Estimating Survival Time of Dengue Haemorrhagic Fever Using Extended Cox Model

IOP Conf. Series: Journal of Physics: Conf. Series **1188** (2019) 012017 doi:10.1088/1742-6596/1188/1/012017

Estimating Survival Time of Dengue Haemorrhagic Fever Using Extended Cox Model

M Muhammad[1], Gunawan[1], and D A Yuwaningsih[2]

[1]Universitas Muhammadiyah Purwokero, Jl. Raya Dukuhwaluh 53182, Purwokerto, Indonesia
[2]Universitas Ahmad Dahlan, Jl. Ringroad Selatan 55191, Yogyakarta, Indonesia

E-mail: malim.muhammad@gmail.com

Abstract. Dengue Haemorrhagic Fever (DHF) is a disease that tends to increase every year around the world and become endemic almost half the world's population. In Indonesia since 1968, DHF has known in Surabaya and Jakarta. Survival analysis is a statistical analysis that specifically used to analyze data or cases related to the time or length of time until a particular event occurs. The aims of this research where to find out the significant variables that influence the rate of death DHF patient at Dr. Pirngadi Hospital in January until December 2017 as many as 100 patients. The result shows that the Extended Cox Model could overcome the assumption of non-proportional hazard on DHF patients at Dr. Pirngadi Hospital, during January until December 2017. The best model is Extended Cox Model time function $g_i(t) = t$, because the model have the smallest score of AIC is 213.0408. Furthemore, Gender variable was the significant factor that influence toward survival time on DHF patients. In this case, Female has exp(0.9162) = 2.5, it means that Female has a higher risk of death rate of 2.5 than Male on DHF patients during January until December 2017 at Dr. Pirngadi Hospital.

1. Introduction

Dengue is a major public health concern throughout the tropical and subtropical regions of the world. Almost half the world's population live in countries where Dengue is endemic. World Health Organization (WHO) estimates that 50-100 million Dengue infections occur every year with 22,000 deaths. It has been identified as one of the 17 neglected tropical diseases by WHO [1]. Dengue and its severe forms, namely, Dengue Haemorrhagic Fever (DHF) and dengue shock syndrome (DSS), caused by four serotypes of dengue virus (DENV), have become a major public health concern that is straining the health systems of both developing and developed countries. More than 50% of the people at risk of being infected are living in the South East Asian Region (SEAR) of the World Health Organization (WHO). Lack of approved vaccines and antivirals for prevention and treatment of the disease and the failure of vector control programs to combat the disease-carrying mosquitoes of Aedes species had contributed to the spread and increased incidence of dengue [2]. It was founded in tropical and subtropical regions around the world, predominantly in urban and semi-urban areas. There is no specific treatment for dengue, but appropriate medical care frequently saves the lives of patients with more serious DHF. The most effective way to prevent dengue virus transmission is to combat the disease-carrying mosquitoes [3].

Indonesia is a tropical country that has two seasons, namely the rainy season and the dry season. In the rainy season, for various reasons, there are floods or puddles that can become a mosquito breeding

and spread various diseases, one of which is dengue fever disease [4]. Most of the regions in Indonesia have tropical climate and sub-tropics. These circumstances make Indonesia as one of the DHF endemic countries in South East Asia [5]. Furthermore, DHF has been known in Indonesia since 1968 were reported in Surabaya and Jakarta [6]. It quickly spread to other areas so that in 1980 all provinces in Indonesia that have been infected with DHF. Indonesia is the country with the highest incidence of DHF in Southeast Asia since 1968-2009 [7]. The number of DHF cases since January until October in 2009 is 121,423 cases, with the number of died patients, are 1,013 and it has been increasing the DHF cases than in 2008. On the other hand, the number of DHF case in 2012 is 90,245 cases which 816 patient died and 8,177 cases of DHF were reported in East Java during 2012 and that cases became the highest rank in Indonesia after West Java with 19,663 cases [8].

