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The Relationship of Fever Onset with NS1 Examination Results, IgM, and IgG in Dengue Hemorrhagic Fever Patients

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Abstract

Fever onset represents the average number of days from the beginning of fever symptoms to the time when IgM and IgG examinations are conducted. Determining the right timing for these examinations can significantly impact their accuracy. In November 2021, there was a notable surge in cases of Dengue Hemorrhagic Fever at the Karawang Health Center, Sukabumi. This study aimed to investigate the relationship between the duration of fever and the results of dengue antigen and antibody tests. The research employed a descriptive analysis with a cross-sectional approach, and a sample of 50 individuals was gathered through consecutive sampling. The data was then analyzed using the Chi-Square test. The study revealed a positive correlation between the duration of fever and the outcomes of the NS1 and IgG Dengue examinations ($p < 0.05$), highlighting the significance of timing when conducting these tests. NS1 was predominantly detected within the first three days of fever, while IgG showed reactivity after more than five days of fever. These findings underscore the importance of timing when conducting these tests and interpreting their results.

Keywords: dengue hemorrhagic fever, duration of fever, IgG dengue, IgM dengue, NS1

Original Research Article

INTRODUCTION

Dengue hemorrhagic fever (DHF) is caused by arbovirus with the help of the mosquito *Aedes aegypti*. Incident of DHF is predicted to rise and spread to wider areas due to climate change, behavioral change, economic rise, and clean water availability. Until now, there are no specific drugs and vaccines are not widely available (Gusti et al., 2017). A lack of sensitive diagnostic methods in the early phase of the illness is one of the challenging problems in clinical practices (Luvira et al., 2023; Pramata et al., 2020).

World Health Organization (WHO) predicted annually there would be 100-400 million cases of DHF globally. In 2020, as reported by the Minister of Health, Indonesia recorded 95,893 cases of DHF, resulting in 661 fatalities. These cases were distributed across 472 cities and districts within 34 provinces, with mortality cases reported in 219 of these cities and districts. The incidence rate (IR) reached 49 per 100,000 people (Rahmi et al., 2019; Sumampouw, 2020).

During 2021, there was a surge of Dengue Hemorrhagic Fever cases at the Karawang Health Center, Sukabumi up to 38%. The highest number of dengue cases occurred in November while in December, the increase was 34%, with a concerning 29% of cases resulting in fatalities.

Early detection should be done to avoid worsening clinical conditions. Non-structural protein 1 antigen (NS1) examination can be performed early as it circulates in blood with high concentration. NS-1 antigen is a glycoprotein and has the ability to replicate the virus (Ndiaye et al., 2023; Pandaibesi, 2017; Rahmi et al., 2019).

Dengue infection stimulates specific antibody production and cellular immune response. IgM and IgG antibodies vary based on the onset of fever. Fever itself is a body mechanism to battle infection by activating the immune system.

A study by Puspitasari in Soetomo Hospital, Surabaya, showed the highest concentration of NS-1 antigen could be seen in fever day 2 until it lowered and was non-reactive before or simultaneously to decreasing body temperature on day 5 (Puspitasari et al., 2017). In 2021, there was a significant rise in DHF cases in Karawang Health Center, Sukabumi, and its peak was in November with a 38% rise and December with a 34% rise and 28% mortality case.

NS1 antigen, IgM, and IgG examination related to the onset of fever could optimize the result. The onset of fever was defined as the average number of days from the day the fever appeared to the day NS1, IgM, and IgG were examined (Libraty et al., 2002; Santos et al., 2020). High IR and Case Fatality Rate (CFR) of DHF in Indonesia related to the onset of fever as the main symptom of the disease motivated the writer to study this topic.

Diagnosis of infection during the first week of fever is extremely important in the clinical management of the patient and in preventing potential outbreaks. The purpose of this study was to determine the relationship between fever duration and dengue antigen and antibody test results, mainly at Karawang Health Center, Sukabumi.

