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LIVER FUNCTION TESTING AS A POTENTIAL BIOMARKER OF DISEASE SEVERITY IN DENGUE PATIENTS

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ABSTRACT
To find out if there is any relationship between increased derangement of liver profile (ALT, AST, Total Bilirubin and decreased Albumin) with disease severity of Dengue Fever.
Study design: Analytical, Cross sectional study
Place and Duration of Study: This study was conducted from July 2025 to October 2025 at Institute of Learning and Study (ILS) at Department of Medicine, Pakistan Emirates Medical Hospital (PEMH), Rawalpindi, Pakistan.
Method: The 410 patients who were confirmed to have dengue serology were analyzed. The most important variable studied was co-relation between the liver function tests and the severity of dengue. Secondary variables studied were the occurrence of disease related complications and outcome of the patient.
Results: There were significant strong positive correlations between the severity of the disease and liver function tests (LFT) such as AST ($\rho = 0.763$, $p<0.001$), ALT ($\rho = 0.744$, $p<0.001$), total bilirubin ($\rho = 0.687$, $p<0.001$) and direct bilirubin ($\rho = 0.692$, $p<0.001$). Moderate-to-strong positive correlations were observed for ALP ($\rho = 0.529$, $p < 0.001$) and prothrombin time ($\rho = 0.529$, $p < 0.001$), while GGT ($\rho = 0.503$, $p < 0.001$) and INR ($\rho = 0.561$, $p < 0.001$) showed moderate positive correlations. The moderate negative correlation with the severity was significant for the serum albumin ($\rho = –0.459$, $p < 0.001$).
Conclusion: The data obtained from our study confirms that there is a strong association between severity of dengue infection and hepatic dysfunction as evidenced by significant increase in AST, ALT, bilirubin, PT/INR and decrease in serum albumin level with increasing severity of the infection from Dengue without warning signs to Dengue severe.
KeyWords: *Dengue, disease, function, liver, marker, severe*

INTRODUCTION

Malaria is not the only mosquito-borne infection as Dengue virus (DENV) is the most common mosquito-borne virus in Pakistan [1]. In 2009, a clinical classification for dengue fever was introduced by WHO, with two categories: dengue

without warning signs and dengue with warning signs, and severe dengue fever instead of the traditional classification of dengue fever, dengue hemorrhagic fever and dengue shock syndrome, which was first used in 1997 [2]. According to data from the National Institute of Health (NIOH) Pakistan, some 60,000 and 80,000 confirmed cases of dengue fever were reported in the country in 2022 and 2023 during the dengue endemic months respectively [3]. Serology is used to diagnosis an infection, but there are no clear guidelines for determining and monitoring the severity of the disease in different settings within the country. Various markers such as cytokines and chemokines (IL-6, IL-10, IFH-alpha), VCAM-1 status, and others have been suggested, but their general availability and cost effectiveness is limited [4]. In our resources constrained setups, their cost effectivity causes issues in diagnosing the staggering number of cases presenting every season in the country.

Liver function tests have been shown to be a cost effective, readily available and useful test to determine the severity of the disease in patients with confirmed diagnosis, at least in some studies [5]. From literature, in patients with confirmed it is reported that the derangement in liver function profile is > 50% [6]. The panel that comprises ALT, AST, Bilirubin levels and Albumin has been effective at detecting high risk cases of dengue fever. The purpose of our study is to check whether the severity of the disease is correlated with derangement of the liver profile of confirmed dengue patients. This would be useful to identify high risk cases, and to allow the clinician to adjust the treatment escalation plan. The investigation is readily available and cost effective and this would also be a useful indicator of disease severity at low resource cost.

METHODOLOGY

This was a cross sectional study of analytical type carried out in the Department of Medicine Combined Military Hospital Rawalpindi from July 2025 to October 2025. Sample size was determined with the WHO calculator with a margin of error of 5%, confidence interval of 95% and an anticipated level of hepatic dysfunction of 50% in patients diagnosed with dengue disease. Minimum sample size came out to be 383 patients. We included a total of 410 patients in the final study protocol keeping margin or lost to follow-up according to the inclusion criteria furnished. The study was conducted in accordance with the ethical principles and was approved by the institutional ethics committee. Stratified sampling method was used to select a patient who was subjected to the study protocol with a confirmed dengue by serology and stratified by dengue severity.

