Hepatic damage associated with dengue infection: insights from the emergency department of a tertiary care centre

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Abstract

Liver involvement is a common but variable manifestation of dengue virus infection. This study aimed to evaluate the clinical and biochemical spectrum of dengue hepatitis and its correlation with disease severity in patients presenting to a tertiary care center. A retrospective cross-sectional study was conducted at a tertiary care center from July 2024 to December 2024, including 130 adult patients with laboratory-confirmed dengue infection. Dengue hepatitis was categorized as mild, moderate, or severe based on serum transaminase levels. Disease severity was assessed according to both the World Health Organization (WHO) 1997 and WHO 2009 classification criteria. Laboratory parameters were analyzed in relation to hepatitis severity. Among the 130 patients, 113 (87%) had elevated liver enzymes. Aspartate Aminotransferase Levels (AST) were consistently higher than Alanine Aminotransferase (ALT). Severe dengue hepatitis was significantly associated with WHO 2009 disease severity classification ($p<0.001$). Total bilirubin levels were significantly elevated in patients with more severe hepatitis, while no significant correlation was observed between platelet count and hepatitis severity. Patients presenting with warning signs and severe dengue had higher frequencies of moderate-to-severe hepatitis. We conclude that hepatic involvement in dengue infection is common and correlates with disease severity. Elevated transaminases, particularly AST, and rising bilirubin levels may serve as early markers of severe dengue. Integration of liver function monitoring into clinical assessment protocols is essential for the timely management of dengue hepatitis.

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Introduction

Dengue, often referred to as "breakbone fever," has become a leading cause of febrile illness in tropical and subtropical regions. After malaria, it ranks as the most prevalent mosquito-borne infection and is currently the foremost cause of arboviral disease worldwide.[1] Dengue is recognized by the WHO (World Health Organization) as a major global public health threat, with cases and deaths rising sharply in recent decades.[2] Currently, about 4 billion people half the world's population are at risk, with an estimated 400 million infections annually, 50-100 million of which are symptomatic.[3] Projections suggest that by 2080, over 6 billion people could be at risk, more than double the 2015 figures.[4]

The Dengue Virus (DENV) comprises four distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 while DENV-2 is most common in India.[5] While all four serotypes were initially identified in Southeast Asia, they have since spread widely and are now endemic across tropical and subtropical regions worldwide.[6] Infection with any one serotype provides lifelong immunity against that specific serotype. However, because the serotypes are antigenically similar, they offer only short-term cross-protection against the others. Notably, a secondary infection with a different serotype increases the risk of developing more severe forms of the disease, such as Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS). The disease is transmitted primarily by *Aedes aegypti* and *Aedes albopictus* mosquitoes, with no direct person-to-person transmission.[7,8]

WHO has proposed two major classifications for the clinical manifestations of dengue. The 1997 WHO classification divides dengue into three clinical entities: Dengue Fever (DF), DHF, and DSS. In contrast, the revised 2009 WHO classification redefines the clinical spectrum by categorizing cases as dengue without warning signs, dengue with warning signs, and severe dengue, with the aim of enhancing clinical management and improving case identification, particularly in resource-limited settings.[9]

Dengue infection can be categorized as asymptomatic or symptomatic. The symptomatic form includes a wide range of clinical presentations, such as undifferentiated fever, classic dengue fever, and DHF, which may occur with or without shock. Additionally, certain cases are classified as expanded dengue syndrome due to atypical or severe organ involvement, with or without plasma leakage or features of DHF.

