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Clinical profile and early severity predictors of dengue fever: Current trends for the deadliest dengue infection in Bangladesh in 2022

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ABSTRACT

Objectives: In 2022, Bangladesh had the highest dengue-related fatality (281). This study evaluated clinical profiles to detect early changes to predict dengue fever severity.

Methods: This prospective observational study was performed in four government hospitals from June to November 2022 in Dhaka. Febrile patients admitted within 4th day of illness were recruited if they had a confirmed dengue viral infection either by by positive dengue nonstructural protein antigen or anti-dengue immunoglobulin (Ig)M antibody.

Results: We divided 308 patients with confirmed dengue into two groups: 232 (74.3%) in nonsevere dengue and 76 (24.7%) in severe dengue. Men were 205 (66.6%), and the most affected age group was 21-30 years (47.7%). Patients with severe dengue reported a higher number of nausea 80.3%, coughs 57.9%, abdominal pain 56.6%, persistent vomitting 53.9%, dyspnea 35.5%, diarrhea 28.9%, and skin rash at 27.6%. In addition, the disease's febrile phase (≤4 days) showed thrombocytopenia (odds ratio [OR] 6.409, 95% CI 2.855-14.386, p <0.001), hemoconcentration (OR 3.428, 95% CI 1.030-11.405, p 0.045), and hypotension (OR 5.896, 95% CI 1.203-28.897, p 0.029) were associated severe disease.

Conclusions: Hypotension, thrombocytopenia, and hemoconcentration during the febrile phase might indicate progression towards severe disease.

Introduction

Between January 01 and December 31, 2022, there were 62,382 dengue cases, including the highest number of 281 related deaths in Bangladesh's history of dengue fever reported by the Ministry of Health & Family Welfare (MOHFW) [1]. Since 2000, the highest number of cases recorded in 2019, 101,354 people diagnosed with the disease, and 164 fatalities [2]. Dengue virus (DENV) transmits to humans through the bite of an *Ades aegypti* or *A. albopictus* containing any of four strains of DENV (DENV1, DENV2, DENV3, DENV4). Since 2019, DENV3 has been the predominant strain; however, a recent investigation in Chattogram, Bangladesh's port city, found DENV4. Contrary to previously reported in Bangladesh, DENV4 was the most prevalent single DENV serotype infection at 41%, followed by DENV2, DENV1, and DENV3 at 25%, 22%, and 13%, respectively [3,4].

"Dengue fever," called "Break-bone fever," is the most common acute systemic viral infection transmitted by arthropods. It is brought on by DENV, which is a type of virus that belongs to the family *Flaviviridae*. Because of the year-round frequency of two mosquito vectors—*Aedes aegypti* and *A. albopictus*—dengue fever is an endemic disease in several countries [5]. *A. aegypti* thrives in densely populated metropolitan areas, whereas *A. albopictus* prefers less densely populated areas. Because of local temperature shifts, fast industrialization, and parallel circulation of numerous DENV serotypes simultaneously, Bangladesh has one of the biggest dengue loads in the world [5,6].

After the first official dengue outbreak in 2000, throughout the decade, several outbreaks occurred with increasing cases each year: 2430 cases (2001), 6232 (2002), 3934 (2004), 3162 (2015), 6060 (2016), and 10,148 (2018). In 2020, amidst the pandemic, 1405 cases of dengue confirmed cases were reported by the authority of Bangladesh [7,8]. Within the ongoing COVID-19 third wave, Bangladesh recorded 28,429 overall cases for 2021, with documented deaths of 105 patients [9].

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Our study highlighted the clinicopathological profiles of the admitted patients in four tertiary care hospitals in Dhaka. Moreover, we aimed to detect early changes in parameters, both clinical and hematologic, to predict the severity of dengue fever.

Methods

Study design

This prospective observational study was conducted at Dhaka City's four public hospitals between June 2022 and November 2022. Dhaka was the critical location affected by the dengue epidemic that began in 2022.

