

## Correlation of Liver Function Test and Total Leukocyte Count with Severity of Disease in Children with Dengue Fever: A Prospective Study

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### Abstract:

**Introduction:** Dengue fever is a vector borne disease manifesting in many clinical ways. It is a well-studied disease, and many research aims to understand various aspects of its severity and prognosis. Hepatic dysfunction, especially when accompanied by encephalopathy, significantly increases the risk of mortality. In addition, liver dysfunction can exacerbate bleeding manifestations and disseminated intravascular coagulation, both of which are associated with poor outcomes. Early detection and prompt supportive care are crucial to reducing mortality and morbidity. This study aims to explore the correlation between the severity of dengue fever in children and their total leukocyte count and liver function test.

**Method:** The prospective observational study was conducted in the Department of Pediatrics at Rohilkhand Medical College and Hospital from November 2022 to October 2023. 55 participants were enrolled after obtaining informed consent from the guardians or parents, with clearance from the institutional ethics committee. Readings of LFTs and total leukocyte count was obtained. All children were further followed up for minimum 3 months or normalized LFT and Total leukocyte count whichever is earlier.

**Result:** Laboratory tests revealed significant changes in the average Total Leukocyte Count (TLC) during the follow-up period, particularly among patients with Dengue Shock Syndrome (DSS). There were also notable differences in liver enzyme levels (SGOT and SGPT) between the initial and follow-up tests, reflecting the considerable impact of dengue on liver function. Additionally, average platelet counts varied with disease severity, highlighting a clear link between thrombocytopenia and the seriousness of dengue.

However, no statistically significant changes were observed in leucocyte count or other laboratory parameters, such as PCV, Alkaline Phosphatase, Total Protein, and Albumin levels, across different forms of dengue.

**Conclusion:** This study underscores the complex diagnostic and laboratory features of dengue virus infection in children, emphasizing the need for careful patient monitoring and tailored care strategies to improve outcomes based on the severity of the disease.

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### Introduction

Dengue is a disease that is transmitted by vectors and can manifest in a variety of ways clinically. It could range from a mild viral disease to a severe condition that endangers one's life and finally leads to the failure of several organs and death.

Because it poses a substantial burden of disease in regions where it is prevalent, the government has implemented substantial measures to decrease the vector control and training programme with the aim of effectively managing the disease. However, there are times when clinical condition worsens to land up in critical phase where child needs PICU and other high-level modalities and treatment.

Although many of the cases admitted in the hospital may get discharged with a single supportive treatment, there are times when clinical condition worsens to land up in critical phase. [1,2]

Dengue has emerged as a significant threat to public health in recent decades due to the high rates of death and illness linked to the disease. [1] It is one of the most important viral diseases that can be transmitted from mosquitoes to humans and can cause illness. It can be found in over a hundred different countries and poses a danger to the wellbeing of over 2.5 billion people living in tropical and subtropical regions. [2] Dengue is

considered an endemic disease in many parts of India [2,3], furthermore, it exists common practice to keep track of both domestic and international epidemics. [4] Patients with dengue experience changes in their complete blood count with each passing day of their fever.

More specifically, these shifts take place on days 3 through 8, beginning with progressive leukopenia and moving on to thrombocytopenia and hemoconcentration due to plasma leakage. [12,13] The data from Brazil revealed that the average white blood cell count (WBC) of individuals infected with dengue was  $4.6 \times 10^9/L$ , with the lowest level recorded at  $0.7 \times 10^9/L$ . Additionally, the average number of platelets was  $26.4 \times 10^9/L$ , and the lowest count observed to be less than  $1 \times 10^9/L$ . Each these kinds of counts exhibited a substantial increase compared to the count recorded for patients without dengue. [14] A prominent and, according to some estimates, the second most common symptom of dengue is leucopenia, This is characterised as an overall leucocyte counts of less than  $4 \times 10^9/l$ . [15,16] It provides sufficient clues throughout the process of diagnosing dengue and aids in distinguishing it from other disorders that are associated with fever that, in the end, helps to bring about a decrease in the morbidity and death rates that are linked with the disease. [17]

While some research has found that total leucocyte counts or leucopenia could be employed as a predictive factor for the severity of dengue, other research has found the opposite to be true. [18] A small number of several investigations have demonstrated that there is a steady decline in the number of white cells along with a sudden drop in platelet counts that occurs prior to plasma leakage. As a consequence of this, it is possible that this is the earliest indicator of severe dengue. [19] As of late, more reports have demonstrated elevated hepatic transaminases or aminotransferase levels in dengue infection.

