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The association between overweight and shock in children with dengue hemorrhagic fever at Wangaya General Hospital, Bali, Indonesia

Jade Irene Linardi[1*], I Wayan Bikin Suryawan[1], Anak Agung Made Widiasa[1]

[1]Department of Child Health, Wangaya General Hospital, Bali, Indonesia

*Correspondence to:
Jade Irene Linardi; Department of Child Health, Wangaya General Hospital, Bali, Indonesia;
jade.irene@yahoo.com

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ABSTRACT

Background: Dengue Hemorrhagic Fever (DHF) which severity varies, has devastating complications and outcomes, especially when shock events appeared and are prolonged. There is no predictor of whether DHF patients would develop into shock (called Dengue Shock Syndrome or DSS). Previous studies claimed overweight as a predictor of DSS, although it remains controversial.

Objective: To find the association between overweight and shock events in children with DHF.

Methods: This was an observational analytic study with a case-control design. Data were taken from medical records with children hospitalized at Wangaya General Hospital from May 2019 through April 2020. Inclusion criteria were children < 18 years who have been diagnosed with DHF grade I through IV. Data were analyzed using the chi-square test in SPSS 24.0 for windows.

Results: Of 126 subjects who fulfilled the inclusion criteria, there were 42 DSS patients as the case group and 84 non-DSS patients as the control group. From the data analysis, there was a significant association between overweight and shock events in children with DHF (p=0.001; OR 3.76; 95% CI 1.72 to 8.20). Furthermore, pleural effusion (p=0.001), highest hematocrit of ≥ 46% (p=0.001), and lowest platelet count of ≤ 50,000/µL (p=0.006) also had significant association with shock events.

Conclusion: Overweight is associated with shock events in children with DHF. Pleural effusion, hematocrit level of ≥ 46%, and platelet count of ≤ 50,000/µL were also counted as risk factors to develop shock.

Keywords: shock, dengue, overweight, nutritional status.

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INTRODUCTION

Dengue hemorrhagic fever (DHF) is one of the spectrums of dengue infection, which has been a global problem for ages, especially in tropical countries, including in Indonesia. The virus itself has been known to have several serotypes includes dengue virus (DEN)-1, DEN-2, DEN-3, and DEN-4. Of all serotypes, DEN-3 is associated with more severe cases, followed by DEN-2.[1] DHF had certain periods where incidence peaked in Indonesia. The last incidence peaked in 2017, in which Bali Province had the highest morbidity of 105.95 cases per 100.000 population.[2] Most dengue infections are self-limiting, but complications that appeared can lead to high morbidity and mortality. According to World Health Organization (WHO) South-Asia Region, DHF is categorized into 4 grades by its severity, grade I and II as non-shock cases, while grade III and IV as dengue shock syndrome (DSS).[3]

Until today, clinicians have difficulties differentiating which DHF patients that will develop into shock. Early recognition of risk factors for shock events is essential in order to provide proper and prompt treatment. One of the risk factors predicted to be associated with shock events is overweight, although it remains controversial.[4-8] Based on theories, there was greater plasma leakage in overweight/obese patients caused by combinations of increased proliferation of dengue virus, increased inflammatory cytokines, and adhesion molecules secondary to a decreased level of adiponectin serum.[6,9,10] Therefore, this study was conducted to find the association between overweight and shock events in children with DHF.

METHODS

This was an observational case-control study performed at Wangaya General Hospital. Study subjects were collected by using consecutive sampling. Subjects were aged less than 18 years, who met WHO (2011) criteria for DHF or DSS that were admitted to Wangaya General Hospital in both the common pediatric unit and pediatric intensive care unit (PICU)

from May 2019 through April 2020. We excluded patients with final diagnoses of dengue fever or who had other infections such as pneumonia, diarrhea with severe dehydration, encephalitis. Patients with a history of hematologic diseases or in an immunocompromised state were also excluded.

Study subjects were divided into case groups and control groups. The control group consisted of patients diagnosed with DHF grade I or II who had 2-7 days of fever, hemorrhagic manifestation (positive tourniquet test), platelet counts < 100,000/μL, and plasma leakage signs such as increased hematocrit, had pleural effusion, or ascites. The case group included patients diagnosed with DHF grade III or IV who fit the criteria above of DHF grade I or II plus shock signs such as weak pulse, narrowed pulse pressure, hypotension, cold, clammy skin, decreased urine output, and restlessness.[3]

The total samples were calculated based on an unpaired case-control study where the case versus control group ratio was 1:2. The proportion of the effect on the control (P2) was 0.24;[11] determined odds ratio (OR) was 3, with Zα value of 1.96 and Zβ value of 0.84. Therefore, the minimum subjects required for the DSS group (case) were 42 children, while for the non-DSS group (control) were 82 children.

