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Time to development of macrovascular complications and its predictors among type 2 diabetes mellitus patients at Jimma University Medical Center

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Abstract

Background Type 2 diabetes mellitus is a serious metabolic disease that is often associated with vascular complications. The increasing prevalence of type 2 diabetes mellitus poses significant public health challenges, particularly in Low and Middle-Income Countries where healthcare resources are often limited. In Africa, the burden of T2DM is rising rapidly, leading to a consequential increase in macrovascular complications such as cardiovascular disease and stroke. These complications not only affect the quality of life but also significantly contribute to morbidity and mortality among affected individuals. The main objective of this study was to assess the time to development of macrovascular complications and identify its predictors among type 2 diabetes mellitus patients in Jimma University medical center from 2018–2022.

Methods Institutional-based retrospective follow-up study was conducted in Jimma University Medical Center among newly diagnosed type 2 diabetes mellitus patient from 2018, to 2022. A systematic sampling technique was used to recruit 452 records of type 2 diabetes mellitus patients. The Kaplan–Meier curve and the log-rank tests were used to determine the time to macro-vascular complications, and evaluate the significant difference in survival probability among predictors respectively. The overall goodness of the Cox proportional hazard model was checked by Cox-Snell residuals. Bivariable and multivariable cox-proportional hazard regression were used to identify the association between the variables and survival time.

Results The median survival time to development of macro vascular complications was 24 months. Urban residence [(Adjusted hazard ratio = 2.02; 95% CI: (1.33, 3.05)], having hypertension at start of diabetic treatment [(AHR = 1.52; 95% CI: (1.06, 2.13)], baseline age ≥ 60 years [(AHR = 4.42; 95% CI: (1.72, 11.29)], having dyslipidemia at baseline [(AHR = 1.82; 95% CI: (1.13, 2.93)], High density lipoprotein cholesterol levels < 40 mg/dl [(AHR = 2.11; (1.16, 3.81)], triglycerides > 150 mg/dl [(AHR = 1.48; 95% CI:(1.02, 2.13)], Hemoglobin A1C level > 7% [(AHR = 1.49; 95% CI: (1.04, 2.14)], and Oral hypoglycemic agents + insulin [(AHR = 2.73; 95% CI: (1.81, 4.09)] were the significant predictors of the time to development of macro vascular complications.

Conclusion Findings in this study indicated that the median time to development of macro vascular complications among type 2 diabetes mellitus patients was 24 months. Baseline age category in years, residence, presence of hypertension, presence of dyslipidemia, High density lipoprotein-cholesterol level < 40 mg/dl, triglyceride > 150 mg/dl,

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HgbA1C > 7% at baseline, and medication regimens were identified as independent significant predictors of the time to development of macro vascular complications among type 2 diabetes mellitus patients. The findings call attention to the role of treatment regimens, particularly the use of combination therapies involving oral hypoglycemic agents and insulin, which were associated with increased hazards for complications. High incidence of macrovascular complications within a short follow-up period underscores the need for proactive, individualized care strategies in T2DM management. By focusing on early identification of at-risk patients and tailoring treatment plans accordingly, healthcare providers can potentially improve outcomes and reduce the burden of macro vascular complications in this population.

Keywords Type 2 diabetes mellitus, Time to macrovascular complications, Predictor

Introduction

Background

Type 2 Diabetes Mellitus (T2DM) is primarily caused by two factors, defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond appropriately to insulin [1]. This serious health condition arises when blood glucose levels are too high due to the body's inability to use insulin effectively. Over time, elevated blood sugar levels can severely damage blood vessels, leading to significant health complications that affect the entire body [2]. One of the main long-term consequences of uncontrolled T2DM is the development of macro vascular complications [3].

Macrovascular complications occur due to damage of large blood vessels and it is a disease that affects the large blood vessels, including the coronary arteries, the aorta, and the large arteries in the brain and limbs [4]. Macrovascular complications mainly refer to atherosclerotic cardiovascular disease, represented by coronary artery disease (CAD), Peripheral artery disease (PAD), and cerebrovascular disease (CBD) [5].

The burden of macro-vascular complications in type 2 diabetes is significant, contributing to increased morbidity and mortality among affected individuals. These complications, which include cardiovascular disease, cerebrovascular disease, and peripheral artery disease, lead to a higher risk of heart attacks, strokes, and amputations [3]. Patients often experience a reduced quality of life due to chronic pain, disability, and the psychological impact of living with these conditions. The economic burden is substantial as well, with increased healthcare costs stemming from hospitalizations, long-term care, and the need for medications and interventions [6].

Globally, Non-communicable diseases kill 41 million people each year, equivalent to 74% of all deaths. From 41 million deaths, diabetes mellitus kills 2 million people per year and ranked as the fourth numeral cause of death from common NCDs [6]. About 32.2% of people with T2DM worldwide are affected by CVD. CVD is a major cause of mortality among people with T2DM [7]. T2DM patients have a 2-to 4- fold increased risk of CVD [8, 9].

The overall prevalence of macrovascular complications among individuals with type 2 diabetes mellitus (T2DM) is 12.7%. This rate is highest in Europe at 26.7% and lowest in South-East Asia at 4.0%. Specific complications include 8.2% for coronary artery disease (CAD), 3.3% for heart failure, 2.2% for stroke, and 1.2% for peripheral arterial diseases (PADs) [10]. In low- and middle-income countries, the estimated prevalence of macrovascular complications in T2DM patients ranges from 1 to 40% for PAD, 5% to 10% for myocardial infarction, and 1% to 27% for ischemic heart disease.

In Africa, the crude prevalence of macrovascular complications is 10.7%, with CAD being the most common complication, ranging from 2.7% to 11.6% across various countries. In Sub-Saharan Africa, the prevalence of diabetes among individuals aged 20 to 79 has increased significantly over the past 25 years, with rates varying from 2.0% in The Gambia, 6.3% in the Congo, 9.3% in South Africa, to as high as 14.8% in Mauritius. In Ethiopia, 42.5% of T2DM patients are affected by cardiovascular disease, which includes hypertensive heart disease (38.99%), heart failure (6.83%), and stroke (2.20%) [8].

In 2019 T2DM the disability-adjusted life-years (DALY) rate was 801.5 per 100,000 people [11]. The anticipated cost of treating diabetes worldwide was estimated to be 966 billion US$ in 2021, and are projected to reach 1,054 billion US$ by 2045 [28]. In Ethiopia the burden of diabetes is exponentially increasing, with more than 68% of people with it being undiagnosed [12]. The death rate from CVD among T2DM patients in Ethiopia was 32% [8, 12]. The average monthly direct and indirect costs of diabetes per patient were US$28.73 and US$9.50, respectively [13].

