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Abella MAG, Ranile BM. Accuracy of the Daily Dengue Severity Score in Assessing Disease Severity in Children
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ORIGINAL ARTICLE

ACCURACY OF THE DAILY DENGUE SEVERITY SCORE IN ASSESSING DISEASE SEVERITY IN CHILDREN

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ABSTRACT

Background*:* Dengue is a global health concern, particularly in tropical regions such as the Philippines. In 2019, Cebu City reported the highest number of dengue cases in Central Visayas with 3,290 cases and 20 deaths, an 11.8% increase compared to 2018[1]. To help predict disease outcomes and provide timely management, a scoring system, the Daily Dengue Severity Score (DDSS)[2] was utilized.

Objective: To determine the clinicodemographic profile of dengue patients, determine the accuracy of the DDSS in assessing disease severity, and determine a cut off score that suggests severe dengue.

Methods: Patients 1 month to 18 years admitted for dengue at Perpetual Succour Hospital from January 2018 to December 2020 were included. Cases were classified as Dengue without Warning Signs, Dengue with Warning Signs, and Severe Dengue, and scored using the DDSS. Statistical analysis used were Geometric mean and Area Under the Receiver Operating Characteristic (AUROC) curves to analyze the discriminative performance of the DDSS among the different disease severity states.

Results: Out of 327 cases, 34 were classified as Dengue without Warning Signs, 271 Dengue with Warning Signs, and 22 Severe Dengue. The highest mean DDSS was 17.7 ±14.0 at Day -4 among those with Severe Dengue, and the lowest mean DDSS was 1.1 ± 2.0 at Day +3 among those with Dengue without Warning Signs. A cut off point of 10 on Day -1 predicted subsequent Severe Dengue among patients with Dengue with Warning Signs. In 91.39% of cases, there was a significant relationship between the DDSS and dengue classification, and the higher the DDSS, the more severe the disease.

Conclusion: Majority of dengue patients were males, aged 8.1 to 9.2 years. DDSS showed 66.67% sensitivity, 92.86% specificity, a positive likelihood ratio of 9.3, and a cutoff of 10 is predictive of severe dengue among patients with dengue with warning signs.

KEYWORDS: Dengue, Scoring Method, Patient Monitoring

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INTRODUCTION

In 2019, Cebu City in the Philippines faced a dengue outbreak, reporting the highest number of cases in Central Visayas. The city had 3,290 cases and 20 deaths, leading to an 11.8% increase from 2018[1]. This surge contributed to the national declaration of a dengue epidemic in the Philippines in 2019[3]. The Department of Health responded with the implementation of evidence-based strategies to prevent dengue through community education and vector control. However, when prevention efforts fall short, use of clinical management tools can help mitigate the impact of dengue.

Scoring systems are routinely used in the Pediatric Intensive Care Unit (PICU) or in the ward to determine disease severity, based on epidemiological information and clinical signs or symptoms. These are not solely used for dengue infection, but also in patients with other critical conditions, such as sepsis. Several attempts were made to find a suitable tool to predict who among patients with Dengue are at risk of subsequent bleeding, plasma leakage, threatened shock and profound shock during the febrile and critical stages. In 2019, the Dengue Severity Index[4] (DSI) was developed in India by K. Koganti et al., which included parameters such as systolic blood pressure, respiratory rate, partial thromboplastin time (PTT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, platelet count and hematocrit. The DSI can help guide in classifying patients and be more cautions with patients having higher scores, especially during seasons with high admission volume. However, it did not consider other factors such as clinical management that may affect the overall prognosis. Another dengue scoring tool, the Dengue Infection Severity Score (DISS)[5] by Surangrat Pongpan et al., focused on clinical and laboratory parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), and partial thromboplastin time (PTT). A validation of the DISS was done and published in 2014[6] which correctly predicted and classified 50.8% of patients into Dengue Fever, Dengue Hemorrhagic Fever, and Dengue Shock Syndrome, with clinically acceptable underestimation of 18.6% and overestimation of 30.8%. After several trials, formulation of the DDSS[2] by Tangnararatchakit et al. followed, which used 14 parameters, namely, comorbid risk factors, pulse rate, lowest systolic blood pressure and pulse pressure, time to achieve pulse pressure of >20 mmHg and normal blood pressure, amount of crystalloids used, amount of colloids used, urine output, number of bleeding sites, amount of packed red blood cell transfused, amount of platelet concentrate transfused, number of major organ dysfunction, status of re-shock or requirement for inotropes, requirement for ventilator support, and requirement for invasive procedure. In this trial, a score of ≥12 accurately assessed those with severe disease.[2] A validation study of the DDSS by Tangnararatchakit et al. was done in two phases where Phase I established the DDSS as an assessment tool for severe manifestations of the disease, and where Phase II, lookedinto the accuracy of the severity score.