Study sites

The inpatient departments of the following four tertiary care government hospitals in Dhaka City were used for this study: (a) Bangabandhu Sheikh Mujib Medical University, (b) Dhaka Medical College, (c) Sir Salimullah Medical College Hospital, (d) Mugda Medical College Hospital. These hospitals are located in the urban part of the Dhaka District and have high-dependency units (HDUs) and intensive care units (ICUs).

Study population

Within the four tertiary institutions that participated in the study, 308 hospitalized patients with dengue were recruited between June and November 2022. All the patients were diagnosed with dengue fever after testing positive for either the nonstructural protein (NS1) antigen or the anti-dengue immunoglobulin (Ig)M antibody. On a uniform case report form, vital clinical and laboratory information was meticulously documented consistently for every hospitalized patient. During a comprehensive clinical examination, the vital signs, skin rashes, pleural effusion, shortness of breath, ascites, hepatomegaly, etc., were among the symptoms that were looked for.

Inclusion and exclusion criteria

Hospitalized patients were recruited as a presumptive dengue fever within the first 4 days of sickness if they had an oral temperature of at least 100.4°F, lived in a dengue-endemic area with at least two of the following: nausea/vomiting, rash, aches/pain, positive tourniquet test, leukopenia, or any warning signs [10]. After recruitment, dengue infection was confirmed by a positive result for either NS1 dengue antigen if the blood sample was taken within 5 days of the onset of fever or IgM antibody if the blood sample was acquired after the 6th day of symptoms utilizing serum samples. Presumptive patients with dengue who were negative for both NS1 antigen or IgM antibody or developed another secondary infection were excluded from the study. Informed written consent was taken for all participants, except for minors (age <18 years), where informed written consent was taken from the legal guardian (parents).

Laboratory test for dengue infection

The enzyme-linked immunosorbent test (ELISA) technique was used to identify the NS1 antigen, anti-dengue IgM, and IgG antibodies for diagnosis. Dengue fever was detected using DENV DetectTM NS1 ELISA Kit (Sensitivity and Specificity: 86.6 % positive percent agreement (PPA) and 97.8 % negative percent agreement (NPA)) (InBios International, Inc., USA) and DENV DetectTM IgM/IgG ELISA Kit (InBios International, Inc., USA). NS1 antigen, anti-dengue IgM, and IgG were interpreted as positive or negative reports only. Other laboratory tests include a complete blood count (using a Sysmex XN-2000TM Hematology Autoanalyzer manufactured by Sysmex Corporation). A required complete blood

count was taken during the febrile period (4 days) to establish a baseline complete blood count (CBC) profile and detect early alterations. It was repeated to track the changes in hematocrit (Hct) and platelet count daily until discharge or death. An anti-dengue IgG antibody was done to see evidence of secondary infection. In addition, other reports of serum alanine transaminase (ALT), serum aspartate aminotransferase (AST), serum creatinine, ultrasonography (USG) of the abdomen, urine routine and microscopy study were collected from the patient's hospital profile. The severity of dengue was categorized during discharge or death according to the World Health Organization's 2009 classification as Group A, Group B, and Group C. Group A includes patients having dengue fever without warning signs, Group B includes dengue fever with warning signs, and Group C includes severe dengue fever (severe plasma leakage, severe bleeding, severe organ involvements) [10]. Groups A and B are combined into the nonsevere group, and Group C is labeled the severe group.

Data collection

Three licensed physicians performed physical examinations and extracted the patient's clinical information from patient profiles. Patients were monitored until discharge or until they died. Clinical characteristics and laboratory indicators were obtained using a structured questionnaire by pretrained registered physicians. The laboratory-based cutoff levels for each investigation's results on reference ranges.

Statistical analyses

SPSS (IBM version 28.0) was used to do statistical analysis. Clinical and laboratory parameters among different groups were compared with the chi-square or Fisher's exact tests, for numerical variables, and independent t test, as applicable for continuous variables. Multivariable logistic regression was done to detect the risk factors and early clinical and hematologic parameter change for developing severe dengue. All tests were interpreted as statistical significance with $p < 0.05$.

