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Original Article

Clinical Spectrum and Risk Factors of Severe Dengue among Hospitalized Patients - A Cross-sectional Study during the 2023 Dengue Epidemic in Bangladesh

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Abstract

Introduction: *Dengue is a significant public health concern for Bangladesh with recurrent epidemics. This study aimed to investigate the clinical and biochemical presentations and identify risk factors for severe dengue among patients admitted to a tertiary care hospital during the 2023 epidemic in Bangladesh.*

Methods: *This cross-sectional study was conducted at a tertiary care hospital in Bangladesh between July and September 2023. Data were collected from 176 adult patients with serologically confirmed dengue infection. Clinical and laboratory parameters were recorded, and severity of dengue was categorized according to WHO guidelines. Logistic regression was performed to identify predictors of severe dengue.*

Results: *Of the 176 patients included, 113 had severe dengue and 63 had non-severe dengue. The mean age was 34.5 (SD 14.3) years, with a male-female ratio of 1:1.07. Conventional symptoms including fever, myalgia, headache, and retro-orbital pain were present in majority of patients, with warning signs present in two-thirds of them. Laboratory findings showed leukocytopenia (53%), thrombocytopenia (25.6%), elevated hematocrit level (4.5%), elevated ALT,AST and ferritin level (36%, 24% and 50% respectively). Logistic regression identified persistent vomiting (aOR 3.22, 95% CI 1.41–8.04), clinical fluid accumulation (aOR 2.23, 95% CI 1.13–5.74), and elevated serum AST (aOR 3.13, 95% CI 1.30–7.79) as predictors of severe dengue.*

Conclusion: *Most dengue cases presented with typical symptoms and warning signs, with associated laboratory abnormalities. Persistent vomiting, clinical fluid accumulation, and elevated serum AST levels upon admission could predict severe dengue.*

Keywords: *Severe dengue, Epidemic, Clinical presentation, Bangladesh*

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Introduction

Dengue is a mosquito-borne febrile disease caused by Dengue virus (DENV), a single-strand RNA virus of the genus Flavivirus, usually spread by *Aedes aegypti* [1]. It is one of the major global health concerns, especially for the lower and middle-income countries of southeast Asia, sub-Saharan Africa, and Latin America affecting more than 390 million people with a number of approximately 40,000 deaths annually [2,3]. Moreover, almost half of the global population living in these areas are at risk of dengue infection[4].

In Bangladesh, which is geographically located within the endemic belt of dengue fever in Southeast Asia, the disease was historically present in a sporadic fashion since mid-twentieth century[5]. The country witnessed its first large scale outbreak of dengue during the year 2000 with a number of 5,521 confirmed cases and 92 deaths[6]. Subsequently, recurrent epidemics occurred in this country, almost annually. Though the initial epidemics were concentrated in the capital city of Dhaka, the recent ones have expanded beyond this geographic limitation, affecting populations across the entire country[7]. Recently, in 2023, Bangladesh encountered a large-scale nationwide epidemic of dengue with approximately

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280,000 confirmed dengue cases and 1,408 confirmed deaths[8].

Dengue infection can present with a varying range of clinical manifestations from self-limiting febrile illness to a potentially fatal dengue hemorrhagic fever or dengue shock syndrome. Classical presentations of dengue infection include fever, arthralgia, myalgia, retro-orbital pain, and rash. Some of the patients also manifest with gastrointestinal disorders (e.g. abdominal pain, diarrhea and vomiting), respiratory symptoms (e.g. cough and respiratory distress) and mucosal bleeding (e.g. sub-conjunctival hemorrhage, petechiae, epistaxis, malena etc.) along with some altered laboratory parameters including increased hematocrit, reduced platelet count, and abnormal liver function tests[8-13]. A small proportion of patients also develop severe complications of dengue including severe plasma leakage and shock, severe hemorrhage and expanded dengue syndrome[8, 12, 14].

