



## **Direct Medical Cost Analysis of Dengue Patients: A Retrospective Study**

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*Submitted: 3 February 2022*

*Accepted: 18 July 2022*

*Published: 31 August 2022*

### **Abstract**

**Background:** Dengue infection is an arboviral disease that could lead to severe illness. The incidence of severe dengue will impact patients' financial aspects. As an important clinical feature, platelet level on admission day might contribute to the direct medical cost. **Objective:** This study aimed to examine the direct medical cost among patients with dengue fever (DF) or dengue hemorrhagic fever (DHF) in Yogyakarta, Indonesia. **Methods:** This study was a retrospective study conducted in two private hospitals in Yogyakarta, Indonesia. Participants included in this study were hospitalized patients diagnosed with DF or DHF. Data were extracted from medical records and finance departments in each hospital. **Results:** Among 174 dengue patients included in this study, the mean age of DHF patients ( $18.44 \pm 14.87$ ) was lower than in DF patients ( $23.47 \pm 18.99$ ). Patients with DHF (4.88 days) also showed prolonged hospitalization compared with DF (4.18 days) patients. In terms of medical cost, DHF patients need a higher dengue treatment cost, which is about 329.74 USD compared to 220.68 USD for DF patients in hospital 2. Mainly related to room charges, which increased by 9.48% in hospital 1 and 66.28% in hospital 2 compared with DF patients. Furthermore, DHF patients with thrombocytopenia on the first day of admission present higher medical costs in terms of laboratory fees (36.08%), medicine (18.17%), and total medical costs (9.84%). **Conclusion:** Severe form of dengue will contribute to economic burden. Therefore, prevention and adequate treatment are essential to reduce the prognosis of severe dengue and higher medical cost.

**Keywords:** dengue, infection, medical cost

### **How to cite this article:**

Faridah, I.N., Syahfitri, T.L., Nugroho, R.A., Supadmi, W., Dania, H. & Perwitasari, D.A. (2022). Direct Medical Cost Analysis of Dengue Patients: A Retrospective Study. *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, 9(2), 177-184. <http://doi.org/10.20473/jfiki.v9i22022.177-184>

## INTRODUCTION

Dengue is a mosquito-borne viral infection caused by four dengue virus serotypes (DENV-1 to DENV-4). This infection, an arboviral disease, has different manifestations in each patient due to the host immunity or the virus serotype (Khan et al., 2020). Based on the manifestations, dengue infection could be divided into an undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF), or other severe forms of dengue due to plasma leakage, which leads to dengue shock syndrome (DSS) and severe organ involvement (Pang et al., 2017; World Health Organization, 1997).

The incidence of infection and disability-adjusted life-years due to dengue increased in the past two decades. Furthermore, the high incidence of dengue in the world suggests that this infectious disease has become a significant public health challenge (Zeng et al., 2021). Data from Indonesia showed that the annual fatality rate declined by half in each decade. However, DHF incidence increases with incidence peaks every 6-8 years (Harapan et al., 2019). Moreover, coronavirus disease 2019 (Covid-19) became a new pandemic in 2019 that occurred globally and impacted health care systems worldwide. Dengue incidence in the Covid-19 pandemic seems to decrease during 2020 and 2021 (World Health Organization, 2022). Recently, the report of dengue incidence in Covid-19 in each country still varies. Some regions (such as Guangzhou, China and Sri Lanka) reported decreasing dengue cases (Jiang et al., 2021; Liyanage et al., 2021). However, other regions experienced an increased incidence of dengue during the Covid-19 pandemic (Lim et al., 2021; Plasencia-Dueñas et al., 2022).

The experience of dengue in patients could be related to reduced quality of life and financial problems (Elson et al., 2020; Panmei et al., 2019). In 2013, the global burden of disease study mentioned that there were 58.40 million symptomatic dengue virus infections, with 13.586 fatal cases, and the total annual international cost of dengue illness was 8.9 billion US\$ (Shepard et al., 2016). The other previous study in India presented that the dengue treatment reached 2.16 million US\$, which was lower than the cost of prevention (8.3 million US\$). Furthermore, the total cost of dengue reached 38 million US\$ (Nujum et al., 2020). A previous systematic review in 2019 stated that the dengue burden still significantly impacts the economic situation in particular countries with specific socioeconomic characteristics and similarities in health management systems (Oliveira et al., 2019).