The DDSS has not been applied in the local setting hence, this study aimed to determine the accuracy of the DDSS in assessing disease severity among admitted patients ages 1 month to 18 years old in Perpetual Succour Hospital, Cebu City, Philippines, and determine its overall accuracy to predict Severe Dengue before the day of defervescence based on its sensitivity, specificity, and positive likelihood ratio. This study also aimed to determine and compare the mean DDSS among patients classified as Dengue with warning signs, Dengue without warning signs, and Severe Dengue and determine a cut off score to predict severe outcome in dengue infection. Lastly, it compared the clinicodemographic profile of patients classified as Dengue without warning signs, Dengue with warning signs, and Severe Dengue.

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MATERIALS AND METHODS

Study Design and Population

This was a cross-sectional study which involved patients 1 month to 18 years old with laboratory confirmed dengue infection admitted from January 2018 to December 2020 at Perpetual Succour Hospital, Cebu City, Philippines. Laboratory confirmation of dengue infection was done using either Dengue NS1 antigen test and/or dengue-specific IgM or IgG serology by Immunochromatographic test or Enzyme-Linked Immunosorbent Assay[7].

Excluded were patients who stayed in the hospital for 24 hours or less due to rapid deterioration leading to demise, transferred to another facility in less than 24 hours, discharged in less than 24 hours, and admitted children who are already in the recovery/defervescence phase.

Sampling Procedure and Sample Size Computation

Medical records of patients who fit the inclusion criteria were retrieved and reviewed, and this comprised the sample size. Based on the total Pediatric hospital admissions of 8,134 and the total number of Dengue cases of 1,034 from 2018 to 2020, a computed estimated proportion of 0.13, 0.14, and 0.10 respectively, were taken from each year, with a Desired Precision of 0.05 (5%) and Confidence Interval (CI) of 0.95 (95%). Sample size for each year were calculated using the formula below:

$$n = [Z2 \times P \times (1 - P)] / e2$$

Where: **Z** = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion

e = desired precision (half desired CI width)

The sample size for each year was summed and a total sample size of 327 was derived. Since Severe Dengue cases comprised only 3% of the total cases, and Dengue Fever with Warning Signs comprised 75% of cases, purposive sampling was applied with the objective of testing the accuracy of the DDSS among those with warning signs to identify patients who will progress to severe dengue.

Data Gathering and Analysis Tools

The DDSS is a 14-parameter scoring tool which utilizes data on the clinical presentation and management of dengue infection. Information on these items were obtained from each patient, with a corresponding score assigned to each item. (Table 1). The DDSS was tabulated in an Excel Worksheet and the duration of hospitalization served as a guide as to the number of columns to be prepared. The timing of hospital admission varied across the reviewed cases and was influenced by the onset of illness and day of defervescence. For those admitted more than two days before and/or after D0, the tabulation of the DDSS was adjusted accordingly. This included adding extra columns before D0, designated as D -3 and D -4, and so on, as well as extra columns after D0, designated as D +3 and D +4, as necessary. If the patient was admitted for seven days, there were seven columns where the day of defervescence was designated as D0. One and two days before defervescence was designated as D −1, and D −2, and one and two days after defervescence was designated as D +1, and D +2. Additionally, collection of baseline characteristics, such as age, sex, duration of fever, duration of hospitalization, complete blood cell count, bleeding sites and complications during admission were done. The patient's general information and medical history were also reviewed for co-morbidities and risk factors. Vital signs monitoring sheets were reviewed taking note of the maximum pulse rate, lowest systolic blood pressure (BP), pulse pressure during the 24-hour shift, and time to achieve pulse pressure >20 mmHg and normal BP if there was any hypotension or hypertension. The Input and Output (I & O) Fluid monitoring sheets were also reviewed, and the total amount given to the patient were calculated in ml/Day (for crystalloids), ml/kg/day (for colloids and packed red blood cell), units/kg/day (for platelet concentrate), and ml/kg/hr (for urine output). Other criteria that were reviewed were presence of

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bleeding sites, presence of major organ dysfunction specifically renal failure, hepatic failure, encephalopathy, and acute respiratory distress syndrome; status of re-shock or requirement for inotropes; requirement for mechanical ventilatory support; and requirement for any invasive procedure.

