Correlates of time to microvascular complications among diabetes mellitus patients using parametric and non-parametric approaches: a case study of Ayder referral hospital, Ethiopia.

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ABSTRACT

Socio-demographic and clinical factors have been known to affect the time to microvascular complications and survival probabilities of diabetes mellitus patients. The objective of this study was to identify risk factors and estimate average survival times for the time to the development of microvascular complications of diabetic patients under follow up at Ayder referral hospital from February 2011 to January 2014. A retrospective follow up study was conducted on diabetic patients during this treatment period of 3 years. Using simple random sampling a total of 277 patients were included in the study. Cox and Weibull proportional hazards models were used to identify risk factors for the time to microvascular complications. Results showed that the prevalence of microvascular complication during the follow up period in the studied population was 42.6% and was more prevalent in women. The estimated overall median survival time was 425 days. Factors associated with increased risk of microvascular complications among the sampled diabetes mellitus patients as identified by the Weibull model were older age (HR=1.025, 95% CI: 1.008-1.043, p=0.003), female sex (HR=1.531, 95% CI: 1.063-2.206, p=0.002), Type 2 diabetes (HR=2.320, 95% CI: 1.121-4.799, p=0.023) and fasting blood sugar (FBS) (HR=1.006, 95% CI: 1.003-1.008, p=0.0000). The results suggest strongly that to minimize the risk of diabetic complications it is necessary to treat blood glucose aggressively.

Key Words: Diabetes Mellitus, Microvascular complications, Survival Analysis, Weibull proportional hazards model, Ayder Referral Hospital.
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INTRODUCTION

Diabetes mellitus is a chronic disease characterized by hyperglycemia and by complications that include microvascular diseases of the eye and kidney and a variety of clinical neuropathies (Natan, 1993). The effects of diabetes mellitus include long term damage, dysfunction and failure of various organs. Based on the revised WHO classification which encompasses both clinical stages and aetiological types, there are three types of diabetes mellitus; Type 1, Type 2 and Type 3. Type 2 is the most common form of diabetes and is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature (Alberti and Zimmet, 1998).

Diabetes mellitus continues to increase in numbers and significance, as changing lifestyles lead to reduced physical activity and increased obesity. According to International Diabetes Federation, an estimated 4.9 million deaths were attributable to diabetes annually (Guariguata *et al*., 2014). The world prevalence of diabetes among adults aged 20–79 years in the year 2014 was estimated to be 8.3%, affecting 387 million people. This is projected to increase to 8.8% affecting 591.9 million adults by 2035. North America and Caribbean is the region with the highest prevalence (regional prevalence of 11.0% in 2013 and estimated prevalence of 12.5% in 2035) followed by Middle East and North Africa

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(regional prevalence of 9.2% in 2013 and estimated prevalence of 11.6% in 2035). The corresponding figures for Africa were 19.8 million people in 2013 (a regional prevalence of 4.9%) and 41.5 million by 2035. The highest prevalence of diabetes in the Africa Region was on the island of Reunion (15.4%), followed by Seychelles (12.1%), Gabon (10.7%) and Zimbabwe (9.7%). In Ethiopia, the report indicated an estimated prevalence of 4.36 %.

People with diabetes are at risk of developing a number of disabling and life-threatening health problems. Consistently high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys, and nerves. People with diabetes are also at increased risk of developing infections.

The long–term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease (Alberti and Zimmet, 1998).

A multinational, open-label, observational study where 66,726 people were enrolled from 28 countries across four continents (Asia, Africa, Europe and South America) and with type 2 diabetes who had begun using insulin, found that 53.5% had microvascular complications (Litwak *et al*., 2013). According to (Naiker, 2009), the prevalence of diabetic nephropathy is estimated to be 14%-16% in South Africa, 23.8% in Zambia, 12.4% in Egypt, 9% in Sudan, and 6.1% in Ethiopia.

Rotimi *et al*. (2003) looked at the prevalence and risk factors for diabetic retinopathy and cataracts in 840 patients with type 2 diabetes and 191 spouse controls, enrolled from 7 centers in Ghana and Nigeria. In this cohort (whose mean age was 46 years), the prevalence of diabetic retinopathy was 18%. A study on the prevalence of diabetic retinopathy in Jimma University Hospital, Ethiopia, showed that the prevalence of diabetic retinopathy was 41.4% (Guadie Sharew *et al*., 2013).

