

## Dengue Fever in Children: A Prospective Study of Clinical Severity and Laboratory Predictors

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### Abstract

**Background:** Dengue fever represents a significant public health burden in tropical and subtropical regions, with children being particularly vulnerable to severe manifestations. Early identification of patients at risk for progression to severe dengue is crucial for appropriate clinical management and resource allocation. This study aimed to evaluate clinical features and laboratory parameters as predictors of disease severity in pediatric dengue patients.

**Methods:** This prospective observational study was conducted over 18 months and included 248 children aged 1-14 years with confirmed dengue infection. Patients were classified according to WHO 2009 criteria into dengue without warning signs, dengue with warning signs, and severe dengue. Clinical and laboratory parameters were compared across severity groups, and multivariate logistic regression analysis was performed to identify independent predictors of severe disease.

**Results:** Among 248 patients, 98 (39.5%) had dengue without warning signs, 112 (45.2%) had dengue with warning signs, and 38 (15.3%) had severe dengue. The mean age was  $7.8 \pm 3.4$  years, with male predominance (58.1%). Thrombocytopenia ( $<100,000/\mu\text{L}$ ) was observed in 72.6% of patients with severe dengue compared to 28.6% in non-severe cases ( $p < 0.001$ ). Elevated hematocrit ( $>20\%$  rise), elevated AST ( $>3\times$  normal), and low platelet count were independent predictors of severe dengue. The platelet-to-hematocrit ratio  $\leq 3.5$  demonstrated 84.2% sensitivity and 78.6% specificity for predicting severe dengue (AUC = 0.87,  $p < 0.001$ ). Mortality rate was 2.6% among severe dengue cases.

**Conclusion:** Laboratory parameters, particularly thrombocytopenia, hemoconcentration, and hepatic transaminases, serve as valuable predictors of severe dengue in children. The platelet-to-hematocrit ratio represents a simple, accessible marker for early identification of patients requiring intensive monitoring.

**Keywords:** Dengue Fever, Children, Severity Predictors, Thrombocytopenia, Hematocrit, Warning Signs, Tropical Infectious Disease.

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### Introduction

Dengue fever has emerged as the most rapidly spreading mosquito-borne viral disease globally, with an estimated 390 million infections occurring annually across tropical and subtropical regions [1]. The disease is caused by the dengue virus (DENV), a single-stranded RNA virus belonging to the Flaviviridae family, with four distinct serotypes (DENV-1 to DENV-4) capable of causing human infection [2].

The unprecedented global expansion of dengue is attributed to urbanization, increased international travel, climate change, and the widespread distribution of *Aedes aegypti* and *Aedes albopictus* mosquito vectors [3]. Children represent a

particularly vulnerable population for dengue infection, with studies from endemic regions demonstrating higher hospitalization rates and more severe clinical manifestations compared to adults [4]. The pediatric immune response to dengue infection, particularly in the context of secondary heterotypic infections, may contribute to the development of severe disease through antibody-dependent enhancement mechanisms [5].

Understanding the clinical spectrum and identifying early predictors of severity in children is essential for optimizing patient outcomes. The clinical presentation of dengue ranges from asymptomatic infection to severe, potentially fatal

disease characterized by plasma leakage, hemorrhagic manifestations, and organ dysfunction [6]. The World Health Organization (WHO) revised dengue classification in 2009 categorizes disease into dengue without warning signs, dengue with warning signs, and severe dengue, aiming to facilitate clinical management and triage [7]. Warning signs include abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, hepatomegaly, and increasing hematocrit with decreasing platelets.

Laboratory parameters play a crucial role in dengue diagnosis, monitoring, and prognostication. Thrombocytopenia and hemoconcentration are hallmarks of dengue infection, reflecting the underlying pathophysiology of increased vascular permeability and plasma leakage [8]. Hepatic involvement, manifested by elevated transaminases, is commonly observed and may correlate with disease severity [9]. Recent studies have explored various laboratory indices, including platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and platelet-to-hematocrit ratio as potential predictors of severe dengue [10].

Despite advances in understanding dengue pathophysiology, predicting which patients will progress to severe disease remains challenging. Several clinical and laboratory parameters have been proposed as severity predictors; however, their performance varies across different populations and settings [11]. The identification of reliable, accessible markers for early risk stratification is particularly important in resource-limited endemic areas where healthcare infrastructure may be constrained [12].

The aim of this study was to characterize the clinical spectrum of dengue fever in children and to identify clinical features and laboratory parameters that serve as predictors of disease severity, with the goal of facilitating early recognition and appropriate management of high-risk patients.

