Original article

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Albumin level as a predictor of shock and recurrent shock in children with dengue hemorrhagic fever

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Abstract

***Background*: The severity of dengue hemorrhagic fever (DHF) can be seen from bleeding and plasma leakage manifestations. Albumin level is one of the markers of plasma leakage in dengue infection. Whether albumin can be used as a predictor of shock in DHF patients or of recurrent shock in dengue shock syndrome (DSS) patients still need to be further evaluated.**

***Objective*: To determine serum albumin level as a predictor of shock in DHF and of recurrent shock in DSS.**

***Design*: A cohort prospective study.**

***Setting*: Department of Child Health, Prof. Dr. RD Kandou Hospital, Manado, Indonesia.**

***Patients and participants*: Sixty-seven DHF patients and 58 DSS patients aged 1- to 14-year-old were enrolled in our study. Sampling was done with consecutive sampling method. The inclusion criteria were patients diagnosed with DHF/DSS based on World Health Organization (WHO) criteria (2011). The exclusion criteria were patients who received corticosteroids, blood transfusion, albumin infusion and patients with severe malnutrition. The dependent variables were shock and recurrent shock. The independent variable was serum albumin level. The relation between serum albumin level and shock or recurrent shock were analyzed using logistic regression test, power 0.80, α 0.05 and was significant if $p<0.05$. We used receiver operating characteristic (ROC) curve to determine prognostic factors. Data was analyzed using software SPSS v 21.0.**

***Results*: There was significant correlation between albumin level and shock in DHF patients (p=0.0001, area under the curve (AUC) 0.865, cut-off 3.05, odds ratio (OR) 17.4, sensitivity 79%, specificity 81%), but there was no correlation between albumin level and recurrent shock in DSS patients.**

***Conclusions*: Serum albumin level can be used as a predictor of shock in DHF patients but it cannot be used as predictor of recurrent shock in DSS patients.**

Key word: Dengue hemorrhagic fever, dengue shock syndrome, predictors, albumin level, plasma leakage.

Background

Dengue hemorrhagic fever (DHF) still remains the main health problem in 100 tropical and subtropical countries (Southeast Asia, West Pasific, Central America and South America). (1,2) There was 1.8 billion people at risk of dengue viral infection in the Asia Pasific and 1.3 billion people were living in South-east Asia. Within the last decade, there was an increase in DHF cases as much as 3.5 times more than previous decades. (2) Case fatality rate (CFR) of DHF in Southeast Asia is 1%. India's, Indonesia's and Myanmar's CFR rised into 3-5% due to the outbreak. (3) According to Halstead, (1) mortality rate of DHF can increase to 40-45% if not treated early and adequately, in contrast to <1% in people who had adequate access to hospital (expert hospital care). (4) Treatment for dengue fever is merely supportive by handling plasma leakage and hemmorage because an effective antiviral or vaccine against dengue virus has not been found yet. (4) Therefore, an early predictor to predict the occurence of shock in DHF and reccurent shock in DSS needs to be studied.

Serum albumin is one of the markers of plasma leakage. Role of mediators become the main focus as the cause of plasma leakage in DHF due to the occurrence is less than 24-48 hours. (2) In vitro, the researchers had proved the role of various cytokines to the decline in transendothelial electrical resistance (TEER) from human umbilical vein endothelial cells line (HUVEC), which lead to in

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crease permeability of the endothelial cells line. (5,6) In addition to increased permeability, endothelial damage was suspected to be the main cause of the worsening course of DHF. (7-9) Nevertheless, both increased permeability due to tight junction stretching and endothelial damage will lead to plasma leakage. (10,11) Therefore, to date plasma leakage was the main concern of dengue virus infection. It has become interesting to study whether or not serum albumin, as a marker of plasma leakage, can be used as predictors of outcome, that were shock in patients with DHF and recurrent shock in DSS patients.

Study methods

Designs

A cross-sectional method was used to gain clinical characteristics data, laboratories and initial serum albumin level in study subjects. The study subjects were divided into two groups: DHF and DSS. After the initial measurement of serum albumin level, we monitored the outcomes in DHF and DSS patients. Outcome for patients with DHF was shock, while patients with DSS was recurrent shock.