Research on estimating the mean survival time to the development of complications on diabetic patients and the determinant factors of time to the development of complications of diabetes mellitus is important to allocate resources and increase access to community health services. In a study to identify causes of end stage renal failure among haemodialysis patients in Khartoum, Sudan (Banaga *et al.* (2015) found that hypertension and diabetes mellitus were the leading causes of End Stage Renal Failure (ESRF) among patients over 40 years old. In a study in Sweden, Svensson *et al.* (2015) reported that older age, Type 2 DM, higher Body Mass Index (BMI) at diagnosis of diabetes and poor glycaemic control were risk markers for one or more of the complications of diabetes mellitus. Liu *et al.* (2010) in a cross-sectional hospital based survey in urban China used generalized linear models to reveal that the prevalence of chronic complications varied between cities, and significantly increased with age and duration of diagnosed diabetes. Kengne *et al*. (2005) found that smoking, diet high in saturated fat; hypertension, obesity, type 2 diabetes mellitus, dyslipidemia, and lack of physical exercise were identified as risk factors for cardiovascular complications of diabetes mellitus in sub-Saharan Africa.

Some research works have been documented in sub Saharan Africa and Ethiopia on the prevalence and determinants of diabetes mellitus and its complications (Yeweyenhareg Feleke and Fikre Enquselassie, 2005; Dawit Worku *et al*., 2010; Solomon Tamiru and Fessahaye Alemseged, 2010; Hall *et al*., 2011; Tilahun Nigatu, 2012; Solomon Mekonnen Abebe *et al*., 2014; Wubareg Seifu *et al*., 2015). However, little work has been reported on estimating the survival time to the development of complications of diabetic patients and its determinant factors. The purpose of this study was therefore to estimate the average time to the development of microvascular complications of diabetes mellitus and its determinant factors using parametric and nonparametric methods of survival analysis.

METHODS

Retrospective follow up study design was used for this study. The cohort was followed from February 2011 to January 2014. The data was collected from individual patients' chart from May to June 2014. The source of population for this study was all diabetes mellitus patients of Ayder referral hospital. Since no similar researches were found in Ethiopia, estimates of hazard ratio (HR) were taken from other countries in the region. Based on the study on "Diabetes in the Middle East and North Africa" by Zabetian *et al*. (2013), the hazard ratio of microvascular events in Iran was HR=2.9 with 95% confidence level compared with those without diabetes. Using these estimates, the sample size for this study with power 0.8 and 10% censored observations computed using Cox proportional hazards model was 277. The 277 sample diabetes mellitus patients for this study were selected by simple random sampling technique using the patient's medical registration number from the population of 1295. The response variable is continuous and describes the duration of time (in days) until the occurrence of microvascular complications.

Inclusion and exclusion criteria

Patients included in this study were only type 1 and type 2 diabetes mellitus patients. Patients who were exposed to gestational diabetes mellitus were not included in the study.

Statistical analysis

The variables like Age, Sex, Body Mass Index (BMI), Place of residence, HIV, Feeding Habit, Albumen, Ketone, Diabetes type, Treatment type, Hypertension, TB status, Parastosis and Pneumonia were considered as potential risk factors. Descriptive statistics were used to describe the percentage and frequency of the patients in reference to all covariates. 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. The Cox PH model and four parametric models (Exponential, Weibull, Log logistic and Lognormal) were used to identify the risk factors for the time to microvascular complications. The model that best fits the data was identified using the AIC and BIC criteria. The plot of $log\{-log\,(\widehat{S(t)}\}$ versus $log\,(t)$, where $\widehat{S(t)}$ is the estimate of the Kaplan-Meier estimate of the survivor function, was checked for linearity which suggests the appropriateness of the Weibull proportional hazards model. Two-tailed P value of less than 0.05 was considered as significant.

