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Incidence of Retinopathy and its Predictors among Adult Type Two Diabetic Patients in Felege Hiwot Referral Hospital, Northwest Ethiopia, 2021

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COLLEGE OF MEDICINE AND HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS

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Jun, 2021

Bahir Dar, Ethiopia

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Thesis Report Submitted to Department of Epidemiology and Biostatistics, School of Public Health, College of Medicine and Health Sciences, Bahir Dar University for Partial Fulfillment of the Requirements for the Degree of Master of Public Health in Epidemiology.

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DECLARATION

This is to certify that the thesis entitled incidence of diabetic retinopathy and its predictors among adult type two diabetic patients in Felege Hiwot referral hospital, Northwest Ethiopia, submitted in partial fulfillment of the requirements for the degree of Master of public health in the Epidemiology within Bahir Dar University, is a record of original work carried out by me and has never been submitted to this or any other institution to get any other degree or certificates. The assistance and help I received during the course of this investigation have been duly acknowledged.

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The undersigned examining committee certify that the thesis report presented by Gebrehiwot Dinku entitled: incidence of retinopathy and its predictors among adult type 2 diabetic patients in Felege Hiwot referral Hospital, Northwest Ethiopia, 2021, submitted to Bahir Dar University, College of Medicine and Health Sciences, School of Public Health, Department of Epidemiology and Biostatistics, in partial fulfillment of the requirements for the master of degree in Epidemiology compiles with the regulation of the University and meets the accepted standards with respects to originality and quality.

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We hereby certify that we have examined this thesis entitled incidence of retinopathy and its predictors among adult type two diabetic patients in Felege Hiwot referral hospital, Northwest Ethiopia, by Gebrehiwot Dinku Admasu. We recommend and appr ove the thesis a degree of master in Epidemiology.

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ABSTRACT

Background: Diabetic retinopathy develops due to the damage of small capillaries of the retina and leaking of blood through these fragile vessels. It has developed via nonproliferative to proliferative retinopathy . It had gradually increased throughout the globe since 1980 and more frequent in Africa that accounted 52%. About 20% Ethiopians was victims of retinopathy and Amhara region was the most affected one. Diabetic retinopathy was gradually increased even if Ethiopia had started projects to prevent in collaboration with the world health organization.

Objective: This study aimed to assess the incidence of retinopathy and its predictors among type 2 diabetic patients in Felege Hiwot Hospital from 2010 to 2020, Northwest Ethiopia.

Methods: Institutional based retrospective cohort study was conducted in Felege Hiwot referral Hospital among 514 newly diagnosed diabetic patients from January 2010 to December 2020 and followed until retinopathy was developed. Data were collected by reviewing patient charts. Patients were followed annually and Person-time at risk was measured in years. Data were entered into Epi Data version 3.1 and transferred to STATA version 14 for analysis. Schoenfeld proportional assumption test and Cox Snell residual model fitting were done and met the criteria. Univariable analysis was done for each predictor of diabetic retinopathy using cox regression at 25% significance level. Finally, five variables were identified using stepwise backward regression as predictors of retinopathy at 0.05 significance level and 95% of confidence level.

Result: The median survival time was 10.58 (CI: 8.49, 12.67) years. The incidence of retinopathy was 37.64 (95% CI: 30.31, 46.73) per 1000 Person-years. Residence (AHR : 2.60 95% CI: 1.41, 4.81), body mass index (AHR:1.053, 95% CI: 1.002, 1.11, p=0.042), Protein urea (AHR:2.13, 95%CI: 1.35, 3.35, p=0.001), high-density lipoprotein (AHR:0.58, 95%CI: 0.36, 0.94, p=0.026) and low-density lipoprotein (AHR:2.28, 95%CI: 1.38, 3.76, p=0.001) times increased the risk of diabetic retinopathy.

Conclusion: The incidence rate of this study was higher. Urban residents, increment of body mass index, positive urine protein, high-density lipoprotein less than 40 mg/dl and low-density lipoprotein more than 100 mg/dl were significant predictors of retinopathy for type 2 diabetic patients.

Key Words: Diabetic retinopathy, incidence, Type two Diabetes mellitus, and predictors

ACRONYMS

AHR	Adjusted Hazard Ratio
ART	Antiretroviral Therapy
BMI	Body Mass Index
BOR	Bed Occupancy Rate
CHR	Crude Hazard Ratio
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
FBG	Fasting Blood Glucose
HDL	High-Density Lipoprotein
IDF	International Diabetes Federation
LDL	Low-Density Lipoprotein
NCD	Non-Communicable Disease
NPDR	Non-Proliferative Diabetic Retinopathy
OHA	Oral Hypoglycemic Agent
OPD	Outpatient Departments
PDR	Proliferative Diabetic Retinopathy
UK	United Kingdom
WHO	World Health Organization

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Background

Micro vascular complications of diabetes are developed secondary to chronic hyperglycemia due to the defects of insulin secretion, resistance, or both of them. Diabetes mellitus can be complicated to micro vascular disorders like retinopathy, nephropathy, and neuropathy involving the peripheral and autonomic nervous system if it is left uncontrolled for a long period. Among these complications; diabetic retinopathy is the commonest microvascular disorder that causes blindness between the ages of 20 and 70 years and damages any part of the eye including the orbital socket and usually progresses towards blindness as a result of proliferative diabetic retinopathy with fractional retinal detachment or clinically significant diabetic macular edema, which were the most sight-threatening conditions of diabetes (1, 2). Diabetic retinopathy is developed due to the damage of small capillaries of the retina and leaking of blood with fluid through these fragile vessels. Progression of these conditions may impair vision and loosen the retina due to retinal detachment and scar tissue (1). It is one of the leading causes of blindness and one of the microvascular complications of diabetes mellitus. It has developed through mild non-proliferative diabetic Retinopathy to Proliferative Diabetic Retinopathy (PDR) and clinically significant macular edema. Non-proliferative diabetic retinopathy (NPDR) is classified into four stages (1, 2). The first stage is mild NPDR that is characterized by at least one microaneurysm, retinal hemorrhages, and hard or soft exudates. The second stage is moderate NPDR that is characterized by microaneurysms at least in one quadrant, dot and/or blot hemorrhages, soft exudates, venous beading, or intraretinal microvascular abnormalities. The third stage is severe NPDR that characterized by at least one of the following triads, which are microaneurysms and intraretinal hemorrhages in all four quadrants, venous bleeding in two or more quadrants, and moderate intraretinal microvascular abnormalities in at least one quadrant. The final stage of NPDR is very severe one that characterized by at least two of the following triads, which are micro aneurysms and intraretinal hemorrhages in all four quadrants, venous bleeding in two or more quadrants and moderate intraretinal micro vascular abnormalities in at least one quadrant. Proliferative Diabetic Retinopathy is usually proliferation of new vessels on the optic disk from veins and new vessels elsewhere on the retina. Finally, macular edema has developed and leads to dimness of vision, retinal edema and hard exudates close to fovea and end up with blindness (2).

1.2. Statement of Problem

Globally, the magnitude of blindness and visual impairment as a result of diabetic retinopathy was increased by 27% and 64% in 2010 respectively as compared to 1990 [3]. Diabetic retinopathy had gradually increased throughout the globe since 1980 and it was more frequent in Africans that accounted for 52% as compared to Europeans that accounted for 26% [4, 5]. The progression of diabetic retinopathy to blindness and visual impairment was increased by 7.7% from 1990 to 2015 in contrast to cataracts, uncorrected refractive error, and glaucoma that were reduced by 13.3% to 16·6% [6].

