

# Association between Clinical Profiles and Severe Dengue Infection in Children in Developing Country

Masayu Amanda Ledika, Djatnika Setiabudi, Meita Dhamayanti\*

Department of Child Health, Hasan Sadikin General Hospital–Universitas Padjadjaran, Bandung, Indonesia

\*Corresponding author: [amanda.ledika@gmail.com](mailto:amanda.ledika@gmail.com)

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**Abstract Background:** Dengue virus infection is endemic and is one of major causes of morbidity and mortality in children. The cause of mortality in children with dengue infection was not limited to shock but also caused by severe bleeding and organ dysfunction. This study aim to examined clinical profiles of children with dengue infection and their association with severe dengue. **Methodology and principal findings:** Cross-sectional study of children with dengue virus infection admitted to Department of Child Health, Hasan Sadikin Hospital Bandung from April 2013 to September 2014. Subjects were patient age 1–14 who fulfilled 2009 WHO criteria for dengue virus infection. Association between clinical profile and severe dengue infection was analyzed in two steps. After bivariate analysis, variable with p value <0.25 was included in the next step by logistic regression. P value <0.05 was consider significant. Of 451 subjects, 24.6% (n=111) had severe dengue infection. Dengue shock syndrome with or without other form of severe dengue was the most common complication and occurred in 65.7% (n=73) of all severe dengue cases. Patient admitted  $\geq 4$ th day of illness (OR 13.25 95%CI 3.45–50.86), persistent vomiting (OR 20.32 95%CI 7.41–55.74); hepatomegaly (OR 21.72 95%CI 7.73–61.01), platelet count  $< 50.000/\text{mm}^3$  (OR 26.54 95%CI 8.59–81.99), and leukocyte  $\geq 5000/\text{mm}^3$  at admission (OR 4.25 95%CI 1.55–11.65) were associated with severe dengue infection. **Conclusion:** Clinical manifestation of severe dengue infection was not limited to dengue shock syndrome. Patient admitted  $\geq 4$ th day of illness, persistent vomiting, hepatomegaly, platelet count  $< 50.000/\text{mm}^3$  and leukocyte  $\geq 5000/\text{mm}^3$  at admission were associated with severe dengue infection in children.

**Keywords:** Children, Clinical Profile, Severe Dengue

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## 1. Introduction

Dengue virus infection is one of the major causes of morbidity and mortality of children in endemic area. The disease is a rapidly spread, mosquito borne viral disease in Southeast Asia including Indonesia. [1] Although the proportion of dengue cases in children and mortality tend to decline over the years but the number of cases are rising. [2,3] Some older children had higher risk of developing shock, but young children had higher mortality rate. [3] This age–group differences in children call for a specific research in children. Clinical manifestation ranged from undifferentiated febrile illness to severe dengue infection including dengue shock syndrome (DSS), severe bleeding, and severe organ involvement. Mortality was not only caused by DSS but also by other severe manifestation. [4] World Health Organization in 2009 developed a diagnostic criteria to differentiate severe manifestation of dengue infection and to help early detection by warning signs. [5] Some of the warning signs such as lethargy and rise in hematocrit with rapid drop in platelet count may happen in late stages of dengue virus infection. Studies are limited to risk factors for dengue shock syndrome and

fewer study discussed the clinical profile and wider manifestation of severe dengue infection in children.

This study aimed to find out the clinical profile of severe dengue infection and association between clinical factors and severe dengue infection in children.

## 2. Methods

This is a cross-sectional study conducted on patient with dengue virus infection at Child Health Department, Medical School, Universitas Padjadjaran/Hasan Sadikin General Hospital in Bandung from April 2013 to September 2014.

