



The Severity and Outcome of Acute Hepatitis in Patients Presenting with Dengue Fever: A Cross sectional Study

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ABSTRACT

Introduction: Dengue fever is an arboviral infection spread by the mosquitoes *Aedes aegypti* and *Aedes albopictus*. The majority of these instances have been documented in Southeast Asian locations, which are popular tourist destinations.

Aim: To assess the severity and outcome of acute hepatitis in patients presenting with dengue fever.

Methodology: The study included all patients under the age of 14 who were hospitalized with a diagnosis of Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), or Dengue Shock Syndrome (DSS). The Chi Square test and, when appropriate, the Fischer exact test were employed to compare categorical variables. For the primary outcome, a survival analysis (Cox regression and log rank) was performed. To compare continuous variables, the student test was utilized. Significance was defined as a p value of less than or equal to 0.05. Cross sectional study. This study was conducted at Suleman Roshan Medical College Hospital Tando Adam Pakistan from January 2020 to January 2021.

Results: Total 500 cases were included in the study, with 87 % (435) having DF and 13% (65) having DHFs or DSS. The median ALT was 87.91 IU/L; IQR 42.78-181 IU/L, the median AST was 179 IU/L; IQR 85-369.3 IU/L, and the median T.Bil was 0.8 mg/dl; IQR 0.6-1.3 mg/dl, according to liver function tests. Total 71 % (355) of the patients had mild to moderate hepatitis, whereas 15 % (75) had severe hepatitis. In patients with mild/moderate hepatitis, the average length of stay (LOS) was 3.63 days, compared to 4.3 days in those with severe hepatitis (P value 0.002). Overall mortality in the mild/moderate hepatitis group was 36.84% (n = 7) compared to 63.15% (n = 12) in the severe hepatitis group (p value 0.001). The severe hepatitis group (H.R (4.91; 95 % CI 1.74-13.87 and P value 0.003), as well as the DHF/DSS group, had substantially increased mortality (H.R (5.43; CI 1.86-15.84 and P value 0.002). In the mild/moderate and severe hepatitis groups, there was a substantial difference in sequelae such as bleeding (P value 0.001), Acute Renal Failure (ARF) (P value 0.002), Acalculous cholecystitis (P value 0.04), and encephalopathy (P value 0.02).

Conclusion: In Dengue fever, severe hepatitis (ALT>300IU) is linked to a longer length of hospital stay, mortality, hemorrhage, and renal failure. Apart from typical hepatotropic viruses, dengue fever should be evaluated when liver tests are abnormal.

Key Words: Dengue fever, Hepatitis, Dengue Hemorrhagic fever, Dengue shock syndrome, sickness, infection.

INTRODUCTION

Dengue fever is an arboviral infection spread by the mosquitoes *Aedes aegypti* and *Aedes albopictus*. It has four stages: asymptomatic, acute febrile sickness, typical Dengue fever (DF), and Dengue Hemorrhagic Fever (DHF), which includes Dengue Shock Syndrome (DSS).¹ Dengue fever has been listed as one of the world's most serious developing ep-

idemics.² This infection causes 100 million cases of DF each year in the tropics, with additional 250,000 cases of DHF and a death rate of 24,000-25,000 each year.³ The majority of these instances have been documented in Southeast Asian locations, which are popular tourist destinations. At least two verified outbreaks have been recorded in Pakistan, the first in 1994 and the second in 2005.⁴

When dengue fever affects the liver and nervous system at

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the same time, it has a terrible prognosis, including death. In DF, atypical symptoms include liver involvement, central nervous system involvement (encephalopathy), and cardiac involvement. In terms of mortality and length of stay, none of the research have reported on the severity of liver involvement in Dengue fever Length of Stay (LOS).⁵ The presence of the liver involvement in dengue fever is shown by an increase in transaminases, which indicates reactive hepatitis. During the current outbreaks in Brazil, this has been noticed during the previous two decades.⁶ According to research from Thailand (Retrospective review), 34.6 % of dengue-infected children had liver damage.⁷

Elevated transaminases in DF can be caused by a variety of factors, including the use of hepatotoxic medications or a direct viral infection, resulting in these uncommon clinical symptoms. As a result, dengue patients have a more catastrophic prognosis. The presence of the liver involvement in dengue fever has been documented in the literature since 1970.⁸ The most prevalent finding observed in Liver Function Tests (LFT) is increased transaminases, which are involved in amino acid metabolism. Aspartate Aminotransferase (AST) levels are greater than Alanine Aminotransferase levels in almost 90% of DF patients (ALT). DF triggers inflammatory reactions in the liver, generating parenchymal alterations and the release of transaminases into the bloodstream.⁹

Since dengue fever is a new condition in our area nothing is known regarding the severity of hepatitis and its consequences in individuals with dengue fever who have a liver infection. As a result, we want to see how common hepatitis is in dengue infection. We also want to see how patients with mild to moderate hepatitis and severe hepatitis in dengue illness behaves (mortality, duration of hospital stay, and comorbidities).

