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Correlation Of Positive IgM or IgG RDT (Rapid Diagnostic Test) Results with CRP (C-Reactive Protein) Levels in Dengue Hemorrhagic Fever Patients

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ABSTRACT

Background: Laboratory diagnosis of Dengue Hemorrhagic Fever includes the IgM & IgG RDT (Rapid Diagnostic Test) examination which differentiates primary and secondary dengue infection. The presence of inflammation in the body caused by the dengue virus needs to be examined for C-Reactive Protein. Methods: This research is an analytical observational study with a cross sectional approach. The sample used is a plasma sample of a patient diagnosed with DHF with a positive IgM or IgG RDT result. Results: Positive IgM RDT results were 6 people (17%) and positive IgG were 30 people (83%). The results of a qualitative CRP study were 24 people (67%) with positive CRP levels. Semi-quantitative CRP average level for positive IgG was 29.33. The results of the Spearman's Rank statistical test obtained a value of p = 0.003 <0.05 which showed a significant result. Conclusion: Clinically it shows that the more positive IgM or IgG RDT results obtained, the higher the CRP level which indicates the severity/inflammation that is formed in the body.

INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is still a major public health problem in Indonesia. DHF is a disease caused by the dengue virus and is transmitted through the bite of a female mosquito or commonly known as the Aedes aegypti mosquito (Oroh et al., 2020).

Symptoms in people affected by DHF usually occur bleeding in the nose, gums, mouth, continuous pain in the pit of the stomach and bruising on the skin. DHF is characterized by fever for 2-7 days accompanied by bleeding manifestations, decreased platelets (thrombocytopenia), presence of hemoconcentration which is characterized by plasma leakage (increased hematocrit, ascites, pleural effusion and hypoalbuminemia) (Kemenkes RI, 2017)

This disease can also be accompanied by atypical symptoms such as headaches, muscle and bone pain, skin rashes or pain behind the eyeballs. Disease transmission in areas affected by dengue cases is due to the large number of eggs, larvae and pupae of the Aedes aegypti mosquito that grow and develop in the water (Oroh et al., 2020).

Dengue fever as an infectious disease, is still a public health problem in NTB Province due to its rapid spread, potential for death and all. Districts/cities have been infected with DHF. The number of dengue cases found in 2021 will be less than the previous year. In 2020 there were 3,919 cases of DHF and decreased by 0.69 times to 2,719 cases in 2021

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with 18 people dying. The most cases of DHF were in East Lombok Regency with 484 cases (Dinas Kesehatan NTB, 2022).

The diagnosis of DHF according to WHO (World Health Organization) can be done by looking at the clinical picture that is typical for DHF (Hidayat et al., 2021). In the acute phase of dengue infection, the method of choice in establishing the diagnosis is IgM antibody serological test as a marker of primary infection (first time) and IgG antibody serological test as a marker of secondary (recurrent) infection. The immune response to primary infection is in the form of IgM antibody production and secondary infection in the form of IgG antibody production (Aziz et al., 2019)

The wide clinical spectrum of dengue infection emphasizes the importance of laboratory tests. One of the laboratory tests that can be used to differentiate primary or secondary dengue infection is the RDT (Rapid Diagnostic Test) method, namely serological examination using the ICT (Immunochromatographic Test) technique with a dipstick that can detect antibodies (IgM or IgG) in serum, plasma. or fresh blood (Saraswati & Mulyantari, 2017).

Examination that can be done to indicate the presence of dengue infection as suspected inflammation is by examining CRP (C-Reactive Protein). CRP levels will increase if trauma, inflammation and infection occur in the body so that it can be used as a marker of inflammation. Inflammation is a response due to damage to tissues caused by physical trauma, damaging chemicals or microbiological substances (Pramonodjati et al., 2019).

CRP examination can also be used to determine inflammation caused by a viral infection such as dengue or due to a bacterial infection such as typhoid. This can help determine the development of the disease and see the effectiveness of the treatment/therapy that has been given by the clinician. Surgical research et al, (2019) yielded a frequency distribution of 66%, namely 33 patients with normal CRP levels in DHF patients aged 3 years and obtained a frequency distribution of 34%, namely 17 patients with CRP levels above normal at 3 years of age (Bedah et al., 2019).