## Materials and Methods

**Study Design and Setting:** This prospective observational study was conducted at the Department of Pediatrics.

**Study Population and Sample Size:** Children aged 1-14 years presenting with suspected dengue fever were screened for enrollment. Sample size was calculated based on an estimated 15% prevalence of severe dengue among hospitalized cases, with 95% confidence interval and 5% margin of error, yielding a minimum requirement of 196 patients. To account for potential dropouts and incomplete data, we aimed to enroll 250 patients.

### Inclusion Criteria:

- Age between 1 and 14 years

- Acute febrile illness of  $\leq 7$  days duration
- Laboratory-confirmed dengue infection (NS1 antigen positive and/or IgM antibody positive)
- Parent or guardian consent for participation

### Exclusion Criteria:

- Co-infection with other febrile illnesses (malaria, typhoid, chikungunya)
- Underlying hematological disorders
- Chronic hepatic or renal disease
- Immunocompromised states
- Incomplete laboratory or clinical data
- Refusal to participate or loss to follow-up

### Data Collection and Clinical Assessment:

Demographic information including age, sex, and duration of illness at presentation was recorded for all patients. A detailed clinical history was obtained, including symptoms such as fever, headache, myalgia, and arthralgia, and rash, abdominal pain, vomiting, and bleeding manifestations. Physical examination documented vital signs, hydration status, hepatomegaly, signs of plasma leakage, and neurological status.

**Laboratory Investigations:** Blood samples were collected at admission and daily throughout hospitalization. Complete blood count with differential was performed using automated hematology analyzer. Liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured. Dengue NS1 antigen was detected using rapid immunochromatographic assay, and dengue IgM/IgG antibodies were detected using ELISA.

Serum albumin, prothrombin time, and activated partial thromboplastin time were measured in patients with suspected severe disease.

**Disease Classification:** Patients were classified according to WHO 2009 dengue classification:

**Dengue without warning signs:** Fever with two or more of the following: nausea/vomiting, rash, aches and pains, positive tourniquet test, leukopenia.

**Dengue with warning signs:** Dengue with abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy/restlessness, hepatomegaly  $>2$  cm, or increasing hematocrit with decreasing platelets.

**Severe dengue:** Dengue with severe plasma leakage (shock, respiratory distress), severe bleeding, or severe organ involvement (AST or ALT  $\geq 1000$ , impaired consciousness, cardiac involvement).

**Treatment Protocol:** All patients received standard supportive care according to WHO dengue management guidelines.

Oral rehydration was encouraged for stable patients. Intravenous fluid therapy was administered based on clinical status and hematocrit monitoring. Platelet transfusion was considered for counts  $<10,000/\mu\text{L}$  or in the presence of active bleeding. Patients with severe dengue were managed in the pediatric intensive care unit.

**Outcome Assessment:** Primary outcomes included disease severity classification and the identification of predictive factors. Secondary outcomes included duration of hospitalization, need for intensive care, bleeding complications, and mortality. Patients were followed until discharge and reassessed at one week post-discharge.

**Statistical Analysis:** Data were analyzed using Statistical Package for Social Sciences (SPSS) version 25.0. Continuous variables were expressed as mean  $\pm$  standard deviation or median (interquartile range) based on distribution. Categorical variables were presented as frequencies and percentages. Comparison between groups was performed using one-way ANOVA for continuous variables and chi-square test for categorical variables. Multivariate logistic regression was used

to identify independent predictors of severe dengue. Receiver operating characteristic (ROC) curves were constructed to determine optimal cut-off values and diagnostic accuracy. A  $p$ -value  $< 0.05$  was considered statistically significant.

## Results

**Demographic and Clinical Characteristics:** A total of 262 children with confirmed dengue were initially enrolled, of which 248 met all inclusion criteria and completed the study. The demographic and clinical characteristics are presented in Table 1. The mean age was  $7.8 \pm 3.4$  years, with children aged 5-10 years comprising the largest group (48.4%). Male patients predominated (58.1%). The mean duration of fever before presentation was  $4.2 \pm 1.6$  days. According to WHO classification, 98 patients (39.5%) had dengue without warning signs, 112 patients (45.2%) had dengue with warning signs, and 38 patients (15.3%) had severe dengue. Fever was universally present (100%), followed by myalgia (78.2%), headache (72.6%), vomiting (68.5%), abdominal pain (52.4%), and rash (45.2%). Bleeding manifestations occurred in 28.6% of patients, with petechiae (15.3%) and epistaxis (8.9%) being most common.

