common symptoms were fever, bleeding, headache, nausea & vomiting.

Symptoms and Signs	Present Study (N=65) (%)	Narayanan et al[40] (n=89) (%)	Mulay S et al[4](n=88) (%)	Jain H et al[2] (n=65) (%)
Fever	100	97	100	100
Vomiting	47.7	83	64.8	46.1
Pain Abdomen	35.4	23.7	62.5	36.9
Hepatomegaly	24.6	54	39.8	90.7
Myalgia	13.85	54.2	53.4	63
Headache	10.77	28.8	48.9	64.6
Splenomegaly	4.6	10	20.5	26.1
Bleeding Manifestations	1.5	66	-	58.4
Icterus	1.5	10	-	-

WARNING SIGNS:

In our study most common warning signs were persistent abdominal pain (30.77%), hepatomegaly (24.6%), abdominal tenderness (23.07%), increase in heamtocrit with decrease in platelet count (7.69%) and persistent vomiting (6.15%) and other fewer signs included bleeding tendencies, ascites, pleural effusion etc. This is comparable to warning signs in study by **Jain H et al[63]**

SEROLOGY TESTS

Of 65 cases NS1 was noted positive in DF (100%), DFWS (90%) & SD (56%). IgM in DF (8%), DFWS (23%) & SD (11%). IgG in DF (20%), DFWS (26%) & SD (22%). These findings are comparable to **Kumar AMK et al [64].** To enrol in the study, positive result in any of the above serological tests is considered.

In present study most of the cases (n=44) are only NS1 positive accounting to 67.7% followed by positivity in NS1+IgG in 7(10.76%) cases, NS1+IgM+IgG in

4(6.15%) cases, NS1+IgM in 3(4.61%) cases, only IgG in 3(4.61%) and only IgM in 2(3.07%) cases. These NS1 findings are comparable to study by **Mishra S et al [62]**.

ELISA IgM was done in 33 cases out of which 22 were positive and 11 were negative. Rapid card test IgM was positive only in 2 out of these 33 cases in which ELISA was done. Both ELISA and Rapid card test were positive in only one case suggesting that ELISA is superior to rapid card test in detecting Dengue.

LABORATORY INVESTIGATIONS:

a) Haematological findings :

Platelets and haematocrit values are commonly measured during the acute stages of dengue infection. A drop of the platelet count below 100 000 per µL may be observed in dengue fever but it is a constant feature of severe dengue. Thrombocytopenia is usually observed in the period between day 3 and day 8 following the onset of illness. Haemoconcentration, as estimated by an increase in haematocrit of 20% or more compared with convalescent values, is suggestive of hypovolaemia due to vascular permeability and plasma leakage.

- Of 65 cases, **thrombocytopenia** was noted in 69.23% of cases, among these Platelet count (PLC) of 1-1.5 lakh/mm^3 is seen in 26.1%, 50000-1 lakh/mm^3 in 16.9% and <50000/mm^3 in 26.1% of cases.

  Mean values of PLC at admission when compared among DF, DFWS & SD showed a decreasing pattern with least value in SD & highest in DF suggesting worsening from DF to SD.

- **Raised hematocrit** of ≥35% is seen in 63.07% cases.

  Mean values at admission when compared among DF, DFWS & SD showed a drop from DF To DFWS but increased to SD with highest value in SD & least in DFWS with no statistical significance (p=0.801).

- **Total leukocyte count** <4000cells/mm^3 i.e **Leukopenia** is seen in 41.5% of cases.

  Mean values of TC at admission when compared among DF, DFWS & SD showed an increasing pattern with highest value in SD & least in DF with statistical significance (p=0.001) suggesting worsening from DF to SD.

- **APTT** of more than 34 seconds is seen in 72.3% of cases. Mean values of APTT when compared among DF, DFWS & SD showed an increasing pattern with similar values in DFWS & SD with least value in DF with no statistical significance was noted.

- **PT** of more than 13.5 seconds is seen in 83% cases. Mean values of PT when compared among DF, DFWS & SD showed an increasing pattern with highest value in SD & least in DF with statistical significance (p=0.001) suggesting worsening from DF to SD.

  This findings are comparable to study by **Pothapregada S et al[89]** & few variables of study by **Jain H et al[63].**

Variable	Present Study (%)	Pothapregada S et al[90](%)	Jain H et al[2] (%)
TLC <4000cells/mm^3	41.5	19.1	44
Raised Hematocrit	63.07	46.4	84
PLC <1.5lakh/mm^3	69.23	82.4	-
PLC <1 lakh/mm^3	43.07	-	80
PLC<50000/mm^3	26.1	16.5	-
PT (>13.5sec)	83	3.4	-
APTT (>34sec)	72.3	1.5	-

b) Biochemical findings :

Biochemical findings include Liver function tests (LFT) & CPK-MB levels.Upon injury to the liver, the enzymes, aspartate aminotranferase(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. In the acute phase of the disease, an increase occurs in aminotranferases, the levels of which subsequently decrease as the liver recovers. AST may be found in high concentrations in the heart muscle, liver cells and skeletal muscle and, in lower concentrations, in the kidneys and pancreas. ALT is mainly found in the liver and in lower concentrations in the kidney. While majority of the patients have only mild or moderate elevation of these transaminases, some of them have levels elevated by 10-fold or greater. In dengue infections, the levels of serum AST are greater than serum ALT, which is in contrast to the normal finding with viral hepatitis. It has been suggested that this may be due to excess release of AST from damaged myocytes during dengue infection. The elevation of the AST level is usually higher than that of ALT in patients with dengue fever during the first week of infection, with a decrease to normal levels within three weeks. Some studies have suggested that the average levels of transaminases were significantly higher in SD patients than in DF patients.

- Mean value of AST was 316.4 IU/L, it was raised (>40IU/L) in 56 cases (86%).On comparison of mean values among DF, DFWS & SD there is an increasing pattern with highest value in SD & least in DF with statistical significance (p<0.001) suggesting high values are specific for SD.

77

- Mean value of ALT was 233.6 IU/L, it was raised (>40IU/L) in 30 cases (46%).On comparison of mean values among DF, DFWS & SD there is an increasing pattern with highest value in SD & least in DF with statistical significance (p<0.001) suggesting high values are specific for SD.

- Mean value of ALP was 179 IU/L. On comparison of mean values among DF, DFWS & SD there is an increasing pattern with highest value in SD & least in DF with statistical significance (p<0.001) suggesting high values are specific for SD.

- Mean value of CPK-MB was 64.5 IU/L. It was raised (>26IU/L) in 55 cases (84.6%). On comparison of mean values among DF, DFWS & SD there is a drop from DF to DFWS and increased in SD with highest value in SD & least in DFWS with statistical significance (p=0.001) suggesting high values are specific for SD.

These findings are comparable to study by **Kulothungan R et al[(94)]**.

Variable	Present study			Kulothungan R et al[5]		
	DF (%)	**DFWS (%)**	**SD (%)**	**DF(%)**	**DFWS (%)**	**SD (%)**
AST(Normal- < 40IU/L)	6(24)	2(6.45)	1(11.1)	42 (79.2)	7 (23.7)	0(0)
41-100	13(52)	12(38.7)	0(0)			
101-200	5(20)	9(29.03)	2 (22.2)	11 (20.8)	23 (76.3)	0 (0)
>200	1(4)	8(25.8)	6 (66.7)	0 (0)	0 (0)	20 (100)
TOTAL	**25(100)**	**31(100)**	**9(100)**	**53 (100)**	**30 (100)**	**20(100)**
ALT (Normal- < 40IU/L)	19(76)	14(45.16)	2(22.2)	48 (90.6)	23 (59)	0 (0)
41-100	6(24)	8(25.8)	1(11.1)			
101-200	0(0)	6(19.3)	1(11.1)	5 (9.4)	16 (41)	0 (0)
>200	0(0)	3(9.6)	5(55.5)	0 (0)	0 (0)	11 (100)
TOTAL	**25(100)**	**31(100)**	**9(100)**	**53 (100)**	**39 (100)**	**11(100)**
CPK-MB - (Normal)	4 (16)	5(16.2)	1 (11.1)	51 (96.2)	1 (6.67)	0 (0)
- (Abnormal)	21 (84)	26 (83.8)	8 (88.9)	2 (3.8)	14 (93.3)	35 (100)
TOTAL	**25(100)**	**31(100)**	**9(100)**	**53(100)**	**15(100)**	**35(100)**

c)   **Serum Albumin & bilirubin:**

Of 65 cases in our study low serum albumin (<3.5g/dl) is noted in 34 cases (52.3%). Mean value was 3.36 g/dl. On comparison of mean values among DF, DFWS & SD there is a drop from DF to DFWS and increased in SD with highest value in DF & least in DFWS with statistical significance (p=0.044) suggesting low values are more common in DFWS & SD.

