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Determinants of Dengue Hemorrhagic Fever Deaths: A Hospital-Based Cross-Sectional Study

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Abstract

Background: The increase in the dengue mortality rate in Indonesia and its risk factors which must be addressed immediately. Brebes Hospital, a hospital that is the primary referral for health centers and clinics in Brebes Regency, has a dengue mortality rate (Case Fatality Rate) of 7.88%, contributing to the first death rate in Brebes Regency. Data related to dengue deaths, such as comorbidities and hematocrit levels in dengue patients, were unavailable at the provincial and Brebes district levels, especially at Brebes Hospital. This study aims to determine the determinants of dengue death in inpatients at Brebes Hospital.
Methods: This cross-sectional study used medical record data of dengue inpatients from September 2021 to August 2022, with as many as 138 respondents using a simple random sampling technique. The research instrument is an observation sheet, including age, gender, incidence of thrombocytopenia, hypotension, hematocrit levels, hemoglobin levels, diabetes mellitus status, hypertension status, comorbidities, and LOS. The data were analyzed in univariate, bivariate with the chi-square test, and multivariate with a logistic regression test.
Results: The bivariate analysis results showed that the variables of hypertension status, DM status, thrombocytopenia, hematocrit levels, and the presence of comorbid diseases were associated with dengue mortality ($p<0.01$). Multivariate analysis showed that after controlling for other variables, the risk of comorbid diseases was significant 27.54 times (p-value <0.001; AOR= 27.54; 95% CI= 7.21-105.07), and hematocrit levels were at risk of 4.96 times increasing dengue mortality (p-value = 0.005; AOR= 4.69; 95% CI= 1.59-13.83).
Conclusion: Hematocrit levels and the presence of comorbid diseases are critical determinants of dengue case mortality. The central comorbid diseases are hypertension, diabetes, and stroke. These two factors must be the primary concern of the clinicians in charge of patients in anticipation of an emergency.

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INTRODUCTION

The incidence of dengue has increased substantially, based on data from 76 countries, with the highest number of infections in Asian countries (Stanaway et al., 2016). Indonesia is one of the countries where dengue cases are still a health problem. The Incidence Rate (IR) of Dengue is still below the national target in 2021, 27 per 100,000 people. Moreover, the Case Fatality Rate (CFR) due to dengue increased in 2021 by 0.96% compared to 2020 by 0.69%. The province with the highest dengue death cases in Indonesia in 2021 is Central Java Province (Kemenkes RI, 2021). The dengue mortality rate in Central Java Province reached 2.71% in 2021, in the high category above 1%, exceeding the national target.

Brebes Regency has a CFR dengue mortality rate above the national target of 2.95% in 2020. There was a significant increase in CFR DHF in Brebes Regency between 2019 and 2020, from 1.43% to 2.95% (Brebes Regency Health Office, 2020). Brebes Regency ranks in the top 16 districts with the highest dengue cases in Central Java. However, the Brebes Regency does not rank highest in Central Java; this certainly does not make the Brebes Regency free from the threat of dengue deaths, with CFR numbers above the national target. Brebes Hospital is the primary referral for dengue patients from health centers and clinics in the Brebes Regency area (Brebes Hospital, 2022), with a mortality rate of 7.88% of dengue cases.

Dengue deaths are influenced by several factors, including age, comorbid diseases, and increased hematocrit levels (Mallhi et al., 2017). Patients with thrombocytopenia are significantly associated with dengue deaths (Pinto et al., 2016). Decreased platelet levels are associated with increased dengue mortality, which is identified as a risk factor for mild to moderate bleeding and causes bleeding complications (Hassan et al., 2020). An increase in hematocrit and a decrease in platelet count increase the likelihood of heavy bleeding (de Cavalcanti, 2014; Htun, 2021).