Table 1	Daily Dengue Severity Scoring Tool (DDSS)[2]							
Items				**Max Score**	**D-2**	**D-1**	**D0**	**D+1**	**D+2**
Illness Day on admission: (check one)									
1. Co-morbid risk factors, score 3 for each factors: - Underlying disease - Obesity (weight for height or weight for age >2) - Infant <1 yr - Ibuprofen or Aspirin ingestion)				6					
2. Maximum pulse rate (/min) depends on age				10					
	1yr	1-5 yr	>5 yr						
Score 10	0	0	0						
Score 8	>150	>130	>120						
Score 5	120-150	100-130	100-120						
Score 0	<120	<100	<100						
3. Lowest systolic BP & pulse pressure		BP	pulse pressure	10					
Score 10		0	0						
Score 8		<90	0-9						
Score 6		>90	≤ 10						
Score 4		>90	<20						
Score 2		>90	20						
Score 0		>90	>20						
4. Time to achieve pulse pressure >20 mmHg and normal BP				10					
Score 10	>24 h								
Score 8	≤24 h								
Score 6	≤12 h								
Score 4	≤ 6 h								
Score 2	≤ 1 h								
Score 0	= 0 h								
5. Amount of crystalloid (mL/day)				10					
Score 10	>maintenance + >10% deficit								
Score 8	>maintenance + >7-10% deficit								
Score 6	>maintenance + >5-10% deficit								
Score 4	>maintenance + >3-5% deficit								
Score 2	>maintenance + <3% deficit								
Score 0	≤ maintenance								
	1yr	>1 yr		10					
Score 10	severe	severe							
Score 8	moderate	severe							
Score 6	moderate	severe							
Score 4	mild	moderate							
Score 2	mild	mild							
Score 0	≤ maintenance	≤ maintenance							
6. Maximum urine output (mL/kg/hr) depends on age				10					
	<1 yr	≥1 yr							
Score 10	<1	<0.5							
Score 6	1-1.5	0.5-1.0							
Score 0	>1.5	>1.0							
7. Number of bleeding sites, petechiae ± ecchymosis, score 2 for each other bleeding: - Epistaxis - Hypermenorrhea - Gross Hematuria - Melena - Hematemesis - Hematochezia				10					
8. Amount of colloid (mL/kg/day)				5					
Score 5	>50								
Score 4	<50								
Score 3	<40								
Score 2	<30								
Score 1	<20								
Score 0	= none								
9. Amount of packed red blood cell transfusion (mL/kg/day)				5					
Score 5	>50								
Score 4	≤50								
Score 3	≤40								
Score 2	≤30								
Score 1	≤20								
Score 0	= none								
10. Amount of platelet concentrate transfusion (units/kg/day)				5					
Score 5	>0.8								
Score 4	>0.6-0.8								
Score 3	<0.4-0.6								
Score 2	<02.-0.4								
Score 1	≤0.2								
Score 0	= none								
11. Number of major organ dysfunction, score 3 for each organ: - Renal failure - Hepatic failure - Encephalopathy - ARDS				6					
12. Status of re-shock or requiring inotropic drug				5					
13. Requiring ventilator support				5					
14. Requiring invasive procedure, score 3 for each procedure: - Central line - Blood exchange				3					
Total score									

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Distribution of patient characteristics among Dengue without warning signs, Dengue with warning signs, and Severe Dengue were analyzed by exact probability test, analysis of variance (ANOVA), or ANOVA by rank based on types of variables. The Bonferonni correction statistical method was then applied to identify specific differences between the DDSS among the dengue classification groups to control the overall error rate and ensure that any identified differences are statistically valid. The Stata/SE (Special Edition) 14.0 (StataCorp. LP. Stata Statistical Software: Revised 2015. College Station, TX: StataCorp LP.) was used for descriptive analysis of the mean and standard deviation, inferential statistics of ANOVA, and analysis of DDSS with expected outliers computed as interquartile range (IQR).

Mean DDSS was calculated using geometric mean. Data for patients with Dengue without warning signs, Dengue with warning signs, and Severe Dengue were assessed using the Area under the Receiver Operating Characteristic Curve (AUROC). A series of multivariate logistic regression models which included age, bleeding episodes, hematocrit, white blood cell count, and platelet count were performed to test for associations between the outcome variable(s), such as development of complications of dengue, progression to severe dengue, and patient prognosis, as suggested in the literature and from preliminary analyses.

The predictive ability of a score for subsequent Severe Dengue during the defervescence phase was analyzed and presented as sensitivity, specificity and positive likelihood ratio. A subgroup analysis was done among patients with Dengue with warning signs to test the predictive ability of the Daily Dengue Severity Score to identify patients who will progress to Severe Dengue.

