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ANALYSIS OF SURVIVAL TIMES OF DIABETIC PATIENTS USING COX PROPORTIONAL HAZARD MODEL: CASE STUDY

Nurudeen A. A., Kolawole I. A. and Nasiru R.

Department of Mathematics and Statistics, Kaduna Polytechnic, Kaduna

Abstract

This study examines the survival times of diabetic patients attending two different diabetes centers. The data used were obtained from clinical studies-Usmanu Danfodiyo University Teaching Hospital, (UDUTH), Sokoto and Barau Dikko Teaching Hospital, (BDTH) Kaduna from 2012-2017, the population-based survey of known diabetes prevalence with a subsequent 6-year mortality follow-up. A cohort of 2,613 diabetic patients' folder was observed on 11th April, 2018 from two different sources: UDUTH, Sokoto and BDTH, Kaduna. As at the dates stated, 1,193 patients in the entire cohort attended UDUTH while the remaining attended BDTH. The life status of the diabetic cohort was ascertained on 11th April, 2018. Using Cox proportional hazard model for sex, age, place of attendance and severity of illness. The regression coefficient 0.179 for explanatory variable; place of attendance reveals that the hazard is higher (prognosis worse) for patients attending BDTH than their counterparts at UDUDTH (P<0.05). The hazard ratio obtained was 1.196 (95% C I 1.000 - 1.429), this indicates that UDUTH attendees are less likely to have shorter time to event of interest (death). The drop line chart on severity of the illness also shows that the mean survival time is slightly higher among the UDUTH attendees' than their counterparts in BDTH.

***Keywords*:** Survival time, Cox model, hazard, diabetic, patients, attendance centre.

1.0 INTRODUCTION

Survival analysis techniques employ methods designed to investigate the amount of study time an experimental unit contributes to a study period from entry until event. The term "survival" may be misleading because the techniques are applicable to any well-defined event although traditionally death is the event of interest and the study period consisted of following the subject until death. Event in survival analysis (also referred to as endpoints or outcomes) are defined by a transition from one discrete state to another at an instantaneous moment in time. Example of events include months until onset of disease, days until remission after cancer therapy, years until stock market crash, hours until equipment failure, days until unemployment or time until failing or passing an examination [1].

Although the origin of survival analysis goes back to mortality tables from centuries ago, recent advancements in survival analytic techniques using non-parametric and semi-parametric approaches have allowed researchers flexibility in their work not properly seen within the confines of parametric methods. These methods have become popular over parametric methods due to the relatively robust modeling approaches without distributional assumptions on the survival times [2].

Diabetes is a chronic disease that arises when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Insulin is a hormone made by the pancreas that enables cells to take in glucose from the blood and use it for energy. Failure to produce insulin, or of insulin to act properly, or both, leads to raise glucose (sugar) levels in the blood (hyperglycemia). This is associated with long term damage to the body and failure of various organs and tissues [3].

Diabetes comes from Greek, and it means a siphon. Aretus the Cappadocian, a Greek physician during the second century A.D., named the condition diabainein. He described patients who were passing too much water (polyuria) - like a siphon. The word became "diabetes" from the English adoption of the Medieval Latin diabetes.

Corresponding Author**:** Nurudeen A.A., Email: nurkarmeds@gmail.com, Tel: +2348032156015

In 1675 Thomas Willis added mellitus to the term, although it is commonly referred to simply as diabetes. Mel in Latin means honey; the urine and blood of people with diabetes has excess glucose, and glucose is sweet like honey. Diabetes mellitus could literally mean "siphoning off sweet water". In ancient China people observed that ants would be attracted to some people's urine, because it was sweet. The term "Sweet Urine Disease" was coined [4].

There are three main types of diabetes, type I diabetes is sometimes called insulin-dependent, immune-mediated or juvenile-onset diabetes. It is caused by an auto-immune reaction where the body defence system attacks the insulin-producing cells. The reason why this occurs is not fully understood. People with type I diabetes produce very little or no insulin. The disease can affect people of any age, but usually occurs in children or young adults. People with this form of diabetes need injections of insulin everyday in order to control the level of glucose in their blood. If people with type I diabetes do not have access to insulin, they will die [5].

Type II diabetes account 90% of all cases of diabetes. Type II diabetes is sometimes called non-insulin dependent diabetes or adult-onset diabetes, and account for at least 90% of all cases of diabetes. It is characterized by insulin resistance and relative insulin deficiency, either of which may be present at the time that diabetes becomes clinically manifest. The diagnosis of type II diabetes usually occurs after the age of 40 but can be detected earlier, especially in population with high diabetes prevalence. Type II diabetes can remain undetected for many years and the diagnosis is often made from associated complications or incidentally through an abnormal blood or urine glucose test. It is often, but not always, associated with obesity, which itself can cause insulin resistance and lead elevated blood glucose levels [4].

