A SURVIVAL ANALYSIS WITH COX REGRESSION INTERACTION MODEL OF TYPE II DIABETES MELLITUS IN INDONESIAN

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ABSTRACT

This study analyzes the survival of patients with type II diabetes mellitus and factors that affect it using survival analysis. The survival analysis was conducted by Kaplan Meier curves and Cox regression equations of interaction models. In this study, 1293 patients with type II diabetes mellitus, with 10.36% (n = 134 patients) death. Patients aged ≥45 years 88.86% (n = 1149), 53.29% women (n = 689), 71.15% (n = 920) with comorbidities, 56.84% (n = 735) high blood glucose levels, and 49.03% (n = 634) received a combination of insulin-oral antidiabetic therapy. Factors related to the patient's survival are the interaction of gender variables with age variables (p <0.05; HR = 0.841; CI 95% 0.711-0.993), variable interaction of blood glucose levels while with variable age (p <0,05; HR = 1,061; CI 95% 1,028-1,096), variable interaction of blood glucose levels with comorbidity variables (p <0,05; HR 1,221; CI 95% 1,036-1,438), and variable interaction of blood glucose levels with variable treatment profiles (p <0,05; HR = 0.824; CI 95% 0.747-0.909). Factors that affect the survival of patients with type II diabetes mellitus are age, gender, diagnosis complications, comorbidity, intermittent blood glucose levels, and treatment profiles.

Keywords: Mortality; Risk-factors; Survival analysis; Type II diabetes mellitus

INTRODUCTION

Type II diabetes mellitus is a group of metabolic diseases with characteristic hyperglycemia[1] that occur due to abnormalities of insulin secretion, insulin work, or both.[2] This disease is one of the world's health threats, including in Indonesia. Based on primary health research data in 2018, the prevalence of diabetes mellitus in the ≥15-year-old population in Indonesia increased from 1.5% in 2013 to 2.0% in 2018.[3] WHO[3] estimates that people with diabetes mellitus will continue to increase up to 2-3 times by 2035.[4] Patients aged 20-79 are expected to increase to 642 million, with most low- and middle-income countries.[5]

The mortality rate due to diabetes mellitus ranges from 0.28-8.24 per 100 patients-years with the highest mortality in older patients and longer.[6] According to the IDF, 5.0 million people died in 2015, while 415 million were injured.[5] Diabetic Mellitus patients who have complications with hypertension and poor blood glucose control have a higher risk of failure.[7] Not only that, renal complications[7-10], cardiovascular[7,11,] and peripheral circulation[14,15] also increase the risk of mortality of type II diabetes mellitus patients.

Survival analysis is a statistical technique that has been widely used in health sciences[16-18] to analyze the chances of death, recurrence, survival, and other events at any given time.[19] Accurate predictions regarding the externality or survival rate of diabetic patients can be critical to levels of prognosis and therapy. Therefore, this study was conducted to assess the length of life, therapy, and factors that affect survival. It is expected to have a linear impact on the length of life of diabetes mellitus patients.

MATERIAL AND METHODS

This research was descriptive research, where the data used was the medical record data of patients with type II diabetes mellitus who undergo hospitalization and outpatient at two hospitals, namely PKU Muhammadiyah Gamping Hospital and PKU Muhammadiyah Hospital Yogyakarta, Indonesia. Inclusion criteria: Patients diagnosed with Type II Diabetes Mellitus are ≥18 years old and undergo treatment from 2015 to 2019. Patients diagnosed with diabetes mellitus type I and gestational diabetes illegible medical records and incomplete data was excluded.

Data retrieval was conducted retrospectively by collecting all data related to this study, from the initial events of patients diagnosed with type II diabetes mellitus to the observation period. It aimed to determine the survival of patients with type II diabetes mellitus and the factors that affect it. The patient's survival was known based on the patient's survival status (life/death) and survival time measured when the patient was diagnosed with type II diabetes mellitus until the time the data was taken. The required data were patient name, gender, age, history of disease, complications, when first diagnosed with Diabetes Mellitus type II, therapy regimen used, and laboratory results in the form of blood glucose levels. This research has obtained ethical clearance from the Research Ethics Commission of PKU Muhammadiyah Hospital Yogyakarta No. 0011/KT.7.4/VIII/2020.

