Original Research Article

Trends in the clinical and hematological profile of patients with dengue fever

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ABSTRACT

Background: World Health Organization (WHO) estimates that 50-100 million dengue infections occur every year with 22000 deaths. The increasing magnitude of the problem together with its changing epidemiology is an important public health concern. The aim of the present study was to evaluate clinical profile, hematological profile, biochemical profile and outcome of dengue fever and to determine the relationship between clinical profile and hematological profile.

Methods: This is a retrospective, observational, hospital-based study. 369 patients, aged more than 12 years, admitted between 1st January to 31st December 2015 with dengue fever were studied for clinical profile including documented bleeding manifestations/bleeding tendencies, hematological profile, biochemical profile and outcome.

Results: Dengue cases occurred at higher frequency in 12-30 year age (81.30%), in males (M: F ratio- 2.35:1) and in rainy season (87.26% from September to November). Common presentations on clinical, radiological, haematological and biochemical profile were: fever (100%), headache (73.98%), bodyache (71.81%); hepatomegaly (66.93%), pericholecystic oedema (48.23%), distended GB (38.21%); thrombocytopenia (92.68%), leucopenia (58.26%) and raised liver enzymes (79.94%) respectively. Bleeding manifestations were observed in 48.61% cases of which petechiae (74.68%) was the commonest followed by epistaxis (7.59%), gum bleeding (2.16%), melena (2.16%) mainly. Mean duration of fever prior to hospitalization was 5.06±1.70 days. Mean nadir of platelet count was on 6.83±1.47 day from onset of illness (1st symptom-fever) and 1.77±0.89 day of hospitalization.100% patients had good recovery.

Conclusions: Maximum prevalence of dengue was in young, in males and in rainy season. Thrombcytopenia, leucopenia, hepatomegaly, raised liver enzymes-aspartate aminotransferase (AST) and alanine aminotransferase (ALT), pericholecystic oedema are prima facie of dengue. Prompt diagnosis and immediate specific treatment with maintenance of platelet count and haemostatic function gives good recovery.

Keywords: Dengue, Hepatomegaly, Leucopenia, Petechiae, Thrombocytopenia

INTRODUCTION

There is clear evidence that the world's climate is changing and that global warming (whatever the cause) is a real phenomenon. There has been much interest in the impact this change will have on the distribution of diseases, particularly vector-borne diseases. Projections for the future spread of dengue using conservative predictions of changes in humidity and population suggest that 4.1 billion people (44% of world's population) will be at risk of dengue by 2055.[1] World Health Organization (WHO) estimates that 50-100 million Dengue infections occur every year with 22000 deaths.[2] It has been identified as one of the 17 neglected

tropical diseases by WHO.[3] The emergence and spread of all four dengue viruses ("serotypes") represent a global pandemic.

The epidemiology of dengue is an intricate phenomenon which depends upon a complex relationship between epidemiological factors viz., host (man and mosquito), agent (virus) and the environment (abiotic and biotic factors).[4] The causative agent dengue virus belongs to genus *Flavivirus* of the family *Flaviviridae*. Dengue virus is a positive-stranded encapsulated RNA virus. The dengue virus genome is composed of three structural protein genes encoding the nucleocapsid of core protein (C), a membrane associated protein (M), an envelope protein (E) and seven non-structural (NS) proteins- NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5.[4] Dengue fever and dengue hemorrhagic fever are caused by four antigenically related dengue viruses 1, 2, 3 and 4.[6] All four viruses have *Aedes aegypti* as their principal vector.[5] The complexity of relationship amongst these factors eventually determines the level of endemicity in an area. During interepidemic period, the transmission of dengue remains low due to extremes of temperature with low relative humidity but during monsoon the environment becomes suitable for vectors, temperature between 25° C and 30° C relative humidity around 80% and innumerable small water collections resulting in high vector density.[4]

All four serotypes have long been endemic in Asia. Co-circulation of several serotypes of dengue virus has resulted in concurrent infection in some patients with multiple serotypes of DV.[7] Infection with any one serotype confers lifelong immunity to that virus serotype.[6] The four dengue virus serotypes can co-circulate in the endemic area because the immunity to one serotype does not protect from the infection by a heterotopous serotype.[4]

