

## **DENGUE HEPATOPATHY AND ITS CORRELATION WITH SEVERITY OF DISEASE FROM WESTERN PART OF INDIA**

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## Abstract:

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**Background and Objectives:** The global incidence of dengue has grown dramatically in recent decades affecting children and young adults mainly in tropical and subtropical countries. Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evaluation and outcome. While most patients recover following a self-limiting non-severe clinical course, a small proportion progress to severe disease, mostly characterised by plasma leakage with or without haemorrhage.

**Methods:** It is a Prospective, observational study including 150 serologically confirmed Dengue fever in a tertiary care centre. The main objective was to study patterns of hepatopathy in dengue fever and to determine whether the patterns of hepatic involvement correlate with clinical, laboratory profile and outcome in Dengue fever according to WHO classification.

**Results:** Younger age groups were found to be more prone to hepatopathy with 46.7% of patients having hepatopathy (transaminases >3x UNL) belonging to ages 21-30 yrs. AST level correlates maximum with severe Dengue, followed by abnormal PT and APTT value. AST is more useful than ALT and AST:ALT Ratio is even more reliable indicator than using the values alone. Risk factors which were statistically significant for mortality: Positive Tourniquet test, Abnormal CNS Examination, Bleeding Manifestations, and thrombocytopenia. Hepatic dysfunction Grade 3 and 4 were not directly related to mortality.

**Interpretation and Conclusion:** Even though hepatopathy does not correlate with the severity of disease directly, its significant association with warning signs, thrombocytopenia and bleeding manifestations make it very important factor to predict which subset of patients will develop severe Dengue fever. Timely diagnosis of hepatopathy in patients with dengue fever and its management may improve patient survival rate.

### Key Words

Dengue Hepatopathy, Severe Dengue, Dengue fever

# INTRODUCTION

The global incidence of dengue has grown dramatically in recent decades affecting children and young adults mainly in tropical and subtropical countries<sup>1,2,3</sup>. Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evaluation and outcome. While most patients recover following a self-limiting non-severe clinical course, a small proportion progress to severe disease, mostly characterised by plasma leakage with or without haemorrhage<sup>4</sup>. Hepatic dysfunction though rare in dengue infection, but can be a cause of death along with Dengue Hemorrhagic fever and Dengue Shock Syndrome or without such involvement<sup>5</sup>. Rise in liver enzymes starts in later part of febrile phase, few days before the development of thrombocytopenia, which occurs during critical phase of illness. In India, dengue is an important cause of hepatic dysfunction manifesting as elevation of transaminases and alteration of other parameters of liver function. Acute liver failure has also been recognized as a complication and an unusual manifestation of dengue.<sup>3,4</sup> The present study assesses the clinical profile, laboratory parameters, magnitude and spectrum of alterations in liver function (hepatopathy) and outcome of patients admitted with dengue fever and whether it correlates with severity of the disease. Understanding pattern of hepatopathy helps in differentiating Dengue from other common causes of hepatitis.

# MATERIAL AND METHODS

The present study was conducted prospectively in the department of General Medicine of a tertiary care hospital in Ahmedabad during a dengue outbreak between the months of July and September 2019.

Patients over the age of 12 who are serologically confirmed (NS1/IgM positive) dengue were included in the study after informed written consent in vernacular language.

Patients with viral hepatitis, alcoholic patients, patients with cirrhosis, patients with other causes of altered LFTs or thrombocytopenia were excluded from the study.

150 patients **Abstract**

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## Results:

Younger age groups were found to be more prone to hepatopathy with 46.7% of patients having hepatopathy (transaminases >3x UNL) belonging to ages 21-30 yrs. AST level correlates maximum with severe Dengue, followed by abnormal PT and APTT

value .AST is more useful than ALT and AST:ALT Ratio is even more reliable indicator than using the values alone. Risk factors which were statistically significant for mortality :Positive Tourniquet test, Abnormal CNS Examination, Bleeding Manifestations, and thrombocytopenia. Hepatic dysfunction Grade 3 and 4 were not directly related to mortality.

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Key Words

Dengue Hepatopathy, Severe Dengue, Dengue fever were subjected to clinical examination and baseline investigations so as to fill in a structured proforma.

The diagnosis of dengue fever, dengue haemorrhagic fever and dengue shock syndrome was based on the WHO criteria<sup>3</sup>. The variables were demographic variables, features on clinical examination, warning signs as per WHO guidelines<sup>3</sup>, laboratory parameters, duration of hospital stay and outcome of the patient.

