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ORIGINAL ARTICLE

Prediction of severity of dengue infection in children based on hepatic involvement

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Abstract

Background and Aim: To assess the spectrum of hepatic involvement in children with dengue fever (DF) and prediction of severity of dengue infection by early detection of elevated liver enzymes.

Methods: This prospective observational study was conducted at a tertiary care hospital from June 2019 to September 2019. Children admitted with DF were included. Severity of DF was graded as dengue without warning sign (DNWS), with warning sign (DWS), and severe dengue fever (SDF) according to WHO criteria. Liver injury (LI) was defined as alanine aminotransferase (ALT) more than upper limit of normal irrespective of sex.

Results: Of 190 children (male, 109) with DF, 60 had DNWS, 49 had DWS, and 81 had SDF. A total of 100 children (52.6%) had LI. The distribution of hepatic involvement spectrum involves hepatomegaly (26.3%), hepatic tenderness (25.2%), features of acute liver failure (1.5%), raised level of ALT (52.6%), raised level of aspartateaminotransferase (AST) (65.8%), prolonged prothrombin time (7.3%), and reduced level of serum albumin (44.7%) in children. Of them, 5.8% and 6.8% of children had >tenfold increase in ALT and AST values. The degree of liver function derangement significantly ($P < 0.05$) increased with DF severity. In our study, ALT at 422 IU/L (10 times upper limit of normal [ULN]) and AST 689 IU/L (17 times ULN) had similar sensitivity and specificity as WHO recommended cutoff of 1000 IU/L (25 times of ULN) to detect SDF.

Conclusion: ALT ≥10 times and AST ≥17 times of ULN are as sensitive as ≥25 times (as recommended by WHO) to detect SDF.

Introduction

Nowadays dengue infection, an arthropod-borne viral fever, has become a major challenge to public health. The global picture is becoming alarming. Every year 100 million new dengue cases are detected and more than 2 billion populations are at risk in tropical and subtropical countries.[1] Annual estimation suggests that over 50 million cases are detected as severe dengue that occurs in Asian countries. The case fatality rate is less than 5%. Among them, less than 15 years of age group children are around 90%.[2] By 2080, around 60% of the world's population is anticipated to be at risk of getting dengue fever (DF).[3] Four closely related but serologically distinct dengue viruses (DENV) which belong to the genus *Flavivirus* are DENV-1, DENV-2, DENV-3, and DENV-4. Dengue virus is usually transmitted by *Aedes aegypti* or *Aedes albopictus* mosquitoes and any one of four subtypes causes dengue infection. A mild variety of dengue infections to more severe forms of the disease (dengue hemorrhagic fever [DHF] or dengue shock syndrome [DSS]) can be induced by all subtypes of DENV. But second-time infection by a different DENV type other than the first one can progress to more severe dengue which is labeled as secondary infection.[4]

Most dengue infections are asymptomatic or minimally symptomatic among children.[5]

The clinical manifestation of dengue has a wide range. From a clinical aspect, dengue infection may be symptomless or demonstrate a wide range of clinical pictures including a mild form of febrile illness to fatal DSS. Dengue virus can affect various organs like the liver, kidney, heart, and central nervous system.[6] Unusual clinical pictures of dengue fever have become more evident in recent years and are frequently associated with more serious states.[7] Though the liver is not a major target organ, derangement in liver function is a well-described feature of dengue infection. Dengue-induced hepatic dysfunction may occur as a result of a direct viral effect on liver cells or a detrimental effect of disrupted host immune response against DENV.[8,9] A wide range of hepatic involvement may occur that is characterized by acute hepatitis, right hypochondriac region pain, hepatomegaly, jaundice, and raised aminotransferase levels.[2,9–12] Every

year the number of DENV-infected patients is expanding but published literature is scarce in this particular field among Bangladeshi children. We get a sizeable number of children with DENV infection with unusual manifestations as our hospital is a tertiary care hospital. So the study aimed to observe the spectrum of DENV-related hepatic involvement in the pediatric age group, and also to predict the severity of dengue infection by early detection of elevated liver enzymes.

Methods

This prospective observational study was conducted at a tertiary care hospital during an outbreak of dengue fever from June 2019 to September 2019. All children, aged up to 18 years, admitted with a diagnosis of DF were included in the study. After taking ethical clearance from the institution and informed written consent from parents/guardians, consecutive 190 children were enrolled. Children having fever for 2–7 days duration, with at least one of the following symptoms like bleeding manifestation, rash, or swelling in the absence of cough and cold were initially screened for dengue.

