

Clinical Profile And Liver Functions In Dengue Fever

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Abstract

Objective: This cross-sectional study explores the complex effects of dengue fever on liver functions in individuals admitted to a Federal Government Polyclinic Hospital (PGMI), in Islamabad.

Methods: This prospective cross-sectional study evaluated 60 children aged 1–12 years with confirmed dengue, categorized into dengue fever and dengue hemorrhagic fever groups, admitted to a hospital in Islamabad over six months in 2022. Liver function tests and clinical parameters were analyzed using SPSS to compare outcomes, with statistical significance set at $p < 0.05$.

Results: With a mean patient age of 7.23 ± 3.58 years and a male-to-female ratio of 1.22:1, our third-day results showed increased ALT in 50% of cases, AST in 71.7%, and STB in 13.3% of patients. By the seventh day, the corresponding percentages had increased to 68.3%, 96.7%, and 81.7%, respectively. Remarkably, AST exceeded ALT in 50% of cases on day three and in 43% of cases on day seven. Except for STB on day three ($p = 0.435$), mean ALT, AST, and STB levels were significantly higher in patients with Dengue Hemorrhagic Fever (DHF) on days three and 7 ($p < 0.000$).

Conclusion: This study demonstrated a significant correlation between liver function and dengue fever, with a more substantial effect observed in patients with plasma leakage or DHF. It becomes clear that monitoring liver function in dengue-infected individuals is essential for prompt intervention and improved clinical care.

Keywords: Hepatomegaly, Severe Dengue, Vomiting, Liver function tests.

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1. Introduction

Arthropods are the primary source of the highly prevalent dengue fever. This is caused by the presence of four distinct serotypes of dengue virus, namely DENV-1, DENV-2, DENV-3, and DENV-4. The dengue virus is responsible for a wide range of illnesses, which can vary from a moderate and self-limiting condition known as dengue fever (DF) to more severe forms, such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).¹ The prevalence of dengue virus infection is increasing globally, posing a significant public health concern. Dengue affects approximately 400 million individuals globally every year.² In Pakistan, the prevalence of this disease remains constant throughout the year in all four provinces; however, the number of cases tends to increase during the rainy season from August to October. The World Health Organization (WHO) has recorded a cumulative total of 25,932 cases, with 62 deaths, in Pakistan in 2022.² In 2021, there were 48,906 cases, with 183 deaths documented in the country.³ The symptomatology of dengue virus infection varies, ranging from asymptomatic cases to dengue shock syndrome. Common symptoms of this

condition include fever, muscle discomfort, joint pain, headache, abdominal pain, and other gastrointestinal symptoms and pain behind the eyes. Illness was categorized into four groups based on the severity level. Asymptomatic infection, acute febrile sickness, typical dengue fever, and dengue hemorrhagic fever are different manifestations of the dengue virus. Serum total bilirubin (STB), alkaline aminotransferase (ALT), and aspartate aminotransferase

(AST) are hepatic function markers that are used to assess the severity of hepatic dysfunction or injury. The primary organ most frequently affected by the dengue virus is the liver.⁴ Dengue virus infection of the liver results in an asymptomatic increase in transaminase levels, which may ultimately lead to severe liver failure. Multiple mechanisms explain the precise potential for damage, including direct viral damage,⁴ immunological injury, and hypoxic injury caused by reduced blood flow during shock.⁵ The liver may show signs like pain in the right hypochondrium, hepatomegaly, different levels of jaundice, and high levels of ALT and AST, which are similar to those seen in people with acute hepatitis caused by viruses A, B, C, D, and E.¹⁵ From August to December 2022, 111 confirmed cases of dengue were admitted to the

pediatric department of the Federal Government Polyclinic Hospital in Islamabad. Liver damage was one of the main reasons for hospital admission.

This study is designed to evaluate the relationship of liver function test during the course of dengue fever.

2. Materials & Methods

This was a prospective cross-sectional study conducted after ethical committee clearance and informed consent Children between 1 to 12 years of age were recruited (the youngest was 1 year of age) admitted to the dengue ward, federal government polyclinic hospital (PGMI), Islamabad were included in the study which took place for a total of six months from July to December 2022.

Those with dengue NS1 positive or with positive dengue serology are considered dengue patients and patients who are admitted to the hospital with platelet count less than 100,000,

or with danger signs i.e. persistent vomiting, severe abdominal, bruising, bleeding from any profiles were included in the study.

Children with other diseases with fever and thrombocytopenia, and drugs causing thrombocytopenia, or patients taking drugs causing thrombocytopenia or direct liver damage and those diseases affecting or damaging the liver directly or indirectly, were excluded from the study.

