



Prevalence and Risk Factors and Efforts to Reduce Dengue Fever and Dengue Hemorrhagic Fever Infections at PKU Muhammadiyah Gamping Hospital, Yogyakarta

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ABSTRACT

The incidence of Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) has increased sharply in recent decades, making these infections endemic in several parts of the world. The purpose of this study was to analyze the prevalence, risk factors, and efforts to reduce DF and DHF infections at PKU Muhammadiyah Gamping Hospital, Yogyakarta. This study employed an observational cross-sectional design. The study sample consisted of patients diagnosed with DF or DHF at general hospitals in Yogyakarta between January 2019 and December 2023 who met the inclusion and exclusion criteria. Patients with a DF or DHF diagnosis but incomplete data were excluded. Sampling was conducted using a consecutive sampling method, retrieving information from patient data recorded in medical records. The research obtained ethical approval from the PKU Muhammadiyah Gamping Hospital Ethics Committee under permit number 054/KEP-PKU/II/2024. A p-value of 0.005 indicates a correlation between the incidence of DF DHF and liver illness. The value of OR is 4.660. A p-value of 0.006 indicates a correlation between the occurrence of DF DHF and corticosteroid therapy. This study found that the incidence of Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) was correlated with diabetes, hypertension, kidney disease, and asthma/chronic lung disease, which were protective factors. However, liver disease and a history of corticosteroid therapy were identified as significant risk factors. These findings suggest that impaired liver function and long-term corticosteroid use may impair the immune response, increasing susceptibility to dengue infection and its severe manifestations. Therefore, clinical management and prevention strategies should prioritize monitoring of patients with liver impairment or those undergoing corticosteroid therapy, especially in dengue-endemic areas.

INTRODUCTION

The Dengue Virus (DENV) is a small, spherical, single-stranded RNA virus with 10,700 bases. This virus belongs to the genus *Flavivirus* under the family *Flaviviridae*. Other well-known viruses of the genus *Flavivirus* include the West Nile virus, Zika virus, and tick-borne encephalitis virus. Three structural proteins and seven non-structural proteins make up DENV. DENV consists of multiple structural and non-structural proteins that vary among its four serotypes (DEN1–DEN4), influencing infection patterns and disease severity across populations. Each serotype provides lifetime immunity only to itself but not to others. Reinfection with a different serotype, on the other hand, often results in more severe illness due to immune cross-reactivity. The causal serotype is given lifetime immunity upon infection with each serotype, but not the other serotypes. Reinfection with a different serotype, on the other hand, results in serious illness.¹ This serotype diversity explains why dengue remains endemic in many regions, including Yogyakarta, where recurring outbreaks occur almost every year.

Five to seven days after infection, dengue fever symptoms typically appear, and in certain situations, severe dengue fever develops. Fever lasting less than a week, the lack of upper respiratory tract symptoms, and at least two of the following symptoms: general discomfort, muscle or joint pain, headache, fever, or pain behind the eyes as well as gastrointestinal symptoms like vomiting or diarrhea, skin rash, petechiae, a positive tourniquet test, leukopenia, thrombocytopenia, or elevated liver enzymes are the primary criteria for diagnosis. Children and adults experience these symptoms differently.²

Depending on the patient's stage of the infectious process, making a clinical diagnosis of dengue fever can be challenging. There are other viruses that induce disease or disease states that are similar to the range of disease caused by dengue infection, depending on the geographic location of the world. Dengue can first manifest as a moderate "flu-like" fever that is difficult to differentiate from other illnesses such as influenza, measles, Zika, chikungunya, yellow fever, and malaria. Since therapy for dengue-related shock and sepsis-related shock have historically required different treatments, it is imperative to

diagnose the pathogen causing the later manifestation of shock correctly.³

Dengue fever has become endemic in many parts of the world due to increased international travel, and over the past few decades, its prevalence has expanded dramatically. Dengue fever is a major public health issue, with an estimated 100 million infections and 20 to 25,000 deaths annually. Disease outbreaks happen anywhere in the world. After getting dengue hemorrhagic fever (DHF), certain individuals who have already been infected with one subtype of the dengue virus (DENV) experience extreme capillary permeability and bleeding. The defining characteristics are covered in the section that follows, even if the signs and symptoms are similar to those of several viral prodromes.⁴ Yogyakarta Province, where PKU Gamping Hospital operates, consistently records high dengue cases, reflecting both environmental and behavioral risk factors that facilitate mosquito breeding.