The burden of diabetic retinopathy was higher among some developing countries as compared to developed countries, which was around 28% to 36% in China, Japan, Bangladesh, Iran, and India [7-11] whereas it was 12% to 21% in Sweden, Mexico, and Ecuador according to their observational studies [12-14]. Similarly; around one retinopathy was developed among ten type 2 diabetic patients in India Sankara [15]. The incidence of diabetic retinopathy was increased in recent years in Singapore that accounted for about 17.6% in 2018 and 21.9% in 2019 [16, 17]. Likewise; it was more rapidly increased in Japanese among type 2 diabetic patients from 5.9% in 2014 to 28.9% in 2021 that was more than four times raise within five years [18, 19]. About one-tenth of new retinopathy cases were developed among type 2 diabetes mellitus (DM) patients in Lebanon and it was almost doubled in Canada within six years [20, 21]. In Spain, the incidence of retinopathy among type 2 DM patients was 2.43% in 2013 and 8.1% in 2017 which was rapidly increased as compared to the former one [22, 23]. Diabetic retinopathy and associated visual impairment had further complicated to depression, anxiety, worsening mental health level, lower vision-related quality of life, and psychosocial instability in general [24, 25].

Even if there has documented the decline of the incidence of diabetic retinopathy among type 1 DM, its trend among type 2 DM patients is still little known and it remains the leading cause of blindness among productive age groups that accounts for about 3 to 7% in the developing countries [26]. Western sub-Saharan and North African countries were accounted for 16% to 18.9% of the global blindness due to diabetic retinopathy which was the highest followed by East African countries which accounted for 13.7% and it was less than 0.1 in other continents [3].

Macular edema had developed from the advanced stage of diabetic retinopathy that accounted for about 16.1% and individuals with more advanced stage of diabetic retinopathy were increased with a longer period of DM exposure and improper blood glucose control in Tanzania

[27]. Diabetic retinopathy was 28.4% in Zimbabwe [28], 82.6% in Sudan, of which Proliferative diabetic retinopathy was 39.9% [29]. The incidence of diabetic retinopathy was 9.7% in Southern Malawi and it was more than doubled and tripled in Kenya and South Africa per year respectively [30-32].

About one in five diabetic patients had developed diabetic retinopathy in Ethiopia. Amhara region had a similar burden as the country level and the most affected region of Ethiopia next to the Oromia region [33]. Patients with type 2 DM were 4 times more likely to develop diabetic retinopathy when compared to type 1 DM in Tikur Anbessa Referral Hospital [34]. The magnitude of diabetic complications including retinopathy was 61% and 70.5% in Gurage and Dessie hospitals respectively [35, 36]. About one-fifth of diabetic patients had retinopathy in Debre Markos referral hospital [37] and sight-threatening retinopathy was 12.5% among type 2 diabetic patients in Debre Tabor general hospital in 2020 [38].

The impact of diabetes on vision was gradually increased even though the world health organization (WHO) and international diabetes federation (IDF) had started projects to prevent diabetic-related visual impairment in low and middle-income countries especially in Sub-Saharan Africa through the adoption of an effective surveillance system, establishing resources to policymakers for implementation, evidence-based information, educating diabetic patients about risk factors of diabetic retinopathy and promoting a healthy lifestyle [3]. There were limited resources to prevent and control the impact of diabetes over the past years in Ethiopia [39] which had a shortage of medicines, basic technologies, and procedures for DM according to the WHO report of 2016 [40]. DM and diabetic retinopathy haven't owned national guidelines even if prevention and control policies and strategies of diabetes mellitus complications are incorporated within non-communicable diseases through proper glycemic control, healthy diet and lifestyles, early detection, and screening [41]. The incidence of diabetic retinopathy among type 2 DM patients wasn't investigated in Africa including Ethiopia in contrast to its burden, which provides poor evidence of association. The incidence of diabetic retinopathy among mixed type 1 and 2 diabetic populations was studied in Jimma, Arbaminch, and Tikur Anbessa referral hospitals even if they couldn't show the association of predictors to retinopathy among each type of diabetic populations independently. Moreover; the study conducted in Arbaminch Referral hospital stated that the major limitation of the study was applying consecutive non-probability sampling technique which leads the findings to be unable to generalize for the target population

as well as unable to show causal relationship among predictors and diabetic retinopathy. So, to fill the above gaps, this study aimed to assess the incidence of diabetic retinopathy among type 2 DM patients and its predictors.

1.3. Significance of the Study

The findings of this study had new important insights for health care providers in the management and follow-up modalities of diabetic retinopathy. It will also equip health care providers with knowledge of predictors, median time, and incidence of DR among type 2 DM patients in Felege Hiwot hospital. Finally, it will be used for program managers and policymakers to develop management and prevention strategies for DR. This study will pull the attention of other researchers to conduct it prospectively or at the community levels.

2. LITERATURE REVIEW

2.1. Incidence of Diabetic Retinopathy

The commonest micro vascular complication of DM is diabetic retinopathy, which is a sight-threatening condition of the eye (40). About one-tenth of new diabetic retinopathy per year was developed in Pakistan and Lebanon among type 2 DM patients in 2016 (20, 42). The incidence of diabetic retinopathy was 1.8% to 8.13% per year in China and Spain according to their cohort studies (22, 43). It was increased from 1.13% per year in 2004 to 4.1% per year in 2011 among type 2 DM in United Kingdom (UK) (44). Likewise; about 3.8% of type 2 diabetic patients had developed retinopathy per year in South Korea in 2016 (45). The incidence of retinopathy was 21.89% and its progression was 33.45% in the Singapore-Indian cohort study (17), which was comparable with the incidence of a community-based cohort study of Israel (46).

Diabetic retinopathy was 224.7 and 380 per 1000 person-years of observation in Kenya and Malawi according to their cohort studies (30, 47). It was 35.9 to 50.2 per 1000 person-years as well as 2.65 per 1000 person month of observation for both type 1 and type 2 DM patients per year in Arbaminch, Jimma, and Tikur Anbessa Referral Hospitals respectively based on their cohort studies (34, 48, 49).

2.2. Time to Diabetic Retinopathy

The median time to develop retinopathy among type 2 DM patients was 9.1 years in the UK and 7 years in Japan (19, 44). Similarly; diabetic retinopathy was developed relatively in a short median time among community-based cohort studies of Israel and Lebanon, which had a median survival time of 4.5 to 5 years (20, 46). In Singapore and South Korea, retinopathy had a median survival time of 6.2 and 11.8 years among type 2 diabetic patients respectively (16, 45). The duration of diabetic follow up was about 4.8 times increase the risk of diabetic retinopathy for those greater than 10 years and 2.6 times increase for 5 to 10 years as compared to diabetic patients who have followed up time of fewer than 5 years in Pakistan according to the findings of its observational study (42). The risk of retinopathy was 1.10 to 1.74 times increased for every one year increment of DM duration in Mexico, Mainland China, and Beijing China respectively (13, 50, 51). Similarly; it was 14.7 times higher for those more than 10 years follow up in the UK which was approximately doubled of the finding of Saudi Arabia and Brazil as well as more than 10 times as compared to the risk within Armenia (44, 52-54). Around one in five type 2 DM

patients had developed diabetic retinopathy within 5 years in the UK (44). Among type 2 diabetic patients of India, those who have more than 15 years of follow up were 9.07 times expose for retinopathy (52) and 1.093 to 1.11 times increased for every one additional follow up time according to the multicenter study of China and Japan respectively (7, 9). It was 1.75 times increased in the Island of Denmark for every 5 years of follow-up (55).