T2DM determines a significant expenditure of the health system and substantial health losses. The expected Quality-Adjusted Life Year of a recently diagnosed T2DMs patient were 12.44 QALYs [14]. The common impacts related to DMs and its effect on patients' quality of life were mostly in the pain/discomfort (67.3%), dimension followed by mobility (60.5%), whereas the usual activities domain (34.1%) was the least health problem

[15]. Despite the fact that the prevalence of type 2 diabetes and its associated macrovascular complications is increasing, there is no current updated information on the survival time to development of macrovascular complications in Ethiopia, including the study area.

Preventing and managing macro-vascular complications in diabetes involves a comprehensive approach that includes regular monitoring and control of blood sugar levels through medications and dietary changes, alongside maintaining healthy blood pressure and lipid levels with lifestyle modifications and prescribed treatments [4]. Engaging in regular physical activity, achieving a healthy weight, and quitting smoking are crucial lifestyle changes. Routine health check-ups, including foot care, are essential for early detection of complications. Additionally, participating in diabetes education programs and adhering to prescribed medications can empower individuals to manage their condition effectively, significantly reducing the risk of developing serious complications [2, 7].

These studies have mentioned factors such as age, sex, residence, body mass index, duration of DM, presence of comorbidity such as dyslipidemia, and hypertension, family history of DM, duration of diagnosis of DM, total cholesterol level, LDL and HDL cholesterol level, and protein urea which were contributed to an increased likelihood of macrovascular complications in people with T2DM [8, 16, 17]. Without including those and similar variables, the clear picture of the determinants of the time to development of macrovascular complications wouldn't be sufficiently described. Therefore, the purpose of this study is to assess the survival time to development of macrovascular complications and identify it's predictors among T2DM patients in Jimma University Medical Center from 2018–2022, Jimma, southwest Ethiopia.

The findings of this study have a significant contribution to health institutions, and different stakeholders that help provide useful information about factors that hinder reduction of T2DM macrovascular complications development, forcing them to consider designing new programs or improving the quality and effectiveness of the current intervention programs on T2DM care practice through identifying the gaps and giving them more attention and decreasing T2DM macrovascular complications mortality. Lastly this study can be used as baseline data by other researchers for further investigation.

Methods and materials

Study area and period

The study was conducted in the Jimma Medical Center, Jimma Town, South-west Ethiopia. Jimma town is located 357 km southwest of Addis Ababa, the capital city of Ethiopia. Jimma Medical Center is the only major tertiary referral teaching hospital in the southwestern part of the country and currently it offers both inpatient and outpatient services to almost 18 million residents of the Jimma Zone and surrounding regions. It has different specialty clinics that give follow-up services; among these diabetic follow-up clinics is one of the chronic follow-up units. Around 1,141 Type 2 diabetes mellitus patients had been newly diagnosed and had undergone DM treatment follow-up between January 1, 2018 and December 31, 2022. All T2DM patients had follow-up visits every month. The study period was from June to July, 2023 G.C.

Study design and population

Institutional-based retrospective cohort study was conducted. The source population included all adult records (age 18 and older) diagnosed with T2DM and enrolled in the DM treatment or medical follow-up program in Jimma Medical Center. The study population included all adult records of T2DM patients who were on DM treatment follow-up programs from January 1, 2018, to December 31, 2022, in Jimma Medical Center.T2DM patient record was the study unit. All medical records of adult (age 18 years and older) T2DM patients registered for and on DM treatment follow-up programs from January 1, 2018, to December 31, 2022, in Jimma Medical Center were included in this study.T2DM patient records with incomplete date of diagnosis/treatment initiation and date of outcomes occurred were excluded from the study.

Sample size determination

The formula for manual calculation of the sample size in survival analysis was as follows. To estimate the sample size Schoenfeld DA group comparison formula is used [18, 19].

$$E = \frac{(Z_\alpha + z\beta)^2}{(\text{In HR})^2\ \text{PQ}}$$

Where:

E: the number of events required to be observed.

P: the proportion of exposed (4.06% or 0.0406 from the previous study) [17].

Q: is the proportion of non-exposed, (1-P), 1–0.0406 = 0.9594.

Zα is the critical value for the test at the specified type 1 error (e.g., 1.96 for a 2-sided test at α = 0.05).

$z\beta$: Power is the upper standard normal quantile at the desired power (0.84 for 80% power).

ln(HR) = the natural logarithm of the hazard ratio.

HR is the hazard ratio (from the previous study duration of diabetes 10 years on antidiabetic treatment was found to be a significant predictor of development of

macrovascular complications (HR: 2.05) [20]. By inserting all, the number of events required to be observed in the study, E = 384.

Then, the total sample size needed in order to achieve the calculated number of events was calculated using the following formula.

$$n = \frac{E}{Pr(E)}$$

n = total sample size.
E = Number of event to be observed.
Pr (E) = probability of success observed (0.95).
n = 384/0.95 = 411.

By inserting all the values in the formula the result is 411. By adding 10% missing data/incomplete data the total sample size has become 452.

Sampling technique and procedure

First, the DM clinic registration log book was reviewed for adults aged 18 and above diagnosed with T2DM and follow-up on DM treatment in Jimma Medical Center from January 1, 2018 to December 31, 2022. A sampling frame was prepared from the registration log book of T2DM patients that were registered at the DM clinic from 2018–2022 G.C. A systematic sampling technique was used to select 452records of T2DM patient from a total of 1,141 eligible T2DM records. Then the medical record numbers of the sampled T2DM records were reviewed.

Data collection procedures and data collection techniques

The study utilized a structured data extraction checklist to gather routinely recorded data from January 1, 2018, to December 31, 2022 G.C. This checklist covered various aspects, including general information, socio-demographic factors, comorbidities, clinical and anthropometric factors, laboratory and treatment-related factors of T2DM patients. Trained health professionals reviewed the records of all enrolled clients, with exclusion criteria applied as needed. Data collection involved identifying the medical record number, obtaining the corresponding chart, and extracting relevant data using a specified format. The primary outcome, macrovascular complications such as cerebrovascular disease, peripheral arterial disease, and coronary artery disease, was determined based on clinical decisions, with baseline characteristics assessed from the patient's records.

Study variables

Dependent variable

The primary outcome, time to development of macrovascular complications such as cerebrovascular disease, peripheral arterial disease, and coronary artery disease, was determined based on clinical decisions, with baseline characteristics assessed from the patient's records.

Independent variables

Socio-demographic variables (age, sex and residence), clinical variables (duration of DM, family history of CVD, types of treatment regimen, HDL-C level, LDL-C level, total cholesterol level, triglyceride level, HgbA1C level and protein urea), comorbidity variables(hypertension, diabetic ketoacidosis and dyslipidemia) and anthropometric variables(initial weight, height and BMI).

