

# Alterations in Hematological Parameters and Liver Function Test with Respect to Severity of Dengue in Pediatric Population

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## ABSTRACT

**Background and Objectives:** Dengue is an arboviral mosquito-borne infection prevalent in tropical and subtropical regions worldwide. The objective of this study was to evaluate the impact of dengue on pediatric hematological and hepatic parameters and to explore their association with the disease's progression.

**Methods:** This retrospective study was conducted in the Department of Paediatrics at SMGS Hospital in Jammu. We evaluated 100 patients under 18 years of age who were clinically diagnosed with dengue fever. Detailed hematological parameters (TLC, hematocrit, platelet count) and liver function tests (AST, ALT) were assessed.

**Results:** A total of 100 patients were included in the study. Among these, 82 patients were diagnosed with dengue fever, 13 with dengue hemorrhagic fever (DHF), and 5 with dengue shock syndrome (DSS). Out of the 100 patients in the study, 70 presented with thrombocytopenia of which 39 had mild thrombocytopenia, 20 had moderate, and 11 had severe thrombocytopenia. Liver function tests revealed elevated ALT and AST levels in 86 and 95 patients, respectively. A statistically significant association was found between the degree of thrombocytopenia and transaminitis with disease severity.

**Conclusion:** Thrombocytopenia and increased transaminases are significant markers for gauging the severity of dengue infection.

**Keywords:** ALT, AST, DF, DHF, DSS

## INTRODUCTION

Dengue, often referred to as "breakbone fever," has increasingly become a major cause of febrile illness. This mosquito-borne disease is now the leading arboviral infection globally, following malaria. Approximately 2.5 billion individuals worldwide are susceptible to dengue virus

infection, and over 50 million new cases are anticipated annually. As the leading arthropod-borne viral illness, dengue presents a major public health concern. [1]

The dengue virus (DENV) is a member of the Flavivirus family and is primarily transmitted to humans by Aedes mosquitoes, especially Aedes aegypti. There

are four distinct serotypes of the virus (DENV-1 to DENV-4), identified through neutralization tests. The World Health Organization (WHO) categorizes dengue hemorrhagic fever (DHF) into four grades (I to IV). Grades III and IV represent the most severe cases, which can involve shock, while grades I and II are milder and do not include shock. Symptoms of dengue hemorrhagic fever (DHF) include those of dengue fever, along with bleeding symptoms (such as a positive tourniquet test or spontaneous bleeding), low platelet count, and signs of increased capillary permeability, which may appear as elevated hematocrit or fluid buildup in the chest or abdomen. [2]

In 2009, the World Health Organization (WHO) categorized "severe" dengue (Group C) as encompassing a range of severity levels, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[3]

Significant changes in patients' hematological profiles are associated with dengue infection. Additionally, liver biopsy samples have shown pathological signs of dengue, such as inflammatory cell infiltration and necrosis. These changes are also evident in abnormal liver enzyme levels.[4]

The most prominent hematological change in dengue is leukopenia, which can sometimes drop below  $2 \times 10^3/L$ . Atypical lymphocytes are commonly observed in cases of lymphocytosis. As the condition progresses to dengue hemorrhagic fever (DHF), there is typically a 20% increase in hematocrit levels from the patient's baseline, accompanied by thrombocytopenia (below  $100 \times 10^9/L$ ). Therefore, hematocrit concentration should be monitored regularly throughout the course of the illness. [5,6]

Hepatic dysfunction during dengue infection can result from direct damage to liver cells by the virus or from dysregulated host immune responses. Children infected with dengue may experience mild liver damage, characterized by elevated transaminases, or severe liver damage leading to jaundice and

liver cell failure. Hepatic dysfunction is more prevalent in cases of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[7]

Recent studies from India and Thailand indicated that acute hepatic failure in children is most frequently caused by dengue infection, representing 18.5% of cases in India and 34.3% in Thailand. [8,9]

Dengue infection can be identified using clinical signs and laboratory tests. There are both nonspecific and specific laboratory tests used, including haematological parameters, liver function tests, serum protein concentration, viral antigen tests, genomic sequences, and serology for antibody detection.