DF was diagnosed in the presence of the following three criteria: (i) probable dengue as suggested by WHO; (ii) either NS1 antigen or DENV-specific immunoglobulin M antibody positive; and (iii) exclusion of other etiology likely to explain the illness, when required. DF severity was graded into dengue without warning sign (DNWS), with warning sign (DWS), and severe dengue fever (SDF) according to WHO criteria. According to WHO, probable dengue is defined as an acute febrile illness in a person who either lived or traveled to a dengue-endemic area with at least two components among the following: vomiting, nausea, rash, pains and aches, leucopenia, and positive tourniquet test. Abdominal pain/tenderness, persistent vomiting, mucosal bleeding, clinical fluid accumulation, lethargy or restlessness, liver enlargement (>2 cm), and an increase in hematocrit with the rapid decrease in platelet count were labeled as warning signs. Severe dengue is defined as the presence of evidence of any of the following three features: (i) severe plasma leakage leading to shock or fluid accumulation with respiratory distress; (ii) features of severe bleeding as judged by a physician; and (iii) severe organ involvement such as liver (suggested by alanine aminotransferase [ALT] or aspartate transaminase [AST] ≥1000 IU/L), central nervous system (suggested by impaired consciousness), heart or other organs. All the children were treated according to the WHO guidelines recommended for the treatment of DF during their course of treatment.[1] Appropriate laboratory tests were done in all children to exclude other etiology of acute febrile illness like enteric fever, malaria, acute hepatitis A virus infection, etc.

A meticulous history and comprehensive physical examination were done in all cases and documentation was done carefully. Following investigations were done in all children: Dengue NS1 antigen, Dengue IgM capture ELISA, hemoglobin level, total leukocyte count, differential leukocyte count, platelet count (PLC), hematocrit (HCT), peripheral blood film, ALT, AST, alkaline phosphatase (ALP), serum bilirubin, serum albumin,

Table 1 Clinical features and outcome in different groups of dengue fever

Parameter	DNWS (60)	DWS (49)	SDF (81)	Total (190)	*P* value
Age in years (mean ± SD)	6.85 ± 3.93	6.86 ± 3.49	7.74 ± 0.042	7.23 ± 3.7	0.279
Fever in days(mean ± SD)	4.47 ± 1.85	4.37 ± 1.32	4.46 ± 1.32	4.44 ± 1.48	0.930
Duration of hospital stay in days (mean ± SD)	4.32 ± 2.02	5.27 ± 2.379	6.30 ± 2.332	5.41 ± 2.39	0.0001†
Vomiting	19	18	38	75	0.169
Pruritus	7	11	11	29	0.255
Diarrhea	6	8	14	28	0.452
Headache	27	18	48	93	0.034†
Rash	10	13	21	44	0.326
Family history	13	12	32	57	0.046†
Ascites	1	2	42	45	0.0001†
Pleural effusion	0	4	44	48	0.0001†
Arthritis	4	4	8	16	0.792
Bleeding manifestation	0	10	17	27	0.001†
Features of carditis	0	0	13	13	0.0001†
Features of shock	0	0	58	58	0.0001†
ALF	0	2	1	3	0.225
Pallor-Mild	12	21	48	81	0.0001†
Moderate	1	7	7	15	
Severe	0	0	1	1	
Hepatomegaly	6	12	32	50	0.001†
Splenomegaly	0	1	8	9	0.014†
Outcome					
Favorable	60	48	77	185	0.185
Adverse	0	1	4	5	

†Significant.

DNWS, dengue without warning sign; DWS, with warning sign; SDF, severe dengue fever.

prothrombin time (PT) with international normalization ratio (INR), activated partial thromboplastin time (APTT), ultrasound abdomen and relevant investigations to exclude other etiology of fever. Serum ALT and AST were preferred as markers of liver injury (LI). LI was defined as ALT more than the upper limit of normal (ULN) irrespective of sex because of its higher specificity for the liver. The cutoff value for ALT and AST was taken at 40 IU/L according to our laboratory value irrespective of sex.

The outcome of the patient was documented as either favorable or adverse. Children discharged in suitable condition had favorable outcomes. Children who either died or taken discharged on parent's request were recorded as having adverse outcomes.

Statistical analysis. Numerical data are presented as mean and SD or median and interquartile range (IQR). Categorical data are expressed as frequency and percentage (%). Continuous or numerical variables between the two groups were compared using Student's *t*-test or the Mann–Whitney *U* test as appropriate. Categorical variables between the two groups were compared using the χ^2 test or Fisher's exact test as appropriate. Receiver operating curves (ROC) were constructed to determine serum ALT and AST levels for the prediction of severe dengue. The area under the ROC (AUROC) was calculated. The cutoff value was determined at the points of highest sensitivity and specificity. A *P* value of <0.05 was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc., Chicago, IL).