In DENV infection, a high level of viremia is often associated with multi-organ involvement, particularly in severe cases.[10] Among these, the liver is the most commonly affected organ. Hepatic involvement in dengue is frequent and may range from mild elevations of liver enzymes to fulminant hepatic failure. The mechanisms contributing to liver damage include: i) ischemic injury due to reduced blood flow in dengue shock syndrome; ii) endothelial dysfunction involving the hepatic sinusoids, leading to impaired microcirculation and hepatic congestion; iii) direct viral cytopathic effects, as the dengue virus can infect hepatocytes and cause cellular damage; and iv) immune-mediated injury, in which host immune responses trigger inflammation and hepatocellular damage through cytokine release and immune cell activation.[11-13] Diabetic patients with dengue exhibit increased inflammatory responses and more severe clinical manifestations. Diabetes independently increases the risk of severe dengue, highlighting its potential role as a predictor of disease severity.[14]

There is currently no universally accepted definition of dengue-related hepatitis. However, an elevation of Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) levels to more than three times the Upper Limit of Normal (ULN) is commonly used as a clinical indicator. The severity of dengue hepatitis is classified according to liver enzyme elevation as mild (ALT or AST 3-5 times ULN), moderate (5-10 times ULN), or severe (>10 times ULN). In most cases, serum AST levels are significantly higher than serum ALT levels. The degree of liver enzyme elevation is closely associated with disease severity. Moreover, markedly elevated ALT levels may serve as a prognostic marker, being associated with an increased risk of adverse clinical outcomes.[15,16]

Transaminases are released into the bloodstream due to inflammation of the liver parenchyma. Although the impact of DENV infection on liver function is well recognized, research in this area remains limited. This study aimed to evaluate liver enzyme abnormalities in dengue fever and to explore their correlation with disease severity. The frequency and clinical presentation of liver injury associated with dengue infection vary significantly across studies, likely due to differences in case definitions, viral serotypes, individual host factors, and underlying conditions such as chronic liver disease.[17]

Materials and Methods

This retrospective observational study was conducted in the Department of Emergency Medicine at Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, in collaboration with the Department of Hepatology. The study included 130 patients with a confirmed diagnosis of dengue infection who presented to the Emergency Department between July 2024 and December 2024. Given the retrospective design, the Institutional Ethics Committee waived the requirement for informed consent in accordance with established ethical guidelines. Patient data were collected from medical records, and the study aimed to evaluate the spectrum and severity of hepatic involvement in dengue fever. Ethical approval for the study was obtained from the Institutional Ethics Committee - Clinical Research & Studies, SGPGIMS, Lucknow, India (IEC Code: 2025-155-IMP-144).

Inclusion and exclusion criteria

Patients were eligible for inclusion if they were between 10 and 70 years of age and had a confirmed diagnosis of dengue infection, based on either Non-Structural protein 1 (NS1) antigen testing or immunoglobulin M (IgM) antibody detection. Patients were excluded if they had co-infection with other viral or tropical diseases, including hepatitis A- E, leptospirosis, malaria, rickettsial infections, tuberculosis, or enteric fever; presence of autoimmune disorders known to affect liver function; a history of hepatotoxic drug use, including paracetamol or other known hepatotoxic agents; pregnancy, due to its influence on disease presentation and laboratory parameters; or pre-existing chronic liver disease, including alcoholic liver disease.

Blood sample collection and analysis

Blood samples were collected from all patients within 24 hours of hospital admission. Data were collected for each patient to ensure a comprehensive clinical and laboratory profile. Demographic information included age and gender. Detailed medical history was documented, with particular emphasis on the presence of dengue infection. Clinical features assessed at presentation included nausea or vomiting, rash, aches and pains, a positive tourniquet test, leukopenia, or the presence of any warning sign. Laboratory investigations encompassed a Complete Blood Count (CBC) and liver function tests, specifically serum AST, serum ALT, and total serum bilirubin (TSB). Samples were processed according to standard laboratory protocols. CBC was performed using an automated hematology analyzer. Liver function tests were measured using standard biochemical assays. Dengue antigen testing was performed using a rapid immunochromatographic test, while antibodies were detected using an Enzyme-Linked Immunosorbent Assay (ELISA).

