Comparison of 2009 and 2011 WHO Guidelines, and Scoring Models for Adult Hospitalized Dengue Infection: A Single Observation in Tangerang, Indonesia

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Abstract

Background: World Health Organization (WHO) published a dengue guideline in 2009 and in 2011 by WHO-SEARO. However, many of dengue cases in early phase do not meet all the criteria by WHO classification. Because of this condition there is a scoring model that was published in 2015, that might help in primary health care. Therefore, a study to compare those diagnostic tools especially in adult dengue patients in Banten is needed.

Aims: This study is to know the comparison between 2009 version and 2011 version of dengue diagnostic guidelines by WHO and scoring model version.

Methods and Material: This study used a descriptive method with a cross-sectional design at 60 adult dengue patients. Each patient is grouped according to diagnostic tools' classification and will be analyzed using Chi-square.

Results: results are grouped according to the WHO diagnosis from 2009 and 2011, presumptive model and probable models where there are 46 (77%), 48 (78%), 31(52%), and 15 (25%) of patients diagnosed with dengue infection. Overall, the diagnosis made by the 2009 WHO and the probable models has the most superior sensitivity and specificity values of 84,6% and 25%, and 82,4% and 97,7% respectively compared to other diagnostic tools. However, from the results of positive predictive values, probable models have a higher percentage than the 2009 WHO diagnosis.

Conclusions: probable model is more sensitive and specific than other diagnostic results. These conclude that probable model is best tool for dengue infection screening in early phase of infection.

Introduction

Dengue illness is a viral disease caused by dengue virus of Flavivirus genus, Flaviviridae family that has four serotypes (DENS-1, DENV2, DENV-3, DENV-4) and spread by *Aedes aegypti* mosquito.[1],[2],[3] For the past 50 years, dengue cases had increase by 30 times with 50 million cases each year and 2.5 million people lived in endemic area.[4],[5] According to World Health Organization (WHO), Asia Pacific has contributed 75% of dengue cases in the world and Indonesia as the second country with the most cases among 30 other endemic countries since 2004 to 2010.[5] In 2017 based on Ministry of Health of the Republic of Indonesia, there were 68.407 and 493 of dengue cases and DHF-associated deaths in Indonesia with 26,12 per 100,000 person-years and 0,72% of incidence rate (IR) and case fatality rate (CFR), respectively.[6] The WHO has published new dengue classification in 2009 that was revised from 1997.[4,7] Then in 2011 WHO-SEARO published their dengue guidelines with different classification.[5,8] Previous study in

2015 also published new screening tool in a form of scoring model with two types of model such as presumptive and probable model. This scoring model was designs to diagnose dengue infection in the early phase of illness with limited resources of laboratory facilities in Indonesia.[9] Early studies in 18 countries also showed that 2009 WHO dengue classification has a higher level of accuracy compared to 1997 and 2011 WHO dengue classification.[10],[11],[12] However, 2009 WHO dengue classification is still rarely used in diagnosing dengue illness.[13] This study used the Standard F Dengue IgM/IgG FIA™ and Standard F Dengue NS1 Ag FIA™, which are fluorescence immunoassays from SD Biosensor. This examination is used to obtain IgM, IgG, and NS-1 antigen to be used as a diagnosis of dengue. Therefore, this studied was to compared diagnosis guidelines of 2009 and 2011 WHO dengue classification and scoring model at adult patients in Siloam Teaching Hospital, Banten, Tangerang.

Subjects And Methods

Data source

The study has passed the ethical review from local institutional ethical committee with number of 192/K-LKJ/ETIK/XI/2019 and was conducted from November 2019 to June 2020 in the Faculty of Medicine, Universitas Pelita Harapan. This study used a descriptive method with a cross-sectional design on 60 adult dengue patients with purposive sampling in Siloam Teaching Hospital. Clinical data such as the patient's sign and symptoms and biological materials were collected through appropriate informed consent and were anonymized. Adult patients (age 18-59-year-old) with fever (≥ 37.5 °C) and thrombocytopenia (≥150 000 cell/mcL), were eligible to participate. Patients with a history of autoimmune disease or immunologic/hematologic disorder were excluded.

Case definition and criteria

The 2009 WHO classifies dengue infection into two groups: uncomplicated and severe. Severe cases are linked to excessive hemorrhage, organ impairment, or severe plasma leakage, and the remaining cases are considered uncomplicated.[4] Meanwhile, according to 2011 WHO classification, dengue cases divided into Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). DHF was further subdivided into grades I-IV, where grade III – IV are considered as Dengue Shock Syndrome (DSS).

