Association between Body Mass Index and Type of Infection on the Severity of Dengue Infection in Bengkulu City, Indonesia

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Abstract
Dengue virus infection is a serious global health problem. Several factors that influence the severity of dengue are Body Mass Index (BMI) and type of infection. The study aimed to determine the association between BMI and type of infection on the severity of dengue infection in adulthood. The study used a cross-sectional design with a total sample of 39 patients diagnosed with dengue infection and fulfilling the inclusion criteria. The sampling technique was consecutive sampling. The data analysis used was the Spearman correlation test. Data collection was conducted by distributing research form which cover sample characteristics, BMI values, clinical manifestations, types of infection and the severity of dengue infection. The total of subject obtained was 37 respondents (23 male and 14 female). The average BMI value was 24.65 ± 5.08. The most common clinical manifestations were fever (100%), nausea/vomiting (91.8%), headache (89.1%), myalgia (89.1%), and arthralgia (72.9%). Most cases of dengue infection were in the normal BMI group and the highest degree of severity was DD. There was a significant relationship with a fairly strong correlation value between BMI and dengue severity (p=0.003; r=0.478). However, there was no significant relationship between the type of infection (p=0.987; r=0.03) with the level of dengue severity. Knowing the risk factors as predictors of dengue severity is very necessary in order to handle dengue infection quickly and accurately.

Keywords: body mass index, dengue, primary infection, secondary infection, severity level of dengue.

Introduction

Dengue infection that occurs worldwide is estimated as 50 million cases with 22,000 deaths every year, there are 2.5 billion people living in dengue infection endemic areas (WHO, 2011). Indonesia is reported as the 2nd country with the largest dengue cases among 30 endemic areas of Southeast Asian countries (Permatasari et al., 2015). Bengkulu Province is one of the three

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provinces with the highest morbidity rate in Indonesia (Kementerian Kesehatan RI, 2018).

There were 1,439 dengue cases found In Bengkulu Province alone. Most cases occurred in Bengkulu City, by numbers of 427 cases. It increased the number of cases from 2017 with a total of 287 cases. Bengkulu Province is also one of the three provinces with the highest morbidity rate in Indonesia.(Kemenkes RI, 2018). Various aspects regarding dengue have been investigated to determine the factors that affect the severity of dengue virus infection. One of them is the Body Mass Index (BMI). Body proportion which is reflected from the BMI value is related to dengue infection, since the bigger a person's body size, the worse the capillary permeability is, which in

the case of DHF can support complications in other organs (Whitehorn & Farrar, 2010).

Obese patients infected with dengue have many clinical parameters that show more severe clinical manifestations, as evidenced by high frequency of hemoconcentration, severe thrombocytopenia, elevated creatinine, liver enzymes, and warning signs of increased hematocrit with the rapid decrease in platelets (Khei Tan et al., 2018).

Body proportion as reflected by the BMI value is often associated with dengue infection. Permatasari's research results in 2015 showed that there was a significant relationship between BMI and dengue severity (Permatasari et al., 2015). Other studies have also stated that obesity is a predisposing factor for dengue infection and tends to cause serious complications and affect the level of dengue severity.(Kaur et al., 2017).

Antibodies to the dengue virus can be found in the blood around day 5 of fever and disappear after 60-90 days. The kinetics of IgG levels are different from those of IgM antibody levels. In primary infection, IgG antibodies increase around day 14 of the fever. In secondary infection, IgG antibody increases on the second day. Therefore, early diagnosis of primary infection can only be confirmed by detecting IgM antibodies after the fifth day of illness. Secondary infection can be established early with a rapid increase in IgG and IgM antibodies (Candra, 2010).

There are two theories or hypotheses of immunopathogenesis in dengue infection that are still controversial, namely the virulence theory and secondary infection (secondary heterologous infection). In virulence theory, the dengue virus can undergo genetic changes as a defense mechanism when the virus replicates both in humans and in mosquitoes. Phenotypic expression of genetic changes in the viral genome may lead to increased viral replication and viremia, increased virulence, and has the potential to cause outbreaks (Syafiqah, 2010).

Secondary infection theory or hypothesis states that when an individual gets an infection by one dengue virus serotype, there will be an immune process against the dengue virus serotype infection for a long time. However, if the individual gets secondary infection by other different dengue virus serotypes, a heavier infection will occur. It is due to the heterologous antibodies that are formed in primary infection developing an antigen-antibody complex with a new serotype dengue virus infection that cannot be neutralized and even tends to form an infectious complex and is internalizing opsonization. The complex will then be activated and produce IL-1, IL-6, Tumor Necrosis Factor-Alpha (TNF-α), Platelet Activating Factor (PAF). Tumor Necrosis Factor-Alpha will cause leakage of blood vessel so that plasma fluid from blood vessels can reach body tissues as a result of damage to blood vessel endothelium (Candra, 2010; Wibowo, 2020).