Wangsa & Lestari's research, (2014) provided the results of analyzing data on 33 patients, it was found that the majority of patients were male (75.8%) and the majority of patients were in the age group over 15 years of 21 patients (63.6%) and also obtained 22 patients (66.7%) showing secondary infection while 6 patients (18.2%) showed primary infection (Wangsa & Lestari, 2014)

Previous research has been carried out by Wangsa & Lestari, (2014), namely determining the type of IgM or IgG according to age and type of infection in patients affected by DHF, while the study by Bedah et al, (2019) found that 34% of patients aged 3 years had CRP levels above normal but there has been no further publication on the results of positive IgM or IgG RDTs with CRP levels in DHF patients. so that the novelty in this study not only saw a positive IgM or IgG RDT serological examination in DHF patients but also correlated it with CRP levels in DHF patients. Therefore, researchers are interested in conducting research on "Correlation of positive IgM or IgG RDT (Rapid Diagnostic Test) results with CRP (C-Reactive Protein) levels in Dengue Hemorrhagic Fever patients".

MATERIALS/METHOD

This study uses Analytical Observational. The samples used were 36 samples. This research was conducted from January to February 2023. This research used the Probability

Sampling technique with the Simple Random Sampling method. Examination in this study used the RDT (Rapid Diagnostic Test) method, namely a serological examination using the ICT (Immunochromatographic Test) technique with a dipstick that can diagnose more quickly which detects antibodies (IgM or IgG) in serum, plasma or fresh blood and on CRP examination using the agglutination method latex. Data analysis of the results of this examination was carried out using the SPSS (Statistical Package For Social Sciences) program with the Non-Parametric Spearman's Rank test.

RESULTS

This study aims to determine the correlation of positive IgM or IgG RDT (Rapid Diagnostic Test) results with CRP (C-Reactive Protein) levels in Dengue Hemorrhagic Fever patients. The research sample consisted of 36 samples from plasma samples that had been collected based on the results of a positive IgM or IgG RDT examination in DHF patients, then CRP was examined using the latex method to determine the levels of CRP using a qualitative method (to determine positive/negative) and then continued with the CRP method. semi-quantitative (for determining levels/titers). The results obtained from a positive IgM or IgG RDT examination with CRP levels in DHF patients were processed to determine whether or not there was a correlation between the two variables.

Table 1. RDT (Rapid Diagnostic Test) Examination Results in Dengue Hemorrhagic Fever Patients and CRP Level Data

	Sample Code	Dengue Hemorrhagic Fever Examination			
		IgM (+)	IgG (+)	CRP levels	
				Qualitative	Semi Quantitative
1.	QH24		√	Positive (+)	12
2.	MA24	√		Negative (-)	0
3.	BU27		√	Positive (+)	96
4.	MU27		√	Positive (+)	12
5.	AK27		√	Positive (+)	12
6.	AL27	√		Negative (-)	0
7.	SA30		√	Positive (+)	12
8.	FA30		√	Negative (-)	0
9.	MI30		√	Negative (-)	0
10.	SA31		√	Positive (+)	96
11.	RE31		√	Positive (+)	12
12.	HE1		√	Positive (+)	12
13.	KA1	√		Positive (+)	24
14.	TA1		√	Positive (+)	96
15.	MR2		√	Positive (+)	12
16.	DA3		√	Positive (+)	12
17	LA3	√		Negative (-)	0

