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Cox Proportional Hazard Regression Survival Analysis for Type 2 Diabetes Mellitus

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***Abstract*—One of the most widely used methods of survival analysis is Cox proportional hazard regression. It is a semiparametric regression used to investigate the effect of a number of variables on the dependent variable based on survival time. Using the Cox proportional hazard regression method, this study aims to estimate the factors that influence the survival of patients with type 2 diabetes mellitus. The estimated parameter values, as well as the Cox Regression equation model, were also investigated. A total of 1293 diabetic patients with type 2 diabetes were studied, with data taken from medical records at PKU Muhammadiyah Hospital in Yogyakarta, Indonesia. These variables have regression coefficients of 1.36, 1.59, -0.63, 0.11, and 0.51, respectively. Furthermore, the results showed the hazard ratio for female patients was 1.16 times male patients. Patients on insulin treatment had a 4.92-fold higher risk of death than those on other therapy profiles. Patients with normal blood sugar levels (GDS 140 mg/dl) had a 1.12 times higher risk of death than those with other blood glucose levels. Type 2 diabetes mellitus is a challenge for many Indonesians, in addition to being a deadly condition that was initially difficult to diagnose. As a result, patient survival analysis is needed to reduce the patient's risk of death.**

***Keywords*—Cox regression; hazard ratio; proportional hazards; survival analysis; diabetes mellitus**

I. INTRODUCTION

Survival analysis is a form of statistical analysis that is widely used in medicine and public health. The occurrence in survival analysis is usually death, which is why it is called survival analysis, but it could also be another outcome. Data analysis in the context of time, from a well-defined starting point to the occurrence of a specific event or endpoint, is referred to as survival analysis [1]. This method is often employed to assess a relationship between variables whose outcome is difficult to predict, such as death [2]. For example, the likelihood that a patient with a disease will survive, whether the patient's treatment will affect the patient's ability to survive, and so on. The goal is to figure out what percentage of people will live to the end of a given follow-up period [3].

In the medical field, survival analysis normally entails looking at diseases that are potentially lethal, such as leukemia, tumors, cancer, and diabetes [4]. In studies of dangerous diseases, survival analysis is used in a variety of ways [5]–[10]. Survival analysis is used to assess their chances of survival for people with heart failure which is a chronic health condition with high morbidity and mortality [11]. It is also been used to look at prostate cancer, which is a major health concern for New Zealand men, using a survey of 42,563 men [12].

Although there have been numerous survival analyses for a variety of fatal diseases, there are still few studies on type 2 diabetes mellitus, especially in Indonesia. Even though, the prognosis of patients with this disease is critical and should be thoroughly investigated. The factors that may increase the survival of patients with type 2 diabetes should be thoroughly investigated and not overlooked. As a result, the growing number of studies focusing on the survival of patients with type 2 diabetes mellitus may provide more useful references and perspectives. The level profile of type 2 diabetes mellitus and its factors were investigated. The profile of type 2 diabetes patients who improved or recovered as a result of treatment was then examined.

Diabetes mellitus type 2 is extremely dangerous since it is rarely detected at first and is only discovered after symptoms such as damage to the skin, kidneys, nerves, gums, teeth, and blood vessels [13]. Diabetes mellitus is also known to cause kidney failure [14]–[16]. Type 2 diabetes affects the majority of diabetics in Indonesia [17], [18]. Therefore, the focus of this study is on people who have type 2 diabetes.

The Cox regression method is frequently used to establish a connection between survival time and the variables estimated to affect it [4]. Probably the most widely used statistical method in survival analysis is the Cox regression model [2]. Cox Proportional Hazards are lifetime data of an individual [19]. Many researchers in the health sector have used survival analysis to apply Cox regression to different aspects [2], [20]–[23]. The Cox Proportional Hazard regression means that the mortality rate is constant over time [4]. The Cox regression model assumes that the underlying hazard function for the two levels of multiple covariates is proportional over the span of follow-up time in regression models for survival results [24]. The Cox regression allows several variables into account and measures their independent effects on the hazard function.

