

Determining The Recurrence of Diabetic Patients Recovery Time in Benishangul-Gumuz Hospitals, Ethiopia

Endalkachew Abebe^{*1} and Zelalem Birku²

¹Department of Statistics, College of Natural & Computational Sciences, Assosa Univeristy, Assosa, Ethiopia

²Department of Mid-wifer, College of Health Sciences, Assosa Univeristy, Assosa, Ethiopia

*Corresponding author:

Endalkachew Abebe, Department of Statistics, College of Natural & Computational Sciences, Assosa Univeristy, Assosa, Ethiopia.

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Abstract

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar). About 90% of people with diabetes around the world have type II diabetes. It is the main global health issues and burden as well with serious health complications including heart disease, blindness, kidney failure, and lower-extremity amputations. In middle- and low-income countries the prevalence of diabetes has been rising more rapidly and needs great attention. The data from such case has been considered as recurrent event data and correlation between events should be taken into account in the analysis. Thus, the aim of the study was to identify risk factors for recurrence of diabetic patient's recovery time in Benishangul-Gumuz hospitals (Assosa, Pawi and Wonbera hospital), Ethiopia. A retrospective study has been applied to obtain data on the recurrence of diabetic patient's recovery time in Benishangul-Gumuz hospitals, Ethiopia, from September 1, 2019 to September 1, 2021. Kaplan-Meier plot (s) and Log-rank test were used for comparison of patient's recovery time from diabetes; Standard Cox-PH and Shared Frailty model were used to identify factors significantly affect the recovery time of diabetic patients, using R version 4.1.1 for data analysis. Of the total diabetic patients in this study 61.87 % experienced recurrence of diabetic. The estimated median recovery time of diabetic patients was 6 months. The Shared Log-normal Frailty model was chosen to be best fit for this data set, based on Likelihood Cross-Validation value. Family history, other medical history and Systolic Blood Pressure of patients were significantly affected the recovery time of diabetic patient's.

Keywords: Diabetic Patients, Recovery Time, Recurrent Event, Shared Frailty Model

Background of the Study

Diabetes is a chronic metabolic disease characterized by elevated levels of blood glucose (or blood sugar). It is due to either the pancreas, an organ that lies near the stomach, making a hormone called insulin to help glucose get into the cells of our body, not producing enough insulin, or the cells of the body not responding properly to the insulin produced [1]. Diabetes leads over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves [2, 3, 1]. There are three main types of diabetes: type 1, type 2, and gestational diabetes (diabetes while pregnant). Type 1 diabetes is characterized by a lack of insulin production and without daily administration of insulin it is rapidly fatal. The majority of type 1 diabetes occurs in children and adolescents. Type 2 diabetes is the most common type of diabetes, which occur in adults and results from the body's ineffective use of insulin. Approximately 10% of diabetic patients have type I diabetes and 90% of diabetic

patients have type II diabetes. Gestational diabetes is hyperglycemia with blood glucose values above normal but below those diagnostic of diabetes. It occurs during pregnancy and women with this type of diabetes are at an increased risk of complications during pregnancy and at delivery. These women and possibly their children are also at increased risk of type 2 diabetes in the future. Gestational diabetes is diagnosed through prenatal screening, rather than through reported symptoms [4, 1].

Diabetes is the main global health issue and a burden as well. About 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades [1]. In 2021, diabetes was the direct cause of 6.7 million deaths and in 2019, 48% of all deaths due to

diabetes occurred before the age of 70 years [4,1]. In middle- and low-income countries, the prevalence of diabetes has been rising more rapidly and an estimated 416,000 deaths occur in 2021. Now a day, diabetes has emanated and emerged as an important clinical, public health, and economic problem throughout the world including developing countries. Ethiopia is one of the developing countries working with complications of diabetes like: substantial economic loss in people, health systems, and national economies through direct medical costs and loss of work [4]. However, due to limited resources and its prevalence growing most rapidly, diabetes is worrying in the country, diabetes needs a major focus in the country; unless when diabetes is not well managed, acute complications are a significant contributor to mortality, costs and poor quality of life [5, 6, 7].

The most common risk factors of diabetes are: age, sex, weight, regimen, family history, other medical history and Blood Pressure [8, 9, 10, 11,12].

The researchers are using logistic regression to identify risk factors for the occurrence of diabetes [13, 14, 15, 16]. However, such data can be more explored using survival models such as: standard Cox-PH, Shared Gamma Frailty, and Shared Log-normal Frailty models. Therefore, the overall aim of this study was to identify risk factors for recurrence of diabetic patient's recovery time in Benishangul-Gumuz hospitals (Assosa, Pawi and Wombera hospital), Ethiopia using the data taken from diabetic patients during follow-up time from September 1, 2019 to September 1, 2021.

Data and Methodology

Study Area

The study was conducted at Benishangul-Gumuz hospitals (Assosa, Pawi and Wombera hospital). Benishangul-Gumuz hospitals are the hospitals found in Benishangul-Gumuz Regional State; in which the region is one of the nine regional states established in 1994 by the constitution of Ethiopia. Assosa hospital is found in Assosa town; Pawi and Wombera hospitals are found in Metekel zone, Benishangul-Gumuz region, Ethiopia. Assosa, the capital city of the region, and Metekel zone are located in the northwestern part of Ethiopia, with 667 km and 792 km distance from Addis Ababa, Ethiopia, respectively. The hospitals have different cases for CNCDS and serves as the biggest referral hospital in the region.