Data processing and analysis procedure

The data were checked manually for completeness and consistency. Then, the data were coded and entered into Epi-Data version 4.6 and transferred to STATA version 17.0, where they were cleaned, edited, recoded, and analyzed. Descriptive statistics were used in order to describe the percentage and frequency of the patients with respect to all variables. The mean with standard deviation and median with interquartile range were used to summarize normally and non-normally distributed continuous variables, respectively. However, the median was determined in the instance of survival time because censoring prevents the mean from providing correct information. The incidence of macrovascular complications with respect to time at risk was calculated for groups.

The time to macrovascular complications was estimated using the Kaplan–Meier method, and the log-rank tests were used to evaluate the significant difference in survival probability among categories of the predictor. A Cox proportional hazard model was used to identify factors contributing to time to development of macrovascular complications in T2DM patients. Variables with a p-value less than 0.25 in the univariable Cox proportional hazard model were included in the multivariable Cox proportional hazard model, and variables with a p-value less than or equal to 0.05 in the multivariable model were considered significantly associated with the response variable. The adjusted hazard ratios (AHR) with their 95% confidence intervals were computed to show the strength of the association.

The graphical examination of KM curves, the graphical examination of log (-log survival), and the presence of a time-dependent covariate were used to check the proportionality assumption of the cox-proportional hazard model. Martingule residuals and deviance residuals were used to check the linearity of the test and the presence or absence of influential observations or outliers respectively. The overall goodness of fit of the Cox proportional hazard model was checked by Cox-Snell residuals. The results were presented in tables, texts, and graphs based on the nature of the variable.

Operational definitions

Comorbidity:—Is the presence of one or more additional diseases co-occurring with a T2DM.

Coronary artery disease:—diagnosed as coronary diseases by the physicians on the client card.

Censored: is considered, lost to follow-up, death, transferred out before developing the event or be event-free at termination of the study.

Event:—development of macrovascular complications among T2DM patients followed from January 1, 2018 to December 31, 2022.

Hypertension diagnosed as HTN by the physicians on the client card.

Peripheral arterial disease (PAD):- diagnosed as Peripheral arterial diseases by the physicians on the client card.

Time to macro-vascular complication: is the time between newly diagnosedT2DM until the development of macro-vascular complications (in months).

Stroke: -diagnosed as stroke/cerebrovascular diseases by the physicians on the client card.

Results

Socio-demographic characteristics of the patients

The total number of 434 records of adult T2DM patients who were registered from January 1, 2018 to December 31, 2022, in JMC were reviewed and incorporated into the final analysis of the study. More than half (53.70%) of the participants were male. The mean (± SD) age of the patients at the beginning of DM treatment follow-up was 54.7 (± 11.80) years. Two hundred twenty-one (50.90%) of the participants were categorized as aged 40–59 years. Majority of the patients (55.76%), were urban dwellers (Table 1).

Table 1 Socio-demographic characteristics of T2DM patients in JMUC, Jimma, Southwest Ethiopia, from January 1, 2018–December 31, 2022 ($n=452$)

Variables	Category	Status at last contact		Total
		Macrovascular Complications	Censored	
Sex	Male	86(36.9%)	147(63.1%)	233(53.7%)
	Female	91(45.3%)	110(54.7%)	201(46.3%)
Age	Mean (SD): 54.7(SD ± 11.8) years			
Age category in years	18–39	5(10.0%)	45(90.0%)	50(11.5%)
	40–59	49(22.2%)	172(77.8)	221(50.9%)
	≥ 60	123(75.5%)	40(24.5%)	163(37.6%)
Residence	Rural	34(17.7%)	158(82.3%)	192(44.24%)
	Urban	143(59.1%)	99(40.9%)	242(55.76%)

Clinical, Comorbidity and Anthropometric characteristics of the patients

At the beginning of T2DM treatments, about 192 (44.2%) of patients had hypertension, and 34 (7.8%) of the study patients had dyslipidemia. At the start of anti-diabetic treatment, the mean (SD) FBS and RBS of T2DM patients were 185.10 (± 33.65) and 399.54 (± 89.16), respectively. Majority of the patients (68.9%) were a normal weight at the initial time of diagnosis, whereas 57 (13.3%) were obese. At baseline, about 250(58.3%) patients had HDL cholesterol levels more than 40 mg/dl, whereas more than half (55.3%) of the patients had triglycerides levels less than or equal to 150 mg/dl. About 200 (46.1%) of the patients had HgbA1C levels higher than 7%. Regarding the antidiabetic agents taken, about two hundred and sixty-four (60.8%) used oral hypoglycemic agents alone, eighty-one (18.7%) used insulin alone, and the remaining eighty-nine (20.5%) used insulin and OHAs together to manage their diabetes (Table 2).

Survival time to development of macrovascular complications among T2DM patients

In the current study, 434 patients with T2DM in total were followed from the point when T2DM was confirmed until the occurrence of macrovascular complications for up to 60 months. One hundred seventy-seven (40.78%) T2DM patients experienced macrovascular complications, and two hundred fifty seven (59.22%) were censored during the study's follow-up period. Following the beginning of anti-diabetic medication, the patients were followed for a minimum of 1 month and a maximum of 55 months, with a median follow-up time of 17.5 months (IQR: 12). The median (IQR) time to develop macrovascular complications was 24(IQR) months as presented in Fig. 1.

The total person-months of observations were found to be 7,929 person-months. The overall incidence rate of macrovascular complications among T2DM patients was 22.4 cases (95% CI: 19.4, 26.0) per 1000 person-months of observation. This lead to estimate the incidence of CAD at 5.9 (95% CI: 4.5, 7.8), PAD at 5.7 (95% CI: 4.6, 7.5), and cerebrovascular diseases (strokes) at 6.8 (95% CI: 5.0, 9.3) per 100 person-months of observation.

The incidence of developing macrovascular complications was higher in patients with dyslipidemia comorbidity at baseline (5.23 cases; 95% CI: 3.6, 7.6), patients greater than or equal to 60 years (4.6 cases; 95% CI: 3.9, 5.5), patients with HDL cholesterol less than 40 mg/dl (4.33 cases; 95% CI: 3.6, 5.1) per 100 persons-months observations, and triglycerides greater than 150 mg/dl (3.3 cases, 95% CI: 2.7, 4.0) per 100 persons-months observations.

