

# Study of Hepatic Involvement and Thrombocytopenia in Dengue

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## Abstract

**Objective:** The purpose of this study was to assess the pattern of hepatic involvement and thrombocytopenia in patients with dengue fever and time taken for clinical/biochemical recovery.

**Methods:** This is a retrospective study done in a tertiary centre. A total of 1111 patients with documented dengue fever, either with NS<sub>1</sub> antigen/IgM antibody positive report who were admitted between January 2016 to December 2016. The aminotransferase levels and platelet counts were measured on day 1,4 and 7. Patients were assessed clinically on day 1,4,7 or till discharge/death accordingly.

**Conclusion:** Out of 1111 patients with dengue infection, 993 had either thrombocytopenia or hepatic involvement or both. Majority of patients with thrombocytopenia and hepatic dysfunction recovered between 4-7 days of admission i.e 53.98% and 29.20%. Statistically significant correlation of platelet count and aminotransferase levels with recovery or death of the patient was seen in our study.

## Introduction

Dengue fever was first reported by Benjamin Rush in 1780 as "break bone fever".

Dengue is an acute vector borne disease caused by flavivirus, which is a RNA virus presenting as four antigenically distinct serotypes (DENV1-4). It is transmitted by the bite of *Aedes aegypti* mosquito. The clinical spectrum varies from Asymptomatic stage, Dengue Fever (DF) and Dengue Hemorrhagic fever (DHF) and Dengue Shock syndrome (DSS).<sup>1</sup> The clinical features in symptomatic patients range from fever, arthralgia, myalgia, thrombocytopenia presenting as petechial rash, gum bleeding and bleeding from muco-cutaneous orifices to severe dengue hemorrhagic shock syndrome. Every year, 100 million people are reported to suffer from dengue fever in the tropical countries with 250,000 cases of DHF taking 24,000-25,000 lives per year.<sup>2</sup> Hepatic dysfunction and thrombocytopenia are common in dengue infection. Some of the patients have severe vomiting and dehydration which can be present due to the hepatic involvement. Mechanisms of liver injury in dengue may be due to direct effects of the

virus or host immune response on the liver cells, circulatory compromise, metabolic acidosis and/or hypoxia caused by hypotension or localized vascular leakage inside the liver.<sup>3,4</sup>

The pathogenesis of thrombocytopenia in dengue fever (DF) is not clearly understood. Increased peripheral destruction of antibody coated platelets is strongly suspected as the possible mechanism. Other modes include acute bone marrow suppression leading to a megakaryolytic condition and enhanced platelet destruction by the reticulo-endothelial system.<sup>5</sup> There are many cases of Dengue which are seen every year in Mumbai with hepatic involvement and thrombocytopenia. Hence we decided to analyse the data of patients admitted in our hospital to study the hepatic involvement and thrombocytopenia in patients of Dengue.

## Materials and Methods

The present retrospective study was conducted in Hindufriday Samrat

Balasaheb Thackeray Medical College and Dr. R N Cooper Hospital Mumbai, in accordance with the ICH/GCP guidelines of ICMR 2006. The study was approved by Institutional Ethics committee (IEC). All patients above 12 years of age, admitted in Medicine wards from 1<sup>st</sup> January 2016 to 31<sup>st</sup> December 2016 with a positive Dengue NS<sub>1</sub> antigen/IgM antibody report were enrolled in the study. Patients with incomplete indoor records, patients with hepatitis/thrombocytopenia due to any other cause like Malaria, Leptospirosis, chronic liver disease and those who had co-infection of dengue with malaria/leptospirosis, were excluded from the study. The data was collected from the available indoor papers and hence waiver of consent was granted by the IEC. Serum transaminases and platelet count on day 1, day 4 and day 7 or till complete recovery or death were analysed.

Hepatic involvement in our study was classified into 3 grades:

Grade A : elevated aminotransferase, with increased levels of at least one of the enzymes, but lesser than 3 times the normal value.

Grade B : elevated aminotransferase with the levels of at least one of the enzymes increased more than three times but less than ten times the reference values.

