

Incidence and Predictors of Cardiovascular Disease among Type 1 and Type 2 Diabetes Mellitus in a Tertiary Health Care Setting of Ethiopia: 8-Year Retrospective Follow-Up Study

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Background: Cardiovascular disease (CVD) is a major cause of death and disability among people with diabetes in the world and it is proving to be a major barrier to sustainable human development. Despite CVD continuing to devastate human survival, few studies in Ethiopia have focused on its prevalence which alone are insufficient to assess the risk of incident cardiovascular events. Therefore, we determined the incidence and predictors of cardiovascular disease among diabetic patients in a selected tertiary healthcare setting of Ethiopia.

Methods: A retrospective cohort study using secondary data was conducted on 399 randomly selected diabetes patients. Data were entered using Epi-Data and analyzed using Stata version 14. Multivariable Weibull proportional hazards regression analysis was used to identify the predictors of CVDs (namely, coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD)) at 5% level of significance.

Results: After a median follow-up of 5.9 years, the overall incidence rate of CVD per 100 person-years (PY) was 2.71 (95% CI=16.9–17.6). The multivariable Weibull proportional hazard regression analysis showed a significant association of chronic kidney disease (CKD); (adjusted hazard ratio (AHR) [95% CI]=2.53 [1.36–4.72]), systolic blood pressure (SBP)≥140; (AHR [95% CI]=4.30 [2.12–8.73]) and triglyceride (TG)≥200 mg/dL; (AHR [95% CI]=5.10 [2.02–12.89]) with risk of incident CVD.

Conclusion: CVD is a public health problem among diabetic patients in Ethiopia. SBP≥140, chronic kidney disease, and high triglyceride were independent predictors of new CVD among diabetic patients. These findings emphasize the need of attention for CVD patients with CKD and hypertension (HTN) comorbidities and a longer follow-up period using a prospective study design to determine the long-term effects of predictors of CVD among diabetic patients.

Keywords: incidence, cardiovascular disease, predictors, type 1 and type 2 diabetes

Introduction

Many Sub-Saharan African (SSA) countries, including Ethiopia, are facing a high burden of noncommunicable diseases (NCDs).¹ Diabetes mellitus (DM) is one global epidemic NCD which has been estimated to affect 463 million peoples globally and 4.3% of Ethiopia's population according to the International diabetic federation in 2019.² Part of the severity of DM is explained by its association with risk of CVD and other clinical complications.³ Individuals with DM have a 2–8-fold

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higher risk of heart disease as well as an increased risk of mortality of up to 3-times,⁴ and CVD is responsible for 80% of the mortality in diabetes.⁵

CVDs are a group of diseases involving the heart or blood vessels and are now the leading cause of diabetes-related morbidity and mortality.⁶ Globally, there were an estimated 422.7 million cases of CVD, and Africa were one of the countries with the highest age-standardized prevalence in 2015.⁷ The age-adjusted incidence rate of CVD was 6,081.6 per 100,000 in 2017.⁸ According to a systematic literature review from 2007 to 2017, the magnitude of CVD among DM was about 32.2% in the world.⁹

CVD is among the world's leading killers, responsible for a combined 15.2 million deaths in 2016, increasing to 17.8 million in 2017, and has remained a leading cause of death in the last 15 years.^{8,10} According to 2015 global burden of disease data there were 418, 285, and 349 deaths per 100,000 due to CVD in central, western, and eastern SSA countries.⁷ CVD death has increased by more than 50% in SSA over the past three decades¹¹ and is inclined to happen at younger ages, leading to a high number of disability adjusted life years and most of them were attributed to DM.^{12,13}

Several epidemiological researchers around the world have identified older age and longer duration of DM,¹⁴ high density lipoprotein cholesterol (HDL-C) level,¹⁵ smoking and heavy alcohol consumption,¹⁶ HTN,^{17,18} poor glycemic control (high glycosylated hemoglobin (HbA1c)¹⁸ and TG¹⁹ to be independent predictors for incident CVD. In response to the recent rise of CVDs in developing countries, the World Health Organization (WHO) has identified very cost-effective interventions that are applicable even in low-resource settings for prevention and control of CVDs.²⁰

Although the WHO predicts a rapid increase of CVDs in SSA by 2030, researchers perceive that CVDs are not a priority public health problem in the region.²¹ This perception is undermining the existing burden of the problem in this continent. Despite CVDs continuing to devastate human survival through the premature deaths of its workforce in developing countries, the few studies in Ethiopia have been limited to cross-sectional studies, which alone are insufficient to assess the risk of incident cardiovascular events. Therefore, we determined the incidence and predictors of cardiovascular disease among diabetic patients, from 2012 to 2020.