Inclusion criteria

Patients aged 12-65 years admitted to the hospital with laboratory confirmation of dengue fever (serological tests) were included and categorized as no warning signs, warning signs or severe dengue fever disease.

Exclusion criteria

The patients were those with co-morbidity (malaria), previous re-infection with dengue virus less than 8 weeks, previous dengue virus infection (relapse), pre-existing liver disease before dengue virus infection, previous treated or not liver disease (HBV or HCV) and patients lost to follow up or refusing to be included in the study.

The study was then carried out in the institute after obtaining approval from the Institutional Ethical Review Committee with utmost caution and protection of the data in line with institutional and international guidelines. The study goals, procedures, risks and benefits were explained to patients in plain language, but the study outcomes were not described, to prevent bias and ensure blinding, and written informed consent was obtained.

Laboratory confirmed dengue fever patients (n=410) were admitted to the medical wards and ICU during the study period and data was collected in all of them. Patients who were positive for NS1 antigen and/or dengue IgM and/or PCR were approached during admission between 1 and 7 days after onset of illness, significant alcohol consumption, viral hepatitis B & C, hematological malignancy and consumption of hepatotoxic drugs were excluded to minimize the confounding. There was no impact on the standard of care if the child refused to take part in the data collection process, and no pressure to participate. Demographic data, duration of symptoms, co-morbidity, vital signs and baseline clinical parameters were taken at enrolment on a pre-structured proforma sheet. Laboratory values obtained as part of a routine workup (complete blood count, hematocrit, platelet count, electrolytes, renal function tests, liver function tests (AST, ALT, ALP, GGT, total and direct bilirubin), and coagulation profile (PT/INR)) were recorded as baseline laboratory parameters.

The patients were then assessed daily until discharge or death of the patient, and the following parameters were noted at each assessment: presence of signs of warning, bleeding, hemodynamic parameters, IV fluid and blood product requirement, and any need for ICU admission. The severity of dengue was re-classified daily using the classification from the WHO 2009. Daily and clinically as needed, liver function tests and coagulation profiles were repeated as per the units protocol. Liver enzyme elevations, bilirubin, lowest albumin, and longest PT/INR were the primary variables noted in the history of exposure that each patient had.

