CLINICAL AND HAEMATOLOGICAL PROFILE OF DENGUE FEVER IN A TERTIARY CARE HOSPITAL AT KAKINADA

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ABSTRACT

BACKGROUND
Dengue fever(DF) with its severe manifestations such as DHF and DSS has emerged as a major public health problem of international concern.The geographical distribution has greatly expanded over the last 30 years, because of increased potential for breeding of Aedes aegypti. This has been prompted by demographic explosion, rapid growth of urban centers with strain on public services, such as potable water and augmented by rain water harvesting in diverse types of containers resulting in multiple storage practices. Today, Dengue ranks as the most important mosquito-borne viral disease in the world. Current estimates report that at least 112 countries are endemic for Dengue and about 40% of the world populations (2.5-3 billion people) are at risk in tropics and sub-tropics. Annually, 100 million cases of dengue fever and half a million cases of DHF occur worldwide. Early recognition and prompt initiation of treatment are vital if disease related morbidity and mortality are to be limited.

METHODS
A total of 100 patients admitted to our hospital with fever (>38.5^{0}F) and IgM Dengue positive were studied at our institute, Rangaraya Medical College, Kakinada during Jan 2013 to Jan 2015. Out of 100 patients, 73(73%) patients were diagnosed to have DF, 22(22%) patients were diagnosed to have DHF and 5(5%) patients were diagnosed to have DSS based on WHO criteria. The present study was conducted in Government General Hospital, Kakinada during 2013-2015. Informed consent was taken from all the patients during the study.

STUDY DESIGN
It is a prospective cohort study over a period of two years through sample and sampling techniques. A total of 100 patients admitted to the hospital with history of fever of more than 38.5 ^{0} C and IgM Dengue positive cases were selected using purposive sampling techniques. They were followed from the onset of fever to time of recovery or discharge according to WHO discharge criteria whichever is earlier. The following investigations were done: Blood counts, IgM Dengue. Clinically, patients were monitored and platelet count, haematocrit, Hess test were repeated daily.

DATA ANALYSIS
Data collected will be analysed by frequency, percentage and mean.

Dengue-IgM Capture ELISA
Detection of dengue virus specific IgM Antibodies in serum.

RESULTS
Male to female ratio was 1.5:1. Majority of the cases having dengue infection belong to the age group of 21-30 years, wherein 48% belong to 21-30 years' group and 24% belong to 31-40 years' group. All the cases had fever (100%). Other common signs and symptoms included are myalgia (85%), headache (80%), joint pains (76%), vomiting (60%), pain abdomen (54%), rash (46%), hepatomegaly (25%), bleeding (21%) and shock (5%). Signs suggestive of plasma leakage such as pedal oedema (12%), ascites (20%), pleural effusion (26%) were present. Hess test was positive in 20% of the patients. Thrombocytopenia was found in 76% patients. Bradycardia was found in 41 %.

CONCLUSIONS
The present study had an objective of studying clinical manifestations and haematological profile associated with dengue fever. A positive Hess test should prompt close observation and early hospital referral, but a negative test does not exclude dengue infection. Bleeding tendencies should be closely watched for. When features of plasma leakage such as pedal oedema, pleural effusion, ascites are present, the patient should be closely watched for and should be immediately managed. The treatment of dengue is mainly supportive. However, appropriate fluid management plays a major role in outcome of the disease. Dengue sero-surveillance studies may give some idea about advent, intensity, transmission season, seasonal incidence, waxing and waning, and impending epidemic of dengue and DHF. A large-scale active longitudinal sero-survey along with the study of vector capacity and vector competence would provide more correct information.

