"To evaluate the outcome of thrombocytopenia with Dengue Fever"

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Abstract: Despite considerable efforts to control the mosquito populations, dengue fever has emerged, spread and established itself rapidly. The most serious manifestations of the infection are Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Though thrombocytopenia is a distinctive characteristic of dengue, few studies have related thrombocytopenia with its clinical severity. Our research aims to study the clinical profile of patients presenting Dengue fever with thrombocytopenia & to study the outcome of patients with respect to severity of thrombocytopenia in Dengue fever and associated co morbid medical conditions. After taking informed consent, data regarding history, examination & investigations were noted & analysed further. Out of enrolled 127 patients 89(70.08%) patients were male and 38 (29.92%) were females. Mean age of presentation was 26.20 ± 10.92 years. Bleeding Tendency was present in 26 (20.47%) patients .   Other complication like Hepatic failure in 7 (5.51 %) patients, Renal failure in 12 (9.44 %) patients , acute respiratory distress syndrome (ARDS) in 9 (7.08%) of patients & Multi Organ Dysfunction Syndrome (MODS)   was observed in 7 (5.51 %) patients . Overall 7 (5.51%) patients died during ward stay of which MODS with disseminated intravascular coagulation (DIC) (71%) was the commonest cause of death followed by ARDS. In conclusion , Severe thrombocytopenia was found to be associated with shock, bleeding tendency, anaemia, renal failure, severe hepatic involvement and ARDS to a significant extent. (Key Words - Thrombocytopenia , Dengue Fever)

I.   INTRODUCTION

"Dengue is one disease caused by an arthropod borne virus with complex clinical presentations and often with unpredictable clinical evolution and outcome, yet management is relatively simple, inexpensive and very effective in saving lives so long as correct and timely interventions are instituted." [1]
While most patients recover following a self-limiting, which may be asymptomatic (50-90%),[2] or result in a nonspecific febrile illness. A small proportion progress to severe disease, mostly characterized by plasma leakage with or without haemorrhage, leading to mortality in approximately 1–5% cases. The fatality rate is less than 1% with adequate treatment; however those who develop shock, may have a fatality rate of up to 26%.[3] A WHO/TDR-supported prospective clinical multicentre study across dengue-endemic regions has classified dengue into levels of severity. By using a set of clinical and/or laboratory parameters, one sees a clear-cut difference between patients with severe dengue and those with non-severe dengue.[1]
1] Non-severe dengue further divided into two subgroups -- patients with warning signs and those without them.
2] Severe dengue characterized by plasma leakage, bleeding or severe organ impairment.
        Of all the complications, bleeding in dengue is one of the dreaded complications and is associated with higher mortality in dengue haemorrhagic fever (DHF)/Dengue shock syndrome (DSS). Factors like degree of disseminated intravascular coagulation (DIC), hepatic derangement and thrombocytopenia act synergistically to cause bleeding in dengue patient[4]. Though thrombocytopenia is a distinctive characteristic of dengue, few studies have related thrombocytopenia with its clinical severity. Platelet transfusion is given in those patients who is either bleeding or having other haemorrhagic symptoms along with thrombocytopenia. [5][6] The aim of our study was to show the relationship between thrombocytopenia and clinical outcome in terms of both morbidity and mortality.

Objectives
1] The primary objective of this prospective cross-sectional study was to study the clinical profile of patients presenting with thrombocytopenia in Dengue fever & complications in patients with Dengue fever and thrombocytopenia.
2] The secondary objective was to study the outcome of patients with respect to severity of thrombocytopenia in Dengue fever and associated co morbid medical conditions.

II . MATERIAL AND METHODS

This study was conducted in a tertiary care centre in Mumbai over 12 months after obtaining approval from the Institutional Ethics Committee. 127 patients of Dengue with thrombocytopenia were enrolled in this study based on the inclusion & exclusion criteria. Once all the criteria were satisfied, a written informed consent was taken and the patient was included in the study. Clinical data was collected through interviewing the patients or their attendants and meticulous physical examination of the patients . Reports of haematological investigations, dengue serology, imaging, platelet requirements and data obtained from daily follow-up were analysed.

Based on the platelet count, patients were classified as[7-9]

Mild : Platelet count between 50,000 to 1,00,00;

Moderate : Platelet count between 20,000 to 50,000;

Severe : Platelet count less than 20,000. Patients were followed till discharge or death .