The Cox proportional hazards model is used in situations where the hazard of death at a particular

time depends on the values of the explanatory variables. The general Cox proportional hazards model is of the form:

$$h_i(t) = \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{3i} + \cdots + \beta_p x_{pi}) h_0(t)$$

where $h_i(t)$, the hazard function at time t for the ith individual, is the product of two functions. The baseline hazard, $h_0(t)$, characterizes how the hazard function changes as a function of survival time; $\exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \beta_p x_{pi})$, where x_i are observable covariates and β_i are estimable coefficients, characterizes how the hazard function changes as a function of covariates. The ratio of the two hazards, called the hazard ratio (HR) is

$$HR = \frac{h_i(t)}{h_0(t)} = \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{3i} + \cdots + \beta_p x_{pi})$$

The HR reveals the time rate of the happening of the event at any time during the study period, compared to the reference category. HR= 1 indicates that the covariates in the model have no effect and do not change the baseline hazard, $h_0(t)$. HR< 1 and HR>1 mean that the time rates are decreased and increased throughout the study period, respectively. The above function can be expressed in the form:

$$log\left\{\frac{h_i(t)}{h_0(t)}\right\} = \beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{3i} + \cdots + \beta_p x_{pi}$$

which is a linear model for the logarithm of the hazard ratio. The method of partial likelihood is used to find estimates of the coefficients, β_i.

Weibull proportional hazards model plays a central role in the analysis of survival data. The probability density function of the Weibull distribution with scale parameter λ and shape parameter γ, W(λ, γ), is given by $W(\lambda,\gamma) = \lambda\gamma t^{\gamma-1}\exp(-\lambda t^{\gamma})$

The survivor and hazard functions of a W(λ, γ) distribution are given by $S(t) = \exp(-\lambda t^{\gamma})$ and $h(t) = \lambda\gamma t^{\gamma-1}$ respectively. If $\gamma = 1$, the hazard will be constant over time and hence is equivalent to exponential survival time. If $\gamma > 1$, the hazard increases with time and if $\gamma < 1$ the hazard decreases as time increases. The method of maximum likelihood is used to find estimates of the parameters λ and γ.

Data management and analysis of this study was carried out using STATA12. The model that best fits the data was selected using the AIC and BIC criteria.

RESULTS

A sample of 277 (168 male and 109 female) diabetes mellitus patients, who were attending regular follow up taking the oral and injectable insulin treatment at Ayder referral hospital during February 2011 to January 2014 were included in this study. Of the 277 patients under follow up at Ayder referral hospital, 42.6% have developed microvascular complications. Seventy one (25.6%) patients have developed only one type of complication, while in 35 (12.6%) and 12 (4.33%) of the patients any two and all the three complications respectively coexisted. Regarding the place of residence, 125 (45.1%) were from rural and the rest 152 (54.9%) were from the urban areas. One hundred and sixty two (58.5%) patients were taking the injectable insulin treatment while 115 (41.5%) were taking the oral treatment. Out of the 162 patients who were taking the injectable insulin treatment, 117 (72.2%) were type 1 and the rest 45 (27.8%) were type 2 diabetes mellitus patients. Females were more susceptible to develop the complication (Table 1).

Table1. The distribution of important socio-demographic and clinical characteristics of diabetes mellitus patients treated at Ayder referral hospital, Ethiopia (2011-2014).

Variables	Category	Censored	Complication (%)	total
Sex	Male	104	64(38.1)	168
	Female	55	54(49.5)	109
Residence	Rural	35	90(72)	125
	Urban	124	28(18.4)	152
HIV	No	159	116(42.2)	275
	Yes	0	2(100)	2
Foot Ulcer	No	156	85(35.3)	241
	Yes	3	33(91.7)	36
Feeding	Sugar free	119	32(21.2)	151
	Salt free	22	31(58.5)	53
	Both sugar & salt free	18	55(75.3)	73
Albumen	Negative	156	53(25.4)	209
	Positive	3	65(95.6)	68
Ketone	Negative	159	53(25)	212
	Positive	0	65(100)	65
Diabetes type	Type I	109	12(9.9)	121
	Type II	50	106(67.9)	156
Hypertension	No	154	59(27.7)	213
	Yes	5	59(92.2)	64
Treatment	Injectable insulin	119	43(26.5)	162
	Oral tablet	40	75(65.2)	115
TB	No	150	111(42.5)	261
	Yes	9	7(43.8)	16
Parastosis	No	146	109(42.4)	255
	Yes	13	9(40.9)	22
Pneumonia	No	149	108(42.1)	257
	Yes	10	10(50)	20

The continuous variables age, BMI, SBP and FBS are described using different summary measures (Table 2). The median age of the patients was 40 years with minimum of 4 years and maximum of 85 years. The median body mass index of the patients was 21.26 with interquartile range of 4.9.

