Original Article

Implementation of *Dengue Recurrent Shock Prediction Score* in pediatric dengue shock syndrome

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Abstract

Background Global morbidities due to dengue viral infection increase yearly. The pediatric mortality rate from dengue shock syndrome (DSS) remains high. Early identification of the risk of recurrent shock may serve to increase awareness and reduce mortality. *The Dengue Recurrent Shock Prediction Score* (DRSPS) is a tool to predict recurrent shock in children with DSS, but the optimal cut-off point in our population is still unknown.

Objective To assess the validity of the DRSPS by determining the optimal cut-off point that can be used in Indonesia

Methods This cross-sectional prospective study was done at Sanglah Hospital, Denpasar, Bali. Risk of reccurent shock were classify based on DRSPS in all DSS patient, and they were observed whether they will experienced recurrent shock or not.

Results Of 56 children with DSS, 27 subjects had recurrent shock and 29 subjects did not. The optimal DRSPS cut-off point was -189.9 for predicting recurrent shock, with 87.4% area under the curve (AUC), 81.5% sensitivity and 82.8% specificity.

Conclusion The optimal cut-off point of DRSPS was -189.9 and it has good validity. The results of this study are expected not only to be used as the basis for further study, but to increase physician awareness in treating DSS patients. [Paediatr Indones. 2020;60:178-85 ; DOI: 10.14238/pi60.4.2020.178-85].

Keywords: *dengue shock syndrome; recurrent shock; DRSPS*

The national mortality rate of dengue hemorrhagic fever (DHF) declined from 41.4% in 1968, to 4% in 1980, to 1.4% in 2000, and to only 0.88% in 2012. However, the number of deaths due to dengue shock syndrome (DSS) remain high. Data from six teaching hospitals in Indonesia in 2008-2013 revealed that the mortality rate due to DSS was about 7.81%, reaching 10-20% if proper initial treatment is lacking.1 Hence, we need to better identify the risk factors of shock in children with dengue infection, with the aim of increasing physician awareness for stricter supervision of patients.[1,2]

Deaths from dengue infections were reported to be fifty times higher in patients with shock than those without shock. About 30% of shock patients experience recurrent shock, affecting subsequent treatment and outcomes. In 2016, there were 245 pediatric DSS cases in RSUP Sanglah, Bali, of whom 119 cases (48.5%) had recurrent shock.[2] Recurrent shock generally occurs during the critical phase of

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dengue infection. Some patients experience several episodes of shock within 24-48 hours before the convalescent period. Risk factors for recurrent shock of DSS include young age, earlier onset of shock, higher body temperature, faster pulse, higher hematocrit rate, and poor hemodynamic status.[2,3-4]

Early identification of the risk factors for recurrent shock can help increase awareness to prevent recurrence of shock episodes in children with DSS. Huy *et al.*[3] in Vietnam developed a model to predict the occurrence of recurrent shock in children with DSS. This model includes physical and laboratory examination results, with 68.3% sensitivity and 68% specificity. *The Dengue Recurrent Shock Prediction Score* (DRSPS) can yield differing results when applied to the population in Indonesia, not only because of the climate difference, but also because of variations in local expertise and health facilities in Indonesia and Vietnam.[3-5]

Despite these differences, the practical reasons for assessing the validity of the Huy's model in Indonesia are: the high mortality rate of DSS in children, the difficulty of identifying the risk of recurrent shock in children with DSS as there is no standard method to predict recurrent shock in children with DSS in Indonesia, and the lack of validity studies on Huy's model (or DRSPS). As such, we aimed to assess the validity of the DRSPS by determining the optimal cut-off point that can be used in Indonesia.

Methods

This diagnostic study was done to determine the optimal DRSPS cut-off point to predict recurrent shock in children with DSS. Patients at Sanglah Hospital, Bali, were selected by consecutive sampling from January 2019 until the minimum required sample size was fulfilled. The inclusion criteria were children aged ≥6 months to 18 years with DSS diagnosed by the 2011 WHO criteria,[6] and whose previous shock episode had been resolved with a maximum of 2 crystalloid bolus administrations at 20 mL/kg body weight. Exclusion criteria were patients with chronic clinical conditions or massive bleeding that required blood transfusions. The minimum required sample size of 56 subjects was based on a 48.5% prevalence of recurrent shock in DSS.

