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A Study on Type 2 Diabetes Mellitus Patients Using Regression Model and Survival Analysis Techniques

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ABSTRACT

Now a day, Non-Communicable Diseases are chronic diseases such as cardiovascular diseases, diabetes mellitus and cancer are increasing worldwide and they are associated with poor quality of life and increased economical burden. Among them, diabetes is a Non-Communicable Disease and is a serious chronic disease. The main objective of this paper is to study the Characteristics of diabetes mellitus patients at diagnosis level, to estimate the survival time of patients and to identify the prognostic factors for diabetes mellitus patient's data. 174 diabetes mellitus patients were collected during the period of February 2016 to April 2016. The Kaplan-Meier analysis was shown that the age group, Systolic Blood Pressure (SBP), family history of diabetes, Diabetic Retinopathy (DR), Diabetic Neuropathy (DN) and Fasting Blood Sugar (FBS) were shown significant difference in the survival curves except for sex, Body Mass Index (BMI) (kg/m^2), Total Cholesterol (TC) (mg/dl) and Triglyceride (TGL) (mg/dl). Cox Proportional Hazard (PH) regression analysis was shown that diabetes mellitus patients who had age group more than 60 years (HR = 2.732, 95% CI: 1.449-5.152, P = 0.002) and diabetic retinopathy (HR = 25.611, 95% CI: 6.248 – 104.983) were identified as significant risk factors. Life time of diabetes mellitus patients can be increased through early detection of risk factors, diagnosis and treatment and maintaining of healthy body weight, by taking healthy diet along with regular physical activity and also by avoiding the tobacco and alcohol use can reduce the morbidity, mortality and improve the quality of life.

Key words: *Chronic diseases, Diabetes mellitus, Survival analysis, Cox regression model*

INTRODUCTION

Chronic diseases such as cardiovascular diseases, diabetes mellitus and cancer are increasing worldwide and they are associated with poor quality of life and increased economical burden; therefore, development of preventive measures against chronic diseases is imperative. For the prevention process, it is important to identify the risk factors of these chronic diseases. Among them, diabetes is a serious chronic disease and Non-Communicable Diseases (NCDs) that occur either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces.

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Hyperglycaemia, or raised blood sugar is a common effect of uncontrolled diabetes and that can damage the body's systems especially the heart, blood vessels, eyes, kidneys, and nerves. Smoking increases the risk of diabetes and cardiovascular diseases[1]. Both the number of incidence and the prevalence of diabetes have been gradually increasing over the past few decades. In the worldwide, the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014[2]. Diabetes is contributing factor and is associated with a variety of long-term complications that can cause death. In 2012, an estimated number of deaths with the cause of diabetes were 1.5 million and another 2.2 million deaths, by increasing the risks of cardiovascular and other diseases were in high blood glucose. WHO projects that diabetes will be the 7th leading cause of death in 2030[2,3]. India is home to the second largest number of adults living with diabetes worldwide, after China. People with diabetes in India, Bangladesh, and Sri Lanka make up 99.0% of the region's total adult diabetes population. There are mainly three types of diabetes, Type 1, Type 2 and Gestational Diabetes. Type 2 diabetes is more common than type 1 diabetes and type 2 diabetes can be preventable with physical activity and health diet. India is home to the second largest number of children with type 1 diabetes in the world (70, 200), after the USA, and accounts for the majority of the children with type 1 diabetes in the region. More than half (53.2%) of these deaths occurred in people under 60 years of age. India was the largest contributor to regional mortality, with one million deaths attributable to diabetes[4,5]. Survival analysis is a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs[6]. The time variable as survival time, because it gives the time that an individual has "survived" over some follow up period. The event may be referred to as failure, because the event of interest usually is death, disease incidence or some other negative individual experience[6-7]. The analysis of survival data from clinical trials and observational studies was given by Marubini and Valsecchi[8]. A Cox regression model for the relative mortality and its application to diabetes mellitus survival data was given by Andersen *et al*[9]. Statistical applications of survival data analysis and identifying the risk factors for mortality can be applied in many health care studies, such as, breast cancer[10], Secondary type of cancer[11], Comparison of parametric methods for regression model by using cardiovascular disease survival data[12], to analyze epidemiological and clinical trends in the incidence and survival of lower extremity amputations among diabetes patients[13], to analyze the survival rate of End Stage Renal Disease (ESRD) patients in Lahore city, and to evaluate the influence of various risk factors and prognostic factors on survival of these patients[14] and many more. The main objective of this paper is to study the Characteristics of diabetes mellitus patients at diagnosis level, to estimate the survival time of patients and to identify the prognostic factors for diabetes mellitus patient's data.