Mean value of total serum bilirubin (<1.3mg/dl) is 0.8mg/dl. On comparison of mean values among DF, DFWS & SD there is an increasing pattern with highest value in SD & least in DF with no statistical significance (p<0.108) suggesting no specific pattern in dengue.

Comparison of 'p values' of laboratory findings among DF, DFWS & SD:

Using Post Hoc test when p values of various laboratory parameters are compared among DF, DFWS &SD to assess the severity and pattern of disease progression following findings were noted:

• In TLC evaluation on comparison of DF v/s DFWS no statistical significance was noted (0.377) where as DF v/s SD (0.001) & SD v/s DFWS (0.009) showed statistical significance suggesting no much difference between DF & DFWS but SD has high TLC values in dengue illness.

• In PT evaluation on comparison of DF v/s DFWS no statistical significance was noted (0.590) where as DF v/s SD (<0.001) & SD v/s DFWS (<0.001) showed statistical significance suggesting no much difference between DF & DFWS but SD has high PT values in dengue illness.

- In AST evaluation on comparison of DF v/s DFWS (0.014), DF v/s SD (<0.001) & SD v/s DFWS (<0.001) showed statistical significance among all three stages suggesting high values in dengue illness are more specific to SD.

- In ALT evaluation on comparison of DF v/s DFWS (0.008), DF v/s SD (<0.001) & SD v/s DFWS (<0.001) showed statistical significance among all three stages suggesting high values in dengue illness are more specific to SD.

- In CPK-MB evaluation on comparison of DF v/s DFWS (0.138) & DF v/s SD (0.132) no statistical significance was noted where as & SD v/s DFWS (0.001) showed statistical significance suggesting but SD has high values in dengue illness.

- In Bilirubin evaluation on comparison of DF v/s DFWS (0.249) & SD v/s DFWS (0.248) no statistical significance was noted where as DF v/s SD (0.018) showed statistical significance suggesting SD has high values in dengue illness due to more liver damage.

- In Albumin evaluation on comparison of DF v/s DFWS (0.003) showed statistical significance where as DF v/s SD (0.163) & SD v/s DFWS (0.819) showed no statistical significance suggesting DFWS has least values in dengue illness.

IMAGING FINDINGS:

a) CHEST X-RAY:

In our study, among 65 cases with dengue infection, 6(9.23%) cases showed abnormal lung findings with lung infiltration, of which 2(6.5%) are of DFWS and 4(44.4%) are of SD. These findings are comparable to study by **Kulothungan R et al[94]**.

In both the studies most cases with positive findings are under severe dengue category. p value is <0.001 which shows statistical significance stating that positive chest x-ray findings are specific for severe dengue.

Chest X-Ray with radiological findings					
Study Series	DF	DFWS	SD	Total	P-value
Present Study	0	2 (6.5%)	4 (44.4%)	6 (9.23%)	0.001
Kulothungan R et al.	4 (7.5%)	0 (0)%	15 (30%)	19 (18.4%)	0.003

b) USG abdomen and pelvis:

In our study of 65 cases with dengue infection, most common ultrasound finding was cholecystitis accounting to 38.4%, followed by ascites (27%), pleural effusion (17%), GB wall thickening (12.3%). This is comparable to studies by **Mulay S et al[65] & Chacko B et al[56].** Pleural effusion was better detected in ultrasound (17%) than in x-ray (0%).

USG Finding	Present Study (n=65) (%)	Mulay S et al[4] (n=88) (%)	Chacko B et al[45] (n=73) (%)
Cholecystitis	38.4	53.4	21.91
GB Wall thickening	12.3		
Ascites	27.07	30.7	16.4
Hepatomegaly	9.23	39.8	17.8
Splenomegaly	4.61	20.5	9.58
Pleural Effusion	16.92	38.6	30.13

Out of 65 cases polyserositis manifestation in the form of ascites (27.07%) and pleural effusion (17%) was noted. These can be further subdivided under DF, DFWS & SD as follows. This is comparable to study by **Kumar AMK et al[(64)].**

Polyserositis	DF (%)	DFWS (%)	SD (%)
Present study	32	87.1	89.9
Kumar AMK et al[1]	20	47.4	57.1

Maximum percentage of polyserositis is noted in SD (89.9%) followed by DFWS (87.1%) and least in DF (32%) suggesting with increase in severity frequency of polyserositis increases.

ROC:

Among the 65 cases reviewed, about 9 cases (13.84%) had severe dengue.

- AST, ALT, BIL, ALP, PT, SGOT[2]/SGPT and total count were found to be good at identification of severe dengue.

- AST (AUC 0.824; 95%CI 0.625-1.000) optimal cut off ≥156 U/L with sensitivity of 77.8% and specificity of 76.8%.

- ALT (AUC 0.824; 95%CI 0.665-0.984) optimal cut off ≥44 U/L with a sensitivity of 66.7% and specificity of 62.5%.

- Bilirubin (AUC 0.81; 95%CI 0.649-0.97) optimal cut off ≥0.45mg/dL with a sensitivity of 88.9% and specificity of 53.6%.

- ALP (AUC 0.756; 95%CI 0.545-0.967) optimal cut off ≥191.5 U/L with a sensitivity of 77.8% and specificity of 75.0%.

- PT (AUC 0.890; 95%CI 0.798-0.983) optimal cut off ≥17.35 sec with a sensitivity of 77.8% and specificity of 75.0%.

- The composite index AST^2/ALT (AUC 0.813; 95% CI 0.615 – 1.000) optimal cut off $\geq$400.4 with a sensitivity of 88.9% and specificity of 76.8%.

- Total count (AUC 0.163; 95%CI 0.044 - 0.281) optimal cut off $\leq$ 6220 cells/mm^3 with sensitivity of 33.3% and specificity of 25%.

In present study the composite index (AST^2/ALT) was the most accurate (AUC 0.813; 95% CI 0.615 – 1.000) when optimal cut off is $\geq$ 400.4 with highest sensitivity (88.9%) and specificity (76.8%) stating that it may be used as a marker for identification of severe dengue based on admission AST and ALT which is comparable to study done by **Sani SS et al**[95]. This is followed by AST, ALP, PT, ALT and BILIRUBIN which can be used to predict severity of dengue infection.

BLOOD PRODUCTS USAGE IN MANAGEMENT:

Types of Dengue	Platelet transfusion			
	Present study		Kumar AMK et al	
	YES	NO	YES	NO
DF	0%	100%	6.7%	93.3%
DFWS	19.4%	81.6%	26.3%	73.7%
SD	33.3%	66.7%	14.3%	85.7%

Platelet transfusion was done in 19.4% of DFWS , 33.3% of SD which is comparable to study by **Kumar AMK et al**[64]**.** Out of 65 cases blood products were transfused in 13(20%) cases of which platelets were transfused in 9(13.8%) of 65 cases of which 3(33.3%) cases are from severe dengue group ,FFP was transfused in 1(11.1%) of severe dengue group and three children required whole blood transfusion which is comparable to study by **Sujatha R et al**[66] in which out of 125(22%) children who received blood products, platelets were transfused in 80 children (14% of 568) out of

which 64 (32.9%) were from SD group. Fresh frozen plasma (FFP) was used in 23 children (11.8%) of severe dengue group. Four children required whole blood transfusion.