Study Population

A retrospective study has been applied to obtain data on recurrence of diabetic patients in Benishangul-Gumuz hospitals (Assosa, Pawi and Wombera hospital). The population of this study was all diabetic patients go for treatment to Benishangul-Gumuz hospital for two years starting from September 1, 2019 to September 1, 2021. The data has been carefully reviewed from the registration log book and patients' registration card; any inadequate information encountered was checked from the file and excluded from analysis if proven to be inadequate. Thus, the data has been collected from patient follow-up records based on the variables in the study.

Inclusion and Exclusion Criteria

Inclusion Criteria: - All diabetic patients who have treatment follow-up in the hospital with full information including study variables eligible for the study are included in the study.

Exclusion criteria: - Gestational diabetes patients are not included in the study.

Data Collection Procedure

Ethical permission has been obtained from the Research Ethics Review Board of Assosa University. Then secondary data has been taken for the recurrence of diabetic patient's recovery time from patient card in the hospital by data collectors. The data collector in each hospital has been collecting the data after they took one-day training on the objective and relevance of the study, how to gather the appropriate information, procedures of data collection techniques, and the whole contents of the interview. The researcher monitored the overall data collection process during the data collection period.

Variables in the Study

The outcome variable in this study was the time to recovery of diabetic patients. Time to recovery (might be one time, two times, or more than two times) means the time until patients come to normal fasting blood sugar levels for recurrent time in the follow-up period, according to WHO scale (80-130 mg/dl) and under 180 mg/dl for two hours after starting a meal. Patient's recovery from diabetes is an event of interest.

The covariates/predictors considered in this study were age (< 30, 30-50, > 50) in years, sex (female, male), educational status (uneducated, educated), marital status (single, married, divorced, widowed), employment status (unemployed, employee), family history (no, yes), other medical history (no, yes), regimen (oral Agents, insulin agents, oral and insulin agents), types of diabetes (T1D, T2D), specific drug used (Doanied, HCT, Metformin, Monotend, Lute, Regular, oral), Systolic Blood Pressure (low, normal, high) in mm/Hg, Diastolic Blood Pressure (low, normal, high) in mm/Hg and weight (underweight, normal, overweight, obesity) in Kg.

Operational Definition of some covariates

Regimen Group: - Diabetic patients were classified into regimen groups according to the medication they took in follow-up time as: -

- **Oral Agents Only:** - all are administered orally in diabetic patients.
- **Insulin Agents Only:** - is provided in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. It is given by injecting patients with the dose level ordered by the physician.
- **Both Oral and Insulin agents:** - is another regimen group when patients are ordered to take both oral and insulin agents at the same time in the follow-up period.

Blood Pressure (BP) in (mm/Hg): - measures the pressure in blood vessels of diabetic patients. It can be classified as Systolic and Diastolic Blood Pressure.

Family History of Diabetes: - having a family who had Diabetic Disease or not.

Other Medical History: - Whether the patients have other medical history before enrollment into a chronic follow-up clinic as a diabetic patient.

Methods of Statistical Analysis

Descriptive Statistics

The description of survival data utilizes non-parametric methods to compare the survival functions of two or more groups and Kaplan-Meier plot(s) would be employed for this purpose [17]. The frequency distribution table was also used to summarize the data obtained from diabetic patients based on the study variables in Benishangul-Gumuz hospitals, Ethiopia.

Survival Data Analysis

Survival analysis is a statistical analytic method used for modeling and analyzing data that have a principal end point - the time until an event occurs. It considers a key analytical problem of censoring that occurs when some information about individual survival time is known, but not the exact survival time [18]. The censoring assumed to occur in this study is right censoring, meaning to say the true observed event is at the right of censoring time.

Standard Cox Proportional Hazard Model

The most frequently applied analysis method for recurrent data is the model by Andersen and Gill, which is based on the common Cox-PH model [19,20]. The Andersen-Gill model assumes independence between all observed event times irrespective whether these event times correspond to the same/different patients. According to Kleinbaum and Klein, modeling recurrent survival data can be carried out using a Cox-PH model with the data layout constructed so that each subject has a line of data corresponding to each recurrent event [21]. The assumption of Cox-PH model were checked by test of correlation (ρ) and global test. The assumption is valid using test correlation (ρ) and global test if the test result is insignificant [22].

Shared Frailty Model

The Shared Frailty model is extended by Pickels and Yashin to allow unobserved heterogeneity that occurs because some observations are more prone to failure, and therefore more “Frail” than others in a data set. It may also use for modeling the degree of correlation within groups [23, 24]. Among different models: Shared Gamma Frailty model and Shared Log-normal Frailty model were used to model the data. The expectation-maximization (EM) algorithm and the penalized likelihood approach were used to estimate parameters in the models [25]. An approximate likelihood cross-validation criterion (LCV), approximately equivalent to Akaike’s criterion, is used to check the goodness of fit for Cox and Frailty models [26]. Lower values of LCV indicate a better fitting model.

Model Building

The methods of selecting a subset of covariates in Standard Cox-PH and Shared Frailty models are essentially similar to those used in any other regression models. Thus, the model was built using Hosmer and Lemeshow recommendation [27].

Model Diagnostics

Residuals are a useful method for checking the fit of a statistical model. The Cox-Snell residuals, provided for checking the overall fit of the model is a residual plot used to check if a parametric distribution fits the observed data or not [28].

