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SURVIVAL ANALYSIS OF DENGUE HEMORRHAGIC FEVER PATIENTS (DHF)

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Abstract. *Dengue Hemorrhagic Fever (DHF) is a dangerous disease transmitted by the Dengue virus. In 2020, along with the occurrence of the Covid-19 pandemic in Indonesia, the number of dengue cases in Indonesia was high. One of the provinces recorded as the highest suspected dengue fever area is North Sumatra. This is evidenced in October 2019 North Sumatra became the province with the highest suspected dengue fever in Indonesia with a total of 250 cases. Based on the medical record data of patients with DHF at the Dr. Pirngadi General Hospital, Medan in 2019, the factors thought to affect the rate of survival of DHF patients were age, gender, platelet count, and hematocrit levels. Furthermore, survival analysis was carried out using the Kaplan-Meier method and Cox Proportional Hazard Regression with the suspected factors to determine the estimated survival function for patients with DHF and to determine the factors that affect the recovery rate of patients with DHF. Based on the survival function curve, it was found that the curve decreased slowly because many patients with DHF were censored and it was found that the chances of survival of patients with DHF were relatively high, ranging from 1 to 0.6352. Based on the selection of the best model, it was found that only the age variable had a significant effect on the model.*

Keywords: *Dengue Hemorrhagic Fever, Survival Analysis, Kaplan-Meier, Cox Proportional Hazard*

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1. INTRODUCTION

Indonesia is an archipelagic country with more than 17,000 islands and a country with a tropical climate that results in relative humidity between 70% to 90%. Therefore, it can cause health problems that usually occur in countries with tropical climates [1].The Law of the Republic of Indonesia Number 36 of 2009 concerning Health states that health is a healthy condition physically, mentally, spiritually and socially so that every individual can engage in social and economic activities. Health conditions can be difficult to control when a disease has become epidemic so that it can cause an Extraordinary Event (EE) [2]. According to the Regulation of the Minister of Health of the Republic of Indonesia Number 1501/MENKES/PER/X/2010, it is stated that an EE is an event within a certain period of time that causes illness to death in a certain group or region. One of the outbreaks in Indonesia that has occurred from year to year is Dengue Hemorrhagic Fever (DHF) [3].

Dengue Hemorrhagic Fever (DHF) is an infectious disease caused by the Dengue virus which is transmitted through the bite of a vector, namely the Aedes Aegypty mosquito. Dengue virus has four serotypes, namely DEN-1, DEN-2, DEN-3, and DEN-4. DHF cases can be found throughout the year, especially during the rainy season and can infect all age groups [4]. According **[1]**, DHF is a disease that is influenced by the Dengue virus. Dengue virus is transmitted through the bite of the Aedes spp. Symptoms that arise from DHF are almost the same as symptoms that arise in Dengue Fever, except that in DHF there are different symptoms, namely heartburn, bleeding and bruising on the skin.

Dengue fever is considered a harmless disease caused by the influence of the tropical climate at first. However, this disease was considered a dangerous disease since the outbreak of dengue fever in 1953 to 1954 in Manila, Philippines. The first appearance of DHF in Indonesia occurred in 1968 in Surabaya. Then in 1968 to 1972, DHF infected people on the island of Java. In 1972 DHF infected Lampung and West Sumatra, then Riau, North Sulawesi, and Bali in 1973. Then, in 1975 DHF had spread to 20 provinces in Indonesia, until 1981 all provinces in Indonesia were infected with DHF [5] .

DHF has always been a major health problem for the people of Indonesia with the number of dominant cases increasing since 1968 until now. This is accompanied by an increase in population, the number of sufferers and the distribution area is increasing [3]. Based on WHO, Asia Pacific has a dengue incidence rate of 75% in the world from 2004 to 2010. Among 30 countries in endemic areas, Indonesia is the 2nd largest country with the incidence of DHF [1].