## **MATERIALS & METHODS**

This study was conducted at the Paediatric Department of SMGS Hospital in Jammu during August 2022 to October 2022. It focused on children under 18 years old who were diagnosed with dengue fever. Patients with confirmed diagnoses of malaria, leishmaniasis, typhoid fever, or other chronic diseases were not included in the study. On a predesigned proforma, detailed history and clinical examination findings were noted. In accordance with the standard diagnostic procedures at our hospital, the following investigations were conducted: complete blood count (CBC), dengue NS1 antigen, Dengue IgM antibody tests, serum bilirubin, SGPT, SGOT, ALP, prothrombin time, serum protein, serum albumin, and abdominal ultrasound (USG). Both NS1 antigen and IGM antibodies for dengue were done by ELISA method.

Clinical criteria for diagnosing dengue fever. Fever of less than 7 days with any 2 of the following: Headache, Arthralgia, Myalgia, Rash, Retroorbital pain & hemorrhagic manifestation.

Dengue was divided into three categories, Dengue fever, Dengue Hemorrhagic Fever (DHF), Dengue Shock Syndrome (DSS), according to Indian National Guidelines for management of Dengue Fever 2015. WBC counts below  $4,000 \text{ cells/mm}^3$  was

considered leukopenia, and platelet counts below 1,50,000 cells/mm<sup>3</sup> was considered. Thrombocytopenia- Thrombocytopenia was further classified as mild moderate and severe with platelets counts 1.5 to 1 lakh/mm<sup>3</sup>, 1 lakh to 50000 mm<sup>3</sup> and <50000 mm<sup>3</sup> respectively. A raised level of AST and ALT was defined as 40 IU or more. Hypoalbuminemia is defined as an albumin level below 3.5 g/dL, hypoglobulinemia as globulin levels under 2.5 g/dL, and hyperbilirubinemia as bilirubin levels exceeding 1.2 mg/dL. It will be tested whether liver enzyme levels (AST and ALT) correlate with dengue severity.

### STATISTICAL ANALYSIS

Descriptive statistics were used to analyze hospital data. The data were entered into a Microsoft excel spreadsheet, and the final analysis was performed using IBM's Statistical package for the Social Sciences (SPSS) software, IBM manufacturer, Chicago, Illinois, USA, version 21.0. The Chi-square test was used to examine qualitative variables. A  $P < 0.05$  was considered statistically significant for statistical significance.

### RESULT

One hundred patients were included in the study. Among them, 52 were NS1 Antigen positive, 3 were Rapid IgM antibody positive, and 39 were positive for both tests. The remaining 6 dengue cases were negative for both NS1 Antigen and Rapid IgM antibody. Age and gender distribution of patients is shown in Table 1. 6.25 days was the average duration of hospitalisation. 82 patients were attributed to be classical dengue fever in which 53 (64.6%) were males and 29 (35.4%) were females. 13 cases diagnosed as dengue haemorrhagic fever and 5 patients as dengue shock syndrome were predominant in male patients. Fatalities reported were due to multi-organ failure likely DSS & mortality rate in our study was 5.0% (5 cases) (FIGURE 1).

Headache and fever was the common presenting symptoms in majority of the patients. Retro-orbital pain, nausea, vomiting, body ache, itching, rashes and bleeding manifestations were also seen. Many of the patients presented as acute gastroenteritis and hepatomegaly. Third-space fluid collections were observed as ascites in a small number of cases.

In this study, from thrombocytopenia (platelet count <1.5 lakh) was found in 70 (70%) cases while rest 30 patients presented with normal platelet count of more than 1.5 lakh. Out of 70 patients with thrombocytopenia, 39 patients had mild thrombocytopenia in which 37(94.9%) had dengue fever and 2 (5.1%) with dengue haemorrhagic fever. 20 patients had moderate thrombocytopenia with 15 (75.0%) diagnosed as dengue fever and 5 (25.0%) with dengue haemorrhagic fever while remaining 11 patients had severe thrombocytopenia in which 6 (54.5%) were dengue haemorrhagic fever and 5 (45.5%) were dengue shock syndrome. A strong correlation was found between the severity of thrombocytopenia and the severity of the disease ( $p < 0.001$ ) as shown in Table (Table 2). The study also revealed a strong correlation between the degree of thrombocytopenia and disease severity, as all patients with dengue shock syndrome (DSS) exhibited severe thrombocytopenia. Similarly, patients with dengue hemorrhagic fever (DHF) showed more severe thrombocytopenia compared to those with dengue fever, which is statistically significant and depicted in the Table 2.