Another theory that is also associated with the pathogenesis of dengue infection is Antibody Dependent Enhancement (ADE), a process that will increase dengue virus infection and replication in mononuclear cells. In response to the infection, secretion of vasoactive mediators occurs which in turn leads to increased vascular permeability, resulting in hypovolemia and shock. This causes an increase/enhancement of dengue virus infection (Syafiqah, 2010; Wibowo, 2020). In addition to activating the complement system, the antibody antigen complex also causes platelet aggregation as a result of adhesion of the antigen-antibody complex to the platelet membrane resulting in thrombocytopenia. This results in impaired platelet function, so that even though the amount of platelet is still quite a lot, it does not function properly (Mayasari et al., 2019; Syafiqah, 2010). Based on this description, the aim of this study was to determine the relationship between BMI and the type of dengue infection on the severity of dengue infection in Bengkulu City, Indonesia.

Methods

This research was conducted in July 2020 and has been approved by Health Research Ethics Commite of the Faculty of Medicine and Health Sciences Universitas Bengkulu, by numbers

306/UN30.14.9/LT/2020. The study used an analytic observational study with cross-sectional design (Dahlan, 2016). The target population in this study was all adult patients with dengue in Bengkulu City. The accessible population in this study was all patient with dengue at Harapan dan Do'a Hospital, Ummi Hospital, Gading Medika Hospital, Dr. M. Yunus Hospital and Bhayangkara Hospital, Bengkulu City, Indonesia, between July 2020 to Desember 2020.

The research sample was 37 repondents. The research sampling technique used consecutive sampling for 6 months at 5 hospitals. Data collection begins with the signing of the consent sheet by the respondent and then completes the identity data sheet, then the characteristics of the research subject. Measurement of thrombocyte, hematocrit, and leukocyte levels in research subjects was carried out by using spectrophotometer method. The respondents' vein bloods were collected from the cubital fossa after disinfection. Dengue diagnosis was performed using NS1 antigen detection and IgG/IgM in the Clinical Pathology Laboratory of Harapan and Do'a Hospital, Bengkulu City. Hypothesis testing used was bivariate analysis with Rank Spearman nonparametric hypothesis testing. Data analysis was performed by using SPSS version 23 software.

Results

The distribution of the frequency of the characteristic data in the form of gender, age, occupation and education are presented in Table 1. The percentage of research subjects with the most gender characteristics was male by 23 people (62.2%). The age of research subjects was mostly in the age range of 16-29 years old, by the number of 18 people (48.6%). Jobs with the most dengue infection were self-employed as many as 8 people (21.6%). The most recent education levels of subjects that experienced dengue infection were high and middle levels, each amounting to 18 people (48.6%).

Table 1. The Distribution of the Characteristics of the Research Category

Characteristics	Category	Frequency (%)
Sex	Male	23 (62.2%)
	Female	14 (37.8%)
Age	16-29 years old	18 (48.6%)
	30-39 years old	8 (21.6%)
	40-49 t years old	4 (10.8%)
	≥50 t years old	7 (18.9%)
Occupation	Doctor	3 (8.1%)
	Nurse	2 (5.4%)
	Laboratory analyst	2 (5.4%)
	Government employees	6 (16.2%)
	Police	4 (10.8%)
	Self-employment	8 (21.6%)
	Private employees	3 (8.1%)
	Laborer	1 (2.7%)
	Housewife	4 (10.8%)
	Student	4 (10.8%)
Education	High	18 (48.6%)
	Middle	18 (48.6%)
	Basic	1 (2.7%)

The frequency distribution of study subjects based on clinical manifestations of dengue infection can be seen in Table 2. The most common manifestations experienced by the subjects were fever as many as 37 people (100%), followed by nausea/vomiting as many as

34 people (91.8%), headache as many as 33 people (89.1%), myalgia as many as 33 people (89.1%), and arthralgia as many as 27 people (72.9%).