Classic dengue fever (break bone fever) is an acute self-limited illness with diphasic fever, headache, arthralgia, myalgia, rash, lymphadenopathy and leukopenia caused by four distinct serotypes of dengue virus, a mosquito-borne *Flavivirus*. DHF is distinguished from classic dengue by haemorrhagic manifestations, thrombo-cytopenia with concurrent hemoconcentration and in severe cases, circulatory failure, shock(dengue shock syndrome), and death in a proportion of cases.[7] The induction of vascular permeability and shock depends on multiple factors such as presence or absence of enhancing and non-neutralizing antibodies, age (susceptibility to severe dengue drops considerably after 12 years of age), sex (females are more often affected than males), race (whites are more often affected than blacks), nutritional status (malnutrition is protective), or sequence of infections (e.g. dengue virus 1 infection followed by dengue virus 2 infection seems to be more dangerous than dengue virus 4 followed by dengue virus 2 infection). [5]

The key to control of both dengue and severe dengue is the control of *A. aegypti*. Control effects have been handicapped by the presence of non-degradable tires and long-lived plastic containers in trash repositories (perfect breeding grounds when filled with water during rainfall) and by insecticide resistance.[5] Although the true impact of dengue is difficult to measure owing to inadequate disease surveillance, lack of diagnostic facilities and poor reporting; the burden of dengue is expected to further rise due to globalization, increase in travel and trade, global warming and lack of vaccine and specific antiviral therapy.[8]

METHODS

This retrospective study was conducted on patients admitted in PDUMC and Civil hospital, Rajkot, Gujarat, India from 1st January 2015 to 31st December 2015. Patients for this study were selected from hospital records based on inclusion and exclusion criteria. All new patients above 12 years of age, Dengue IgM Ab test and/or Dengue NS1 Ag test positive cases irrespective of clinical presentation and all clinically stable and complicated dengue cases were included in the study. Exclusion criteria were patients with age less than 12 years, pyrexia with/without thrombocytopenia due to other causes. Complete history, clinical findings and investigations as noted in the medical record were analyzed statistically. Mean value and ±SD were calculated for each group and compared with other studies. P value <0.001 was taken as a point of minimal statistical significance.

RESULTS

During the period of 1st January 2015 to 31st December 2015, 369 patients were included in the study.

Age and sex distribution

Out of 369 patients of dengue, 259 were males and 110 were females. Males were affected more than females in present study. Patients of 12 to 30 years of age were affected the most (300, 81.30%) followed by 30 to 40 years of age group (33, 8.94%), 40 to 50 years of age group (19, 5.14%), 50 to 60 year group (12, 3.25%), 60-70 year group (2, 0.54%) and more than 70 year age group (3, 0.81%) as given in Table 1.

Effect of seasonal variation on incidence of dengue

In the present study, 322(87.26%) of 369 cases of Dengue were seen during monsoon and post-monsoon season (September to November) as presented in Table 1 and Figure 1.

Clinical profile

In the present study, symptoms observed in descending order of frequency were: fever (369), headache (273,

73.98%), bodyache (265, 71.81%), backache (129, 34.95%), vomiting (114, 30.89%), nausea (105, 28.45%), Retro-orbital pain (96, 26.01%), joint pain (76, 20.59%), abdominal pain (53, 14.36%), breathlessness (44, 11.92%), loose motion (19, 5.14%), giddiness (11, 2.98%), decreased urine output (7, 1.89%), altered sensorium (4, 1.08%), convulsion (1, 0.27%). Bleeding manifestations were mentioned separately with corresponding frequency under the heading of platelet count and bleeding manifestations. Mean duration of fever prior to hospitalization was 5.06 ± 1.70 days.

Table 1: Demographic profile of dengue fever.