MEAN DURATION OF STAY:

Out of 65 cases mean stay of duration of DF, DFWS & SD are 4.92, 6 & 7.78 days respectively. The overall mean duration of stay of all the cases together is 6.2 days. The duration is categorised into 3 groups viz; 0-3 days, 4-6 days & >6 days. Under this non severe dengue (includes DF & DFWS) the number of cases registered are 5(8.93%), 32(57.14%) & 19(33.93%) respectively where as under SD the number of cases are 1(11.1%), 3(33.3%) & 5(55.6%) respectively. This is comparable to studies by **Mishra S et al[62]** & **Natwar lal Sharma et al[67].**

		Non severe dengue	Severe dengue	Mean
		Dengue fever without warning signs & Dengue fever with warning signs		duration
Present study	0-3 days	5(8.93%)	1(11.1%)	6.23 days
	4-6 days	32(57.14%)	3(33.3%)	
	>6 days	19(33.93%)	5(55.6%)	
Natwar lal Sharma et al	0-3 days	45(25.42%)	0(0%)	4.61days
	4-6 days	128(72.32%)	2(8.7%)	
	>6 days	4(2.26)	21(91.3%)	
Mishra S et al	0-3 days	27(32.1%)	1(7.7%)	3.8 days
	4-6 days	57(67.9%)	5(38.5%)	
	>6 days	0(0%)	7(53.8%)	

OUTCOME:

Outcome in present study was comparable to studies by **K.S. Sahana et al**[61] ,

Sujatha R et al[66] and **Mulay S et al**[65] .

Types of Dengue	Present Study n (%)		K.S.Sahana et al n (%)		Sujatha R et al n (%)		Mulay S et al n (%)	
	Improved	Expired	Improved	Expired	Improved	Expired	Improved	Expired
DF	25(100)	0(0)	39(100)	0(0)	66(100)	0(0)	14(100)	0(0)
DFWS	31(100)	0(0)	22(100)	0(0)	308(100)	0(0)	49(100)	0(0)
SD	7(77.8)	2(22.2)	18(90)	2(10)	187(96.4)	7(3.6)	23(92)	2(8)

LIMITATIONS OF MY STUDY:

1. Study participants present to the hospital on different days after the onset of illness which may alter the levels of various parameters at admission.

2. ELISA test for IgM could be done only in 33 cases as Bijapur was proven to be dengue positive region by the district surveillance officers and they didn't collect samples further.

3. Sample size of the present study is small.

SUMMARY

A prospective study of 65 patients of confirmed dengue cases was carried out over a period of 18 months clinically, haematologically, biochemically and radiologically to predict the severity and outcome in Dengue infection at time of admission. Based on 2009 WHO classification criteria these 65 cases were divided into 3 categories

1. Dengue fever without warning signs (DF) (n=25) (38.5%)

2. Dengue fever with warning signs (DFWS) (n=31) (47.7%) and

3. Severe dengue (SD) (n=9) (13.8%)

1. DENGUE FEVER (DF) :

- Out of 25 cases of dengue fever, majority of the cases (n=11) belong to 6-10 years with mean age of 8.91 years.

- Majority of them were males (n=15) and rest are females (n=10) with a M: F sex ratio of 1.5:1.

- Most common clinical symptoms were fever (100%), vomiting (32%), myalgia (24%), arthralgia (12%), nausea (8%), pain abdomen (8%), headache (8%), loose stools (8%) etc.

- Most of the cases of DF presented to hospital between 3-4 days (60%) followed by 5-7 days(28%) after the onset of illness.

- Out of 25 cases of DF 19(76%) were only NS1 positive, 1(4%) was NS1 & IgM positive, 4(16%) were NS1 & IgG positive & 1(4%) was NS1, IgM, IgG positive

- NS1 is positive in all 25cases of DF, IgM is positive in 2 cases, IgG is positive in 5 cases.

- Mean value of Total count at admission was 4490.40, platelet at admission was 138160.00, PCV was 36.80, PT was 15.5, APTT was 47.9, AST & ALT are 82.9, 31.7 respectively, Albumin was 3.6, CPK-MB was 51.3.

- Out of 25 patients chest x-ray was found to be normal in all cases. On ultrasound majority of cases showed ascites (n=8) and cholecystitis (n=5).

- Blood components usage was not there in any of the cases.

- Mean duration of stay was 4.92 days and all cases improved at the time of discharge.

2. DENGUE FEVER WITH WARNING SIGNS (DFWS) :

- Out of 31 cases of dengue fever with warning signs, majority of the cases (n=13) belong to 11-14 years with mean age of 9.0 years.

- Majority of them were males (n=20) and rest are females (n=11) with a M: F sex ratio of ~ 2:1.

- Most common clinical symptoms were fever (100%), vomiting (61.2%), pain abdomen (61.2%), hepatomegaly (41.9%) etc.

- Most common warning signs were abdominal pain (58.1%), hepatomegaly (41.94%), abdomen tenderness (41.94%), vomiting (9.7%) & ascites (6.45%) etc.

- Most of the cases of DFWS presented to hospital between 3-4 days (54.8%) followed by 5-7 days (29.03%) after the onset of illness.

- Out of 31 cases of DFWS 20(64.51%) were only NS1 positive, 1(3.22%) was only IgM positive, 1(3.22%) was only IgG positive, 2(6.45%) were NS1 & IgM positive , 3(9.68%) were NS1 & IgG positive, 1(3.22%) was IgM & IgG positive & 3(9.68%) were NS1, IgM, IgG positive.

- NS1 is positive in 28cases, IgM is positive in 7 cases & IgG is positive in 8 cases.

- Mean value of Total count at admission was 5700.32, platelet at admission was 110161.32, PCV was 36.16, PT was 16.0, APTT was 51.4, AST & ALT are 140.5, 80.7 respectively, Albumin was 3.2, CPK-MB was 41.4.

- Out of 31 patients chest x-ray was found to be normal in 29 cases and consolidation in 2 cases. On chest and abdominal ultrasound majority of cases showed ascites (n=19), cholecystitis (n=16) and pleural effusion (n=8).

- Blood component usage was done in 9 out of 31 cases. Of which FFP were used in 2 cases, platelet transfusion in 6 cases and whole blood was used in 1 case.

- Mean duration of stay was 6.0 days and all cases improved at the time of discharge.

3. **SEVERE DENGUE (SD) :**

- Out of 09 cases of severe dengue, majority of the cases (n=4) belong to 0-5 years with mean age of 4.88 years.

- Majority of them were males (n=6) and rest are females (n=3) with a M: F sex ratio of ~ 2:1.

- Most common clinical symptoms were fever (100%), vomiting (44.4%), hepatomegaly (33.3%) & pain abdomen/hurried breathing/headache/ loose stools (22.2%) & drowsiness/convulsions (11.1%) etc.

- Most common warning signs were hepatomegaly (33.3%), abdominal pain (22.2%), abdomen tenderness (22.2%), convulsions/oedema/hematemesis/comatose (11.1%) etc.

- Most of the cases of SD presented to hospital between 5-7 days (44.44%) followed by 3-4 days (33.33%) after the onset of illness.

- Out of 9 cases of SD only NS1 is positive in 5(55.56%) cases, only IgM is positive in 1(11.11%) case, IgG is positive in 2(22.22%) cases and ELISA IgM is positive in 1(11.11%) case.

- Mean value of Total count at admission was 9544.44, platelet at admission was 77777.78, PCV was 37.44, PT was 22.6, APTT was 51.0, AST & ALT are 725.9, 588.4 respectively, Albumin was 3.3, CPK-MB was 100.8.

- Out of 9 patients chest x-ray was found to be normal in 5 cases with consolidation in 4 cases. On chest and abdominal ultrasound majority of cases showed ascites (n=5), cholecystitis (n=4) and pleural effusion (n=3).

- Blood component usage was done in 6 cases of SD condition. Of which FFP was used in 1 case, platelet transfusion in 3 cases and whole blood was used in 2 cases.

- Mean duration of stay was 7.78 days.

- Out of 9 SD cases, 7 cases (77.7%) improved at the time of discharge while 2 cases expired (22.2%).

DIAGNOSTIC EFFICACY OF CARD TEST TO DETECT IGM POSITIVE COMPARED TO ELISA TEST:

- In present study out of 65 cases ELISA IgM was done in 33 cases and is compared to rapid card test IgM of the same cases. ELISA is more efficacious in detecting dengue IgM with a100% sensitivity and 100% specificity than rapid card test whose sensitivity and specificity are 4.55% and 90.91% respectively.

4. HEMATOLOGICAL PARAMETERS:

Among the various haematological parameters:

- Thrombocytopenia (<1.5lakh/mm^3) was noted in 69.23% & leucopoenia(Tc < 4000cells/mm^3) in 41.5% of cases.

- Raised hematocrit was noted in 63.07% of cases.

- Increased PT & APTT in 83% & 72.3% of cases respectively.

