

## Original Research Article

# Derangement of liver function tests in dengue patients

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## ABSTRACT

**Background:** Changes in the liver function test may serve as an early marker for timely diagnosis and identification of patients who may develop severe dengue. The purpose of this study was to examine the link between dengue fever severity and liver function test.

**Methods:** This prospective observational study was conducted in the Department of General Medicine, Madhesh Institute of health sciences, provincial hospital, Janakpurdham in which we included dengue positive patients (aged 18 years or more) based on NS1 antigen or high titer on IgM/IgG testing from July 2023 till August 2023. We excluded patients with diseases like malaria, cirrhosis of liver, enteric fever, viral hepatitis or any other disease or taking any medication which can derange LFT.

**Results:** We included 96 patients fulfilling the study criteria. Of these, 71% had DF, 22% had DHF and 7% had DSS. Among liver enzymes, mean AST of the patients was significantly higher in DSS group of patients ( $775.19 \pm 39.65$  U/l), as compared to those in the DF and DHF group of patients,  $p$  value  $< 0.01$ . Similarly, mean ALT of the patients was significantly higher in DSS group of patients ( $387.8 \pm 18.6$  U/l), as compared to those in the DF and DHF group of patients,  $p$  value  $< 0.01$ . On the contrary, mean alkaline phosphatase levels were similar between the three patient groups.

**Conclusions:** Based on the results our study, we conclude that raised AST and ALT levels were significantly associated with severity of DSS and DHF. Patients with dengue infection should have a baseline liver function test and subsequent LFT monitoring to detect early hepatic impairment.

**Keywords:** Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome, Septicemia, Hepatic encephalopathy, Liver function test

## INTRODUCTION

In the last three decades, the global burden of dengue fever has more than doubled, and there are approximately 2.5 billion people at risk of contracting the disease.<sup>1</sup> Dengue virus infections can cause a wide spectrum of clinical symptoms, ranging from a mild febrile illness known as 'dengue fever' to 'severe dengue,' also known as

dengue haemorrhagic fever (DHF), which is characterised by capillary leakage, hypovolaemic shock, organ dysfunction, and bleeding issues.<sup>2</sup> Plasma leakage is indicated by a rapid rise in haematocrit, hypoproteinemia, pleural effusions and ascites, and a reduction in plasma volume, all of which lead to haemodynamic compromise and hypovolaemic shock. Dengue may manifest with a wide spectrum of clinical manifestations, ranging from a

moderate febrile illness to an abrupt plasma leakage that results in life-threatening shock.<sup>3</sup> Hepatic impairment is a prominent feature of DENV infection. Infection with DENV affects hepatocytes and Kupffer cells preferentially. It is believed that the pathophysiology of dengue liver injury is mostly a T cell-mediated process involving antibody-endothelial interaction and a concomitant cytokine storm.<sup>4</sup> Elevated transaminase values are the most frequent abnormality. In 63-97% of patients, aspartate transaminase (AST) levels are elevated, while alanine transaminase (ALT) levels are elevated in 45-96% of patients. The levels of liver enzymes were surprisingly higher throughout the feverish and severe phases of dengue fever. Keeping this in mind, changes in the liver function test may serve as an early marker for timely diagnosis and identification of patients who may develop severe complications such as Dengue shock syndrome, septicemia, hepatic encephalopathy, and Dengue hemorrhagic fever, and therefore serve as an early biochemical predictor of the severity of the outcome of Dengue fever. The purpose of this study was to examine the link between dengue fever severity and liver function test.

## METHODS

### *Study design and sample size*

This prospective observational study was conducted in the department of general medicine, Madhesh Institute of health sciences, provincial hospital, Janakpur, which we included dengue positive patients (aged 18 years or more) based on NS1 antigen or high titer on IgM/IgG testing from July 2023 till August 2023. We excluded patients with diseases like malaria, cirrhosis of liver, enteric fever, viral hepatitis or any other disease or taking any medication which can derange LFT. Informed written consent was obtained before the patients were enrolled in the study.