The diabetes mellitus patients were followed up for a median time of 425 days with the minimum follow up time of 1 day and maximum follow up time of 1095 days. The overall estimated mean survival time was 462.6 days.

The simplest and informative way to compare the survival times obtained from different groups of individuals is to plot the corresponding estimates of the two survivor functions on the same axis. The estimates of the Kaplan-Meier survival functions of DM patients for different categories of the study variables are displayed using different graphs (Figure 1).

Table 2. Summary statistics of continuous variables included in the study of diabetes mellitus patients at Ayder referral hospital, Ethiopia (2011-2014).

Variable	Mean	Std. Dev	Min	Max	Median	IQR
Age	39.92	16.43	4	85	40	27
Body mass index (BMI)	21.25	3.78	12.82	38.73	21.26	4.91
Systolic blood pressure (SBP)	119.45	20.33	80	190	120	20
Fasting blood sugar (FBS)	154.11	66.00	67	424	122	79

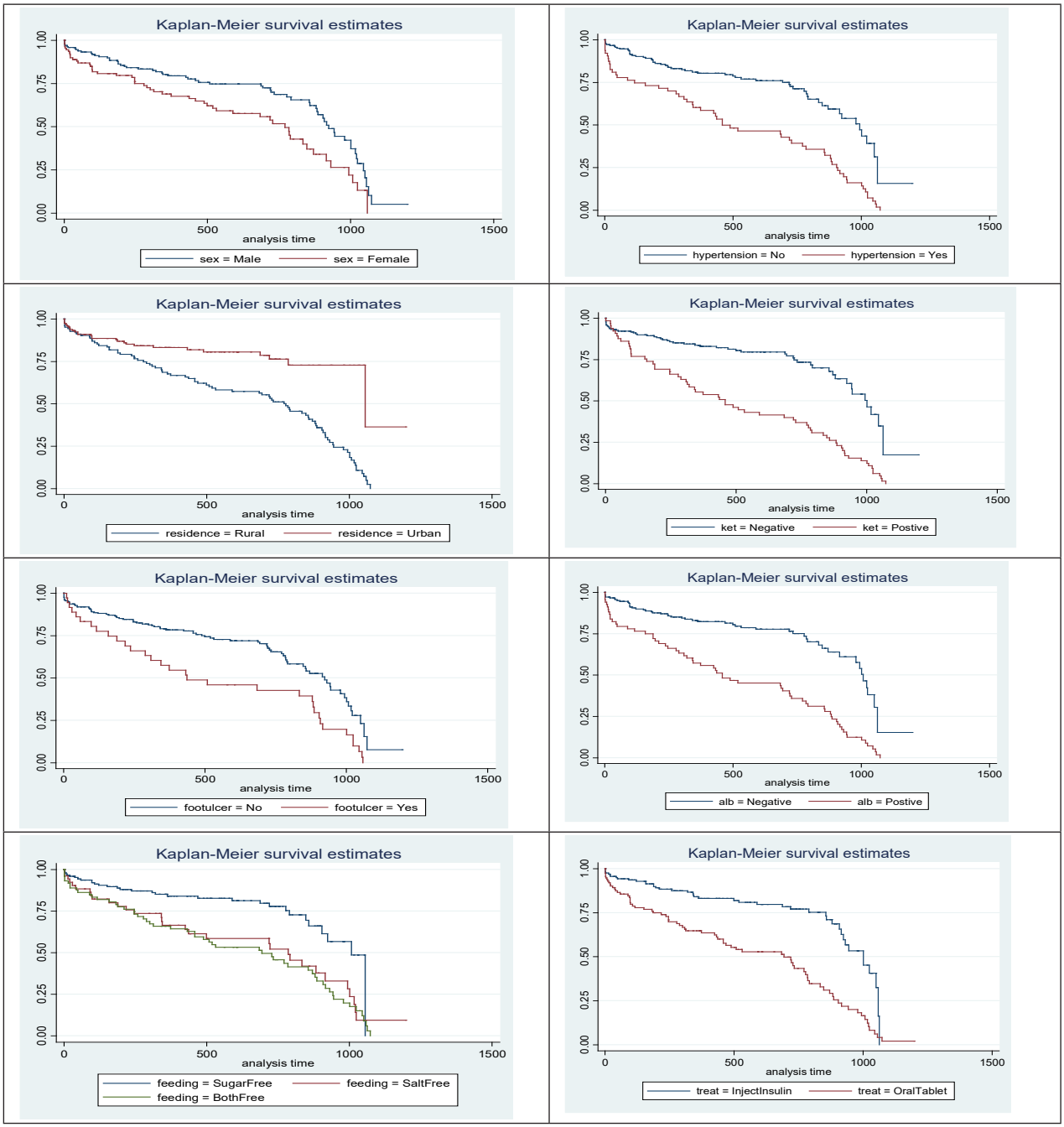

Figure 1. Kaplan-Meier survival estimates of different groups of diabetes mellitus patients at Ayder referral hospital, Ethiopia.