Ethical Considerations

This study was reviewed by the Institutional and Ethics Review Board of Perpetual Succour Hospital. Upon approval, the research study commenced, with strict adherence to patient data confidentiality protocols. Each medical case record was assigned a number code to ensure anonymity. There was no external funding received and the principal investigator declare no conflicts of interest with any external agency in the conduct of the study. Permission to utilize the Daily Dengue Severity Score (DDSS) was requested and granted by the original author.

RESULTS

Patient Classification and Demographics

Medical records of eligible patients from 2018 to 2020 were reviewed and a total of 327 patients were categorized following the 2009 WHO Dengue Case Classification as Dengue without Warning Signs (N=34), Dengue with Warning Signs (N=271), and Severe Dengue (N=22). The clinicodemographic profile of patients is seen in Table 2. Mean duration of fever showed that those with Dengue without Warning Signs had fever for 3.9 ±2.0 days; Dengue with Warning Signs, 4.2±1.5 days, and Severe Dengue, 5.1±3.5 days. Complete blood count showed that the highest hematocrit and lowest platelet counts have a significant p-value of <0.05 among all the disease categories. Complications during admission showed that 63.6% of Severe Dengue developed pleural effusion and 18.2% had myocarditis.

Table 2 Clinicodemographic Profile of Patients Ages 1 Month to 18 Years Old Admitted With Dengue Infection (N=327)

Patient Profiles	Diagnosis			
	Dengue without Warning Signs (N=34)	Dengue with warning signs (N=271)	Severe Dengue (N=22)	P-value
Demographic				
Male, %	50.0	58.3	50.0	0.521
Age (yr) (Mean ± SD) (month)(n=4)	9.2±5.0	8.2 ± 4.2	8.14±3.3	0.46 -
Duration of fever (day) (Mean ± SD)	3.9±2.0[a]	4.2±1.5	5.1±3.5[a]	0.03
Duration of hospitalization (day) (Mean ± SD)	5.6± 1.5[a]	5.8± 2.7[b]	7.5 ± 2.4[a,b]	0.008
Hematological Status (Complete Blood Count)				
Initial Hematocrit (%)	41.2±4.2	39.6±4.8	40.5±5.0	0.16
Highest Hematocrit (%)	42.2±4.5[a]	41.7±4.3[b]	46.3±6.0[a,b]	0.000
Initial White Blood Cell count (10^3/ μL)	1.18.7±5.87	1.11.8±6.48	1.29.6±6.80	0.41
Initial platelet count (×10^3/μL)	159.7±61.7	139.7±64.5	140.9±93.0	0.25
Lowest platelet count (×10^3/μL)	86.8±43.6[a,c]	60.2±39.7[b,c]	22.5±21.1[a,b]	0.000

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Bleeding sites (n,%)				
Epistaxis	2(5.9)	26(9.6)	1(4.6)	0.59
Petechiae ± ecchymosis	7(20.6)	39(14.4)	9(40.9)	0.005
Hypermenorrhea	0(0)	2(0.74)	0(0)	-
Gross hematuria	0(0)	0(0)	0(0)	-
Melena	0(0)	0(0)	0(0)	-
Hematemesis	0(0)	0(0)	0(0)	-
Hematochezia	0(0)	0(0)	0(0)	-
Mode of presentation (n,%)				
Hepatomegaly	0(0)	20(7.4)	9(40.9)	
Headache	8(23.5)	41(15.1)	8(36.4)	
Myalgia	1(2.9)	24(8.9)	4(18.2)	
Vomiting	13(38.2)	118(43.5)	15(68.2)	
Cough	23(32.4)	219(19.2)	9(59.1)	
Abdominal pain	6(17.6)	100(36.9)	17(77.3)	
Hemodynamic status (Mean ± SD)				
Pulse pressure	32.6± 5.1	33.8±6.2[b]	29.5±8.4[b]	0.01
Systolic Blood Pressure	98.8±9.1[a]	98.3±9.4[b]	90.4±23.4[a,b]	0.005
Diastolic Blood Pressure	65.6±7.0	64.3±6.6	60.9±16.6	0.08
Complications during admission (n,%)				
Myocarditis	0.0 (0)	3(1.1)	4(18.2)	
Pleural effusion	0(0)	9(3.3)	14(63.6)	
Encephalitis	0 (0)	0 (0)	0 (0)	
Presence of comorbidities (n,%)	1 (3.0)	2(0.7)	1(4.6)	-
Discharged (n,%)	33(100.0)	271(100)	22(100)	0.05

[a,b,c] statistical significance at p-value <0.05

Daily Dengue Severity Scores and Score Distribution

Daily Dengue Severity Scores differed in relation to the days before and after defervescence. DDSS was highest in those with severe dengue at D-4 (mean ±SD: 17.7 ±14.0) and lowest at D+3 (mean ±SD: 4.6±8.4). Scores were likewise higher for Severe Dengue when compared with those classified under Dengue without warning signs and Dengue with warning signs (Table 3).