Methods and Materials

Study Setting, Design, and Period

This was a retrospective follow-up study done at Jimma University Medical Center (JUMC) to assess the incidence and predictors of CVD among diabetic patients from September 5, 2012 to February 25, 2020. JUMC is one of the largest public hospitals in Jimma zone, Oromia regional state, Ethiopia. It is about 352 kilometers from Addis Ababa, the capital city of Ethiopia. Every year approximately 9,000 inpatients and 80,000 outpatients are served in the hospital, coming from a catchment population of about 15 million people. In addition to other services, chronic disease follow-up services are being provided and diabetic clinic is found separated from other chronic disease.

Study Population

Our reference population involves all type 1 DM (T1DM) and type 2 DM (T2DM) patients (age of 15 years and above) who had follow-up at JUMC and all newly-diagnosed T1DM and T2DM patients during the study period were our study population. The study population was recruited from September 5, 2012 to September 8, 2015 and each case was followed until February 25, 2020. Once diagnosed for T1DM or T2DM, follow-up immediately started for all patients. We followed our cohort of DM patients to measure the primary outcomes, and new cases of CVD were recorded among diabetic patients during the follow-up period. Diabetic patients with no history of CVD at baseline were included in the study. Patients with unknown date of diabetes and cardiovascular disease diagnosis were excluded from the study.

Measurements and Operational Definition

Our primary outcome was CVD and defined as the first non-fatal CHD, stroke, or PAD, diagnosed by specialized physicians based on the clinical assessment and confirmed using diagnostic tests. We excluded sudden death from the definition and only non-fatal CVD was included. A non-fatal CHD was confirmed using the WHO's criteria in the case of raised levels of cardiac biomarkers with either symptoms or electrocardiograms suggestive of ischemia.²² A non-fatal stroke was defined as typical dysfunction of neurology that lasts >24 hours excluding other diagnoses and was taken from patients records. Peripheral arterial occlusion was defined as an sudden onset arterial event with a duration of greater than 2

weeks, and resulted in symptomatic limb ischemia.²³ In cases when a subject had experienced greater than one endpoint, the first event was used to define the onset of CVD. Once patients were diagnosed with T1DM or T2DM they immediately started follow-up. Our independent variables include: socio-demographics, clinical parameters, laboratory, and comorbidities characteristics. Socio-demographics include: age, sex, and residence. Clinical and laboratory characteristics include: type of DM, type of treatment, family history of diabetes, body mass index (BMI), classified as low (<18.5 kg/m²), normal (18.5–24.9 kg/m²), and high (≥ 25 kg/m²) according to WHO criteria²⁴, HDL-C, low density lipoprotein cholesterol (LDL-C), TG, total cholesterol (TC), diastolic blood pressure (DBP), SBP, baseline fasting blood sugar (FBS), creatinine, and history of acute complication. The third characteristic assessed was the comorbidities and this includes HTN (based on physician-registered diagnosis on the medical record when SBP ≥ 140 mmHg and DBP ≥ 90 mmHg), diabetic retinopathy, CKD, and diabetic retinopathy.

Sample Size and Sampling Procedure

The final sample size of 424 was calculated using Schoenfeld formula for survival analysis²⁵ using 8.1% probability of events and 2.74 AHR of TG from previous studies.^{14,19} We assumed a 95% confidence level, 80% power and 10% of withdrawal probability, and this sample was computed using Stata version 14. Then subjects were selected using simple random sampling technique by collecting the identification number of DM patients from the registration book.

Data Collection and Quality Control

This secondary data was collected by trained nurses from the medical records of the study participants using a preliminary reviewed uniform checklist. This checklist was checked for consistency and completeness. Data was cross-checked and clarified for any missing data. We followed subjects from the date of enrolment (September 5, 2012) until they were diagnosed to have CVD or February 25, 2020 (study exit date). Patients with diagnosed CVD before the date of enrolment were excluded. Those who died or were lost to follow-up before the study exit date and were event free at the exit date were considered as censored during analysis.