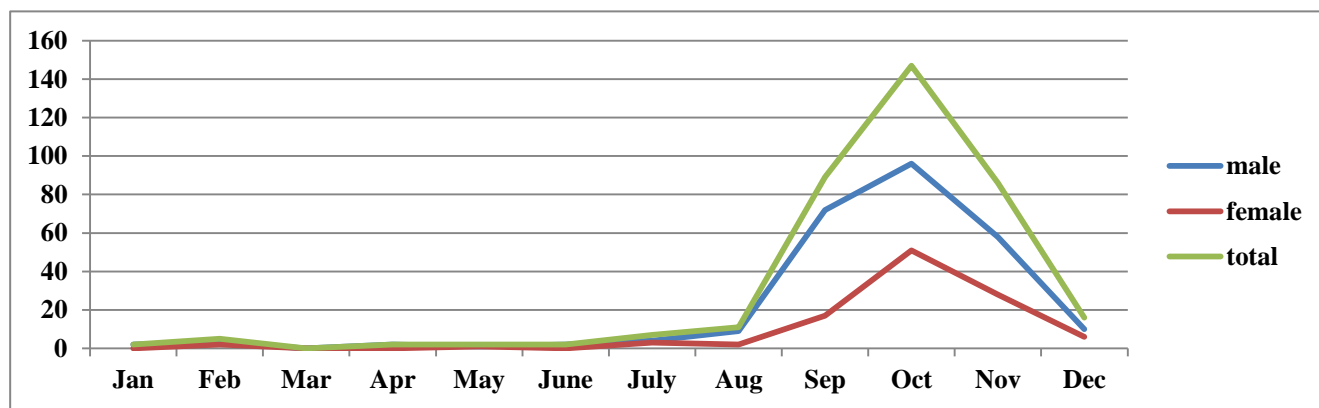| Month	12-20 years		21-30 years		31-40 years		41-50 years		51-60 years		61-70 years		>70 years		Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
January	1		1												2
February	1		1	1			1			1					5
March															0
April	1				1										2
May	1					1									2
June			1				1								2
July	1	2	1	1					1				1		7
August	1		7		1	2									11
September	33	7	25	4	7	4	4	2	3						89
October	45	15	39	25	7	5	3	3	1	2		1		1	147
November	29	10	21	13	3	1	1	3	3	1	1				86
December	2	1	6	4	1			1						1	16
	115	35	102	48	20	13	10	9	8	4	1	1	3		369

Figure 1: Seasonal trend in dengue fever (2015).

Radiological profile

In the present study, positive findings on ultrasonography of chest, abdomen and pelvis were : pericholecystic oedema 178 (48.23%), distended GB 141 (38.21%), GB collapse 72 (19.51%), splenomegaly 82 (22.22%), hepatomegaly 247 (66.93%), fatty changes 35 (9.48%), ascites 45 (12.19%), fluid in Morrison's pouch 8 (2.16%), pleural effusion 39 (10.56%) and perirenal thin strip of collection 7 (1.89%) as shown in Table 2.

Platelet count and bleeding manifestations

As in Table 3 and Figure 2, in the present study, dengue fever was presented with thrombocytopenia on admission in 342 (92.68%) cases. Mean Nadir of platelet count was on 6.83±1.47 day from onset of illness (1st symptom - fever) and 1.77±0.89 day of hospitalization. 158 of 369 patients, presented with or developed bleeding manifestations. Petechiae were seen in 118 patients as a major bleeding manifestation followed by epistaxis (12), gum bleeding (8), melena (8), bleeding per rectum (4), hemoptysis (3), hematemesis (2), subconjunctival

haemorrhage (2) and hematuria (1). Petechiae, gum bleeding, epistaxis, hematemesis, hemoptysis, bleeding per rectum, hematuria, melena, subconjunctival hemorrhage occured at an average platelet count (mean in 10^3) of 31000/mm^3, 16000/mm^3, 20000/mm^3, 21000/mm^3, 35000/mm^3, 28000/mm^3, 9000/mm^3, 34000/mm^3, 44000/mm^3 respectively.

Table 2: Ultrasonographic findings of the study population comparision between present study and Mia et al study.