A total of 100 patients admitted to our hospital with fever (>38.50 F) and IgM Dengue positive were studied at our Institute, Rangaraya Medical College, Kakinada during Jan 2013 to Jan 2015. Out of 100 patients, 73(73%) patients were diagnosed to have DF, 22(22%) patients were diagnosed to have DHF and 5(5%) patients were diagnosed to have DSS based on WHO criteria. Male to female ratio was 1.5:1. Majority of the cases having dengue infection belong to the age group of 21-30 years, wherein 48% belong to 21-30 years' group and 24% belong to 31-40 years' group. All the cases had fever (100%). Other common signs and symptoms included are myalgia (85%), headache (80%), joint pains (76%), vomiting (60%), pain in abdomen (54%), rash (46%), hepatomegaly (25%), bleeding (21%) and shock (5%). Signs suggestive of plasma leakage such as pedal oedema (12%), ascites (20%), pleural effusion (26%) were present. Hess test was positive in 20% of the patients. Thrombocytopenia was found in 76% patients. Bradycardia was found in 41%.

KEYWORDS
Dengue C02.081.270 , Severe Dengue C02.081.270.200

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INTRODUCTION: Dengue fever (DF) with its severe manifestations such as DHF and DSS has emerged as a major public health problem of international concern. The geographical distribution has greatly expanded over the last 30 years because of increased potential for breeding of Aedes aegypti. This has been prompted by demographic explosion, rapid growth of urban centers with strain on public services, such as potable water and augmented by rain water harvesting in diverse types of containers resulting in multiple storage practices. Today, Dengue ranks as the most important mosquito-borne viral disease in the world. Current estimates report that at least 112 countries are endemic for Dengue and about 40% of the world populations (2.5-3 billion people) are at risk in tropics and sub-tropics. Annually, 100 million cases of dengue fever and half a million cases of DHF occur worldwide. Early recognition and prompt initiation of treatment are vital if disease related morbidity and mortality are to be limited. Dengue fever is an acute febrile disease characterized by sudden onset of fever of 3-5 days, intense headache, myalgia, retro-orbital pain, anorexia, gastro intestinal disturbances and rash. Dengue virus is a flavivirus, which includes four serotypes 1, 2, 3 and 4. The virus is transmitted to man by the bite of infective mosquitoes, mainly Aedes aegypti. The incubation period is 4-7 days, but may range from 3 to 14 days. The disease is now endemic in most tropical and subtropical countries

Pathogenesis: Humans are the main amplifying host of the virus**.** Following the bite of an infectious mosquito, virus replicates in the local lymph nodes and within 2-3 days disseminates to the blood and various tissues. During the stage of viremia, patient manifests with fever and as the virus is cleared from blood, the fever decreases. Primary infection is thought to induce lifelong protective immunity to the infecting serotype.[1,2] In secondary infections with a virus of a different serotype from that causing the primary infection, the clinical manifestations are severe. This is due to antibody dependent enhancement. In this model, non-neutralizing, cross-reactive antibodies raised during a primary infection, or acquired passively at birth, bind to epitopes on the surface of heterologous infecting virus and facilitate virus entry into Fc-receptor-bearing cells. During a secondary infection, cross-reactive memory T cells are also rapidly activated, proliferate, express cytokines and die by apoptosis in a manner that generally correlates with overall disease severity. Plasma leakage, haemoconcentration and abnormalities in homeostasis characterise severe dengue. Both decreased production and increased utilisation of platelets may contribute to bleeding early in infection.[3,4] Shock in DSS occurs due to sudden extravasation of plasma to extravascular sites like the pleural and abdominal cavity. This occurs because of increased vascular permeability due to immune activation.[4](Fig. 1)

AIM AND OBJECTIVES:

1. To study the various clinical presentations of dengue fever.
2. To study the haematological features of dengue fever.

MATERIAL AND METHOD: The present study was conducted in Government General Hospital, Kakinada during 2013-2015. Informed consent was taken from all the patients during the study.

Study Design: It is a prospective cohort study over a period of two years through sample and sampling techniques. A total of 100 patients admitted to the hospital with the history of fever of more than 38.5 ^{0} C and IgM Dengue-positive cases were selected using purposive sampling techniques. They were followed from the onset of fever to time of recovery or discharge according to WHO discharge criteria whichever is earlier. The following investigations were done: Blood counts, IgM Dengue. Clinically, patients were monitored and platelet count, haematocrit, Hess test were repeated daily.

Data Analysis: Data collected will be analyzed by frequency, percentage and mean.

Dengue-IgM Capture ELISA: Detection of dengue virus specific IgM Antibodies in serum.