Data Management and Statistical Analysis

Data were entered using Epi-Data version 4.6 and then exported to Stata version 14 for further data cleaning and analysis. Descriptive statistics like mean (standard deviation) or median (inter-quartile range) for continuous variables and frequencies (%) for categorical variables were used to describe the population. Cumulative incidence was computed by the number of new cases (CVD) per total initial population and incidence rate was calculated as the number of new cases per by PY at risk. Bivariable analysis with a *p*-value less than 0.2 were included in the multivariable regression. The Kaplan-Meier procedure was used to estimate the survival curves and Log rank test to compare survival time between groups of categorical variables. Schoenfeld residuals method was used to assess proportional hazard assumptions (PHA). The parsimonious survival model was selected based on Akaike Information Criterion (AIC) and goodness of fitness of the model was checked using Cox Snell residual plot. To deal with missing data, we compared the model for multiple imputed data with complete case analysis and the model with the lowest AIC was used for analysis. Finally, Weibull regression analysis was used to calculate the hazard ratios and variables with a significance level of <0.05 were used to identify the predictors of CVD.

Results

Out of 424 total sample, 25 (5.9%) subjects with incomplete records (unknown date of DM and CVD diagnosis and diagnosed CVD before the diabetes) were excluded, making a 94.1% response rate. Then 399 T1DM and T2DM patients were retrospectively followed from September 5, 2012, to February 25, 2020.

Socio-Demographic and Clinical Characteristics

The mean age at baseline was 43.93 ± 15.87 years, with minimum and maximum ages of 15 and 90 years, respectively. Male patients accounted for 61.4% and urban residents accounted for 59.15% of study participants, and a high proportion of CVD were from urban areas (65.6%). The majority (70.4%) of subjects had T2DM and SBP ≥ 140 constituted 36.8% of study participants. A high percentage of CVDs happened in T2DM (82.0%) and SBP ≥ 140 (77.1%). Further details on the socio-demographic and baseline clinical characteristics of the study sample are shown in Table 1.

Table 1 Socio-Demographic and Clinical Characteristics of Study Participants, 2020

Variables	Status of Cardiovascular Disease		Total (n=399)
	CVD (n=61)	No CVD (n=338)	
Age (mean±SD)	50.19±14.59	42.79±5.78	43.93±15.87
Sex			
Male	38 (62.3)	207 (61.2)	245 (61.4)
Female	23 (37.7)	131 (38.8)	154 (38.6)
Residence			
Urban	40 (65.6)	196 (58.0)	236 (59.2)
Rural	21 (34.4)	142 (42.0)	163 (40.8)
Family history of DM			
No	50 (82.0)	238 (70.4)	288 (72.2)
Yes	11 (18.0)	100 (29.6)	111 (27.8)
Type of DM			
T1DM	11 (18.0)	107 (31.7)	118 (29.6)
T2DM	50 (82.0)	231 (68.3)	281 (70.4)
Type of treatment			
OHA	37 (60.6)	176 (52.1)	213 (53.4)
Insulin	12 (19.7)	108 (31.9)	120 (30.1)
Both	12 (19.7)	54 (16.0)	66 (16.5)
Acute Complication			
No	31 (50.8)	198 (58.6)	229 (57.5)
Yes	30 (49.2)	139 (41.1)	169 (42.5)
BMI (kg/m ²)			
<18.5	2 (3.3)	24 (7.1)	26 (6.5)
18.5–24.9	12 (19.7)	238 (70.4)	250 (62.7)
≥25	47 (77.0)	76 (22.5)	123 (30.8)
DBP			
<90	31 (50.8)	240 (71.0)	271 (67.9)
≥90	30 (49.2)	98 (29.0)	128 (32.1)
SBP			
<140	14 (22.9)	238 (70.4)	252 (63.2)
≥140	47 (77.1)	100 (29.6)	147 (36.8)

Abbreviations: CVD, cardiovascular disease; SD, standard deviation; DM, diabetes mellitus; T1DM, type one diabetes; T2DM, type two diabetes; OHA, oral hypoglycemic agent; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; Kg/m², kilograms per meter squared.

