RESEARCH PAPER

Development and Validation of a Bedside Dengue Severity Score for Predicting Severe Dengue in Children

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Objective: To develop and validate a bedside dengue severity score in children less than 12 years for predicting severe dengue disease.

Methods: We carried out an analysis of data on the clinical and laboratory parameters of patients with confirmed dengue, hospitalized in October, 2019 at our center. A comprehensive patient's score was developed. Predictive models for severity were built using a forward step-wise method. This model was validated on the data of 312 children with dengue admitted during September- October, 2021.

Results: Severe dengue was predicted by the dengue severity score with a sensitivity of 86.75% (95% CI 77.52%-93.19%), specificity of 98.25% (95% CI 95.56-99.52%), a positive predictive value of 95.34% (95% CI 92.18%-97.26%) and a negative predictive value of 94.74% (95% CI 87.16%-97.95%). The overall predictive accuracy was 95.2% (95% CI 92.19%-97.28%).

Conclusion: The proposed bedside dengue severity scoring system was found to have good validity. Validating the score in different settings and patient populations is suggested.

Keywords: *Management, Mortality, Obesity, Outcome, Prognosis*.

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Dengue fever is the most prevalent human arboviral infection and a major public health issue in the tropics [1]. In 2021, the National Vector Borne Disease Control Program (NVBDCP) reported 1,93,254 laboratory-confirmed cases of dengue in the country [2]. With monsoon epidemics overwhelming our hospitals, it is crucial to identify the risk factors for severe dengue. By assessing the validity of such predictors, operational solutions can be established, thereby, reducing the burden on the health care system [3].

Previously available dengue severity scores, proposed from other countries, involve laborious calculations. With modest specificity and sensitivity, these scores rely on extensive laboratory parameters [4]. Derived scores that aim to classify patients into different categories, have overlapping scores amongst the severity categories, thereby limiting their clinical applicability [5]. There is tremendous diversity in dengue endemicity in different parts of the world and even within the same country [6].

We, herein, report the development and validation of a bedside dengue severity score in children less than 12 years, for prediction of severe dengue disease.

METHODS

A model scoring system was built for predicting severe dengue using data from hospital records for 125 children who were admitted with dengue in the month of October, 2019. The derived score was deployed in children with dengue prospectively for validation. Based on total number of dengue cases admitted during peak dengue season (September, 2019 to January, 2021), an initial sample size of 380 was determined. Pilot research was conducted using 10% of this sample size, and the findings of the pilot research were used to estimate the actual sample size for the study. Using G*Power software (version 3.1.9.2), a power of 80%, a level of significance (*P* value) set at 5%, a confidence interval of 95% and prevalence data obtained from the pilot study (5.1%), the sample size was estimated to be 312 for the final study group.

Invited Commentary: Pages 341-42.

The study was approved by the institutional ethics committee of our institute. For the model prediction and validation, the same inclusion and exclusion criteria were used. The study population included children admitted in the inpatient wards of the Institute of Child Heath,

Chennai, with fever and positive NS1 Ag and/or IgM Elisa dengue in the age group of 2 month - 12 year. Co-infection with other tropical diseases, and fever with any identified focus of infection were excluded. Further, for score validation, the children were enrolled in the febrile phase.

Fourteen risk factors for severe dengue were taken from the National guidelines on dengue (2020) [7] to develop the severity score (**Web Box I)**. Obesity, which is claimed to be positively associated with severe dengue [8], was also included. Narrow pulse pressure (≤20 mm /Hg) in the absence of circulatory shock is indicative for fluid leak from the intravascular compartment. Pulse pressure is also considered a reliable indicator of fluid responsiveness [9]. Hence, narrow pulse pressure in the absence of shock was considered as one of the possible risk factors for severe dengue.

Severe dengue was defined by the revised World Health Organization (WHO) 2009 disease classification [10] and NVBDCP 2020 criteria (**Web Box II**) [7]. Disease outcome was primarily classified as severe and non-severe.

Statistical analysis: Data were analyzed using IBM SPSS version 20.0 (IBM Corp). Binary logistic regression was used to develop the prediction severity model. A forward stepwise method was used by the model in three steps to identify three variables as significantly predicting the dependent variable. The Nagelkerke square was used to quantify how much the predicted variables influenced the result. Hosmer-Lemeshow test was used to determine the fitness of the regression model. Using Canonical discriminant function coefficient, the ability of the identified (significantly associated) risk factors to effectively discriminate between severe and non-severe dengue were calculated. Linear discriminant analysis was used for the estimation of coefficients as the risk factors are not completely independent of each other and a predictive score was developed. The means of the discriminant function was given by Functions at group centroids and the score value necessary to differentiate between severe and non-severe dengue were given. Validity of the constructed model was deployed on 2021 data; sensitivity, specificity and predictive accuracy were calculated.