Time and place setting

This study was done in Pediatric ward of Prof. Dr. RD Kandou Hospital, Manado, between July 2012 and July 2014.

Population and study subjects

Population of this study were children with DHF who had been hospitalized in Department of Child Health of Prof. Dr. RD Kandou Hospital, Manado. Study subjects were children who fulfilled the inclusion criteria. The inclusion criteria were DHF patients according to WHO (2011) criteria and whose parents consented their participation in the study. The exclusion criteria were children with bacterial infection, has received corticosteroids, blood transfusion, albumin infusion and had severe malnutrition. Minimun sample size was 38 (assumed r=0.4, power 0.80 and α 0.05) and study subjects recruitment was by consecutive sampling methods according to lines of inquiry (**Figure 1**). This study has received approval from the Ethics Committee of Prof. Dr. RD Kandou Hospital, Manado.

Statistical analysis

Data was analyzed using t-test or Mann Whitney test, logistic regresssion and ROC curves with SPSS v 21.0.

Results

We enrolled 67 children with DHF and 58 children with DSS. Characteristics of the study subjects were shown on **Table 1**. Based on follow up in DHF group, there were 34 children who developed shock (DSS) (**Figure 2**) and in DSS group there were 28 children who developed recurrent shock (**Figure 3**). The initial serum albumin level in DHF group who developed shock was significantly lower compared to those who did not develop shock (2.8 vs 3.6 g/dL) (**Table 2**). We did not find significant difference in serum albumin level between children who developed and did not develop recurrent shock in DSS group (2.7 vs 2.6 g/dL) (**Table 2**).

The results of statistical analysis with receiver operating characteristic (ROC) curves showed that to predict outcome of shock in DHF group, the cut-off of serum albumin level was 3.05 g/dl, with odds ratio (OR) 17.4, area under the curve (AUC) 0.865, sensitivity 79.4%, specificity 81.8%, positive predictive value (PPV) 81.8 and negative predictive value (NPV) 79.4, p=0.0001 and 95% CI 0.779-0.951 (**Table 3**). Meanwhile, in DSS group, albumin did not have prognostic value (p=0.630) (**Table 3**). The results from cross-analysis between DHF patients that deteriorated and DSS that did not deteriorate showed that there was no significant difference of initial serum albumin levels in the two groups (p=0.524) (**Figure 4**).

Discussion

Endothelial involvement in dengue could cause plasma leakage and hemostatic disturbances. (7,11) Plasma leakage is known to hold several important roles in course of disease and also prognosis of patient with dengue viral infection. (2,7) Albumin is the biggest colloid osmotic pressure in intravascular space (around 80%). Therefore, level of serum albumin plays an important role in managing plasma oncotic pressure compared with other proteins such as globulin and fibrinogen. (12) Interesting phenomenon in this study was the difference of initial serum albumin levels in DHF group who did not deteriorate compared to them who deteriorated/developed shock. Nevertheless, there was no significant difference between DHF group who did not deteriorate, DSS group who did not deteriorate and DSS group who deteriorated (**Figure 4**). This results showed that in severe cases, level of albumin was no longer decreased. Serum albumin level in intravascular space and extravascular space have reached new balance

according to osmolarity law. Increased permeability up to a certain point will not change the level of serum albumin. This caused albumin cannot be used as a predictor in the DSS group or in any larger leakage. Prior to the increase in permeability, there is a difference in oncotic pressure between intravascular space and interstitital space, which is about 20 mmHg. (12) Intravascular space has oncotic pressure about 28 mmHg consisting of 19 mmHg molecular effects and 19 mmHg Donnan effects, whereas the interstitial space is only about 8 mmHg. (12) These findings provide clinical meaning that in more severe condition, plasma leakage is no longer the centre of the pathomechanism in deterioration of DHF and DSS. This result was consistent with research conducted by Juffrie et al (2000) and Bethel et al (1989). (7,8) There are other factors that hold more important roles in DHF prognosis other than plasma leakage itself. Therefore, administration of albumin or any smaller molecules have no longer benefits on DSS management.