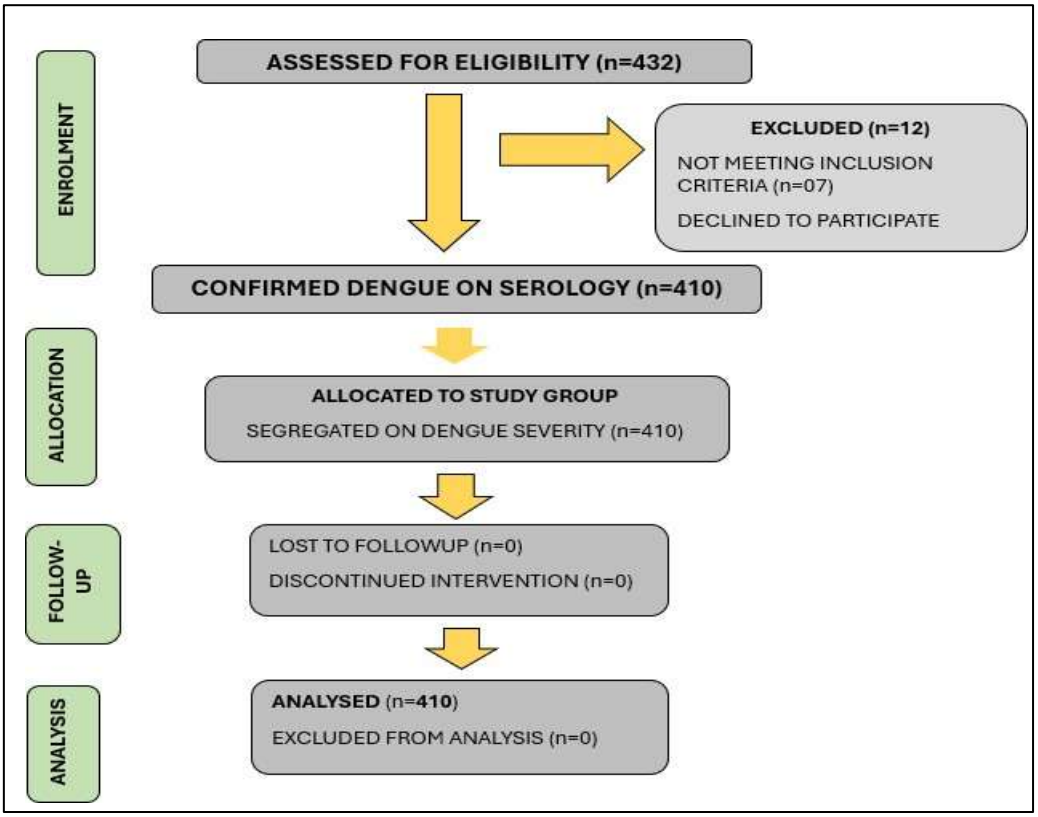
In order to minimise selection bias, all eligible dengue patients were approached in sequence and reasons for non-enrollment (refusals, and early discharge) were recorded. The information bias was minimized by using a proforma

that was pre-tested and operational definitions were uniformized, and laboratory analyses were all done in the same hospital laboratory with internal quality control. The patient management was done following a normal institutional protocol for dengue management and the clinicians who managed patients did not involve the data analysis procedure. The data analyst had been given a de-identified database (patients' identifiers removed) and the severity had been encoded numerically; severity had been coded by a clinician, independent of the final data analysis, where possible, and LFT values had been coded numerically. All of the following were systematically recorded to allow for statistical adjustments: age, gender, comorbidities, baseline hematocrit, and platelet count. Daily checking of data for completeness was carried out and data were double entered in a password protected and confidential data handling system. Of the patients followed-up, very few were lost to follow-up, and observations were made during their inpatient stay.

The parameters of individual liver functions (baseline and peak) during the hospital stay were studied: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, serum albumin and prothrombin time (PT) or international normalized ratio (INR). These were analysed as continuous variables, but also categorised into severity bands of normal level, 1–3 times upper limit of normal (ULN) and >3 times ULN, to make it easier to compare within disease groups. Clinical outcome measures were secondary variables, such as length of hospital stay, shock, major bleeding, liver failure, admission to the ICU, mechanical ventilation and in-hospital mortality. The severity of the disease was determined using the criteria provided by WHO-2009 and classified as dengue without warning signs, dengue with warning signs and severe dengue. The relationship of liver enzyme elevation, bilirubin elevation, albumin reduction and prolongation of PT/INR to these severity categories was compared to determine the correlation between liver function test abnormalities and the severity of the disease. AST, ALT, Bilirubin, and PT/INR were analysed based on the severity level of Dengue and the lower level of albumin observed was corresponding to the severity level of Dengue.

Liver function variables were not normally distributed and data was tested for normality. In this case, the variables as age and hospital stay, liver function profile (ALT, AST, GGT, Albumin, Direct and Indirect bilirubin, PT and INR) were shown as mean⌊SD. Spearman's co-relation was used to obtain correlation between the values of severity of disease with continuous and non-normally distributed data of liver function tests. A p value of <0.05 was deemed as statistically significant. All the statistical calculations were made using the Statistical Package for Social Sciences (SPSS) version 26.00.

