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Evaluation of Liver Function Tests and Clinical Outcomes in Dengue Patients: Elevated Alkaline Phosphatase Levels as a Predictor of Mortality

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ABSTRACT

Objectives: To evaluate liver function test abnormalities in patients with dengue infection and determine whether elevated alkaline phosphatase (ALP) levels are associated with mortality and adverse clinical outcomes.

Study Design and Setting: A prospective, descriptive observational study conducted over four months, from April 2 to July 31, 2022, at PNS Shifa Hospital (BUHSC).

Methodology: Demographic, clinical, and laboratory data of confirmed dengue patients were recorded using a structured proforma. Liver function parameters including alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum bilirubin were analyzed. Data were entered and analyzed using SPSS version 29.

Results: The study included 135 patients with a mean age of 30.9 ± 12.1 years: the majority (60.7%) were under 30. Liver involvement was common, with 64 patients (48.8%) exhibiting liver function test abnormalities. Among these, 27 (42.2%) had elevated ALT, seven (10.9%) showed increased bilirubin, and 30 (46.9%) had elevated ALP. Most patients (83%) maintained normal bilirubin levels, with a mean bilirubin level of 11.7 ± 8.6 µmol/L. Mean ALT was 107 ± 240 IU/L, and mean ALP was 113.6 ± 59.9 IU/L, both above normal ranges. Among liver function parameters, elevated alkaline phosphatase (ALP) levels showed a statistically significant association with mortality (Pearson's r = 0.282, p = 0.01), whereas ALT and bilirubin levels were not significantly associated with death.

Conclusions: Hepatic dysfunction is a frequent finding in dengue patients, with elevated ALP positively correlating with mortality. Although ALT and bilirubin abnormalities are often observed, they do not significantly predict patient outcomes.

Keywords: Alkaline Phosphatase, Dengue, Dengue Hemorrhagic Fever, Hepatic Insufficiency, Liver Function Tests

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INTRODUCTION

In the Post-COVID era, dengue fever, transmitted by the *Aedes aegypti* mosquito, has resurfaced as a severe health crisis, especially in underdeveloped countries. In Pakistan, dengue transmission is exacerbated by poor drainage systems, accumulation of solid waste, inadequate sanitation, and densely populated urban areas, all of which create favourable breeding conditions for *Aedes* mosquitoes.[1] These challenging conditions make dengue a persistent and significant threat to communities already facing numerous health and socioeconomic hardships. As the disease continues to thrive, particularly among poorer communities with limited access to timely medical intervention and preventive measures, it is expected to impose a sustained burden on public health and economic stability.[1]

According to the World Health Organization, 4.2 million cases were reported in 2019, up from 2.4 million in 2010 and 505,430 cases in 2000.[2] Dengue transmission is increasingly reported in both endemic and previously low-risk regions, driven by environmental factors such as poor drainage systems, accumulation of solid waste, and inadequate sanitation, which promote *Aedes* mosquito

breeding.[3] Within Pakistan, dengue has transitioned from a sporadic illness to a recurring epidemic, with all four serotypes now in circulation, increasing the risk of severe secondary infections.[8] The co-circulation of multiple serotypes is a major public health concern, as a secondary infection with a heterologous serotype is a primary risk factor for developing severe dengue through mechanisms like antibody-dependent enhancement (ADE).[8]

It is believed that dengue has changed its behaviour over the decades in terms of clinical representation and organ involvement.[3] Liver involvement in dengue fever has gained increasing recognition in recent years, as a notable portion of patients present with symptoms such as jaundice, pain in the hypochondriac region, and liver enlargement. These symptoms indicate that the liver is significantly affected in many dengue cases, reflecting a growing understanding of the disease's impact on this vital organ.[4,5]