The survival time is time that is within an object from the beginning to the time of occurrence of an event. These events may include the development of the disease, response to treatment, the recurrence of the disease, or death [9]. The time of each individual does not have to be the same and the unit can be either year, month, week or day. The survival time was not be observed in full that can be caused by the expiration of individual observations, which are observed to disappear in times of observations, died or cause other than research. When the survival time can be observed during the period of observation it is called complete data, whereas when it is not fully observable data then it is called censor [10]. In the hazard ratio model, the resulting value is no longer time-dependent so that the ratio of the two objects remains at all times proportional hazard. The proportional Cox regression model emphasizes the fulfillment of the proportional hazard assumption which means that the ratio between individual hazard functions of one and other individual hazard functions is constant [11].

2. Materials and Methods

2.1. Cox Proportional Hazard Model

The most common approach to model covariate effects on survival is the Cox Proportional Hazard (PH) Model, which can handle censored and or truncated observations [12]. Regression analysis generally used for identifying the risk factors, but due to the presence of censoring in survival data, ordinary regression models cannot use. In addition, simple logistic regression analysis has the limitation of only allowing a view of survival probability over the entire study period as a single time interval and it assumes that every patient is at risk over the entire study period. This is not valid for studies with longer follow up or other situations where patients have variable time at risk. For this purpose, in survival analysis, Cox regression model is widely applicable [13]. The distinguishing feature of the Cox PH Model is its ability to estimate the relationship between the hazard rate and explanatory variables without having to make any assumptions about the shape of the baseline hazard function. Hence, the Cox PH Model referred to as a semi-parametric model. Let $x_1, x_2, ..., x_p$ be the values of p covariates $X_1, X_2, ..., X_p$, the Cox PH regression model relates covariates to the hazard function as follows:

$$h(t) = h_0(t) \exp\left(\sum_{i=1}^{p} \beta_i x_i \right) \tag{1}$$

Where $\beta = \left(\beta_1, \beta_2, ..., \beta_p \right)$ is a $1 \times p$ vector of regression parameters (independent variables) and $h_0(t)$ is the baseline hazard function at that time. Coefficient vectors of the covariates estimated using a Maximum Likelihood procedure. Maximum Likelihood estimates are obtained by maximizing a (partial) likelihood function [14].

2.2. Testing Parameter Estimator

Testing parameter estimator performed to examine the role of the independent variables in the Cox PH Model. Testing the parameters β simultaneously using G-test, while testing partially using Wald-test.

2.2.1. G-Test. This test is the likelihood ratio test used to test the parameters β (independent variables) in the model simultaneously. Under the null hypothesis, used significant levels alpha (α), H_0 was rejected if $G \geq \chi^2_{(\alpha;df)}$ or p-value less than alpha (α). Where $G = -2[\ln(L_0) - \ln(L_p)]$, L_0 is the likelihood function without independent variables and L_p is the likelihood function with *p* independent variables. It indicates that there are at least one independent variables which influence significantly to the survival time [14].

2.2.2. Wald-Test. This test used to test the parameters β (independent variables) in the model partially. Under the null hypothesis, used significant levels alpha (α), H_0 was rejected if $W \geq \chi^2_{(\alpha;df)}$ or p-value less than alpha (α). Where $W = \left(\frac{\hat{\beta}_i}{SE\left(\hat{\beta}_i\right)} \right)^2$, it indicates that there is the independent variable which influences significantly partially to the survival time [14].

2.3. Assessment of Proportional Hazards Assumption

In Cox PH Model there is a proportional hazard assumption to be satisfy i.e. function hazard an individual against function hazard another individual is proportional or the ratio of the hazard function two different individuals is constant over time [15]. The interpretation of coefficients on a Cox PH Model seen through the hazard rate ratio. If there are two individuals with variables x and x^*, then the hazard rate ratio is given as follows [16]:

$$HR = \frac{h(t_1)}{h(t_2)} = \frac{h_0(t)\exp\left(\sum_{i=1}^{p}\beta_i x_i\right)}{h_0(t)\exp\left(\sum_{i=1}^{p}\beta_i x_i^*\right)} = \exp\left[\sum_{i=1}^{p}\beta_j\left(x_i - x_i^*\right)\right] \tag{2}$$

The above equation is the relative risk of an individual with risk factor x experience event than any other individuals with risk factors of x^* [17]. The main assumption of the Cox PH Model is proportional hazards, which mean that the hazard ratio is constant over time. There are several methods for verifying that a model satisfies the assumption proportionality (Graphical Method, Scaled Schoenfeld Residuals, and Adding Time-Dependent Covariate). In this case, used Graphical Method, and Scaled Schoenfeld Residuals.