### *Data collection and data analysis*

Data were collected using a pre-designed semi-structured study proforma. Demographic information of the patients like age and gender was noted from the medical records. Clinical information included presenting complaints, past medical history and family history. The findings of the general physical examination and systemic examination were noted. The NS1 early dengue ELISA was used to confirm acute dengue infection in serum samples. The commercial capture-IgM and IgG enzyme-linked immunosorbent test (ELISA) was performed to identify whether the patients had a primary or secondary dengue infection. For the diagnosis of dengue infection: Dengue fever: febrile illness associated with one of the following laboratory confirmation tests: Detection of dengue specific IgM capture antibody or NS1 antigen; or A four-fold or greater increase of dengue-specific IgG capture antibody by ELISA and hemoagglutination inhibition assay in paired serum samples. Dengue Hemorrhagic

Fever: patients who have DF and hemorrhagic manifestations, low platelet count, and objective evidence of leaky capillaries ( $\geq 20\%$  elevation in hematocrit, lower serum albumin, and pleural or other effusions) were classified as having DHF (WHO grades I/II). Dengue Shock Syndrome: Those with evidence of circulatory failure (pulse pressure  $\leq 20$  mmHg, hypotension, or frank shock) were classified as having DSS (WHO classification, DHF grades III/IV). Biomarkers will be collected into appropriate Vacutainers®, as is routine procedure at our centre. The fully automatic Biochemistry analyser (Mindray 480) will be used to assess liver function tests. while bromocresol green was used to analyse serum albumin (Roche Diagnostics, Malaysia).

Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data were expressed as absolute number and percentage. Cross tables were generated and chi square test was used for testing of associations and ANOVA test was used for comparison of quantitative parameters between DF, DHF and DSS group of patients, p value  $< 0.05$  is considered statistically significant. All analysis were done using SPSS software, version 24.0.

## RESULTS

During the study period, we included 96 patients fulfilling the study criteria. Of these, 71% had DF, 22% had DHF and 7% had DSS. We observed a significant association between increasing age and increasing severity of dengue ( $p < 0.01$ ). Also, DHF and DSS were significantly more common among female patients as compared to DF ( $p < 0.05$ ), whereas in males dengue fever is seen more in comparison of female (Table 1). The most common presenting complaint was fever (79%). Other common presenting complaints were pain abdomen (73%), vomiting (63%), headache (56%) and joint pain (53%). Furthermore, we observed that bleeding was significantly more common among DHF (90.4%) and DSS (85.7%) as compared to DF group (0%),  $p < 0.01$ . Analysis of hematological investigations revealed that mean hematocrit, haemoglobin and total leucocyte count were significantly high in DSS patients as compared to DF and DHF patients (Table 2). Similarly, mean bilirubin levels were significantly higher among DSS patients as compared to DF and DHF patients. Among liver enzymes, mean AST of the patients was significantly higher in DSS group of patients ( $775.19 \pm 39.65$  U/l), as compared to those in the DF and DHF group of patients,  $p < 0.01$ . Similarly, mean ALT of the patients was significantly higher in DSS group of patients ( $387.8 \pm 18.6$  U/l), as compared to those in the DF and DHF group of patients,  $p < 0.01$ . On the contrary, mean alkaline phosphatase levels were similar between the three patient groups. Based on raised levels, raised AST and ALT were significantly associated with DSS, as all patients of DSS had more than 40 U/l AST and ALT (Table 3).

**Table 1: Association of clinical presentation of patients with dengue severity.**

Parameters	Dengue severity				Total	P value
	DF	DHF	DSS			
<b>Age groups (years)</b>	N					
	%					
<b>&lt;20</b>	N	11	0	0	11	
	%	16.18	0.00	0.00	11	
<b>21 to 40</b>	N	38	1	0	39	<0.01
	%	55.88	4.76	0.00	41	
<b>41 to 60</b>	N	16	13	4	33	
	%	23.53	61.90	57.14	34	
<b>61 to 80</b>	N	3	7	3	13	
	%	4.41	33.33	42.86	14	
<b>Gender</b>						
<b>Female</b>	N	11	17	4	32	<0.05
	%	16.18	80.95	57.14	33	
<b>Male</b>	N	57	4	3	64	
	%	83.82	19.05	42.86	67	
<b>Symptoms</b>						
<b>Fever</b>	N	51	18	7	76	0.54
	%	75.00	85.71	100.0	79	
<b>Pain in abdomen</b>	N	47	17	6	70	0.62
	%	69.12	80.95	85.71	73	
<b>Vomiting</b>	N	36	20	4	60	<0.05
	%	52.94	95.24	57.14	63	
<b>Headache</b>	N	28	20	6	54	0.71
	%	41.18	95.24	85.71	56	
<b>Joint pain</b>	N	28	17	6	51	<0.05
	%	41.18	80.95	85.71	53	
<b>Clinical findings</b>						
<b>Bleeding</b>	N	0	19	6	44	<0.01
	%	0.00	90.48	85.71	46	
<b>Shock</b>	N	4	11	7	20	<0.05
	%	5.88	52.38	100.0	21	
<b>Hematuria</b>	N	5	10	4	11	0.53
	%	7.35	47.62	57.14	11	
<b>Proteinuria</b>	N	3	11	6	11	<0.05
	%	4.41	52.38	85.71	11	
<b>Total</b>	N	68	21	7	96	<0.05
	%	100.0	100.0	100.0	100	

