ORIGINAL ARTICLE

# Correlation Between Liver Function Test and Severity of Dengue Fever at a Tertiary Care Hospital, Rawalpindi

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**ABSTRACT**

**Objective:** To evaluate the correlation between changes in serum liver function tests and the severity of dengue fever.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** This study was conducted at the Department of Medicine, Pak Emirates Military Hospital, from 1st May 2023 till 30th October 2023

**Methods:** Patients aged 18 years and above who had dengue NS1 rapid test assay or dengue IgM/IgG rapid test positive were included in the study using convenience sampling. Participants with pre-existing liver conditions, chronic kidney disease, pregnant women, and those with concurrent infectious illness were excluded. The World Health Organization classification system was used to classify the patient's disease severity into Dengue Fever and Severe dengue.

**Results:** One hundred and seventy-one patients, including 131 (76.61%) males, had a mean age of 35.91±12.86 years. Severe dengue was observed in 15 (8.8%), while 156 (91.2%) had dengue fever. The dengue NS1 protein assay was positive in 169 (98.8%) and dengue serology was positive only in 2 (1.2%). All liver enzymes, including serum alanine transaminase, serum alkaline phosphatase, serum albumin, and serum bilirubin, had significant relation amongst the dengue disease severity groups. The severity of hepatic impairment was also significantly related to the World Health Organization classification ($P = 0.02$).

**Conclusion:** Dengue fever severity can be predicted early by derangements in liver function tests as they statistically correlate with the severity of the disease.

**Keywords:** *Aedes-Borne Diseases, Dengue Fever, Hepatitis, Liver, Liver Dysfunction.*

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## Introduction

Dengue fever has evolved as one of the leading causes of acute febrile illness in the last two decades in Southeast Asia. After malaria, dengue is the second most frequent mosquito-borne illness that affects people.[1] Pakistan is one of the countries where the burden of disease related to dengue fever is very high as compared to other neighboring countries. Dengue fever is a viral illness and has four serotypes, which are transmitted through Aedes Mosquito. That's why it is an arthropod borne disease. It can present in a spectrum of diseases ranging from self-limiting illness to a life-threatening disease.[2] Although an initial natural dengue infection is frequently asymptomatic, the biggest risk factor for developing a severe form of the disease is thought to be a secondary dengue infection with

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a heterologous serotype.[3] According to the World Health Organization (WHO) it can be classified as Dengue Fever or Severe Dengue.[4]

Dengue infection occurs in a series of phases: fever, acute illness, and recovery. Symptoms, including arthralgia, vomiting, headaches, high fever, and the flu, are common during the febrile phase, which typically lasts for a week. "Critical phase" also refers to the potentially lethal stage that is marked by the appearance of more severe symptoms such as internal hemorrhage and leakage of plasma. As vascular permeability recovers throughout the recovery period, symptoms get milder.[5]

In symptomatic patients with dengue, symptoms often start from the 4th day of illness and usually present with high-grade fever (up to 104°F), joint and muscle pains, nausea, vomiting, headache, retro-orbital pain, rash, and glandular swellings. In severe dengue, symptoms usually include severe pain in the abdomen, persistent vomiting, dyspnoea-dyspnea, gums or nose bleed nosebleed, fatigue, restlessness, haematemesis or haematochezia, polydipsia, pale and cold skin, and generalized weakness.[4]

Dengue usually gets better over time only with symptomatic treatment but in severe cases patient may need hospitalization and indoor management.[6] Dengue affects multiple systems, including the hepatobiliary system, and can cause encephalitis, carditis, liver failure, and shock in severe cases.[7] Liver injury can be due to direct viral injury to the hepatocytes or due to the weak immune system of the host and can be observed through liver function tests, mainly transaminase levels.[2] While the liver is not the key target organ, individuals with Dengue fever have been shown to have abnormalities such as fatty alterations, centrilobular necrosis, kupffer defense system, and leukocytic intrusion of the portal system. It is believed that either a direct viral action on liver cells or a dysregulated immune response of the affected causes liver function impairment or injury.[8]

A particular antiviral medication and an authorized vaccination to treat and prevent DENV infection are still lacking.[9] Until the COVID-19 pandemic, dengue has several turning points in its history where the disease's intensity transformed to more severe versions and attracted the greatest attention from worldwide writers.[10] Limited data is available in our resource-constrained country on liver injury and its correlation with dengue disease spectra. we have focused ourselves on conducting a study in order to help clinicians to relate dengue severity based on liver transaminase levels and management of the patients in an effective way.

