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Factors Affecting Time to Return to a Normal Level of Hba1c Among Diabetes Mellitus Patients at Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia

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Abstract

Background: This study aims to fill the information gap on factors affecting time to return to normal HbA1c level and expected survival times in Ethiopia, as studies on these aspects are scarce, particularly in diabetic patients.

Methods: A cross-sectional study was conducted on the patients with Diabetes Mellitus who follow-up the diabetic clinic at HUCSH, Ethiopia, between May to July 2021. The 382 diabetic patients were recruited into the study using simple random sampling techniques from the recorded frame of the hospital and were interviewed using structured interview schedule. The Cox regression analysis is applied on time to time to return normal HbA1c level. Data were entered, using EPI – info and analyzed by using STATA 16 computer software.

Result: Diabetic patient expected survival times to return normal HbA1c had an average of 52.678 weeks with a standard error of 0.144. HbA1c level return to normal on patients of age below 18 year-old is reduced by 91.7% as compared to those who are older than 54 years. Similarly, the recovery time of patients in the age groups 18-36 year and 36-54 year is reduced by 44.1% and 55.6%, respectively compared to patients of age above 54 year-old. Moreover, when compared to patients with no medication side effects and patients with nausea/vomiting, headache, fatigue, and stomach upset have 43.8%, 57.3%, 44.1%, and 64.3% longer time to return to normal HbA1c level. Additionally, patient with low adherence level of patients were increased by 47.8 % time to return to normal HbA1c level compared to high adherence.

Conclusion: It is advisable for clinicians that special consideration should be given for diabetic patients with medication-related side effects, elderly patients, and for poor treatment adherence diabetic patient.

Keywords: Cox regression model; Diabetes Patient; Glycemic control; HbA1c; Ethiopia

Abbreviations: HbA1c- Glycated Hemoglobin A1c; DM- Diabetes Mellitus; and OHA- Oral Hypoglycemic Agents

Background

Diabetes mellitus (DM) is a metabolic disorder brought on by either decreased insulin sensitivity, insufficient production of insulin by pancreatic beta cells, or both [1]. It classified based on the cause in to two as Type 1 diabetes (DM1), which is brought on by insufficient or decreased insulin production, and type 2 diabetes (DM2), which is typically diagnosed in adulthood and is carried on by impaired insulin sensitivity [2]. The main symptom of diabetes is hyperglycemia; Hyperglycemia, is a condition in which blood glucose levels are unusually high, is the primary sign of diabetes [1].

Currently around 300 million people are living with diabetes; in each year, the number increases by seven million. This number projected to be 438 million by 2030 which means 7.8% of the adult population [3]. Globally diabetes killed nearly 10,000 people per day. It is constitute 6.8% of deaths from all causes [4]. In 2013 diabetes has killed 4.6 million people [5]. More than 77 % of morbidity [6] and 88 % of mortality [7] due to DM occur in low and middle-income countries. Moreover, diabetes accounts for large annual healthcare expenditures globally. In 2021 alone around 13 billion USD was spent on healthcare for people with diabetes in Africa [8].

As well, complications resulting from diabetes also further contribute to annual expenditures approximately 88 million disability in occupational settings [9]. Likewise, diabetes presents during the peak income earning period in individual's life, those affected individuals are main source of income of their families. This shown despite its tremendous effect on health expenditure, morbidity and mortality little concern had given in comparison to HIV/AIDS [4].

Diabetes used to be considered a rare condition in Sub-Saharan Africa. However, in 2010 only above 12 million people were living with diabetes, and the condition was expected to be responsible for a death of 330,000 people. In addition, the prevalence of diabetes is rising quickly due to a number of reasons: aging, expanding population, fast urbanization and its accompanying [4]. Surprisingly, compared the rest region of the world the rate of diabetics in Sub-Saharan Africa will be the highest in the next 20 years; by 2030, the projection from 2010 was expected to nearly double, reaching 23.9 million[4]. Ethiopia is one of the most impacted country by diabetes among sub-Saharan countries. The number of cases was estimated to be 800,000 in 2000 and projected to 1.8 million by 2030 [10]. About 21,000 deaths in Ethiopia were attributed to diabetes in 2007 [3].

