

# Spectrum of Liver Injury in Dengue Fever: Cause or Effect of Severe Dengue?

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## ABSTRACT

The study aimed to determine if deranged liver function tests (LFTs) can predict severe dengue or mortality. It included 135 dengue patients, with a mean age of  $30.9 \pm 12.09$  years. Among the patients, 82 (60.7%) were under 30 years of age. Nearly half of the patients (64, 47.4%) had some degree of liver damage indicated by deranged LFTs, 27 (42.1%) had elevated alanine transaminase (ALT), 7 (10.9%) had increased bilirubin, and 30 (46.9%) had high values of alkaline phosphatase (ALP). However, only elevated ALP levels were positively correlated with mortality (Pearson's  $R = 0.282$ ,  $p = <0.05$ ). The mean bilirubin was  $11.711 \pm 8.602$   $\mu\text{mol/L}$ , and the mean values of ALT and ALP were  $107 \pm 240$  and  $113.571 \pm 59.91$  IU/L, respectively, which were higher than the normal. The study findings suggested that hepatic derangement is a common occurrence in dengue patients, and increased ALP levels could be an indicator of a higher risk of mortality. These findings can help improve patient care by identifying the potential risk factors for mortality.

**Key Words:** Dengue, Liver function tests, Alanine transaminase, Alkaline phosphatase.

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Dengue fever has re-emerged as a major health disaster in the underdeveloped countries, particularly in Pakistan. Dengue is a rapidly spreading infectious disease that can cause severe health and economic instability, with a fatality rate of 3-5%.<sup>1</sup> According to the WHO, 4.2 million cases were reported in 2019, up from 2.4 million in 2010 and 505,430 cases in 2000.<sup>1</sup>

Dengue fever has changed its behaviour over time in terms of the clinical presentation and organ involvement. Liver involvement is increasingly recognised, with patients presenting with jaundice, hypochondriac pain, and liver enlargement. Pancreatitis, cholecystitis, severe pruritis, and even fulminant hepatic failure have been linked to liver involvement, which has been identified as a separate entity called Dengue expanded syndrome.<sup>2</sup>

There is increasing evidence that severe derangement of liver function during dengue fever is associated with poor prognosis and outcomes, and derangement of liver functions may be used as a predictor of poor outcomes in dengue patients.

In the mid of 2021, there was an outbreak of dengue in the province of Sindh with the majority of cases from Karachi. The authors studied the derangement of LFTs and the pattern of liver involvement in dengue fever. The main goals were to establish a correlation between the pattern of liver involvement and clinical outcomes, and to compile information on dengue that could aid in future patient management strategies and a better understanding of the disease.<sup>2</sup>

This research was conducted at PNS Shifa Hospital, Karachi, Pakistan, spanning from 4<sup>th</sup> February 2022, to 31<sup>st</sup> July, 2022. The sample size was calculated using WHO sample size calculator version 2, keeping 95% confidence interval and 5% margin for error and previously reported incidence of 3-5% in the local literature.<sup>3,4</sup> Non-probability convenience sampling technique was used. The permission of the ethical committee was taken vide letter no ERC/2022/MEDICINE/11. Liver involvement was evaluated in patients with dengue by measuring the levels of alanine transferase (ALT), alkaline phosphatase (ALP), and serum bilirubin. Any value above the normal range were considered abnormal LFT. Patients with recent hepatitis, regular use of hepatotoxic medications, or prior cirrhosis were excluded. Data were collected through an online proforma and analysed using SPSS v29. The descriptive statistics were used to calculate means for numerical data and frequencies for the categorical data. The study utilised Pearson's correlation coefficient to determine the correlation between elevated (ALP) and patient mortality. The  $p$ -value  $<0.05$  was considered statistically significant.

