ASSOCIATION BETWEEN NUTRITIONAL STATUS AND THE OUTCOME OF PEDIATRIC PATIENT WITH DENGUE SHOCK SYNDROME

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ABSTRACT

Background: *The association between nutritional status and dengue infection is still considered controversial. Researches that study obesity and shock in pediatric patients with dengue hemmorhagic fever (DHF) has been widely carried out. However, researches that study the association between obesity and the outcome of patients with dengue shock syndrome (DSS) are still rarely done.* ***Objective:*** *The objective is to study the association of obesity in body mass index-for-age (BMI-for-age), gender, and age to the outcome of patients with dengue shock syndrome (recurrent shock or death).* ***Material and method:*** *The research was analytical retrospective observational research with a case-control design using secondary data from the medical records of pediatric patients with DSS in Dr. Soetomo General Hospital during 2015. The analyses used to test the association of obesity (BMI-for-age), gender, age and the outcome of patients with dengue shock syndrome (recurrent shock or death) were the Chi Square or Fisher Exact test.* ***Result:*** *The sample acquired was 60 data, consisting of 46 patients with DSS without recurrent shock or death and 14 pediatric patients with DSS experiencing recurrent shock or mortality. The frequency of boys and girls were found in equal numbers. Age group >5-10 years was found more common (45%). The results of the analyses test found no asssiation between gender (p=0.542), age (p=0.314), and obesity (p=1,000) and the outcome of pediatric patients with dengue shock syndrome.* ***Conclusion:*** *There were no association found between obesity, age, and gender to the outcomes of pediatric patients with DSS at Dr. Soetomo General Hospital.*

Keywords: Obesity, children, age, dengue shock syndrome, outcome.

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Background

Dengue hemorrhagic fever (DHF) is a tropical disease that has become a major problem in subtropical countries in the Western Pacific, Southeast Asia, Central and South America (WHO, 2011). According to the data in 2015, 126,675 people in Indonesia had been infected with dengue virus and a total of 1,229 people have died (Kemenkes RI, 2016). According to the World Health Organization (WHO), DHF patients with dengue shock syndrome (DSS), have the most severe form of dengue infection (WHO, 2011).

Pathophysiology of DHF/DSS involves various inflammatory cytokines as IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-18, TGF-1β , TNF-α, and IFN-γ (Martina, et al., 2009). These cytokines affect vascular permeability and trigger plasma leakage. A research has shown that TNF-α synergize with dengue virus to modify adhesion molecule on endothelial cell and increases vascular permeability (Inyoo, et al., 2017). Cytokine IL-8 was initially known to increase vascular permeability and cause thrombocytopenia in patients with dengue infection (Iani, et al., 2016). Another research also found that IL-6 has pro-inflammatory properties and enhances antibody production of B cell (Scheller, et al., 2011). These cytokines would form 'cytokine storms' that will increase vascular permeability and cause vascular leakage (Rathakrishnan, et al., 2012). Children were found to be more susceptible to shock than adults (The, et al., 2012). This finding could be explained because children have greater vascular permeability than adults, which makes them more vulnerable to vascular leakage during dengue infection (Gamble et al., 2001). Also in children, it required much less significant fluid loss to induce shock in their hemodynamic system compared with adults, thus explaining why children were more vulnerable to hypovolemic shock (Elbarbary et al., 2015). Another opinion suggested that children have less well-developed mechanism in minimizing heart decompensation against increasing vascular permeability, thus making children more vulnerable to hemodynamic instability (The, et al., 2012).

Objective

Obesity was initially thought to induce shock in DHF patients because adipose tissue express inflammatory cytokines such as TNF-α, IL-6, IL-8 and IL-1β, that may play a role in increasing vascular permeability and plasma leakage (Makki, et al., 2013). Many studies have discussed the relationship of obesity to shock in patients with DHF. However, this relationship is still controversial given the many variations of the research design, as well as variables used in research. Meanwhile, researches that study the relationship between obesity and the outcomes of pediatric patients with DSS are still very rarely conducted. Therefore, this research aims to find the relationship between the nutritional status of obesity on the outcome of pediatric patients with DSS.

Methods and Material

This research used a retrospective case-control design and used secondary data from medical records that was stored in Marketing and Medical Records Department of Regional Public Hospital of Dr. Soetomo, Surabaya, East Java. Medical record acquired in this study was all pediatric patients with DHF who were hospitalized from 1 January 2015 to 31 December 2015. Cases were all pediatric patients aged 0-18 years with DSS that fulfill WHO Dengue 2011 standards and the inclusion and exclusion criteria. Variables taken from this research were nutritional status, age, gender, and outcome of patients with recurrent shock or death. The inclusion criteria were DSS patients, diagnosed with DHF grade III or IV that fulfill WHO 2011 standards, had complete information of weight, height and age, who were hospitalized in the Bona and/or Pediatric Intensive Care Unit (PICU) wards. Exclusion criteria were patients with comorbid such as varicella, typhoid, sepsis, pneumonia, kidney failure, severe dehydration, hypertension, or patients who left the hospital against medical advice.