However, this study showed that measured levels of serum albumin still have meaning in predicting the disease course in the early stage of DHF, which is within the cut-off point of 3.05 g/dl, with OR 17.4. The next question, which is whether or not albumin could benefit DHF in the early stage still needs further research.

Table 1. Clinical characteristics of study subjects

	Course of disease			
	DHF		DSS	
	DHF to DHF (n=33)	DHF to DSS (n=34)	DSS to DSS (n=30)	DSS to recurrent DSS (n=28)
Gender				
Male (n=67),%	54.5	35.3	67.7	59.3
Female (n=58),%	45.5	64.7	32.3	40.7
Age (year)				
Mean	6.9	7.5	7.4	6.1
Median	6	7.5	7	5.5
Range	1-12	3-13	3-12	1-11
Day of fever on admission (n, %)				
Day 3	17 (51.5)	1 (2.9)	12 (40.0)	6 (21.4)
Day 4	10 (30.3)	13 (38.2)	15 (50.0)	11 (39.3)
Day 5	6 (18.2)	14 (41.2)	1 (3.3)	8 (28.6)
Day 6	0	6 (17.6)	2 (6.7)	3 (10.7)

Table 2. Laboratories characterictics of study subjects

	Course of disease			
	DHF		DSS	
	Shock - n=33	Shock + n=34	Recurrent shock - n=30	Recurrent shock + n=28
Albumin (g/dL)				
Mean	3.6	2.8	2.7	2.6
Median	3.6	2.8	2.7	2.7
Range	2.6-4.5	2.0-3.9	1.5-4.0	2.0-3.2

Table 3. Initial serum albumin levels in outcomes of DHF and DSS

Course of disease	Albumin								
	AUC	Cutoff	Sn (%)	Sp (%)	PPV (%)	NPV (%)	OR	p	95% CI
DHF to DSS	0.865	3.05	79.4	81.8	81.8	79.4	17.4	0.0001	0.779-0.951
DSS to recurrent DSS	0.541	2.55	42.9	63.3	52.2	54.3	1.3	0.630	5.2-58.4

Legend: Sn=sensitivity; Sp=specificity; PPV=positive predictive value; NPV=negative predictive value; OR=odds ratio; CI=confidence interval.