2.3.1. A graphical method using log (-log (survival)). According to the Cox PH Model, the survival function for the *ith* individual is given by:

$$S_i(t) = \left[S_0(t)\right]\exp\left(\sum_{i=1}^{p}\beta_i x_i\right) \tag{3}$$

Where $x_1, x_2, ..., x_p$ be the values of p covariates, by taking the logarithm twice as follow:

$$\ln\left[-\ln S_i(t)\right] = \left(\sum_{i=1}^{p}\beta_i x_i\right) + \ln\left[-\ln S_0(t)\right] \tag{4}$$

Then the difference in log-log curves corresponding to two different individuals with variables $x_1 = (x_{11}, x_{12}, ..., x_{1p})$ and $x_2 = (x_{21}, x_{22}, ..., x_{2p})$ not depend on the *t* given by:

$$\ln\left[-\ln S_i(t, x_1)\right] - \ln\left[-\ln S_i(t, x_2)\right] = \sum_{i=1}^{p} \beta\left(x_{1i} - x_{2i}\right) \tag{5}$$

This provides the basis for assessing the validity of the Cox PH assumption. By plotting estimated *log (-log(survival))* versus survival time for two groups, it would see parallel curves if the hazards are proportional [18]. This method did not work well for categorical predictors with many levels because the graph cluttered.

2.3.2. Scaled Schoenfeld Residuals. Scaled Schoenfeld Residuals are defined as the product of the inverse of the estimated variance-covariance matrix of the *kth* Schoenfeld Residual and the *kth* Schoenfeld Residual [19]. The Scaled Schoenfeld Residual used to assess time trends and lack of proportional hazard.

$$r_{pji}^{*} = \left(V^{-1}\right) r_{pji} \tag{6}$$

Where r_{pji}^{*} is the Scaled Schoenfeld Residual and r_{pji} is the Schoenfeld Residual. Under the null hypothesis, expected to see a constant function over time. When the proportional hazards assumption holds, straight horizontal line with zero slopes is expected.

2.4. Extended Cox Model

If the proportional hazard assumption did not satisfy, so Extended Cox Model was the solution to overcome the independent variables when the hazard ratio is not constant over time. Extended Cox Model is called non-proportional hazard model because this model was an alternative model if the proportional hazard was not fulfilled [9].

$$h(t, X(t)) = h_0(t) \exp\left(\sum_{i=1}^{p1} \beta_i X_i + \sum_{j=1}^{p2} \delta_j X_j(t)\right) \tag{7}$$

With $X(t) = (X_1, X_2, ..., X_{p1}, X_1(t), X_2(t), ..., X_{p2}(t))$, $X_1, X_2, ..., X_{p1}$ covariates variables that do not depend on time and $X_1(t), X_2(t), ..., X_{p2}(t)$ covariates variables that depend on time. The notation δ is a parameter of covariate variables for each time *t* and β is a vector of regression parameters not depend on time. To assess that the proportional hazard regression model, the function of this hazard satisfy proportional hazard assumption, we can use the function of time $g_i(t)$, so that this model written as:

$$h(t, X(t)) = h_0(t) \exp\left(\sum_{i=1}^{p1} \beta_i X_i + \sum_{j=1}^{p2} \delta_j X_j g_i(t)\right) \tag{8}$$

Value of the parameter $\hat{\delta}_i$ will be varying on each of the explanatory variables that depend to time and the parameter $\hat{\delta}_i$ to interpret the overall influence of the relationship between the explanatory variables to time to see at all the time on the variables used in the study. If the value of the parameter $\hat{\delta}_i < 0$ then the hazard ratio will decline simultaneously with the rise, time and vice versa. It caused hazard ratio inconsistent, it means that the proportional hazard assumption is not satisfied for Extended Cox Model. A function of time $g_i(t)$ is used in Extended Cox Model are $g_i(t) = 0, g_i(t) = t, g_i(t) = \ln t$, and $g_i(t)$ is heavy side function.