Based on the characteristics of dengue patients, Sangkaew (2021) noted that the female sex has a higher risk of becoming severe than men. This risk is related to differences in health-seeking behavior and the immunological system. Another study revealed that low hemoglobin levels and length of stay (LOS) were significantly associated with dengue deaths associated with plasma leakage (Farida, 2022; Shahid Ansari, 2021). The presence of diabetes increases the risk of dengue severity by 2.12 times more (Agrawal et al., 2018) because there is a disorder of the immune system that causes proinflammation with endothelial discourse (N. S. N. Htun et al., 2015), while the existence of hypertension is significantly related to dengue deaths (Baqi, 2022; Foed-Portilla, 2021). The analysis report on the determinants of dengue cases in Indonesia has not been found, so it is essential to understand this. This study aims to determine the determinants of dengue deaths, analyzed from data of inpatients at Brebes Regency Hospital.

METHODS

This type of research was observational analytical with cross-sectional studies. The population of this study was 1334 respondents. The sample in this study was patients with a primary diagnosis of dengue fever recorded in the medical record data of Brebes Hospital in September 2021-August 2022. One hundred thirty-eight samples consisted of 43 deceased dengue patients and 95 recovered dengue patients obtained using simple random sampling techniques. The flow chart of patient selection and grouping is shown in Figure 1.

The data used is secondary data on the medical records of dengue inpatients from September 2021 to August 2022 at Brebes Hospital and is recorded in the reporting of dengue domestic hospitals from September 2021 to August 2022. The variables studied were dengue death, age, gender, incidence of thrombocytopenia, hypotension, hematocrit levels, hemoglobin levels, diabetes mellitus status, hypertension status, comorbidities, and LOS.

This research instrument was an observation sheet used to record data on the variables of the research part. Univariate and bivariate data processing applications, such as the chi-square test and Fisher test, carried out data analysis. This research has been approved by the Health Research Ethics Commission, Faculty of Sports Sciences, Semarang State University with Number 429//KEPK/EC/2022.