MATERIALS AND METHODS

Data was collected from the registries of medical records in the Department of Endocrinology, Narayana Superspeciality Hospital, Nellore, Andhra Pradesh, India over a period of three months i.e., from February 2016 to April 2016. Data were entered into MS-Excel and analyzed by using statistical software IBM SPSS Version 22.0 (SPSS Inc., Chicago, USA). By analyzing the data, Kaplan-Meier Method was used for estimating the survivorship function, to compare the probability of survival curves of two groups log rank test was used and for identifying the prognostic factors, Cox Proportional Hazard (PH) regression model was used. All the p-values are having less than 0.05 are considered as statistical significance.

Kaplan-Meier Product-Limit (PL) method:

The Product-Limit (PL) method of estimating the survivorship function was developed by

Kaplan and Meier (1958). This method can be applicable to small, moderate and large samples. These estimates are developed based on individual survival time[7]. Let 'n' patients are put under the treatment with similar disease and let the survival times of all patients are known. i.e., consider the case where all patients are observed to death. Let $t_1, t_2, \ldots, t_n$ indicates the survival times of 'n' patients under study. Then we can arrange these survival times in increasing order of magnitude $t_{(1)} \leq t_{(2)} \leq \ldots \leq t_{(n)}$.

Then the survival function at time point 't_i' is given by

$$\hat{S}(t_{(i)}) = \frac{\text{Number of patients surviving surviving larger than } t_{(i)}}{\text{Total number of patients}}$$

$$= \frac{n-i}{n} = 1 - \frac{i}{n}; \qquad (1)$$

where i indicates the number of deaths.

Since every individual alive in the beginning of study and no one survives longer than $t_{(n)}$. Then we have $\hat{S}(t_{(0)}) = 1$ and $\hat{S}(t_{(n)}) = 0$. Generally, the value of $\hat{S}(t)$ is computed at every distinct time point, the graph of $\hat{S}(t)$ shown that it is a step function starting at '1' and decreases to zero in the steps of 1/n.Let n be the total number of patients whose survival times, censored or not, are available. Relabel the n survival times in order of increasing magnitude such that $t_{(1)} \leq t_{(2)} \leq \ldots \leq t_{(n)}$.

Then

$$\hat{S}(t) = \prod_{t_{(r)} \leq t} \frac{n-r}{n-r+1} \qquad (2)$$

The estimated median survival time is the 50th percentile, which is the value of t at $\hat{S}(t) = 0.50$.

Log rank test:

Mantel's (1966) generalization of the Savage (1956) test, often referred to as the Log rank test (Peto and Peto, 1972), it is based on a set of scores w_i assigned to the observations. The scores are functions of the logarithm of the survival function[7]. Altshuler (1970) estimates the log survival function at $t_{(i)}$ using

$$-e(t_{(i)}) = -\sum_{j \leq t_{(i)}} \frac{m_{(j)}}{r_{(j)}} \qquad (3)$$

Where $m_{(j)}$ = Number of times uncensored observation repeated and

$r_{(j)}$ = Number of observations in risk set in both groups.

Then the score suggested by peto and peto's is given by $w_i = 1 - e(t_{(i)})$ for uncensored observation $t_{(i)}$(or) $w_i = - e(t_{(j)})$, where t(j) is largest uncensored observation such that $t_{(j)} \leq t_i^+$.Further the w scores sum identically zero for the two groups together. Then the test statistic for testing the null hypothesis

H_0: $S_1(t) = S_2(t)$ against

H_1: $S_1(t) > S_2(t)$, (or) H_2: $S_1(t) < S_2(t)$ (or) H_3: $S_1(t) \neq S_2(t)$

is given by

$$L = \frac{S}{\sqrt{Var(S)}} \qquad (4)$$

Here S = sum of scores assigned to group-II observations $= \sum_{i=1}^{n_2} w_i$

Under H_0, it is assumed that L is a standard normal variate. If S is obtained from group I then critical region is $L < - Z_\alpha$. If S is obtained from group II then critical region is $L > Z_\alpha$.

