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Review Article

Comparative Diagnostic Value of Anti-Dengue IgG, Anti-Dengue IgM of Two Rapid Tests in Dengue Virus Infection

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ABSTRACT

Introduction: Diagnosis of Dengue Virus Infection (DVI) is based on combination of clinical manifestation, hematological, serological, and molecular examination. This study aims to compare the diagnostic value of anti-dengue IgG and anti-dengue IgM by two rapid tests with RT-PCR Dengue and ELISA as the gold standards.

Methods: This was an observational cross-sectional study. Serum was collected from 80 febrile patients (3-7 day fever), who were suspected Dengue Virus Infection (DVI). Serum was examined by STANDARD Q-SD and SD BIOLINE as rapid tests and RT-PCR and or NS1 Ag Dengue (ELISA) and anti-dengue IgG/IgM ELISA as the gold standards.

Results: The most common serotype identification was DENV 3. The positive results of NS1 Ag Dengue were common on day 3 of fever in primary infection and day 4 of fever in secondary infection. The antibody examination was dominated by positive anti-dengue IgM and positive anti-dengue IgG in 27 patients (54%) in secondary infection. Sensitivity anti-dengue IgG STANDARD Q was 68%, and SD BIOLINE was 87%. Specificity anti-dengue IgG STANDARD Q was 80%, and SD BIOLINE was 76.7%. Sensitivity IgM anti-dengue STANDARD Q was 44%, and SD BIOLINE was 48%. Specificity anti-dengue IgM of two rapid tests was 100%.

Conclusion: The serological examination with rapid tests is not enough to establish a diagnosis of DVI, so the combination with NS1 Ag Dengue and RT-PCR examination is needed.

Keywords: *Dengue virus, diagnosis, rapid test, ELISA*

INTRODUCTION

Dengue virus infection (DVI) is an infectious disease caused by the dengue virus (DENV), which is transmitted by *Aedes aegypti* mosquitoes influenced by climate and environmental [1, 2]. DVI is still a public health challenge because Indonesia is a tropical country hyperendemic of DVI. Public awareness regarding DVI, perception of the problem, and prevention practices are essential factors in the epidemiology of DVI [3]. The clinical manifestations are various, from dengue fever to other serious conditions, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome [4–6]. This diseases also have potential risk factors, including personal life activities, sanitation, housing situation, living conditions and hygiene, as similar other infection such as *Helicobacter pylori* [7].

DVI is divided into primary and secondary infections based on the produced antibody response. In primary infection, anti-dengue IgM first appears slowly and has a low concentration. Thus, anti-dengue IgG is produced in 2 weeks after infection. However, in secondary infection, there is a rapidly increased concentration of anti-dengue IgG two days after fever onset. In contrast, anti-

dengue IgM takes a long time or even goes undetected [5, 8–10].

Diagnosis of DVI is based on a combination of clinical manifestations and laboratory examinations, such as hematology, serology, virology [11]. Several methods have limitations for early detection of DVI because it needs complete laboratory facilities, high cost, and time-consuming. Rapid and accurate diagnosis is very needed for epidemiologic surveillance, treatment strategy, and vaccine development. The serology examination with the immunochromatography method (rapid test) is faster and practical. However, each serology parameter by various methods, including immunochromatography (rapid test), has various diagnostic values correlating with time of onset and the produced antibody response [12–17]. This research aims to compare the diagnostic value of anti-dengue IgG and anti-dengue IgM by two rapid tests with RT-PCR and ELISA as the gold standards in DVI.

METHODS

Ethics approval was obtained from Ethics Committee of Dr. Soetomo General Hospital with letter number 1747/KEPK/XII/2019. Informed consent was obtained from all participants following the administration of the participation information sheet. This was an observational cross-sectional research. Serum was collected from 80 febrile patients (3-7 day fever), who were suspected DVI at the Tropic and Infectious Disease Ward, Dr. Soetomo General Hospital, Surabaya from February until August 2016. The criteria used in suspecting Dengue in this study is based on WHO 2011 criteria, includes 3-7 day fever with or without specific signs and symptoms of DVI such as headaches, nausea, vomiting, abdominal pain, rash, hemorrhagic manifestations, positive tourniquet test, and supporting with laboratory examination results includes thrombocytopenia, leukopenia, hematocrit rise [11].

