

ORIGINAL ARTICLE

Clinical Profile, Hepatic Dysfunctions, and Outcome of Dengue Patients in a Tertiary Care Hospital of Eastern India

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Abstract

Background: Dengue is one of the commonest tropical infections in India. This study was aimed to evaluate clinical profile, magnitude and spectrum of hepatic dysfunctions, outcome and clinical predictors of mortality in patients with dengue.

Methods: In an observational study, data of 183 consecutive admitted dengue patients were prospectively collected. The magnitude of hepatitis and its association with outcome were studied.

Results: The transaminases elevation was seen in 156 (85%) patients, with 21 (11.4%) patients had levels above 10 times the upper normal limit (UNL). Aspartate aminotransferase (AST) showed greater elevation as compared to Alanine aminotransferase (ALT) in 136 (87%) patients. Patients who died (n=8), compared with those who survived (n=175) had higher mean serum bilirubin (3.4 vs. 0.7 mg/dl, p= 0.01), median AST (8791 vs. 138 IU/L, p=0.02), median ALT (2692 vs 81 IU/L, p=0.02), median serum creatinine (2.0 vs 1.0 mg/dl, p=0.007), mean International normalized ratio (3.5 vs 1.1, p= 0.04), and lower median platelet count (20000 vs 60000/mm³, p <0.001). Among patients who died 87.5% (n= 7) had AST levels greater than 100 times UNL while among patients who survived 93% (n=162) had AST levels lower than 10 times UNL. In a multivariate analysis, serum bilirubin (≥ 2.2 mg/dl, OR 4.8) and creatinine (≥ 1.65 mg/dl, OR 2.8) were found to be independent predictors of mortality.

Conclusions: Hepatitis is very frequent in patients with dengue. AST elevation is usually more than ALT elevation. Presence of jaundice and renal dysfunction at presentation are ominous signs in predicting mortality.

Introduction

Dengue is as an important arboviral disease in tropical countries. It is one of the commonest mosquito-transmitted diseases, second only to malaria, and it 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 year.² The loss to the economy is 264 disability-adjusted life years (DALY) per million of population.

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.² Despite being one of the commonest tropical infections in India, published data on clinical profile, spectrum of liver involvement, and outcome is still scant in the English literature. Therefore, this study was conducted to evaluate the clinical profile, magnitude and spectrum of hepatic dysfunctions, outcome and clinical predictors of mortality in patients with dengue.

Material and Method

The study was conducted at Paras-HMRI hospital Patna, a tertiary care hospital in eastern India, between July

2015 July to December 2015. During this period, 183 consecutive patients with dengue who required hospitalization were included in this study. Patients with mild uncomplicated dengue fever who did not require hospitalization were excluded from study. The diagnosis of dengue was made on the basis of clinical feature along with positive NS1 antigen and/or positive IgM antibody against dengue virus. The severity of dengue was defined using modified categorization of WHO in 2012 which included dengue with or without warning signs or severe dengue.³ The consent for including data for the purpose of study was obtained from each patient at the time of enrollment

A thorough clinical history and examinations were done in all patients at the initial visit. The blood sample were collected for a complete blood count and biochemical investigations including a liver function test, kidney function tests, coagulation profiles, blood glucose, and other test as and when needed. A uniform management protocol was followed which included antibiotics, stress ulcer prophylaxis, monitoring and correction of blood sugar levels, maintenance of mean arterial pressure >60 mm Hg and other supportive treatment. The microbiological surveillance was done to detect infection. Renal replacement therapy was used when required.

Statistical Analysis

Normally distributed continuous variables were expressed as mean (\pm SD), and the continuous variables with skewed distribution were expressed as median (range). Categorical data were presented as proportion. Comparisons were done using t test for continuous variables and the Chi square (χ^2)

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or Fishers exact test for discrete variables, wherever applicable. The baseline variables that independently predicted deaths were identified using multiple regression analysis. The variables with significance $p < 0.10$ in the univariate analysis were taken in the multivariable analysis. A receiver operating characteristic (ROC) curve technique was used to identify an appropriate cut off value of predictive variable. Data were analyzed by using GNU PSPP Statistical analysis software.