Grade C : Elevated aminotransferase levels in one or both enzymes increased to at least 10 times their normal values.

Thrombocytopenia was defined as platelet count less than 1,50,000/mm<sup>3</sup>. Recovery was defined in the form of clinical/biochemical improvement. Clinical improvement was defined as relief from the presenting symptoms like fever, vomiting, arthralgia/myalgia, rash and hypotension. Biochemical

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**Table 1: Age distribution of the study sample**

Category	Number	Percentage
12-19 years	302	27.18
20-29 years	407	36.63
30-39 years	201	18.09
40-49 years	107	9.63
50-59 years	50	4.50
60-69 years	39	3.51
70-79 years	4	0.36
80 years and above	1	0.09
Total	1111	100

**Table 2: Gender distribution of study sample**

Category	Number	Percentage
Male	656	59.05
Female	455	40.95
Total	1111	100

**Table 3: Method of diagnosis of Dengue infection in the study sample (n = 1111)**

Method of diagnosis	Number	Percentage
NS <sub>1</sub> Antigen	743	66.88
Rapid IgM antibody test	368	33.12
Total	1111	100

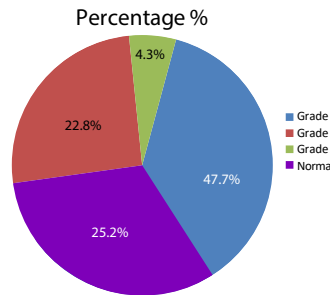
improvement was defined as normalisation of platelet count (above 1,50,000/mm<sup>3</sup>) and transaminases (< 35IU/l). Platelet transfusion was given to those patients whose platelet counts were <10,000/mm<sup>3</sup> and to those patients with signs of bleeding manifestations in the form of gum bleeding, epistaxis, hemoptysis, hematemesis, melena etc.

The numerical data was analysed by percentages, graphs and pie diagrams. Paired t test was applied to find out the outcome of hepatic involvement on day 1, day 4 and day 7. Paired t test was also applied to find out the outcome of thrombocytopenia on day 1, day 4 and day 7. Chi squared test was applied to find the trends in recovery time from thrombocytopenia and hepatic involvement.

**Results**

In our study, 1140 patients of dengue fever were admitted during the study period. But, only 1111 patients fulfilled the Inclusion and Exclusion criteria and hence only their records were analysed.

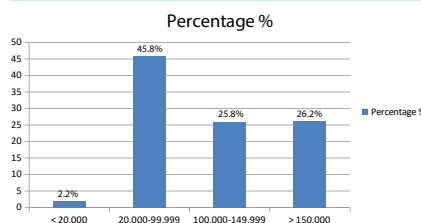
Table 1 shows the age distribution of the study participants and Table 2 shows gender distribution. Table 3 shows the methods of detection of the Dengue infection. The patients were diagnosed by NS<sub>1</sub> antigen or IgM rapid antibody test.



**Fig. 1: Percentage distribution of grade of hepatitis**

**Table 4: Grade of Hepatic involvement and time taken to recovery (n = 832)**

Grade of Hepatic Involvement	Time to recovery			Total
	Within 4 days	Between 4 days and a week	A week or more	
Grade A	156	164	210	530
Grade B	4	77	173	254
Grade C	0	2	43 (3 deaths)= 46	48
Total	160	243	429 (and 3 deaths) = 432	832



**Fig. 2: Percentage distribution of patients according to platelet count**

**Hepatic involvement**

279/1111 (25.11%) had normal transaminase levels. 530/1111 (47.7%) had Grade A, 254/1111(22.86%) had Grade B and 48/1111(4.32%) had grade C hepatic involvement (Figure 1).

**Thrombocytopenia**

Figure 2 shows the distribution of patient according to the platelet count.