In 2020, along with the occurrence of the Covid-19 pandemic in Indonesia, the number of dengue cases was high. According to data from the Indonesian Ministry of Health, the number of dengue cases in Indonesia as of July 2020 was 71,633 cases with 459 deaths. The number of DHF cases in 2019 was 112,954, this number is more when compared to DHF cases in July 2020 [**6**]. One of the provinces recorded as the highest suspected dengue fever area is North Sumatra Province. In October 2019, there were 250 suspected dengue cases in North Sumatra, this number makes North Sumatra the highest dengue suspect area in October 2019 in Indonesia **[**7**]**.

The North Sumatra Provincial Health Office in 2013 stated that the spread of DHF had spread widely in all areas of North Sumatra Province. DHF cases in North Sumatra are outbreaks that result in relatively high morbidity and mortality rates. The area in North Sumatra is divided into three classifications based on the number of dengue cases that occurred in the region. Karo District, Tebing Tinggi City, Pematang Siantar City, Asahan District, Langkat District, Binjai City, Deli Serdang District and Medan City are included in dengue endemic areas. Samosir District, Pak-Pak District, Serdang Bedagai District, Humbang Hasundutan District, Labuhan Batu District, Padang Sidempuan City, Tapanuli Selatan District, Mandailing Natal District, Tapanuli Utara District, Dairi District, Tapanuli Utara District, Toba Samosir District, Simalungun District, Tanjung Balai City and Sibolga City are included in the sporadic areas of DHF. While the Nias Selatan District and Nias District are included in the potential areas/free of DHF **[**8**]**.

The city of Medan is an endemic area for dengue fever, dengue cases are still a serious problem for the people in the city of Medan. It can be seen that in 2017 there were 1,214 cases **[**9**]**, in 2018 there were 1,490 cases of which 13 people died and as of January to October 2019 there were 913 cases of which 6 people died in Medan City. Compared to other areas in North Sumatra, Medan City is the area with the highest dengue cases in North Sumatra **[**10**].**

The healing factor for DHF patients can also be influenced by clinical symptoms suffered by DHF patients, including high fever, bleeding, thrombocytopenia, and an increase in hematocrit. These clinical symptoms also have a relationship and are influenced by the age and sex of DHF sufferers [11]. So it is necessary to do a survival analysis to determine the factors that affect the rate of recovery of patients with DHF.

Survival analysis is generally defined as statistical steps in analyzing data measured from the beginning of time to the occurrence of certain events. In survival analysis there is data censorship, namely data failures that may occur when research is carried out. Failure in this case has several possibilities, namely the patient dies, the patient leaves the hospital before recovering and others [12].

Cox Proportional Hazard Regression was carried out to determine the relationship between the dependent variable and the independent variable using data on the survive of an individual. In estimating and describing the graph of the resistance function, the Kaplan-Meier method can be used. This method can be used in nonparametric research [12]. Furthermore, in comparing the relationship between the dependent variable and the independent variable and comparing the graphs of the resistance function, the Log-Rank test is performed. In the Log-Rank test, a hypothesis will be made to draw a decision [13].

Based on the above conditions, the authors are interested in conducting a **survival analysis of Dengue Hemorrhagic Fever (DHF)** by analyzing the factors that affect the recovery time of DHF patients.

2. RESEARCH METHODS

2.1 Survival Analysis

Survival analysis is a statistical term that is defined as a statistical step to analyze a random variable that has a positive value [14]. Survival analysis is a statistical method in analyzing data from the beginning of time until the emergence of a certain event. Certain events are usually referred to as failures [15].

2.2 Censored Data

Censored data is incomplete data caused by the subject not being observed or missing information. This makes survival analysis different from other statistical analyzes [15]. Censored is a part of survival analysis which is generally used when the observed lifetime of the individual is unknown [16].

In general, censored data consists of three types, namely right censored, left censored, and interval censored [17]:

1. Right censored occurs if a subject leaves the observation before the event occurs, or the observation ends before the event occurs.
2. Left censored occurs when the event has occurred before the observation begins.
3. Interval censored occurs when the failure event that occurs cannot be observed directly but is only known during the time interval.