Table 2 Comorbidity, clinical, and Anthropometric characteristics of T2DM patients in Jimma University Medical Center, Jimma, Southwest Ethiopia, from January 1, 2018 to December 31, 2022 G.C. ($n=434$)

Variables	Category	Status at last contact		Total
		Macrovascular complications	Censored	
Hypertension	No	59(24.4%)	183(75.6%)	242(55.8%)
	Yes	118(61.5%)	74(38.5%)	192(44.2%)
Diabetic ketoacidosis	No	125(38.5%)	200(61.5%)	325(74.9%)
	Yes	5247.7%)	57(52.3%)	109(25.1%)
Chronic kidney diseases	No	154(37.8%)	253(62.2%)	407(93.8%)
	Yes	23(85.2%)	4(14.8%)	27(6.2%)
Dyslipidemia	No	147(36.8%)	251(63.2%)	400(92.2%)
	Yes	28(82.4%)	6(17.6%)	34(7.8%)
DM duration	Mean(SD) DM duration:1.09(±0.78)			
BMI	Under weight	2(40%)	3(60%)	5(1.2%)
	Normal weight	73(24.4%)	226(75.6%)	299(68.9%)
	Over weight	54(74%)	19(26%)	73(16.8%)
	Obese	48(84.3%)	9(15.7%)	57(13.1%)
Medication regimen	OHA	63(23.9%)	201(76.1)	264(60.8%)
	Injection	45(55.6%)	36(44.4%)	81(18.7%)
	Both	69(55%)	20(45%)	89(20.5%)
SBP	Mean(SD): 129.51 (±18.60)			
DBP	Mean(SD): 84.64 (±11.04)			
FBS	Mean(SD): 185.10 (±33.65)			
RBS	Mean(SD): 399.54 (±89.16)			
Total cholesterol	≤200 mg/dl	44(17.5%)	207(82.5%)	251(57.8%)
	>200 mg/dl	133(72.7%)	50(27.3%)	183(42.2%)
HDL-cholesterol	≥40 mg/dl	42(16.6%)	211(83.4%)	253(58.3%)
	<40 mg/dl	135(74.6%)	46(25.6%)	181(41.7%)
LDL-cholesterol	≤100 mg/dl	64(24.0%%)	202(76.0%)	266(61.3%)
	>100 mg/dl	113(67.3%)	55(32.7%)	168(38.7%)
Triglyceride	≤150 mg/dl	64(26.7%)	176(73.3%)	240(55.3%)
	>150 mg/dl	113(58.2%)	81(41.8%)	194(44.7%)
Protein urea	Negative	115(32.6%)	238(67.4%)	353(81.3%)
	Positive	62(76.5%)	19(23.5%)	81(18.7%)
HgbA1C	≤7%	54(23.1%)	180(76.9%)	234(53.9%)
	>7%	123(61.5%)	77(38.5%)	200(46.1%)
History of CVD	No	135(34.6%)	255(65.4%)	390(89.9%)
	Yes	42(95.5%)	2(4.5%)	44(10.1%)

Among the censored T2DM patients, one hundred fifty-six (34.94%) had no macrovascular complications or terminated the follow-up period; forty-one (9.45%) were transferred out; twenty-three (5.30%) dead; and thirty-seven (8.53%) were lost to follow-up as presented in Fig. 2.

Comparison of Median survival time among different covariates

Kaplan–Meier survival curves were performed to compare survival probabilities between categories of different covariates. Additionally, log-rank tests were used to evaluate the significant difference in survival probability among predictors. In this study, the median survival time to the development of macrovascular complications in T2DM patients aged ≥60 years was shorter than that of patients aged 18–39 years. T2DM patients aged 18–39 years had high survival probability than T2DM patients aged ≥60 years. This was a statistically significant difference, with test statistics X^2 = 135.00 and P.Value < 0.001 as presented in Fig. 3.

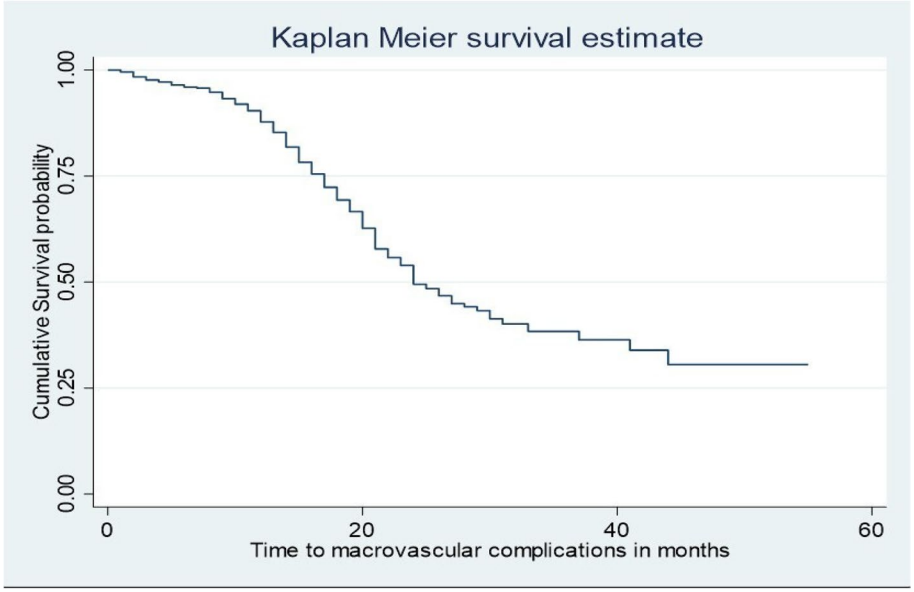

Fig. 1 Kaplan Meier graph for overall Survival functions for time to development of macrovascular complications among T2DM patients in JMUC, Jimma, Southwest Ethiopia from January 1, 2018 to December 31, 2022 G.C.(*n* = 434)

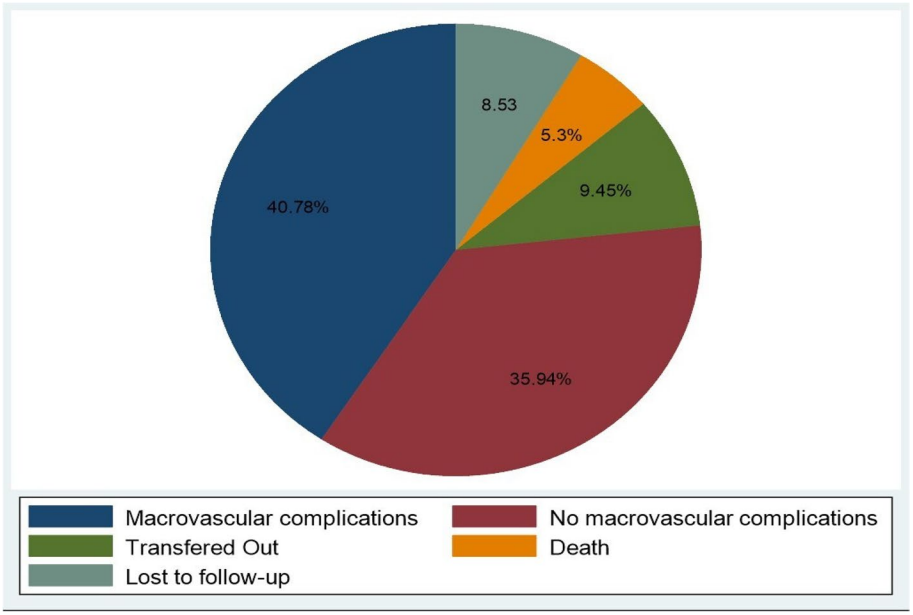

Fig. 2 Overall outcomes of adult Type 2 DM patients in JMUC, from January 1, 2018 to December 31, 2022 G.C