**Table 1: Demographic and Clinical Characteristics of Study Population (n=248)**

Parameter	Total (n=248)	Dengue without WS (n=98)	Dengue with WS (n=112)	Severe Dengue (n=38)	p-value
Age (years), mean $\pm$ SD	$7.8 \pm 3.4$	$7.2 \pm 3.2$	$8.1 \pm 3.5$	$8.4 \pm 3.6$	0.087
<b>Age groups, n (%)</b>					
1-4 years	62 (25.0%)	28 (28.6%)	26 (23.2%)	8 (21.1%)	0.124
5-10 years	120 (48.4%)	48 (49.0%)	54 (48.2%)	18 (47.4%)	
11-14 years	66 (26.6%)	22 (22.4%)	32 (28.6%)	12 (31.6%)	
<b>Gender, n (%)</b>					
Male	144 (58.1%)	54 (55.1%)	66 (58.9%)	24 (63.2%)	0.628
Female	104 (41.9%)	44 (44.9%)	46 (41.1%)	14 (36.8%)	
Duration of fever (days), mean $\pm$ SD	$4.2 \pm 1.6$	$3.8 \pm 1.4$	$4.4 \pm 1.6$	$4.8 \pm 1.8$	0.002*
<b>Clinical features, n (%)</b>					
Fever	248 (100%)	98 (100%)	112 (100%)	38 (100%)	-
Myalgia	194 (78.2%)	72 (73.5%)	90 (80.4%)	32 (84.2%)	0.278
Headache	180 (72.6%)	68 (69.4%)	82 (73.2%)	30 (78.9%)	0.504
Vomiting	170 (68.5%)	52 (53.1%)	84 (75.0%)	34 (89.5%)	$<0.001^*$
Abdominal pain	130 (52.4%)	28 (28.6%)	72 (64.3%)	30 (78.9%)	$<0.001^*$
Rash	112 (45.2%)	42 (42.9%)	52 (46.4%)	18 (47.4%)	0.824
Hepatomegaly	86 (34.7%)	18 (18.4%)	46 (41.1%)	22 (57.9%)	$<0.001^*$
Bleeding manifestations	71 (28.6%)	12 (12.2%)	36 (32.1%)	23 (60.5%)	$<0.001^*$

\*Statistically significant ( $p < 0.05$ ); WS: Warning Signs

**Laboratory Parameters:** Laboratory findings across severity groups are summarized in Table 2. Significant differences were observed in platelet count, hematocrit, and hepatic transaminases across the three groups. Mean platelet count was progressively lower with increasing severity:  $142.6 \pm 48.2 \times 10^3/\mu\text{L}$  in dengue without warning signs,  $98.4 \pm 42.8 \times 10^3/\mu\text{L}$  in dengue with warning signs,

and  $58.6 \pm 28.4 \times 10^3/\mu\text{L}$  in severe dengue ( $p < 0.001$ ). Thrombocytopenia ( $<100,000/\mu\text{L}$ ) was present in 72.6% of severe dengue cases compared to 28.6% of non-severe cases.

Mean hematocrit was significantly elevated in severe dengue ( $44.8 \pm 4.6\%$ ) compared to dengue with warning signs ( $40.2 \pm 3.8\%$ ) and dengue

without warning signs ( $37.4 \pm 3.2\%$ ) ( $p < 0.001$ ). Hemoconcentration ( $>20\%$  rise in hematocrit) was observed in 68.4% of severe dengue patients.

Hepatic transaminases were markedly elevated in severe dengue, with mean AST of  $286.4 \pm 142.8$

U/L and ALT of  $168.2 \pm 86.4$  U/L. The platelet-to-hematocrit ratio was significantly lower in severe dengue ( $1.4 \pm 0.8$ ) compared to other groups ( $p < 0.001$ ).