Result

Baseline characteristics of dengue cases

At the outset, we enrolled 350 individuals with suspected dengue fever. However, we had to eliminate 42 patients from the study because their NS1 antigen or anti-dengue IgM antibody tests returned negative or because they had confirmed infection with another disease. Finally, 308 hospitalized patients had a confirmed dengue fever that was verified by serology. Patients were enrolled in our study between July 2022 and November 2022, corresponding to the height of the dengue outbreak in 2022. We separated the 308 patients who had dengue fever into two groups: 232 (74.3%) of them had nonsevere dengue (Groups A and B), while 76 patients (24.7%) were diagnosed with severe dengue fever (Group C). In total, 262 of 308 patients had positive dengue NS1 antigen tests, which accounts for 85.1% of the total, and 46 of the patients, which accounts for 14.7% of the total, had positive dengue-specific IgM antibody tests. There was a total of 249 reports that were accessible for anti-dengue IgG antibody testing; 44 (14.3%) of these reports were positive in the overall cohort, and 19 (23%) of these reports were in the severe category (p 0.01). A total of 205 patients were male, with 59.2% and 69% of patients from severe and nonsevere groups, respectively. The most vulnerable age range was between 21 and 30 years (47.7% in total and 39.5% in severe). In the severe group, the mean age was 34.09 (16.6) years, while 30.09 (12.1) years were in the nonsevere group (p 0.02). A total of 79.9% of patients were residents of metropolitan areas, while the remaining 20.1% were from either semi-urban or rural areas. In terms of comorbidities, 115 patients, or 37.3% of the total, were found to have at least one, with 35 patients (46.05%) coming from the severe group and 80 patients (34.4%) coming from the nonsevere

Table 1
Baseline characteristics of the patients.

Characteristics	Total n (%) [n = 308]	Severe dengue n (%) [n = 76 (24.7%)]	Nonsevere dengue n (%) [n = 232 (74.3%)]	p-value[a]
Age (years), mean (SD)		34.09 (16.6)	30.09 (12.1)	0.02
Age category (years)				
12-20	32 (10.4)	8 (10.5)	24 (10.3)	
21-30	147 (47.7)	30 (39.5)	117 (50.4)	
31-40	69 (22.4)	21 (27.6)	48 (20.7)	
41-50	34 (11)	6 (7.9)	28 (12.1)	
51-60	17 (5.5)	5 (6.6)	12 (5.2)	
>60	9 (2.9)	6 (7.9)	3 (1.3)	
Sex				
Male	205 (66.6)	45 (59.2)	160 (69)	0.12
Domicile				
Dhaka	246 (79.9)	49 (64.5)	197 (84.9)	
Outside Dhaka	62 (20.1)	27 (35.5)	35 (15.1)	
Comorbidities (Yes)	115 (37.3)	35 (46.05)	80 (34.48)	0.07
DM	29 (9.4)	12 (15.8)	17 (7.3)	0.03
HTN	36 (11.7)	15 (19.7)	21 (9.1)	0.01
MACE	10 (3.2)	7 (9.2)	3 (1.3)	0.001
CPD (BA/COPD)	9 (2.9)	3 (3.9)	6 (2.6)	0.54
CLD	1 (0.3)	1 (1.3)	0	0.08
CKD	9 (2.9)	5 (6.6)	4 (1.7)	0.03
Malignancy	3 (1)	2 (2.6)	1 (0.4)	0.09
Obesity	84 (27.27)	23 (30.26)	61 (26.29)	0.08
Dengue NS1 Antigen				
Positive	262 (85.1)	62 (81.6)	200 (86.2)	
Anti-dengue IgM Ab				
Positive	46 (14.7)	14 (18.4)	32 (13.8)	
Anti-dengue IgG Ab				
Positive	44 (14.3)	19 (23)	25 (10.8)	0.01

Ab, antibody; BA, bronchial asthma; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CPD, chronic pulmonary disease; DM, diabetes mellitus; HTN, hypertension; Ig, immunoglobulin; MACE, major adverse cardiovascular events; NS1, nonstructural protein 1.