The median survival time for the development of macrovascular complications among urban residents was 21 months, whereas rural residents had no median survival time. Urban residence had a shorter survival time than rural residence. This was a statistically significant difference, with the test statistics X^2 = 53.85 and *P*. Value < 0.001 as presented in Fig. 4.

Test of proportional assumption (Model diagnosis)

When the necessary assumption of the Cox proportional hazard model was checked using the graphical examination of KM curve, they didn't cross each other. The graphical examination of log (-log survival) versus log (survival time) confirmed that the curves are roughly parallel, and the presence of a time-dependent covariate

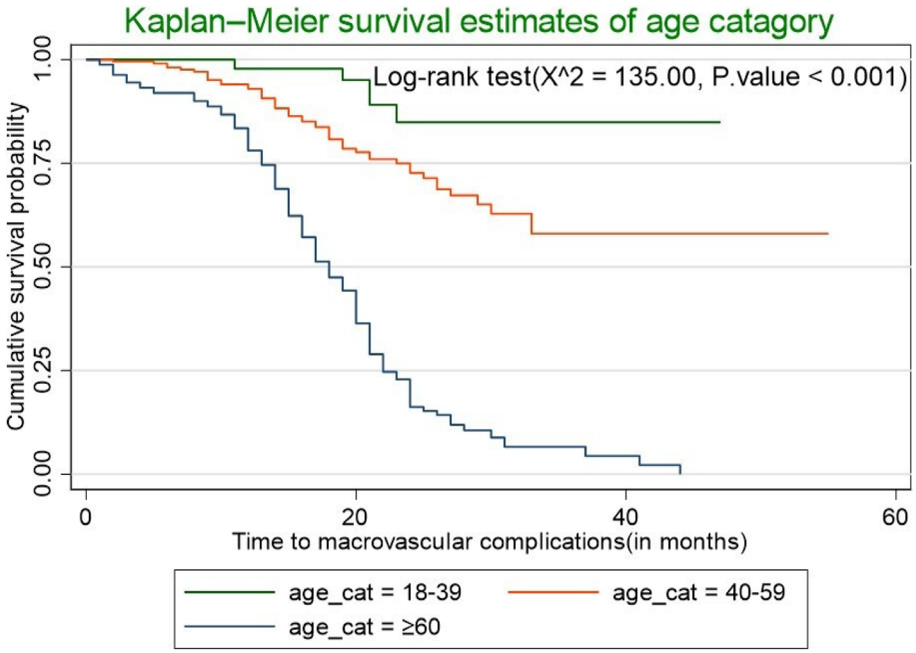

Fig. 3 Kaplan Meier and log rank survival estimated graph of time to development of macrovascular complications among T2DM patients by age category in JMUC, January 1, 2018 to December 31, 2022 G.C.(*n* = 434)

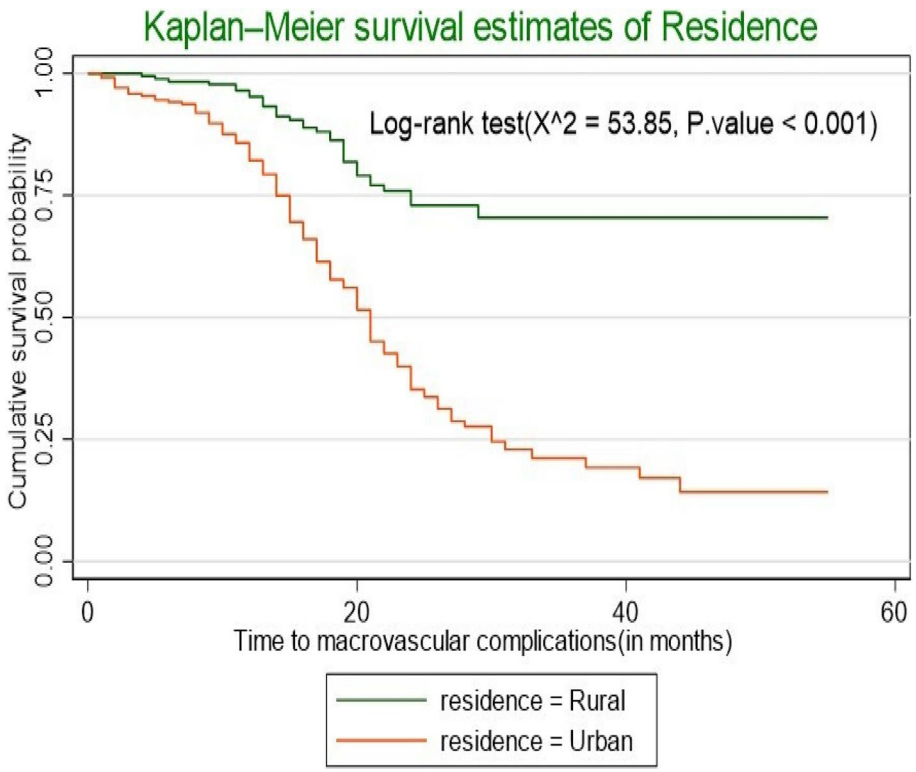

Fig. 4 Kaplan Meier and log rank survival estimated graph of time to development of macrovascular complications among T2DM patients by residence in JMC, January 1, 2018 to December 31, 2022 G.C.(*n* = 434)

in the model indicated the proportionality assumption of the cox-proportional hazard model. Martingale residuals and deviance residuals showed the linearity of the test and the absence of influential observations or outliers, respectively. The assumption of the Cox proportional hazard regression model was not violated, and the overall global test was 0.6799 with rho = 17.51 and 21 degrees of freedom.

Test of model goodness of fit

For the test of model fitness cox-Snell residual was used. The Cox-Snell residual plot indicated the goodness of fitness of the model was satisfied because the cumulative hazard plot followed 45 degrees, or a straight line, through the origin with slope one as presented in Fig. 5.