Figure 1. Flowchart

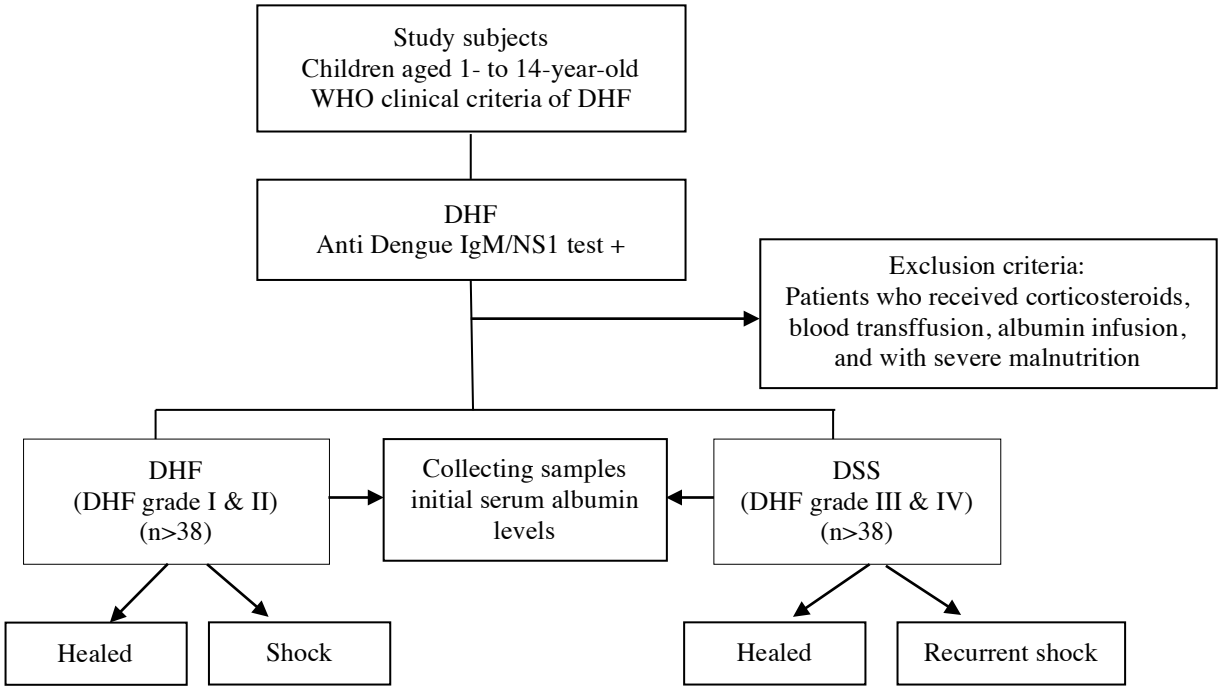


Figure 2. Course of disease in DHF group

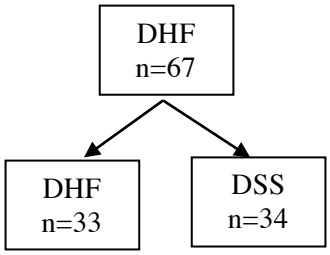


Figure 3. Course of disease in DSS group

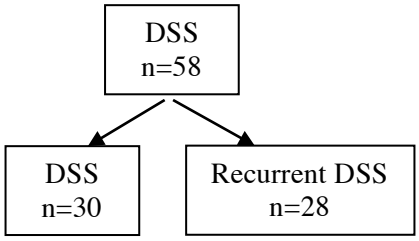
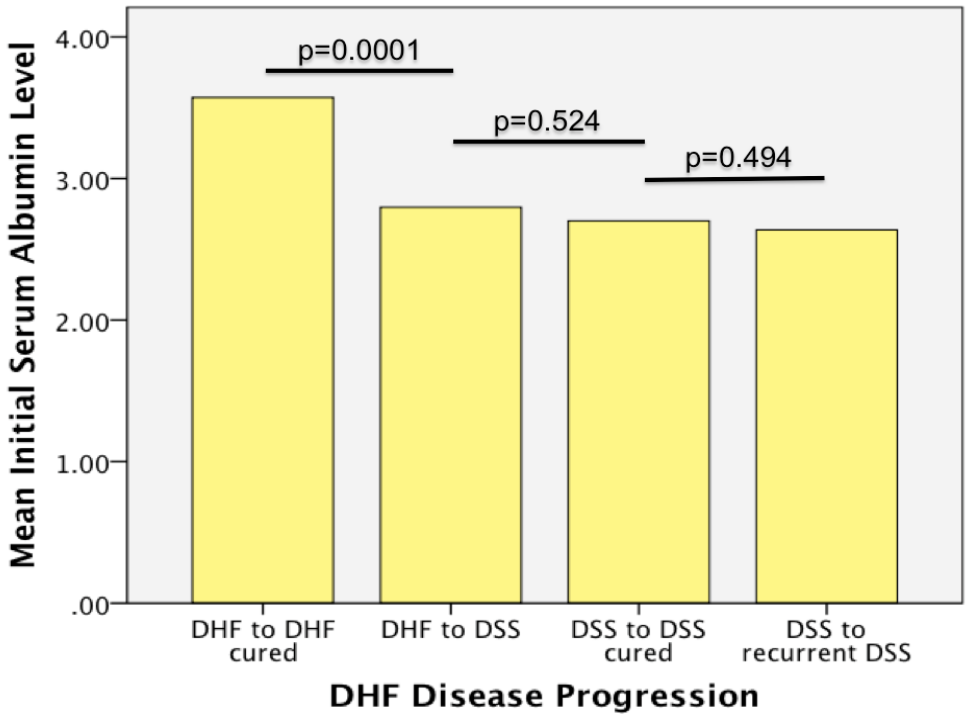


Figure 4. Comparison of mean initial serum albumin level in each group based on disease's outcome



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