Results

Descriptive Analysis

The data for this study has been taken from 575 diabetic patients that have received treatments for more than one time in Benishangul-Gumuz hospitals (Assosa, Pawi and Wonbera hospital), Ethiopia between September 1, 2019 and September 1, 2021. The outcome was time to recovery from diabetic’s disease. From the total of 1516 events, 938 (61.87 %) experienced recurrence of diabetic and the remaining 578 (38.13%) were censored. The minimum and maximum recovery times of patient’s diabetes were 1 and 24 months, respectively. Of all total diabetic patients in the hospitals, 90.10% have type II diabetes and the remaining 9.90% have type I diabetes. The median recovery time of diabetic patients was 6 months.

Table 1: Show Median Recovery Time for Diabetic Data

Here is the estimated probability of recovery time for recurrence of diabetic patients

Time	n.risk	n.event	Recovery	std.err	lower 95%CI	upper 95%CI	n	events	median
1	1516	1	0.9993	0.000659	0.99805	1.0000			
2	1514	73	0.9512	0.005538	0.94036	0.9621			
3	1416	132	0.8625	0.008901	0.84522	0.8801			
4	1207	182	0.7324	0.011664	0.70993	0.7557			
5	920	190	0.5812	0.013462	0.55538	0.6082			
6	635	163	0.4320	0.014199	0.40504	0.4607			
7	376	82	0.3378	0.014419	0.31067	0.3673	1516	938	6
8	219	51	0.2591	0.014677	0.23189	0.2895			
9	114	49	0.1477	0.014641	0.12166	0.1794			
10	39	6	0.1250	0.015045	0.09875	0.1583			
11	16	3	0.1016	0.017269	0.07279	0.1417			
12	8	2	0.0762	0.020238	0.04526	0.1282			
13	6	3	0.0381	0.018553	0.01466	0.0989			
14	3	1	0.0254	0.016138	0.00731	0.0882			

As observed in Table 2 below, most of the diabetic patients in the hospitals, age lies between 30 and 50 years. 53.60% diabetic patients in the hospital were female and the remaining 46.40% were male patients. Looking at the education status of diabetic patients in the hospital, 51.50% diabetic patients were uneducated. The recovery time for diabetic patients who have been married seems higher than rest of categories. More of the diabetic patients receiving treatment in the hospitals had a family history of diabetes. By observing the medication given to diabetic patients in the hospitals, the recovery time for patients receiving insulin agents only

was seemed higher than other regimen groups.

By considering the specific drug given to diabetic patients in the hospitals, 63.30% diabetic patients took metformin. Diabetic patients who have other medical history before enrollment in to a chronic follow-up in the hospital as a diabetic patient was 52.50%. Most of the diabetic patients receiving treatment from the hospitals had high (130/80 mmHg) Blood Pressure. The weights of diabetic patients in the underweight, normal, overweight, and obesity categories were 16.50%, 17.20%, 35.50%, and 30.80%, respectively.

Table 2: Descriptive Statistics Summary

Covariates	Categories	Patients Recovery Status		Total (%)
		Censored (%)	Event (%)	
Age	<30	112 (7.40)	182 (12.00)	294(19.40)
	30 - 50	294 (19.40)	469(30.90)	763 (50.30)
	>50	172(11.30)	287(18.90)	459(30.30)
Sex	Female	313(20.60)	499(32.90)	812 (53.60)
	Male	265(17.50)	439(29.00)	704(46.40)
Education Status	Uneducated	301(19.90)	479(31.60)	780(51.50)
	Educated	277(18.30)	459(30.30)	736(48.50)
Marital Status	Single	152(10.00)	242(16.00)	394(26.00)
	Married	362(23.90)	590(38.90)	952(62.80)
	Divorced	32 (2.10)	54(3.60)	86(5.70)
	Widowed	32 (2.10)	52(3.40)	84(5.50)
Employment Status	Unemployed	307(20.30)	484(31.90)	791(52.20)
	Employed	270(17.80)	454(30.00)	724(47.80)
Family History of diabetic	No	290(19.10)	439(29.00)	729(48.10)
	Yes	288(19.00)	499(32.90)	787(51.90)

Regimen	Oral Agents	39(2.60)	58(3.80)	97(6.40)
	Insulin Agents	436(28.80)	720(47.50)	1156(76.30)
	Oral & Insulin Agents	103(6.80)	160(10.60)	263(17.30)
Specific drug Used	Doanied	66(4.40)	117(7.70)	183(12.10)
	HCT	31(2.00)	52(3.40)	83(5.50)
	Metformin	366(24.10)	594(39.20)	960(63.30)
	Monotend	16(1.10)	26(1.70)	42(2.80)
	Lute	12(0.80)	14(0.90)	26(1.70)
	Regular	9(0.60)	16(1.10)	25(1.60)
	Oral	78(5.10)	119(7.80)	197(13.00)
Other Medical History	No	290(19.10)	430(28.40)	720(47.50)
	Yes	288(19.00)	508(33.50)	796(52.50)
Systolic Blood Pressure	Low(<110)	58(3.80)	184(12.10)	242(16.00)
	Normal (110-130)	363(23.90)	202(13.30)	565(37.30)
	High(>130)	157(10.30)	552(36.40)	709(46.70)
Diastolic Blood Pressure	Low(<60)	48(3.10)	135(8.90)	183(12.00)
	Normal (60-80)	308(20.30)	210(13.90)	518(34.20)
	High(>80)	222(14.60)	593(39.10)	815(53.80)
Weight	Underweight	92(6.10)	158(10.40)	250(16.50)
	Normal weight	101(6.70)	159(10.50)	260(17.20)
	Overweight	209(13.80)	330(21.70)	539(35.60)
	Obesity	176(11.60)	291(19.20)	467(30.80)
Type of Diabetes	Type I	58(3.80)	92(6.10)	150(9.90)
	Type II	520(34.30)	846(55.80)	1366(90.10)

Comparison of Recovery Time of Diabetic Patients

As it can be observed from log-rank test Table 3 below, there is difference in the recovery time of diabetic patients for their family

history, regimen, other medical history, and Blood Pressure of the patients since their corresponding p-values are smaller than the common level of significance (5%).