The research subjects consisted of two groups. There were DVI (n = 50) and non-DVI (n = 30) groups based on WHO 2011 criteria and the results of RT-PCR Dengue or NS1 Ag Dengue (ELISA method). The DVI group consisted of febrile patients who have been proven DVI (confirmed dengue RT-PCR and or NS1 Ag Dengue positive). The non-DVI group consisted of febrile patients who are not proven DVI (RT-PCR and or negative NS1 Ag Dengue) but caused by other diseases.

Examinations of NS1 Ag Dengue (Panbio Dengue Early (NS1) ELISA, Panbio Diagnostics), anti-dengue IgG, IgM (Panbio Dengue Duo IgM and IgG capture ELISA, Panbio Diagnostics) were conducted at the Laboratory of the Infection Hospital, Universitas Airlangga, Surabaya in August 2016. RNA extraction was carried out using automatic MagNA Pure LC 2.0, MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche) reagent. Detection of RNA, DENV serotypes was conducted using the RT-PCR (Focus Diagnostics) real-time Simplexa Dengue, 3M Integrated Cycler, in August 2016 at the Dengue Laboratory, Eijkman Molecular Biology Institute, Jakarta. Serum samples were stored in 4-5 microtubes at -80°C. Examination of anti-dengue IgG, IgM with two rapid tests (STANDARD Q-SD Biosensor, Korea, and SD BIOLINE-Standard Diagnostics, Korea) in this research was conducted at the Clinical Pathology Laboratory, Dr. Soetomo General Hospital, Surabaya in January 2020, using stored biological material. One microtube was only thawed once and only for one rapid test.

The principle of STANDARD Q anti-dengue IgM/IgG is as follows: Anti-dengue IgM, anti-dengue IgG in serum (10μL) will migrate and react with monoclonal anti-human IgM and monoclonal anti-human IgG on the test line. The goat anti-mouse IgG was immobilized in the control line on the nitrocellulose membrane. Inactive Dengue virus and monoclonal anti-dengue-gold complex will be released when diluent (3 drops/90μL) is added and react with antibodies in serum. The results are read after 15-20 minutes until the red color appeared on the test line and the control line [8].

The principle of SD BIOLINE Dengue IgG/IgM is immunochromatography. The antibodies in the serum (5μL) will be captured by anti-human IgG and or anti-human IgM, which are immobilized on the test line. Anti-human IgG monoclonal mouse conjugate, IgM-colloidal gold reacts with the DENV envelope protein to form antibody (Ab)-antigen (Ag) complex when added a diluent (4 drops 120μL). The Ab-Ag complex will migrate and react with antibodies on the test line and produce a red color change after 15-20 minutes. The red color on the control line indicates the correct working process.

Quality assurance before inspection included checking the expiration date, lot number, storage of reagents according to the insert kit. The inspection was carried out according to the procedure in the insert kit. Quality assurance of the results of both rapid tests was ensuring by the appearance of the test line and the control line (in red) during the reading. The interpretation was done blindly by 3 independent observers. The conclusion of the results was determined based on the interpretation of the most results.

Statistical Analysis

Statistical analysis was carried out using SPSS version 20.0. Confidence intervals were

determined 95%, and p-value <0.05 was significant. Kappa (κ) values were interpreted as very good (κ = 0.81-1.00), good (κ = 0.61-0.80), adequate (κ = 0.41-0.60), bad (κ = 0.21-0.40), and very bad (κ <0.20) [18].