Dengue diagnosis and spectrum of clinical manifestations

Dengue infection was confirmed using both NS1 antigen testing and IgM antibody detection. NS1 antigen testing was performed using a rapid immunochromatographic test, while IgM antibodies were detected using an ELISA. A positive result in either test, along with compatible clinical features, was considered diagnostic of dengue infection. Dengue virus-specific IgM antibodies were detected using the Panbio™ Dengue IgM Capture ELISA kit (Catalog No. 01PE20, Abbott Laboratories, Brisbane, Australia). This qualitative ELISA is intended to support the diagnosis of dengue infection in patients presenting with clinically consistent symptoms. As per the manufacturer's data, the assay has a serological sensitivity of 94.7% for primary dengue infections and 55.7% for secondary infections, with a serological specificity of 100% in negative samples. Although the assay does not report a numerical detection limit, it is optimized for identifying IgM anti-

bodies during the acute phase of infection. The reported intra-assay variability is <10%, and inter-assay variability is <15%.

Criteria for dengue hemorrhagic fever, warning signs, and severe dengue

DHF is defined by the presence of fever, hemorrhagic manifestations (e.g., positive tourniquet test), and evidence of plasma leakage or spontaneous bleeding. It may be accompanied by signs of circulatory compromise, such as weak pulse, narrow pulse pressure (≤20 mmHg), or profound shock with undetectable blood pressure and pulse.

Warning signs of dengue include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, hepatomegaly (>2 cm), and laboratory evidence of hemoconcentration with a concurrent rapid decline in platelet count.

Severe dengue is diagnosed when one or more of the following are present: i) severe plasma leakage leading to hypovolemic shock (dengue shock syndrome) and/or respiratory distress from pleural effusion or ascites; ii) severe bleeding that is clinically significant; iii) severe organ involvement**,** such as markedly elevated transaminases (AST or ALT ≥1000 IU/L), impaired consciousness due to central nervous system involvement, myocarditis, or acute kidney injury.

Hepatitis classification

Dengue-associated hepatitis is classified by liver enzyme (ALT, AST) elevation relative to the upper limit of normal (ULN=40 U/L): Mild: 3 to 5× ULN (120-200 U/L), Moderate: >5 - 10× ULN (200-400 U/L), Severe: >10× ULN (>400 U/L). In all cases, the higher of the two transaminase values (ALT or AST) was used to determine the severity category.

Statistical analysis

Continuous variables were expressed as mean±Standard Deviation (SD), and categorical variables as frequencies and percentages. Group differences in categorical data were assessed using the Chi-square or Fisher's exact test. Continuous variables, including age, hemoglobin (Hb), total leukocyte count (TLC), platelet count, and liver function parameters ALT and AST, and TSB, were compared across dengue hepatitis severity groups using one-way analysis of variance (ANOVA). Significant ANOVA results were followed by Bonferroni-adjusted post-hoc tests. All analyses were performed with IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value <0.05 was considered statistically significant.

The distribution of hepatic involvement (categorized as no hepatitis, mild, moderate, or severe) across the different clinical spectrum of dengue infection: Dengue Fever, DHF, and DSS are summarized in Table 1. Among DF cases, hepatic involvement is fairly distributed, with the highest proportion exhibiting moderate hepatitis (37.5%). In contrast, DHF and DSS cases show a trend toward more frequent mild hepatic involvement (47.1% and 66.7%, respectively). However, none of the patients with DHF or DSS had normal liver transaminase levels thus patients with DSS or DHF group had hepatitis, indicating that liver involvement may be a consistent feature in severe dengue cases. Although variations in hepatitis severity were noted across the clinical categories, the differences were not statistically significant (p=0.083). These findings suggest that while dengue hepatitis can occur across all forms of dengue infection, its severity does not differ significantly among the clinical classifications.

