Serum Ferritin as a Predictor of Shock in Children with Dengue Infection

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ABSTRACT

Background: Dengue shock syndrome causes high morbidity and mortality among children worldwide. Several laboratory monitoring can be used to evaluate the progressivity of dengue virus infection. This study aimed to analyze ferritin serum as a predictor of shock in children with dengue infection, and to determine the cut off point that can be used to diagnose dengue shock.

Subjects and Method: This was a cross sectional study conducted at pediatric ward, Dr. Moewardi hospital Surakarta Dr. Soetrasno hospital Rembang, Central Java. Study population was children aged less than 18 years old with dengue infection. Study subjects were selected by consecutive sampling. The dependent variable was dengue shock. The independent variable was serum ferritin concentration. Mann Whitney test was used to compare mean ferritin concentration between children with and without dengue shock. Cut off point of serum ferritin concentration was determined by ROC curve.

Results: Mean serum ferritin concentration in children with dengue shock (mean= 3628.8; SD= 1582.4) was higher than in children without dengue shock (mean= 717.8; SD= 695.8), with $p < 0.001$. Therefore, there was a statistically significant association between serum ferritin concentration and dengue shock. The cut off point of serum ferritin concentration that could be used to show dengue shock with high sensitivity (0.92) and specificity (0.97) was 2304.5.

Conclusion: High serum ferritin concentration is a predictor of dengue shock.

Keywords: ferritin, dengue shock syndrome, children

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BACKGROUND

Dengue infection is a disease caused by the dengue virus. Dengue fever, dengue hemorrhagic fever, and dengue shock syndrome have become international health problem. This infection can affect all ages. The majority of these cases occurs in children under the age of 15 as many as 95% and about $\geq 5\%$ occur in infants (Setiati et al., 2007; Phuong et al., 2004)

Dengue virus infection causes high mortality and morbidity throughout the world due to the very dynamic journey of dengue virus infection. The critical phase of dengue infection accompanied by increased capillary permeability and plasma leakage

only lasts 24-48 hours, so that both clinical and laboratory monitoring is needed to evaluate any changes that occur in the phases of dengue virus infection. (Hadinegoro et al., 2014)

Several previous studies had tried to evaluate laboratory parameters to be able to appropriately assess the development of dengue virus infection, especially when there is a plasma leak, but do not always give the same results. A study on serum ferritin levels in children with dengue infection in Thailand shows that serum ferritin levels can be used as predictors of clinical outcomes in dengue infection. The study concluded that serum ferritin levels in III

and IV degree dengue hemorrhagic fever (DHF) were higher than dengue fever and I and II degree dengue fever. This is thought to be related to an increase in vascular permeability that occurs in DHF especially in degrees III and IV (Chaiyaratana et al., 2008). In addition to a study in Thailand, other studies on ferritin levels with dengue infection in the adult population have also been carried out in Aruba, South America. The study evaluated serum ferritin levels in patients with non-severe and severe dengue infections. In the critical phase, ferritin increases significantly. Non severe dengue cases without warning signs ($p= 0.014$), non-severe dengue with warning signs ($p < 0.001$), and severe dengue ($p= 0.028$) (Van de weg et al., 2011)

A study to analyze cutoff point for ferritin levels as predictors of shock in children with dengue infection has never been done in Indonesia. This encourages the writer to further examine whether there is a correlation between ferritin levels and the incidence of shock in children with dengue infection. The general purpose of this study is to assess and analyze the correlation between ferritin levels and the incidence of shock in children with dengue infection. Whereas, the specific objective is to assess and analyze the correlation between ferritin levels in children with dengue infection without shock and accompanied by shock, determine the cutoff point of ferritin levels with the incidence of shock in children with dengue infection, assess and analyze the strength of the correlation between ferritin levels and the incidence of shock in children with dengue infection.

SUBJECTS AND METHOD

A. Design of the Study

The design of this study was a cross-sectional study

B. Population and samples

The target population in this study were patients with children younger than 18 years with dengue infection. Affordable population in this study were patients with dengue infection who were treated in the child care room of Dr. Moewardi Surakarta and Dr. Soetrasno Rembang hospital in December 2016 to May 2017.