Cox Proportional Hazard (PH) regression model:

The Cox (1972) proportional hazards model does not require knowledge of the underlying distribution. The hazard function in this model can take on any form, including that of a step function, but the hazard functions of different individuals are assumed to be proportional and independent of time. The Cox proportional hazards model possesses the property that different individuals have hazard functions that are proportional, i.e., $[h(t|\mathbf{x}_1) / h(t|\mathbf{x}_2)]$, the ratio of the hazard functions of two individuals with prognostic factors or covariates $\mathbf{x}_1 = (x_{11}, x_{21}, .., x_{p1})'$, and $\mathbf{x}_2 = (x_{12}, x_{22}, ., x_{p2})'$ is a constant[7]. The hazard function for a given set of covariates $\mathbf{x} = (x_1, x_2, ..., x_p)'$ can be written as a function of anunderlying hazard function and also a function, say $g(x_1, ..., x_p)$, of only the covariates, that is,

$$h(t \mid x_1,\ldots., x_p) = h_0(t)\, g(x_1, \ldots., x_p) \text{ or } h(t \mid \mathbf{x}) = h_0(t)\, g(\mathbf{x}) \qquad (5)$$

The underlying hazard function, $h_0(t)$, represents how the risk changes with time, and $g(\mathbf{x})$ represents the effect of covariates. $h_0(t)$ can be interpreted as the hazard function when all covariates are ignored or when $g(\mathbf{x}) = 1$, and is also called the *baseline hazard function*. The hazard ratio of two individuals with different covariates $\mathbf{x}_1$and $\mathbf{x}_2$ is

$$\frac{h(t|\mathbf{x}_1)}{h(t|\mathbf{x}_2)} = \frac{h_0(t)g(\mathbf{x}_1)}{h_0(t)g(\mathbf{x}_2)} = \frac{g(\mathbf{x}_1)}{g(\mathbf{x}_2)} \qquad (6)$$

Which t is a constant, independent of time.

The Cox (1972) proportional hazard model assumes that $g(\mathbf{x})$ in (5) is an exponential function of the covariates, that is,

$$g(x) = e^{\sum_{j=1}^{p} b_j x_j} = e^{\boldsymbol{b}'\mathbf{x}} \qquad (7)$$

and the hazard function is

$$h(t|\mathbf{X}) = h_0(t) e^{\sum_{j=1}^{p} b_j x_j} = h_0(t) e^{\boldsymbol{b}'\mathbf{X}} \qquad (8)$$

Where $\mathbf{b} = (b_1, b_2, \ldots, b_p)$ denotes the coefficients of covariates.

Dividing both sides of (7) by $h_0(t)$ and taking its logarithm, we obtain

$$\log \frac{h_i(t)}{h_0(t)} = b_1 x_{1i} + b_2 x_{2i} + \cdots + b_p x_{pi} = \sum_{j=1}^{p} b_j x_{ji} = \boldsymbol{b}'\mathbf{X_i} \qquad (9)$$

Where the x's are covariates for the i^{th} individual. The left side of equation (9) is a function of hazard ratio (or relative risk) and the right side is a linear function of the covariates and their respective coefficients.The use of equation (9) is used to identify important prognostic factors. If b_i is zero, the corresponding covariate is not related to survival. If b_i is not zero, it represents the magnitude of the effect of x_i on hazard when the other covariates are considered simultaneously[7].