Principle: IgM antibodies in patient's blood are captured by anti-human IgM that are coated on to the solid surface (wells). In the next step, DEN antigen is added which bind to capture IgM, if the IgM and antigen are homologous. Unbound antigen is removed during the washing steps. In the subsequent step, biotinylated flavivirus cross-reactive monoclonal antibody (Hx-B) is added followed by avidin-HRP. Subsequently, substrate/chromogen is added and watched for development of colour. The reaction is stopped by 1N H2SO4. The intensity of colour/optical density is monitored at 450 nm. OD readings are directly proportional to the amount of dengue virus specific IgM antibodies in the sample.

Quality Control: Each kit is supplied with one positive control and one negative control. These are mainly for validation of the kit. Expected values are given below;
Positive: OD values > 0.5.
Negative: OD value < 0.18.

Interpretation of the Results: If the OD value of sample tested exceeds OD of negative control by a factor 2.1 (sample OD > negative OD x 2.1), the sample should be considered as positive.

Estimation of Platelet Count and Hematocrit: Platelet count and haematocrit were determined using patients EDTA blood, modified Dacie Leurs method, using automated counter, HORIBA-ABX Diagnostics, MICROS-60.

Estimation of Haemoglobin Estimation: Haemoglobin estimation by cyan-methemoglobin method.

Estimation Of TLC: Total and differential leukocyte count using Neubauer's chamber.

LABORATORY DIAGNOSIS OF DF/DHF[5,6,7,2]

Hematological criteria for diagnosis:

Thrombocytopenia - ≤ 100,000 cells/mm^3.

Hemoconcentration – (> 20% of rise in average hematocrit for age and sex).

Inclusion Criteria:

1. Those admitted in Government General Hospital having fever more than 38.5 ^{0}C.
2. IgM Dengue positive.

Exclusion Criteria:

1. Age less than 15 years or more than 60 years.
2. Preexisting substantial chronic liver, kidney or heart disease.
3. Patients with history of hematological disorders.

RESULTS & OBSERVATIONS:

Study Design: A total of 100 patients admitted to our hospital with fever (>38.5^{0}C) and IgM dengue positive cases were studied. Out of 100 patients, 72 (72%) patients were diagnosed to have DF, 23(23%) patients were diagnosed to have DHF and 5(5%) patients were diagnosed to have DSS based on WHO criteria. The present study included 40(40%) female and 60 (60%) male patients (fig-2). Dengue infection was more seen in males, DF cases were more among males i.e., 42(58.33%) than in females i.e., 30 (41.67%). DHF cases were more among males i.e., 15 (65.3%) than in females 8 (34.7%). DSS cases were more among males i.e., 3 (60%) and females 2 (40%). Majority of the cases having dengue infection belong to the age group of 21-30 years' group (48%). It is more common in younger population. Fever was present in 100 (100%) cases, myalgia in 85 (85%) cases. Likewise, headache was present in 80 (80%) cases, joint pains in 76 (76%)cases, vomiting in 60 (60%) cases, pain in abdomen in 54 (54%) cases, rash in 46 (46%) cases, hepatomegaly in 25 (25%) cases, bleeding in 21 (21%) cases and shock in 5 (5%) cases. Association of Hess test was studied. It shows that Hess test was positive in 20 (20%) patients. (fig-10 & 11)

As per WHO criteria, 76(76%) patients had low platelet counts. Out of 100 patients, 55 (55%) patients had total leukocyte counts between 4,000 and 11,000. A total leukocyte count of less than 4,000 was present in 40 (40%) patients. A total leukocyte count of more than 11,000 was present in 5 (5%) patients. The haematocrit value ranged from 34-49% with a mean value of 39.29%. Among 100 (100%) patients, 41 (41%) patients had bradycardia. The present study showed the evidence of plasma leakage such as pedal oedema in 12 (12%), pleural effusion in 26 (26%), ascites in 20 (20%) of patients.