The plot of the survivor functions of the different groups gives only an idea as to how the survival experiences of the groups may be compared. The log-rank test for the equality of survivor functions among different groups of patients is a formal test of the differences. The results of this test show that there was significant difference in survival experience of the categories of sex, residence, foot ulcer, feeding habit, albumin level, ketone level, diabetes type, hypertension and treatment, whereas the survival experience of patients do not differ significantly in the variables TB, HIV/AIDS, parasitosis and pneumonia (Table 3).

Table 3. Results of the Log-rank test for the significant categorical variables of diabetes mellitus patients treated at Ayder referral Hospital, Tigrai, Ethiopia. (2011-2014).

Variables	Status	Observed (n)	Expected	Pr>chi2	Chi-square
Sex	Male	64	79	0.0030	8.80
	Female	54	39		
Residence	Rural	90	64	0.0000	23.32
	Urban	28	54		
Foot Ulcer	No	85	99	0.0006	11.70
	Yes	33	19		
Feeding	Sugar free	32	56	0.0001	20.65
	Salt free	31	24		
	Both sugar & salt free	55	38		
Alb	Negative	53	84	0.0000	40.49
	Positive	65	34		
Ket	Negative	53	84	0.0000	39.54
	Positive	65	34		
Diabetes type	Type 1	12	51	0.0000	52.41
	Type 2	106	67		
Hypertension	No	59	85	0.0000	28.87
	Yes	59	33		
Treatment	Injectable insulin	43	71	0.0000	29.39
	Oral tablet	75	47		
	Yes	10	9		
Total		118	118		

To select the variables associated with the survival time to the occurrence of complications, a univariable analysis was first conducted at the 0.20 level of significance. Variables significant at this level were then included in the multivariable analysis. The four variables age, sex, fasting blood sugar (FBS) and diabetes type, which were significant in the multivariate analysis were then included in the final main effects model. The Cox proportional hazards model and different parametric models were fitted and compared as to which model best fits the data. As can be seen from Table 4 below, the Weibull model having the smallest values of AIC and BIC was the best model to fit the given data. Following this, all two and three way interaction terms were checked for their importance in predicting the time to microvascular complications. However, none of them had significant contribution. Interpretations and conclusions will thus be based on the Weibull model. However, as it was intended to use parametric and non parametric models for the analysis, the Cox proportional hazards model with Breslow method for the treatment of tied observations, was also fitted.

Table 4. AIC and BIC values for the different models proposed for the data on microvascular complications of diabetic patients at Ayder referral hospital, February 2011- January, 2014.

	Model				
	Cox PH model	Exponential	Weibull	Log logistic	Lognormal
Log likelihood	-490.71664	-266.6302	-264.69076	-275.64479	-283.07628
AIC (smallest better)	27.39173	26.17173	26.15712	26.23823	26.29143
BIC (smallest better)	40.51182	39.29181	39.27721	39.35831	39.41152

The scale parameter of the Weibull distribution was found to be γ=0.824 with a standard error of 0.061 and 95% C.I. [0.70444, 0.94356]. This interval does not include γ=1.0 suggesting that the Weibull model is more appropriate than the exponential model. Since γ=0.824 which is less than 1, the hazard of developing complications decrease as survival time increases.

Table 5. Multivariable Cox proportional hazards regression analysis of microvascular complications of diabetic patients at Ayder referral hospital, February 2011- January, 2014.

Variable	Hazard Ratio	Std. Err.	Z	D.F.	P>|z|	95.0% CI	
						Lower	Upper
Age	1.024	.0092	2.69	1	.007	1.007	1.042
Sex (Female)	1.856	.3582	3.21	1	.001	1.27	0.786
FBS	1.005	.0014	3.42	1	.001	1.002	1.008
Diabetes type (Type II)	2.356	.8815	2.29	1	.022	1.131	4.905

Table 5. Multivariable Weibull proportional hazards regression Analysis of microvascular complications of diabetic patients at Ayder referral hospital, February 2011- January, 2014.