Management of dengue cases during an outbreak is a challenge for the resource-limited and non-resilient healthcare setting of Bangladesh[15]. The World Health Organization (WHO) introduced a comprehensive dengue classification in 2009 guideline for more convenient clinical management and it has set a rational approach for early prediction of severe dengue, triage, and management of patients based on clinical and laboratory parameters[1]. Despite the fact, it was observed that the hospitals of the country surged with a large portion of potentially non-complicated cases during the outbreaks who could be managed with less intensive follow up in outpatient settings[8, 12, 13].

In this context, understanding the spectrum of clinical and laboratory parameters of the patients with severe and non-severe dengue would be beneficial for early identification of the patients at risk for development of severe dengue infection. This can help in reducing admission and economic burden on health care facilities of the low-risk patients. Hence, the present study aimed to investigate the clinical and biochemical presentations as well as to identify the risk factors of severe dengue among the patients admitted in a tertiary care hospital during the dengue epidemic in 2023.

Materials and Methods

This cross-sectional study was conducted between July and September 2023 at the Department of Medicine of Shaheed Suhrawardy Medical College Hospital. A total of 176 adult patients with serologically confirmed diagnosis of dengue infection who were admitted during the study period were included in the study. The inclusion criteria for this study were (i) patients presenting with clinical criteria of dengue fever and (ii) confirmed dengue viral infection as defined by positive tests for either dengue specific NS1 antigen or IgM antibody upon admission. Patients with mixed infections (simultaneous infection by other organisms such as Plasmodium or the Chikungunya virus along with DENV) or females who were pregnant were excluded from the study.

All the potential patients were screened for inclusion and exclusion criteria and gave consent, clinical history was taken examined thoroughly, and the findings were recorded in the case report form. Other Laboratory investigations, including complete blood count, serum albumin, serum ferritin, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) etc. were requested within 48 hours of admission and repeated based on clinical requirements.

The severity of dengue was categorized in according to the WHO's 2009 classification as non-severe and severe dengue during discharge or upon death of the patient[1]. Patients with non-severe dengue were then categorized into two groups depending on the presence or absence of warning signs. All patients with dengue in our study received standard care according to WHO guidelines.

A confirmed diagnosis of dengue viral infection was established based on the presence of acute fever along with a combination of two or more of the following symptoms: headache, retro-orbital or ocular pain, myalgia, arthralgia, rash, a positive tourniquet test (defined as the presence of >20 petechiae per 1 inch^2), or leukopenia (defined as a white blood cell count of 5,000 cells/mm^3), coupled with a positive result from either specific dengue NS1 antigen testing (if the blood sample was obtained within six days of symptom onset) or IgM antibody testing (if the blood sample was obtained after six days of symptom onset) via enzyme-linked immunosorbent assay (ELISA) conducted on serum samples upon admission[1].

Non severe dengue without warning signs was defined as having acute fever with at least two of the following criteria: headache, myalgia, arthralgia, nausea, vomiting, rash, a positive tourniquet test, or leukopenia. Warning signs included abdominal pain or tenderness, persistent vomiting (vomiting with signs of dehydration); clinical fluid accumulation; bleeding from mucosal areas including the nose, gums, gastrointestinal tract, or vagina; lethargy; restlessness; liver enlargement of more than 2 cm; and increased hematocrit (>20%) concurrent with a rapid decrease in platelet count (<100,000 platelets/mL)[1].

Severe dengue was defined as having (i) severe plasma leakage, defined as plasma leakage with shock or respiratory

distress (respiratory rate 24 breaths/minute with oxygen saturation ,95% in room air and/or requiring oxygen therapy); (ii) severe clinical bleeding, defined as spontaneous bleeding from mucosal areas that necessitated a blood transfusion; or (iii) severe organ involvement, defined as AST >1,000 IU/L and/or ALT >1,000 IU/L, serum creatinine levels two times or more above baseline, myocarditis, and/or encephalitis[1].

All statistical analyses were conducted by using STATA version 17.0 (StataCorp LLC, College Station, TX). Both descriptive and inferential statistics were used. Continuous variables were presented as mean and standard deviation (SD), whereas categorical variables were presented as frequency with percentages. Clinical and laboratory parameters for the severe and non-severe dengue patients were compared using the x^2 test, Fisher's exact test or independent t-test as appropriate. A logistic regression model was constructed including the variables which were significant in bivariate analysis to determine the risk factors of developing sever dengue. Statistical significance level was set at p-value <0.05.