Gestational diabetes (GDM) is a form of diabetes consisting of high blood glucose levels during pregnancy. It develops in one in a 25 pregnancies world wide and is associated with complications in the period immediately before and after birth. GDM usually disappears after pregnancy but women with GDM they are at an increase risk of developing type II diabetes later in life. Approximately half of women with a history of GDM go on to develop type II diabetes within five to ten years after delivery [6]

Warning signs of diabetes, Individuals can experience different warning signs and sometimes there may be no obvious warning, but some of the signs of diabetes are commonly experienced:

Frequent urination, Excessive thirst, Increased hunger, Weight loss, Tiredness, Lack of interest and concentration, Vomiting and stomach pain (often mistaken as the flu), A tingling sensation or numbness in the hand or feet, Blurred vision, Frequent infections, Slow-healing wounds,. The onset of type I diabetes is usually sudden and dramatic while the symptoms can often be mild or absent in people with type II diabetes, making this type of diabetes gradual in onset and hard to detect. If you show these signs, consult a health professional.

The risk factors, for type I diabetes are still being researched. However, having a family member with type I diabetes increases the risks for developing the condition, as do the presence of some genetic factors. Environmental factors increased height and weight development, increased maternal age at delivery, and exposure to some viral infections have also been linked to the risk of developing type I diabetes. Several risk factors have been associated with type II diabetes and include: Obesity, Diet and Physical inactivity, Increasing age, Insulin resistance, Family history of diabetes, Ethnicity. Changes in diet and physical activity related to rapid development and urbanization have led to sharp increases in the numbers of people developing diabetes. Pregnant women who are overweight, have been diagnosed with Impaired Glucose Tolerance (IGT), or have a family history of diabetes are all at risk of developing Gestational diabetes (GDM). In addition, having been previously diagnosed with gestational diabetes or being of certain ethnicities put women at risk of developing the condition [4].

The aim of this paper is to analyse the survival time of diabetic patients attending two different diabetic centers. The objective of the study is to determine the survival of patients with emphasis on place of attendance and severity of illness.

2.0 Materials and Methods

2.1 Method of Data Collection

The data used for this study were obtained from clinical studies-Usmanu Danfodiyo University Teaching Hospital, (UDUTH),Sokoto and Barau Dikko Teaching Hospital, (BDTH) Kaduna from 2013-2018, the population-based survey of known diabetes prevalence with a subsequent 6-year mortality follow-up. Time from diagnosis of the disease to death defines the failure time while those whose records read “alive” were right-censored because such patients had not died as at the time of the study. The hospital set-up for the case study are tertiary health centres in which the medical facilities for the treatment of diabetes are the same. A cohort of 2,613 diabetic patients’ folder was observed on 11th April, 2018 from two different sources: UDUTH, Sokoto and BDSH, Kaduna. As at the dates stated, 1,193 patients in the entire cohort attended UDUTH while the remaining attended BDTH. Severities of illness were categorized into stages namely 1, 2, 3A and 3B. Stage 1and 2 being the early stages of the diabetes while stage 3A and 3B are the late stages of the illness. The life status of the diabetic cohort was ascertained on 11th April, 2018.

2.2 Statistical Analysis

In this paper, Cox proportional hazard model (multivariate survival analysis) was employed to analyse clinical variables of diabetic patients which includes sex, age, severity of illness and attendance centre and also we obtained demographic characteristics of diabetic patients. All analyses were performed using SPSS (version 20.0),

2.2.1 Model Specification

2.2.2 Cox Proportional Hazard Model

Suppose that the data collected on n subjects are denoted by (t_i, δ_i, Z_i)(t, j, c_j), where t_i is the failure time of the i[th] subject, δ_i is the censoring indicator such that such that for the i[th] subject, δ_i = 1 if a subject is observed to fail and δ_i =0 if the time is right censored, the model assumes that the hazard function for the i[th] subject with covariate value Z_i has the form

$$\lambda(t_i, Z_i) = \lambda_0(t)\exp(\beta' Z_i) \quad \ldots\ldots (2.1)$$ **[2]**

Where $\lambda_0(t)$ is an arbitrary baseline hazard function and β is a p x 1 vector of unknown regression coefficients (parameters). Model (2.1) is semi-parametric because the dependence function $\exp(\beta' Z_i)$ is modeled explicitly but no specific probability distribution is assumed for the survival times.