\*analyzed using Chi-square test

## DISCUSSION

We identified a strong correlation ( $p < 0.01$ ) between increasing age and higher dengue severity. We found that DHF and DSS were much more frequent among female patients than among male patients ( $p < 0.05$ ). A similar study by Bandopadhyaya et al included 110 cases, 61 (55.5%) of which were male and 49 (44.5%), female. 59 (26.6%) of these 59 (53.6% of the total) patients had

DF, 25 (22.7%) had DHF, and 25 (22.7%) had DSS.<sup>5</sup> They observed the biggest number of instances in individuals aged 46 to 61. Soni et al. reported that 188 (67 percent) of the 281 patients in their research were male and 93 were female (33 percent).<sup>6</sup> In addition, the most prevalent presenting symptom in our research was fever. According to Bandopadhyaya et al the most frequent presenting illness in all 110 instances is fever (100 percent). Other common presenting symptoms were stomach discomfort in 52 patients (47.2%), vomiting in 44 patients (40%) and headache in 34 patients (30.9%), as well as joint pain in 63 individuals (57.2 percent). In a separate study, Kittittrakul and colleagues discovered that fever was present in all 127 patients prior to admission.<sup>7</sup> Patients also had stomach discomfort in 27.5%, rash in 15.7%, vomiting in 84.2%, headache in 75%, and joint pain in 71. (55.9%). The major presenting symptoms in the study by Singh et al were fever in 214 (100%) patients, myalgia in 92 (43%) patients, vomiting in 80 (37.3%) patients, and stomach pain in 43 (20%) patients.<sup>8</sup> In the prior studies, fever was the most frequently observed symptom of dengue fever, which mirrored our study; however, in the prior studies, fever was found in all patients prior to admission or at the time of admission, whereas in our study, we only include symptoms that were present at the time of admission. Typically, the illness starts with a quick onset of fever accompanied by a strong headache and any of the following symptoms: chills, discomfort behind the eyes, especially with eye movement, backache, and pain in the muscles, bones, and joints, 5-8 days after an infective mosquito bite. Based on recent research demonstrating that DSS, DHF, and DF increased hematocrit levels while lowering platelet count in dengue patients, we designed our study in a similar fashion. A rise in hematocrit suggests that plasma leakage has occurred due to extensive capillary leak, hypotension, rhabdomyolysis, hemolysis, and severe DIC, culminating in ischemia, hypoxia, and multiorgan failure, and that proper fluid management is required.<sup>9</sup> Additionally, vasculopathy and thrombocytopenia may contribute to bleeding in dengue. Reabsorption of plasma leakage occurs throughout the recovery phase. As a consequence, dengue patients are needed to undergo hematocrit monitoring.<sup>10</sup> In our patient sample, 86% of the patients demonstrated high AST levels ( $>40$  U/l). Likewise, 90% of the patients had increased ALT levels ( $>40$  U/l). Bandyopadhyay et al found that 103 patients (93.6%) had increased AST levels, with 52 patients (88.1%) having DF, 26 patients (100%) having DHF, and 25 patients (100%) having DSS ( $p=0.01$ ). 89 out of 110 patients had increased ALT levels, with 41 (69.4%) having DF, 23 (88.4%) having DHF, and 25 (100%) having DSS ( $p$  value=0.01); DF accounted for 69.4 percent, DHF for 88.4 percent, and DSS for 100 percent. In their study, the mean ALP levels for the DF, DHF, and DSS groups were  $132.7 \pm 16.86$ ,  $138.3 \pm 18.02$ , and  $139.29 \pm 19.3$  U/l, respectively ( $p=0.8$ ). Amit Soni and colleagues discovered that 93.6 percent of 281 people had increased AST levels and 270 had elevated ALT values. The ALP levels of 61 research participants were not increased. 209

patients (97.7%) had increased AST levels, with 169 patients (97.1%) having DF, 29 patients (100%) having DHF, and 11 patients (100%) having DSS, according to the study of Singh et al. In 199 patients (93.9%), 65 ALT

levels were found to be high, with 161 patients (92.5%) having DF, 27 patients (93.1%) having DHF, and 11 patients (100%) having DSS.