Every one-year increment of diabetic duration was associated with 1.06 and 2.8 times increment of the risk of diabetic retinopathy in Zimbabwe and Sudan respectively (28, 29). Tikur Anbessa and Jimma Referral Hospitals had a median survival time of approximately 6 years whereas it took as long as 10 years in Arbaminch referral Hospital according to their cohort studies (34, 48, 49). The observational studies of Debre Tabor and Debre Markos Referral Hospitals showed that the risk of diabetic retinopathy was 3.54 and 3.91 times increased because of diabetic duration more than 10 years respectively (37, 38) whereas diabetic duration greater than or equal to 6 years was 92% decreased the risk of retinopathy as compared to its counterpart in Arbaminch referral hospital (48).

2.3. Predictors

2.3.1. Demographic Characteristics

The Cross-sectional study conducted in Saudi showed that the risk of diabetic retinopathy was 1.35 times higher among male patients as compared to females among type 2 DM patients (53). The progression of diabetes to diabetic retinopathy was 7% decreased among female patients in the UK whereas it was 1.29 to 1.45 times increased in Japan and Taiwan (9, 44, 56). However; age hadn't associated with retinopathy in Singapore-Indian cohort study, Taiwan, Mainland, and Beijing China, Japan, Lebanon, and UK (9, 17, 20, 44, 50, 51, 56). One year increment of age was associated with a 3% decrement to develop retinopathy in Mainland China (50) Even though age more than or equal to 60 years was 1.23 to 2.65 times increase the risk of diabetic retinopathy in South Korea, Spain, Saudi Arabia, and Armenia when compared to their counter parts respectively (22, 45, 53, 54). The risk of retinopathy was 5.98 times higher among diabetic patients older than 50 years in Bangladesh whereas urban residents were 59% decreased the risk of retinopathy (10). It was 6% decreased for every 10 years increment of age in the Island of Denmark (55) and 8.14 times increased for every one-year increment of age in Ecuador (8). Age was neither a protective nor risk factor in Lebanon, Japan, Taiwan, Pakistan,

and Israel as the findings of their observational studies (9, 20, 42, 46, 56). Sex and residence weren't associated with retinopathy in Lebanon, South Korea, Japan, the Island of Denmark, Spain, Mainland, and Beijing China (9, 20, 22, 45, 50, 51, 55).

Diabetic retinopathy was 1.75 times higher among urban residents in Kenya and 6.9 times for age greater than or equal to 60 years in Arbaminch Referral Hospital (30, 48). It was also approximately doubled among male patients in Tikur Anbessa Referral Hospital whereas it wasn't associated with age and residence in Tikur Anbessa referral Hospital (34). On the other hand; no one of the place of residence, sex, and age were associated with diabetic retinopathy in Jimma, Debre Tabor, and Debre Markos referral Hospitals (37, 38, 49).

2.3.2. Clinical factors

Neuropathy was a risk factor for diabetic retinopathy in Saudi Arabia, which accounted for about 2.5 whereas it hadn't yet been associated among the studies conducted in India and Lebanon (20, 53, 57). Poor glycemic control was expose diabetic patients for diabetic retinopathy about 1.27, 1.8, and 3.83 times in China, Saudi Arabia, and Brazil respectively (43, 52, 53). Insulin treatment was 1.68 to 4.51 times increase the risk of retinopathy as compared to non-users in Singapore, Japan, Armenia, and Saudi (9, 17, 53, 54). Retinopathy was 6.86 times increased among oral hypoglycemic agent users as compared to its counterpart in Mainland China and it was 3.74 for insulin users (50). On the other hand; this factor hadn't associated with retinopathy in South Korea and Israel (45, 46). The risk of diabetic retinopathy had neither increase nor decrease because of the anti-DM regimen and family history of DM in Sudan, Debre Tabor, Debre Markos, and Arbaminch referral hospitals (29, 37, 38, 48).

2.3.3. Comorbidities

In Israel, the risk of diabetic retinopathy was increased due to hypertension and obesity (46). Similarly; body mass index of more than 25 mg/dl was 6%, 37%, and 26% decrease the risk of retinopathy among type 2 DM patients in Japan, Saudi Arabia, and Singapore respectively whereas it was 1.58 and 1.05 times increase the risk of retinopathy as compared to normal body weight in China Beijing and Island of Denmark respectively (9, 17, 51, 53, 55).

Diabetic patients with hypertensive conditions had a 1.44 and 3.2 times higher risk of retinopathy in Saudi and India respectively (53, 57). Unlikely; none of the studies conducted in South Korea, Lebanon, Bangladesh, Brazil, and Armenia had shown an association between retinopathy and hypertension (10, 20, 45, 52, 54). Obesity and overweight were 3% decreased for every one unit

increment of body mass index in Sweden (12) whereas it was 1.7 to 1.88 times increase in Southern Iran and 6.83 to 6.69 times increase the risk of retinopathy in Kenya as compared to normal weight even though it was adjusted only for age (30, 58). The risk of diabetic retinopathy had neither increased nor decreased because of obesity or overweight in Zimbabwe, Tanzania, and Sudan (27-29).

Hypertension was a 3.1 time increase the risk of retinopathy in Sudan and a 46% decrease in Jimma referral hospital (29, 49). It was 3.4 and 5.86 times in Debre Tabor and Debre Markos referral hospitals when compared to non-hypertensive patients respectively (37, 38). Body mass index (BMI) wasn't associated with diabetic retinopathy in Jimma, Arbaminch, and Tikur Anbessa Referral Hospitals (34, 48, 49). One unit increment of BMI was about 3.74 to 4.8 times increase the risk of retinopathy among patients more than 25kg/m^2 and 30 kg/ m^2 in Debre Tabor and Debre Markos referral hospitals when compared to their counterpart respectively (37, 38).

2.3.4. Biomarkers

Low-density lipoprotein (LDL) was 1.004 to 4.4 times exposing diabetic patients for diabetic retinopathy in Taiwan, Indonesia, Mainland China, and Bangladesh (10, 50, 56, 59) whereas it was 3% decreased in Spain (22). Protein urea was 1.003 to 10.3 times increase the risk of retinopathy in China, the UK, South Korea, Mexico, and Lebanon respectively (13, 20, 45, 60, 61). However; it was neither positively nor negatively associated with retinopathy among the studies conducted in Japan, the Island of Denmark, and Israel (9, 46, 55). When the concentration of high-density lipoprotein (HDL) had increased every 1 mg/dl, the incidence of retinopathy was 3%, 7%, and 12% decreased according to the study conducted in Japan, Indonesia and UK respectively (9, 59, 61). Every one mg/dl fasting blood glucose (FBG) increment was associated with 1.076 times the risk of retinopathy in Mainland China and this risk was 2.4 times higher among diabetic patients who had FBG concentration greater than 130 mg/dl in India (8). On the other hand; no one of cholesterol level, creatinine, and triglyceride were related with diabetic retinopathy in Lebanon, Japan, Bangladesh, and Mainland China (9, 10, 20, 50).

