



## Research Article

# Thrombocyte count in male and female adult of Dengue hemorrhagic fever patients

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## Abstract

The trend of dengue virus infection in Indonesia has changed from children to older groups. Some studies suggested that different gender might affect the different progression of dengue infection, but its mechanism was unclear. This study analyzed the difference by evaluating the daily thrombocyte count pattern. An analytic observational study with a retrospective design was conducted using the secondary data collected from medical records in Dr. Soetomo General Hospital Surabaya during 2017-2018. The samples were adult patients in the age range of 18-55 years old with DHF but without comorbidity or coinfection. The total number of samples was 40 patients. The average of thrombocyte count in both male and female patients decreased since the 3<sup>rd</sup> day of illness and reached the lowest level on the 6<sup>th</sup> day of illness then increased on the 7<sup>th</sup> day but did not reach the normal range. Although the majority of thrombocyte count in females was lower than males, there was no significant difference in thrombocyte count pattern between them.



## INTRODUCTION

Dengue virus is classified as a Flaviviridae family, which has four serotypes, DEN-1, DEN-2, DEN-3, and DEN-4 (Jawetz, E., Melnick, J.L., & Adelberg, 2016). It is transmitted by the bite of an *Aedes* mosquito infected with dengue virus (CDC, 2012). Dengue virus transmission is only through the bite of female *Aedes* mosquitos (Greenwood D, Slack R., Barer M, Irving, 2012). *Aedes* mosquitos prefer to lay eggs in artificial water containers, to live in closer to humans and to feed on human rather than other vertebrates with high preference to the urban environment (Murray, Rosenthal, 2016; Haryanto, 2018)

Dengue virus infection is one of the most contagious arboviral infections with a massive burden consequent public health in more than 100 tropical and subtropical countries in South East Asia, Western Pacific, and South America (WHO, 2011). In Indonesia, during 2016, the IR of dengue cases was high up to 77.96 for every 100,000 populations in each province with the Case Fatality Rate (CFR) was 0.79% (Kemenkes RI, 2016). The trend of dengue virus infection in Indonesia has changed from children to older groups (Karyanti et al., 2014). An adult patient has the possibility of more severe clinical manifestations like headaches, bone pain, depression, and pathetic (WHO Media Centre, 2017).

*Aedes aegypti* is commonly found in a particular location such as water disposal or water storage. Exposure to such an environment may be related to specific demographic factors such as gender (Aamir et al., 2014). Gender and sex differences may contribute to the differences in the pathogenesis of infectious disease in males and females. Analysis and studies in Singapore, Vietnam, and Malaysia found that female gender was associated with severe dengue (Huy et al., 2013). However, a study in France and Lahore showed that the

male gender was associated with severe dengue manifestations (Aamir et al., 2014). Both sexes that refers to the genetic and biological status of XX or XY organism and gender that refers to the social and cultural differences play together in immunological dimorphism. Females typically develop higher innate immunity, humoral, and cellular response to viral infections than males (Ruggieri et al., 2016 ; Jones et al., 2018), while testosterone appears to inhibit IgM and IgG production (Kanda, Tsuchida, & Medicine, 1996). In addition to biological differences, gender refers to the differences between male and female regulated by cultural and social factors, involving the area of human life. In developing countrywoman spends more time at home than male, thus are more exposed to indoor pollution. Inadequate nutrition and less accessibility to appropriate health care service are also more frequent in the woman (Ruggieri et al., 2016). These differences could play in discrepancies between males and males in response to infection.

As gender roles and the exposure change over the human life span, it is crucial to know the different progression of DHF between male and female adult patients by observing laboratory parameters such as thrombocyte. Daily thrombocyte count was used because it is an important laboratory parameter to help identify patients at the high-risk condition of Dengue Shocked Syndrome (DSS) (Lam et al., 2017). The pattern of thrombocyte count in both male and female patients will give new information about the different progression of the disease in both groups. This data is also important to improve the alertness to the patient's condition.