Comorbidities and Laboratory Characteristics

Table 2 shows the study baseline laboratory and comorbidities characteristics of study participants. The median (IQR) of baseline FBS and creatinine was 186 (99) and 0.86 (0.52), respectively. Regarding the lipid profile of the study participants: 30.8%, 38.8%, and 23.6% of patients had TG ≥200 md/dL, LDL-C ≥100 md/dL, and HDL-C <40 md/dL, respectively. Nearly one fifth (20.3%)

Table 2 Laboratory and Comorbidities Characteristics of Study Participants, 2020

Variables	Status of Cardiovascular Disease		Total (n=399)
	CVD (n=61)	No CVD (n=338)	
Baseline FBS, Median (IQR)			
	178 (92)	242 (115)	186 (99)
Creatinine, Median (IQR)			
	1.1 (1.55)	0.81 (0.39)	0.86 (0.52)
Total cholesterol (mg/dL)			
<200	30 (49.2)	224 (66.3)	254 (64.3)
200–239	9 (14.7)	65 (19.2)	74 (18.7)
≥240	22 (30.1)	45 (13.3)	67 (17.0)
Triglyceride (md/dL)			
<150	9 (14.8)	183 (54.1)	192 (48.1)
150–199	11 (18.0)	73 (21.6)	84 (21.1)
≥200	41 (67.2)	82 (24.3)	123 (30.8)
LDL-C (md/dL)			
<100	24 (39.3)	217 (64.2)	241 (61.2)
≥100	37 (60.7)	116 (34.3)	153 (38.8)
HDL-C (md/dL)			
≥40	33 (54.1)	268 (79.3)	301 (76.4)
<40	28 (45.9)	65 (19.2)	93 (23.6)
Chronic kidney disease			
No	27 (44.3)	309 (91.4)	336 (84.2)
Yes	34 (55.7)	29 (8.6)	63 (15.8)
Diabetic retinopathy			
No	39 (63.9)	279 (82.5)	318 (79.7)
Yes	22 (36.1)	59 (17.5)	81 (20.3)

Notes: TC for 4, LDL-C for five and HDL-C for five subjects were missed.

Abbreviations: FBS, fasting blood sugar; IQR, interquartile range; mg/dL, milligram per Deciliter; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

and 15.8% of patients had diabetic retinopathy (DR) and CKD comorbid, respectively.

Incidence of Cardiovascular Disease among Diabetic Patients

We followed study subjects for a median follow-up period of 5.89 years (minimum of 0.66 and maximum of 7.50 years) after initiation of treatment for a total of 2,250.4 PY. The entire cumulative incidence of CVD in this study was 15.29% (61/399; 95% CI=12.07–19.18). The total incidence density was 2.71; 95% CI=2.11–3.48, with 2.82;

95% CI=2.05–, 3.87, and 2.55; 95% CI=1.69–, 3.83 per 100 PY among males and females, respectively (no significant difference, $p=0.876$). The incidence density was found to be 15.78; 95% CI=8.74–28.49, and 32.18; 95% CI=24.39–42.47, 1,000 PY in type 1 and type 2 diabetes respectively. Among diabetic patients who were free from any type of CVD at the start of study, the cumulative proportion of developing CVD was 0.0452, 0.0862, 0.1394, and 0.2511 at year 2, 4, 6, and at the end of the study, respectively (Figure 1).

Predictors of CVD among Diabetic Patients

To evaluate the effect of the number of factors on the risk of patients to develop new-onset CVD we fitted Weibull regression which has the lowest AIC compared to all other models (Cox, exponential, and Gompertz models). The tolerance of factors ranged from 0.48 to 0.89 and variance inflation ranged from 1.12 to 2.10, indicating an absence of multicollinearity. Schoenfeld residual to test the proportional hazards assumption was not significant (P -value for each variable ranged from 0.111 to 0.777, with a global P -value of 0.535) and indicates that PHA was satisfied. As well, the Cox Snell residual plot showed the goodness of fitness of the model was satisfied because the cumulative hazard plot follows 45 degrees or a straight line through the origin with slope one (Figure 2). As shown in Table 3, bivariate Weibull regression (95% CI of CHR) shows a significant association with age, type of DM, CKD, DR, DBP, SBP, BMI, HDL, LDL, TC, and TG with risk of CVD. But after adjusting for other variables in multivariable Weibull