HbA1c level is important indicator for glycemic control in diabetic patient. The higher the HbA1c or above 7% associated with the higher risk complications. Variety of research findings had shown that poor glycemic control of DM leads to micro vascular and macro vascular complications [11]. However, lowering HbA1c concentrations by tight glycemic control significantly reduces the rate of progression of micro vascular complications [11, 12].

Thus, for provision of standard care for the diabetic patients, objective information regarding the factor affecting time to return normal HbA1c level is needed. However, studies on the assessment of factor affecting time to return normal HbA1c level and expected survival times to return normal HbA1c in Ethiopia are very scarce. Therefore, the finding of this study will fill the information gap about affecting time to return normal HbA1c level and expected survival times to return normal HbA1c in diabetic patients as a point of care testing. In addition, it will assist to improve for development and evaluation of health plans for diabetic patients in order to decrease the time needed return to normal HbA1c level.

Methods

Study Area and Period

The study was conducted at Hawassa University Comprehensive specialized Hospital (HUCSH) located in Sidama region. Sidama region is located at the southern part of Ethiopia. Hawassa is the capital city of Sidama region, located 273 km to the south

of Addis Ababa. Based on reports from the Central Statistical Agency of Ethiopia, Hawassa city has an estimated total population of 159,013 out of which 81,984 are male and 77,029 female. The data collection for this study was conducted between May and July 2021 for diabetic patient has follow up starting from March 2008 to November 2021 at HUCSH.

Study Design and Target Population

Institutional based cross sectional study was conducted. The target population for the study is patients under the diabetes follow up from March 2008 to November 2021 at HUCSH.

Inclusion and Exclusion Criteria

The study considered all diabetes patients under ADT who have been on anti-diabetic medications for at least three months at HUCSH. The study excluded individuals refused to participate in the study.

Sample Size Determination and Sampling Technique

The sample size was determined using cochran formula [13]. By considering the N=900 diabetic patient, non-response rate of 5%, degree of precision 0.03 and a study conducted at Jimma University [14] indicated that the proportion of non-adherent patients is 17.3%. Final calculated sample size for study were 382. Study participants were included using a simple random sampling method.

Data Source

Data were collected by reviewing medical cards/charts and interviews using structured questionnaire. The structured questionnaire was developed from different published articles. Structure questioned used to collected demographic and clinical data of diabetic patients during their follow-up time. The secondary data of the study were collected from the patients' medical records**.** Data were collected by four nurse and supervised by one Medical surgical specialist Nurse working at Hawassa University College of Medicine and Health Science.

Data Quality Assurance

Data quality was assured by developing structured questioner in English based on objective of the study. A one-day training was given for data collectors and supervisor. Collected data were checked by supervisor and principal investigator every day for its completeness. The checklists were pretested by reviewing charts and interviewing 38 of diabetic patient has follow up at Adare Primary Hospital. The final pretested checklist was used for data collection.

Study Variables

Dependent Variable

In this study, the response (event) variable was return to normal HbA1c level.

Independent Variables

Independent variables were: age, religion, employment status, marital status, ethnicity, housing, monthly income, diabetes type, medication burden, side effects, type of ADT drugs, length of treatment, and patient adherence level.

Operational of Definitions

Return to normal HbA1c: Considered for diabetic patient blood plasma level HbA1c level than 7% was used.

Medication Burden: Multiple medicines routines for non-communicable diseases can be burdensome to patients and this burden is influenced by numerous factors such as medication regimens, formulations, side effects, experiences with healthcare, and social burden (15). Thus, in this study medication burden is classified based on the type of medication taken by diabetic patient.

Adherence classification: To measure adherence level as high, medium and low for the study**,** a multi-method tool approach has been adopted as the world health organization recommendations and was administered for the first time to patients in routine follow-up care at two South African hospitals for ART [16].

Data analysis

Data collected from the medical records and interviews were coded and entered to epi info version 3.5.1 software and exported to STATA 16 for analysis. An event in this study is defined as the first time following the start of treatment normal or less than 7% of blood plasma of in HbA1c. Collett D. [17] recommended doing a single covariate analysis first to screen to select potentially significant variables for consideration in the multi-covariate model. Thus, our study's model building started with a single covariate analysis based on Collett D. All variables that were significant at the 25% level were included in multivariable analysis model. The stepwise statistical method was used to identify the independent variable affects time to return normal HbA1c level. Using forward variable selection method variables were added successively (the most significant at each step) until add variable statistically insignificant.