DISCUSSION: A total of 100 patients admitted to our hospital with fever > 38.5^0 F and IgM Dengue positive were studied. The study included 40(40%) female and 60(60%) male patients, out of which 30(30%) females and 42(42%) males were diagnosed to have DF. Male to female ratio was 1.5:1(fig-3).This was corresponding to the other studies by Dash PK et al and Neerja M et al i.e., 1.28:1, 2:1 respectively (fig-22) [8,9]. In present study, DSS and DHF were also more common in males than females. 8(20%) females and 15(25%) males were diagnosed to have DHF. 2(5%) females and 3(5%) males were diagnosed to have DSS(fig-4 & fig-5). In the present study, Dengue fever was seen in 73% of the study population. The incidence of DHF and DSS was 22% and 5% respectively. In a study done by Neerja M et al, the prevalence of DF, DHF, DSS was 85%, 5%, 10% respectively. In a study done by Pancharoen et al, there was high incidence of DHF i.e., 60.4%.[10] These observations imply that the incidence of each clinical spectrum varies with geographical area.(fig-22). Fever was the presenting complaint in all cases in our current study. In the study conducted by Aggarwal et al, Dash PK et al, Neerja et al, Khan et al, fever was present in 93%, 100%, 100%, 98.3% respectively.(fig-24).[8,9] Myalgia was seen in 85% of cases. In the studies conducted by Dash PK et al, Neerja et al, Farhan et al, myalgia was present in 70%, 53%, 61% respectively.[8,9] This correlated with other studies. Myalgia is seen in majority of cases of viral fever. Joint pain was found in 76% of cases in the study. It was found in 55%, 15% and 54% of patients in studies done by Dash PK et al, Neerja M et al and Farhan et al respectively.[8,9] It was noted that headache was seen in 80% of patients in our study. Similar incidence was present in other studies too. In the studies conducted by Dash PK et al, Neerja et al and Khan et al, headache was present in 85%, 74%, 75% respectively.[8,9] Bleeding was a presenting complaint in 21% of patients. In the study conducted by Neerja et al and Farhan et al, the percentage of bleeding was 7%and 21% respectively. In present study, 76(76%) patients had thrombocytopenia. Studies by Cherian T et al, Singh NP et al and Khan E et al showed the incidence of thrombocytopenia in 94.7%, 61.39%, 81.4% respectively. This correlated with the above-mentioned studies.[11,12,13] Present study showed features of shock in 5(5%) patients. Study conducted by Nimmanitya et al, Nandini et al, Farhan et al showed the incidence of shock in 35%, 11.5% and 8% respectively. From these observations, we can conclude that the incidence of each clinical spectrum varies with the geographical area. (fig-8 & 9).[14] Platelet count and tourniquet test did not consistently correlate with each other. Tourniquet test was positive in (20%) 20 cases. Other studies have noted varying results in this test. Tourniquet test is not a reliable test for diagnosis as observed in many other Indian studies. This correlated with other studies. (Fig-12 & 13). The present study showed hepatomegaly in 25% of patients. Studies conducted by Aggarwal et al, Neerja et al, Nimmanitya et al[15], Mohan et al showed incidence of hepatomegaly in 90%, 74%, 71% and 72% patients respectively. The haematocrit ranged from 34 - 49%. The mean haematocrit value of dengue positive cases in my study was 39.29%. In DHF and DSS, an increase in haematocrit levels was noted due to plasma leak. This correlated as per the WHO guidelines. (fig-16 & 17).

Out of 100 patients in the study, 26 (26%) patients showed evidence of pleural effusion, 12 (12%) patients were found to have pedal oedema, 20 (20%) patients were found to have ascites. This correlated with the studies done by Neerja et al and Dash P K et al.[9,8] As per WHO guidelines,

pedal oedema, ascites and pleural effusion are the supporting evidence of plasma leakage, the distinguishing feature of DHF.

CONCLUSION: The present study had an objective of studying clinical manifestations and haematological profile associated with dengue fever. A positive Hess test should prompt close observation and early hospital referral, but a negative test does not exclude dengue infection. Bleeding tendencies should be closely watched for. When features of plasma leakage such as pedal oedema, pleural effusion, ascites are present, the patient should be closely watched for and should be immediately managed. The treatment of dengue is mainly supportive. However, appropriate fluid management plays a major role in outcome of the disease. Dengue sero-surveillance studies may give some idea about advent, intensity, transmission season, seasonal incidence, waxing and waning, and impending epidemic of dengue and DHF. A large-scale active longitudinal sero-survey along with the study of vector capacity and vector competence would provide more correct information.