2.3 Kaplan-Meier

According to **[**18**]**, the Kaplan-Meier estimation was carried out to calculate the survival function and describe it in the form of a curve to see the relationship between the survival function and survival time. The survival function is denoted by S(t), then the general form is as follows:

$$\hat{S}\left(t_{(j-1)}\right) = \prod_{i=1}^{j-1} \hat{P}r(T > t_{(i)} | T \geq t_{(i)}) \quad (1)$$

The Kaplan-Meier method is a simple method that does not assume distribution, in this case the observed resistance time in a study. This method is very useful for summarizing survival data and making simple comparisons but cannot easily deal with more complex situations [19].

2.4 Log-Rank Test

The Log-Rank test is a statistical technique to see the difference between two or more resistance tables or curve graphs in the survival function. The Log-Rank test is a chi square test on large sample data, the hypothesis is [15]:

H_0 : There is no difference between survival function

H_1 : There is at least one difference between survival functions

This test was conducted to test the survival curve equations to detect significant differences in survival times with the various categorical variables considered in this study. The Log-Rank test showed that survival time varied significantly according to different categorical variables [20].

The test statistics on the Log-Rank test are as follows [13]:

$$\chi^2 = \sum_{i=1}^{G} \frac{(O_i - E_i)^2}{E_i} \; ; i = 1,2,3,\dots,G \tag{2}$$

And with :

$$O_i - E_i = \sum_{j=1}^{n} \sum_{i=1}^{G} (m_{ij} - e_{ij}) \tag{3}$$

$$e_{ij} = \left(\frac{n_{ij}}{\sum_{j=1}^{n} \sum_{i=1}^{\cdot} n_{ij}}\right) \left(\sum_{j=1}^{n} \sum_{i=1}^{G} m_{ij}\right) \tag{4}$$

Description :

m_{ij} = total subjects who failed in group i at time $t_{(j)}$

n_{ij} = total subjects at risk of temporary failure in group i at time $t_{(j)}$

e_{ij} = expected value in group i at time $t_{(j)}$

G = total group

With the decision criteria:

Reject H_0 if χ^2_{count} greater than $\chi^2_{a,df}$

2.5 Cox Regression (Cox Proportional Hazard)

The Cox regression model defines that the hazard function of different subjects is constant. The Cox regression model is as follows [21] :

$$h(t,x) = h_0(t) exp \; (\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p) \tag{5}$$

Description :

$h_0(t)$: baseline hazard function

$\beta_1, \beta_2, \dots, \beta_p$: regression parameters

$x_1, x_2, \dots, x_p$: the value of the independent variable $X_1, X_2, \dots, X_p$

2.6 Cox Stratified Model

Independent variables that do not meet the proportional hazard assumption can be overcome by using a modification of the Cox Proportional Hazard model, namely the Stratisfied Cox model. In the Cox Stratisfied model, it is done by stratifying the independent variables that do not meet the proportional hazard assumption [22].

2.6.1 Cox Stratisfied Model Without Interaction

To see that there is no interaction for each independent variable, it is done using the Cox Stratisfied model without interaction, then the general form of the hazard function is:

$$h_s(t,X) = h_{0s}(t). exp \; [\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k] \tag{6}$$

Description :

s = declared strata of Z^* ; s = 1, 2,..., m.

$h_{0s}(t)$ = baseline failure function for each stratum

$\beta_1, \beta_2, \dots, \beta_k$ = regression parameters

2.6.2 Cox Stratisfied Model with Interaction

The interaction between the variables Z* and X in this model is stated as follows:

$$h_s(t,X) = h_{0s}(t). exp \; [\beta_{1s} X_1 + \beta_{2s} X_2 + \cdots + \beta_{ks} X_k] \tag{7}$$

Description :

s = declared strata of Z^* ; s = 1, 2,..., m^*.