Leukocytopenia, with a white blood cell count below 4,000, was observed in 29% of cases (29 patients). This suggests that, along with thrombocytopenia, leukocytopenia is another indicator of this viral infection and should be included in the differential diagnosis. In 67 cases (67%) leukocyte count was normal between 4000- 11,000 and only 4 cases (4%) presented with leukocyte count > 11,000. Out of 100 patients, 59 patients had haematocrit value of less than 40, followed by 24 patients with

haematocrit in the range of 40-45 and only 17 patients had haematocrit value more than 45. (Table 3)

For liver function tests, 86% of patients (86 cases) had elevated ALT levels, and 95% of patients (95 cases) had elevated AST levels. All five cases of dengue shock syndrome (DSS) showed elevated levels of both ALT and AST. Specifically, three cases (60%) had ALT values between 490-700 IU/L, while two cases (40%) had values ranging from 70-490 IU/L. Similarly, two cases (40%) had AST values between 590-800 IU/L, and the remaining three cases (60%) showed values between 70-590 IU/L.

Among the 13 diagnosed cases of dengue hemorrhagic fever (DHF), 12 patients exhibited elevated ALT levels. Of these, 10 cases (76.9%) had ALT values ranging from 70 IU/L to 490 IU/L, while the remaining 2 cases (15.4%) had values between 490 and

700 IU/L. (FIGURE 2) Similarly, 86 patients exhibited elevated AST values. Among them, 11 cases (84.6%) had values ranging from 70 IU/L to 590 IU/L, while the remaining 2 cases (15.4%) had values between 590 IU/L and 800 IU/L (FIGURE 3). From a total of 82 patients with Dengue fever, 32 patients (39%) showed ALT value between 31-70 IU/L, 50 patients (61%) showed value between 70-490 IU/L. Similarly, AST levels among whom 23 cases (28%) had value between 31-70 IU/L, and 59 cases (72%) showed value between 70-590 IU/L, with a significance of lesser hepatic injury in cases of dengue fever in comparison to DHF and DSS. Higher levels of both transaminases were significantly associated with increased disease severity. as shown in Table and Chart 2. This emphasizes the substantial role of liver tissue in the viral infection.

**Table-1 Age-wise and Gender-wise distribution of patients**

Age Group	Male		Female		Total Patients	
	Number	%	Number	%	Number	%
1-4 years	4	57.1	3	42.9	7	100.0
5-9 years	25	92.6	2	7.4	27	100.0
10-14 years	30	71.4	12	28.6	42	100.0
15-18 years	12	50.0	12	50.0	24	100.0
Total	71	29.0	29	71.0	100	100.0

**Table-2 Degree of thrombocytopenia & its association with Dengue fever, DHF, DSS**

Severity of Dengue	Thrombocytopenia						$\chi^2$	p-value
	Mild		Moderate		Severe			
	No.	%	No.	%	No.	%		
Dengue Fever	37	94.9	15	75.0	0	-	74.147	<0.001
Dengue Hemorrhagic Fever	2	5.1	5	25.0	6	54.5		
Dengue Shock Syndrome	0	-	0	-	5	45.5		
Total	39	100	20	100	11	100		

**Table 3 Platelet, TLC & Haematocrit values of the patients**

Parameters		Normal Reference Range	Number (%)
Platelet Count	<150,000	150,000-400,000 per microlitre	70 (70)
	≥150,000		30 (30)
	Total		100 (100)
Total Leukocyte Count	<4,000	4,000-11,000 cu.mm	29 (29)
	4,000-11,000		67 (67)
	>11,000		4 (4)
	Total		100 (100)
Hematocrit	Below 40	35.5% to 44.9%	59 (59)
	40-45		24 (24)
	Above 45		17 (17)
	Total		100 (100)