Results

A total of 190 (male, 109) admitted serologically confirmed dengue virus-infected children were analyzed for the study. Among them, 60 (31.5%) children were in the DNWS group, 20 (15.2%) children were in the DWS group, and the remaining 81 (42.6%) children were in SDF group. Most of them (103 children, 54.2%) were in the 5–10 years age group. Rest of the children, 47 (24.7%) and 40 (21.1%) were in less than 5 years and more than 10 years age groups, respectively. The mean age of the total participant was 7.23 ± 3.7 years. The mean duration of hospital stay was more in SD group (6.3 ± 2.33 days) which was statistically significant (*P* value 0.0001). Table 1 shows the clinical parameters in different groups of dengue fever. Fever was present in all children (100%) and mean duration was 4.44 ± 1.48 days. Vomiting, pruritus, diarrhea, and rash were seen in 75 (39.4%), 29 (15.2%), 28 (14.7%), and 44 (23.1%) children, respectively. Headache was more common in the SD group which was statistically significant between the three groups. 57 (30%) children had a history of other family members affected with DF simultaneously and among them, 56.1% were in the SD group which was statistically significant. Pallor, ascites, pleural effusion, bleeding manifestation, feature of carditis, features of shock, hepatomegaly, and splenomegaly were present in 97 (51%), 45 (23.6%), 48 (25.2%), 27 (14.2%), 13 (6.8%), 58 (30.5%), 50 (26.3%), and 9 (4.7%) children, respectively. All these parameters are statistically significant in SD group. Among three (1.5%) children who developed acute liver failure, two children were in the DWS group (one child died) and one in the SD

Table 2 Hematological and biochemical parameters in different groups of DF

	DNWS (*n* = 60)	DWS (*n* = 49)	SDF (*n* = 81)	Total (*n* = 190)	*P* value
Hemoglobin (gm/dL)	11.683 ± 1.05	10.563 ± 1.17	10.877 ± 1.60	11.051 ± 1.41	0.0001†
Total leukocyte count (×10^6/L)	5802.17 ± 2639.22	5868.37 ± 2914.39	6390.99 ± 49	6070.26 ± 3869.03	0.616
Platelet count (×10^9/L)	94 383.33 ± 50 710.58	56 500 ± 39 333.78	56 264 ± 49 289.74	68 362.63 ± 50 380.54	0.0001†
Hematocrit %	36.40 ± 2.88	35.19 ± 4.72	36.39 ± 4.42	36.09 ± 4.09	0.211
ALT (IU/L)	58.25 ± 76.55	166.04 ± 337.27	215.30 ± 544.84	153 ± 401.16	0.068
AST (IU/L)	74.30 ± 86.45	270.76 ± 670.32	253.11 ± 610.4	201.19 ± 530.73	0.080
PT (s)	11.68 ± 1.105	12.98 ± 3.47	13.01 ± 3.11	12.59 ± 2.82	0.013
INR	1.068 ± 1.33	1.190 ± 0.34	1.317 ± 1.36	1.21 ± 0.91	0.293
Albumin (mg/dL)	3.745 ± 0.57	3.574 ± 0.60	3.599 ± 3.28	3.636 ± 2.25	0.924
Na + (mmol/L)	136.10 ± 3.72	134.50 ± 2.74	136.30 ± 4.33	135.97 ± 3.94	0.616
K+(mmol/L)	4.39 ± 0.63	4.21 ± 0.53	3.92 ± 0.88	4.09 ± 0.79	0.280
Calcium (mg/dL)	8.31 ± 0.80	7.64 ± 0.80	7.53 ± 1.89	7.78 ± 1.47	0.440
Creatinine (mg/dL)	0.481 ± 0.18	0.614 ± 0.15	0.685 ± 0.54	0.613 ± 0.41	0.436

†Significant.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DNWS, dengue without warning sign; DWS, with warning sign; SDF, severe dengue fever.