2.7 Cox Extended Model

According [26], Cox Extended regression is used if there are independent variables that depend on time. The independent variable that depends on time must be related to the time function *g(t)*. Functions containing *t*, *t*, and *ln t* can be used for time functions. For each time-dependent variable in the Cox Extended model, there is only one coefficient that applies to each t of $x_j(t)$during the study. The general equation for the Cox Extended model is as follows:

$$h\big(t,x(t)\big) = h_0(t)exp\left[\sum_{i=1}^{p}\beta_j x_{ji} + \sum_{j=1}^{q}\beta_j x_j g_j(t)\right] \quad (8)$$

Description :

$g_j(t)$ = function with respect to time which plays an important role in determining the exact form of $g_j(t)$

2.8 Research Locations and Samples

This research was conducted at Dr. General Hospital. Pirngadi Medan located in Jl. Prof. HM. Yamin Sh No. 47, Perintis, Kec. Medan Timur, Kota Medan, Sumatera Utara. The sample used in this study were 54 DHF patients who were hospitalized at Dr. General Hospital. Pirngadi Medan in 2019.

2.9 Research Variable

In this study using 2 variables, namely:

1. The dependent variable (dependent variable)
   The dependent variable (dependent variable) is Y, where this variable is a variable that is influenced by the independent variable. In this study, the dependent variable is the length of time the patient survives with Dengue Hemorrhagic Fever (DHF) starting from the beginning of the study until the occurrence of the incident.
2. Independent variable (independent variable)
   The independent variable is X, where this variable is a variable that affects the dependent variable. In this study, the independent variables were age, gender, platelet count, and hematocrit level.

3. RESULTS AND DISCUSSION

3.1 Descriptive Statistical Analysis

In this study, descriptive statistical analysis describes the characteristics of patients with Dengue Hemorrhagic Fever (DHF) who are hospitalized at RSU Dr. Pirngadi Medan in 2019 based on the factors that influence the length of survival for DHF patients. The following are the results of descriptive statistical analysis:

Table 1. Descriptive statistics on the survival time of patients with DHF

Variable	N	Minimum	Maximum	Mean	Std. Deviation
Long Survival Time of Patients with DHF (Y)	54	2	16	5,52	2,538

Table 2. Descriptive statistics on the age of patients with DHF

	Frequency	Percent (%)
Children	11	20,4
Teenager	17	31,5
Mature	23	42,6
Elderly	3	5,6
Total	**54**	**100**