In this study, there were several research variables, namely patient survival status, survival time, gender (X1), age (X2), concomitant disease (X3), complications (X4), treatment profile (X5), and current blood glucose levels (X6). The data that has been obtained is classified and coded according to existing variables. Variables of patient survival status, gender, and accompanying disease are grouped into dichotomous data. Survival time was expressed in units of years. The age variable was grouped into two levels, namely <45 years and ≥45 years. Variable complications were divided into: without complications, renal complications, peripheral circulation complications, multi complication, coma, cardiovascular complications, and other complications. The variable profile of treatment was divided into insulin, oral antidiabetics, and a combination of oral insulin-antidiabetics. Variable blood glucose levels was divided into: Normal (<140 mg/dL), Moderate (140-199 mg/dL), and High (≥ 200 mg/dL).

In this study, the Kaplan Meier method was used to know the characteristics of survival time. In addition, the Log Rank test was used to determine the difference in survival curve between groups of factors that affect the survival of patients with type II diabetes mellitus with $p < 0.05$. Proportional hazard assumption testing was conducted with two tests, namely visual test using Kaplan Meier method and formal test using Goodness of fit test. The total covariate result of cox regression p<0.05 was included in the equation model. The data was analyzed using SPSS 25 software.

The models or formulas for predicting hazard functions and survival functions are as follows.

a. Hazard Function

$$H(t)= H0(t)e^{y} \qquad (1)$$

$$H(t)= H0(t)e^{0.337\ (X6-X2)\ -0.199\ (X6-X3)-0.059\ (X4-X6)-0{,}174\ (X1-X2)-0.193\ (X6-X5)}$$

b. Survival Function

$$S(t)=S0(t)^{(e\hat{\ }y)} \qquad (2)$$

$$S(t)=S0(t)^{e\hat{\ }0{,}337(X6*X2)+0{,}199(X6*X3)+0{,}059(X4*X6)-0{,}174(X1*X2)-0{,}193(X6*X5)}$$

RESULT

In this study, there were 1293 data of type II diabetes mellitus patients as seen in Table 1, 10.36% (n = 134) were non-survivor patients or died, and 89.64% (n = 1159) were survivor patients or still surviving during the period 2015-2019. In non-survivor patients, there were 70 male patients and 64 female patients; 126 patients were ≥45 years old, 76 patients were diagnosed with complications, 109 patients with comorbidity, and moderately elevated blood glucose levels were identified.

Based on research that has been done, obtained data on the overall number of patients with type II diabetes mellitus aged ≥45 years more (88.86%) than patients who are <45 years old. In the sex variables, 53.29% of type II diabetes mellitus patients were female, while 46.71% were male. The most common complications are peripheral circulation complications. The majority of patients (71.15%) had comorbidity, and 56.84 percent of type II diabetes mellitus patients had hyperglycemia, while 49.03 percent received insulin-oral antidiabetic combination therapy, 44.01 percent received oral antidiabetic therapy, and 6.96 percent received insulin therapy.

Table 1. Frequency Distribution of Characteristics of Type II Diabetes Mellitus Patients at PKU Muhammadiyah Gamping Hospital and Yogyakarta City

Variable	***n***	**(%)**
Survival Status		
• Life	1159	89,64
• Died	134	10,36
Gender		
• Male	604	46,71
• Women	689	53,29
Age		
• <45 years old	144	11,14
• ≥45 years old	1149	88,86
Diagnosis of Complications		
• Without Complications	719	55,61
• Renal Complications	56	4,33
• Neurology Complications	171	13,23
• Peripheral Circulation Complications	199	15,39
• Multicomplication	37	15,39
• Coma	34	2,63
• Cardiovascular Complications	76	5,33
• Other Complications	1	0,08
Comorbidity		
• Without Comorbidity	373	28,85
• With Comorbidity	920	71,15
Treatment Profile		
• Insulin	90	6,96
• Oral antidiabetics	569	44,01
• Combination	634	49,03
Blood Glucose Levels		
• Normal	102	7,89
• Moderate	456	35,27
• High	735	56,84