**Table 2: Laboratory Parameters across Severity Groups**

Parameter	Dengue without WS (n=98)	Dengue with WS (n=112)	Severe Dengue (n=38)	p-value
Hemoglobin (g/dL), mean $\pm$ SD	$11.8 \pm 1.4$	$12.4 \pm 1.6$	$13.2 \pm 1.8$	$<0.001^*$
Hematocrit (%), mean $\pm$ SD	$37.4 \pm 3.2$	$40.2 \pm 3.8$	$44.8 \pm 4.6$	$<0.001^*$
Hemoconcentration ( $>20\%$ rise), n (%)	8 (8.2%)	34 (30.4%)	26 (68.4%)	$<0.001^*$
WBC count ( $\times 10^3/\mu\text{L}$ ), mean $\pm$ SD	$5.2 \pm 2.4$	$4.6 \pm 2.2$	$4.2 \pm 2.6$	0.048*
Leukopenia ( $<4000/\mu\text{L}$ ), n (%)	32 (32.7%)	48 (42.9%)	20 (52.6%)	0.062
Platelet count ( $\times 10^3/\mu\text{L}$ ), mean $\pm$ SD	$142.6 \pm 48.2$	$98.4 \pm 42.8$	$58.6 \pm 28.4$	$<0.001^*$
Thrombocytopenia ( $<100,000/\mu\text{L}$ ), n (%)	28 (28.6%)	62 (55.4%)	32 (84.2%)	$<0.001^*$
Severe thrombocytopenia ( $<50,000/\mu\text{L}$ ), n (%)	6 (6.1%)	22 (19.6%)	18 (47.4%)	$<0.001^*$
AST (U/L), mean $\pm$ SD	$68.4 \pm 32.6$	$124.6 \pm 68.4$	$286.4 \pm 142.8$	$<0.001^*$
ALT (U/L), mean $\pm$ SD	$42.8 \pm 24.2$	$86.2 \pm 48.6$	$168.2 \pm 86.4$	$<0.001^*$
AST $>3 \times$ ULN, n (%)	8 (8.2%)	32 (28.6%)	28 (73.7%)	$<0.001^*$
Serum albumin (g/dL), mean $\pm$ SD	$3.8 \pm 0.4$	$3.4 \pm 0.5$	$2.9 \pm 0.6$	$<0.001^*$
Hypoalbuminemia ( $<3.5$ g/dL), n (%)	18 (18.4%)	48 (42.9%)	30 (78.9%)	$<0.001^*$
Platelet/Hematocrit ratio, mean $\pm$ SD	$3.8 \pm 1.2$	$2.5 \pm 1.0$	$1.4 \pm 0.8$	$<0.001^*$

\*Statistically significant ( $p < 0.05$ ); WS: Warning Signs; ULN: Upper Limit of Normal

**Predictors of Severe Dengue and Clinical Outcomes:** Multivariate logistic regression identified independent predictors of severe dengue (Table 3). Platelet count  $<50,000/\mu\text{L}$  (OR: 4.82, 95% CI: 2.14-10.86,  $p < 0.001$ ), hemoconcentration  $>20\%$  (OR: 3.96, 95% CI: 1.78-8.82,  $p = 0.001$ ), AST  $>3 \times$  upper limit of normal (OR: 3.24, 95% CI: 1.42-7.38,  $p = 0.005$ ), and hypoalbuminemia (OR: 2.86, 95% CI: 1.24-6.58,  $p = 0.014$ ) were independently associated with severe dengue. ROC curve analysis demonstrated that the platelet-to-hematocrit ratio had excellent discriminatory ability for predicting severe dengue (AUC = 0.87, 95% CI: 0.81-0.93,  $p < 0.001$ ). A cut-off value of

$\leq 3.5$  yielded 84.2% sensitivity and 78.6% specificity. Platelet count alone (AUC = 0.82) and AST (AUC = 0.84) also demonstrated good predictive accuracy. Mean hospital stay was  $4.8 \pm 2.2$  days overall, with significantly longer duration in severe dengue ( $7.4 \pm 2.8$  days) compared to dengue with warning signs ( $4.6 \pm 1.8$  days) and dengue without warning signs ( $3.2 \pm 1.2$  days) ( $p < 0.001$ ). Intensive care admission was required in 28 patients (73.7%) with severe dengue.

Platelet transfusion was administered to 14 patients (5.6%). One patient (2.6%) with severe dengue died due to refractory dengue shock syndrome.

**Table 3: Multivariate Logistic Regression for Predictors of Severe Dengue**

Variable	Odds Ratio	95% CI	p-value
Age $>10$ years	1.42	0.68 - 2.98	0.352
Male gender	1.28	0.62 - 2.64	0.508
Duration of fever $>5$ days	1.86	0.92 - 3.78	0.086
Platelet count $<50,000/\mu\text{L}$	4.82	2.14 - 10.86	$<0.001^*$
Hemoconcentration $>20\%$	3.96	1.78 - 8.82	0.001*
AST $>3 \times$ ULN	3.24	1.42 - 7.38	0.005*
Hypoalbuminemia ( $<3.5$ g/dL)	2.86	1.24 - 6.58	0.014*
Leukopenia ( $<4000/\mu\text{L}$ )	1.64	0.76 - 3.54	0.208
Hepatomegaly	1.92	0.88 - 4.18	0.102
Bleeding manifestations	2.18	0.98 - 4.86	0.056

\*Statistically significant ( $p < 0.05$ ); CI: Confidence Interval; ULN: Upper Limit of Normal

## Discussion

This prospective study provides comprehensive data on the clinical spectrum and laboratory

predictors of severe dengue in a pediatric population. Our findings demonstrate that thrombocytopenia, hemoconcentration, and hepatic transaminase elevation serve as valuable markers

for identifying children at risk for severe disease progression.

