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Original Research Article

Relationship between the degree of dengue hemorrhagic fever and comorbid in patients at Wangaya general teaching hospital

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ABSTRACT

Background: Dengue fever has become a major international public health problem in recent decades. Clinical manifestations of DENV infection can range from asymptomatic (no symptoms) or mild flu-like syndrome, also known as Dengue Fever (DF), to more severe and life-threatening forms, Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Comorbidities can make the primary disease more severe and worsen the prognosis. The aim of this research is to find out the relationship between the degree of dengue fever and comorbid in inpatients.
Methods: This study used an analytical approach and was conducted at Wangaya Regional General Hospital from January to May 2024. Medical records were the main data source for this study. A total of 425 patient samples were collected based on inclusion and exclusion criteria. The sampling technique used in this study was total sampling that met the inclusion and exclusion criteria. The data was processed using SPSS with the Fisher's Exact Test statistical test.
Results: In the group of dengue fever patients with comorbid hypertension, diabetes mellitus, CVD, and CLD, there is a higher risk of developing DHF than patients with comorbid COPD, CKD, Stroke, HIV.
Conclusion: Dengue fever with hypertension, diabetes mellitus, CVD, and CLD have a higher risk of developing DHF when compared with patients with dengue fever with other comorbidities. This finding helps us in triaging patients with comorbidities who develop dengue fever for specialized care and closer clinical monitoring.

Keywords: Dengue hemorrhagic fever, Diabetes mellitus**,** Chronic obstructive pulmonary disease, Cardiovascular disease, Chronic kidney disease, Stroke, Chronic liver disease

INTRODUCTION

Dengue fever is one of the most common tropical diseases affecting humans. Dengue fever has become a major international public health problem in recent decades. The World Health Organization (WHO) estimates that around 2.5-3 billion people currently live in dengue fever transmission zones. Dengue fever is an acute febrile disease triggered by dengue virus (DENV) infection. DENV is a single positive-stranded RNA flavivirus, a member of the Flaviviridae family. This virus has four main serotypes (DENV-1, DENV-2, DENV-3, and DENV-4).[1] If an infection occurs with 1 serotype, the sufferer has lifelong immunity against that serotype. However, reinfection with another serotype can occur and the second infection increases the risk of more severe dengue fever. Humans contract dengue fever through the bite of DENV-carrying female Aedes mosquitoes, including Aedes albopictus and Aedes aegypti.[2] It is estimated that there are more than 390 million DENV infections per year, of which 96 million have clinical

manifestations of varying degrees of severity and 3.9 billion people in 128 countries are at risk of infection.[3] Over the last 50 years, the incidence of dengue fever has increased 30-fold. DENV epidemics occur every year in America, Asia, Africa and Australia, and also attack travelers from endemic areas. Apart from its impact on public health, this epidemic also has a huge economic impact in the affected countries.[4]

Over a 50-year period, there has been a sharp increase in the annual incidence rate (IR) of dengue fever in Indonesia, from only 0.05 cases per 100,000 people/year in 1968 to 77.96 cases per 100,000 people/year in 2016. DHF IR has experienced a cyclical pattern, with peaks occurring approximately every 6-8 years. The peak incidence occurred in 1973, 1988, 1998, 2009, and 2016. In 2017, there were 59,047 cases of dengue fever and 444 deaths related to dengue fever in Indonesia with an IR of 22.55 per 100,000 people/year and a Case Fatality Rate (CFR) of 0, 75%.[5]

The prevalence of dengue hemorrhagic fever in Bali Province fluctuated between 2015 and 2020. The highest number of dengue fever cases was in 2016 at 20,306 cases and decreased from 2017 to 2019. Cases doubled in 2020, namely 12,173 cases. The endemic areas with the highest prevalence of cases are in Buleleng and Badung Regencies. The highest incidence rate occurred in 2016 at 483/100,000 population, and over the last five years it has not met the national target of 49/100,000 population. The highest CFR figure in 2020 was 0.43%, an increase of 1.5 times during the COVID-19 pandemic.[6]