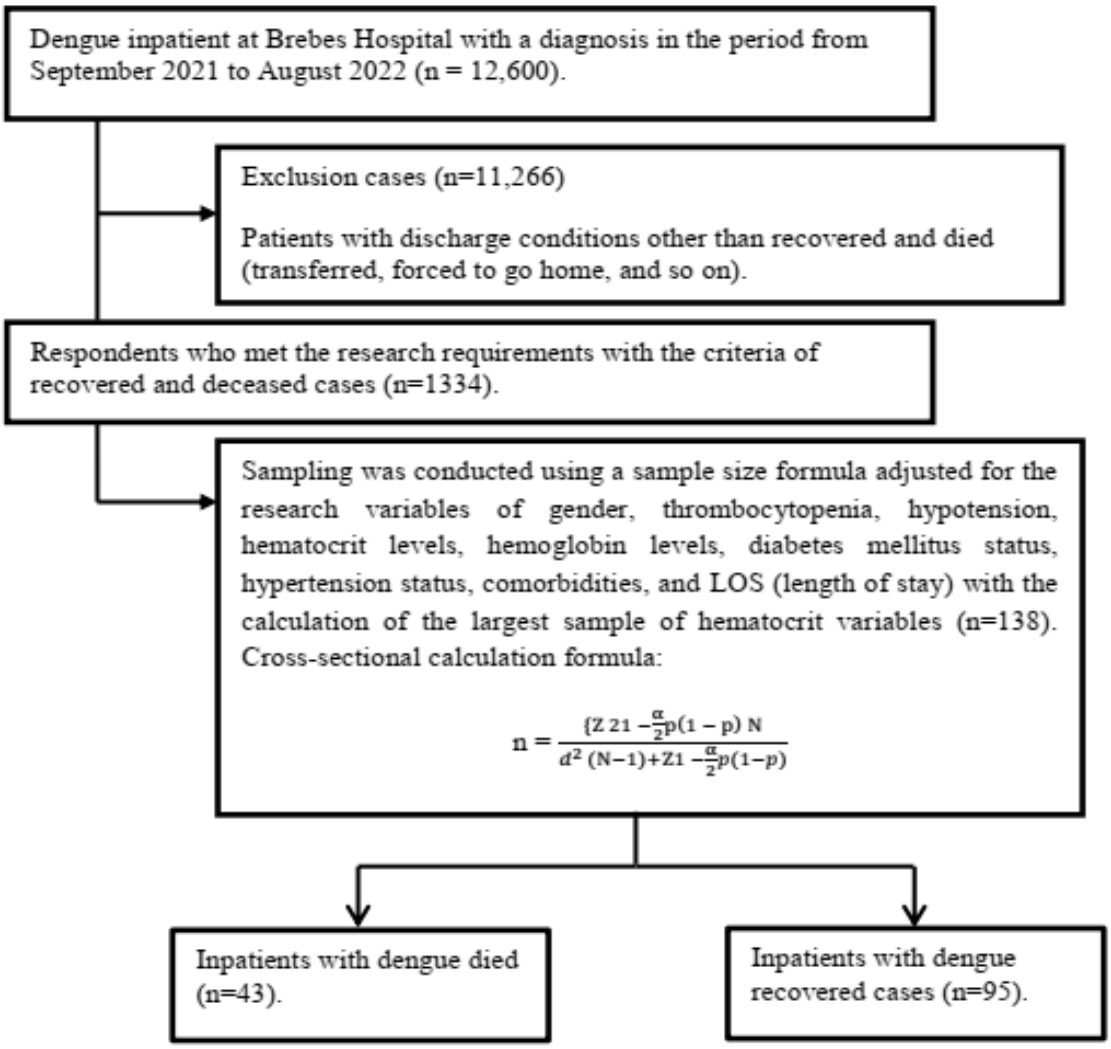

Figure 1. Patient Selection and Grouping Flow Diagram

RESULTS AND DISCUSSION

The results of data analysis from 138 patients showed that female patients were more than male patients, predominantly children of age, and had not worked. About a quarter of patients have comorbid diseases, with the identified types of diseases being hypertension and DM, with a proportion below 10%. The clinical condition of most patients with mild/ typical thrombocytopenia, more than half with low Hb levels of ≤12 dl, almost a quarter with an increase in hematocrit >42%, and most patients are treated <5 days.

Bivariate analysis shown in Table 2, eplain the results were obtained that the status of diabetes mellitus, hypertension status, thrombocytopenia, and the presence of comorbidities were significantly correlated to the risk of dengue death in hospitalized patients. These results were inversely to gender, hemoglobin levels, hematocrit levels, hypotension, and LOS (length of stay), which showed insignificant results related to dengue death in hospitalized patients.

The relationship between gender and dengue mortality in this study showed no significant relationship with a value of p=0.26 (PR=1.40; 95% CI: 0.84-2.33). The results of this study were align with the research conducted by Abualamah (2020), indicating that there was no difference between gender and dengue deaths. However, it is different from the results of the research by Sangkaew (2021), that gender is a factor in the occurrence of dengue deaths. The female sex is associated with a higher risk for severe dengue due to differences in the immune systems of men and women.

Table 1. Distribution of Research Respondents

Variable	Frequency (n)	Percent (%)
Gender		
Woman	72	52.2
Legal Law	66	47.8
Age		
1-14 years	78	56.5
15 – 55 years old	31	22.5
>55 years	29	21.0
Work		
Unemployed	87	63.0
Housewives	20	14.5
Labor	1	0.7
Merchant	2	1.4
Farmer	4	2.9
Driver	2	14.0
Self-employed	10	7.2
Retired	7	5.1
Civil Servant	5	3.6
Hypertension Status		
Yes	13	9.4
No	125	90.6
Diabetes Mellitus Status		
Yes	8	5.8
No	130	94.2
Thrombocytopenia		
Severe	5	3.6
Light/Normal	133	96.4
Hemoglobin		
≤12 g/dl	71	51.4
>12 g/dl	67	48.6
Hematocrit		
≥42%	32	23.2
<42%	106	76.8
Hypotension		
Yes	14	10.1
No	124	89.9
Existence of Comorbid Diseases		
Yes	36	26.1
No	102	73.9
LOS		
>5 days	29	21.0
≤5 days	109	79.0