Figure 1 Pie Chart showing severity of the disease among patients

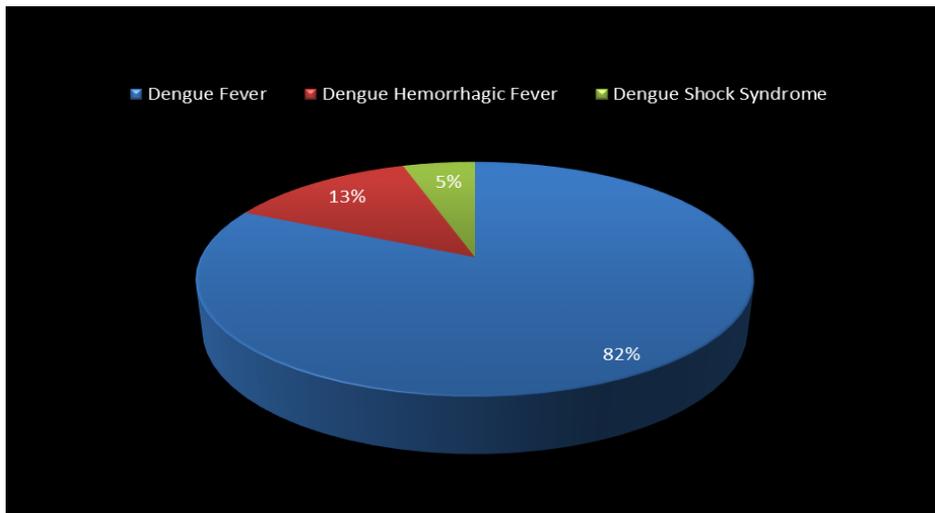


Figure 2 Correlation of raised Aspartate aminotransferase (AST) values with severity of disease

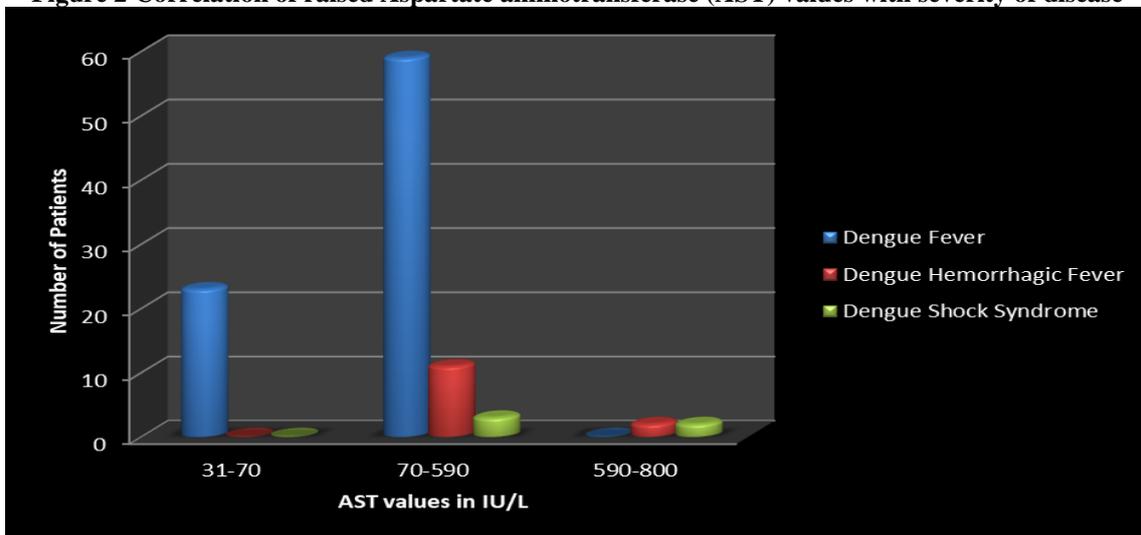
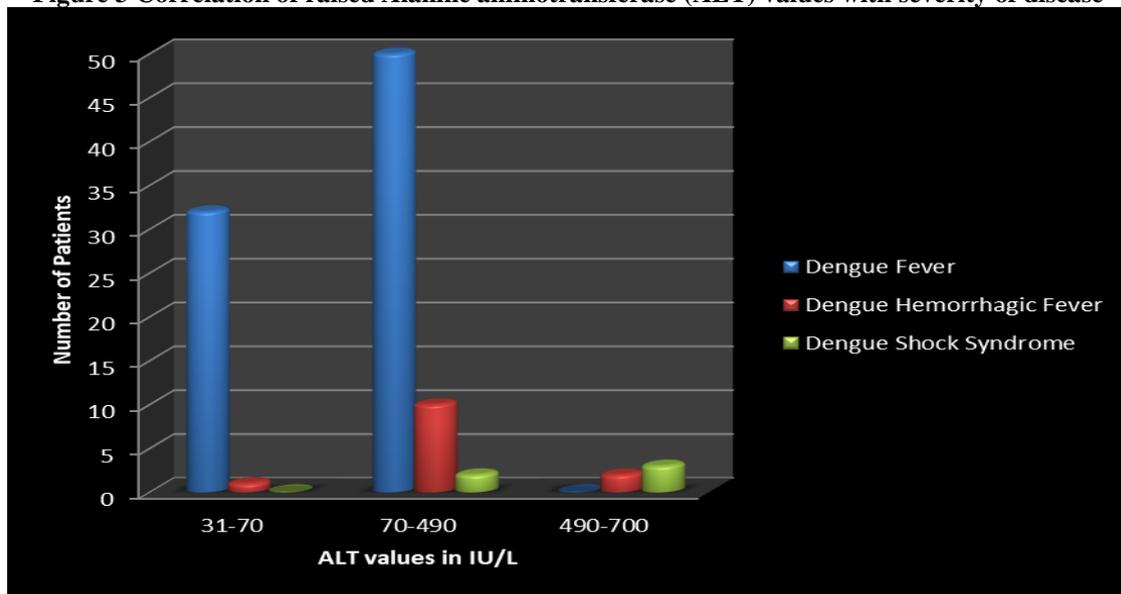