All patients underwent investigations like complete haemogram, urea, creatinine, liver function tests, chest X ray, ECG and ultrasound of abdomen, along with prothrombin time, INR and activated partial thromboplastin time.

To study patterns of hepatopathy in dengue fever and to determine whether the patterns of hepatic involvement correlate with clinical & laboratory profile and outcome and severity according to WHO classification , we classified the 150 participants into 4 groups based on elevations of transaminases<sup>1,2</sup>.

To gauge the severity of the illness and classify the patients according to a standard classification, we used the revised WHO classification as given in the WHO guidelines. Patient's clinical and lab. parameters were studied during hospital stay. Factors associated with mortality were noted.

## RESULT

A total of 150 patients were enrolled in this study. The Age (Years) ranged from 12 - 77. The mean (SD) of Age <https://smallseotools.com/plagiarism-checker/> in Years was 27.16 (13.92). The median (IQR) of Age in years was 23.00 (10.00). Majority of the participants (45.3%) were aged 21-30 Years.

64.7% of the participants were males and 35.3% of the participants were females. There was no significant difference between the groups in terms of Age and gender compared to the WHO classification ( $\chi^2 = 3.544$ ,  $p = 0.315$ ) ; ( $\chi^2 = 2.946$ ,  $p = 0.229$ ) . TABLE 1 shows association between hepatopathy and age.

We compared the distribution of various clinical signs on general examination and abnormal systemic examination in all patients and in patients classified as per grading of hepatopathy. There was a significant difference between the various groups in terms of distribution of Vomiting ( $\chi^2 = 8.143$ ,  $p = 0.043$ ) with participants in group B having high proportion of vomiting, suggesting that association of vomiting with hepatopathy was statistically significant. Blanching erythema (51.3%) was the most common feature observed on general examination followed by pallor (12.0%) and maculopapular rash (6.7%). Out of warning signs (as per WHO guidelines) the most common ones were Clinical Fluid Accumulation found in 73 patients (48.7%), Abdominal Pain in 24 patients (16.0%). Bleeding Manifestations and Rise in Haematocrit with Fall in Platelet Count present in 10 patients each (6.7%). Table 2 shows association between Hepatopathy and Clinical Features

Fisher's exact test was used to explore the association between Hepatopathy and bleeding manifestations as more than 20% of the total number of cells had an expected count of less than 5. There was a significant difference between the various groups in terms of distribution of Positive Tourniquet test ( $\chi^2 = 8.270$ ,  $p = 0.035$ ). Participants in Group D (Severe Hepatopathy) had the largest proportion of Positive Tourniquet test.

There was a significant difference between the various groups in terms of distribution of Gross Bleeding ( $\chi^2 = 19.353$ ,  $p = <0.001$ ). Participants in Group D (Severe Hepatopathy) had the largest proportion of Gross Bleeding. Table 3 shows association between Hepatopathy and Bleeding manifestations

Raised Hematocrit was observed in 5 (3.3%) out of which 3 belonged to category C and 1 belonged to category D. All patients with even mild form of hepatopathy (category B), had thrombocytopenia. The average levels of AST and ALT were 93.3 U/L ( $\pm 117$ ) and 86.0 U/L ( $\pm 93.7$ ), respectively. Both of these enzymes were normal in 34.8% of the patients (grade A); 44.5% had altered levels of at least one of the enzymes (grade B); 16.9% had at least one of the enzymes increased to three times its reference level (grade C) and 3.8% of the cases had acute hepatitis (grade D). The average levels of AST and ALT were greater in DHF (127.1 U/L and 100.2 U/L, respectively) than in classic dengue (89.8 U/L and 84.6 U/L, respectively) Table 4 Shows hepatopathy Grades and Liver Enzymes

There was a difference between the 4 groups in terms of APTT (Seconds) with the median APTT (Seconds) being highest in the Hepatopathy: D (Severe Hepatopathy) group, though statistically not significant. Same trend was observed for Prothrombin time. Under haematological parameters, the mean  $\pm$  SD Hemoglobin was  $13.02 \pm 2.14$ , mean  $\pm$  SD Hematocrit was  $40.48 \pm 6.63$ , mean  $\pm$  SD total WBC counts were  $4940.93 \pm 3793.71$  and mean  $\pm$  SD platelets were  $79353.33 \pm 46509.89$ . Out of these, association of low platelet Counts ( $p = <0.001$ ) with hepatopathy was found out to be statistically significant. Table 5 shows correlation of Dengue hepatopathy with disease severity as per revised WHO classification

The mean of Duration of Hospital Stay was 4.91 days (around 5 days). The Duration of Hospital Stay ranged from 1 - 11 days. Out of 150 patients included in the study 4

patients died during the course of illness, because of dengue shock syndrome and haemorrhagic manifestations. One patient died of fulminant hepatic failure.

