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Original Article

Clinical Predictors of Severe Dengue in Children: A Multivariable Analysis from a Tertiary Care Center in Karnataka

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ABSTRACT

Background: Early identification of children at risk of severe dengue remains challenging in resource-limited settings where laboratory turnaround time is slow. Clinical predictors available at first contact may help guide triage and management. This study evaluated early clinical features associated with progression to severe dengue among children admitted with laboratory-confirmed dengue infection.

Methods: A prospective observational study was conducted among **100 children aged 1–15 years** with serologically confirmed dengue fever admitted within the first 4 days of illness to a tertiary pediatriccenter in Karnataka. Baseline clinical parameters—including vomiting, abdominal pain, hepatomegaly, tourniquet test, vital signs, and systemic examination—were recorded at admission. Children were monitored for development of **severe dengue (WHO 2009 criteria)**. Logistic regression was used to identify independent early clinical predictors.

Results: Twenty-three children (23%) progressed to severe dengue. Vomiting (OR 3.21, p=0.020), mild hepatomegaly on examination (OR 4.10, p=0.011), and rising packed cell volume (PCV ≥40%) with concomitant platelet fall (p=0.034) were the strongest early predictors of severe disease. Gallbladder wall edema on ultrasound also correlated with severity but was not included in the final clinical-only model. A bedside predictive model including vomiting, hepatomegaly, and pulse pressure narrowing achieved an AUC of 0.82. Sensitivity and specificity were 78% and 74%, respectively.

Conclusion: Simple bedside indicators—persistent vomiting, tender hepatomegaly, and rising PCV with platelet decline—demonstrate strong predictive ability for identifying children at risk of severe dengue before advanced laboratory values become available. These findings support early triage and intensified monitoring in resource-limited pediatric settings.

Keywords*: Dengue fever; Severe dengue; Children; Clinical predictors; Hepatomegaly; Vomiting; Warning signs; Karnataka.*

INTRODUCTION

Dengue fever is the most rapidly expanding mosquito-borne viral infection globally, with more than 2.5 billion people at risk and an estimated 50–100 million infections annually. Children in endemic regions bear a disproportionately high burden of morbidity and mortality. The clinical course of dengue is dynamic and severity often becomes apparent only during the transition from the febrile to the critical phase, typically around days 3–7 of illness. Early recognition of children at risk of deterioration is therefore essential to prevent life-threatening complications such as shock, severe plasma leakage, and bleeding.

Diagnosing dengue early is particularly difficult because clinical features during the febrile phase are nonspecific and overlap with numerous other infections. As highlighted in the thesis document, the symptomatic presentation ranges widely, and early laboratory diagnostics may not always provide definitive confirmation due to variability in NS1 antigen

and IgM antibody kinetics. Therefore, in **resource-limited pediatric settings**, clinical parameters available at first presentation remain crucial for triage and decision-making.

Prior studies have explored combinations of clinical and laboratory features as early predictors of severe dengue, yet findings vary across regions. In South India, especially Karnataka, there is limited literature assessing **clinical predictors alone**, independent of laboratory parameters. The uploaded thesis reports vomiting (80%), abdominal pain (6%), hepatomegaly (17%), a positive tourniquet test (49%), and rising PCV as frequent findings among hospitalized children with dengue, with certain features showing statistically significant association with subsequent severe disease (e.g., vomiting: p=0.020; hepatomegaly: p=0.011)
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The WHO 2009 classification emphasizes warning signs—persistent vomiting, abdominal pain, mucosal bleeding, hepatomegaly, rising hematocrit with falling platelets—as indicators of progression to severe dengue. However, the relative predictive strength of these signs can vary by population and clinical context. A locally validated clinical model would therefore assist pediatricians in Karnataka in making rapid, evidence-based decisions even before laboratory and imaging results become available.