Figure 3 Correlation of raised Alanine aminotransferase (ALT) values with severity of disease



## DISCUSSION

In our study, all patients (100%) reported fever, while 40-50% experienced headache and 50-60% had retro-orbital pain. Laul et al. also found that 87% of their patients complained of headache, with 41% experiencing retro-orbital pain (10). Abdominal symptoms are common in dengue fever. In our study, 40% of patients presented with acute gastroenteritis, and 50% experienced nausea and vomiting. Nimgadda et al. reported similar issues in 70% of their patients. (11)

In our study, thrombocytopenia was found in 70% of cases, while the remaining 30% had normal platelet counts. Among those with thrombocytopenia, 39% had mild thrombocytopenia, 20% had moderate thrombocytopenia, and 11% had severe thrombocytopenia. Similar results were reported in previous studies. For instance, K. Jayashree et al. found that 70% of cases had thrombocytopenia (platelet count <1.5 lakh). Among these, 36 patients (48.64%) had mild thrombocytopenia (1 lakh to <1.5 lakh), 31 patients (41.89%) had moderate thrombocytopenia (50,000 to 1 lakh), and 7 patients (9.45%) had severe thrombocytopenia (less than 50,000). Other studies have also shown similar findings. For example, in a study by Khan et al., among 76 patients with thrombocytopenia (platelet count <1.5 lakh), 38 (50.0%) had mild thrombocytopenia (1 lakh – <1.5 lakh), 28 (36.8%) had moderate thrombocytopenia (50,000 – 1 lakh), and 10 (13.2%) had severe thrombocytopenia (platelet count <50,000). In addition, Kishore et al. found thrombocytopenia in 80% of cases. (12) A study examining the correlation between leukocyte count, platelet count, and disease progression found the following low blood count values during the illness: hemoglobin (Hb) at  $13.2 \pm 1.9$  gm/dL, white blood cells (WBC) at  $(2.77 \pm 1.63) \times 10^3/\text{mm}^3$ , and platelets at  $(8.7 \pm 5.5) \times 10^4/\text{mm}^3$ . Leukopenia (WBC less than  $4000/\text{mm}^3$ ) was observed in 76% of cases (38 patients), which is consistent with our findings, as 29% of cases in our study also showed