Table 3	Comparison of the Mean Daily Dengue Severity Scores between Disease Categories		
Day of illness (D)	Dengue without warning signs	Dengue with warning signs	Severe Dengue
D-4	4.7±2.5 (4.1)[3]	6±3.3 (5.6) [29]	17.7 ±14.0(10.8) [3]
D-3	5.1±4.1(5.5) [9]	6.1±3.2(5.4) [65]	12.8±4.0 (12.3) [5]
D-2	6±3.6 (5.4) [21]	6.3 ±2.8 (5.8) [142]	14±6.7(11.8) [9]
D-1	5.0±3.2 (5.2) [33]	5.9±2.7(5.4) [252]	12.1±5.2(11.1) [15]
D0	4.4±2.9 (4.5) [33]	4.7±2.8 (4.7) [270]	8.3±5.4(6.7) [21]
D+1	3.2± 3.0 (4.6) [32]	3.3 ±2.7 (4.2) [269]	6.5±4.9(5.8)[22]
D+2	2.2±2.6 (4.1) [29]	2.6±2.6(3.8) [244]	4.6±4.4(4.3)[22]
D+3	1.1±2.0 (2.6) [16]	2.2 ±2.4(3.6) [169]	4.6±8.4(3.4)[20]

*mean ± SD (geometric mean) [N]
*D = defervescence

Distribution of severity scores by Dengue Classification was analyzed using geometric mean and is further illustrated in Figure 1. This is useful when numbers in the series are independent of each other, or if the numbers tend to make large fluctuations.

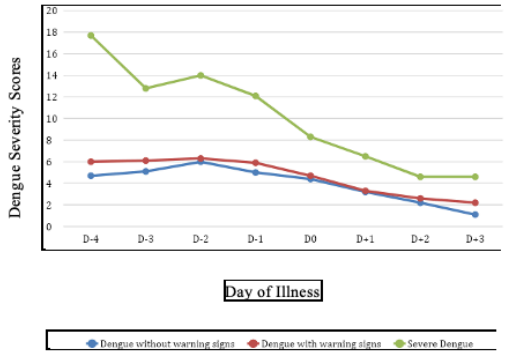
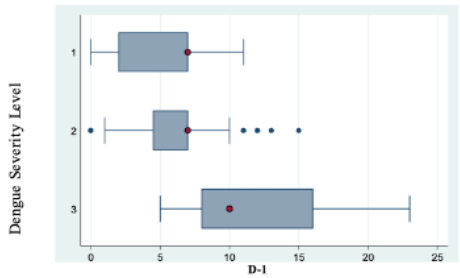


Figure 1 Comparison of the Mean Daily Dengue Severity Score between Disease Categories

Dengue Severity Scores at D-1 (One Day Before Defervescence)

The DDSS at D-1 varied across the three dengue disease severity categories (Figure 2). The mean, standard deviation (mean±SD), geometric mean, and interquartile range (IQR) are as follows: Dengue without warning signs 5.0±3.2 (5.2), IQR 5; Dengue with warning signs 5.9±2.7 (5.4) IQR 2.5; and Severe Dengue 12.1±5.2 (11.1), IQR 8. Red dot marks in the box represent medians and box boundaries represent the 25th and 75th percentile. Blue dot marks represent other scores beyond the range of the aforementioned percentiles and standard deviations.



*1= Dengue without Warning Signs, 2 = Dengue with Warning Signs, 3 = Severe Dengue
*Box boundaries = represent the 25th and 75th percentiles
*Red marks in box = Medians
*Blue marks = other scores beyond range of the 25th and 75th percentiles

Figure 2 Distribution of Dengue Severity Scores at D-1 by Severity Levels

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Figure 3 illustrates the relationship of the Dengue Severity Classification and Positive Likelihood Ratio seen in the DDSS at D-1 (Table 4). It is observed in the line graph that as scores were increasing, there is a higher likelihood of going into Severe Dengue.