2.2.2.1 Estimation Specification

Suppose that of the n subjects in the study, r of them are observed to fail while the remaining n-r are right censored. Let $t_{(1)} < \ldots < t_{(r)}$ be ordered failure times and $Z_{(i)}$ be the vector of covariate associated with the individual whose survival time is $t_{(1)}$. Define $R(t_{(i)})$, the risk set at $t_{(i)}$ as the set of all individuals who are still under study at the time just prior to $t_{(1)}$, then the probability that the individual with covariate $Z_{(i)}$ dies at $t_{(1)}$ given that one person from R $t_{(1)}$ dies at $t_{(1)}$ is

$$\frac{\lambda(t_{(i)}, Z_{(i)})}{\sum_{j\varepsilon R(t_{(i)})} \lambda(t_{(i)}, Z_{(i)})} \quad \ldots\ldots (2.2)$$

Which is from (2.1), is

$$\frac{\exp(\beta', Z_{(i)})}{\sum_{j\varepsilon R(t_{(i)})} \exp(\beta', Z_{(i)})} \quad \ldots\ldots (2.3)$$

Cox (1972), on the assumption of no tied events, gave likelihood function as

$$L(\beta) = \prod_{i=1}^{r} \frac{\exp(\beta', Z_{(i)})}{\sum_{j\varepsilon R(t_{(i)})} \exp(\beta', Z_{(i)})} \quad \ldots\ldots (2.4)$$

Hence the required log likelihood function is

$$L(\beta) = \sum_{i=r}^{r} Z_{(i)}\beta - \sum_{j\varepsilon R(t_{(i)})}^{r} \log\left[\sum\right] \quad \ldots\ldots (2.5)$$

Table 1: Main clinical characteristics of the diabetic patients.

	Diabetic patients attending UDUTH, Sokoto	Diabetic patients attending BDTH,Kaduna
Cases	1,193	1,420
(Male)	642 (53.8)	765 (53.9)
Sex :		
(Female)	551 (46.2)	655 (46.1)
Age (years ± SD)	56.9 ± 17.3	52.1 ± 21.7
Age (Group)		
0-19	35 (2.9)	157 (11.1)
20-39	155 (13.0)	195 (13.7)
40-59	461 (38.7)	526 (37.0)
60-79	405 (33.9)	395 (27.8)
≥ 80	137 (11.5)	147 (10.4)
Severity of illness		
Stage1	159 (13.3)	199 (14.0)
Stage2	397 (33.3)	475 (33.5)
Stage3A	495 (41.5)	576 (40.6)
Stage3B	142 (11.9)	170 (11.9)

Data are mean ± SD for continuous variable and absolute frequency (percent) for categorical variables.

3.0 Results

The main clinical characteristics of the cohort under study are summarized in table 1. With respect to age, the patients that attended UDUTH were slightly older ($p<0.000$) than the patients that attended BDTH. By the end of the study, 504 diabetic patients were deceased. Of these, 210 were among the 1,193 patients that attended UDUTH (17.6%) and 294 were among the 1,420 attendees' of BDTH (20.7%). On the length of attendance (months), there was no significant difference between the patients that attended UDUTH and that of BDTH.

The difference in survival as a function of attendance at the diabetes clinic was well appreciable, since this is an adjusting for confounder model, our interest is only in the variable attendance. the regression coefficient 0.179 for explanatory variable; place of attendance reveals that the hazard is higher (prognosis worse) for patients attending BDTH than their counterparts at UDUDTH ($P<0.05$).The drop line chart on severity of the illness also shows that the mean survival time is slightly higher among the UDUTH attendees' than their counterparts in BDSH especially for stage1 and stage2. Surprisingly, reverse was the case for stage3A and stage3B. (Fig.6).The hazard ratio obtained was 1.196 (95% C I 1.000 - 1.429), this indicates that UDUTH attendees are less likely to have shorter time to event of interest (death).

However, on the overall, the survival time was slightly higher in UDUTH, Sokoto centre than in BDTH, Kaduna. Persisted after adjustment for sex, age, severity of illness and places of attendance in the Cox model.

Patients attending BDSH and UDUTH belonging to stage 1 of illness have 25.1 months and 26.5 months survival time respectively, for stage 2 they have (24.4 months and 24.8 months respectively), for stage 3A (24.9 months and 24.8 months respectively) and for stage 3B we have (25 months and 24.5 months respectively).