The etiology of liver damage in dengue involves multiple complex mechanisms, including a pronounced cytokine storm, immune-mediated hepatocyte injury, and the direct cytopathic action of dengue virus (DENV) itself, which induces hepatocyte apoptosis.[4] DENV primarily targets hepatocytes and Kupffer cells, leading to cellular stress and the release of pro-inflammatory signals that recruit immune cells, further perpetuating the inflammatory cascade. Additionally, hepatic hypoperfusion, resulting from compromised blood flow to the liver, is another significant factor. This hepatic dysfunction can range from mild, asymptomatic transaminase elevation to fulminant acute liver failure, a rare but life-threatening complication.[6,10]

Derangement of liver functions may be used as a predictor of poor outcome in dengue patients.[6] However, while elevated aminotransferases are a hallmark of dengue-related hepatitis, their direct correlation with disease severity and mortality remains inconsistent across studies.[11,13,15] Some research suggests a strong link, while other studies have found that the degree of LFT derangement does not reliably predict the development of severe dengue.[17] This lack of consensus highlights a critical gap in understanding which specific laboratory markers can reliably identify patients at the highest risk. For instance, while some large cohort studies have correlated peak transaminase levels with the development of DHF, others, particularly those focusing on paediatric populations, have found that the degree of elevation does not reliably predict progression to shock.[12,11,13] Similarly, the significance of alkaline phosphatase (ALP) and bilirubin remains contentious. An elevated ALP has been linked to severe outcomes in some adult cohorts, yet it is often considered a non-specific marker of inflammation. This clinical equipoise underscores the need for more granular data from diverse patient populations.[6]

In the mid of 2021 there was outbreak of dengue in Sindh province with majority of cases from provincial capital Karachi.[7] Our primary objective was to investigate various parameters associated with liver involvement in dengue fever and to establish a correlation between the observed patterns of liver involvement and corresponding clinical outcomes. By analyzing these factors, we aimed to gain insights into how liver complications influence the progression and severity of dengue within our local population, contributing to the broader effort to identify reliable prognostic markers. Given the unique epidemiological and demographic characteristics of the region, local data is essential to validate or challenge the prognostic models developed in other parts of the world and to ultimately refine patient management strategies.

METHODOLOGY

This prospective, descriptive observational study was conducted within the Department of Medicine at PNS Shifa Hospital, a major tertiary care teaching hospital affiliated with Bahria University of Medical Sciences in Karachi, Pakistan. The patient enrollment and data collection were carried out over a four-month period corresponding with the regional dengue season, from April 2, 2022, to July 31, 2022. The study protocol, consent forms, and all related documents were formally approved by an independent local review body, the hospital's Institutional Review Board (IRB) and Ethics Committee (Ref: ERC/2022/medicine/11), ensuring full compliance with the ethical principles of the Declaration of Helsinki.

The sample size was prospectively calculated using the WHO sample size calculator (version 2). The calculation based on an anticipated incidence of severe hepatic involvement in dengue infection of approximately 3–5%, as reported in regional literature. This estimate refers to clinically significant hepatic complications such as severe hepatitis or acute liver failure, rather than mild biochemical liver function abnormalities.[8,9] A non-probability convenience sampling technique was utilized for patient enrollment, wherein all consecutive patients meeting the eligibility criteria during the study period were invited to participate. After a thorough explanation of the research objectives, procedures, and potential risks, written informed consent was obtained from all participants or their legal guardians prior to any study-related activities.

A total of 135 patients who fulfilled the established inclusion and exclusion criteria were included in the final analysis. Inclusion criteria required patients to be adults presenting with a clinical syndrome consistent with classic dengue—including symptoms such as headache, retro-orbital pain, myalgias, and high-grade fever—and to have a definitive laboratory-confirmed diagnosis. This confirmation was achieved via a positive result for either the dengue non-structural protein 1 (NS-1) antigen or the presence of IgM antibodies on serology testing. Exclusion criteria were applied to patients with a documented history of any form

of acute or chronic viral hepatitis within the past three months, a known history of regular use of hepatotoxic medications (e.g., high-dose paracetamol, anti-tuberculosis drugs), or a prior diagnosis of cirrhosis from any cause, in order to isolate the hepatic effects of the dengue virus.