II. PROPORTIONAL HAZARD COX REGRESSION MODEL

A Cox regression model can be used to investigate the relationship between patient survival experience and explanatory variables. It can be used to investigate how the survival of a group of patients is affected by the value of one or more explanatory variables, the values of which were reported for each patient at the time of origin [1]. Suppose a group of patients has received either normal or novel care. Suppose that their respective hazard functions (failure functions) at time t are denoted by $h_S(t)$ and $h_N(t)$, respectively. Thus, according to a basic model of survival analysis for two patient groups, the hazard function for patients receiving new treatment at time t was equivalent to the hazard function for patients receiving standard care at the same time. Equation (1) below illustrates this proportional hazard model [1].

$$h_N(t) = \psi h_S(t) \qquad 1$$

where ψ is the hazard ratio or relative hazard and every t is non-negative, then ψ is constant. It is the ratio of each person in new care compared to the individual in standard care at any given time. If $\psi > 1$, the new drug's users face a higher risk of death at time t, although standard treatment is preferable. Individuals receiving the new medication, on the other hand, had a lower risk of death at time t than those receiving the standard treatment. The new treatment is then referred to as a step forward from the current treatment [1]. Higher survival rates are associated with lower hazard levels.

Suppose X is an indicator variable that has a value of zero when a person is on standard medications. If x_i is the X value for the i-th individual, and $i = 1,2,\dots,n$. Then the hazard function for that individual can be written in the following equation:

$$h_i(t) = e^{\beta x_i} h_0(t) \qquad 2$$

Where

$$\begin{cases} 1 & if\ the\ i-th\ individual\ receives\ a\ new\ treatment \\ 0 & otherwise \end{cases}$$

In equation (2), the hazard function for individuals providing standard treatment is denoted by $h_0(t)$. Meanwhile, the hazard function for individuals receiving new treatment is symbolized by $\psi h_0(t)$. Since the hazard ratio ψ cannot be negative, it can also be written as $\psi = exp\ exp\ (\beta)$. Because the parameter β is a logarithmic function of the hazard ratio, it is written $\beta = \log \psi$, which also implies that each value of β in the interval $(-\infty, \infty)$ will produce a positive value of ψ. Equation (2) is also known as the proportional hazards model to compare two treatment groups [1]. When the hazard function at a certain time depends on the explanatory variables $x_1, x_2, \dots x_p$ and because $\psi(x_i)$ is not negative, it can also be written as $exp\ (\eta_i)$, where $\eta_i = \sum_{j=1}^{p} \beta_j x_{ij}$ is a linear combination of explanatory variables. Then, the general model for proportional hazard can be written in equation (3) below [1].

$$h_i(t) = h_0(t)\ exp\ exp\ (\beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi}) \qquad 3$$
$$h_i(t) = h_0(t) e^{\sum_{j=1}^{p} \beta_j x_{ji}}$$

Where

$h_i(t)$: the i-th individual hazard function
$h_0(t)$: Basic hazard function
x_{ji} : The value of the j-th variable of the i-th individual, $i = 1,2,\dots,n$ and $j = 1,2,\dots,p$
β_j : The regression coefficient, where $j = 1,2,\dots,p$

The hazard ratio is also described as the failure of one group of people divided by the failure of another group of people. The following equation can be used to calculate the hazard ratio [25]:

$$\widehat{HR} = \frac{h_0(t) e^{\sum_{j=1}^{p} \beta_j x_j^*}}{h_0(t) e^{\sum_{j=1}^{p} \beta_j x_j}} \qquad 4$$
$$\widehat{HR} = e^{\sum_{j=1}^{p} \hat{\beta}_j \left(x_j^* - x_j\right)}$$

β is regression coefficient, $x^* = (x_1^*, x_2^*, \dots x_p^*)$ the independent variable for one group of individuals, and $x = (x_1, x_2, \dots, x_p)$ is an independent variable for one group of other individuals. Hazard ratios can be interpreted as relative risk, namely comparing the risk of an event occurring in two groups [26].

III. DATA AND VARIABLES

This study relies on secondary data from Type 2 diabetes inpatient medical records. The information was gathered at PKU Muhammadiyah Hospital in Yogyakarta, Indonesia. A total of 1293 diabetic patients with type 2 were analyzed in this study. The patient data were collected from February to April 2020.