These elevated levels of Aspartate Transaminase (AST) and Alanine Transaminase (ALT) suggest that the liver is primary targets for the dengue virus. It is possible for the degree of the liver injury to range from a minor rise of transaminases that is asymptomatic to acute liver failure, which can be fatal with the latter being more typical in the children, females, and certain ethnic groups.

In addition, children who have had dengue before are a greater likelihood of having significant involvement of the liver. [22]

### Material and Methods

This study was conducted at Rohilkhand Medical College and Hospital in Bareilly. The study included both inpatients and outpatients receiving

treatment from November 1, 2022, to October 30, 2023.

### Inclusion Criteria:

1. All the patient falling under the age of 18.
2. Children who are diagnosed via serology tests as having dengue fever.

### Exclusion Criteria:

1. Patients above 18 years of age.
2. Children having malaria, enteric fever, dengue like illness.
3. Children having drug induced liver toxicity

After approval from the Institutional Ethical committee the subjects were selected as per inclusion and exclusion criteria. A detailed history, complete physical examination and routine & appropriate investigations were done for all patients. Study was carried out in the Department of Paediatrics, RMCH after taking approval from institutional ethics committee and consent from patients and included all the serologically proven dengue positive patients under the age of 18 years. Agreement was taken from all subjects for clinical examination. Readings of LFTs and total leucocyte count was obtained. All children were further followed up for minimum 3 months or normalized LFT and Total leukocyte count whichever is earlier.

**Statistical Analysis:** The statistical evaluation was conducted by the statistical software SPSS version 25.0 after the data had been loaded into the Microsoft excel spreadsheet.

The quantitative (numerical variables) information was presented as the averages and levels of standard deviation, while the qualitative (categorical variables) information was presented as the occurrence and percentage of each category. Using chi square test the data analysis will be done to prove the association of both LFT and total leukocyte count with severity of disease in kids with dengue fever. If the p-value was less than 0.05, then it was regarded to be of statistical significance.

### Results

**Age:** Major Findings: The age range between 6 and 10 years had the highest occurrence of all forms of dengue infections, with dengue fever (DF) being the most prevalent among all age groups. The significance level of 0.723 indicates that there is no statistically significant variation in illness type distribution based on age.

**Important Values:** 20 DF patients in the age range of 6 to 10 years group (highest incidence).

**Gender:** Major Findings: Males were significantly more affected by dengue infections than females, with 41 male cases out of 57. There was no

statistically significant variation in the distribution of infection types between genders (p-value: 0.344).

Important Values: 26 DF cases among males (highest).

### Symptoms

Major Findings: Fever was the predominant symptom for both Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF), although vomiting was notably more prevalent in cases of DHF and Dengue Shock Syndrome (DSS).

The spectrum of symptoms demonstrates the variability in clinical presentations among different kinds of dengue.

Important Values: Vomiting observed in 70% of DHF and 73% of DSS cases.

### Mean Hospital Stay

Major Findings: DSS patients showed the lengthiest hospital stays on average, but the variation in stay length across dengue types wasn't statistically significant (p-value: 0.634).

Important Values: Mean stay of 7.55 days for DSS patients.

### Mean TLC Count

Major Findings: There were substantial alterations in the average total lung capacity (TLC) from the initial measurement to the subsequent evaluation, especially among patients with DSS. The follow-up analysis revealed a noteworthy p-value of 0.001, showing significant disparities between the groups.

Important Values: Baseline mean TLC for DSS was 8180.75; follow-up showed significant changes.

### Lab Findings

Major Findings: While there were trends in increasing PCV and variable levels of Alkaline Phosphatase, Total Protein, and Albumin along with severity of disease, none showed statistically significant differences across dengue types.

Important Values: The packed cell volume (PCV) showed an increase from 34.45 in the DF condition

to 37.00 in the DSS condition, however this increase was not of statistical significance (p-value: 0.067).

### LFT

Major Findings: Trends suggest higher total and direct bilirubin levels in more severe dengue types, but differences were not of significance statistically.

Important Values: Highest mean total bilirubin in DHF (57.68%).

### SGOT Levels

Major Findings: There were notable disparities in SGOT levels between the initial measurement and the subsequent with DSS patients exhibiting considerably elevated levels initially (p-value: 0.001).

Important Values: Baseline SGOT for DSS was 678.38 U/L.

### SGPT Levels

Major Findings: Like SGOT, notable disparities in the SGPT levels were noted, suggesting that liver strain fluctuates depending on the severity of dengue (p value: 0.001).