Clinical manifestations of DENV infection can range from asymptomatic (no symptoms) or mild flu-like syndrome, also known as Dengue Fever (DF), to more severe and life-threatening forms, Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Then WHO in 2011 classified dengue infection into undifferentiated fever, DD, and DHF. DHF itself is divided into degrees I-IV.[7,8]

Comorbid is the term used to describe a person who has many diseases or conditions that affect them simultaneously. Comorbid illnesses are defined as persistent or chronic ailments. Comorbidities can make the primary disease more severe and worsen the prognosis. People who suffer from chronic illnesses will have reduced immune systems, which will leave them more vulnerable to infections and other illnesses. In Indonesia, heart disease, diabetes, hypertension, and obesity are common co-occurring conditions.

The Indonesian Ministry of Health projects that there will be 63,309,620 cases of hypertension in the country in 2021, with a death rate of 427,218. In 2020, the percentage of Indonesians with diabetes was 6.2%, or over 10.8 million cases. In the meantime, Indonesia's obesity rate increased from 19.1% in 2017 to 35.4% in 2018.[9] The aim of this research is to find out the relationship between the degree of dengue fever and comorbid in inpatients.

METHODS

Study place

This research used an analytical approach and was conducted at the Wangaya General Teaching Hospital

Study duration

The study was conducted from January to May 2024.

Sample size

Medical records were the main data source for this research. A total of 425 patient samples were collected based on inclusion and exclusion criteria.

Inclusion criteria

The inclusion criteria were adults (>18 years old) who were treated at Wangaya General Teaching Hospital.

Exclusion criteria

The exclusion criteria were incomplete medical record data.

The degree of dengue fever is classified based on the criteria WHO into DD, grade 1 dengue fever, grade 2 dengue fever, grade 3 dengue fever and grade 4 dengue fever. The comorbidities studied are hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), chronic kidney disease (CKD), stroke, chronic liver disease (CLD), human immunodeficiency virus (HIV).

Data collection

Data collection was carried out meticulously using a standardized data collection form designed for this study. The form was developed after a thorough review of relevant literature and consultation with experts in the field of dengue research. Data were extracted from the electronic medical records of eligible patients, ensuring confidentiality and adherence to ethical guidelines.

Ethical approval

This research had obtained ethical approval from the Wangaya General Teaching Hospital research ethics committee with reference number 000.9.2/3642/RSUDW.

Statistical analysis

The following information was systematically collected for each patient: demographic data, degree of dengue fever and comorbidities. The sampling technique used in this research was total sampling which met the inclusion and

exclusion criteria. Data were processed using SPSS 27 with the Fisher's Exact Test statistical test.

RESULTS

Table 1 provides details of the demographic characteristics of the 410 patients included in the dengue hemorrhagic fever (DHF) study in Bali. There was a slight male predominance, with 56.5% male patients and 43.5% female. This indicates that males have a higher risk of developing DHF, which could be due to work and behavior that cause more frequent exposure to mosquitoes. The most affected age group is <50 year (88.8%) This indicates that DHF primarily affects young adults in Bali. This could be related to factors such as increased outdoor activities, occupational exposures, or differences in immune responses. Based on the presence of comorbid diseases in Table 1, the majority of patients at Wangaya General Teaching Hospital experienced DF is 16 patients, DHF grade 1 is 266 patients, DHF grade 2 is 132 patients, dan DHF grade 3 is 11 patients.

Total DHF patients with comorbid hypertension is 30 patients. The majority of patients with comorbid diseases had DHF grade 2, with 3 patients (10%) experiencing DHF grade 1, 25 patients (83.3%) with dengue fever grade 2, and 2 patients (6.7%) with dengue fever grade 3. Descriptively, it can be concluded that 7% of DHF patients also had hypertension. Based on the results of statistical tests using Fisher's Exact Test, the p-value was <0.001($p<0.05$). Therefore, it can be concluded that the comorbid factor of hypertension has significant relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital.