[a] Chi-squared test was done.

group (p 0.07). In the severe category, obesity was the most common comorbidity, affecting 30.3% of patients (p 0.08), followed by 19.7% who had hypertension (p 0.01), while 15.8% were diabetic (p 0.03) (Table 1).

Clinical profile of patients with dengue

We documented the patient's clinical features since the beginning of the illness. Fever was found in 100% of the cases, followed by body aches in 72.1%, nausea in 67.9%, vomiting in 63.6%, headache in 62%, and joint pain in 26%. Among other symptoms, cough was present in 41.2%, dyspnea in 16.9%, sore throat in 5.2%, diarrhea in 25.6%, and jaundice in 3.2% of the patients. Among the warning signs, abdominal pain 50.3% was most common, followed by persistent vomiting 37%, and diarrhea was documented in about 79 (26%) instances. Epistaxis and melena 5.2% for each, were the most common clinical presentations, followed by gum bleeding 3.9%, hematuria 2.3%, hematemesis 2.3%, hemoptysis 1.3%, hematochezia 1.3%, vaginal bleeding 1%, and melena with hematemesis both were present 1.6% of the cases. Hematemesis, hematochezia, melena, and hematemesis were present only in severe dengue cases. Patients with severe dengue also reported a higher number of joint pain 26.3% (p 0.91), cough 57.9% (p <0.001), dyspnea 35.5% (p <0.001), abdominal pain 56.6% (p 0.21), nausea 80.3% (p 0.008), vomiting 76.3% (p 0.008), diarrhea 28.9% (p 0.45), and skin rash 27.6% (p 0.001). Severe organ involvement was found in 22 (7.1%), all severe dengue cases. Among these, the most common were pneumonia 2.3%, followed by hepatitis 1.6%, pancreatitis 1.3%, neurologic involvement 0.6%, and cardiac involvement 0.6% of the cases. (Table 2). Two reported neurologic involvement included Guillain-Barré syndrome (GBS) and meningitis; both cardiac involvements were myocarditis.

Hematologic, biochemical, and radiological parameters of dengue cases during the critical period

On hematologic parameters, the overall mean (±SD) of platelet count was $71 \times 10^9/l$ (±59.7); the mean was lower, $49.6 \times 10^9/l$ (45.9) in the severe group (p 0.001). Total leucocyte count (mean ± SD) was $5.9 \times 10^9/l$ (3.6) in the entire cohort and the lowered mean found in the nonsevere group was $5.7 \times 10^9/l$ (3.0) (p 0.07). The mean Hct was 40.2% (±6.8) in the overall cohort, with a lowered mean in the severe group of 39.2% (9.5) (p 0.15). In severe dengue cases, the rise of Hct was observed in 36.8% of cases, whereas the fall of Hct was in 31.6% of cases, having a p value of 0.003 and 0.001, respectively. Leucopenia ($<4 \times 10^9/l$) was observed in 36.7% of instances overall, having almost similar distribution among severe and nonsevere cases (p 0.56). Severe thrombocytopenia ($<50 \times 10^9/l$) occurred more in the severe group, 61.8% of the patients (p 0.04). Regarding liver function tests, ALT and AST reports were available in 157 and 52 patients, respectively. The total cohort mean (± SD) serum ALT was 153.7 International Units Per Liter (IU/l) (±284) and for serum AST 376 IU/L (±846). The mean was higher in the severe group, ALT 273 IU/L (500) and AST 637 IU/L (1229), with a *P*-value of 0.001 and 0.04, respectively. Serum creatinine reports of 175 patients were available where the mean (±SD) was 1.39 mg/dl (±1.6) with 2.1 mg/dl (±2) in the severe dengue group (p 0.001). Overall, raised serum creatinine (>1.3 [mg/dl]) was observed in 36 (20.6%) patients, among them 17 (35.4%) in severe and 19 (15%) in nonsevere groups (p 0.003). Proteinuria was found in 16 (5.2%) cases of 141 available urinary samples and was higher in severe dengue group 10 (3.2%) (p 0.001). Of the available 112 patient's USG of the abdomen and lower chest, evidence of fluid leakage was found in 55 (49.1%) patients; among them, the severe group had 35 (53%) patients and 20 (43.4%) in nonsevere (p 0.32). In the USG profile, concomitant ascites and pleural effusion were the most common finding in 8.1% of the cases, followed by only pleural effusion in 6.5% and only ascites in 3.2% of

Table 2
Clinical presentations.