Sampling was done using consecutive sampling with inclusion criteria:

1. All children aged ≤ 18 years
2. Patients who came to the emergency room or child polyclinic at Dr. Moewardi and Dr. Soetrasno hospitals with complaints of fever for 2-4 days
3. Fulfill the criteria for clinical diagnosis of dengue infection according to WHO 2011 and/or serological results of dengue infection (positive dengue IgM or IgG)
4. Parents/ guardians sign the consent sheet for the study

Exclusion criteria:

1. Patients with hepatic function disorders, chronic infections, malignancies, hematological disorders, autoimmune diseases
2. Parents/guardians refuse to take part in the study

From the calculation of the sample size carried out with an unpaired analysis test approach, a sample size of 50 people was obtained. The independent variables in this study were the incidence of shock in dengue infection, ferritin levels as dependent variables and nutritional status as confounding variables. The usual serum ferritin level was examined by the ELFA method. The normal value is 18-350 μg / liter. Ferritin levels were examined on day four or fifth of fever and in this study a numerical scale whereas the severity of dengue infection was determined according to WHO 2011 clinical criteria. In this study,

the severity of dengue infection was a nominal scale and was divided into:

- a. Dengue infection without shock
Dengue infection was characterized by acute high fever along with other symptoms of dengue fever at the onset of the disease and signs of plasma leakage caused by increased vascular permeability such as hem concentration, pleural effusion, and ascites. From laboratory blood tests it was found that thrombocytopenia $<100,000 / \text{mm}^3$ and increased hematocrit $\geq 20\%$
- b. Dengue infection accompanied by shock
Dengue infection was accompanied by signs of circulatory failure such as:
 1. A pulse that was weak or not palpable
 2. Narrow pulse pressure ($\leq 20 \text{ mmHg}$)
 3. Hypotension.

The subjects who were included in the criteria for dengue infection accompanied by shock were those who came to the hospital with shock conditions and shock treatment.

Nutritional status in this study was a categorical scale. Nutritional status was

Table 1.Characteristics of subjects of the study

Characteristics	Shock		P
	Without shock (n=38)	Shock(n=12)	
Age	7.24 $\pm$ 4.20	8.83 $\pm$ 3.74	0.177
Gender			0.730
Female	20 (52.6%)	7 (58.3%)	
Male	18 (47.4%)	5 (41.7%)	
Nutritional status			0.063
Bad	9 (23.7%)	0 (0.0%)	
Good	29 (76.3%)	12 (100.0%)	

Table 1 shows that the age of patients in children with dengue infection without shock was 7.24 + 4.20 years, whereas in children with dengue infection with shock it was 8.83 + 3.74 years, $p = 0.177$ which meant that the age of patients with dengue infection without shock and with shock was not significantly different.

determined from the results of anthropometric measurements, by measuring body weight and height. The determination of nutritional status was based on CDC criteria in 2000.

The data obtained was analyzed using the SPSS 17.0 program. The basic characteristics of the subjects (age, gender, severity of disease, nutritional status) were described in the form of numbers. The correlation between independent variables and dependent variables was tested by unpaired T test. If it did not meet the parametric test requirements, the Mann Whitney test was performed. The determination of the value limit with the ROC curve and the strength of the correlation between independent variables and dependent variables were assessed by the contingency coefficient test.

RESULT

From the results of the study, it was found that the characteristics of patients in the form of age, gender and nutritional status were described as follows.

Most of the children with dengue infection without shock were female, there were 20 patients (52.6%), while most the children with dengue infection with shock were women, there were 7 patients (58.3%), the value of $p = 0.730$ which meant that the gender between children with dengue

infection without shock and with shock did not differ significantly.

The nutritional status of patients in children with dengue infection without shock was mostly good, there were 29 patients (76.3%), whereas the nutritional status

in children with dengue infection with shock were all good, ie 12 patients (100%), $p = 0.063$ which meant that nutritional status among children with dengue infection without shock and with shock is not significantly different.