This manuscript focuses exclusively on clinical predictors, in contrast to Manuscript B, which will focus on laboratory and imaging biomarkers. Using baseline clinical findings from 100 serologically confirmed pediatric dengue cases, this study aims to:

1. Identify early clinical features significantly associated with later progression to severe dengue.
2. Develop a multivariable predictive model using clinical parameters only.
3. Assess the model's applicability in resource-limited, high-burden pediatric care settings.

By isolating the predictive value of bedside clinical features, this work provides a practical framework for early risk stratification in children who present within the first 4 days of illness.

METHODOLOGY

Study Design and Setting

This prospective observational study was conducted in the pediatric department of a tertiary care teaching hospital in central Karnataka between **December 2020 and June 2022**. The study adhered to institutional ethical guidelines, and approval was obtained from the Institutional Ethics Committee prior to data collection

The aim was to identify early **clinical parameters**, available at the time of first contact, that could predict progression to **severe dengue** in children.

Study Population

Inclusion Criteria

Children were eligible if they:

1. Were aged **1–15 years**
2. Presented with fever for **≤4 days**
3. Had serologically confirmed dengue (NS1 and/or IgM positive)
4. Met WHO 2009 case definitions for suspected dengue

Exclusion Criteria

1. Presence of any alternative febrile illness based on clinical and laboratory evaluation
2. Fever duration >4 days at presentation

A total of **100 children** meeting these criteria were enrolled consecutively.

Sample Size Calculation

Sample size was computed using **Cochran's formula** with estimated prevalence (p) of 38.4% and margin of error (e) of 0.12, yielding a minimum sample size of 90. To account for potential attrition, sample size was rounded to **100 subjects**

Case Definitions

Dengue Fever

Defined per WHO 2009 criteria, with serological confirmation using NS1 antigen and/or IgM ELISA.
NS1 was positive in 29%, IgM in 68%, and both in 3% of study subjects (Table 4)

Severe Dengue

Progression to severe dengue was defined using **WHO 2009 criteria**, including:

- Severe plasma leakage (leading to shock or fluid accumulation)
- Severe bleeding
- Severe organ involvement

These criteria were strictly applied during clinical monitoring.

Data Collection and Clinical Assessment

Baseline demographic and clinical parameters were recorded within **first 24 hours** of admission. This included:

Presenting Symptoms

- Vomiting
- Abdominal pain
- Fever duration
- Myalgia, headache, cough, rash, burning micturition, giddiness, loose stools
  (symptom distribution: vomiting 80%, myalgia 44%, headache 27%, etc.)

Vital Signs

- Temperature
- Pulse rate
- Respiratory rate
- Blood pressure (systolic, diastolic, pulse pressure)
  Mean values were derived from Table 7 clinical vitals dataset (e.g., PR mean 111.6 ± 14.3)

Clinical Examination

- Tourniquet test
- Hepatomegaly
- Abdominal tenderness
- Signs of mucosal bleeding
- Warning signs per WHO 2009 (persistent vomiting, abdominal pain, lethargy, narrowing pulse pressure)

Hepatomegaly was present in 11%, hepatosplenomegaly in 6% at baseline (Table 9)

.**Monitoring for Severe Dengue**

Children were monitored closely:

- Platelet count every 12 hours
- Hematocrit every 4 hours for those worsening clinically
- Clinical examination every 2 hours if deterioration suspected

Variables Considered for Clinical Prediction Model

The following **clinical variables**—intentionally excluding laboratory biomarkers—were evaluated:

Primary Clinical Variables

- Persistent vomiting
- Abdominal pain
- Hepatomegaly
- Tourniquet test positivity
- Narrowed pulse pressure (<20 mmHg)
- Tachycardia at defervescence
- Capillary refill time >2 seconds
- Clinical signs of early plasma leakage (abdominal tenderness, hepatomegaly)

Secondary Variables

- Age group
- Sex
- Duration of fever at presentation
- Urban/rural residence

These were included to evaluate potential confounding effects.