Table 3. Descriptive statistics on gender of patients with DHF

	Frequency	Percent (%)
Man	32	59,3
Woman	22	40,7
Total	**54**	**100**

Table 4. Descriptive statistics on the platelet count of patients with DHF

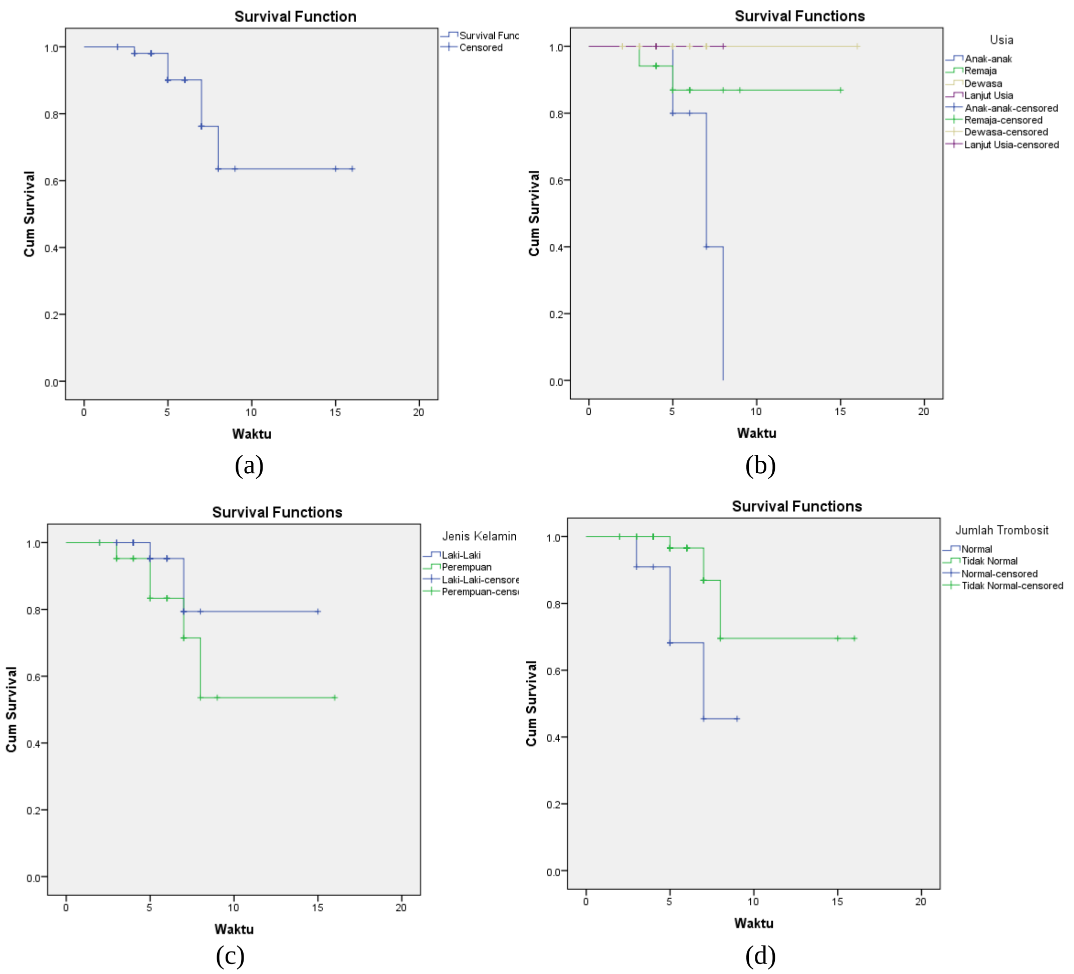
	Frequency	Percent (%)
Normal	11	20,4
Abnormal	43	79,6
Total	**54**	**100**

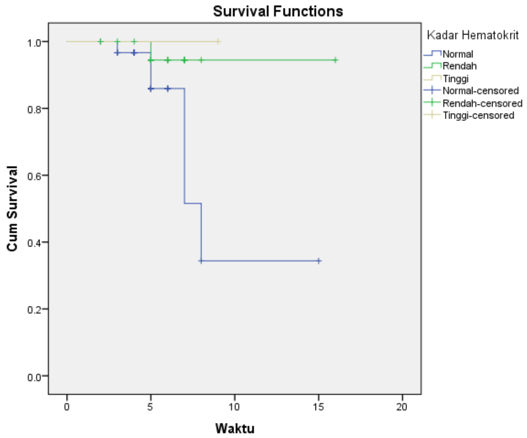
Table 5. Descriptive statistics of hematocrit levels in patients with DHF

	Frequency	Percent (%)
Normal	31	57,4
Low	22	40,7
High	1	1,9
Total	**54**	**100**

3.2 Kaplan-Meier method

In this study, the Kaplan-Meier method was used to estimate the survival function of patients with DHF and to determine the outcome curve for the estimated survival of patients with DHF based on the factors that affect the resilience of patients with DHF. The curve of the estimated survival results is shown in Figure 1 below:





(e)

Figure 1. Estimating curve of survival of patients with DHF at Dr. Pirngadi General Hospital Medan in 2019, where: a) overall survival curve b) survival estimation curve based on age factor c) survival estimation curve based on sex factor d) curve estimation of survival based on platelet count factor e) curve estimation of survival based on factor of hematocrit level

