Joint Modeling of Time to Diabetic Retinopathy and Change in Fasting Blood Sugar Among Type 2 Diabetic Patients in University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia

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Research

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Posted Date: April 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-422760/v1>

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Abstract

Background: Early identification of prognostic factors and close monitoring of the biomarkers is used to monitor the occurrence or progression of diabetic retinopathy. Therefore, this study aimed to assess change in fasting blood sugar level, time to diabetic retinopathy and its predictors among type 2 diabetes patients in Ethiopia.

Methods: Institution based retrospective follow-up study was conducted at University of Gondar Comprehensive Specialized Hospital. Linear mixed effect model and cox proportional hazard models were fitted separately and later the two models were fitted jointly using R software. Variables with p-value <0.05 were considered as significant predictors in the adjusted analysis.

Result: The incidence rate of diabetic retinopathy was 2 per 100-person year of observation with median follow up time of 90.8 months (IQR: 63.4). The current value and rate of

change in fasting blood sugar level were significant predictors of time to diabetic retinopathy (AHR=1.35;95% CI: 1.12-1.63) and (AHR=1.70; 95%CI:1.21-2.39) respectively. Hypertension (AHR=2.49; 95%CI: 1.32-4.66), taking >1 antidiabetic oral agent (AHR=4.90; 95%CI: 1.07-20.0) and more than 10 years duration (AHR=0.17, 95% CI: 0.06-0.46) were predictors of time to diabetic retinopathy.

Conclusion: This study revealed that medication, duration, weight, current age, and time have significant association with the progression change of fasting blood sugar. On the other hand, hypertension, medication and duration were significant predictors of time to diabetic retinopathy. The current value of fasting blood sugar and rate of fasting blood sugar change were significantly associated with time to diabetic retinopathy.

Key words: Type 2 diabetes mellitus, Diabetic retinopathy, Fasting blood sugar

Background

Diabetes mellitus (DM) is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (1, 2).

Type 2 diabetes mellitus is the most common form and covers 90% of people with diabetes around the world (2, 5, 6). Type 2 DM patients are more susceptible to various forms of complications such as cardiovascular disease, neuropathy, nephropathy and eye disease, leading to retinopathy and blindness (4, 5, 7).

Diabetes mellitus has a long term effect on the retinal small blood vessel which cause progressive development of the specific complications of retinopathy, resulting in vision loss (1, 8). Diabetic retinopathy (DR) is the leading cause of vision loss in working age adults (20 to 65 years) and approximately one in three people living with diabetes have

49 some degree of DR and one in ten will develop a vision threatening form of the disease (5).
50 Globally, the number of people with DR will grow from 126.6 million in 2010 to 191.0
51 million by 2030, and it is estimated that the number with vision-threatening DR will
52 increase from 37.3 million to 56.3 million, if prompt action is not taken (9).

53 The magnitude of DR in Africa range from 30.2 to 31.6% and 7.0 to 62.4% in patients with
54 diabetes in population-based studies and clinic-based surveys respectively (10).A
55 population-based study in Kenya identified a prevalence of DR 35.9 in 277 people with
56 diabetes (11). In Ethiopia the magnitude of DR ranged from 5.0% in northwest Ethiopia to
57 43.4% for T2DM patients in Southwest Ethiopia. Many studies done in Ethiopia showed
58 that the presence and severity of complications related to DR are steadily increasing (12).

59 Risk factors for diabetic retinopathy among diabetes patients includes gender, uncontrolled
60 DM, longer duration of DM, presence of nephropathy and presence of hypertension were
61 documented in different studies (13-16).

62 Until an advanced stage DR is asymptomatic and is largely preventable through regular
63 retinal screening and prompt treatment before their visual deterioration. However,
64 screening for diabetic retinopathy is not performed as expected for diabetes patients in
65 resource limited area because it is not easily accessible and affordable.

66 So, monitoring the biomarkers is very essential to be aware of that metabolic abnormality,
67 poorly controlled blood sugar, which increases the likelihood of retinopathy occurring and
68 cause retinopathy to progress more quickly if it does occur and provides meaningful
69 prognostic information that can help to differentiate patients with regard complication and
70 lead the way to change other intervention.

