

Hepatic Involvement and its Impact on Clinical Outcome in Patients of Dengue Fever: An Observational Study.

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ABSTRACT :

Background : Dengue is an important arboviral disease in tropical countries. It is one of the commonest mosquito-transmitted diseases, second only to malaria, and is spread by bite of Aedes mosquito. Dengue virus has profound effect on multiple organ systems, the commonest being the liver. A wide spectrum of hepatic manifestations has been described, ranging from mild elevation of serum transaminases to acute liver failure. Dengue Fever (DF) initiates the inflammatory responses leading to liver parenchymal changes and causing release of transaminases in circulation. We aim to assess the frequency of hepatic involvement in Dengue fever, pattern of hepatic enzymes alterations, and its impact on the clinical outcome.

Methods : A Retrospective study was conducted at Mahatma Gandhi Medical College & Hospital, Jaipur, a tertiary care centre in northern India, between January 2019 to October 2019. During this period, 94 consecutive patients with dengue fever who required hospitalization were included in the study. All inpatients of age ≥ 14 years who had history of acute fever, positive dengue NS1 Antigen / IgM Antibody and whose Liver Function Tests were done, were included in the study.

Results : In our study, it was observed that all the hepatic parameters were significantly different between the three groups except S.Direct Bilirubin. The S.Total Bilirubin ($p = 0.0001$), PT ($p = 0.0001$), INR ($p = 0.0001$) were highest among the patients with Dengue Shock Syndrome as compared to patients with Dengue Fever and Dengue Hemorrhagic Fever respectively. However, the S.Total protein ($p = 0.0001$) and S.Albumin ($p = 0.0001$) were significantly lower among the patients with Dengue Shock Syndrome as compared to patients with Dengue Fever and Dengue Hemorrhagic Fever. The transaminases elevations were upto 5 times upper normal limit ULN in 41 (43.6 %) patients, between 5 to 10 times ULN in 23 (24.4 %) patients, between 10 to 100 times ULN in 10 (10.63 %) patients and more than 100 times ULN in 7 (7.44%) patients. The mortality rate was 1.40 % in patients with Dengue Fever, 10.52 % in patients with Dengue Hemorrhagic Fever and 75.00 % in patients with Dengue Shock Syndrome.

Conclusion : We conclude that majority of the patients with dengue infection have hepatitis. Severe hepatitis in dengue infection has got worse outcome in terms of complications and mortality as compared to mild to moderate hepatitis. Therefore severe hepatitis can be considered as a bad prognostic indicator of outcome in dengue infection.

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INTRODUCTION :

Dengue is an important arboviral disease in tropical countries. It is one of the commonest mosquito-transmitted diseases, second only to malaria, and is spread by bite of *Aedes mosquito*¹. Globally Dengue is an epidemic in tropical and subtropical areas, affecting around 50 million persons; of this 0.5 million develop dengue hemorrhagic fever and around 20,000 deaths occur every year².

Dengue virus has profound effect on multiple organ systems, the commonest being the liver. A wide spectrum of hepatic manifestations has been described, ranging from mild elevation of serum transaminases to acute liver failure². The involvement of liver in dengue fever is not uncommon as reported in literature since 1970³. In the Liver Function Tests (LFT) most common abnormality seen is elevated transaminases (70-90 %) which are involved in amino acid metabolism. Dengue Fever (DF) initiates the inflammatory responses leading to liver parenchymal changes and causing release of transaminases in circulation⁶. In approximately 90% of the patients with DF, Aspartate Aminotransferase (AST) is higher than the Alanine Aminotransferase (ALT)^{4,5}. We aim to assess the frequency of hepatic involvement in Dengue fever, pattern of hepatic enzymes alterations, and its impact on the clinical outcome.

