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## Dengue hemorrhagic fever and the liver

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### Abstract

Dengue hemorrhagic fever (DHF) is one of the most rapidly emerging infections of tropical and subtropical regions worldwide. It affects more rural and urban areas due to many factors, including climate change. Although most people with dengue viral infection are asymptomatic, approximately 25% experience a self-limited febrile illness with mild to moderate biochemical abnormalities. Severe dengue diseases develop in a small proportion of these patients, and the common organ involvement is the liver. The hepatocellular injury was found in 60%-90% of DHF patients manifested as hepatomegaly, jaundice, elevated aminotransferase enzymes, and critical condition as an acute liver failure (ALF). Even the incidence of ALF in DHF is very low (0.31%-1.1%), but it is associated with a relatively high mortality rate (20%-68.3%). The pathophysiology of liver injury in DHF included the direct cytopathic effect of the DENV causing hepatocytes apoptosis, immune-mediated hepatocyte injury induced hepatitis, and cytokine storm. Hepatic hypoperfusion is another contributing factor in dengue shock syndrome. The reduction of morbidity and mortality in DHF with liver involvement is dependent on the early detection of warning signs before the development of ALF.

**Key Words:** Dengue hemorrhagic fever; Dengue viral infection; Liver involvement; Liver injury; Acute liver failure; Hepatocyte apoptosis; Cytokine storm; Severe dengue disease

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**Core Tip:** The liver is the most common organ involvement in dengue hemorrhagic fever (DHF) patients with ranges from mild subclinical biochemical changes to severe liver disease as an acute liver failure (ALF). However, the low incidence of ALF in

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DHF with liver injury is associated with a high fatality rate. The hepatocyte injury is caused by direct viral cytopathic, immune-mediated, and poor hepatic perfusion. Early detection of severe hepatocellular injury development may reduce the morbidity and mortality in DHF patients with liver involvement.

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## INTRODUCTION

Dengue virus (DENV) is a mosquito-borne flavivirus that consists of four serotypes (1-4) circulating in endemic areas. Most DENV infections are asymptomatic. However, the clinical manifestation of DENV infections could be dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Dengue is one of the most rapidly evolving vector-borne infections, affecting 129 countries, 70% of the actual burden is in Asia, causing nearly 390 million affected patients each year, of which 96 million manifests clinically. The number of dengue cases reported to World Health Organization increased over eightfold during the last two decades, from 505430 cases in 2000 to over 2.4 million in 2010 and 4.2 million in 2019[1]. It is predicted that the transmission of dengue will be more strengthened in dengue-endemic countries, and due to climate change and increases in international traveling, the infection may spread to countries in Europe and the US that are currently not significantly affected by DENV[2,3]. Liver injury associated with DENV infection was first reported in 1967 [4]. The liver is one of the common organs involved in dengue infection. Hepatic complications were found in 60%-90% of infected patients included hepatomegaly, jaundice, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), and acute liver failure (ALF). All four serotypes have been associated with dengue-related liver injury, but DENV-1 and DENV-3 have more significant injuries[5]. Abnormal liver function in DENV infections resulted from the direct viral effect on hepatocytes or a dysregulated immunologic injury against the virus[6]. Moreover, underlying chronic diseases common among adults in several tropical and sub-tropical countries potentially compound the effects of acute dengue-related liver injury. However, the evidence to date is still conflicting and needs to be elucidated. We review the current evidence on liver injury in DHF patients and discuss the association between clinical manifestations, laboratory findings, pathological findings, and molecular evidence with the pathophysiology of a derangement of the liver in DHF.

## GENOMIC ORGANIZATION OF THE DENGUE VIRUS

DENV genome is a linear, single-stranded, positive-sense RNA which translated as a single open reading frame. It was bordered by 5' and 3' untranslated regions on each side. DENV particle was a spherical 50 nm virion. The ssRNA genome was encapsulated by multiple copies of the capsid (C) protein to form a nucleocapsid core. This core is covered by a lipid bilayer forming an outer glycoprotein envelop (E) protective casing. When DENV enters the host cell, the positive ssRNA genome is released from the capsid and translated to a polyprotein of 3400 amino acids. The polyprotein is subsequently cleaved by viral and host proteases to 10 kinds of protein. These proteins are three structural proteins [C, E, pre-membrane (prM)] and seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5)[7,8]. The structural proteins are essential in virion assembly, release, maturation, and infectivity. In comparison, viral replication and eluding a host cell's immune response are the NS proteins' primary functions. DENV has four serotypes (DEN 1-4), each sharing 60%-70% amino acid sequence homology.