Table 3: Log-rank Test for each of the Covariates

Covariates	Chi-square Value	Degree of Freedom	P -value
Age	4.70	2	0.100
Sex	0.30	1	0.600
Education	0.9	1	0.600
Marital Status	1.9	3	0.600
Employment Status	2.70	1	0.100
Family History	10.80	1	0.001
Regimen	9.20	2	0.010
Specific Drug Used	9.00	6	0.200
Other Medical History	15.50	1	<0.0001
Systolic Blood Pressure	139.00	2	<0.0001
Diastolic Blood Pressure	78.20	2	<0.0001
Weight	2.50	3	0.500

Recurrent Model
Standard Cox Proportional Hazard Model

To determine the effect of each covariate on the recovery time of diabetic patients, Cox proportional hazard model was fitted before proceeding to more complicated models. Result of the univariable

standard Cox-PH model is shown in the Appendix [Table 4]. As this result shows, family history, other medical history, and Blood Pressure of patients are significantly affecting the recovery time of diabetic patients.

Appendix

Table 4: Shows Univariate Analysis of Recurrent Model

Covariates	Categories	Model Used					
		Standard Cox-PH		Shared Gamma Frailty		Shared Log-normal Frailty	
		β^{\wedge} [SE(β^{\wedge})]	P-value	β^{\wedge} [SE(β^{\wedge})]	P-value	β^{\wedge} [SE(β^{\wedge})]	P-value
Age	<30						
	30 - 50	-0.135 [0.087]	0.123	-0.126[0.087]	0.148	-0.137[0.094]	0.144
	>50	-0.019[0.095]	0.844	-0.021[0.095]	0.828	-0.018[0.102]	0.859
Sex	Female						
	Male	0.048[0.065]	0.464	0.033[0.066]	0.611	0.0480[0.0703]	0.4948
Education Status	Uneducated						
	Educated	0.043[0.065]	0.509	0.031[0.065]	0.611	0.040[0.0702]	0.5698
Family History of diabetic	No						
	Yes	0.172[0.066]	0.009	0.144[0.066]	0.028	0.176[0.070]	0.012
Regimen	Oral Agents						
	Insulin Agents	0.301[0.136]	0.028	0.285[0.137]	0.037	0.312[0.146]	0.032
	Both	0.170[0.153]	0.268	0.164[0.153]	0.286	0.182[0.1637]	0.266
Specific drug Used	Doanied						
	HCT	-0.120 [0.167]	0.231	-0.192[0.167]	0.251	-0.207[0.179]	0.249
	Metformin	-0.060[0.101]	0.551	-0.042[0.101]	0.681	-0.064[0.109]	0.560
	Monotend	0.194[0.217]	0.371	0.165[0.217]	0.448	0.208[0.236]	0.377
	Lute	-0.426[0.283]	0.133	-0.378[0.283]	0.182	-0.438[0.299]	0.143
	Regular	0.155[0.267]	0.560	0.138[0.267]	0.607	0.149[0.287]	0.603
	Oral	-0.116[0.130]	0.374	-0.082[0.130]	0.530	-0.123[0.140]	0.378
Other Medical History	No						
	Yes	0.160[0.066]	0.015	0.142[0.066]	0.031	0.164[0.071]	0.021
Systolic Blood Pressure	Low						
	Normal	-0.470[0.104]	<0.0001	-0.489[0.104]	<0.0001	-0.496[0.108]	<0.0001
	High	-0.006[0.085]	0.095	-0.018[0.085]	0.083	-0.020[0.090]	0.081
Diastolic Blood Pres- sure	Low						
	Normal	-0.303[0.111]	0.007	0.327[0.111]	0.003	-0.322[0.116]	0.005
	High	0.070[0.096]	0.467	0.045[0.096]	0.638	0.054[0.100]	0.589
Weight	Underweight						
	Normal	-0.060[0.112]	0.596	-0.051[0.112]	0.652	-0.058[0.121]	0.628
	Overweight	-0.071[0.097]	0.462	-0.067[0.097]	0.489	-0.072[0.104]	0.489
	Obesity	-0.010[0.099]	0.920	-0.014[0.099]	0.887	-0.012[0.107]	0.912

The fitted Standard Cox-PH model, as shown in Table 5 below, shows that the recovery time of the diabetic patient's significant-ly affected by family history, other medical history, and Systolic

Blood Pressure of patients. The Standard Cox-PH model considers different lines of data contributed by the same subjects as independ-ent contributions from different subjects.