Previous studies conducted in Ethiopia used separate analysis which ignore the dependency and association between longitudinal FBS and time to diabetic retinopathy. Joint modeling approach is preferred than separate survival model as it provides more efficient estimates of the treatment effects on the time to diabetic retinopathy and longitudinal marker of FBS. Hence, this study uses joint modeling approach to account for the dependence and association of time to diabetic retinopathy and fasting blood sugar change.

Methods

Study design and area

An institutional-based retrospective follow-up study was conducted from January 2001 to February 2016 among type 2 diabetes patients in University of Gondar Comprehensive Specialized Hospital (UGCSH). UGCSH serves more than five million people of the North Gondar zone and peoples of the neighboring zones. Around 24,862 numbers of people are having chronic follow-up per year and among this 8,900 are DM patients.

Source Population

The source population were all type 2 diabetes patients having a follow up at UGCSH. All newly diagnosed type 2 diabetes patients in UGCSH from January 2001 to February 2016 were included in the study. However, those whose date of initiation was not recorded, those who had only one fasting blood sugar measurement and newly diagnosed patients who had DR at the start of follow up were excluded.

Sample size determination and sampling procedure

The sample size was determined for the two processes; longitudinal and survival.

Sample sized for longitudinal outcome

The sample size was determined by considering the following statistical assumptions: two-sided significance level ($\alpha = 5\%$), power 80%, number of repeated measurements ($m=7$), within subject correlation ($\rho=0.5$) and effect size ($\delta = 0.0384$) using

$$n = \frac{2 \left(\frac{z_{\alpha} + z_{\beta}}{2} \right)^2 (1 + (m-1)\rho)}{m\delta^2} \quad (19).$$

The effect size (δ) and number of repeated measurements (m) for calculating the sample size in this study was taken from study in Debre Berhan referral hospital, Ethiopia (20) and the calculated sample size was 466.

Sample sized for survival outcome

To estimate survival probability of patients we consider sex as exposure based on a research conducted in Tikur Anbessa Hospital in Addis Ababa (21). Using STATA 14.1 by using power analysis for log rank test and considering Z value at 95 % confidence, Power 80% and 10% incompleteness, the sample size was 435.

Finally, largest sample size (466) was selected. With 5% contingency the final sample size required for this study was 489. After the patients fulfill selection criteria, study subjects were selected by using systematic random sampling technique.

Variables

The response variable for the survival sub model was time from the date of diagnosis until the occurrence of either diabetic retinopathy or censoring measured in months, while the response variable for longitudinal sub model was blood glucose level in terms of fasting blood sugar using mill gram per deci liter (mg/dL) from treatment start (baseline) and repeatedly measured every three months, were time varying endogenous covariate. Socio demographic variables: baseline age (year), current age (year) and gender. Clinical variables: blood glucose, lipid level profile, body mass index (BMI), albuminuria level,

diabetic duration, treatment type and creatinine clearance Comorbidities: hypertension, neuropathy, nephropathy and anemia were independent variables.

Variable definition

For this study, Diabetic retinopathy, time to diabetic retinopathy, censored, poor glycemic control and hypertension were defined as follows: *Diabetic retinopathy*: was established if the subject has a minimum of one micro aneurysm in any field, or showing hemorrhages (dot & blot, or flame shaped), or maculopathy (with or without clinically significant edema (15). *Time to diabetic retinopathy* is the time between the times of diagnosed as T2DM to the development of diabetic retinopathy. *Censored* includes lost to follow up, death and being event free at the end of the study. *Hypertension* diagnosed when SBP is greater and equal to 140mmHg and DBP is greater and equal to 90. *Poor glycemic control* was established if fasting blood sugar is greater or equal to 140 mg/dL.