RESULTS

The characteristics of the research subjects are shown in Table 1. The mean days of fever in the DVI group (4.68±1.22) were shorter than the non-DVI group (5.93±1.26). The most duration of fever in the DVI group was day 4 (28%), whereas in the non-DVI group was day 7 (53.3%). The most common serotype identification and NS1 Ag Dengue results were dominated by DENV 3. The positive results of NS1 Ag Dengue were common on day 3 of fever in primary infection and day 4 of fever in secondary infection (Table 1).

Table 1: Characteristics of research subjects

Variables	DVI (n = 50)	Non-DVI (n = 30)
Age*	24.72 ± 10.53	35.9 ± 18.38
Male, n (%)	30 (60)	12 (40)
Female, n (%)	20 (40)	18 (60)
Duration of fever* :	4.68 ± 1.22	5.93 ± 1.26
• 3 days, n (%)	10 (20)	1 (3.33)
• 4 days, n (%)	14 (28)	4 (13.33)
• 5 days, n (%)	12 (24)	7 (23.33)
• 6 days, n (%)	10 (20)	2 (6.67)
• 7 days, n (%)	4 (8)	16 (53.33)
Thrombocyte count* :	61,335 ± 35,238.15	246,426.67±223,707.73
Group of DVI :		
• Dengue fever, n (%)		
• DHF stage I, n (%)	6 (12)	
• DHF stage II, n (%)	26 (52)	
• DHF stage III, n (%)	13 (26)	
• DHF stage IV, n (%)	5 (10)	
Group of non-DVI :		
• Leptospirosis, n (%)		1 (3.33)
• Typhoid fever, n (%)		12 (40)
• Upper respiratory tract infection, n (%)		1 (3.33)
• UTI, n (%)		6 (20)
• Hepatitis A, n (%)		1 (3.33)
• Hepatitis B, n (%)		2. (6.67)
• Hepatitis C, n (%)		1 (3.33)
• Malaria, n (%)		2 (6.67)
• Morbili, n (%)		1 (3.33)
• Sepsis, n (%)		1 (3.33)
• Fever caused by other virus, n (%)		2 (6.67)
• Positive RT-PCR of Dengue, n (%)	41 (82)	0 (0)
• Negative RT-PCR of Dengue, n (%)	9 (18)	30 (100)
Dengue virus serotype :		
• DENV 1, n (%)	7 (14)	0 (0)
• DENV 2, n (%)	7 (14)	0 (0)
• DENV 3, n (%)	26 (52)	0 (0)
• DENV 4, n (%)	0 (0)	0 (0)
• Mixed DENV 1 and DENV 3, n (%)	1 (2)	0 (0)
• Positive NS1 Ag Dengue, n (%)	38 (76)	0 (0)
• Negative NS1 Ag Dengue, n (%)	12 (24)	30 (100)
• Positive anti-dengue IgM (ELISA), n (%)	33 (66)	2 (6.67)
• Negative anti-dengue IgM (ELISA), n (%)	17 (34)	28 (93.33)
• Positive anti-dengue IgG (ELISA), n (%)	29 (58)	24 (80)
• Negative anti-dengue IgG (ELISA), n (%)	21 (42)	6 (20)

Dengue primary infection, n (%)	14 (28)	
Dengue secondary infection, n (%)	36 (72)	
*Mean ± SD (standard deviation); DVI: Dengue Virus Infection (febrile patients which are Dengue confirmed with NS1 Antigen Dengue and or RNA RT-PCR Dengue), non-DVI: non Dengue Virus Infection (febrile patients which are not confirmed with NS1 Antigen Dengue and or RNA RT-PCR Dengue, but confirmed with the other diseases)		

The results of positive anti-dengue IgM, positive anti-dengue IgG in the DENV 3 serotype were more detectable on day 5 of fever in secondary infection. The antibody results in this study were dominated by secondary infection, positive anti-dengue IgM, positive anti-dengue IgG in 27 patients (54%), followed by negative anti-dengue IgM, negative anti-dengue IgG in 13 patients (26%) (Table 2).