Lastly, for statistical significant variables counted in the multivariate model were verified by different model fitness assessment techniques. The assumption of the proportional hazards model is evaluated using formal tests. Additionally, proportional hazards evaluated by plots of cumulative hazard functions against time for each of the model covariates [18, 19]. Furthermore, model fitness and assumptions for Cox regression models was checked by martingale residuals. A martingale residuals plot can be used to check linearity with respect to the covariate values. If there is no visible pattern in the plot or the smoothed curve is almost horizontal through the origin, the covariate is roughly linear. Our finding fulfill the mention assumptions of model fitness tests (detail of model fitness test result is available on supplementary file).

Ethical Consideration

The study was approved by College of Natural and Computational Sciences Research Ethics Review Committee (RERC) of Hawassa University (RERC/005/21). All participants provided written informed consent. All methods were performed following the relevant guidelines and regulations expressed in the Declaration of Helsinki.

Results

Socio-Demographic Characteristics Study Participants

Nearly half 188 (51.65%) of the study participants were male. Majority of study participants were in age range of 37-54 year-old 174 (47.80%); 156 (42.6%) of participants were government employees and 164 (45.05%) were married. Moreover, one hundred twenty nine (35.4%) of diabetic patients were educated primary or secondary school (Table 1).

Table 1: Socio-demographic characteristics of study participant patients at Hawassa University Comprehensive specialized Hospital, July 2021

Variables		Frequency	Percentage (%)
Sex	Male	188	51.65
	Female	176	48.35
Age (in years)	< 18	52	14.30
	18-36	99	27.20
	37- 54	174	47.80
	> 54	39	10.70
Religion	Orthodox	105	28.85
	Catholic	130	35.70
	Muslim	71	19.5
	Protestant	38	10.40
	Others	20	5.50
Marital status	Never	129	35.40
	Married	164	45.05
	Divorced	46	12.60
	Widowed	25	6.87%
Ethnicity	Amhara	113	31.04
	Oromo	55	15.11%
	Sidama	90	24.72%
	Wolyta	66	18.13%
	Others	40	11.00%
Education level	No formal education	48	13.20
	Basic education	85	23.40
	Primary or secondary school	129	35.40
	Certificate & above	102	28.00
Employment status	Government employee	156	42.86
	Self-employee	121	33.24
	Unemployed	87	23.90
Housing status	Own	116	31.90
	Rent	191	52.50
	Other	57	15.66
Income per monthin ETB	<500	83	22.80
	500-1500	154	42.30
	1501-2500	100	27.50

	>2500	27	7.40
Family support	Yes	216	59.34
	No	148	40.66

Clinical Characteristics of Study Participants

Three hundred fourteen study participants were type-II diabetic patients. And, 142 (39%) and 86 (23.6%) were head ache and fatigue complain respectively. Majority 124 (34.05%) diabetic patients had high level adherence. Similarly, 122 (33.52%) study participants were on two types of hypoglycemic agent and 163 (44.8%) diabetic patient were on oral hypoglycemic agent (Table 2).

Table 2: Clinical characteristics of study participants at Hawassa University Comprehensive Specialized Hospital, July 2021

Variables		Frequency	Percentage (%)
Diabetes type	Type I	50	13.70
	Type II	314	86.30
Side effect	Nausea and vomiting	41	11.11
	Headache	86	23.60
	Fatigue	142	39.00
	Stomach upset	28	7.70
	Others	30	8.20
	No side effects	37	10.16
Status of Adherence Level	Low	93	25.55
	Moderate	124	34.05
	High	147	40.40
Medication burden	1	156	42.86
	2	122	33.52
	>=3	86	23.63
ADT in use	Oral hypoglycemic agent	163	44.80
	Both (Insulin + OHA)	76	20.88
	Insulin alone	125	34.30
YearsonADT(Treatment duration)	< 1 year	63	17.31
	1-2 years	108	29.67
	2-5 years	184	50.55
	≥ 5years	9	2.50

Non-parametric survival analysis

Kaplan-Meier Estimate of Time to Return Normal Hemoglobin Ac1 Level

The patients undergoing ADT had their time for HbA1c level return to normal value using techniques of survival analysis.