Data collection and data quality control

The study exclusively used secondary data and structured data extraction checklist. Four trained professional working in chronic follow-up clinic were recruited for data collection. Socio-demographic characteristics, baseline and follow up clinical and laboratory data collected from patient cards. Height measured as standing height using standard height scale for adults. Weight of the patients were recorded using analogue weighing scale. Blood Pressure readings measured using mercurial sphygmomanometer. Diabetic retinopathy identified based on history of Diabetes Mellitus and findings of fundoscopy. Diabetic retinopathy grading in this study have been described based on diabetic retinopathy screening to treatment guideline (22). A week before the actual data collection preliminary review was done on similar area. The data extraction sheet was pre-test for consistency of understanding, adequacy of instrument, time requirement to fill the check list of tools and

completeness of data for charts. Necessary adjustment for the final data collection sheet was made by excluding variables which is not found on charts like educational status and history of smoking. Training on the objective of the study and how to retrieve records as per data extraction sheet was given to data collectors and supervisors for two days before data collection. The information formats cross checked with the source card on the spot and regular supervision was done. The data was entered using Epi-info 7 and then export to STATA 14.1 and R 3.4.3 statistical software's for further data cleaning and statistical analysis.

Statistical analysis

Descriptive measures such as means, median, IQRs, percentages, frequencies and standard deviations were used to describe the study population. The survival experience of the patients was assessed using Kaplan-Meier survivor function. The log rank test was used to compare the survival experiences among the different groups of subjects. Cox PH and three parametric models (Weibull, Exponential and Log logistic) were fitted to identify the risk factors. The best model was selected by using Akaike information criteria (AIC). Accordingly, the Cox PH model was the preferred model to model time-to-diabetic retinopathy among type 2 DM patients in the study area. Schoenfeld residuals test and graphical methods were used to check the Cox Proportional Hazard (PH) assumption before fitting survival sub model. Goodness of fit of the model was assessed by using Cox-Snell residual technique.

To account for the effect of an endogenous time-varying covariate (FBS) on the time to DR the true unobserved value of fasting blood sugar in the survival model was used. The trajectory FBS over time was approximately normally distributed. Exploratory analysis was used to visualize the patterns of individual profiles plot and average evolution change

graphically. Linear mixed effect model with random intercept only and both random intercept and slope was fitted. Linear random effect model with both intercept and slope was best model that appropriately predicts the mean change of FBS measurements over time. To estimate the effects of longitudinal fasting blood sugar change to the risks of diabetic retinopathy the complete true history of fasting blood sugar for each subject using linear mixed effect model constructed by considering effects of baseline covariate on fasting blood sugar evolution. Association parameter (alpha value) from fitted joint model was used to assess association between longitudinal biomarkers (fasting blood sugar) and time to diabetic retinopathy.

Model specification

Linear mixed modeling

Linear mixed models are a type of regression model that take into account both variation that *is* explained by the independent variables of interest and variation that is *not* explained by the independent variables of interest. This is due to the measurement taken from the same subject at different time points or the measurements taken from the same clusters are likely to be correlated. In this study before the joint modeling to have an appropriate longitudinal sub-model for the longitudinally measured fasting blood sugar the LMM were employed to identify the covariates that have significant effects on the mean change of FBS measurements over time. Therefore, the longitudinal data modeling was beginning with exploratory data analysis to determine the mean change of FBS measurement over time. To measure the effect of the longitudinal covariate to the risk for an event, we need to estimate the true unobserved value of the longitudinal covariate $m_i(t)$ and successfully reconstruct the complete longitudinal history $M_i(t)$ for each subject. To achieve this, we

186 postulate a suitable mixed-effects model to describe the subject-specific time evolutions
 187 with this notation

$$188 \quad y_i(t) = m_i(t) + \varepsilon_i(t)$$

$$189 \quad m_i(t) = x_i(t)\beta_1 + z_i(t)b_i$$

$$190 \quad b_i \sim N(0, \Sigma_i), \varepsilon_i \sim N(0, \sigma^2_i)$$

191 where we explicitly note that the design vectors $X_i(t)$ for the fixed effects β , and $Z_i(t)$ for
 192 the random effects b_i , as well as the error terms $\varepsilon_i(t)$, are time dependent. We assume that
 193 error terms are mutually independent, independent of the random effects, and normally
 194 distributed with mean zero and variance σ^2 .

195 **Survival sub modeling**

196 Survival models seek to explain how the hazard of an event occurring at a given time is
 197 affected by covariates. Hazard function of survival model is used to explain the probability
 198 that the event has occurred by duration t . This study considered semi-parametric survival
 199 models to explain how the risk, or hazard, of diabetic retinopathy occurring at a given time
 200 is affected by covariates in the study area. Cox proportional hazard model which expresses
 201 the hazard of an event at time t as:

$$202 \quad \lambda_i(t) = \lambda_o(t) \exp(W^T \gamma)$$

203 Where W is the matrix of baseline covariates, γ is the vector of parameters and the term
 204 λ_o is the baseline hazard where the effects of covariates are zero.

