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Clinical spectrum and risk factors of severe dengue infection: findings from the 2023 dengue outbreak in Bangladesh

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Abstract

Background Since the first detection of dengue in 2000, Bangladesh has been facing an increasing number of dengue patients and related deaths every year. This situation warrants the importance of quickly identifying severe dengue patients to expedite necessary medical interventions which could potentially reduce the adverse consequences. The aim of this study was to identify clinical features and laboratory parameters of the severe dengue patients in the 2023 dengue outbreak in Bangladesh.

Methods This hospital based cross-sectional study included the demographic, clinical and laboratory data of 1313 Dengue patients from several secondary and tertiary hospitals across Bangladesh from August 2023 to December 2023. According to the 2009 WHO classification, dengue cases were classified into severe dengue and non-severe dengue (with and without warning signs). Chi-square test, Fischer's exact test and multiple logistic regression analyses were conducted to identify potential risk factors associated with severe dengue cases.

Results Of the 1313 patients included in this study, nearly 20% had severe dengue, 36.71% of them were from the 16–25 year age bracket and nearly two-thirds were male. Fever (99.54%) was the most common clinical symptom followed by anorexia (69.54%) and severe headache (66.03%); whereas most common warning signs were severe lethargy (43.64%), persistent vomiting (27.57%), and severe abdominal pain and tenderness (20.03%) across all patients. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are significantly more common in severe dengue cases compared to non-severe ones. Among the laboratory parameters, decrease of platelet level and increased ALT level was more prominent in severe patients. Multiple logistic regression analysis found that severe abdominal pain, severe lethargy, respiratory distress, altered mental status, decreased urine output, pleural effusion and ascites were positively associated with the development of severe dengue.

Conclusion This study presents warning signs, clinical symptoms and trends of laboratory parameters associated with severe cases of dengue in Bangladesh that can be used in improving patient management in the future.

Keywords Dengue, Outbreak, Bangladesh, Dengue fever

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Introduction

Dengue is a mosquito-borne disease that is heavily endemic in tropical and subtropical regions, with its increasing prevalence placing nearly half of the world's population at risk [1]. The dengue virus (DENV), a member of the Flaviviridae family, transmitted by Aedes mosquitoes, is the cause of dengue fever. It is reported in more than 100 countries, with 400 million cases and 22,000 deaths worldwide each year [2]. DENV is a positive-stranded RNA virus with four serotypes (DENV-1 to DENV-4) separated antigenically from each other [2]. Although each dengue virus serotype provides long-lasting immunity against the same serotype by producing virus-neutralizing antibodies, protection against other serotypes is partial or short-lasting. Cross-reactive antibodies can accelerate DENV entry into host cells during secondary infection, contributing to antibody-dependent enhancement (ADE) [2]. The complex interplay between virus, host genes, and immune responses significantly affects disease pathogenicity [2, 3]. The severity of the dengue infection depends on hyperactivation of T helper 2 (Th2) cells, which causes disproportionate cytokine production and results in a cytokine storm. Moreover, excessive cytokine upregulates the production of free radicals, which can increase plasma permeability with severe plasma leakage [2, 3]. Researchers have concluded that secondary dengue infection is more likely to result in dengue hemorrhagic fever or dengue shock syndrome than primary dengue infection. It has been established that ADE in secondary dengue infection can cause a high degree of viremia while also suppressing the activation of antiviral responses, significantly affecting the severity of dengue [3]. Clinically severe dengue is identified as a dengue patient with signs and symptoms suggestive of severe plasma leakages, such as severe bleeding and severe organ involvement, as per the World Health Organization's (WHO) 2009 dengue guideline [4].

Being one of the most dangerous mosquito-borne viral diseases, dengue is endemic to Latin American and Caribbean countries along with South-East Asia. According to the WHO, from 2015 to 2019, the number of dengue cases in Southeast Asia increased by 46%, and this region bears more than half of the world's burden of dengue [5]. Bangladesh saw its first dengue outbreak almost two decades ago, in 2000, and is currently one of the major dengue-endemic countries in Asia [6–8]. In recent years, the fatality ratio (0.37–0.50) of dengue in Bangladesh (2020–2023) has been higher than that of any other dengue-endemic country in Latin America and Southeast Asia [9, 10]. Bangladesh faced a major epidemic of DENV in 2019, followed by a heterogenic pause; there was another significant upsurge in 2022–2023, with a record number of fatalities [9]. Although dengue is common in Bangladesh, the same pattern of DENV surge has not been observed in neighboring India or other Southeast Asian countries. In India, Malaysia, and Vietnam, dengue fatality is decreasing from 2021 to 2023, and Bangladesh and the Philippines are seeing an increase in the fatality ratio [9]. This warrants further investigation of recent dengue outbreaks to prevent their spread and limit severe dengue with the appropriate usage of healthcare services in resource-limited settings.

Understanding clinical features and its trends of dengue is critical. While primary dengue infection is typically asymptomatic or causes mild illness, severe or secondary infection can result in hemostatic dysfunction and multi-organ failure. The presence of symptoms also aids clinicians in distinguishing between the different phases of dengue infection, which include febrile, critical, and convalescent or recovery. Sudden high-grade fever and dehydration are present during the febrile phase, and rash, itching, and increased appetite are present during the recovery phase [2].