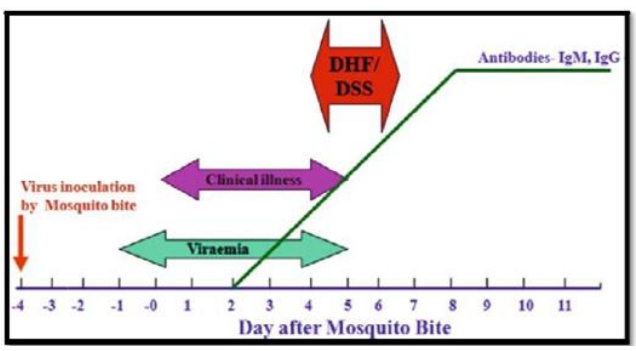

Fig. 1: Temporal sequence of pathology of DHF

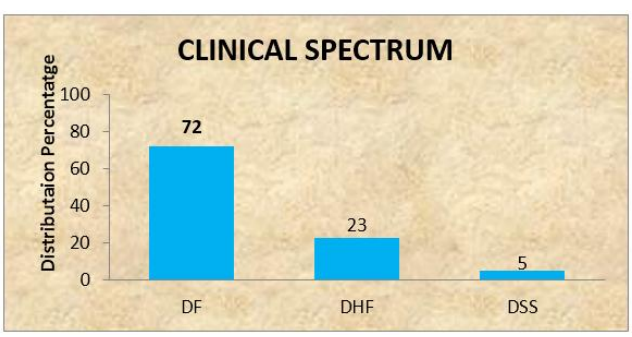

Fig. 2: Clinical spectrum

Sex	Number	Percentage
Male	60	60%
Female	40	40%
Total	**100**	**100%**

Fig. 3: Gender wise distribution

Sex	DF		DHF		DSS	
	No.	%	No.	%	No.	%
Female	30	41.67%	8	34.7%	2	40%
Male	42	58.33%	15	65.3%	3	60%
Total	72	100%	23	100%	5	100%

