

Association Between Anti-Dengue IgM/IgG Serological Profile Results and the Severity of Dengue Infection

Hubungan Hasil Pemeriksaan Profil Serologi Anti-Dengue IgM/IgG dan Derajat Keparahan Infeksi Dengue

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ABSTRACT

Background: Dengue infection is a disease caused by the Dengue virus, which is transmitted by Aedes mosquito vectors and can cause Dengue fever (DF) and even Dengue shock syndrome (DSS).

Objective: The aim of this study was to determine the relationship between serological profiles and the severity of Dengue.

Methods: Variations in IgM and IgG serological profiles distinguish between primary infection (predominantly increased IgM) and secondary infection (decreased IgM and rapid increase in IgG), which are associated with differences in clinical manifestations and the severity of Dengue infection. This retrospective analytical descriptive study was conducted at KRMT Wongsonegoro Hospital with 160 dengue patient samples (period 2021-2022) selected by simple random sampling, followed by data analysis using the Chi-Square and Fisher Exact tests.

Results: The results showed a significant association between anti-Dengue serological tests and severity, with IgM (+), IgG (+), and the combination of IgM (+) IgG (+) each having a p-value <0.05. Patients with IgM (+) had a 4 times higher risk of severe dengue, while IgG (+) increased the risk up to 7 times, and the combination of IgM (+) IgG (+) increased the risk 5 times.

Conclusion: These results confirm that serological profiles can serve as early predictive indicators of severity, thereby supporting early triage and appropriate treatment for high-risk patients.

Keywords: dengue infection, dengue severity degree, IgM IgG serology profile

ABSTRAK

Latar Belakang: Infeksi Dengue merupakan penyakit akibat virus Dengue yang ditularkan oleh vektor nyamuk Aedes dan dapat menimbulkan demam Dengue (DD) hingga Dengue shock syndrome (DSS).

Tujuan: Tujuan dari penelitian ini untuk mengetahui kaitan antara profil serologi dengan derajat keparahan Dengue.

Metode: Variasi profil serologi IgM dan IgG, membedakan infeksi primer (dominan peningkatan IgM) dan infeksi sekunder (penurunan IgM dan peningkatan cepat IgG), yang berkaitan dengan perbedaan manifestasi klinis serta tingkat keparahan infeksi Dengue. Penelitian deskriptif analitik retrospektif ini dilakukan di RSD KRMT Wongsonegoro dengan 160 sampel pasien dengue (periode 2021-2022) yang dipilih secara *simple random sampling* yang selanjutnya dilakukan analisis data menggunakan uji Chi-Square dan Fisher Exact.

Hasil: Hasil penelitian menunjukkan keterkaitan bermakna antara pemeriksaan serologi anti-Dengue dan derajat keparahan, dengan IgM (+), IgG (+), serta kombinasi IgM (+)

IgG (+) masing-masing memiliki nilai $p < 0,05$. Pasien dengan IgM (+) memiliki risiko 4 kali lebih tinggi mengalami severe Dengue, sedangkan IgG (+) meningkatkan risiko hingga 7 kali, dan kombinasi IgM (+) IgG (+) meningkatkan risiko 5 kali.

Kesimpulan: Hasil ini menegaskan bahwa profil serologi dapat berperan sebagai indikator prediktif awal keparahan sehingga mendukung triase dini dan penanganan tepat pada pasien berisiko tinggi.

Kata kunci: infeksi dengue, derajat keparahan dengue, profil serologi IgM IgG

INTRODUCTION

Dengue infection is an infectious disease caused by the Dengue virus (DENV) and is transmitted through the bite of the *Aedes aegypti* mosquito as the primary vector and *Aedes albopictus* as the secondary vector.¹ This disease can cause a wide spectrum of clinical manifestations, ranging from mild symptoms such as dengue fever (DF) to severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). These infections are classified as dengue without warning signs or with warning signs, and severe dengue.² Dengue infection is endemic in tropical and subtropical regions, including Indonesia, with cases increasing during the rainy season (November to May). WHO data shows that the Asia Pacific region has the highest caseload globally, with 451,422 cases reported in Southeast Asia in 2015 (14.11% of the global total), which increased to 658,301 cases in 2019.³⁻⁶ In 2024, the Southeast Asia region recorded a high dengue burden, with more than 1.16 million cases and thousands of deaths reported according to the World Health Organization.⁷