Table 2. The Goodness of Fit Test Results of Type II Diabetes Mellitus Patients at PKU Muhammadiyah Gamping Hospital and Yogyakarta City

	T	**G**	**Age**	**DC**	**C**	**BGL (mg/dL)**
Chi-Square	409,592	5,588	781,148	2402,23	231,407	467,012
Df	2	1	1	7	1	2
Asymp. Sig	0,000	0,018	0,000	0,000	0,000	0,000

Note : T = Therapy, G = Gender, DC = Diagnose of Complications, C = Comorbidity, BGL = Blood Glucose Level, df = degree of freedom

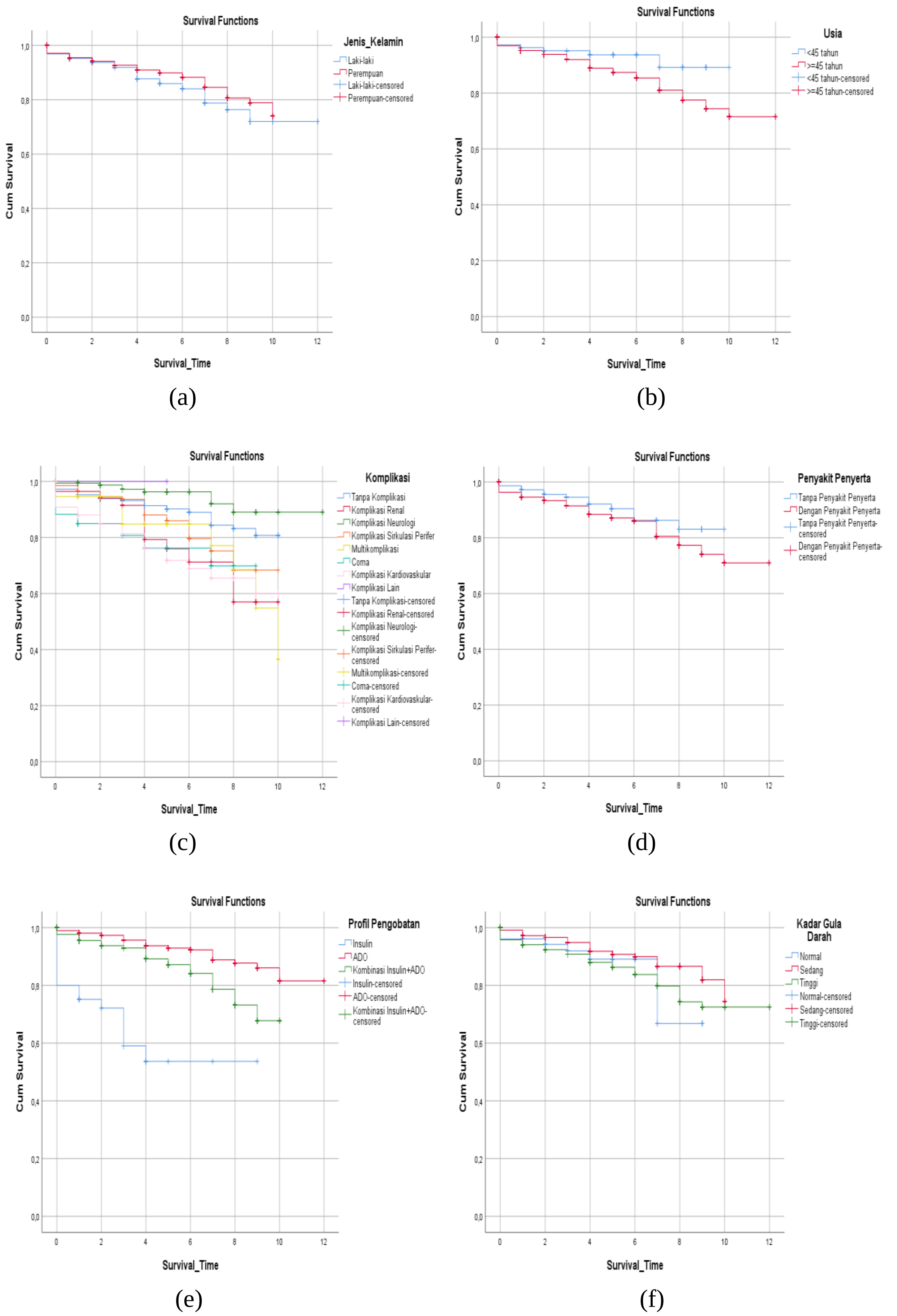

Figure 1. Kaplan Meier curves each factor. (a) Gender; (b) Age; (c) Complications; (d) Comorbidity; (e) Treatment Profile; (f) Blood Glucose Levels.

Table 3. Cox Regression Results of Type II Diabetes Mellitus Patient Interaction Model at PKU Muhammadiyah Gamping Hospital and Yogyakarta City

	B	SE	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
						Lower	Upper
Sex*Age	-0,174	0,085	1	0,041	0,841	0,711	0,993
Blood Glucose Levels *Age	0,337	0,092	1	0,000	1,401	1,169	1,678
Complications*Treatment Profile	0,059	0,016	1	0,000	1,061	1,028	1,096
Blood Glucose Levels* Comorbidity	0,199	0,083	1	0,017	1,221	1,036	1,438
Blood Glucose Levels* Treatment Profile	-0,193	0,050	1	0,000	0,824	0,747	0,909

Description: B = Slope Value or Beta Coefficient of Constants; SE = Standard Error; df = degree of freedom; Sig. = Significance or *p*-value Wald test; Exp(B) = Exponential Beta Coefficient

Hazard proportional assumption testing was also conducted with the Goodness of Fit test approach. This test was conducted to obtain more objective decisions. In this test, H_0 means factors that were suspected to affect the survival of patients with diabetes mellitus type II meet the assumption of proportional hazard, while H_1 means that factors that were suspected to affect the survival of patients with type II diabetes mellitus do not meet the assumption of