	Present study (369)	Mia et al study (100)
Sonographic characteristics	No. of patients (%)	No. of patients (%)
Pericholecystic oedema	178 (48.23)	Thickened GB wall 38 (38) Pericholecystic fluid 2 (2)
GB distended	141 (38.21)	
GB collapse	72 (19.51)	
Hepatomegaly	247 (66.93)	54 (54)
Fatty changes of liver	35 (9.48)	-------
Hepatic intraparenchymal fluid	-------	2 (2)
Spleenomegaly	82 (22.22)	18 (18)
Splenic subcapsular fluid	-------	3 (3)
Pancreatic enlargement	-------	11 (11)
Peripancreatic fluid	-------	1 (1)
Peri-renal fluid collection	7 (1.89)	15 (15)
Ascites	45 (12.19)	41 (41)
Fluid in morrison's pouch	8 (2.16)	-------
Pleural effusion	39 (10.56)	42 (42)
Pericardial effusion	-------	6 (6)

Table 3: Correlation of bleeding manifestation with platelet count and statistical analysis in dengue fever.

Bleeding manifestation	Platelet count/mm^3			Total
	<20000/mm^3	20000-50000/mm^3	50000-150000/mm^3	
Petechiae	41 (69.49%)	56 (78.87%)	21(75%)	118 (74.68%)
Subconjunctival hemorrhage	0	1 (1.40%)	1 (3.57%)	2 (1.26%)
Gum bleeding	6 (10.16%)	2 (2.81%)	0	8 (5.06%)
Hematuria	1 (1.69%)	0	0	1 (0.63%)
Bleeding per rectum	1 (1.69%)	2 (2.81%)	1 (3.57%)	4 (2.53%)
Hemoptysis	1 (1.69%)	1 (1.40%)	1 (3.57%)	3 (1.89%)
Hematemesis	1 (1.69%)	1 (1.40%)	0	2 (1.26%)
Melena	3 (5.08%)	2 (2.81%)	3 (10.71%)	8 (5.06%)
Epistaxis	5 (8.47%)	6 (8.45%)	1 (3.57%)	12 (7.59%)
Total	**59**	**71**	**28**	**158**
*platelet count <20000/mm^3, 20000-50000/mm^3, 50000-150000/mm^3 were labelled as group A, B and C respectively				
	A	**B**	**C**	**Total**
Bleeding manifestation	59 (96.72%)	71 (60.16%)	28 (14.73%)	158 (42.81%)
No bleeding	2	47	162	211
Total	**61**	**118**	**190**	**369**

**platelet count <20000/mm^3, 20000-50000/mm^3, 50000-150000/mm^3 were labelled as group A, B and C for statistical analysis. Chi square value=148.092, p value<0.0001, degree of freedom (df) =2 indicates significant difference between all the 3(A, B and C) groups. Chi square value (A vs B+C) =86.725, p value<0.0001, df= 1 indicates strong association of occurrence of bleeding at platelet count <20000/mm^3.