2.5. Likelihood Ratio (LR) Test

Likelihood Ratio (LR) Test is a comparison test of log likelihood for Stratified Cox Model and Extended Cox Model. LR Test as follows:

$$LR = -2\ln L_R - (-2\ln L_F) \tag{9}$$

Where,

LR is Likelihood Ratio

L_R is without interaction model (*Reduced* Model)

L_F is with interaction model (*Full* Model)

Rejection Area: H_0 rejected if $LR > \chi^2_{(\alpha;df)}$ or *p-value* < 0.05 [14].

2.6. Selection of the Best Models

Similar to classical regression analysis. Cox regression analysis also needs to determine the best models. The best models have the smallest score of Akaike Information's Criterion (AIC).

$$AIC = -2\log \hat{L} + \alpha q \tag{10}$$

Where,

$\hat{L}$ = Maximum likelihood function of cox regression model

α = The large number of independent variables of cox regression model

q = Predetermined constant

2.7. Research Data

Data used in this research is secondary data on Dengue Haemorrhagic Fever (DHF) patients at Dr. Pirngadi Hospital, in January until December 2017, obtained from medical record of Dr. Pirngadi Hospital as many as 100 patients [20].

2.8. Research Variable

In this research, the variables used are response variables and predictor variables, with the description as follows:

2.8.1. Response Variable. Response variable in this research is survival time, which is time needed by the patient to survive from the time early of DHF patients in the hospital (start point) until patient stated recover (failure). The patient observed in 6 days, the patient recover within 6 days observation called event. If the patient has not recovered until the end of observation, the patient dies, the patient resigns or lost to follow up is called censor, which is classified into two categories where 0 is event (recover) and 1 is censor (still sick at the end of the observation, died, resign or lost to follow up).

2.8.2. Predictor Variables. Predictive variables in this study are data predicted to affect the survival time of DHF patients obtained from medical record data at Dr. Pirngadi Hospital, the description for predictor variables provided in Figure 1.

- **Age (X1)**: The age variable is the age of DHF patients at the beginning of admission to hospitalization at Dr. Pirngadi Hospital, which is classified into two categories:
  0 = more than equal 20 years
  1 = less than 20 years
- **Gender (X2)**: The gender variable is the sex of DHF patients who are hospitalized at Dr. Pirngadi Hospital, which is classified into two categories:
  0 = Male
  1 = Female

- **Duration of DHF (X3)**: Time interval that started the fever until treated at Dr. Pirngadi Hospital, which is classified into two categories:
  0 = less than equal 4 days
  1 = more than 4 days
- **Grade of DHF (X4)**: The severity of DHF experienced by a patient is determined when the patient is first time came to the Hospital based on the medical record, which is classified into four categories:
  0 = Level I
  1 = Level II
  2 = Level III
  3 = Level IV
- **Platelet (X5)**: Platelet variable is the number of thrombocyte of DHF patients during undergoing inpatient at Dr. Pirngadi Hospital, which is divided into two categories:
  0 = more than 100,000/mm^3
  1 = less than equal 100,000/mm^3

Figure 1. Classification of the predictor variables on DHF patients at Dr. Pirngadi Hospital.

3. Results

3.1. Testing Parameter Estimator of Cox PH Model

Testing parameter estimator performed to examine the role of the independent variables in the Cox PH Model. Table 3.1 is the result of Cox PH model parameter estimation of DHF patients during undergoing inpatient at Dr. Pirngadi Hospital as many as 100 patient. Estimation of Cox PH Model parameters done using Efron Method approach.

Table 3.1 Cox PH Model Parameter Estimation with Efron Method

Variables	Coef	*Exp(Coef)*	Se(Coef)	*z*	Pr(>|z|)
Age	0.1708	1.1863	0.3894	0.439	0.6609
Gender	0.6838	1.9815	0.3963	1.725	0.0844
Duration	-0.4557	0.634	0.4428	-1.029	0.3034
Grade	0.1602	1.1738	0.24	0.668	0.5044
Platelet	1.2014	3.3249	0.6406	1.875	0.0607

From table 3.1, it assumed that all the independent variables to the model, then all variables included in the general equation of Cox PH Model, obtained estimated Cox PH model with the Efron method as follows:

$$h(t) = h_0(t)\exp(0.1708X_1 + 0.6838X_2 - 0.4557X_3 + 0.1602X_4 + 1.2014X_5) \qquad (11)$$

3.2. Testing Parameter Estimator

Testing the independent's parameters simultaneously using G-test, while testing partially using Wald test. Cox PH model was conducted to determine the relationship between survival time and the independent variables. It obtained, $G = 10.269 < \chi^2_{(0,05;6)} = 12,592$ and $\text{p-value} = 0.113 > 0.05$, so H_0 is accepted and inferred that the independent variables have no effect simultaneously in the model. The table 3.2 shows that the Wald-Test estimator used to test the parameter β partially.

