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Hepatic Dysfunction in Pediatric Dengue Fever: A Prospective Study from Central India

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ABSTRACT:
Background: Dengue fever is the most rapidly spreading mosquito-borne viral disease globally. Hepatic dysfunction is a well-recognized complication of dengue infection in children, ranging from mild transaminase elevation to acute liver failure. There is limited published data from the Chhattisgarh region of Central India on this aspect. **Methods:** This was a prospective observational study conducted at the Department of Paediatrics, Jawaharlal Nehru Hospital and Research Centre, Bhilai, Chhattisgarh, from November 2018 to October 2019. Ninety-two serologically confirmed dengue patients below 18 years of age were enrolled. All cases underwent detailed clinical evaluation and liver function tests including AST, ALT, total bilirubin, serum albumin, and INR. Cases were classified per 2009 WHO dengue guidelines. **Results:** Of 92 children (mean age 11.15 ± 4.73 years; male-to-female ratio 1.25:1), 52.2% had hepatic dysfunction. Cases were classified as dengue without warning signs (46.7%), dengue with warning signs (46.7%), and severe dengue (6.5%). Hepatic dysfunction was present in 46.5%, 53.5%, and 83.3% of the three groups respectively. Elevated liver enzymes (>2×ULN) were the most common hepatic manifestation (70.83%), followed by hepatomegaly (56.25%) and elevated INR ≥1.5 (20.83%). Mean AST was 68.23 ± 46.12 U/L and mean ALT was 44.92 ± 29.56 U/L. AST elevation was disproportionately higher than ALT. Severe hepatitis and acute liver failure were not observed. Elevated INR was significantly more prevalent in severe dengue (p=0.007). **Conclusion:** Hepatic dysfunction is common in pediatric dengue (52.2%), predominantly anicteric, and correlates positively with disease severity. Early assessment of liver function tests should be incorporated into the routine management of all dengue-positive children. Deranged coagulation profile is an important marker of severe dengue.

INTRODUCTION:
Dengue fever (DF) is a mosquito-borne viral illness caused by the dengue virus (DENV), a single-stranded RNA

virus of the Flaviviridae family with four serologically distinct serotypes (DENV-1 to DENV-4). It is currently the most rapidly spreading vector-borne viral disease worldwide, with a 30-fold increase in global incidence over the past five decades. The World Health Organization (WHO) estimates 50–100 million dengue infections occur annually, placing approximately 3.97 billion people across 128 countries at risk. The WHO Southeast Asian and Western Pacific regions bear approximately 75% of this global burden.

India is among the seven South-East Asian countries with regular dengue fever/dengue hemorrhagic fever (DHF) outbreaks. The first virologically confirmed dengue epidemic in India occurred in Calcutta and on the Eastern Coast in 1963–64. Since then, the disease has expanded geographically, with all four serotypes now reported from multiple states. Despite significant advances in understanding dengue pathogenesis, hepatic involvement in dengue — one of its most clinically significant extra-vascular manifestations — remains inadequately characterized in the pediatric population, particularly in Central India.

The spectrum of dengue-associated hepatic injury in children ranges from asymptomatic transaminase elevation to fulminant hepatic failure. Several mechanisms have been proposed, including direct cytopathic effects of DENV on hepatocytes, immune-mediated injury via cytokine-induced hepatocellular apoptosis, microcirculatory disturbances secondary to plasma leakage, hypoxia from hemodynamic compromise, and metabolic acidosis. Clinically, dengue hepatitis is characteristically anicteric, distinguishing it from classical viral hepatitis. The degree of hepatic injury tends to parallel the severity of dengue infection and is a recognized predictor of poor outcomes.

In recent studies from India and Thailand, dengue infection accounted for 18.5% and 34.3% of acute hepatic failure cases in children respectively, underscoring its clinical significance. Children with DHF and dengue shock syndrome (DSS) are particularly predisposed to severe hepatic compromise. Despite the high dengue burden in Chhattisgarh, a state in Central India, published literature documenting the pattern and prevalence of hepatic dysfunction in pediatric dengue from this region is sparse. The present study was therefore undertaken to systematically evaluate the prevalence, spectrum, and severity of hepatic dysfunction in children admitted with confirmed dengue fever at a tertiary care centre in Central India.