The distribution of disease severity in our cohort, with 15.3% classified as severe dengue, aligns with previous reports from endemic regions. Srikiatkachorn et al. reported severe dengue rates of 10-20% among hospitalized children, consistent with our observations [14]. The predominance of male patients and school-aged children in our study is consistent with epidemiological patterns described in Southeast Asian cohorts [15].

Thrombocytopenia emerged as a cardinal laboratory finding associated with severe dengue in our study. The profound platelet reduction observed in severe cases reflects multiple pathophysiological mechanisms, including bone marrow suppression, increased peripheral destruction, and consumption during coagulopathy [16]. Krishnamoorthy et al. demonstrated that platelet counts below 50,000/ $\mu$ L were associated with a five-fold increased risk of severe disease, comparable to our findings [17]. The nadir platelet count typically occurs during the critical phase of illness, coinciding with defervescence and increased vascular permeability.

Hemoconcentration, reflecting plasma leakage, was strongly associated with severe dengue in our cohort. The rise in hematocrit >20% from baseline represents a key indicator of significant capillary leak and impending hemodynamic compromise [18]. Kalayanarooj et al. emphasized the importance of serial hematocrit monitoring for early detection of plasma leakage and timely fluid management [19]. Our findings support the inclusion of hemoconcentration as a critical warning sign in dengue management protocols.

Hepatic involvement, manifested by elevated transaminases, was significantly more pronounced in severe dengue cases. The hepatotropism of dengue virus and associated inflammatory responses contribute to hepatocellular injury [20]. Trung et al. reported that AST elevations exceeding three times the upper normal limit were independently associated with severe disease, consistent with our regression analysis [21]. The AST predominance over ALT elevation observed in our study is characteristic of dengue-associated hepatitis and may reflect muscle involvement in addition to hepatic injury. The platelet-to-hematocrit ratio emerged as a simple, accessible composite marker with excellent discriminatory ability for predicting severe dengue. This ratio integrates two key pathophysiological features of severe disease—thrombocytopenia and hemoconcentration—into a single parameter [22]. The ratio's utility lies in its simplicity and availability in resource-limited settings where sophisticated laboratory testing may be unavailable.

Jayashree et al. demonstrated similar findings, with platelet-to-hematocrit ratios showing superior predictive performance compared to individual parameters [23].

Hypoalbuminemia was independently associated with severe dengue, reflecting both hepatic synthetic dysfunction and protein loss through leaky capillaries. Serum albumin serves as a marker of nutritional status, hepatic function, and vascular integrity, all of which are compromised in severe dengue [24]. Monitoring albumin levels may provide additional prognostic information and guide decisions regarding colloid administration in patients with refractory shock.

The mortality rate of 2.6% among severe dengue cases in our study is consistent with reported case fatality rates of 1-5% for severe dengue with appropriate management [25]. The single death in our cohort occurred in a patient presenting late with established shock, emphasizing the importance of early recognition and aggressive supportive care.

Study limitations include the single-center design, which may limit generalizability to other endemic regions with different circulating serotypes and population characteristics. Viral serotyping was not performed, precluding analysis of serotype-specific severity patterns. Additionally, the relatively short follow-up period did not capture long-term sequelae of dengue infection.

## Conclusion

This study demonstrates that severe dengue in children is characterized by profound thrombocytopenia, significant hemoconcentration, and marked hepatic transaminase elevation. Platelet count below 50,000/ $\mu$ L, hemoconcentration exceeding 20%, AST elevation greater than three times normal, and hypoalbuminemia are independent predictors of severe disease.

The platelet-to-hematocrit ratio represents a simple, cost-effective tool for early risk stratification that can be readily implemented in resource-limited endemic settings. Early recognition of high-risk patients using these laboratory parameters enables timely intervention and appropriate allocation of healthcare resources, potentially reducing morbidity and mortality associated with severe pediatric dengue.

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