According to a previous study, DHF patients have relatively high direct and indirect medical costs (due to productivity loss) due to the severity (Supadmi et al., 2019). Another study found that DHF patients require more extended hospitalization than DF patients (Faridah et al., 2022), implying that DHF medical costs will rise. Another factor contributing to increased direct medical costs is crucial clinical aspects of severe dengue, such as platelet count. As a result, this study aims to look at the direct medical costs of dengue patients of varying severity (DF or DHF) in Yogyakarta, Indonesia.

## MATERIALS AND METHODS

This study was a retrospective study conducted in two private hospitals in Yogyakarta, Indonesia. Participants included in this study were hospitalized patients diagnosed with dengue (dengue fever, dengue hemorrhagic fever, or dengue shock syndrome) using ICD code A90/A91. The data were randomly collected from 2018 to 2020. The sample size was calculated using the formula: Expected proportion of patients with dengue fever ( $p$ ) = 0.33 based on the ratio of dengue patients aged 5-14 years old = 33%, expected precision = 0.1 and confidence interval at 95% (Pourhoseingholi et al., 2013; Rafikahmed et al., 2021). The minimum sample size was about 85.

$$n = \frac{Z_{1-\alpha/2}^2 pq}{d^2}$$

$$Z_{1-\alpha/2} = 1.96$$

$$p = 0.33$$

$$q = 0.67$$

$$d = 0.1$$

This study was approved by Health Research Ethics Committee of *Fakultas Kedokteran dan Ilmu Kesehatan Universitas Muhammadiyah Yogyakarta* (Ref : 063/EC-KEPK FKIK UMY/XII/2020) and Ethics Committee Approval from *PKU Muhammadiyah Yogyakarta Hospital* (Ref : 00101/KT.7.4/III/2021).

Classification of dengue manifestation was divided into undifferentiated fever, dengue fever, and dengue hemorrhagic fever. The definition of dengue fever is an acute febrile illness with two or more manifestations such as headache, myalgia, rash, hemorrhagic manifestations, or leukopenia. However, dengue haemorrhagic fever is fever with hemorrhagic manifestations (positive tourniquet test, petechiae, bleeding from the mucosa, gastrointestinal tract, or melena), thrombocytopenia ( $<100,000$  cells per  $\text{mm}^3$ ), and the sign of plasma leakage which manifested by

rising hematocrit, pleural effusion, ascites, or hypoproteinemia (World Health Organization, 1997).

Data were extracted from medical records about sociodemographic and clinical features using a data extraction form. Sociodemographic data includes age, gender, education, mode of payment, room of stay and duration of hospitalization. Furthermore, each hospital's finance department obtained data on direct medical costs. The direct medical cost was defined as room stay charges, cost of laboratory tests, medicine, service fee, and a total of payment based on the hospital perspective.

Analysis of the data was performed using SAS 9.4. The characteristics and clinical features of the patients were described descriptively with percentages; however, age and length of hospitalization were summarized as mean and standard deviation (SD). A direct medical cost between DF and DHF was analyzed using the Mann-Whitney test or t-test, and the significance level was set at P-value < 0.05.

## RESULTS AND DISCUSSION

A total of 174 dengue patients were screened and included in this study, which are 85 patients diagnosed with DF and 89 patients with DHF. Of the total 174 dengue patients, the mean age was 20.9 years ( $\pm$  SD 17.14) which the mean age of DHF patients was lower than in DF patients. This data also represents the group of age, in which 37.65% of DF patients were adults (21

to 60 years old); however, 40.45% of DHF patients were children below 12 years old. Other characteristics of our respondents are the majority having lower than senior high school for education (95.97%), male gender (57.47%), and using government insurance (72.41%). The average stay in the hospital for all patients was 4.53 days (+ SD 1.5), and the mean stay in the hospital was longer in DHF patients than in DF patients (Table 1).