- Grade I (DHF I): Fever with bleeding manifestation and evidence of plasma leakage.
- Grade 2 (DHF II): Fever with spontaneous bleeding.
- Grade 3 (DHF III): Clinical sign of circulatory failure or shock.
- Grade 4 (DHF IV): Profound shock with undetectable blood pressure and pulse.[5]

The Scoring Model is a scoring formed using the Roc tab analysis method which gives the results of two models, namely presumptive dengue illness and probable dengue illness with a total value of total ≥14 dan ≥7, respectively. The presumptive model variables are duration of fever, torniquet test, myalgia, monocyte, white blood cell, and thrombocytes examination results. The probable model also have the same variables however, this model is distinguished by the presence of laboratory test result of NS-1 antigen[9].

Standard F Dengue

All eligible patients were screened with Standard F Dengue IgM/IgG FIA™ and NS1 Ag FIA™. Positive NS1 Ag FIA or IgM detection results following either positive or negative IgG FIA results were confirmed dengue. Each patient is grouped according to diagnostic tools' classification and will be analyzed using Chi-square to determine the sensitivity, specificity, likelihood ratio, and negative and predictive value of each diagnostic tool. The sensitivity and specificity value of WHO diagnosis from

2009 and 2011, the presumptive model, and probable model were compared to decide the best screening tool for dengue diagnosis. The examination was carried out according to the protocol provided by SD Biosensor as follows:

Standard F Dengue IgM/IgG FIA™:

1. Store the probe and sample at 15-30°C for at least 30 minutes
2. Set up the Standard F analyzer and select "standard test" mode.
3. Prepare 10μl of sample serum / plasma / blood on the standard black line Ezi Tube^{+}.
4. Enter the sample that has been prepared on the inspection tool.
5. Add 3 drops of dilution liquid to the probe
6. Press "start" to start diagnosis
7. The inspection tool will process and provide results after 15 minutes.

Standard F Dengue NS1 Ag FIA™

1. Store the probe and sample at 15-30°C for at least 30 minutes.
2. Set up the Standard F analyzer and select "standard test" mode.
3. Prepare 100μl of sample serum / plasma / blood sample with a dropper and mix it with dilution liquid.
4. Enter the sample that has been prepared on the inspection tool.
5. Add 3 drops of mixed dilution liquid.
6. Press "start" to start diagnosis.
7. The inspection tool will process and provide results after 15 or 5 minutes on samples that have a strong positive result.

Result

There were 60 dengue infection cases were included in this study. The demographic characteristic, patients' clinical features, and laboratory results such as hematocrit, white blood cell, thrombocyte, neutrophil, and monocyte level were shown in **Table 1.** There are 32 (53%) male and 28 (47%) female patients with an average age of 34,57-year-old. Nausea/vomiting, myalgia, arthralgia, and anorexia were the most common associated symptoms with acute fever. The laboratory results show the mean hematocrit level of 40,29%, indicating that there were no patients with plasma leakages condition. In the early phase, the mean total white blood cell (WBC) count was 4741± 2109,739 cell/mcL and thrombocyte count was 120133 ± 59488 cell/mcL. Moreover, the mean band and segment neutrophils count was 2,75±0,728% and 63±14,924% respectively, and the mean monocyte count was 6,82±1,578%.

Table 1. Demographic results, patients' clinical features, and laboratory results of the participants

Characteristics	N[a]	Min	Max
Demographic information			
a. Age (year)	34,57±12,24	18	59
b. Male	7		
c. Female	32(53)		
Clinical features	28(47)		
Fever			
Retro-orbital pain	58(97)		
Nausea/vomiting	24(40)		
Myalgia	46(77)		
Arthralgia	46(77)		
Anorexia	42(70)		
Constipation	42(70)		
Abdominal pain	8(13)		
Sore throat	22(37)		
Redness	25(42)		
Hepatomegaly	15(25)		
Bleeding manifestation	1(2)		
a. Petechiae			
b. Epistaxis	9(15)		
c. Gastrointestinal	2(3)		
bleeding	2(3)		
d. Gum bleeding	5(8)		
e. Hematoma	2(3)		
Laboratory results		23	57
Hematocrit (%)	40,29±6,326	138	12500
Total WBC count	4741±2109,7	9	27600
(cell/mcL)	39	600	0
Thrombocyte count	120133±594	0	5
(cell/mcL)	88	2	87
Band neutrophils count	2,75±0,728	18	10
(%)	63±14,924	2	
Segment neutrophils	6,82±1,578		
count (%)			
Monocyte count (%)			