And, the association between the covariate variables with the dependent variable time to HbA1c level return to normal was examined using the Cox proportional hazard model. From the total sample size 364; 80 (22%) diabetic patient the period to return normal level of HbA1c was not monitored and considered as censored. Whereas, two hundred eighty four (78%) diabetic patient of observed incidents are listed below. Diabetic patient expected survival times to return normal HbA1c had an average of 52.678 weeks with a standard error of 0.144.

The Kaplan-Meier method involves tracking the fates of individuals over time and estimating how long it takes for an event to occur (20). Survival curves show, for each time point plotted on the X-axis, the portion of all individuals surviving on the y-axis. Plots of the Kaplan-Meier estimation is applied to estimate survival curves and compare the survival (return normal HbA1c) times of diabetes patients based on their levels of adherence using the log-rank test is presented in figure 1. The Kaplan-Meier survival curve shown that the higher the adherence, the faster their recovery to normal value.

Univariate and Multivariate Analysis of the Covariates

The Cox proportional hazards model was utilized to calculate the regression coefficients. From the Cox proportional hazards model; age, ethnicity, housing, monthly income, medication burden, side effects, years on medication, level of adherence, and use of ADT drugs were significantly associated with treatment success at 25% level of significance (Tabe-1). Then, all significant covariates were included in the multivariable analysis. Covariates which were insignificant in the multivariate analysis were removed from the model by using forward stepwise (likelihood ratio) variable selection method. Finally, ethnicity, housing status, monthly income, medication burden, ADT drug use, and years on ADT, were excluded. And, the final model kept the main effect of the covariates were age, side effects, and level of adherence (Table 3).

Table 3 shown HbA1c level return to normal on patients of age below 18 years is reduced by 91.7% as compared to those who are older than 54 years. Similarly, the recovery time of patients in the age groups 18-36 year and 36-54 year is reduced by 44.1% and 55.6%, respectively compared to patients of age above 54 year-old. Moreover, the presence of side effects was significantly associated with the time to return to normal HbA1c of patients. When compared to patients with no medication side effects and patients with nausea/vomiting, headache, fatigue, and stomach upset have 43.8%, 57.3%, 44.1%, and 64.3% longer time to return to normal HbA1c level. Additionally, patient with low adherence level of patients were increased by 47.8

% time to return to normal HbA1c level compared to high adherence.

Table 3: Univariate analysis of variables for diabetic patients at Hawassa University Comprehensive Specialized Hospital, July 2021

Effect	Wald Chi-Square	P-value
Age	6.9896	0.0722
Marital status	1.1199	0.7723
Employment status	0.7837	0.6758
Ethnicity	5.9413	0.2036
Religion	1.7596	0.7799
Housing status	2.8168	0.2445
Income	4.3800	0.2232
Medication burden	7.1367	0.0282
Diabetes type	0.9377	0.3329

Family support	0.6950	0.4045
Side effect type	14.9760	0.0105
ADT in use	3.2796	0.1940
Treatment duration	5.6040	0.1326
Adherence level	22.5033	<.0001

Table 4: Multivariate analysis of diabetic patients at Hawassa University Comprehensive Specialized Hospital, July 2021

Variable	Estimate	Stan. Error	Wald Chi- Square	P-value	Hazard ratio	95% CI
Age group						
<18 year-old	0.65081	0.20655	9.9283	0.0016	1.917	(1.279, 2.874)
18-36 year-old	0.36545	0.18048	4.1000	0.0429	1.441	(1.012, 2.053)
36-54 year-old	0.44180	0.17317	6.5089	0.0107	1.556	(1.108, 2.184)
>54 year-old	1	1	1			
Side effect types						
Nausea/vomiting	-0.57607	0.25009	5.3058	0.0213	0.562	(0.344, 0.918)
Headache	-0.85088	0.21939	15.0420	0.0001	0.427	(0.278, 0.656)
Fatigue	-0.58128	0.19859	8.5672	0.0034	0.559	(0.379, 0.825)
Stomach upset	-1.02904	0.30432	11.4340	0.0007	0.357	(0.197, 0.649)
Other s/effects	-0.95213	0.27989	11.5724	0.0007	0.386	(0.223, 0.668)
No side effects	1	1	1			
Adherence level						
Low	-0.73890	0.15604	22.4227	<.0001	0.478	(0.352, 0.649)
Moderate	-0.40019	0.14287	7.8457	0.0051	0.670	(0.507, 0.887)
High	1	1	1			

Discussion

A total of 364 diabetic patients were included in the trial; 284 (78.02%) of these patients' HbA1c levels returned to normal, and 80 (21.98%) of these patients were censored because their HbA1c levels were not tracked or monitored and considered as censored. At Hawassa University Comprehensive Specialty Hospital, the overall median time to reach a normal HbA1c level for diabetic patients was 52.678 weeks, with a standard error of 0.144. Patients with diabetes who are younger than 54 year-old, complain a side effects of the drugs, low and moderate adherence level of drugs significantly associated with time to return normal HbA1c level.