Table 2: Distribution of DENV serotype, the positive results of NS1 Ag Dengue, anti-dengue IgG, anti-dengue IgM (ELISA) each serotype, serological profile DVI group according to the day of fever

STATE OF INFECTION	DAY OF FEVER (days)				
	3	4	5	6	7
	P / S	P / S	P / S	P / S	P / S
DEN-1	0	1	2	1	3
• NS1 (+)	0 / 0	0 / 0	0 / 0	0 / 0	0 / 1
• IgM (+)	0 / 0	0 / 1	0 / 2	0 / 1	0 / 2
• IgG (+)	0 / 0	0 / 1	0 / 2	0 / 1	0 / 2
DEN-2	2	3	2	0	0
• NS1 (+)	1 / 0	1 / 2	1 / 1	0 / 0	0 / 0
• IgM (+)	1 / 0	1 / 2	1 / 1	0 / 0	0 / 0
• IgG (+)	0 / 0	0 / 2	0 / 1	0 / 0	0 / 0
DEN-3	8	8	5	4	1
• NS1 (+)	5 / 2	2 / 5	0 / 4	2 / 0	0 / 1
• IgM (+)	2 / 0	0 / 3	0 / 4	1 / 1	0 / 1
• IgG (+)	0 / 0	0 / 4	0 / 5	0 / 2	0 / 1
Mixed DEN-1 and DEN-3	0	1	0	0	0
• NS1 (+)	0 / 0	0 / 1	0 / 0	0 / 0	0 / 0
• IgM (+)	0 / 0	0 / 1	0 / 0	0 / 0	0 / 0
• IgG (+)	0 / 0	0 / 1	0 / 0	0 / 0	0 / 0
STANDARD Q					
IgM (+), IgG (+)	0 (0)	5 (10)	8 (16)	7 (14)	1 (2)
IgM (-), IgG (+)	2 (4)	4 (8)	3 (6)	2 (4)	2 (4)
IgM (+), IgG (-)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
IgM (-), IgG (-)	8 (16)	4 (8)	1 (2)	1 (2)	1 (2)
SD BIOLINE					
IgM (+), IgG (+)	2 (4)	6 (12)	8 (16)	6 (12)	2 (4)
IgM (-), IgG (+)	5 (10)	6 (12)	3 (6)	2 (4)	2 (4)
IgM (+), IgG (-)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
IgM (-), IgG (-)	3 (6)	2 (4)	1 (2)	1 (2)	0 (0)
ELISA					
IgM (+), IgG (+)	0 (0)	8 (16)	9 (18)	7 (14)	3 (6)
IgM (-), IgG (+)	1 (2)	1 (2)	1 (2)	1 (2)	0 (0)
IgM (+), IgG (-)	3 (6)	1 (2)	1 (2)	1 (2)	0 (0)
IgM (-), IgG (-)	6 (12)	4 (8)	1 (2)	1 (2)	1 (2)
P = Primary infection; S = Secondary infection					

The diagnostic value of both rapid tests with anti-dengue IgG, anti-dengue IgM ELISA, RT-PCR and or NS1 Ag Dengue method as the gold standard is shown in Table 3. Sensitivity anti-dengue IgG

STANDARD Q was 68%, and SD BIOLINE was 87%. Specificity IgG anti-dengue STANDARD Q was 80%, and SD BIOLINE was 76.7%. Sensitivity IgM anti-dengue STANDARD Q was 44%, and SD BIOLINE was 48%. Specificity IgM anti-dengue of two rapid tests was 100% (Table 3).