3.3 Log-Rank Test

The Log-Rank test is carried out to compare two or more survival tables and curve graphs in the survival function, so the hypothesis used in the Log-Rank test is as follows:

H_0 : No difference between different groups on the survival curve
H_1 : There is at least 1 difference between different groups on the survival curve

The results of the Log-Rank test are shown in Table 6, below:

Table 6. Log-rank test results

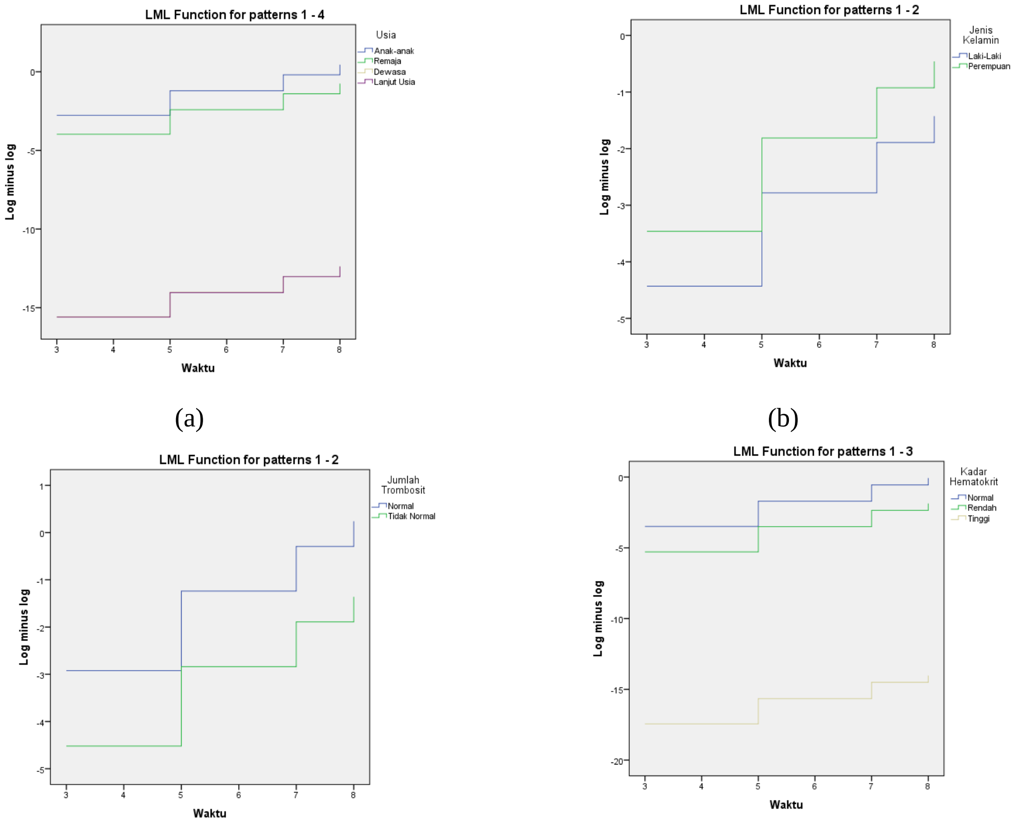
	Chi-Square	**df**	**Sig.**	**Decision**
Age	9,035	3	0,029	Reject H_0
Gender	1,482	1	0,223	Accept H_0
Platelet Count	5,646	1	0,017	Reject H_0
Hematocrit Level	4,445	2	0,108	Accept H_0

Based on Table 6, it can be seen that by using α value of 0.05 there are differences in age and platelet count variables on the survival curve, while on the survival curve there is no difference between gender and hematocrit levels.