Hematological and biochemical profile

In the present study, the following patterns were observed in the haematological and biochemical profile: pancytopenia (23, 6.23%), bicytopenia (252, 68.29%) and thrombocytopenia (342, 92.68%). Mean haemoglobin (12.89), mean hematocrit (39.58), hematocrit >44 (43, 11.65%), mean total leucocyte count (on admission 5481.57 and on nadir 4974.58), mean platelet count (on admission 78679.13 and on nadir 52769.65), leucopenia (215/369, 58.26% on admission), raised liver enzymes-AST, ALT (295,79.94%), altered renal function tests (blood urea, serum creatinine) (19, 5.14%) were observed as in Table 4,5 and Figure 3,4.
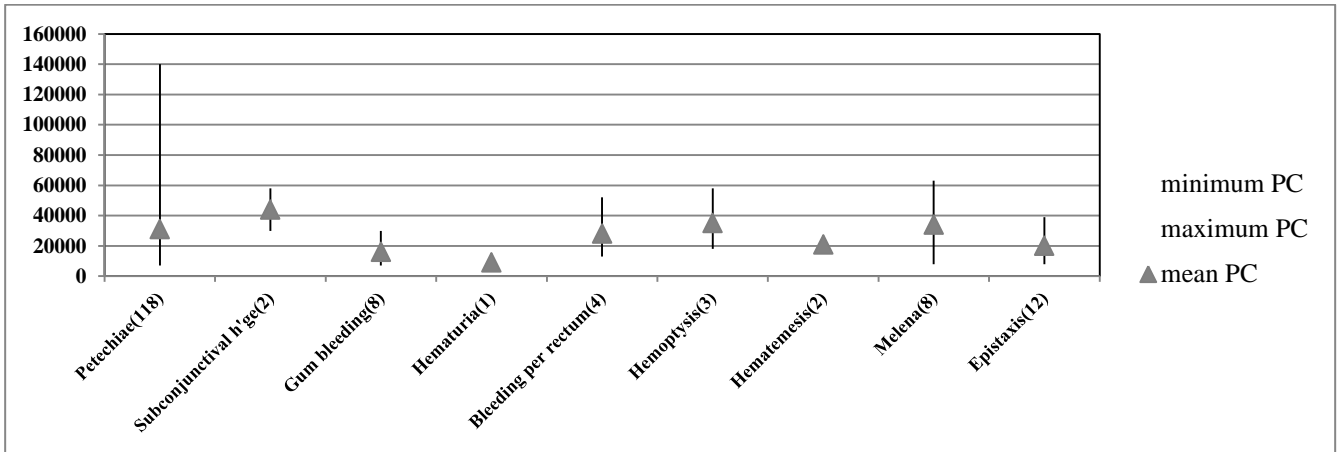
PET=petechiae, SCH=subconjunctival hemorrhage, GB=gum bleeding, HU=hematuria, BPR=bleeding per rectum, HPT=hemoptysis, HTM=hematemesis, M=melena, EPT = epistaxis. Figure in parenthesis indicate frequency of bleeding manifestation in present study.

Figure 2: Spectrum of bleeding manifestation with maximum, minimum and mean platelet count in dengue.

Table 4: Platelet count (PC) on admission and nadir.

Platelet count (PC)	On admission (PC2)	Nadir (PC1)
<20000	15	61
20-50000	75	118
>50000	279	190
Total	**369**	**369**
Mean ±SD	78679.13±34858.93	52769.65±35657.92

Paired t-test: t = (-) 22.637, df 368, Sig. (2 tailed) 0.000, p <0.001 indicates statistically significant difference between two groups on admission and nadir
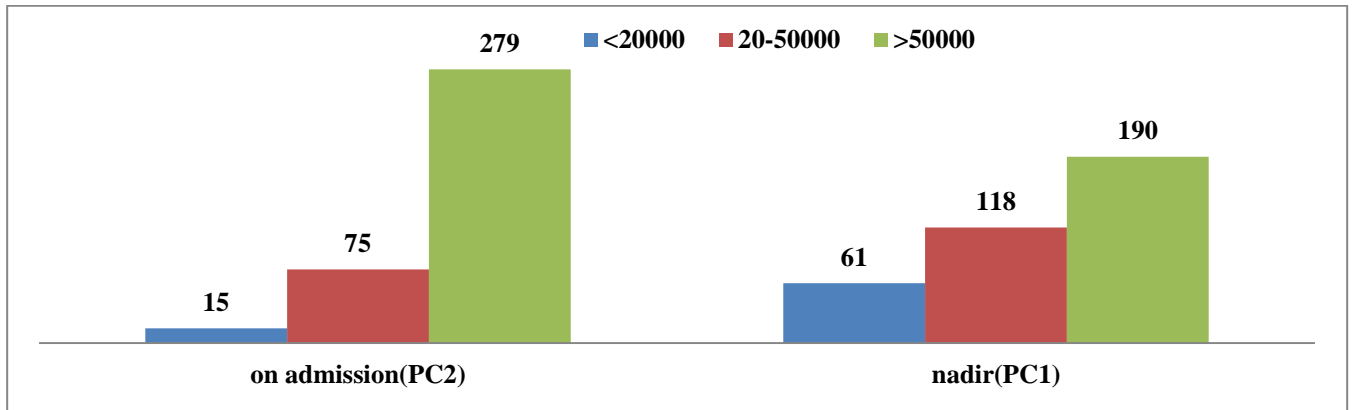

Figure 3: Platelet count (PC) on admission and nadir.