Table 2. Results of Bivariate Analysis of Research

Variable	Status Responding				*p-value*	PR (95% CI)
	Die		Recover			
	N	%	N	%		
Gender						
Woman	26	36.1	46	63.9	0.25	1.40 (0.84-2.33)
Man	17	25.8	49	74.2		
Hypertension Status						
Ys	11	84.6	2	15.4	<0.001*	3.30 (2.26-4.82)
No	32	25.6	93	74.4		
Diabetes Mellitus Status						
Yes	7	87.5	1	12.5	0.001*	3.16 (2.15-4.62)
No	36	27.7	94	72.3		
Thrombocytopenia						
Severe	4	80	1	3.4	0.03*	2.72 (1.63-4.55)
Light/Normal	39	29.3	94	70.7		
Up to Hemoglobin						
≤12 g/dl	25	35.2	46	64.8	0.38	1.31 (0.79-2.17)
>12 g/dL	18	26.9	49	73.1		
Up to Hematocrit						
≥42%	16	50.0	16	50.0	0.01*	1.96 (1.22-3.15)
<42%	27	25.5	79	74.5		
Hypotension						
Yes	5	35.7	9	64.3	0.76	1.16 (0.55-2.47)
No	38	30.6	86	69.4		
Existence of Comorbid Diseases						
Yes	29	80.6	7	19.4	<0.001*	5.86 (3.51-9.79)
No	14	13.7	88	86.3		
LOS						
>5 days	11	37.9	18	62.1	0.51	1.29 (0.74-2.23)
≤5 days	32	29.4	77	70.6		

*Significant (p<0,05); LOS (*Length of stay*)

Table 3. Multivariate Analysis of Determinants of Dengue Death in Hospitalized Patients

Variable	B	Wald	p-value	AOR (95% CI)
The existence of comorbid diseases	3.316	23.553	<0.001	27.54 (7.21-105.07)
Hematocrit Level	1.546	7.857	0.005	4.69 (1.59-13.83)

Based on the results of the study, 84.6% of cases died in patients with hypertension status, and 74.4% of patients with recovered cases tended to patients who did not have hypertension status. The statistical test results in Table 1 showed an effect between hypertension status and dengue mortality with a p-value of <0.001 (PR=3.30; 95% CI: 2.26-4.82). This research is in line with the research done by Fonseca-Portilla (2021) 24,495 cases of dengue were identified, indicating that people with hypertension had a 2.45 times higher risk of death than patients without hypertension.

Other studies by Baqi (2022), also stated that patients with hypertension are 5.76 times more likely to die than non-hypertensive patients. Hypertension often appears with underlying risk factors such as glucose disorders or diabetes mellitus, obesity, and high blood cholesterol levels (Fauzi et al., 2019). Hypertension causes damage to blood vessels and endothelial dysfunction, as well as inflammation of the endothelium and changes in vascular flow (Wang et al., 2019). Damage

of endotel in blood vessels as an indicator of plasma leakage refers to hypovolemic shock, which results in tissue anoxia, metabolic acidosis, and death (Nurminha et al., 2018).