Important Values: Baseline SGPT for DSS was 314.13 U/L.

### Leucocyte Count

Major Findings: Leucopenia was common across dengue types, but the occurrence didn't significantly vary with the severity of dengue fever.

Important Values: 52.63% DF patients had leucopenia.

### Average Platelet Count

Major Findings: Significant variations in average platelet counts were seen among different forms of dengue, with numbers falling in more severe cases (p value: 0.001).

Important Values: An average platelet count for DF was 98675.21/ $\mu$  L, much higher compared to DHF and DSS.

**Table 1: Describing the study groups as per Age**

Age	DF (Dengue Fever)	DHF (Dengue Hemorrhagic Fever)	DSS (Dengue Shock Syndrome)	Total	p-value
1 to 5 years	10 (17.54)	3 (5.26)	2 (3.51)	15 (26.32)	0.723
6 to 10 years	20 (35.09)	7 (12.28)	3 (5.26)	30 (52.63)	
11 to 15 years	7 (12.28)	2 (3.51)	1(1.75)	10 (17.54)	
16 to 18 Years	1(1.75)	1(1.75)	0 (0.00)	2 (3.51)	
Total	38 (66.67)	13 (22.81)	6 (10.53)	57 (100.0)	

**Table 2: Describing the study groups as per Gender**

Gender	DF	DHF	DSS	Total	p-value
Male	26 (45.61)	11 (19.30)	4 (7.02)	41 (71.93)	0.344
Female	12 (21.05)	2(3.51)	2(3.51)	16 (28.07)	
Total	38 (66.67)	13 (22.81)	6 (10.53)	57 (100.0)	

**Table 3: Describing the study groups as per Symptoms**

Symptoms	DF	DHF	DSS
Fever	60%	50%	50%
Headache	9.6%	5%	45%
Myalgia	9.6%	16.57%	27%
Arthralgia rash	7.5%	0.00%	0.00%
Diarrhea	9.65%	15%	0.00%
Vomiting	43%	70%	73%
Skin Bleeding	0.00%	0.00%	27%
Cough	24%	56%	6%
Convulsion	3%	16%	0.00%

**Table 4: Describing the study groups as per Mean Hospital Stay**

Hospital Stay	DF	DHF	DSS	p-value
Mean±SD	6.34±1.11	6.78±1.30	7.55±1.75	0.634

**Table 5: Describing the study groups as per Mean TLC count**

Mean TLC count	DF		DHF		DSS		Total		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Baseline	6433.79	6295.91	5818.54	7189.51	8180.75	7149.11	6495.60	6786.33	0.786
Follow- up	5482.07	1484.82	6252.31	2313.96	7051.00	1563.88	5807.28	1812.49	0.001

**Table 6: Describing the study groups as per Lab findings**

Lab findings	DF		DHF		DSS		Total		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
PCV	34.45	8.67	35.45	7.67	37.00	6.26	37.43	6.93	0.067
Alkaline Phosphates e	168.22	122.75	164.77	98.65	142.13	64.64	159.97	109.37	0.783
Total Protein	6.20	0.93	6.67	0.91	6.15	1.01	6.36	0.93	0.503
Albumin level	3.05	0.66	3.33	0.79	3.10	0.59	3.15	0.68	0.430

**Table 7: Describing the study groups as per LFT**

LFT	DF		DHF		DSS		p-value
	Mean	SD	Mean	SD	Mean	SD	
Total Bilirubin	37.45%	22.99%	57.68%	35.24%	55.25%	23.66%	0.057
Direct Bilirubin	17.53%	6.09%	23.46%	11.67%	20.88%	8.93%	0.214

**Table 8: Describing the study groups as per SGOT**

SGOT	DF		DHF		DSS		p-value
	Mean	SD	Mean	SD	Mean	SD	
Baseline	124.62	150.89	167.82	89.56	678.38	796.27	0.001
Follow-up	26.28	3.80	30.77	6.19	35.88	10.62	0.001

**Table 9: Describing the study groups as per SGPT**

SGPT	DF		DHF		DSS		p-value
	Mean	SD	Mean	SD	Mean	SD	
Baseline	68.93	38.36	114.25	48.72	314.13	282.13	0.001
Follow-up	35.31	4.38	37.62	7.64	48.38	14.61	0.001

**Table 10: Describing the study groups as per Leucocyte count**

Leucocyte count	DF N= 38		DHF N=13		DSS N=6		Total N=57		p-value
	n	%	n	%	n	%	n	%	
Leukocytosis	2	5.26	1	7.69	0	0.0	3	5.26	0.796
Leucopenia	20	52.63	7	53.85	1	16.67	28	49.12	0.328