Dengue infection has been classified into three categories by the WHO in its most recent clinical classification: dengue without warning signs, dengue with warning signs, and severe dengue. This classification based on dengue signs and symptoms is essential as it helps clinicians decide where and how to observe and treat patients [4]. As dengue symptoms are often very similar to febrile illnesses, it became essential to identify dengue in resource limited rural endemic areas [11]. For instance, researchers in Taiwan have developed a dengue diagnosis scoring tool based on clinical features to estimate dengue infection with 79.7–88.1% sensitivity and 68.0–94.9% specificity, minimizing urgent need of laboratory tests for decision making [12].

A meta-analysis published by Tshten et al. reported that age, secondary infection, comorbidities such as diabetes, renal disease, increased hematocrit, decreased platelets along with warning signs such as abdominal pain, lethargy, vomiting, hepatomegaly, ascites, pleural effusion, and melena are strongly associated with the severe dengue infection [13]. Furthermore, several systematic reviews have presented that clinical features of vomiting, abdominal pain, spontaneous mucosal bleeding, and presence of clinical fluid accumulation are significantly related to severe dengue [14, 15]. During the 2019 dengue outbreak in Bangladesh, vomiting, respiratory distress, plasma leakage (low platelets) and hemorrhage (bleeding manifestations) were significantly associated with severe dengue in adult and pediatric patients [16, 17]. In 2022, according to Sami et al., severe dengue patients had a high frequency of nausea, cough, abdominal pain, persistent vomiting, respiratory distress, diarrhea, and skin rash [18].

The aim of this study is to investigate the 2023 dengue outbreak in Bangladesh, present the signs and symptoms of severe dengue infection compared to non-severe dengue, and identify potential risk factors for developing severe dengue infection in Bangladesh.

Materials and methods

Study setting and data source

This hospital-based cross-sectional study was conducted at selected secondary and tertiary hospitals in Bangladesh. All data were collected from patients diagnosed with dengue infection from inpatient (dedicated dengue wards) and outpatient departments of two tertiary and one secondary hospital in these divisions [19]. Data collection started in August 2023 and ended in December 2023, the most critical period of dengue infection transmission, given the highest number of cases recorded in this time frame for the past several years in Bangladesh [20, 21]. All the hospitals were public hospitals funded by the government of Bangladesh [19]. The study sites in two major Bangladesh divisions (Dhaka and Chittagong) cover 40.21% of the national population, according to the Population and Housing Census 2022 by the Bangladesh Bureau of Statistics [22]. Ethical clearance was collected from the institutional review board of Chittagong Medical College (Memo no. 59.27.0000.013.19. PG.2023.009.288).

Data collection

Data were collected through face-to-face interviews with dengue patients or their parents upon receiving written informed consent. The clinical data were assessed and included in medical records. The data collection team members, comprised of experienced medical doctors and students, questioned the patients. The dengue patients' symptoms, warning signs, and comorbidities were gathered by asking open-ended questions and reviewing clinical notes. The case record form contained a detailed list of possible symptoms developed by researchers after a literature review of the recently published articles [23, 24]. The questionnaire used in this was simultaneously utilized for data collection in several other studies to investigate the separate outcomes of the same dengue outbreak [25, 26]. The team members followed up with individuals till 10/14th day from the onset of the first symptoms (day 1) to confirm the severity of dengue as per existing guidelines of the WHO adopted by the Directorate General of Health Services (DGHS), Bangladesh [4, 27].

Laboratory tests

People who tested positive for Nonstructural NS1 Antigen and or IgM for dengue during the first 7 days of symptom onset with clinical symptoms suggestive of dengue were included in the study, as in dengue-endemic countries, these two diagnostic tests are used primarily [28, 29]. Since the study area is within resource limited settings with limited capability to perform positive reverse transcriptase–polymerase chain reaction (RT-PCR) and enzyme linked immunosorbent assay (ELISA) in all suspected patients, rapid diagnostic tests (RDTs) such as immunochromatographic (ICT) assays to detect dengue NS1 and IgM were also considered in selecting study participants. For the majority of the study participants, RDT using SD Bioline ® rapid immunochromatographic test kit (SD Bioline, Abbott Diagnostics, Korea) were performed according to the protocol provided. However, a wide range of commercially available RDT kits were used for a limited number of participants who needed their tests result out of hours.

According to recent systematic review published in 2022, the cumulative sensitivity and specificity of the various ICT tests used in dengue endemic area for detecting NS1 antigen were 70.97% and 94.73% respectively during the acute phase. Similarly for IgM the sensitivity and specificity of ICTs were 40.32% and 93.01% respectively [30]. Another study from Dhaka, Bangladesh found that the dengue NS1 ICT test has a sensitivity of 68.29%, a specificity of 100%, and an accuracy of 83.95% when compared to the NS1 ELISA test [31]. It is important to highlight that NS1 and IgM antibodies are less sensitive to secondary dengue than primary dengue [32, 33]. However, given the magnitude of the 2023 outbreak, this study did not distinguish between primary and secondary dengue infections. Furthermore, IgM can test positive after other flavivirus infections such as Zika, yellow fever, and tick-borne encephalitis but can still be classified as probable dengue following the current guidelines (Supplementary Table 1) [34].