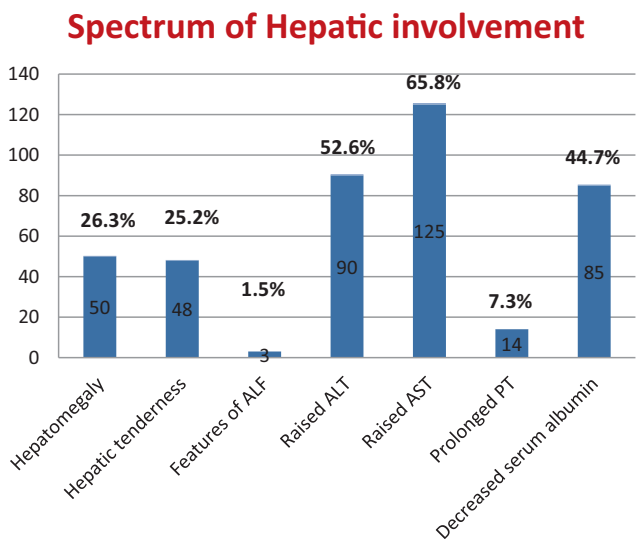

Figure 1 Spectrum of hepatic involvement in dengue fever. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time.

group. Five (2.6%) children had adverse outcomes. Among them, three children died (DWS 1, SD 2) and two children were discharged on request (DWS 1, SD 1). Table 2 shows hematological and biochemical parameters in different groups of DF. Low hemoglobin levels and low platelet count were more evident in DWS and SD groups that were statistically significant. Mean ALT, AST, PT, and serum albumin values were 153 IU/L, 201 IU/L, 12.5 s, and 3.4 mg/dl. Out of 190 children, 100 children (52.6%) had LI. The distribution of the hepatic involvement spectrum is hepatomegaly 50 (26.3%), hepatic tenderness 48 (25.2%), features of acute liver failure 3 (1.5%), a raised level of ALT 90 (52.6%), a raised level of AST 125 (65.8%), prolonged prothrombin time (PT) 14 (7.3%), and reduced level of serum albumin 85 (44.7%) children (Fig. 1). Of them, 5.8% and 6.8% of children had >tenfold increase in ALT and AST values. The degree of liver function derangement significantly ($P < 0.05$) increased with DF severity (Table 3). WHO recommended cutoff value ≥1000 IU/L had sensitivity and specificity of 6.2% and 97.2%, respectively for ALT, and of 4.9% and 97.2%, respectively for AST for detection of SD. Among the total study population (n, 190), ALT and AST < 1000 IU/L, the area under receiver operating curves for detection of SD were 0.627 (95% CI, 0.545–0.708; $P < 0.05$) for ALT and 0.600 (95% CI, 0.517–0.682; $P < 0.05$) for AST. In our study, ALT at ≥422 IU/L (10 times ULN) and AST ≥689 IU/L (17 times ULN) had similar sensitivity and specificity as WHO recommended cutoff of ≥1000 IU/L (25 times of ULN) to detect SD (Fig. 2).

Discussion

This single-center, prospective study included 190 children diagnosed with DF during an epidemic, June 2019 to September 2019, in Bangladesh. Various degree of liver involvement is well documented in acute dengue infection. In our study, approximately half (51%) of the children developed LI. LI in children

Table 3 Range of aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) elevations in different groups of dengue fever

Parameter	DNWS (60)	DWS (49)	SDF (81)	*P* value
ALT (IU/L)				
<40	41	20	29	
40–400	18	25	46	0.002†
>400	1	4	6	
AST (IU/L)				
<40	30	12	23	
40–400	28	32	52	0.03†
>400	2	5	6	

†Significant.
DNWS, dengue without warning sign; DWS, with warning sign; SDF, severe dengue fever.

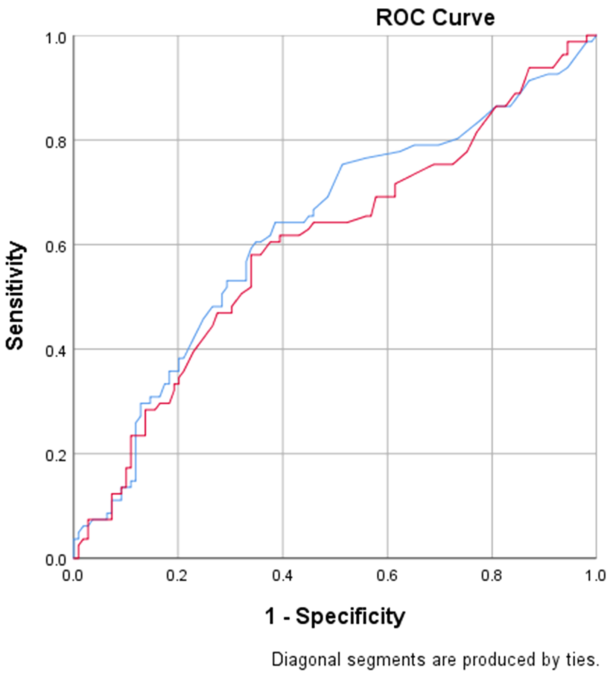

Figure 2 Receiver operating curve (ROC) revealing serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level for prediction of severe dengue. Source of the curve: (——), ALT; (——), AST.

