Survival Analysis on Time-To-Recovery of Diabetic Patients at Minlik Referral Hospital, Ethiopia: Retrospective Cohort Study

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Abstract

Aim

The study aimed to determine the time to recovery of diabetic patients who have been treated in the hospital under follow-up.

Subject and Methods

A retrospective cohort study design was carried out. The fast blood glucose level of diabetic patients who are under follow-up in the hospital was measured from 2016 to 2020. One thousand seven hundred diabetic patients were included in the study. Kaplan-Meier, Log-rank test, global test, Schoenfeld residuals, and Cox-PH model were used for statistical analysis.

Results

Out of the total of 1278 patients, 27.4% were censored (withdrawal from follow-up) and 72.6% recovered from the diabetic disease. For sex, the expected hazard is 1.322 times higher in males than female diabetic patients or there is a 32.2% increase in the expected hazard in males relative to female diabetic patients. For Spdrt, The expected hazard is 1.164 times higher in the patients who had taken leute than diabetic patients who took doanied. For regimen, the expected hazard is 1.495 times higher in the patients who had been treated by insulin agent only than diabetic patients who were treated by oral agents only.

Conclusion

The intensive-therapy regimen, Spdrt, and gender differences were statistically significant and critically contribute to the survival time to recovery of diabetic patients.

Introduction

Diabetes is an incurable and genealogical disease (Tarekegne et al., 2018; Berhanie, Mihretie and Anandapandian, 2019; Handayani, Nugroho and Hermawati, 2020; Fikadu et al., 2021). Chronic hyperglycemia is associated with micro-vascular and macro-vascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage, amputations, heart disease, and stroke (Lea and Nicholas, 2002; Sileshi Bekele Hordofa* and Olani Debelo, 2020).

There are three main types of diabetes: type I, type II, and gestational age. Of these, type II occurs in almost all cases (Grossman and Grossman, 2017; Ababa, Id and Id, 2019; ‘Comparative Study Of Some Immunological Aspects Between Type I And Type II Diabetic Mellitus In Iraqi Patients Of Thi-Qar’, 2020). Income(Rabi et al., 2006), education(Whitaker et al., 2014), age(Selvin and Parrinello, 2013), gender(Siddiqui, Khan and Carline, 2013), past medical history(Tattersall, 2010), family history(Ard, Tettey and Feresu, 2020), health complication(Abejew, Belay and Kerje, 2015), types of medication(Stubbs, Levy
and Dhatariya, 2017) and Spdrt(Lv and Guo, 2020) are associated with diabetes. With age, the body’s sugar level may drop, and the disease can be fatal. The internal structure of the body can be the cause of the disease, and there is a difference between men and women (Negash Terefe, Abiyot, 2017).

Diabetes is directly related to high blood pressure so that it is important to measure and treat the blood pressure (Grossman and Messerli, 2011; Muleta et al., 2017; Akalu and Belsti, 2020).

- In summary, it is important to identify and treat the causes, as the disease may not be cured by nature, but may be treated with a variety of therapies and interventions. Therefore, the aim of the study is to assess the time to recovery of diabetic patients who have been treated in the hospital under follow-up.

Materials And Methods

Study design, setting and Sample size

The study was conducted at Minlik Referral Hospital, Ethiopia, found in the capital city of Ethiopia, Addis Ababa. The data was measured by the blood glucose level of diabetic patients at the hospital, covering the period from 2009 to 2016, and 1278 patients were eligible for the study.

Data collection, procedure and quality control

Data collectors also participated in the hospital's staff and experts in the field. The data has been monitored and verified by experts based on the questionnaire checklist developed by the researchers. Data were categorized, compiled, coded, and checked for completeness, accuracy.

Data processing and analysis

The data were entered into SPSS (version 20) and exported to R-software (version 4.06) for analysis. Descriptive statistics have been applied to analyze patient characteristics such as mean, variance, median, percentile, and proportions of two groups (Kaplan-Meir). A survival model such as the Cox-proportional model was used to assess the hazard effect of seemingly significant predictors of the outcome variable. The p-value <0.05 was considered statistically significant.