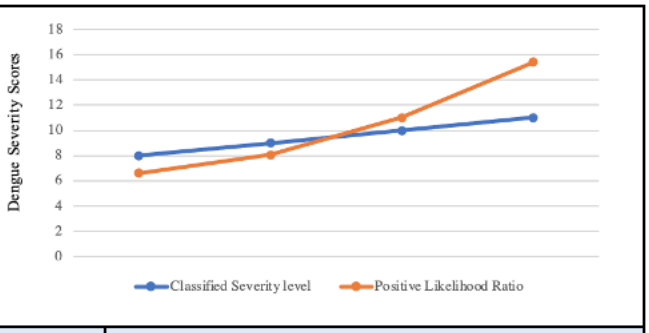

Figure 3 Relationship of the Dengue Severity Classification and Positive Likelihood Ratio

Predictive Ability of the Daily Dengue Severity Score

Scores 8, 9, and 10 were noted to have the ability to predict subsequent Severe Dengue at D-1 (Table 4). These set points had the highest sensitivity of 66.7-80% and specificity of 87.88-93.94%. A score of 8 has a positive likelihood ratio of 6.6, while a score of 11 has the highest positive likelihood ratio of 15.4. Scores 13 and 15 do not have a positive likelihood ratio listed, as both have a specificity of 100%. Although scores ≥11 had higher specificity of 96.97-100% and higher positive likelihood ratio of 15.4, but had a lower percentage of correctly classifying cases, ranging from 79.17-81.25%.

Table 4 Score-Classified Dengue Severity Level to Predict Subsequent Severe Dengue at Day –1 (One Day Before Defervescence)

Score-Classified Severity Level	Sensitivity (%)	Specificity (%)	Correctively Classified (%)	Positive Likelihood Ratio
8	80.0	87.88	85.42	6.6
9	73.3	90.91	85.42	8.07
10	66.67	93.94	85.42	11.0
11	46.67	96.97	81.25	15.4
13	40.0	100.0	81.25	-
15	33.3	100.0	79.17	-

Subgroup Analysis (Dengue with Warning Signs)

Since majority of cases were classified as Dengue with Warning Signs (N=271) and comprised 82% of cases, a subgroup analysis was done. The lower threshold scores (4 to 7), have high sensitivity of up to 100%, however they have low specificity of 22.2-38.9%. Intermediate threshold Scores (8 to 10) have moderate sensitivity of 66.67-80% and high specificity of 82.14-92.86%, with higher positive likelihood ratio of 9.3, with 91.39% correctively classified patients. Higher threshold scores (11 to 15) have lower sensitivity of 33.33-46.67%, a very high specificity of 97.22-99.6%, correctly classified patients at 94.38-95.88%, with high overall accuracy due to the high specificity, and a very high positive likelihood ratio (16.8-84). The possibility of subsequent Severe Dengue was more observed upon analyzing patients diagnosed with Dengue with warning signs (Table 5).

Table 5 Score-Classified Dengue Severity Level and Subgroup Analysis on Dengue with Warning Signs to Predict Subsequent Severe Dengue

Score-Classified Severity Level	Sensitivity (%)	Specificity (%)	Correctively Classified (%)	Positive Likelihood Ratio
4	100.0%	22.2%	26.6	1.3
5	100.0%	25.0%	29.21	1.3
6	93.3%	35.3%	38.6	1.4
7	93.3%	38.9%	41.95%	1.5
8	80%	82.14%	82.02%	4.4
9	73.33%	87.70%	86.89%	5.9
10	66.67%	92.86%	91.39%	9.3
11	46.6%	97.22%	94.38%	16.8
12	40%	98.02%	94.76%	20.1
13	40%	99.21%	95.88%	50.39
15	33.33%	99.6%	95.88%	84.0

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Discriminative Performance Using AUROC Curves

The discriminative performance of the Daily Dengue Severity Score among Dengue with Warning signs and Severe Dengue using AUROC curves were analyzed (Table 6). It is shown that the daily Dengue Severity score had the ability to assess subsequent Severe Dengue at D-1 compared with other days. Severe Dengue showed a higher AUROC curve of 0.89 at D-1 compared to Dengue with warning signs (0.58), with a 95% confidence interval between 0.47-0.68 and 0.8-0.99, respectively.

Table 6	Discriminative Performance of Daily Dengue Severity Score Among Patients with Dengue With Warning Signs and Severe Dengue Using Area Under the Receiver Operating Characteristic (AUROC) Curves			
Days of illness	Dengue with warning signs		Severe Dengue	
	AUROC	95% CI	AUROC	95% CI
D-4	0.66	0.42,0.91	0.72	0.17,1.0
D-3	0.52	0.26,0.79	0.92	0.77,1.00
D-2	0.54	0.39,0.68	0.86	0.67, 1.00
D-1	0.58	0.47,0.68	0.89	0.80, 0.99
D0	0.54	0.44,0.644	0.73	0.59, 0.87
D+1	0.53	0.42,0.63	0.75	0.62,0.88
D+2	0.55	0.45,0.66	0.68	0.54,0.83
D+3	0.63	0.52,0.75	0.71	0.55,0.87