Liver involvement was biochemically evaluated by obtaining the levels of ALT (reference <45 IU/L), alkaline phosphatase (reference <145 IU/L), and Serum Bilirubin (reference <17 µmol/L), with any value above the institutional laboratory's normal range classified as an abnormal LFT. All laboratory analyses were performed using standardized automated analyzers in the hospital's central laboratory. All demographic, clinical, and laboratory data were entered into a secure database and analyzed using SPSS Statistics (Version 29.0). Descriptive statistics were used to summarize the data, and a p-value of <0.05 was considered statistically significant for all inferential analyses.

RESULTS

A total of 135 patients were included in the study. The mean age of the participants was 30.9 ± 12.09 years. Most patients belonged to the younger age group, with 82 (60.7%) patients aged less than 30 years, while 106 (80%) were younger than 40 years. The majority of patients were male (107: 79.3%), whereas 28 (20.7%) were female. The male gender and younger age were preferentially involved in dengue fever as there were 107 (79.3 %) males and only 28(20.7%) females in the study.

Overall, 64 (48.8%) patients had some degree of liver involvement indicated by deranged LFTs. These abnormalities predominantly represented mild to moderate biochemical derangements, and no cases of severe hepatitis or acute liver failure were observed during the study period. Among these patients, 27 (42.2%) had elevated ALT, seven (10.9%) had increased bilirubin, and 30 (46.9%) had elevated ALP. Serum bilirubin remained normal in most patients, with 112 (83%) showing values within the reference range and a mean bilirubin level of 11.71 ± 8.60 µmol/L. Mean ALT was 107 ± 240 IU/L, and mean ALP was 113.57 ± 59.91 IU/L. The large standard deviation observed for ALT reflects wide variability in transaminase levels, likely due to a small number of patients with markedly elevated values, consistent with outlier patterns commonly reported in dengue-associated hepatitis (Table I). Regarding hematological parameters, platelet levels were expectedly low, with a mean of 79.71 ± 47.82 $\times 10^3/\mu L$. Total leukocyte count remained within the normal range (4.67 ± 2.61 $\times 10^3/\mu L$), and mean hemoglobin level was also normal at 13.46 ± 1.88 g/dL. Evidence of coagulopathy was observed, with a mean prothrombin time of 14.45 ± 2.17 seconds and activated partial thromboplastin time of 35.87 ± 6.67 seconds. On correlation analysis, elevated alkaline phosphatase (ALP) was the only liver function parameter found to be associated with mortality (Pearson's $r = 0.282$, $p < 0.05$), whereas ALT and bilirubin derangements did not show a significant association with death (Table II). The number of observations (n) varied across liver function parameters due to incomplete laboratory testing in some patients, primarily resulting from early discharge, patient transfer, or unavailability of specific assays at the time of sampling. Among 105 male participants, two (1.9%) patients died, while one death (3.7%) was observed among 27 female participants. The overall mortality rate in the study population was 2.2% (3/135 patients).

Table 1. Descriptive statistics of demographic and laboratory parameters of the study population

	N	Mean	Std. Deviation	Variance
Serum Bilirubin µmol/L	128	11.711	8.602	73.987
AGE	128	30.984	12.029	144.687
Platelets 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

