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

Armand Setiady Liwan, I Wayan Gustawan, Eka Gunawijaya, Soetjiningsih, Ketut Ariawati, I Nyoman Budi Hartawan

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 recurrent 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 DRPS 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 2 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.

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
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 35x103/µL, ranging from 21 to 44x103/µL. The most common difference in pulse pressure in our 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’ 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 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        |
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      | 0.072       | 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 | -39.855 | 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
A previous study reported that the prevalence of recurrent shock was 28% in children with DSS in Vietnam. However, another study reported 48.5% prevalence in Bali, similar to a previous study (48.3%). In addition, a Vietnam study reported 35.9% prevalence of recurrent shock. The Vietnamese studies had slightly different results, perhaps because Lam et al. sourced their sample population from one hospital, while Huy et al. 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. In fact, Tarigan et al. 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

\[ \text{Figure 2. ROC curve} \]

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
DRSPS & Recurrent shock (Optimal cut-off -189.9) & & Recurrent shock (Original cut-off) & & \\
\hline & Yes & No & Total & Yes & No & Total \\
\hline Risk & 22 & 5 & 27 & 23 & 3 & 26 \\
No risk & 5 & 24 & 29 & 4 & 26 & 30 \\
Total & 27 & 29 & 56 & 27 & 29 & 56 \\
\hline
\end{tabular}
\caption{Cross-tabulation of DRSPS}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Values & Accuracy & \\
& Optimal cut-off -189.9 (%) & Original cut-off (%) \\
\hline
Sensitivity & 81.5 & 85.2 \\
Specificity & 82.8 & 89.7 \\
Positive predictive value & 81.5 & 88.5 \\
Negative predictive value & 82.8 & 86.7 \\
\hline
\end{tabular}
\caption{Diagnostic values of dengue recurrent shock prediction score}
\end{table}
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 study9 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 DRPS, 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/echymosis 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.

Acknowledgments

Special thanks to I Wayan Gustawan, MD, Paed as a Consultant of Infectious & Tropical Diseases and Eka Gunawijaya, MD, Paed as a Consultant of Cardiology, Department of Child Health, Udayana University/Sanglah Hospital. Many thanks to all inpatient staff, especially in the PICU and Infectious Disease Ward at Sanglah Hospital/Udayana University.

Funding acknowledgement

The author(s) received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Junia J, Garna H, Setiabudi D. Clinical risk factors for dengue shock syndrome in children. Paediatrica Indonesiana. 2007;47:7-11. DOI: 10.14238/pi47.1.2007.7-11.
2. Tarigan AD, Gustawan IW, Utama IMD. Risk factors of recurrent shock in children with dengue shock syndrome. Poster presented at: Excellence in clinical practice. 11th International Congress of Tropical Pediatrics; 2017 Aug 4-7; Yogyakarta.
3. Huy NT, Thao NT, Ha TT, Lan NT, Nga PT, Thuy TT, et al. Development of clinical decision rules to predict recurrent shock in dengue. Crit Care. 2013;17:1-8. DOI: 10.1186/cc13135.
4. Raihan, Hadinegoro SRS, Tumbelaka AR. Faktor prognosis terjadinya syok pada demam berdarah dengue. Sari Pediatri. 2010;12:47-52. DOI: 10.14238/sp12.1.2010.47-52.
5. Lam PK, Tam DT, Dung NM, Tien NT, Kieu NT, Simmons C, et al. A prognostic model for development of profound shock among children presenting with dengue shock syndrome. PLoS One. 2015;10:1-13. DOI: 10.1371/journal.pone.0126134.
6. World Health Organization. Comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever. Revised and expanded edition. New Delhi: WHO Regional Office for Southeast Asia; 2011.
7. Tatura SNN, Kalensang P, Mandei JM, Wahyuni S, Yusuf I, Daud D. Albumin level as a predictor of shock and recurrent shock in children with dengue hemorrhagic fever. Crit Care Shock. 2017;20:24-29. Downloaded from: http://criticalcareshock.org/2017/05/albumin-level-predictor-shock-recurrent-shock-children-dengue-hemorrhagic-fever/albumin-level-as-a-predictor-of-shock-and-recurrent-shock-in-children-with-dengue-hemorrhagic-fever/
8. Halstead SB. Dengue fever and dengue hemorrhagic fever. In: Kliegman RM, Stanton BF, St. Geme JW, Schor FN, Behrman RE, editors. Nelson textbook of pediatrics. 20th ed. Philadelphia: WB Saunders; 2016. p. 1147-50.
9. Ebi KL, Nealon J. Dengue in a changing climate. Environ Res. 2016;151:115-23. DOI: 10.1016/j.envres.2016.07.026.
10. Md-Sani SS, Md-Noor J, Han WH, Gan SP, Rani NS, Tan HL, et al. Prediction of mortality in severe dengue cases. BMC Infect Dis. 2018;18:232. DOI:10.1186/s12879-018-3141-6.
11. Sastroasmoro S, Ismael S. Dasar-dasar metodologi penelitian klinis. 5th ed. Jakarta: CV Sagung Seto; 2014. p. 219-43.
12. Megawati D, Masyeni S, Yohan B, Lestarini A, Hayati RF, Meutiaiati F, et al. Dengue in Bali: clinical characteristics and genetic diversity of circulating dengue viruses. PLoS Negl Trop Dis. 2017;11:e0005483. DOI: 10.1371/journal.pntd.0005483.