Table 2. Frequency Distribution Based on Clinical Manifestations of Dengue Infection

Clinical manifestations	Severity Level of Dengue Infection			
	DF	DHF grade I	DHF grade II	Total
	N (%)	N (%)	N (%)	N (%)
Fever	18 (100%)	13 (100%)	6 (100%)	37 (100%)
Nausea/Vomiting	16 (88.8%)	13 (100%)	5 (83.3%)	34 (91.8%)
Retroorbital pain	10 (55.5%)	10 (76.9%)	3 (50%)	23 (62.1%)
Headache	14 (77.7%)	13 (100%)	6 (100%)	33 (89.1%)
Myalgia	14 (77.7%)	13 (100%)	6 (100%)	33 (89.1%)
Arthralgia	11 (61.1%)	11 (84.6%)	5 (83.3%)	27 (72.9%)
Petechia	5 (27.7%)	7 (53.8%)	4 (66.6%)	16 (43.2%)
Tourniquet test	6 (33.3 %)	10 (76.9%)	2 (33.3%)	18 (48.6%)
Nosebleed	1 (5.5%)	0 (0%)	1 (16.6%)	2 (5.4%)
Bleeding gums	0 (0%)	0 (0%)	4 (66.6%)	4 (10.8%)
Black bowel movements	0 (0%)	0 (0%)	2 (33.3%)	2 (5.4%)
Dyspnea	0 (0%)	1 (7.6%)	0 (0%)	1 (2.7%)
Heartburn	8 (44.4%)	10 (76.9%)	2 (33.3%)	20 (54%)

The distribution of study subjects based on BMI and the level of severity of dengue infection can be seen in Table 3.

Table 3. Distribution of Study Subjects Based on BMI, Type of Infection and Level of Severity of Dengue Infection

Variable	Category	Frequency (%)
Body Mass Index	Underweight	3 (8.1%)
	Normal	19 (51.4%)
	Overweight	10 (27%)
	Obese	5 (13.5%)
Type of Infection	Primary	15 (40.5%)
	Secondary	22 (59.5%)
Severity Level of Dengue	DF	18 (48.6%)
	DHF grade I	13 (35.1%)
	DHF grade II	6 (16.2%)

Variable	Category	Frequency (%)
Severity Level of Dengue	DHF grade III	0 (0%)
	DHF grade IV	0 (0%)

The percentage of BMI categories with the most dengue infections was normal as many as 19 people (51.4%). Obtained the mean value of BMI is 24.65 ± 5.08. The most severity level of dengue infection was Dengue Fever (DF), which occurred on 18 people (48.6%). Bivariate analysis of BMI on the severity of dengue infection can be seen in Table 4.

Table 4. Relationship between BMI and the Severity of Dengue Infection

		Severity Level of Dengue Infection			P value	r value
		DF	DHF grade I	DHF grade II		
		N (%)	N (%)	N (%)		
BMI	*Underweight*	2 (11.1%)	1 (7.6%)	0 (0%)	0.003	0.478
	Normal	13 (72.2%)	4 (30.7%)	2 (33.3%)		
	Overweight	3 (16.6%)	5 (38.4%)	2 (33.3%)		
	Obese	0 (0%)	3 (23%)	2 (33.3%)		
Total		18 (100%)	13 (100%)	6 (100%)		

The results of the correlation test between BMI and the severity of dengue infection. The Spearman test results showed that p = 0.003 (p <0.05) and the correlation value was 0.478. A bivariate analysis of the type of infection on the severity of dengue infection can be seen in Table 5.

Table 5. Relationship between Type of Infection and the Severity of Dengue Infection

		Severity Level of Dengue Infection			P value	r value
		DF	DHF grade I	DHF grade II		
		N (%)	N (%)	N (%)		
Type of Infection	*Primary*	9 (50%)	4 (30.8%)	2 (33,3%)	0.987	0.03
	Secondary	9 (50%)	9 (69.2%)	4 (66.7%)		
Total		18 (100%)	13 (100%)	6 (100%)		

The results of the correlation test between BMI and the severity of dengue infection. The Spearman test results showed that p = 0.987 (p> 0.05) and the correlation value was 0.03.

Discussion

This study found that the male (62.2%) suffered the most from dengue infection. Other studies have also stated that dengue infection in Indonesia is slightly more dominated by men than women.(Made Susila Utama et al., 2019) Men were more affected by DHF than women with a ratio of 1.4: 1 (Pranata & Artini, 2017). This is due to the factor of mobility where men basically spend more time outdoors, so the risk

of being bitten by mosquitoes is greater (Kasman. & Ishak, 2018).

The age of most adult dengue patients was 16-29 years old. It is known that there has been a shift in the age of patients with dengue infection towards the age of 15 and over or the adolescent and adult categories, they were in the 16-20 years and 21-25 years age group (Divy et al., 2018). It is suspected that this happened because of a change in transmission, from transmissions at home to transmissions in public facilities (Safri, 2017).

In this study, self-employment was the occupation that experienced the most dengue infection. There is no relationship between occupation and the incidence of dengue infection. This is because the spread of dengue virus transmission vectors is almost evenly distributed in all places so that everyone has almost the same chance of getting dengue infection (Umaya et al., 2013). Another study states that there is a relationship between work and the incidence of dengue infection where people who work are 2 times more likely to contract DHF than people who do not work. This is influenced by the level of a person's mobility which is supported by an increasingly advanced transportation system, so that people tend to do more outdoor activities (Novrita et al., 2017).