## METHODS

This is an analytic observational study with a retrospective design using the secondary data collected from the medical records in Dr. Soetomo General Hospital Surabaya during 2017-2018. The sample used was adult patients



in the age range of 18-55 years old with Dengue Haemorrhagic Fever (DHF) grade I until III, hospitalized at the tropical ward, Dr. Soetomo hospital, Surabaya. The patients included in this study did not have comorbid or coinfection that might interfere with the thrombocyte count. They were a healthy person before or having no other disease during hospitalized. Sysmex XN-1000 Hematology Analyzer analyzed the thrombocyte count. The blood samples result on the 3<sup>rd</sup> until the 10<sup>th</sup> day of illness were taken for this study. The sampling technique was total sampling and obtained 40 samples. The collected data was presented in tables, graphics, and narratives. Statistical analysis used descriptive calculations and analytical calculations (Chi-square and independent t-test). A 'p' value less than 0.05 was taken to be statistically significant. This study has passed the ethical clearance number 0500/KEPK/VIII/2018 from Dr. Soetomo Hospital.

## RESULTS

### Patients Characteristics

The total number of patients in the age range of 18-55 years old who infected with Dengue virus

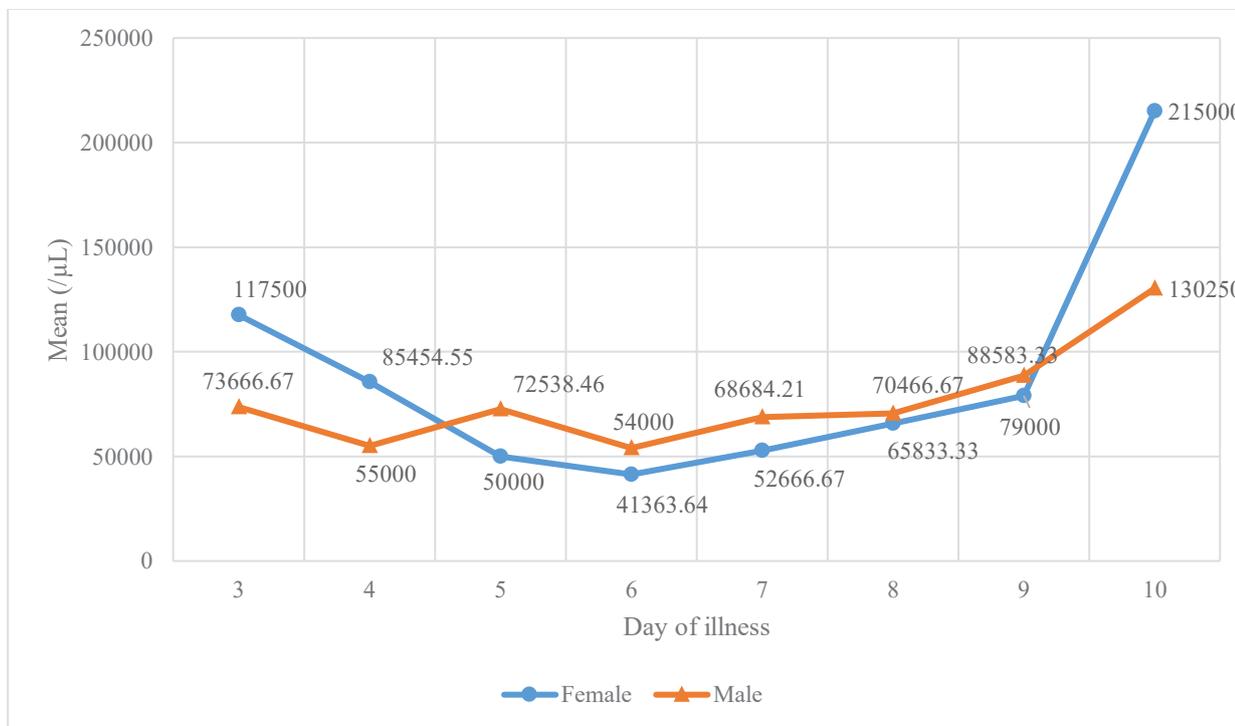
was 122 patients. Of them, 40 patients showed a clinical manifestation of Dengue Hemorrhagic Fever (DHF), and 22 patients were Dengue Fever (DF). Sixty out of 122 patients were excluded from this research because there were underlying diseases such as typhoid fever, myocarditis, urinary tract infections, varicella, hepatitis, and leukemia accompanying dengue infection. There were 16 (40%) female patients and 24 (60%) male patients. Among a total of 16 (40%) female patients with DHF, 5(12.5%) were DHF grade I, 10 (25%) were DHF grade II, and 1(2.5%) was DHF grade III. Of them, 14 (35%) were at 18-35 years old, and 2(5%) were at 36-55 years old. From eleven (27.5%) out of 24 (60%), male patients were DHF grade I, 12(30%) were DHF grade II, and 1 (2.5%) was DHF grade III (**Table 1**). Of them, 20 were at 18-35 years old, and four patients were at 36-55 years old. The results of the Chi-Square statistical analysis showed that there was no significant difference between the number of male and female patients with  $p > 0.05$  (0.206) (**Table 2**). This result indicated that DHF was not affected by gender; either male or female could undergo DHF.