Routine hematological investigations such as complete blood count (CBC) and alanine transferase (ALT) tests were done at the tertiary centers during their hospital stay using automated blood and biochemistry analyzer. To maintain uniformity and accuracy, laboratories utilized standard operating procedures and uniform methods for sample collection, handling, and processing. Biochemical markers were graded as febrile, critical, or recovery phase during the first three days, between the fourth and seventh days, and after the seventh day of symptom onset, respectively.

Case definitions

Before the 2009 WHO dengue classification, dengue was clinically divided into undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever (DHF), while DHF was further classified into four different grades I, II, III & IV. Grade III & IV DHFs were labeled as dengue shock

syndrome [4]. However, this classification confused diagnosing clinically severe dengue patients with DHF [35]. Later, with prospective multi-center studies across dengue endemic zones by WHO, dengue patients were classified as non-severe and severe dengue in 2009 [4]. A set of clinical and laboratory parameters named "warning signs" were used to further divide non-severe dengue into those with warning signs and those without warning signs. Warnings signs were abdominal pain and tenderness, persistent vomiting (> 3 times/day), persistent diarrhea (> 3 times/day), severe prostration, severe lethargy, respiratory distress, liver enlargement, altered mental status, and decreased urine output [4].

This study categorized the dengue patients into non severe and severe dengue combined with 2009 WHO dengue guideline and 2018 revised dengue clinical management guideline published by the Directorate General of Health Services in Bangladesh [4, 27]. Severe dengue cases were defined as severe plasma leakage (resulting in shock, fluid accumulation, and respiratory distress), severe bleeding (as evaluated by treating clinicians), severe organ involvement (such as acute renal failure, acute liver failure, encephalopathy or encephalitis, cardiomyopathy, or other unusual manifestations), and laboratory findings of organ damage (such as ALT or AST > 1000, raised creatinine, etc.). For the purposes of our research, we have combined the first two groups into non-severe dengue. Those who were diagnosed with a concurrent infection with Zika virus, Chikungunya virus, or Typhoid fever were excluded from the study. Participants who did not provide written informed consent were also excluded. The detailed case definition for dengue applied to the present study is provided in Supplementary Table 1.

Inclusion and exclusion criteria

This study includes the hospitalized patients of all ages with confirmed or probable dengue infection diagnosed by suggestive sign, symptoms and confirmatory tests mainly by ELISA, RT-PCR or RDT methods. Patient demographics, laboratory test and disease progression over their period of hospitalization were collected. Patients with serology tests suggesting chronic infection (positive IgG but negative IgM and or negative NS1) or coinfection with Zika, Typhoid and Chikungunya were excluded from the study. Additionally, those who declined to provide consent were omitted (Supplementary Table 1).

Statistical analysis

Sociodemographic variables were examined using the chi-square or fischer's exact test to identify significant differences in dengue severity categories. Age and gender-adjusted multiple logistic regression analyses were performed to risk factors of severe dengue infection as a dichotomous dependent variable while symptoms, warning signs, comorbidities, bleeding manifestations, and clinical fluid accumulations as independent variables. Stata/SE version 15.1 was used for statistical analysis [36].

Results

Demography of the study respondents

In this study, 1313 people with dengue fever were interviewed, and the average and median age of all respondents were 29.49 years and 26 years, respectively. While young patients (16–25 years old) were the most common (36.71%, $n = 482$), followed by middle-aged (26–40 years old) (32.67%, $n = 429$), nearly two-thirds (66.64%, $n = 875$) of the total study participants were male.

Over one-third (36.48%, $n = 479$) have completed or are presently pursuing primary school, followed by the Secondary School Examination Level (22.77%, $n = 299$). Only 54 (4.11%) patients had finished a postgraduate (masters/PhD) degree. Almost one-third (32.22%, $n = 423$) of our study participants worked as service providers, while 17.44% ($n = 229$), 17.36% ($n = 228$), and 15.84% ($n = 208$) were housewives, unemployed, and students, respectively. Most dengue patients (41.89%, $n = 550$) had a monthly family income of less than 20,000 BDT (182.38 USD as of 1st August 2023), and 34.73% ($n = 456$) had a family income of 20,000 to 35,000 BDT (182.38 to 319.20 USD) (Table 1) [37].

Symptomatic presentation

From Fig. 1, Fever (99.54%, $n = 1307$), Anorexia (69.54%, $n = 913$) & Severe headache (66.03%, $n = 867$) were the three most common symptoms of dengue fever. However, gastrointestinal symptoms such as vomiting (62.2%, $n = 158$ vs 50.05%, $n = 530$) and diarrhea (34.65%, $n = 88$ vs 28.33%, $n = 300$) were significantly more common in severe dengue cases compared to non-severe dengue. Contrarily, severe headache (68.08%, $n = 721$) and joint pain (7.37%, $n = 78$) were significantly more common in non-severe dengue patients (Supplementary Table 2). Mouth soreness (9.75%, $n = 128$), rash (9.75%, $n = 128$), and joint pain (6.63%, $n = 87$) were the least three symptoms that present in dengue, with less than 10% frequency.

