

# Liver Damage during Dengue Fever in Ouagadougou

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## Abstract

Dengue fever is widespread in all tropical and subtropical areas of the world and is the main public health problem posed by arboviroses. In Burkina Faso, an outbreak of dengue serotype “DENV-2”, which is responsible for severe forms of dengue, has been reported. In this study, we will discuss liver damage during this disease. The aim of this study was to describe the sociodemographic, diagnostic, therapeutic and evolutionary aspects of dengue patients with hepatic cytolysis. **Patients and Methods:** This was a prospective cross-sectional study of dengue disease in 2 facilities in the city of Ouagadougou. The study was spread over a period of 3 months from August to November 2019. The study population consisted of all patients hospitalised for dengue with a positive AgNS1 and/or IgM rapid diagnostic test (RDT) and presenting signs of liver damage. **Results:** During our study period we recruited 134 patients with dengue fever of which 93 or 69.4% had at least one elevated transaminase. The sex ratio was 1.90 and the average age was 35 years. Symptoms of liver damage were rare with right hypochondrial pain in 4.30% of cases and jaundice in 1.07% of cases. Dengue haemorrhagic fever was found in 5 patients. IgG was negative in 77.42%. The majority of patients (44% or 47.31%) had at least one transaminase value elevated to the upper limit of normal (ULN); and a minority, 14 patients or 15.06%, had transaminases above 10 ULN. A small proportion of patients had hepatocellular failure 26.92% with a lowered prothrombin level. Ninety-four per cent (94.62%) of the patients received analgesics. Level 1 analgesic (paracetamol) was the most widely administered, particularly in 76 patients (86.36%). More than half of the patients (57.14%) had a length of stay of less than or equal to 3 days and the outcome was favourable in 91.40%. **Conclusion:** Dengue virus causes alterations in the liver parenchyma. The degree of liver damage is variable. As clinical symptoms are almost non-existent, the measurement of transaminases

es remains important.

## Keywords

Dengue Fever, Liver Damage, Cytolysis, Hemorrhagic Fever

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## 1. Introduction

According to the WHO, 3.9 billion people in 128 countries are at risk of infection, representing 40% - 50% of the world's population, with 390 million cases of dengue per year, 96 million of which have clinical manifestations and 20,000 deaths per year [1].

In 2015, there was an increase in the number of reported cases from 2.2 million in 2010 to 3.2 million. Before 1970, only 9 countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific; the latter two regions being the most affected [1].

Several studies around the world are interested in liver damage related to dengue and it is recognized as an important cause of acute hepatic failure in endemic countries [2] [3]. Dengue should be considered as a differential in the assessment of acute hepatic impairment and as an element promoting acute flare-ups in patients with chronic hepatic impairment. The spectrum of involvement includes asymptomatic elevation of hepatic transaminases to occurrence of severe manifestation in form of ALF. However, very few studies have been conducted in black Africans.

Since August 2016, suspected dengue cases and deaths have been reported in Ouagadougou, the capital of Burkina Faso. From 5 August to 12 November 2016, a total of 1061 probable cases (positive to the Dengue Rapid Diagnostic Test: RDT) out of 1266 suspected cases were notified with a cumulative total of 15 deaths (case fatality rate of 1.2%) [4]. In 2018, 1636 cases of Dengue fever were recorded in Burkina, including 26 deaths [5].

There are 4 serotypes of dengue recorded worldwide. In Burkina Faso an outbreak of dengue serotype DENV-2 [1] [6], which is responsible for severe forms of dengue, has been reported.

There are several forms of dengue: asymptomatic dengue, classical dengue and severe forms (severe dengue or dengue haemorrhagic fever and dengue with shock syndrome which can lead to death, especially in children). The main complication is dengue haemorrhagic fever, but mortality is mainly due to the occurrence of shock syndrome.

The most common complications are hepatic and neurological, which can lead to bone marrow failure. Studies have been carried out in Burkina Faso on dengue fever [7] [8] [9]. They have focused on the clinical and evolutionary aspects of the disease, particularly haemorrhagic aspects. In this study, we propose

to address the hepatic damage during this disease.