Results

The mean age of participants was 34.5 (SD 14.3) years with a male-female ratio of 1:1.07 without any significant difference between patients with severe and non-severe dengue. Majority of the patients (89.20%) hailed from urban areas and more than two-thirds of them belonged to middle-income families. Hypertension was the most prevalent comorbidity among these patients (19%) followed by type 2 diabetes mellitus (10%), and coronary artery disease (2.3%). The distribution pattern of comorbidities was similar in both severe and non-severe group of patients (Table 1).

Table 1. Sociodemographic characteristics of patients with dengue (n = 176)

Characteristics	Overall, n = 176	Severe dengue, n = 113	Non-severe dengue, n = 63	p-value
Age	34.47 (14.32)	33.54 (13.31)	36.14 (15.95)	0.322
Sex				0.15
Male	85 (48.30)	50 (44.25)	35 (55.56)	
Female	91 (51.70)	63 (55.75)	28 (44.44)	
Marital status				0.988
Married	137 (77.84)	88 (77.88)	49 (77.78)	
Unmarried	39 (22.16)	25 (22.12)	14 (22.22)	
Religion				0.288
Islam	165 (93.75)	105 (92.92)	60 (95.24)	
Hinduism	10 (5.68)	8 (7.08)	2 (3.17)	
Others	1 (0.57)	0 (0.00)	1 (1.59)	
Occupation				0.424
Service holder	34 (19.32)	22 (19.47)	12 (19.05)	
Business man	23 (13.07)	14 (12.39)	9 (14.29)	
Housewife	71 (40.34)	45 (39.82)	26 (41.27)	
Student	33 (18.75)	25 (22.12)	8 (12.70)	
Farmer	1 (0.57)	0 (0.00)	1 (1.59)	
Day labourer	2 (1.14)	1 (0.88)	1 (1.59)	
Unemployed	4 (2.27)	1 (0.88)	3 (4.76)	
Others	8 (4.55)	5 (4.42)	3 (4.76)	
Socioeconomic status				0.143
Low	37 (21.02)	22 (19.47)	15 (23.81)	
Middle	118 (67.05)	81 (71.68)	37 (58.73)	
High	21 (11.93)	10 (8.85)	11 (17.46)	
Residence				0.008
Urban	157 (89.20)	106 (93.81)	51 (80.95)	
Rural	19 (10.80)	7 (6.19)	12 (19.05)	
Comorbidities				
Hypertension	18 (10.23)	14 (12.39)	4 (6.35)	0.205
Diabetes	33 (18.75)	26 (23.01)	7 (11.11)	0.053
Coronary artery disease	4 (2.27)	3 (2.65)	1 (1.59)	>0.999
Others	2 (1.14)	2 (1.77)	0 (0.00)	0.538

Conventional symptoms such as fever, myalgia, headache, and retro-orbital pain were present in majority of patients without any significant difference with severe and non-severe dengue. Two-thirds of the patients were presented with warning signs, among which, abdominal pain was most commonly presented (48%) followed by diarrhea (33%), persistent vomiting (27%) and hepatomegaly (14%). Besides, signs of clinical fluid accumulation were present in 25% of the patients (ascites 20.5% and pleural effusion 14%) while manifestations of mucosal bleeding were present in 21.6% of the patients. Persistent vomiting and signs of clinical fluid accumulation were more commonly present among the patients with severe dengue ($p<0.05$) compared to non-severe dengue (Table 2).

Among the hematological parameters, leukocytopenia was most commonly observed (53%) followed by thrombocytopenia (25.6%) and raised hematocrit level (4.5%). On the other hand, altered biochemical parameters like raised serum ALT and AST level was observed in 36%, 24% of the patients respectively while reduced serum albumin and raised serum ferritin level was observed in almost half of the patients. Among these parameters, raised serum ALT and AST level, reduced serum albumin and raised serum ferritin level were associated with severe dengue($p<0.05$) (Table 3).