METHODOLOGY

The institutional Ethical Review Committee provided ethical approval. The research included 500 inpatients under the age of 14 with a history of acute fever, positive dengue IgM, and an elevated ALT level. All individuals with underlying Chronic Liver Disease (CLD) or known positive serology for viral hepatitis (HBsAg or HCV Antibodies) as well as those with malaria were excluded from the study. Hepatitis was labelled as Mild hepatitis (ALT levels upto 5 times normal), Moderate hepatitis (ALT levels 5- 10 times normal) and severe hepatitis (ALT > 300 IU/L or 10 times normal). Mortality and length of hospital stay were the primary outcome metrics. Different complications were specified as secondary outcome measures: a) Bleeding was classified as either mucosal bleeding (epistaxis or gum bleed) or gastrointestinal bleed b) Acute

Renal Failure (ARF) was defined as a rise in creatinine (Cr) of more than three times the normal level. c) Encephalopathy was defined as a change in mental status (drowsiness, lethargy, agitation, or coma) lasting more than eight hours. d) Shock was defined as a systolic blood pressure of less than 90 mm Hg. For the key outcome metrics, we additionally divided the data into Dengue Fever and Dengue Hemorrhagic Fever/Dengue Shock Syndrome depending on diagnosis.

People who have dengue fever are more likely to have liver problems than people who don't have the disease, so a minimum sample size of 250 people was needed, with a 0.05 error limit and a 95% confidence level. Data was collected on a predesigned form that included demographics, clinical presentation, laboratory parameters, and the outcome of the study (in hospital mortality, length of hospital stay and complications). All patients who met the criteria were taken to the medical ward through the emergency room or clinic were included. Each patient was put into mild, moderate or severe hepatitis groups based on their ALT levels, and these patients were kept track of until the end of their stay in the hospital.

For the study, the Statistical Package for Social Sciences (SPSS) version 16 was utilized. For continuous variables, the results are reported as mean standard deviation (SD), whereas qualitative variables are presented as frequency and percentage. The median and interquartile ranges (IQR) were utilized for non-normally distributed quantitative data. The Chi-Square test was used to compare categorical variables, and the Fischer exact test was employed when the numbers were too small for the Chi-Square test to be performed. To compare continuous variables, the student test was utilized. After satisfying the proportional hazard ratio assumption, the cox proportion hazard ratio (Cox regression) was calculated for mortality in DHF/DSS and severe hepatitis in a survival study. The log rank test and the Kaplan Meir plot of survival over time were also utilized. A p value of less than 0.05 was considered significant. The mortality rates for 10 days in each group were determined, as well as the 95 % confidence interval for the death rate ratio.

RESULTS

A total of 500 individuals with DF were enrolled in the study, with 61 % of them being men. The average age of the patients was 30.87 ± 13.75 years. Approximately 82 % (n = 410) of the patients were diagnosed with DF, 14 % with DHF, and just 4 % with DSS. All of the patients tested negative for the malaria parasite. Fever lasted an average of 6 ± 3.17 days, with a mean temperature of $38.0 \pm 1.5^{\circ}\text{C}$. Total 46.9% patients experienced nausea/ vomiting, 19.4% had abdominal pain, 18.2% had rash, 15.8% had body ache, 12.3% had diarrhea, 9.7% had cough, 6.5% had hematemesis, 4.8 % had bleeding gums, 5.1% had malena, 7.2% had changed mental

status, and 3% had jaundice, among other clinical characteristics. 7% experienced right hypochondric discomfort and 2.1% had epigastric soreness on abdominal examination.

In terms of hemodynamics, the average pulse rate was 94 ± 16.5 beats per minute, the average systolic blood pressure was 116 ± 14 mmHg, and the average diastolic blood pressure was 77 ± 13 mmHg. The complete blood work revealed a mean hemoglobin of 13.26 ± 2.41 gm/l, a mean hematocrit of $39.07 \pm 7.1\%$, a mean white blood cell count of 5.8 ± 7 cmm, and a median platelet count of 46/cmm, with an IQR of 22-93/cmm. The mean Activated Partial Thromboplastin Time (APTT) was 35.39 ± 10.92 seconds, compared to 40 seconds for the control group. Cr was 1.21 mg/dl on average. The median ALT is 87.91 IU/L; IQR 42.78-181 IU/L, the median AST is 179 IU/L; IQR 85-369.3 IU/L, the median ALK.Phos is 79 IU/L; IQR 52-125 IU/L, and the median T.Bil is 0.78 mg/dl; IQR 0.5-1.1 mg/dl, according to liver function tests. ALT levels were increased in about 82 % (410) of the patients (hepatitis). In this population, the mean LOS was 3.20 2.7 days.