Dengue's varied severity is thought to be caused by a process called Antibody-Dependent Enhancement (ADE), while the precise explanation is uncertain. This idea was first proposed in 1964 when a case of severe dengue occurred in a secondary dengue infection. The immune system creates antibodies that can bind and neutralize subsequent infections with the same virus serotype (monologous secondary infection) following a primary infection with a particular dengue virus serotype. However, if a subsequent infection with a different serotype occurs (heterologous secondary infection), the illness will be more severe. Although they can bind the virus, antibodies produced during the initial infection cannot neutralize it. By binding to cells with Fcγ receptors, such as monocytes, macrophages, and dendritic cells, these cross-reactive antibodies can create a virus-antibody complex that opsonizes the virus and promotes its replication. According to Marvianto D, Ratih OD, and Wijaya KFN, this phenomenon is referred to as Antibody-Dependent Enhancement (ADE).⁵

The occurrence of dengue fever is influenced by several factors, including age, nutritional status, vectors presence, residence, environment, breeding and resting places, hanging clothing habits, climate, insect repellent use, profession, attitude and knowledge, and 3M practices.⁶

The physical environment, which includes temperature, humidity, and rainfall; the biological environment, which includes the presence of mosquito larvae and vectors as well as breeding and resting places; community behavioral factors, population density, and the number of mobile residents; and the biogenic factors of mosquito vectors, weather, and climate conditions are risk factors that can impact the rise in the number of DHF cases. Meanwhile, several factors, including the existence of mosquito vectors, might affect the pattern of DHF transmission. The House Index (HI), Container Index (CI), Breteau Index (BI), and Larvae Free Rate (ABJ) are entomological indicators that can be used to analyze these parameters. The high number of *Aedes aegypti* mosquitoes contributes to the increased transmission or spread of DHF.⁷

Therefore, this study aims to analyze the prevalence, risk factors, and ongoing hospital-based initiatives to reduce Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) cases at PKU Muhammadiyah Gamping Hospital, Yogyakarta. By linking virological, environmental, and behavioral determinants with clinical data, this research aims to provide a more comprehensive understanding of dengue control in a hospital context.

MATERIAL AND METHOD

This study used a cross-sectional observational design. The population was inpatients at PKU Muhammadiyah Gamping Hospital, Yogyakarta. The sample consisted of patients diagnosed with Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) and treated at PKU Muhammadiyah Gamping Hospital, Yogyakarta, during a four-year period, from 2019 to 2023, who met the inclusion and exclusion criteria. Inclusion criteria were inpatients at the hospital from January 1, 2019, to December 31, 2023, and patients diagnosed with dengue fever and dengue hemorrhagic fever according to hospital protocol. Exclusion criteria were patients diagnosed with dengue fever and dengue hemorrhagic fever but with incomplete data. Consecutive sampling was used as the sampling technique. A total of 820 samples were obtained. Data were collected from the medical records of patients with DF and DHF. Statistical analysis was performed using multivariate logistic regression. Prior to the study, ethical clearance

and research permit applications were submitted. After the research permit was issued, data were collected from medical records by the medical records staff. The collected data were then processed by the researchers and statistical tests were performed. Ethics approval was obtained from PKU Muhammadiyah Gamping Hospital, number 054/KEP-PKU/II/2024.

RESULTS

The results present the research outputs by describing factual and valid findings in relation to the study objectives, including respondent characteristics and the results of statistical analyses. The data presented in Table 1 describe the clinical characteristics of the study participants, including the presence of liver disease and a history of corticosteroid therapy. Liver disease encompasses conditions such as hepatitis, cirrhosis, fatty liver disease, liver cancer, and liver failure. A history of corticosteroid therapy refers to prior treatment involving corticosteroid agents, which are synthetic compounds that mimic the effects of cortisol, a hormone naturally produced by the adrenal glands located above the kidneys.

Table 1. Characteristics of Respondent

Variabel	n = 820	%
Diabetes		
Yes	107	13.0
No	713	87.0
Hypertension		
Yes	141	17.2
No	679	82.8
Heart Disease		
Yes	30	3.7
No	790	96.3
Asthma/Chronic Lung Disease		
Yes	41	5.0
No	779	95.0
Kidney Disease		
Yes	22	2.7
No	798	97.3
Liver Disease		
Yes	31	3.8
No	789	96.2
Undergoing Chemotherapy		
Yes	2	0.2
No	818	99.8
Undergoing Corticosteroid Therapy		
Yes	70	8.5
No	750	91.5
Occurrence of DF/DHF		
Yes	350	42.7
No	470	57.3