**Methods**

This cross-sectional study was carried out at the Pak Emirates Military Hospital in Rawalpindi, along with specialized dengue treatment facilities. To account for the dengue fever severity in our setup, a month worth of data was collected, i.e., 1st May 2023 to 30th October 2023. Before the study began, the Pak Emirates Military Hospital Ethics Committee's clearance was obtained via letter no. A/28/EC/516/23. Every research participant was provided with informed consent. Patient identification and data were treated with strict confidentiality and were never disclosed. Using the following formula:

$$n = \frac{\left[(Z_\alpha + Z_\beta)^2 + pq\right]}{d^2}$$

The sample size was determined to be 120, assuming that the expected prevalence of hepatic dysfunction in dengue would be around 50%, assuming α error of 5% and β error of 20%, and a power of 80% with a precision of 5%.[2] Non-probability convenience sampling was used for enrolment. Patients aged 18 years and above from both genders, who had dengue non-structural protein-1 rapid test assay or dengue Immunoglobulin M and G rapid test positive were included in the study. Participants with pre-existing liver conditions, chronic kidney disease, pregnant women, and those with concurrent infectious & chronic illnesses affecting liver enzymes and causing thrombocytopenia were excluded. Individuals who did

not give consent were also excluded.

The relevant clinical attributes, which encompassed age, gender, medical background, symptoms, and duration of illness, were recorded. The blood samples were collected and analyzed for complete blood counts and liver function tests. The Cobas® 6000 analyzer series was used to analyse liver functions. A 3-part semi-automated hematology analyzer Sysmex XP100 was used to perform complete blood count analysis. The two groups were made Dengue Fever (DF) and Severe Dengue (SD). WHO classification system was used to classify the patient's disease severity i.e. Dengue Fever and Severe dengue.[4]

The Statistical Package for Social Sciences (SPSS) Version 24.0 was utilised to analyse the data. The qualitative variables and quantitative were expressed as frequency, percentages and mean ± SD respectively. The correlation between transaminases, bilirubin, platelet count and dengue severity were determined using independent sample *t*- test. *P*-value <0.05 were taken as significant.

**Results**

Total of one hundred and seventy-one (n=171) patients were enrolled into the study. Among them 131 (76.61%) were males while 40 (23.39%) were females. On assessment 24 (14.04%) patients had previous history of dengue fever. There were 15 (8.77%) patients who had severe dengue and 156 (91.23%) had dengue fever. Extended details of demographic attributes are shown in table-1.

All study variables except lymphocytes and neutrophils showed a statistically significant association with dengue fever severity, while the liver function test showed a very strong relationship with the disease. Details are shown in table-2.WHO Dengue Fever Class is significantly associated with hepatitis severity (*P*=0.020) as shown in table-3.

**Discussion**

This research has shown inciteful results. As expected, there was a significantly greater risk of hepatic dysfunction amongst patients with more severe dengue infection as assessed clinically using the criteria laid down by the World Health Organization. Different liver enzymes had higher values in patients with severe dengue as compared to dengue fever. Dengue fever, an

**Table-1: Demographic and clinical attributes of study population (n=171)**

| Variables | Frequency (%) |
|---|---|
| Age (Years) | 35.91±12.86 (mean±SD) |
| Gender | |
| • Male | 131 (76.61%) |
| • Female | 40 (23.39%) |
| Comorbid Conditions | |
| • Hypertension | 22 (12.87%) |
| • Diabetes Mellitus | 17 (9.94%) |
| • Ischaemic Heart Disease | 17 (9.94%) |
| • Others | 01 (0.58%) |
| Dengue Classification | |
| • Severe Dengue | 15 (8.77%) |
| • Dengue Fever | 156 (91.23%) |
| Previous History of Dengue | 24 (14.04%) |
| Dengue Workup | |
| • Dengue NS1 | 169 (98.83%) |
| • Dengue Serology | 2 (1.17%) |