Table 5: Total leucocyte count (TLC) on admission and nadir.

Total leucocyte count (TLC)	On admission (TC2)	Nadir (TC1)
<3000	52	73
3000-4000	72	85
4000-5000	91	78
>5000	154	133
Total	369	369
Mean±SD	5481.57±3129.94	4974.58±2743.32

Paired t-test: t= (-) 4.720, df 368, Sig.(2 tailed) 0.000, p<0.001 indicates statistically significant difference between two groups on admission and nadir
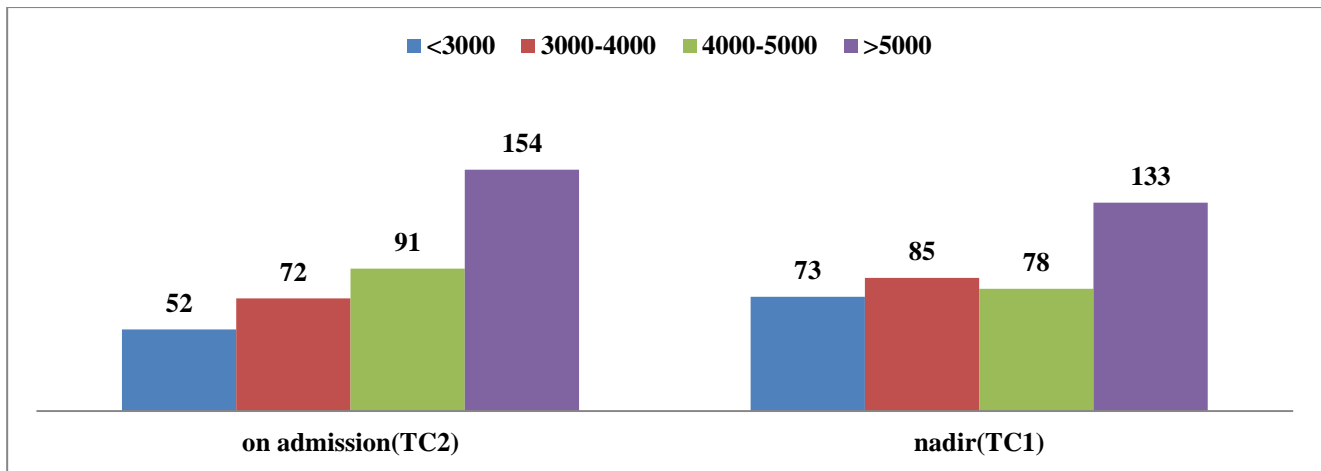
Figure 4: Total leucocyte count (TLC) on admission and nadir.

Outcome

In present study, no mortality was recorded in dengue fever in 2015. All the patients had good recovery.

DISCUSSION

During the period of 1st January 2015 to 31st December 2015, 369 patients admitted to PDUMC and Civil hospital, Rajkot were included in this study.

Out of 369 patients of dengue, 259 were males and 110 were females. Males (259) were affected more than females (110) in the present study with ratio of 2.35:1. Similar observation was made by others (2.67:1 in Deshwal et al, 2.07:1 in Patil et al, 1.8:1 in Kumar et al, 1.7:1 in Kauser et al) showed increased preponderance among males due to increased outdoor activities of male and more exposure to the environment causing dengue.[9-12] Patients of 12 to 30 years of age were affected the most (300,81.30%) as given in Table 1 as also observed by Patil et al (73.01% in <30 years group), Sharma et al (65.81% in 11-30 years patients), Parmar et al (76%).[10,13,14] Monthly-based analysis of data was done to identify seasonal pattern of disease. In the present study, 322 (87.26%) of 369 cases of dengue were seen during rainy season (September to November). The increased occurrence of dengue cases in the monsoon season is evident in this study and is further supported by Kumar et al, Kausher et al, Sharma et al, as well as studies from Kerala, Ludhiana and Karachi.[11-13,15-17] These findings suggest that preventive measures against dengue should start well before the monsoon and continue till the end of the season. A rise in number of cases was observed from the month of July, with 92.68% (342) cases occurring in between June and November, which corresponds to monsoon and post-monsoon season in our country as in Table 1 and Figure 1. The mosquito breeding was maximum during this period due to abundance of water bodies. Wongkoon et al have described seasonal pattern of dengue which corresponds with the rainy season due to abundance of mosquito breeding in this season.[18] Every year during the period of July-November, an upsurge in the cases of dengue/DHF has been observed. The disease has a seasonal pattern i.e., the cases peak after monsoon and it is not uniformly distributed throughout the year.[4]