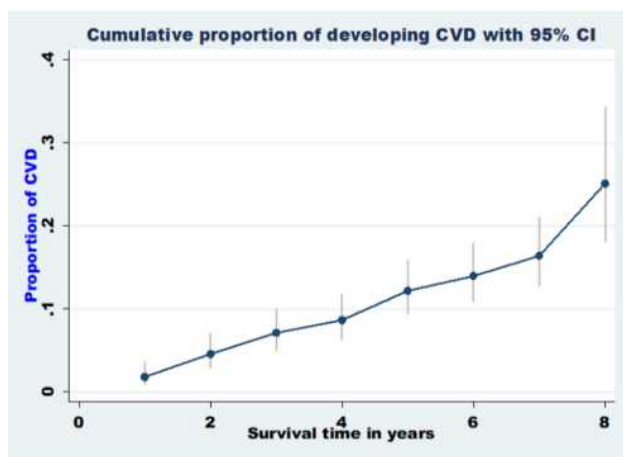


Figure 1 The life table graph showing cumulative proportion of CVD among diabetic patients over time with 95% confidence interval, 2020.

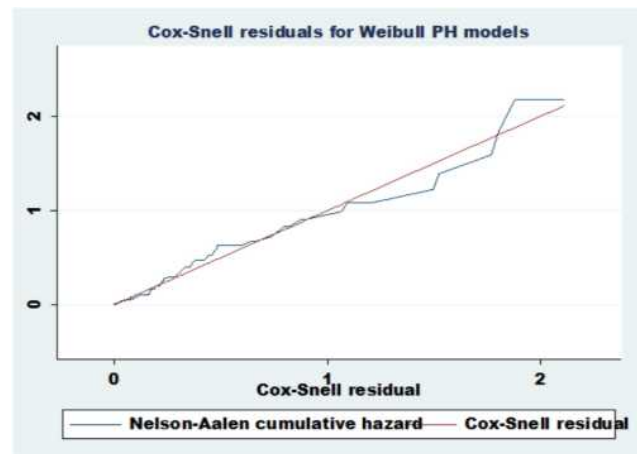


Figure 2 Cox-Snell residuals for Weibull PH models of incidence and predictors of incident CVD among diabetic patients, 2020.

regression, there are three independent variables (CKD, systolic HTN, and TG) that significantly determine the risk of CVD in diabetic patients. The risk of CVD was 2.53-times higher among diabetic patients with CKD as compared to those who have no CKD. The hazard of CVD among DM was 4.30-times higher for patients with systolic HTN as compared to their counterparts. Compared to patients with TG <150 mg/dL, diabetic patients with TG >200 mg/dL had a 5.10-fold higher risk for the incident CVD.

Discussion

CVD among patients with diabetes is a life-threatening disease with poor survival rates and it is associated with high healthcare expenditure. Thus, the current study investigated the incidence of CVD and its predictors among type 1 and type 2 diabetes mellitus in Ethiopia. A total of three factors were identified to determine the incidence of CVD and these factors include: CKD, systolic HTN, and TG.

The current study revealed 15.29% (95% CI=12.07–19.18) of cumulative incidence and 2.71 (95% CI=2.11–3.48) per 100PY of incidence density CVD among T1DM and T2DM patients during the median follow-up time of 5.89 years. Incidence of CVD differs substantially across different populations with diabetes based on the study setting, inclusion criteria, CVD outcome definition, and duration of the follow-up. Unfortunately, to our knowledge there were no longitudinal studies found in the literature related to CVD incidence among diabetic patients in the countries near to Ethiopia. However, worldwide, some studies showed a higher and others a much lower incidence of CVD compared to our study. The incidence of CVD in our study is in

Table 3 Multivariable Weibull Regression for Predictors of Incident CVD among Diabetes Mellitus Patients, 2020

