Clinical Warning Signs and Their Association with Severe Dengue Outcomes in Adult Patients

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Abstract

Background: Dengue is a viral illness that can fluctuate from mild sickness to severe dengue. Indicators such as stomach discomfort, nausea, and fluid build-up assist in forecasting serious results. Lab tests are frequently restricted, making clinical characteristics crucial. This study evaluates the correlation of warning signs with severe dengue in adults.

Methods: A forward-looking study at Dinajpur Medical Hospital (Jan–Dec 2024) recruited 120 adults with verified dengue, excluding people with long-term illnesses, pregnancy, or other infections. Demographics, clinical warning signs, and lab parameters were recorded. Severe dengue was categorized according to WHO criteria from 2009. Data were analyzed using SPSS 25, with ethics approval and informed consent obtained.

Results: Among 120 adult dengue patients, most were male (65.8%), middle-aged or older, and urban residents (56.7%), with 71.7% having no co-morbidities and 18.3% reporting prior dengue. Severe dengue occurred in 15% of patients. Common warning signs were abdominal pain (54.2%), rising hematocrit (39.2%), and rapid platelet fall (37.5%). Critical instances were notably linked to comorbidities, prior dengue, abdominal pain, vomiting, mucosal bleeding, fluid accumulation, thrombocytopenia, hemoconcentration, and elevated AST/ALT, reflecting more pronounced hematological and hepatic involvement compared with non-severe cases.

Conclusion: Severe dengue occurred more frequently in individuals with comorbid conditions or past infections. Warning signs like abdominal pain, vomiting, and fluid accumulation, along with low platelets, rising hematocrit, and elevated liver enzymes, were linked to severity, emphasizing the importance of thorough clinical and laboratory observation for prompt intervention.

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Introduction

Dengue is an arboviral disease resulting from the dengue virus (DENV) belonging to the Flaviviridae family; four serotypes (DENV1–4) circulate worldwide and lead to conditions that vary from asymptomatic infection to severe dengue or dengue shock syndrome.[1] Dengue is common in tropical and subtropical regions worldwide, particularly in urban and semi-urban areas.[2] It impacts approximately 50 million individuals each year globally; the majority are self-limiting, but under 1% experience serious, possibly lethal complications if not addressed. [3]

The 1997 WHO classification (DF, DHF, DSS) had drawbacks, as serious illness could arise outside the DHF/DSS criteria. Therefore, the 2009 WHO guidelines reclassified dengue into dengue with or without cautionary indicators and severe dengue, with cautionary indicators encompassing abdominal discomfort, ongoing vomiting, fluid buildup, mucosal hemorrhage, fatigue, hepatomegaly (>2 cm), and rising hematocrit with falling platelet count. [4] Laboratory diagnosis of dengue relies on detecting viral components in serum, including RT-PCR for viral nucleic acid, NS1 antigen, and dengue-specific IgM or IgG antibodies. These tests are expensive, require a lot of time, and are frequently inaccessible in areas with limited resources; as a result, diagnosing dengue typically relies on clinical characteristics. [5]

Global evidence suggests that WHO-defined clinical warning signs are strong predictors of advancement to severe dengue in adult individuals. In a substantial prospective cohort study of adult dengue cases, the existence of any warning signs significantly heightened the risk of severe dengue, whereas their lack demonstrated a strong negative predictive value. [6]

In Indonesia, researchers ndicated that having three or more indicators of warnings (such as vomiting, fluid accumulation, mucosal bleeding, and lethargy) was strongly predictive of severe dengue, with high sensitivity and specificity, indicating that a greater number of warning signs increases predictive accuracy. [7] In adult dengue cases in Sri Lanka, studies showed that abdominal pain, persistent vomiting, and Clinical fluid buildup occurred more frequently in severe dengue patients, verifying that these warning signs serve as valuable indicators of disease advancement in adults as well.[8]

A study of adult dengue patients in Dhaka (2019) found that severe dengue, mainly from plasma leakage was linked to WHO warning signs - abdominal pain, fluid accumulation, and persistent vomiting - along with thrombocytopenia, leukopenia, and elevated hematocrit and liver enzymes. [9] Analyses of dengue outbreaks in Bangladesh showed that gastrointestinal symptoms—particularly abdominal pain, nausea, and vomiting—were common, and severity-indicating signs like hypotension and fluid accumulation were more frequent in larger outbreaks, supporting the use of warning signs for severity assessment.[10] Another study of dengue patients in Bangladesh and discovered that dyspnea, plasma leakage, and bleeding were closely linked to severe dengue. Risk of severe disease ranged from 7% in older patients without plasma leakage to 92.9% in younger patients with both dyspnea and plasma leakage, with age, plasma leakage, platelet count, and dyspnea identified as key predictors. [11]

In Bangladesh, the investigation of severe dengue is hindered by a scarcity of prospective adult studies, inconsistent application of WHO 2009 criteria, limited incorporation of laboratory biomarkers, and insufficient data from community

environments. The timing of warning signs, serotype-specific effects, and long-term outcomes remain underexplored. Therefore, this study aims to assess clinical warning signs and their link to severe outcomes of dengue in adult patients.