The survival time data used in this analysis is a ratio scale that depicts how long a patient lives from the time he or she is diagnosed with type 2 diabetes mellitus before the data is obtained (in years). The patient's survival status, which shows the patient's status at the end of the observation, is then used as the response variable in this analysis. This variable is divided into two categories, namely 0 (censors) and 1 (event).

The term sensor refers to the fact that the patient does not experience the event being studied, while the term event refers to the fact that the patient experiencing the event being studied (died).

Furthermore, the explanatory variables used are gender (X1), age (X2), diagnosis of complications (X3), comorbid diagnosis (X4), therapy profile (X5), and blood glucose levels (X6), all of which are variables grouped into two or more categories. The nominal measurement scale form is used for the gender variable (X1), where 1 represents a female patient and 2 represents a male patient. The age variable (X2) is calculated using an ordinal measurement scale of two categories: less than 45 years and greater than or equal to 45 years. The complication diagnosis variable (X3) denotes the occurrence of a new disease as a result of the effects of type 2 diabetes mellitus, as measured by a nominal type measurement scale. This variable has eight categories (0 = no complications, 1 = renal complications, 2 = neurological complications, 3 = peripheral circulation complications, 4 = multiple complications, 5 = coma, 6 = cardiovascular complications, and 7 = other complications).

The comorbidity diagnostic variable (X4) employs a nominal form measurement scale to depict the patient's non-diabetes mellitus type 2 disease, which is divided into two categories (0 = without comorbidities and 1 = with comorbidities). Data form with a nominal measurement scale is also used in the variable therapy profile (X5). From the time the patient was diagnosed with type 2 diabetes mellitus until the end of the observation period, this indicator indicates the type of treatment he or she got. Treatment profiles were divided into three categories (1 = Insulin, 2 = Oral Anti-diabetics, and 3 = Combined Insulin and Oral Anti-diabetics). The last independent variable, blood glucose levels (X6), shows the status of type 2 diabetes mellitus patients by monitoring glucose levels at any time. The average blood sugar during hospitalization was used to generate this information (if the patient is hospitalized more than once). Variable blood glucose levels were measured using an ordinal scale data form, which was divided into three categories: 1 = Normal (if the GDS <140 mg/dl); 2 = Moderate (if the GDS is between 140 and 199 mg/dl); and 3 = High (if the GDS ≥200 mg/dl).

Proportional hazard models in cox regression were used to analyze the data. The death group is used as the baseline for analyzing the response variable, which is the variable of type 2 diabetes mellitus patients' survival status.

IV. RESULTS AND DISCUSSION

A. Data Descriptions

A sample description showing a general description of type 2 diabetes patients is given in this section. A total of 1293 patients with type 2 diabetes were studied in this study. The age of the respondents was divided into two groups; those under 45 years old and those who were 45 years old or older. Most respondents were type 2 diabetes patients who were in the age group of more than or equal to 45 years, with 1149 patients total (88.86 percent). Meanwhile, only 144 patients in the age group of fewer than 45 years were included in this study (11.14 percent). The proportion of respondents based on the gender of the patient is shown in Figure 1, with 604 patients being male and 689 being female.

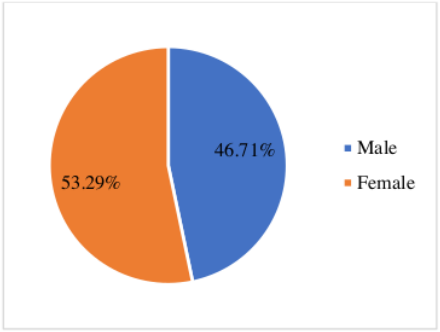

Fig. 1 Proportion of respondents by gender

Variables diagnosis of complications is divided into eight groups, with the majority of patients (719) falling into the category of no complications, followed by 199 patients in the category of Peripheral Circulation Complications. Other complication category was the complication diagnosis group with the smallest number of patients, only one. The proportion of patients based on the diagnosis of complications is shown in detail in Figure 2.