Indonesia has been an endemic country since the first case was discovered in 1968.³ Indonesia has experienced fluctuating dengue incidence in recent years, increasing from 50.8 to 78.9 per 100,000 population in 2015–2016, then decreasing to 27 per 100,000 in 2021. Although Central Java has reduced incidence rates below the national target, the dengue Case Fatality Rate (CFR) remains high at 2.71%, exceeding the national target of 0.7%, indicating that dengue remains a significant health problem in Indonesia.⁸ Indonesia's tropical climate supports the growth of the *Aedes* mosquito vector and the transmission of the Dengue virus through the human-mosquito-human cycle.^{6,9} Dengue virus has four antigenic serotypes (DENV-1 to DENV-4), each of which only provides lifelong immunity against that same serotype.^{4,10}

Reinfection with a different dengue serotype can cause more severe manifestations through Antibody-Dependent Enhancement (ADE), in which antibodies from a previous infection fail to neutralize the new serotype and instead enhance viral replication in monocytes and macrophages. This process increases viral load and triggers immunopathogenic responses leading to vascular leakage, commonly observed in severe dengue infections such as DHF and DSS.¹¹ Clinical manifestations of dengue infection generally appear after an incubation period of 3-14 days. Initial symptoms include acute fever, headache, myalgia, fatigue, anorexia, skin rash, and retro-orbital pain.^{12,13} In DHF, more severe clinical manifestations are found, namely bleeding and a decrease in the number of platelets (thrombocytopenia).^{2,12} DENV will stimulate T-cells to increase cytokine production (TNF- α , IFN-g, and chemokines).^{6,14} Excessive cytokine production will cause tissue damage and plasma leakage, which triggers hypovolemia.¹⁵ Antibody serology testing is generally performed on days 3–5 of fever to support early diagnosis. In primary infection, IgM is the first marker to appear after day 5 of clinical manifestations and is usually found at higher levels than IgG.^{2,16} Conversely, in secondary infections, IgG levels increase sharply while IgM levels begin to decline. This results in a positive IgG result, whether with or without IgM, in secondary infections.^{2,17}

Previous research showed that positive IgM was most often found in grade I DHF, while IgG titers were higher in Dengue shock patients compared to DHF patients without

shock.¹⁸ Research in Bali showed that positive IgG with or without IgM was more common in patients with secondary infections than in patients with primary infections. Furthermore, the IgM/IgG ratio did not differ significantly between patients with dengue shock and those without dengue fever, according to a study at Dr. Kariadi Hospital.¹⁹ However, these findings still show inconsistent results regarding the relationship between serological profiles and clinical severity. Some studies have focused on comparing primary and secondary infections or shock status; however, they have not comprehensively evaluated the association between serological parameters and the full spectrum of dengue infection severity. Early diagnosis of dengue infection is essential for disease control and effective supportive therapy, which can reduce mortality to less than 1%.²⁰ Accurate anti-Dengue serology testing can help health workers increase awareness of the severity of the disease.

Furthermore, limitations in the location and population of previous studies indicate the need for more representative data. Therefore, further research is needed to clarify the role of anti-dengue IgM and IgG serology as predictors of dengue severity and to support dengue management strategies in Indonesia. This study aims to analyze the relationship between anti-dengue IgM and IgG serology and the severity of dengue infection.

METHODS

Study design

The type of research used was analytical with a retrospective design using data from the medical records section of KMRT Wongsonegoro Regional Hospital from August to September 2023.

Data sources and sampling procedures

The study population was Dengue infection patients at KRMT Wongsonegoro Regional Hospital, Semarang City, during the 2021–2022 period. A sample of 160 patients was obtained through simple random sampling based on the formula $N = Z^2 \alpha p(1-p)/d^2$. Inclusion criteria included patients with a clinical diagnosis according to WHO 2012, being treated, and having complete medical record data (gender, age, address, clinical symptoms, diagnosis, serological profile, and blood tests). Exclusion criteria were incomplete or damaged medical records.