Variable	Hazard Ratio	Std. Err.	Z	D.F.	P>|z|	95.0% CI	
						Lower	Upper
Age	1.025	.0087	2.94	1	.003	1.008	1.043
Sex (Female)	1.531	.2852	2.29	1	.022	1.063	2.206
FBS	1.006	.0014	4.21	1	.000	1.003	1.008
Diabetes type (Type II)	2.320	.86o4	2.27	1	.023	1.121	4.799
Constant	.00011	.00006	-15.49	1	.000	.00004	.0004

Before interpreting the results it is important to assess the adequacy of the fitted model in terms the appropriateness of the Weibull model and the validity of the proportionality assumption. The value of the likelihood ratio statistic for the model was 113.91 (p=0.0000) indicating overall significance of the model. Figure 2 shows the plot of *log[-log(survival probability)]* versus log of survival time for the two groups of DM patients and the two categories of sex. It can be observed that in both plots the two lines are approximately straight indicating that the Weibull model is plausible for the data. Moreover the two lines are nearly parallel which means that the proportional hazards assumption is valid.

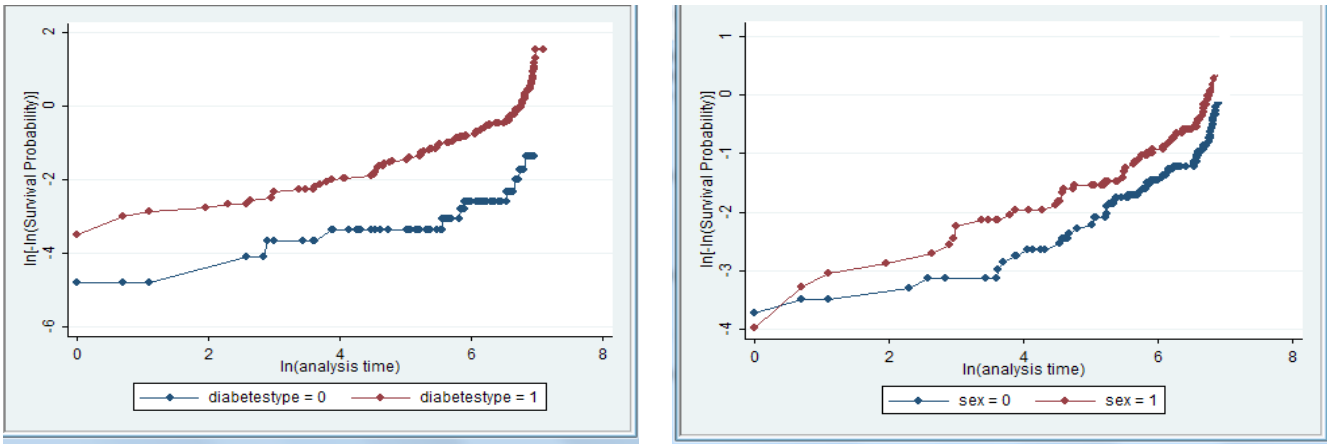

Figure 2. Graphical evaluation of Weibull model and proportional hazards assumption using the plot of ln (-ln(S (t))) versus ln (t).

The assumption of proportionality was also assessed graphically by plotting the scaled Schoenfeld residuals of each covariate against time. Figures 3 shows the plots of scaled Schoenfeld residuals of each covariate in the model against survival times along with the LOESS smoothed curves. The residuals are more or less random and LOESS smoothed curves have basically zero slope which is an indication that there is no evidence of non-proportionality. The interaction of covariates with time was also checked. The conclusion is that all of the time-dependent interaction variables are not significant either collectively or individually thus supporting the assumption of proportional hazards.

The global test of proportional-hazards assumption based on the Schoenfeld residuals also gives a chi-square value of 2.86 with 4 degrees of freedom (p=0.5818) indicating validity of assumption of proportional hazards.

The results of multivariable analysis showed that age of a patient at the start of follow up is significantly associated with the development of microvascular complication (HR=1.025, 95% CI: 1.008-1.043, p=0.003). Since the estimated hazard ratio is greater than unity, other factors being fixed, the higher the age of a patient, the greater the hazard of developing complication at any given time. In particular, an increase of one year of age of a patient increases the hazard of developing complication by 2.5%. The 95% CI indicates that the hazard ratio could be as low as 1.008 or as large as 1.043.