*Data presents as n (%) or mean ± standard deviation

All dengue patients are grouped based on WHO diagnosis from 2009 and 2011, presumptive and probable model. There are 46 (77%) patients were diagnosed with dengue infection using WHO diagnoses from 2009 where 24 (47%) patients classified as dengue without warning signs and later 22 (37%) patients classified as dengue with warning signs. On the other hand, based on 2011 WHO there are 47 (78%) patients diagnosed with dengue infection, 28 (47%) of them are classified as dengue fever and 19(32%) patients classified as dengue hemorrhagic fever. Diagnosis by presumptive and probable model shows 31(52%) and 29(48%) patients are positive with dengue infection. All diagnosis results were compared to Standard F Dengue IgM/IgG FIA and NS1 Ag FIA test results to obtain sensitivity and specificity value, log likelihood ratio (LLR), and negative and positive predictive value. The 2009 WHO classification had a sensitivity and specificity of 84,6% and 25,5% respectively. These results have a value of 23,9% and 85,7% for positive predictive value (PPV) and negative predictive value (NPV), and LLR of 0,428. On the other hand, 2011 WHO classification had the sensitivity value of 84,6% and specificity value of 23,4%. The PPV, NPV, and LLR value of 2011 WHO are 23,9%, 84,6%, and 0,522. Furthermore, the comparison between the presumptive model and the results of the Standard F Dengue NS-1 and/or IgM and IgG examination showed a sensitivity of 61.5% and a specificity of 51.1% with PPV, NPV, and LLR, namely 25.8%, 82.8%. , and 0.419, respectively. Next, the probable model has a sensitivity and specificity of 82.4% and 97.7%. The sensitivity and specificity had a PPV and NPV of 93.3% and LLR of 0.00. The comparison between the proposed scoring model and WHO classification is presented in **Table 2.**

Table 2. Comparison Dengue Diagnostic Value of WHO Classification and Scoring Model

	NS-1 (+)/(-) and/or IgM (+) and IgG (+)/(-)				
	Sen (%)	Spe (%)	PPV (+)	NPV (-)	LLR
2009 WHO Dengue Classification	84,6	25,5	23,9	85,7	0,428
2011 WHO Dengue Classification	84,6	23,4	23,4	84,6	0,522
Presumptive Model	61,5	51,1	25,8	82,8	0,419
Probable Model	82,4	97,7	93,3	93,3	0,00

Sen = Sensitivity, Spec = Specivicity, PPV = Positive Predictive Value, NPV = Negative Predictive Value, LLR = Log Likelihood Ratio

Discussion

From those comparisons, the 2009 WHO classification and probable model had a sensitivity of 84,6% and 82,4%, and specificity of 25,5% and 97,7% respectively. These values showed that the 2009 WHO and probable model were higher than the other diagnostic results. Previous studies about these scoring models also determined that 2009 WHO and probable had higher results of sensitivity and specificity.[9],[13],[14] However, it should be seen from the ppv based on WHO diagnosis guidelines, although it has high sensitivity and specificity value, however, the PPV is low at 23.9% compared to the probable model which has a PPV of 93.3% On the other hand, the llr of the probable model is 0,00, in which the diagnostic tools such as Standard F Dengue IgM/IgG FIA and NS1 Ag FIA test are still needed for patients' early diagnosis in dengue infection. In addition, keep in mind that the probable scoring model itself also has a variable of NS-1 antigen examination results. This diagnostic study shows that the probable model could predict dengue illness better than 2009 and 2011 WHO classification, and presumptive model. However, diagnostic tools such as the serologic test of Standard F Dengue IgM/IgG FIA and NS1 Ag FIA test are still needed to further diagnose dengue illness.

Conclusion

Probable model scoring type tool has the highest sensitivity and specificity values than other diagnostic results. In conclusion, the probable model is the best tool for dengue infection screening in early phase of infection. However, serologic test of Standard F Dengue IgM/IgG FIA and NS1 Ag FIA are still needed in determining the diagnosis of dengue illness.

Conflict of Interests

The authors declare no conflict of interests and approve for this manuscript.

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