At the time of initial diagnosis, all subject were classified into compensated and decompensated shock. Subjects' data were documented on the DRSPS form. The DRSPS included several components: duration of fever before admission, purpura/ecchymosis, ascites/pleural effusion, platelet count at shock, and pulse pressure during shock. Each component had its own corresponding value **(Table 1)**. The total corresponding value of each sample was analyzed to find the optimal cut-off point. Based on new optimal cut-off point, subjects were grouped into either the risk of recurrent shock group or the no risk of recurrent shock group. Subjects were followed until they were discharged or died, whether they had recurrent shock or not. The outcomes of this study were a new optimal cut-off point based on sample population, AUC value, and accuracy (sensitivity, specificity; positive and negative predictive value) based on the original and new optimal cut-off point.

Table 1. Dengue recurrent shock prediction score (Huy's model)[3]

Variables	Results	Score
Fever duration before admission (in days)		
Purpura/ecchymosis		
Ascites/pleural effusion		
Platelet count at shock (/µL)		
Pulse pressure at shock		
Total		

Notes: Fever duration before admission (-40 per day), purpura/ecchymosis (+50 if positive), ascites/pleural effusion (+150 if positive), platelet count at shock (-7 per 10,000 platelets), pulse pressure at shock (-4 per 1 mmHg). Total score >-154.5 (Huy's cut-off) was considered to be at risk of recurrent shock.

The characteristics of subjects were presented in tables and narration. The optimal cut-off point analysis was presented in graphs and tables. The accuracy of DRSPS was assessed by 2x2 cross-tabulation. The data obtained were analyzed by *SPSS Statistic 22*. This study was approved by the Research Ethics Committee of the Universitas Udayana Medical School/Sanglah Hospital, Denpasar.

Results

During the study period, 56 DSS patients met the inclusion criteria. Subjects' mean age was 9 years,

ranging from 2-16 years. Subjects' mean length of hospitalization was 3 days; two subjects required prolonged hospitalization of up to 14 and 15 days due to secondary bacterial infections. At the initial diagnosis, most subjects were in the compensated DSS group (51%). Recurrent shock prevalence was 48.2%, and 15 out of 27 recurrent shock subjects were in the decompensated DSS group. Most children experienced the first shock after a 4-day fever, ranging from 2 to 6 days of fever. Subjects' mean platelet count was $35x10^3/\mu L$, ranging from 21 to $44x10^3/\mu L$. The most common difference in pulse pressure in our

Table 2. Subjects' characteristics

Characteristics	Recurrent shock	
	Yes (n=27)	No (n=29)
Gender, n		
Male	17	10
Female	17	12
Age, n		
Toddler	3	2
Preschool	4	3
School-age	9	9
Teenager	11	15
Nutritional status, n		
Mild-moderate malnutrition	5	3
Well-nourished	17	14
Overweight	1	3
Obese	4	9
Ascites/pleural effusion, n		
Yes	12	29
No	15	0
Purpura/ ecchymosis, n		
Yes	13	20
No	14	9
Length of stay, n (%)		
<3 days	5	4
3-5 days	19	22
>5 days	3	3
Outcomes, n		
Died	5	0
Survived	22	29

subjects was 20 mmHg, with a mean of 14 mmHg. The basic characteristics of subjects are shown in **Table 2**.

Using the numeric DRSPS of subjects in **Table 3**, we calculated the optimal cut-off point for the local population to be -189.9. It was started from the optimal cut-off point formed in **Figure 1**, then the pseudo line was drawn perpendicular down and showed exactly

number 29. The ROC curve had 87.4% AUC, with 81.5% sensitivity and 82.8% specificity (**Figure 1** and **Figure 2**). The diagnostic value of DRSPS using the original and new optimal cut-off point in predicting the occurrence of recurrent shock is shown in **Table 4**. Based on cross-tabulation data in **Table 4**, we calculated several accuracy parameters of DRSPS. The accuracy of this model using both cut-off point is shown in **Table 5**.

The value of diagnostics depended not only on sensitivity and specificity, but also the predictive value based on the prevalence of the diseases. Low prevalence in a population could lead to a high level of false positive, so more specific tests were needed. The higher the prevalence of a disease, the higher the positive predictive value (PPV). When the prevalence of the diseases dropped below 45%, it showed that the PPV based on optimal cut-off also dropped below 80%. **Figure 3** shows the effect of the prevalence on positive predictive value when DRSPS was applied to different populations's prevalence.