Diabetes mellitus is one of the leading comorbidities of mortality and morbidity globally, especially in Asia. Table 2 shows a relationship between diabetes mellitus status and dengue mortality with a value of p=0.001 (PR=3.16; 95% CI: 2.15-4.62). Patients who experienced dengue death mostly had DM status (87.5%), while patients with recovered cases mostly did not have DM status (72.3%). Based on the analysis, the result of PR = 3.16 was given, meaning that patients with DM status had a 3.16 times risk of experiencing dengue death compared to patients without DM status. This research is aligned with the research conducted by Mallhi (2015), that people with DM status are at 2.8 times the risk of death from dengue. Diabetes mellitus can cause immune disorders and endothelial damage that affects the death of dengue (Pang et al., 2012).

Decreased platelet levels are closely related to the incidence of dengue, which can cause thrombocytopenia in dengue patients. Table 2 shows an association between thrombocytopenia and dengue mortality with p= 0.03 (PR=2.72; 95% CI: 1.63-4.5). Severe thrombocytopenia has a 2.72 times risk of dying from dengue fever. The results of this study are the research by Faridah (2022) It was revealed that patients with thrombocytopenia were associated with dengue death. Dengue in patients with low platelet levels will experience plasma leakage, which results in dengue death (Talukdar et al., 2021). In this study, 80% of patients who experienced death had severe thrombocytopenia, and in patients with recovered cases, mostly 70.7% had moderate and regular thrombocytopenia.

In the hemoglobin variable, a value of p=1.31 (PR = 1.31; 95% CI: 0.79-2.17) was obtained, meaning there was no relationship between hemoglobin levels and dengue death. The results of this study are not in line with the research by Faridah (2022) that hemoglobin levels have a significant effect on dengue mortality. However, the results of this study are in line with the research done by Hsieh (2017) stated that there was no association between hemoglobin levels and dengue death. Based on this study, 25 patients died by having hemoglobin levels ≤12 g/dL, and 18 patients died of dengue fever by having hemoglobin levels >12 g/dL.

Analysis of hematocrit levels and dengue mortality showed a significant relationship with a value of p=0.01 (PR=1.96; 95% CI: 1.22-3.15). This research is similar with the results conducted by Agrawal (2018), hematocrit levels ≥42%, causing a risk of death of 3.14 times that of dengue deaths. This research is not aligned with Married (2021),stated that there was no significant difference between hematocrit levels and dengue deaths, but an increase in hematocrit was related to the patient's platelet transfusion attempt. Based on this study, there were 16 patients with high hematocrit levels (≥42%) who died of dengue fever, while in recovered cases, there were 79 patients with low hematocrit levels (<42%).

Hypotension is systolic blood pressure <90mmHg (Rhodes et al., 2017). There were five patients (35.7%) who died of dengue fever by having hypotension, while 38 patients (30.6%) died without hypotension status. In Table 2, the analysis between hypotension and dengue mortality showed no relationship with a p-value 0.76 (PR 1.16; 95% CI: 0.55-2.47). The results of this study were not aligned with study done by General (2015) that the presence of hypotension in patients is associated with the risk of death from dengue. However, the results of this study are in line with study done by Agrawal (2018) showed that there was no difference between patients with hypotension status and patients without hypotension to dengue death.

Comorbidities such as hypertension, diabetes, chronic kidney disease, liver disease, and stroke are related to the risk of developing dengue that is getting worse (Guo et al., 2017; Kulkarni et al., 2019; Lee et al., 2020). In this study, 29 patients died with comorbidities, and 88 cases recovered without comorbidities. Table 2 shows a comorbid association with the death of dengue fever with p<0.001 (PR=5.86; 95% CI: 3.51-9.79). The results of this study were similar with the research by Werneck (2018) stated that comorbidities are associated with dengue deaths and research by Mallhi (2017)

that comorbidities are an essential condition that affects dengue patients. The existence of comorbidities that occur in the elderly contributes to the severity of dengue, apart from infection of dengue fever virus in dengue patients (Wei et al., 2016).