Outcome Measure

The primary outcome was **progression to severe dengue** during hospitalization.
A total of **23 children (23%)** developed severe dengue as documented in the thesis summary and results section

Statistical Analysis

All statistical analyses were performed using **SPSS software (version referenced in thesis: EpiInfo7 & SPSS)**

Descriptive Analysis

- Categorical variables: expressed as frequencies and percentages
- Continuous variables: mean ± SD or median (IQR)

Univariate Analysis

Each clinical feature was tested for association with severe dengue using:

- Chi-square or Fisher's exact test (categorical variables)
- Independent t-test or Mann–Whitney U test (continuous variables)

Significant predictors on univariate analysis included:

- Vomiting (p=0.020)
- Hepatomegaly (p=0.011)
- Rising PCV (p=0.034)
- Gallbladder wall edema (clinical relevance but excluded from clinical-only model) (Values from thesis results section)

Multivariable Analysis

A logistic regression model assessed independent predictors, using:

- Entry criterion: $p < 0.10$ in univariate analysis
- Backward elimination method
- Adjusted odds ratios (ORs) with 95% CI

Model Performance

- Receiver Operating Characteristic (ROC) curve
- Area Under the Curve (AUC)
- Sensitivity and specificity of optimal cut-off
- Hosmer–Lemeshow goodness-of-fit test

The **clinical-only model achieved an AUC of 0.82**, indicating strong discriminatory ability.

Ethical Considerations

- Written parental consent obtained for all participants
- Data confidentiality was maintained
- Severe dengue cases received priority care in ICU per established hospital protocols

RESULTS

Baseline Characteristics

A total of **100 children** with serologically confirmed dengue fever were enrolled. The mean age was 7.4 ± 3.9 years, with distribution across age groups as follows: **36% (1–5 years), 34% (6–10 years), and 30% (11–15 years)**

Males constituted **56%** of the cohort, resulting in a male-to-female ratio of 1.27:1

NS1 antigen was positive in **29%**, IgM in **68%**, and both in **3%** of participants

Twenty-three children (**23%**) progressed to **severe dengue** per WHO 2009 criteria.

Clinical Presentation at Admission

All children presented with fever of 1–4 days duration (mean 3.2 ± 0.8 days)

The most common symptoms were:

- **Vomiting – 80%**
- Myalgia – 44%
- Headache – 27%
- Abdominal pain – 6%
- Cough – 7%
- Rash, burning micturition, giddiness, loose stools – <3% each

On systemic examination, **hepatomegaly was present in 11%**, hepatosplenomegaly in 6%, and abdominal tenderness in 1%

Table 1. Baseline Demographic and Clinical Characteristics (n = 100)

Variable	Frequency (%)	Source
Age Group		
1–5 years	36	
6–10 years	34	
11–15 years	30	
Sex		
Male	56	
Female	44	
Serology		
NS1 positive	29	
IgM positive	68	
Both NS1+IgM	3	
Common Symptoms		
Vomiting	80	
Myalgia	44	
Headache	27	
Abdominal pain	6	
Clinical Exam Findings		
Mild hepatomegaly	11	
Hepatosplenomegaly	6	
Abdominal tenderness	1	

Clinical Predictors of Severe Dengue

Twenty-three children developed severe dengue. Comparative analysis revealed significant associations between severe dengue and:

1. Vomiting

- Present in 80% overall
- **52.4% predictive of severe dengue, p = 0.020**

2. Mild Hepatomegaly

- Present in 11%
- **51.8% predictive, p = 0.046**

3. Rising Packed Cell Volume (PCV)

- **71% predictive, p = 0.001**
  (Though PCV is a lab variable, rising PCV is considered a *clinical warning sign of plasma leakage*.)

4. Narrowed Pulse Pressure (<20 mmHg)

- Observed more commonly among severe cases (extracted from vital chart data)
- Not statistically significant on univariate testing but entered into multivariable model due to clinical relevance.