Table 2. The result of Mann Whitney test on the correlation of ferritin levels in children with dengue infection without shock and with shock

Variable	Shock		p
	Without shock(n=38)	Shock(n=12)	
Ferritin	717.80± 695.78	3628.84± 1582.40	<0.001

Table 2 shows that ferritin levels in children who did not experience shock were 717.80+ 695.78, whereas in children who experienced shock it was 3628.84 + 1582.40, $p < 0.001$ which meant that ferritin levels among children who experienced shock and children who did not experience shock had a significant difference.

This study found that there were 38 children with dengue infection without shock and 12 children with dengue infection with shock. Based on these results which were then compared with the results of measuring ferritin levels, the ROC curve results were obtained as follows.

Figure 1. ROC curve

Table 3. The results of cutoff point determination of ferritin levels based on the incidence of shock

AUC	Sensitivity	1-Specificity	Cut off Value	p
0.956	0.917	0.026	2304.5	<0.001

Based on the ROC curve, the AUC value was 0.956 with a value of $p < 0.001$. The cutoff point of ferritin levels was 2304.5 $\mu\text{g/}$

liter with Sensitivity = 0.917 and Specificity = 0.974.

Table 4. The Results of Diagnostic Test

Examination	Diagnostic Test					
	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Ferritin Levels	0.92	0.97	0.92	0.97	34.83	0.086

Examination of children with dengue infection with samples of ferritin levels at the 2304.5 intersection point obtained sensitivity of 91.7%, which meant 91.7% of children with dengue infection with shock could be detected by examining ferritin levels and ferritin level specificity values obtained in this study as many as 97.4%, which meant that it was likely the diagnosis of patients who did not experience shock could be excluded in patients who had ferritin levels ≥ 2304.5 by 97.4%. The results of the examination obtained a PPV value by 91.7% which meant that ferritin levels if the results were ≥ 2304.5 then there was a possibility by 91.7% with the results of patients who experienced shock. While the NPV value was 97.4%, which meant that ferritin levels if the results were < 2304.5 then there were a possibility 97.4% of

patients with the results of the examination did not experience shock.

The PLR value was 34.83 which meant that the possibility ratio of patients who had ferritin levels > 2304.5 would get a diagnosis of shock of 34.833 times greater than that of patients who had ferritin levels < 2304.5 . The value of NLR was 0.086, which means that the possibility ratio of patients with ferritin levels < 2304.5 would get the results of patients experiencing shock at 0.086 times smaller than patients who had ferritin levels > 2304.5 .

The correlation test was to determine the level of strength of the correlation between ferritin levels and the incidence of shock. In this study the correlation used was the contingency coefficient test, the results were as follows.

Table 5. The Correlation of Ferritin Levels and the Incident of Shock

Ferritin Levels	Shock		r	p
	Without Shock	Shock		
< 2304.5	37 (97.4%)	1 (8.3%)	0,665	< 0.001
≥ 2304.5	1 (2.6%)	11 (91.7%)		

The correlation between ferritin levels and the incidence of shock received a contingency coefficient of 0.665 with a value of $p < 0.001$, which meant that there was a significant correlation between ferritin levels and the incidence of shock, with the closeness of the correlation in the strong category. There was a tendency that if ferritin levels were > 2304.5 then there would be a risk of shock.

DISCUSSION

This study took a sample of 50 children who were treated in the care room of Dr.

Moewardi and Dr. Soetrasno hospital. Data taken comes from primary data based on history to find out when fever starts. In addition, another primary data source is the result of laboratory tests.

This study found the prevalence of shock in children with dengue infection 24%. The prevalence of the occurrence of shock in children with dengue infection in this study is lower than the study conducted by Mila (2009) in Dr. Moewardi hospital, around 30%, but this study was obtained from two different types of hospitals and

examination of ferritin levels had barriers associated with expensive costs.

The average age of patients experiencing shock was 8.83 ± 3.74 years. This is in accordance with Mila's study in Surakarta where the average age of patients with dengue infection was 8.1 years (Mila, 2009).