DHF patients with comorbid diabetes mellitus most frequently experienced DHF grade 2 at 69.2%, DHF grade I at 15.4%, and DHF grade II at 15.4%. Meanwhile, the majority of DHF patients without diabetes mellitus experienced dengue fever at 3.9%, 64% for grade I DHF, 29.9% for grade II DHF, and 2.2% for grade III DHF. Descriptively, it can be concluded that 7% of DHF patients also had diabetes mellitus. Based on the results of statistical tests using Fisher's Exact Test, the p value was <0.001($p<0.05$), so it can be concluded that the comorbid factor of diabetes mellitus had relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital. mDHF patients with comorbid COPD most frequently experienced DHF grade 1 at 52.4%, and DHF grade II at 47.6%. Descriptively, it can be concluded that 5% of DHF patients also had COPD. Based on the results of statistical tests using Fisher's Exact Test, the p value was 0.408 ($p>0.05$), so it can be concluded that the comorbid factor of COPD had no relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital. DHF patients with comorbid CVD most frequently experienced DHF grade 2 at 57.1%, DF at 14.3%, DHF grade I at 14.3%, and DHF grade III at 14.3%. Descriptively, it can be concluded that 1.6% of DHF patients also had CVD. Based on the results of statistical tests using Fisher's Exact Test, the p-value was 0.010 ($p<0.05$), so it can be concluded that the comorbid factor of CVD had relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital.

DHF patients with comorbid CKD most frequently experienced DHF grade 1 and 2 at 50% and 50%, DF at 0%, and DHF grade III at 0%. Descriptively, it can be concluded that 2.3% of DHF patients also had CKD. Based on the results of statistical tests using Fisher's Exact Test, the p-value was 0.645 ($p>0.05$), so it can be concluded that the comorbid factor of CKD had no relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital.

DHF patients with comorbid stroke most frequently experienced DHF grade 2 with 2 patients. Descriptively, it can be concluded that 0.4% of DHF patients also had stroke. Based on the results of statistical tests using Fisher's Exact Test, the p value was 0.219 ($p>0.05$), so it can be concluded that the comorbid factor of stroke had no relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital. DHF patients with comorbid CLD most frequently experienced DHF grade 2 at 61.5%, DHF grade I at 30.8%, and DHF grade III at 7.7%. Descriptively, it can be concluded that 3% of DHF patients also had CLD. Based on the results of statistical tests using Fisher's Exact Test, the p-value was 0.039 ($p<0.05$), so it can be concluded that the comorbid factor of CLD had relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital.

Table 1: Patient demographics.

Characteristic		Number of patients (N)	(%)
Gender	Male	240	56.5
	Female	185	43.5
Age (in years)	<50	377	88.8
	>50	48	11.2
DHF grading	DF	16	3.8
	DHF grade 1	266	62.6
	DHF grade 2	132	31.0
	DHF grade 3	11	2.6

Table 2: Comorbid based on DHF severity.