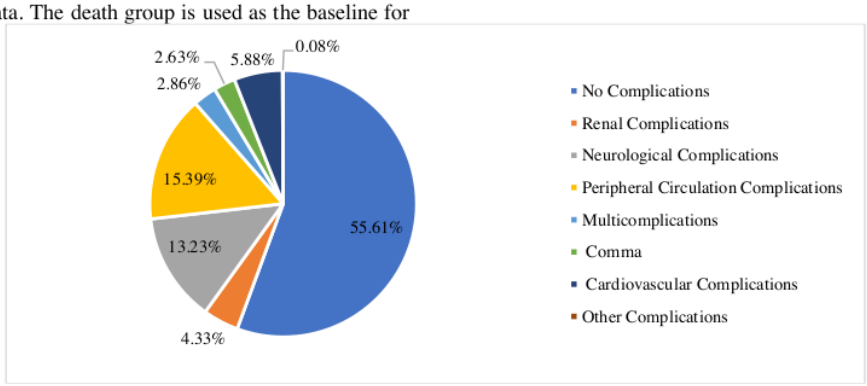

Fig. 2 Proportion of by diagnosis of complications

The majority of patients in the comorbidity diagnosis group were in group 1 (with comorbidities), with 920 patients (71.15 percent), while group 0 (without comorbidities) had just 373 patients (28.85 percent). Furthermore, the majority of patients (634 patients) were in the combined insulin and oral anti-diabetics community on the predictor of therapy profile. Meanwhile, insulin therapy is the least common, accounting for 90 patients. Figure 3 shows the proportion of type 2 diabetes patients according to the type of treatment they got.

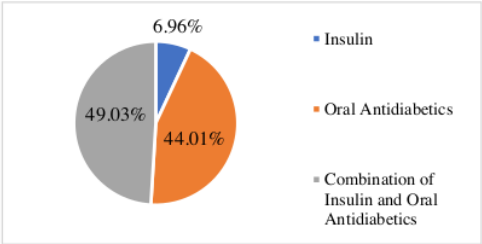

Fig. 3 Proportion of respondents by therapeutic profiles

Figure 4 illustrates the proportion of type 2 diabetes mellitus patients depending on the condition of type 2 diabetes mellitus patients with blood glucose measurements, which are divided into three categories.

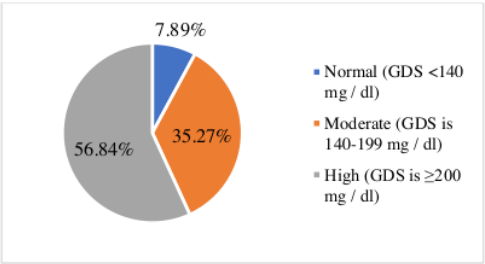

Fig. 4 Proportion of respondents by blood glucose levels

Figure 4 shows that the majority of patients are in the high category (GDS 200 mg/dl), with 735 patients, followed by patients in the moderate category (GDS 200 mg/dl), with 456 patients. Meanwhile, 102 patients had blood glucose levels below 140 mg/dl (GDS).

B. Results of the Analysis

This study used six independent variables, namely gender (X1), age (X2), diagnosis of complications (X3), comorbidity diagnosis (X4), therapy profile (X5), and glucose levels (X6). The results of the parameter significance test on the Cox proportional hazard regression, which was carried out partially and as a whole, are presented in Table 1.

TABLE I
SIGNIFICANCE TEST

Likelihood ratio	Chi-square	df	Sig.	Decision
1631.82	153.72	14	0.00	Reject Ho

Table 1 clearly shows that the cox regression with proportional hazard produces a likelihood ratio of 1631.82 and a chi-square value of 153.72 with 14 degrees of freedom (*df*). The significance value, which indicates that the *p*-value is 0.00 less than the alpha value determined in this study ($\alpha = 0.05$). The decision to reject H0 is based on the value of $Sig. < \alpha = 0.0$ which indicates that at least one independent variable has a significant impact on the survival of type 2 diabetes patients. Based on the data and variables calculated in this analysis, the Cox proportional hazard regression model is declared suitable for use in assessing the survival of type 2 diabetes patients.

The results of the Cox proportional hazard regression analysis partially can be seen in Table II. This partial test aims to decide the independent variables that contribute significantly to the model presented, namely, type 2 diabetes patient survival.