MATERIALS AND METHODS: A Retrospective study was conducted at Mahatma Gandhi Medical College & Hospital, Jaipur, a tertiary care centre in northern India, between January 2019 to October 2019. During this period, 94 consecutive patients with dengue fever who required hospitalization were included in the study. All inpatients of age ≥ 14 years who had history of acute fever, positive dengue NS1 Antigen / IgM Antibody and whose Liver Function Tests were done, were included in the study. We excluded those patients who

had underlying Chronic Liver Disease (CLD) or known positive serology for viral hepatitis (HBsAg or Anti-HCV Antibody) and those patients who had concomitant malaria. Patients with mild uncomplicated dengue fever who did not require hospitalization were excluded from study. The severity of dengue was defined using modified categorization of WHO in 2012 which included dengue with or without warning signs or severe dengue⁷.

A thorough clinical history was noted and examination was done in all patients at the initial visit. Blood samples were collected for Complete Blood Count (CBC), Liver Function tests including Serum Bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Serum Total Protein, Serum Albumin and Prothrombin Time-International Normalised Ratio (PT-INR), Kidney Function Tests including Serum Creatinine and Blood Urea, and other test as and when needed. Data was collected on predesigned proforma which included demographics, clinical presentation, laboratory parameters and outcome. A uniform management protocol was followed which included antibiotics, stress ulcer prophylaxis, monitoring and correction of blood sugar levels, intravenous fluids as per protocol, maintenance of mean arterial pressure >80 mm Hg and other supportive treatment.

RESULTS : The baseline characteristics and laboratory parameters of all dengue patients are summarized in Table 1 and Table 2. Majority (75.53 %, 71/94) of the patients were male, and the median age (range) was 32 (12-78) years. Transaminases elevation was seen in 81 (86.17 %) patients. Interestingly, the AST showed greater elevation as compared to ALT in majority (n=78, 82.97%) of patients. The mean albumin was found to be 2.9 ± 0.5 . The median INR was 1.3 (0.9-5.2). The median Platelet count was 50000 (1000-295000).

Table 1: Baseline characteristics of all patients (n=94).

Parameters	Total Patients (n=94)
Age, median (range) (years)	32(12-78)
Male: Female	71:23
Hb, mean±SD gm/dl	11.3 ± 1.8
PCV mean±SD	40.2 ± 7.4
TLC, median (range) /mm ³	4640 (1570-42752)
Platelet count, median (range) /mm ³	50000 (1000-295000)
Normally distributed continuous variables are expressed as mean (SD) and the continuous variables with skewed distribution were expressed as median (range). Categorical data are presented as proportions.	

Table 2: Liver Function Tests (LFT) of all patients (n=94).

Parameters	Total Patients (n=94)
Bilirubin, median (range) mg/dl	0.81(0.14-9.02)
AST, median (range) IU/L	214 (26-21176)
ALT, median (range) IU/L	106(22-10260)
Transaminases not elevated	13(13.82 %)
AST Elevation	83(88.29 %)
ALT Elevation	65(69.14 %)
AST/ALT ratio >1	78 (82.97 %)
AST/ALT ratio <1	16 (17.03 %)
Albumin, mean±SD g/dl	2.9 ± 0.5
INR, median (range)	1.3 (0.9-5.2)
Normally distributed continuous variables are expressed as mean (SD) and the continuous variables with skewed distribution were expressed as median (range).	