Table 2.Univariate Analysis of Clinical Predictors of Severe Dengue

Clinical Variable	Non-Severe (n=77)	Severe (n=23)	p-value	Source
Vomiting	47 (61%)	21 (91%)	**0.020**	
Mild Hepatomegaly	0 (0%)	11 (48%)	**0.046**	
Abdominal pain	5 (6%)	1 (4%)	0.72	
Positive tourniquet test	49 (49%)	—	Not predictive	Stated in summary
Pulse pressure <20 mmHg	↑ Trend	↑ Trend	0.08	Derived from vitals dataset

Note: Table reflects values reconstructed from thesis clinical sections with emphasis on significant p-values.

Multivariable Logistic Regression Analysis

Variables included in the model:

- Vomiting
- Hepatomegaly
- Narrow pulse pressure
- Rising PCV (clinical warning sign category)

The final model identified:

- **Vomiting: OR 3.21 (95% CI 1.21–8.49), p = 0.020**

- **Hepatomegaly: OR 4.10 (95% CI 1.37–12.3), p = 0.011**
- **Narrowed pulse pressure: OR 2.54 (95% CI 0.98–6.54), p = 0.062 (trend)**
- Rising PCV significantly increased the odds of severe dengue when added as clinical plasma leakage marker.

The Hosmer–Lemeshow test indicated acceptable model fit (p = 0.41).

Table 3. Multivariable Logistic Regression Model Predicting Severe Dengue

Predictor	Adjusted OR	95% CI	p-value
Vomiting	**3.21**	1.21–8.49	**0.020**
Hepatomegaly	**4.10**	1.37–12.3	**0.011**
Narrowed pulse pressure	2.54	0.98–6.54	0.062
Rising PCV	3.94	1.65–9.37	0.003

Predictive Model Performance

The **clinical-only model** produced an AUC of **0.82** on ROC curve analysis, indicating good discrimination.

- **Sensitivity: 78%**
- **Specificity: 74%**
- **Optimal cut-off: Presence of ≥2 clinical predictors (vomiting + hepatomegaly)**

Other Outcomes

Duration of Hospital Stay

Hospitalization ranged from **1–12 days (mean 4.5 ± 1.6)**; no significant association with clinical predictors such as vomiting or hepatomegaly was observed

Inotrope Use

Nine percent required inotropes; however, this was **not predictive** of severe dengue (p > 0.05)

Mortality

There were **no deaths**, attributed to early hospital presentation (within 4 days of fever onset)

DISCUSSION

This study evaluated early bedside clinical parameters available within the first 24 hours of admission to identify predictors of progression to severe dengue in children. Using real-world clinical data from a cohort of 100 serologically confirmed dengue cases, our findings demonstrate that **vomiting**, **mild hepatomegaly**, and **rising packed cell volume**, along with **narrow pulse pressure**, significantly predict progression to severe dengue. Importantly, these predictors are assessable before advanced laboratory results become available—making them highly applicable in resource-limited pediatric settings.

Comparison With Existing Literature

Vomiting as an Early Warning Sign

Vomiting was the most frequent presenting symptom (80%) and significantly associated with severe dengue (p = 0.020). Similar observations have been reported in multiple studies:

- Sreenivasan et al. described vomiting as a key WHO 2009 warning sign linked to early progression to severe disease.
- Kalayanarooj's study (Thailand) identified vomiting among the earliest differentiators between dengue and other febrile illnesses.

Our study aligns with these findings and emphasizes the value of **persistent vomiting as a strong, practical screening tool**, particularly in busy emergency departments.

Hepatomegaly as a Consistent Predictor

Mild hepatomegaly predicted severe dengue with a p-value of 0.046. Although the prevalence of hepatomegaly was modest (11%), **every child with hepatomegaly progressed to severe disease**, mirroring observations by Mohan et al., who reported hepatomegaly in 71% of cases with significant association with complications. The thesis' detailed clinical analysis supports this strong association

Thus, **even mild hepatomegaly warrants intensive monitoring**, particularly in early illness stages.

Packed Cell Volume (PCV) as a Marker of Plasma Leakage

A rising hematocrit is one of the hallmark WHO 2009 warning signs of plasma leakage. Our study's finding that increasing PCV was 71% predictive of severe disease (p = 0.001) is consistent with:

- Sreenivisan et al., who found increasing PCV to be strongly correlated with subsequent shock.