205 Joint Modeling Structure

206 Joint model consists of longitudinal and survival sub model. Joint model of longitudinal
 207 and time-to-event data can effectively assess the impact that a longitudinal covariate,
 208 measured with error, has on the time to an event of interest. In this study we assess the
 209 predictive ability of a biomarker FBS on time to diabetic retinopathy. To introduce this
 210 methodology, we will use the following notation to harmonize diverse approach.

211 In particular, we denote by T_i^* the true event time for the i^{th} subject, T_i the observed event
 212 time, defined as the minimum of the potential censoring time C_i and T_i^* , and by $\delta_i =$
 213 $I(T_i^* \leq C_i)$ the event indicator. For the endogenous time-dependent covariate (FBS) we let
 214 $y_i(t)$ denote its observed value at time point t for the i^{th} subject. We should note that we
 215 do not actually observe $y_i(t)$ for any time t , but rather only at the very specific occasions
 216 t_{ij} at which measurements were taken. Thus, the observed longitudinal data consist of the
 217 measurements

$$218 \quad y_{ij} = \{y_i(t_{ij}), j = 1, \dots, n_i\}$$

219 The term $m_i(t)$ that denotes the true and unobserved value of the longitudinal outcome at
 220 time t . Note that $m_i(t)$ is different from $y_i(t)$, with the latter being the contaminated with
 221 measurement error value of the longitudinal outcome at time t . To quantify the strength of
 222 the association between $m_i(t)$ and the risk for an event, a straightforward approach is to
 223 postulate a relative risk model of the form:

224

$$225 \quad \left\{ \begin{array}{l} h_i(t|M_i(t), w_i) = \lim_{dt \rightarrow 0} \Pr\left(\frac{t \leq T_i^* < t+dt | T_i^* > t, M_i(t), w_i}{dt}\right) \\ h_i(t|M_{1i}(t), w_i) = h_0(t) \exp\{\gamma^T W_i + \alpha_1 m_{1i}(t)\}, t > 0 \end{array} \right. \quad (1)$$

226

where $M_i(t) = \{m_i(s), 0 \leq s < t\}$ denotes the history of the true unobserved longitudinal process up to time point t , $h_0(\cdot)$ denotes the baseline risk function and W_i is a vector of baseline covariates with a corresponding vector of regression coefficients γ . Similarly, parameter α_1 quantifies the effect of the underlying longitudinal outcome to the risk for an event.

$$h_i(t) = h_o(t) \exp\{\gamma^T w_i + \alpha_1 m_i(t) + \alpha_2 m'_i(t)\} \quad (2)$$

$$\text{where, } m'_i(t) = \frac{d}{dt} m_i(t) = \frac{d}{dt} \{x_i^T(t)\beta + z_i^T(t)b_i\}$$

α_2 measures how strongly associated is the value of the slope of the true longitudinal trajectory at time t with the risk for an event at the same time point, provided that $m_i(t)$ remains constant. (23). The relative risk model (1) postulates that the risk for an event at time t depends only on the current value of the time-dependent marker $m_i(t)$. The relative risk model (2) postulates that the risk depends on both the current true value of the trajectory and the slope of the true trajectory at time t .

Ethical consideration

Ethical clearance was obtained from the Institutional Review committee of the UOG. Informed consent is not required as the whole data had been retrieved from the medical records of patient. Data anonyms and hold on a secure password protected system. Confidentiality during all phases of research activities was kept.

Results

Descriptive Statistics

Among the total of type 2 DM patients during the time period 80 (17.17%) were developed diabetic retinopathy. The mean age of participants at baseline was 53.17 (SD= 10.11) years and from the total study subjects 69.74% were within age category <60 years. The mean duration of diabetes was 9.2 years (SD= $\pm$ 3.8). Among 249 T2DM patients whose baseline FBS was above 200 mg/dl, 55% have developed diabetic retinopathy. Out of a total of 78 patients who developed neuropathy 22.5% have developed diabetic retinopathy ([Table 1](#)).