Table 5: Parameter Estimates of Standard Cox-PH Model

Covariates	Categories	Coef	Exp(coef)	SE [Coef(HIH)]	95% CI	P-value
Family History of diabetic	No					
	Yes	0.1329	1.1421	0.0663	[1.00 , 1.30]	0.0393
Regimen	Oral Agents					
	Insulin Agents	0.1836	1.2016	0.1376	[0.92 , 1.57]	0.1902
	Both	0.1029	1.1084	0.1537	[0.82 , 1.50]	0.5030
Other Medical History	No					
	Yes	0.1315	1.1406	0.0663	[1.00 , 1.30]	0.0472
Systolic Blood Pressure	Low					
	Normal	-0.4237	0.6546	0.1170	[0.52 , 0.82]	0.0003
	High	-0.0903	0.913656	0.0986	[0.75 , 1.11]	0.3596
Diastolic Blood Pressure	Low					
	Normal	-0.0925	0.9116	0.1254	[0.71 , 1.17]	0.4605
	High	0.1259	1.1341	0.1102	[0.91 , 1.41]	0.2537
<i>penalized marginal log-likelihood = -2517.41; Convergence criteria: parameters = 2.33e-06; likelihood = 4.05e-05 gradient = 1.77e-07; LCV = the approximate likelihood cross-validation criterion in the semi parametrical case = 1.67106</i>						
<i>Coef: estimated coefficient for each covariates; Exp (coef): exponentiation value of coefficient, se coef (H) and hr is hazard ratio.</i>						

Checking the Assumption of Cox-PH

The assumption of Cox-PH model by considering a variable included in the model was checked using the Schoenfeld residuals as described in Table 6 below. Observing the results from this Table

the covariates are not statistically significant, implying that the covariates are time independent. The overall proportionality test is also not statistically significant, implying that the proportionality assumption was not violated.

Table 6: Test of Assumption for Cox-PH Model

Covariates	rho	Chi-square Value	Degree of Freedom	P-value
Family History	0.033	0.529	1	0.470
Regimen	-0.002	1.625	2	0.440
Other Medical History	0.042	1.046	1	0.310
Systolic Blood Pressure	0.147	1.649	2	0.440
Diastolic Blood Pressure	0.131	1.076	2	0.580
GLOBAL	NA	6.530	8	0.590

Shared Gamma Frailty Model

In the Shared Gamma Frailty model, the clustered structure of the data is taken into account with interest of considering the heterogeneity between subjects. As usual, the first univariable analysis was conducted and significant variables at 25% level of significance were taken in the multiple Shared Gamma Frailty model.

The result of the univariable Shared Gamma Frailty model is

shown in the Appendix (Table 4). As it can be observed from the result, family history, regimen, other medical history, and Blood Pressure of patients are significantly affecting the recovery time of diabetic patients. The fitted Shared Gamma Frailty model, as shown in Table 7 below, showed that the recovery time of the diabetic patient's significantly affected by family history, other medical history and Systolic Blood Pressure of patients.

Table 7: Parameter Estimates of Shared Gamma Frailty Model

Covariates	Categories	Coef	Exp(coef)	SE [Coef(HIH)]	95% CI	P-value
Family History of diabetic	No					
	Yes	0.1223	1.1301	0.0662	[1.00 , 1.29]	0.0065
Regimen	Oral Agents					
	Insulin Agents	0.2004	1.2219	0.1378	[0.93 , 1.60]	0.1550
	Both	0.1407	1.1510	0.1540	[0.85 , 1.56]	0.3658
Other Medi-cal History	No					
	Yes	0.1358	1.1454	0.0663	[1.01 , 1.30]	0.0040
Systolic Blood Pressure	Low					
	Normal	-0.4540	0.6351	0.1165	[0.51 , 0.80]	<0.0001
	High	-0.0846	0.9189	0.0979	[0.76 , 1.11]	0.0387
Diastolic Blood Pressure	Low					
	Normal	-0.1231	0.8841	0.1247	[0.69 , 1.13]	0.2577
	High	0.1205	1.1281	0.1095	[0.91 , 1.40]	0.3020
<i>Frailty parameter, 2.66283e-17; SE (H): 4.27331e-10; p = 0.5</i>						
<i>penalized marginal log-likelihood = -2508.6; Convergence criteria: parameters = 2.29e-08; likelihood = 3.07e-07; gradient = 1.12e-12; LCV = the approximate likelihood cross-validation criterion in the semi parametrical case = 1.66661</i>						
<i>Coef: estimated coefficient for each covariates; Exp (coef): exponentiation value of coefficient, se coef (H) and hr is hazard ratio.</i>						

Shared Log-Normal Frailty Model

As in Shared Gamma Frailty model, for Shared Log-Normal Frailty model, the clustered structure of the data is taken into account with the interest in considering the heterogeneity between subjects. The result of the univariable Shared Gamma Frailty model is shown in the Appendix (Table 4). As it can be observed from the result, family history, regimen, other medical history, and Blood

Pressure of patients are significantly affecting the recovery time of diabetic patients. The multivariable Shared Log-Normal Frailty model is shown as in Table 8 below. Thus, the result shows that the recovery time of diabetic patient’s significantly affected by family history, other medical history, and Systolic Blood Pressure of patients.

Table 8: Parameter Estimates of Shared Log-Normal Frailty Model

Covariates	Categories	Coef	Exp(coef)	SE [Coef(HIH)]	95% CI	P-value
Family History of diabetic	No					
	Yes	0.1527	1.1650	0.0711	[1.01 , 1.34]	0.0318
Regimen	Oral Agents					
	Insulin Agents	0.2177	1.2432	0.1467	[0.93 , 1.66]	0.1379
	Both	0.1547	1.1672	0.1640	[0.85 , 1.61]	0.3460
Other Medical History	No					
	Yes	0.1616	1.1754	0.0711	[1.02 , 1.35]	0.0230
Systolic Blood Pressure	Low					
	Normal	-0.4601	0.6312	0.1220	[0.50 , 0.80]	0.0003
	High	-0.0907	0.9133	0.1036	[0.75 , 1.12]	0.3814
Diastolic Blood Pressure	Low					
	Normal	-0.1101	0.8957	0.1308	[0.69 , 1.16]	0.3997
	High	0.1346	1.1441	0.1156	[0.91 , 1.43]	0.2442
<i>Frailty parameter, Sigma Square: 0.0757467; SE (H): 0.00742001; p = < 1e-16</i>						
<i>penalized marginal log-likelihood = -2506.04; Convergence criteria: parameters = 5.54e-11; likelihood = 1.35e-07; gradient = 6.92e-16; LCV = the approximate likelihood cross-validation criterion in the semi parametrical case = 1.66625</i>						
<i>Coef: estimated coefficient for each covariates; Exp (coef): exponentiation value of coefficient, se coef (H) and hr is hazard ratio.</i>						