MATERIAL AND METHODS

The study was a descriptive-analytic study. Primary data such as laboratory results NS1, IgM, and IgG Dengue were collected. The study was held in May- July 2022 in Laboratory Karawang Health Center, Sukabumi. Samples were taken from patients who had pathognomonic symptoms of DHF. We used purposive sampling which the process was decided by the researcher. We then performed NS1, IgM, and IgG examinations on the samples. The inclusion criteria were positive results of NS1, IgM, and IgG Dengue examination. The exclusion criteria were a sample from patients with co-infection or comorbid disease which could misinterpret the main results, for example, typhoid fever.

We used rapid test dengue combo *Indec Diagnostic* which NS1, IgM, and IgG Dengue were examined simultaneously. Baseline tests were performed when a patient came to the health center. On the 5th day of fever, we re-examined the tests. Samples were blood plasma to perform the NS1

test and 15 minutes of centrifugated serum for IgM and IgG Dengue. We collected 50 samples. Data was analyzed using IBM SPSS 25. We performed a Chi-Square analysis to prove the correlation among days of fever, NS1, IgM, and IgG Dengue

RESULTS

Table 1. Respondent’s Demography Data

Variable	Frequency	Percentage (%)
Gender		
Male	19	38%
Female	31	62%
Age (years old)		
0-5	3	6%
6-11	15	30%
12-16	2	4%
17-25	7	14%
26-35	9	18%
36-57	14	28%
Baseline Days of Fever		
1 day	6	12%
2 days	23	46%
3 days	21	42%
Baseline NS1		
Reactive	47	94%
Non-Reactive	3	6%
Baseline IgM		
Reactive	3	6%
Non-Reactive	47	94%
Baseline IgG		
Reactive	0	0%
Non-Reactive	50	100%
Follow Up Days of Fever		
5 days	44	88%
6 days	4	8%
7 days	2	4%
Follow Up NS1		
Reactive	0	0%
Non-Reactive	50	100%
Follow Up IgM		
Reactive	4	8%
Non-Reactive	46	92%
Follow Up IgG		
Reactive	48	96%
Non-Reactive	2	4%

Based on Table 1, we collected 50 patients. Out of all patients, 62% of them were females and most of them were children 6-11 years old (30%). At the baseline, most of them had already experienced fever for 2 days (46%), reactive NS1 (94%), non-reactive IgM (94%), and non-reactive IgG (100%). Five days

later, we re-examined all the tests. All of them were non-reactive NS1, 92% of them were non-reactive IgM and 96% were reactive IgG.

We performed a Chi-Square test to analyze the correlation between days of fever to NS1, IgM, and IgG Dengue examination. Table 2 illustrates that among the 50 patients who experienced a three-day fever, there was a positive reaction to the NS1 test. Conversely, patients with a fever lasting more than five days did not show a reaction to the NS1 test. A Chi-Square test revealed a statistically significant correlation between the duration of fever and the outcome of the NS1 dengue examination ($p < 0.05$).

Table 2. Correlation Days of Fever to NS1 Dengue Examination

Days of Fever	NS1		Total	<i>p- value</i>
	Reactive	Non- Reactive		
3 days	47	3	50	0.0001
>5 days	0	50	50	

Table 3 outlines that among the 50 patients experiencing a three-day fever, the majority exhibited a positive reaction to the IgM test, while all patients with a five-day fever did not. However, a Chi-Square test indicated that the duration of fever was not significantly correlated with the outcome of the IgM dengue examination.

Table 3. Correlation Days of Fever to IgM Dengue Examination

Days of Fever	IgM		Total	<i>P value</i>
	Reactive	Non- Reactive		
3 days	3	47	50	0.695
>5 days	4	46	50	

Table 4 indicates none of the patients with a three-day fever exhibited a reaction to IgG, whereas the majority of patients with a fever lasting more than five days tested positive for IgG. The Chi-Square test results revealed the duration of fever was not significantly correlated to the outcome of the IgG dengue examination.

Table 4. Correlation Days of Fever to IgG Dengue Examination

Days of Fever	IgG		Total	<i>P value</i>
	Reactive	Non- Reactive		
3 days	0	50	50	0.0001
>5 days	48	2	50	

DISCUSSION

The participants were dominated by females (62 %). It was in line with Ngwe Tun's study which was also dominated by females. He stated that females were put at higher risk of getting infected than males (Ngwe Tun et al., 2013). Other studies by Nguyet et al also showed female was put at higher risk. Permatasari proved, based on statistical analysis, that there was a significant correlation between gender and DHF incidence. She stated that females had a chance 3,333x more than males to be infected with DHF (Permatasari et al., 2015).