Predictors of time to development of macrovascular complications among type 2 DM patients

In this study, the development of macrovascular complications was classified as a failure event, while other outcomes were treated as censored data. To identify potential candidate variables for further analysis, univariable Cox proportional hazards regression analyses were conducted, revealing significant differences among the predictors. The multivariable analysis subsequently included variables with a p-value of less than 0.25 from the univariable analysis, ensuring that potentially relevant predictors were examined to provide a clearer understanding of the factors influencing the risk of developing macrovascular complications.

According to Table 3, the results of the univariable analysis indicated that several factors were associated with the development of macrovascular complications among T2DM patients. These factors included gender, baseline age category, residence, and comorbidities such as hypertension, diabetic ketoacidosis (DKA), and dyslipidemia at baseline. Additionally, lipid profiles including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, along with HgbA1C levels, proteinuria, family history of cardiovascular disease (CVD), and the medication regimen were also found to be significant predictors of macrovascular complications in this population.

According to the results of the multivariable analysis, several factors were identified as significant independent predictors for the time to development of macrovascular complications among T2DM patients after controlling for the effects of other variables. These predictors included a baseline age of 60 years or older, residence, the presence of baseline hypertension, baseline dyslipidemia, a baseline HDL cholesterol level of less than 40 mg/dl, a baseline triglyceride level greater than 150 mg/dl, a baseline HgbA1C level exceeding 7%, and the specific medication regimens prescribed to the patients.

The hazard of developing macrovascular complications among T2DM patients aged 60 years or older at

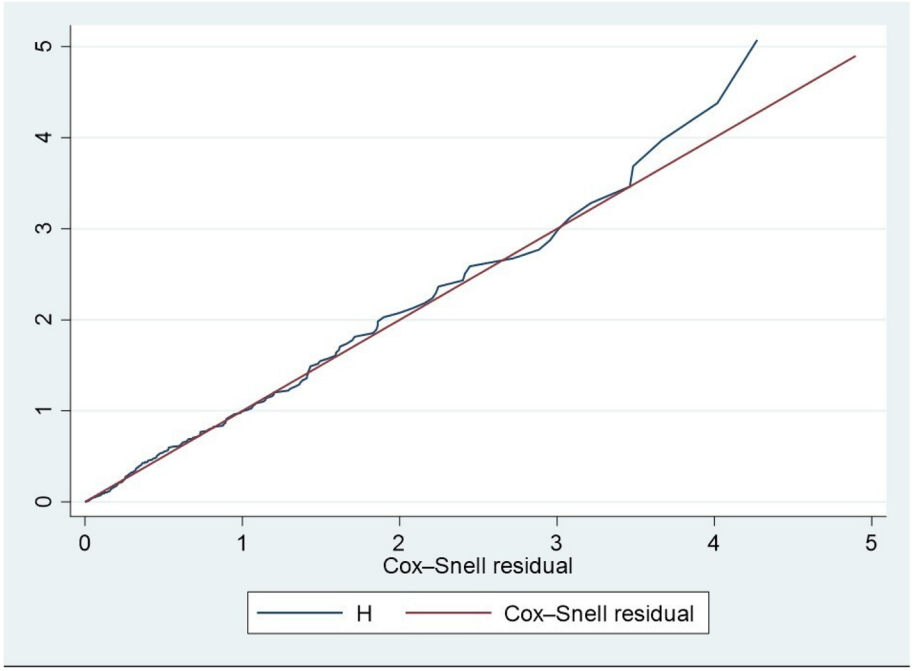

Fig. 5 Cox-Snell residual graph, based on the Kaplan Meier estimated survivor function, to test the overall goodness of fit cox-proportional model of time to macrovascular complications among T2DM patients in JMUC, January 1, 2018 to December 31, 2022 G.C

Table 3 Univariable and multivariable analyses using the Cox-proportional hazard model for predictor's of macrovascular complications among T2DM patients in JMC, Oromia Region, Southwest Ethiopia from January 1, 2018 to December 31, 2022 G.C

Variables	Category	Status at last contact		CHR(95% CI)	*P*. Value	AHR(95%CI)	*P*. Value
		Macrovascular Complications	Censored				
Gender	Female	91	110	1.27(0.95,1.70)	0.113	0.80(0.58,1.11)	0.188
	Male	86	147	1			
Age-category in years	≥ 60 years	123	40	13.81(5.62,33.93)	0.000	4.42(1.72,11.29)	0.002
	40–59 years	49	172	3.42(1.20,7.61)	0.018	2.28(0.89,5.82)	0.083
	18–39 years	5	45	1			
Residence	Urban	143	99	3.63(2.49,5.27)	0.000	2.02(1.34,3.05)	0.001
	Rural	34	158	1			
Hypertension	Yes	118	74	2.66(1.94,3.63)	0.000	1.50(1.06,2.14)	0.020
	No	59	183	1			
Dyslipidemia	Yes	23	4	3.11(2.07,4.68)	0.000	1.82(1.13,2.93)	0.014
	No	154	253	1			
BMI	Obese	48	9	2.99(0.72,12.38)	0.129	1.31(0.28,6.08)	0.733
	Overweight	54	19	2.99(0.72,12.38)	0.129	1.33(0.28,6.08)	0.733
	Normal weight	73	226	0.94(0.23,3.85)	0.935	1.40(1.13,2.93)	0.659
	Underweight	2	3	1			
Cholesterol	> 200 mg/dl	133	50	4.73(3.36,6.67)	0.000	1.38(0.75,2.53)	0.300
	≤ 200 mg/dl	44	207	1			
HDL-C	< 40 mg/dl	135	46	5.31(3.74,7.55)	0.000	2.11(1.16,3.81)	0.013
	≥ 40 mg/dl	42	211	1			
LDL-C	> 100 mg/dl	113	55	3.14(2.30,4.27)	0.000	0.73(0.48,1.11)	0.144
	≤ 100 mg/dl	64	202	1			
Triglyceride	> 150 mg/dl	113	81	2.43(1.78,3.31)	0.000	1.48(1.02,2.13)	0.037
	≤ 150 mg/dl	64	176	1			
Protein urea	Positive	62	19	2.76(2.02,3.77)	0.000	1.06(0.74,1.51)	0.737
	Negative	115	238	1			
HgbA1C	7%	123	77	2.84(2.06,3.92)	0.000	1.49(1.04,2.14)	0.029
	≤ 7%	54	180	1			
Family history of CVD	Yes	42	2	3.18(2.24,4.52)	0.000	1.25(0.84,1.88)	0.268
	No	135	255	1			
Medications	Both	69	20	5.39(3.79,7.66)	0.000	2.73(1.81,4.09)	0.0001
	Injections	45	36	2.47(1.68,3.63)	0.000	1.49(0.97,2.27)	0.062
	OHA	63	201	1			

the baseline of anti-diabetic treatment follow-up was found to be 4.42 times higher compared to those aged 18–39 years (AHR: 4.42; 95% CI: 1.72, 11.29). Additionally, T2DM patients residing in urban areas faced a 2.02 times greater risk of developing macrovascular complications than those living in rural areas (AHR: 2.02; 95% CI: 1.33, 3.05).