Testing Frailty Effect of Shared Frailty Model

Test hypothesis for the variance term of both Shared Gamma and Log-Normal Frailty terms is given by:

$$H_0: \theta=0 \text{ or } H_0: \delta^2=0 \text{ Vs } H_1: \theta>0 \text{ or } H_1: \delta^2>0$$

The variance of the Frailty Term Theta and Sigma Square are significantly different from zero, meaning that there is heterogeneity between subjects. The modified Wald Test Values for Shared Gamma Frailty and Shared Log-Normal Frailty model are $W_m(\theta)=7.564\exp(-12)$ and $W_m \delta^2=10.216$, respectively. Looking at Table 7 and Table 8 above, the p-value for the Shared Log-normal Frailty model, but not for Shared Gamma Frailty model, is less than 5%. This means that there is a significant Frailty effect; that is, within-subject the correlation cannot be ignored for Shared Log-normal Frailty model but not for Shared Gamma Frailty model.

Comparison of Standard Cox-PH and Shared Frailty Model

In this study, the model based and empirically corrected standard errors (H^{-1} and $H^{-1} IH^{-1}$) were almost identical for each model used. Comparing the estimated standard errors presented in Table 6, Table 7, and Table 8 above, slight differences were observed in the standard error for Standard Cox-PH model and Shared Frailty model. As expected, the standard errors of the Shared Gamma Frailty and Shared Log-Normal Frailty model were slightly larger than standard errors of the Standard Cox-PH model.

Efficiency of the fitted models was compared using penalized marginal log-likelihood and LCV (likelihood cross-validation) criterion. The likelihood cross-validation criterion assesses the goodness of fit of a statistical model and approximately equivalent to Akaike Information criterion (AIC) for the parametric models [26]. Table 9 below shows the LCV result of standard Cox- PH, Shared Gamma Frailty and Shared Log-Normal Frailty models. Accordingly, the Shared Log-Normal Frailty model was chosen as the best fit for the data in this study.

Table 9: Comparison of Standard Cox-PH and Shared Frailty Model

Model	Frailty Parameter	Standard Error	Penalized Marginal Log-Likelihood	LCV
Standard Cox-PH	-	-	-2517.41	1.67106
Shared Gamma Frailty	2.66283e-17	4.27331e-11	-2508.60	1.66661
Shared Log-Normal Frailty	0.0757467	0.00742001	-2506.04	1.66625

Interpretation of Final Fitted Model

The Shared Log-normal Frailty model was chosen as the best fit for the recurrent events data of diabetes based on the LCV. Therefore, the final fitted model was Shared Log-Normal Frailty model as shown in Table 8 above. Family history, other medical history, and Systolic Blood Pressure were the only significant covariates selected from the saturated multiple Shared Log-normal Frailty model.

The estimated hazard rate for Patients with family history of diabetes is 1.1650 with [95% CI: 1.01, 1.34]. This result shows that the expected hazard rate of diabetic patients to have a normal fasting Blood Sugar Level who have a family history of diabetes is 1.650 times higher than patients who have no family history of diabetes by keeping the effect of other factors constant and accounting for frailty. The 95% confidence interval for hazard rate of patient's family history of diabetes did not include one and p-value is small (p-value= 0.0318), which implies that patient's family history of diabetes had a significant effect on the recovery time of diabetic patients.

Looking at other medical history, keeping the effect of other factors constant and accounting for frailty, the expected hazard rate of diabetic patients to have a normal fasting Blood Sugar Level who have other medical history of diabetes is 1.1754 times higher than patients who have no other medical history of diabetes, since the estimated hazard rate for patients with other medical history of the

diabetes is 1.1754 with [95% CI: 1.02, 1.35]. The 95% confidence interval for the hazard rate of patients with other medical history of diabetes did not include one and p-value is small (p-value= 0.0230), which implies that patients with other medical history of diabetes have a significant effect on the recovery time of diabetic patients.

Finally, observing for Systolic Blood Pressure, keeping the effect of other factors constant, and accounting for frailty, the expected hazard rate of diabetic patients to have normal fasting Blood Sugar Level who have normal systolic blood pressure is 0.6312 times less than patients who have low systolic blood pressure, since the estimated hazard rate for patient's normal systolic blood pressure of the diabetes is with [95% CI: 0.50, 0.80]. The 95% confidence interval for the hazard rate of patients with normal systolic blood pressure of the diabetes did not include one and p-value is small (p-value= 0.0003), which implies that patients systolic blood pressure of diabetes had a significant effect on the recovery time of diabetic patients.

Model Diagnostic

By observing Cox-Snell residuals plot Figure 1 below, the Shared Log-normal Frailty model fits the recurrent data of diabetic patients; since the plot of Cox-Snell residuals against the cumulative hazard function of residuals is approximately a straight line with slope one.