In our investigation, the mortality rate was 2.76 %. We discovered 1.54 % hemorrhage, 1.41 % shock, and 2.63 % ARF

among the consequences. Acalculous cholecystitis, 3.79 %, and encephalopathy, 2.83 %. (As shown in table 2) Severe hepatitis was found in 15% of the participants, mild to moderate hepatitis in 71%, and normal ALT in 14%.

Overall mortality in the severe hepatitis group (63.15 %; n = 12) was substantially greater than in the mild to moderate hepatitis group (36.84 %; n = 7). Picture 1 depicts the Kaplan-Meier curve's survival probability for the mild to moderate and severe hepatitis groups, with numbers at risk below the figure. There are substantial differences in overall survival between these two groups (P value 0.005; log rank). Patients with mild/moderate hepatitis stayed 3.63 days on average, compared to 4.3 days for those with severe hepatitis. With regard to mild to moderate hepatitis and DF, Cox regression (survival analysis) revealed substantially greater mortality in the severe hepatitis group (H.R 4.91; 95 % CI 1.74-13.87 and P value 0.003) and DHF/DSS group (H.R 5.43; CI 1.86-15.84 and P value 0.002). In a subgroup study of DF and DHF/DSS for mortality, severe hepatitis was shown to have considerably greater mortality than mild to moderate hepatitis (3/436 compared 3/81, P value 0.04 in DF; 3/60 versus 9/22, p value 0.001 in DHF/DSS group).(As shown in table 1)

Table 1: Primary outcome measures according to severity of hepatitis

Diagnosis Categories	Severity of hepatitis	Deaths	Death rate (Deaths/10 day)	H.R (95% CI; UCI, LCI) ^	P value (Difference in death rate)	LOS $\pm$ SD	P value
Dengue fever (n = 355)	Mild to Moderate Hepatitis (n = 270)	3	0.011	2.76 (0.37,17.4)	0.194	3.20 $\pm$ 1.24	>0.029
	Severe hepatitis (n = 85)	4	0.047			3.46 $\pm$ 2.07	
DHF/DSS (n = 145)	Mild to Moderate Hepatitis (n = 113)	4	0.035	5 (1.4,17)	0.005	4.61 $\pm$ 2.78	0.221
	Severe hepatitis (n = 32)	8	0.25			5.70 $\pm$ 3.58	

Table 2: Complications in two groups of severity of hepatitis

Complications	Mild to moderate-hepatitis (n = 496)	Severe hepatitis (n = 103)	P value
Bleeding	2	6	0.001
Renal failure	7	7	0.002
Encephalopathy	6	10	0.02
Shock	5	1	0.40
Acalculous cholecystitis	13	6	0.04

DISCUSSION

The biggest cross sectional research on hepatitis in dengue fever patients and its relationship with outcome from

south Asia (Pakistan) is presented. Dengue fever is now the world's most prevalent rapidly developing virus, with Pakistan reporting its first epidemic in 1994.¹⁰ Due to direct assault on liver cells or an uncontrolled host immunological response to the virus, individuals with dengue infection often have abnormal liver functions. As a result, AST and ALT levels must be measured to determine if the liver is involved. Deranged liver functions are an essential hallmark in individuals with dengue infection, according to our findings. Hepatitis (raised ALT) was found in about 86 % of the patients in our research, while elevated AST was found in 95 %. Sameer Gulati et al., found that AST anomaly was more common than ALT abnormality, with 91 % and 72 %, respectively, which is consistent with our findings.¹¹

However, the AST and ALT levels in our research sample are greater than those reported by Sameer Gulati et al. and

other investigations. Souza et al. observed a similar AST/ALT trend in dengue fever, albeit at a considerably lower level than our study. This disparity may be explained by the fact that all the patients in our research were inpatients, while all of the patients in their study were outpatients with less severe illness.¹²

Furthermore, research from the Asia-Pacific area (Taiwan) by Parkash et al. found that roughly 90% of dengue patients had an abnormal AST, which is consistent with our findings. Higher ALT or AST readings in our group are most likely related to a more virulent strain of dengue illness or a virus that is more hepatotoxic. As a result, further research is needed to determine if this virus is hepatotropic, as well as its virulence and kind. Immune responses, both innate and acquired, play a significant role in deciding how a virus is responded to.¹¹ The notion of immunological enhancement and the virulent characteristic of the virus has been proposed as a cause of the severity of dengue illness. In their investigation, Chaturvedi et al. colleagues discovered that various helper cell cytokines appeared in human white blood cell cultures infected in vitro with dengue virus type 2.¹³ Because an unregulated host immune response may play a role in the severity of dengue illness, severe infection may be avoided by modulating the immune response.¹⁴