5. **BOCHEMICAL PARAMETERS:**

- Among the various biochemical parameters, raised AST were noted in 76% of DF, 93.55% of DFWS & 88.9% of SD cases.

- Raised ALT was noted in 24% of DF, 54.84% of DFWS & 78.8% of SD cases.

- Abnormal CPK-MB was noted in 84% of DF, 83.8% of DFWS & 88.9% of SD cases.

COMPARISON OF 'P VALUES' OF LABORATORY FINDINGS AMONG DF, DFWS & SD:

Using Post Hoc test when p values of various laboratory parameters are compared among DF, DFWS &SD to assess the severity and pattern of disease progression following findings were noted:

- In TLC evaluation on comparison of DF v/s SD (p=0.001) & SD v/s DFWS (p=0.009) showed statistical significance suggesting high TLC values are more specific to SD in dengue illness.

- In PT evaluation on comparison of DF v/s SD (p<0.001) & SD v/s DFWS (p<0.001) showed statistical significance suggesting SD has high PT values in dengue illness.

- In AST evaluation on comparison of DF v/s DFWS (p=0.014), DF v/s SD (p<0.001) & SD v/s DFWS (p<0.001) showed statistical significance among all three stages suggesting that AST increases as dengue illness worsens and is highest in severe dengue.

- In ALT evaluation on comparison of DF v/s DFWS (p=0.008), DF v/s SD (p<0.001) & SD v/s DFWS (p<0.001) showed statistical significance among all three stages suggesting that ALT increases as dengue illness worsens and is highest in severe dengue.

- In CPK-MB evaluation SD v/s DFWS (p=0.001) showed statistical significance suggesting but SD has high values in dengue illness.

- In Bilirubin evaluation DF v/s SD (p=0.018) showed statistical significance suggesting SD has high values in dengue illness due to more liver damage.

- In Albumin evaluation on comparison of DF v/s DFWS (p=0.003) showed statistical significance suggesting DFWS has least values in dengue illness.

6. **USG FINDINGS:**

   Maximum percentage of polyserositis (Ascites and Pleural Effusion) is noted in SD (89.9%) followed by DFWS (87.1%) and least in DF (32%) suggesting with increase in severity frequency of polyserositis increases.

ROC in SEVERE DENGUE:

In present study of the 65 cases, about 9 cases (13.84%) had severe dengue. The composite index (AST^2/ALT) was the most accurate (AUC 0.813; 95% CI 0.615 – 1.000) when optimal cut off is $\geq$ 400.4 with highest sensitivity (88.9%) and specificity (76.8%) stating that it may be used as a marker for identification of severity of dengue illness based on admission AST and ALT . This is followed by AST, ALP, PT, ALT and bilirubin which can be used to predict severity of dengue infection.

CONCLUSION

PCV $\geq$ 35.95%, TLC< 6200/mm^3, deranged coagulation profile, AST $\geq$ 156U/L, ALT $\geq$ 44U/L ,the composite index AST^2/ALT (AUC 0.813; 95% CI 0.615 – 1.000) optimal cut off $\geq$400.4 with a sensitivity of 88.9% and specificity of 76.8% and presence of polyserositis on USG/X-ray are predictive of Severe Dengue and should alert the clinician for more vigilant monitoring. Early prediction and anticipation of Severe Dengue and its prompt management can reduce the mortality associated with the disease and for proper counseling of the patients and their relatives.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE
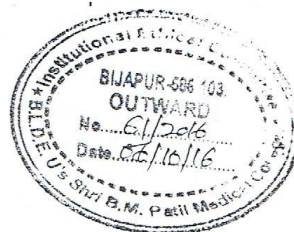
B.L.D.E. UNIVERSITY'S

SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on _04-10-2016_ at _03 pm_ to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title _"Clinical, Hematological, Biochemical and radiological predictors of severity and outcome in dengue infection"_

Name of P.G. student _Dr. Gogineni Ankita_
Dept of pediatrics

Name of Guide/Co-investigator Dr _M.M. Patil_
Assoc. prof of pediatrics

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

RESEARCH INFORMED CONSENT FORM

B.L.D.E (DEEMED TO BE UNIVERSITY)

SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPUR - 586103.

TITLE OF THE PROJECT : CLINICAL, HEMATOLOGICAL, BIOCHEMICAL AND RADIOLOGICAL

PREDICTORS OF SEVERITY AND OUTCOME IN DENGUE INFECTION.

GUIDE : Dr. M.M.PATIL MD;
ASSOCIATE PROFESSOR
DEPARTMENT OF PEDIATRICS

PRINCIPAL INVESTIGATOR : DR. GOGINENI ANKITA
PG DEPARTMENT OF
PEDIATRICS

PURPOSE OF RESEARCH:

There are so many studies on predictors of severity and prognosis of dengue in adults. But there are very few studies available in children. This study is being conducted to know the prognosis and outcome of dengue in children based on clinical features, AST, ALT, CPK-MB, ultrasound.

PROCEDURE:

I/We are aware that in addition to routine care received, I/We will be asked series of questions by the investigator. I/We have been asked to undergo the necessary investigations which will help the investigator in this study.

RISK AND DISCOMFORTS:

I/Weunderstand there is no risk involved and that the patient may experience some pain and discomforts during the examination. This is mainly the result of the condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I/We understand that participation in the study will help the investigator in early prediction of prognosis and outcome of dengue infection.

CONFIDENTIALITY:

I/We understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I/We understand that I/We may ask more questions about the study at any time; Dr. Gogineni Ankita at the department of pediatrics is available to answer my questions or concerns. I/We understand that I/We will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I/We understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I/We also understand that Dr. Gogineni Ankita may terminate my participation in the study after he has explained the reasons for doing so.

<u>INJURY STATEMENT:</u>

I/We understand that in the unlikely event of injury to the baby resulting directly from participation in this study, if such injury were reported promptly, the appropriate treatment would be available to the baby. But, no further compensation would be provided by the hospital. I/We understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____   _____

 Dr. Gogineni Ankita   Date
  (Investigator)

PARENTS / GUARDIAN CONSENT STATEMENT:

I/We confirm that Dr. Gogineni Ankita is doing a study on **CLINICAL, HEMATOLOGICAL, BIOCHEMICAL AND RADIOLOGICAL PREDICTORS OF SEVERITY AND OUTCOME IN DENGUE INFECTION**. Dr. Gogineni Ankita has explained to us the purpose of research and the study procedure. I/We are willing to allow our child to undergo all the investigations and the possible discomforts as well as benefits. I/We have been explained all the above in detail in our own language and we understand the same. Therefore I/we agree to give consent for our child's participation as a subject in this research project.

_____   _____

      (Parents / Guardian)   Date

_____   _____

      (Witness to signature)   Date

<u>ಪಾಲಕರು / ಪೋಷಕರು ಒಪ್ಪಿಗೆಯನ್ನು ಸೂಚಿಸುವ ಹೇಳಿಕೆ:</u>

ನಾನು/ನಾವು ಈ ಮೂಲಕ ಧೃಢ ಪಡಿಸುವುದೇನೆಂದರೆ, ಡಾ. ಅಂಕಿತಾ ಗೊಗಿಸೆನಿ ಅವರು

"CLINICAL, HEMATOLOGICAL, BIOCHEMICAL AND RADIOLOGICAL PREDICTORS OF SEVERITY AND OUTCOME IN DENGUE INFECTION." ವಿಷಯದ ಮೇಲೆ ಅಧ್ಯಯನ ಮಾಡುತಿದ್ದಾರೆ.