TABLE III
ESTIMATED COX REGRESSION

Variables	B	Wald	Sig.	Exp (B)	Decision
Gender	1.36	5.85	0.02	1.16	Reject H0
Age	-0.54	4.09	0.10	0.58	Accept H0
DK(1)	5.61	0.01	0.91	272.12	Accept H0
DK(2)	5.95	0.01	0.91	382.76	Accept H0
DK(3)	4.72	0.01	0.93	112.41	Accept H0
DK(4)	5.86	0.01	0.91	350.26	Accept H0
DK(5)	6.12	0.01	0.91	455.4	Accept H0
DK(6)	6.32	0.02	0.90	557.17	Accept H0
DK(7)	6.38	0.02	0.90	588.2	Accept H0
DP	-0.4	2.72	0.10	0.67	Accept H0
PT(1)	1.59	41.52	0.00	4.92	Reject H0
PT(2)	-0.63	8.31	0.00	0.53	Reject H0
KG(1)	0.11	3.78	0.05	1.12	Reject H0

KG(2)	0.51	5.84	0.02	0.6	Reject H0

From table II, DK stands for complication diagnosis variable (X3), DP for the comorbid diagnostic variable (X4), PT for therapy profile (X5), and KG for blood glucose (X6). Based on equation (3) and according to the results of the analysis in table II, the final model of Cox regression in this study is written as follows:

$$h_i(t) = h_0(t)\, exp\, exp\,(1.36X_1 - 0.54X_2 + 5.61X_3(1) + 5.95X_3(2) + 4.72X_3(3) + 5.86\,X_3(4) + 6.12\,X_3(5) + 6.32\,X_3(6) + 6.38\,X_3(7) - 0.407X_4 + 1.59X_5(1) - 0.63X_5(2) + 0.11X_6(1) + 0.51X_6(2))$$

The majority of independent variables generate regression coefficients with a positive sign, with only three variables having a negative effect, namely age, comorbid diagnosis, and therapy profile(2), as shown in the equation model and regression coefficient (B) in Table II. According to table 2, rejecting H0 suggests that the independent variable in question has a significant impact on the dependent variable in this analysis, namely, type 2 diabetes mellitus patient survival. The p-value is used to search for a meaningful impact, i.e. to reject H0 (significance). Compare the p-value with the standard significance level of 0.05, that is, rejecting H0 when Sig. <α (0.05).

Table 2 clearly shows that the partial analysis reveals there are 5 (five) variables that have a statistically significant impact on the survival of type 2 diabetes patients, with all of these variables having a significance value of less than 0.05. Sex, therapy profile (1), therapy profile (2), glucose level (1), and glucose level (2) are the variables to consider. The p-values of the five variables are 0.02, 0.00, 0.00, 0.05, and 0.02 respectively. These findings suggest that these five variables play an important role in patient survival. Alternatively, it may be suggested that there is substantial evidence that the increased risk of death is due to gender, the patient's treatment history from the time of diagnosis of type 2 diabetes to the time of observation, and the condition of type 2 diabetes mellitus by measuring blood glucose. Additionally, other factors have been shown to have no statistically meaningful impact on type 2 diabetes patient survival. This also implies that there is insufficient evidence that the patient's gender and age affect the risk of death.

C. Hazard Ratio

The hazard ratio is the risk of failure for one group of individuals separated by the risk of failure for another group. Only the independent variable with a statistically important effect on the survival of type 2 diabetes patients is used to measure the hazard ratio. Thus, only five variables were analyzed in terms of their hazard ratios. They were used to compare the risk of failure of individual patients for each category of the variable. As a result, only five variables were examined in terms of their hazard ratios. For of type of variable, hazard ratios were used to compare the risk of failure of individual patients. The failure ratio for each independent variable that has a major contribution to patient survival can be determined from table II, as seen in Table III below.