Variables	Categories	CHR (95% CI)	AHR (95% CI)	P-value
Age	<45	1	1	
	≥45	2.21 (1.27–3.82)	1.30 (0.62–2.74)	0.483
Type of DM	T1DM	1	1	
	T2DM	2.07 (1.08–3.97)	0.43 (0.17–1.08)	0.072
CKD	No	1	1	
	Yes	8.15 (4.91–13.51)	2.53 (1.36–4.72)	0.003**
DR	No	1	1	
	Yes	2.19 (1.30–3.69)	1.07 (0.59–1.95)	0.815
DBP (mmHg)	<90	1	1)	
	≥90	2.31 (1.40–3.82)	0.82 (0.46–1.44)	0.485
SBP (mmHg)	<140	1	1	
	≥140	6.77 (3.73–12.30)	4.30 (2.12–8.73)	<0.001***
BMI (Kg/m ²)	<18.5	1	1	
	18.5–24.9	1.36 (0.18–10.43)	1.09 (0.14–8.39)	0.937
	≥25	11.27 (1.55–16.6)	3.39 (0.44–5.86)	0.239
HDL-C (mg/dL)	≥40	1	1	
	<40	2.82 (1.71–4.67)	0.69 (0.37–1.27)	0.234
LDL-C (mg/dL)	<100	1	1	
	≥100	2.46 (1.47–4.12)	0.95 (0.53–1.72)	0.869
TC (mg/dL)	<200	1	1	
	200–239	0.95 (0.45–2.01)	1.43 (0.19–1.97)	0.063
	≥240	3.02 (1.74–5.24)	1.82 (0.44–1.54)	0.539
TG (mg/dL)	<150	1	1	
	150–199	2.83 (1.17–6.83)	2.50 (0.91–6.88)	0.075
	≥200	7.96 (3.87–16.38)	5.10 (2.02–12.89)	0.001***

Notes: ** P-value<0.01 and *** P-value <0.001.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; DR, diabetic retinopathy; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; mg/dL, milligram per deciliter; TC, total cholesterol; TG: triglyceride; SBP, systolic blood pressure; T1DM, type one diabetes mellitus; T2DM, type two diabetes mellitus.

line with recent studies conducted in Italy (incidence rates of 28.8 and 23.3 per 1,000 PYs among men and women, respectively),²⁶ Sweden (25.4 per 1,000 PY),²⁷ and Africa (22.5 per 1,000 PY).²⁸ Our study revealed a higher incidence of CVD among diabetic patients as compared with studies conducted in the world. Studies in China¹⁴ and Oman²⁹ showed that 17.2 and 17.6 per 1,000 PY of CVD among DM within median follow-up periods of 5.3 and 5.6 years,

respectively. This difference was probably because of the higher proportion of DM patients in our study who had HTN, which contributes to the risk for developing CVD, compared to the general population.⁶ A facility-based study in Ethiopia¹⁹ and a population-based study in Italy²⁶ revealed an incidence rate of 16.7 per 1,000 PY and a cumulative incidence of 7.6%, respectively. Nevertheless, these two studies considered CHD alone as an outcome,

which might be the reason for the lower incidence of CVD compared to our study. However, our estimates of incident CVD were lower than those reported in Finland (cumulative incidence of 20.2%) with a mean age of 59.1 years³⁰ and a New Zealand cohort (incidence rate of 44.5 per 1,000 PY) with a mean age of 59.2 years.³¹ The possible reason for this lower incidence of CVD in our study could be due to the lower mean age of our study participants (43.93 years) compared to the studies in Finland and New Zealand. Age plays an important role in the deterioration of cardiovascular functionality.³² These functional changes in aging adult hearts have been characterized by diastolic, systolic, and electrical dysfunction, resulting in an increased risk of CVD in older adults.³³ For example, the American Heart Association (AHA) reported the incidence of CVD: approximately 40% among those aged 40–59 years, 75% among those aged 60–79 years, and 86% in those above the age of 80 years.³⁴ Another possible reason might be because our study included CHD, PAD, and stroke as CVD outcomes and excluded sudden death from the definition of the outcome. Due to methodological differences such as the methods of CVD diagnosis and study design, direct comparisons of study findings may not be feasible.

In our study, we found that, the presence of chronic kidney disease comorbid increased the incidence of CVD among diabetes by more than 2-fold as compared with their counterparts. The finding of increased incident CVD among DM patients with CKD in our study is consistent with previous reports in different parts of the world.^{14,35,36} Our finding also supports the current American Diabetes Association direction that regular assessment of estimated glomerular filtration rate (eGFR) and urine albumin creatinine ratio is part of routine care for DM patients and used for early identification of patients at high risk of CVD.³⁷ This study also revealed that renal function impairment (low eGFR and increased albuminuria) can increase the risk of CVD by 2–4-fold.³⁸ CKD is not only associated with risk of CVD, but also increases the CVD mortality by 2-fold in patients with stage 3 CKD and 3-fold in patients with stage 4 CKD when compared to patients with normal renal function.³⁹ CKD causes CVD through alteration of salt and water balance which predisposes to volume retention and alterations in vascular tone that together contribute to HTN.⁴⁰ Elevation in blood pressure initially causes extracellular fluid volume expansion and a rise in cardiac output. Subsequently, arterial pressure remains elevated and increases peripheral resistance which leads to CVD.⁴¹ The other means of CVD in CKD is through activation of renin, angiotensin, and aldosterone that

contributes to abnormal vascular tone, HTN, nephron loss, and finally leads to CVD.⁴²