Table 3.2 Cox Regression Model Parameter Estimation Partially with Efron Method

Variables	Coef	*Se(Coef)*	W	χ^2	Pr(>|z|)	Decision
Age	0.3162	0.3815	0.69	3,841	0.407	Accepted H_0
Gender	0.7470	0.3946	3.58	3,841	0.058	Accepted H_0

Duration	-0.1010	0.3992	0.06	3,841	0.800	Accepted H_0
Grade	0.2390	0.2036	1.38	3,841	0.240	Accepted H_0
Platelet	1.2385	0.6146	4.06	3,841	0.043	Rejected H_0

From table 3.2, the Wald-Test shows the variable Platelet effected to the model partially. Because $W = 4.06 \geq \chi^2_{(0.05;1)} = 3,841$ or p-value $= 0.043 < \alpha = 0.05$. However, to make sure that the independent variable fulfilled the proportional hazards assumption. It assess this model using several methods for verifying that the model satisfies the assumption of proportional hazard, in this case, Graphical Method using plot log (-log(survival)) and Scaled Schoenfeld Residuals was provided.

3.3. Assessment of Proportional Hazards Assumption

There is two approaches method to assess Cox PH assumption. There are Graphical Method and Scaled Schoenfeld Residuals.

3.3.1. Graphical method using plot log (-log (survival)). According to [15], if the plot log-minus-log of survival parallel means that the assumption of proportional hazard is not violated. Each independent variables from the plot log-minus-log of survival indicated that the resulting curve parallel between categories, then it satisfies the proportional hazard assumption. Conversely, if the curve of log-minus-log of survival for independent variables occurs intersection indicated that the resulting does not satisfy the assumptions.