Warning signs and comorbidities

Severe lethargy (43.64%, $n = 573$), persistent vomiting (27.57%, $n = 362$), and severe abdominal pain and tenderness (20.03%, $n = 263$) were the overall three most common warning signs presented in our study participants. All the warning signs were comparatively more common

Table 1 Demographic distribution of the study participants

Characteristics	Categories	Frequency (%)
Age	Mean (SD)	29.49 (± 14.49)
	Median (IQR)	26 (20–36)
Age Category	0–15 years	154 (11.73)
	16–25 years	482 (36.71)
	26–40 years	429 (32.67)
	41–60 years	205 (15.61)
	above 60 years	43 (3.27)
Gender	Female	438 (33.36)
	Male	875 (66.64)
Religion	Islam	1107 (84.31)
	Hindu	187 (14.24)
	Buddhist	19 (1.45)
Educational Status	Never been to school	110 (8.38)
	Primary	479 (36.48)
	SSC	299 (22.77)
	HSC	220 (16.76)
	Bachelor/Hons	151 (11.5)
	Masters/PhD	54 (4.11)
Occupation	Farmer	10 (0.76)
	Driver	15 (1.14)
	Retired	17 (1.29)
	Business	156 (11.88)
	Student	208 (15.84)
	Unemployed	228 (17.36)
	Housewife	229 (17.44)
	Service	423 (32.22)
	Others	27 (2.06)
Marital Status	Married	713 (54.3)
	Never married	573 (43.64)
	Separated/Divorced	2 (0.15)
	Widow/widower	25 (1.9)
Family income	< 20 K BDT (< 182.38 USD)	550 (41.89)
	20 K- < 35 K BDT (182.38—< 319.20 USD)	456 (34.73)
	35 K- < 50 K BDT (319.20—< 455.94 USD)	187 (14.24)
	50 K- < 75 K BDT (455.94—< 683.91 USD)	74 (5.64)
	75 K- < l Lac BDT (683.91—< 911.89 USD)	28 (2.13)
	> = 1 Lac BDT (> = 911.89 USD)	18 (1.37)

in severe dengue patients. Severe abdominal pain and tenderness (28.35% vs 18.04%, p =< 0.001), severe lethargy (59.84% vs 39.75%, p =< 0.001), respiratory distress (11.42% vs 4.25%, p =< 0.001), altered mental status (9.06% vs 3.31%, p =< 0.001), and decreased urine output (12.6% vs 4.06%, p = < 0.001) were significantly more common in severe cases. While most (49.61%, n= 126) of the severe dengue patients had two or more warning signs, the majority (39.09%, n= 414) of the non-severe patients had no warning signs (Table 2).

Among 1313 respondents, 188 (12.10%) of our dengue patients had at least one comorbidity (Supplementary Table 3). The most common comorbidity among dengue patients was hypertension (HTN) (7.16%, n= 94), followed by diabetes mellitus (DM) (5.41%, n= 71), heart disease (2.59%, n= 34), asthma/chronic obstructive pulmonary disease (COPD) (2.36%, n= 31), cancer (0.61%, n= 8), and thyroid issues (0.53%, n= 7), such as hypothyroidism or hyperthyroidism. Around 6.78% (n= 89) of the study participants were diagnosed with either

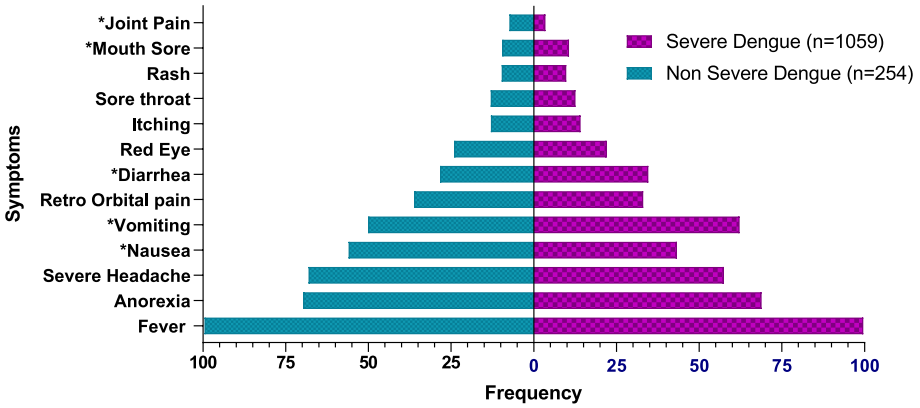

Fig. 1 Symptomatic presentation of the dengue patients according to their severity (* *p*-value < 0.05)

Table 2 Frequency of warning signs among the dengue patients according to their severity

Warning Signs	Non severe dengue (%) (*n*= 1059)	Severe dengue (%) (*n*= 254)	Total (%) (*n*= 1313)	*p*-value
Severe abdominal pain and tenderness	191 (18.04)	72 (28.35)	263 (20.03)	< 0.001
Persistent vomiting	281 (26.53)	81 (31.89)	362 (27.57)	0.086
Persistent Diarrhea	168 (15.86)	49 (19.29)	217 (16.53)	0.187
Severe Prostration	133 (12.56)	34 (13.39)	167 (12.72)	0.722
Severe Lethargy	421 (39.75)	152 (59.84)	573 (43.64)	< 0.001
Respiratory Distress	45 (4.25)	29 (11.42)	74 (5.64)	< 0.001
Liver enlargement	7 (0.66)	4 (1.57)	11 (0.84)	0.239*
Altered mental status	35 (3.31)	23 (9.06)	58 (4.42)	< 0.001
Decreased urine output	43 (4.06)	32 (12.6)	75 (5.71)	< 0.001
No warning signs	414 (39.09)	54 (21.26)	468 (35.64)	< 0.001
Single warning sign	291 (27.48)	74 (29.13)	365 (27.8)	
Two or more warnings	354 (33.43)	126 (49.61)	480 (36.56)	