Patients with severe hepatitis have a much greater death rate. Our research population had a death rate of 2.7 %. Previous research from Pakistan found a similar death rate (2.6%) but with a smaller sample size (n = 225). There is a scarcity of literature on the mortality of dengue infection in those who have poor liver function. In a study of 45 patients in Vietnam, Nguyen et al., colleagues found that DHF causes mild to moderate liver dysfunction in most cases; nevertheless, some individuals may develop acute liver failure, resulting in encephalopathy and death.¹¹

However, the impact of liver disease on mortality was not investigated. Dengue patients with hepatitis and encephalopathy have a significant fatality rate, according to Shah. However, this was limited research conducted in India, with just four juvenile patients. Ours is the first big research from the South Asian area to reveal the increased risk of death in dengue patients with abnormal liver function.¹⁵ When the liver is implicated, the self-limiting clinical course of dengue infection may be extended, according to Souza et al. As a result, when there is extensive hepatic involvement, we have noticed a poorer outcome in our research participants. Further subgroup analysis revealed that mortality in the severe category of hepatitis was considerably greater in both DF and DSS. We might speculate that severe hepatitis is a substantial contributor to death in dengue infected patients.

Nevertheless, further immunologic research is needed to determine the origin of liver involvement, whether it is related to the virus or an immune response (reactive hepatitis). Our

research population with dengue infection had a mean length of stay of around 4 days, although Lye et al reported a mean LOS of 3 days in a study from Singapore. In their research (166 patients) in the Saudi population, Parkash et al found that the median length of hospital stay in dengue patients was 4 days, although there was no contrast based on liver functions. There has yet to be research that compares LOS to liver involvement. When the illness is light (DF), severe hepatitis affects the LOS; however, when the disease becomes more severe, severe hepatitis has no effect on the LOS. Clinical consequences such as hemorrhage, renal failure, encephalopathy, and Acalculous cholecystitis were shown to be more common in patients with severe hepatitis. Parkash et al. found a link between high AST levels and this problem in a Saudi population research. However, issues with hepatitis based on blood ALT levels have been seen.¹⁰

Patients with severe hepatitis have a much greater risk of bleeding complications. Similarly, Parkash CH et colleagues found that those with high AST, ALT, and GGT levels had more bleeding episodes. In another research, individuals with increased ALT and Alk.Phos had considerably more spontaneous bleeding episodes. AST and ALT levels were also observed to be considerably higher in DHF patients with gastrointestinal bleeding, according to Thach et al.¹⁸ We might speculate that, in addition to thrombocytopenia, abnormal liver functions may play a role in bleeding. We discovered that individuals with renal insufficiency had a considerably greater rate of severe hepatitis. Although there are case reports of acute renal failure/injury in dengue fever, none of these have been examined in adults with liver involvement. Encephalopathy was also considerably greater in the severe hepatitis group in our research sample.¹⁶ Encephalopathy caused by dengue infection in adults has been documented in case reports. Encephalopathy, on the other hand, has been extensively researched in the pediatric population. Patients with severe hepatitis had a considerably higher rate of acalculous cholecystitis.¹⁷ A calculous cholecystitis is a well-known complication of dengue fever, although no studies have compared it to the severity of hepatitis. In our research population, 3% of the patients exhibited jaundice. In their investigation on hepatic change in dengue fever, Ferguson T et al found jaundice in just two out of 63 patients.

Strength and Limitations: This is the largest study of dengue fever patients from South Asia. This is the first study to compare the outcomes of dengue and hepatitis patients. Because this is research of inpatients, it has low external validity because it excludes patients who have attended outpatient and other hospitals in the city. The study population in our tertiary care hospital is made up of people with middle to high incomes, who make up a tiny fraction of the city's population. We didn't look for the kind of dengue virus, either.

CONCLUSION

With comparison to mild to moderate hepatitis, severe hepatitis in dengue infection has a poorer prognosis in terms of duration of stay, death, and comorbidities. As a result, severe hepatitis might be regarded a poor predictive indication of dengue infection prognosis. Even though the majority of the patients had a self-resolving sickness, they might be at risk for acute fulminant hepatic failure. Apart from typical hepatotropic viruses, dengue fever should be evaluated when liver tests are abnormal. More research is needed to determine if liver harm is caused by the virus's hepatotropic nature or by immunologic injury.

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Nothing to declare

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