Discussion

In the last three decades, there has been an increase in the frequency of dengue infections worldwide. The number of cases of dengue infection has continued to increase since the 1950s. In 2008 there has been an increase of almost ¾ times from the previous decade. Around 2.5 billion of the world's population lives in dengue endemic areas and more than half are in 10 countries in Southeast Asia. There were 156,052 cases of dengue infection with 1396 deaths occurred in Indonesia and the highest number of deaths in Southeast Asia. In 2016, there were 245 pediatric DSS cases in RSUP Sanglah, Bali, of whom 119 cases (48.5%) had recurrent shock. Some patients experience several episodes of shock within 24-48 hours before the convalescent period. Early identification of the risk factors for recurrent shock can help increase awareness to prevent recurrence of shock episodes in children with DSS. A simple model which found by Huy *et al.*[3] can be used to predict the occurrence of recurrent shock in children with DSS. In this study we try to assess the validity of the DRSPS by determining the optimal cut-off point that can be used in Indonesia.[1,2,6,8]

Table 3. Sensitivity and specificity of each subject

| No	Value	Sensitivity	Specificity	No	Value	Sensitivity	Specificity
1	-315.3	1	0	29	-189.9	0.815	0.828
2	-308.65	1	0.034	30	-188.75	0.815	0.862
3	-298.765	1	0.069	31	-179.35	0.815	0.897
4	-294.16	0.963	0.069	32	-170.35	0.778	0.897
5	-293.545	0.963	0.103	33	-152.9	0.741	0.897
6	-292.05	0.963	0.138	34	-133.95	0.704	0.897
7	-289.9	0.963	0172	35	-130.9	0.667	0.897
8	-287.8	0.963	0.207	36	-128.05	0.63	0.897
9	-283.25	0.963	0.241	37	-125	0.593	0.897
10	-272.8	0.963	0.276	38	-122.9	0.593	0.931
11	-263.7	0.963	0.31	39	-121.865	0.556	0.931
12	-261.35	0.926	0.31	40	-119.565	0.556	0.966
13	-259.075	0.926	0.345	41	-115.45	0.519	0.966
14	-255.875	0.926	0.379	42	-110.2	0.481	0.966
15	-254.25	0.926	0.414	43	-105.05	0.444	0.966
16	-252.95	0.926	0.448	44	-102.2	0.407	0.966
17	-251.915	0.926	0.483	45	-99.265	0.37	0.966
18	-248.055	0.926	0.517	46	-77.815	0.37	1
19	-237.54	0.926	0.552	47	-54	0.333	1
20	-228.25	0.889	0.552	48	-46.9	0.296	1
21	-223.88	0.889	0.586	49	-39.85	0.259	1
22	-220.895	0.889	0.621	50	-28.1	0.222	1
23	-218.23	0.889	0.655	51	-19.2	0.185	1
24	-213.215	0.889	0.69	52	-5.4	0.148	1
25	-206.4	0.889	0.724	53	22.3	0.111	1
26	-201.82	0.889	0.759	54	37.525	0.074	1
27	-197.07	0.852	0.759	55	73.175	0.037	1
28	-191.8	0.815	0.793	56	109.8	0	1
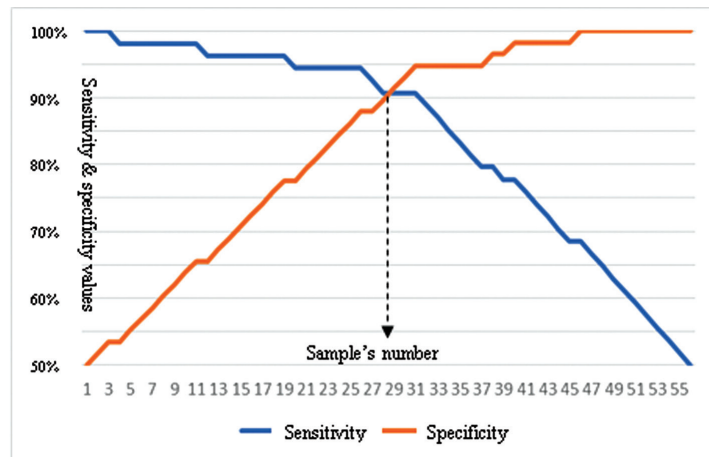
Figure 1. Optimal cut-off point
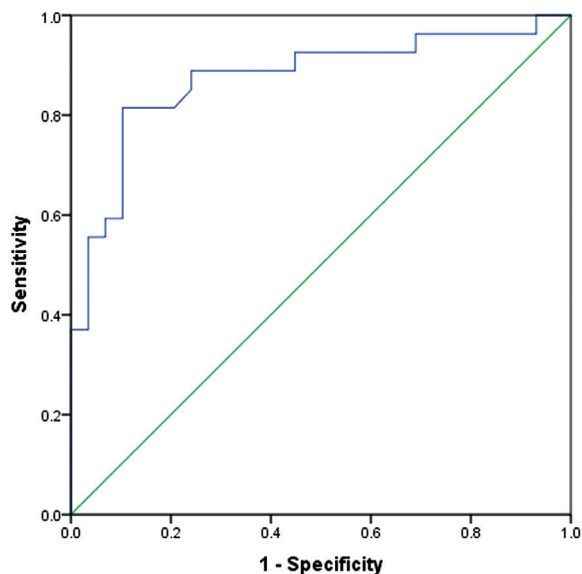
Figure 2. ROC curve