All Percentages are within Column

*Fischer's exact test

hypertension or diabetes, and 2.89% (*n*= 38) of them shared both comorbidities (Table 3). Where 9.6% (*n*= 126) of the dengue patients had at least one comorbidity, 4.72% (*n*= 62) had two or more comorbidities. The proportion of severe dengue in patients with two or more comorbidities (17.74%. *n*= 11) is higher compared to dengue patients with a single comorbidity (13.49%, *n*= 17) (Supplementary Table 3). Overall, dengue patients with comorbidities such as diabetes, hypertension, asthma/COPD have an increased frequency of developing warning signs. Respondents with two or more comorbidities (45.16%) were more likely to have two or more warning signs compared to single comorbidity (38.89%) (Fig. 2).

Gum bleeding (4.72%, *n*= 62), per-rectal bleeding (1.98%, *n*= 26), and hemoptysis (1.75%, *n*= 23) were the three most common bleeding manifestations of dengue infection. Furthermore, gum bleeding (7.09% vs 4.15%, *p*= 0.048), per-rectal bleeding (4.33% vs 1.42%, $p = 0.003$), hematuria (2.36% vs 0.76%, $p = 0.025$), epistaxis (2.76% vs 0.57%, $p = 0.002$), pleural effusion (16.14% vs 2.17%, $p = < 0.001$) and ascites (15.35% vs 1.32%, $p = < 0.001$) were significantly more frequent in severe dengue compared to non-severe dengue (Table 4).

Laboratory parameters

Figure 3 portrays the distribution of the four biochemical parameters (platelet count, hemoglobin, hematocrit, and alanine aminotransferase) in different phases of dengue infection based on their severity. Although hemoglobin and hematocrit charts didn't represent any visible differences, exciting differences were observed for platelet count and ALT. From the febrile phase to the critical phase, platelet count for both non-severe and severe dengue experienced a decrease, followed by an increase

Table 3 Comorbidities of the dengue patient according to their severity

Comorbidities	Non severe dengue (%) (*n*= 1059)	Severe dengue (%) (*n*= 254)	Total (%) (*n*= 1313)	*p*-value
Hypertension	79 (7.46)	15 (5.91)	94 (7.16)	0.388
Diabetes	62 (5.85)	9 (3.54)	71 (5.41)	0.144
DM/ HTN	77 (7.27)	12 (4.72)	89 (6.78)	0.286
DM with HTN	32 (3.02)	6 (2.36)	38 (2.89)	
Heart Diseases	27 (2.55)	7 (2.76)	34 (2.59)	0.852
Asthma/COPD	29 (2.74)	2 (0.79)	31 (2.36)	0.582
Cancer	6 (0.57)	2 (0.79)	8 (0.61)	0.685
Thyroid issues	6 (0.57)	1 (0.39)	7 (0.53)	0.734
Single comorbidities	109 (10.29)	17 (6.69)	126 (9.6)	0.195
Two or more comorbidities	51 (4.82)	11 (4.33)	62 (4.72)	

All Percentages are within Column

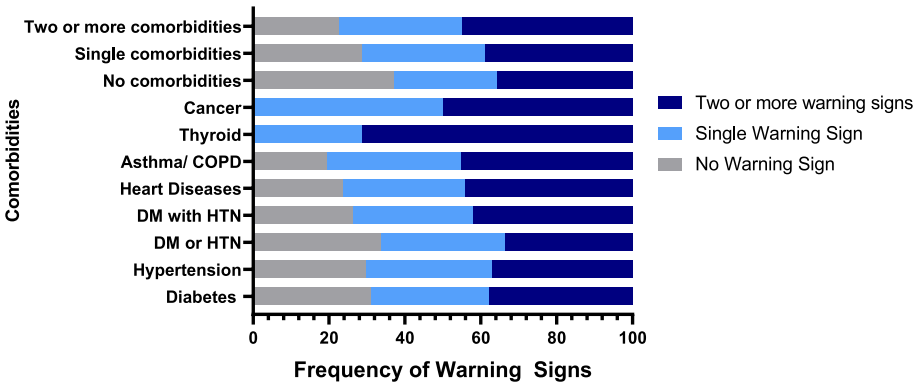

Fig. 2 Frequency of warning signs in patients with comorbidities

during the recovery phase. However, in all scenarios, platelets in severe dengue patients were always low compared to non-severe dengue patients. The decrease in platelet count (below 100 K) doubled in both non-severe and severe dengue as patients progressed from the febrile phase to the critical phase. Additionally, ALT levels increased more in severe dengue patients from the febrile to the recovery phase compared to non-severe dengue.