Regarding the age with the incidence of dengue, the results of this study were similar to previous studies. Paediatric patients significantly have more risk of developing a severe form of dengue than adult patients (Hegazi et al., 2020). A previous study in Brazil summarized that complicated dengue, DHF, or DSS were higher in younger age classes than in adults (Burattini et al., 2016). However, a severe form of dengue could occur at an older or younger age. Older age patients who suffered severe dengue and were admitted to the Intensive Care Unit (ICU) were correlated with multiple comorbidities (including hypertension, diabetes mellitus, and chronic kidney disease) and high case-fatality rate (Hsieh et al., 2017). Meanwhile, pediatric patients tend to present hypovolemic shock or DSS, and daily monitoring of platelet count can help identify patients that are at high risk of DSS (Lam et al., 2017).

**Table 1.** Characteristics of dengue patients

	Dengue Fever (n = 85)	Dengue Hemorrhagic Fever (n = 89)	Total
Age (years), mean $\pm$ SD	23.47 + 18.99	18.44 + 14.87	20.90 + 17.14
< 12 years old	23 (27.06)	36 (40.45)	59 (33.91)
12 - 21 years old	23 (27.06)	24 (26.97)	47 (27.01)
21 - 60 years old	32 (37.65)	27 (30.34)	59 (33.91)
> 60 years old	7 (8.24)	2 (2.25)	9 (5.17)
Male Gender	50 (58.82)	50 (56.18)	100 (57.47)
Education			
< Senior High School	82 (96.47)	85 (95.51)	167 (95.97)
> Senior High School	3 (3.53)	4 (4.49)	7 (4.02)
Payment			
Indonesia's National Health Insurance	59 (69.41)	67 (75.28)	126 (72.41)
Self-paid	21 (24.71)	16 (17.98)	37 (21.26)
Others	5 (5.88)	6 (6.74)	11 (6.32)
Length of Hospitalization (days), mean+SD	4.18 + 1.28	4.88 + 1.62	4.53 + 1.50
Room			
3	29 (34.12)	20 (22.47)	49 (28.16)
3A	9 (10.59)	7 (7.87)	16 (9.20)
2	19 (22.35)	33 (37.08)	52 (29.89)
1	17 (20)	12 (13.48)	29 (16.67)
VIP	8 (9.41)	13 (14.61)	21 (12.07)
VVIP	3 (3.53)	4 (4.49)	7 (4.02)

SD : Standard Deviation

**Table 2.** Clinical features of dengue patients

Symptom	Dengue Fever (n = 85)	Dengue Hemorrhagic Fever (n = 89)	Total
Headache	26 (30.59)	30 (33.71)	56 (32.18)
Rash	2 (2.35)	1 (1.12)	3 (1.72)
Fatigue	0	1 (1.12)	1 (0.57)
Diarrhea	7 (8.24)	3 (3.37)	10 (5.75)
Gum Bleeding	0	1 (1.12)	1 (0.57)
Nausea/Vomiting	48 (56.47)	46 (51.69)	94 (54.02)
Abdominal Pain	16 (18.82)	15 (16.85)	31 (17.82)
Bone Pain	6 (7.06)	2 (2.25)	8 (4.60)
Gastric Bleeding	0	1 (1.12)	1 (0.57)
Hemoptysis	1 (1.18)	6 (6.74)	7 (4.02)
Thrombocytopenia	32 (37.65)	48 (53.93)	80 (45.98)
High Hematocrit	41 (48.24)	37 (41.57)	78 (44.83)

Prolonged hospital stays are also represented in DHF patients in this study. This result was in line with previous research that fatal cases of DHF patients had prolonged hospital stays than controls (Thein et al., 2013). Other predictors than DHF, such as an elevated liver enzyme, prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT) and the presence of multiple organ disorders, are also known to contribute to prolonged hospitalization (Mallhi et al., 2017).