Fig. 4: Sex distribution of DF, DHF and DSS

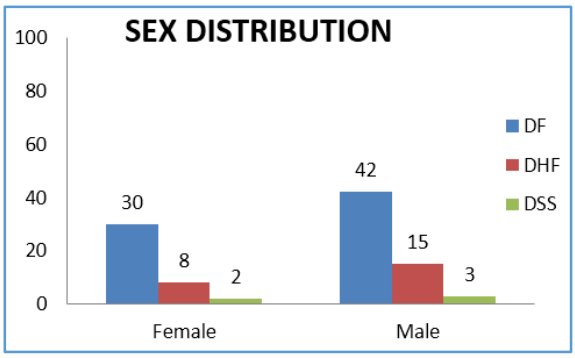

Fig. 5

Age	15-20	21-30	31-40	41-50	51-60
Frequency(n)	15	48	24	11	2

Fig. 6: Age wise distribution

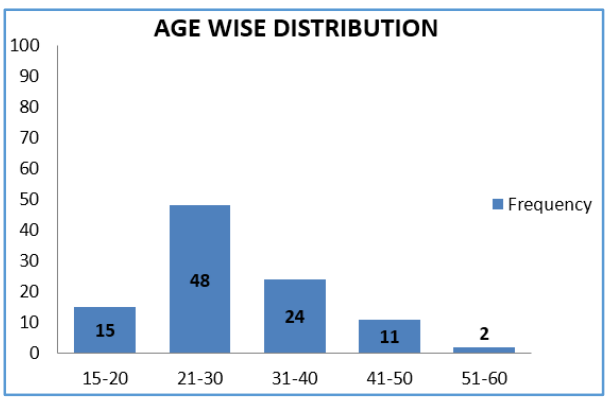

Fig. 7

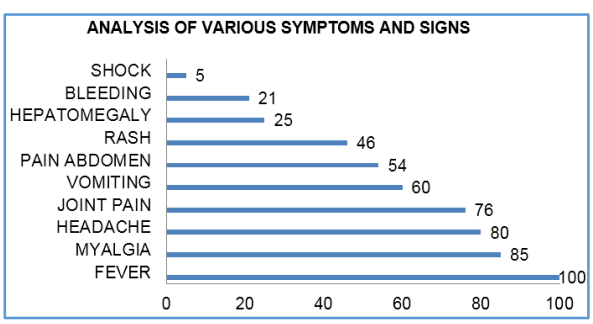

Fig. 8

	Present		Absent	
Symptoms and signs	**No. of patients**	**Perce-ntage**	**No. of patients**	**Percen-tage**
Fever	100	100%	0	0%
Myalgia	85	85%	15	15%
Joint pain	76	76%	24	24%
Vomiting	60	60%	40	40%
Pain Abdomen	54	54%	46	46%
Rash	46	46%	54	54%
Bleeding	21	21%	79	79%
Headache	80	80%	20	20%
Hepatomegaly	25	25%	75	75%
Shock	5	5%	95	95%

Fig. 9: Analysis of various symptoms and signs

	Present		Absent	
	No. of patients	Percent	No. of patients	Percent
HESS	20	20	80	80

Fig. 10: Hess test

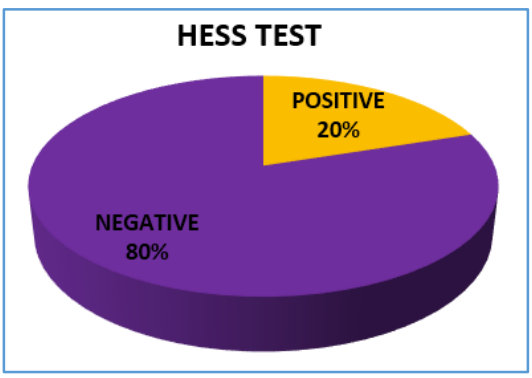

Fig. 11

Platelet	Frequency	Percentage
<100,000	76	76%
>/=100,000	24	24%
TOTAL	**100**	**100%**

Fig. 12: Platelet count

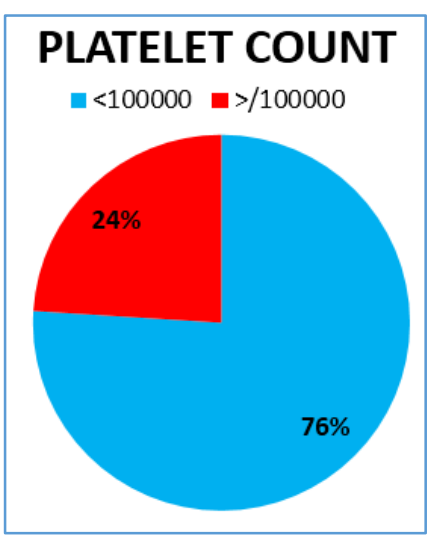

Fig. 13: As per WHO criteria 76(76%) patients had low platelet counts

TLC	Number	Percent
< 4000	40	40%
4000 - 11000	55	55%
> 11000	5	5%
Total	100	100%

Fig. 14: Total leukocyte count

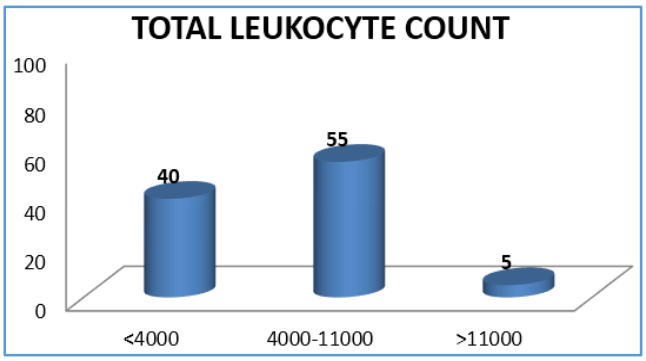

Fig. 15

Haematocrit	Number	Percent (%)
Below 40	52	52
40 - 45	40	40
Above 45	8	8
Total	**100**	**100**