RESULTS AND DISCUSSION

In the analysis, the treatment outcome of the diabetes mellitus patients, 123 (70.7%) were alive, 51 (29.30%) were dead patients. Patients' Characteristics at diagnosis by the patient status and Kaplan-Meier survival analysis for diabetes mellitus patients and the median survival time and log-rank test results are shown were shown in table-1. Out of 174 diabetes mellitus patients, number of female patients 92 (52.87%) are higher than the male patients 82 (47.13%). However, the number of

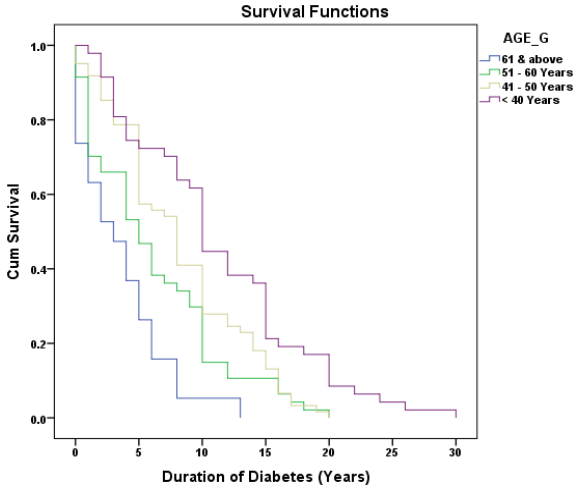
male deaths is more 38 (46.3%) than the female deaths 13 (14.1%). The number of patients having age group ≤ 40 years is 19 (10.92%), 41-50 years 47 (27.01%), 51-60 years is 61 (35.06%), > 60 years is 47 (27.01%). Moreover, the number of deaths in the age group of > 60 years 24 (51.1%) is high when compared with other age groups. In our study, Age is increases then survival lifetime of patients is gradually decreases. The number of patients of BMI groups are of Normal is 61 (35.06%), Over weight is 72 (41.38%) and Obese is 41 (23.56%). However, the number of deaths in Obese group 22 (53.7%) is more than the over weight group 21 (29.2%) and normal group 8 (13.1%).The number of patients having Systolic Blood Pressure (SBP) (< 140 mmHg) is 103 (59.2%), and systolic blood pressure (≥ 140 mmHg) is 71 (40.8%). The percentage of deaths is significantly higher in systolic blood pressure (≥ 140 mmHg) 29 (40.8%) than the systolic blood pressure (< 140 mmHg) 22 (21.4%). The number of patients having family history of diabetes is less 79 (45.40%) when compared with family history of non-diabetes patients 95 (54.60%). However, the number of deaths in family history of diabetes patients 33 (41.8%) is more than the family history of non-diabetes patients 18 (18.9%).The number of patients having diabetic retinopathy is less 38 (21.84%) when compared with diabetic non-retinopathies 136 (78.16%). However, the number of deaths in diabetic retinopathy patients 36 (94.7%) is more than the diabetic non-retinopathy patients 15 (11.0%). The number of patients having diabetic neuropathy 117 (67.24%) is high when compared with diabetic non-neuropathy 57 (32.76%). Similarly, the number of deaths in diabetic neuropathy patients 45 (38.46%) is more than the diabetic non- neuropathy patients 6 (10.53%). The number of patients having Fasting Blood Sugar (FBS) (≥ 110 mg/dl) is more 139 (79.89%) than the fasting blood sugar (< 110 mg/dl) 35 (20.11%). Similarly, the number of deaths of fasting blood sugar (≥ 110 mg/dl) patients 42 (30.2%) is high when compared with fasting blood sugar (< 110 mg/dl) patients 9 (25.7%).The number of patients having Total Cholesterol (TC) (< 200 mg/dl) is higher 127 (79.89%) than the total cholesterol (≥ 200 mg/dl) 47 (20.11%). Similarly, the number of deaths of total cholesterol (< 200 mg/dl) patients 40 (30.5%) is more when compared with total cholesterol (≥ 200 mg/dl) patients 11 (23.4%). The number of patients having Triglyceride (TGL) (< 150 mg/dl) is higher 25 (14.37%) than the Triglyceride (≥ 150 mg/dl) 149 (85.63%). However, the number of deaths of Triglyceride (< 150 mg/dl) patients 7 (28.0%) is less when compared with Triglyceride (≥ 150 mg/dl) patients 44 (29.53%).Kaplan-Meier survival analysis and Log-rank test values for diabetes mellitus patients are shown in Table-1 and Kaplan-Meier estimate for survival probability curves for Age group, Systolic Blood Pressure (SBP), Family History, Diabetic Retinopathy (DR), Diabetic Neuropathy (DN) and Fasting Blood Sugar (FBS) are shown Figure-1.