Table 3: Diagnostic value of anti-dengue IgG, anti-dengue IgM 2 rapid tests with anti-dengue IgG, anti-dengue IgM ELISA method as the gold standard and with RT-PCR and or NS1 Ag Dengue (ELISA) as the gold standard

Anti-dengue IgG, anti-dengue IgM ELISA (gold standard)				
Variable	STANDARD Q		SD BIOLINE	
	IgG	IgM	IgG	IgM
Sensitivity	84.4 %	50 %	96.9 %	52.6 %
Specificity	72.9 %	92.9 %	60.4 %	90.5 %
PPV	67.5 %	86.4 %	62 %	83.3 %
NPV	87.5 %	67.2 %	96.7 %	67.9 %
LR +	3.114	7.042	2.447	5.537
LR -	0.214	0.538	0.051	0.524
κ value	0.550	0.437	0.524	0.439
P value	<0.001	<0.001	<0.001	<0.001
RT-PCR and or NS1 Ag Dengue (ELISA) (gold standard)				
Variable	STANDARD Q		SD BIOLINE	
	IgG	IgM	IgG	IgM
Sensitivity	68 %	44 %	87 %	48 %
Specificity	80 %	100 %	76.7 %	100 %
PPV	85 %	100 %	87 %	100 %
NPV	60 %	51.7 %	76.7 %	53.6 %
LR +	3.4	Infinity	3.734	Infinity
LR -	0.4	0.56	0.169	0.52
κ value	0.450	0.371	0.627	0.409
P value	<0.001	<0.001	<0.001	<0.001

The kappa coefficient (κ) of anti-dengue IgG STANDARD Q and SD BIOLINE against the gold standard of anti-dengue IgG (ELISA) was 0.550 (p = 0.000) and 0.524 (p = 0.000), respectively. While in anti-dengue IgM STANDARD Q and SD BIOLINE against the gold standard of anti-dengue IgM (ELISA) was 0.437 (p = 0.000) and 0.439 (p = 0.000), respectively. The kappa coefficient of anti-dengue IgG STANDARD Q and SD BIOLINE against the gold standard RT-PCR or NS1 Ag Dengue (ELISA) was 0.450 (p = 0.000) and 0.627(p = 0.000), respectively. While in anti-dengue IgM STANDARD Q and SD BIOLINE against the gold standard RT-PCR or NS1 Ag Dengue (ELISA) was 0.371 (p = 0.000) and 0.409 (p = 0.000), respectively (Table 3).

DISCUSSION

The mean days of fever in the DVI group (4.68±1.22) were shorter than the non-DVI group (5.93±1.26). The most duration of fever in the DVI group was day 4 (28%). The results of anti-dengue IgM in all DENV serotypes were predominant in secondary infection than primary infection. Most DENV 3 serotype was detected in day 5 of fever. The most serological profile in this study was positive IgM and positive IgG. The conformity between both rapid tests with anti-dengue IgG, anti-dengue IgM with ELISA method was good and significant. STANDARD Q anti-dengue IgG had relatively good and significant conformity with RT-PCR and or NS1 Ag Dengue (ELISA) as the gold standard, whereas SD BIOLINE anti-dengue IgG had good and significant conformity. However, anti-dengue IgM both rapid tests had poor conformity.

These results were following the fever pattern theory of DVI, which was peak fever on day 4. On day 5, fever will decrease, but it was still needed to watch out because it was a critical phase [8, 11]. The platelet count of the DVI group was lower than the non-DVI group. Thrombocytopenia occurred due to changes in megakaryocytopoiesis by hematopoietic cell infection and disruption of progenitor cell growth, resulting in platelet dysfunction, peripheral sequestration, and increased platelet consumption [4, 19]. The DENV serotype in this research was dominated by DENV 3 (52%). Several studies had shown a shift in DENV serotypes in Surabaya, Indonesia, over the past few years. In 2003-2007, it was dominated by DENV 2. The prevalence of DENV 1 was increased in 2008–2012. In 2012, the prevalence of DENV 3 was increased [4, 10]. The NS1 Ag Dengue has

detected mostly in DENV 3 serotype, both primary and secondary infections from day 3-7 fever. These results showed that NS1 Ag Dengue secretion was influenced by humoral immune responses, sampling time and also serotype differences [4, 17].