Results

The baseline characteristics laboratory parameters and outcome of all dengue patients in all are summarized in Table 1. Majorities

Table 1: Baseline characteristics of all patients (N=183)

Parameters*	Total N=183
Age, median (range) (years)	35 (13-78)
Male: Female	141:42
Bilirubin, median (range) mg/dl	0.7 (0.1- 9.02)
Aspartate transaminase (AST), median (range) IU/L	144 (11-45176)
Alanine transaminase (ALT), median (range) IU/L	86 (12-12260)
Transaminases Not elevated	27 (15%)
elevation upto 5 times UNL#	97 (53%)
5-10 times UNL	38 (21%)
10 -100 times UNL	14 (7.6%)
>100 times UNL	07 (3.8%)
AST/ALT ratio >1	136 (87%)
AST/ALT ratio <1	20 (13%)
Albumin, mean±SD g/dl	3.4 ± 0.5
Sodium, mean±SD meq/dl	133 ± 7.6
Potassium, mean±SD meq/dl	4.6 ± 0.9
Serum creatinine, median (range) (mg/dl)	1.0 (0.4-3.2)
Hb, mean±SD gm/dl	13.3 ± 1.9
PCV mean±SD	41.4 ± 6.4
TLC, median (range) /mm ³	4980 (1620-35430)
Platelet count, median (range) /mm ³	60000 (4000-325000)
INR, median (range)	1.2 (0.9-5.5)
Outcome, n (%)	
Died	08 (4.4%)
Survived	175 (95.6%)

*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.; #Upper normal limit

Table 3: Sensitivity, specificity, positive predictive value, negative predictive values, and likelihood ratio for predictive variables in isolation and in combination

Variable	n	Death	Sensitivity%	Specificity%	PPV%	NPV%	LR+	LR-
Bilirubin ≥2.2	9	6	75	98	66.7	98.8	43.5	0.25
Creatinine ≥1.65	9	5	62.5	97.7	55.5	98.2	27.3	0.38
Bilirubin ≥2.2 + creatinine ≥1.65	6	5	62	99.4	83	98	113	0.37

PPV, positive predictive value; NPV, negative predictive value; LR(+), positive likelihood ratio; LR(-), negative likelihood ratio.

(77%, 171/183) of the patients were male, and the median age (range) was 35 (13-78) years. Twenty patients had evidence of severe dengue as per modified WHO criteria.³ The transaminases elevation was seen in 156 (85%) patients. The transaminases elevations were upto 5 times upper normal limit UNL in 97 (53%) patients, between 5 to 10 times UNL in 38 (21%) patients, and more than 10 times UNL in 21 (11.4%) patients. Interestingly, the aspartate aminotransferase (AST) showed greater elevation as compared to alanine aminotransferase (ALT) in majority (n=136, 87%) of patients. Eight of 183 (4.4%) admitted dengue patients died. Of these 8 patients, 7 died within 24 hrs of admission. Patients who died (n=8), compared with those who survived (n=175) had higher mean serum bilirubin (3.4 vs. 0.7 mg/dl, $p = 0.01$), median AST (8791 vs. 138 IU/L, $p = 0.02$), median ALT (2692 vs 81 IU/L, $p = 0.02$), median serum creatinine (2.0 vs 1.0 mg/dl, $p = 0.007$), mean International normalized ratio (3.5 vs 1.1, $p = 0.04$), and lower median platelet count (20000 vs 60000/mm³, $p < 0.001$). Among patients who died 87.5% (n= 7) had AST levels greater than 100 times UNL while among patients who

survived 93% (n=162) had AST levels lower than 10 times UNL (Table 2). The mean hemoglobin and hematocrit levels were not significantly different between died and survived patients. In a multivariate analysis only serum bilirubin and serum creatinine were found to be independent predictors of mortality. The best cut-off values for serum bilirubin and serum creatinine discriminating between those who died and those who survived were 2.2 mg/dl, and 1.65 mg/dl, respectively. The Odds ratio (OR) for each independent predictor and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) at relevant cut-off values in different combinations are shown in Table 3.

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 annually.⁴ Near about 75% of exposed people live in Asia pacific region. In India the first case was reported in 1780 in madras (Chennai). Since 1970, several epidemics of dengue

Table 2: Comparison of variables between died and survived patients (univariate analysis)

Parameters	Survived N= 175	Died N=08	p
Age, median (range) (years)	35 (13-78)	44 (25-62)	0.25
Male: Female	136: 39	05:03	0.28
Dengue shock Syndrome (n %)	0	4	<0.001
Bilirubin, median (range) mg/dl	0.7 (0.1- 6.7)	3.4 (1.4-9.02)	0.01
Aspartate transaminase, median (range) IU/L	138 (11-37191)	8791 (2420-45176)	0.024
Alanine transaminase, median (range) IU/L	81 (12-932)	2692 (897-12260)	0.026
Transaminases levels Within normal limit	27 (15.7%)	00	
upto 5 times UNL	97 (55.4%)	0	
5-10 times UNL	38 (21.7%)	00	<0.001
10 -100 times UNL	13 (07.2%)	01 (12.5%)	
>100 times UNL	00	07 (87.5)	
Albumin, mean±SD g/dl	3.8 ± 0.5	3.2 ± 0.6	
Sodium, mean±SD meq/dl	135 ± 4.0	130 ± 9.8	0.27
Potassium, mean±SD meq/dl	4.2 ± 0.7	5.1 ± 0.9	0.09
Serum creatinine, median (range) (mg/dl)	1.0 (0.4-2.9)	2.0 (1.3 -3.2)	0.007
Hb, mean±SD gm/dl	13.3 ± 1.9	13.3 ± 2.0	0.94
PCV mean±SD	41.3 ± 6.4	43.1 ± 6.1	0.43
TLC, median (range) /mm ³	4900 (1620-35430)	9365 (3090- 27310)	0.062
Platelet count, median (range) /mm ³	60000 (4000-325000)	20000 (5000-43000)	<0.001
INR, median (range)	1.1 (0.9 - 1.4)	3.5 (1.5 -5.5)	0.04