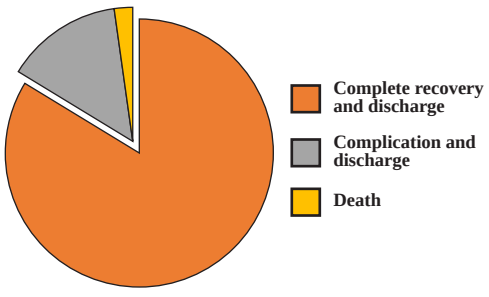

Figure 2: Major presenting complaints of dengue in males and females

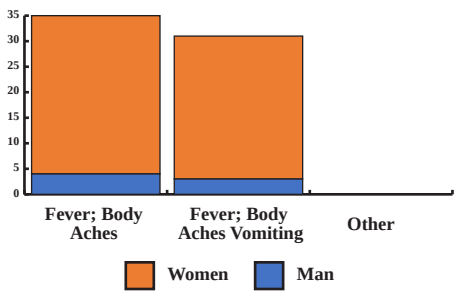

Table 2: Correlation analysis of deranged LFTS with mortality

Liver Parameter	LFTS group		Survived	Death	Total	Pearson's R	Significance
Bilirubin	Normal	Count	125	3	128	0.03	0.68
		% Within Normal values	97.7%	2.3%	100.0%		
	Abnormal	Count	7	0	7		
		% Within deranged values	100.0%	0.0%	100.0%		
	Total	Count	132	3	135		
		% Within Total population	97.8%	2.2%	100.0%		
ALT	Normal	Count	106	2	108	0.05	0.55
		% WithinNormal values	98.1%	1.9%	100.0%		
	Abnormal	Count	26	1	27		
		% Withinderanged values	96.3%	3.7%	100.0%		
	Total	Count	132	3	135		
		% Within Total population	97.8%	2.2%	100.0%		
ALP	Normal	Count	105	0	105	0.282	0.01
		% WithinNormal values	100.0%	0.0%	100.0%		
	Abnormal	Count	27	3	30		
		% Within deranged values	90.0%	10.0%	100.0%		
	Total	Count	132	3	135		
		% Within total population	97.8%	2.2%	100.0%		

DISCUSSION

The consensus in the literature is that liver involvement is an almost universal feature in dengue patients, though the extent of this involvement varies widely.[1°] In our study, nearly half of the patients (47.4%) exhibited some form of hepatic derangement, with most experiencing mild to moderate liver involvement and no cases of fulminant liver failure, a finding consistent with many observational cohorts.[3] The majority of patients in our study presented with clinical features consistent with uncomplicated dengue fever as defined by the World Health Organization severity framework, while severe forms such as dengue haemorrhagic fever or dengue shock syndrome were uncommon. In this context, hepatic involvement typically manifested as a transient, self-limiting elevation in liver enzymes without evidence of significant synthetic dysfunction, such as coagulopathy or hypoalbuminemia directly attributable to liver failure. This rate, while clinically significant, underscores that severe hepatitis remains a less common, albeit critical, complication of the disease. The absence of acute liver failure in our cohort is a positive prognostic indicator for the general patient population in this outbreak, but it also highlights that the most severe manifestations of dengue may be underrepresented in single-center studies, particularly those conducted outside of specialized intensive care or transplant units.

The principal finding of this study is the observed positive association between elevated serum alkaline phosphatase (ALP) levels and mortality. While elevated aminotransferases are the most frequently discussed markers of liver injury in dengue, our data suggest that ALP may hold distinct prognostic value. This aligns with findings from Teerasarntipan et al., who identified significant hepatic derangement as a predictor of mortality, particularly in cases progressing to acute liver failure.6 Aspartate aminotransferase (AST), which is often reported to be more markedly elevated than ALT in dengue and has been described as a potential prognostic marker, was not routinely measured in this study due to limitations in the standard laboratory testing protocol during the study period. Consequently, analysis of AST levels and AST/ALT ratios could not be performed and represents an important area for future research[6].The potential mechanism for this association is not fully understood but may reflect a more profound systemic inflammatory response or a degree of cholestatic injury that is not captured by transaminase levels alone. It is plausible that an elevated ALP signifies a more severe, systemic insult rather than isolated hepatocellular damage. This is a critical distinction, as ALT elevation primarily reflects direct hepatocyte damage, whereas ALP can also be released from the biliary epithelium, which may be affected by the systemic inflammation and capillary leakage characteristic of severe dengue. In contrast, our study found no significant association between elevated ALT or bilirubin levels and mortality. This contributes to an ongoing debate in the literature. While some studies have correlated high transaminase levels with severe dengue,[11,13] others have found them to be poor predictors of adverse outcomes, especially when considered in isolation.[15,17] For example, a large study by Samad et al. found a clear pattern