In present study, fever is universal. Mean duration of fever prior to hospitalization was 5.06±1.70 days as compared to 5.2±1.5 days in Singapore 1992 study.[19] Fever (369, 100%) and headache (273, 73.98%) were the two most common clinical presentations on admission in present study as well as in studies of Deshwal et al, Mandal et al, Daniel et al.[9,20,21] Other symptoms observed in descending order of frequency were: bodyache (265, 71.81%), backache (129, 34.95%), vomiting (114, 30.89%), nausea (105, 28.45%), retro-orbital pain (96, 26.01%), joint pain (76, 20.59%) mainly.

In the present study, positive findings on ultrasonography of chest, abdomen and pelvis are : pericholecystic oedema 178 (48.23%), distended GB 141 (38.21%), GB collapse 72 (19.51%), spleenomegaly 82 (22.22%), hepatomegaly 247 (66.93%), fatty changes 35 (9.48%), ascites 45 (12.19%), fluid in Morrison's pouch 8 (2.16%), pleural effusion 39 (10.56%) and perirenal thin strip of collection 7 (1.89%) in comparision to Mia et al study (Bangladesh study) in which ultrasonographic findings of thickened GB wall, hepatomegaly, spleenomegaly, perirenal fluid collection, pleural effusion, ascites occurred at a frequency of 38%, 54%, 18%, 15%, 42%, 41% respectively.[22] Pericholecystic oedema (48.23%) was a common sonographic characteristic reported in present study as in Table 2.

In present study, raised liver enzymes (AST, ALT) were reported in (295) 79.94% of cases in comparison with Kularatne et al study (88%), Karoli et al (92%).[23,26] Kuo et al (Taiwan study), Nimmagadda et al reported raised AST at frequency of 93.3%,92.7% and raised ALT at

82.2%,85.3% respectively.[24,25] Involvement of liver in the pathobiology of dengue virus infection of human as concluded by Smith et al is supported by present study (raised liver enzymes AST, ALT in (295) 79.94% , hepatomegaly in (247) 66.93%.[27]

In the present study, leucopenia on admission (215, 58.26%) is also a feature of dengue infection and is felt to be related to bone marrow suppression.[28] The observed mean total leucocyte count on admission was 5481.57 ± 3129.94 and on nadir was 4974.58 ± 2743.32. Paired t-test of two groups TC2 (total leucocyte count on admission) and TC1 (total leucocyte count nadir) with results of t= (-) 4.720, degree of freedom (df) 368, Sig (2 tailed) 0.000, p <0.001 indicates significant difference between the concerned groups statistically as seen in Figure 4 with Table 5.

Thrombocytopenia was present in 342/369 (92.68%)of cases on admission, this finding was consistent with observations made by Daniel et al study (90%), Karoli et al (89%), Varsarani et al (90.53%), Tejushree et al (88%).[20,26,2,9,30] Dengue causes thrombocytopenia by destruction of platelet (antiplatelet antibodies), DIC, bone marrow suppression, peripheral sequestration of platelets.[4] The observed mean platelet count on admission was 78679.13 ± 34858.93 and on nadir was 52769.65 ± 35657.92. Mean Nadir of platelet count was observed on day 6.83±1.47 from onset of illness (1st symptom-fever) in dengue as compared to 6.4±1.6 in Singapore (1992) study.[23] Paired t-test of two groups PC2 (Platelet count on admission) and PC1 (Platelet count nadir) with results of t= (-) 22.637, degree of freedom (df) 368, Sig (2 tailed) 0.000, p <0.001 indicates significant difference between the concerned groups statistically as in Figure 3 with Table 4.