TABLE IIIII
HAZARD RATIO

Variables	B	Sig.	Exp (B)
Gender	1.36	0.02	1.16
PT(1)	1.59	0.00	4.92
PT(2)	-0.63	0.00	0.53
KG(1)	0.11	0.05	1.12
KG(2)	0.51	0.02	0.60

For gender variables, there are two groups of categories, namely male and female patients. Since the reference category in this study was male patients, so the hazard ratio is defined as $\frac{h_{females}(t)}{h_{males}(t)}$. Table III shows that the gender variable's value of Exp(B) is 1.16, so it can be written as $\frac{h_{females}(t)}{h_{males}(t)} = 1.16$. The hazard ratio for female patients is 1.16 times that of male patients, according to this value. To put it another way, the mortality rate of female patients is roughly equal to that of male patients.

The value of PT(1), which reflects insulin treatment therapy, is Exp(B) = 4.92. This means that patients with type 2 diabetes mellitus who use insulin treatment therapy have a 4.92 percent risk of dying compared to patients who use other therapy profiles. The value of Exp(B) in the PT(2) is 0.53, indicating that respondents with type 2 diabetes mellitus who are taking oral antidiabetics have a death rate of 0.53 times of type 2 diabetes mellitus patients who are taking other therapy profiles. Furthermore, the variable KG(1) yields an Exp(B) value of 1.12, indicating that patients with type 2 diabetes who have normal blood sugar levels (GDS < 140 mg / dl) have a 1.12 times greater risk of dying than those with other blood glucose levels. Patients with type 2 diabetes with moderate sugar levels (GDS 140-199 mg/dl) as represented by KG(2) are estimated to have 0.60 times the risk of patients with type 2 diabetes with other blood sugar levels. In addition, Figures 3 and 6 below show the survival function and hazard function of type 2 diabetes patients in this study.

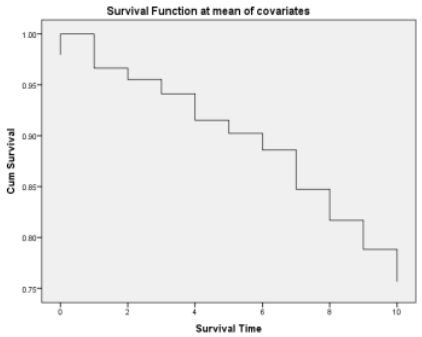

Fig. 5 Survival function

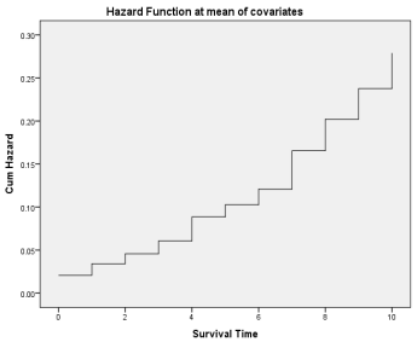

Fig. 6 Hazard function

The baseline survival curve, shown in Figure 5, is a visual representation of the model's approximate time. The time to event is shown on the horizontal axis, while the probability of survival for a patient with type 2 diabetes is shown on the vertical axis. Figure 5 also clearly demonstrates that the survival risk of patients with type 2 diabetes decreases as time passes. The horizontal axis in Figure 6 depicts the event's duration, while the vertical axis depicts the cumulative hazard, which is proportional to the negative log of the probability of survival. The accumulated hazard continues to increase with longer time, as seen in Figure 6, which is the opposite of the survival function curve.

V. Conclusion

A Cox proportional hazard regression model was used to examine the survival of type 2 diabetes patients in this study. The results of the analysis indicated that gender, insulin therapy treatment profile, oral antidiabetic treatment profile, normal and moderate blood glucose levels all had a statistically significant impact on the survival of patients with type 2 diabetes. Patient gender seems to have a positive impact on survival, with female patients having a higher hazard ratio than male patients. This suggests that women are more likely to die than men. Furthermore, the profile of insulin therapy is considered to have a favorable contribution to patient survival, with a hazard ratio is higher than other treatment approaches. According to the findings, insulin therapy had a fivefold risk of death compared to any other therapy profile. Then it was discovered that patients with normal glucose levels had a higher risk of dying than those with other glucose levels. Further research can be done by adding other factors that have the ability to cause the survival of type 2 diabetes patients. Additionally, other survival analysis approaches may be used.

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