Diabetes is estimated to be responsible for 3.96 million adult deaths per year at global level [21] and it has significant associated morbidity and mortality. Patients with diabetes have a 2 to 4 fold increase in the risk of both cardiovascular and cerebrovascular disease, resulting in an increased mortality rate among patients with diabetes compared to the general population [22]. Therefore, glycemic control is essential in diabetes management [23].

Looking at the effect of age after controlling for other confounding factors, patients under the age of 18 have a 91.7% shorter

time to return to a normal HbA1c level than patients over the age of 54. Similar to this, patients between the ages of 18 and 36 and 36 and 54 recover faster than those over the age of 54, with reductions of 44.1% and 55.6%, respectively. Likewise, similar finding were seen in study conducted Ethiopia [24], India [25] , England [26], and France [27], advanced diabetic age is associated with poor glycemic control result.

For diabetic patients, the length of time it takes to return to a normal HbA1c is highly correlated with the presence of side effects. When compared to individuals who did not experience any drug side effects, diabetic patients who experienced nausea/vomiting, headache, fatigue, and stomach upset took longer to return to a normal HbA1c by 43.8%, 57.3%, 44.1%, and 64.3%, respectively. This result is consistent with research conducted at Louisiana State University [28]. Thus, early management of the side effects or complains is advisable.

As comparison to patients who are highly adherent to treatment, the time to normal HbA1 is increased by 52.2% and 33%, respectively, in low- and moderate-adherence patients. Likewise, a study carried out at the University of Gondar Referral Hospital in Ethiopia found that patients with poor adherence had poor glycemic control [29]. Moreover, investigations from the Asian and Western worlds; Jordan [30], Malaysia [31], Virginia America [32], and France [27] revealed that a simillar conclusions.

Moreover, studies reveal that a significant barrier to adequate glycemic control for many diabetic patient is still low medication adherence. Glycemic control improvements in healthcare are linked to higher compliance [33]. Adherence may be impacted by the difficulty of managing many medications, a diminished sense of urgency brought on by asymptomatic illnesses in Type 2 DM patients, traditional beliefs in rural communities, and their comprehension of their disease status. Studies have also revealed that DM patients who frequently attend clinic appointments and receive regular counseling are more likely to stick to their treatment regimens [34, 35]. Continuous education is important in motivating patients to cultivate healthy lifestyles and maintain good treatment adherence [30, 36]. Patient motivation to adopt healthy lifestyles and maintain good treatment compliance requires ongoing education [37]. Lastly, income, family support diabetic type were not associated with time to return with HbA1c.

Limitation

The data were extracted from medical records, with variations in the level of completeness of documentation of the demographic and medical parameters affecting the time to return a normal HbA1c. Additionally, important covariates like the extent of body mass index, blood pressure, alcohol intake, and cholesterol level were not included in the study.

Conclusion

The Cox regression analysis revealed diabetic patients' time to return normal HbA1c level were affected by their age, medication side effects, and level of adherence. Diabetic patients who are older than 54-year-old, and experience medication-related side effects take a longer time to return to normal HbA1c level. However, patients who had high adherence to their treatment regimen were a short time to return to normal HbA1c level. Therefore, we advised clinicians that special consideration should be given to diabetic patients with medication-related side effects, elderly patients, and poor treatment adherence.

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Consent to Publish

Not applicable

Data Availability

The datasets used in this study are available from the authors upon reasonable request

Funding

No funding was used in this study

Conflict of Interests

No conflict of interest to declare

Authors' Contribution

Melisew Wuchew: designed and conceived the study, supervised the data collection, perform the analysis and write the first draft of the manuscript. H.M., M.W.W., A.A.Y., and S.F.M assisted the data collection and analysis, critically revised and edited the manuscript. Authors are read and approved the final paper.

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