2. MATERIALS AND METHODS:

2.1 Study Design and Setting:

This was a time-bound prospective observational study conducted in the Department of Paediatrics, Jawaharlal Nehru Hospital and Research Centre (JLNH & RC), Bhilai Steel Plant, Bhilai, Chhattisgarh — a tertiary care hospital in Central India — from 1st November 2018 to 31st October 2019. Ethical clearance was obtained from the Institutional Ethics Committee of JLNH & RC prior to commencement of the study.

2.2 Study Population and Eligibility Criteria:

Children below 18 years of age admitted to the Paediatrics department with serologically confirmed dengue fever were eligible for inclusion. Dengue was confirmed by dengue NS1 antigen detection or dengue IgM MAC-ELISA, as per WHO 2009 diagnostic criteria. Cases with pre-existing or concurrent hepatic conditions including drug-induced hepatitis, malaria, hepatitis A, hepatitis B, and enteric fever were excluded based on history, clinical examination, and relevant investigations. Isolated dengue IgG-positive cases (indicative of past infection without active disease) were also excluded.

2.3 Sample Size:

Sample size was calculated using the Cochran formula for observational studies. Based on a prior estimate of hepatic dysfunction prevalence of 67.31% in dengue, a Z-value of 1.96 (5% confidence level), and an allowable error of 10%, the minimum required sample size was 85. To improve statistical power and account for potential data loss, 92 patients were enrolled.

2.4 Clinical Assessment and Classification:

All enrolled children underwent a standardized clinical assessment with detailed history and physical examination documented in a predesigned proforma. All cases were classified into three groups per the WHO 2009 dengue classification: (1) Dengue Without Warning Signs (DWNS), (2) Dengue With Warning Signs (DWWS), and (3) Severe Dengue (SD). Children were managed per WHO dengue treatment guidelines.

2.5 Laboratory Investigations:
All patients underwent complete liver function testing using an Olympus AU 400 fully computerized auto-analyzer. Parameters assessed included total serum bilirubin (TSB), direct and indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, and serum albumin. Prothrombin time (PT) and International Normalized Ratio (INR) were measured using a Stago Start 4 Coagulometer with Liquiplastin as reagent. Complete blood count was performed using a Coulter UniCel DxH 800 analyzer. Ultrasonography (USG) of the abdomen was performed in all cases as clinically indicated.

2.6 Definition of Hepatic Dysfunction:
Hepatic dysfunction was defined by the presence of any one or more of the following criteria: (1) elevation of AST and/or ALT more than twice the upper limit of normal (ULN) with or without hepatomegaly; (2) clinical jaundice; or (3) INR ≥1.5. Further grading was applied: liver function impairment was defined as AST/ALT 2–4×ULN; hepatitis as AST/ALT 4–10×ULN; and severe hepatitis as AST/ALT >10×ULN.

2.7 Statistical Analysis:
Data were tabulated using Microsoft Excel. Categorical variables were expressed as frequency and percentage and compared using the chi-square test. Continuous variables were expressed as mean ± standard deviation (SD) and compared across groups using one-way ANOVA. All analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY). A p-value <0.05 was considered statistically significant and p<0.001 strongly significant.

3. RESULTS:
3.1 Demographic Profile:
A total of 92 children with serologically confirmed dengue fever were enrolled during the study period. The mean age of the study cohort was 11.15 ± 4.73 years. The age group of 12–17 years was most frequently affected, accounting for 52 cases (56.5%), followed by the 6–11-year group (23 cases; 25.0%), and the 0–5-year group (17 cases; 18.5%). Males predominated, with 51 males (55.4%) and 41 females (44.6%), yielding a male-to-female ratio of 1.25:1.

Table 1: Age Distribution of Dengue Cases (n=92)

Age Group	Number of Cases	Percentage (%)
0–5 years	17	18.5
6–11 years	23	25.0
12–17 years	52	56.5
Total	92	100.0

3.2 Serological Profile:
Among the 92 confirmed cases, NS1 antigen reactivity was the most common positive test, found in 83 cases (90.2%). Three cases (3.3%) were positive for IgM antibody alone, five cases (5.4%) were positive for both NS1 antigen and IgM, and one case (1.1%) was positive for both NS1 and IgG, suggesting a secondary dengue infection.

3.3 Clinical Features:
Fever was universally present in all 92 cases (100%). Other symptoms in descending order of frequency were: vomiting in 29 patients (31.52%), abdominal pain in 27 patients (29.34%), skin rashes in 20 patients (21.7%), lethargy and shock each in 4 patients (4.34%), and retro-orbital pain, epistaxis, and hematemesis each in 2 patients (2.17%). No patient manifested clinical jaundice during the study period.