### 2.1. Patient Population

Children age 1–14 who fulfilled 2009 WHO criteria for dengue virus infection with laboratory confirmation on either non-structural protein 1 (NS1) or anti dengue antibody (IgM, IgG, or both) positive for dengue infection was included in this study. Exclusion criteria were simultaneous infection, severe malnutrition, long term steroid use, hemolytic diseases such as thalassemia, and malignant diseases. (Figure 1)

## 2.2. Case Definition

Diagnostic criteria for dengue infection was using 2009 WHO criteria. Non-severe dengue was defined as those with probable dengue, stay or visiting and endemic dengue area, with febrile and at least two of the following: nausea, vomiting, rash, pain, positive tourniquet test, and laboratory confirmation for dengue infection. Severe dengue infection in this study include plasma leakage resulting in severe dengue shock syndrome, which meets the criteria for dengue hemorrhagic fever with signs of shock, including: tachycardia, cold extremities, decreased capillary refill, weak pulse, lethargic or anxiety can be a sign of decline in brain perfusion, pulse pressure  $\leq 20$  mmHg diastolic pressure, hypotension with age, defined by systolic pressure  $< 80$  mmHg for aged  $< 5$  years, or  $80-90$  mmHg for older children and adults; or fluid accumulation with respiratory distress without evidence of pulmonary complications such as pneumonia; heavy bleeding as assessed by physician; and severe organ involvement, SGOT/AST or SGPT/ALT  $\geq 1000$  u/L, and central nervous system manifestations of at least altered consciousness, and cardiac involvement or organ involvement elsewhere. [5] Age group was classified by using a cut-off point of  $\geq 1$  year (12 months)–old to 5 year–old (60 months) and  $> 5$  year–old (61 months) to  $< 14$  year–old (167 months). [6] Days of illness was counted from the first symptoms of fever appear in patients. Critical phase of dengue infection commonly started at 4th day of illness, thus, group was divided between patient who was admitted from less than 4 days since first symptoms or 4 days or more. [5] Overweight/obesity was defined as weight-for-height or length (in children aged  $< 2$  years) more than 2 standard deviations (SD) based on the WHO growth charts or body mass index per–age in children aged  $\geq 5$  year more than 2 SD based WHO growth reference curve. Persistent vomiting was defined as repeated vomiting that occurred two or more consecutive days. [7] Spontaneous bleeding was any bleeding that occurs without previous interventions, including spontaneous petechial bleeding, bleeding gums, epistaxis, excluding positive tourniquet tests. [8] Hepatomegaly was defined as liver size palpable at  $\geq 3$  cm in patient  $< 5$  year–old, or any liver palpable for patient  $\geq 5$  year–old. Platelet and leukocyte count was the first laboratory value taken when patient was admitted, and value of  $< 50.000/\text{mm}^3$  and  $\geq 5000/\text{mm}^3$  was used respectively as cut–off point. [6]

## 2.3. Statistical Analysis

Association between clinical profiles and severe dengue infection was analyzed in two steps. Bivariate analysis was using Chi-Square or Fisher's Exact test for kategorical variable and  $p < 0.25$  was included in the logistic regression analysis. Association between clinical profiles and severe dengue virus infection in children was determined when  $p$  value  $< 0.05$  and result was also presented in odds ratio (OR) with 95% confidence interval (CI). The study was approved by ethical committee at Medical School Universitas Padjadjaran/Hasan Sadikin General Hospital Bandung.

## 3. Result

During April 2013 to September 2014 there were 493 cases of DF and DHF recorded in the department of Child Health, Dr. Hasan Sadikin Hospital with a diagnosis of dengue virus infection. We found 451 cases who fulfilled the inclusion criteria and were included as subject of the research. The prevalence of severe dengue virus infection was 24.6% ( $n=111$ ). Confirmation of dengue virus infection in this study was either positive NS1 ( $n=50$ ; 11%) or positive antidengue antibody (IgG and IgM) ( $n=401$ ; 89%). The ratio of male and female was similar in dengue infection group, while in severe dengue virus infection group, the ratio was 1:1.7. The average age of children with severe dengue infection was slightly older than in children with non-severe dengue infection ( $78.42 \pm 48.18$  vs  $70.06 \pm 45.93$ ). Three cases died due to complications of dengue virus during the study period (0.66%).