Source: Primary Data, 2024

The statistical test results were obtained through a multivariate analysis using logistic regression, as presented in Table 2. The analysis showed a significant association between liver disease and the incidence of Dengue Fever (DF), with a p-value of 0.005 and an Odds Ratio (OR) of 4.660 (95% CI: 1.577–13.768), indicating that patients with liver disease were approximately 4.7 times more likely to develop DF than those without liver disease. A significant relationship was also observed between a history of corticosteroid therapy and the incidence of DF, with a p-value of 0.006 and an OR of 2.412 (95% CI: 1.295–4.494), suggesting a higher risk of DF or DHF among patients with prior corticosteroid use. Diabetes was significantly associated with the incidence of DF/DHF (p=0.001; OR=0.044; 95% CI: 0.014–0.145), indicating a protective effect. Hypertension also demonstrated a significant protective association with DF/DHF incidence (p=0.001; OR=0.083; 95% CI: 0.040–0.170). Asthma or chronic lung disease was significantly associated with a reduced risk of DF/DHF (p=0.042; OR=0.472; 95% CI: 0.229–0.974). Furthermore, kidney disease showed a significant protective association with the occurrence of DF/DHF (p=0.031; OR=0.240; 95% CI: 0.065–0.880). However, no significant association was found between heart disease and the incidence of DF/DHF (p=0.997).

DISCUSSION

A p-value of 0.005 indicates a correlation between dengue fever (DF) incidence and liver disease. An OR of 4.660 indicates that patients with liver disease are 4.7 times more likely to

develop dengue fever compared to patients without liver disease. A p-value of 0.006 indicates a correlation between dengue fever incidence and a history of corticosteroid therapy. An OR of 2.412 indicates that patients on corticosteroid therapy are 2 times more likely to develop dengue fever compared to patients without a history of corticosteroid therapy. Diabetes mellitus, hypertension, asthma or Chronic Obstructive Pulmonary Disease (COPD), and kidney disease are associated with the incidence of dengue fever and act as protective factors. These conditions need to be compared with conditions in various countries.

The liver is the most commonly affected organ in fatal dengue cases. Hepatitis is the most common feature.⁸ The pathophysiology of liver damage in dengue virus infection remains unclear. Liver damage in dengue is thought to occur due to direct viral toxicity or dysregulated immunological injury in response to the virus. Hepatocytes and Kupffer cells are the primary targets for DENV infection, as demonstrated by biopsies and autopsies of fatal cases. Dengue virus antigens are detected in hepatocytes and Kupffer cells by immunohistochemistry and in situ hybridization, and dengue virus nucleic acid in hepatocytes by PCR. Virus entry into hepatocytes and Kupffer cells is mediated by phagocytosis and receptor-mediated endocytosis. Protein E plays a role in viral attachment. Cells infected by the virus essentially require viral entry and a conducive environment for the invader to grow within the host cell. This property is influenced by the viral strain, serotype, and cell type.⁹

Table 2. Statistical Test Results

Variabel	p	OR	95% C.I.for EXP(B)	
			Lower	Upper
Diabetes	0.001	0.044	0.014	0.145
Hypertension	0.001	0.083	0.040	0.170
Heart Disease	0.997	0.001	0.001	-
Asthma/Chronic Lung Disease	0.042	0.472	0.229	0.974
Kidney Disease	0.031	0.238	0.065	0.880
Liver Disease	0.005	4.660	1.577	13.768
Undergoing Corticosteroid Therapy	0.006	2.412	1.295	4.494

Source: Primary Data, 2024

In addition to existing fluid management for dengue, this immunopharmacological approach is suggested as a treatment option to suppress the immune dysfunction that causes DHF and other dengue complications. The value of steroids in dengue immune pathology cannot be underestimated, and this could open up an entirely new scientific approach and be recommended for the management of the more than 250,000–500,000 patients worldwide who suffer from severe dengue each year. This can be further tested with a double-blind controlled trial using a standard steroid protocol, taking into account the stages of dengue immunopathology. This review article (a) provides an immunological link between dengue and steroid treatment (b) offers scope for corticosteroid-based treatment as an approach for DF and DHF (DSS), (c) provides a better understanding of corticosteroid action in dengue immune pathology, and (d) provides and opens a well-known, entirely new argument for dengue, but with strong scientific evidence, to reconsider the use of steroids for managing dengue and its complications.¹⁰