RESULTS

With forward stepwise regression, three variables were identified as significantly predicting the disease outcome viz., the presence of mucosal bleed [OR (95% CI) 29.81 (6.49-136.85); *P*<0.001], narrow pulse pressure [OR (95%CI) 287.48 (80.27-1029.62); P<0.001] and third space fluid accumulation [OR (95% CI) 6.42 (2.11-19.48); *P*= 0.001]. Other risk factors studied were not significantly associated with severe disease in the 125 children used for score development. Nagelkerke R Square showed that these three predictors influenced dengue severity by 80.8%.

Hosmer-Lemeshow test assessed the goodness of fit of the model. In Step 3, the model strengthened and became significant (*P*=0.026), when three variables of good significance were added (narrow pulse pressure, minor mucosal bleed and third space fluid accumulation). Using Canonical discriminant function for all the three variables, the equation for scoring was calculated as follows:

Bedside Dengue Severity Score = -1.297+ 4.234 (narrow pulse pressure) + 1.284 (mucosal bleed) + 0.489 (third space fluid loss)

In the score, -1.297 is the constant and 4.234, 1.284, and 0.489 were the coefficient of narrow pulse pressure, mucosal bleed and third space fluid loss, respectively. The score was calculated, by applying the variables in the formula as number 1 and 0 for presence and absence, respectively. From functions at the group centroid, values closer to -1.056 were predicted to devlop non severe dengue and values closer to 2.913 were proposed to develop severe dengue; the midpoint being 0.9285.

Table I Characteristics of Children With Dengue Fever (*N*=312)

Characteristics	*Value*
Age (y)[a]	6.4 (3.44)
Infants	19 (6)
Obese children	12 (3.8)
Immunodeficient children	9 (2.8)
Chronic illness	7 (2.2)
Bleeding tendency	1 (0.3)
Abdominal tenderness	111 (35.5)
Hepatomegaly	53 (16.9)
Persistent vomiting	148 (47.4)
Lethargy	92 (29.4)
Narrow pulse pressure	73 (23.4)
Hematocrit rise	56 (17.9)
Rapid fall in platelets	39 (12.5)
Minor mucosal bleed	20 (6.4)
Third space fluid loss	122 (39.1)
Dengue severity	
Mild dengue	110 (35.5)
Dengue with warning signs	119 (38.14)
Severe dengue	83 (26.6)
Dengue deaths	8 (2.5)

Values in no. (%) or [a]mean (SD).