One unit increment of creatinine level of diabetic patients was associated with a 1% decrease in the risk of retinopathy in Zimbabwe in contrast to Tikur Anbessa Referral Hospital, which was a 2.59 times increase in the risk of retinopathy (28, 34). The risk of retinopathy was 49% decreased among diabetic patients who have a high concentration of HDL less than 40 mg/dl in

Jimma referral hospital in contrast to Tikur Anbessa referral hospital, which wasn't significantly associated (34, 49). The risk of retinopathy was around 2.6 to 2.9 times increased among diabetic patients with a borderline and high concentration of triglyceride respectively in Tikur Anbessa referral hospital and 37% decreased among diabetic patients with borderline total cholesterol in Jimma referral hospital according to their cohort studies (34, 49). It was also 1.002 times higher when FBG concentration had increased every 1mg/dl in Arbaminch referral hospital (48).

2.4. CONCEPTUAL FRAMEWORK

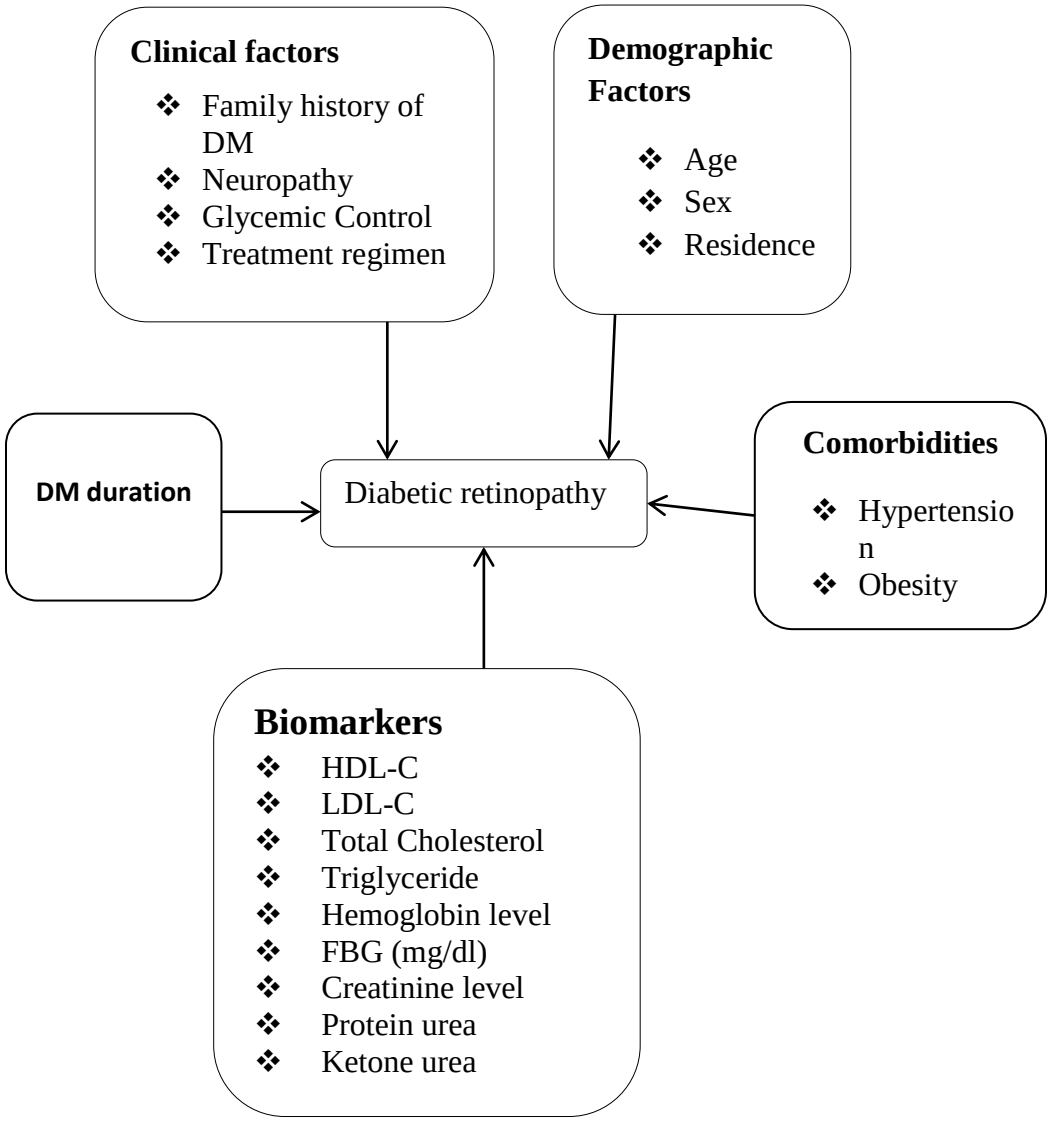

Figure 1. Conceptual framework of diabetic retinopathy among type 2 DM and predictors in Felege Hiwot Hospital, Northwest Ethiopia, 2021.

3. OBJECTIVES

3.1. General Objectives

To assess the incidence of retinopathy and its predictors among adult type 2 diabetes patients in Felege Hiwot referral Hospital, Northwest Ethiopia, 2021.

3.2. Specific Objectives

To determine the incidence of retinopathy among type 2 diabetic patients in Felege Hiwot referral Hospital, Northwest Ethiopia, 2021.

To identify the predictors of time to retinopathy among type 2 diabetic patients in Felege Hiwot referral Hospital, Northwest Ethiopia, 2021.

4. METHODS AND MATERIALS

4.1. Study design

The institution-based retrospective cohort study was conducted in Felege Hiwot comprehensive specialized Hospital.

4.2. Study area and period

This study was conducted from January 2010 to December 2020 in Felege Hiwot referral Hospital, Northwest Ethiopia. Felege Hiwot Referral Hospital is located in Bahir Dar city, the capital city of the Amhara National Regional State. Bahir Dar is found 565 km North West far from Addis Ababa. It gives a referral service for the Amhara region and it has 500 beds as well as around 15 adult outpatient departments (OPD) serving over 15 million people from the surrounding area. The hospital serves around 935 patients per month within each OPD. It has antiretroviral therapy (ART), psychiatry, internal medical, gynecologic and obstetric, pediatric, orthopedic, surgery, oncologic, radiologic, laboratory, pharmacy, and ophthalmology services. Felege Hiwot Referral Hospital had a 95.5% bed occupancy rate (BOR) and 4.7 days of the length of stay in admission. According to the report of the plan office of Felege Hiwot Referral Hospital, there were around 7114 diabetic patients on follow-up, of which 4675 were type 2 DM patients.

4.3. Source Population

The source populations were all 18 and above years of type 2 DM patients within Felege Hiwot referral Hospital.

4.4. Study Population

The study populations were all type 2 diabetic patients aged 18 and above years diagnosed within the study period of 2010 to 2019 in Felege Hiwot Hospital.

4.5. Eligibility Criteria

4.5.1. Inclusion criteria

All type 2 DM patients that newly diagnosed from January 1st, 2010 to December 31th, 2019 in Felege Hiwot Hospital were included in this study.