Table 1: Kaplan-Meier survival analysis & Log-rank test values for diabetes mellitus patients

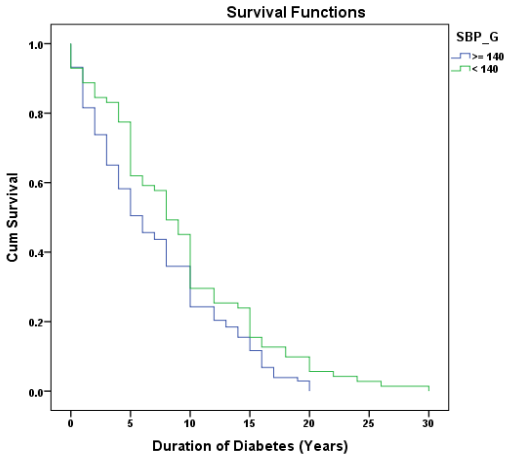
Variables	No. of Patients	No. of Deaths [n (%)]	Median for survival time (Years)		95% Confidence Interval		Chi square	P value
			Estimate	Std. Error	Lower Bound	Upper Bound		
Sex								
Males	82	38 (46.3)	15	0.45	14.12	15.89	2.963	0.085
Females	92	13 (14.1)	16	1.01	14.02	17.99		
Age (Years)								
≤ 40	19	0 (0.0)	10	0.43	9.17	10.84		
41 – 50	47	11 (23.4)	8	0.85	6.33	9.67	34.47	< 0.0001*
51 – 60	61	16 (26.2)	5	1.05	2.94	7.06		
> 60	47	24 (51.1)	3	1.31	0.44	5.56		
Body Mass Index (BMI) [kg/m^2]								
Normal	61	8 (13.1)	16	2.08	11.93	20.08	1.72	0.423
Over weight	72	21 (29.2)	16	1.09	13.87	18.14		
Obese	41	22 (53.7)	15	1.34	12.37	17.63		
Systolic Blood Pressure (SBP) [mmHg]								
< 140	103	22 (21.4)	8	0.63	6.76	9.24	5.022	0.025*
≥ 140	71	29 (40.9)	6	1.01	4.02	7.98		

Family History of diabetes								
Yes	79	33 (41.8)	5	0.97	3.09	6.91	11.598	0.001*
No	95	18 (18.9)	8	0.99	6.07	9.93		
Diabetic Retinopathy								
Yes	38	36 (94.7)	5	0.53	3.96	6.04	28.35	< 0.0001*
No	136	15 (11.0)	15	1.27	12.51	17.49		
Diabetic Neuropathy								
Yes	117	45 (38.5)	3	0.69	1.66	4.35	32.48	< 0.0001*
No	57	6 (10.5)	10	0.45	9.11	10.89		
Fasting Blood Sugar (FBS) [mg/dl]								
< 110	35	9 (25.7)	8	1.04	5.97	10.03	12.09	0.001*
≥ 110	139	42 (30.2)	3	0.81	1.42	4.58		
Total Cholesterol (TC) [mg/dl]								
< 200	127	40 (30.5)	8	1.05	5.94	10.06	0.835	0.361
≥ 200	47	11 (23.4)	5	1.37	2.31	7.69		
Triglyceride (TGL) [mg/dl]								
< 150	25	7 (28.0)	6	0.83	4.38	7.62	0.037	0.848
≥ 150	149	44 (29.5)	6	0.83	4.38	7.62		

**** P < 0.05 - Significant***



(a)