Variables of Study

The dependent variable would be divided into two categories: Time to recovery of diabetic patients is an event while withdrawal from follow-up from different reasons and death are considered as censored. When the variable is properly measured, it serves as a key pillar for data analysis and discussion, as well as conclusions. The following are the main factors that affect the outcome variable: Sex of Patients, Types of Diabetes, Age of Patients, Past Medical History, Family History, Complication, Marital Status, Employee Status, Spdrt, SBP, DBP, Weight, and Time.

Operational definitions
Diabetic mellitus: primarily characterized by high blood glucose levels (hyperglycemia), polydipsia, and polyphagia (Alam et al., 2021).

Type II diabetic mellitus: Type 2 diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world (Olokoba, Obateru and Olokoba, 2015).

Type I diabetic mellitus: It often starts in childhood. However, it can start in adulthood (Johns Hopkins University and Johns Hopkins Health System, 2011).

Hypertension: Hypertension is defined as a systolic blood pressure of 140 mm Hg or greater and/or a diastolic pressure of 90 mm Hg or greater in subjects who are not taking antihypertensive medication (Pardi et al., 2009).

**Results**

Out of the total of 1278 participants, 27.4% were censored (withdrawal from follow-up, death), and 72.6% recovered from the diabetic disease (Table 1).

| Status     | Frequency | Percent |
|------------|-----------|---------|
| Censored   | 350       | 27.4    |
| Event      | 928       | 72.6    |
| Total      | 1278      | 100.0   |

The overall mean and median estimated survival time of diabetic patients under the follow-up study respectively was 50.48 and 32 (Table 2).

**Table 2: Time to recovery in weeks**

| Status | Mean | Median | Std.deviation | Min | Max |
|--------|------|--------|---------------|-----|-----|
| Time   | 50.48| 32     | 52.52         | 0   | 318 |

Table 2 also presents the minimum and maximum follow-up per week were respectively 0 and 318. 15.6% of female patients and 11.7 % of male patients lost follow-up.

33.3% of male and 39.4% female patients recovered from diabetic disease. Generally, female patients had more time to recover from the diabetic disease (Table 2, Figure 1).

Age of the patients with intervals 15 to 29, 30 to 44, 45 to 59,60 to 74, and more than 74 were 3.8 %,6%,9.9%,7.3% and 0.5 % respectively censored, and 10.8 %,15.2%,25.2%,20% and 1.5 % of patients were recovered from the disease(Table 3, Figure 2).
5.9% of Type I DM and 21.4% of Type II DM patients were censored whereas 16.4% and 56.2% of patients with Type I and Type II had been recovered from the diabetic disease. Generally, patients with type II had more recovered from the disease (Table 2, Figure 3).

Table 3: Baseline patient’s characteristics

| Variable               | Category | Patient status | Censored | Event |
|------------------------|----------|----------------|----------|-------|
| Sex                    | Male     |                | 150(11.7)| 424(33.3) |
|                        | Female   |                | 200(15.6)| 504(39.4) |
| Types of DM            | Type I   |                | 76(5.9)  | 210(16.4) |
|                        | Type II  |                | 274(21.4)| 718(56.2) |
| Past medical history   | yes      |                | 96(7.5)  | 267(20.9) |
|                        | no       |                | 254(19.4)| 661(51.7) |
| Family history         | yes      |                | 64(5)    | 182(14.2) |
|                        | no       |                | 286(22.4)| 746(58.4) |
| Is there complication  | yes      |                | 235(18.4)| 621(48.6) |
|                        | no       |                | 115(9)   | 307(24) |
| Marital status         | Married  |                | 217(17)  | 573(44.8) |
|                        | single   |                | 133(10.4)| 355(27.8) |
| Educational status     | educated |                | 265(20.7)| 705(55.2) |
|                        | uneducated |            | 85(27.4) | 223(72.6) |
| Employee status        | employee |                | 171(13.4)| 463(36.2) |
|                        | unemployed|              | 179(14)  | 465(36.4) |

7.2%, 15.8%, 4.4% of patients respectively took oral agents only, insulin agents only, and insulin and oral agents were censored whereas 15.6%, 45.9%, and 11% patients respectively who had taken oral agents only, insulin agents and insulin and oral agents only recovered from the disease (Table 3, Figure 7).