**Table 11: Describing the study groups as per Mean platelet count**

Mean platelet count	DF		DHF		DSS		Total		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
	98675.	71515.	38846.	19560.	45027.	34185.	67800.	72917.	0.00
	21	99	15	92	00	84	00	50	1

## Discussion

Patients with dengue infection exhibit an abrupt onset of fever without any specific local signs or symptoms. The clinical manifestations may bear resemblance to other infections, posing challenges in distinguishing it from tropical diseases (such as rickettsial illness, a condition known as leptospirosis, or malaria as well as other infections caused by viruses, and primary bacteremia. Our study discovered significant differences in clinical features and CBC parameters that can help distinguish dengue infection from other causes. [24]

The symptoms of dengue infection encompass fever, headache, reduced appetite, nausea, bleeding tendency, muscle pain, abdominal discomfort, throat irritation, and diarrhoea. These symptoms are nonspecific and may be seen in different types of illnesses. We observed that headache, nausea, lack of hunger, and haemorrhage diathesis were prevalent among dengue patients, whereas chills were notably more prevalent in the placebo group. Consequently, these observable symptoms can help differentiate dengue illness from other infections when initially observed. [24]

## Leucocyte Count

Based on the findings of our research, the array of white cell counts was between 1.4 and 35.0 x 10<sup>9</sup>/l, and there was leucopenia in 49.12% of the subjects while 5.26 % of the subjects had leukocytosis. In a study that was undertaken by Joshi et al.[10], the total leucocyte count ranged from 1.1 x 10<sup>9</sup> /l to 14.3 x 10<sup>9</sup> /l ( 4 x 10<sup>9</sup> /l), and leucopenia and leukocytosis were observed in 36% and 9% of the cases, respectively. These % ages were significantly lower than the ones seen in our study. Leucopenia was found in 26 % of the study subjects, according to Natasha Ali et al.[11] , while spoorthy vulavula et al.[22 ] and Geetika dhir et al.[93] found it in 34.19% and 37.8% of the cases, respectively. In a study that was undertaken by Priyanka M. Patel et al.[14], leucopenia was observed in approximately 44% of the patients. Meena KC et al.[90], on the other hand, reported leucopenia in 51% of patients, which was not in lieu with our study. The % age of people with leucopenia found in Kinjal Patel et al.[25]'s study was 56.92%, which was greater than the %age found in the present study.

Dengue is a prominent factor in the development of leucopenia, a condition resulting from the virus's

ability to inhibit bone marrow function. [20] Leucopenia is helpful in diagnosing, differentiating, and determining the prognosis for dengue. [24, 25] Upon analysing the dengue group with the control group, it was found that the dengue fever group exhibited a significantly reduced total count of white blood cells. Leukopenia in the dengue fever group commenced on the second day of the illness and reached its nadir on the fifth day of the fever. A bone marrow examination revealed a slight decrease in cell count during the initial seven days of fever, followed by a return to normal cell count during the recovery phase. Based on this, one possible explanation for the development of leukopenia in dengue infection cases is the destruction or suppression of the myeloid progenitor cells. The determination was made based on the observation because the marrow's examination revealed a normal level of cellularity during the recovery phase. [24]

## Liver enzymes

In children who have a dengue infection, the severity of liver dysfunction can range from mild injury with an elevated level of transaminases to severe injury with jaundice and the death of liver cells. Pain in the right hypochondrium, hepatomegaly, varying degrees of jaundice, and a rise in liver markers, primarily AST and ALT, are some of the manifestations that may be indicative of liver involvement. In patients with dengue shock syndrome and dengue hemorrhagic fever, the occurrence of hepatic dysfunction is significantly higher. [15]

In the current research, increased levels of both SGOT and SGPT, plus alkaline phosphatase. In a study that was very similar to ours, Kuo and colleagues[18] reported that elevated levels of AST, ALT, and ALP were found in 93.3%, 82.2%, and 16.3% of cases respectively. Although the most of the patients had only mild to moderately elevated levels of these transaminases, approximately 10% of patients (11% for AST and 7% for ALT respectively) had levels that were elevated by almost multiplied by 10 or more than normal. Both the AST and ALT levels were found to be altered in 63 and 45% of patients, respectively, based on the findings of DeSouza and colleagues [14]. They found that the levels of AST and ALT in patients with DHF were noticeably higher on average than those found in patients with DF. Wahid SF et al.[11] discovered that patients with DHF exhibited higher levels of blood alanine

aminotransferase (ALT) and alkaline phosphatase (ALP) compared to patients with DF. The % age of patients with DHF who had these elevated levels was 80% and 48%, respectively (64% and 32% patients respectively). Concomitant elevation of ALT and ALP levels was found in 36% of patients with DHF and 24% of patients with DF.