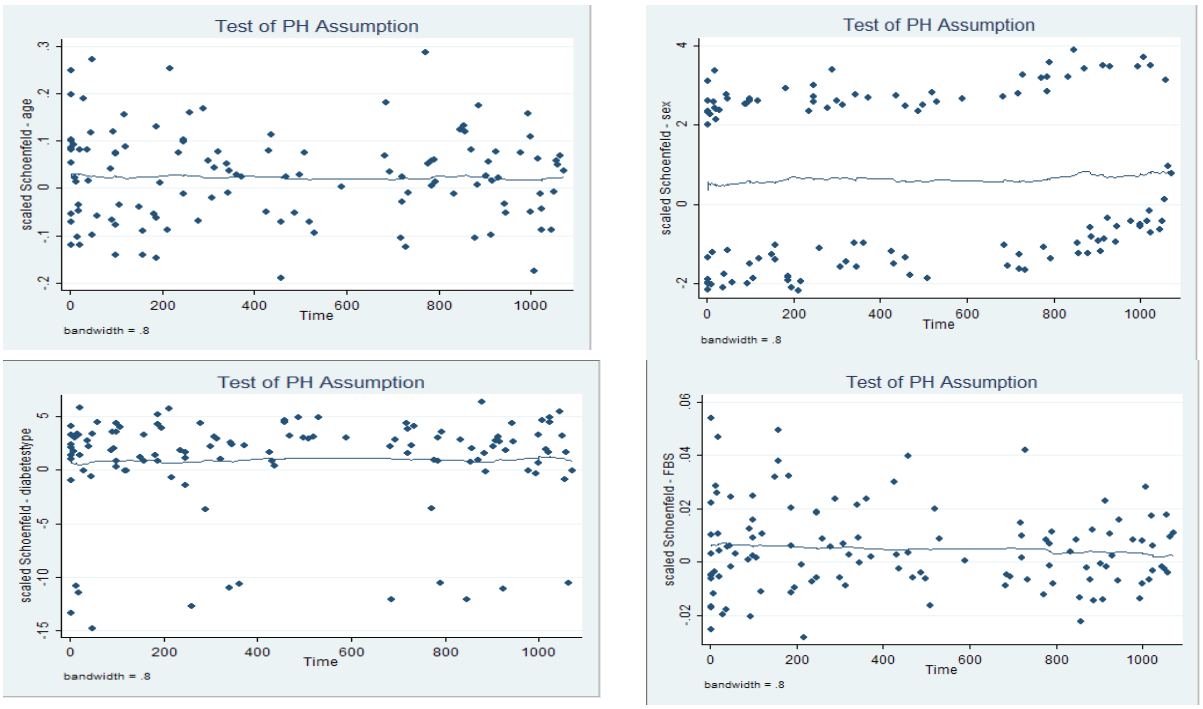

Figure 3. Graphs of scaled Schoenfeld residuals of the covariates in the model.

Sex of the patients was also a significant factor in determining the development of microvascular complication of diabetes mellitus patients (HR=1.531, 95% CI: 1.063-2.206, p=0.022). Being female posed an increased risk which is 53% higher than male patients for developing microvascular complications. The 95% confidence interval suggests that the risk of development of microvascular complication for females is as low as 1.063 times and as large as 2.206 times compared to males after adjusting for other variables in the model.

The risk of microvascular complication was also significantly associated with higher level of fasting blood sugar. Other factors being fixed, patients with higher fasting blood glucose had higher risk of developing complications (HR=1.006, 95% CI: 1.003-1.008, p=0.000). That means the hazard of developing complications increase by 10.06 when the fasting blood glucose increases by 10mg/dl. When compared with patients with type 1 diabetes mellitus, patients with type 2 diabetes mellitus had higher risk of developing microvascular complications. The estimated hazard of the developing complication for patients with type 2 diabetes mellitus was 2.32 times that of type 1 patients (95% CI: 1.121-4.799, p=0.023).