## 2. Patients and Methods

This was a prospective cross-sectional study of dengue disease at Yalgado Ouédraogo University Hospital (CHU-YO) and Philadelphie Center. The study was conducted over a period of 3 months from August to November 2019. The study population consisted of all hospitalized patients with a diagnosis of dengue disease during the study period who also presented with liver signs. We included in our study all patients in whom a rapid diagnostic test (RDT: AgNS1 and/or IgM positive) allowed us to retain the diagnosis of dengue disease associated with changes in the liver biology (transaminases, prothrombin level). Patients were followed for a fortnight from diagnosis until improvement of liver tests. The periodicity of the examinations depended on the severity of the dengue (daily for severe dengue and every 48 hours for non-severe dengue). The follow-up variables were mainly clinical and biological. On the clinical level: search for external bleeding, signs of shock. In terms of biology, we monitored: transaminases (ALT, ASAT), prothrombin rate, blood count (haemoglobin, platelets and leucocyte count). These patients were classified into 3 groups. In group A, at least one transaminase value (AST or ALT) was elevated up to 3 times the upper limit of normal; in group B, one of the two transaminases (AST or ALT) was between 3 and 10 times the upper limit of normal; in group C, one of the two enzymes was greater than 10 times the upper limit of normal.

The data collected on a paper collection sheet and then entered and analyzed with the Epi-Info version 7 software (French version). These were essentially descriptive analyses and cross-tabulations were performed to describe the results. Patients had given informed consent to conduct the study. Anonymity was respected.

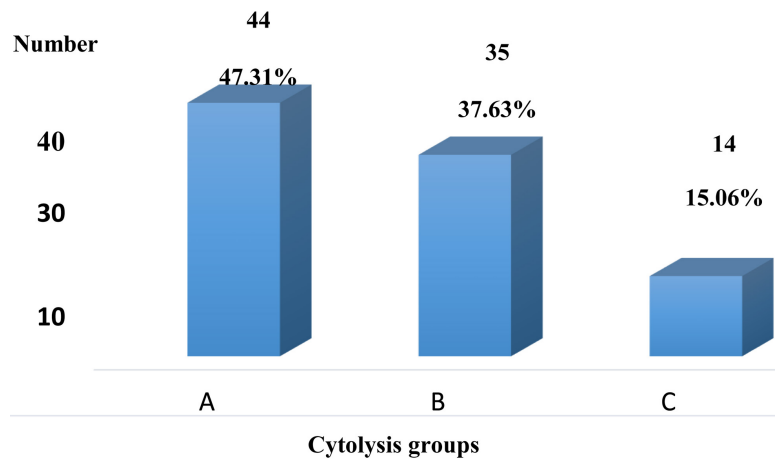
## 3. Results

During our study period we enrolled 134 dengue patients of whom 93% or 69.4% had at least one elevated transaminase. Patients with cytolysis less than 3 ULN accounted for half (47.31%). **Figure 1** shows the distribution of patients according to the different cytolysis groups.

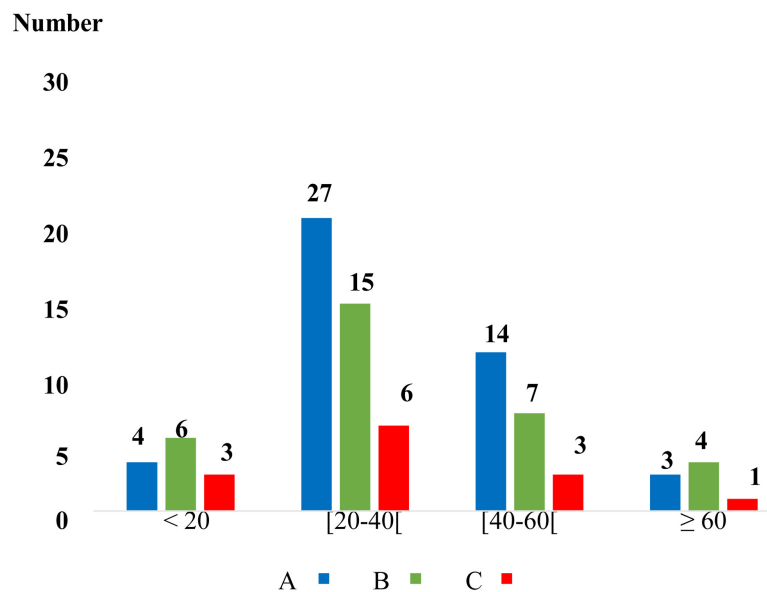
Our study population consisted of 61 men, *i.e.* two-thirds of the total number of patients. The sex-ratio was 1.90. The average age was 35.12 years. The youngest patient was 15 years old and the oldest 84 years old. Patients between the ages of 20 and 40 made up half of the total number of 48 patients. Young people between 20 and 40 years of age with cytolysis less than 3 ULN were the most represented in half (54.55%) of the cases.