Similar to the previous findings, T2DM patients with hypertension comorbidity at baseline had a 1.50-fold increased risk of developing macrovascular complications compared to those who were non-hypertensive (AHR: 1.50; 95% CI: 1.06, 2.13). Furthermore, the risk of developing macrovascular complications was 2.11 times higher among T2DM patients with baseline HDL cholesterol levels of less than 40 mg/dl compared to those with levels of 40 mg/dl or higher (AHR: 2.11; 95% CI: 1.16, 3.81). Additionally, the hazard of developing macrovascular complications was 1.82 times greater among T2DM patients with baseline dyslipidemia at the start of diabetic treatment follow-up compared to those without dyslipidemia (AHR: 1.82; 95% CI: 1.13, 2.93).

By controlling for other variables as constants, the analysis revealed that HgbA1C levels of 7% or higher at the beginning of anti-diabetic treatment significantly

increased the risk of developing macrovascular complications by 1.49 times when compared to patients with HgbA1C levels below 7%. This finding underscores the importance of maintaining optimal glycemic control in T2DM patients to mitigate the risk of severe complications. Additionally, the study found that triglyceride levels greater than 150 mg/dl at the initiation of diabetic treatment were linked to a 52% increase in the hazard of developing macrovascular complications compared to those with triglyceride levels of 150 mg/dl or lower. This highlights the critical role of lipid management in the overall treatment strategy for T2DM patients.

Moreover, patients who were prescribed a combination of oral hypoglycemic agents (OHA) and insulin faced a significantly higher risk, with hazards being 2.73 times greater than those for patients using oral hypoglycemic agents alone (AHR: 2.73; 95% CI: 1.81, 4.09). This suggests that the complexity of treatment regimens may be associated with increased risk, potentially indicating that more intensive management is necessary for patients requiring combination therapy. Overall, these findings emphasize the need for comprehensive monitoring and management of glycemic and lipid levels, as well as careful consideration of treatment strategies in T2DM patients to reduce the risk of macrovascular complications.

Discussion

The results of this retrospective cohort study provide crucial insights into the time to development of macrovascular complications among adult T2DM patients at JMC, revealing significant implications for clinical practice and patient management. With a follow-up of 434 patients over 7,929 person-months, the study observed that 177 patients developed macrovascular complications, resulting in an incidence rate of 22.4 cases (95% CI: 19.4, 26.0) per 1,000 person-month observations. This indicates a considerable risk of complications in a relatively short period, highlighting the urgency for early intervention strategies. The median survival time of 24 months before the onset of macrovascular complications suggests that many patients may experience significant health deterioration soon after initiating anti-diabetic treatment. This finding emphasizes the need for healthcare providers to closely monitor patients during the early stages of treatment, particularly those with identified risk factors such as older age, hypertension, dyslipidemia, and poor glycemic control.

Baseline age category in years, residence, presence of hypertension at the beginning, presence of dyslipidemia at baseline, HDL-cholesterol level < 40 mg/dl at baseline, triglyceride > 150 mg/dl at baseline, HgbA1C > 7% at baseline, and medication regimens were identified as independent significant predictors for the time to development of macrovascular complications among T2DM patients.

The median survival time to the development of macrovascular complications in our study was significantly lower than that reported in studies from Kaiser Permanente Southern California (3.0 to 5.2 years) [21], the University of Gondar Referral Hospital (6.8 years) [17], and Felege Hiwot Referral Hospital at Bahir Dar (95 months) [22] respectivily. This variation may largely be attributed to differences in follow-up duration, as our study's 24-month follow-up period was considerably shorter than those in the aforementioned studies. Additionally, variations in patient demographics, such as age and comorbidities, as well as healthcare access and treatment protocols, could influence the progression of complications. Regions with better healthcare infrastructure may provide more effective management, potentially delaying the onset of complications, whereas limited resources may accelerate disease progression. Furthermore, lifestyle factors, including diet and physical activity, can significantly impact metabolic control and the risk of developing macrovascular complications. Collectively, these factors underscore the complexity of T2DM management and the necessity for tailored interventions that consider the unique characteristics of diverse patient populations to enhance long-term outcomes.

The findings in this study revealed an overall incidence rate of macrovascular complications among T2DM patients of 22.4 cases per 1,000 person-months of observation, which contrasts with the lower incidence rate of 11.9 cases per 1,000 person-year observations reported at Kaiser Permanente Southern California [21]. This discrepancy may be attributed to the differences in healthcare systems and the organization of diabetic care between developed countries and low- and middle-income (LMI) countries like Ethiopia. In more developed settings, diabetic care is often more structured and comprehensive, benefiting from better resource allocation, advanced treatment protocols, and a focus on preventive care. In contrast, the high incidence observed in our study may be linked to several systemic issues, including fragmentation of healthcare services, which can lead to inconsistent patient management; limited resources that hinder access to essential medications and monitoring equipment; inadequate training among healthcare professionals that affects the quality of care; and low health literacy among diabetes patients, which can impede effective self-management. These factors collectively contribute to the elevated risk of macrovascular complications in LMI countries, highlighting the urgent need for targeted interventions to improve diabetes care and patient outcomes in these settings.

In this study, baseline age greater than or equal to 60 years and urban residence were associated with an increased hazard of developing macrovascular complications among T2DM patients. This finding aligns with studies conducted in Ningbo, China [23], the Harari Region of Eastern Ethiopia [8], and Mettu Karl Referral Hospital [20], which similarly identified age and urban living as risk factors for vascular complications. The increased risk associated with aging can be attributed to physiological changes in the heart and blood vessels, which elevate the likelihood of developing cardiovascular disease (CVD) [24]. Additionally, older age is often linked to a higher prevalence of atherosclerosis and arteriosclerosis, exacerbated by the progression of diabetes. Urban residents tend to have a greater likelihood of experiencing risk factors such as obesity, physical inactivity, and irregular eating patterns, all of which further contribute to the risk of T2DM complications [20].