Regression analysis

From Table 5, multiple logistic regression analysis adjusted for age, gender, family income and comorbidities portrayed that severe headache (OR = 0.59, 95% CI = 0.42–0.82, p= 0.002) and nausea (OR = 0.50, 95% CI = 0.36–0.69, p= < 0.001) are negatively associated with severe dengue. However, dengue patients with vomiting had 1.79 times more odds (OR = 1.79, 95% CI = 1.24–2.59, p = 0.002) of presenting with severe dengue. Similarly, warning signs such as severe abdominal pain (OR = 1.54, 95% CI = 0.96–2.49, p = 0.07), severe lethargy (OR = 2.69, 95% CI = 1.60–4.53, p = < 0.001), respiratory distress (OR = 2.14, 95% CI = 1.10–4.15, p = 0.025), altered mental status (OR = 1.98, 95% CI = 1.00–3.92, p = 0.049), and decreased urine output (OR = 2.24, 95% CI = 1.20–4.17, p = 0.011) are positively associated with severe dengue infection. Moreover, pleural effusion (OR = 3.35, 95% CI = 1.51–7.46, p = < 0.001) and ascites (OR = 3.47, 95% CI = 3.47–20.89, p = < 0.001) increased the odds of severe dengue (Table 5).

Discussion

In this study, we investigated the clinical features, and the signs and symptoms associated with severe cases of dengue patients. We compared them to those in non-severe cases during the 2023 dengue outbreak in Bangladesh. Our findings demonstrate that severe abdominal pain and tenderness, severe lethargy, decreased urine output, pleural effusion, and ascites were significantly more prevalent among severe dengue patients than among

Table 4 Bleeding manifestation and clinical fluid accumulation in dengue patients according to their severity

Bleeding manifestation and clinical fluid accumulations	Non severe dengue (*n*= 1059)	Severe dengue (*n*= 254)	Total (*n*= 1313)	*p*-value
Gum bleeding	44 (4.15)	18 (7.09)	62 (4.72)	0.048
Per-rectal bleeding	15 (1.42)	11 (4.33)	26 (1.98)	0.003
Hemoptysis	21 (1.98)	2 (0.79)	23 (1.75)	0.192
Sub-conjunctival hemorrhage	17 (1.61)	4 (1.57)	21 (1.6)	0.972
Hematuria	8 (0.76)	6 (2.36)	14 (1.07)	0.025
Epistaxis	6 (0.57)	7 (2.76)	13 (0.99)	0.002
Menorrhagia	8 (0.76)	1 (0.39)	9 (0.69)	0.53
Per-vaginal bleeding	6 (0.57)	2 (0.79)	8 (0.61)	0.685
Pleural effusion	23 (2.17)	41 (16.14)	64 (4.87)	< 0.001
Ascites	14 (1.32)	39 (15.35)	53 (4.04)	< 0.001