Table 4 shows the categorization of patients according to their time to recovery and also according to grade of hepatic involvement. The chi-squared test for trend for the above data yielded a p value of < 0.001 which is highly statistically significant. This might be suggestive of a strong association between hepatic involvement and a longer time to recovery. The median values of SGOT were 62 (8 – 4340) and SGPT were 41(7

**Table 5: Platelet count at presentation and time to recovery (n = 1111)**

Level of platelet deficiency	Time to recovery			Total
	Within 4 days	Between 4 days and a week	A week or more	
Below 20,000	2	0	21	23
20,000 – 99,999	25	168	316	509
100,000 – 149,999	111	96	80	287
150,000 and above (Normal)	97	37	158	292
Total	235	301	575	1111

**Table 6: Distribution of patients with the parameter studied**

Parameter	Number of patients
Only thrombocytopenia	161
Both TCP and hepatic involvement	658
Only hepatic involvement	174
Neither thrombocytopenia nor hepatic involvement	118

– 2580). Three patients with grade C hepatic involvement succumbed to death. All three of them had severe thrombocytopenia, hypotension and acalculous cholecystitis.

Proportion of patients recovering within 4 days = 235 / 993 = 23.67%

Proportion of patients recovering after 4 days but before a week = 301 / remaining 758 = 39.71%

Cumulative proportion of patients recovering within a week = 536 / 993 = 53.98%

Proportion of patients recovering after a week = 457 / 993 = 46.02 %.

Table 5 shows the trends of time to recovery of a patient from thrombocytopenia-an indicator of prognosis. The chi-squared test for trends for the above table yielded a p value of < 0.001 which is statistically very significant. This is in agreement with the previously known fact that severity of platelet deficiency at presentation is a poor prognostic indicator of recovery as well as of poor outcomes.

Table 6 shows the distribution of patient with the parameter studied (only thrombocytopenia, only hepatic involvement, both thrombocytopenia and hepatic involvement; and neither thrombocytopenia nor hepatic involvement). Incidence of only thrombocytopenia (platelet count < 150,000 / cu. mm.) (no hepatic involvement) among diagnosed

dengue fever cases =  $161 / 1111 = 145$  per 1000 cases of dengue fever. Incidence of only hepatic involvement (SGOT and / or SGPT > 35 IU/L) (no thrombocytopenia) among diagnosed dengue fever cases =  $174 / 1111 = 163$  per 1000 cases of dengue fever. Incidence of both thrombocytopenia and hepatic involvement among diagnosed dengue fever cases =  $658 / 1111 = 592$  per 1000 cases of dengue fever. Overall incidence of thrombocytopenia among diagnosed dengue fever cases =  $819 / 1111 = 737$  per 1000 cases of dengue fever. Overall incidence of hepatic involvement among diagnosed dengue fever cases =  $832 / 1111 = 748$  per 1000 cases of dengue fever.

Out of 1111 patients, 118 patients (10.6%) did not have thrombocytopenia or hepatic involvement. Thus, out of the 1111 patients with dengue infection, 993 had either thrombocytopenia or hepatic involvement or both. Apart from thrombocytopenia and hepatic involvement in our study, Hypotension was present in 321 (28.8%) of patients on admission. Gall bladder wall oedema was present in 115 (10.3%). Serositis was present in 145 (13%) patients.

## Discussion

There is abundance of clinical cases of dengue but scanty published data on information about hepatic involvement and thrombocytopenia occurring simultaneously in dengue patients in India, majority of the reported studies are from the Asian countries outside India.

This was a retrospective observational study done in a municipal medical college and tertiary care centre. In our study out of 1111 patients, 656 (59.05%) were males and 455 (40.95%) were females, which was similar to a study done by Om Prakash et al, out of 699 patients, 65% were males and 35% were females.<sup>6</sup> In another study done by Souza et al of 1585 patients there was a female preponderance of 58.3 percent.<sup>7</sup> Francisca from Brazil reported 53.25% males and 46.75% females. Jehangir and Asar Khan studied the incidence of Dengue and found 68.6% were males and 31.3% were females.<sup>8</sup> The gender distribution varies from place to place, and country to country. It depends on the health care seeking tendencies and available outreach facilities and awareness about the illness amongst the

patients themselves and their primary care givers.