Table 2. Clinical presentations of patients with dengue (n = 176)

Clinical presentations	Overall, n = 176	Severe dengue, n = 113	Non-severe dengue, n = 63	p-value
Fever	153 (86.93)	100 (88.50)	53 (84.13)	0.410
Myalgia	125 (71.02)	78 (69.03)	47 (74.60)	0.434
Headache	96 (54.55)	60 (53.10)	36 (57.14)	0.605
Retro-orbital pain	35 (19.89)	19 (16.81)	16 (25.40)	0.171
Warning signs				
Abdominal pain	84 (47.73)	51 (45.13)	33 (52.38)	0.356
Diarrhea	56 (33.14)	34 (31.19)	22 (36.67)	0.469
Persistent vomiting	48 (27.27)	39 (34.51)	9 (14.29)	0.004
Hepatomegaly	25 (14.20)	15 (13.27)	10 (15.87)	0.636
Clinical fluid accumulation				
Ascites	36 (20.45)	20 (17.70)	16 (25.40)	0.225
Pleural effusion	25 (14.20)	12 (10.62)	13 (20.63)	0.068
Any fluid accumulation	44 (25.00)	35 (30.97)	9 (14.29)	0.014
Mucosal bleeding	38 (21.59)	22 (19.47)	16 (25.40)	0.360
Any warning sign	112 (63.64)	75 (66.37)	37 (58.73)	0.312

Table 3. Laboratory parameters of patients with dengue (n = 176)

Laboratory parameters	Overall, n = 176	Severe dengue, n = 113	Non-severe dengue, n = 63	p-value
Hemoglobin (g/dL)	12.73 (1.99)	12.64 (1.89)	12.77 (2.04)	0.705
Leukocyte ($10^3/mm^3$)	5.63 (2.97)	5.87 (3.15)	5.46 (2.86)	0.380
Platelet ($10^3/mm^3$)	76.02 (69.42)	88.67 (90.11)	69.01 (53.92)	0.675
Hematocrit (%)	38.07 (6.16)	37.24 (6.77)	38.51 (5.79)	0.414
Serum ALT (U/L)	89.78 (87.92)	75.27 (73.03)	97.92 (94.61)	0.027
Serum AST (U/L)	117.20 (140.12)	75.63 (64.80)	139.56 (163.13)	<0.001
Serum albumin (g/dL)	3.43 (0.53)	3.60 (0.61)	3.34 (0.46)	0.002
Serum ferritin (μg/L)	2,051.70 (2,769.97)	1,951.43 (3,676.75)	2,108.09 (2,113.70)	0.004

Table 3. Laboratory parameters of patients with dengue (n = 176) *(Cont'd)*

Laboratory parameters	Overall, n = 176	Severe dengue, n = 113	Non-severe dengue, n = 63	p-value
Hemoglobin (g/dL)				0.592
<12	108 (61.36)	37 (58.73)	71 (62.83)	
≥12	68 (38.64)	26 (41.27)	42 (37.17)	
Leukocyte (/mm^3)				0.291
<5,000	94 (53.41)	37 (58.73)	57 (50.44)	
≥5,000	82 (46.59)	26 (41.27)	56 (49.56)	
Platelet (/mm^3)				0.078
<100,000	45 (25.57)	21 (33.33)	24 (21.24)	
≥100,000	131 (74.43)	42 (66.67)	89 (78.76)	
Hematocrit (%)				0.713
≤48	168 (95.45)	61 (96.83)	107 (94.69)	
>48	8 (4.55)	2 (3.17)	6 (5.31)	
Serum ALT (U/L)				0.015
≤42	113 (64.20)	33 (52.38)	80 (70.80)	
>42	63 (35.80)	30 (47.62)	33 (29.20)	
Serum AST (U/L)				<0.001
≤42	134 (76.14)	39 (61.90)	95 (84.07)	
>42	42 (23.86)	24 (38.10)	18 (15.93)	
Serum albumin (g/dL)				
<3.5	88 (50.00)	25 (39.68)	63 (55.75)	0.041
≥3.5	88 (50.00)	38 (60.32)	50 (44.25)	
Serum ferritin (ìg/L)				0.010
<1500	89 (50.57)	40 (63.49)	49 (43.36)	
≥1500	87 (49.43)	23 (36.51)	64 (56.64)	

In the logistic regression model, having persistent vomiting and symptoms of clinical fluid accumulation on admission were predictors of severe dengue (aOR 3.22, 95% CI 1.41, 8.04, p-value 0.008 and aOR 2.23, 95% CI 1.13, 5.74, p-value 0.018 respectively). Besides, among the laboratory parameters, raised serum AST was a predictor of severe dengue (aOR 3.13, 95% CI 1.30, 7.79, p-value 0.012) (Table 4).