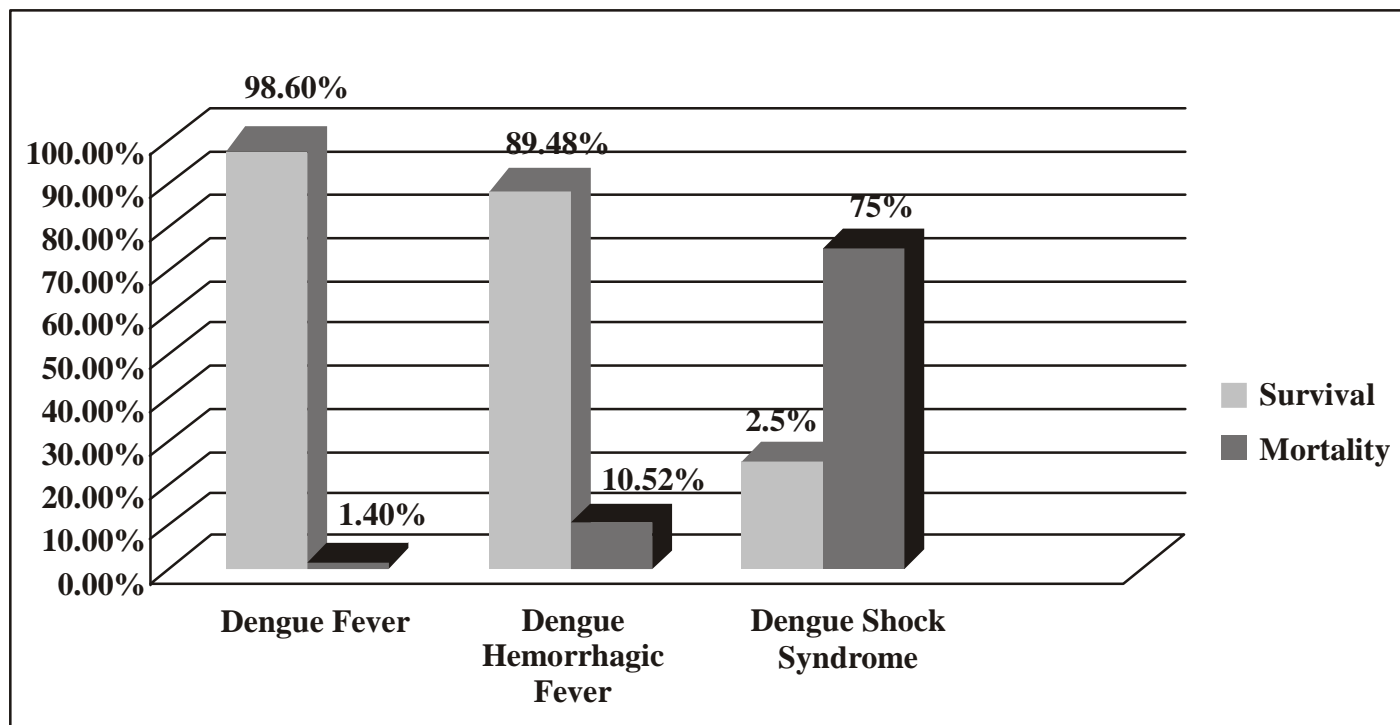


Figure 1 : Comparison of Survival rates among the different clinical types of Dengue Fever.

Table 3: Comparison of patient characteristics and outcomes among the different clinical types of Dengue Fever.

Parameters	Dengue Fever (n= 71)	Dengue Hemorrhagic fever (n= 19)	Dengue Shock Syndrome (n=4)	p- Value
Age (years)	29.70±13.21	30.22±10.32	39.20±18.66	0.001
Hepatomegaly	19 (26.76 %)	6 (31.57 %)	2 (50.0 %)	0.0001
Peritoneal collection	22 (30.98 %)	13 (68.40 %)	4 (100.0%)	0.0001
S.Total Bilirubin, mean±SD* mg/dl	1.50±0.92	1.62±1.21	2.71±1.96	0.0001
S.Direct Bilirubin, mean±SD mg/dl	0.78±0.31	0.91±0.47	2.32±1.75	0.468
Transaminases elevation				
Not elevated	11 (15.49 %)	2(10.52 %)	0	
Upto 5 x ULN#	37 (52.11 %)	3(15.78 %)	1 (25.00 %)	
5-10 x ULN	15 (21.12 %)	7(36.84 %)	1 (25.00 %)	
10-100 x ULN	6 (8.45 %)	4(21.05 %)	0	
>100 x ULN	2 (2.81 %)	3(15.78 %)	2 (50.00 %)	
S. Total protein, mean±SD g/dl	6.27±0.88	5.98±0.97	4.99±1.06	0.0001
S. Albumin, mean±SD g/dl	3.21±0.52	3.00±0.48	2.51±1.16	0.0001
PT, mean±SD seconds	16.42±2.31	15.91±3.12	25.19±9.66	0.0001
INR	1.21±0.82	1.45±0.51	2.03±1.51	0.0001
Mortality	1 (1.40 %)	2 (10.52 %)	3 (75.00 %)	0.0001
*SD - Standard Deviation #ULN - Upper Limit of Normal				