The following variables were significantly associated ( $p < 0.05$ ) with the Mortality: Positive Tourniquet test, Gross Bleeding, Abnormal CNS Examination, Raised AST more than five times upper normal limits, DHF grade IV and longer duration of ICU Stay (Days)

## DISCUSSION

- The spectrum of dengue fever in the patients included in our study classified as per the revised WHO classification ( $n = 150$ ), consisted of : 90 patients (60%) of Dengue fever without warning signs , 53 patients (35.3%) of Dengue with warning signs and 7 patients (4.7%) with severe dengue. Clinical profile of patients included in our study was similar to other studies<sup>6,7</sup> with fever as a universal symptom (present in 100%) followed by myalgia ( 76.7%) , decreased appetite (66%) and headache (52%) .  
Out of symptoms, the association of vomiting with hepatopathy was found out to be statistically significant ( $p = 0.043$ ) Most common clinical signs in patients included in our study were Blanching erythema (51.3%) followed by pallor (12.0%) and maculopapular rash (6.7%). Abnormal CNS examination in the form of lethargy, restlessness and altered sensorium was present in 4 patients (2.7%) and its association with hepatopathy was found out to be statistically significant ( $p = 0.030$ ).
- Out of hemorrhagic manifestations, Positive Tourniquet test was present in 35 (23.3%) patients, gross bleeding in 10 (6.7%) patients and their association with hepatopathy was not statistically significant. Thrombocytopenia and Hepatopathy has statistically significant association . However association of thrombocytopenia and mortality was not statistically significant.
- Mean  $\pm$  SD of PT (prothrombin time) in our patients was  $14.99 \pm 4.57$  seconds and Mean  $\pm$  SD aPTT was  $34.47 \pm 8.10$
- The association of aPTT with hepatopathy was found out to be statistically significant with  $p = 0.048$ , suggesting that higher aPTT values were associated with hepatopathy.
- In other parameters of Liver function, Mean  $\pm$  SD albumin of patients included in our study was  $3.80 \pm 0.59$  , with lowest values in Grade IV hepatopathy. Correlation of Low albumin with hepatopathy was also found to be statistically significant ( $p = < 0.001$  )
- The association of aPTT and PT with hepatopathy was found out to be statistically significant with  $p = 0.048$ , suggesting that higher aPTT values were associated with hepatopathy. Similar study shows that prolonged INR and acute liver failure correlates with mortality in severe Dengue<sup>10</sup>.
- In our study, amongst all Liver function parameters, AST level correlates maximum with severe Dengue .AST is more useful than ALT and AST:ALT Ratio is even more reliable indicator than using the values alone, according to study published in BMC Infectious Disease<sup>8</sup>. It is important to note that rise in SGPT and reaching to peak level occurs 1-2 days earlier before platelets starts falling<sup>9,10</sup>.
- Association of Positive Tourniquet test, Abnormal CNS Examination, Bleeding Manifestations, and thrombocytopenia were associated with mortality and found to be statistically significant. Hepatic dysfunction Grade 3 and 4 were not directly related to mortality.

## CONCLUSION

- Even though hepatopathy does not correlate with the severity of disease directly, its significant association with warning signs ,thrombocytopenia and bleeding manifestations make it very important factor to predict which subset of patients will develop severe Dengue fever. AST level correlates maximum with severe Dengue ,followed by abnormal PT and APTT value .AST is more useful than ALT and AST:ALT Ratio is even more reliable indicator than using the values alone.Timely diagnosis of hepatopathy in patients with dengue fever and its management may improve patient survival rate.Large scale studies should be done to establish role of LFT as an early prognostic indicator in severe Dengue.
- FUNDING AND CONFLICT OF INTEREST none

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Table 1 ASSOCIATION BETWEEN HEPATOPATHY AND AGE

Age	Hepatopathy			Fisher's Exact Test	
	Present (Grade B+C+D)	Absent (Grade A)	Total	X <sup>2</sup>	P Value
12-20 Years	24 (40.0%)	28 (31.1%)	52 (34.7%)	11.287	0.025
21-30 Years	28 (46.7%)	40 (44.4%)	68 (45.3%)		
31-40 Years	6 (10.0%)	7 (7.8%)	13 (8.7%)		
41-50 Years	2 (3.3%)	1 (1.1%)	3 (2.0%)		
51-60 Years	0 (0.0%)	5 (5.6%)	5 (3.3%)		
>60 Years	0 (0.0%)	9 (10.0%)	9 (6.0%)		
Total	60 (100.0%)	90 (100.0%)	150 (100.0%)		