## DENGUE HEMORRHAGIC FEVER AND LIVER INVOLVEMENT

### **Clinical manifestations and laboratory findings**

The spectrum of symptoms in DHF patients is very diverse, ranging from mild to severe dengue disease (SDD). DENV infection (DVI) has an incubation period of 3-14 d with the same symptom as a common cold and gastroenteritis. The patients usually have an abrupt fever, retro-orbital pain, headache, muscle ache, arthralgia, nausea, vomiting, diarrhea, and rashes. Less than 5% of DVI patients progress to severe life-threatening manifestations, particularly those previously infected with different serotypes. DHF has 3 distinct phases comprise of febrile, critical, and recovery. The patient has a biphasic fever commonly over 40°C with retro-orbital pain and headache ranging 2-7 d for the febrile phase. Fifty to eighty percent of the patients exhibit rashes or petechiae. The critical phase is characterized by plasma leakage with or without bleeding, which starts abruptly after defervescence. During this phase, an increase in capillary permeability with the rising of hematocrit can occur[9,10]. Moreover, the accumulation of fluids in the abdominal cavities and thoracic could be detected, leading to hypovolemic shock resulting in multiple organ dysfunctions, metabolic acidosis, disseminated intravascular coagulation (DIC), and severe bleeding. The mortality rate of SDD is relatively high at 20%, while early and appropriate treatment with intravenous fluid can decrease mortality to less than 1%. The recovery phase lasts for a few days with rash and a fluid overload, affecting the brain as a reduced level of consciousness or seizures[11,12].

Hepatic injury in DVI is more common in DHF than DF. Moreover, it is more severe in children patients, especially in previous dengue infection (primary infection), high hematocrit values, low platelet counts, and vascular leakage[13-15]. The clinical manifestations of DHF with hepatic involvement were from mild biochemical changes without symptoms to ALF. It manifests as right subcostal pain, hepatomegaly with tenderness, elevated aminotransferase enzymes, hyper-bilirubinemia, hypoalbuminemia, or ALF. The prevalence of liver involvement in DHF has many variations across different investigators (Table 1). This variation probably from the difference in DENV serotypes, case definition, age group, host susceptibilities, pre-existing diseases, especially chronic liver diseases (CLD). The most common symptoms associated with liver involvement in DHF are anorexia, nausea, vomiting, and abdominal pain[16-19, 23,25-27,29]. The most common physical sign is hepatomegaly, with a wide range from several studies between 10.0 to 80.8% of the patients. The smaller number of DHF patients are clinically jaundiced (3.6%-48%)[16,21,26,28,29,31]. The hepatomegaly demonstrated an increased risk for SDD with an odds ratio of 4.75 (95%CI: 1.76-12.57) [32].

The elevation of AST and ALT is the commonest finding of DHF with liver involvement[16-31]. The elevated AST is usually modest and greater than ALT. The greater elevation in AST than ALT is partly due to AST release from muscles damaged. Mean AST and ALT concentrations ranged from 2-fold to 5-fold rises, which demonstrated mild hepatitis with self-limited. The 10-fold elevation of AST and ALT was reported in 4%-15% of the patients associated with SDD and may deteriorate to be ALF[33,34]. The physical sign of hepatomegaly with hepatic tenderness did not predict the rising of AST and ALT[16]. The highest level of AST and ALT occurs approximately day 7 of fever and should return to the normal level within 21 d of illness. The elevation of AST and ALT appears to correlate with SDD[30,35]. Hypoalbuminemia has been reported in broad ranges from 35.3%-76.0% in several studies due to the population heterogeneity and the disease severity[16,20,27-29]. The meta-analysis conducted by Huy and colleagues revealed that hypoalbuminemia was significantly associated with DSS[35]. Abnormal coagulation has been found in many studies with 34.0%-42.5% of prolonged prothrombin time (PT) and partial thromboplastin time (PTT)[16,21,26]. Notably, consumptive coagulopathy may also contribute to DSS.