The distribution of dengue hepatitis severity across three clinical categories: dengue fever without warning signs, dengue fever with warning signs, and severe dengue are illustrated in Table 2. A statistically significant association (p<0.001) was observed between dengue severity and the degree of hepatitis. Among patients with dengue fever without warning signs (n=30), the majority had moderate hepatitis (43.3%), followed by severe (23.3%), and mild or no hepatitis (each 16.7%). In patients with dengue fever with warning signs (n=61), moderate (37.7%) and severe hepatitis (31.1%) were predominant, with no cases of no hepatitis. Among those with severe dengue (n=39), mild hepatitis was most common (41.0%), followed by equal proportions of no and moderate hepatitis (20.5% each), and severe hepatitis (17.9%). These findings suggest that as dengue severity increases, there is a corresponding increase in the severity of liver involvement, high-

Table 1. Distribution of severity of dengue hepatitis among clinical categories of dengue (N=130). Data are presented as number (%). Comparisons of severity of dengue hepatitis across clinical categories (DF, DHF, DSS) were performed using Fisher's exact test (p=0.083). A p-value <0.05 was considered statistically significant.

Dengue category	No hepatitis n=13 (%)	Mild n=40 (%)	Moderate n=44 (%)	Severe n=33 (%)	Total n=130
DF	13 (12.5)	26 (25)	39 (37.5)	26 (25)	104
DHF	0	8 (47.1)	4 (23.5)	5 (29.4)	17
DSS	0	6 (66.7)	1 (11.1)	2 (22.2)	9

DF, Dengue Fever; DHF, Dengue Hemorrhagic Fever; DSS, Dengue Shock Syndrome.

Table 2. Distribution of dengue hepatitis severity across clinical presentations of dengue (N=130). Data are expressed as number (%). Comparisons among groups were performed using Fisher's exact test (p <0.001). A p-value <0.05 was considered statistically significant.

Dengue category	No hepatitis n=13 (%)	Mild n=40 (%)	Moderate n=44 (%)	Severe n=33 (%)	Total n=130
DF	5 (16.7)	5 (16.7)	13 (43.3)	7 (23.3)	30
DHF	0	19 (31.1%)	23 (37.7)	19 (31.1)	61
DSS	8 (20.5)	16 (41)	8 (20.5)	7 (17.9)	39

DF, Dengue Fever; DHF, Dengue Hemorrhagic Fever; DSS, Dengue Shock Syndrome.

lighting the importance of monitoring hepatic function in dengue patients.

The clinical and laboratory parameters associated with varying severity levels of dengue hepatitis (no hepatitis, mild, moderate, and severe) are summarized in Table 3. The mean age did not significantly differ among the groups, with values of 39.92±23.00 years in the no hepatitis group, 35.40±15.84 years in the mild group, 40.07±16.39 years in the moderate group, and 34.36±12.86 years in the severe group (p=0.357). Hb levels also showed no statistically significant variation across the groups. Similarly, TLC values did not differ significantly (p=0.141), although a slight decrease was observed in the severe group. In contrast, platelet counts varied significantly across hepatitis severity (p=0.011), with the highest mean count seen in the severe group (11.76±10.51 $\times 10^3/\mu L$), potentially reflecting a reactive thrombocytosis or differential immune response.

Liver enzyme levels showed marked differences with increasing severity. AST levels increased dramatically from 35.42±16.26 U/L in the no hepatitis group to 139.50±261.21 U/L in mild, 181.58±77.91 U/L in moderate, and 1136.87±1996.68 U/L in severe hepatitis, with a highly significant p-value of <0.001. Although ALT levels also appeared elevated, the variation was not statistically significant (p=0.252). TSB levels showed a significant increase with hepatitis severity (p=0.006), rising from 48.69±20.79 µmol/L in the no hepatitis group to 3079.86±7834.73 µmol/L in the severe group. Direct bilirubin also demonstrated a progressive increase across groups (p<0.001). The TLC value was significantly different between moderate to severe dengue patients. Similarly, ALT (Max) was significantly different between severe dengue patients and no hepatitis, mild and moderate dengue patients. These findings suggest that elevated liver enzymes and bilirubin levels are strongly associated with the severity of hepatic involvement in dengue infection and may serve as important prognostic indicators.