proportional hazard. Reject decision H0 if p-value < α = 5%. Here were the results of the hazard proportional assumption test using the Goodness of Fit test. Based on table 2, it is concluded that all variables do not meet proportional hazard assumptions because the significance value of all variables was less than the α value of 0.05.

Based on the analysis, the variables related to the survival of Type II Diabetes Mellitus patients are the interaction of gender variables with age variables (p<0.05; HR = 0.841; CI 95% 0.711-0.993), variable interaction of blood glucose levels during with variable age (p <0.05; HR = 1,061; CI 95% 1,028-1,096), variable interaction of blood glucose levels when with concomitant disease variables (p <0.05; HR 1,221; CI 95% 1,036-1,438), and variable interaction of blood glucose levels with variable treatment profiles (p <0.05; HR = 0.824; CI 95% 0.747-0.909).

DISCUSSION

The Kaplan-Meier survival curve analysis aims to find out an overview of the characteristics of survival time. In addition, the Kaplan Meier curve is also used to assess proportional hazard assumptions. To see the difference in survival curve can be made statistically testing by using the Log Rank test. Log-Rank test is intended to determine the difference in survival curve between groups of factors that affect the survival of patients with type II diabetes mellitus. In addition to using the Kaplan Meier curve, to see the difference in survival curve can be done statistically testing by using the Log Rank test. Test value of 2.010 with a degree of freedom of 1 and *p*-value of Log Rank test result of 0.156. The results of this test will be compared to the α value of 5%. The *p*-value value is greater than the α hence the decision to accept H_0, which means there is no difference in the survival curve based on gender.