fever (DF) have occurred in different parts of country. Dengue can present as mild self-limiting illness DF, or as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁵ Though, dengue has been traditionally classified into DF, DHF, and DSS (WHO 1997 Classification), the modified categorization of WHO in 2009 and 2012 include dengue with or without warning sign and severe dengue. The warning signs include abdominal pain or tenderness, persistent vomiting, fluid accumulation like effusions and ascites, bleeding, lassitude, hepatomegaly, or rise in hematocrit ($\geq 20\%$) with rapid reduction in platelet count ($< 50000/\text{mm}^3$). The severe dengue which includes DHF and DSS has evidence of severe plasma leakage, bleeding and organ impairment.

Dengue was initially believed to be a disease of childhood but now nearly similar incidences has been seen in older age group. In our study, patients' age varied from 13-78 years with median age being 35 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, 77% of patients were male. Studies in India by Shekhar et al; and in Malaysia by Kabra et al; have reported a higher mortality rates in females which could be due to different pathogenesis and immune response⁽⁶⁾ In our study, the mortality rates in female was 7.1% (03/42) compared to 3.5% (05/141) among male patients. The case fatality due to dengue has declined from 3.3% in 1996 to 0.3 % in 2013.⁽⁷⁾ In our study, the mortality rate was 4.4%. This higher figure is not only because of referral bias, but also because of the fact that we selectively excluded uncomplicated patients from the study.

The course of illness involves 3 phases-febrile, critical and recovery. Febrile phase last for 2-7 days and is characterized by fever, retro orbital pain, headache, myalgia, arthralgia, nausea, and vomiting. Critical period starts after 3-5 days of fever subsides and patient developed capillary leak, hepatitis, and may leads to DHF. Clinical deterioration often occur in this phase.⁸ The DHF is characterised by haemoconcentration, thrombocytopenia and coagulation abnormalities. The DSS

which is accompanied by narrow pulse pressure or hypotension has grave prognosis. In our study none of the survived patients had DSS at admission whereas 50% died patients had it at admission.

The prominent gastrohepatic manifestation in dengue involves acute abdomen due to hepatitis, acalculous cholecystitis, shock and pancreatitis. Abdominal pain is an early sign of plasma leakage and become more severe as hypovolemia progresses. The commonest involvement of liver is asymptomatic elevation of transaminases but acute liver failure can also occur in severe DF.^{9,10} In our study, transaminases elevation was seen in 85% patients. Interestingly and contrary to what is seen in viral hepatitis, AST elevation was higher than ALT, and AST/ALT ratio was >1 in 87% of patients. This could be due to extrahepatic release of AST. The AST has various sources such as the liver, heart, muscle, erythrocytes, whilst ALT primarily is hepatic in origin. Similar findings were reported by Chung et al in a large series of patients, and it was attributed to be due to release of AST from damaged monocytes.⁽¹¹⁾ All patients who did not survive had massive elevation of transaminases, 85% had levels >100 times UNL, and the median serum AST level was 8791 IU/L which was much higher than the median AST levels in survived patients (138 IU/L). The thrombocytopenia was more severe in patients who died than who survived (table 2). However, neither transaminases nor platelet count at presentation had independent role in predicting mortality. In multivariate analysis only serum bilirubin and serum creatinine were found to be independent predictors of mortality. The best discriminatory cut-off values for serum bilirubin and serum creatinine between died and survived patients were 2.2 mg/dl, and 1.65 mg/dl, respectively. When both poor prognostic markers were present at admission, the mortality rate was 83% with sensitivity of 62%, specificity of 99.4%, PPV 83%, and NPV 98%. Therefore, the presence of jaundice and renal dysfunctions at presentation are ominous signs in patients with dengue.

In conclusion, our study found a high prevalence of hepatitis in hospitalized patients with dengue.

AST elevation was greater than ALT elevation. The mortality in our study cohort was 4.4%, and the presence of jaundice and renal dysfunctions at presentation predicted mortality independently. An obvious limitation of our study is the hospital based observational study, small sample size and restrictive selection of variables predicting mortality. A confirmatory study using larger sample is needed.

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