Obesity is determined based on body-mass-index-for-age (BMI-for-age), which is predetermined by weight-for-height charts. If the weight-for-height chart measurement shows that there is a potential for an overweight (>+1 SD) according to WHO 2006 growth chart for children aged 0-5 years, or weight-for-height ratio >110% based on the CDC 2000 growth chart for children aged >5-18 years, the BMI–for-age chart is used to differentiate overweight or obesity. Children aged 0-2 years use the WHO 2006 BMI-for-

age growth chart, while for those aged >2-18 years, the CDC 2000 BMI-for-age growth are used instead. The nutritional status of obesity is determined if the area is >+3SD on the 2006 WHO chart. While the 2000 CDC chart defines obesity if the area is found in $>P_{95}$ (Unit Kerja Koordinasi Nutrisi dan Penyakit Metabolik, 2011). The age variable is calculated by substracting hospital admission date and the patient's birth date. Gender is determined based on medical records.

The patients were all DHF pediatric patients who experience DSS. The control group was patients that did not experience recurrent shock or death and the case group were patients that experience recurrent shock or death. Recurrent shock is defined as a condition characterized by pulse pressure ≤20 mmHg with impaired perfusion (cold acral, prolonged capillary refill time, tachycardia), or accompanied by hypotension-by-age with cold and wet extremities, or irreversible pulse and blood pressure, which occur in patients who have experienced the condition before, have been resuscitated, and have had clinical improvement such as improved blood pressure, capillary refill time <2, and warm and red extremities (WHO, 2011).

The sampling technique used in this researched is total sampling. The collected data is analyzed with International Business Machine Statistical Product and Service Solution version 25 (IBM SPSS 25), with a significance level of $p<0.05$ and a 95% confidence interval. The test used in this research was the Chi Square or Fischer Exact test.

Result

The research was conducted from August 2018 to January 2019, and had obtained a research permit at the Health Research Ethics Committee of Regional Public Hospital of Dr. Soetomo. Data collection was carried out by observing medical records of DHF pediatric patients with DSS who were treated in the Bona ward or PICU Dr. Soetomo in 2015. The data successfully obtained were 114 medical records. Medical records that fulfill the inclusion criteria were 70 medical records, and 44 medical records did not fulfill the inclusion criteria. Medical records excluded after inclusion criteria were 10 medical records, which excluded patients presenting with varicella, typhoid, sepsis, pneumonia, or left the hospital against medical advice. Patients that experienced recurrent shock or death were 14 patients and 46 patients did not experience recurrent shock and death.

Table 1. Gender and age characteristic of DSS pediatric patient hospitalized in Regional General Public Hospital of Dr. Soetomo Surabaya in 2015.

Patient characteristic	**Patient without recurrent shock or died**	**Patient with recurrent shock or died**	**Total n (%)**	**p-value**
Gender				
Female	24 (52,2%)	6 (42,9%)	30 (50%)	0,542[a]
Male	22 (47,8%)	8 (57,1%)	30 (50%)	
Age				
0-2	5 (10,9%)	0 (0,0%)	5 (8,3%)	0,314[b]
>2-5	14 (30,4%)	2 (14,3%)	16 (26,7%)	
>5-10	19 (41,3%)	8 (57,1%)	27 (45%)	
>10-18	8 (17,4%)	4 (28,6%)	12 (20%)	

[a] *Chi Square Test*
[b] *Fisher Exact Test*

Table.1 showed that Chi Square statistical tests found no significant relationship between gender and the outcome of pediatric patients with DSS (p> 0.05). Between the gender of female and male were found to have the same number. As for the age variable, the statistical test used was the Fischer Exact test and found no significant relationship with the outcome of pediatric patients with DSS (p>0.05). The age group> 5-10 years (45%) was found more common.

Table 2. Statistical analysis of nutritional status using *Fischer's Exact Test*, of pediatric patients hospitalized in Bona or PICU ward of Regional General Public Hospital of Dr. Soetomo Surabaya in 2015.