**Table 1.** Patients characteristic according to gender and clinical manifestation

Gender	Clinical Manifestation			Total
	DHF I	DHF II	DHF III	
Female	5 (12.5%)	10(25%)	1(2.5%)	16(40%)
Male	11(27.5%)	12(30%)	1(2.5%)	24(60%)
Total	16(40%)	22(55%)	2(5%)	40(100%)

**Table 2.** Distribution of DHF patient according to gender and age range

Gender	Number of patients by age range		Total	p
	18 – 35 years old	36 – 55 years old		
Female	14(35%)	2(5 %)	16(40%)	0.206
Male	20(50%)	4(10%)	24(60%)	
Total	34(85%)	6(15%)	40(100%)	



**Graphic 1.**Thrombocyte count pattern in DHF patient according to the day of illness

**Table 3.** The difference of thrombocyte count between male and female patient according to the day of illness

Day of illness	Female			Male			p
	n	Mean(/µL)	SD	n	Mean(/µL)	SD	
3	4	117,500.00	57,645.468	3	73,666.67	62,819.848	
4	11	85,454.55	44,824.912	9	55,000.00	38,421.999	0.125
5	10	50,000.00	34,140.234	13	72,538.46	49,304.522	0.231
6	11	41,363.64	29,513.633	18	54,000.00	39,615.802	0.370
7	9	52,666.67	39,764.934	19	68,684.21	59,091.316	0.623
8	6	65,833.33	31,801.992	15	70,466.67	34,073.171	0.778
9	1	79,000.00		12	88,583.33	44,935.223	
10	1	215,000.00		8	130,250.00	73,976.348	



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## DISCUSSION

### *Sample Characteristic*

Dengue virus infection remains a significant challenge in Indonesian public health. This condition is supported by the fact that Indonesia has a tropical climate and subsequent relative high humidity. It makes a favorable condition for vector-borne disease transmission, such as dengue. An epidemiology study reported that the incidence of DHF over the past 45 years increased rapidly, with the peak incidence changing from young children to 15 years old or more. The number of males was higher than females in both age ranges, but there was no significant difference between them ( $p = 0.206$ ). Of the 40 patients, 85% were in the age range, 18-35 years old (Karyanti et al., 2014). This result was concordance with the studies carried out by Payyappilly, Karunakaran, & Adilat (2017); Mubarak, Alghasali, & Bahashwan (2017) and Raza et al. (2014). These consistent results reinforce some factors that might contribute to the more number of male patients suffered from DHF rather than females. It is widely known that in Asian countries and Saudi Arabia, males in reproductive age spend more time outside their houses and thus more likely to be exposed with the vector of dengue (Rathore et al., 2005; Shahina, et al., 2009). However, in Indonesia, the fewer female of DHF patients was not only due to the rarely spent their time out of the house, but also related to the increase in hijab usage.