	DHF Severity								Total			
Comorbid	**DF**		**DHF 1**		**DHF 2**		**DHF 3**		∑	**%**	**α**	**P value**
Hypertense	∑	%	∑	%	∑	%	∑	%				
Yes	0	0	3	10	25	83.3	2	6.7	30	100	0.05	<0.001
No	16	4	263	67	107	27	9	2	395	100		
Diabetes mellitus	∑	%	∑	%	∑	%	∑	%				
Yes	0	0	2	15.4	9	69.2	2	15.4	13	100	0.05	<0.001
No	16	3.9	264	64	123	29.9	9	2.2	412	100		
COPD	∑	%	∑	%	∑	%	∑	%				
Yes	0	0	11	52.4	10	47.6	0	0	21	100	0.05	0.408
No	16	3.9	255	63.1	122	30.2	11	2.8	404	100		
CVD	∑	%	∑	%	∑	%	∑	%				
Yes	1	14.3	1	14.3	4	57.1	1	14.3	7	100	0.05	0.010
No	15	3.6	265	63.4	128	30.6	10	2.4	418	100		
CKD	∑	%	∑	%	∑	%	∑	%				
Yes	0	0	5	50	5	50	0	0	10	100	0.05	0.645
No	16	3.9	261	62.8	127	30.6	11	2.7	415	100		
Stroke	∑	%	∑	%	∑	%	∑	%				
Yes	0	0	0	0	2	100	0	0	2	100	0.05	0.219
No	16	3.8	266	62.8	130	30.8	11	2.6	423	100		
CLD	∑	%	∑	%	∑	%	∑	%				
Yes	0	0	4	30.8	8	61.5	1	7.7	13	100	0.05	0.039
No	16	4	262	63.6	124	30	10	2.4	412	100		
HIV	∑	%	∑	%	∑	%	∑	%				
Yes	0	0	2	66.7	1	33.3	0	0	3	100	0.05	1.000
No	16	3.8	264	62.6	131	31	11	2.6	422	100		

DHF patients with comorbid HIV most frequently experienced DHF grade 1 at 66.7%, and DHF grade II at 33.3%. Descriptively, it can be concluded that 0.7% of DHF patients also had HIV. Based on the results of statistical tests using Fisher's Exact Test, the p value was 1.000 ($p>0.05$), so it can be concluded that the comorbid factor of HIV had no relationship with the severity of DHF in patients treated at Wangaya General Teaching Hospital.

DISCUSSION

There are a few reasonable theories for the apparent mechanism that connects hypertension to an increased risk of severe dengue, even though it is not fully understood. The overactivation of the host immune system is a common feature of both severe dengue and hypertension. Studies have shown a considerable rise of inflammatory markers such as interleukin-6 (IL-6) and c-reactive protein (CRP) in hypertensive patients, suggesting a relationship between hypertension and a pro-inflammatory state. Severe dengue symptoms may result from the pro-inflammatory condition observed in hypertension patients, which has been connected to vascular endothelium dysfunction.[9-12] The effects of severe dengue on the endothelial glycocalyx (EG) layer may also be related to hypertension. Studies on humans and animals have shown that comorbidities like hypertension and diabetes mellitus are disrupted in the EG layer. The vascular endothelium's luminal side is lined with EG, a semipermeable membrane that is essential to the hemostatic regulation of fluid exchange between intravascular and extracellular areas. In a test on animals, the mean EG thickness of the choroidal and retinal capillaries was significantly lower in hypertensive mice than in control mice.

Therefore, in patients with diabetes mellitus and hypertension, disturbance of EG and the ensuing disturbance to fluid homeostasis may have a role in the development of severe dengue.[13-15] In the meta-analysis and systematic review research conducted by Padhi et al, a significant association was found between CVD and an increased risk of severe dengue, with a calculated RR of 2.71 (95% CI: 1.03 to 7.10) so that the importance of closely monitoring individuals with pre-existing cardiovascular disease and providing them with targeted interventions upon dengue diagnosis to mitigate the risk of severe outcomes.[16] Most cross-sectional studies do not conclude on the effect of HBV or HCV chronic infection on dengue-associated liver damage because of the low prevalence of coinfections. However, ALT levels in the crucial period were considerably higher in patients with chronic HBV co-infection in one cross-sectional investigation, where 69 (11%) of 618 dengue patients also had chronic HBV infection.[17]

There are limitations in this study, this study was conducted in a single center so the results may not be able to be replicated exactly in a study conducted at a multicenter level due to the wide demographic variation of Indonesia and the study was conducted in Bali. Further studies are needed with a larger sample size of patients in other areas.

CONCLUSION

Dengue fever with hypertension, diabetes mellitus, CVD, and CLD have a higher risk of developing DHF when compared with patients with dengue fever with other comorbidities. This finding helps us in triaging patients with comorbidities who develop dengue fever for specialized care and closer clinical monitoring.