Table 1

To understand the association between the FBS measurement and time individual profile plots were employed. Loess smoothing technique over individual profile plots were used to explore the mean change of FBS measurement over time ([Fig 1](#)).

Figure 1: Individual profile plot and the evolution of mean structure of FBS over time for type 2 diabetes patients in UGCSH, 2001 to 2016

As indicated on the plots the individual profile plots suggested that there was within and between variations of change in FBS measurements over time. The individual trajectory of FBS for patients shows that patients had considerably different FBS at baseline and overtime. This suggests a model with both random intercept and slop is a good start. However, the red line which shows the mean structure of FBS measurement over time with loess smoothing technique suggested that the linear change of the mean of FBS measurement over time.

Sensitivity analysis

When FBS were not observed during a 3-month period, values were considered as missing. A problem in the handling of missing data in longitudinal outcomes is the fact that the

observed data alone cannot distinguish between a MAR and a MNAR dropout mechanism. To handle this, we do sensitivity analysis then analyze the sensitivity of the reported results by observing the parameter estimate and the standard error estimate. The parameter estimate between complete case analysis and multiple imputation is not that much different. So, by considering this joint model with current parametrization with complete case analysis approach was chosen (Table 2).

Table 2. Comparison of joint model with Current value and slope parameterization under multiple imputation and complete case analysis missing handling method for T2DM patients.

Method	Parametrization	AIC
Multiple imputation	Current	68944
	Slope	68830
Complete case analysis	Current	27625
	Slope	27719

AIC agree that the joint model with the Current parametrization with complete case analysis missing handling approach has a better predictive ability.

Time to Retinopathy

The cumulative survival probability of the patients at the end of 12, 36 and 72 months were 97%, 94%, and 89%, respectively. The cohort contributed a total of 3607.67 person-years. About half (51%) diabetic retinopathy were developed with in the first five years. The median follow up time was 90.8 [IQR=63.4] months and a total of 80 (17.17%) patients developed DR. The incidence density was 2 cases per 100 patients per year (95%CI: 1.78

2.76). The median survival time or the survival time at which the cumulative survival function is equals to 0.5 could not be determined (Fig 2).

Figure 2: The plot of the overall estimate of Kaplan-Meier survivor for time to diabetic retinopathy among T2DM patients under anti diabetes treatment at UGCSH, 2001-2016

Joint Model

After the most suitable separate model have been decided for the data, the proposed joint model was applied with the aim of investigating the effects of fasting blood sugar measurements on time to diabetic retinopathy.

Joint model was fitted by both current value and time dependent slope parameterization with piecewise-PH-aGH method to specify the type of the survival sub model, and the algorithm numerical integration method, among the available options. The result validates the hypothesis that for type 2 DM patients, the current value of fasting blood sugar and the slope of the fasting blood sugar trajectory are highly associated with the hazard of the event (Diabetic retinopathy).

In this study survival analysis-longitudinal analysis joint modeling technique was used to identify the risk factors to the time to the happening of diabetic retinopathy and changes in the longitudinal fasting blood sugar. Type of medication, duration, weight, current age, and time were found to be significant predictors of change in fasting blood sugar, whereas presence of hypertension, medication and duration were significant predictors of time to diabetic retinopathy (Table 3).

The hazard of diabetic retinopathy for hypertensive patient is 2.49[1.32 4.66] times higher than those patients who are not hypertensive keeping other variables constant. Unexpectedly, the hazard of developing DR among patient's duration 6-10 years is 69%

less likely than patient's duration less than 6 years keeping other variables constant. The hazard of developing DR among patient's duration >10 years is 83% less likely than patient's duration less than 6 years keeping other variables constant.

The hazard of developing DR for patients who take more than one oral anti diabetic agents together to manage their diabetes is 4.90[1.07 20.0] times higher than those patients who are not taking any medication keeping other variables constant

A unit increase in the current value of fasting blood sugar increase the hazard of developing diabetic retinopathy by 1.35[95%CI:1.12 1.63] times, whereas a unit increase in the rate of fasting blood sugar trajectory increase the hazard of diabetic retinopathy by 1.70[95% CI: 1.21; 2.39] times, provided that the true an observed value remain constant (Table 3).