### **Pathological findings**

Pathological studies in humans DHF are uncommon and limited as the liver biopsy is invasive and hazardous. The human hepatocytes are an essential site for replication of DENV[36]. In 2014, Aye and colleagues reported an autopsy study of 13 patients who died of severe DHF. They found that the liver had significant levels of DENV RNA and histopathological changes consisting of microvesicular and macrovesicular steatosis, Councilman bodies, hepatocellular necrosis, and lack of inflammatory cell infiltrates[37]. In the liver, DENV infection occurred in hepatocytes and Kupffer cells but not in endothelial cells. Other studies reported the same pathological findings[34, 38,39]. Recently, Win and colleagues reported that the prominent findings of the ultrastructure features of human liver specimens from patients who died of DHF were



**Table 1 Clinical and laboratory findings of Dengue hemorrhagic fever with liver involvement**

Investigators	No. of patients	Hepatomegaly (%)	Elevated AST (%)	Elevated ALT (%)	Hyper-bilirubinemia (%)	Low albumin (%)
Bandyopadhyay <i>et al</i> [16]	110	79.1	92.7	78.2	4.5	66.4
Kittitrakul <i>et al</i> [17]	127	34.6	88.2	69.3	N/A	N/A
Saha <i>et al</i> [18]	570	28.6	N/A	N/A	N/A	N/A
Roy <i>et al</i> [19]	120	80.8	94.2	89.2	N/A	N/A
Nascimento <i>et al</i> [20]	68	N/A	83.8	73.5	N/A	35.3
Karoli <i>et al</i> [21]	138	N/A	N/A	92.0	48.0	N/A
Lee <i>et al</i> [22]	690	N/A	86.0	46.0	N/A	N/A
Jagadishkumar <i>et al</i> [23]	110	79.0	93.6	78.2	N/A	N/A
Parkash <i>et al</i> [24]	699	N/A	95.0	86.0	N/A	N/A
Trung <i>et al</i> [25]	644	34.8	97.0	97.0	N/A	N/A
Wong and Shen [26]	127	11.8	90.6	71.7	13.4	N/A
Uehara <i>et al</i> [27]	41	10.0	80.5	61.0	N/A	48.4
Itha <i>et al</i> [28]	45	N/A	96.0	96.0	30.0	76.0
Fernando <i>et al</i> [29]	55	36.4	90.1	81.8	3.6	72.7
Souza <i>et al</i> [30]	1585	N/A	63.4	45.0	N/A	N/A
Kuo <i>et al</i> [31]	270	N/A	93.3	82.2	7.2	N/A

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; N/A: Not applicable.

extensive cellular damage and steatosis. Moreover, no virus-induced endoplasmic replicating structures have been identified in the hepatocytes. They postulated that DENV in the hepatocytes and Kupffer cells might not be the key contributor to hepatic steatosis[40]. Hepatic steatosis was the significant pathologic finding in acute alcoholic and non-alcoholic steatohepatitis[41]. The hypotheses on the mechanism of hepatic steatosis were the breakdown of the intestinal barrier, allowing bacterial pathogens to reach the liver (microbial translocation). Recent studies demonstrated that elevated lipopolysaccharide (LPS) levels during DVIs correlated with disease severity, primarily when determined in plasma leakage[42,43].

## DHF AND ACUTE LIVER FAILURE

ALF is a rare condition in DHF patients. Kye Mon and colleagues conducted a retrospective cohort study to evaluate the incidence and clinical outcome in 1926 patients with DHF. They reported the 0.31% incidence of ALF associated with DHF. It was most common among young adults with the median duration from onset of fever to ALF development was 7.5 d. The patients with the severe stage of dengue had a higher risk of developing ALF. They concluded that although the development of ALF is relatively rare in patients with DHF, it is associated with a high mortality rate (66.7%) (Table 2)[44]. In 2010, Trung and colleagues conducted a study to evaluate the liver involvement associated with DVI in 644 adults and found that ALF was 0.77% with a 20.0% mortality rate. They concluded that clinically severe liver involvement was infrequent but usually resulted in severe clinical outcomes[25]. In 2016, Laoprasopwattana and colleagues reported the study of clinical course and outcomes of liver functions in children with dengue viral infection-caused ALF. They found that 41 patients (1.1%) of 3630 DHF children had ALF. The fatality rate of DVI-caused ALF in this study was 28 of 41 (68.3%) compared with 2 of 197 (1.0%) in severe dengue patients without ALF. They concluded that the DHF patients with ALF had the major cause from the profound shock, which induced microcirculatory abnormality in the liver cells[45]. In 2020, Devarbhavi and colleagues conducted the study to determine the incidence and clinical outcome in 10108 DHF patients. They found that 36 patients