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18.	MA3		√	Positive (+)	24
19.	KA6		√	Negative (-)	0
20.	VA6		√	Positive (+)	96
21.	AZ8		√	Positive (+)	32
22.	IR 8		√	Positive (+)	24
23.	LU9	√		Negative (-)	0
24.	LI10		√	Positive (+)	12
25.	IS10		√	Negative (-)	0
26.	MA11		√	Positive (+)	24
27.	DR13		√	Positive (+)	12
28.	GE13		√	Negative (-)	0
29.	YU13		√	Positive (+)	32
30.	NI13		√	Positive (+)	192
31.	AN14	√		Negative (-)	0
32.	AZ14		√	Positive (+)	24
33.	NI15		√	Negative (-)	0
34.	MJ15		√	Negative (-)	0
35.	AL16		√	Positive (+)	12
36.	IN22		√	Positive (+)	12
	Number/Percentage of Negative Results (-)	30 (83%)	6 (17%)	12 (33%)	12 (33%)
	Number/Percentage of Positive Results (+)	6 (17%)	30 (83%)	24 (67%)	24 (67%)

Information:
Positive IgM value (+) : the appearance of a line on the RDT IgM strip test well Negative IgG value (-) : the appearance of a line on the RDT IgG strip test well C – Reactive Protein Level : <6 mg/L

Based on table 1 it shows that the number of positive IgM RDT samples in patients infected with DHF was 6 people (17%) and continued for Qualitative CRP examination with positive results of 1 person then the remaining 5 people with negative results, After that it was continued with Semi Quantitative CRP examination which produced the highest agglutination at 1:4 dilution which is equivalent to 24 levels in the results of the Semi Quantitative CRP examination.

The number of positive RDT IgG samples in patients infected with DHF was 30 people (83%) and continued for Qualitative CRP examination with positive results of 23 people and the remaining 7 people with negative results. dilution of 1:32 which is equivalent to the level of 192 and at the lowest agglutination at a dilution of 1:2 which is equivalent to the level of 12 on the results of the Semi Quantitative CRP examination. The number of Qualitative CRP examination results that were examined in patients infected with DHF were 12 people (33%) with negative results resulting in levels <6 mg/L while 24 people (67%) with positive results resulting in levels >6 mg/L.

DISCUSSION

Of the 36 samples obtained in this study, 6 people (17%) had positive IgM results and 30 people (83%) had positive IgG results. The results of this study are in line with the results of the study by Wila & Nusa (2020) with the results of serological tests with the research title Clinical Features and Immune Responses of Dengue Hemorrhagic Fever Sufferers at Lindi Mara Christian Hospital, East Sumba From January to December 2018 as many as 10 people (19, 2%), was a primary infection (positive IgM) indicating that it was the first time infected with dengue virus and there were 42 people (80.7%) secondary infections (positive IgG with positive or negative IgM) (Wila & Nusa, 2020).

The results of Putri & Nilapsari's research (2015) with the results of serological tests on the research title Overview of Dengue Rapid Test Results Based on Clinical Phase and Thrombocytopenic Events in Dengue Fever Patients at Al-Ihsan Hospital Bandung Period 2015 showed that most patients experienced secondary infections, namely with IgM results & IgG positive 66 people (52.8%) and positive IgG results in 20 people (22.4%) while the remaining 28 people (22.8%) were positive IgM (primary infection) (Putri & Nilapsari, 2015).

From the results of studies published in several journals, the average outcome of secondary dengue infection was found to be the most common, because people who had been previously infected with dengue with the same antibody, namely IgG, were reinfected by the same virus from a different serotype. Therefore, it causes more patients who are infected with positive IgG (secondary infection) than patients who are IgM positive (primary infection), the same as the results of previous studies, namely that there are more positive IgG patients than positive IgM. The examination that can be done to indicate the presence of dengue infection as suspected inflammation is by examining CRP (C-Reactive Protein).

The results of the study related to CRP levels were obtained from the results of Qualitative CRP examination which had been carried out on 12 patients infected with DHF with negative results yielding levels
<6 mg/L while 24 people (67%) with positive results yielding levels >6 mg /L, then proceed with a Semi Quantitative CRP examination for positive IgM resulting in the highest agglutination at a 1:4 dilution which is equivalent to 24 levels in the Semi Quantitative CRP examination results while a Semi Quantitative CRP examination for positive IgG produces

the highest agglutination at a 1:32 dilution which equivalent to 192 levels and at the lowest agglutination at a 1:2 dilution which is equivalent to 12 levels.