In our study, majority of the study population (36.63%) were in the age group of 20 to 29 years with a mean age of 24.5 years, which was comparable to a study reported by Trung et al, where the mean age ranged between 15 to 35 years.<sup>9</sup> In a study by Somia Iqtadar, the average age was reported as 31 years.<sup>2</sup> Lifestyle habits of youngsters like improperly covered extremities with clothes, sleeping in open air without mosquito nets or mosquito repellants may be the reason for higher study population in the age group of 20-29 years.

In our study hepatic involvement was studied on the basis of aminotransferase elevation. Total of 74.88% (832/1111) of patients had elevated aminotransferase. Grade A in 47.70 %, Grade B in 22.86 %, Grade C in 4.32% of patients. Transaminase levels started improving within the first week of illness but recovery occurred in majority of the patients by the end of 7 days or more. There were 3 deaths in patients who had severe hepatitis grade C alongwith thrombocytopenia and hypotension and acalculous cholecystitis. The postulated pathogenetic mechanisms of hepatic involvement in dengue are direct hepatotoxic effects of the virus, immune response of the host on the hepatocytes, ischaemic hepatitis, hypoxia mediated hepatic injury, tissue tropism of the dengue viral serotypes.

In a study by Wong et al 91% had AST elevation and 72% had ALT elevation. Kuo et al reported 90% had abnormal AST and 80% had abnormal ALT. In our study 77% had AST elevation and 59.7% had ALT elevation. In a study by Iqtadar S, which consisted of 220 patients, hepatic dysfunction was seen in 38.15% of those suffering from Dengue fever and 18.6% in those suffering from Dengue Hemorrhagic fever.<sup>2</sup> AST elevation was seen in 85% and ALT elevation was seen in 51%. A study by Ahmed et al found AST elevation twice as much as ALT.<sup>23</sup> These studies show that hepatic involvement in Dengue fever is not uncommon as it was thought to be. Although Dengue Virus is not hepatotropic virus, the above postulated mechanisms are responsible for the pathogenic effects. In a study by Parkash in Karachi, AST was reported as high as 95% and ALT 86%. This study included only DHF

patients so the hepatic involvement was high in this study.<sup>6</sup> There were 3 deaths in patients who had severe hepatitis grade C alongwith thrombocytopenia and hypotension and acalculous cholecystitis.

Thrombocytopenia is a common manifestation of Dengue fever. It may remain asymptomatic or cause clinical manifestations ranging from petechial rash to bleeding from mucosal sites to frank dengue hemorrhagic fever or dengue shock syndrome. Studies suggest that the cause for thrombocytopenia is multifactorial which includes decreased formation due to suppression of megakaryocytopoiesis; as well as increased destruction of platelets due to clearance by DENV-induced apoptosis and antiplatelet antibodies.<sup>11</sup> In our study thrombocytopenia was based on platelet count at the time of admission. Total of 73.71% (819 / 1111) of patients had thrombocytopenia during presentation. According to study done by Nandini Chatterjee et al, 55% of patients had thrombocytopenia which is similar to our study.<sup>12</sup> Study done by Rachel Daniel et al. also demonstrated thrombocytopenia was present in (225 / 250) 90% cases.<sup>13</sup>

Majority of the patients in our study (45.81%) had a platelet count ranging from 20,000-99,000, which was similar to other studies where the median platelet counts were 48,000. Platelet count less than 20,000 in 2.25% cases, 20,000-99,999 in 45.81% cases, 1,00,000-1,49,000 in 25.83% cases.

In a study done by Amitava Acharyya, Total 36.9% (141) cases had platelet count between 36,000 and 1,00,000; while 10.5% (40) patients platelet count went below 35,000 which was similar to the findings in our study.<sup>14</sup>

The study also showed that majority of people (91 %) with platelet count of below 20,000 took a week or more for recovery, similarly among 509 patients with platelet count between 20,000-99,999, 168 people (33%) took 4 days to 1 week for recovery while 316 patients (62%) took 1 week or more for recovery. 58% of patients with platelet counts of 1,00,000 and more recovered within 1 week as compared to patients with platelet count of less than 1 lakh. In majority of patients with thrombocytopenia the time taken for recovery was 4 to 7 days i.e 536 /

993 = 53.98%.