Characteristics	Total n (%)	Severe dengue n (%)	Nonsevere dengue n (%)	p-value
Fever	308 (100)	76 (100)	232 (100)	-
Headache	191 (62)	44 (57.9)	147 (63.4)	0.39
Body ache	222 (72.1)	53 (69.7)	169 (72.8)	0.6
Joint pain	80 (26)	20 (26.3)	66 (25.9)	0.91
Cough	127 (41.2)	44 (57.9)	83 (35.8)	<0.001
Dyspnea	52 (16.9)	27 (35.5)	25 (10.8)	<0.001
Abdominal pain	155 (50.3)	43 (56.6)	112 (48.3)	0.21
Nausea	209 (67.9)	61 (80.3)	148 (63.8)	0.008
Vomiting	196 (63.6)	58 (76.3)	138 (59.5)	0.008
Diarrhea	79 (25.6)	22 (28.9)	57 (24.6)	0.45
Skin rash	42 (13.6)	21 (27.6)	21 (9.1)	<0.001
Sore throat	16 (5.2)	3 (3.9)	13 (5.6)	0.57
Jaundice	10 (3.2)	7 (9.2)	3 (1.3)	<0.001
Persistent vomiting	114 (37)	41 (53.9)	73 (31.5)	<0.001
Bleeding Manifestation				
Gum bleeding	12 (3.9)	4 (5.3)	8 (3.4)	0.01
Epistaxis	16 (5.2)	6 (7.9)	10 (4.3)	0.009
Per vaginal bleeding	3 (1)	3 (3.9)	-	
Melena	16 (5.2)	13 (17.1)	3 (1.3)	0.001
Hematuria	7 (2.3)	6 (7.9)	1 (0.4)	0.001
Hemoptysis	4 (1.3)	3 (3.9)	1 (0.4)	0.001
Hematemesis	7 (2.3)	7 (9.2)	-	
Hematochezia	4 (1.3)	4 (5.3)	-	
Melena + Hematemesis	5 (1.6)	5 (6.6)	-	
Severe organ involvement	22 (7.1)	22 (28.9)	-	
Neurologic involvement	2 (0.6)	2 (2.6)	-	
Cardiac involvement	2 (0.6)	2 (2.6)	-	
Pancreatic involvement	4 (1.3)	4 (5.3)	-	
Pulmonary involvement	7 (2.3)	7 (9.2)	-	
Liver involvement	5 (1.6)	5 (6.6)	-	

Table 3
Hematological, biochemical, and radiological parameters during critical period.