ಡಾ. ಅಂಕಿತಾ ಗೊಗಿಸೆನಿ ರವರು ನಮಗೆ ಈ ವಿಷಯದ ಕುರಿತು ಸಂಶೋಧನೆ ನಡೆಸುವ ಉದ್ದೇಶ ಹಾಗು ಅಧ್ಯಯನದ ಕಾರ್ಯ ಪದ್ಧತಿ ಬಗ್ಗೆ ವಿವರಿಸಿರುತ್ತಾರೆ. ನಾನು/ನಾವು ಈ ಅಧ್ಯಯನದ ಸಲುವಾಗಿ ಅವಶ್ಯಕವಿರುವ ಮಾಹಿತಿಗಳನ್ನು ಎಷ್ಟು ಸಾಧ್ಯವೋ ಅಷ್ಟೂ ಮಾಹಿತಿ ನೀಡಲು ಹಾಗು ಈ ಅಧ್ಯಯನದಿಂದ ಆಗಬಹುದಾದ ತೊಂದರೆಗಳು ಹಾಗು ಲಾಭಗಳ ಕುರಿತು ಪತ್ತೆ ಹಚ್ಚಲು ಅವಶ್ಯಕ ಮಾಹಿತಿಗಳನ್ನು ನೀಡಲು ನಮ್ಮ ಸಮ್ಮತಿ ಇರುತ್ತದೆ. ನನಗೆ/ನಮಗೆ ಮೇಲೆ ತಿಳಿಸಿದ ಅಧ್ಯಯನದ ಕುರಿತು ಎಲ್ಲ ಮಾಹಿತಿಗಳನ್ನು ನಮ್ಮ ಮಾತೃಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಿದ್ದು, ನಾವು ಇದನ್ನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇವೆ. ಆದ್ದರಿಂದ ನಾವು ಈ ಸಂಶೋಧನೆಯಲ್ಲಿನ ಒಂದು ವಿಷಯವಾಗಿ ನಮ್ಮ ಮಗುವಿನ ಭಾಗವಹಿಸುವಿಕೆಯ ಕುರಿತು ಸಮ್ಮತಿಯನ್ನು ನೀಡಿರುತ್ತೇವೆ.

_____   _____
(ತಂದೆತಾಯಿಗಳು / ಪೋಷಕರು)   ದಿನಾಂಕ

_____   _____
ಸಾಕ್ಷಿದಾರರ ಸಹಿ   ದಿನಾಂಕ

PROFORMA

1. Name   **:**

2. Age   **:**

3. Sex   **:**

4. Address   **:**

5. IP No   **:**

6. DOA   **:**

7. DOD   **:**

CHIEF COMPLAINTS:

VITAL SIGNS

DATE								
PR								
BP								
RR								

GENERAL PHYSICAL EXAMINATION

Pallor   **:**

Icterus   **:**

Cyanosis   **:**

Clubbing   **:**

Lymphadenopathy   **:**

Pedal edema   **:**

Rash   **:**

Other Features   **:**

SYSTEMIC EXAMINATION

PER ABDOMEN
INSPECTION

1. Shape   -

2. Skin over the abdomen   -

3. Movement with respiration   -

4. Umbilicus   -

5. Any scars, sinuses or   -

    dilated veins

6. Visible lump, pulsations   -

or peristalsis

PALPATION

1.Feel of abdomen					
2.Areas of tenderness/mass					
3.Liver					
4.Spleen					

PERCUSSION

1. Puddle sign   -

2. Shifting dullness   -

3. Fluid thrill   -

AUSCULTATION

1. Bowel sounds   -

OTHER SYSTEMS

Respiratory System   -

Cardiovascular System   -

Central Nervous System   -

INVESTIGATIONS

1. COMPLETE HEMOGRAM

PARAMETERS			
TC(cells/mm^3)			
N L E M B			
RBC (millions/mm^3)			
Hb (gm)			
PCV (%)			
MCV(fl)			
MCH(pg)			
MCHC			
Platelet count (lakhs/mm^3)			
ESR(mm 1st hr)			
RDW (%)			
PDW(fl)			
MPV(fl)			
CH-Others			

PERIPHERAL SMEAR -

2. DENGUE SEROLOGY:

DENGUE SEROLOGY	CARD TEST	ELISA
Ns1		
IgM		
IgG		

3. <u>LIVER FUNCTION TESTS</u>

DATE			
TOTAL BILURUBIN(mg/dl)			
COAGULATED BILURUBIN(mg/dl)			
UNCONJUGATED BILURUBIN(mg/dl)			
TOTAL PROTEINS(g/dl)			
SERUM ALBUMIN(g/dl)			
SERUM GLOBULIN(g/dl)			
A:G RATIO			
AST(U/L)			
ALT(U/L)			
ALP(U/L)			

4. <u>COAGULATION PROFILE</u> :

	PT(Sec)	APTT(Sec)
TEST		
CONTROL		
INR		

5. BLOOD GROUP :

6. USG ABDOMEN AND

   PELVIS   :

7. CPK-MB :

8. CXR:

9. OTHER

   INVESTIGATIONS:

TREATMENT HISTORY :

OUTCOME:

KEY TO MASTER CHART

SERIAL NO	ABBREVIATION	FULL FORM
1	ALP	Alkaline phosphatase
2	ALT	Alanine transaminase
3	APTT	Activated partial thromboplastin time
4	AST	Aspartate transaminase
5	BIL	Bilirubin
6	BL	Bilateral
7	CPK-MB	Creatine phosphokinase- muscle/brain
8	DF	Dengue fever without warning signs
9	DFWS	Dengue fever with warning signs
10	DOA	Date of Admission
11	DOD	Date of discharge
12	ELISA	Enzyme linked immunosorbent assay
13	F	Female
14	FFP	Fresh frozen plasma
15	GB	Gall Bladder
16	IgG	Immunoglobulin G
17	IgM	Immunogloblin M
18	IP NO	Inpatient Number
19	M	Male
20	MOD	Moderate
21	NS 1	Nonstructural protein 1
22	PCV	Packed cell volume
23	PE	Pleural effusion
24	PT	Prothrombin time
25	RT	Right
26	SD	Severe dengue
27	USG	Ultrasonography

MASTER CHART

NAME	AGE YEARS	SEX	IP NO	DOA	DOD	SYMPTOMS	DAY OF START OF FEVER AT TIME OF PRESENT ATION	TOTAL LEUK OCYTE COUNT	PLATE LET	PCV	CARD TEST NS1	CARD TEST IGM	CARD TEST IGG	ELI SA	AST	ALT	BIL	ALBU MIN	ALP	PT	APTT	CPK- MB	USG ABDOMEN & PELVIS	CHEST X RAY	BLOOD	WARNING SIGNS	DIAGNO SIS	DURA TION OF STAY(DAYS)	OUTC OME
AISHWAR YA	4	F	31141	18-9-16	23-9-16	FEVER , LOOSE STOOLS , VOMITINGS	7	8010	19000	35.9	+	-	-	+	1246	580	0.8	4.2	203	20	80	NOT DONE	HORSE SHOE KIDNEY, MILD ASCITES, MESENTERIC LYMPHADENOPATHY	NORMAL	NO	BLOODY VOMITING S	SD	6	IMPRO VED
RAVI	3	M	32448	28/9/16	2/10/16	FEVER, COLD, COUGH	4	15650	29000	32.4	-	-	-	+	500	500	1.3	3	251	35.6	77.8	145	GROSS ASCITES ,BILATERAL PLEURAL EFFUSION	RT CONSOLID ATION	PLATE LET, WHOLE BLOOD	NECK RIGIDITY, COMATOS E	SD WITH ENCEPH ALITIS	5	EXPIR ED
SANMITH	5 /12	M	32421	28-9-16	29-9-16	FEVER, COLD, COUGH	7	9870	22000	41.9	+	-	-	-	892	1959	0.6	3.4	244	22.5	27.2	229	ACUTE CHOLECYSTITIS ,MODERATE ASCITES, MILD RIGHT SIDED PLEURAL EFFUSION	RT LUNG CONSOLID ATION	PLATE LET	HEPATOM EGALY, TACHYPN OEA	SD WITH MYOCA RDITIS WITH CARDIO GENIC SHOCK	2	EXPIR ED
CHANDRA SEKHAR GURU GACHINA MATH	11	M	32718	30/9/16	2/10/2016	FEVER	5	6830	91000	37.7	+	-	-	+	63	20	0.4	3.7	127	11.3	39.5	17	THICKENED GB WALL, MILD ASCITES	NORMAL	NO	NO	DF	3	IMPRO VED
LAXMAN DEVAGIRI	14	M	32790	1/10/2016	5/10/2016	FEVER, PAIN ABDOMEN	5	3000	161000	39	+	-	-	+	63	37	0.5	3.8	112	13.7	35.6	31	DISTENDED GALL BLADDER	NORMAL	NO	PAIN ABDOMEN	DFWS	5	IMPRO VED
MAYUR	3	M	33222	5/10/2016	8/10/2016	FEVER	5	3100	142000	30.7	+	-	-	+	38	28	0.4	4	123	13.6	41.2	40	NORMAL	NORMAL	NO	NO	DF	4	IMPRO VED
SUMAYYA	6	F	33531	8/10/2016	12/10/2016	FEVER, HEADACHE , ARTHRALG IA	3	3570	199000	36	+	-	-	+	46	21	0.4	4.2	188	13.7	38.9	36	MILD ASCITES	NORMAL	NO	NO	DF	5	IMPRO VED
PRERANA VALASAN GA	14	F	33548	8/10/2016	12/10/2016	FEVER, VOMITING , ABDOMINA L PAIN	4	2700	115000	37	+	+	+	+	252	172	0.5	4.2	210	14.9	66.3	55	MESENTERIC LYMPHADENOPATHY	NORMAL	NO	VOMITING S,PAIN ABDOMEN	DFWS	5	IMPRO VED
ANKITA MAHESH KABADE	5	F	34083	13-10-16	15-10-16	FEVER, VOMITING,I TCHING	3	5900	107000	30.4	+	-	+	-	82	41	0.4	4.2	111	13.3	31.2	110	MILD HEPATOMEGALY , MILD ASCITES	NORMAL	NO	NO	DF	3	IMPRO VED
LAXMI CHANAPP A KABADAGI	13	F	34112	13-10-16	19-10-16	FEVER, GIDDINESS	5	3500	40000	44	+	-	-	+	57	17	0.5	4	83	13.9	42.2	46	CHOLECYSTITIS, MOD ASCITES, LEFT ECTOPIC PELVIC KIDNEY	NORMAL	NO	NO	DF	7	IMPRO VED