4.5.2. Exclusion Criteria

Study Subjects with gestational diabetes, patients who hadn't visual assessment and hadn't at least one followed up profile or transfer out immediately after diagnosis were excluded from the study.

4.6. Sample Size Determination

The accrual period of the study subjects was from 2010 to 2019 with one year additional study period. The minimum sample size was calculated among predictor variables independently. Firstly, the required minimum sample size was determined for predictor variables by using the log-rank test method with STATA version 14 software. Where n is the sample size, z is 1.96 which is standard normal distribution at the significant level of 5% and confidence level of 95%, power (1-β) is 80% and the hazard ratio of each predictor variable was taken independently. The sample size of the study was taken as 514 since it was the maximum sample size from the samples of predictors as shown from the table below (Table 1).

Table 1: Sample size determination among predictors for Felege Hiwot Hospital, Northwest Ethiopia, 2021.

Variable	HR	P-value	P(event)	event	sample size	Survival probability	
						Exposed	Unexposed
Sex (34)	1.94	<0.05	0.200	71	356	0.740	0.86
Borderline triglyceride (34)	2.87	<0.05	0.199	103	514	0.750	0.85
High level triglyceride (34)	2.59	<0.05	0.200	99	492	0.748	0.85

4.7. Sampling Technique and Sampling Procedure

The study subjects were selected among newly diagnosed type 2 diabetic patients from 2010 to 2019 within Felege Hiwot Hospital. The sampling frame was prepared among type 2 diabetic patients' medical registration numbers that were collected from medical OPDs, non-communicable disease (NCD), and ophthalmology. The patients' medical registration numbers were arranged in ascending order using Microsoft offices excel. Simple random sampling technique was used to select study subjects. Random numbers were generated using Microsoft offices Excel's random number formula and arranged in the smallest to largest order to randomize card numbers. Finally, the first 514 medical registration numbers were selected among ordered random numbers.

4.8. Data Collection Tool and Procedure

Data were extracted from the document by using a pre-tested structured checklist that adapted from studies of Kenya, Arbaminch, and Tikur Anbessa Referral Hospitals [30, 34, 48]. The checklist was used as a data collection tool since the study question utilized secondary data. The adapted Checklist was prepared in English language and didn't translate to Amharic since the data collectors were health professionals and the source of the data was chart review. Newly diagnosed type 2 diabetic patients from January 2010 to December 2019 who had followed up within Felege Hiwot Referral Hospital were included in the study and then followed until December 31th 2020. The data extraction tool had demographic, clinical, comorbidities, DM duration, and biomarkers. Data was collected by one diabetic focal person under the supervision of one health officer. This diabetic focal person was collected the data during his off time to accommodate the routine service. The data collector and supervisor were given orientation for one day about sample size, data extraction, ethical issues, and way of supervision. Incidence of diabetic retinopathy was the outcome of interest for this study. However; it was considered as censored when diabetic cases were lost to follow-up, died, and transferred out before they develop diabetic retinopathy and patients who didn't develop diabetic retinopathy at the end of the study. The checklist was validated for completeness and the whole data collection process on daily basis.

4.9. Study Variables

4.9.1. Dependent variables

The outcome variable of this study was diabetic retinopathy.

4.9.2. Independent variables

The independent variables that used to affect the development of diabetic retinopathy were the followings;

Demographic Factors: age, sex, and residence.

Clinical Factors: family DM history, neuropathy, Treatment, and glycemic control.

Comorbidities: hypertension and obesity.

Duration of DM: the time taken for DM patients to develop DR.

Biomarkers: those were HDL-C, LDL-C, total cholesterol level, triglyceride, FBG (mg/dl), ketone bodies, protein urea, creatinine level, and hemoglobin level.

4.10. Operational Definition.

Event: when type 2 DM patient develops diabetic retinopathy for the first time.

Survival time: the total time from the diagnosis of DM to diabetic retinopathy or censoring.

Protein urea: it was positive if urine albumin is 2 or more and negative if it is 1 or less.

Ketone urea: it was positive if urine ketone is 2 or more and negative if it is 1 or less.

Poor glycemic control: it was identified if the average six consequent follow up fast blood glucose level greater than 130 mg/dl.

Censored: DM cases were taken as censored when they did not develop DR throughout the study period, lost to follow up, died before they develop DR, and transfer out to other health facilities before they develop DR.

Study period: The time interval between 21/12/2010 to 21/12/2020.

4.11. Data Processing and Analysis Procedure

The data were extracted from individual patient charts using a pre-tested-structured checklist that was taken from previous studies. After the end of data extraction, it was entered into Epi Data version 3.1 and transferred to STATA SE version 14 for cleaning, coding, categorizing, merging, and to check completeness, consistency, and outliers or extreme values. Descriptive analysis was carried out using frequency tables for categorical variables, median and interquartile range for continuous variables, and Kaplan Meier cumulative curve to summarize survival probability. Person-time at risk was measured in years starting from the time of diabetic diagnosis until each patient ended the follow-up. Schoenfeld proportional assumption test (both global and individual) was used to check the cox proportional hazards assumption (Annex 1). The assumption was not violated since the test value was 0.8948, which was insignificant at the 5% α level. Cox Snell residual method of model fitting was done and better fitted the observed data (Annex 1). Secondly, univariable survival analysis was done for each predictor of diabetic retinopathy and seven candidate variables were selected at a 25% significance level for the multivariable cox regression analysis. Cox proportional hazard regression was conducted using

the stepwise backward regression method to show the causal association between predictors and incidence of diabetic retinopathy as far as the assumption wasn't violated. Finally, five variables that had less than or equal to 0.05 significance at 95% of confidence were considered as predictors of diabetic retinopathy. The incidence rate was measured with person-years of observation. Finally, the findings of the study were presented using text, tables, and graphs.

4.12. Data Quality Management

The collected data were checked for completeness and consistency. It was also cleaned, coded, entered to Epi data version 3.1, and then exported to Stata version 14 software for analysis. To achieve the quality of the data, the data extraction checklist was pretested about 5% of the sample size in Felege Hiwot Referral Hospital. The data collector and supervisor were given orientation about the sample size, ethical issues, data collection instrument, and procedure. Simple random sampling technique and multivariate analysis were used to minimize selection bias and to control confounder effects respectively.

4.13. Ethical Consideration

Ethical permission for this study was obtained from Bahir Dar University College of medicine and health science Ethical Review Board. The official letter was also obtained from the Department of Epidemiology and Biostatistics and submitted to Felege Hiwot referral hospital to get their cooperation during the data collection process. The confidentiality was assured of the information respected to patient folders. Explanation regarding the purpose of this study was informed for data collectors and concerned officials within the hospitals.

5. RESULT

5.1. Baseline characteristics of study participants

Among type 2 diabetic patients that had followed up within Felege Hiwot Referral hospital from January 2010 to December 2019, all of 514 patients were included in the final analysis. The median BMI of diabetic patients was 23.75 kg/m^2 and its middle 50% was lay in between 21.59 kg/m^2 to 26.54 kg/m^2. The median FBG of diabetic patients was 173 mg/dl and its 50% was lay in between 70 to 457 mg/dl. The median creatinine of diabetic patients was 0.9 mg/dl and its 50% was lay in between 0.75 to 1.15 mg/dl. The median age of diabetic patients was 55 years and its 50% was lay in between 48 to 64 years. Among 514 study subjects, 265 (51.56%) were male, 351 (68.29%) were urban residents and 233 (45.33%) had hypertension (Table 2).