Table 4. Cross-tabulation of DRSPS

DRSPS	Recurrent shock (Optimal cut-off -189.9)			Recurrent shock (Original cut-off)		
	Yes	No	Total	Yes	No	Total
Risk	22	5	27	23	3	26
No risk	5	24	29	4	26	30
Total	27	29	56	27	29	56

Table 5. Diagnostic values of dengue recurrent shock prediction score

Values	Accuracy	
	Optimal cut-off -189.9 (%)	Original cut-off (%)
Sensitivity	81.5	85.2
Specificity	82.8	89.7
Positive predictive value	81.5	88.5
Negative predictive value	82.8	86.7

A previous study reported that the prevalence of recurrent shock was 28% in children with DSS in Vietnam.[3] However, another study reported 48.5% prevalence in Bali,[2] similar to a previous study (48.3%).[7] In addition, a Vietnam study reported 35.9% prevalence of recurrent shock.[5] The Vietnamese studies had slightly different results, perhaps because Lam *et al.*[5] sourced their sample population from one hospital, while Huy *et al.*[3] sourced their sample from public health centers in a small province and referral center hospitals in major cities. In our study, 27 of 56 children suffered recurrent shock (48.2%). Two Indonesian studies had similar results, probably because they were conducted in referral center hospitals and were located in regions of Indonesia, which has a tropical climate.[4,6] In fact, Tarigan *et al.*[2] study was done in our institution, Sanglah Hospital (referral center hospital). In addition, the Indonesian studies reported higher prevalences compared to the Vietnamese studies. This difference may have been
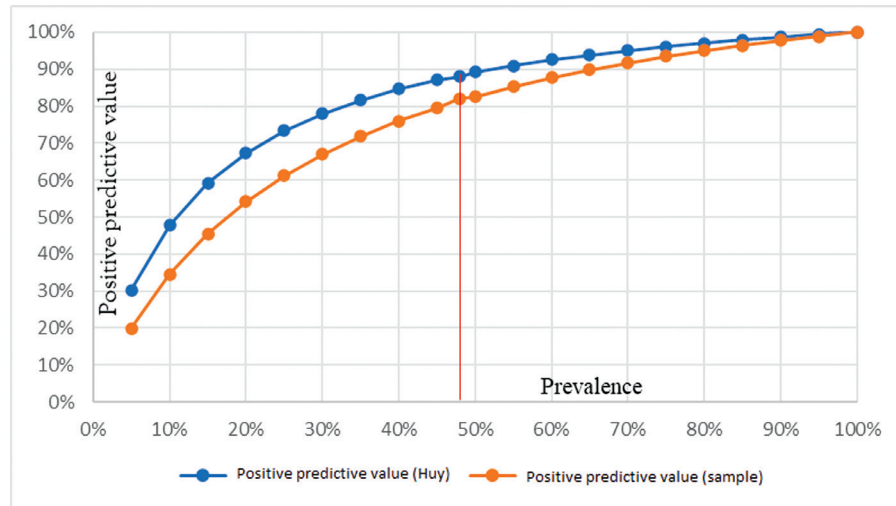
Figure 3. Prevalence effect on positive predictive value

due to (subtropical), regional climate differences (tropical *vs.* sub-tropical, respectively). Warmer air temperatures in tropical regions have been associated with increased spread of dengue viruses, as they directly affect the life cycle of *Aedes aegypti* and *Aedes albopictus* mosquitoes which are the primary vectors of dengue virus transmission.[6-8]