**Figure 2** shows the age distribution of patients according to the three cytolysis groups A (<3 LSN), B (3 - 10 LSN) and C (>10 LSN).

Civil servants and students were the most represented, with 37.63% and 27.95% of the population respectively. Regarding the patients' history, no patient



**Figure 1.** Distribution of patients according to cytolysis groups.



**Figure 2.** Age distribution of patients according to the three cytolysis groups.

was known to have chronic liver disease. There was no evidence of non-steroidal anti-inflammatory drug (NSAID) use. A few rare cases of traditional treatment (5.37%) and treatment with hepatotoxic potential (paracetamol in 3.22%) were reported and are presented in **Table 1**.

Clinically, fever and headache were the most frequently reported symptoms in four-fifths of the cases respectively. Symptoms related to liver damage were rare, such as right hypochondrial pain (4.30%), pruritus (3.2%) and jaundice (1.07%) and are presented in **Table 2**.

Anemia was found in one tenth (9.67%) of cases. The general condition was altered in two thirds (63.44%) of cases. On physical examination, two patients (2.15%) had hepatomegaly and five patients (5.37%) had haemorrhage. Classic dengue accounted for more than nine-tenths (94.62%) of the cases. Severe dengue haemorrhagic fever was reported in 5.38% of cases.

**Table 1.** Distribution of patients by history and lifestyle.

History and lifestyle	Number	Percentage (%)
Hepatopathy	0	0
HTA	6	6.45
Diabetes	2	2.15
Lifestyle		
Alcohol	4	4.30
Tobacco	6	6.45
Previous treatment		
NSAIDs	0	0
Paracetamol	3	3.22
Traditional treatment	5	5.37

**Table 2.** Distribution of patients according to functional signs.

Functional signs	Number	Percentage (%)
Fever	77	82.79
Headaches	74	79.56
Nausea or vomiting	54	58.06
Joint pain	37	39.78
Muscle pain	36	38.70
Retro-orbital pain	11	11.82
Pain in the right hypochondrium	4	4.30
Bleeding	14	15.05
Dark urine	3	3.22
Pruritus	3	3.22
Icterus	1	1.07
Discoloured stools	1	1.07

A positive Ag NS1 serological diagnosis associated with a negative immunoglobulin test was present in more than half of the cases (56%). **Figure 3** shows the distribution according to the serological diagnosis of the patients.

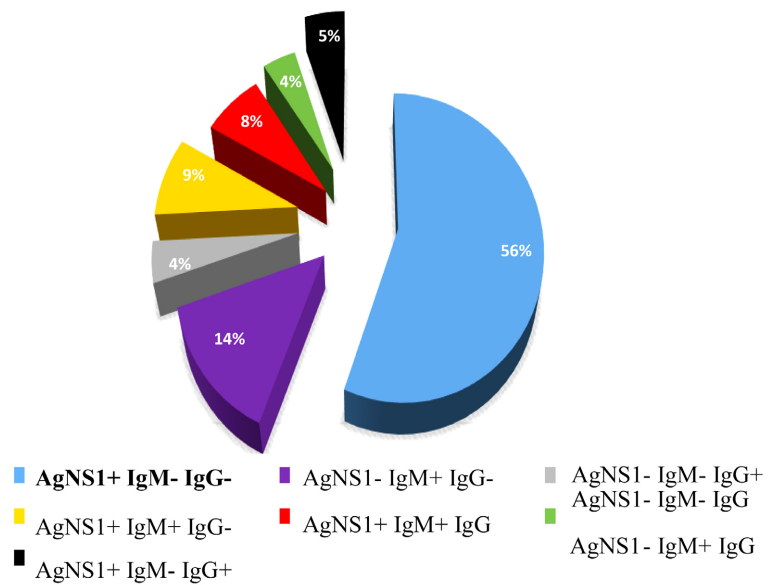
Indeed, 91.39% of patients had elevated AST versus 82.79% who had elevated ALT. The average AST, 248.66 IU/ml was higher than the average ALT which was 166.66 IU/ml. Twenty six patients (27.96%) measured their prothrombin level and among these 7 patients either 26.92% of them had a lower rate in **Table 3**.