The results of anti-dengue IgM in all DENV serotypes were predominant in secondary infection than primary infection. Most DENV 3 serotype was detected in day 5 of fever. Primary infection was defined as a negative anti-dengue IgG (ELISA method), positive anti-dengue IgM (ELISA method) and or IgM/IgG ratio >1.2. Secondary infection was defined as a positive anti-dengue IgG, positive or negative anti-dengue IgM, and or IgM/IgG ratio <1.2 [11, 13]. This was contradictive with the theory that anti-dengue IgM concentrations were higher in primary infection than that in secondary infection. This was possible because there were only six patients with positive anti-dengue IgM in primary infection. Humoral immune response in primary infection characterized by anti-dengue IgM which was formed on day 3 of fever, but generally could be detected in day 7 of fever or more and increased within 1-3 weeks later [20]. The results of negative anti-dengue IgM, negative anti-dengue IgG (26%) were likely primary infection, but anti-dengue IgM had not yet been formed. Anti-dengue IgG results were positive in all DENV serotypes. The humoral immune response of anti-dengue IgG in secondary infection appeared faster because of the amnestic IgG reaction so that on day 2 of fever, anti-dengue IgG could already appear [5, 9, 13, 15].

Profile of anti-dengue IgG, anti-dengue IgM in primary and secondary infections were different [12, 13]. Sampling time based on the duration of the day of fever had an important role. Day 3-5 of fever was the best time for serological examination because antibodies had begun to be produced. In contrast, on day 2 of fever, there was generally no change in hemodynamics and antibody production. However, often antibodies had not been produced on days 3-7 of fever so that the results of anti-dengue IgG and anti-dengue IgM were false negatives. Anti-dengue IgM in primary infection was detected on day 3-5 of fever in about 50% of patients, then increased on day 5 (80%) and became 99% on day 10. After day 10 of fever, usually, DHF patients entered the convalescence phase, and serological examination was rarely performed. The concentration of anti-dengue IgG in primary infection of day 7 of fever was still low, increasing slowly and lasting several months or even for life. Conversely, in secondary infection, in the body, amnestic IgG had been formed so that anti-dengue IgG was detected high in the acute phase and could last up to 10 months or even for a lifetime [12, 14–16, 18, 21].

Most of the serological profile was positive IgM and positive IgG. The response of IgG formation could occur quickly before or concurrently with the production of IgM and would be the dominant immunoglobulin isotype in secondary infection. Serological profile of negative IgM, positive IgG was interpreted as secondary infection with the possibility of anti-dengue IgM which had not yet been produced or patients with a history of secondary infection in the past and had been now cured. If clinical and other tests supported DVI, negative IgM could occur because the concentration of anti-dengue IgM in secondary infection was significantly lower than primary infection. At the same time, amnestic IgG rose sharply and showed positive IgG profile. However, if it appeared in patients who had recovered in secondary infection, anti-dengue IgM only lasted 14 days and then was not detected, whereas anti-dengue IgG could last for a lifetime [12].

Profile of positive IgM and negative IgG showed primary or secondary infection, but anti-dengue IgG had not yet been produced because anti-dengue IgG had not yet formed in the critical phase (day 3-5 of fever) [22]. Positive seroconversion of anti-dengue IgG occurred in the convalescence phase (fever 7 days or more). Serological profiles of negative IgM, negative IgG indicated the possibility of patient not infected with DENV or antibodies not yet been produced so that a serological examination was needed in the healing phase to see positive seroconversion of anti-dengue IgM, IgG anti-dengue [12].