Figure 1a shows the curve position of type II diabetes mellitus patients who were female and male close to each other in the 0th to 3rd year. In year 4, the curve position of the patient with the male gender is below the curve of the female patient. This revealed that in the 0th to 3rd year, both women and men have a relatively similar level of survival probability, while in the 4th year, the probability of survival of male patients is lower than that of female patients, so descriptively there was a difference in the survival curve of type II diabetes mellitus patients based on the gender suffered

Kaplan Meier's curve in Figure 1 shows the curve position of patients diagnosed with type II diabetes mellitus at the age of ≥45 years is below the curve of patients who are recorded as diagnosed with type II diabetes mellitus aged <45 years. The <45 years old patient curve also showed a reasonably slow decline until the 10th year was still above 0.8. These results state that the probability of survival of patients diagnosed at the age of <45 years is higher than patients diagnosed with type II diabetes mellitus at the age of ≥45 years. The Log Rank test analysis obtained a result of 2,899 with a degree of freedom of 1 and a p-value of 0.089. This result is then compared to α by 5%, then obtained a p-value more significant than α. Hence, the decision to accept H0 means there is no difference in the survival curve of type II diabetes mellitus patients based on the initial age of diagnosis.

Figure 1c, the curve of a multi-diagnosed patient is at the very bottom compared to the curve of the patient diagnosed with other complications. This indicates that patients with multiplication have a lower probability of survival than other complications. Statistically, the Log Rank test obtained 36,627 with a degree of freedom of 7 and a p-value of 0.000. This value is compared to the α value of 5%. The results showed that the value of p-value is less than α, hence the decision to reject $H_{0,}$ which means there is a difference in the survival curve of type II diabetes mellitus patients based on complications suffered.

Figure 1d shows the curve position of type II diabetes mellitus patients with comorbidity below the curve of type II diabetes mellitus patients without comorbidity. It appears that the survival curve of patients without comorbidity is above 0.8. In contrast, the survival curve of patients with comorbidity continues to decrease below the line of 0.8. This result shows that the probability of survival of type II diabetes mellitus patients without comorbidity is better compared to patients with type II diabetes mellitus with comorbidity. However, based on statistics, the Log Rank test results from 3,444, a degree of freedom of 1, and a value *p*-value is 0.064. Thus, the value of *p*-value is greater than the value of α 5%, which states that there is no difference in the curve of type II diabetes mellitus patients based on comorbidity.

Based on Figure 1e, type II diabetes mellitus II patients with insulin therapy are well below the curve of type II diabetes mellitus patients with oral antidiabetics. It is also below the curve type II diabetes mellitus patients who receive insulin-oral antidiabetic combination therapy. This indicates that the survival of patients with insulin therapy is lower than patients with oral antidiabetics or insulin-oral antidiabetics combination. The curve of patients receiving oral antidiabetic therapy dropped quite slowly until the 10th year was still above the 0.8 line. This means the probability of survival of type II diabetes mellitus patients receiving oral antidiabetic therapy is high. Statistical analysis using Log Rank shows a test result of 117.655 with a degree of freedom of 2 and a value *p*-value of 0.001. This value is then compared to the α value of 0.05%. The results showed a value of *p*-value more minor than the value of α, so the decision to reject H_0 means there is a difference in the survival curve of type II diabetes mellitus patients based on treatment profile.

In Figure 1f, the curve position of type II diabetes mellitus patients who have normal blood glucose levels is below the curve of type II diabetes mellitus patients who have moderate and high blood glucose levels. These results show that the survival of type II diabetes mellitus patients who have average blood glucose tends to below. In statistical analysis, Log Rank test results were obtained at 7,793 with a degree of freedom of 2 and a *p*-value value of 0.020. This value is then compared with an α value of 5%, where the *p*-value is less than α. Hence, the decision to reject H_0 means there is a difference in the survival curve of type II diabetes mellitus patients based on current blood glucose levels.