LOS is the time that indicates the length of care for the patient, from being recorded as an inpatient to being discharged from the hospital, either dead or recovered. In this study, patients who experienced death tended to have LOS >5 days (37.9%), and patients who recovered tended to have LOS ≤5 days (70.6%). Table 2 shows no association between LOS and dengue mortality with a value of p=0.51 (PR=1.29; 95% CI: 0.74-2.23). According to Ang (2019) A prolonged LOS is related to the incidence of dengue fever and affects the severity of the disease. Nevertheless, a study conducted in Trinidad showed that more severe diseases in patients can shorten LOS in hospitals. (Pooransingh et al., 2016).

The results of the analysis in Table 3 show that comorbidities (p-value <0.001; AOR= 27.54; 95% CI= 7.21-105.07) from hematocrit (p-value= 0.005; AOR= 4.69; 95% CI= 1.59-13.83) is the primary variable for dengue mortality in inpatients. Thus, it can be concluded that the most significant variable after controlling for other variables is the comorbid variable. The results of the analysis showed that dengue patients with comorbidities were 27.54 times at risk of dying from dengue compared to dengue patients who did not have comorbidities. The results of this study are in line with Toledo (2016) that comorbidities are associated with dengue deaths and research by Werneck (2018) people with comorbidities are 11 times at risk of dying from dengue fever. The existence of comorbidities such as cardiovascular disease, stroke, diabetes, hypertension, kidney disease, and respiratory diseases shows the potential for morbidity and mortality of dengue (Limkittikul, 2014; Pang, 2012; Toledo, 2016).

Hematocrit was a significant variable contributing 4.69 times increasing the risk of death of dengue patients. The results of this study are in line with the research conducted by Agrawal (2018), which found that increased hematocrit levels ≥42% in dengue patients cause a risk of death of 3.14 times that of dengue. An increase in hematocrit levels is a predictor that causes plasma leakage and results in death. (Huy & Toan, 2022). In addition, increased hematocrit is one of the laboratory parameters related to dengue infection's severity and severe organ involvement. (Lam, 2017; Pang, 2012).

The mortality rate in dengue patients with a history of comorbidities requires appropriate treatment strategies and appropriate clinical care (WHO, 2012). The existence of comorbidities requires better protective measures against infection dengue fever in patients who have comorbidities without specific antiviral treatment. (Macias et al., 2021). An increase in hematocrit in patients can result in bleeding during dengue infection; therefore, monitoring the incidence of dengue fever is very important to determine the risk of hemoconcentration, which is an indicator of plasma leakage (Huy & Toan, 2022). Timely clinical management and early laboratory diagnosis in dengue patients with comorbidities are necessary for early detection of dengue case severity (WHO, 2012). In addition, medical treatment by doctors and nurses who have experience in developing dengue disease can reduce the mortality rate by less than 1% in most countries (WHO, 2018).

The strength of this study was the addition of new variables, such as the presence of comorbid diseases and the percentage of hematocrit levels in dengue patients, especially in Brebes Regency, where there has been no further research on the determinants of dengue mortality at Brebes Hospital so that further treatment can be carried out in dengue patients with comorbid diseases and high hematocrit levels. In addition, there were some limitations to this study. The use of medical record data that has not been computerized makes data lost, incomplete, and difficult to read. This study only used 138 respondents in one hospital, so it was insufficient to describe the determinants of dengue deaths in other regions. In addition, the study had not considered several factors related to dengue mortality due to unavailable data. The next researcher is expected to examine other variables through data collected by health professionals to analyze the clinical and epidemiological profile along with the determinants of dengue deaths.

CONCLUSION

The existence of comorbid diseases was at risk 27.54 times, while increased hematocrit levels contribute 4.69 times to the death of dengue cases. Clinicians and paramedics need to pay special attention and care to dengue patients with comorbid diseases and have elevated hematocrit levels to reduce the risk of death. Further research on the types of comorbid diseases and the critical value of hematocrit levels that affect the mortality of dengue cases.

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