Characteristics	Total n (%)	Severe dengue n (%)	Nonsevere dengue n (%)	p-value
Hematological, mean (SD)				
Hct %	40.2 (6.8)	39.2 (9.5)	40.5 (5.6)	0.15
Leucocyte count (cells $\times 10^9$/l)	5.9 (3.6)	6.6 (4.9)	5.7 (3.0)	0.07
Platelet count (cells $\times 10^9$/l)	71 (59.7)	49.6 (45.9)	78.9 (61.9)	0.001
Biochemical parameters, mean (SD)				
Serum ALT (IU/l), n = 157	153.7 (284)	273 (500)	107 (94)	0.001
Serum AST (IU/l), n = 52	376 (846)	637 (1229)	169 (126)	0.04
Serum Creatinine (mg/dl), n = 176	1.39 (1.6)	2.1 (2)	1.2 (1.1)	0.001
Categorical data				
Rise of Hct >45, n (%)	75 (24.3)	28 (36.8)	47 (20.2)	0.003
Fall of Hct <35, n (%)	53 (17.3)	24 (31.6)	29 (12.5)	0.001
Leucocyte count (≤4000), n (%)	113 (36.7)	30 (39.4)	83 (35.7)	0.56
Platelet count (≤50,000), n (%)	156 (51.1)	47 (61.8)	112 (48.3)	0.04
Serum ALT (> 45 [IU/l]), n = 157	117 (75)	35 (79.5)	82 (73.2)	0.41
Serum AST (> 45 [IU/l]), n = 52	49 (15.91)	21 (91.3)	28 (96.6)	0.51
Serum Creatinine (>1.3 [mg/dl]) n = 176	36 (20.6)	17 (35.4)	19 (15)	0.003
Proteinuria, n = 141	16 (5.2)	10 (3.2)	6 (2.6)	0.001
Fluid leakage (ultrasonogram)	55 (49.1)	35 (53)	20 (43.4)	0.32
n = 112				
Only Ascites	10 (3.2)	4 (5.3)	6 (2.6)	
Only Pleural effusion	20 (6.5)	15 (19.7)	5 (2.2)	
Ascites + pleural effusion	25 (8.1)	16 (21.1)	9 (3.9)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hct, hematocrit.

the cases. The nonsevere group consists of Group B, where evidence of fluid leakage can be found, thus increasing the number of patients with fluid leakage (Table 3).

Febrile period (≤ 4 days of illness) parameters and known risk factors associated with severe dengue

Multivariable logistic regression showed febrile phase parameters (≤4 days), high Hct (odds ratio [OR] 3.428, 95% confidence interval [CI] 1.030-11.405, p 0.045), hypotension (OR 5.896, 95% CI 1.203-28.897, p 0.029), thrombocytopenia (OR 6.409, 95% CI 2.855-14.386, p <0.001) were significantly associated with the development of severe dengue fever. Other known comorbidities, hypertension (OR 2.019, 95% CI 0.734-5.54, p 0.173), overweight (OR 4.688, 95% CI 0.949-23.147, p 0.058), diabetes mellitus (DM) (OR 2.179, 95% CI 0.740-6.419, p 0.015), anti-dengue IgG (+ve) (OR 1.673, 95% CI 0.761-3.681, p 0.201) showed higher OR but only DM was statistically significant in our study (Table 4).

Table 4
Severity risk factors for dengue with early markers during febrile period (≤4 days).

Risk factors	Odds ratio	Confidence interval	p-value[a]
High hematocrit ≤4 days of illness	3.428	1.030-11.405	0.045
Hypotension ≤4 days of illness	5.896	1.203-28.897	0.029
Thrombocytopenia ≤4 days of illness	6.409	2.855-14.386	<0.001
Hypertension	2.019	0.734-5.54	0.173
Overweight	4.688	0.949-23.147	0.058
Diabetes mellitus	2.179	0.740-6.419	0.015
Anti-dengue immunoglobulin G (+ve)	1.673	0.761-3.681	0.201

[a] Multivariable logistic regression analysis was done.

Table 5
Outcome of patients.

Characteristics	Total n (%)	Severe dengue	Nonsevere dengue	p-value
Death, n (%)	13 (4.2)	13 (17.1)		
Intensive care unit admission, n (%)	7 (2.3)	7 (9.2)		
Duration of hospital (days), mean (SD)	4.9 (2.1)	6.5 (3)	4.3 (1.5)	0.001

Outcome of patients

The mean hospital stay duration of the patients was 4.9 (±2.1) days. Most of the patients recovered well and were discharged. A total of 27 (8.8%) patients required the transfusion of blood products. Among them, 22 (7.1%) were transfused with platelet concentrations, four required whole blood (1.3%), and one patient (0.3%) required red cell concentrate. ICU admission was required for seven (2.3%) cases, all of which belonged to the severe group. A total of 13 (4.2%) case fatalities were reported, all with severe dengue infection among them, five patients died in ICU (Table 5).