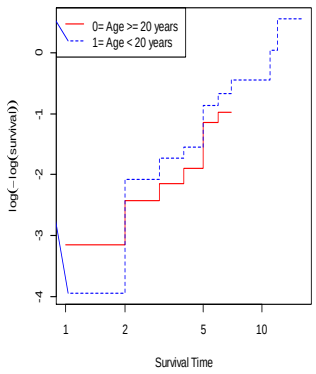

Figure 2. Plot log-minus-log survival of Age variable

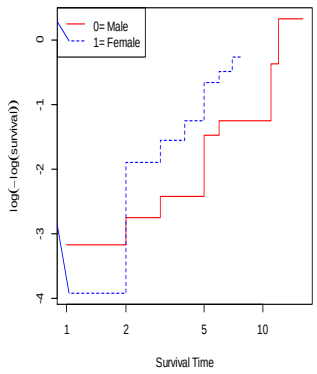

Figure 3. Plot log-minus-log survival of Gender variable

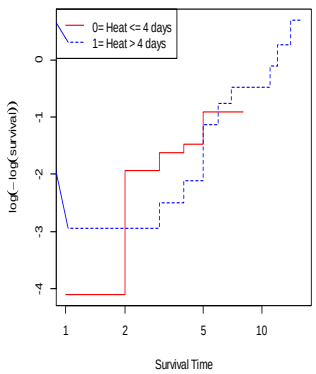

Figure 4. Plot log-minus-log survival of Duration variable

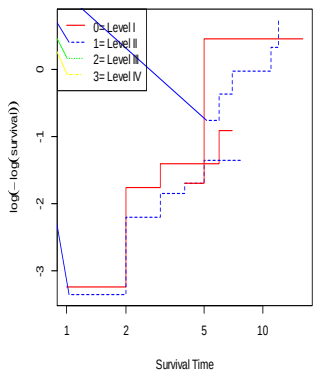

Figure 5. Plot log-minus-log survival of Grade variable

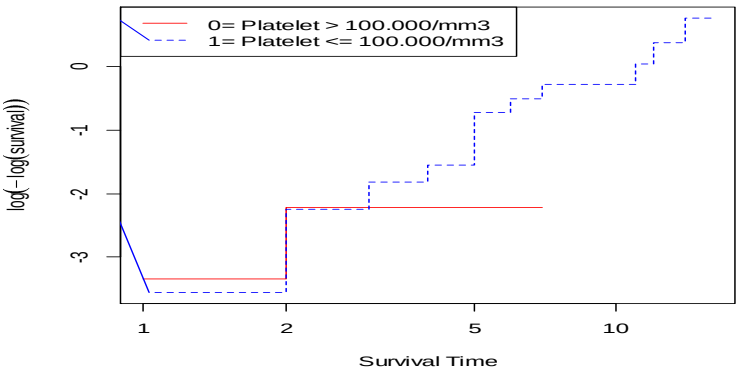

Figure 6. Plot log-minus-log survival of Platelet variable

In Figure 2 shows that plot log-minus-log of survival for Age variable with plot more than equal 20 years and less than 20 years intersected, so the Age variable was not satisfied the assumption. In Figure 3 shows that plot log-minus-log of survival for Gender variable with plot Male and Female intersected, so the Gender variable was not satisfied the assumption. In Figure 4 shows that plot log-minus-log of survival for Duration variable with plot less than equal 4 days and more than 4 days intersected, so the Duration variable was not satisfied the assumption. In Figure 5 shows that plot log-minus-log of survival for Grade variable with plot Level I, Level II, Level III, and Level IV intersected, so the Grade variable was not satisfied the assumption. In Figure 6 shows that plot log-minus-log of survival for Platelet variable approach curve parallel. In this case, based on Collett [14], it can be said to have a little reason to doubt the plot for satisfied proportional hazard assumption [21]. Furthermore, for more detail, it can be used Scaled Schoenfeld Residuals.

3.3.2. Scaled Schoenfeld Residuals. The value of Scaled Schoenfeld Residuals towards survival time provide information about the shape of coefficient independent variables over the time. The curve approaches horizontal or has approach zero slopes with indicated that the independent variables constant over the time and proportional hazard assumption fulfilled. Given plot Scaled Schoenfeld Residuals towards survival time of each independent variables as follow.