Inclusion criteria

All patients with age >12 year diagnosed to have clinical and serologic (positive IgM or NS1 Antigen) diagnosis of dengue with platelet count less than 1,00,000 were included.

Exclusion criteria

i) Patients diagnosed to have Dengue fever with platelet count greater than 1,00,000.

ii) Patients with thrombocytopenia of aetiology other than Dengue fever .

iii)Patients with mixed infections were excluded from the studies.

Data Analysis

Data was analysed using statistical software SPSS version 20. Tests applied were z test of proportion and chi square test. p value of < 0.05 was considered significant at 95% confidence level.The results were statistically analysed, compared with previous studies and conclusions derived appropriately.

III . RESULT

Figure 1 : Pie chart depicting gender wise distribution of cases of dengue fever (n = 127)

Figure 2 : Bar diagram showing age wise distribution of cases of dengue fever (n = 127)

Figure 3 : Symptoms In Descending Order Of Frequency

Figure 4 : Bleeding Symptoms In Order Of Frequency.

Figure 5 : Platelet count and bleeding tendency in cases of dengue fever.

Figure 6 : Organ system involvement among the cases with dengue fever

Out of the 127 patients with dengue fever, 70.08% (89) of patients were males and 29.92%(38) were females (Figure 1) . Mean age of presentation was 26.20 ± 10.92 years. Majority of the patients were from the third decade (50), followed by the second decade(38), contributing to 69.29% of cases (Figure 2). In this study, varied complications were known to occur in patients having dengue with thrombocytopenia during its clinical course. Of the 127patients in this study, Bleeding diathesis was present in 20.47% (n=26) of patients (Figure3). Among the patients with bleeding tendency, petechiae (n=17) and occult gastrointestinal bleed(n=16) were most common which was followed by haematuria (n=15). One patient had intracranial bleed secondary to thrombocytopenia (Figure 4).

Figure 7 : Case fatality and aetiology of death in patients with dengue & Gender wise outcome of patients with dengue fever.

| Hemoglobin	Discharge	Death
< 10 (N=10)	6 (60)	4 (40)
10 - 16 (N=101)	98 (97.02)	3 (2.97)
> 16 g (N=16)	16 (100))	0

Mortality was seen in 40% cases with Hemoglobin < 10g% (p<0.0001)
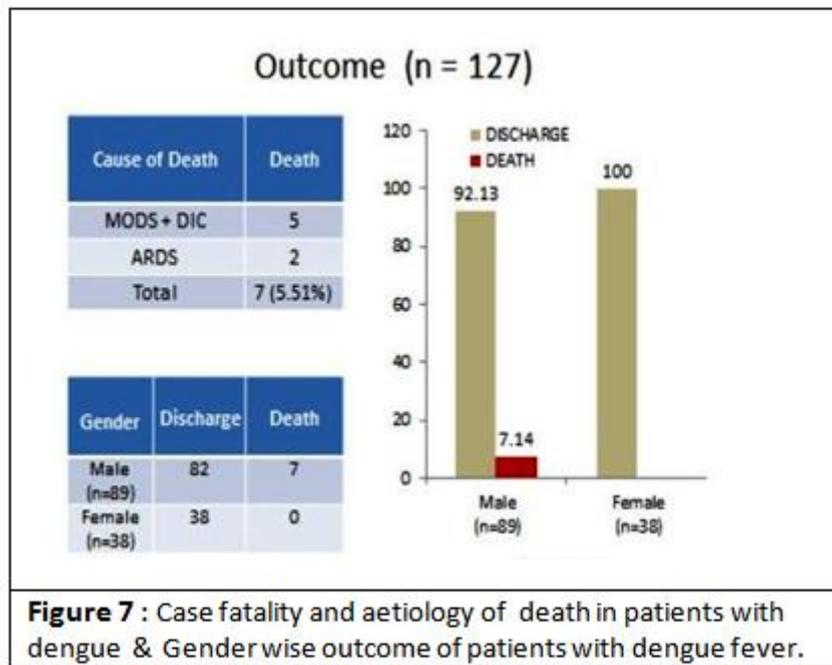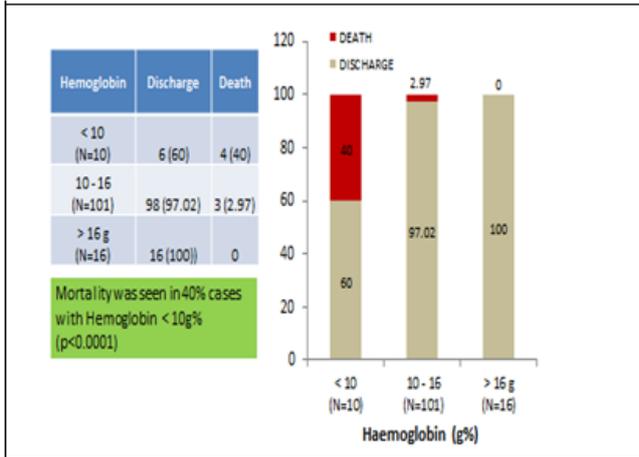
Figure 8 : Relation of Haemoglobin to prognosis