Methods

Study Design and Setting

This was a prospective observational study conducted at Dinajpur medical Hospital, Bangladesh, from January 2024 to December 2024. The research sought to assess the clinical warning indicators in adult dengue patients and their relationship with severe dengue results.

Study Population

Inclusion criteria

- Individuals 18 years and older diagnosed with dengue, verified through NS1 antigen or IgM/IgG serological tests.
- Patients admitted to the medical facility throughout the research duration.

Exclusion criteria

- Patients with chronic liver, kidney, or hematological disorders.
- Pregnant women.
- Individuals with co-infections (e.g., malaria, chikungunya)

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Sample Size

A total of 120 adult individuals diagnosed with dengue were sequentially enrolled throughout the study duration.

Data Collection

Data were collected using a pre-tested structured questionnaire and clinical record review**.** Information included:

- Sociodemographic data (age, sex, residence)
- Medical history and co-morbidities (e.g., diabetes, hypertension, asthma, ischemic heart disease)
- History of previous dengue infection
- Clinical alert indicators, documented in accordance with the **WHO 2009 dengue guidelines.**
- Laboratory metrics such as platelet count, hematocrit, WBC count, AST, and ALT at admission and their highest/lowest values during the hospital stay.

Clinical warning signs were documented in phases.**:**

- **Febrile phase (Day 1–3)**
- **Critical phase (Day 4–6)**
- **Recovery phase (Day 7–10)**

Definition of Variables

Dengue Severity

Severe dengue: Characterized by the WHO 2009 standards, which encompass significant plasma leakage, intense bleeding, or serious organ involvement.

Non-severe dengue: Patients exhibiting warning signs or not, yet lacking severe symptoms.

*Clinical Warning Signs***:** Symptoms encompassed abdominal pain or tenderness, ongoing vomiting, mucosal hemorrhage, clinical fluid build-up, hepatomegaly (>2 cm), lethargy or restlessness, rapid decrease in platelets (<100,000/mm³), increased hematocrit (>20%), and heightened liver enzymes (AST/ALT >2× ULN).

Laboratory Parameters

• Platelet nadir: Minimum platelet count observed while hospitalized.

• Hematocrit maximum: Highest hematocrit level noted during the illness.

• AST/ALT peak: Maximum liver enzyme levels noted during the hospital stay.

• WBC nadir: Minimum WBC count noted during the disease.

Statistical Analysis

Data was entered and analyzed with SPSS version 25.0. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were reported as

counts and percentages. The Chi-square test or Fisher's exact test was used for categorical variables, while the independent t-test or Mann–Whitney U test was applied for continuous variables when comparing severe and non-severe dengue patients, as applicable. A p-value of less than 0.05 was deemed statistically significant.

Ethical Considerations

- The Institutional Ethics Committee of Dinajpur Medical Hospital approved the study.
- All participants provided written informed consent.
- Confidentiality of patients was preserved during the entire study.

Results

The study included a total of 120 adult patients with dengue. Following the WHO 2009 classification, 18 (15%) patients were diagnosed with severe dengue while 102 (85%) had non-severe dengue. Sociodemographic features, clinical indicators, and laboratory measurements were examined and contrasted based on the severity of the disease. The tables and figure below display the phase-wise allocation of warning signs and elements linked to severe dengue.

Table I: Sociodemographic and Clinical Characteristics of Study Participants (n = 120)

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	18–30	35	29.2
	31–45	42	35.0
	>45	43	35.8
Sex	Male	79	65.8
	Female	41	34.2
Residence	Urban	68	56.7
	Rural	52	43.3
Co-morbidities	Diabetes mellitus	17	14.2
	Hypertension	14	11.7
	Bronchial asthma	5	4.2
	Ischemic heart disease	3	2.5
	No co-morbidity	**86**	**71.7**
History of Previous Dengue Infection	Yes	22	18.3
	No	98	81.7

Table I shows the sociodemographic and clinical features of the 120 study participants. The majority were middle-aged or older adults, male (65.8%), and urban residents (56.7%). Most participants (71.7%) had no co-morbidities, with diabetes mellitus (14.2%) and hypertension (11.7%) being the most common underlying conditions. Only 18.3% reported a previous dengue infection, indicating limited prior exposure in the cohort.