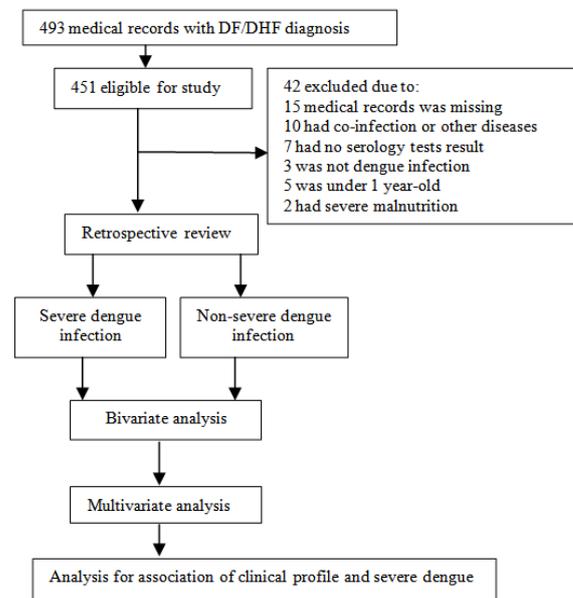


Figure 1. Study's Flow Diagram

Based on the examination of dengue antibodies on severe dengue cases ( $n=104$ ), we found that 97.1% ( $n=102$ ) were secondary dengue virus infections with positive IgG results. Dengue shock syndrome is the most frequent cause of severe dengue virus infection, and DSS alone covered more than one third of cases of severe dengue virus infection in this study ( $n=41$ ). Dengue shock syndrome was also seen in patients with with respiratory distress due to fluid accumulation and other multiple complication with the total of 73 (65.7%) with severe dengue infection experienced shock. Multiple complications and respiratory distress due to fluid accumulation without shock also happened quite frequently, 19 (17.1%) and 14 (12.6%) patients respectively. Two cases of menorrhagia occurred in girls aged 12 and 13 years. Multiple complications that occur most often are combination of severe plasma leakage and encephalopathy in 11 cases, while the rest were combination of severe plasma leakage and myocarditis. (Table 1)

Association between clinical profile and severe dengue infection in children was examined for age, sex, days of illness, overweight/obesity, persistent vomiting, hepatomegaly, spontaneous bleeding, platelet count  $< 50.000/\text{mm}^3$  and leukocyte  $\geq 5000/\text{mm}^3$  at admission

(Table 2). All variables with  $p < 0.25$  was included in multivariate analysis.

Patient admitted  $\geq 4$ th day of illness (OR 13.25 95%CI 3.45–50.86), persistent vomiting (OR 20.32 95%CI 7.41–55.74); hepatomegaly (OR 21.72 95%CI 7.73–61.01), platelet count  $< 50,000/\text{mm}^3$  (OR 26.54 95%CI 8.59–81.99), and leukocyte  $\geq 5000/\text{mm}^3$  at admission (OR 4.25 95%CI 1.55–11.65) were associated with severe dengue infection.

**Table 1. Complications of children with severe dengue infection**

Severe dengue criteria	n (111)	%
Severe plasma leakage		
• Dengue shock syndrome	41	37%
• Fluid accumulation with respiratory distress	16	14.4%
• Both SSD and fluid accumulation	13	11.7%
Severe bleeding		
• Gastrointestinal bleeding	6	5.4%
• Menorrhagia	2	1.8%
• Hematuria	1	0.9%
Severe organ involvement		
• Liver, with ALT/AST $> 1000$ U/L	1	0.9%
• Central nervous system, impaired consciousness	9	8.1%
• Heart and other organs	2	1.8%
• Multiple severe organ involvement	1	0.9%
Multiple complications		
• Severe plasma leakage+ Severe bleeding	1	0.9%
• Severe plasma leakage + severe organ involvement	14	12.6%
• Severe plasma leakage + Severe organ involvement + Severe bleeding	4	3.6%

## 4. Discussion

From 493 cases diagnosed as dengue virus infection, 42 was excluded due to several reasons. (Figure 1). There were 451 cases included and 24.6% ( $n=111$ ) patients were diagnosed as severe dengue infection. This result is slightly higher than prevalence of severe dengue infection of children in Surabaya of 19.3%. [9] The most frequent complication in severe dengue infection is dengue shock syndrome (DSS) with and without respiratory distress due to fluid accumulation which happened in 48.6% of all severe dengue virus infection cases. Shock also contributed to 14 cases of multiple complications, with a total of 69 out of 111 cases (62.1%) of severe dengue virus infection experienced DSS. These results indicated that severe dengue virus infection was not limited to dengue shock syndrome and WHO classification for dengue virus infection in 2009 can help to detect severe dengue virus infection without DSS. There were 3 death cases (0.66%) during the study period, much lower than in a similar study 20 years ago with a case fatality rate (CFR) of 2.5%, resembling CFR in Southeast Asia about 1%, but still below the CFR in Thailand of less than 0.2%. [5,10] Two of the 3 died cases experienced multiple complications of all plasma leakage, severe bleeding, and severe organ involvement. This study excluded infants under 1 year of age as the infants were suspected to carry passive maternal dengue antibodies and were at risk of severe dengue virus infection. [11]