Discussion

In our prospective observational study, we have included 308 patients with confirmed dengue serology during the peak wave of 2022's dengue epidemic from July to November. There was a clear predominance of male patients 66.6% and young age (21-30 years) group, 47.7% of the total cohort. This difference between men and women is consistent with the previous dengue outbreak of 2019 (64.11% men vs 35.89% women), supported by other studies conducted in Bangladesh [11] and in Saudi Arabia [12]. Our study shows the highest number of cases (47.7%) belong to the 21-30-year-old group, among them, severe dengue occurred in 39.5%. The mean (±SD) age for severe dengue was 34.09 (±16.6) years, and it was statistically significant (p 0.02). In Bangladesh, Rahman et al. [13] and Mahmood et al. [11] recorded the highest proportion of cases in the 18-33 and 20-40 age groups, respectively. Also, El-Gilani et al. [12] found that the most affected dengue age group in Saudi Arabia was between 16-44 years. Toledo et al. [6] demonstrated in a meta-analysis, that older age was related to severe disease, our investigation showed that dengue severity was high among the young. One possible explanation is that the maximum patients recruited were young, while only nine (2.9%) patients were more than 60 years old. Therefore, most severe dengue cases belong to the young age group.

Our study showed at least one comorbidity was present in 35 patients in the severe (46.05%) and in nonsevere group 80 patients (34.4%) (p 0.07). However, hypertension (19.7%) and DM (15.8%), major cardiovascular adverse events (MACE) (9.2%), and chronic kidney disease CKD (6.6%) were significantly associated with disease severity (p 0.01, 0.03, 0.001, 0.03; respectively). Different systematic reviews and meta-analyses support these findings of comorbidities related to disease severity [6,14].

Since 2010, atypical symptoms have become the rule [15]. Our investigation illustrates the diverse clinical presentation of dengue fever. As in previous research from India and Bangladesh, we observed that fever (100%) was the most common presenting symptom [16,17]. Followed by body aches (72.1%) and headaches (62%), similar to studies from Saudi Arabia [12]. Gastrointestinal symptoms were greater, with abdominal pain occurring in 50.3%, nausea in 67.9%, vomiting in 63.66%, and diarrhea in 25.6% of the study population. DENV-mediated liver damage could be responsible for nausea, vomiting, and abdominal pain [18]. In the current study, cough (41.2%) and dyspnea (16.9%) were the most prevalent respiratory symptoms associated with dengue, however, 8.1% of patients had combined pleural effusion and ascites, lower than study conducted in India (11%) (2013) [19], but higher than a 2019 study from Bangladesh (1.8%) [15], although later found fluid leakage evidence as per clinical examination, unlike ours where we documented by ultrasonographical evidence, which, might explain the differences. The rest of our cohort's clinical manifestations and laboratory profiles were similar to previous dengue epidemics in Bangladesh [15,20,21]. Cough, dyspnea, jaundice, persistent vomiting, and mucosal bleeding were significantly associated with severe dengue fever during the 2022 outbreak, which differed from the 2019 outbreak [7].

Hematologic parameters showed that thrombocytopenia was most common, and 51.1% of patients had platelet counts below 50×10^9/l; this parameter was most significantly related to severe dengue infection (61.8%). In Bangladesh, Pakistan, and India, thrombocytopenia is patients' most prevalent hematologic anomaly [11,22]. Dengue fever causes thrombocytopenia by a process that is caused by bone marrow depression and the degradation of peripheral platelets; however, the specific origin of this condition is not yet understood [23]. Leukopenia was the second most prevalent hematologic finding in the present investigation, occurring in 36.7% of patients, roughly similar to the findings of Mahmood et al. [12]. In keeping with the findings of Humayoun et al. [22], our investigation revealed greater Hct and raised AST and ALT levels, mainly in the severe dengue group. We have also observed a lower Hct (<35%) among 31.6% in the critical period of the disease. Renal involvement had been remarked in terms of raised creatinine (>1.3 [mg/dl]) and proteinuria. Among 175 available samples, 20.6% of cases had elevated creatinine, primarily in the severe dengue group (35.4%) (p 0.003). Consistent with the findings of Vasanwala et al. [24], proteinuria was detected in 5.2% of the 141 urine samples and 3.2% of the severe dengue group (p 0.001). The etiopathogenesis of dengue fever-induced kidney injury has been hypothesized to be caused by several different mechanisms, some of which include the virus's direct activity, hemodynamic instability, rhabdomyolysis, hemolysis, and acute glomerular injury. These mechanisms can act independently or in combination [25].

