INDONESIAN COUNCIL OF PREMIER STATISTICAL SCIENCE

Indonesian Council of Premier Statistical Science
ISSN: 3030-9956/https://dx.doi.org/10.24014/icopss.v4i2.37878

Volume 4 Issue 2, 74 – 80, August 2025

Application of the Cox Proportional Hazard Model with the Breslow Method in Inpatients with Type 2 Diabetes Mellitus at XYZ Hospital

Puteri Nuraisyah[1], Zahra Zakiyah[2]

[1,2]*Department of Matematika, Faculty of Sciences and Technology, Universitas Islam Negeri Sultan Syarif Kasim Riau, Indonesia*

Received: 23 July 2025 Revised: 27 August 2025 Accepted: 30 August 2025 Published: 31 August 2025

Abstract - *Type 2 Diabetes Mellitus (DMT2) is a chronic disease that is often accompanied by complications such as hypertension, anemia, and infection, which can affect the length of hospitalization and the time of clinical occurrence. The purpose of this study is to analyze the clinical factors that affect the time of occurrence in DMT2 inpatients at XYZ Hospital using the Cox Proportional Hazard regression model using the Breslow method. Secondary data from 33 patients were analyzed by including variables of age, sex, comorbidities, blood pressure, blood sugar levels, diabetes mellitus diet program, diabetic feet, and pain. Results showed that age (p = 0.076), comorbidities (p = 0.058), and pain complaints (p = 0.101) had a significant effect on the time of occurrence, while other variables were insignificant. Thus, the Cox model of the Breslow method has been shown to be effective in identifying risk factors in the clinical data of survival of DMT2 patients.*

Keywords: Survival Analysis, Cox Proportional Hazard Model, Type 2 Diabetes Mellitus

1. Introduction

Type 2 Diabetes Mellitus (DMT2) is a non-communicable type of disease, which is generally triggered by an unbalanced diet and accompanied by a lack of activity [1]. This condition causes impaired glucose metabolism in the body, characterized by a chronic increase in blood sugar levels caused by insulin resistance [2]. The disease is characterized by impaired glucose metabolism that causes chronically high blood sugar levels, especially due to insulin resistance or inadequate insulin production [3]. In Indonesia, the prevalence of type 2 diabetes mellitus is also high, reaching 10.9% based on Riskesdas data (2018) [4]. Complications due to DMT2 are very complex and can include impaired kidney function, heart, eyes, and limb amputation [5]. Therefore, it is necessary to identify factors that affect the cause of complications or death due to DMT2 so that patient treatment can be carried out more effectively.

Several previous studies have revealed a significant influence between various clinical factors and the risk of complications and death in patients with type 2 diabetes mellitus (DMT2). One of the studies [6] showed a relationship between age and fasting blood sugar levels in DMT2 patients at KPRJ Proklamasi, Depok, West Java. In addition, research by [7] It also identifies that blood sugar levels have a significant relationship with blood pressure, indicating that uncontrolled glucose levels can worsen the patient's clinical condition. Other factors such as hypertension have also been shown to be related to the incidence of DMT2 in Jambi Province [8]. Other research [9] found a significant association between sex factors and DMT2 incidence. However, not all of the results showed consistency, there were studies that stated that age, gender, and hypertension did not have a significant relationship with the incidence of DMT2 [10][11]. On the other hand, many previous studies have focused only on prevalence or simple relationships between variables, without considering the time of occurrence or the multiple events that often occur in clinical data.

Therefore, an analysis method is needed that not only identifies the influencing factors, but also takes into account the time of occurrence and the censored nature of the patient data. Type cox proportional hazard is one of the most widely used approaches in analysis survival because it is semiparametric and flexible, and does not require the assumption of a specific distribution of time survival [12]. This model allows researchers to measure the relative influence of variables on the risk of events in a given unit of time through estimation hazard ratio [13]. In the application of the model cox proportional hazardmethod Breslow chosen as an approach to estimating the function baseline hazard because of its excellence in handling data with events occurring at the same time [14].

Method Breslow provides a more stable and simple estimation compared to other methods such as Efron or Exact, so it is very suitable for use in clinical datasets that often have events tied to observation time [15]. This advantage is what makes the Breslow is the right choice in this study, because it is able to produce accurate risk estimates while making it easier to interpret the results of the analysis survival in patients with type 2 diabetes mellitus. So that the use of this method is expected to provide more complex and reliable knowledge about the factors that affect the time of complications or death in DMT2 patients, as well as support more effective clinical decision-making.