Table 2: Clinical Symptoms and Signs (n=92)

Clinical Feature	Number	Percentage (%)
Fever	92	100.0
Vomiting	29	31.52
Abdominal pain	27	29.34
Rashes	20	21.70
Lethargy	4	4.34
Shock	4	4.34
Epistaxis	2	2.17
Hematemesis	2	2.17
Retro-orbital pain	2	2.17
Jaundice	0	0

3.4 WHO Clinical Classification:

According to WHO 2009 dengue classification, 43 children (46.7%) were in the DWNS group, 43 children (46.7%) in the DWWS group, and 6 children (6.5%) in the Severe Dengue group.

3.5 Prevalence and Spectrum of Hepatic Dysfunction:

Of the 92 enrolled children, hepatic dysfunction was present in 48 patients (52.2%). The most common criterion fulfilled was elevated liver enzymes (AST and/or ALT >2×ULN) in 34 patients (70.83% of those with hepatic dysfunction), followed by hepatomegaly in 27 patients (56.25%), and elevated INR (≥1.5) in 10 patients (20.83%). Notably, no patient in the study developed jaundice, acute hepatic failure, or hepatic encephalopathy.

Table 3: Causes of Hepatic Dysfunction (n=48)

Parameter	Number	Percentage of HD cases (%)
Elevated liver enzymes (>2×ULN)	34	70.83
Hepatomegaly	27	56.25
INR ≥1.5	10	20.83
Jaundice	0	0

3.6 Hepatic Dysfunction by Disease Severity:

Hepatic dysfunction was present in 20 of 43 (46.5%) patients in the DWNS group, 23 of 43 (53.5%) in the DWWS group, and 5 of 6 (83.3%) in the Severe Dengue group, demonstrating a clear gradient with increasing disease severity. Hepatomegaly was present in 9 (20.9%) DWNS, 13 (30.23%) DWWS, and 5 (83.3%) Severe Dengue patients, a statistically significant association.

Table 4: Hepatic Dysfunction by WHO Disease Classification (n=92)

Disease Group	n	Hepatic Dysfunction Present	Percentage (%)
Dengue Without Warning Signs	43	20	46.5
Dengue With Warning Signs	43	23	53.5
Severe Dengue	6	5	83.3
Total	92	48	52.2

3.7 Liver Enzyme Profile:

The overall mean AST was 68.23 ± 46.12 U/L and mean ALT was 44.92 ± 29.56 U/L. AST elevation (>2×ULN) was found in 34 patients (37%), while ALT elevation was found in 18 patients (19.6%). Among those with elevated transaminases, 16 patients (17.4%) had isolated AST elevation, 17 (18.5%) had elevation of both AST and ALT, and only one patient (1.1%) had isolated ALT elevation. AST elevation was consistently disproportionately greater than ALT, a pattern distinct from classical viral hepatitis in which ALT typically predominates or is equal.

Mean AST was highest in the Severe Dengue group (101.67 ± 59.13 U/L) compared to DWWS (64.6 ± 45.01 U/L) and DWNS (67.19 ± 44.62 U/L). Hepatitis-grade enzyme elevation (4–10×ULN) was observed in 33.3% of Severe Dengue patients for AST. No case in the study met criteria for severe hepatitis (>10×ULN).

Table 5: Liver Enzyme Elevation Pattern (n=92)

Pattern	Number	Percentage (%)
Both AST and ALT normal	58	63.0
AST elevated only	16	17.4
AST and ALT both elevated	17	18.5
ALT elevated only	1	1.1
Total	92	100.0

3.8 Bilirubin, Albumin, and Coagulation Profile:

The mean total serum bilirubin (TSB) was 0.538 ± 0.201 mg/dL, with no significant difference across disease groups (Severe Dengue: 0.667 mg/dL; DWWS: 0.505 mg/dL; DWNS: 0.553 mg/dL). No patient developed clinical jaundice, consistent with predominant anicteric hepatitis.

Mean serum albumin showed a progressive decline with disease severity: 3.67 mg/dL overall, and 3.03 mg/dL in the Severe Dengue group. This reduction was statistically significant ($p<0.001$) and attributed to plasma leakage-mediated protein loss characteristic of severe dengue.

The mean INR was 1.18 ± 0.23 overall. Elevated INR (≥1.5) was observed in 10 patients (10.9%). Distribution by disease group revealed no elevated INR in the DWNS group, 7 patients (16.2%) in the DWWS group, and 3 patients (50%) in the Severe Dengue group. This distribution was statistically significant (p=0.007). Mean PT was highest in the Severe Dengue group (17.5 seconds) compared to the other groups.