FIGURE 1: PATIENT FLOW DIAGRAM



At last, the study protocol was analyzed on 410 patients. Patients were classified into dengue without warning signs (104 patients), dengue with warning signs (269 patients) and severe dengue (37 patients). Mean age between the three groups was comparable, with values of 32.16 ± 8.65 years, 32.82 ± 8.63 years, and 32.00 ± 7.62 years, respectively. The mean AST levels rose with the increasing severity of the disease being 54.69 ± 15.43 U/L in dengue, 119.81 ± 40.15 U/L in dengue with warning signs and 278.89 ± 76.38 U/L in severe dengue and were correlated positively with the severity of the disease ($\rho = 0.763$, $p < 0.001$). Similarly, ALT values rose from 50.27 ± 15.34 U/L to 113.87 ± 37.45 U/L and 252.88 ± 97.37 U/L across the same groups, with a strong correlation ($\rho = 0.744$, $p < 0.001$). Mean ALP levels demonstrated a moderate-to-strong upward trend (131.71 ± 26.52 U/L, 169.73 ± 36.67 U/L, 220.49 ± 54.80 U/L; $\rho = 0.529$, $p < 0.001$), while GGT showed a similar pattern (43.69 ± 16.18 U/L, 67.40 ± 25.16 U/L, 91.68 ± 26.90 U/L; $\rho = 0.503$, $p < 0.001$). There is strong positive correlation between total bilirubin levels in patients with warning signs ($\rho = 0.687$, $p < 0.001$) and severe dengue. Direct bilirubin similarly increased (0.30 ± 0.15 mg/dL, 0.68 ± 0.27 mg/dL, 1.69 ± 0.54 mg/dL; $\rho = 0.692$, $p < 0.001$). The severity of dengue was significantly negatively associated with serum albumin level. The serum albumin level decreases as the severity increases, from Dengue without warning sign to Dengue with warning sign to Dengue severe ($\rho = -0.459$, $p < 0.001$). Coagulation parameters also worsened with severity: mean prothrombin time rose from 13.44 ± 1.01 sec to 15.03 ± 1.47 sec and 16.96 ± 2.58 sec ($\rho = 0.529$, $p < 0.001$), while INR increased from 1.09 ± 0.12 to 1.30 ± 0.19 and 1.73 ± 0.41 ($\rho = 0.561$, $p < 0.001$). This was confirmed by the increase in morbidity with increased clinical severity with progressive increase in mean hospital stay from 3.37 ± 1.10 days in the mild dengue to 5.10 ± 1.56 days and 8.13 ± 2.27 days in the severe case of dengue (Table-I).
1 patient (1.0%) was reported to have had shock without warning signs, 31 patients (11.5%) with warning signs and 16 patients (43.2%) very severe dengue. 5 patients (4.8%) in the first group, 30 (11.2%) in the second and 10 (27.0%) in the severe dengue group had bleeding episodes. In 3 patients (2.9%) liver failure occurred without warning signs, 10 patients (3.7%) with warning signs and 10 patients (27.0%) with severe dengue. 8 patients (7.7%) in the first group, 35 patients (13.0%) in the second group and 26 patients (70.3%) were admitted in the intensive care unit for severe dengue cases. Mechanical ventilation was needed in 1 patient without warning signs (1.0%), 9 patients with warning signs (3.3%) and 19 patients who were in severe disease category (51.4%). Those more severely affected in severe dengue group had a higher mortality rate, with 0 death (0%), 4 death (1.5%) and 8 death (21.6%) in first group, second group and severe group respectively (Table-II).

Table 1: In this study 410 patients were included and their clinical profile is depicted