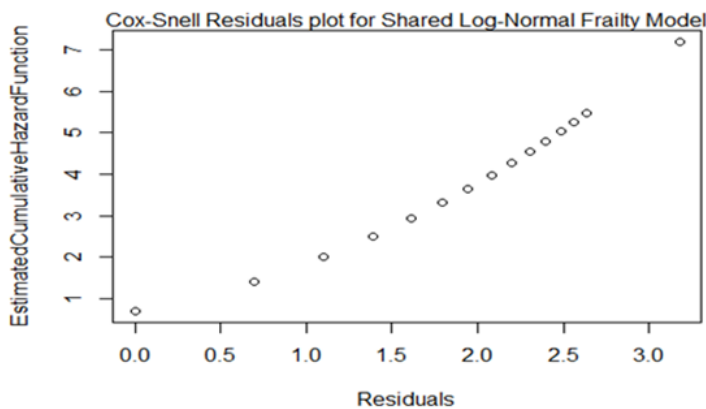


Figure 1: Cox-Snell Residuals Plot

Discussion

The main aim of this study was to identify factors affecting the recurrence of patients diabetes data set, which was obtained from Benishangul-Gumuz hospitals (Assosa, Pawi and Wonbera hospital). The Cox-PH model was applied for this data since the assumption of Cox-PH model was not violated. However, the common Cox model only considers the time until the first occurring event, meaning that all events after the first are neglected. The most frequently applied analysis method for recurrent time-to-event data is the model by Andersen and Gill, which is based on the common Cox proportional hazards model [19, 20]. The Andersen-Gill model assumes independence between all observed event times irrespective whether these event times correspond to the same patient or to different patients. In addition, Frailty models will be used to account for the dependence among the recurrent event times based on Andersen-Gill (A-G) survival model.

From 575 diabetic patients, 518(90.10%) were Type-II diabetic and the remaining 57 (9.90%) were Type-I diabetic. Of all 1516 events, 938 (61.87 %) experienced recurrence of diabetic and the remaining 578 (38.13%) were censored. The minimum and maximum recovery times of patient's diabetes were 1 and 24, month respectively. The median recovering time of the diabetic patients was 6 months.

Under univariable analysis, the Shared Log-normal Frailty model shows that family history, regimen, other medical history, and Blood Pressure were significantly associated with recurrence of diabetic patients at 5% level of significance.

By considering multivariable analysis result from Standard Cox-PH, Shared Gamma Frailty and Shared Log-normal Frailty model the recovery time of diabetic patient's significantly affected by family history, other medical history and Systolic Blood Pressure of patients. LCV values of for the standard Cox-PH, Shared

Gamma Frailty and for Shared Log-normal Frailty models were 1.67106, 1.66661 and 1.66625 respectively. Thus, the Shared Log-normal Frailty model was chosen to be best fit for this data set, since LCV value for the Shared Log-normal Frailty model was minimum as compared to the Standard Cox-PH and Shared Gamma Frailty models.

The heterogeneity parameters of θ and σ^2 are estimated to be: $2.66283e-17$ [with SE (H) = $4.27331e-10$; $p = 0.5$] and: 0.0757467 [with SE (H): 0.00742001 ; $p = < 1e-16$] for the Shared Gamma Frailty and Shared Log-normal Frailty models respectively. This result suggests that there is a significant Frailty effect for Shared Log-normal Frailty model but not for Shared Gamma Frailty model. This means that, in the Shared Log-normal Frailty model the correlation within the cluster patients cannot be ignored.

The study done by InterAct Consortium: Scott et al. (2013) showed that the recovery time of diabetic patients was significantly affected by family history of diabetes and the expected recovery time of diabetic patients to have a normal fasting Blood Sugar Level who have a family history of diabetes was less than patients who have no family history of diabetes [10]. This study was consistent with the current study.

The recovery time of diabetic patients was significantly affected by other medical history of diabetes; the expected recovery time of diabetic patients to have normal fasting Blood Sugar Level who have other medical history of diabetes was less than patients who have no other medical history of diabetes. This study was justified by the study done by Leon and Maddox (2015) [12].

On the other hand, the study done by showed that systolic blood pressure was significantly affected the recovery time of diabetic patients [11]. The recovery time of diabetic patients to have normal fasting Blood Sugar Level who have normal systolic blood pressure was less than patients who have low systolic blood pressure. This study was agreed with the current study.