Days of illness was count from the first febrile symptoms appear in patient. Guidelines from WHO

showed critical phase of dengue infection commonly started from day 4 to 6 where severe plasma leakage usually started. [5] Children at  $\geq 4$ th day of illness by the time they were admitted to hospital was associated with severe dengue infection (OR 13.24 95%CI 3.45–50.86). This study showed that children with suspected dengue infection who come at earlier days of illness (i.e day  $< 72$  hours from the start of fever) should receive repeated assessment and optimal counseling of critical phase in dengue virus infection, moreover, awareness should be raised to people living in dengue endemic area to seek medical counsel before critical phase, to avoid severe dengue infection and to receive optimal management to prevent mortality of dengue infection.

Persistent vomiting is a warning sign that has been released by WHO for the occurrence of severe dengue virus infection. [5] Persistent vomiting was associated with severe dengue virus infection in children (OR 20.32 95%CI 7.41–55.74). Vomiting in dengue infection could be a sign of gastrointestinal involvement or early neurological signs. A study showed vomiting was associated with DSS. [14] Persistent vomiting in adult with dengue infection was associated with higher risk for severe dengue infection and predictors of combined form of severe dengue. [7] Brazilian study showed persistent vomiting was associated with death in children with severe dengue virus infection, so more attention should be given in children with persistent vomiting in early dengue virus infection. [15]

Hepatomegaly is a warning sign of severe dengue virus infections that have been issued by WHO. This study showed hepatomegaly was associated with severe dengue virus infection (OR 21.72 95%CI 7.73–61.01). Hepatomegaly has been shown in dengue infection cases due to direct involvement of dengue virus in the liver. [16] This result was supported by previous studies that showed hepatomegaly as a risk factor for shock in children, as well as a risk factor for severe dengue virus infection. [6,13,17] Liver size in children in this study used a limit of  $\geq 3$  cm in children under 5 years, because smaller children with palpable liver size up to 2 cm may be found in normal conditions. This result showed an enlarged liver requires special attention in children with dengue virus infection.

Platelets  $< 50,000/\text{mm}^3$  at admission was associated with severe dengue virus infection in this study (OR 26.54 95%CI 8.59–81.99). Low platelet count has been the hallmark for dengue virus infection and could vary very widely in each cases. Lower platelet value at admission had an association with more severe dengue spectrum. [13] Platelet count  $< 50,000/\text{mm}^3$  had a risk of DSS two times higher. [18] This suggested children who presented with lower platelet levels, or patients with progression of changes rapidly decreased platelet levels required special attention to the development of severe dengue virus infection. Platelet levels at admission became very important in the planning and management of severe dengue virus infection to obtain optimal outcomes for all children with dengue virus infection.

This study showed an association between leukocytes  $\geq 5000/\text{mm}^3$  and severe dengue infection in children (OR 4.25 95%CI 1.55–11.65) Previous studies that demonstrated the role of leukocytes in severe dengue virus infection was diversified. [6,18,19] A study in 2011 showed

leukopenia as a predictor of progression in children with DHF into DSS and another study also showed leukocyte  $<4000/\text{mm}^3$  as a risk factor for DSS. [6,19]