Case Definitions:

Dengue fever: Patient with constitutional signs and symptoms of dengue fever such as high-grade fever, headache, and retro-orbital pain along with positive serology either dengue NS1 positive or positive IgM antibodies.¹⁷

Severe dengue (or dengue hemorrhagic fever): As per WHO criteria, severe dengue include symptoms of dengue fever along with signs of plasma , as rising hematocrit (HCT), fluids in closed spaces as pleural effusion and/ or ascites, bleeding from the skin as purpura or bruises, or from orifices i.e. hematemesis, epistaxis or melena , thrombocytopenia and liver damage leading to liver failure.¹⁷

The children who came into the pediatric department having symptoms of dengue fever i.e. high fever, severe headache, complaints of muscle/joint pain, and nausea/vomiting were further investigated through NS1Antigen test for confirmation of dengue. Plasma leakage were also assessed clinically through fluid

accumulation in the closed spaces as pleural effusion, ascites.

Hepatomegaly was assessed based on observation of liver size and liver edge below the costal margin also by ultrasonography. 30 diagnosed cases of dengue fever and 30 were further categorized into dengue hemorrhagic fever. Thus two study groups were formed. Liver function tests of all patients were performed on day 3 and day 7 of the admission and ALT, AST and STB were noted down. Patients were advised to follow the study protocols strictly and remain hospitalized till the 7th day irrespective of their condition.

Statistical Package for social sciences (SPSS) version 28 was used to analyze the data. Initial symptoms of the patients i.e. vomiting, nausea, body aches, the status of plasma leakage and hepatomegaly were presented in frequency and percentage. Mean and standard deviation was used for quantitative variables i.e. age, ALT, AST and STB. Independent sample t test was used

to compare the LFTs between two groups. Patient's sex was used for stratification of the result. P value < 0.05 was considered significant.

The sample size of the study was calculated with the help of WHO sample size calculator 7.1, based on the stats mentioned in the study conducted by Manohar et al,¹⁶ where the mean total bilirubin was reported as 1.17 ± 0.45 in patients came with diagnosis of dengue with warning signs. Keeping the given statistics as a reference for the population, with a confidence level of 95% and relative precision of 10%, the minimum sample size to estimate the mean total bilirubin level in the concerned population was 57. Sixty confirmed cases of dengue were included in our study.

The sample size of the study was calculated with the help of WHO sample size calculator 7.4b, based on the stats mentioned in the study conducted by Manohar et al, where the mean aspartate aminotransferase in patients with DHF was 471.36 ± 223.08 (U/L) whereas in patients with DF, mean platelet was observed 108.19 ± 29.87 (U/L). Keeping the given statistics as a reference for the population, with a confidence level of 95% and power of test of 99%, the minimum sample size to compare the mean AST level was 13 in each group. Sixty confirmed cases (30 in each group) were included.

3. Results

The patient's mean age was 7.23 ± 3.58 years, with a minimum age of 1 year and a maximum age of 12 years,

respectively. The average age of patients with DHF was 7.25 ± 3.71 years, which did not show a significant difference compared to the average age of patients with DF, which was 7.21 ± 3.50 years, with a p-value of 0.966.

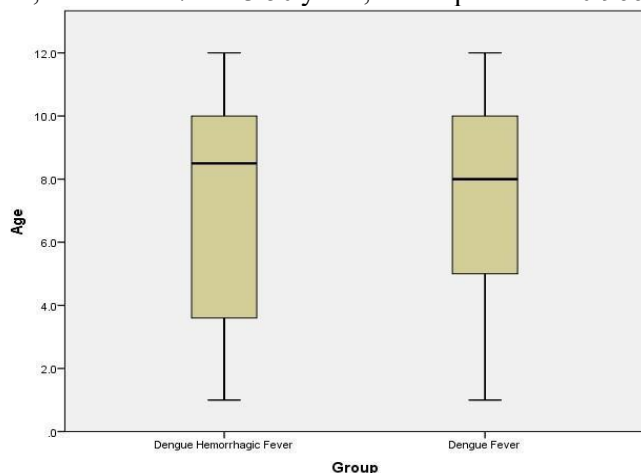


Figure 1: Comparison of age between two groups

The average age of patients in both groups was not statistically significant in males ($p = 0.559$) or females ($p = 0.552$). The shortest and longest durations of fever reported were 1 day and 14 days, respectively, with an average duration of fever of 6.30 ± 3.04 days. (Figure 1) Out of the total number of patients, 33 (55 %) were male (Figure 2).