leukopenia. In our study, hepatomegaly was present in 50% of patients, with elevated ALT levels in 86% and elevated AST levels in 95%. All five cases of dengue shock syndrome (DSS) exhibited elevated ALT and AST values. Of these, three cases had ALT levels between 490 IU/L and 700 IU/L, while the other two had ALT values ranging from 70 IU/L to 490 IU/L. For these same patients, AST values were between 70 IU/L and 590 IU/L in three patients and between 590 IU/L and 800 IU/L in two patients. Among the 13 patients with dengue hemorrhagic fever (DHF), all cases exhibited elevated ALT levels. Specifically, 2 cases had ALT levels between 490 IU/L and 700 IU/L, while the other 11 patients had values ranging from 30 IU/L to 490 IU/L. AST levels were also elevated, with 2 cases falling between 590 IU/L and 800 IU/L, and 11 cases showing values between 70 IU/L and 590 IU/L. In the cohort of 82 patients with dengue fever, 64% had raised transaminase values, although these elevations were less significant, with ALT ranging from 50 IU/L to 500 IU/L and AST from 59 IU/L to 590 IU/L. This suggests a lower degree of liver damage in dengue fever cases compared to those with DHF and DSS. The elevation of both transaminase levels was strongly correlated with disease severity ( $p < 0.001$ ), highlighting the liver's significant role in the viral infection. Kuo et al. studied liver enzymes in 270 dengue patients and found abnormal AST and ALT levels in 93.3% and 82.2%, respectively. Most cases showed mild to moderate increases in transaminase levels. In 11.1% of patients, AST levels were ten times higher than the normal upper limit, and 7.4% had similarly elevated ALT levels. The study observed that AST levels generally rose more than ALT levels, and both returned to normal within three weeks. This finding was attributed to the damage of heart muscle cells during dengue infection, resulting in the release of AST. (13) Similarly, a study by Souza LJ et al. found that liver damage was more severe in patients with dengue hemorrhagic fever

(DHF), with acute hepatitis (grade D) diagnosed in 8.5% of these cases. The hemorrhagic form of the disease showed higher average levels of AST and ALT. (14) Wahid et al. studied 50 serologically confirmed cases—25 with classic dengue and 25 with DHF—and found significantly higher serum levels of AST and ALT in patients with DHF. (15) Linda K et al. found that 86% of cases (595) had AST levels above the normal upper limit, while 46% of cases (316) had elevated ALT levels. According to the WHO 2009 criteria, seven patients (1.0%) were classified as having severe dengue due to concurrent AST or ALT levels  $\geq 1000$  U/L, and three additional patients met the criteria based solely on elevated AST or ALT levels  $\geq 1000$  U/L. (16)

### LIMITATION

The sample size included in the study was limited keeping in view duration of the study. Also there was no information on whether the infection was primary or secondary and dengue serotype. Having a bigger sample size & involvement of other centres about the disease would yield more better conclusions.

### CONCLUSION

Several studies have investigated the connection between blood cell counts, liver involvement, and the severity of dengue disease. However, no single marker has been established for assessing overall disease severity. Furthermore, atypical symptoms have made managing and predicting patient outcomes more challenging. Our study aimed to explore the relationships between different parameters and disease severity and prognosis. Among the blood cell counts, platelet count demonstrated a significant correlation with disease severity, making it valuable for assessing severity and adjusting treatment plans. Notably, all three fatal cases in our study also had severe thrombocytopenia. Similarly, hepatic involvement assessed through liver enzyme assays indicated that

severe cases had significantly elevated enzyme levels, suggesting more intense liver tissue involvement in severe dengue. In conclusion, low platelet counts and elevated liver enzymes are reliable indicators of the severity of dengue fever.

### Declaration by Authors

**Ethical Approval:** Approved

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**Conflict of Interest:** The authors declare no conflict of interest.

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