Similarly, diabetic patients with systolic HTN comorbid had more than 4-fold higher risk of developing CVD than those who had no systolic HTN, which agrees with the findings from other longitudinal studies.^{14,18,43} Even though the recent guidelines by the American College of Cardiology and AHA showed importance of detection, evaluation and management of high blood pressure in reducing the risk of CVD,⁴⁴ a significant number of patients fail to achieve blood pressure targets in developing countries.⁴⁵ As an example, the findings from a regional survey of Middle East countries showed that, out of all HTN patients in the countries only 47% were being treated with antihypertensives and, of these, only 19% had blood pressures <140/90 mmHg.⁴⁶ Though there is no literature on how many hypertensive patients achieved the target blood pressures in Ethiopia, it is expected that an important number of patients target blood pressures are not being achieved. The other possible reason could be the damage of endothelial cell structure and functioning by high blood pressure that leads to abnormal growth of endothelial cells and vasoconstriction that predispose DM patients for vascular complications.⁴⁷

Another important finding of this study was that DM patients with TG \geq 200 mg/dL were around 5-times at higher risk of developing CVD than triglyceride <150 mg/dL and the association between CVD and TG 150–199 mg/dL was not significant. Such studies showing the high risk of developing CVD among diabetes with high TG has been previously reported.^{15,48} Due to the scarce amount of studies on causal associations between TG and CVD, attention was not given by researchers and physicians, mainly from cardiologists who should carefully assess patients at risk of CVD.⁴⁹ However, high levels of TG are common in DM patients due to the overproduction of TG-rich and reduced hepatic clearance for TG.⁵⁰ Mendelian randomization studies showed a significant association of triglyceride with the risk of CVD.⁵¹ Remarkably, the gene-based testing indicated that a rare genetic variation with lower TG was consistently associated with a reduced risk for CVD.⁵² Despite the above facts, a study reported that significantly elevated TG level (>1,000 mg/dL) is not always associated with CVD.⁵³ Therefore, further investigation about this issue is needed.

In spite of its strength, this study was not done without limitations. First, due to the retrospective nature of the data, we have not considered other potential predictors such as HbA1c, exercise, smoking, alcohol drinking, and diet due to their unavailability in the patients' card. Exclusion of fatal myocardial infarction and fatal stroke from the CVD definition may underestimate the incidence of CVD among DM patients. Also, a longer follow-up of 10 years and above would be required to determine the long-term predictors of CVD, while our study participants were only followed for a median of 5.89 years.

Conclusion

In conclusion, CVD is a public health problem among diabetic patients in Ethiopia and systolic HTN, chronic kidney disease, and high triglyceride were found to be independent modifiable predictors of incident CVD among DM patients. More attention should be given to diabetic patients, who had HTN, CKD, and high TG level. Studies with a longer follow-up period using a prospective study design are required to determine the long-term effects of predictors of CVD among diabetic patients.

Abbreviations

AHR, adjusted hazard ratio; AIC, Akaike Information Criterion; AHA, American Heart Association; BMI, body mass index; CI, confidence interval; CHR, crude hazard ratio; CKD, chronic kidney disease; CHD, cardiac heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IHD, ischemic heart disease; JUMC, Jimma University Medical Center; Kg/m², kilogram per square meters; KM, Kaplan–Meier; LDL-C, low-density lipoprotein cholesterol; NCDs, noncommunicable diseases; OHA, oral hypoglycemic agent; PAD, peripheral arterial disease; PHA, proportional hazard assumption; PY, person years; SSA, Sub-Saharan African; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; T1DM, type one diabetes mellitus; T2DM, type two diabetes mellitus; WHO, World Health Organization.

Data Sharing Statement

Data will be available from the corresponding author upon request.

Ethical Approval and Consent to Participate

Ethical approval for the study was obtained from the Ethical Review Board of University of Gondar and permission or waiver letter was obtained from the medical directors of JUMC to review the medical charts. Data confidentiality was kept during all phases of research activities and held on secured password protected system. This study was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors contributed to designation of the study, supervision of data collection, data analysis and interpretation, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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The authors reported no conflicts of interest for this work.

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