2. Research Methods

2.1. Research Data and Variables

The secondary data used in this study was obtained through the medical records of inpatients with a diagnosis of DMT2 at XYZ Hospital. The total number of patients in the dataset was 33 people, each of whom was observed based on the time of hospitalization until they experienced complications or were declared complete without incident (censored). Data were collected from patient records during a specific period of hospitalization.

Table 1. Diagnosis Data of Type 2 Diabetes Mellitus (DMT2) at XYZ Hospital

		Frequency	Percentage
Event	Uncensored	27	81,8%
	Tersensor	6	18,2%
Total		33	100%

The variables in this study are as follows:

Table 2 Variable Data of Diagnosis of Type 2 Diabetes Mellitus (DMT2) at XYZ Hospital

Variable Name	Unit	Data Type
X_1 = Age	Year	Category 0: Year$\leq$ 45 1: Year$>$ 45
X_2 = Gender	-	Category 0: Female 1: Male
X_3 = Comorbidity Disease	-	Category 1: Anemia 2: Hypertension 3: THAT 4: Pneumonia 5: Complications 6: Others
X_4 = Blood Pressure	mmHg	Category 0: mmHg$\leq$ 99 1: mmHg$\geq$ 100
X_5 = Blood Sugar Level	mg/dL	Category 0: mg/dL$<$ 200 1: mg/dL$\geq$ 200
X_6 = Program Diet Diabetes Melitus	-	Category 0: Ya 1: No
X_7 = Diabetic Foot	-	Category 0: Ya 1: No
X_8 = Rasa Nyeri	-	Category 0: Ya 1: No
Status	-	Category 0: Censored Data 1: Uncensored Data (Improved)
Y = Patient's *Survival* Time or Length of Hospitalization	Day	Numerik

2.2 Theoretical Foundations

2.2.1. Survival Function

Function *survival* $S\ (t)$, is the chance that the survival time exceeds or is equal to t[16], so that the function can be formulated as follows:

$$S(t) = P(T > t) = 1 - P(T \leq t) \quad (1)$$

2.2.2. Hazard Function

The hazard function expresses the rate of risk or likelihood of an event occurring at a time, provided that the individual has not experienced an event up to that time t[16]. Here are the similarities of functions *hazard*:

$$h(t) \ = \ \lim_{\Delta t \to 0} \left(\frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \right) \quad (2)$$

Functions can be expressed in the following forms:

$$h(t) \ = \frac{f(t)}{S(t)} \quad (3)$$

2.2.3. Model Regresi Cox proportional hazard

Model cox proportional hazard is a semiparametric model used in the analysis survival to assess the influence of independent variables on the timing of an event. This model is widely used because it does not require any specific distribution assumptions of time survival. Model regresi cox proportional hazard Was [16]:

$$h(t, x) = h_0(t) \exp\ (\beta_1 X_1 + \ \beta_2 X_2 + \cdots + \ \beta_p X_p)$$
$$\exp () = h_0(t) \sum_i^p \beta_i X_i \quad (4)$$

Information:

$h(t, x)$: the speed at which the individual experiences an occurrence at the time t with characteristics x
$h_0(t)$: Basic hazard function
β_i : the parameters of the regression model with i = 1, 2, ⋯, p
X_i : the value of an independent variable, with i = 1, 2, ⋯, p

2.2.4. Asumsi Regresi Cox proportional hazard

The main assumption of the cox model is that the hazard ratio between two individuals is constant to time. Testing of this assumption can be done through statistical approaches such as the likelihood ratio test or the Schoenfeld residual test. When this assumption is achieved, then the *cox proportional hazard* can be validly used for hazard ratio interpretation [17].

2.2.5. Parameter Estimation on Joint Occurrence with the Breslow Method

Method approach Breslow is more commonly used because the partial likelihood function is simpler than other methods. This is because, in every case that occurs at the same time, it is impossible to determine the sequence of events. Method *Breslow* Assuming that the size of each set of risks is of equal value. Approach *Breslow* have the following equations [18]:

$$L(\beta)_{breslow} \ = \ \prod_{i=1}^{r} \frac{exp(\sum_{j=1}^{p} \beta_j S_k)}{(\sum_{i \in R(ti)} exp(\sum_{j=1}^{p} \beta_j X_{1j}))^{d_i}} \quad (5)$$

Information:

S_k : total covariance x In the case of ties
d_i : the number of ties cases at the time t_i
$R(t)$: a set of individuals who are at risk of experiencing an event at the time of the t_i
k : TIES value
r : number of uncensored individuals

2.2.6. Parameter Significance Testing

To validate independent variables that affect a model, it is necessary to test the significance of the parameters. The parameter test in this study uses the *partial likelihood ratio* to test *Overall* and *WALD Test* used for testing *Partial* [18].