**Table 2** The incidence and mortality rate of acute liver failure in Dengue hemorrhagic fever patients with liver involvement

Investigators	Countries	Study population	Incidence rate (%)	Mortality rate (%)
Teerasarntipan <i>et al</i> [46]	Thailand	2311 adults	0.71	58.82
Devarbhavi <i>et al</i> [34]	Qatar	10108 adults	0.35	58.30
Laoprasopwattana <i>et al</i> [45]	Thailand	3630 children	1.10	68.30
Trung <i>et al</i> [25]	Vietnam	644 adults	0.77	20.00
Kye Mon <i>et al</i> [44]	Thailand	1926 age ≥ 15 yr	0.31	66.70

(0.35%) developed ALF with a 58.3% mortality rate. They concluded that dengue hepatitis progressing to ALF is rare and were seen in only 0.35%. However, the development of ALF is associated with a very high mortality rate. Lactate levels, pH, and model for end-stage liver disease (MELD) score at admission were the only predictors of mortality[34]. Recently, Teerasarntipan and colleagues conducted a retrospective study of 2311 serologically confirmed adult dengue patients to evaluate ALF and fatality rate incidence. They found that ALF incidence in their study was 17 of 2396 DHF patients (0.71%). The mortality rate of ALF was 10 of 17 SDD patients (58.82%). They concluded that the MELD score is the best predictor of ALF in dengue-induced severe hepatitis (DISH) patients[46].

## PATHOPHYSIOLOGY OF LIVER DAMAGE IN DHF

The mechanism of hepatocellular injury in DHF is poorly understood. Several findings include the direct cytopathic effect of the DENV causing hepatocytes apoptosis, immune-mediated hepatocyte injury by CD4 lymphocyte induced hepatitis, and cytokine storm. Poor hepatic perfusion is also a potential contributing factor in SDD patients.

### **Direct cytopathic effect**

There have been very few studies reporting the presence of DENV in hepatocytes of DHF patients. Moreover, the association between DENV replication and hepatocellular damage has never been concluded. In 1989, Rosen and colleagues firstly demonstrated the recovery of DENV from 5 of 17 livers of children who died from DHF[47]. In 1995, Kangwanpong and colleagues detected DENV RNA in hepatocytes located in the mid-zonal region of the DHF patients' liver by in situ PCR method[48]. In 1999, Couvelard and colleagues confirmed that DENV RNA was found in liver specimens of DHF patient. They concluded that nested PCR was the most sensitive method to identify the DENV RNA in clinical specimens[49]. Furthermore, Huerre and colleagues identified dengue antigens in formalin-fixed paraffin-embedded human liver by immunohistochemical analysis in 2001[50]. Several studies could demonstrate the cytopathic effects of DENV, which induced hepatocytes apoptosis[51-54]. Therefore, the exact effect of DENV in direct cytopathic effect and caused hepatocytes apoptosis is be confirmed. Although hepatocyte apoptosis could contribute to liver injury in DHF patients, it probably has a beneficial effect in inhibiting DENV replication and spread.