Thrombocytopenia was found in 68 patients (73.12%), leukopenia in 41 patients (44.09%) and anaemia in 13 patients (13.98%) on the blood count. Seventy-eight patients (83.87%) had a plasma creatinine measurement and five patients or 6.41% had acute renal failure. Twelve patients (11.94%) had an ultra-

sound scan. Homogeneous hepatomegaly was present in 4 of them (33.33%). Nine tenths (94.62%) of the patients received analgesics. Level 1 analgesic (paracetamol) was the most widely administered, particularly in 76 patients (86.36%) in **Table 4**.

Sixty-one patients, *i.e.* two thirds (65.59%), received parenteral rehydration with crystalloids. In addition, two patients were transfused with packed red blood cells and six with platelet concentrates.

The length of stay varied from 1 to 19 days with an average of 3.54 days. About two thirds (60.22%) of the patients had a short stay of between 1 and 3 days show in **Table 5**.



**Figure 3.** Distribution of patients by serological diagnosis.

**Table 3.** Distribution of patients by prothrombin level.

TP (%)	Number	Percentage (%)
≥70	19	73.08
]70 - 50]	6	23.08
<50	1	3.84
<b>Total</b>	<b>26</b>	<b>100</b>

**Table 4.** Distribution of patients according to analgesic treatment.

Analgesics	Number	Percentage (%)
Level 1	76	86.36
Level 2	11	12.50
Level 3	1	1.13
<b>Total</b>	<b>88</b>	<b>100</b>

**Table 5.** Distribution of patients by length of stay.

Duration of hospital stay (days)	Number	Percentage (%)
[1 - 3]	56	60.22
[4 - 7]	35	37.63
≥8	2	2.15
<b>Total</b>	<b>93</b>	<b>100</b>

The outcome was favourable for 85 patients (91.4%) and four patients (4.30%) were lost to follow-up. Four other patients (4.30%) died as a result of upper gastrointestinal haemorrhage.

#### 4. Discussion

Our study took place over a 4-month period when there is often an upsurge of dengue, 93 patients were collected, an average of 24 patients per month. The dengue virus has a tropism for the liver, nervous system and muscles where it is likely to create cellular alterations. Data from the literature suggest that 65% - 96% of dengue patients have elevated transaminases with persistence up to 60 days after the onset of symptoms [10]. This is consistent with the results of our study. Dengue fever with cytolysis can occur in all age groups. Hepatic manifestations are either a result of direct viral toxicity or dysregulated immunologic injury in response to the virus [11] [12].

Our study found right hypochondrial pain, hepatomegaly and jaundice in 4.30%, 2.15% and 1.07% of cases respectively. These results are weaker than those of other studies conducted in Asia, where almost 40% tenderness to palpation of the right hypochondrium was reported [10], 24% - 100% hepatomegaly [13] [14] [15], 29% jaundice [16] [17]. In a 2013 meta-analysis, hepatomegaly was preferentially associated with severe dengue [18].

A positive Ag NS1 serological diagnosis associated with a negative immunoglobulin test was present in more than half the cases (56%). The qualitative immunoglobulin G assay was negative in 77.42% of cases in our study. Souza in his study found an almost similar result of 65.5% [19]. This high frequency of negative IgG could mean that the patients in the study were received relatively early in the course of the disease. The generally noisy symptoms of dengue fever may lead to early consultation. However, it should be remembered that in our study the diagnosis of dengue was made by RDT with the risk of false positives for patients without AgNS1 and false negatives due to the lack of IgG titration.