Platelet Count	Discharge	Death
< 20000 N=11	7	4 (36.36%)
20000 - <50000 N=46	44	2 (4.34%)
50000 - 100000 N=70	69	1 (1.42%)

Mortality was more in cases with platelet count less than 20000 (36.3%) (p<0.0001)
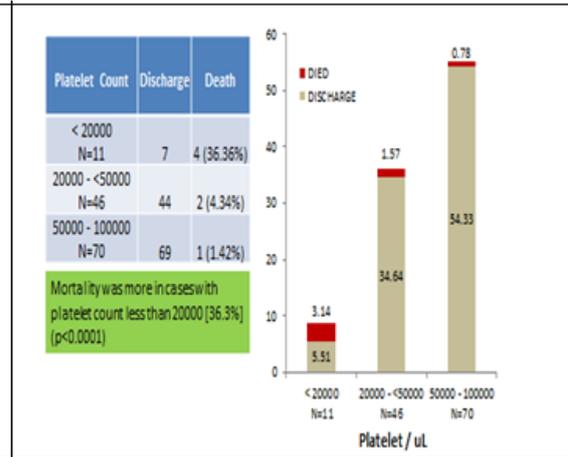
Figure 9 : Relation of platelet count to prognosis

Platelet Count	Leucko Cytosis	Normal	Leucko Cytopenia
< 20000 N=11	3 (27.27)	4 (36.36)	4 (36.36)
20000 - <50000 N=46	0	20 (43.47)	26 (56.52)
50000 - 100000 N=70	1 (1.42)	29 (41.42)	40 (57.14)

Leucocytopenia was seen in all class of thrombocytopenia (p=0.71)
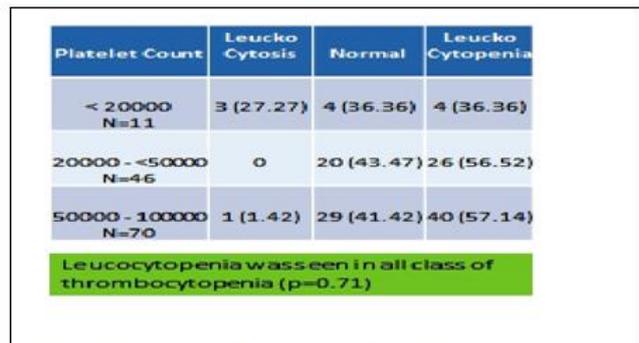
Figure 10: Relation of TLC and platelet count among the cases with dengue fever.

TLC (/uL)	percentage
< 1500	0
1500 – <2500	23 (18.11)
2500 – <4000	49 (38.58)
4000 – <11000	52 (40.94)
≥ 11000	4 (3.14)
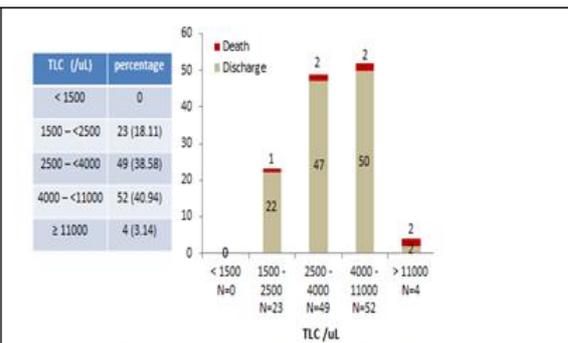
Figure 11: Relation of Total Leucocyte count to prognosis.