Table 2: Baseline characteristics of study subjects in Felege Hiwot hospital, Northwest Ethiopia, 2021.

Variables	Categories	Retinopathy		Total(n=514)
		Yes (n=82)	Censored(n=432)	
Sex	Female	40 (48.78%)	209 (48.38%)	249 (48.44%)
	Male	42 (51.22%)	223 (51.62%)	265 (51.56%)
Residence	Urban	69 (84.15%)	282 (65.28%)	351 (68.29%)
	Rural	13 (15.85%)	150 (34.72%)	163 (31.71%)
Hypertension	Yes	44 (53.66%)	189 (43.75%)	233 (45.33%)
	No	38 (46.34%)	243 (56.25%)	281 (54.67%)
Family History of DM	Yes	29 (35.37%)	148 (34.26%)	177 (34.44%)
	No	43 (52.44%)	232 (53.70%)	275 (53.50%)
	Unknown	10 (12.20%)	52 (12.04%)	62 (12.06%)
Neuropathy	Yes	19 (23.17%)	88 (20.37%)	107 (20.82%)
	No	63 (76.83%)	344 (79.63%)	407 (79.18%)
Treatment	Insulin	12 (14.63%)	61 (14.12%)	73 (14.20%)
	OHA	56 (68.29%)	266 (61.57%)	322 (62.65%)
	Insulin + OHA	14 (17.07%)	105 (24.31%)	119 (23.15%)
Duration of DM	< 5 years	33 (40.24%)	282 (65.28%)	315 (61.28%)
	≥ 10 years	49 (59.76%)	150 (34.73%)	199 (38.72%)
Glycemic Control	poor	72 (87.80%)	362 (83.80%)	434 (84.44%)
	good	10 (12.20%)	70 (16.20%)	80 (15.56%)
Protein urea	Positive	38 (46.34%)	121 (28.01%)	159 (30.93%)
	Negative	44 (53.66%)	311 (71.99%)	355 (69.07%)
Ketone urea	Positive	18 (21.95%)	81 (18.75%)	99 (19.26%)
	Negative	64 (78.05%)	351 (81.25%)	415 (80.74%)
Hemoglobin	<12 mg/dl	11 (13.41%)	39 (9.03%)	50 (9.73%)
	≥ 12 mg/dl	71 (86.59%)	393 (90.97%)	464 (90.27%)
HDL-C	≥ 40 mg/dl	51 (62.20%)	346 (80.09%)	397 (77.24%)
	< 40 mg/dl	31 (37.80%)	86 (19.91%)	117 (22.76%)
LDL-C	≥100 mg/dl	45 (54.88%)	124 (28.70%)	169 (32.88%)
	<100 mg/dl	37 (45.12%)	308 (71.30%)	345 (67.12%)
Triglyceride	≥150 mg/dl	37 (45.12%)	141 (32.64%)	178 (34.63%)
	<150 mg/dl	45 (54.88%)	291 (67.36%)	336 (65.37%)
Total Cholesterol	≥200 mg/dl	28 (34.15%)	146 (33.80%)	174 (33.85%)
	<200 mg/dl	54 (65.85%)	286 (66.20%)	340 (66.15%)

Expressed as BMI: body mass index, DM: diabetes mellitus, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

5.2. Incidence of Retinopathy among Type 2 Diabetic Patients

During the total 11 years study period of patients on follow-up in Felege Hiwot Referral hospital, 82 (16%) had developed diabetic retinopathy. The incidence rate was 37.64 (95% CI: 30.31, 46.73) per 1000 person-years of observation. About 238 (43.80%) of type 2 diabetic patients were survived beyond the study period. The median survival time of the study subjects was 10.58 years (CI=8.49, 12.67) years with 2181.81 person-years of observation.

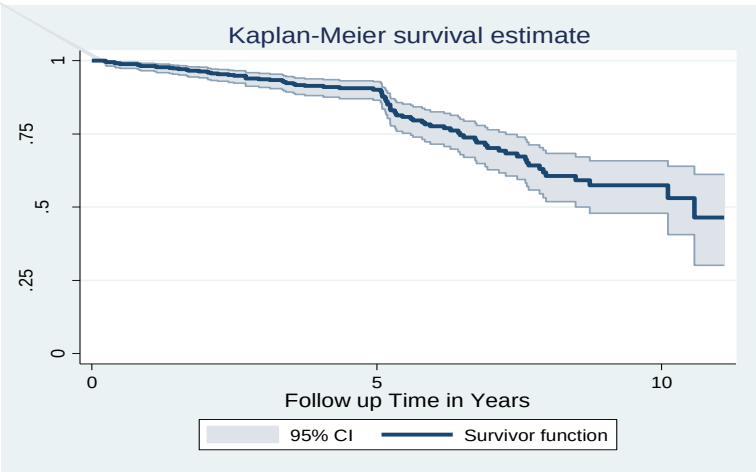

Figure 2: The Kaplan Meier cumulative survival probability curve among type 2 diabetic patients for retinopathy at Felege Hiwot Hospital, Northwest Ethiopia, 2021.

5.3. Predictors of Retinopathy among Type 2 Diabetic patients

Among 514 study subjects, 8.54% of observations were missing from the patient's chart and replaced using multiple imputations. Among predictors: sex, age, treatment, neuropathy, hypertension, fasting blood glucose level, triglyceride, cholesterol, creatinine, hemoglobin, and ketone level hadn't yet been associated with diabetic retinopathy. According to multivariable analysis using cox proportional hazard regression; baseline Residence, Body mass index, High-density lipoprotein level, Low-density lipoprotein level, and urine protein status were statistically significantly associated with diabetic retinopathy. Residence and protein status were moderately associated with retinopathy, which was 2.60 and 2.13 times higher among urban residents and positive protein urea when compared to rural residents and negative protein urea respectively (AHR:2.60, 95%CI: 1.41, 4.81, p=0.002) and (AHR:2.13, 95%CI: 1.35, 3.35, p=0.001). It was also 42% decreased and 2.28 times increased because of high and low-density lipoprotein greater than or equal to 40 mg/dl and 100 mg/dl as compared to their counter parts respectively (AHR=0.58, 95%CI: 0.36, 0.94, p=0.026) and (AHR=2.28, 95%CI: 1.38, 3.76, p=0.001). One

unit increment in body mass index was associated with a 1.053 times increment of retinopathy (AHR:1.053, 95% CI: 1.002, 1.11, p=0.042) (Table 4).

Table 3: Bivariable and multivariable Cox proportional hazards regression analysis of predictors of retinopathy in Felege Hiwot hospital, Northwest Ethiopia, 2021.