The small number of samples in this study because of the exclusion of patients with comorbid conditions or coinfection such as typhoid fever, myocarditis, urinary tract infections, acute kidney injury, varicella, hepatitis, and leukemia. The comorbid condition in DHF patients was reported that the risk of dying of 326,380 hospitalized dengue cases in Brazil was 11-times higher in the presence of common underlying comorbidities (Werneck et

al., 2018). In addition, co-infection with typhoid fever was often found in dengue infection caused by overlapping symptoms creating a diagnostic dilemma (Sharma et al., 2014). Major underlying diseases caused fatality cases of refractory shock in an elderly patient infected with dengue included hypertension, diabetes mellitus type 2, neoplasm, and chronic kidney disease (Kuo, Lee, & Liu, 2018). Those factors were considered to cause bias; therefore, patients with comorbid conditions or co-infection were excluded from this study.

### *Thrombocyte Count*

This study found that the pattern of thrombocyte count in both male and female with DHF were similar. The average of thrombocyte was  $< 100000/\mu\text{L}$  in both genders on the 4th till the 9th day of illness. The lowest level of thrombocyte in both genders was found on the sixth day or later than in the children who found earlier on the 5th day of illness (Sari, Kahar, & Puspitasari, 2017). This finding indicated that alertness has to be taken cautiously earlier in DHF pediatric patients rather than the adult.

The androgen promotes Th1 type immune response with the production of pro-inflammatory cytokines such as IL-2, IFN- $\gamma$ , and enhanced cytotoxic T lymphocytes (CTL) activity (Fairweather & Frisancho-kiss, 2008). At serum level, estrogen also stimulates Th1 type immune response in males and females in the luteal phase or post-menopause, while at a high level as in pregnancy or pre-ovulatory periods, it promotes anti-inflammatory, Th2 type immune response (Payyappilly et al., 2017). These mechanisms are supposed to be the causes of the wide spreading of DENV and a greater decrease of thrombocyte count in the male patient rather than female patients at reproductive age in some studies. As thrombocytopenia is associated with clinical outcome and severity of the disease (Azeredo, Monteiro, & Pinto, 2015), it was assumed that



the lower of thrombocyte count, the more severe the disease. However, in this study, we found that the average of thrombocyte count on 5th till 9th day in female patients was precisely lower than male patients. As we know, the critical phase in DHF usually happens on the 3rd till the 7th day of illness. Also, there were no significant differences of thrombocyte count between male and female in early, critical or convalescence phases ( $p > 0,05$ ). These finding was similar to result reported by Acharya, Khan, Kosuru, & Mallya (2018) where there was no relation of mortality with gender of the dengue patient ( $p = 0.534$ ).

Although some studies have explained that sex and gender difference might affect the progressivity of the disease, there was no clear explanation by which mechanism it affects the disease. The male patient might have greater exposure to the vector of dengue, but it did not mean they had worse outcome or shock condition because of its biological or gender factor. Whereas a female patient who has a better immune response to viral infection and less exposure did not mean they had a better outcome. We considered comorbid factors or coinfection as a major factor that might contribute to the possibility of the severe outcomes of the disease rather than sex or gender difference itself.

There are some limitations to our study. Our data lacked primary and secondary dengue infection data, which might interfere with the thrombocyte count in both genders. The thrombocyte count was not checked daily, and this made our sample size was inconsistent day by day. The other factor, such as the menstrual cycle and psychological condition, could not be evaluated. Thus, the following study is necessary to validate our findings.

## CONCLUSION

The average of thrombocyte count in both male and female patients decreased since the 3<sup>rd</sup> day of illness and reached the lowest level on the 6<sup>th</sup> day of illness, then increased on the 7<sup>th</sup> day but did not reach the normal range. Although the majority of thrombocyte count in females was lower than males, there was no significant difference in thrombocyte count between them.

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