Platelet Count	Creat > 3	Creat 1.5 - 3	Creat < 1.5
< 20000 N=11	45.45	0	54.54
20000 - <50000 N=46	4.34	8.69	86.95
50000 - 100000 N=70	0	1.42	98.57

Serum Creatinine >3mg/dL was significantly more common in subjects with platelet counts < 20000 (p<0.001)
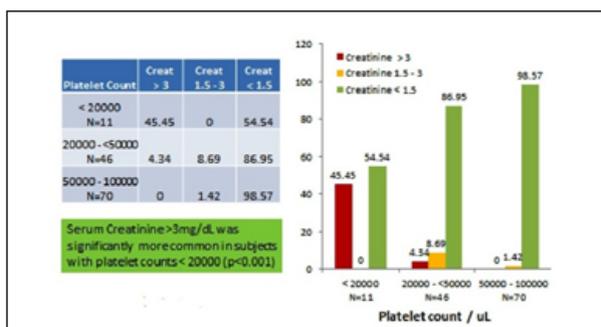
Figure 12: Relation of renal function and platelet count among the cases with dengue fever

Creatinine	Discharge	Death
< 1.5 (N=115)	113 (88.9)	2 (1.57)
1.5 -3 (N=4)	4 (3.14)	0
> 3 (N=8)	4 (3.14)	4 (3.14)
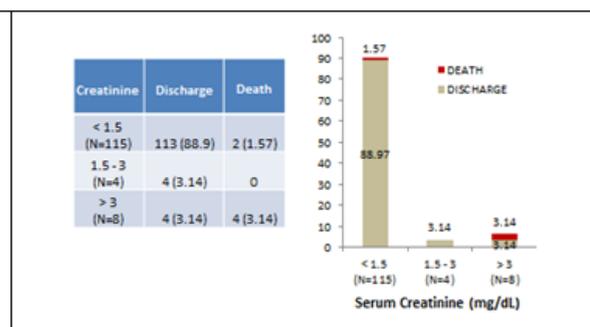
Figure 13 : Relation of renal function to prognosis

SGPT (IU/uL)	Discharge	Died
< 45 (N=48)	46	2 (4.16%)
45 - <200 (N=42)	41	1 (2.38%)
200 - <1000 (N=33)	32	1 (3.03%)
1000 - <2000 (N=2)	1	1 (50%)
≥ 2000 (N=2)	0	2 (100%)
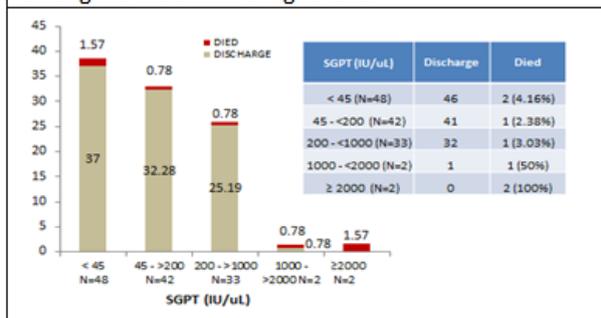
Figure 14 : Relation of Liver function (SGPT) to prognosis

Bilirubin	Discharge	Death
< 1.5 (N=107)	105	2 (1.86%)
1.5 -3 (N=12)	12	0
> 3 (N=8)	3	5 (62.5%)