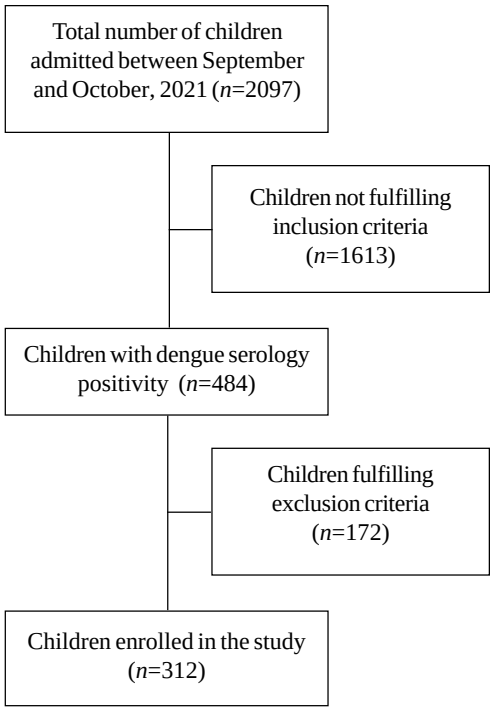


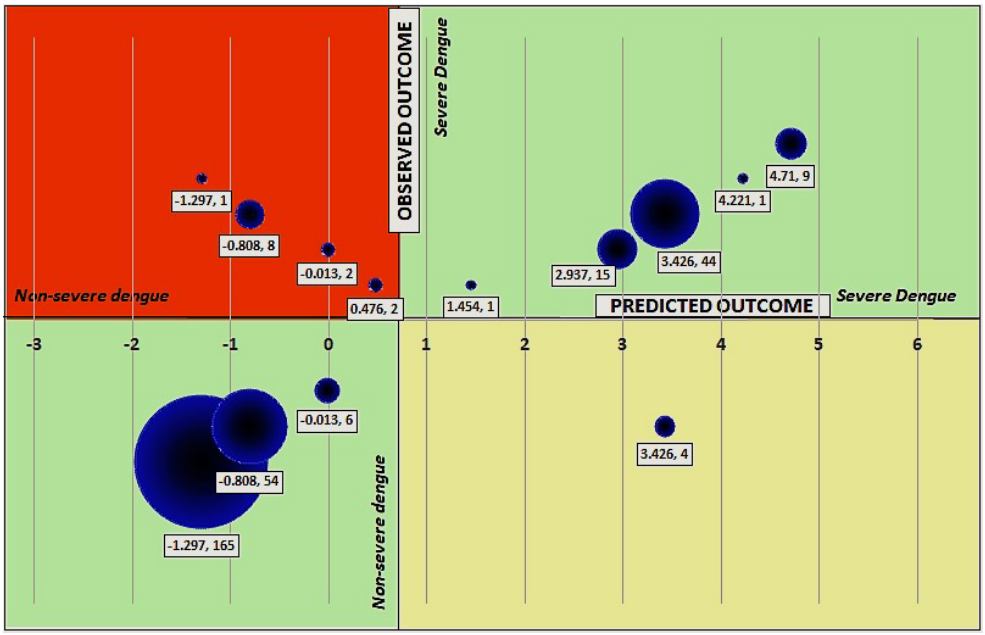
Fig.1 *Flow of patients in the study.*

Table II Diagnostic Performance of the Bedside Dengue Severity Scoring System in Children

Measure	*Value (95% CI)*
Sensitivity	86.75% (77.52-93.19)
Specificity	98.25% (95.59-99.52)
Positive predictive value	95.34% (92.18-97.26)
Negative predictive value	94.74% (87.16-97.95)
Accuracy	95.19% (92.19-97.28)

The score was validated by applying it on the data collected in the year 2021. The clinical characteristics of the 312 children (62.8% boys) enrolled is given in **Table I** and the flow of patients in the study for validation is given in **Fig. 1**. There was no loss to follow-up and no patient was discharged against medical advice in the cohort. Mean (SD) age was 6.4 (3.44) years.

Fig. 2 shows the bubble chart graph illustrating outcome of study sample. Non-severe dengue was predicted by the score in 236 children, and was observed in 225 children; whereas, severe dengue was predicted in 78 and observed in 72 children. The score identified severe dengue with 86.7% sensitivity and 98.25% specificity, and 95.2% overall predictive accuracy (**Table II**).



The label beneath each bubble reads the score, followed by the number of children with that score, from left to right. The size of the bubble is proportionate to the number of children with the specific score. The X-axis represents the outcome predicted by the score as severe and non-severe dengue with values closer to 2.913 being severe and values closer to -1.056 being non-severe dengue with the midpoint being 0.9285. The Y-axis depicts the observed disease outcome, categorized as severe or non-severe. The green quadrants (left lower and right upper) reflect those cases in which the predicted outcome matched the observed outcome. The orange (left upper) quadrant shows those cases where the predicted outcome was non-severe but was observed to have severe dengue. The yellow (right lower) quadrant displays the cases where the cases were predicted to have severe dengue but were observed to have non-severe dengue.

Fig. 2 *Bubble chart graph illustrates the outcome of the study sample.*

WHAT IS ALREADY KNOWN?

- Co morbidities and presence of warning signs predispose to severe dengue, but there is no operational tool to predict the severity.

WHAT THIS STUDY ADDS?

- A scoring system is provided that can be generated rapidly at the bedside and can predict severe dengue with good accuracy.

DISCUSSION

In this study, we devised a severity score that could be reliably performed at the bedside with three validated risk factors. Narrow pulse pressure in the absence of circulatory shock was considered as an important predictor of severe dengue, as it may be an early marker of reduced effective circulating volume. The existing criteria for admission, diagnosis, and discharge were not altered. If the values of 0 and 1 are substituted in the formula, for the presence or absence of narrow pulse pressure, mucosal bleed and third space fluid loss, the score can be calculated manually in less than a minute.

Several researchers have devised scoring system to predict dengue severity, but most of them require extensive investigatory backup. The score developed by Phakounthong, et al. [13] from Cambodia had modest sensitivity and specificity and also requires a good laboratory backup, which may not be available at all levels of care. Compared to this, the score currently described has good specificity and positive predictive values, relies solely on clinical criteria, and can be adapted to most levels of care. Tangnararatchakit, et al. [4] had devised a daily dengue severity score, which consisted of 14 parameters, making the application tedious and cumbersome. In this study, the clinical outcomes depended on quality of patient care. Further, there was a possibility of variation in each parameter for scoring that could affect the final score [4]. Pongpan, et al. [5] had devised a score on a large scale for children in Thailand but the generated score could correctly classify patients into their original severity levels only 60% of the time, and had an unacceptable under-estimation and over-estimation levels of 25.7 % and 13.5 %, respectively [5].