Patients who had taken the specific types of drugs at Time such as doanied, HCT, metformin, monotend, leute, regular and all orals respectively were 0.3%, 0.7%, 0.6%, 15.3%, 0.8%, 1.1%, and 1.6% censored, and 17.5%, 1.6%, 1.6%, 45%2%, 1.9% and 3.1% were recovered from the disease (Table 3, Figure 8).

Patients with systolic blood pressure below, normal and high were 5.2%, 8.7%, and 13.5% respectively censored, and 13.5%, 22.5%, and 36.6% of patients with systolic blood pressure respectively were recovered from the disease (Table 3, Figure 10).

Table 4: Baseline Descriptive statistics of patient’s characteristics
| Variable | Category          | Patient status in% |
|----------|-------------------|--------------------|
|          |                   | Censored | Event |
| Regimen  | Oral agents only  | 92(7.2)  | 200(15.6) |
|          | Insulin agents only | 202(15.8) | 587(45.9) |
|          | Insulin and oral agents | 56(4.4) | 141(11) |
| Spdrt    | Doanied           | 93(.3)   | 224(17.5) |
|          | HCT               | 9(0.7)   | 20(1.6)   |
|          | Metformin         | 8(0.6)   | 20(1.6)   |
|          | Monotend          | 196(15.3)| 575(45)   |
|          | Leute             | 10(0.8)  | 25(2)     |
|          | Regular           | 14(1.1)  | 24(1.9)   |
|          | All orals         | 20(1.6)  | 40(3.1)   |
| SBP      | <=110(below)      | 66(5.2)  | 173(13.5) |
|          | 110-130(normal)   | 111(8.7) | 287(22.5) |
|          | >=130(high)       | 173(13.5)| 468(36.6) |
| DBP      | <=60(below)       | 7(0.5)   | 15(1.2)   |
|          | 60-80(normal)     | 134(10.5)| 348(27.2) |
|          | >=80(high)        | 350(27.4)| 928(72.6) |
| Age category | 15-29         | 48(3.8)  | 138(10.8) |
|          | 30-44            | 77(6)    | 194(15.2) |
|          | 45-59            | 126(9.9) | 322(25.2) |
|          | 60-74            | 93(7.3)  | 255(20)   |
|          | >74              | 6(0.5)   | 19(1.5)   |

Patients with diastolic pressure below, normal and high were 0.5%, 10.5%, and 27.4% respectively censored, and 1.2%, 27.2%, and 72.6% of patients with systolic blood pressure respectively were recovered from the disease (Table 3, Figure 9).

7.5% of patients who had a past medical history and 19.4% of patients who had no past medical history lost to follow-up. 20.9% of patients who had past medical history recovered from the disease, and 51.7% of patients who had no past medical history had recovered from diabetic disease (Table 2, Figure 4).
5% of Patients that family history and 22.4% of patients whose family history was censored. 14.2 % of patients whose family history recovered from the disease, and 58.4% of patients who had family history recovered from the disease (Table 2, Figure 5).

**Discussion**

The diabetic disease or diabetes is not curable. The cause of the disease is high blood sugar in the blood. However, it is possible to treat through medication and traditional methods. The aim of the study focused on determining the time to recurrence of diabetic patients over the entire follow-up period at Minlik Referral Hospital, Ethiopia, found in Addis Ababa, headquarter of Ethiopia. The retrospective cohort study was conducted. The data were analyzed by R-software (version 4.05).

Among the total of 1278, 72.6% of diabetic patients experienced to time to recovery of diabetic patients and 27.4% loss to follow up from study. The mean and median of time to recurrence of diabetic patients respectively are 50.48 and 32.