### **Immune mediated hepatocyte injury and cytokine storm**

Macrophages and Kupffer cells recognize DENV particles and release cytokines and chemokines, which activated the inflammatory cells and act as antigen-presenting cells. Furthermore, Th1 cells released pro-inflammatory cytokines, which induce parenchymal cell damage and vascular vasodilatation. Moreover, NK cells induced TNF-related apoptosis-inducing ligand (TRAIL) expression and contribute to hepatocytes apoptosis[55,56]. Cells involved in the immune response for DVI include CD8+ cells, NK cells, and Th1 cells. The different immune cells caused hepatocyte damage at different stages of the disease. CD8+ cells are attracted to hepatocytes by regulated inactivation, and normal T cell expressed and secreted have been shown to recognize the NS4B<sub>99-17</sub> epitope expressed on infected hepatocytes[57]. NK cell infiltration correlated with a rise in cleaved caspase 3 in liver tissue, meaning that it could induce hepatocytes apoptosis. Although the exact mechanisms of NK cell-mediated apoptosis are not well understood, up-regulation of TRAIL maybe a significant role

[56]. During a secondary DVI, memory T cells from the previous infection were rapidly stimulated, leading to a potent inflammatory response. However, the cross-reactive memory T cells have less specificity to the new DENV strain. Hence, the T cell activation would be insufficient to inhibit the virus but potent enough to cause immunopathogenesis[58]. Monocytes have been recognized as important targets of DVI and amplification, particularly in low concentrations of dengue-specific antibodies. The dramatic enhancement by dengue antibody of DENV replication in monocytes and other cells is known as antibody-dependent enhancement (ADE). During a secondary DVI, ADE contributes to severe manifestations caused by IgG antibodies from the primary infection. It fails to neutralize the different strains of DENV, but it could opsonize the viral particles and facilitate the viral uptake into the immune cells. DENV infection of monocytes stimulates the release of numerous immunological factors, some of which modulate the function of other cells, particularly vascular endothelial cells. TNF released by antibody-enhanced DENV-infected monocytes activates endothelial cells. Circulating TNF levels are altered in severely afflicted dengue patients, and TNF is a crucial factor in DENV-induced hemorrhage. This phenomenon could promote a severe inflammatory response with numerous cytokines released as cytokine storms[59,60].

### Poor hepatic perfusion

ALF frequently occurs in SDD with shock. Poor hepatic perfusion has been considered a causative factor. However, extensive research regarding the role of microcirculatory injury resulting in hepatocyte ischemia has not been adequately studied[29,61].

In 2019, Kulkarni and colleagues conducted a study to compare the manifestations of DVI in 95 patients with and without the liver disease [group A (without liver disease) = 71, group B (chronic hepatitis) = 12, and group C (cirrhosis = 12)]. They found that one patient in group A had ALF with renal failure and shock. Another one in group A had DHF with multiorgan failure and ARDS. A total of 3 patients expired in group C compared to 1 in group A and none in group B. Moreover, patients in group C required prolonged hospital stay compared to those in group A and group B. They concluded that DVI could have varied manifestations, ranging from simple fever to acute-on-chronic liver failure (ACLF) and ALF[62]. In 2013, Jha *et al*[63] conducted a prospective study to evaluate the etiology, clinical profile, and in-hospital mortality of ACLF in 52 ACLF patients. They found 46.1% hepatitis virus infection and 36.5% bacterial infection were the most common acute infection. The other acute injuries were drugs, autoimmune disease, surgery, malaria, and dengue. The mortality rate was higher in patients with dual insults than single insult (66.6% *vs* 51.1%). They concluded that dual acute insult is not uncommon and may increase mortality in these patients. DVI may be associated with ACLF[63]. In 2019, Galante and colleagues reported the first case in the world of liver transplantation performed in a patient with severe ALF due to DF. Liver transplantation may be considered as a treatment option for patients presenting with acute ALF secondary to DVI[64].

## CONCLUSION

The clinical manifestations, laboratory, and pathological findings suggest that liver involvement is very common in DHF. The extent of liver damage may range from asymptomatic with slightly elevated AST and ALT to ALF. Hepatic injury in DHF could be from the direct cytopathic effects of DENV and caused hepatocytes apoptosis. Moreover, the immune-mediated hepatocytes injury by CD4 lymphocyte induced hepatitis and cytokine storm are also crucial factors. Notably, poor hepatic perfusion in SDD with shock is another co-factor in hepatocellular damage. Host defense mechanisms may overcome DVI with a less virulent strain and low viral loads. Infection with a more virulent DENV serotype with high viral loads would lead to extensive hepatocyte damage. Although ALF is a rare condition in DHF patients, the mortality rate in these patients is very high. The early detection of warning signs before the development of ALF in DHF is a critical issue, reducing the fatality rate.

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