Discussion

This study evaluated liver enzyme abnormalities in 130 hospitalized patients with confirmed dengue fever and explored their correlation with disease severity. Hepatic involvement was observed in nearly 90% of cases, with an overall mortality rate of 6.15%. The classification of hepatitis into mild, moderate, and severe categories based on AST/ALT levels provided a practical framework for assessing hepatic dysfunction.

Hepatic dysfunction in dengue is widely reported, occurring in 60–90% of patients.[17] It is attributed to both direct viral effects on hepatocytes and Kupffer cells, and to immune-mediated injury.[18,19] Elevated aminotransferases remain the most common biochemical abnormality.[20,21] Consistent with previous studies, AST was more frequently and markedly elevated than ALT.[22-24] Narasimhan *et al.* reported AST elevation in 92% and ALT elevation in 82% of cases, findings closely aligned with ours.[21] In dengue infection, AST typically rises higher than ALT, unlike viral hepatitis A, B, and C, where ALT predominates. Enzyme elevation begins around day three of illness, peaks by day seven or eight, and normalizes within three to eight weeks.[25] The disproportionately higher AST may be explained by its presence in hepatic and extrahepatic tissues, including muscle and erythrocytes, with contributions from myocyte damage, hemolysis, and ischemia-induced mitochondrial injury.[20,21,26] Although common, elevated transaminases have limited predictive value for severity, though some studies link higher ALT levels to poorer outcomes in dengue.[16] Despite their frequency, aminotransferase elevations did not predict disease severity in our cohort, consistent with Priyangika *et al.* and others who found limited prognostic value for transaminases.[27,28] Shivkar *et al.* noted a negative correlation between platelet count and aminotransferases, which we also observed, though without significant clinical impact.[29]

In the 2009 WHO classification, markedly elevated transaminases (AST or ALT >1000 U/L) were incorporated as one of the criteria for severe dengue. However, Lee LK et al. reported that aminotransferase elevations alone did not reliably differentiate between DF and DHF or between non-severe and severe dengue.[30] Our findings are consistent with this observation, further suggesting that liver enzyme levels, while frequently deranged, have limited value as standalone markers of disease severity.

Interestingly, while hepatitis severity did not differ significantly across the older WHO 1997 categories of DF, DHF, and DSS (p=0.083), all DHF and DSS patients had enzyme elevations, suggesting liver injury is a near-universal feature of severe disease. This aligns with earlier studies attributing liver dysfunction in severe dengue to systemic inflammation, viral cytopathic effects, ischemia from shock, and immune-mediated injury.[11-13] Importantly, the WHO 2009 classification showed a clear correlation with hepatitis severity (p<0.001), with patients presenting warning signs more often exhibiting moderate-to-severe hepatitis. This reinforces the greater clinical utility of the revised classification in reflecting organ involvement.

Beyond transaminases, bilirubin levels rose progressively with increasing hepatitis severity (p=0.006 and <0.001, respectively), suggesting cholestatic or mixed liver injury patterns in advanced

Table 3. Clinical and laboratory parameters by severity of dengue hepatitis (N=130).

Parameters	No hepatitis n=13 (%)	Mild n=40 (%)	Moderate n=44 (%)	Severe n=33 (%)	p	PHT (p<0.05)
Age (years)	39.92±23.00	35.40±15.84	40.07±16.39	34.36±12.86	0.357	--
Hb (g/dL)	11.24±2.65	12.37±2.55	12.09±2.38	11.10±2.71	0.141	--
TLC	6.60±6.94	7.43±7.14	6.06±5.39	11.77±10.51	0.011	Severe *vs* Moderate
Platelet count ($\times 10^3/\mu L$)	146.92±130.63	103.5±69.43	92.52±79.26	114.58±99.16	0.252	--
ALT (U/L, max)	35.42±16.26	139.5±261.22	181.58±77.91	1136.86±1996.67	0.001	Severe *vs* No Hepatitis, Severe *vs* Mild, Severe *vs* Moderate
AST (U/L, max)	48.69±20.79	188.48±250.80	256.27±81.28	3079.86±7834.74	0.006	Severe *vs* Mild, Severe vs Moderate
TSB (mg/dL, max)	0.74±0.56	0.88±0.83	1.49±2.42	2.71±2.84	0.001	Severe *vs* No Hepatitis, Mild