Name	Age	Sex	No.	Date 1	Date 2	Symptoms					+	-	-	+									Findings 1	Findings 2		Findings 3	Dx		Outcome
SAMARTH	6	M	35275	23-10-16	25-10-16	FEVER, VOMITINGS	5	2900	141000	26.8	+	-	-	+	133	45	0.5	3.6	112	13	31.6	24	NORMAL	NORMAL	NO	NO	DF	3	IMPROVED
SHIVANAG OUDA	8	M	35274	23/10/16	27/10/16	FEVER, VOMITING	4	4800	123000	28.2	+	-	-	+	113	43	0.6	3.1	238	12	29.4	59	MODERATE ASCITES, RT PLEURAL EFFUSION	RT LUNG CONSOLIDATION	NO	ABDOMINAL TENDERNESS, INCREASE IN HEMATOCRIT WITH DECREASE IN PLATELET COUNT	DFWS	5	IMPROVED
SIDDANAG OUDA	14	M	35553	25/10/16	1/11/2016	FEVER, HEADACHE, VOMITINGS, MYALGIA	3	1800	161000	34.8	+	-	-	+	184	67	0.5	3.8	256	12.1	38.4	47	MODERATE ASCITES, THICKENED GALL BLADDER WALL	NORMAL	NO	ASCITES	DF	8	IMPROVED
MIJBA	7/12	F	35619	26/10/16	1/11/2016	FEVER, LOOSE STOOLS	3	5600	186000	29.5	+	-	-	-	110	24	0.5	3.4	181	12.1	48.3	74	MODERATE ASCITES	RT LUNG CONSOLIDATION	NO	ASCITES, HEPATOMEGALY	DFWS	7	IMPROVED
AHLOK DILEEP PAWAR	6/12	M	39411	28/11/16	2/12/2016	FEVER, IRRITABILITY	4	14300	85000	30.3	+	+	-	-	111	31	0.5	3.4	147	12.9	54	57	NORMAL	NORMAL	NO	NO	DF	5	IMPROVED
VARUN MAHESH	12	M	11566	11/4/2017	18/04/17	FEVER, VOMITINGS, MYALGIA, HEADACHE	5	2000	25000	46.2	+	-	+	-	500	230	0.4	3.4	209	19.7	31.6	28	NORMAL	NORMAL	NO	ABDOMINAL TENDERNESS, PERSISTENT VOMITING, INCREASE IN HEMATOCRIT WITH DECREASE IN PLT	DFWS	8	IMPROVED
PAVAN RAMESH	5	M	11556	11/4/2017	16/4/17	FEVER, MYALGIA	4	3800	168000	36.9	+	-	-	+	57	37	0.4	3.8	94	11.4	28.4	104	NORMAL	NORMAL	NO	NO	DF	6	IMPROVED
VAISHNAVI BOMMANALLI	6/12	F	12243	17/4/17	23/4/17	FEVER, LOOSE STOOLS	7	3900	68000	40.5	+	-	-	+	151	51	0.4	3.2	105	17.1	51.2	38	NORMAL	NORMAL	NO	HEPATOMEGALY	DF WITH DIPHTHERIAE	7	IMPROVED
KARTHIK MATHAPATI	10	M	12900	22/4/17	26/4/17	FEVER, VOMITINGS, MYALGIA, ARTHRALGIA	3	4900	112000	37.3	+	-	-	+	88	17	0.5	3.8	137	14.6	35	45	NORMAL	NORMAL	NO	NO	DF	5	IMPROVED

Name	Age	Sex	IP No	DOA	DOD	Symptoms																	USG	CXR		Signs	Dx		Outcome
MANISH PARASAPPA GAVARI	9	M	14892	10/5/2017	14/5/2017	FEVER, PAIN ABDOMEN , VOMITINGS , MYALGIA	3	3300	154000	34.8	+	-	-	-	51	40	0.4	3.7	148	14.4	50	117	THICKENED GALL BLADDER WALL	NORMAL	NO	ABDOMINAL PAIN & TENDERNESS, HEPATOMEGALY	DFWS	5	IMPROVED
AKSHATA RAYAGOND SIDDAPUR	12	F	16948	26/5/17	2/6/2017	HEADACHE , FEVER, VOMITINGS , ABDOMINAL PAIN	5	5720	30000	39.4	-	-	+	+	161	36	0.5	2.3	235	21.3	48.1	56	MILD ASCITES, THICKENED GB WALL	NORMAL	PLATELET,FFP	ABDOMINAL PAIN & TENDERNESS, HEMATEMESIS	SD	7	IMPROVED
MALLIKARJUN MULAWAD	5	M	18599	9/6/2017	13/6/17	FEVER, ABDOMINAL PAIN, VOMITINGS , RASHES	5	15500	63000	34.2	-	-	+	+	249	103	0.5	3.1	148	16.6	26.3	44	HEPATOSPLENOMEGALY, ACALCULUS CHOLECYSTITIS,MILD ASCITES,BL PE	NORMAL	NO	PAIN &TENDERNESS IN ABDOMEN, PERSISTENT VOMITINGS, HEPATOMEGALY	DFWS	5	IMPROVED
SUMIT SHIVU KUMAR	13	M	21738	3/7/2017	9/7/2017	FEVER, MYALGIA	4	2800	127000	31	+	-	-	+	61	10	0.4	3.4	235	16.8	76.9	43	ACUTE CHOLECYSTITIS	NORMAL	NO	PAIN ABDOMEN, RAISE IN HEMATOCRIT WITH RAPID FALL IN PLATELET COUNT	DFWS	7	IMPROVED
SWATI BIRADAR	7	F	21695	3/7/2017	6/7/2017	FEVER, BDOMINAL PAIN	3	1900	94000	44.6	+	-	+	+	79	30	0.4	3	121	14.2	30.1	13	ACUTE CHOLECYSTITIS,MILD ASCITES,MILD RT PE	NORMAL	PLATELET	ABDOMINAL PAIN, HEPATOMEGALY	DFWS	4	IMPROVED
AISHWARYA CHANDRA SEKHAR	10	F	22525	10/7/2017	13/7/17	FEVER, VOMITINGS	2	4780	37000	41.5	+	-	+	+	216	144	0.4	2.9	216	17.5	52	29	MODERATE ASCITES, RT PE	NORMAL	NO	PAIN AND TENDERNESS IN ABDOMEN, HEPATOMEGALY, PERSISTENT VOMITINGS	DFWS	4	IMPROVED
OMSWARUP RAJASEKHAR	14	M	22599	10/7/2017	14/7/17	FEVER, PERI ORBITAL PAIN	2	2530	121000	37.4	+	-	+	+	30	17	0.5	3.5	218	21.3	44	38	NORMAL	NORMAL	NO	NO	DF	4	IMPROVED
BHAGYASHRI SIDDARAM	9	F	24360	25/7/17	27/7/17	FEVER, ABDOMINAL PAIN	3	3550	168000	36.9	+	-	-	+	59	16	0.4	3.6	142	14.2	50.9	87	NORMAL	NORMAL	NO	NO	DF	3	IMPROVED
NISHAJA MUMIN	11	F	25025	30/7/17	7/8/2017	FEVER	8	7600	317000	34.5	+	-	-	+	28	22	0.4	3.5	175	17.4	62.9	50	ACUTE CHOLECYSTITIS, MILD ASCITES	NORMAL	PLATELET	PAIN ABDOMEN , TENDERNESS,	DFWS	9	IMPROVED