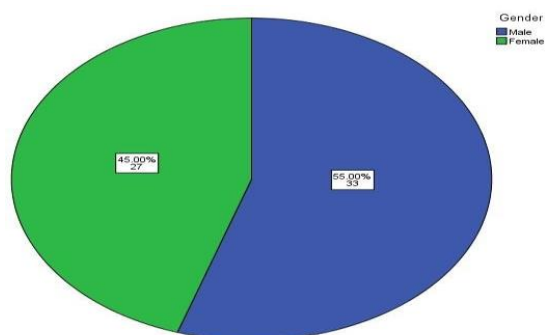


Figure 2: Gender distribution of the patients in the study

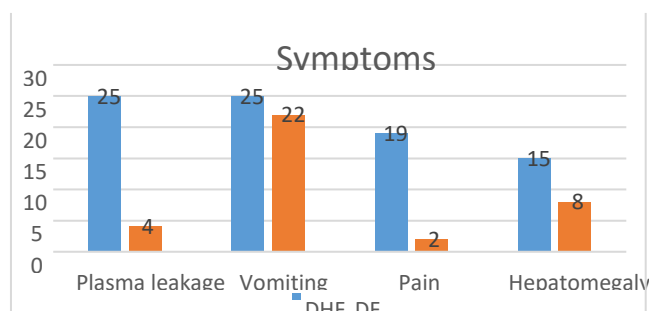
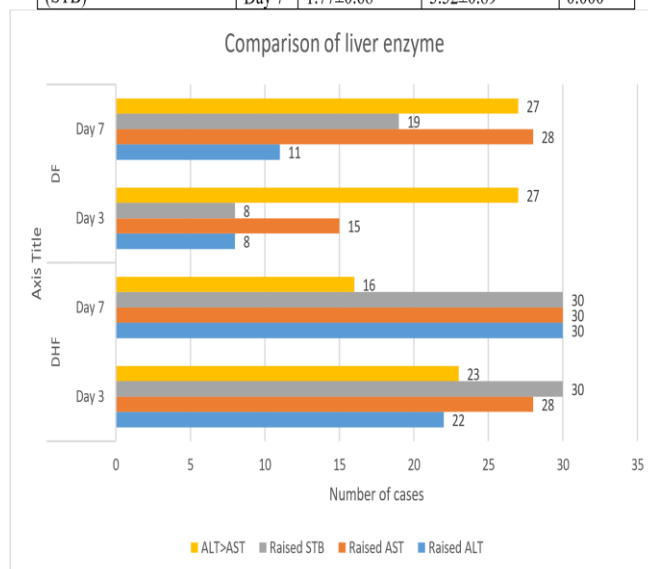


Figure 3: Distribution of different symptoms between two groups

Table 1: Comparison of liver enzyme between two study groups

Variables		DF	DHF	p value
Alanine Aminotransferase (ALT)	Day 3	36.17 $\pm$ 25.03	69.47 $\pm$ 25.05	0.000
	Day 7	59.09 $\pm$ 51.39	149.90 $\pm$ 38.16	0.000
Aspartate Aminotransferase (AST)	Day 3	60.80 $\pm$ 41.30	91.93 $\pm$ 31.33	0.000
	Day 7	93.13 $\pm$ 47.90	158.10 $\pm$ 55.43	0.000
Serum Total Bilirubin (STB)	Day 3	1.03 $\pm$ 0.33	1.08 $\pm$ 0.12	0.435
	Day 7	1.77 $\pm$ 0.68	3.32 $\pm$ 0.89	0.000



The ratio of males to females was 1.22:1. Both research groups were sex-independent as there was no significant difference in the proportion of male patients between the two groups. Out of the patients with DHF, 17 of them (56.7%) had a certain condition, while out of the patients with DF, 16 of them (53.3%) had the same condition. The p-value for this comparison is 0.795. In patients with DHF, the incidence of plasma leakage and severe abdominal pain was higher than in patients with DF, with a P value of 0.000 for both variables. However, there was no significant difference in the incidence of persistent vomiting (at least three times) or hepatomegaly between the two groups, with p-values = 0.347 and 0.063, respectively). (Figure 3) In patients with DHF, the levels of ALT, AST, and STB were all significantly elevated on the 7th day of fever, with a p-value of 0.000 for each. The same trend was observed on the 3rd day of fever, except for STB, which had a p-value of 0.435. The results were identical when comparing the two research groups concerning age stratification (Table 1 & 2). ALT, AST and STB all were significantly high in patients with DHF with p value 0.000 for each at 7day of fever, whereas the result was same at 3rd day of fever except STB with p value 0.435.

(Table 1). The results were same when we compare the two study groups with stratification age.