1. Uji *Overall*

   The overall test is carried out with a partial likelihood ratio test commonly called the GG test, this test is used to see if independent variables have an effect simultaneously with dependent variables.

   a. Hipotesis

   $H_0 :\ \beta_1 \ = \ \beta_2 = \cdots = \ \beta_p = 0$

   $H_1 : minimal\ ada\ satu\ dari\ \beta_j \ \neq \ 0, dengan\ j = 1,2, \dots, p$

   b. Taraf signifikan $\propto = 5\% = 0{,}05$.

   c. Test Statistics

$$G = \ -2[ln\, L_R - ln\, L_f] \quad (6)$$

d. Test Criteria
Subtract if or p-value$H_0 G \geq X^2_{(db;0,05)}$ ≤ α
e. Conclusion
When accepted, it shows that there is no independent variable that affects survival timeH_0.
2. Partial Test
The partial test performed for *the wald* test is used to find out whether the independent variable has a significant influence on the dependent variable.
a. Hipotesis
$H_0 : \beta_j = 0, dengan\ j = 1,2, \dots, p$
$H_1 : \beta_j = 0, dengan\ j = 1,2, \dots, p$
b. Side signifiance 5%.
c. Test Statistics

$$X_w^2 = [\frac{\beta_j}{S_e(\beta_j)}]^2 \tag{7}$$

d. Test Criteria
Subtract if or p-value$H_0 X_w^2 \geq X^2_{(db;0,05)}$ ≤ α
e. Conclusion
When accepted, it means that the independent variables have no effect on H_0*survival time*.

2.2.7. Best Model Selection

Parameter estimation from regression models, the Cox proportional hazard, is best obtained through the reverse elimination method (backward elimination). The elimination process is done backward by eliminating independent non-significant variables one by one, and is stopped when all variables in the model are significant [19].

2.3. Research Methodology

The following are the steps of analysis in this study.

1. Descriptive analysis
Presents the amount of data, the proportion of events and censored, and detects whether or not data is missing or invalid.
2. Pemodelan awal cox proportional hazard
Establish an initial regression model by including all independent variables using the Breslow method to handle data ties.
3. Testing of cox proportional hazard assumptions
Using the Omnibus Test to see if the initial model as a whole is significant and worth continuing. The proportional hazard assumption is tested through p-values for all variables.
4. Parameter significance test
A partial test (Wald test) was carried out for each variable and a simultaneous test (likelihood ratio test) to assess the collective significance of the variables in the model.
5. Backward Deletion
If insignificant variables are found, a backward elimination process is carried out to obtain a simpler and more significant model.
6. Determination of the final model
The best model is selected based on the final result of elimination and the significance value of the parameters. The final model leaves only the variables that contribute significantly to the hazard.
7. Model interpretation
Interpret the regression coefficient in the form of hazard ratio (exp(β)) to understand the magnitude of the influence of each variable on the time of occurrence.

The entire analysis process was carried out using IBM SPSS Statistical software, with the Breslow estimation method to accommodate the possibility of co-occurrences (ties) at survival time.

3. Analysis

3.1. Descriptive Analysis

The total data used in this study is 33 observations. Of these, 27 cases (81.8%) patients were discharged from the hospital when the condition improved, and the remaining 6 cases (18.2%) patients did not go home or went home in a condition that did not improve, and if the patient died. No data is lost, so all data can be used in the process of modeling Cox proportional hazard regression.

3.2. Early Modeling of Cox Regression Proportional Hazard

Modeling using the Breslow method yielded a -2 Log Likelihood value of 127.526, which decreased from the model without independent variables, at 139.578. This decrease indicates an increase in model fit when independent variables are included.

Table 3 Results of the Initial Model of Cox Regression Proportional Hazard

Block	-2 *Log Likelihood*	*Chi-Square*	Df	Sig. (p-*value*)	Information
Block 0	139,578	-	-	-	Initial model without independent variables
Block 1	127,526	14,667	8	0,066	There is a potential variable to time

3.3. Testing Cox Proportional Hazard Assumptions

The test of proportional hazard assumptions is carried out through the Omnibus Test. The results showed a chi-square value of 14.667 with a degree of freedom of 8 and a p-value of 0.066. Because the p-value > 0.05, in general, the model is not statistically significant, although it is close. Nevertheless, this suggests that there is at least the potential for models to be developed with more relevant variables.