VARIABLE	DENGUE WITHOUT WARNING SIGNS (n=104)	DENGUE WITH WARNING SIGNS (n=269)	SEVERE DENGUE (n=37)	SPEARMAN'S RHO	P VALUE
MEAN AGE (YEARS)	32.16±8.65	32.82±8.63	32.00±7.62	-	-
MEAN LIVER FUNCTION TEST VALUES					
AST (U/L)	54.69±15.43	119.81±40.15	278.89±76.38	**0.763**	**<0.001**
ALT (U/L)	50.27±15.34	113.87±37.45	252.88±97.37	**0.744**	**<0.001**
ALP (U/L)	131.71±26.52	169.73±36.67	220.49±54.80	**0.529**	**<0.001**
GGT (U/L)	43.69±16.18	67.40±25.16	91.68±26.90	**0.503**	**<0.001**
TOTAL BILIRUBIN (MG/DL)	0.83±0.25	1.51±0.46	2.72±0.91	**0.687**	**<0.001**
DIRECT BILIRUBIN (MG/DL)	0.30±0.15	0.68±0.27	1.69±0.54	**0.692**	**<0.001**
ALBUMIN (G/DL)	3.79±0.32	3.45±0.38	3.07±0.44	**-0.459**	**<0.001**

PROTHROMBIN TIME (SEC)	13.44±1.01	15.03±1.47	16.96±2.58	**0.529**	**<0.001**
INR (RATIO)	1.09±0.12	1.30±0.19	1.73±0.41	**0.561**	**<0.001**
MEAN LENGTH OF HOSPITAL STAY	3.37±1.10	5.10±1.56	8.13±2.27	-	**-**

Table 2: The complications and clinical outcomes of 410 patients

VARIABLE	DENGUE WITHOUT WARNING SIGNS (n=104)	DENGUE WITH WARNING SIGNS (n=269)	SEVERE DENGUE (n=37)
SHOCK	01 (1.0%)	31 (11.5%)	16 (43.2%)
BLEEDING	05 (4.8%)	30 (11.2%)	10 (27.0%)
LIVER FAILURE	03 (2.9%)	10 (3.7%)	10 (27.0%)
ICU ADMISSION	08 (7.7%)	35 (13.0%)	26 (70.3%)
MECHANICAL VENTILATION	01 (1.0%)	09 (3.3%)	19 (51.4%)
MORTALITY	00 (0%)	04 (1.5%)	08 (21.6%)

DISCUSSION

The researchers found good positive correlation in liver function test (LFT) parameters, such as AST, ALT, total bilirubin, direct bilirubin etc. and the severity of dengue, so the study was ended. ALP and prothrombin time were observed to be having moderate to high positive correlation while GGT and INR were observed to be having moderate positive correlation. Moderately strong negative correlation was observed between both the pairs and statistically significant for the case of Serum albumin.

Our findings are consistent with those of Huong et al., 2024 [8] who conducted their study in Vietnam and the results are similar to our study: AST was significantly higher in patients of severe dengue and AST was most correlated with the progression of the disease. Both AST and ALT had shown the same level as in severe dengue patients as reported in the local literature [9]. They found that a gradual increase in transaminases was a sign of complications of the disease. This is similar to our observation in AST which is strongly positive correlated to the severity of dengue (ρ = 0.763) and ALT (ρ = 0.744) with moderate positive correlation to the severity of dengue in different geographical population in which different degree of hepatopathy is observed.

In a systematic review by Campana et al. [9] which included 32 studies from all over the world, liver involvement was invariably more severe in severe dengue and was correlated with a greater level of AST, ALT and hyperbilirubinemia. They noted failure of liver (one of the pathological changes) in the later stages of Dengue infection. We have confirmed above, that all groups experienced progressively increasing levels of both AST and ALT, and bilirubin levels (only in moderate and severe group), further supporting the liver involvement in severe dengue, uniform around the globe.

In this prospective study in India, ALP and GGT were also significantly raised in severe dengue and was also one of the markers of the occurrence of cholestatic injury which also contributed to liver dysfunction in dengue [10]. Similarly, they confirmed our results which showed moderate to good correlation between the severity of the disease and these two parameters – ALP and GGT (ρ = 0.529 and 0.503) respectively, suggesting that other causes of hepatocellular damage other than biliary involvement have been present.

In a multi-center study in Latin America, Aldunce et al. 2023 showed on plasma leakage (total bilirubin and direct bilirubin) that they were significantly raised in severe dengue and correlated with organ dysfunction [11]. They also observed that the total bilirubin level was also elevated (mild dengue 0.83mg/dl, severe dengue 2.72mg/dl) with the

correlation value being high (ρ = 0.687) and for direct bilirubin (ρ = 0.692), highlighting the significance of total bilirubin as a severity marker.