The sensitivity of IgG anti-dengue of both rapid tests tended to be high, but the sensitivity of IgG anti-dengue STANDARD Q compared with RT-PCR or NS1 Ag Dengue was only 68%. High anti-dengue IgG sensitivity could be used as screening for a dengue vaccination program [23]. The specificity of anti-dengue of both rapid tests IgG was generally lower, which may be due to a history of DVI in the past [18]. The sensitivity of IgM of both rapid tests was low according to the theory that anti-dengue IgM was detected on days 3-5 of fever. Examination of anti-dengue IgM before day 5 of fever was often false negative so that the sensitivity of anti-dengue IgM tended to be low and could increase case fatality rates [11, 18, 21]. The sensitivity and specificity of rapid tests to detect antibodies were also influenced by the quality of the antigen used. Generally, the antigen used was a recombinant DENV envelope protein that tended to lose its antigenic properties such as natural structure and glycosylation pattern, causing false-negative results and decreased sensitivity. Native antigenicity was maintained, and there was no

change in antigen structure when using DENV antigens. Both rapid tests showed no cross-reaction with malaria parasites, leptospirosis, *Hepadnaviruses, Salmonella typhi,* and other disease-causing microorganisms. This was indicated by the specificity of anti-dengue IgM of both rapid tests as much as 100%.

The choice of method was determined by the purpose of the examination, laboratory facilities, skills, costs, and time of sampling [11]. Examination of anti-dengue IgG, anti-dengue IgM alone was not enough to diagnose DVI because anti-dengue IgG could last a lifetime. The concentration of anti-dengue IgM in secondary infection was lower than in primary infection could even be undetected. Negative anti-dengue IgM did not rule out DVI [13, 14, 18, 21, 23, 24]. A combination with the virological examination (NS1 Ag Dengue, PCR) was highly recommended for DVI diagnosis. The combination of NS1 Ag Dengue and anti-dengue IgM could increase the sensitivity and specificity of DVI diagnosis [13, 14, 18]. PCR confirmation was recommended for positive NS1 Ag results, especially when there were cross-reactions and in hyperendemic areas [14, 21]. Direct methods (virus isolation, detection nucleic acid, NS1 Ag Dengue) were used to diagnose DVI in the early stages because the virus was detected in serum, plasma, blood circulation and body tissues in 4-5 days after onset, while the indirect method (anti-dengue IgG, anti-dengue IgM) at the end of acute phase. The accessibility level of DVI laboratory examination was inversely related to the level of confidence. Anti-Dengue IgG and IgM examination had a high level of accessibility with a low level of confidence. Virus isolation, detection of nucleic acids, NS1 Ag Dengue had a high level of confidence (higher sensitivity and specificity than serological examinations) but a low level of accessibility (required complex laboratory technology and special skills) [11].

The limitation of this research was the insufficient number of samples. There were no samples with the DENV 4 serotype. The number of samples with a mixed DENV serotype 1, 3 was small. There was no follow-up or re-serology examination so it was not possible to know the possibility of seroconversion of negative anti-dengue IgG and IgM to become positive. Positive anti-dengue IgM result in the endemic area was sometimes difficult to interpret as DVI because there was possibility that positive anti-dengue IgM was DVI profile eight months ago. Anti-dengue IgA examination was better than anti-dengue IgM to diagnose acute secondary infection because anti-dengue IgA had a short time in circulation 5 16. However, the anti-dengue IgA examination in this research was not yet done.

CONCLUSION

Serological examination of anti-dengue IgG and IgM with rapid test has high level of accessibility but low level of confidence. It is not enough to establish a diagnosis of DVI. A combination with NS1 Ag Dengue and RT-PCR examination is needed.

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AUTHOR CONTRIBUTIONS

MFT contributed at all stages of study include investigation, acquisition data, analysis and interpretation of data, drafting the article and revising it, final approval the version of the published. NZ contributed to investigation, acquisition data, analysis and interpretation data. IGAAEPS, BJW, FH, PW, DH, AR, SNT contributed to investigation, acquisition data, analysis data. A contributed to supervision, conception and design, analysis and interpretation of data, validation, and final approval the version of the published. All the authors have read and agreed to the final manuscript.

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