In contrast to hepatitis B and C virus infections (HBV and HCV), AST levels in dengue patients are often found to be higher than ALT levels. The involvement of cardiac and skeletal muscle in flavivirus infections may explain this observation [20]. Kuo *et al.* reported elevated AST and ALT levels in 90% and 80% of patients respectively [21]. The results of our study were in agreement with the literature. The prevalences of HBV (9.1%) and HCV (3.6%) infection are high in

our context. The contribution of these viruses in the genesis of cytolysis could not be evaluated in our work.

In endemic countries such as Burkina Faso, *Plasmodium falciparum*, hepatitis viruses (A, B, C, D, E) and human immunodeficiency virus, *Mycobacterium tuberculosis* are responsible for the majority of infectious deaths [22]. Co-infections with dengue virus and these pathogens may contribute to the worsening of both cytolysis and prognosis during dengue disease. This highlights the importance of studying the epidemiology and pathophysiology of these co-infections. These studies could help to improve the management of patients.

Many clinical studies have established the degree of severity of liver damage according to the level of transaminases detected in the blood. Thus, when the transaminase level reaches at least 10 times the upper limit of normal (group C), then the liver damage is the most severe. This is the case in almost 4% of patients [23] [24] compared to 15.05% in our study. This could be due to the abuse of self-medication. Indeed, the use of paracetamol, NSAIDs and traditional treatment was reported in 3.22%, 0%, 5.37% and 6.9% of patients respectively.

This is a common practice as NSAIDs and paracetamol are commonly self-medicated. This is a frequent practice because NSAIDs and paracetamol are commonly used in self-medication. In addition to being available without prescription in pharmacies and also illegally sold in the street, they also seem to be frequently prescribed more in nursing practice (prescription of drugs delegated to nurses) than in medical practice in cases of infectious syndrome, with or without pain. The hepatotoxic risk of phytotherapies, whose exact composition is often unknown, must also be taken into account in our context.

It was lowered in 26.92% in our study. Similar frequencies ranging from 34% to 42% have been found in other studies [25] [26]. Although bleeding (5.38% in our study) may be observed with elevated transaminases [21] [27], studies have shown a weak correlation between prothrombin levels and transaminases. Therefore, the hepatic function of coagulation factor synthesis would generally be well compensated. The factors associated with the occurrence of severe forms of dengue have been researched in Burkina Faso. In this study, risk factors for severe dengue included age, male sex, primary dengue, haemoglobin S, diabetes and hypertension. Adults were at greater risk of severe dengue compared with children (age  $\leq 15$  years) [7].

In addition to the liver, dengue fever can affect various organs including the kidney [25]. The kidney is affected in a variety of ways and may involve one or more of its structures. Among the renal complications, acute renal failure (ARF) is the most frequent; it is found in at least 48.4% of dengue cases [28]. The majority of studies on renal involvement in dengue are from Asian countries and South America. These studies show that ARF is often associated with severe dengue [28]. Coulibaly in Burkina Faso found that 73.8% of patients with ARF due to dengue had liver cytolysis. In our study, 80% of patients with ARF had cytolysis greater than 10 LSN. This finding may suggest a link between the fail-



ures of the two viscera.

The treatment of dengue is symptomatic by combating dehydration (oral and parenteral rehydration), fever (paracetamol) and the algic syndrome. The onset of cytolysis raises concerns that the use of paracetamol or any other potentially hepatotoxic drug may accentuate liver damage. Strict adherence to dosage regimens is essential [29].

Ninety-one percent (91.40) of patients had a favourable outcome and four percent (4.30%) died. Deaths accounted for 80% of haemorrhagic dengues. These data are consistent with the literature. Severe forms of dengue fever have the highest case fatality rate [29] [30].

This study has some limitations: the sites were chosen in relation to the availability of RDTs, which may lead to selection bias. The tests (transaminases, RDTs, haemograms, creatininemia) were paid for by the patients and were not always performed.

## 5. Conclusion

Dengue virus causes damage to the liver parenchyma and other organs. The degree of liver damage is variable. The measurement of transaminases is of great importance, on the one hand to assess the severity of liver damage and on the other hand to facilitate better follow-up. Liver damage, although frequent, can be multifactorial and should be considered in our context.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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