In present study, bleeding manifestations were reported in158 (42.81%) cases. Similar observations were reported by Mittal et al (48.8%).[31] While Kumar et al, Mandal et al, Karoli et al reported bleeding manifestations in 26.6%, 11.48%, 40% respectively. In present study, petechiae was the major bleeding manifestation (74.68%) followed by spontaneous bleeding (25.31%) which was consistent with Kumar et al study and Varsharani et al study.[11,29] When bleeding due to thrombocytopenia does occur, it usually begins in the skin or mucous membranes.[32]

A platelet count of approximately 5000-10000/microL is required to maintain vascular integrity in the microcirculation. When the count is markedly decreased, petechiae first appear in areas of increased venous pressure, the ankle and feet in an ambulatory patient. Petechiae are pinpoint, non-blanching haemorrhages and are usually a sign of decreased platelet number and not platelet dysfunction.[33] Petechiae, gum bleeding, epistaxis, hematemesis, hemoptysis, bleeding per rectum, hematuria, melena and subconjunctival hemorrhage occurred at an average platelet count (mean in 10^3) of 31000/mm^3, 16000/mm^3, 20000/mm^3, 21000/mm^3, 35000/mm^3, 28000/mm^3, 9000/mm^3, 34000/mm^3, 44000/mm^3 respectively. Platelet count <20000/mm^3, 20000-50000/mm^3, 50000-150000/mm^3 were labelled as group A, B and C for statistical analysis. Chi square value=148.092, p value <0.0001, degree of freedom (df) 2 indicates significant difference between all the 3 (A, B and C) groups. Chi square value (A vs B+C) =86.725, p value <0.0001, degree of freedom df =1 indicates strong association of occurrence of bleeding at platelet count <20000/mm^3.

The risk of bleeding increases exponentially as the platelet count falls below 20000/microL, at which point patient may begin to complain of easy bruisability. Spontaneous bruising and petechiae, generally starting in dependant areas, gingival bleeding after bruising, menorrhagia and epistaxis become progressively more common if the platelet count falls below 10000 to 20000/microL. Spontaneous bleeding is rare at platelet counts above 30000/microL. Bleeding may occur at higher platelet counts when qualitative platelet defects, such as those caused by medication that impair platelet function, have been superimposed or when underlying anatomic defects that predispose to bleeding are present.[31] Figure 2 with Table-3 indicates bleeding manifestations reported at varied platelet count in present study. Causes of bleeding in DF/DHF are abnormal coagulogram, thrombocytopenia, platelet dysfunction, prothrombin complex deficiency secondary to liver involvement, endothelial cellular injury, DIC and prolonged aPTT, decreased fibrinogen level, increased level of FDP, increased level of D-dimer, consumptive coagulopathy(activation of mononuclear phagocytes), sequestration of platelets.[4]

CONCLUSION

Maximum prevalence of dengue is in young, in males, in rainy season with summative effect of endemicity of disease in particular geographical region. Young population bears greater burden of disease with increased magnitude in monsoon and post-monsoon period.

Thrombocytopenia, leucopenia (hematological profile), hepatomegaly (clinical and radiological profile), Raised liver enzymes (biochemical profile), pericholecystic oedema (radiological profile) are prima facie of dengue, and constitute immense value as indicators for provisional diagnosis of dengue, individually or in combination. Although bleeding manifestations can occur at varied platelet counts in dengue due to multiple mechanisms, risk of bleeding increases when platelet count decreases below 20000.

There is no absolute relationship between platelet count and severity of bleeding. Thrombocytopenia has no correlation to mortality and morbidity. Prompt diagnosis and immediate specific treatment with maintenance of platelet count and hemostatic function gives good recovery.

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