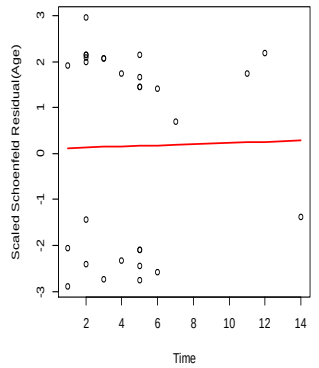

Figure 7. Plot Scaled Residual Schoenfeld Age variable

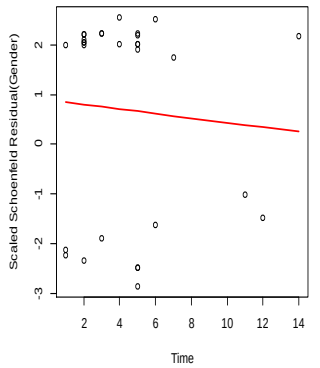

Figure 8. Plot Scaled Residual Schoenfeld Gender variable

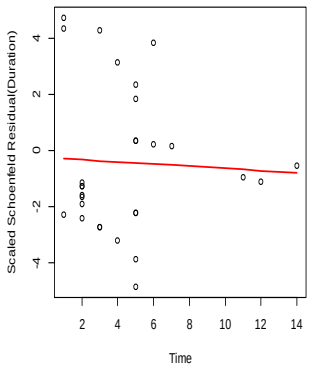

Figure 9. Plot Scaled Residual Schoenfeld Duration variable

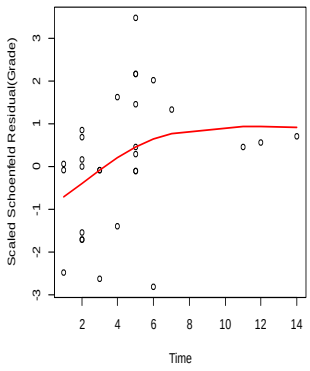

Figure 10. Plot Scaled Residual Schoenfeld Grade variable

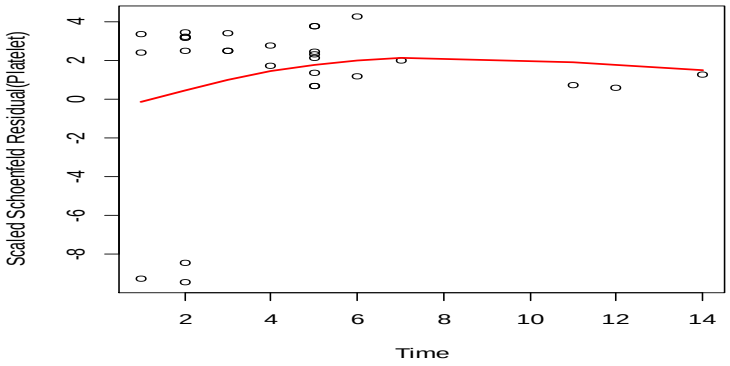

Figure 11. Plot Scaled Residual Schoenfeld Platelet variable

Based on Figure 7, it can see clearly that plot Scaled Schoenfeld Residual toward survival time for Age variable approaches horizontal or has approach zero slopes, so that it said that proportional hazard assumption for Age variable fulfilled. Based on figure 8 and figure 9, likewise with Gender variable and Duration variable approaches horizontal or have approach zero slopes, so that it can be said that proportional hazard assumption for Gender variable and Duration variable was fulfilled. On the contrary, In figure 10 and figure 11, Grade variable and Platelet variable did not approach the horizontal and has a slope that did not approach zero, in other words, proportional hazard assumption for Gender variable and Platelet variable using Scaled Schoenfeld Residuals was not satisfied.

Based on plot log-minus-log and Scaled Schoenfeld Residuals it can be inferred that Platelet variable did not fulfill the assumption of proportional hazard so in this study was continued to the Extended Cox Model.

3.4. Cox Extended Model

Based on the assumption of proportional hazard, it founded that Platelet did not fulfill the assumption, so new model needed to overcome the variable that does not satisfy the Cox PH, in this case using Cox Extended Model. In this research, Platelet variable interacted with time function. Therefore, added the time function $g(t)$ on Platelet variable in Extended Cox Model as follow.

1. $g_i(t) = t$
2. $g_i(t) = ln\, t$

3. $g_i(t) = \begin{cases} 1, if\ t \geq 6 \\ 0, if\ t < 6 \end{cases}$ is heavy side function (12)

From equation (12), Testing parameters simultaneously using likelihood ratio test obtained p-value significant. It means that at least one independent variable influence the model. More detail shows on table 3.3 as follow.

Table 3.3 Comparison Cox Extended Model with time function using Efron Method

	$g_i(t) = t$ *Parameter Estimation*	*p-value*	$g_i(t) = ln\ t$ *Parameter Estimation*	*p-value*	*Heavyside Parameter Estimation*	*p-value*
Age1	0.2066	0.601	0.20972	0.5956	0.2261	0.569
Gender1	0.9162	0.0263	0.90889	0.0272	0.8641	0.0335
Duration1	-0.7724	0.1074	-0.77395	0.1064	-0.7757	0.1045
Grade1	-0.9678	0.0757	-0.96806	0.0752	-0.9506	0.0777
Grade2	-0.1321	0.8495	-0.13187	0.8495	-0.1075	0.8756
Grade3	0.0668	0.9201	0.07545	0.9096	0.1451	0.8247
Platelet1	-2.2422	0.1821	-1.04211	0.3194	1.0300	0.1117
Platelet.gt	1.3177	0.1156	2.48668	0.0546	-15.7400	0.9979
Likelihood Ratio Test	20.81	0.0076	19.85	0.0109	15.14	0.04645
AIC	213.0408		214.002		218.7095	

3.5. Interpretation of Cox Extended Model

The best model from table 3.3 is Extended Cox Model time function $g_i(t) = t$ because the model have the smallest score of Akaike Information's Criterion (AIC) is 213.0408. The best model expressed in the following equation:

$$h(t) = h_0(t)\exp(0.2066X_1 + 0.9162X_2 - 0.7724X_3 - 0.9678X_4 - 0.1321X_5 + 0.0668X_6 - 2.2422X_7 + 1.3177X_7 g_i(t)) \quad (13)$$

Based on table 3.3, only Gender variable was the significant factor that influence toward survival time on DHF patients. In this case, Female has exp(0.9162) = 2.5, it means that Female has a higher risk of death rate of 2.5 than Male on DHF patients during January until December 2017 at Dr. Pirngadi Hospital.