Fig. 16: Hematocrit

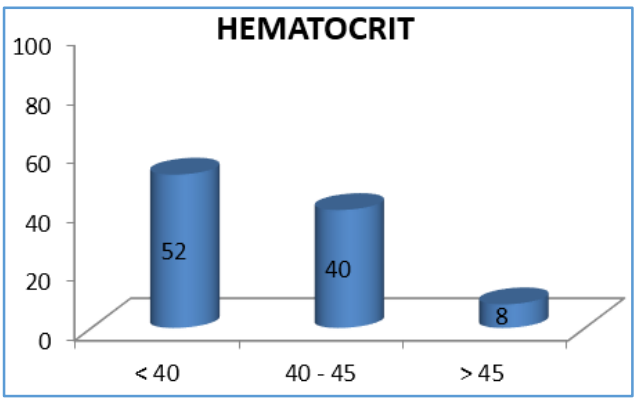

Fig. 17

Bradycardia	Number	Percentage
Present	41	41%
Absent	59	59%

Fig. 18: Bradycardia

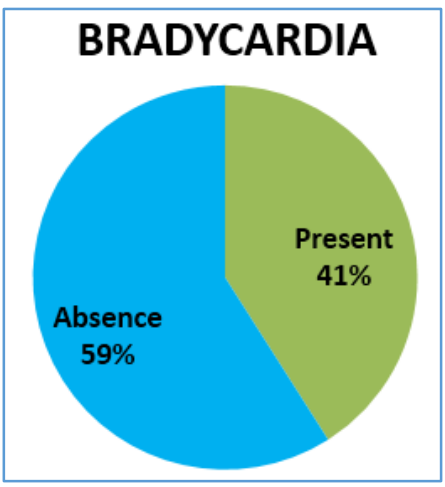

Fig. 19

Sl. No.	Evidence of plasma leakage	Number	Percentage
1.	Pleural effusion	26	26%
2.	Ascites	20	20%
3.	Pedal oedema	12	12%
4.	Shock	5	5%

Fig. 20: Plasma leakage

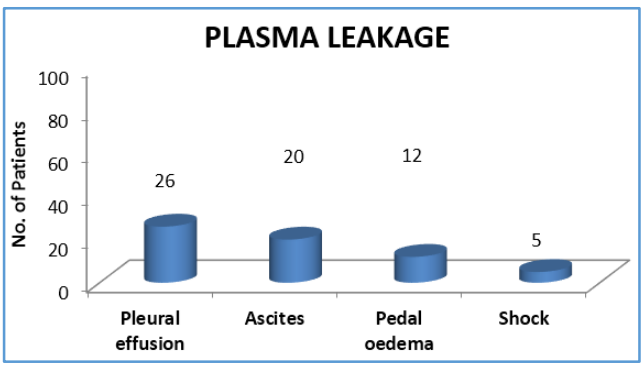

Fig. 21

Comparison of sex distribution with other studies:

Sl. No.	Study	Year	Place	M:F
1.	Kamal S et al	2002	Warangal	0.72:1
2.	Dash PK et al	2003	Gwalior	1.28:1
3.	Neerja M et al	2004	Hyderabad	2:1
4.	Present study	2013	Kakinada	1.5:1

Fig. 22: Compared sex distribution

Sl. No.	Author	Year	Place	Clinical profile
1.	Pancharoen et al	1995	Thailand	DF: 22.3% DHF: 60.4% DSS: 17.3%
2.	Neerja et al	2004	Hyderabad	DF: 85% DHF: 5% DSS: 10%
3.	Present study	2013	Kakinada	DF: 73% DHF: 22% DSS: 5%

Fig. 23: Comparing incidence of each clinical spectrum in various studies

Sl. No.	Study	Fever
1	Aggarwal et al 1996	93%
2.	Dash PK et al 2003	100%
3.	Neerja M et al 2004	100%
4.	Khan E et al 2006	98.3%
5.	Present study 2013	100%

Fig. 24: Comparing incidence of fever with other studies

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