DISCUSSION

Diabetes mellitus represents one of the most detrimental diseases and significant public health problems due its increasingly high incidence and prevalence as well as high risk of macro- and microvascular complications. This three years retrospective follow up study gives insights into the covariates that are significantly associated with the time to the development of microvascular complications of diabetes mellitus. The data was obtained from a follow-up study of diabetes

mellitus patients at Ayder referral hospital, Mekelle, Ethiopia. The significant predictors for higher risk of microvascular complication for diabetes mellitus patients were found to be the patients' age, gender, the level of fasting blood sugar (FBS) and diabetes type.

In this study it was found that older age was positively associated with the higher risk of developing any or all of the three microvascular complications. This finding is consistent with the large evidence base showing that the risk of developing these complications is positively associated with older age. A study conducted in Tikur Anbesa specialized hospital, Ethiopia, by Kalayou Kidanu Berhe *et al*. (2012) and another study conducted in 28 countries across four continents (Asia, Africa, Europe and South America) by Litwak *et al*. (2013) and several other works in different parts of the world are in line with this finding (Tesfaye *et al*. 1996; Wändell 1999; Moore *et al*., 2009; Bansal *et al*., 2014; Svensson *et al*., 2015). This is a reasonable finding, because age itself may be an independent risk factor as aging is associated with decline in fat oxidation and insulin resistance or may have other risk factors related to aging or exposure to risk factors during their lifetime.

Another important risk factor for the development of microvascular complications in patients with type-1 and type-2 diabetes is the level of fasting blood sugar. Glucose is the driving force in microvascular complications of diabetes (Reusch, 2003). Patients with higher fasting blood sugar had higher risk of developing complications. Findings from other studies also support that higher blood glucose is related to microvascular complications (Klien, 1995; Cade, 2008; Group, 1998; Cardoso and Salles 2008; Nazimek-Siewniak *et al*., 2002; Ali *et al*., 2013; Glycemic control is the primary mediator of diabetic microvascular complications. Therefore improved blood glucose control decreases the progression of diabetic microvascular disease (Ali *et al*., 2013).

Sex of the patient was also found to be a significant factor for the development of microvascular complication of diabetes mellitus patients. It was found in this study that female patients have more risk of developing all the three complications than males. This is supported by a similar study conducted in middle-east and North Africa (Zabetian *et al*., 2013) and India (Brasad and Robinson, 1995). Some other studies reported the associations between sex of a patient and specific complications. In this regard Margaret *et al.* (2015) reported that women had an increased risk of incident CKD compared with men after adjustment for other variables. This may be because mothers are family caretakers and hence may have high chance of exposures and less resistance to infections. In another study in India, Bansal *et al.* (2014) reported that being male posed high risk for nephropathy. Additional work is needed to determine if these sex differences contribute to worse outcomes in women with diabetes.

Diabetes type of the patients (type 1 and type 2) was found to be strongly associated with development of microvascular complication in this study. Many other studies also support that the type 2 diabetes mellitus patients are more likely to develop the microvascular complications than type 1 diabetes mellitus patients (Brassrad and Robinson, 1995; Herman *et al*., 1998).

Many research findings across the globe have reported that any increase in body mass index (BMI) above normal weight levels is positively

associated with an increased risk of being diagnosed as having complications of diabetes mellitus (Wändell, 1999; Moore *et al*. 2009; Zoppini *et al*., 2012; Litwak *et al*., 2013; Gray *et al*., 2015). However this study found no significant association between BMI and the risk of development of microvascular complication of diabetes mellitus patients. One possible explanation for this surprising result may be the study design. Because this was as a retrospective follow-up study, all patient data could not be fully retrieved and hence some important variables that may have interactions with BMI were not recorded. In addition to this, for this study, the values of the covariates were recorded at baseline values, while repeated measurements should have been taken and analyzed. Another possibility may be the existing diagnostic facilities at the Ayder referral hospital.

CONCLUSION

The present study was aimed to determine the mean survival time and identify the risk factors that are significantly associated with the risk of development of microvascular complications in diabetes mellitus patients under follow up at Ayder referral hospital, Mekelle, Ethiopia, using the method of survival analysis. The mean and median survival times were 462.6 (95% C.I= 421.8-503.5) days and 425 (95% C.I. 350.1-501) days. The results of the multivariable Weibull proportional hazards regression model showed that age, sex, fasting blood glucose level and diabetes type were significant determinants of the time to the development of microvascular complications of diabetes mellitus patients. The results suggest strongly that to minimize the risk of diabetic complications it is necessary to treat blood glucose aggressively.

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