Hb, hemoglobin; TLC, total leukocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TSB, total serum bilirubin; PHT, post hoc test. Values are expressed as mean±standard deviation. Group comparisons were performed using one-way ANOVA, followed by post hoc multiple comparison tests. A p-value <0.05 was considered statistically significant.

cases. Total leukocyte counts also correlated with severe hepatitis (p=0.011), possibly reflecting exaggerated systemic inflammation or stress responses. By contrast, platelet count, hemoglobin, and age did not significantly vary with hepatitis severity, highlighting the multifactorial basis of these hematological changes in dengue. Platelet count did not significantly correlate with hepatitis severity (p=0.252), despite thrombocytopenia being typical in dengue. This likely reflects its multifactorial causes bone marrow suppression, immune-mediated destruction, and hemorrhagic consumption rather than direct hepatic involvement

Taken together, our findings confirm that while liver enzyme derangements are highly prevalent in dengue, their magnitude alone does not predict disease severity. In summary, the novel contribution of this study is demonstrating that the WHO 2009 classification correlates more strongly with dengue-associated hepatitis than the 1997 classification**,** underscoring the need for routine liver function monitoring in dengue patients, particularly those with warning signs or severe disease.

Limitations

This study has several limitations. First, its retrospective design limits the ability to establish causality and is susceptible to incomplete documentation or missing data. Second, we focused solely on patients who presented to the emergency department, potentially excluding milder outpatient cases. Third, serial liver function tests beyond the peak values were not consistently available, limiting the assessment of recovery patterns or long-term outcomes. Fourth, dengue serotyping was not performed, which could have provided further insights. Fifth, Point-Of-Care Ultrasound (POCUS) was not performed in all patients, limiting assessment of fluid status and organ involvement. Lastly, Hepatic markers (PT, INR) and key clinical outcomes such as encephalopathy, bleeding, coagulopathy, and acute liver failure were not systematically assessed, limiting a comprehensive understanding of hepatic involvement.

Practical implications for emergency clinicians

From an emergency medicine perspective, managing fever in dengue hepatitis requires a careful balance between providing symptomatic relief and minimizing the risk of drug-induced liver injury. Paracetamol is the antipyretic of choice due to its lower risk of bleeding and renal complications compared with NSAIDs. In patients with hepatic involvement, it should be used at the lowest effective dose (≤60 mg/kg/day, maximum 3 g/day in adults) and avoided in those with marked transaminase elevations or clinical liver dysfunction.[31] A randomized trial in 123 adults with dengue reported increased transaminases without improvement in fever or pain, highlighting the need for caution, although other studies suggest paracetamol rarely worsens liver function in severe dengue hepatitis.[32,33] Supportive measures, including tepid sponging, hydration, and close vital monitoring, remain essential.

WHO and the European Association for the Study of the Liver recommend N-acetylcysteine (NAC) for managing acute liver failure and acetaminophen overdose.[34] Emergency physicians should assess liver function routinely in patients with warning signs or severe disease and adjust therapy accordingly. Early recognition of hepatic dysfunction and judicious use of paracetamol are essential to prevent liver injury and optimize patient outcomes in the emergency setting.

Conclusions

Hepatic involvement is a common and clinically significant feature of dengue infection, often appearing early and in parallel with disease severity. Elevated AST, disproportionately higher than ALT, and rising bilirubin levels serve as early markers of severe disease and warrant vigilant monitoring. The severity of dengue-associated hepatitis aligns more closely with the 2009 WHO dengue classification than with the 1997 criteria. Prompt recognition and regular assessment of liver function are essential for early identification of severe dengue and for guiding supportive care strategies to reduce morbidity and mortality.

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