Dengue hemorrhagic fever is a severe form of dengue. Data from Table 2 represent the clinical features of dengue patients, and the top three features are nausea/vomiting, headache, and abdominal pain. This result was similar to the previous result that dengue patients included nausea/vomiting, headache, and abdominal pain in the top five clinical characteristics. However, in contrast to the previous study, nausea/vomiting and abdominal pain showed a higher percentage in DF patients than in DHF patients due to a small number of patients (Jayarajah et al., 2020).

Other presentations, gum and gastric bleeding, showed only in DHF patients. Gum/gingival bleeding includes minor bleeding that usually happens in a critical phase of dengue. Bleeding in dengue patients could be associated with coagulation abnormalities and vascular leak syndrome. Moreover, severe haemorrhages are shown by gastrointestinal bleeding or severe vaginal bleeding (Azeredo et al., 2015). However, due to the small sample size in this study, the number of patients suffering from bleeding was very small (Table 2).

Although the mechanism of thrombocytopenia and bleeding in dengue patients is not fully understood, it is

known that platelets play a role in thrombus formation. The decreasing number of platelets in dengue could be associated with dengue severity and bleeding in dengue patients (Wilder-smith et al., 2019). Furthermore, anti-platelet antibodies in patients with dengue virus (DENV) cause platelet lysis or dysfunction and contribute to some clinical features of DHF (Azeredo et al., 2015). Our study also revealed that patients with low platelet count on on-admission day were significantly higher in DHF patients (53.93%) rather than in DF patients (37.65%) (p-value=0.0312) (Table 2).

Figure 1 shows the direct medical cost percentage compared with the total cost for DF and DHF patients, while Table 3 summarizes the direct medical cost data comparison between DF and DHF at two private hospitals in Yogyakarta. The percentage of the cost was higher in room charge (26%) and medicine cost (26%) for DF patients, while in DHF patients, the higher percentage of the price was in room charge (31%) and laboratory cost (25%). In sub-analysis data between two different hospitals, our study result showed that DHF patients need a higher cost of dengue treatment, which is about 329.74 USD, compared to 220.68 USD for DF patients in hospital 2. This is especially related to room charges, which are higher at 9.48% in private hospital 1 and 66.28% in private hospital 2. Higher costs also showed in the service fee of DHF patients, which were higher at 8.65% in private hospital 1 and higher at 16.87% in private hospital 2. This result was statistically significant in private hospital 2 (p-value=0.0028 for room charge and p-value=0.0498 for service fee), and although it present insignificant in private hospital 1, the trend was similar in that DHF patients need extra payment for room charges and service fees. A previous study in India also revealed that adults or paediatrics

with severe dengue need higher costs than dengue patients with or without warning signs (Panmei et al., 2019). As an expectation, a severe form of the disease will increase the medical cost, such as hospitalization, laboratory fee, and fee for professional services. Based on the data from private hospital 2, the cost for laboratory testing and comprehensive treatment also showed significant differences between DF and DHF patients, but the result showed differences in private hospital 1. This study showed that in private hospital 1, laboratory costs, medicine, and treatment total were higher in DF patients than in DHF patients. This happened due to the distribution of room class 28% of DF patients stayed in class 1 and VIP, while only 22% of DHF patients stayed in the same class. The difference in classroom distribution impacts some costs that are higher in DF than in DHF patients.

Platelet is one of the factors that contribute to the severity of dengue. Bone marrow depression induced by DENV causes thrombocytopenia. Thrombocytopenia in dengue patients increases the risk of bleeding

manifestation and other severe complications. However, not all patients present thrombocytopenia, a previous study in Brazil showed that thrombocytopenia happened in 40.3% of respondents (Castilho et al., 2020). Platelet count during the febrile phase can be used as a risk factor for developing shock syndrome, and monitoring of the changes in platelet count over time is also related to the development of shock syndrome (Lam et al., 2017). Hence, platelet counts on admission day could be related to dengue prognosis and higher medical costs. Considering the previous results that DHF needs extra payment for medical costs, data in Table 4 emphasized that DHF patients with low platelet levels present higher medical costs (236.11 USD) than DHF with normal platelet patients (214.95 USD). The significant result showed higher laboratory cost, medicine, and total medical cost (p-value=0.0003, 0.0033, and 0.0106, respectively). Although the cost for room charges in DHF presents insignificant results, the average of room charges was higher in DHF with low platelet than normal platelet count.