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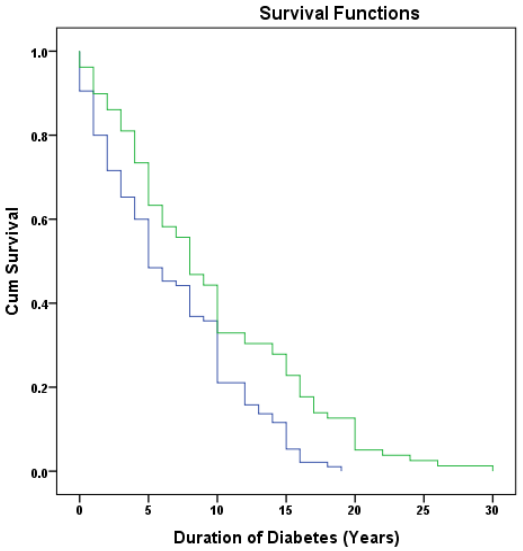

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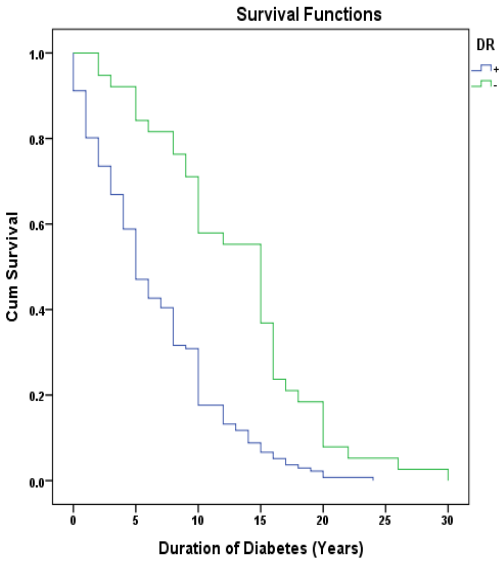

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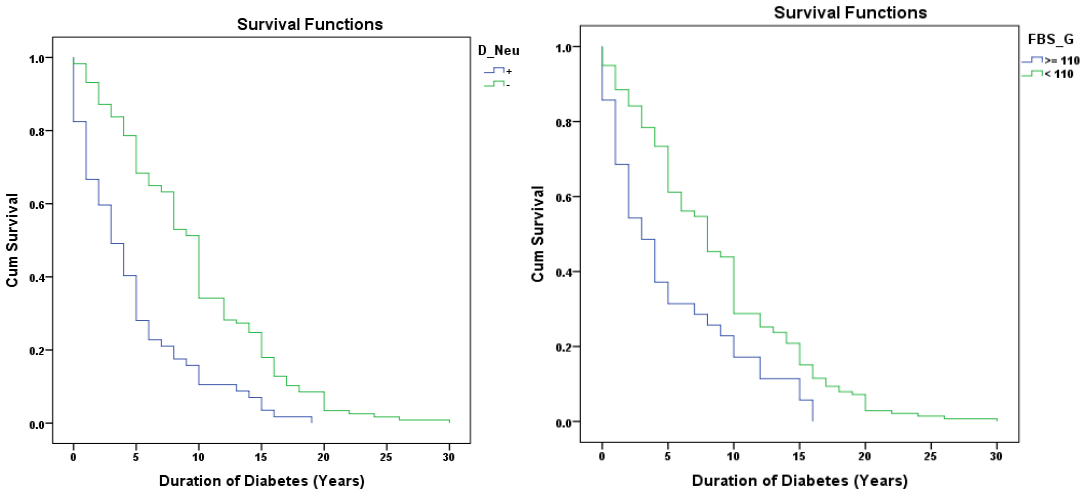

(e) **(f)**

Fig. 1: Kaplan-Meier estimate for survival probability curve for (a) Age group, (b) SBP, (c) Family History, (d) Diabetic Retinopathy, (e) Diabetic Neuropathy and (f) fasting blood sugar for diabetes mellitus patient's data