When compared to the DF group, the hepatic enzyme levels of those with DSS and DHF in the hospital study were significantly higher than those in the DF group. In a study conducted by Srivenuithae et al. [16], it was observed that the level of hepatic enzymes increased fivefold in cases of dengue fever contrasted to severe dengue (DHF and DSS). Petdachai109 discovered markedly elevated levels of liver enzymes in individuals with DSS in comparison to those with dengue fever.

In our study, we noted that the level of ALT rose by more than tenfold in 16% of the DSS group, 7.7% of the DHF group, and none of the DF group. When compared to the DF group, it was discovered that most of the transaminases were significantly elevated in the DSS and DHF groups, which was statistically significant. Similar to our study, Kuo et al. [18] discovered a rise in AST of more than >10fold in 11.1% of patients and ALT in 7.4%. Out of 1585 dengue patients, De Souza et al. 24 discovered that a >10fold rise in AST and ALT levels is seen in 3.4% and 1.8% of the cases respectively/y. In their study, Wong et al.[16] discovered a greater than 10-fold increase in AST levels in 10.2% of the cases and ALT levels in 9.5% of the cases.

The increase in transaminases by a factor of 10 was more pronounced in children than in adults, suggesting a higher level of liver involvement in children compared to adults. If the patient had an unusually elevated amount of an enzyme called transaminase, there was a substantial likelihood that they were experiencing hepatic encephalopathy. [13]

Khan et al.[19] in Saudi Arabia reached the same conclusion about the correlation between elevated AST levels and problems. Hepatic injury induced by dengue often initiates within the initial week of sickness and resolves back to normal within a span of between two and three weeks. It has been observed that the level of transaminase starts to rise within the initial three days of the sickness and reaches its highest point around the fifth day. Fernando et al.[17] observed that the most elevated levels of AST were observed on the sixth day of illness in a group of 55 adults diagnosed with dengue. Furthermore, they noted that these values were higher in individuals with Severe Dengue. These findings are very similar to the results that have been shown by other researchers.

According to Jagdish Kumar and colleagues [23], prolonged PT values (INR>1.5) were found in 20%

of the cases. This % age was significantly higher in the DHF group (31%), compared to the DSS group (13%). In 66 % of the cases, hypoalbumenemia was found to be present. The incidence of hypoglobinemia was substantially greater in the DHF group (69%) and DSS group (60%) compared to the DF group (17%). Wong et al. [16] found low globulin levels in 14.2% of their adult patients, low albumin levels in 16.5% of their patients, and abnormalities in PT and APTT in 42.5% of their adult patients.

When fever and hepatic failure are present in children in regions where dengue is endemic, the primary differential diagnosis that must be considered is dengue. This is especially true for cases involving young children. Damage can be caused to liver cells either by the virus itself or by the immune response of the host to the virus. Also, the compromise in mechanism of circulation, hypoxia, acidosis and vascular leakage in liver. Instances have been documented wherein the virus that causes dengue fever was detected in hepatocytes, resulting in elevated mortality rates. An analogous experiment was conducted on mice, and then replicated on people.

Wong et al.[95]'s research indicates that the occurrence of DHF, as well as DSS, subsequent infection, thrombocytopenia, high haematocrit, being female, and being a youngster are all prognostic variables for liver injury. At an early stage in the fever phase, the transaminases are important predictors of dengue fever added with other viral markers.

## Conclusion

Lab tests revealed substantial alterations in the average Total Leukocyte Count (TLC) during the follow-up period, especially in patients with Dengue Shock Syndrome (DSS). Additionally, there were notable differences in the levels of liver enzymes (SGOT and SGPT) between the initial and follow-up tests, indicating the considerable effect of dengue on liver function. Moreover, there were notable differences in average platelet counts that corresponded to the severity of the disease, providing further evidence of the link between thrombocytopenia and the seriousness of dengue.

Nevertheless, there were no statistically significant changes observed in the leucocyte count and other laboratory findings, such as PCV, Alkaline Phosphatase, Total Protein, and Albumin levels, among the different forms of dengue. This study highlights the intricate diagnostic and lab characteristics of dengue virus infection in children, underlining the importance of closely monitoring patients and implementing comprehensive care regimens that are specifically designed for the extent of the disease in order to improve patient outcomes.

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