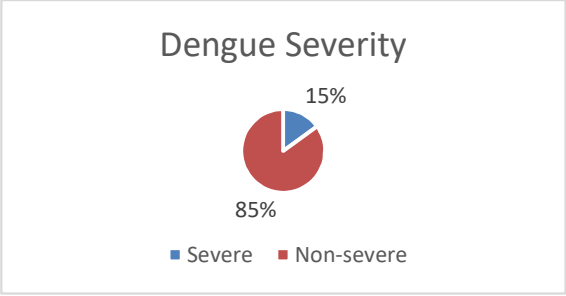

Figure 1. Severity of Dengue patients

Based on WHO 2009 classification, 18 patients (15%) were classified as severe dengue, while 102 (85%) had non-severe dengue (Figure 1).

Table II: Phase-wise Distribution of Clinical and Laboratory Warning Signs in Adult Dengue Patients (n = 120)

Warning Sign	Febrile Phase (Day 1–3)	Critical Phase (Day 4–6)	Recovery Phase (Day 7–10)	Total Patients n (%)
Abdominal pain/tenderness	21	38	6	65 (54.2)
Persistent vomiting	12	22	3	37 (30.8)
Mucosal bleeding	8	28	1	37 (30.8)
Clinical fluid accumulation	2	15	3	20 (16.7)
Hepatomegaly (>2 cm)	0	14	2	16 (13.3)
Lethargy / Restlessness	5	25	10	40 (33.3)
Rapid platelet fall (<100,000/mm³)	6	25	14	45 (37.5)
Rising hematocrit (>20%)	4	30	13	47 (39.2)
Elevated liver enzymes (AST/ALT >2× ULN)	2	10	4	16 (13.3)

Table II shows the phase-wise distribution of clinical and laboratory warning signs among 120 grown-up dengue patients. Abdominal discomfort or sensitivity was the most commonly noted warning symptom, present in 54.2% of patients, mainly during the critical phase (38 patients). Rising hematocrit (>20%) and rapid platelet fall (<100,000/mm³) were the most common laboratory indicators of severe disease, seen in 39.2% and 37.5% of patients, respectively, predominantly during the critical phase. Lethargy or restlessness occurred in one-third of patients (33.3%), while persistent vomiting and mucosal bleeding were each observed in 30.8%. Clinical fluid accumulation (16.7%), hepatomegaly >2 cm (13.3%), and elevated liver enzymes (AST/ALT >2× ULN) (13.3%) were less frequent.

Table III: Comparison of Sociodemographic and Clinical Characteristics Between Severe and Non-Severe Dengue Patients (n = 120)

Variable	Category	Severe Dengue (n = 18), n (%)	Non-Severe Dengue (n = 102), n (%)	p-value
Age (years)	18–30	3 (16.7)	32 (31.4)	0.21
	31–45	5 (27.8)	37 (36.3)	
	>45	10 (55.5)	33 (32.3)	
Sex	Male	13 (72.2)	66 (64.7)	0.52
	Female	5 (27.8)	36 (35.3)	
Residence	Urban	11 (61.1)	57 (55.9)	0.68
	Rural	7 (38.9)	45 (44.1)	
Co-morbidities	≥1 present	9 (50.0)	25 (24.5)	0.03*
	None	9 (50.0)	77 (75.5)	
History of Previous Dengue	Yes	6 (33.3)	16 (15.7)	0.04*
	No	12 (66.7)	86 (84.3)	

Table III indicates that severe dengue occurred more frequently in patients with comorbid conditions (50% vs. 24.5%) and those with a prior history of dengue (33.3% vs. 15.7%), whereas age, gender, and living location were not significantly related to disease severity.