3.4. Parameter Significance Test

The table below shows the estimated coefficient, significance value, and hazard ratio (exp(β)) interpretation of each variable:

Table 4 Parameter Significance Test

Variabel	Coefficients (β)	Sig. (p-*value*)	Exp(b)	Test Results	Information
() AgeX_1	-1,557	0,076	0,211	Less H_0	Risk decreases with age
() GenderX_2	-0,287	0,521	0,750	Receive H_0	No significant effect
() Comorbidity DiseaseX_3	0,352	0,058	1,421	Less H_0	Increased risk of incidents, significant marginal
() Blood PressureX_4	-1,198	0,131	0,302	Receive H_0	No significant effect
() Blood Sugar LevelX_5	0,412	0,381	1,510	Receive H_0	No significant effect
() X_6Program Diet Diabetes Melitus	2,101	0,107	8,175	Receive H_0	Large but insignificant effects
() Diabetic FootX_7	-1,057	0,230	0,347	Receive H_0	Insignificant
() PainX_8	0,776	0,101	2,174	Reject H_0	The risk increases if the patient experiences pain

3.5. Backward Elimination and Best Model Determination

Because not all variables are significant, a backward elimination process is carried out to eliminate variables with a p-value of > 0.1. This process results in a final model that consists only of age variables, comorbidities, and pain. The final model is considered simpler and better at explaining the timing variation of events.

3.6. Final Model Interpretation

The final model of cox regression proportional hazard with the Breslow method is:

$$h(t,x) = h_0(t)\exp\ (0{,}211 \cdot Usia +\ 1{,}421 \cdot Penyakit\ Penyerta +\ 2{,}174 \cdot Rasa\ Nyeri)$$

4. Discussion

The purpose of this study is to find out the clinical factors that affect the timing of complications or important events that occur in hospitalized patients with Type 2 Diabetes Mellitus (DMT2). From the results of the analysis carried out with the Cox Proportional Hazard Using the Breslow, it was found that age, comorbidities, and pain were the factors that most affected the timing of the event. Older patients actually have a lower risk of events. This can be seen from the negative relationship between age and risk. Although this seems to contradict the common assumption that older people are more vulnerable, previous research [6] It mentioned that elderly patients tend to be more compliant in undergoing treatment and maintaining blood sugar levels, thereby reducing the risk of sudden complications, although the hospitalization time can be longer.

The existence of comorbidities has also been shown to significantly affect the timing of the occurrence. These results are in line with research [8], which explains that the presence of other diseases outside of diabetes will worsen the body's condition and accelerate the occurrence of complications or deterioration of health. These additional complications make the body work harder, so the patient's condition can deteriorate quickly. In addition, pain also affects the risk of an event, although not very strong. Pain usually indicates complications, such as infections, muscle and joint disorders, or nerve damage due to diabetes (diabetic neuropathy). This is in accordance with the explanation in [5] that DMT2 complications often affect many body systems and can cause pain, both acute and chronic.

On the other hand, factors such as gender, blood pressure, blood sugar levels, diet, and diabetic feet did not show a significant influence in the study. These results support other studies[10][11], which suggests that the influence of such factors can vary depending on the condition of the patient and the group being studied. The Cox Proportional Hazard model used has proven to be effective in handling censored data and accounting for the time of occurrence, in accordance with the methodological recommendations in the [12][13]. Method Breslow used to estimate parameters as they are more suitable for handling joint events (ties), which are common in hospital clinical data [14][15]. Overall, the results of this study show that special attention needs to be paid to patients with comorbidities and pain complaints, as well as to the management of elderly patients, so that inpatient management can be more effective and focused on real risks.

5. Conclusion

This study concluded that of the eight variables tested, only three variables had a significant effect on the timing of DMT2 hospitalization, namely age, pulse pressure (comorbidities), and new pain. Age variables lower the risk of events, while high pulse pressure and pain complaints increase the risk of events during the hospitalization. The variables of gender, blood pressure, blood sugar levels, diet program, and diabetic feet had no statistically significant influence. The Cox Proportional Hazard regression model with the Breslow method has proven to be effective in analyzing clinical data with time of occurrence and censored data. These results are expected to be used as a guideline in improving the quality of treatment of inpatient DMT2 patients as well as in the development of risk-based clinical protocols.

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