Variables of study

The independent variables in this study were the anti-Dengue IgM and IgG serological profiles, and the dependent variable was the severity of the infection. The hypothesis of this study was that there is a relationship between anti-Dengue serology and the severity of Dengue infection.

Measurement and instrument

The research instrument used was the patient's medical record document, which included data on anti-Dengue serological examination results as well as clinical information related to the severity of Dengue infection.

Data collection

Data collection was conducted using a simple random sampling method based on the inclusion and exclusion criteria. The selected data were then entered into Microsoft Excel tables for organization and coding. Subsequently, the data were imported into IBM SPSS Statistics for further statistical analysis.

Ethical consideration

This research has obtained Ethical Clearance issued by the Health Research Ethics Commission (KEPK) of RSD KRMT Wongsonegoro Semarang with Number 001/Kom.EtikRSWN/VII/2023.

Data analysis

The analysis used in this study was the Chi Square and Fisher Exact Tests with SPSS software.

RESULTS

Respondent characteristics

A medical record search revealed that 2,523 cases of dengue infection were diagnosed at KRMT Wongsonegoro Regional Hospital (RSD) during 2021–2022. A total of 160 subjects meeting the inclusion and exclusion criteria were selected through simple random sampling. Univariate analysis was performed on all variables, with the results presented in Table 1 and Figure 1.

Table 1. Characteristics of Respondent

Variables	n(%)	Mean ± SD
Gender		
Male	78 (48.8)	
Female	82 (51.3)	
Age		15.78 ± 13.73
Residential area		
Tembalang	71 (44.4)	
Pedurungan	20 (12.5)	
Genuk	11 (6.9)	
Candisari	5 (3.1)	
Gayamsari	2 (1,3)	
Banyumanik	2 (1,3)	
Gunungpati	1 (0.6)	
Semarang Barat	1 (0.6)	
Semarang Tengah	1 (0.6)	
Luar Semarang	44 (27.5)	
Serological profile		
IgM (-), IgG (-)	29 (18.1)	
IgM (+), IgG (-)	15 (9.4)	
IgG (+), IgM (-)	60 (37.5)	
IgM (+), IgG (+)	56 (35.0)	
Increased Hb	42 (26.3)	
Increased Ht	52 (32.5)	
Thrombocytopenia	145 (90.6)	
Degree of severity		
DD	80 (50.0)	
Grade I DHF	28 (17.5)	
Grade II DHF	30 (18.8)	
Grade III dengue fever	8 (5.0)	
Grade IV dengue fever	14 (8.8)	
Fever	82 (51.3)	
Headache	50 (31.3)	
Rash	18 (11.3)	
Onset of fever		
0 – 3 days	42 (26.3)	
4 – 5 days	89 (55.6)	
> 5 days	29 (18.1)	

Table 1 shows that of the 160 subjects, the gender distribution was relatively balanced, with 78 males (48.8%) and 82 females (51.3%). The average age of the patients was 15 years, with the majority residing in Tembalang (71 cases; 44.4%).

The most frequently found serological profile was IgM (-) IgG (+) (37.5%). Blood tests showed no increase in Hb in 42 cases (26.3%) and hematocrit in 52 cases (32.5%), while thrombocytopenia was found in 145 cases (90.6%). The most severe degree of fever was DF (80 cases) (50%). The main complaint was fever in 82 cases (51.3%), and 89 patients (26.3%) came to the hospital on the 4th–5th day of fever.