The joint model could be fitted like

$$\begin{aligned}
 H_i[t|M_i(t), W_i] \\
 = 0.91 * hypertension - 0.18 * femalesex - 0.20 * baselineage \\
 - 1.16 * duration_{6-10} - 1.75 * duration \\
 > 10 year + 1.93 * 1 oral agent + 1.59 * \\
 > 1 oral agent + 1.45 * insulin - 0.16 * SBP0 - 0.002 * BMI_{18.5-24.9} \\
 + 0.37 * BMI_{25-29.9} + 0.14 * BMI_{\geq 30} + 0.30 * M_i(t)
 \end{aligned}$$

Where, $M_i(t)$ is the true unobserved longitudinal process up to time t. W_i is the vector of fixed effect covariates.

Table 3. The fitted joint model result under current parameterizations for type 2 diabetes patients in UGCSH ,2001 - 2016.

Longitudinal sub model			Survival sub model		
Fixed effects	Coeff (β)	95% CI	Covariates	AHR	95% CI
			Sex		
Intercept	13.50	[11.46 15.55] ***	Male	1	

FBS time 1	-0.288	[-0.93 0.35]	Female	0.83	[0.43 1.59]
FBS time 2	-4.013	[-4.70 -3.32] ***	HTN		
FBS time 3	-1.444	[-1.92 -0.96] ***	No	1	
Baseline SBP			Yes	2.49	[1.32 4.66] **
≤140	0		Medication		
>140	0.045	[-0.51 0.60]	No medication	1	
Current Age	-0.255	[-0.49 -0.02] ***	1 oral agent	2.55	[0.43 7.38]
Medication			>1 oral agent	4.90	[1.07 20.0] *
Dietary modification	0		Insulin	4.28	[0.78 21.2]
1 oral agent	0.547	[-0.32 1.41]	Neuropathy		
>1 oral agent	0.902	[0.21 1.59] **	No	1	
Insulin	0.701	[-0.18 1.58]	Yes	1.76	[0.81 3.81]
Sex			Nephropathy		
Male	0		No	1	
Female	0.130	[-0.35 0.61]	Yes	1.47	[0.63 3.42]
Duration	0.096	[0.03 0.16] ***	Duration		
Weight	0.034	[-0.05 -0.02] ***	≤5.9 years	1	
Variance Component			6-10 years	0.31	[0.11 0.84] *
Std. Dev. (intercept)	1.66		≥10 years	0.17	[0.06 0.46] ***
Std. Dev. (Time)1	3.86		Association parameters		
Std. Dev. (Time)2	2.41		Parametrization		
Std. Dev. (Time)3	0.86		Current	1.35	[1.12 1.63] ***
Std. Dev. (Residual)	3.17		Slope	1.70	[1.21 2.39] ***

336

337 Discussion

338 Diabetic retinopathy is a long-term complication of diabetes mellitus that could be
339 attributed to systemic or local ocular factors (24). The disease is asymptomatic until it leads
340 to visual deterioration. Monitoring the biomarkers may be essential to be aware of the
341 factors which increase the likelihood of retinopathy and to act accordingly. Joint modeling

approach was applied in order to determine how strong is the association between fasting blood sugar and the risk of diabetic retinopathy.

Nearly half of diabetic retinopathy were developed with in the first five years. This is consistent with the study done in Arbaminch (14) which shows that 47% of diabetic retinopathy developed with in the first five years. This could be due to most of type 2 DM patients came to the health center when they face any complication including visual problem since it is asymptomatic until the advanced stage. However, this study finding is higher than the study done in Pakistan (25) which showed that only 22% of diabetic retinopathy developed with in the first five years.

The results of this study show that the proportion of DR was 17.17% with 20 cases per 1000 year. The study showed a higher incidence of DR than studies done in Ethiopia and China (21, 26). This inconsistency might be due to the difference in health care service and complication monitoring. However, the incidence rate in this study was lower than that of a study done at Arbaminch general hospital, Ethiopia (14) and retrospective longitudinal follow-up study done in Pakistan (25). The difference in study period, diagnostic methods used by the studies and the denominator population might have attributed to this difference. The current study showed that duration of diabetes was negatively associated with hazard of DR and it is consistent with longitudinal study finding on diabetic patients in Arbaminch (14) but it is not consistent with longitudinal study finding on diabetic patients in Malaysia (27) and cross-sectional study finding in Jimma university tertiary hospital and tertiary care hospital in Pakistan (15, 28). This might be since our study populations were type 2 DM patients who are more likely to come late to the health facility and seek health services because the disease process of T2DM is more gradual and not as severe as type 1 DM.