**Table 2: Association of laboratory investigations of patients with dengue severity.**

Parameters	DF		DHF		DSS		P value*
	Mean	SD	Mean	SD	Mean	SD	
<b>Hematological investigations</b>							
Hematocrit (%)	45.07	5.23	46.34	3.61	47.01	5.13	<0.05
Hemoglobin (gm%)	10.15	3.18	13.16	4.08	15.09	3.11	<0.01
Platelet (per ml)	83115.17	11284.01	71195.93	22701.01	45053.20	24046.19	<0.01
Total leucocyte count (per cumm)	12485.15	2304.25	12129.12	3316.13	18024.13	3244.05	<0.05
Prothrombin time (sec)	12.19	1.40	12.72	3.41	12.19	4.72	0.86
<b>Bilirubin</b>							
Total bilirubin (mg/dl)	1.90	0.47	1.88	0.15	3.01	0.33	<0.05
Direct bilirubin (mg/dl)	0.58	0.08	0.55	0.07	1.92	0.71	<0.05
<b>Serum protein</b>							
Total protein (gm/dl)	6.24	0.49	6.96	0.53	6.44	0.36	0.88
Albumin (gm/dl)	3.16	0.42	3.24	0.35	3.78	0.31	0.75
Globulin (gm/dl)	2.97	0.69	2.89	0.59	2.88	0.48	0.71
<b>Liver enzymes</b>							
AST (U/l)	139.47	49.13	384.87	11.26	775.19	39.65	<0.01
ALT (U/l)	89.77	28.55	184.60	9.76	387.86	18.63	<0.01
Alkaline phosphatase (U/l)	131.20	18.16	163.30	14.02	177.79	14.21	0.76

\*analyzed using ANOVA test

**Table 3: Association of raised liver enzymes of patients with dengue severity.**

Parameters		Dengue severity			Total	P value*
		DF	DHF	DSS		
<b>Raised AST (&gt; 40 U/l)</b>						
Yes	N	58	18	7	83	<0.01
	%	85.29	85.71	100.00	86	
No	N	10	3	0	13	
	%	14.71	14.29	0.00	14	
Total	N	68	21	7	96	
	%	100.00	100.00	100.00	100	
<b>Raised ALT (&gt; 40 U/l)</b>						
Yes	N	59	20	7	86	<0.05
	%	86.76	95.24	100.00	90	
No	N	9	1	0	10	
	%	13.24	4.76	0.00	10	
Total	N	68	21	7	96	
	%	100.00	100.00	100.00	100	

\*analyzed using Chi-square test

Because AST and ALT levels were significantly raised in dengue patients, our study was based on prior research. AST is found in erythrocytes, cardiac and skeletal muscle, kidney, liver, and brain tissue, while ALT is mostly found in liver tissue. In muscle, ALT has a diminished effect. Prior studies indicated that elevated AST levels were more widespread than elevated ALT levels. This trend is seen in alcoholic hepatitis but not in viral hepatitis. It has been hypothesised that the release of AST from a variety of sites during dengue sickness was the reason. Increased infection of hepatocytes, which

leads to apoptosis, and high levels of endoplasmic reticulum stress-driven apoptosis, which is an example of dengue-induced hepatocyte apoptosis, are the causes of the change in liver function tests in Dengue patients. The portal system is characterised by fatty changes (micro vesicular), hepatocyte necrosis, hyperplasia, and the death of Kupffer cells, Councilman Bodies, and mononuclear cell infiltrates.<sup>11</sup> The most common location for hepatocyte damage, including necrotic changes, is the midzonal area, followed by the centrilobular region.<sup>12</sup> According to one potential explanation, the liver cells in

this region may be more susceptible to the effects of anoxia or immune response, or they may be a target zone for dengue viruses. Induction of apoptosis has also been related to the transcription factor NF- $\kappa$ B. This study has a few drawbacks. First, this was a single centre study, so the results of our study might not be applicable to other geographical regions. Second, we could not perform a long term follow up of the patients to know their long term complications.

## CONCLUSION

Based on the results our study, we conclude that raised AST and ALT levels were significantly associated with severity of DSS and DHF. In our study we also observed that AST level was more increase in compared to ALT level in dengue patients. Hepatic involvement in dengue fever may vary from mild biochemical involvement to severe acute liver cell destruction. In addition to haematological problems, dengue virus infection is associated with severe abnormalities in liver function, such as elevated liver enzyme levels. Patients with dengue infection should have a baseline liver function test (LFT) and subsequent LFT monitoring to detect early hepatic impairment. Future studies should investigate the risk factors for hepatic impairment in dengue infection patients.

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