The results of this study are different from the research conducted by Bedah et al (2021) with the results of the CRP study entitled C-Reactive Protein (CRP) Response and Blood Sedimentation Rate (ESR) as Inflammatory Markers in Covid-19 Patients who obtained high CRP results. above the normal value (>0.5 mg/dL) which is 92.85% in 65 patients (Bedah et al., 2021).

In a study conducted by Aini et al (2020) with CRP results in the research title Relationship Between Blood Sedimentation Rate (ESR) and C-Reactive Protein (CRP) Levels in Tuberculosis (TB) Patients who obtained results from TB patients with smear examination results positive had an average CRP level of 36 mg/L, TB patients with positive smear results had ESR levels that showed abnormal results, while TB patients whose smear results were negative had abnormal ESR levels but had normal CRP levels of 6 people (100 %) (Aini et al., 2020).

CRP levels can be affected by the severity of the disease, as previously stated that CRP levels will increase in a relatively short time after an acute inflammatory reaction or damage occurs and decrease rapidly when the stimulus has disappeared, but will continue to increase if the stimulus continues (Purwanto & Astrawinata, 2019).

This is in accordance with the results of a study conducted by Angriany (2021) which stated that the median CRP level in severe cases was 96.15 (4.9-436.6) while non-severe cases was 3.35 (0.02-263.1) with The AUC area on examination of CRP levels for the degree of COVID-19 was 87.3%. Even though the research is about CRP in COVID-19, this data can be used because it is still a viral infection. However, it is necessary to carry out further research on the relationship between CRP levels and the severity of DHF (Angriany, 2021).

In line with the CRP examination if the IgM and IgG examination can also be a predictor of the severity of a disease. The bond between antibodies and dengue virus antigens can trigger the appearance of cytokines which cause increased vascular permeability resulting in plasma leakage. If plasma leakage occurs continuously, it has the potential to cause dengue shock syndrome. In addition, IgM and IgG examinations can also help diagnose DHF if the complaints experienced by the patient and the investigations carried out do not meet WHO criteria. These antibodies can last longer in the body so that they can be a marker for a history of previous infections (Satriadi et al., 2020).

So automatically also in the acute inflammatory response, the increase in the concentration of components will vary according to the cause. Thus DHF patients can also have different CRP levels. This variation suggests that acute phase protein production is dependent on differences in specific cytokines and the pathophysiology of the underlying cause. Therefore CRP can be used as a diagnostic tool in acute fever that is affordable, fast and inexpensive (Bedah et al., 2019).

It can be seen that the more positive IgM or IgG RDT results, the higher the CRP level that is formed, but in the research that has been done, positive IgG results are more dominant. The results show that the average patient with positive IgG RDT results at Mataram City Hospital is included in secondary infection from the results of this study and the highest agglutination result was obtained at a dilution of 1:32 which is equivalent to a level of 192 indicating the severity/inflammation that occurs in the body in patients is quite high (but not always with high dilution/titers on average with dilution ½ which is equivalent to the 12 level obtained from the CRP results) therefore not all positive IgM or IgG RDT results are positive CRP results because there are also negative results out of 36 samples obtained 24 people are positive for CRP and 12 people are negative from the results that have been done.

The limitation of the research that has been done is that this research only examined CRP using the qualitative & semi-quantitative latex agglutination method, so it cannot know CRP levels with certainty. This study also only looked for a correlation of positive IgM or IgG RDT results with CRP levels in DHF patients without differentiating gender, age, nutritional status, and degree of severity, and did not differentiate positive IgM or IgG with the length of time of fever and DHF infection, so it could not be to know the variation and the effect of the results of the examination of some of these parameters on the positive IgM or IgG RDT results with CRP levels in DHF patients.

CONCLUSIONS

From the results of research that has been carried out clinically, it shows that the more results obtained from positive IgM or IgG RDT examinations, the higher the CRP level which indicates the severity/inflammation that is formed in the body.

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