We collected 0-60 years old participants, mainly 6-11 years old (30%). This is in line with a study by Sudarmo that found more than 5-year-old children or more at higher risk of getting infected as they were actively being outdoors as the reservoir activity (Nguyet et al., 2011) DHF transmission could

spread widely. Generally, all age groups and genders are at risk of getting infected. Prevention programs in residential areas, schools, and workplaces should be held in order to avoid transmission (Anwar et al., 2019; Kurnia, 2022).

NS1 is produced in both membrane-associated and secreted forms and may play an essential role in viral replication. The amount of secreted NS1 (sNS1) in the serum of individuals infected with DENV has been shown to directly correlate with viremia and the pathogenesis of dengue infection (Duong et al., 2011; Library et al., 2002). Our study showed NS1 was mainly reactive at the baseline (94%) and 5 days later was non-reactive (100%). Our study also described different results based on the day NS1 examination. Ahmed and Shobha's research revealed that the efficiency of the NS1 antigen test depended on the onset of fever. On the first day of fever, the sensitivity of the test was 50%, with the highest sensitivity observed on the second day of fever. However, on the third and fourth days of fever, the sensitivity decreased to 71.4% and 75%, respectively. Specificity NS1 antigen dengue reached 100% (Ahmed & Broor, 2014; Khairinisa et al., 2018). We found that days of fever were significantly correlated to NS1 Dengue (p-value = 0,0001). The study did not identify any patients with reactive NS1 after experiencing fever from day 4 to day 7. This emphasizes that NS1 is primarily detected during the acute phase of dengue and becomes non-reactive as the disease resolves (Apriliana et al., 2019; van de Weg et al., 2015). It suggests that NS1 reactivity is highest in the early stages of the disease and decreases as the infection progresses. These findings contribute to our understanding of how the NS1 antigen test can be effectively utilized in diagnosing dengue cases (Ghosh et al., 2022; Mora-Cárdenas et al., 2020). However, some findings stated cross-reactivity between Dengue and Zika virus (Zaidi et al., 2020).

At baseline, IgM was not detected in most participants (97%). Our data showed based on Chi Square analysis, that no correlation occurred between the day of fever and to IgM antibody (p>0.05). Another study held by Agarwal et al., demonstrated IgM, combined with IgG dengue (IgM/IgG ratio), as a laboratory parameter to predict severe infection and dengue shock syndrome, mainly in a secondary infection (Agarwal et al., 2022; Satriadi et al., 2021).

We found most IgG reactive in >5 days of fever, while at baseline mostly were non-reactive. IgM/IgG serologic tests could be used to classify primary and secondary infections (Lei et al., 2022). Primary infection was dengue virus infection without any history of dengue infection, while secondary infection was with prior dengue infection. IgG in primary infection appears slower with low titer thus in some cases, it could not be detected using combo dengue rapid test (Singhal & Kothari, 2020). In this study, 48 participants experienced secondary infection. IgG was detected clearly while IgM was really low so that was not detected by the combo dengue rapid test. Chi-square analysis showed a significant difference between IgG performed on day 3 and day >5 of fever (p-value <0,05). The timing of the serologic test was essential to interpret the result. Day 3-5 of fever is the best time to perform the test since the production of antibodies had been able to detect in the blood. On days 0-2 of fever, there are no hemodynamic changes that are able to be detected. IgG dengue was mostly detected on Day 5 of fever (Liang et al., 2021; Masykur, 2022; Mata et al., 2020; Sharada et al., 2021).

The study's constraint is primarily related to the relatively small sample size of participants. This limitation means that the findings and conclusions drawn from the study may not be as broadly applicable or generalizable as they would be if a larger and more diverse group of participants especially area, were included.

CONCLUSION

We found NS1 and IgG dengue examination to be significantly related to days of fever. NS1 was detected mostly in the first three days of fever while IgG was reactive in more than five days of fever. This showed the importance of timing to perform the tests and their interpretation.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this study

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