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REFERENCES

1. Wang H. Dengue hemorrhagic fever-a systemic literature review of current perspectives on pathogenesis, prevention and Control. J Microbiol, Immunol Infect. 2020;53(6):963–78.
2. Tayal A, Kabra SK, Lodha R. Management of Dengue: An Updated Review. Ind J Pediat. 2023;90(2):168–77.
3. Badawi A, Velummailum R, Ryoo SG, Senthinathan A, Yaghoubi S, Vasileva D. Prevalence of chronic comorbidities in dengue fever and west nile virus: A systematic review and meta-analysis. In PLoS ONE. 2018;13(7):1371.
4. Roy SK, Bhattacharjee S. Dengue virus: Epidemiology, biology, and disease aetiology. In Canadian J Microbiol. 2018;67(10):687–702.
5. Harapan H, Michie A, Mudatsir M, Sasmono RT, Imrie A. Epidemiology of dengue hemorrhagic fever in Indonesia: Analysis of five decades data from the National Disease Surveillance. BMC Research. 2018;12(1):4379-9.
6. Adnyana IM, Azhari FS, Sudaryati NL. Prevalence of dengue hemorrhagic fever in Bali from 2015 to 2020 and during the COVID-19 pandemic. J Berkala Epidemiol. 2010;10(2):169–78.
7. Kementerian Kesehatan RI. 2020. Keputusan Menteri Kesehatan Republik Indonesia Nomor Hk.01.07/Menkes/9845/2020 Tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana Infeksi Dengue Pada Dewasa. Available at: Available at: https://www.kemkes.go.id/id/pnpk-2020---tata-laksana-infeksi-dengue-pada-dewasa. Accessed on 17 March 2024.
8. World Health Organization. (2011). Comprehensive guideline for prevention and control of dengue and dengue haemorrhagic fever. Available at: https://iris.who.int/handle/10665/204894. Accessed on 17 March 2024.
9. Singh MV, Chapleau MW, Harwani SC, Abboud FM. The immune system and hypertension. Immunol Res. 2014;59(0):243–53.
10. Sprokholt J, Helgers LC, Geijtenbeek TB. Innate immune receptors drive dengue virus immune activation and disease. Future Virol. 2017;13(4):287–305.
11. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. Hypertens Dallas Tex 1979. 2001;38(3):399–403.
12. Schillaci G, Pirro M, Gemelli F, Pasqualini L, Vaudo G, Marchesi S, et al. Increased C-reactive protein concentrations in never-treated hypertension: the role of systolic and pulse pressures. J Hypertens. 2003;21(10):1841–6.
13. Yeung W, Lye DCB, Thein TL, Chen Y, Leo YS. Blood pressure trends in hospitalized adult dengue patients. Plos One. 2020;15(7):235166.
14. Broekhuizen LN, Lemkes BA, Mooij HL, Meuwese MC, Verberne H, Holleman F, et al. Effect of sulodexide on endothelial glycocalyx and vascular permeability in patients with type 2 diabetes mellitus. Diabetology. 2010;53(12):2646–55.
15. Kumase F, Morizane Y, Mohri S, Takasu I, Ohtsuka A, Ohtsuki H. Glycocalyx degradation in retinal and choroidal capillary endothelium in rats with diabetes and hypertension. Acta Med Okayama. 2010;64(5):277–83.
16. Padhi BK, Khatib MN, Gaidhane S, Zahiruddin QS, Satapathy P, Rabaan AA, et al. Association of cardiovascular disease with severe dengue: A systematic review and meta-analysis. Current Problems in Cardiol. 2023;10:2346.
17. Campana V, Inizan C, Pommier JD, Menudier LY, Vincent M, Lecuit M, et al. Liver involvement in dengue: A systematic review. Reviews in Medical Virol. 2024;34(4):2564

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