The virus that spreads the fastest in the world is dengue fever, which is spread by mosquitoes. Along with its rising geographic expansion into new countries and, in this decade, from urban to rural regions, its incidence has climbed thirty-fold during the past fifty years. Approximately 2.5 billion people reside in dengue-endemic nations, and an estimated 50 million cases of dengue are reported each year. WHO and its member states were urged to increase their commitment to dengue in the 2002 World Health Assembly resolution. Dengue is one of the diseases that may qualify as a public health emergency of worldwide concern with public health implications, according to the World Health Assembly's 2005 resolution on the modification of the worldwide Health Regulations. health security as a result of the epidemic's disruption and its international expansion.¹¹

Dengue has spread significantly around the world in recent decades; in 2000, 505,430 cases were reported to the WHO; by 2019, that figure had risen to 5.2 million. The actual number of dengue cases is underreported since the majority of cases are self-managed and mild or asymptomatic. Furthermore, a lot of cases are mistakenly identified as other feverish illnesses. In

2023, more than 80 countries from all WHO regions reported the most dengue cases. Owing to continuous transmission and an unanticipated rise in dengue cases, there have been over 7,300 dengue-related deaths and a record high of over 6.5 million cases since early 2023.¹²

Risk factors for severe Dengue Fever (DF), including bleeding, vomiting, diarrhea, gastrointestinal distress, secondary infection, and intravascular leakage, have been documented to assist clinicians in assessing the likelihood of severe illness. The search for prognostic indicators for severe dengue has been ongoing. Despite the fact that dengue with warning signs is mentioned in the newly updated WHO guidelines, a multicenter investigation revealed that only 10% of people with DF had SD and roughly 30% had WS. A different study found that WS had a sensitivity of 41–99% and a specificity of 59–98% in identifying SD. Some of the numerous possible indicators for SD that have been identified are not conclusive. We carried out this systematic review and meta-analysis to try to identify some relevant prognostic factors and differentiate SD from DF early in the illness.¹³

A total of 129 countries are at risk of dengue fever, with 70% in Asia. There are eight Asian countries with the highest total number of dengue fever cases, including Indonesia. Dengue fever cases in Southeast Asia increased by 46% from 2015 to 2019, and the high numbers in some parts of the region are more due to the unavailability of appropriate treatment. Indonesia is the country that has always been at the top of the list for dengue fever cases during the period 1990-2015 with reference to the Incidence Rate (IR) and Case Fatality Rate (CFR).¹⁴

According to the World Health Organization, there were more than 7.6 million dengue fever cases globally as of April 30, 2024, with 3.4 million confirmed cases, more than 16,000 severe cases, and more than 3,000 fatalities. Dengue cases have sharply climbed worldwide over the last five years; however, this growth is most pronounced in the Region of the Americas, where by the end of April 2024, there were over seven million cases, surpassing the 4.6 million annual record set in 2023. Although not all of them have been officially reported, 90 countries are now known to be experiencing active dengue transmission in 2024.¹⁵

The most prevalent and significant arbovirus illness worldwide is dengue fever (DF), which is brought on by the dengue virus (DENV). Approximately 390 million infections are thought to happen each year, of which 96 million are clinically noticeable. The cycle of the dengue virus includes transmission of the virus between mosquitoes that are common in forests and nonhuman primates, but in the urban transmission cycle, urban-dwelling insects like *Aedes aegypti* keep the virus alive in human populations. DENV is probably going to spread farther as this vector's geographic range grows. A person is likely to be exposed to the virus more than once during their lifetime because there are four different serotypes of DENV (DENV1-4). According to recent models of dengue transmission, 4 million cases result in hospitalization annually, with an estimated global cost of US\$8.9 billion. 6.1 billion people could be affected by DENV transmission by 2080, according to some predictions, as a result of growing urbanization and climatic change that favors the development of mosquito vectors.¹⁶

About 20% of dengue infections result in symptoms, while the infection can also be asymptomatic. After a person is bitten by an infected mosquito, DF usually resolves on its own. A dengue infection in its early stages may manifest as a moderate "flu-like" sickness that shares symptoms with Zika, chikungunya, influenza, and malaria. Dengue can occasionally cause more severe symptoms, such as bleeding and subsequent vascular leaks, in addition to the self-limiting sickness. The WHO revised its guidelines for the clinical care and classification of dengue into two categories in 2009: dengue and severe dengue. The goal of this change is to provide universal, straightforward criteria that will result in a global standard approach to the illness. Even if the updated criteria are more accurate in identifying severe dengue, there are still issues with their use in clinical settings.¹⁷