Figures (1-10) present the Kaplan–Meier survival functions of categorical variables among diabetic Patients under follow-up at Tepi General Referral Hospital, Ethiopia, found in the capital city of Ethiopia, from 2009 to 2016. The plot shows that the estimated survival function curve for female diabetic patients is above that of male diabetic patients over the entire follow-up period, giving evidence for a higher probability of survival and lower risk of recovery for females as compared with males. It indicated that female patients have better recovery time than male diabetic patients (Figure 1). Thus, females are more prevalent in this study, which is consistent with the study done in a hospital-based cross-sectional study at Harar and Dire Dawa (Ayele, Mengesha and Tesfa, 2019).

The estimated survival function curve for patients with Type II DM is above that of diabetic patients with type I DM over the entire follow-up period, giving evidence for the higher probability of survival and lower risk of recovery for patients with type II DM as compared with patients with type IDM. It indicated that patients with type II DM have better recovery time than diabetic patients with type I DM, which is consistent with the study in Palestinian(Salameh et al., 2019), Gurage Zone(Migora et al., 2021), Amhara region(Getie et al., 2021), Rwanda (Bavuma et al., 2020).

Patients with high systolic blood pressure (SBP) are high percentage to time-to-recovery of diabetic patients as compared to patients with below and normal systolic blood pressure and similar results from patients with high diastolic blood pressure (Muleta et al., 2017).

**Table 5: Log-rank test for the categorical variables**
Table 5 presented us for comparing the group of categorical variables revealed that the survival time of male and female to diabetic disease is different (chi-squared value=20, df=1, p-value=0.0198. It is statistically significant) (Table 5). All factors except sex are not statistically significant. Thus, there are no more differences between groups on survival time of diabetic patients (Table 5, Figures (2-10)).

**Table 6: Global test for Assumption of Cox proportional model**
| Variables           | Chi-square | df | p-value |
|--------------------|------------|----|---------|
| Sex                | 1.4407     | 1  | 0.230   |
| Age categories     | 5.780      | 4  | 0.216   |
| Types of DM        | 0.9823     | 1  | 0.322   |
| Past Medical History| 0.1309     | 1  | 0.718   |
| Family history     | 0.0169     | 1  | 0.897   |
| Complication       | 1.6431     | 1  | 0.200   |
| Marital status     | 1.1073     | 1  | 0.293   |
| Educational Status | 0.9911     | 1  | 0.319   |
| Employee           | 1.1297     | 1  | 0.288   |
| Regime             | 0.6300     | 2  | 0.730   |
| Spdrtys            | 9.4169     | 6  | 0.151   |
| SBP                | 3.1085     | 2  | 0.211   |
| DBP                | 3.4618     | 2  | 0.177   |
| Wight              | 0.9052     | 1  | 0.341   |
| GLOBAL-test        | 37.3800    | 25 | 0.053   |

It is the fact that the violation of proportionality of hazard is the critical problem of assumption of Cox proportional hazard analysis. Thus, checking the assumption of the model and its validity is a must. The assumption of the Cox proportional hazard model can be checked by global test and graphical techniques (Schoenfeld residuals). The chi-square =37.38 with the degree of freedom 25 and p-value=0.053 is statistically insignificant. Thus, the assumption of the Cox proportional model is met (Table 6).

Figures (11-13) presented Schoenfeld residuals for the categorical variables to show whether the assumption of the Cox proportional hazard model is violated or not.

The graphs for all categorical variables are fairly flat; the assumption of proportionality is not (much) violated (Figures 11, 12, 13). Thus, the global test and Schoenfeld residuals showed the assumption of the Cox proportional model is met.