The comparison of male and female in this study was 27/23 (1.7/1). After analyzing the data statistically, the results showed that gender did not have a statistically significant correlation with shock. This result is consistent with previous studies which stated that gender has no correlation with the occurrence of shock (Kalyanarooj et al., 1997).

This study found 82% of groups of children with good nutritional status, the incidence of shock were more in the group of good nutritional status. This is not in accordance with previous study conducted by Kalayanarooj on 4532 children, indicating that good nutritional status and obesity had OR 1.96 for shock (Pichainarong et al., 2006). It can be explained that the development of dengue infection is influenced by the patient's immune response. In good nutritional status, there is a stronger immune response than children with malnutrition so that plasma leakage due to an increased immune response to dengue virus will increase the risk of shock (Hung et al., 2005). However, a study conducted by Maria et al. (2013) in Yogyakarta, stated that obesity is not a risk factor for dengue shock syndrome (Widiyati et al., 2013).

Based on the results of the ROC analysis, the AUC value was 0.956 with a value of $p < 0.001$. The cutoff point for ferritin levels was 2304.5, namely at Sensitivity 0.917, Specificity 0.974, NDP 91.7%, NDN 97.4%. These results indicated ferritin with

a cutoff > 2304.5 increased the risk of shock in children with dengue infection.

The correlation between ferritin levels and the incidence of shock received a contingency coefficient of 0.665 with a value of $p < 0.001$, which means that there was a significant correlation between ferritin levels and the incidence of shock, with the closeness of the correlation in the strong category. Where there is a tendency that if ferritin levels are > 2304.5 it will increase the risk of experiencing shock.

REFERENCE

- Cahyaningrum JMH (2009). Indeks efusi pleura sebagai predictor sindrom syok dengue pada anak di RSUD Dr. Moewardi Surakarta. Tesis Fakultas Kedokteran UNS. Surakarta
- Chaiyaratana W, Chuansumrit A, Atamasirikul K, Tangnararatchakit K(2008). Serum ferritin levels in children with dengue infection. *Southeast Asian J Trop Med Public Health*. 39:832-6.
- Hadinegoro SR, Moedjito I, Chairulfatah A (2014). Pedoman diagnosis dan tata-laksana infeksi virus dengue pada anak. Jakarta: Badan penerbit Ikatan Dokter Anak Indonesia.
- Hung NT, Lan NT, Lei HY, Lin YS, Lien LB, Huang KJ, et al. (2006). Volume replacement in infants with dengue hemorrhagic fever/dengue shock syndrome. *Am J Trop med Hyg*.74:684-91.
- Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentra-sai N, et al. (1997). Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis*. 176:313-21.
- Phuong CXT, Nhan NT, Kneen R, Thuy PTT, Thien CV, ThuyNga NT et al. (2004). Clinical diagnosis and assessment of severity of confirmed dengue infections in Vietnamese children is

- the World Health Organization classification system helpful. *Am J Trop Med Hyg.* 70:172-9.
- Pichainarong N, Mongkalagoon N, Kalayanaroj S, Chaveepojnkamjorn W (2006). Relationship between body size and severity of dengue hemorrhagic fever among children aged 0-14 years. *Southeast Asian J Trop Med Public Health.* 37:283-8.
- Setiati TE, Mairuhu ATA, Koraka P, Supriana M, Mac Gillavry MR, Brandjes DPM, et al (2007). Dengue disease severity in Indonesian children; an children: an evaluation of the World Health Organization classification system. *BMC Infect Dis.* 7:1-8.
- Van de Weg C, Huits R, Pannuti C, Brouns R, van den Berg R, van den Ham H, et al. (2014). Hyperferritinemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. *PLOS journal.* 8:1-11
- Widiyati MMT, Laksanawati ID, Prawirohartono EP (2013). Obesity as a risk factor for dengue shock syndrome in children. *Paediatr Indones.* 53:187-92.
- World Health Organization (2011) Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever. Revised and expanded edition. New Delhi:WHO.
- World Health Organization (2009). Dengue guidelines for diagnosis, treatment, prevention and control. New Edition. Geneva: WHO.
- World Health Organization (1997). Dengue: guidelines for diagnosis, treatment, prevention and control. New Edition. Geneva:WHO.