DISCUSSION

In our study, clinicodemographic profile of patients showed that dengue cases were predominantly males, with a mean age ranging from 8.1 to 9.2 years. However, neither age nor gender appeared to have an influence on the severity scores. Mean duration of fever for Dengue Fever with warning signs was 3.9 ±2.0 days, with less severe illness, compared to Severe Dengue where the mean duration extends to 5.1±3.5 days. Hospitalization trends also follow a similar pattern. Patients with Dengue without warning signs had a mean hospitalization of 5.6± 1.5 days. In contrast, Severe Dengue cases required a longer hospital stay, averaging 7.5 ± 2.4 days. The longer hospital stay is likely due to the critical condition of these patients, necessitating more intensive care to manage complications. This observation aligns with findings from the study of Tangnanaratchakit et al.[2] which also documented prolonged hospitalization in Severe Dengue. While all dengue cases require utmost medical attention, Severe Dengue clearly presents a longer and more complicated course, requiring more resources and time for patient management.

Complete blood count analysis demonstrated that initial hematocrit levels did not significantly differ across the three severity levels. This suggests that, at the onset of the disease, hematocrit may not be a distinguishing marker for classifying disease severity. As the disease progressed, the highest hematocrit levels (significant p-value of <0.05), indicative of hemoconcentration was seen in patients with Severe Dengue. Thrombocytopenia (significant p-value of <0.05), was another marker strongly associated with severe disease. Our data also showed that patients with Severe Dengue had the lowest platelet counts which contributed to bleeding manifestations.

Several clinical parameters were notably present in patients with Severe Dengue. Abdominal pain (77.3%) and vomiting (68.2%) were the most common symptoms, both of which were associated with hepatomegaly (enlarged liver). Hepatomegaly emerged as a significant clinical predictor of dengue severity, consistent with the findings of Surangrat Pongpan et al.[8] who developed the Dengue Infection Severity Score. This study emphasized the importance of hepatic involvement as a marker of disease progression. As to complications, pleural effusion occurred in 63.7% of patients with Severe Dengue, while 18.2% developed myocarditis which can result in impaired cardiac function. Cardiac Troponin I, a serum marker indicative of myocyte injury,[9] was tested in Severe Dengue cases. Our study found elevated levels reaching up to 300 ng/L, which is significantly higher from the reference range of <19 ng/L. While this biomarker showed a sensitivity of 34% and specificity of 84% for detecting cardiac injury, it has not been extensively utilized in previous studies. By searching for hepatomegaly, pleural effusion, myocarditis, and performing Cardiac

Troponin I, our study provided a more comprehensive understanding of dengue and its systemic complications and emphasized the importance of vigilant monitoring for organ-specific involvement especially in severe cases.

In the analysis of DDSS and its distribution, patients diagnosed with Severe Dengue consistently showed higher scores compared to those with less severe forms of the disease. Scores for Severe Dengue peaked on D-4 (mean ± SD of 17.7 ± 14.0) and was lowest at D+3 (mean ± SD of 4.6 ± 8.4). These scores were significantly higher indicating a more severe condition when compared with other categories.

The distribution of DDSS at D-1 varied considerably across the three severity levels. Patients with Dengue without warning signs had a mean ± SD of 5.0 ± 3.2 (geometric mean of 5.2) with interquartile range (IQR) of 5, indicating some variability within the mild cases but generally clustered around this central value. Those with Dengue with warning signs had a mean ± SD of 5.9 ± 2.7 (geometric mean of 5.4) and IQR was narrower at 2.5. This suggests that the scores for this group were tightly distributed compared to those without warning signs. Patients with lower DDSS were classified as having Dengue without warning signs, which is consistent with the finding that a lower score corresponds to less severe manifestation of the disease. These highlight the value of the DDSS which can help distinguish between varying levels of disease severity in dengue cases and provide insight into disease progression.

In contrast, patients with Severe Dengue had markedly high scores, with a mean ± SD of 12.1±5.2 (geometric mean of 11.1) and an IQR of 8. This variation in DDSS distribution relates to disease severity, with the highest scores corresponding to Severe Dengue cases. Significant differences in both mean and IQR highlight how the scoring system effectively differentiates between different clinical severity states. Patients with very high DDSS, reflected significant hemoconcentration, bleeding, or organ dysfunction. A high score typically indicates a higher risk of developing life-threatening complications. The wider IQR in Severe Dengue pointed to greater variability, and the degree of severity and potential complications varied significantly within this group.