Non-linearity assumption is not the problem for categorical variables, however, non-linearity assumption is a problem of continuous variables. Plotting martingale residuals is to detect the non-linearity assumption of the Cox proportional hazard model. Thus, there is no specific pattern for the dependent variable versus the weight of patients, therefore the assumption of the model is not violated (Figure 14).
### Table 7: Multivariable Cox-PH model for diabetic patients

| Variables                        | Category       | Coef  | HR       | Se(coef) | z      | p-value     |
|---------------------------------|----------------|-------|----------|----------|--------|-------------|
| Sex(ref=female)                 | Male           | 0.279 | 1.322    | 0.074    | 3.777  | 0.0001      |
| Age(ref=15-29)                  | 30-44          | -0.128| 0.880    | 0.142    | -0.898 | 0.3689      |
|                                 | 45-59          | 0.067 | 1.069    | 0.180    | 0.374  | 0.7085      |
|                                 | 60-74          | 0.172 | 1.188    | 0.185    | 0.929  | 0.8453      |
|                                 | >74            | 0.005 | 1.005    | 0.298    | 0.015  | 0.9879      |
| TypeDM(ref=type I)              | Type II        | -0.014| 0.986    | 0.133    | -0.104 | 0.9173      |
| PMedh(ref=yes)                  | No             | 0.021 | 1.021    | 0.086    | 0.246  | 0.8054      |
| FamH(ref=yes)                   | No             | -0.072| 0.931    | 0.098    | -0.735 | 0.4624      |
| Comp(ref=yes)                   | No             | 0.004 | 1.004    | 0.079    | 0.056  | 0.9551      |
| Marst(ref=marrid)               | Single         | 0.025 | 1.026    | 0.075    | 0.340  | 0.7339      |
| Educst(ref=educated)            | uneducated     | 0.037 | 1.038    | 0.096    | 0.390  | 0.6966      |
| Empst(ref=employe)              | Unemployed     | -0.042| 0.959    | 0.084    | -0.496 | 0.6202      |
| Regimen(ref=oral)               | Insulin        | 0.402 | 1.495    | 0.193    | 2.085  | 0.0370      |
|                                 | Insul and oral | -0.016| 0.984    | 0.116    | -0.136 | 0.8914      |
| Spdrt(ref= Doanied)             | HCT            | -0.012| 0.988    | 0.248    | -0.049 | 0.9606      |
|                                 | Metformin      | -0.080| 0.923    | 0.239    | -0.336 | 0.7371      |
|                                 | Monotend       | -0.131| 0.877    | 0.188    | -0.697 | 0.4859      |
|                                 | Leute          | 0.152 | 1.164    | 0.235    | 0.647  | 0.0178      |
|                                 | Regular        | -0.182| 0.834    | 0.235    | -0.773 | 0.4393      |
|                                 | All            | -0.031| 0.969    | 0.178    | -0.175 | 0.8614      |
| SBP(ref=below)                  | Normal         | -0.049| 0.951    | 0.109    | -0.457 | 0.6474      |
|                                 | high           | -0.072| 0.931    | 0.1201   | -0.597 | 0.5503      |
| DBP(ref=below)                  | Normal         | 0.192 | 1.213    | 0.279    | 0.686  | 0.4929      |
|                                 | high           | 0.257 | 1.293    | 0.283    | 0.907  | 0.3641      |
| Weight                          | continuous     | 0.002 | 1.002    | 0.003    | 0.667  | 0.5049      |

Likelihood ratio test=44.77 on 25 df, p=0.008892, n= 1278, number of events= 928
Sex, regimen, and Sport are significant factors associated time to Recurrence of diabetic Patients whereas age group (30-44, 45-59, 60-74,>74), past medical history, family history, health complication, education status, marital status, SBP and DBP and types of diabetic Mellitus at baseline are not significant effect for time to recurrence of diabetic patients, hence these variables are not included in multivariable analysis (Table 7). Considered Cox-PH model and the result of multivariable analysis, the fitted model can be:

For interpretability, the hazard ratio for the parameter estimates estimated. For sex, the expected hazard is 1.322 times higher in male than female diabetic patients or there is a 32.2% increase in the expected hazard in males relative to female diabetic patients holding other variables are constant, which is consistent with the study done (Hanefeld et al., 1996; Icks et al., 2012; Whitaker et al., 2014; Muleta et al., 2017; Tachkov et al., 2020).

For Spdrt, exp(0.152) = 1.164. The expected hazard is 1.164 times higher in the patients who had taken leute than diabetic patients who took doanied. Or, there is a 16.4% increase in the expected hazard in the patients who took leute relative to diabetic patients those who had taken doanied holding other variables constant.