Table 4. Predictors of developing severe dengue (logistic regression models)

Variables	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Persistent vomiting	3.16 (1.47, 7.46)	0.005	3.22 (1.41, 8.04)	0.008
Clinical fluid accumulation	2.69 (1.24, 6.38)	0.017	2.23 (1.13, 5.74)	0.018
Serum ALT (>42 U/L)	2.20 (1.16, 4.20)	0.015	1.16 (0.51, 2.56)	0.723
Serum AST (>42 U/L)	3.25 (1.60, 6.73)	0.001	3.13 (1.30, 7.79)	0.012
Serum albumin (<3.5 g/dL)	1.92 (1.03, 3.61)	0.042	1.68 (0.84, 3.38)	0.145
Serum ferritin (≥1500 µg/L)	2.27 (1.21, 4.33)	0.011	1.61 (0.80, 3.26)	0.183

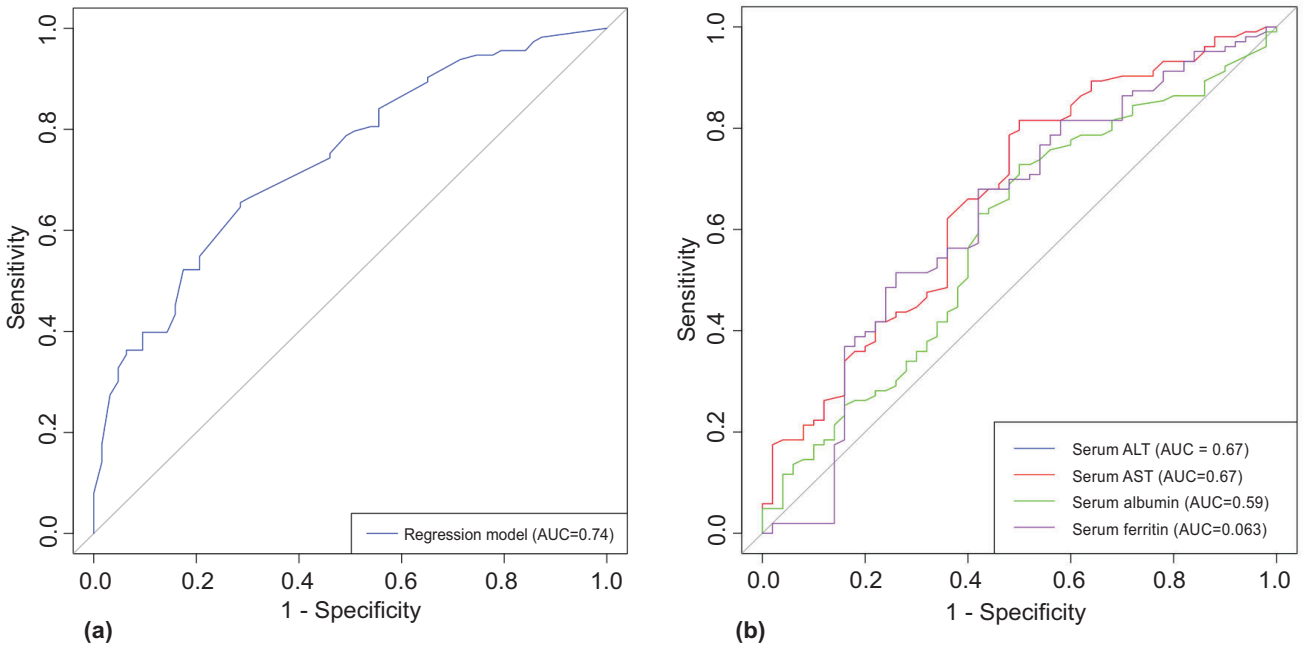

Figure 1: ROC analysis for logistic regression model and individual laboratory parameters for prediction of severe dengue

Figure 1(a) demonstrated the ROC curves for the sensitivity and specificity of the logistic regression model for prediction of severe dengue with an AUC of 0.74. On the other hand, figure 1(b) demonstrated the ROC curves for the sensitivity and specificity of different laboratory parameters for prediction of severe dengue with an AUC of 0.67 for serum ALT and AST, 0.59 for serum albumin and 0.63 for serum ferritin.