Detection of third space fluid accumulation and gall bladder wall thickening can be easily done by point of care ultrasonogram (POCUS) [14]. The current score can be calculated based on history, clinical examination and POCUS, and can be derived at the bedside with the widespread availability of POCUS, and improved competency and training of pediatricians.

Due to the dynamic nature of the disease, which may vary in different phases of illness, it is encouraged that the score be applied frequently in children with proven or suspected dengue, especially in the critical phase, so that, severe disease can be anticipated earlier. Owing to this score's high sensitivity and positive predictive value, it can be used in triaging children with predicted severe dengue to facilitate prompt referral to higher centers. In tertiary care centers, this could be used for better monitoring of children, and improved utilization of resources/infrastructure to increase the survival of children with life threatening disease.

Limitations of the study include that the study subjects predominately were from the poor socio-economic status and may not be representative of the general population. The generation of the score was done from retrospective data, and therefore the fluctuating nature of the risk factors was not accounted for during score formulation. Serum IgG dengue was not performed in our hospital routinely and this was not assessed as a risk factor for severe dengue. Since the study requires performing bedside ultrasound to identify third space fluid accumulation, its utility in primary healthcare facilities remains uncertain.

The Bedside Dengue Severity Scoring developed reliably predicted severe dengue with scores closer to 2.913. It is believed that by promoting early referral, aiding vigilant observation, and better resource allocation in resource-limited settings, this scoring system might contribute to a reduction in morbidity and death associated with severe illness. It is suggested that similar studies may be conducted at different levels of care, before application to the general population.

Ethics clearance: EIC, Madras Medical College; No. 15112021 dated Nov 3, 2021.
Contributors: VG: conceptualized the study, was involved in collecting data, analyzing data, manuscript preparation and case management; SVL: was involved in case management and manuscript preparation; SS: was involved in case management and manuscript preparation; VP: was involved in data collection, management of cases and manuscript preparation; SK: was involved in manuscript preparation, critical review of manuscript and data analysis. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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Note: Additional material related to the study is available with the online version at *www.indianpediatrics.net*

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Web Box I Risk Factors for Severe Dengue Used for Development of Dengue Severity Score

- Infancy
- Lethargy
- Obesity (BMI >27th adult equivalent)
- Persistent vomiting (≥2 times/d) [10]
- Third space fluid loss[a]
- Narrow pulse pressure (≤20 mm Hg) in the absence of circulatory shock
- Immunosuppressed condition[b]
- Hematocrit rise ≥20% from baseline
- Chronic illness[c]
- Rapid fall in platelets (to <50000/µL from ≥100000/µL taken 24 h apart)
- Bleeding tendency (primary or acquired due to drugs/ diseases)
- Abdominal tenderness
- Mucosal bleeding[d]
- Hepatomegaly[e]

[a]Periorbital puffiness, gall bladder wall edema, Free fluid in pleural/peritoneal cavity identified clinically or by imaging; [b]Primary or acquired due to conditions like SAM, Nephrotic syndrome, drugs like steroids/chemotherapeutic drugs other immunosuppressant drugs; [c]Chronic conditions like Chronic liver/GI disease, chronic kidney disease, chronic lung disease/hematological conditions etc.; [d]bleeding from sites other than skin and visceral organs e.g.epistaxis, gum bleed, not causing hemodynamic compromise; [e]by palpation/percussion method or ultrasonography.

Web Box II Severity Classification

Patients were classified as severe if they had at least one of the following:

- shock – compensated and decompensated;[a]
- fluid accumulation causing respiratory distress;
- severe hemorrhage;
- severe organ failure (central nervous system,[b] acute kidney injury,[c] liver,[d] heart,[e] etc).

[a]defined as per Pediatric emergency medicine course (PEMC) guidelines, which is the standard protocol followed in our institution [11]. [b]impaired consciousness/seizure/altered behavior [Dengue encephalitis- detecting anti DENV IgM/Viral RNA/NS1and exclusion of other causative agents of viral encephalitis by cerebrospinal fluid analysis and/or magnetic resonance imaging findings; Dengue encephalopathy- altered sensorium due to edema/ severe hypo-natremia/renal or liver dysfunction/metabolic acidosis/release of toxic substance even if there is no CSF abnormality]. [c]defined as an abrupt reduction in kidney function defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL,≥50% increase in serum creatinine from baseline, or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than six hours). (as per AKIN criteria)[12]. [d]defined by transaminase levels above 1000IU/L. (aspartate transaminase or alanine transaminase).[e]defined as clinical evidence of congestive cardiac failure with cardiomegaly on chest X-ray and ECHO by trained intensivist or cardiologist showing reduced ejection fraction <55% or left ventricular wall motion abnormality.