Mortality was more common in subjects with Bilirubin > 3 mg/dL (p <0.0001)
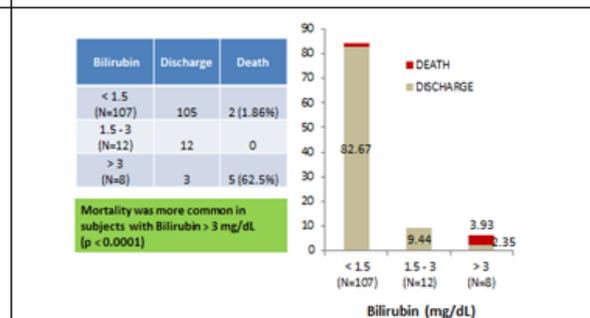
Figure 15 : Relation of bilirubin to prognosis.
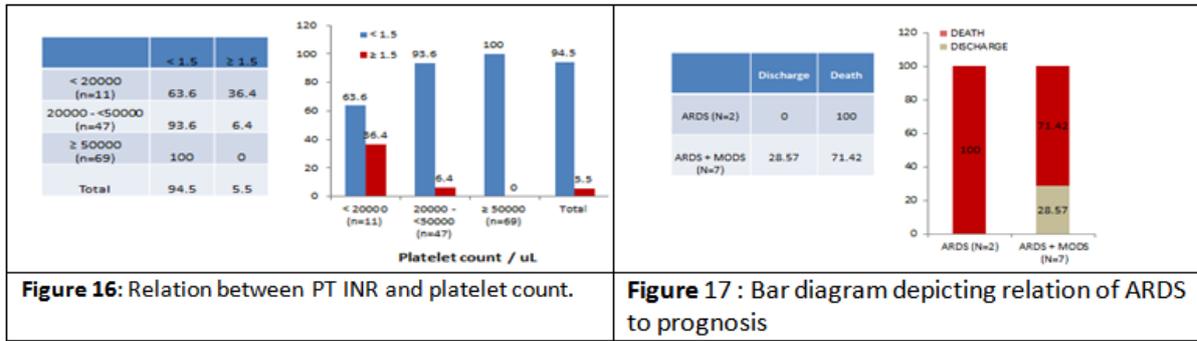
Figure 16: Relation between PT INR and platelet count.
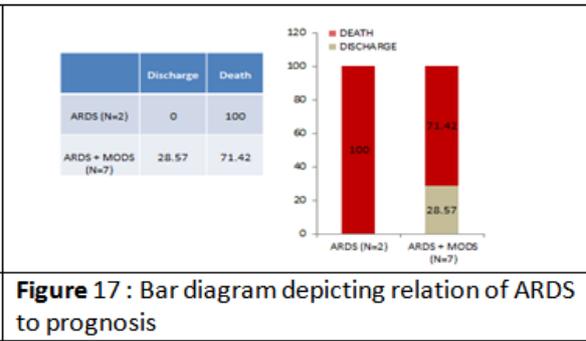
Figure 17 : Bar diagram depicting relation of ARDS to prognosis
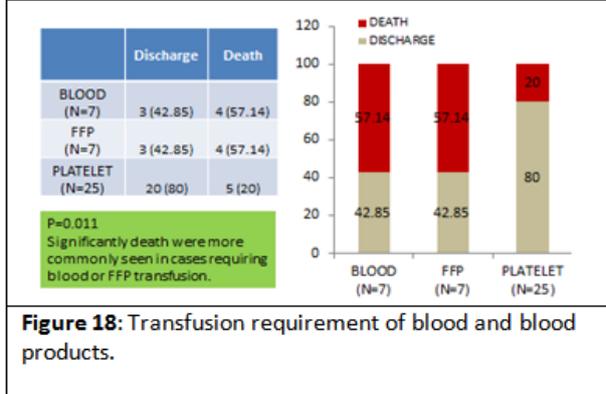
Figure 18: Transfusion requirement of blood and blood products.

Chart 1 : Comparison of mortality and survival groups in dengue infection.

Variables	Died [n=7]		Survived [n=120]		p value
	Mean	± SD	Mean	± SD	
Age	22.57	6.40	26.42	11.11	0.36
Fever Duration	5.14	1.57	4.82	1.28	0.59
Haemoglobin	9.61	3.03	13.55	2.03	<0.001
TLC	7800.00	6558.20	4086.08	1926.53	<0.001
Creatinine	4.34	2.58	1.13	0.88	<0.001
SGOT	2383.29	3456.37	231.65	401.46	<0.001
SGPT	1028.86	1195.20	108.30	176.73	<0.001
Total Bilirubin	5.08	2.11	2.31	0.83	<0.001
PT INR	4.08	1.63	1.12	0.55	<0.001

23% patients were in shock at some point of time. Out of 127 patients, 70 had mild, 46 moderate & 11 severe thrombocytopenia (Figure 5) and leukopenia was found observed in 56.69 % (n=72) of patients & lymphocytosis in 3.14% (n=4) (Figure 11) . 90.09% (10) of patients with platelet count less than 20,000 had bleeding tendency and was found to be statistically significant; while only 2.85% (2) of patients with platelet count greater than 50,000 had bleeding tendency (Figure 5). In our study, 5.51 % of patients had MODS, Hepatic failure in 5.51 % ,Renal failure in 9.44 % of patients & ARDS was observed in 7.08% of patients (Figure 6). 7 of 9 patients had ARDS as a part of MODS. Of these 7 patients with ARDS, all 7 had concomitant renal involvement; while 6 of them had hepatic involvment as well. Other complications like acute kidney injury were noted in 9.43 % patients (n= 12) (Figure no 13), deranged liver function tests in 62.3% patients (n= 79) out of which 3.1% (n=4) of patients had severe hepatitis (SGPT > 1000 IU/L) (Figure 14) and coagulopathy (PTINR >1.5) in 5.5% (Figure 16) . Out of 26 patients with bleeding tendency, 25 patients received platelet transfusion. There was 20% morality among the group that required platelet transfusion. Higher mortality at 42.85% was observed in the group of patients who required either blood or FFP during their course of illness (Figure 18).