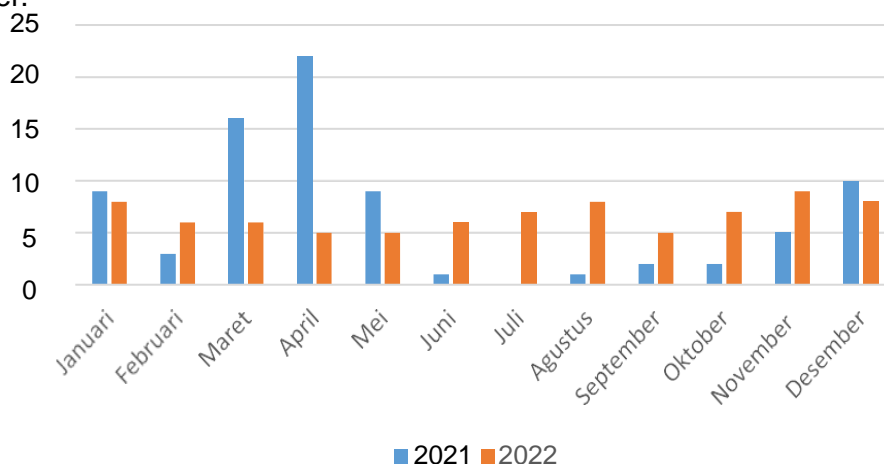


Figure 1. Monthly diagram of Dengue infection incidence.

Figure 1 shows that the highest number of Dengue infections occurred in April 2021, with 22 cases (27.5%), and in November 2022, with 10 cases (11.25%).

Table 2. Relationship of Anti-Dengue Serology to the Severity of Dengue Infection.

Serological profile	Degree of Severity		p	PR	95% Confidence Interval	
	Severe Dengue n (%)	Dengue without/with warning signs n (%)			Lower	Upper
IgM (+)						
Positive	17 (23.9)	54 (76.1)	<0.001*¥	4,262	1, 653	10,988
Negative	5 (5.6)	84 (94.4)				
IgG (+)						
Positive	21 (17.9)	95 (82.1)	0.009*¥	7,966	1,104	57,443
Negative	1 (2,3)	43 (97.7)				
IgM (+), IgG (-)						
Positive	1 (6.6)	14 (93.4)	0.696^	0.406	0.067	3,185
Negative	21 (14.5)	124 (85.5)				
IgM (-), IgG (+)						
Positive	5 (8.3)	55 (91.7)	0.123¥	0.490	0.191	1,260
Negative	17 (17)	83 (83)				
IgM (-), IgG (-)						
Positive	0 (0)	29 (100)	0.015*^	-	-	-
Negative	22 (16.7)	109 (83.3)				
IgM (+), IgG (+)						
Positive	16 (28.5)	40 (71.5)	<0.001*¥	4,952	2,054	11,942
Negative	6 (5.7)	98 (94.3)				

Description: * Significant (p < 0.05); ¥Chi-Square Test ^Fisher's Exact Test

The results of the Chi-Square and Fisher's Exact tests in Table 2 show a significant association between single IgM and IgG serological profiles with the severity of Dengue

infection, with a p-value < 0.05. The prevalence risk value of 4.262 indicates that patients with IgM (+) have a 4.2 times higher risk of experiencing severe dengue, while patients with IgG (+), with a prevalence ratio value of 7.966, have a 7.7 times higher risk than patients with IgM (-) or IgG (-). The combination of IgM (+) and IgG (+) serology with a value (prevalence ratio = 4.952) also increases the risk of Dengue severity by 4.952 times.

The relationship between complete blood count results and the severity of dengue infection

Table 3. The Relationship Between Increased Hemoglobin, Hematocrit, and Platelets and the Severity of Dengue Infection

Blood Test	Degree of Severity		p	PR	95% Confidence Interval	
	Severe Dengue n (%)	Dengue without/with warning signs n(%)			Lower	Upper
Increased Hb						
Yes	13 (59.1)	29 (21)	<0.001*¥	4,058	1,872	8,796
No	9 (40.9)	109 (79)				
Increased Ht						
Yes	2 (9.1)	50 (36.2)	0.012*¥	0.208	0.050	0.855
No	20 (90.9)	88 (63.8)				
Thrombocytopenia						
Yes	21 (95.5)	124 (89.9)	0.696^	2,174	0.314	15,032
No	1 (4.5)	14 (10.1)				

Description: * Significant (p < 0.05); ¥Chi-Square Test ^Fisher's Exact Test

Increased hemoglobin levels showed a significant association with the severity of Dengue infection (p<0.001) based on Table 3, with a 4.0 times greater risk (PR=4.058) of experiencing severe dengue compared to normal levels. A relative risk of more than 1 indicates that increased hemoglobin occurs more frequently in severe dengue than in dengue without/with warning signs. Increased hematocrit was also significantly associated (p=0.012) (p<0.05); however, increased hematocrit tended to occur more frequently in Dengue without/with warning signs, as indicated by a relative risk value of less than 1. In contrast, thrombocytopenia did not show a significant association with severity (p=0.696).