3.4 Testing the Assumption of Proportional Hazard (PH)

The proportional hazard assumption test was conducted to determine whether the factors thought to affect the survival of patients with DHF at Dr. Pirngadi General Hospital Medan were constant or changed with time. In this study, the approach used is the graphical method and the time-dependent variable approach. The time-dependent variable method is used to obtain more objective results if the graph is difficult to observe visually in checking the proportional hazard assumption. The following are the hypotheses in testing using time-dependent variables:

H_0 : The independent variable fulfills the proportional hazard assumption
H_1 : The independent variable doesn't fulfill the proportional hazard assumption



(c) (d)

Figure 2. Plot log(-log S(t)) of DHF patients, where: a) age factor d) sex factor c) platelet count factor d) hematocrit level factor

Based on Figure 2, it is found that the entire log(-log S(t)) plot is difficult to observe visually, then proceed with a time-dependent variable approach to obtain more objective results. Below are the results of the time-dependent variable approach:

Table 7. Approach of time-dependent variable

	Wald	**df**	**Sig.**
T_COV*X_1	1,647	1	0,199
T_COV*X_2	0,449	1	0,503
T_COV*X_3	1,435	1	0,231
T_COV*X_4	0,385	1	0,535

By using α value of 0.05, it can be concluded that all independent variables meet the proportional hazard assumption.

3.5 Cox Regression Model

The Cox regression model is a robustness analysis that meets the proportional hazard assumption. The estimation results of the Cox regression model parameters are shown in Table 8 below:

Table 8. Cox regression model estimation results

	β	**SE**	**Df**	**Sig.**	**Exp(β)**
X_1	-0,974	0,804	1	0,226	0,378
X_2	0,627	0,924	1	0,498	1,872
X_3	-1,339	0,881	1	0,128	0,262
X_4	-1,194	1,023	1	0,243	0,303

Based on Table 8, the Cox Proportional Hazard Regression model is obtained as follows:

$$h(t) = h_0(t)\, exp\, exp\, (-0{,}974x_1 + 0{,}627x_2 - 1{,}339x_3 - 1{,}194x_4)$$

3.6 Parameter Significance Test

Parameter significance testing was conducted to determine whether the model had a significant effect or not on the recovery rate of patients with DHF at Dr. Pirngadi General Hospital Medan.

1. Simultan test

This test is carried out to see in its entirety whether there are independent variables that have a significant influence on the model. The hypothesis is as follows:

H_0 : There is no independent variable that has a significant effect on the model

H_1 : There is at least one independent variable that has a significant effect on the model

Test statistics:

$$G^2 = -2\,(lnL_R - lnL_F) = 43{,}372 - 29{,}590$$
$$= 13{,}782$$

With α = 0,05 obtained:

$$\chi^2_{table} = \chi^2_{\alpha,4} = 9{,}4877$$

Because $G^2 > \chi^2_{table}$ (13,782 > 9,4877), then reject H_0. So that there are independent variables that have a significant influence on the model.

2. Partial test

This test is carried out to see whether there are independent variables that have a significant influence on the model. The hypothesis is as follows:

H_0 : There is no independent variable that has a significant effect on the model

H_1 : There are independent variables that have a significant effect on the model

Test statistics:

$$W^2 = \left(\frac{\beta}{SE(\beta)}\right)^2$$

With α = 0,05 obtained:

$$\chi^2_{tabLE} = \chi^2_{\alpha,1} = 3{,}841$$

Partial test results are shown in Table 9, below:

Table 9. Partial test results

	Wald	χ^2_{tabel}	**Test Criteria**	**Decision**
X_1	1,469	3,841	$W^2 < \chi^2_{table}$	Accept H_0
X_2	0,460	3,841	$W^2 < \chi^2_{table}$	Accept H_0
X_3	2,311	3,841	$W^2 < \chi^2_{table}$	Accept H_0
X_4	1,361	3,841	$W^2 < \chi^2_{table}$	Accept H_0

Based on Table 9, it shows that all the independent variables used in this model have no significant effect on the recovery rate of DHF patients at Dr. Pirngadi General Hospital Medan.