In this study, 4 large groups of risk factors were found that were widely studied, namely sociodemographic, climatological, environmental, and behavioral. The most widely studied sociodemographic factor with the incidence of DHF in Indonesia is the level of education. Temperature is one of the key and crucial climatic variables in the vector breeding process. The most widely studied environmental aspect

is the mosquito breeding ground. The practice of hanging clothes is the behavioral factor most frequently found to be significant and the one most at risk in the transmission of DHF cases. Out of the 27 research publications that were reviewed, 69.5% of them looked at preventive behavioral factors.¹⁴

From the results of the study, 4 large groups of risk factors were found that were widely studied, namely sociodemographic, place of dwelling, environment and behavior. Sociodemographic factors related to DHF incidence are age. Urban areas are the place of dwelling where most DHF cases are found. The environmental aspect that is widely studied is the type of house. The behavioral factor that is at risk of transmission that is most often found to be significant is the Mosquito Nest Eradication or *Pemberantasan Sarang Nyamuk (PSN)* behavior. Based on a systematic review, the risk factor that consistently has the highest percentage of significance and is most analyzed from 10 articles is the Environment (37.5%).¹⁸

Humans contract dengue fever when bitten by an infected mosquito. Both during the day and at night, mosquitoes bite. To avoid contracting dengue, there isn't a readily accessible vaccine. The best method to prevent dengue fever is to protect yourself from mosquito bites, including applying mosquito repellent, wearing loose-fitting long-sleeved shirts and pants, and taking actions to reduce mosquitoes in and around your home.¹⁹

Since 1968, the Indonesian Ministry of Health (MoH) has implemented nationwide initiatives to prevent and control dengue fever through the Directorate General of Communicable Disease Control. These initiatives include mass larviciding, adult perifocal spraying, and community education on disease control. Despite these efforts at control, dengue has spread geographically and in incidence over time, becoming hyperendemic with several DENV serotypes co-circulating across the country. The nation has seen a number of significant dengue outbreaks.²⁰

A community's members are categorized into various groups according to their degree of expertise and comprehension. The significance of neighborhood-based initiatives in Mexico and Cuba in reducing dengue mosquitoes. In Cuba, the importance of community-based efforts to

eradicate dengue mosquitoes has been made evident through heightened community awareness. Different methods can be used with community involvement to achieve maximal vector population reduction; in Cuba, for instance, a combination of chemical control of *A. aegypti* and community-based programs has produced notable results.²¹

Vector control is the cornerstone of dengue prevention, with measures including insecticide use, elimination of mosquito breeding sites, and larval control having proven effective in reducing mosquito populations (2). However, these interventions require sustained community engagement and may face challenges such as insecticide resistance and logistical barriers in resource-limited settings (3). Recent studies have highlighted the efficacy of community-led initiatives and environmental management in achieving sustainable vector control. For example, (4) emphasized the role of community awareness campaigns in reducing dengue transmission by encouraging behavioral changes to limit mosquito breeding habitats.²²

CONCLUSION AND RECOMMENDATION

The presence of liver disease and a history of corticosteroid therapy are risk factors for DF and DHF. The presence of diabetes mellitus, hypertension, asthma, Chronic Obstructive Pulmonary Disease (COPD), and kidney disease are associated with the occurrence of DF and DHF and act as protective factors. The presence of heart disease is not associated with the occurrence of DF and DHF.

Globally, dengue remains an infectious disease with a high incidence rate, a significant increase in cases over the past two decades, and a significant public health burden, particularly in Southeast Asia, including Indonesia. Risk factors widely studied in the literature include sociodemographic, environmental, behavioral, and climatic aspects. However, the results of this study confirm that certain comorbidities, particularly liver disease and the use of corticosteroid therapy, require greater attention in patient clinical management. DF or DHF prevention efforts must continue to prioritize vector control through mosquito breeding site eradication, public education, and community involvement. This strategy must continue to be implemented because the dengue vaccine is not yet widely available and

treatment is still supportive. Therefore, the results of this study can contribute to strengthening prevention and management strategies for dengue/dengue hemorrhagic fever patients by considering comorbid risk factors.

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AUTHOR CONTRIBUTIONS

K: designed and developed the study, supervised the research process, contributed to data interpretation and analysis, and drafted the manuscript; ABA: contributed to clinical insights and interpretation of medical findings; EL: contributed to study methodology and manuscript editing; YAR: contributed to data collection and interpretation of results; AR: contributed to data collection and preparation of the initial draft of the manuscript. The authors read and approved the final manuscript. K = Kusbaryanto; ABA = Abdurraiyid bin Abdurrahman; EL = Ekorini Listiowati; YAR = Yusuf Alam Romadhon; AR = Aisyah Rosyida.

CONFLICTS OF INTERES

The research is free of conflicts of interest.

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