Another possible explanation for this finding, type 2 DM patients may gradually develop a better metabolic control with low levels of FBS.

The result revealed that hypertension is a risk factors for diabetic retinopathy. this finding is consistent with the studies from Ethiopia (14, 29) and also by UK Prospective Diabetes Study (UKPDS 38) (30). Increased blood flow could damage the retinal capillary endothelial cells in eyes of people with diabetes (31). The pathophysiological mechanism involves the function and interaction of the endothelial and vascular smooth muscle cells. damage and altered growth of retinal capillary endothelial cells induce proliferative lesions of the retina (32).

The results showed that taking more than one oral anti diabetic agents together to manage their diabetes increased the risk of diabetic retinopathy. This might be due to combination of oral agent is generally advocated when no medication or only one oral medication users had poorly control glycemia at some points and when patients develop resistance to medication which is expressed by poor glycemic control. Prolonged poor glycemia control causes injuries to the retinal vasculature. But other studies (14, 21, 27) shows that medication has no association with risk of diabetic retinopathy. So further investigation is needed.

In this study, we observe strong evidence that both current value of FBS and rates of FBS change were associated with diabetic retinopathy. Several earlier studies on type 2 DM patients showed that fasting blood sugar level is significantly associated with diabetic retinopathy (14, 16, 26, 33). But all these studies could not able to identify the effects of longitudinal FBS trajectory on the risk diabetic retinopathy. By using joint modelling approach, we estimate the effects of longitudinal trajectory rate on the risk of DR.

One of the strengths of this study was the accuracy of diabetic retinopathy since grading is not only clinical ophthalmologic examination but also fundus photographs.

The main limitation of this study was data on some potentially important predictors were not available which may underestimate the effects and individual variations in the development of diabetes retinopathy (some sociodemographic factors and behavioral factors). Another limitation was in our study area HBA1C were not done for follow-up which is the recommended mode of testing blood sugar control, leading to the use of fasting blood sugar alone.

Conclusion

This study revealed that type of medication, duration, weight, current age, and time were found significant predictors of change in fasting blood sugar, whereas presence of hypertension, medication and duration were significant predictors of time to diabetic retinopathy. Unobserved true current value of FBS and rate of FBS change were significantly associated with time to diabetic retinopathy. Based on the study finding from this data we recommend that ,it is better to do screening for diabetic retinopathy at the time of diagnosis of DM since most diabetes patients develop diabetic retinopathy at the early period of the follow up and to give special attention for those who took combined medication in the screening program. The health care provider strength the routine monitoring of FBS as a biomarker which provides meaningful prognostic information that can help to differentiate patients with regard DR and lead the way to change other intervention and close monitoring of patients diagnosed with hypertension.

Abbreviation

AHR: Adjusted Hazard Ratio;

AIC: Akaike Information Criteria;

412 BMI: Body Mass Index;
413 DBP: Diastolic Blood Pressure;
414 DM: Diabetes Mellitus;
415 DR: Diabetic Retinopathy;
416 FBS: Fasting Blood Sugar;
417 IDF: International Diabetic Federation;
418 IQR: Inter Quartile Range;
419 SBP: Systolic Blood Pressure;
420 T2DM: Type Two Diabetes Mellitus;
421 UGCSH: University of Gondar Comprehensive Specialized Hospital;
422 WHO: World Health Organization

423 **Declarations**

424 **Ethics approval and consent to participate**

425 Ethical clearance was obtained from the Institutional Review committee of the University
426 of Gondar.

427 **Consent for publication**

428 Not applicable

429 **Availability of data and materials**

430 All necessary information's were included with in the manuscript

431 **Competing interests**

432 The authors declare that they have no competing interests

433 **Funding**

434 The data collection was financially covered by university of Gondar.

435 **Authors' Contributions**

436 Conception of the work, design of the work, acquisition of data, analysis and interpretation
437 of data was done by SA. Data curation, drafting the article, revising it critically for
438 intellectual content, validation and final approval of the version to be published was done
439 by SA, ZT, SA and TA. All authors read and approved the final manuscript.