	Retinopathy			
Variables	Yes	Censored	CHR (95% CI)	AHR (95% CI)
Residence				
Rural	13	150	1	1
Urban	69	282	2.52 (CI:1.39, 4.56)	2.60 (CI: 1.41, 4.81)**
Protein urea				
Negative	44	311	1	1
Positive	38	121	1.70 (CI: 1.10, 2.62)	2.13 (CI: 1.35, 3.35)**
HDL				
< 40 mg/dl	31	86	1	1
≥ 40 mg/dl	51	346	0.53 (CI: 0.34, 0.83)	0.58 (CI: 0.36, 0.94)*
LDL				
<100 mg/dl	37	308	1	1
≥100 mg/dl	45	124	2.24 (CI: 1.45, 3.47)	2.28 (CI: 1.38, 3.76)**
Creatinine in mg/dl	**0.9**	0.9	0.61 (CI: 0.3, 1.22)	0.64 (CI: 0.33, 1.24)
BMI in kg/m^2	25.67	23.54	1.085 (CI: 1.032, 1.14)	1.053 (CI: 1.002, 1.11)*
FBG in mg/dl	214	168	1.002 (CI: 0.99, 1.004)	0.99 (CI: 0.99, 1.002)

**expressed as p-value< 0.01, *p-value< 0.05. Expressed as BMI: body mass index, FBS: fasting blood sugar, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, CHR: crude hazard ratio, AHR: adjusted hazard ratio

6. DISCUSSION

This study assessed the incidence of retinopathy and its predictors among type 2 diabetic patients in Felege Hiwot referral hospital from January 2010 to December 2020. This retrospective cohort study identified the risk factors of diabetic retinopathy after multiple cox proportional regression analyses, which were body mass index, residence, protein urea, high and low-density lipoprotein level among type 2 DM patients. On the other hand; age, sex, family history of DM, neuropathy, hypertension, treatment modalities, fasting blood glucose level, triglyceride, total cholesterol, creatinine, hemoglobin, and urine ketone weren't significantly associated with retinopathy. The incidence rate of this study was 37.64 cases per 1000 persons per year with a median follow-up time of 10.58 years. It was consistent with the study done in Jimma and Arbaminch referral hospitals [48, 49]. This consistency might be due to similar health services provided for diabetic patients since the studies done within the same level of the health system and clinical practices. It was also much higher than the study done in Tikur Anbessa referral hospital which was 2.65 cases per 1000 months of observation with a median follow-up time of 6.2 years (34). This might be due to a longer follow-up period and incidence was measured in person-years of observation in this study as compared to Tikur Anbessa referral hospital. However; It was much lower than the study conducted in Kenya, Singapore, and Malawi (16, 30, 47). This might be due to a population-based prospective study of Kenya that addresses many sub-clinical cases within the community and the study focuses on those aged greater than 50 years that are more vulnerable for retinopathy because the natural aging process exposes diabetic patients for retinal degeneration. The possible explanation for the discrepancy with Malawi might be due short study period and diagnostic differences. The incidence of this study was consistent with South Korea whereas it was much lower than the study conducted in Pakistan even if the study period was almost similar (42). This difference may be due to diabetic patients of the current study was coming from elsewhere from the Amhara region either new or old cases whereas, in Pakistan, the study was conducted in a tertiary care unit having diabetic patients with longer duration. Another possible explanation might be due to the difference in health care systems and the quality of care provided for diabetic patients.

The finding of this study reported that urban residents had a higher hazard of retinopathy as compared to rural residents, which was consistent with a community-based prospective cohort study of Kenya (30). However; the finding of this study was inconsistent with the study done in

Bangladesh (10). The possible explanation might be due to increasing sedentary life, psychosocial and behavioral factors among urban residents, and these factors were poorly documented within patient charts, which they weren't fully collected and controlled with the current study. Even if the incidence of diabetic retinopathy was significantly associated with the residence status of the study subjects for the current study it hadn't yet been associated with several studies in Africa (27, 29, 37, 38, 48, 49). Since it wasn't studied as a predictor of retinopathy other than Africa it needs to be further studied.

This study showed that increment of body mass index increased the hazard of retinopathy, which was consistent with the studies done in Debre Tabor (38) and Debre Markos hospitals (37), Kenya (30), Southern Iran (58), China Beijing (51) and Island of Denmark (55). This positive association may be due to overweight and obesity are directly associated with insulin resistance during glucose metabolism that aggravates the progression of retinopathy through the infiltration of glucose molecules within retinal blood vessels (1). However, it was inconsistent with the studies done in Sweden (12), Saudi (53), Iran (62), Iraq (63), Singapore (17), and Japan (9). This discrepancy might be due to prospective community-based studies among older than 40 years diabetic patients in Singapore and Japan whereas all adult ages were used in the current study. Another possible explanation might be due to one center study of the current one whereas, in Japan, it was a multicenter study including clinics to teaching hospitals. Moreover; behavioral factors like smoking and alcoholism were controlled in other studies unlikely to the current study.

Protein urea increased the hazard of diabetic retinopathy in Felege Hiwot referral hospital that was supported by the studies conducted in South Korea (45), China (60), UK (61), Mexico (13), and Lebanon (20). This might be due to the high concentration of protein within the blood system that increases the formation of fibrosis, neovascularization, and retinal detachment(64). Protein urea wasn't significantly associated with retinopathy in Debre Tabor (38), Debre Markos (37), and Jimma (49) referral hospitals, Singapore (17), Japan (9), Taiwan (56), and Spain (22) in contrast of the current study. This might be due to the diagnostic difference of albumin urea, which was urine dipstick for the current study, and urine chemistry for other studies. High and low-density lipoprotein were significantly increased the hazard of retinopathy in this study whereas triglyceride and total cholesterol were neither positively nor negatively associated with it. Higher concentration of low-density lipoprotein was more likely to develop retinopathy

among type 2 diabetic patients according to this study, which was supported by the study done in three different study areas of China (7, 50, 60), Taiwan (56), Indonesia (59) and Bangladesh (10). This might be due to insulin resistance that leads to increase LDL concentration and aggravates the progression of retinopathy (1). This study showed that HDL-C level greater than or equal to 40 mg/dl was negatively associated with diabetic retinopathy, which was consistent with the study done in the UK (61), Iran (11), Japan (9), and Indonesia (59). It was inconsistent with the study done in Jimma referral hospital (49). This discrepancy might be due to the difference between the study populations that is mixed type 1 and 2 DM patients for Jimma hospital whereas only type 2 DM patients for this study. Another possible explanation might be due to the difference in the median survival times, which were 5.9 years in Jimma referral hospital and 10.58 in the current study. Even if there were significant association among triglyceride and hypertension with the diabetic retinopathy in Debre Tabor (38), Gondar (65), Tikur Anbessa (34) and Arbaminch hospitals (48) as well as in Pakistan (42) and Saudi (53) they were insignificant in the current study. This might be occurred because of the retrospective nature of the study design since not all patient characteristics could be fully retrieved and hence behavioral and some important sociodemographic variables weren't be assessed.

7. STRENGTH AND LIMITATION

7.1. Strength

Data collectors were health professionals who were easily trained and could retrieve the data properly. Recall bias was minimized because data was collected from the information recorded in the past during the patient's subsequent follow-up time. Missing values were imputed to maintain the power of the study and to decrease the bias due to missingness.

7.2. Limitation

The major drawback of this study was the absence of most socio-demographic, nutritional and behavioral factors that may underestimate or overestimate the effect of the studied factors on the progression of diabetic retinopathy. It was challenging to prepare a sampling frame since the type of DM wasn't specified for some diabetic patients.