																											PETECHIAE		
ADITYA HIREMATH	10	M	25925	6/8/2017	13/8/17	FEVER, ABDOMINAL PAIN, VOMITINGS	7	3830	251000	38.7	+	-	-	-	257	55	0.4	3.7	144	15.2	100	71	HEPATOMEGALY, ACUTE CHOLECYSTITIS,MINIMAL ASCITES,RT PE	NORMAL	FFP	PAIN AND TENDERNESS IN ABDOMEN, HEPATOMEGALY	DFWS	8	IMPROVED
RUKAYYA SHEIKH	5	F	25932	6/8/2017	11/8/2017	FEVER, VOMITING, ABDOMINAL PIN	5	11300	40000	45.9	+	+	+	NOT DONE	200	69	0.5	2.5	68	14.1	54.5	68	ACUTE CHOLECYSTITIS, MILD ASCITES,B/L PE	NORMAL	PLATELET	PAIN &TENDERNESS IN ABDOMEN, PERSISTENT VOMITINGS	DFWS	6	IMPROVED
VEDA KABADE	9	F	26266	9/8/2017	13/8/17	FEVER, VOMITINGS	4	2000	124000	37.8	+	-	-	NOT DONE	36	24	0.4	3.5	115	12.1	37.8	49	NORMAL	NORMAL	NO	NO	DF	5	IMPROVED
SANNADHI DOMARI	4	F	26734	12/8/2017	17/08/17	FEVER, VOMITINGS, MYALGIA, ARTHRALGIA	3	4500	211000	35.4	+	-	-	-	41	20	0.5	3.9	213	27.3	31.4	95	NORMAL	NORMAL	NO	NO	DF	6	IMPROVED
SAMARTH LOKESH HALLI	8	M	26793	13/8/17	21/8/17	FEVER, ARTHRALGI, VOMITINGS	3	5500	205000	35.9	+	-	-	NOT DONE	35	14	0.4	3.8	153	14.2	28.4	44	ACUTE CHOLECYSTITIS, MILD ASCITES	NORMAL	NO	HEPATOMEGALY, PERSISTENT VOMITING	DFWS	9	IMPROVED
SOUBHAGYA BALLARI	7	F	27042	15/08/17	21/08/17	FEVER, VOMITINGS	5	6100	46000	36.6	+	-	-	NOT DONE	309	95	0.5	3.3	165	17.9	63.2	115	ACUTE CHOLECYSTITIS, MILD ASCITES	NORMAL	NO	NO	DF	7	IMPROVED
SARVESH DESHPANDE	4	M	27211	16/08/17	19/8/17	FEVER, VOMITINGS, ABDOMINAL PAIN, COUGH	4	5600	62000	38.9	+	-	-	-	89	29	0.4	3.3	145	11.5	69.1	36	HEPATOMEGALY,AC ALCULOUS CHOLECYSTITIS	NORMAL	NO	PAIN ABDOMEN AND TENDERNESS, PERSISTENT VOMITING, HEPATOMEGALY	DFWS	4	IMPROVED
PRADYUMNA TS	14	M	27243	17/8/2017	20/08/2017	FEVER, LOOSE STOOLS	4	4270	17000	47.2	+	-	-	-	82	21	0.6	3	98	14.3	60.3	63	ACUTE CHOLECYSTITIS, MILD ASCITES	NORMAL	NO	NO	DF	4	IMPROVED

Name	Age	Sex	ID	Date 1	Date 2	Symptoms	Duration	WBC	Platelet	HCT	NS1	IgM	IgG	Widal	SGOT	SGPT	Bilirubin	Albumin	Alb2	Hb	PCV	Other	USG	CXR	Finding	Sign	Exam	Diagnosis	Days	Outcome
SUMA SAJJAN	12	F	27245	17/8/17	20/8/17	FEVER	6	2800	139000	42.9	+	-	-	NOT DONE	62	25	0.5	3.7	152	15.8	78.8	29	NORMAL	NORMAL	NO	NO	DF	4	IMPROVED
PRUTVI JAGADISH MULASAVALAGI	5	M	27335	17/8/17	26/8/17	FEVER, PAIN ABDOMEN, LOOSE STOOLS	60	7270	301000	31.4	-	+	-	NOT DONE	1650	1678	5.9	3	281	16.7	46.3	32	CHOLECYSTITIS	NORMAL	NO	ABD PAIN & TENDERNESS, HEPATOMEGALY	SD WITH HEPATITIS	10	IMPROVED
SANDEEP BHEEMARAJ NANDARAGI	9	M	27474	18/8/17	22/8/17	FEVER, PAIN ABDOMEN , MYLGIA	5	5400	239000	38.9	+	-	-	-	87	38	0.4	3.9	185	17.3	66.7	61	NORMAL	NORMAL	NO	NO	DF	5	IMPROVED
PRADNYA WADEYAR	8	F	27636	20/8/17	25/8/17	FEVER, HEADACHE , ABDOMINAL PAIN ,VOMITINGS	4	1970	71000	37.3	+	-	-	NOT DONE	228	106	0.4	3.7	123	15.7	100	51	NORMAL	NORMAL	PLATELET	ABD PAIN & TENDERNESS, HEPATOMEGALY	DFWS	6	IMPROVED
JOYA NABIRASUL SHAIKH	5	F	27707	21/8/17	28/8/17	FEVER, LETHARGY, VOMITING, HEADACHE	4	6140	36000	48.8	+	-	-	NOT DONE	110	30	0.6	2.4	80	22.7	30.2	37	NORMAL	NORMAL	NO	DECREASED ACTIVITY & INTAKE OF FOOD, KERNIGS SIGN & BRUDZINSKIS SIGN - POSITIVE, NECK RIGIDITY	SD WITH MENINGITIS WITH RICKETTSIAL FEVER	8	IMPROVED
BILAL MULLA	10	M	28245	24/08/17	28/08/17	FEVER	4	3800	47000	44.5	+	-	-	NOT DONE	138	55	0.4	3	117	14	69.1	43	MODERATE ASCITES	NORMAL	NO	ABDOMINAL TENDERNESS	DFWS	5	IMPROVED
PREMA RAJASHEKAR KYADI	7	F	29656	5/9/2017	11/9/2017	FEVER, COLD	4	6700	278000	36.6	+	-	+	NOT DONE	39	15	0.4	3.7	112	17.7	53.2	29	NORMAL	NORMAL	NO	NO	DF	7	IMPROVED