Discussion

In the present study, we provided an overview regarding the socio-demographic characteristics, clinical presentations and laboratory parameters of the patients diagnosed with severe and non-severe dengue during the epidemic of 2023 in Bangladesh. Moreover, we investigated into the potential early predictors on admission for development of severe dengue during the course of disease.

We found that, majority of our patients were young adults. This trend has been observed in the current as well as previous dengue epidemics in Bangladesh[8,9]. Conventional clinical manifestations like fever, myalgia, headache, and retro-orbital pain were presented commonly irrespective of severity status. A substantial number of patients were presented with warning signs including abdominal pain, diarrhea, persistent vomiting, hepatomegaly, signs of clinical fluid accumulation like ascites and pleural effusion and manifestations of mucosal bleeding. However, no warning signs other than persistent vomiting and clinical fluid accumulation had any significant difference in case of patients with severe and non-severe dengue. In the present study, we included only admitted dengue cases from a tertiary care hospital with a majority of severe cases. Hence, the high prevalence of warning signs was an obvious finding. This phenomenon corroborates with previous studies conducted in similar settings[8,10-13].

We observed that leukocytopenia was present in almost half of the patients while thrombocytopenia and raised hematocrit level was present in around 25% and 4.5% of the patients respectively. Though, prevalence of leukocytopenia was in line with the findings of previous studies from Bangladesh, thrombocytopenia was present in comparatively fewer number of patients in our study[8,10]. According to the recent reports, DEN-2 and DEN-3 serotypes were more prevalent during the epidemics in Bangladesh which are more responsible for plasma leakage rather than thrombocytopenia and dengue hemorrhagic fever which might explain the finding of less prevalence of thrombocytopenia among our patients[16]. Besides, altered levels of liver enzymes like serum ALT and AST were present in almost one-third of the patients which also coincide with the findings of previous studies[8,10,12].

From the present study, we found that presence of persistent vomiting and signs of clinical fluid accumulation as well as raised serum AST level on admission could predict severe dengue in further course of disease. Multiple studies

described these factors as significant predictors of dengue severity[17-20]. Also, these studies had identified some other warning signs like abdominal pain, raised hematocrit value, thrombocytopenia etc. as the predictors of severe dengue infection. Besides, we also explored another potential biomarker for prediction of severe dengue, serum ferritin level, as suggested by several studies[21,22]. However, though we found that patients with severe dengue had a higher level of serum ferritin compared to those with non-severe dengue, in regression model, it could to draw any statistically robust inference (AUC 0.63).

Our study had several limitations. Firstly, we exclusively included hospitalized cases of dengue from a tertiary care facility which resulted in inclusion of large number of severe cases which could limit the generalizability of our findings. Confirmation of dengue infection in the present study relied on clinical manifestations and serological assays, excluding advanced techniques like reverse transcription–polymerase chain reaction for viral RNA detection or DENV serotyping. Consequently, we were unable to determine the specific serotype of the dengue virus responsible for the infection. Furthermore, the impact of hydration and volume expansion on hematocrit levels may have obscured the accurate assessment of hematocrit levels in our patients.

Conclusions

Majority of the patients with dengue presented with conventional symptoms like fever, myalgia, headache, and retro-orbital pain as well as warning signs like abdominal pain, diarrhea, persistent vomiting and hepatomegaly irrespective of severity. Commonly presented altered laboratory parameters were leukocytopenia, thrombocytopenia, raised serum ALLT and AST levels, reduced serum albumin and raised serum ferritin level. Persistent vomiting, clinical fluid accumulation and raised serum AST on admission were predictors of severe dengue.

Declarations

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