The length of hospital stay in our study ranged from 4 to 7 days with an average of 5 days. In a study by Lye et al the length of stay was 3 days and in a study by Khan et al the length of stay was 4 days. The length of stay depends on the severity of thrombocytopenia, hepatic involvement, correction of hypotension, symptomatic improvement from fever, bodyache, arthralgias, nausea, vomiting and abdominal pain. Patients of Dengue hemorrhagic fever and dengue shock syndrome require a prolonged stay in the hospital.

#### Limitations of our study

1. The serotype of Dengue Virus was not studied in our study.
2. Low serum globulin levels result in a loss of fluid in the extravascular compartment. This causes reduction in the gradient of the pressures in the intra and extravascular compartment. Thus, low serum globulin levels can

predict the severity of Dengue. Serum globulin levels were not studied in the present study.

#### Conclusion

Therefore more studies from the Indian subcontinent should be carried out to correlate the serotype of Dengue Virus and the hepatic involvement and thrombocytopenia in dengue fever.

#### References

1. World Health Organization Special. Programme for Research, Training in Tropical Diseases, World Health Organization. Department of Control of Neglected Tropical Diseases, World Health Organization. Epidemic, Pandemic Alert. Dengue: guidelines for diagnosis, treatment, prevention and control. World Health Organization. 2009
2. Iqtadar S, Akbar N, Naima H, Randhava FA. Profile of Hepatic Involvement in Dengue Infections in adult Pakistani population. *Pak J Med Sci* 2017; 33:963–967.
3. Itha S, Kashyap R, Krishnani N, Saraswat VA, Choudhuri G, Aggarwal R. Profile of liver involvement in dengue virus infection. *Natl Med J India* 2005; 18:127.
4. Fernando S, Wijewickrama A, Gomes L, et al. Patterns and Causes of Liver Involvement in Acute Dengue infection. *BMC Inf Dis* 2016; 16:319.
5. Chikkaveeraiah SK, Srinath KM, Kumar SK, ReddyPK. Hepatic profile and platelet count as a prognostic indicator in Dengue fever, from a tertiary care hospital in south India.

*Int Journal Appl Basic Med Res* 2016; 5:54-31.

6. Parkash O, Almas A, Jafri SM, et al. Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (south asia). *BMC Gastroenterol* 2010; 10:43-47.
7. Souza LJ, Alves JG, Nogueira RM et al. Aminotransferase changes and acute hepatitis in patients with dengue fever: Analysis of 1,585 cases. *Braz J Infect Dis* 2004; 8:156-163.
9. Trung DT, Le ThiThu T, Nguyen Minh D, et al. Clinical Features of Dengue in a Large Vietnamese Cohort: Intrinsically Lower Platelet Counts and Greater Risk for Bleeding in Adults than Children. *Plos Negl Trop Dis* 2012; 6:e179.
10. Ahmad S, Dhar M, Srivastava S, Bhat NK, Shirazi N, Biswas D, Kadian M, Ghai S. Dengue Hepatitis sans dysfunction: experience of a single tertiary referral centre in the north Indian State of Uttarakhand. *Trop Doct* 2013; 43:62-5.
11. Schexneider KI, Reedy EA. Thrombocytopenia in Dengue: *Current Hematology Reports* 2005; 4:145-8.
12. Chatterjee N, Mukhopadhyay M, Ghosh S, Mondol M, Das C, Patar K. An Observational Study of Dengue Fever in a Tertiary Care Hospital of Eastern India. *J Assoc Physicians India* 2014; 62:12-15.
13. Daniel R, Rajamohanam, Philip AZ. A Study of Clinical Profile of Dengue Fever in Kollam, Kerala, India. *Dengue Bulletin* 2005; 29:197-202.
14. Acharyya A, Ghosh K, Bhattacharyya A, Ghosh M, Chakraborty S, Ghosh S, Pal M. The dengue fever and its complication: A scenario in a tertiary-level hospital of greater Kolkata. *Annals of Tropical Medicine and Public Health* 2016; 9:92-96.