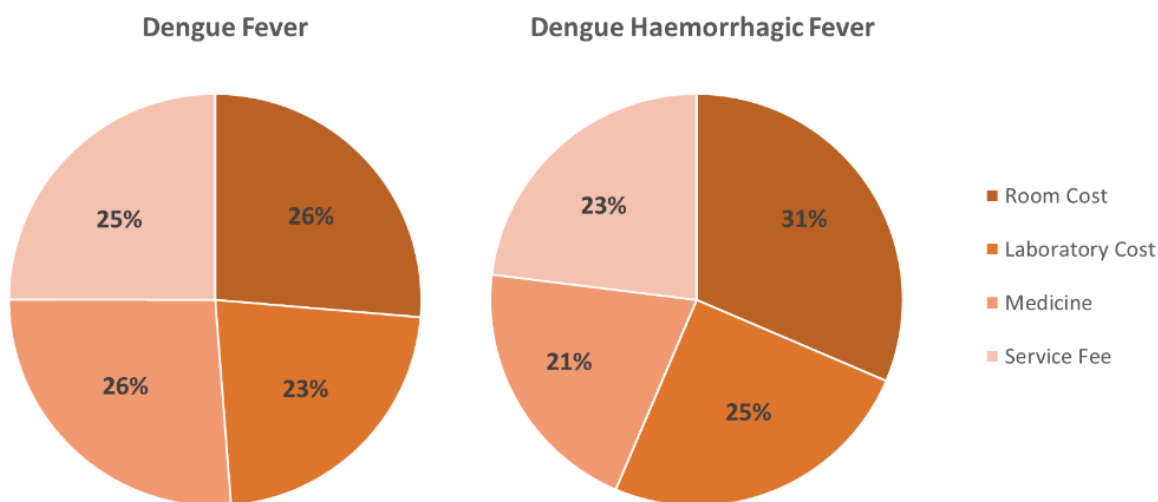


Figure 1. The percentage of direct medical cost for dengue fever and dengue hemorrhagic fever patients

Table 3. Direct medical costs in US Dollars (USD) for dengue fever and dengue hemorrhagic fever in different private hospitals in Yogyakarta

	Private Hospital 1 (n = 100)		P-value*	Private Hospital 2 (n = 74)		P-value*
	DF (n = 50)	DHF (n = 50)		DF (n = 35)	DHF (n = 39)	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Room Cost	36.80 ± 22.21	40.29 ± 19.28	0.0992	66.58 ± 61.15	110.71 ± 94.75	<b>0.0028</b>
Laboratory Cost	33.98 ± 20.76	29.07 ± 13.16	0.7987	52.91 ± 41.90	91.79 ± 105.89	<b>0.0064</b>
Medicine	43.64 ± 41.81	25.29 ± 26.53	<b>0.0032</b>	56.41 ± 38.23	73.71 ± 72.94	0.6729
Service Fee	47.00 ± 14.76	51.07 ± 13.12	0.1392	45.80 ± 15.53	53.53 ± 17.58	<b>0.0498</b>
<b>TOTAL</b>	<b>161.42 ± 68.93</b>	<b>145.73 ± 48.28</b>	0.3683	<b>220.68 ± 107.92</b>	<b>329.74 ± 191.44</b>	<b>0.0087</b>

Exchange rate during the study period: 14499 IDR to 1 USD

\*Calculated using the Mann Whitney Test

**Table 4.** Subgroup analysis of direct medical costs (in US Dollars (USD)) for dengue fever and dengue hemorrhagic fever based on on-admission day platelet