The education levels of the subjects with the most dengue infections are high and middle. This is different from previous research which states that people with low education are most affected by dengue infection. However, there is no relationship between education and the incidence of dengue infection. This is because knowledge and information about dengue infection can be obtained from anywhere so that people do not have to have high education to obtain this information (Umaya et al., 2013). In contrast to other studies which state that there is a relationship between education and the incidence of dengue fever, where the higher a person's education level, the easier it is to receive information and the more knowledge one has, especially in relation to dengue infection (Novrita et al., 2017).

The most common clinical manifestations experienced by the subjects were fever, followed by nausea/vomiting, headache, myalgia, and arthralgia. This is consistent with the results of previous studies that fever is the most frequent clinical manifestation of dengue infection (96.9% of cases, 95% CI: 92.5–98.8%). In some cases, dengue infection can develop into a range of clinical symptoms ranging from mild flu-like syndromes such as fever, skin rash, headache, myalgia and arthralgia, to severe forms of illness.(Badawi et al., 2018) Persistent vomiting symptoms can be used to predict the progression of a severe dengue infection. This is consistent with previous findings that persistent vomiting is a warning sign for severe dengue fever (Thanachartwet et al., 2015).

The result of this study shows a relationship between BMI and the severity of adult dengue infection in Bengkulu City. Body Mass index can affect the severity of dengue infection, where the higher the BMI, the higher the tendency for a person to experience an increase in the severity of dengue infection. The greater a person's body mass index, the greater the capillary permeability, making it easier for hypovolemia to occur and fall into a state of shock. It is in line with previous studies which stated that patients with excess body size have an increased risk of more severe dengue infection (Kaur et al., 2017). Other studies have also suggested that obese patients have a higher frequency of increased hematocrit when treated. Peak hematocrit levels were significantly higher in the obese group (Khei Tan et al., 2018). However, other studies mention different things where the BMI value is not related to the degree of dengue severity (Nurjannah, 2010). It was also stated that there was no relationship between being overweight/obese and dengue (Trang et al., 2016). The differences in observations regarding the effect of BMI on dengue infection may be influenced by several factors, namely comorbidity, organopathy, and drug consumption. (Triana et al., 2020)

Excess BMI value is associated with the severity of dengue infection as a risk factor for

Dengue Shock Syndrome (DSS). This finding is supported by the theory that obesity can affect the severity of dengue infection. It is associated with chronic low-grade inflammation and vascular endothelial dysfunction as a result of increased production of white adipose tissue leading to increased production of inflammatory mediators. The inflammatory mediators are TNF-α and several interleukins (IL) such as IL-1 β, IL-6, and IL-8. In obese patients, there is an increase in TNF α and IL-6. These inflammatory mediators will increase capillary permeability which in turn can lead to progressive plasma leakage leading to a higher risk of DSS (Jayani et al., 2018).

The most common type of dengue infection in this study was secondary infection (59.5%). This study is in line with the research of Ulandari (Ulandari et al., 2020) and Jatmiko (Jatmiko et al., 2017), who showed that there were no patients with primary infection. These results are the same as the results of a study by Khurram which showed that the proportion of patients with secondary infection was higher than that of primary infection (Khurram et al., 2014). Research by Trisnadewi also showed that the prevalence of secondary infection to dengue fever was higher than primary infection (Trisnadewi & Wande, 2016).

Although the distribution of primary infection patients tends to be found at mild severity and secondary infection patients can be found at all severity levels, the Spearman Rank test of this study has a value of p> 0.05 which indicates that there is no significant relationship between serological examination results and the severity of patients with dengue infection. The results of this study are in line with those of Khurram and Ulandari which showed that there was no difference in the degree of severity between patients with primary infection and patients with secondary infection (Khurram et al., 2014; Ulandari et al., 2020). The cause can be several factors that affect the degree of severity, including age, genetics, nutrition, and serotype and genotype of the dengue virus.

The limitation in this study was that there were no cases of dengue infection with grade III and IV severity. This is because the sample size only meets the minimum sample size due to limited access and the number of dengue infection patients is decreasing in hospitals as a result of the ongoing Covid-19 pandemic. For further research on related topics, it is hoped that a larger number of samples can be used, and it is also needed to determine other factors that affect the severity of dengue infection.

Conclusions

This study shows that the higher the BMI value, the higher the tendency for a person to experience an increase in the severity of dengue infection. Knowing risk factors as predictors of dengue severity is very necessary in order to handle dengue infection quickly and accurately.

Conflict of interest

The authors declare no potential conflict of interest.

Acknowledgement

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