Table 6: INR Distribution by Disease Group

Disease Group	INR ≥1.5	INR <1.5
Dengue Without Warning Signs (n=43)	0 (0%)	43 (100%)
Dengue With Warning Signs (n=43)	7 (16.2%)	36 (83.8%)
Severe Dengue (n=6)	3 (50%)	3 (50%)

3.9 Hematological Parameters:

The mean hemoglobin level was 12.17 ± 1.86 g/dL. Five of six severe dengue patients had hemoglobin below 12 g/dL. Leucopenia (TLC <4000 cells/mm³) was observed in 46 patients (50%), with a mean TLC of 4704 ± 2284 cells/mm³. Thrombocytopenia (platelet count <100,000/mm³) was present in 46 patients (50%). The mean platelet count was 1,23,000 ± 84,811 cells/mm³. Four patients had bleeding manifestations (epistaxis and hematemesis), all of whom had thrombocytopenia, with two having platelet counts below 50,000/mm³.

3.10 Ultrasonographic Findings:

Abdominal ultrasonography revealed gall bladder wall edema in 10 cases and ascites in 10 cases, predominantly in the DWWS and Severe Dengue groups. Pleural effusion was observed in 3 cases, hepatomegaly on imaging in 3 cases, and splenomegaly in 2 cases. No USG abnormality was detected in the DWNS group. Five of six Severe Dengue patients had sonographic abnormalities.

3.11 Hepatic Dysfunction by Sex and Age:

Among the 48 patients with hepatic dysfunction, 30 (58.8%) were male and 18 (43.9%) were female, with a male-to-female ratio of 1.66:1. However, this gender difference was not statistically significant (p=0.154). Hepatic dysfunction was present in 47.1% of the 0–5-year age group, 56.5% of the 6–11-year group, and 52.2% of the 12–17-year group, with no statistically significant difference across age groups (p=0.838).

4. DISCUSSION:

The present study is among the few prospective investigations of hepatic dysfunction in pediatric dengue fever from the Central Indian subcontinent, specifically from the Chhattisgarh region. The overall prevalence of hepatic dysfunction in our cohort was 52.2%, a finding consistent with the wide range (34.6%–93%) reported from various parts of Asia, and notably higher than the 34.6% reported by Wiwanitkit et al. in a Thai pediatric series, yet lower than the 93% AST elevation reported by Jagadishkumar et al. from South India.

The predominance of older children (12–17 years; 56.5%) in our cohort contrasts with several studies from Southern India and Thailand, where younger age groups were more commonly affected, reflecting possible regional differences in exposure patterns, vector ecology, and healthcare-seeking behavior. The male predominance (M:F 1.25:1) aligns with findings from Selvan et al. and others, though it is likely an incidental finding rather than a biologically determined susceptibility.

Of particular clinical interest is the complete absence of jaundice in our cohort. This is consistent with the concept of anicteric dengue hepatitis, in which significant hepatocellular injury occurs in the absence of overt hyperbilirubinemia. The mean TSB was below 1.0 mg/dL across all disease groups, confirming that dengue hepatitis frequently masquerades as a non-hepatic febrile illness. This underscores the danger of relying solely on clinical signs of hepatic dysfunction in dengue patients and reinforces the need for routine biochemical liver function evaluation in all dengue-positive children, including those without warning signs.

The disproportionate elevation of AST compared to ALT is a well-recognized feature of dengue hepatitis and was confirmed in our study. This AST-ALT dissociation, in contrast to the ALT-dominant pattern seen in classical viral hepatitis, reflects the multi-organ affection in dengue: AST is derived not only from hepatocytes but also from skeletal muscle, cardiac muscle, erythrocytes, and the brain — all of which may sustain injury from dengue viremia, immune activation, or microvascular compromise. This biochemical pattern, therefore, not only reflects hepatic involvement but also signals systemic multi-organ dysfunction in severe dengue.

The association between disease severity and hepatic dysfunction was clearly demonstrated. Hepatomegaly was found in 83.3% of Severe Dengue patients, compared to 30.23% and 20.9% in the DWWS and DWNS groups respectively. A similar escalating trend was observed by Tambolkar et al. (hepatomegaly in 69% with DF and 100% with DSS) and Jagadishkumar et al. (hepatomegaly in 21% DF and 48% DHF). Hepatomegaly in dengue may result from hepatocellular swelling due to viral injury, Kupffer cell hyperplasia, or secondary to plasma leakage-related periportal edema. Its presence should therefore be considered a marker of hepatic involvement warranting closer monitoring.