The table shows that every year of age increases in type II diabetes mellitus patients, both male and female, the probability of death increases by 0.841 times. Meanwhile, every one year of diabetes mellitus type II patients followed by consistently high blood glucose levels, the probability of death increased by 1,401 times. Sanusi *et al.*, in their research, stated that the younger the patient's age, the longer his life-assurance time will be. Patients under 45 had a 0.015 times lower risk of failure than patients over 45.[20] Shaik *et al.* state that if the age of diabetic patients increases, then the risk of death also increases simultaneously.[21] Based on blood glucose levels, patients with high blood glucose levels had a 1,128 times greater risk of failure than patients with low/normal blood glucose levels. Dewi *et al.* also stated that patients with type II diabetes mellitus with high and low blood glucose levels have a 1,587 times faster risk than patients with regular/stable blood glucose levels. In addition, female type II diabetes mellitus patients had a 1,557-fold risk of failure than male type II diabetes mellitus patients.[22] The amount of comparison between the composition of estradiol will make the estrogen receptor gene (ER), and estradiol receptor in women activated. It causes the metabolic process to work, and both genes will coordinate insulin sensitivity and increased glucose uptake in the blood. In line with the increasing age of humans, the hormone estrogen will decrease, causing insulin sensitivity, and blood glucose uptake will drop.[23]

Patients with complications and received a treatment profile of insulin combination therapy + oral antidiabetics, the probability of experiencing the event of death 1,061 times. The hazard ratio for the interaction of blood glucose levels during and treatment profile was 0.824. This result means patients with current blood glucose levels and receiving insulin-oral antidiabetic combination therapy have a 0.824 chance of dying compared to patients with regular/moderate blood glucose levels and receiving oral/insulin antidiabetic therapy. In addition, the patient's death probability with high blood glucose levels and comorbidity increased by 1,221 times compared to patients with normal blood glucose levels and without comorbidity. Dewi *et al.* stated that patients with type II diabetes mellitus without the concomitant disease had a 0.640 times lower risk of failure than type II diabetes mellitus patients with the concomitant disease.[22] Another study conducted by Putri stated the chances of diabetes mellitus patients who did not have another diagnosis 3.60 times compared to diabetes mellitus patients who had a diagnosis of lain.[24]

According to research, 84.1% of type II diabetes mellitus patients with complications have a poor quality of life. The longer a patient has diabetes, the greater the risk of developing complications.[25] In contrast, Derebew stated that patients who received only oral antidiabetic therapy and received oral antidiabetic therapy combined with insulin had a longer recovery time than patients who received only insulin therapy.[26] Combination therapy with multitarget more provides the benefits of treatment achieved aggressively. According to the Directorate General of Pharmaceutical and Medical Devices, the combination of insulin-oral antidiabetic and the combination between oral antidiabetic is used to obtain controlled blood glucose effects at all times and minimize side effects as well as reduce the risk of acute complications and inhibit the progression of microangiopathy and macroangiopathy.[27]

Hazard H(t) function shows that patients with type II diabetes mellitus in the 0th to 10th year have increased, meaning that the risk of patients experiencing failure (death) is higher (Table 4). S(t) from year 0 to year 10 decreased in survival function, which means the patient's probability of survival is lower. This is not following Putri's research, which states that the longer the patient suffers from diabetes mellitus, the higher the patient's survival ability to diabetes mellitus.[24] The greater the t value, the smaller the S(t) value, while the cumulative hazard indicates that the greater the t time, the greater the H(t) value will tend to be the more significant. This means that the patient's probability of surviving until t time will be more negligible (close to zero), and the risk of dying will be greater.[28]

Table 4. Survival Table of Type II Diabetes Mellitus Patients at PKU Muhammadiyah Gamping Hospital and Yogyakarta City

Time (year)	H(*t*)	S(*t*)
0	0,017	0,973
1	0,027	0,959
2	0,035	0,947
3	0,045	0,933
4	0,063	0,908
5	0,071	0,896
6	0,082	0,880
7	0,109	0,844
8	0,130	0,817
9	0,148	0,795
10	0,165	0,775

Description: H(*t*) = *hazard* function; S(*t*) = *survival* function

CONCLUSION

Factors that affect the survival of patients with type II diabetes mellitus are gender, age, diagnosis of complications, comorbidity, intermittent blood glucose levels, and treatment profile.

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