has a wide range which manifests either clinically (hepatomegaly, mild icteric hepatitis) or biochemically (asymptomatic elevation in transaminase levels), or even features of acute liver failure. Hepatomegaly is the commonest feature of hepatic manifestation among children which ranges from 12% to 80%.[12–16] Fifty children (26.3%) had hepatomegaly in our cohort. Among them, 32 children (64%) were in the SD group. Elevated liver transaminases level are frequently observed findings in childhood DF which ranges from 38.7% to 94%.[12,14–16] Our study showed 90 (52.6%) and 125 (65.8%) children had raised levels of ALT and AST, respectively. Like our observation, AST is more markedly raised than ALT in other pediatric studies. The mechanism

is not clearly described. It has been hypothesized that AST has various sources other than the liver like the heart, erythrocytes, and striated muscle, whereas ALT is hepatic in origin. Moreover, the release of AST from damaged myocytes also could explain the higher elevation of AST than ALT in children with acute dengue infection.[17] In our series, mean ALT and AST were 153 IU/L and 201 IU/L. Different pediatric studies showed mean levels of ALT ranged from 52 U/L[12] to 253 U/L[18] and AST from 78 U/L[12] to 415 U/L.[18] Deranged transaminase level is a dominant feature in our study. ALT was increased up to 10 times more than normal in 18 children with DNWS, 25 children with DWS, and 25 children with severe dengue. We also observed ALT more than 10 times of upper limit of normal (one child in the DNWS group, four children in the DWS group, and six children in the SD group). AST elevation showed a similar trend. AST was increased up to 10 times more than normal in 28 children with DNWS, 32 children with DWS, and 52 children with severe dengue. Also, two children with DNWS, five children with DWS, and six children with severe dengue were found to have AST levels more than 10 times of upper limit of normal. Both AST and ALT elevation were increased with severity with a significant *P* value. We found ALT and AST levels more than tenfold rise in 6.1% and 6.8% of children, respectively. Several researchers from different geographical regions found more than 10 times elevation transaminases level in 1.8%, 3.8%, and 11.1% of the pediatric population in their studies.[8,19,20] In our study, eight children (4.2%) had both AST and ALT levels ≥1000 IU/L and all of them were in the SD group. A large pediatric study comprising 372 subjects also observed 4.8% of children had ALT/AST ≥1000 IU/L for defining severe dengue according to WHO guidelines which are similar to our study.[12] We also observed if we reduce the cutoff value to ≥422 IU/L for ALT and ≥689 IU/L for AST, sensitivity and specificity would almost remain the same as the WHO recommended cutoff value of ≥1000 IU/L. Srivastava *et al.*[12] found similar findings to ours, by lowering the cutoff value to ≥376 IU/L for ALT and ≥635 IU/L for AST to define SD. This cutoff value (≥1000 IU/L) is recommended for all age groups. A recent study from Thailand compared LI between children and adults suffering from DF, and revealed higher levels of ALT and AST in adults than children.[21] The exact mechanism of relatively lower levels of transaminases in children than in adults is not known. It can be hypothesized that because of their smaller body size, there may be an insult to a smaller amount of liver tissue mass or a different pathogenic mechanism may be involved to develop LI. From our data, we can suggest lowering the WHO-recommended cutoff value of ALT and AST to define SD for the pediatric age group. Also establishing a separate cutoff value for both ALT and AST for the prediction of the severity of the disease is essential for children.

Dengue-induced acute liver failure is more common in children than adults. The incidence of dengue-associated ALF has shown 14%, 18.5%, and 34.3% in different reported pediatric literature from our subcontinent.[22–24] Our study showed a lower trend of ALF than the reported studies. We found only 1.5% (three children) developed ALF. Among them, two children were in the DWS group (one child died) and one in SD group. A high mortality rate was shown in different studies which ranges from 50% to 68.3%.[7,24,25] One child who developed ALF at presentation (in DWS group), died on the ninth day of hospital stay in our cohort. And the child with ALF in SD group was discharged on request and lost follow-up.

Our study has some limitations. We have enrolled only hospitalized children as study subjects. A single value of aminotransferase level on admission was assessed and repetition of the test was not done. We did not follow up on the children after discharge to see the normalization of liver function test.

In conclusion, dengue-associated LI is frequent in children. Even dengue-associated ALF is not so uncommon. AST is more markedly elevated than ALT in the presence of LI. A significant rise in liver enzymes helps in the recognition of severe DF. ALT ≥10 times and AST ≥17 times of upper limit of normal are as sensitive as ≥25 times (as recommended by WHO) to pick up severe dengue in the pediatric age group.

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