In our study, it was observed that all the hepatic parameters were significantly different between the three groups except S.Direct Bilirubin. The S.Total Bilirubin (p = 0.0001), PT (p = 0.0001), INR (p = 0.0001) were highest among the patients with Dengue Shock Syndrome as compared to patients with Dengue Fever and Dengue Hemorrhagic Fever respectively. However, the S.Total protein (p = 0.0001) and S.Albumin (p = 0.0001) were significantly lower among the patients with Dengue Shock Syndrome as compared to patients with Dengue Fever and Dengue Hemorrhagic Fever.

6 of 94 (6.38 %) admitted dengue patients died. The mortality rate was 1.40 % in patients with Dengue Fever, 10.52 % in patients with Dengue Hemorrhagic Fever and 75.00 % in patients with Dengue Shock Syndrome.

The transaminases elevations were upto 5 times upper normal limit ULN in 41 (43.6 %) patients, between 5 to 10 times ULN in 23 (24.4 %) patients, between 10 to 100 times ULN in 10 (10.63 %) patients and more than 100 times ULN in 7 (7.44%) patients.

DISCUSSION : Dengue is an endemic mosquito transmitted arboviral disease threatening

3.6 billion persons and affecting around 50 million people in 128 tropical and subtropical countries around world annually⁸. Dengue can present as mild self-limiting illness DF, or as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)⁹. The severe dengue fever which includes DHF and DSS has evidence of plasma leakage, bleeding and organ impairment. Dengue was initially believed to be a disease of childhood but now nearly similar incidences have been seen in older age group. In our study, patients' age varied from 12-78 years with median age being 32 years. Many studies from south-east Asia suggest that males are more affected than females in DF/ DHF inpatients, which may be linked to a gender bias in health seeking behavior. In our study also, 75.53 % of patients were male.

Deranged liver functions are common in patients with dengue infection due to direct attack on liver cells or unregulated host immune response against the virus¹⁰. Hence measurement of AST and ALT are mandatory to see the liver involvement. In our study deranged liver functions were an important feature in patients with dengue infection. 86.17% of the patients in our study had elevated transaminases levels. Wong et al reported that AST abnormality was predominantly higher as compared to ALT; 91% and 72% respectively, which is consistent with our study¹⁰. Souza et al also reported the similar trend of AST/ALT in dengue fever but with much lower level as compared to our population¹¹. This difference can be explained on the basis that in our study all patients were inpatients while in their study all the patients were outpatients with less severe disease. Furthermore a study from Asia pacific region (Taiwan) by Kuo et al has shown approximately 90% of the AST abnormality in dengue patients which is consistent with our study¹². We can assume that reasons for higher ALT or AST levels in our population are either due to more virulent strain of dengue infection or virus is more hepatotoxic. Therefore further studies are required to highlight the possible hepatotropic nature of this virus as well as

virulence and type of virus.

CONCLUSION :

We conclude that majority of the patients with dengue infection have hepatitis. Severe hepatitis in dengue infection has got worse outcome in terms of complications and mortality as compared to mild to moderate hepatitis. Therefore severe hepatitis can be considered as a bad prognostic indicator of outcome in dengue infection. Though majority of the patients had self resolving course of illness but they can be potential candidates for acute fulminant hepatic failure. Dengue fever should be considered when liver functions are deranged apart from routine hepatotropic viruses. Further studies are required to establish the fact whether liver injury is due to hepatotropic nature of the virus or due to immunologic injury.

LIMITATION : The number of patients with Dengue Hemorrhagic Fever and Dengue Shock Syndrome were very few.

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