*NS1: Non-structural protein-1*

**Table-2: Cross Tabulation on Dengue Fever Classification and study variables (n=171)**

| | WHO Classification | | | |
|---|---|---|---|---|
| | DF (n=156) | SD (n=15) | *t-test Statistic* | |
| **Variables** | **Mean±SD** | **Mean±SD** | | ***P*-value** |
| Age (years) | 35.45±12.56 | 40.67±15.38 | -1.274 | 0.221 |
| Day of Illness | 4.28±1.60 | 6.60±1.92 | -4.527 | <0.001 |
| Platelets ($10^9$/L) | 109.39±40.37 | 24.33±11.74 | 8.107 | <0.001 |
| Bilirubin (µmol/L) | 9.06±3.82 | 22.27±12.15 | -9.654 | <0.001 |
| ALT (U/L) | 70.21±41.11 | 123.0±64.41 | -4.487 | <0.001 |
| ALP (U/L) | 79.51±21.97 | 105.06±24.22 | -3.934 | 0.001 |
| Albumin (g/l) | 38.22±3.01 | 35.07±2.08 | 5.341 | <0.001 |
| Hb (g/dL) | 13.30±1.14 | 11.92±11.61 | 3.245 | 0.005 |
| Hct/PCV (l/L | 0.40±0.352 | 0.3707±0.52 | 2.431 | 0.028 |
| Neutrophils (%) | 64.39±12.57 | 57.87±19.43 | 1.818 | 0.071 |
| Lymphocytes (%) | 29.38±12.39 | 35.47±18.50 | -1.730 | 0.085 |

*WHO: World Health Organization; DF: Dengue Fever; SD: Severe Dengue; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; Hb: Haemoglobin; PCV: Pack Cell Volume; Hct: Haematocrit*

**Table-3: Frequency of Dengue Fever Class and Hepatitis Severity (n=171)**

| | | Hepatitis Severity Class | | | |
|---|---|---|---|---|---|
| | | **Normal** | **Mild to Moderate** | **Severe** | **Total** |
| WHO | DF | 18 | 135 | 3 | 156 |
| Class | SD | 0 | 13 | 2 | 15 |
| Total | | 18 | 148 | 5 | 171 |

*WHO: World Health Organization; DF: Dengue Fever; SD: Severe Dengue*

acute febrile illness caused by flavivirus, is spreading at an exponential rate in our region and is of grave concern.[11] It has been suggested that the pathogenic pathways for increased transaminases are hepatocyte destruction caused by the dengue virus, hypoxia, shock, or related liver disease.[12] In our study, the majority of the patients were Dengue NS1 positive, making up 98.8% of the sample size. Only 24 (14.0%) of them had a history of previous dengue infection. We performed statistical analysis based on WHO Dengue classification. We found out that all the liver function test parameters, i.e., ALT, AST, bilirubin, and albumin showed positive statistical significance. However, lymphocytes and neutrophils didn't show any statistical significance. Furthermore, hepatic involvement was also found to be related ($P$=0.020), as shown in figure 1.

These results correspond to comparable research by Ravilla S et al. in Visakhapatnam, South-East India.[13] More than 90% of patients with Severe Dengue Fever had a significantly higher hepatic impairment in comparison to other subtypes ($P$<0.001). Similarly, in coherence with our research, hepatic enzymeenzyme derangements were also significantly disturbed when intra-group comparison was made with SDF ($P$<0.001). In another study conducted by Shravya Dhanwada et al. in Andhra Pradesh, India, dengue seropositivity was associated with hepatic enzyme derangements such that impairment was higher in the seropositive group.[14] Comparable results were reported in a study conducted in Pakistan in 2010, which found