Patient Characteristic	**Patient without recurrent shock or died**	**Patient with recurrent shock or died**	**Total n (%)**	**p-value**
Nutritional Status				
Obese	11 (23,9%)	3 (21,4%)	14 (23%)	1,000[b]
Non-obese	35 (76,1%)	11 (78,6%)	46 (77%)	

[b] *Fisher Exact Test*

Table 2. showed that Fisher Exact statistical test found an insignificant relationship between the nutritional status of obesity and the outcome of pediatric patients with DSS (p> 0.05).

Discussion

The relationship of age to the outcome of repeated shock or death in this research was found to be insignificant. Previous studies also reported, that age had no relationship with recurrent shock events in children with DHF (Huy, et al., 2013). In contrast, other research showed there was an association between younger age and recurrent shock in children (Lam, et al., 2015). A research found that children over the age of 5 years are more at risk of suffering from shock compared with children under 5 years (Gupta, et al., 2011). This is different from other studies which found that children aged 0-5 years are more likely to develop DSS (Yolanda & Alfan, 2017). This shows that the relationship between age and shock is still controversial. In terms of numbers, pediatric patients with age group >5-18 years had more shock events compared to the 0-5 years age group. Another research also found that pediatric patients with DSS aged ≥5 years were found to be more common than pediatric patients aged <5 years (Buntubatu, et al., 2016). A research found that bleeding manifestation and organ involvement were more common in adult than in children (The, et al., 2012). This finding is supported by a research which explained that adult patient with dengue infection require more blood tranfusion than in children, so that it may be suspected that the risk of severe hemorrhage is increased in adolescent (Namvongsa, et al., 2013). In addition, another research showed that secondary infection is found more common in older children, thus they might have higher risk of getting dengue shock due to antibody in past infection (Thai, et al., 2011).

Gender did not show a significant relationship to the outcome of recurrent shock or death in patients with DSS. A research also found that gender was not associated with recurrent shock in DSS pediatric patients (Huy et al., 2013). This could be due to the absence of differences in cytokine levels that play a role in the pathophysiology of DHF between the gender, which indicated that the severity of clinical manifestations does not depend on gender (Hung, et al., 2005). Another research supported this founding, that there is no clear evidence that gender has any effect on cytokine levels in patients with dengue infection (Hernández et al., 2016) In contrast, another research found that female was more associated with recurrent shock events (Lam et al., 2015). It was thought that women were more susceptible to shock due to having

greater vascular permeability and greater immune response (Anders, et al., 2011). A research has shown that women have a greater $CD4^+$ and $CD8^+$ ratio than men, thus theoretically women would have stronger immune response than men (Klein et al., 2016). However, women's age also affects the immunity of women, because of the influence of receptors on female reproductive hormones on immune cells, may affect the individual's immune response (Klein et al., 2015).

Obesity was also found to have no significant relationship with the outcome of recurrent shock or death in pediatric patients with DSS. Obese children with DHF, had been previously found to have an increased risk to develop shock (Saniathi, et al., 2009). This was presumably caused by adipose tissue that can express TNF-α, IL-6, IL-8 and IL-1β cytokines that play a role in the inflammatory process, thereby causing more severe plasma leakage in DHF patients with excess adipose tissue (Makki, et al., 2013). However, a research found that cytokine levels in children with obesity, is influenced by the gender,and age of the individual, so it can be inferred that obesity does not always cause severe clinical manifestations in children with DHF (Tam, et al., 2010). Another research found that obesity was not a risk factor for shock, but an extremely low platelet counts were a more important factor in shock (Widiyati, et al., 2013). Adipose tissue is also known to have a local Renin-Angiotensin system capable of producing mediators such as renin, angiotensinogen, angiotensin I, angiotensin II, angiotensin type I (AT1) and type II (AT2) receptors, angiotensine converting enzyme (ACE), which might play a role in hemodynamics, and compensate shock condition in pediatric patients with DSS (Frigolet et al., 2013). Although in this research the nutritional status of obesity did not affect the outcome of pediatric patients with DSS, it should be noted that in this research, there were 2 patients died and both were obese. Other studies found that obese patients with dengue virus infection have a higher frequency to show hemoconcentration, severe thrombocytopenia, increased creatinine, elevated liver enzymes, rapid hemoconcentration increase, rapid rise in platelet levels, and longer hospital stay (Tan, et al., 2018). A research also found that patients with obesity have more unusual clinical manifestations such as encephalopathy, had infection, and fluid overload than other nutritional status (Kalayanarooj & Nimmanitya, 2005). Regardless of the result of this research, it is important to carefully observe DHF patients with obesity, and further research is required to find the explanation behind this phenomenon.

Conclusion

In this research, there is no relationship between obesity, gender, and age with the outcome of pediatric patient with DSS.

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