**Table 2. Bivariate analysis on association between clinical profiles and severe dengue infection**

Variable		Severe dengue		Non-Severe Dengue		P
		(n=11)	%	(n=340)	%	
Age	$\geq 60$ mo	67	60.4	185	54.4	0.162*
	$< 60$ mo	44	39.6	155	45.6	
Day of Illness	$\geq 4$ days	100	90.1	159	46.8	$<0.001^*$
	$< 4$ days	11	9.9	181	53.2	
Sex	Male	41	36.9	170	50	0.011*
	Female	70	63.1	170	50	
Overweight/obesity	Yes	9	8.1	4	1.2	0.01**
	No	102	91.9	336	98.8	
Persistent vomiting	Yes	91	82.0	30	8.8	$<0.001^*$
	No	20	18.0	310	91.2	
Hepato-megaly	Yes	83	74.8	14	4.1	$<0.001^*$
	No	28	25.2	326	95.9	
Spontaneous bleeding	Yes	81	73.0	92	27.1	$<0.001^*$
	No	30	27.0	248	72.9	
Platelet ( $\text{mm}^3$ )	$<50.000$	78	70.3	41	12.1	$<0.001^*$
	$\geq 50.000$	33	29.7	299	87.9	
Leukocyte ( $\text{mm}^3$ )	$<5000$	23	20.7	256	75.3	$<0.001^*$
	$\geq 5000$	88	79.3	84	24.7	

\*p value was determined using chi-square, \*\*p value was determined using fisher-exact test ; p value  $<0.25$  was included in multivariate analysis

On contrary, another study in 2010 showed patient with leukocytes  $>5.000/\text{mm}^3$  had a risk of shock 2 times higher. [18] Normal-high leukocyte at early fever was associated with low risk for dengue virus infection and recovery of leukocyte value from leukopenia to normal/near-normal value in dengue virus infection was shown to precede the recovery of low platelet count. [20,21] This study showed no association between leukocyte value and time of sampling, leukocyte result of  $<5000/\text{mm}^3$  was taken at  $3.65\pm 1.28$  day of illness while leukocyte  $\geq 5000/\text{mm}^3$  at  $3.7\pm 1.50$  day of illness ( $p=0.680$ ), and thus limited the possible bias of sampling time and leukocyte value. This study was also done in retrospective, and so the laboratory examination was done with different physicians and could effect the validity of the results, especially when not all blood smear for leukocyte was confirmed by a clinical pathologist. Another study that showed leukocytosis in shock tendency was not statistically tested and further study is still needed to support the study results. [18]

Age  $>5$  year-old, overweight/obesity and spontaneous bleeding was not associated with severe dengue infection in children in multivariate analysis in this study. Older children was suspected to be more likely to have secondary infection, and although another study showed age  $>5$  year as a significant risk factor for shock in children with dengue haemorrhagic fever, but other study showed no difference in dengue severity in different age group. [6,11,13] Nutritional status has previously been shown as a risk factors for DSS, but meta-analysis study have shown that nutritional status is not a significant risk for DSS. [14,23] Spontaneous bleeding in this study was limited to spontaneous petechial bleeding, epistaxis, and bleeding gums. Nevertheless, spontaneous bleeding still needed to be considered as part of the WHO warning sign.

Spontaneous bleeding in children with dengue virus infection might be related to studies that showed adult patients with dengue virus infection had a greater risk of bleeding compared to children. [11] The limitation of this study was using secondary data from tertiary hospital. Dengue virus patient was treated and recorded by different physicians, and may compromised the quality of data presented, but even so, our hospital is a teaching hospital in which all cases would be reviewed by a pediatric consultant in infectious diseases. Other limitation was that in our resource-limited facility, dengue virus infection was not routinely checked for virus genotyping which could have added important information on clinical profile of children with severe dengue infection.

**Table 3. Logistic regression analysis on association between clinical profiles and severe dengue infection**

Variable	p	OR	95%CI	
			Min	Max
Days of Illness	$<0.001$	13.24	3.45	50.86
Persistent vomiting	$<0.001$	20.32	7.41	55.74
Hepatomegaly	$<0.001$	21.72	7.73	61.01
Platelet count	$<0.001$	26.54	8.59	81.99
Leukocyte count	0.005	4.25	1.55	11.65

## 5. Conclusion

Clinical profile of children with dengue virus infection at admission could be used to help clinician to assess their possible association with severe dengue virus infection. Day of illness at admission, persistent vomiting, hepatomegaly, platelet count  $<50.000/\text{mm}^3$ , and leukocyte count  $\geq 5000/\text{mm}^3$  at admission were associated with severe dengue infection in children. More studies are needed in regard of association between leukocyte value and severe dengue infection in children.

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## Competing Interest

The authors declare no competing interests.

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