Name	Age	Sex	Reg No	Date 1	Date 2	Symptoms								NS1									Ultrasound		Platelet	Signs	Dx	Days	Outcome
SAI KUMAR	8	M	38686	10/11/2017	13/11/2017	FEVER, MYALGIA, NAUSEA	15	3500	180000	36.3	+	-	+	NOT DONE	62	29	0.4	3.2	171	15.7	63.6	36	ACUTE CHOLECYSTITIS,MILD ASCITES,NONOBSTRUCTIVE LEFT RENAL CALCULUS	NORMAL	NO	NO	DF	4	IMPROVED
KRISHNA PAWAR	14	M	38710	10/11/2017	13/11/17	FEVER, ARTHRALGIA	4	3390	187000	40.8	+	-	-	NOT DONE	40	24	0.5	3.4	162	15.4	68.2	25	NORMAL	NORMAL	NO	NO	DF	4	IMPROVED
BIBIAYESHA	5	F	38798	11/11/2017	13/11/17	FEVER, ABDOMINAL PAIN	7	6300	127000	36	-	+	+	NOT DONE	85	53	0.4	3.8	148	13.6	45.4	41	NORMAL	NORMAL	NO	PAIN ABDOMEN & TENDERNESS	DFWS	3	IMPROVED
ANKUSH SINDAGE	9	M	38910	12/11/2017	15/11/17	FEVER, VOMITING	4	3900	109000	29.6	+	-	-	NOT DONE	65	17	0.4	3.2	136	17.7	29.6	35	ACUTE CHOLECYSTITIS	NORMAL	NO	NO	DF	4	IMPROVED
YASH INGALE	3	M	38937	12/11/2017	17/11/17	FEVER	3	3900	240000	42.3	+	+	+	NOT DONE	38	24	0.4	3.5	156	18	58.6	24	NORMAL	NORMAL	NO	NO	DF	6	IMPROVED
SANKETKUMAR	6	M	39715	17/11/17	30/11/17	FEVER, VOMITINGS	5	4300	110000	33.9	+	-	-	NOT DONE	1410	284	0.4	2.6	137	16.4	30.4	77	CHOLECYSTITIS, MILD ASCITES,BILATERAL PLEURAL EFFUSION	NORMAL	NO	TENDERNESS IN RT HYPOCHONDRIUM ,HEPATOMEGALY	SD WITH HEPATITIS	14	IMPROVED
MANOJ MAHESH	4	M	39876	18/11/17	26/11/17	FEVER, ABDOMINAL PAIN	4	5200	35000	32	+	-	-	NOT DONE	184	49	1.1	3.7	206	13.6	32	25	THICKENED GALLBLADDER WALL,MODERATE ASCITES, BILATERAL PLEURAL EFFUSION	NORMAL	PLATELET	PAIN ABDOMEN, HEPATOMEGALY	DFWS	9	IMPROVED
MOHAMMAD FAIM	6/12	M	39924	19/11/17	25/11/17	FEVER , LOOSE STOOLS	4	7100	182000	24	+	-	-	NOT DONE	143	47	0.5	2.5	148	15	36.7	22	ACUTE CHOLECYSTITIS,MILD ASCITES	NORMAL	PLATELET	NO	DFWS	7	IMPROVED
SHIVARAJ KATTIMANI	13	M	40502	23/11/17	28/11/17	FEVER, ABDOMINAL PAIN, VOMITINGS	3	11300	329000	37.4	+	-	-	NOT DONE	49	26	0.5	3.1	195	14.6	31.2	27	NORMAL	NORMAL	NO	VOMITINGS, PAIN ABDOMEN	DFWS	6	IMPROVED
VIJAY DORKAR	12	M	40793	25/11/17	28/11/17	FEVER, VOMITINGS , GIDDINESS	4	2550	115000	39.9	+	-	-	NOT DONE	75	36	0.8	3	117	20.4	100	33	ACUTE CHOLECYSTITIS, MODERATE ASCITES	NORMAL	NO	NO	DFWS	4	IMPROVED
SOMANATH KODLAPUR	10	M	42384	8/12/2017	11/12/2017	FEVER, VOMITING	3	10400	48000	24.9	+	-	-	NOT DONE	254	310	0.9	2.4	452	13.9	38.2	17	ACUTE CHOLECYSTITIS , MILD ASCITES, HEPATOMEGALY	NORMAL	NO	NO	DFWS	4	IMPROVED

Name	Age	Sex	No	Date Adm	Date Dis	Symptoms								Serology									USG	CXR	Transfusion	Findings	Dx	Days	Outcome
NINGAMMA SIDRAM	13	F	43596	20/12/17	23/12/17	FEVER, VOMITINGS, MYALGIA, ARTHRALGIA	4	8100	40000	43.6	+	+	+	NOT DONE	54	33	0.4	2.8	63	18	51.3	28	MILD ASCITES,ACALCULUS CHOLECYSTITIS	NORMAL	NO	VOMITINGS, TENDERNESS IN RIGHT HYPOCHONDRIUM	DFWS	4	IMPROVED
BHAGYALAKSHMI SADDAYYAMATH	7	F	43690	20/12/17	26/12/2017	FEVER, ABD PAIN	5	6500	144000	35	+	-	-	NOT DONE	59	33	0.6	3.9	146	15.6	37.6	34	NORMAL	NORMAL	NO	ABDOMINAL PAIN, INCREASE IN HCT WITH DECREASE IN PLT COUNT	DFWS	7	IMPROVED
MALLIKARJUN SADAYYAMATH	8	M	43691	20/12/17	26/12/7	FEVER, VOMITING , HEADACHE	5	5500	112000	32.7	+	-	-	NOT DONE	148	15	1	3.9	269	16.3	72.1	35	MILD SPLENOMEGALY	NORMAL	NO	PERSISTENT VOMITING, INCREASE IN HEMATOCRIT WITH DECREASE IN PLT	DFWS	7	IMPROVED
REHAN DUNDARI	11	M	43878	22/12/2017	25/12/2017	FEVER, PAIN ABDOMEN , VOMITINGS , MYALGIA	5	2500	80000	44.7	+	+	-	NOT DONE	169	144	0.5	2.5	153	27.2	31.8	40	ACUTE CHOLECYSTITIS, MODERATEERATE ASCITES, MODERATE BL PE	NORMAL	NO	ASCITES, PLEURAL EFFUSION, PAIN AND TENDERNESS IN THE ABDOMEN, HCT INC C PLT REDUCTION	DFWS	4	IMPROVED
B/O RANJITH RAJU BAJANTRI	1	M	4127	2/2/2018	7/2/2018	FEVER, DROWSINESS, HURRIED BREATHING	2	10720	55000	40.5	+	-	-	NOT DONE	528	188	0.5	3.1	258	21.5	90.1	256	NORMAL	RT LUNG CONSOLIDATION	WHOLE BLOOD	NO	SD	6	IMPROVED
REVANASIDDAPPA	8/12	M	4775	7/2/2018	13/02/18	FEVER, RASH, VOMITINGS	4	6580	29000	32.1	+	-	-	NOT DONE	93	39	0.4	2.7	120	13.3	46.6	33	HEPATOSPLENOMEGALY,CHOLECYSTITIS, MOD ASCITES	NORMAL	WHOLE BLOOD	TENDERNESS IN THE ABDOMEN, HEPATOMEGALY	DFWS	7	IMPROVED
MUTTANNA BAJANTRI	3	M	6777	23/02/18	6/3/18	FEVER, EDEMA, CONVULSION, RESP DISTRESS	4	18220	98000	33.6	-	-	+	NOT DONE	36	41	1.1	5.6	266	26.3	29	16	ACUTE CHOLECYSTITIS	RT UPPERLOBE & MIDDLE LOBE CONSOLIDATION	NO	HEPATOMEGALY, EDEMA, UNCONSCIOUS, CONVULSIONS	SD WITH MENINGITIS	12	IMPROVED
MAILARILINGA SUKADEV PUJARI	6	M	7066	26/02/18	5/3/18	FEVER, ABDOMINAL PAIN, COUGH	8	3490	125000	32.7	+	-	-	NOT DONE	115	48	0.4	2	86	20.4	31.4	38	MOD TO GROSS ASCITES, ACUTE CHOLECYSTITIS	NORMAL	NO	ABDOMINAL PAIN, HEPATOMEGALY	DFWS	8	IMPROVED

NIKHIL MADAGOND	6	M	8227	8/3/2018	14/03/18	LOSS OF APPETITE, ICTERUS, FEVER, BLEEDING PER NOSE	1	5700	56000	30.1	-	+	-	NOT DONE	210	376	6.9	3.8	318	23.3	80	13	ALTERED ECHOTEXTURE, MILD ASCITES, THICKENED EDEMATOUS GB WALL	NORMAL	FFP	BLEEDING PER NOSE,HEPATOMEGALY	DFWS WITH HEPATITIS A	7	IMPROVED
ZUBERAH AMMED	14	M	8431	9/3/2018	12/3/2018	FEVER, NAUSEA,LOSS OF APPETITE	5	5220	81000	36.3	+	-	-	NOT DONE	113	53	0.4	3.3	195	14.9	60.2	33	THICKENED GB WALL	NORMAL	NO	NO	DF	4	IMPROVED
ARCHANA YALLAPPA	8/12	F	8535	10/3/2018	16/03/18	FEVER, VOMITINGS	8	9510	40000	33.2	+	+	-	NOT DONE	48	109	0.4	2.5	160	15.5	30	40	ACUTE CHOLECYSTITIS	NORMAL	NO	PERSISTENT VOMITINGS	DFWS	7	IMPROVED