Table IV: Distribution of Clinical and Laboratory Warning Signs Between Severe and Non-Severe Dengue Patients (n = 120)

Warning Sign	Severe Dengue (n = 18), n (%)	Non-Severe Dengue (n = 102), n (%)	Total n (%), n (%)	p-value
Abdominal pain/tenderness	13 (72.2)	52 (51.0)	65 (54.2)	0.04*
Persistent vomiting	10 (55.6)	27 (26.5)	37 (30.8)	0.01*
Mucosal bleeding	8 (44.4)	29 (28.4)	37 (30.8)	0.05*
Clinical fluid accumulation	7 (38.9)	13 (12.7)	20 (16.7)	<0.001*
Hepatomegaly (>2 cm)	4 (22.2)	12 (11.8)	16 (13.3)	0.18
Lethargy / Restlessness	9 (50.0)	31 (30.4)	40 (33.3)	0.09
Rapid platelet fall (<100,000/mm³)	11 (61.1)	34 (33.3)	45 (37.5)	0.02*
Rising hematocrit (>20%)	12 (66.7)	35 (34.3)	47 (39.2)	0.01*
Elevated liver enzymes (AST/ALT >2× ULN)	6 (33.3)	10 (9.8)	16 (13.3)	0.005*

*Statistically significant at $p < 0.05$

Table IV compares the distribution of clinical and laboratory warning signs between severe (n = 18) and non-severe dengue patients (n = 102). Abdominal pain/tenderness was more frequent in severe cases (72.2% vs. 51.0%, p = 0.04), as were persistent vomiting (55.6% vs. 26.5%, p = 0.01), mucosal bleeding (44.4% vs. 28.4%, p = 0.05), clinical fluid accumulation (38.9% vs. 12.7%, p < 0.001), rapid platelet fall (61.1% vs. 33.3%, p = 0.02), rising hematocrit (66.7% vs. 34.3%, p = 0.01), and elevated liver enzymes (33.3% vs. 9.8%, p = 0.005), all demonstrating statistically meaningful correlations with severe dengue. Additional warning indicators, such as hepatomegaly and lethargy/restlessness, were more prevalent in severe instances but did not achieve statistical significance.

Table V: Laboratory Parameters in Severe and Non-Severe Dengue Patients (n = 120)

Parameter	Severe Dengue (n = 18)	Non-Severe Dengue (n = 102)	p-value*
Platelet count (×10³/μL)			
Admission	132 ± 60	145 ± 57	0.32
Nadir	52 ± 28	72 ± 35	0.01*
Hematocrit (%)			
Admission	42.5 ± 4.8	41.0 ± 4.4	0.15
Peak	54.0 ± 5.5	50.9 ± 5.0	0.03*
WBC count (×10³/μL)			
Admission	5.5 ± 2.0	5.9 ± 2.1	0.48
Nadir	3.8 ± 1.5	4.3 ± 1.8	0.12
AST (U/L)			
Admission	50 ± 30	44 ± 28	0.40
Peak	130 ± 80	105 ± 70	0.04*
ALT (U/L)			
Admission	40 ± 25	37 ± 22	0.55
Peak	110 ± 65	90 ± 58	0.05*

*Statistically significant at p < 0.05

Table V shows that patients with severe dengue experienced markedly lower nadir platelet counts (52 ± 28 vs. 72 ± 35 $\times 10^3/\mu L$, $p = 0.01$), higher peak hematocrit ($54.0 \pm 5.5\%$ vs. $50.9 \pm 5.0\%$, $p = 0.03$), and elevated peak liver enzymes (AST 130 ± 80 vs. 105 ± 70 U/L, $p = 0.04$; ALT 110 ± 65 vs. 90 ± 58 U/L, $p = 0.05$) compared with non-severe cases, while admission values and WBC counts were similar, highlighting more pronounced hematological and hepatic involvement in severe disease**.**

Discussion

The study population was fairly balanced among age categories, with a slight increase in participants aged 31–45 and >45 years. Age influences dengue risk and severity, with studies from Brazil demonstrating greater prevalence among adults in the age group 20–39 years.[12] The male predominance (65.8%) is consistent with Asian dengue studies, where males aged ≥15 years show higher incidence due to greater exposure and activity patterns.[13] Urban residence predominated (56.7%), consistent with Al-Dubai et al. (2013), where urban participants formed the largest subgroup of 300 surveyed in Malaysia.[14] In this study, most participants (71.7%) had no co-morbidities, while diabetes (14.2%), hypertension (11.7%), bronchial asthma (4.2%), and ischemic heart disease (2.5%) were less common. Literature reports pooled prevalence of 13.3% for diabetes, 17.1% for hypertension, and 25.6% (95% CI: 19.5–32.7%) for heart diseases, all associated with 2–4-fold higher risk of severe dengue.[15] In this study, 18.3% of participants reported a past dengue infection. Evidence from a population-based cohort in Taiwan showed that the likelihood of severe dengue was considerably greater in individuals with secondary infection-7.8% experienced severe disease compared with 3.8% after primary infection.[16] Our study found, 15%of patients had severe dengue and 85% non-severe, consistent with WHO 2009-based studies reporting 4.6–28% severe cases in endemic settings, underscoring the classification's clinical utility.[17]