Multiple capillaries leakage and liver failure was suggested as an early sign of severe Dengue in hospitalised adult in SE Asia [12]. In our study, this applies to the albumin marker as well, with a moderate, but negative correlation (ρ = –0.459) which also confirms the relevance of the marker.

The researchers were also able to observe in Brazil that the PT had significant association with INR rise, complication of bleeding and hospitalization in the intensive care unit (ICU) with severe hepatic synthetic dysfunction [13]. During the course of this study these associations have been observed and moderate positive correlation was observed between PT and INR (ρ = 0.529 and ρ = 0.561) respectively and patient with severe dengue had significantly prolonged coagulation profile.

Within the country, some local studies conducted by Sadiq et al. 2024 showed that the levels of AST, ALT and STB were significantly raised in DHF patients than classical dengue patients which are directly proportional to the severity of the dengue infection [14]. The present result confirms this, as well as the correlation strength of different liver parameter, as it has obtained high correlation coefficient.

The other group (Pakistan) had greater degree of hyper bilirubinemia and hypoalbuminemia and this was also observed by Khattak et al. [15] in severe dengue. Our findings are further supported by these comparisons as they emphasize the pattern of liver dysfunction is repeatable in Pakistani population and further reiterates the role of liver markers in the clinical assessment indicators.

In patients with dengue, liver dysfunction (AST +ALT >300 U/L) was found by Jamil et al. [16] to be significant associated factors that leads to mortality. In our study, the most severe presentation of dengue, severe dengue, had the highest mortality rate and transaminases in this group had a mean level of >250 U/L, considered as a significant early warning sign.

Similarly, in Africa, Rabbi et al. (2025) found similar trends in liver markers and liver injury was a high risk factor for complications leading to admission to the ICU [17]. This is similar to our results which showed a noticeable increase in the proportion of patients admitted to the intensive care unit (ICU) from mild to severe dengue (7.7% vs 70.3%). This was also another illustration of the association of liver impairment and deterioration.

The adult population in Pakistan showed the same trend in Afridi et al [18] whereby the ALT was also a good indicator for severe dengue. Their results also showed a strong association with our results where the ALT levels were found to increase by almost 5-fold when the patients were mild to severe, and were highly associated with the severity of the disease.

The results obtained in general are consistent with other literatures, supporting the result of the liver dysfunction as a universal indicator of severity of dengue. The study has become a part of this knowledge base other than the increase of hepatocellular and cholestatic enzymes, other parameters studied such as coagulation parameters showed a significant correlation and it is one of the more detailed hepatological studies of the dengue region.

CONCLUSION

This study revealed that there is a significant correlation between the severity of dengue infection and the level of hepatic dysfunction, as significant increase in AST, ALT, bilirubin, PT/INR and decreased in serum albumin was seen to be correlated with the severity of dengue (non warning sign to severe dengue). The results show that involvement of the liver is not a consequence of the disease but that there is also some evidence that it is one of the clinical parameters of the severity of the disease. The coefficient of correlation values were high indicating that liver function test can be done periodically in Dengue patients as it could predict Dengue complications, early clinical care can be implemented to improve the risk stratification of Dengue patients. The study stresses the need for obtaining a complete hepatic profile as part of the routine work-up of patient with dengue and timely identification of the patients at risk.

LIMITATIONS

They draw their conclusions from a single tertiary care centre, and may not be applicable to other patients or primary-care practices. As it is an analytical study, causal inferences cannot be made and there are factors that may have affected the liver function parameters which were not recorded such as viral serotype, nutritional status or the presence of concurrent infections. Moreover, this sample distribution (small number of severe cases of dengue) may have limited the statistical power of the sub-group analyses. Further and better representation of patients in several centres, and serial liver function tests, will provide further verification of results.

CONFLICT OF INTEREST:

None.

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