All data were taken from medical records where the patient's history, nutritional status, clinical presentation, and laboratory profiles were noted. Nutritional status was assessed by the weight-for-height percentage of > 110% as overweight, while the percentage of ≤ 110% was categorized as non-overweight. Clinical presentations such as abdominal pain, hepatomegaly, and pleural effusion were noted. Laboratory profiles that were assessed were highest hematocrit (cut-off ≥ 46%) and lowest platelet count (cut-off ≤ 50,000/μL) during hospitalization.

Data were analyzed using the chi-square test by SPSS version 24.0 for Windows. P-value was counted with < 0.05 value considered statistically significant. The odds ratio with a 95% confidence interval was also calculated to evaluate the association between overweight and shock events in DHF.

Table 1. Study subject characteristics

Characteristics	DSS group (n = 42)	Non-DSS group (n = 84)
Gender, n (%)		
Female	14 (33.3)	37 (44)
Male	28 (66.7)	47 (56)
Age (year), median (min-max)	10 (3-17)	11 (1-17)
Weight (kg), median (min-max)	35 (17-70)	39 (8-85)
Height (cm), median (min-max)	136 (105-170)	145 (69-182)
Nutritional status, n (%)		
Overweight	24 (57.1)	22 (26.2)
Non-overweight	18 (42.9)	62 (73.8)
Abdominal pain, n (%)		
Yes	19 (45.2)	23 (26.4)
No	23 (54.8)	61 (72.6)
Hepatomegaly, n (%)		
Yes	5 (11.9)	5 (6)
No	37 (88.1)	79 (94)
Pleural effusion, n (%)		
Yes	10 (23.8)	0 (0)
No	32 (76.2)	84 (100)
Highest hematocrit level, n (%)		
≥ 46%	24 (57.1)	21 (25)
< 46%	18 (42.9)	63 (75)
Days of highest hematocrit level, median (min-max)	5 (3-8)	5 (2-9)
Lowest platelet count, n (%)		
≤ 50,000/μL	32 (76.2)	41 (48.8)
> 50,000/μL	10 (23.8)	43 (51.2)
Days of lowest platelet count, median (min-max)	6 (3-8)	6 (3-8)

RESULTS

There were 126 subjects included in this study. Of all study subjects, 61 subjects (48.4%) were diagnosed with DHF grade I; 23 subjects (18.3%) with DHF grade II; 31 subjects (24.6%) with DHF grade III; and 11 subjects with DHF grade IV. They were classified into 2 groups: the DSS group (n=42) and the non-DSS group (n=84). There were basic characteristics from both of the groups, as shown in **Table 1**.

In this study, bivariate analyzes using chi-square test was performed to find the association between overweight and shock events in DHF. From the data analysis, overweight was statistically significantly related to shock events in children with DHF (p=0.001; OR 3.76; 95% CI 1.72 to 8.20) (Table 2).

Moreover, other factors that might be related to shock events in DHF were also analyzed. We found that pleural effusion (p=0.001), highest hematocrit level of ≥ 46% (p=0.001; OR 4; 95% CI 1.82 to 8.77), and lowest platelet count of ≤ 50,000/μL (p=0.006; OR 3.35; 95% CI 1.47 to 7.69) also had significant association with shock events (Table 3).

DISCUSSION

In this study, we found that there is an association between overweight and shock in children with DHF, which is similar to previous studies that also found the association with OR varies from 1.9 to 4.9.[4-6,12] Anthropometry parameter used in studies from Junia *et al.*, and Saniathi *et*

Table 2. Association between overweight and shock events in DHF

Nutritional status	DSS group	Non-DSS group	p-value	OR (95% CI)
Overweight	24 (57.1%)	22 (26.2%)	0.001	3.76 (1.72-8.20)
Non-overweight	18 (42.9%)	62 (73.8%)		

Table 3. Bivariate analysis of other factors associated with shock events in DHF

Factors	p-value	OR (95% CI)
Female	0.248	0.64 (0.29-1.38)
Age > 5 years	0.25	2 (0.74-5.4)
Abdominal pain	0.071	2.19 (1.01-4.75)
Hepatomegaly	0.299	2,14 (0.58-7.83)
Pleural effusion	0.001	-
Highest hematocrit level ≥ 46%	0.001	4 (1.82-8.77)
Lowest platelet count ≤ 50,000/µL	0.006	3.35 (1.47-7.69)