In our study, abdominal pain/tenderness was the most frequent indicator (54.2%), followed by lethargy/restlessness (33.3%), persistent vomiting (30.8%), mucosal bleeding (30.8%), and hepatomegaly >2 cm (13.3%). These results align with Leo *et al.* (2013), who reported abdominal pain in ≈45%, mucosal bleeding in ≈30%, persistent vomiting in ≈25%, lethargy/restlessness in ≈35%, and hepatomegaly in ≈12% of adult dengue patients progressing to severe disease.[4] In our study, rapid platelet fall (<100,000/mm³) was observed in 45 patients (37.5%), rising hematocrit (>20%) in 47 patients (39.2%), elevated liver enzymes (AST/ALT >2× ULN) in 16 patients (13.3%), and clinical fluid accumulation in 20 patients (16.7%), primarily during the critical phase. Leo *et al.* (2013) reported similar frequencies in adult dengue patients progressing to severe disease: thrombocytopenia in 36%, hematocrit rise >20% in 38%, elevated liver enzymes in 14%, and fluid accumulation in 18%.[6]

In our research, age and gender were not notably linked with dengue severity, consistent with Southeast Asian data showing variable effects of these factors once clinical risk factors are taken into account.[18] Co-morbidities were strongly linked to severe dengue (50% vs. 24.5%, $p = 0.03$), with hypertension and diabetes increasing the odds of severe disease 2.46-fold (95% CI: 1.09–5.53).[19] In our study, severe dengue patients more frequently exhibited abdominal pain/tenderness (72.2% vs. 51.0%), persistent vomiting (55.6% vs. 26.5%), clinical fluid accumulation (38.9% vs. 12.7%), rapid platelet fall (61.1% vs. 33.3%), rising hematocrit (66.7% vs. 34.3%), and elevated liver enzymes (33.3% vs. 9.8%) compared

with non-severe cases. These findings are consistent with Idrus *et al.* (2023), who reported in a paediatric cohort that abdominal pain occurred in 70% of severe cases vs. 45% of non-severe, persistent vomiting in 60% vs. 25%, fluid accumulation (ascites/pleural effusion) in 40% vs. 15%, rapid platelet fall in 65% vs. 35%, rising hematocrit >20% in 68% vs. 32%, and elevated liver enzymes in 35% of severe vs. 10% of non-severe cases, all significantly associated with severity.[20] The significant laboratory differences between severe and non-severe dengue in our study mirror patterns identified in the pediatric cohort studied by Idrus et al. (2023). In our adults, severe dengue was associated with lower nadir platelet counts (52 ± 28 vs. $72 \pm 35 \times 10^3/\mu L$, $p = 0.01$) and higher peak hematocrit ($54.0 \pm 5.5\%$ vs. $50.9 \pm 5.0\%$, $p = 0.03$), reflecting more pronounced thrombocytopenia and hemoconcentration—hallmarks of plasma leakage and severity. Although Idrus et al. focused on children, they similarly found that laboratory alterations, including hematological changes and evidence of fluid leakage (ascites), were significantly associated with severe dengue: in their cohort of 254 pediatric patients, 15.4% developed severe disease, and features such as ascites and hepatomegaly were independently linked to severity. Elevated liver enzymes in our severe cases (peak AST 130 ± 80 vs. 105 ± 70 U/L, $p = 0.04$; ALT 110 ± 65 vs. 90 ± 58 U/L, $p = 0.05$) further support systemic involvement, consistent with the broader laboratory profiles described by Idrus et al.[20]

This research has constraints, which include its single-center design, modest sample size, and focus on hospitalized adults, which may limit generalizability. Seasonal variations and mild community cases were not captured, and previous dengue history was self-reported. Despite these limitations, the results offer important perspectives on warning indicators linked to severe dengue in adults in Bangladesh.

Conclusion

In this study of adult dengue patients, a notable proportion developed severe disease, with the presence of underlying health conditions and a history of prior dengue infection increasing the likelihood of severe outcomes. Clinical warning signs such as abdominal pain, persistent vomiting, and fluid accumulation, along with laboratory indicators including low platelet counts, rising hematocrit, and elevated liver enzymes, were more frequent in severe cases. These results highlight the significance of careful monitoring of both clinical symptoms and laboratory parameters to identify patients at risk, enabling timely intervention and improved management of severe dengue.

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