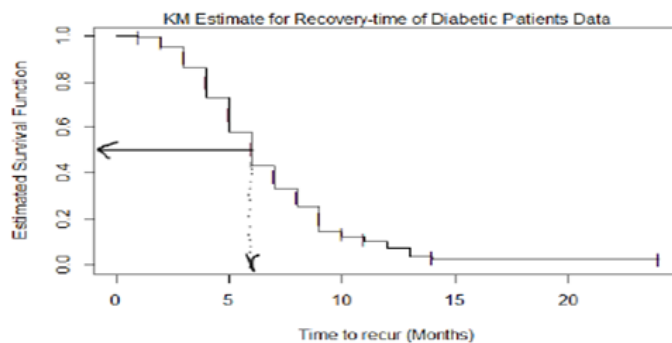


Figure 2: Kaplan-Meier Estimate plot for Recovery Time of Diabetic Patients Data

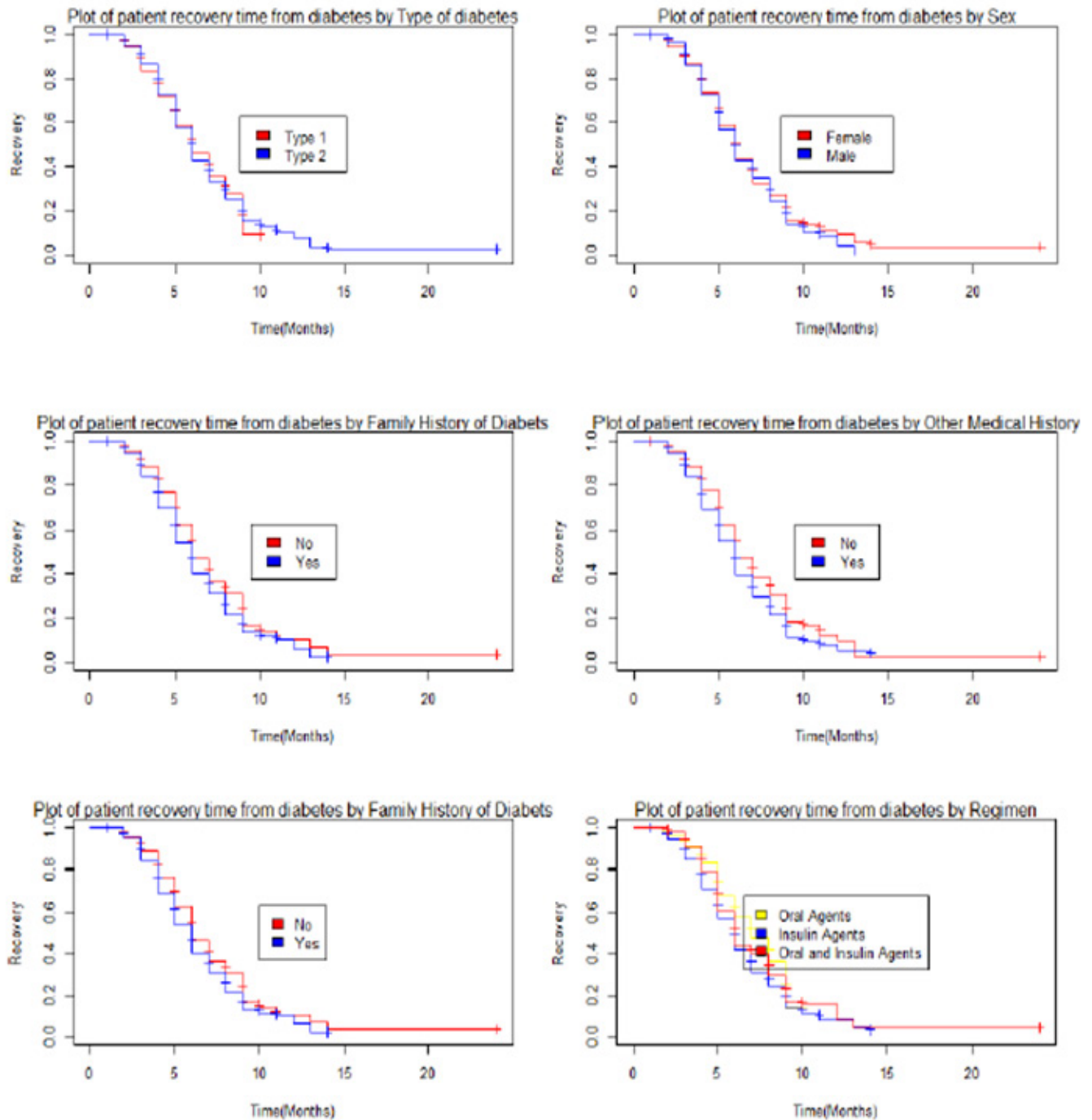


Figure 3: Kaplan-Meier Plot for different variables

Conclusion

This study used the recurrent data sets that have been taken from diabetic patients, for those patients who were receiving treatment for more than one time from September 1, 2019 to September 1, 2021, in Benishangul-Gumuz hospitals (Assosa, Pawi and Wombera hospital); with the aim to identify risk factors for recurrence of diabetic patient's recovery time. From the total of 575 diabetic patients, 61.87 % experienced recurrence of diabetic and the remaining 38.13% were censored. Fifty percent of the diabetic patient's recovery time was 6 months or above it.

To identify risk factors for recurrence of diabetic patient's recovery time, recurrent models: standard Cox-PH, Shared Gamma Frailty and Shared Log-normal Frailty were fitted. The Shared Log-normal Frailty model was chosen to be the best fit for this data set, based on LCV values. Family history, other medical history, and Systolic Blood Pressure of patients were significantly affected the recovery time of diabetic patient's.

Abbreviations

AMECA: Alex's Medical and Educational Clinic in Africa; CNCDS: Non-Communicable Chronic Diseases; Cox-PH: Cox Proportional Hazard; FGD: Focus Group Discussion; IDF International Diabetes Federation; LCV: Likelihood Cross-Validation; NCD-RisC: Non-Communicable Diseases Risk Factor Collaboration; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; WHO: World Health Organization

Declarations

Acknowledgment

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Funding

Not applicable

Availability of Data

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

Ethical Consideration

The Research Ethics Review Board of Assosa University would provide an ethical clearance for the study. The data has been collected after written permission was given to Benishangul- Gumuz hospitals and Assosa University Research Directors write an official cooperation letter to the hospitals for the permission. The data obtained from the hospitals were kept confidentially.

Consent for Publication

Not applicable

Conflict of interest

The authors do not have any conflict of interest.

Authors' Contributions

Both researchers conduct the research and write the manuscript.

Statistical Software Used

SPSS version 20 for data coding and entry; R version 4.1.1 for data analysis

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