al. was the percentage of weight-for-height (Waterlow classification) whereas weight-for-height standard deviation for children ≤ 2 years old and body mass index (BMI) for age were used for children above 2 years old in the study from Buntubatu *et al.*[5,6,12] Nevertheless, they have drawn the same conclusion. On the other hand, other studies found that there was no significant association between nutritional status (overweight/obesity) and shock (DSS).[7,8,13-15] Meta-analysis performed by Trang *et al.* found no solid consistency finding regarding the association between nutritional status (malnourished; normal nutrition; and overweight/obesity) and dengue infection.[11] Other meta-analysis performed by Zulkipli *et al.*, which more specific in analyzing the association between obesity and dengue severity, found that obesity is a risk factor for severe dengue infection (DSS) in children (OR 1.38; 95% CI 1.1 to 1.73), although there were differences in obesity classification. Furthermore, complications such as encephalopathy, co-infection, and fluid overload were found among obese children.[16]

Based on the theory, children with overweight/obesity were more prone to develop complications and even mortality because their immune systems were better than children with malnutrition. Thus, the immune reaction also became greater. In children with obesity, white adipose tissue (WAT) was increased, as well as in overweight, presumably. The WAT gives feedback signal in metabolism resulting in the reduction of adiponectin level. Adiponectin itself functioned as an anti-inflammatory that inhibits the secretion of interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α, as they made capillary permeability increased. Moreover, reduction of adiponectin level also made an impact on increasing adhesion molecule expression; thus, the pro-inflammatory condition occurs. Invasion of the dengue virus to the cell affects endothelial cells. Therefore, local inflammation occurs combined with increased capillary permeability, resulting in vascular leakage and lead to shock events.[6,9,10]

Other factors that had been thought to contribute to shock in DHF in previous studies were also analyzed. We found that pleural effusion had a significant association with shock events. In fact, pleural effusion manifestation only occurred in 7.9% of study subjects where all of them classified as DSS group. Most of them had right pleural effusion, while only 20% of them had bilateral effusion. The hematocrit level of ≥ 46% was also related to shock in children with DHF, concurrent with other studies.[7,14] Studies performed by Cecilia *et al.* and Dewi *et al.* used different cut-off hematocrit levels of > 41% and ≥ 41.5%, respectively.[15,17] However, hematocrit level could not be used as a shock indicator, cause those level was affected by spontaneous bleeding and also the administration of intravenous fluids. Massive bleeding could lower the hematocrit level, while dehydration and plasma leakage could raise it instead. Furthermore, we found that platelet count of ≤ 50,000/µL had a significant association to shock in DHF. Previous studies claimed various findings, and several studies found similar results,[7,14,15] while others found no significant association.[13,17,18] This could affect by impaired platelet function regardless of its quantity.[19]

Factors that might be related to shocks, such as female gender, age above 5 years old, abdominal pain, and hepatomegaly, had no association to shock events in DHF in this study, unlike several prior studies. In the context of gender, some studies found male gender had a higher risk of developing shock manifestation in DHF,[7,18,20] while a study from Lam *et al.* found otherwise.[21]

In this study, age > 5 years old had the highest percentage among the DSS group (85.7%), although it had no significant association with the shock events itself. On the contrary, prior studies found that children below 5 years old were more at risk of developing shock.[12,20] Hammond *et al.* analyzed more specific age ranges and found that infants age 4 to 9 months and children age 5 to 9 years were the age groups who experienced severe dengue (shock). Theoretically, this was related to antibody-dependent enhancement, where infant age 4 to 9 months got antibody enhancement from maternal (vertical) antibody transfer, while children age 5 to 9 years got it from previous dengue infection.[22]

Abdominal pain and hepatomegaly manifestation were also analyzed in this study, where both were not risked factors in developing shock. Although, several studies claimed abdominal pain and hepatomegaly as predictors of shock in children with DHF.[7,12,14,15,18,20]

We found several limitations while conducting this study, including incomplete data collection as the consequence of using secondary data (from medical records) where we could not obtain complete blood count that was ideally performed daily to get better analysis, serological tests for dengue infection diagnoses, and for distinguishing the infection type. Those could lead to bias and affect the study results.

CONCLUSION

In conclusion, observation and monitoring in overweight children with DHF should be done thoroughly because they were more prone to develop shock, which could lead to mortality. Furthermore, children with pleural effusion, hematocrit level of ≥ 46%, and platelet count of ≤ 50,000/μL were also at risk of developing shock.

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CONFLICT OF INTEREST

None declared.

ETHICS CONSIDERATION

This study was approved by the Health Research Ethics Committee, Wangaya General Hospital, Bali, Indonesia, prior to the study being conducted.

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AUTHOR CONTRIBUTIONS

All the authors are responsible for the study from the conceptual framework.

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