Table 2: Comparison of liver enzyme between two study groups with stratification of the gender of the patient

Variables		DF	DHF	p-value
Male				
Alanine Aminotransferase (ALT)	Day	35.69	65.76 ±25.48	0.00
	3	±24.54		2
	Day	54.38±31.45	148.12±37.9	0.00
	7		3	0
Aspartate Aminotransferase (AST)	Day	59.06	88.94 ±31.89	0.02
	3	±39.40		3
	Day	91.38±49.12	156.82±55.4	0.00
	7		3	3
Serum Total Bilirubin (STB)	Day	1.09±0.33	1.08±0.14	0.95
	3			3
	Day	1.77±0.68	3.34±0.89	0.00
	7			0
Female				
Alanine Aminotransferase (ALT)	Day	36.71	74.31 ±24.62	0.00
	3	±26.50		1
	Day	64.48±68.49	152.23±39.8	0.00
	7		8	0
Aspartate Aminotransferase (AST)	Day	62.79	95.85 ±31.42	0.03
	3	±44.78		7
	Day	95.14±48.22	159.77±44.6	0.00
	7		6	1
Serum Total Bilirubin (STB)	Day	0.96±0.32	1.08±0.09	0.22
	3			6
	Day	1.79±0.81	3.29±1.01	0.00
	7			0

4. Discussion

Dengue has become a health issue worldwide and is characterized by the fastest spreading viral disease transmitted by mosquitoes.⁵ The increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels observed in our study is consistent with the findings of Parkesh et al., who reported elevated ALT and AST levels in 95% and 85% of cases, respectively.⁶ Significantly, the liver's involvement in dengue displays minor differences between children and adults, with a greater proportion of liver enlargement reported in children. A review article by Alam, R., et al. highlighted dengue as a significant contributor to acute liver failure in children.⁷ This study found that acute liver failure can range from 14-34% of the cases that are tested positive for dengue serology in different regions i.e. in India and Thailand. Hepatic involvement frequently results in apoptosis,⁸ which is the final outcome. In their investigation, Smith Soni et al. observed a wide range of patterns of AST elevation, with elevations of less than 3-fold to greater than 10-fold occurring in 45.6%, 36.7%, and 16.4% of the patients, respectively.⁹ Although we

didn't do any biopsy or histological analysis of these patients, study done by Ahmad A et. al., showed in his histological analyses, including biopsies performed on individuals with fever, have identified characteristic patterns, such as microvascular necrosis, Councilman bodies, and portal tract inflammation.¹⁰ Our study found that in patients without symptoms of plasma leakage, the average AST level was 190.93 with a standard deviation of 50.88. In contrast, individuals with plasma leakage had an average AST level of 188.37 with a standard deviation of 65.36. Shivbalan et al. highlighted the importance of elevated alanine aminotransferase (ALT) levels, enlarged liver with tenderness (hepatomegaly), and abdominal pain as reliable signs of bleeding in patients with dengue fever.¹¹ In our investigation, 39% of individuals encountered the occurrence of plasma leakage, whereas 38% of the entire patient population under scrutiny displayed hepatomegaly. Our study's mean serum total bilirubin levels were 0.87 with a standard deviation of 0.49 for non-leakers and 0.89 with a standard deviation of 0.40 for leakers. A study conducted in Bangkok found that 74% of the children diagnosed with dengue fever showed liver enlargement, which is known as hepatomegaly.¹² Additionally, aminotransferase and alkaline phosphatase levels were found to be between 80% and 87% higher than normal values. In their study, Kuo et al. found that over 90% of patients had abnormal AST levels.¹³ Similarly, ALT, bilirubin, alkaline phosphatase, and gamma-glutamyl transferase (GGT) were abnormally elevated in 80%, 7%, 16%, and 83% of patients with classic dengue, respectively. Nguyen et al. emphasized that AST levels were often aberrant, exceeding those of ALT (97.7% vs. 37.3% above normal levels).¹⁴ In addition, dengue can manifest as asymptomatic enlargement of the liver without a noticeable increase in liver enzyme levels. Certain individuals may exhibit sudden abdominal discomfort, jaundice, and vomiting, which closely resemble symptoms of acute viral hepatitis. Alternatively, some individuals may have hepatomegaly, jaundice, or discomfort in the right hypochondrium.¹⁶ In a recent year, study conducted in India showed alanine aminotransferase was raised in 99% of cases and hepatomegaly was noticed in 66% of cases.¹⁸ It is crucial to emphasize that none of the patients enrolled in our study had pre-existing liver illness. The various ways in which dengue affects the liver highlight its intricate nature, which requires a

thorough understanding of successful therapeutic treatments.

5. Conclusion

This study demonstrated a significant correlation between liver function and dengue fever, with a more substantial effect observed in patients with plasma leakage or DHF. It becomes clear that monitoring liver function in dengue-infected individuals is essential for prompt intervention and improved clinical care.

Institutional Review Board Approval

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Contributions:

S.S, A.M, F.H, S.M - Conception of study

S.S, A.M - Experimentation/Study Conduction

S.S, A.M, N.A, A.A -

Analysis/Interpretation/Discussion

S.S, A.M, F.H - Manuscript Writing

S.S, A.M, N.A, F.H, S.M, A.A - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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