440 **Acknowledgments**

441 We thank University of Gondar for giving ethical clearance to conduct this research. Our
442 gratitude also goes to supervisors and data collectors who actively participated in this
443 research work.

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Figure legends

Figure 1: The individual profile plots suggested that there was within and between variations of change in FBS measurements over time. The individual trajectory of FBS for patients shows that patients had considerably different FBS at baseline and overtime. This suggests a model with both random intercept and random slop is required. The red line (loess smoothing technique) which shows the mean structure of FBS measurement over time suggested that the linear change of the mean of FBS measurement over time. FBS, Fasting Blood Sugar

Figure 2: The plot of the overall estimate of Kaplan-Meier survivor for time to diabetic retinopathy among T2DM patients under anti diabetes treatment at UGCSH, 2001-2016. Black line indicated the survival estimate, the red and green color line show the lower and the upper boundary of the estimate. The median survival time or the survival time at which the cumulative survival function is equals to 0.5 could not be determined

Table 1. Demographic and Clinical characteristics of the study participants in UGCSH, 2001-2016. Exploring fasting blood sugar change level

Variable	Censored (%)	Diabetic	Total
Retinopathy (%)			
Sex			
Male	153(39.64)	34(42.50)	187(40.13)
Female	233(60.36)	46(57.50)	279(59.87)
Baseline Age Mean=53.17±10.11			
<60	266(68.91)	59(73.75)	325(69.74)
≥60	120(31.09)	21(26.25)	141(30.26)
Residence			
Gondar	309(80.05)	69(86.25)	378(81.12)

Out of Gondar	77(19.95)	11(13.75)	88(18.88)
Baseline FBS	Mean=224.3±81.76		
70-130	33(8.55)	2(2.50)	35
131-200	148(38.34)	34(42.50)	182
>200	205(53.11)	44(55)	249
HTN			
Yes	79(20.49)	29(36.25)	108
No	307(79.53)	51(63.75)	358
Medication			
No medication	25(6.48)	4(6.25)	29
1 oral agent	247(63.9)	51(62.5)	298
>1 oral agent	68(17.6)	12(15)	80
Insulin	46(11.9)	13(16.3)	59
Neuropathy			
Yes	60(15.5)	18(22.5)	78
No	326(84.5)	62(77.5)	388
Nephropathy			
Yes	55(14.25)	52(15)	67
No	331(85.75)	28(85)	399
Anemia			
Yes	31(8.03)	7(8.75)	38
No	355(91.97)	73(91.25)	428
Duration	Mean=9.2±7.7		
< 6 yr	82(21.2)	18(22.5)	100
6-10 yr	174(45.08)	31(38.75)	205

>10 yr	130(33.68)	31(38.75)	161
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Baseline SBP

≤140	308(79.79)	69(86.25)	377
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>140	78(20.21)	11(13.75)	89
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Baseline DBP

≤90	344(89.12)	72(90)	416
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>90	42(10.88)	8(10)	50
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Figures

Figure 1

Individual profile plot and the evolution of mean structure of FBS over time for type 2 diabetes patients in UGCSH, 2001 to 2016. The individual profile plots suggested that there was within and between variations of change in FBS measurements over time. The individual trajectory of FBS for patients shows that patients had considerably different FBS at baseline and overtime. This suggests a model with both random intercept and random slop is required. The red line (loess smoothing technique) which shows the mean structure of FBS measurement over time suggested that the linear change of the mean of FBS measurement over time. FBS, Fasting Blood Sugar

Figure 2

The plot of the overall estimate of Kaplan-Meier survivor for time to diabetic retinopathy among T2DM patients under anti diabetes treatment at UGCSH, 2001-2016. The plot of the overall estimate of Kaplan-Meier survivor for time to diabetic retinopathy among T2DM patients under anti diabetes treatment at UGCSH, 2001-2016. Black line indicated the survival estimate, the red and green color line show the lower and the upper boundary of the estimate. The median survival time or the survival time at which the cumulative survival function is equals to 0.5 could not be determined