DISCUSSION

Characteristics of research subjects

The gender distribution in this study showed a relatively equal proportion of males and females, consistent with several studies that reported no significant difference in susceptibility to Dengue infection based on gender.^{21,22}The average age of Dengue infection patients in this study was 15 years, in line with the results of research conducted at Sanglah General Hospital in 2016 which reported an age range of 5-18 years in Dengue infection patients as well as other studies which showed a dominance of cases in the 4-23 year age group.²³

The timing of dengue infections in this study showed a peak in April 2021 with 22 cases (27.5%) and November 2022 with 10 cases (11.25%). This trend aligns with data from the Central Java Statistics Agency, which recorded high rainfall from November to May in 2021-2022.²⁴ The incidence in that month is closely related to the rainy season,

temperature, mosquito breeding sites, vector fluctuations, and differences in physiographic conditions, which cause the peak of the endemic to vary.²⁵

The majority of the study subjects came from the Tembalang District. This indicates that Tembalang is an area susceptible to dengue infection. KRMT Wongsonegoro Regional Hospital is located in Tembalang District, allowing for higher patient mobility. Data from the Semarang City Health Office for 2021-2022 shows that one of the sub-districts in Tembalang, Kedungmundu, had the highest incidence rate compared to other sub-districts.²⁶

The description of the results of the IgG and IgM serological profile examination is mostly IgG (+), IgM (–) which shows that most patients infected with Dengue have secondary infections according to research conducted at Lewoleba Regional Hospital.³ Similar results were also found in research conducted at Sanglah General Hospital.²⁷ Likewise, research conducted in Denpasar showed that around 33 samples (92%) of 50 samples showed secondary infections.²⁸

A complete blood count (CBC) showed elevated hemoglobin in 42 cases (26.3%), suggesting that elevated hemoglobin levels are not always present in dengue infection. Previous studies have also reported a normal mean hemoglobin level (12.3 g/dL). Elevated hematocrit was identified in 52 cases (32.5%), indicating that most patients did not experience clinically significant hemoconcentration. This finding is consistent with a study at Lewoleba Regional Hospital, which showed hematocrit values within normal limits without any indication of significant plasma leakage.³ In contrast, thrombocytopenia was found in 145 cases (90.6%). This is consistent with research conducted at Dr. H. Abdul Moeloek Regional Hospital, where the majority experienced thrombocytopenia.²⁹

The majority of dengue patients treated at KRMT Wongsonegoro Regional Hospital were diagnosed with dengue fever, accounting for 80 out of 160 cases (50%). This predominance of cases may be influenced by the distribution of circulating DENV serotypes, with infections without warning signs more frequently associated with DENV-1 and DENV-3 serotypes.^{13,30}

Fever is the most dominant clinical manifestation, consistent with a study in Pakistan that reported fever in all subjects. This condition is triggered by DENV replication, which activates macrophages and phagocytes, increasing the release of TNF- α , IL-1, and IL-6, which stimulate prostaglandin production in the hypothalamus and induce a pyrogenic response.³¹

In this study, the majority of patients came to the hospital after experiencing fever for 4-5 days, consistent with the findings at Lewoleba Regional Hospital, which showed the most frequent onset of fever on the 5th day.³ The febrile phase will last for 3-7 days with clinical symptoms of sudden high fever and sometimes biphasic, thus encouraging patients to seek help at health facilities.⁶

The Relationship of Anti-Dengue Serology Test Results to the Severity of Dengue Infection