The predictive ability of DDSS previously seen in the study of Tangnararatchakit et al.[2] was similar to our findings, in terms of sensitivity (86%) and specificity (84%), and closely mirrored the performance of DDSS in our study. In the same study, the mean DDSS during hospitalization related to defervescence among patients with Dengue Hemorrhagic Fever (DHF) grade III (scores 10–20) and DHF grade IV (scores 31–47) were significantly higher than those of Dengue Fever (scores 5–13), DHF grade I (scores 2–10) and DHF grade II (scores 6–11). In our study, a score of ≥12 had a sensitivity of 86.2%, specificity of 84.3%, positive likelihood ratio of 5.66%, with 85.07% of patients correctively classified into their severity levels based on the DDSS.

Given that majority of cases were classified as Dengue with warning signs (N=271, 82% of total cases), a subgroup analysis was conducted to assess the predictive value of DDSS thresholds for identifying severe dengue within this group. At higher threshold scores (11-15), the sensitivity ranged between 33.33-46.67%, which indicates that while the DDSS is less effective in detecting all cases of Severe Dengue, it correctly identified a substantial portion of cases who will progress to severe dengue. However, the specificity of 97.22-99.6% is exceptionally high, which signifies that the DDSS was excellent in identifying patients who did not progress to Severe Dengue, greatly reducing the number of false positives. The proportion of patients correctly classified as severe or not was very high with 94.38-95.88% accuracy, suggesting that the overall classification performance was excellent, despite the lower sensitivity. The positive likelihood ratio ranging from 16.8 to 84 was also very high. A high likelihood ratio indicates that these higher threshold scores are extremely effective in predicting patients who will progress to Severe Dengue. The possibility of subsequent Severe Dengue was more observed upon

analyzing patients diagnosed with Dengue with warning signs. Despite its lower sensitivity, the higher thresholds were accurate in predicting Severe Dengue, emphasizing the importance of using DDSS to better manage patients with warning signs, and anticipate disease progression.

The AUROC curves in this study showed that the DDSS was most effective in predicting Severe Dengue on D-1, the day before severe symptoms fully manifested. At D-1, Severe Dengue had a higher AUROC curve of 0.89, indicating a strong ability to differentiate between patients who will progress to Severe Dengue and those who will not. This is in contrast to Dengue with warning signs, which had a lower AUROC of 0.58. An AUROC score near 0.5 suggests that the prediction is no better than random chance, indicating that the severity score is not as effective in predicting less severe cases. The 95% confidence intervals for the AUROC values were 0.47-0.68 for Dengue with warning signs, and 0.8-0.99 for Severe Dengue. This supports that the scoring system is far more reliable in predicting severe forms of dengue. These findings are consistent with a previous study by Tangnararatchakit et al., which observed that the risk of threatened shock in DHF grades III and IV increased significantly on D-1 compared to other days.[2] This suggests that the DDSS is particularly useful for early detection of Severe Dengue, allowing for timely management.

CONCLUSION

The clinicodemographic profile of patients showed that majority of admitted patients were males with a mean age of 8.1 to 9.2 years old. The mean fever duration for Dengue fever ranged from 3.9 to 5.1 days. The mean duration of hospitalization for Dengue Fever ranged from 5.6 to 7.5 days and a longer duration of hospitalization in Severe Dengue was observed. Initial hematocrit levels did not significantly differ between the three severity states, however, the mean initial hematocrit of 40.5±5.0 in cases of Severe Dengue is significantly different from the highest hematocrit of 46.3±6.0, with a significant hemoconcentration of ≥ 20%.

The DDSS had the ability to predict subsequent Severe Dengue at D-1 (one day before defervescence) compared to other days.

The cut off points of 8, 9, and 10 predict subsequent Severe Dengue at D-1 (one day before defervescence) with a sensitivity of 66.7 to 80%, specificity of 87.88 to 93.94%, positive likelihood ratio of 6.6 to 11, and with 85.42% of patients correctively classified into their severity level based on the DDSS.

A cut off point of 10 was observed to predict subsequent severe outcome among majority of Dengue with Warning Signs which had a 66.67% sensitivity, 92.86% specificity, positive likelihood ratio of 9.3, and with 91.39% of patients correctively classified into their severity level.

RECOMMENDATIONS

It is suggested to adapt such an evaluation tool in clinical practice particularly in the Emergency Room, PICU, or wards to help clinicians monitor for disease progression. Close monitoring should be done as the patient approaches defervescence. It is recommended that a prospective study be pursued with at least 3 scoring frequencies to be done every 8 hours within a 24-hour shift for more conclusive and reliable results.

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CONFLICT OF INTEREST

None declared.

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