8. CONCLUSIONS AND RECOMMENDATION

8.1. Conclusion

This study aimed to assess incidence rate and identify the predictors, which were significantly associated with retinopathy among type 2 diabetic patients. The incidence of retinopathy in this study was higher. The retrospective cohort study findings showed that diabetic retinopathy was significantly associated with residence, body mass index, urine protein status, HDL-C, and LDL-C among type 2 diabetic patients.

8.2. Recommendation

To combat diabetic retinopathy, the followings are recommended:

i. Health professionals in the DM follow up clinics should give targeted intervention for type 2 DM patients with urban residents, overweight and above, LDL-C above 100 mg/dl and HDL-C less than 40 mg/dl.
ii. Patients with urban residents, overweight and above, LDL-C above 100 mg/dl and HDL-C less than 40 mg/dl should strictly control their risk factors of DM.
iii. Diabetic patients who are urban residents, overweight and above, LDL-C above 100 mg/dl and HDL-C less than 40 mg/dl should be screened for DR more frequently
iv. Further studies should be conducted particularly prospective and community-based to assess the most socio-demographic and behavioral factors of retinopathy.

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ANNEX 1: PROPORTIONAL HAZARD ASSUMPTION AND COX SNELL MODEL FITTING

Table 4: proportional hazards assumption test based on Schoenfeld residuals for multivariable cox regression fitted variables in Felege Hiwot hospital, Northwest Ethiopia, 2021.

Variables	rho	chi2	df	Prob>chi2
BMI in kg/M^2	0.06007	0.27	1	0.6066
Fasting blood glucose	-0.09074	0.46	1	0.4976
Creatinine	-0.14485	1.4	1	0.2360
Residence	-0.08404	0.64	1	0.4253
Protein urea	0.01011	0.01	1	0.9250
HDL-C	-0.04800	0.21	1	0.6449
LDL-C	-0.03531	0.11	1	0.7383
Global test		2.89	7	0.8948

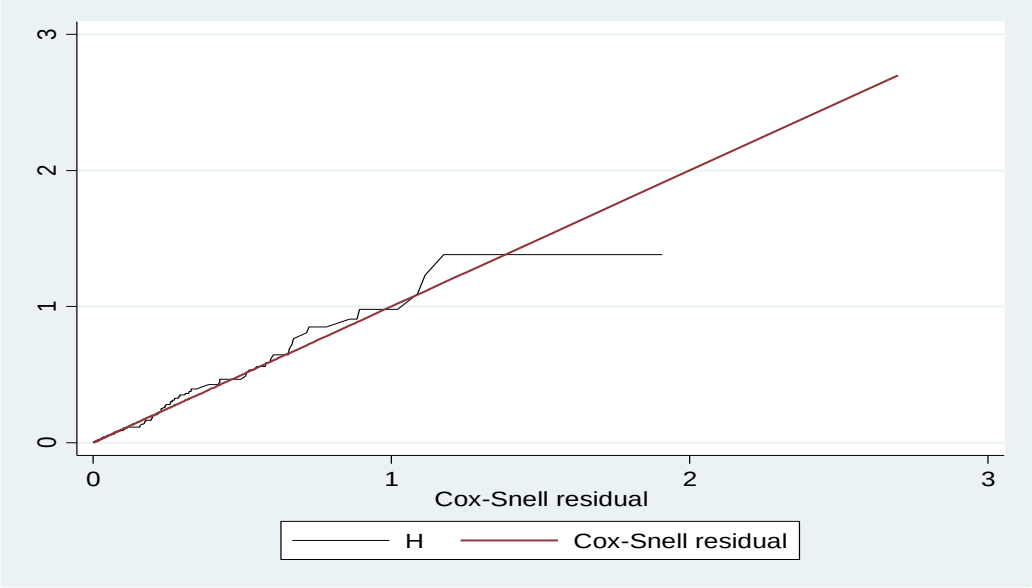

Figure 3: Cox Snell residuals for model fitting of proportional hazards of multivariable Cox regression in Felege Hiwot referral hospital, Northwest Ethiopia, 2021.

ANNEX 2: INFORMATION SHEET

Title of the research: Incidence to retinopathy and predictors among adult type two diabetic patients in Felege Hiwot Referral Hospital, Northwest Ethiopia, 2021.

Name of Principal Investigator: Gebrehiwot Dinku Admasu

Phone number: +251932911461

E-mail: gebrehiwot389@gmail.com

Name of the Organization: Bahir Dar University, collage of medicine and health science, school of public health, Department of Epidemiology and Biostatistics.

Sponsor for the project: Amhara Regional State civil service and human resource commission and Bahir Dar University in collaboration.

Purpose of the Research Project: - to assess the incidence of retinopathy and predictors among adult type two diabetic patients.

Risk: The study wasn't harmed patients and retrieved information was used for only the study purpose since the information for the study was collected from patient charts. The name of the patient wasn't recorded during data extraction and all information taken from patient charts was kept confidential.

Benefit: It had no direct benefit for one whose chart was included in this study. However; it will have direct benefits for health professionals and program managers.

ANNEX 3: DATA EXTRACTION TOOLS

This was data collection checklists intended to incidence to retinopathy and predictors among adult type 2 diabetic patients in Felege Hiwot comprehensive specialized Hospital from January 1st, 2010 to December 31st, 2019.

Name of data collector: _____date:_____sign:_____

Name of field supervisor: _____date: _____sign:_____

Checklist code _____ MRN _____

Principal Investigator: Gebrehiwot Dinku Admasu Phone number: +251932911461

Table 5: Baseline characteristics of type two diabetic patients in Felege Hiwot Hospital, Northwest Ethiopia, 2021.

Code	Checklist	Response	Skip if
01	Age in years		
02	Sex	1. Male 2. Female	
03	Residence	1. Urban 2. Rural	
04	Date of diabetic diagnosis (dd/mm/yy)		
05	Has the patient developed diabetic retinopathy?	1. Yes 2. No	
06	If the answer for Q_5 is yes, when was retinopathy diagnosed? (dd/mm/yy)		Q_5 is no
07	If the answer for Q_5 is no, what was the other outcome of the patient?	1. Not develop retinopathy 2. Loss to follow up 3. Transferred out 4. Death	Q_5 is yes
08	For Q_7, when was the outcome developed? (dd/mm/yy)		Q_5 is yes
09	How many years has the patient followed up?		
10	Family history of DM	1. Yes 2. No	

		3. unknown		
11	Type of treatment	. Insulin . OHA . Insulin + OHA		
Code	Checklist	Baseline	Last	Skip if
12	History of neuropathy	1. Yes 2. No	1. Yes 2. No	
13	BMI in kg/m2			
14	Hypertension	1. Yes 2. No	1. Yes 2. No	
15	Systolic blood pressure in mmHg			
16	Diastolic blood pressure in mmHg			
17	Poor glycemic control	1. Yes 2. No	1. Yes 2. No	
18	Fasting blood sugar in mg/dl			
19	HDL-C in mg/dl			
20	LDL-C in mg/dl			
21	Triglyceride in mg/dl			
22	Total Cholesterol in mg/dl			
23	Creatinine in mg/dl			
24	Hemoglobin level in mg/dl			
25	Protein urea	1. Positive 2. Negative	1. Positive 2. Negative	
26	Ketone bodies	1. Positive 2. Negative	1. Positive 2. Negative	