4. Conclusion

In this study, it inferred that Extended Cox Model could overcome the assumption of non-proportional hazard on DHF patients at Dr. Pirngadi Hospital, during January until December 2017. The best model is Extended Cox Model time function $g_i(t) = t$ because the model have the smallest score of AIC is 213.0408.

5. Acknowledgment

The authors thank to Universitas Muhammadiyah Purwokerto and Universitas Ahmad Dahlan for giving us the opportunity to encourage and facilitate the authors to complete this research.

References

[1] World Health Organization Country Office for India 2015 *National Guidelines for Clinical Management of Dengue Fever* (New Delhi, India)

[2] World Health Organization 2012 *Global Strategy for Dengue Prevention and Control 2012-2020* (Geneva, Switzerland: WHO Press)

[3] World Health Organization Regional Office for South-East Asia 2011 *Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever*

[4] Handayani L, Fatekurohman M and Anggraeni D 2017 Survival Analysis in Patients with Dengue Hemorrhagic Fever (DHF) Using Cox Proportional Hazard Regression *Int. J. Adv. Eng. Res. Sci.* **6495** 138–45

[5] Ali K and Ma'rufi I 2016 Study of Factors Caused Dengue Haemorrhagic Fever Case Study: Pasuruan, Jawa Timur-Indonesia *J. Med. Bioeng.* **5** 108–12

[6] Dinkes Provinsi Jawa Timur 2013 *Profil Kesehatan Provinsi Jawa Timur Tahun 2012* (Surabaya, Jawa Timur)

[7] World Health Organization 2009 *Dengue, Guidelines For Diagnosis, Treatment, Prevention, and Control* (Geneva, Switzerland)

[8] Ministry of Health Republic of Indonesia 2014 Indonesia Health Profile 2013 *Minist. Heal. Repub. Indones* 1–386

[9] Lee E T and Wang J W 2003 *Statistical Methods for Survival Data Analysis* (Hoboken, NJ, USA: John Wiley & Sons, Inc.)

[10] Kleinbaum D G and Klein M 2012 *Survival Analysis A Self-Learning Text* ed M Gail, K Krickeberg, W Wong, A Tsiatis and J M Samet (New York: Springer Science+Business Media)

[11] Husain H, Thamrin S A, Tahir S and Mukhlisin A 2018 The Application of Extended Cox Proportional Hazard Method for Estimating Survival Time of Breast Cancer The Application of Extended Cox Proportional Hazard Method for Estimating Survival Time of Breast Cancer

[12] Therneau T M and Grambsch P M 2000 *Modeling Survival Data: Extending the Cox Model* (New York: Springer Science+Business Media)

[13] Mohamed M, Abdelaal A, Eldin S H, Zakria A, Hossam S, Ahmed E and Modeling Z 2015 Survival Data by Using Cox Regression Model *Am. J. Theor. Appl. Stat.* **4** 504–12

[14] Collett D 2004 *Modelling Survival Data in Medical Research* vol 46 (Chapman & Hall/CRC Texts in Statistical Science)

[15] Guo S 2010 *Survival Analysis* (New York: Oxford University Press)

[16] Kurniawan I 2016 Analisis Daya Tahan Debitur Menggunakan Perluasan Model Cox Dan Cox Stratifikasi

[17] Klein J P and Moeschberger M L 2003 *Survival Analysis Techniques for Censored and Truncated Data* (New York: Springer-Verlag New York Inc.)

[18] Kleinbaum D G 1996 *Survival Analysis* (New York: Springer-Verlag New York Inc.)

[19] Therneau T M and Grambsch P M 1994 Proportional Hazards Tests and Diagnostics Based on Weighted Residuals *Biometrika* **81** 515–26

[20] Hasibuan P H 2018 Analisis Survival Dengan Regresi Cox Pada Laju Kesembuhan Penderita Demam Berdarah Dengue (DBD) di RSUD Dr. Pirngadi Medan

[21] Vittinghoff E, Glidden D V., Shiboski S C and McCulloch C E 2012 *Regression Methods in Biostatistics* (Boston, MA: Springer US)