The coagulation profile findings deserve particular emphasis. Elevated INR (≥1.5) was significantly more prevalent in the Severe Dengue group (50%) compared to the DWWS (16.2%) and DWNS (0%) groups (p=0.007). This finding mirrors observations by Singh et al., who reported PT/INR derangement in 11.11% of all dengue cases, with the highest rates in severe dengue. Coagulopathy in dengue arises from multiple mechanisms: reduced hepatic synthesis of clotting factors (secondary to hepatocellular injury), thrombocytopenia, platelet dysfunction, and disseminated intravascular coagulation (DIC) in severe cases. Importantly, bleeding manifestations in our study were confined to patients with thrombocytopenia and, where present, severe thrombocytopenia (platelet count <50,000/mm^3), suggesting that platelet count rather than coagulation factor deficiency may be the predominant bleeding risk in non-severe dengue.

Hypoalbuminemia, observed most severely in the Severe Dengue group (mean albumin 3.03 mg/dL vs. 3.67 mg/dL overall, p<0.001), reflects both hepatic synthetic failure and the characteristic plasma leakage of severe dengue. This protein extravasation into third spaces contributes to the hemodynamic instability, pleural effusions, and ascites seen in DHF and DSS. The significant correlation between albumin reduction and dengue severity has been similarly documented by Rahman et al. and supports the role of serum albumin as a useful prognostic marker.

The absence of hepatic encephalopathy and acute liver failure in our study, despite a significant prevalence of hepatic dysfunction, is reassuring and likely reflects the moderate severity distribution of our cohort (only 6.5% Severe Dengue) and the relatively milder hepatic injury pattern. This contrasts with studies such as Laopresopwattana et al., who reported acute liver failure in 1.1% of a large Thai dengue cohort, and Wiwanitkit et al., who found hepatic encephalopathy in 8% of patients with hepatic dysfunction. Our relatively low severe dengue proportion may have been influenced by tertiary-centre referral patterns and effective early management.

The sonographic findings in our study corroborate published literature, with gall bladder wall edema and ascites being the predominant abnormalities in DWWS and Severe Dengue groups and no USG abnormalities detected in the DWNS group. Gall bladder wall edema in dengue results from subserosal edema secondary to vascular permeability changes and is a sensitive ultrasonographic marker of dengue, particularly DHF, even in the absence of frank ascites. These findings support the role of abdominal ultrasound as a non-invasive adjunct in dengue severity assessment.

5. CONCLUSION:

This prospective study from Central India demonstrates that hepatic dysfunction is a common and clinically significant complication of pediatric dengue fever, occurring in 52.2% of confirmed dengue cases. The hepatic involvement is predominantly anicteric, with elevated transaminases (AST > ALT), hepatomegaly, and coagulopathy as the cardinal manifestations. The severity of hepatic dysfunction correlates positively and significantly with the WHO clinical classification of dengue severity. Elevated INR is a particularly important marker, confined to dengue with warning signs and severe dengue cases, and its presence should prompt intensive clinical monitoring and aggressive supportive care.

The absence of acute liver failure and hepatic encephalopathy in our cohort, despite widespread hepatic enzyme abnormalities, suggests that most pediatric dengue-associated hepatic injury is self-limiting with appropriate supportive management. However, the potential for severe hepatic decompensation in a subset of patients mandates routine assessment of liver function tests, coagulation profile, and serum albumin in all dengue-positive children, irrespective of clinical severity category. Hepatomegaly and hypoalbuminemia should be recognized as early clinical surrogates of hepatic and systemic disease severity.

Prospective multicentric studies from Central India with larger sample sizes and extended follow-up are warranted to further characterize the hepatic natural history in pediatric dengue and to validate predictive biomarkers for

hepatic severity progression.

6. LIMITATIONS:

This study was conducted at a single tertiary care centre, which may introduce referral bias towards more severe cases and may not reflect the true community-level prevalence of hepatic dysfunction in dengue. The study was time-bound with a sample size of 92, limiting statistical power for subgroup analyses, particularly the Severe Dengue group (n=6). A proportion of patients were lost to follow-up due to referral or discharge against medical advice, potentially affecting outcome assessment. Liver biopsy for histopathological correlation was not performed. A prospective multicentric study with a larger population is recommended to validate and extend these findings.

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CONFLICT OF INTEREST:

None declared.

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