Table 2 Association between Hepatopathy and Clinical Features

<b>Parameters</b>	<b>Hepatopathy : A (No Hepatopathy) (n = 90)</b>	<b>Hepatopathy : B (Mild Hepatopathy) (n = 17)</b>	<b>Hepatopathy: C (Moderate Hepatopathy) (n = 26)</b>	<b>Hepatopathy : D (Severe Hepatopathy) (n = 17)</b>	<b>p value</b>
<b>Fever</b>	90	17	26	17	-
<b>Myalgia</b>	70 (77.8%)	15 (88.2%)	20 (76.9%)	10 (58.8%)	0.25 2 <sup>2</sup>
<b>Headache</b>	42(46.7%)	12(70.6% )	16(61.5%)	8(47.1%)	0.2 13
<b>Vomiting</b>	25 (27.8%)	10 (58.8%)	7 (26.9%)	8 (47.1%)	0.0 433

TABLE 3 Association between Hepatopathy and Bleeding manifestations

Parameters	Group A (No Hepatopathy) (n = 90)	Group B (Mild Hepatopathy) (n = 17)	Group C (Moderate Hepatopathy) (n = 26)	Group D (Severe Hepatopathy) (n = 17)	p value
<b>Positive Tourniquet test</b>	14 (15.6%)	5 (29.4%)	9 (34.6%)	7 (41.2%)	<b>0.035<sup>2</sup></b>
<b>Petechiae</b>	5 (5.6%)	1 (5.9%)	1 (3.8%)	1 (5.9%)	1.000 <sup>2</sup>
<b>Purpura</b>	0 (0.0%)	0 (0.0%)	2 (7.7%)	1 (5.9%)	<b>0.062</b>
<b>Ecchymosis</b>	2 (2.2%)	1 (5.9%)	0 (0.0%)	2 (11.8%)	0.124 <sup>2</sup>
<b>Gross Bleeding</b>	1 (1.1%)	2 (11.8%)	2 (7.7%)	5 (29.4%)	<b>&lt;0.001<sup>2</sup></b>

**TABLE 4 Hepatopathy Grades and Liver Enzymes**

<b>Liver Enzymes</b>	<b>Hepatopathy: A (No Hepatopathy) (n = 90)  (Mean ± SD)</b>	<b>Hepatopathy: B (Mild Hepatopathy) (n = 17) (Mean ± SD)</b>	<b>Hepatopathy: C (Moderate Hepatopathy) (n = 26) (Mean ± SD)</b>	<b>Hepatopathy: D (Severe Hepatopathy) (n = 17) (Mean ± SD)</b>
<b>AST (IU/L)</b>	56.99 ± 27.35	143.88 ± 23.87	254.27 ± 59.77	792.00 ± 835.35
<b>AST</b>				
<3 xULN	90 (100.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
3-5 xULN	0 (0.0%)	16 (94.1%)	2 (7.7%)	0 (0.0%)
5-10 xULN	0 (0.0%)	0 (0.0%)	24 (92.3%)	0 (0.0%)
>10 xULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (100.0%)
<b>ALT</b>				
<3 xULN	90 (100.0%)	11 (64.7%)	4 (15.4%)	0 (0.0%)
3-5 xULN	0 (0.0%)	6 (35.3%)	11 (42.3%)	3 (17.6%)
5-10 xULN	0 (0.0%)	0 (0.0%)	11 (42.3%)	8 (47.1%)
>10 xULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (35.3%)

Table 5 Correlation of Dengue hepatopathy with disease severity as per revised WHO classification

Classification	Hepatopathy					Fisher's Exact Test	
	A (No Hepatopathy)	B (Mild Hepatopathy)	C (Moderate Hepatopathy)	D (Severe Hepatopathy)	Total	X <sup>2</sup>	P Value
DF Without Warning Signs	60 (66.7%)	9 (52.9%)	13 (50.0%)	8 (47.1%)	90 (60.0%)	6.408	0.227
DF With Warning Signs	28 (31.1%)	7 (41.2%)	11 (42.3%)	7 (41.2%)	53 (35.3%)		
Severe Dengue	2 (2.2%)	1 (5.9%)	2 (7.7%)	2 (11.8%)	7 (4.7%)		
Total	90 (100.0%)	17 (100.0%)	26 (100.0%)	17 (100.0%)	150 (100.0%)		