IV . DISCUSSION

In our study, on univariate logistic regression analysis, low haemoglobin (p<0.001), higher total leucocyte count (p<0.001), severe hepatitis (p<0.001), renal failure (p<0.001), and coagulopathy (p <0.001) were significantly associated with mortality as (Chart 1) . Similar observations were made in a study by Almas et al [11]. It was observed that overall mortality associated with dengue fever with thrombocytopenia was 5.51 % (n=7) (Figure 7).Though all patients were males, there was no significant difference between mortality among males and females. (p=0.071).Case fatality was found to be 3.2 % in the study by Daniel et al[10]. Multi organ dysfunction syndrome (MODS) (71%) was the commonest cause of death followed by acute respiratory distress syndrome (ARDS), which was found to be statistically significant (p=0.013).

There was no significant association seen between co morbid illnesses and outcome. All subjects recovered without any complications. A 40%(n=4) mortality was observed in patients with haemoglobin less than 10gm%, which was found to statistically significant (p<0.0001) (Figure 8). Fall in haemoglobin as a result of blood loss through bleeding (internal or external) with associated DIC and multi organ dysfunction are the cause of mortality. Bleeding as an independent risk factor has been shown in studies by Khan et al [12]. Similar observation noted in patients with platelet count less than 20,000,higher mortality (36.36%)(n=4) which was statistically significant (p<0.0001) (Figure 9). Leukopenia was observed in 56.6% of subjects. Higher counts were found to be more common in group with severe thrombocytopenia & was statistically significant (p<0.001). Study by Mishra et al[16] showed relationship between high TLC and poor outcome in patients with dengue.

Deranged renal function was found in 9.43 % of cases, Higher mortality was observed in cases with Serum creatinine > 3 mg/dL (p<0.001). Similar observations were made by Khalil et al [13] and Mehra et al [14]. Deranged liver function was found in 62.3% of cases. Though patients with severe hepatitis had higher mortality, no statistically significant relationship was found between deranged LFTs and the final outcome. (p=0.58). Studies by Khan et al and Mehra et al show SGPT as an independent predictor of mortality. Total bilirubin of > 3mg/dL in patients with dengue fever, was associated with higher mortality. This was found to be statistically significant. (p = 0.0001) Similar observation was made in a study by Chowdhury et al[15]. ARDS was found in 9 (7.08%) patients. In 7 (5.51%) of cases it was associated with MODS. Though two (100%) patients, who presented with only ARDS succumbed to their illness, 71% of patients with ARDS and MODS died. Mortality rate was not found to be significantly different in both groups (p=0.39). Presence of MODS and ARDS were found to be significant independent factors affecting outcome in studies by Khalil et al and Mehra et al. Out of 26 patients with bleeding tendency, 25 patients received platelet transfusion. There was 20% morality among the group that required platelet transfusion. Higher mortality at 42.85% was observed in the group of patients who required either blood or FFP during their course of illness (p=<0.011). Bleeding as an independent risk factor has been shown in studies by Khan et al and Almas et al. Platelet transfusion was done in all patients with platelet count less than 20,000 (irrespective of bleeding) and all patients with platelet count between 20,000 and 50,000 with bleeding tendencies. Bleeding was present only in 90.09% of patients with platelet count less than 20,000 and 30.43% of patients with platelet count between 20,000 and 50,000. Only 2 (2.85%) patients with platelet count greater than 50,000 had bleeding tendency.

V . CONCLUSION

In our study, Severe thrombocytopenia was found to be associated with shock, bleeding tendency, anaemia, renal failure, severe hepatic involvement and ARDS to a significant extent and low haemoglobin, higher total leucocyte count, severe hepatitis, renal failure, and coagulopathy were significantly associated with mortality. So, thrombocytopenia can be used as predictor of complications in a patient with dengue fever. So both Clinical as well as laboratory monitoring of Dengue patients for hemorrhagic manifestations and marked thrombocytopenia is strongly recommended.

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