For regimen, exp(0.402) = 1.495. the expected hazard is 1.495 times higher in the patients who had been treated by insulin agent only than diabetic patients who were treated by oral agents only. Or, patients who had been treated by insulin agents only is 49.5% increase as compared to diabetic patients those who treated by oral only holding other variables constant, which is consistent with the study done in American Diabetes Association (Care and Suppl, 2019).

**Conclusion**

Diabetes is an incurable and genealogical disease. The cause of Diabetes is defects in insulin imbalances. It can cause health complications to death, but it can be possible to control and minimize the risk of the complication through medication. Hence, the objective of the study aimed to determine the time-to-recovery of diabetic patients and associated factors on the entire follow-up period at Tepi General Hospital.

From statistical results, among medication of regimen, 45.9% of patients who had taken insulin agents are recovered from the disease while 15.8% of patients had interrupted their follow up from study. Under Kaplan-Meier survival curves and Log-rank test, the survival times of patients among gender groups are different, hence females are more likely to survive as compared to males. The assumption of the Cox-PH model has been checked by Schoenfeld residuals and GLOBAL-test and the assumption of the model is not violated. In the multivariable Cox-PH model, sex being male; regimen being insulin agents only and Sport being leute are statistically significant. Thus, gender being male is a high risk than female, regimen being insulting agents is high risk and Sport being Leute is high risk for time to recovery of diabetic patients.
Abbreviations

**Cox-PH** - Cox proportional hazard; **DM** - Diabetic Mellitus; **KM** - Kaplan-Meier; **Sport** - Specific drug at the time; **BP** - systolic blood pressure; **BP** - diastolic blood pressure

Declarations

**Acknowledgment**

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**Availability Data and materials**

The data will be given upon request on behalf of the corresponding author

**Declarations**

**Ethical approval and Consent to participate**

The institutional review board of the hospital approved Ethical clearance. The informed consent was obtained from the hospital manager for representing the patients' profiles seated in the hospital. The data obtained from the hospital were kept confidentially and put the questionnaire in a safe place

**Consent for publication**

Not applicable

**Conflict of interest**

The authors do not have any conflict of interest.

**Authors’ contributions**

All authors conducted the research, and write in the manuscript.

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Figures
Figure 1

Kaplar-Meir survival function of diabetic patients with sex
Figure 2

Strata: Age (0=15-29, 1=30-44, 2=45-59, 3=60-74, 4=74+) K-M of Survival function of Diabetic patients with Age categories
Figure 3

Strata: Types of diabetic mellitus (0=Type I, 1=Type II) Kaplan-Meir survival function of diabetic patients with types of DM

Figure 4

Past medical history (0=Yes, 1=No) Kaplan-Meir survival function of diabetic patients with past medical history
Figure 5

Strata; family history (0=Yes, 1=No) Kaplar-Meir survival function of diabetic patients with family history

Figure 6

Strata: Complication (0=Yes, 1=No) Kaplar-Meir survival function of diabetic patients with complication
Figure 7

Strata: Regimen (0=oral agents only,1=insulin agents only,2=oral and insulin agents only) Kaplan-Meier survival function of diabetic patients Regimen

Figure 8

Strata: Specific types of drugs at Time (0=doanied,1=HCT,2=Metformin,3=Monotend,4=leute,5=Regular,6=all orals) Kaplan-Meier survival function of diabetic patients Spdrt
Figure 9

Strata: Diastolic blood pressure (0=below, 1=Normal, 2=High) Kaplan-Meier survival function of diabetic patients DBP

Figure 10

Strata: Systolic blood pressure (0=below, 1=Normal, 2=High) Kaplan-Meier survival function of diabetic patients SBP
Figure 11

Schoenfeld residuals of Types of DM, Age category and Sex
Figure 12

Schoenfeld residuals of Complication, past medical history, Family history and marital status
Figure 13

Schoenfeld residuals for Weight, Spdrt, educational status, SBP, Employe status, DBP and Regimen

Figure 14
Martingale for non linearity assumption of proportional Cox model

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