	DF (n=85)		P-value*	DHF (n=89)		P-value*
	Thrombocytopenia (n=32)	Normal Platelet (n=53)		Thrombocytopenia (n=48)	Normal Platelet (n=41)	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Room Cost	40.22 ± 37.74	54.40 ± 48.31	0.1380	71.38 ± 65.31	70.88 ± 81.78	0.1857
Laboratory Cost	54.35 ± 43.39	34.19 ± 20.43	<b>0.0105</b>	64.42 ± 74.22	47.34 ± 79.91	<b>0.0003</b>
Medicine	47.19 ± 32.05	49.93 ± 45.30	0.6275	50.06 ± 42.09	42.36 ± 71.32	<b>0.0033</b>
Service Fee	47.98 ± 12.47	45.61 ± 16.39	0.3295	50.25 ± 14.36	54.37 ± 15.99	0.2033
<b>TOTAL</b>	<b>189.75 ± 88.09</b>	<b>183.45 ± 94.03</b>	<b>0.5770</b>	<b>236.11 ± 142.91</b>	<b>214.95 ± 178.81</b>	<b>0.0106</b>

Exchange rate during the study period: 14499 IDR to 1 USD

\*Calculated using the Mann-Whitney Test

Considering the different health management settings and geographical situations in other countries, ten years ago, the costs for dengue outbreaks in Indonesia, Peru, and Vietnam were 6.75 million US \$, 4.5 million US\$ and 12 million US\$, respectively. The cost components were vector control, surveillance, information, education and communication, and direct and indirect medical costs (Stahl et al., 2013). Previously study in Indonesia mentioned that the aggregate cost of dengue was 73% higher than the estimation. The study also presented that dengue costs in hospital settings and non-fatal cases were the highest compared to ambulatory and not medically attended settings (Wilastonegoro et al., 2020). In addition, a previous study in Taiwan compared dengue's economical cost and disease burden during epidemic and non-epidemic. The cost in the epidemic year was 12.3 times higher than in the non-epidemic year, and the highest was the cost of hospitalization (86.09%). However, the drug cost was the lowest (0.03%) (Luh et al., 2018).

Based on previous information, analysis of direct medical costs for hospitalized dengue patients is essential. This study highlights that severity of dengue will impact the economic aspect. Thus, identifying the high risk of severe dengue patients is potentially valuable for preventing mortality and reducing direct medical cost. Results of this study showed similar to other studies, in which severe dengue patients had higher costs for treatment than different grades of dengue (Panmei et al., 2019; Vieira Machado et al., 2014). The key to successful treatment and lowering the treatment cost correlates with a better triage system for hospitalization and the availability of technical or laboratory support that is useful for predicting high-risk dengue patients (Bajwala et al., 2019; Ministry of Health Republic of Indonesia, 2021).

The design of the present study was limited. This was a retrospective study with a small number of samples in each hospital or group. Therefore, we could not find consistent results between the two hospitals. Additionally, the limitation of the retrospective study was incomplete data, so some variables related to medical cost cannot be evaluated in this study. Thus, the indirect costs associated with the loss of productivity, such as travel, food, and the absence of families or caregivers from school or activities, cannot be analyzed. This study only estimated direct medical costs of hospitalization.

### CONCLUSION

In conclusion, a severe form of dengue will contribute to the economic burden. DHF patients with a low platelet level on the first day of admission showed need higher cost on specific variables than DHF patients with normal platelets. Hence, prevention and adequate treatment are essential to reducing severe dengue prognosis and higher medical costs.

### ACKNOWLEDGMENT

We thank all the directors and staff at two private hospitals in Yogyakarta.

### AUTHOR CONTRIBUTIONS

Conceptualization, W.S., D.A.P.; Methodology, H.D., I.N.F.; Validation, W.S., D.A.P.; Formal Analysis, I.N.F., H.D.; Investigation, H.D., D.A.P., W.S., I.N.F.; Resources, I.N.F., T.L.S., R.A.N.; Data Curation, T.L.S., R.A.N.; Writing - Original Draft, I.N.F., W.S., D.A.P. ; Writing - Review & Editing, I.N.F., W.S., D.A.P.; Supervision, D.A.P., W.S.; Project Administration, H.D., I.N.F., W.S., D.A.P.; Funding Acquisition, W.S., D.A.P.

**CONFLICT OF INTEREST**

The authors report no conflict of interest in this study.

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