Most children in our study experienced the first shock after a 4-day fever, with the earliest shock occurring after 2 days of fever. Fever is one of five variables of the DRSPS, with one day of fever contributing a negative value of 40 points. Huy *et al.*[3] noted that shorter fever duration before 1st shock relates to the risk of recurrence of shock in children with DSS. Since DSS generally occurs after 4 days of fever, an earlier onset of shock indicates a higher likelihood of severe disease and risk of recurrent shock events.[5,7]

A previous study developed a model for predicting mortality in severe dengue cases. The states of lethargy, bleeding, increased heart rate, decreased bicarbonate levels, and elevated lactate levels were predictors of death in severe dengue cases, but the best predictive model of mortality was obtained by combining the bicarbonate rate with ALT (AUC 83.5%).[9] Another study found that albumin could be used as a predictor of shock in dengue patients (OR 17.4; AUC 86.5%; sensitivity 79%; specificity 81%), but not as a predictor of recurrent shock in DSS.[6] Our independent variables (DRSPS) differed from variables in the two aforementioned studies.[6,9] In

addition, the sample was comprised of adult patients in a previous study[9] making it difficult to compare to the variables in the Lam and Huy's models, as children have different characteristics and immunity from adults.

The DRSPS, a simple model developed by Huy *et al.*[3] has relatively good precision with an AUC of 73%, sensitivity of 68.3%, and specificity of 68.2%. Another model by Lam *et al.*[5] in Vietnam to predict recurrent and prolonged shock had an AUC of 69%. They applied the DRSPS to their study population and obtained a relatively low AUC of 54%.[5] The Huy *et al.*[3] and Lam *et al.*[5] studies reported purpura/ecchymosis in 36% and 3% of subjects, respectively. The proportions of the ascites/pleural effusion also differed (44% *vs.* 1%, respectively).[3,5]

Our validation of the DRSPS showed different results. The new optimal cut-off point of -189.9 from our sample population had 81.5% sensitivity, 82.8% specificity, and 87.4% AUC. It was difficult to compare the validity of DRSPS of this study with the study by Huy due to the distinct prevalence of recurrent shock. In addition, the proportions of pleural effusion and purpura/ecchymosis differed from the Huy *et al.*[3] study. The proportions of the ascites/pleural effusion in our study was 58.9%, and the proportions of ascites/pleural effusion 73,2%. These two variables in DRSPS score (Huy's model) which gives a positive significance of recurrent shock (+50 if purpura/ ecchymosis was occured, and +150 if ascites/pleural effusion was occured).

The original cut-off and our optimal cut-off differed by 35.4 points, leading to a different positive predictive value of 81.5%. The value of type I error or false positive (α) with original cut-off was 5.4%, while that of our optimal cut-off point was 8.9%. This finding indicates that up to 2 children in 100 would be falsely positive for risk of recurrent shock. The type II error or false negative (β) with original cut-off was 7.1%, while that of our cut-off point was 8.9%. This finding indicates that 1 child out of 100 not predicted to experience recurrent shock, will experience it.[11]

The accuracy of the DRSPS depends not only on the sensitivity and specificity, but also on the prevalence of diseases in a population. The higher the prevalence of a disease, the higher the positive predictive value. This model applied to a place with differing prevalence will yield a different result. In populations with a low prevalence of recurrent shock, the DRSPS could lead to high false positive values and low positive predictive values, whereas in populations with a high prevalence of recurrent shock, more sensitive tests are needed than specific tests. With a decrease in prevalence of <35%, the positive predictive value (based on our optimal cut-off point) begin to decline below 70%. The prevalence of recurrent shock was 48.2%, indicating that positive predictive values remained above 80% for both cut-offs. We expect that response times would differ, as Huy *et al.*[3] did not report the time of first fluid administration. The level of parental understanding, awareness, and education in different populations may also reveal different values. The most common dengue serotype in the two Vietnamese studies was DENV-2.[3,5] We did not identify serotypes, which may have differed from the Vietnamese studies. Balinese dengue serotypes are reportedly predominantly DENV-3, followed by DENV-1, DENV-2, and DENV-4.[12] Other limitations were that subjects were diagnosed solely based on 2011 WHO criteria without further investigation of dengue serotypes/PCR examination; timing of the initial fluid resuscitation was not documented; and subjects who died before the seventh day of fever onset did not undergo anti-dengue serological examinations.

In conclusion, the DRSPS can be used to predict recurrent shock in children with DSS. Without underestimating the need for clinical judgment, the DRSPS can be used in daily practice to increase doctor awareness. Therefore, it is expected to reduce morbidity and mortality from recurrent shock in children with DSS.

Conflict of Interest

None declared.

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