Table 2- Categorical Variable Coding

Categorical Variables Coding	Categorical Variables Coding
Age : 1= 0-19	Severity of illness : 1= Stage 1
2= 20-39	2= Stage 2
3= 40-59	3= Stage 3A
4= 60-79	4= Stage 3B
5= >= 80	
Sex : 0= Female	Place of attendance : 0= UDUTH
1= Male	1= BDTH

Table 3- Estimates of variables in Cox regression model

	B	SE	Wald	d.f	Sig.	Exp (B)	Lower	Upper
Sex	-0.056	0.090	0.386	1	0.002	0.946	0.793	1.127
Age	-0.002	0.002	0.516	1	0.036	0.998	0.994	1.003
Severity Of illness	-0.006	0.050	0.014	1	0.514	0.994	0.901	1.097
Attendance	0.179	0.091	3.851	1	0.041	1.196	1.000	1.429

4.0 CONCLUSION

On the overall, the survival time was slightly higher at UDUTH, Sokoto centre than at BDTH, Kaduna. Persisted after adjustment for sex, age, severity of illness and places of attendance in the Cox model. The drop line chart shows that the mean survival time is slightly higher among the UDUTH attendees' than their counterparts in BDTH especially for stage1 and stage2. Surprisingly, reverse was the case for stage3 and stage4 (Fig. 3). However, patients attending BDTH and UDUTH belonging to stage 1 of illness have 25.1 months and 26.5 months survival time respectively, for stage 2 we have (24.4 months and 24.8 months respectively), for stage 3 (24.9 months and 24.8 months) and for stage 4 we have (25 months and 24.5 months respectively). However,

Some limitations are to be considered in the interpretation of our results. In particular, because the selection of location of attendance under study was not randomized, it is not possible to rule out a self-selection bias. To our knowledge, there are no other reports on the effect of level of health care on survival in diabetic patients. Other studies tried to evaluate metabolic control in diabetes patients which is essential to prevent complications and improve survival. Some studies have shown that the degree of metabolic control was greatly improved when patients' care was provided by the family physicians and diabetes centers in collaboration.

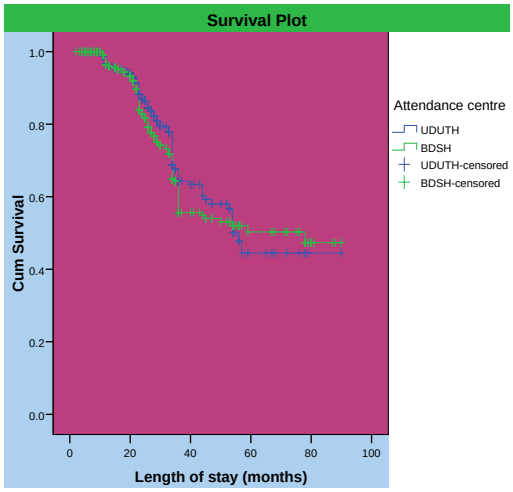

Figure 1: Survival plot for 2,613 diabetic patients data at UDUTH and BDSH from 2012-2017.

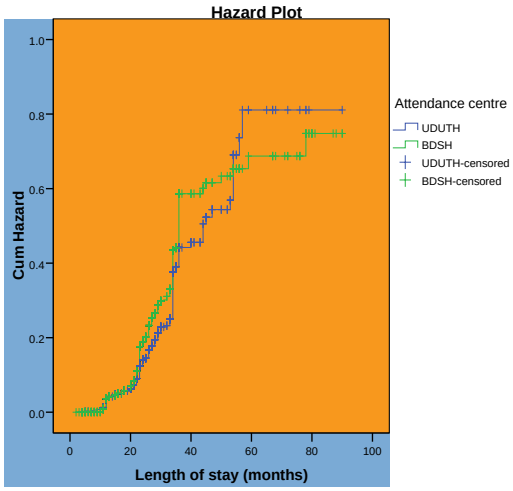

Figure 2: Hazard plot for 2,613 diabetic patients at UDUTH and BDTH from 2012-2017.

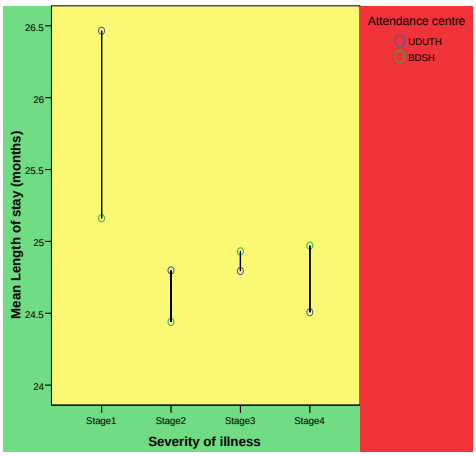

Figure 3: Drop line chart for severity of illness for 2,613 diabetic patients at UDUTH and BDTH from 2012-2017.

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