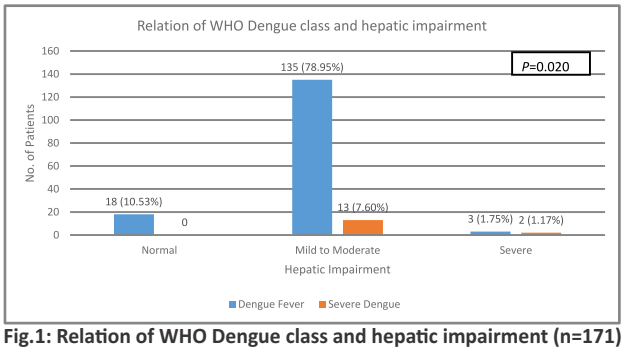


**Fig.1: Relation of WHO Dengue class and hepatic impairment (n=171)**

moderate degree of hepatic impairment occurred the most in up to 75% of the patients, and we also obtained similar results with 86.5 % mild to moderate hepatitis with dengue fever and 13.3% had severe hepatitis, these results varied because of the different severity parameters for hepatitis in both the studies.[8] In a study conducted at Abbasi Shaheed Hospital Karachi, Irfan et al. found serum AST and ALT were raised in 62 of 106 patients tested, but in our study, these results were higher because of the fact that we took a larger sample size and most of the patients included on our study reported mainly at 4$^{th}$ day and more than 4 days of illness which also contributed to have a higher incidence of LFTs derangement.[15] A study by Ayyub et al. observed that both AST and ALT were significantly elevated in 66.7% of patients, almost the same as in our study.[16] Our results also fall in comparison with the research steered by Luiz José et al., Kuo C et al. thus further substantiating our findings and making it a strong study.[17-19] All these studies have shown that liver derangement can help as a predictive marker for SDF, as in our study, we got similar results.

A study was recently conducted on a somewhat similar topic at our hospital.[20] It to evaluate the correlation between serological markers and hepatic ultra-sonographic features amongst patients with a positive dengue serology. Amongst 166 individuals, it was revealed that the different parameters, i.e., the duration of illness, platelets count, blood hemoglobin levels, and TLC, were statistically related to sonographic findings. The mean levels of platelets and haemoglobin were found to be low from reference ranges. In our study, we also found a significant relationship between hemoglobin levels, platelets count, and duration of illness with disease severity groups, and a similar trend was observed for serological markers. However, in their study, they didn't establish a relationship between the severity of disease and different classes of dengue fever as per WHO classification or otherwise. Moreover, comparing these two studies leaves a research gap in seeing the association amongst serological markers, ultra-sonographic features, and severity of the disease among different classes of dengue fever.

A systematic review conducted by Kalluru et al. found that derangements in serum amino-transferases were significantly associated with dengue severity and can be used as useful predictors.[21] In coherence with their findings, we also found a very strong relationship between LFTs and disease severity. These abnormalities in LFTs can be attributed to toxic metabolic effects and host immunological responses to dengue and its viral proteins. In another study conducted in India, the researchers found hepatic enzyme derangements commonly found among different dengue groups ($P$<0.001), similar to our research findings.[22] The plausible reason remains the damage to muscle tissue, hepatocytes, and cardiac muscles by the viral components.

There are certain limitations in our study. This is a single-center study that includes the population of our entitled clientele who were residing in the area at the time of illness and not indeed the population of the twin cities. Moreover, the study has an inherent bias of being a cross-sectional study as there was no follow-up, so comments cannot be made on trends of LFTs. We suggest that extensive multicentre studies should be done to see trends of liver function tests as the disease progresses to generalize results for masses. We also found a gap for further research to see the correlation between LFTs, sonological markers,

and different classes of dengue fever.

**Conclusion**

This study signifies the importance of simple liver function tests in Dengue Fever severity as it can be predicted early by liver function tests (ALT, AST, Bilirubin, Albumin) derangement as they correlate with the severity of the disease as shown by statistical significance in this study. This can help and guide the early admission of severe cases and their management effectively by preventing complications and decreasing morbidity and mortality overall. Early Dengue NS1 testing and clinical examination with relevant lab investigations can help in the early segregation of dengue's Dengue Fever (DF) and severe Dengue (SD) cases.

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

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**WR:** Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing and proofreading

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