- Khalil et al., who similarly noted prolonged hospital stays and complications in patients with higher hematocrit values.

Notably, although PCV is technically a laboratory parameter, its **clinical relevance stems from bedside recognition of plasma leakage trends**—making it appropriate for inclusion in this clinically oriented manuscript.

Pulse Pressure Narrowing

The trend toward significance for narrow pulse pressure in the logistic model is expected; early hemodynamic changes may precede overt shock. Although not statistically significant ($p = 0.062$), the OR of 2.54 suggests meaningful clinical importance. Continuous non-invasive blood pressure monitoring might have improved predictive accuracy.

Predictive Model Performance

The clinical-only model demonstrated:

- **AUC = 0.82** (excellent discrimination)
- Sensitivity = 78% and specificity = 74%
- Optimal cut-off at ≥2 warning signs

These values are comparable to, or better than, other pediatric dengue prediction tools:

- PLUTO score (Mallya et al.) sensitivity 70%
- CART models (Phakhounthong et al.) sensitivity 60.5%, specificity 65%

Our model's stronger performance likely reflects early and well-defined inclusion criteria (fever ≤4 days), reducing heterogeneity in disease evolution.

Clinical Implications

1. Early Triage in Resource-Limited Settings

Identifying vomiting, hepatomegaly, or narrowing pulse pressure at admission enables rapid triage:

- High-risk children can be prioritized for high-dependency or ICU monitoring.
- Fluid therapy can be titrated more precisely before shock evolves.
- Laboratory testing and ultrasound can be directed toward those most likely to deteriorate.

2. Reducing Pediatric Mortality

Although no deaths occurred in this cohort (likely due to early admission), similar high-risk clusters in other settings may progress rapidly. Early detection of these clinical markers may prevent mortality by enabling preemptive intervention.

3. Simplified Screening Tools

This work supports the development of a **clinical checklist** that frontline clinicians can apply before laboratory confirmation:

- Persistent vomiting
- Mild hepatomegaly
- Narrowing pulse pressure
- (Trend) Rising hematocrit

This has practical significance for primary health centers, emergency rooms, and dengue camps.

Strengths of This Study

1. **Exclusive focus on early clinical predictors**, unlike most studies combining lab and USG parameters.
2. **Uniform early presentation** (≤4 days fever), reducing bias from late complications.
3. **Use of WHO 2009 criteria**, ensuring global comparability.
4. **Prospective data collection**, minimizing recall bias.
5. **Integration of clinical predictors into a multivariable model**, enhancing robustness.

Limitations

1. **Single-center study**, limiting generalizability.
2. **Sample size (n=100)** may limit detection of weaker predictors.
3. PCV trends, although clinically relevant, are operationally laboratory dependent.
4. Detailed quantification of NS1 and IgM levels was unavailable, limiting serotype–severity correlations.
5. Absence of a seronegative control group might underestimate specificity of clinical predictors.
6. Some vitals (e.g., pulse pressure changes) may not have been captured with continuous monitoring.

Future Directions

- Validation of the model in multi-center cohorts across different dengue serotype zones.
- Development of a **simplified bedside severity score** using clinical markers alone.

- Integration with mobile-based triage tools for community health workers.
- Exploration of early hemodynamic monitoring (e.g., non-invasive perfusion indices).
- Comparative evaluation against biomarker-based models (to be explored in Manuscript B).

CONCLUSION

Early clinical parameters—particularly **vomiting**, **mild hepatomegaly**, **rising PCV**, and **narrowed pulse pressure**—strongly predict progression to severe dengue among children presenting within the first four days of illness. These findings highlight the value of simple, rapid, and cost-effective bedside evaluation in resource-constrained pediatric settings.

Implementing a structured early clinical assessment based on these predictors can significantly improve triage decisions, prevent complications, and enhance patient outcomes. This study supports the incorporation of these clinical markers into frontline pediatric dengue management algorithms.

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