The Kaplan-Meier analysis was shown that the age group [Log rank test=34.47, d.f. = 3, P < 0.0001], systolic blood pressure [log rank test=5.022, d.f.=1, P =0.025], family history of diabetes [Log rank test=11.598, d.f. = 1, P=0.001], diabetic retinopathy [Log rank test= 28.35, d.f. = 1, P<0.0001], diabetic neuropathy [Log rank test = 32.48, d.f. = 1, P < 0.0001] and Fasting Blood Sugar [Log rank test = 12.09, d.f. = 1, P = 0.001] were having significant difference in the survival curves except for sex [Log rank test = 2.963, d.f.=1, P=0.085], BMI (kg/m^2) [Log rank test = 1.72, d.f. = 2, P = 0.423], total cholesterol (mg/dl) [Log rank test= 0.835, d.f. = 1, P = 0.361] and Triglyceride (mg/dl) [Log rank test = 0.037, d.f. = 1, P = 0.848]. Cox Proportional Hazard (PH) regression analysis of diabetes mellitus patients for death is shown in table 2.

Table 2: Cox Proportional Hazard (PH) regression model analysis in diabetes mellitus patients for death

Variables	Regression Coefficient	Standard Error	Wald Statistic	P value	Hazard Ratio (HR)	95.0% CI for HR	
						Lower Bound	Upper Bound
41-50 Yrs Vs ≤ 40 Yrs	0.155	0.262	0.352	0.553	1.168	0.699	1.950
51-60 Yrs Vs ≤ 40 Yrs	0.325	0.278	1.370	0.242	1.384	0.803	2.386
< 60 Yrs Vs ≤ 40 Yrs	1.005	0.324	9.646	0.002*	2.732	1.449	5.152
Diabetic Retinopathy (Yes Vs No)	3.243	0.720	20.299	0.000*	25.611	6.248	104.983
Diabetic Neuropathy (Yes Vs No)	0.778	0.192	16.374	0.000*	2.178	1.494	3.174

**** p < 0.05 - Significant***

The result of Cox Proportional Hazard (PH) regression analysis are stated that diabetes mellitus patients who had age group 41-50 years (HR = 1.168, 95% CI: 0.699 - 1.950, P = 0.553) were having 1.168 time more at risk of death as compared with the age group < 40 years, Age group 51-60 years (HR = 1.384, 95% CI: 0.803-2.386, P = 0.242) were having 1.384 times more at risk of death as compared with the age group < 40 years and who had age

group > 60 years (HR = 2.732, 95% CI: 1.449 – 5.152, P = 0.002) were having 2.732 times significantly more at risk of death as compared with the age group < 40 years. Diabetes mellitus patients who had diabetic retinopathy (HR = 25.611, 95% CI: 6.248 – 104.983) were having 25.611 times more at risk of death compared with those who had no diabetic retinopathy. Figure 2 showed hazard function at mean of covariates of diabetes Mellitus patients for death and we observed that if the patient duration of diabetes is increases then their risk of death is also increased.

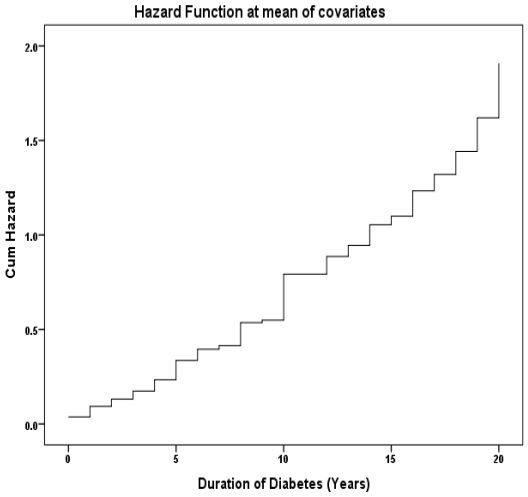

Fig. 2: Hazard function at mean of covariates of diabetes Mellitus patients' death

CONCLUSION

The results are stated that if the diabetic patients age increases then the risk of death is also increases, simultaneously, diabetic patients those who are having diabetic retinopathy and diabetic neuropathy are getting high risk of death in their life. Survival time of diabetes mellitus patients can be increased through early detection of risk factors, diagnosis and treatment and maintaining of healthy body weight, by taking healthy diet and regular physical activity along with lower blood glucose levels and avoiding the tobacco use can reduce the morbidity, mortality and improve the quality of life.

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