Patients who have dengue can potentially develop a condition known as localized plasma leakage, which is characterized by fluid accumulation in the pleural and abdominal cavities and hemoconcentration

around the time of defervescence [26]. In the severe group, we observed three early clinical and hematologic parameters changes during the febrile period (≤ 4 days) of illness: thrombocytopenia (OR 6.409), hemoconcentration (OR 3.428), and hypotension (OR 5.896). One possible explanation can be due to the secondary dengue infection of 23% of the severe patients, as evidenced by positive anti-dengue IgG ab positivity, although an IgG/IgM ratio would confirm the secondary infection [27]. If an infecting serotype of DENV binds to a previously formed antibody from a different serotype, the antibody-dependent condition worsens dramatically because of the release of various proinflammatory cytokines during this period. These cytokines include tumor necrosis factor, interleukin (IL)-6, IL-8, and various chemokines. This, in turn, leads to greater viral replication, which in turn leads to increased permeability and the potential for more severe disease [26,28].

This research has several drawbacks. An important drawback of the study was the missing data from supporting investigations, such as AST, ALT, serum creatinine, serum albumin, and USG profiles. Also, information was lost on multiple clinical profiles, including symptoms such as itching, retroorbital pain, conjunctival congestion, etc. We did not routinely perform any chest x-rays or echocardiography on patients with cough/dyspnea. Only high clinical suspicion was raised to further the possibility of investigation to exclude cardiac causes or other infections. Furthermore, the total number of children was relatively small. In addition, the exclusion of outpatient patients with dengue and the selection of patients from a particular geographical region, even though it was a dengue-endemic region, may not be representative of the overall population. We could not assess the ratio of IgG/IgM anti-dengue antibodies to confirm secondary dengue cases. The serological test confirmed dengue, although reverse transcriptase polymerase chain reaction to detect viral RNA and DENV serotyping was not performed.

Conclusion

Countries with few resources, such as Bangladesh, face formidable challenges regarding the clinical management of many patients during an epidemic. Identifying individuals at risk for developing severe diseases requires greater clinical and primary laboratory surveillance. This study found that younger age groups are more susceptible to severe dengue infection, and DM is the most common comorbidity associated with severe disease. During the febrile phase, an early drop in blood pressure, a decrease in platelets, and an increase in Hct have higher odds of a patient's deterioration and developing severe dengue. Despite its limitations, the study provides evidence of clinical and hematologic profiles for early severity prediction and profiles of current trends of dengue in Bangladesh.

Declarations of competing interests

The authors have no competing interest to declare.

Author contributions

CAS: Study design, Data analysis, and writing the original draft. RT: Data collection, data analysis, writing the original draft. SSH: data collection. AHK: supervision, design, RY: manuscript preparation, MMZ: manuscript review, MAS: data analysis, manuscript review, SMA: concept, design, supervision. All authors read and approved the manuscript.

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Ethical approval

Participants or their legal guardians (younger than 18) explained in detail the purpose and nature of the study. Before enrollment, in-

formed and understood written consent was taken from every participant. Ethical approval was taken from the "Institutional Review Board" of BSMMU. Being an observational study, it entailed no additional risk to the patients. All research data were coded and kept confidential. Each patient was given a unique ID no to safeguard confidentiality and anonymity. All the information collected from the patients, including the laboratory test results, was kept confidential under the principal investigator's responsibility.

Data sharing

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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