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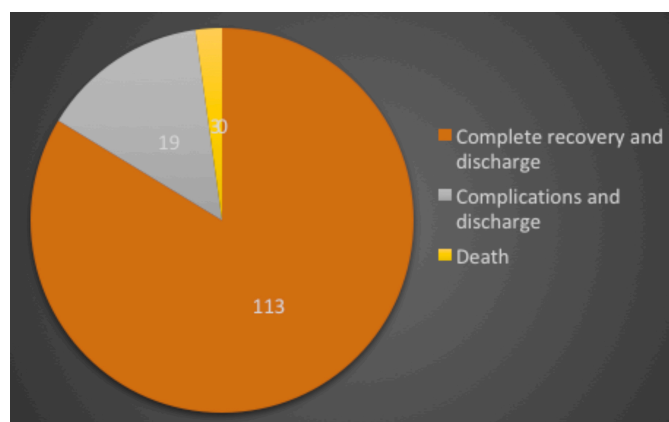
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**Table I: Descriptive statistics of study population.**

	n	Mean	Std. Deviation	Variance
Serum bilirubin $\mu\text{mol/L}$	128	11.711	8.602	73.987
Age	128	30.984	12.029	144.687
PLT lowest recorded	135	79.711	47.821	2286.813
PT	103	14.447	2.167	4.694
APTT	103	35.874	6.668	44.460
CRP	30	16.747	20.281	411.312
Serum alanine transferase (U/L)	128	107.078	240.305	57746.603

**Figure 1: Outcomes of dengue patients.**

This study included 135 patients with dengue fever, with a mean age of  $30.9 \pm 12.09$  years. Most of the patients were under 40 years of age, with 80% being below this age. Males were more commonly affected, accounting for 79.3% of cases. Liver involvement was observed in 48.8% of patients, as indicated by deranged LFTs with elevated ALP (46.9%) being the most common abnormality. Platelet levels were low (mean  $79.71 \pm 47.82/\text{mm}^3$ ), and coagulopathy was present, as evidenced by prolonged prothrombin time (mean  $14.447 \pm 2.167$  seconds) and APTT (mean  $35.874 \pm 6.668$  seconds). However, the mean haemoglobin level remained normal ( $13.464 \pm 1.88$  g/dl). Serum ferritin was elevated (mean  $720 \pm 702.952$  micrograms/L). The analysis found a significant correlation ( $p < 0.05$ ) between these variables. Only elevated ALP levels correlated with patient mortality (Pearson's  $R = 0.282$ ,  $p < 0.05$ ), while ALT and bilirubin derangements did not. The overall mortality rate was approximately 3% in this study, with 2.4% of male participants and 0.6% of female participants succumbing to the disease.

The study found that liver involvement is a common occurrence in dengue patients, with elevated ALT being the most obvious indication of liver involvement. The extent of liver involvement varied widely among different studies, with this study finding of mild-to-moderate liver involvement in most patients, but no cases of fulminant liver failure.<sup>5</sup> A study by Swamy *et al.* correlated hepatic pathologies in dengue patients with bleeding tendency and risk of death and reported that 74.2% of dengue patients had liver damage in the form of increased transaminases.<sup>1</sup> However, it is possible that platelet count is not the only factor responsible for severe dengue and bleeding tendency. This study found that

liver involvement was less common (48%) than in some other studies, which may be due to differences in the hepatic derangement parameters used.

The study also found that the most important hepatic derangement parameter to monitor in dengue patients is ALP, which was positively correlated with the risk of mortality. This finding was consistent with a study by Tongluk *et al.*<sup>6</sup> Elevated APTT was also documented in this study, but its correlation with mortality was unclear. In terms of gender, the current study found a very small number of female patients in comparison to other studies. Further research will be needed to determine if Pakistani women are protected from dengue through their clothing customs or other mechanisms.

The study was limited in that long-term follow-up of patients was not performed, and ultrasound and clinical examination of liver enlargement were not given due representation. Therefore, it is possible that liver damage was under-reported in the study. Only three patients died in the study, which is a small number to draw confident conclusions about mortality in dengue patients with liver involvement. Overall, it is important to closely monitor patients with hepatic derangement in dengue to identify and manage complications related to the disease.

#### ETHICAL APPROVAL:

An approval was granted by Ethical Committee PNS Shifa Hospital, Karachi (ERC/2022/MEDICINE).

#### PATIENTS' CONSENT:

Informed, written consents were obtained from all patients.

#### COMPETING INTEREST:

The authors declared no conflict of interest.

#### AUTHORS' CONTRIBUTION:

IK: Designed the study, managed the data.

SK: Collection the data, conceived the study.

NK: Provided technical support, conducted data interpretative drafting.

SN: Provided consultant expert advice on designing.

MR: Provided administrative and financial support and played critical role in data collection and coordination.

SB: Typed the draft, collected the data and patients' consent.

All authors approved the final version of the manuscript to be published.

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