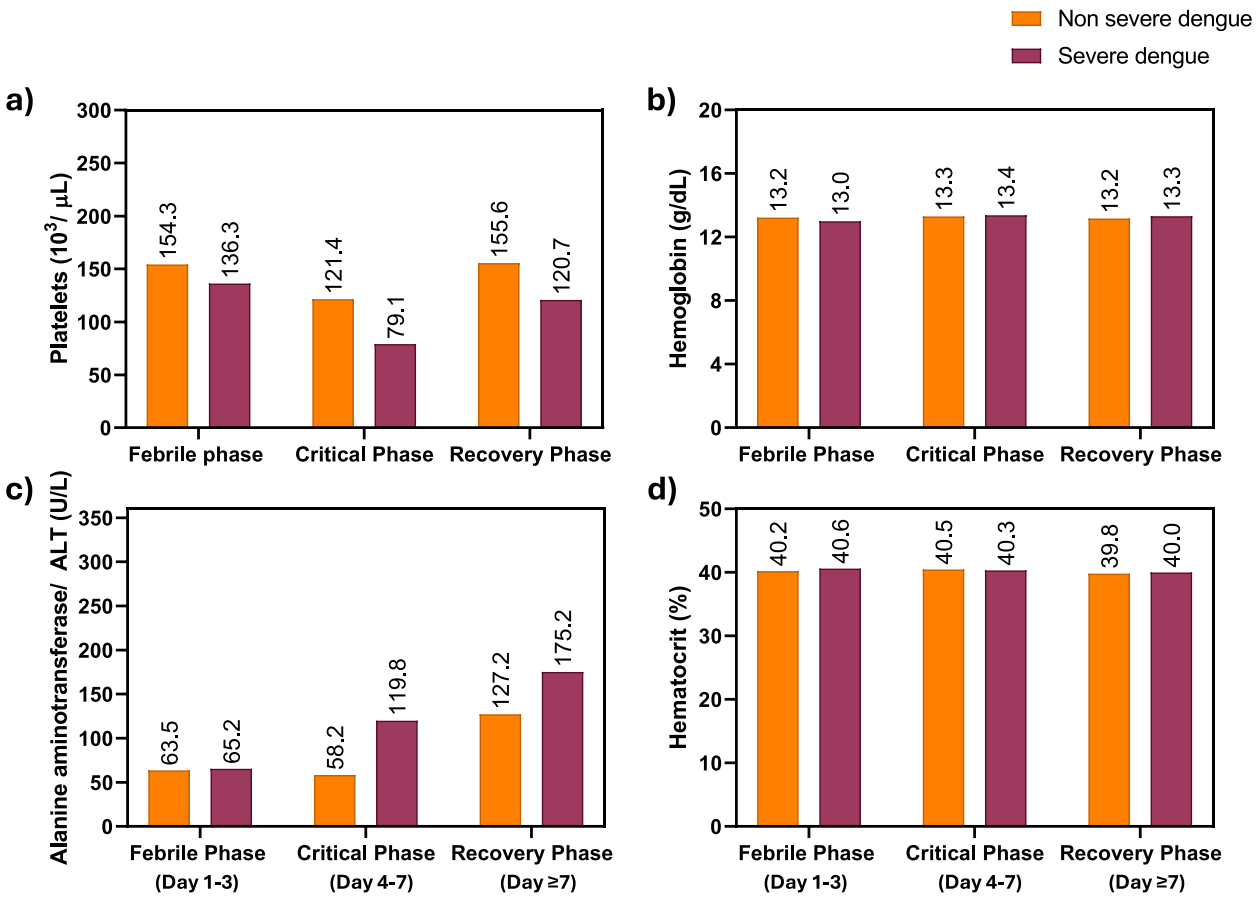

Fig. 3 Distribution of Biochemical Parameters (**a**. Platelets o, **b**. Hemoglobin **c**. Alanine aminotransferase, **d**. Hematocrit) in Non-severe and Severe dengue depending upon different phase of the infection

non-severe ones. This may suggest that these symptoms are associated with the body's response to infection and the extent of the disease severity.

We found that most of the patients in this study were male and from young adults (16–25 years) and middle-aged (26–40 years) group, consistent with previous studies of earlier outbreaks in Bangladesh and neighboring countries [38–41]. In line with the results of this study, Brazil has seen a surge in dengue cases among those aged 21 to 35 years between 2000 and 2014

Table 5 Multiple logistic regression (age, gender and family income adjusted)

Variables	Unadjusted			Adjusted		
	OR	*p*-value	95% CI	OR	*p*-value	95% CI
Dependent variable: Severe dengue (compared to non-severe dengue)						
Severe headache	0.63	0.001**	0.48, 0.84	0.59	0.002*	0.42, 0.82
Nausea	0.60	< 0.001**	0.46, 0.79	0.50	< 0.001**	0.36, 0.69
Vomiting	1.64	0.001**	1.24, 2.16	1.79	0.002*	1.24, 2.59
Diarrhoea	1.34	0.048*	1.00, 1.79			
Joint Pain	0.46	0.032*	0.23, 0.93			
Warning signs and comorbidities						
Severe abdominal pain	1.80	< 0.001**	1.31, 2.46	1.54	0.07*	0.96, 2.49
Severe lethargy	2.26	< 0.001**	1.71, 2.99	2.69	< 0.001**	1.60, 4.53
Respiratory distress	2.90	< 0.001**	1.78, 4.73	2.14	0.025*	1.10, 4.15
Altered mental status	2.91	< 0.001**	1.69, 5.02	1.98	0.049*	1.00, 3.92
Decreased urine output	3.40	< 0.001**	2.11, 5.50	2.24	0.011*	1.20, 4.17
Persistent diarrhoea	1.27	0.187	0.89, 1.80			
Persistent vomiting	1.30	0.087	0.96, 1.75			
Single warning sign	1.95	0.001**	1.33, 2.86			
Two or more warning signs	2.73	< 0.001**	1.925, 3.87			
HTN	0.78	0.389	0.44, 1.38			
DM	0.60	0.148	0.29, 1.21			
Clinical fluid accumulations						
Pleural effusion	8.67	< 0.001**	5.10, 14.75	3.35	0.003*	1.51, 7.46
Ascites	13.54	< 0.001**	7.22, 25.37	5.51	< 0.001**	3.47, 20.89

* $p < 0.05$

** $p < 0.001$

[42]. This is aligned with the shift in global trends of dengue incidence from 1990 to 2019 across different age groups, regardless of gender. In 1990, the incidence rate was highest among the 0–24-year age group, whereas in 2019, it was highest among the 10–49-year age group [43]. During the first outbreak of dengue in 2000 in Bangladesh, mean age of the study respondents among the hospitalized patients was 25.4 years [7]. This high prevalence of dengue in particular age group of 16–25 years of age also correlates with Bangladesh's current population distribution. According to its latest population census in 2022, the most common age groups was those aged 15–19 years (8.49%) followed by 20–24 years of age (8.27%) [22]. The clinical basis of male predominance in dengue cases is still unclear. This might be a combined effect of hospital-based nature of this study and male population's tendency to seek medical care more than females in South Asian countries [44].

Many patients in this study were from low-income backgrounds, suggesting that socioeconomic factors may increase vulnerability to exposure and limit access to preventive care resources. A study conducted in Brazil found that areas with lower income experienced higher relative risks for dengue infection and more significant economic impacts, which has also been reflected in our result [45].

Fever, pain, and rash are typically recognized as the classic triad of dengue symptoms. In our study, the most common symptoms among all dengue cases were fever, followed by anorexia and severe headache, which were consistent with findings from previous research [46, 47]. Notably, several studies have reported a decline in the prevalence of rash as a symptom, alongside an increase in gastrointestinal (GI) symptoms such as abdominal pain, vomiting, nausea, and diarrhea [40, 48]. Similarly, our findings indicate that rash was among the least common symptoms. In contrast, GI symptoms—particularly nausea, vomiting, and diarrhea—were frequently observed, with significantly higher prevalence in severe dengue cases. Studies from other regions such as Mexico, Spain, Brazil, China, Cambodia, Malaysia and Thailand also depicted significant relationship between vomiting and severe dengue infection [24]. The underlying cause might be related to inflammation and damage to the GI tract, which compromises the gut barrier and exacerbates the disease, which has been reported in a study on mice model [49].