This study shows that IgM and IgG serological profiles are significantly associated with the severity of dengue infection, with some combinations increasing the risk of severe dengue by 4.2–7.9 times compared to dengue with/without warning signs. This finding is in line with studies reporting a significant correlation between IgG titers and severity, although other studies have found no significant association between IgM and IgG and severity. Furthermore, some studies have shown that IgM is more sensitive for diagnosis, while IgG correlates with severe dengue symptoms.¹⁸

Dengue antibodies have two antagonistic roles: they act as a protective factor against DENV infection and trigger viral replication through the Antibody-Dependent Enhancement (ADE) mechanism. A positive IgM generally indicates a primary infection,

with a sharp increase in IgM followed by IgG after day 10. Conversely, secondary infections experience a more rapid and higher increase in IgG.³²

A study in Thailand showed that plasma leakage correlates with the presence of afucosylated IgG. Physiologically, most IgG is fucosylated at the N-linked glycan in the Fc region, which decreases affinity for the FcγRIII receptor. Conversely, afucosylated IgG has a higher affinity for FcγRIII, thereby increasing DENV internalization and triggering antibody-dependent enhancement (ADE), especially in secondary infections. In these conditions, antibodies from different serotypes bind to the virus and induce the release of proinflammatory cytokines such as IL-6 and IL-8, which contribute to increased viral replication, vascular permeability, and the risk of disease severity. Higher levels of afucosylated IgG in secondary infections are also associated with severe clinical manifestations, including plasma leakage, pleural effusion, and shock.³³

Thus, serological profiles in the form of IgM (+), IgG (+), or a combination of IgM (+) IgG (+) can be considered as early indicators for predicting the severity of Dengue infection. Meanwhile, the combination profiles of IgM (+) IgG (-) and IgM (-) IgG (+) in this study did not show a significant relationship, possibly influenced by the time of sampling, variability in antibody titers, and cross-reactivity with other infections such as COVID-19, Zika, malaria, leptospira, and tick-borne encephalitis.³⁴

The Relationship of Complete Blood Test Results to the Severity of Dengue Infection

Dengue infection severity correlated significantly with increased hemoglobin and hematocrit, but not with thrombocytopenia, likely due to sample size imbalances. This finding aligns with previous research that has confirmed the role of hemoglobin and hematocrit as important parameters in assessing dengue severity.³⁵

The course of dengue infection consists of three phases: febrile, critical, and recovery. The critical phase is characterized by an increase or persistently high hematocrit accompanied by thrombocytopenia. The increase in hematocrit reflects hemoconcentration due to plasma leakage into the extravascular space, triggered by increased vascular permeability through activation of complement C3a and C5a as an immune response to DENV.⁶ In this study, it is not known when the blood tests were performed, which could affect the results of the study.

An elevated hematocrit level in dengue infection indicates hemoconcentration. Hemoconcentration can occur before or after a decrease in platelets. A hematocrit increase of $\geq 20\%$ can be a strong indicator of plasma leakage. This condition can progress to hypovolemic shock and circulatory failure, ultimately worsening the severity of the dengue infection.⁶

This study used clinical data from medical records with an adequate sample size and appropriate statistical analysis to evaluate the relationship between anti-dengue serologic profiles and infection severity. The results indicate that IgM, IgG, and their combination tests have predictive value for the risk of severe dengue, thus potentially being used not only as a diagnostic tool but also as an early indicator of severity to support patient triage and management in endemic areas.

However, limitations of this study include the use of secondary data with varying completeness and the lack of a relationship between thrombocytopenia and disease severity, which may be influenced by variations in the timing and conditions of blood sampling. Therefore, prospective studies with more controlled designs are needed to obtain more comprehensive and accurate evidence.

CONCLUSION

This study demonstrates a relationship between anti-Dengue IgM and IgG serology and the severity of Dengue infection. These findings support the role of IgM and IgG testing in predicting the risk of disease severity, making early serological evaluation crucial to aid management and prevent patient deterioration. Future studies are recommended to use a prospective design with a larger sample size, take into account the time of fever onset, and integrate additional biomarkers such as NS1 antigen and inflammatory markers, to improve the accuracy of predicting the severity of Dengue virus infection.

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