3.7 Best Model Selection

The Akaike Information Criterion (AIC) criteria were used in selecting the best model. Before calculating the AIC value, first form a model from several variations of the independent variables. The number of variations of the independent variables formed is $2^p - 1$, where *p* is many independent variables. So that the number of models formed is as follows :

$2^p - 1 = 2^4 – 1 = 15$

Of the 15 models formed, the parameter significance test was carried out. Then the results are shown in Table 10 below:

Table 10. Parameter Significance Test Results From 15 Models Formed

No	Model	Simultan Test	Variable	Partial Test
1.	X_1	Significant	X_1	Significant
2.	X_2	Not Significant	X_2	Not Significant
3.	X_3	Significant	X_3	Significant
4.	X_4	Significant	X_4	Not Significant
5.	X_1 , X_2	Significant	X_1	Significant
			X_2	Not Significant
6.	X_1 , X_3	Significant	X_1	Significant
			X_3	Not Significant
7.	X_1 , X_4	Significant	X_1	Significant
			X_4	Not Significant
8.	X_2 , X_3	Not Significant	X_2	Not Significant
			X_3	Not Significant
9.	X_2 , X_4	Significant	X_2	Not Significant
			X_4	Significant
10.	X_3 , X_4	Significant	X_3	Significant
			X_4	Not Significant
11.	X_1 , X_2 , X_3	Significant	X_1	Significant
			X_2	Not Significant
			X_3	Not Significant
12	X_1 , X_2 , X_4	Significant	X_1	Not Significant
			X_2	Not Significant
			X_3	Not Significant
13.	X_1 , X_3 , X_4	Significant	X_1	Not Significant
			X_3	Not Significant
			X_4	Not Significant
14.	X_2 , X_3 , X_4	Significant	X_2	Not Significant
			X_3	Not Significant
			X_4	Significant
15.	X_1 , X_2 , X_3 , X_4	Significant	X_1	Not Significant
			X_2	Not Significant
			X_3	Not Significant
			X_4	Not Significant

Based on Table 10, it shows that there are 6 models whose all variables are not significant when the partial test is carried out, so these models are not the appropriate models. And the other 9 models have significant variables when the partial test is carried out. Then the 9 models calculated the AIC value to get the best model. Here are the AIC values generated from 9 models:

Table 11. AIC Value

Model	AIC
X_1	36,612
X_3	41,117
X_1 , X_2	37,725
X_1 , X_3	35,960
X_1 , X_4	37,070
X_2 , X_4	38,848
X_3 , X_4	36,741
X_1 , X_2 , X_3	37,559
X_2 , X_3 , X_4	37,272

Based on Table 11 shows that the X_3 model produces the largest AIC value of 41.117, while the model X_1 , X_3 produces the smallest AIC value of 35.960. So it can be interpreted that the model X_1 , X_3 is the best model. Parameter estimation of the model X_1 , X_3 shown in Table 12 below :

Table 12. Estimation Results of the Best Cox Regression Model

	β	SE	Df	Sig.	Exp(β)
X_1	-1,550	0,730	1	0,034	0,212
X_3	-1,273	0,781	1	0,103	1,280

Based on the partial test conducted for this model, it was found that the platelet count variable (X_3) had no significant effect on the model while the age variable (X_1) had a significant effect on the model, so only the age variable (X_1) was included in the model. So the final Cox proportional hazard regression model is as follows:

$$h(t) = h_0(t)\ exp\ exp\ (-1{,}550x_1)$$

Then the hazard ratio of the age variable (X_1) is obtained as follows:

$$\widehat{HR} = e^{\beta} = 0{,}212$$

Based on the hazard ratio value of the age variable, it is stated that adolescent DHF patients have a 0.212 times greater chance of survival than children with DHF.

4. CONCLUSIONS

In this study it can be concluded that the estimation of the results of survival analysis using the Kaplan-Meier method on data on DHF patients in RSUD Dr. Pirngadi Medan found that the chances of survival of DHF patients ranged from 1 to 0.6532 and in the significance test of the best model parameters, it was found that the age variable had a significant effect on the cure rate of DHF patients. Dengue Hemorrhagic Fever (DHF).

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