of LFT derangement correlating with severity,[13] whereas our findings are more aligned with studies like Patel et al., which suggest that while transaminitis is common, its prognostic power for mortality is limited.[15] Our results suggest that in our patient population, ALT elevation is a common marker of hepatic inflammation but not necessarily a reliable indicator of impending mortality. This finding encourages clinicians to look beyond transaminase levels and consider a broader panel of markers when assessing risk, potentially moving towards a multi-marker approach for prognostication.

The demographic profile of our cohort, predominantly young males, is consistent with other regional studies from Pakistan and South Asia.[8] This may reflect occupational and social patterns that increase exposure to the *Aedes* vector in this demographic. For example, men in this age group are more likely to have occupations that involve outdoor work or travel during the day when the Aedes mosquito is most active, leading to a higher probability of exposure. The overall rate of liver involvement in our study (47.4%) was lower than the 70-80% reported in some other series.[11,15] This difference may be attributable to variations in the definition of hepatic dysfunction, as our study relied solely on elevations in ALT, ALP, and bilirubin, whereas others have included a broader range of parameters, such as the albumin-to-globulin ratio. Furthermore, host genetic factors and the virulence of the circulating DENV serotype could also contribute to this observed difference in the prevalence of hepatic injury. This highlights the need for standardized definitions of dengue-associated liver injury to allow for more accurate comparisons across studies.

This study has several important limitations. First, as a single-center observational study, the findings may not be generalizable to other populations or healthcare settings. Different regions may have varying circulating viral serotypes, host genetics, and healthcare resources, all of which can influence clinical outcomes. Specifically, DENV-2 and DENV-3 serotypes are often associated with more severe disease and hepatic dysfunction compared to DENV-1 and DENV-4: our study did not perform serotyping, which is a key unmeasured variable. Therefore, the prognostic value of ALP observed here requires validation in larger, multi-center cohorts before it can be widely adopted into clinical guidelines. Second, the small number of mortality events (n=3) limits the statistical power of our correlation analysis and prevents us from drawing definitive conclusions about mortality predictors. A larger, multi-center study would be required to validate the prognostic significance of ALP. While a statistically significant correlation was found, the low event rate means this finding should be interpreted with caution as it may be susceptible to type I error, and the true strength of the association may be different in a larger sample. Third, our reliance on laboratory parameters alone, without standardized data on clinical findings like hepatomegaly or liver ultrasound results, may have led to an underestimation of the true extent of liver involvement. Another laboratory limitation was the lack of AST measurement, which prevented calculation of the AST/ALT ratio: this was due to the study's reliance on routine hospital liver function testing protocols during the outbreak period, in which AST was not included as part of the standard biochemical panel. Finally, the absence of long-term follow-up means the chronic implications of dengue-related liver injury could not be assessed.

CONCLUSION

Hepatic dysfunction is a common finding among patients with dengue fever. In this study, elevated alkaline phosphatase (ALP) levels showed a statistically significant association with mortality, whereas ALT and bilirubin abnormalities were not significantly related to patient outcomes. These findings suggest that ALP may serve as a potential marker of disease severity in dengue patients. However, larger multicenter studies are required to confirm its prognostic value.

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Authors Contribution:
Sherbano Baloch: Data Collection
Muhammad Bilal Arif: Management of Dengue Cases
Muhammad Irfan Khattak: Nephrological Consultation coordinator
Jamal Azfar Khan: Study design and data analysis
Saeed Akhtar Khan Khattak: Hematologic Consultation
Mohammad Tufail: Data Collection

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