Our study has found that all warning signs of dengue, according to WHO 2009 guidelines, were more prevalent in severe dengue patients in comparison to non-severe ones, with severe abdominal pain and tenderness, severe lethargy, respiratory distress, altered mental status and decreased urine output, gum bleeding, per-rectal bleeding, pleural effusion, and ascites being significantly more common in severe cases [4]. These warning signs were significantly associated with severe dengue in previous dengue outbreaks of 2019 and 2022 in Bangladesh [16–18]. Similarly, from a global systematic review study, pleural effusion, gastro-intestinal hemorrhage were highly linked, while abdominal pain and tenderness, lethargy and restlessness were modestly associated with severe dengue [24]. Another significant finding of this study was the presence of more than two warning signs in nearly half of the severe dengue patients. This indicates the need to emphasize the presence and the number of warning signs to better predict severe dengue outcomes.

In this study, hypertension, diabetes, and cardiovascular disease were the most common comorbidities among the patients. Although participants with two or more comorbidities had higher chances of developing warning signs, no significant association has been found between particular comorbidities such as DM, HTN and the possibility of developing severe dengue, aligning with the findings of Ahmad et al. and Mahmood et al. [47, 50]. However, this finding differs from the results of another study conducted on the Chinese population, where the investigators found a significant association between severe dengue (predominantly with DENV2 serotype) and DM or DM with HTN [51]. This disparity might be due to differences in the study design, with the study mentioned above being conducted in a case–control manner and the case subjects being exclusively hospitalized patients.

Our study found no significant difference in the hemoglobin level and hematocrit in the three different phases of dengue between severe and non-severe patients. However, a clear distinction was seen in the platelet count, especially in the critical phase, which was comparatively lower than the other two. Thrombocytopenia has long been associated as a parameter associated with severe dengue, and our study reflects the same result [52, 53]. Although the mechanical relation between thrombocytopenia and the development of severe dengue is yet poorly understood, it is hypothesized that the NS1 protein of the Dengue virus might mediate this process [54]. As organ involvement and damage is a common and serious complications of severe dengue, the level of liver enzymes is considered a valuable predictive marker in determining the severity of the disease condition [55, 56]. In this study, the Alanine aminotransferase (ALT) level was elevated gradually from the febrile phase to the recovery phase in all patients. ALT level was notably higher in severe dengue cases. These findings are consistent with the previous studies that found that liver enzymes (ALT) were significantly higher in severe dengue patients [51, 52]. In discordance with our findings related to hematocrit, another hospital based study on 2022 dengue outbreak in Bangladesh found notable differences in hematocrit in severe dengue patients [57]. This is possibly due to the variable cut-off when reporting hematocrit increase.

This study has a few limitations. First, due to its cross-sectional nature, this cannot establish a causal relationship between the associated factors and progression of severe dengue from non-severe dengue. However, this study may provide useful insights for designing longitudinal studies to further investigate and determine the causes of severe dengue. Secondly, this study introduces selection bias, as the study participants were gathered from the hospital setting. This also might overestimate the dengue severity compared to community. Thirdly, most of our study participants were young adults and older, thus making the findings less representative of pediatric dengue cases. Finally, the study did not analyze the serotype-specific distribution of the symptoms, warning signs and dengue severity.

Conclusion

This study revealed several critical warning signs associated with severe dengue cases in the 2023 Dengue outbreak in Bangladesh which will help to manage and diagnose severe patients and reduce adverse outcomes in patients' health outcomes. This highlights the importance of additional longitudinal research in dengue-endemic nations to comprehend the course of severe dengue and establish a causal link. Future studies should comprehensively examine the distribution of clinical signs and symptoms across different dengue serotypes to understand their role in dengue severity.

Abbreviations

ADE	Antibody Dependent Enhancement
ALT	Alanine Transferase
CBC	Complete Blood Count
COPD	Chronic Obstructive Pulmonary Disease
DENV	Dengue Virus
DF	Dengue Fever
DGHS	Directorate General of Health Services
DHF	Dengue Hemorrhagic Fever
DM	Diabetes Mellitus
ELISA	Enzyme Linked Immunosorbent Assay
GI	Gastrointestinal
HTN	Hypertension
ICT	Immunochromatographic Tests
RT-PCR	Reverse Transcriptase–Polymerase Chain Reaction
RDTs	Rapid Diagnostic Tests
Th2	T helper 2
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Conceptualization: O.S.P., A.M., A.F.M.N.C., N.A., and M.A.S.; Methodology: O.S.P., A.M., H.M.H.M, E.K., A.H.S., A.S., A.H.T.M, N.A., and M.A.S.; Formal Analysis: O.S.P., A.M., G.T., K.M. and N.A.; Writing-Original Draft Preparation: O.S.P., A.M., G.T., K.M., S.M., and S.N.E.; Writing – Review & Editing: A.M., A.S., H.M.H.M., A.H.T.M, and S.N.E. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval for this study was obtained from Institutional Review Board of Chittagong Medical College (Memo no.59.27.0000.013.19.PG.2023.009.288). This study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Chittagong Medical College. Written informed consent was collected for publication of information relating to them or a relative.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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