This study found that T2DM patients with a history of hypertension at the onset of treatment are at a higher risk of developing macrovascular complications, a result consistent with findings from studies in in Ningbo, China [23], South India [25], Saudi Arabia [26], Ethiopia [20], and the University of Gondar Referral Hospital [17]. The increased risk is largely due to hypertension's detrimental effects on endothelial function, which leads to reduced nitric oxide production and promotes vascular resistance. Moreover, chronic hypertension contributes to the development of atherosclerosis, a condition where plaque builds up in the arterial walls. The persistent high pressure can cause injury to the endothelium, facilitating the infiltration of lipids and inflammatory cells into the vessel wall. This process not only promotes plaque formation but also leads to vascular remodeling, which narrows the arteries and reduces blood flow to vital organs. Consequently, patients with both T2DM and hypertension are more susceptible to ischemic events, such as heart attacks and strokes, due to the compounded effects of these conditions. Additionally, hypertension often coexists with other cardiovascular risk factors, compounding the overall risk [27]. Therefore, effective management of hypertension in T2DM patients is crucial to prevent vascular complications, necessitating regular monitoring and comprehensive treatment strategies.

The study findings indicate that T2DM patients with a history of dyslipidemia at the onset of treatment are at an increased risk of developing macrovascular complications, consistent with research conducted in Jimma [28]. Dyslipidemia, characterized by elevated triglycerides and LDL cholesterol alongside reduced HDL cholesterol, is closely linked to insulin resistance, a key feature of T2DM. This insulin resistance leads to an increase in free fatty acid flow into the bloodstream, promoting lipid accumulation in arterial walls and fostering the formation of atherosclerotic plaques. Such plaques narrow arteries and restrict blood flow, heightening the risk of ischemic events like heart attacks and strokes [1]. Additionally, dyslipidemia can exacerbate inflammation and contribute to endothelial dysfunction, further compromising vascular health. The coexistence of dyslipidemia with other metabolic abnormalities, such as hypertension and obesity, complicates the risk profile for T2DM patients. Therefore, early detection and comprehensive management of lipid abnormalities through lifestyle modifications and pharmacological interventions are crucial to reducing the risk of macrovascular complications in this population.

This study showed that the risk of having macrovascular complications was increased by elevated triglyceride levels > 150 mg/dl and HDL-C levels < 40 mg/dl. This result was consistent with earlier research conducted at the University of Gondar Referral Hospital [17],which reported that patients with higher triglyceride and lower HDL cholesterol levels increased the risk of developing macrovascular complications. This might be a result of the fact that the function of HDL-C is to transport cholesterol away from the arterial wall and into the liver. Low HDL-C levels eventually increase the likelihood of fat accumulation and arthrosclerosis within the artery wall and damage the inner lining of the arteries, raising the risk of CHD, stroke, and other vascular complications. Excessive levels of triglyceride above the normal range (> 150 mg/dl) produce plaque in the arteries, increasing the risk of macrovascular complications [29].

This study revealed that T2DM patients with elevated HgbA1C levels greater than 7% are at an increased risk of developing macrovascular complications, a finding consistent with a Moroccan study [30]. Higher HgbA1C levels indicate poor glycemic control, which is linked to various vascular complications, including cardiovascular diseases. Additionally, the study found that the use of insulin and oral hypoglycemic agents (OHA) correlates with an increased risk of macrovascular complications, aligning with findings from studies in Ningbo, China [23] and Morocco [30], respectively. The Ethiopian T2DM management guideline recommends a stepwise approach, initiating treatment with lifestyle modifications, followed by the introduction of OHAs and insulin as the disease progresses. This suggests that the observed association between medication use and complications may reflect greater disease severity and chronicity rather than direct medication effects, as patients requiring insulin or multiple OHAs typically have more advanced diabetes [31]. Therefore, effective glycemic control and proactive management strategies are crucial for mitigating the risk of macrovascular issues, emphasizing the need for regular

monitoring of HgbA1C levels and tailored treatment plans to improve patient outcomes.

Conclusion and recommendation

The results of this retrospective cohort study provide crucial insights into the time to development of macrovascular complications among adult T2DM patients at JMC, revealing significant implications for clinical practice and patient management. With a follow-up of 434 patients over 7,929 person-months, the study observed that 177 patients developed macrovascular complications, resulting in an incidence rate of 22.4 cases per 1,000 person-month observations. The median survival time for the development of macrovascular complications among patients with type 2 diabetes mellitus (T2DM) was found to be 24 months. This finding underscores the relatively rapid onset of macrovascular complications in this patient population, highlighting the critical need for proactive and vigilant management strategies to mitigate the risk and impact of these complications.

The identified predictors, including baseline age category in years, residence, presence of hypertension at baseline, presence of dyslipidemia at baseline, HDL-cholesterol level < 40 mg/dl at baseline, triglyceride > 150 mg/dl at baseline, HgbA1C > 7% at baseline, and medication regimens were identified as independent significant predictors for the time to development of macrovascular complications among T2DM patients in Jimma University Medical Center. These factors can serve as crucial indicators for healthcare professionals in identifying individuals at higher risk and tailoring interventions to address modifiable risk factors early on. Overall, these findings emphasize the significance of early and comprehensive management strategies, including regular monitoring of relevant risk factors and timely intervention, to mitigate the development of macrovascular complications in individuals with type 2 diabetes mellitus.

The study's recommendations underscore the critical need for proactive and comprehensive measures to address macrovascular complications in patients with type 2 diabetes mellitus (T2DM). By emphasizing the importance of strengthening follow-up, continuous training, and supportive supervision programs for healthcare professionals, the study aims to enhance patient survival and reduce the incidence of macrovascular complications. This proactive and multidisciplinary approach to patient care and management reflects a commitment to improving the quality of care and outcomes for individuals living with T2DM. Furthermore, the study's findings, which identify significant predictors for the development of macrovascular complications, provide valuable insights for tailoring targeted interventions and early management strategies. In addition, the study's emphasis on the urgency of early intervention aligns with the broader goal of advancing the understanding and management of T2DM and its associated complications. These efforts are essential for improving the quality of care and outcomes for individuals living with T2DM and addressing the complex challenges posed by this prevalent and impactful disease.

Strength of the study

This study's exploration of the incidence and timing of macrovascular complications, as well as the identification of their predictors among patients with type 2 diabetes mellitus in clinical settings, may represent a pioneering effort within the country. Consequently, it has the potential to inform interventions aimed at addressing this critical issue. The study adds information to the existing body of knowledge on type 2 diabetes mellitus and its associated complications, paving the way for further research and clinical advancements. Furthermore, the study's findings align with the natural history of type 2 diabetes mellitus, thereby adding coherence and validity to the accepted facts about the occurrence of this disease.

Limitation of the study

The duration of diabetes reported in our study reflects the time from diagnosis at JMC. We acknowledge that this may not accurately represent the true onset of the disease, as many patients often seek treatment only after significant health deterioration. Additional the study has some limitations due to its retrospective nature, and it is unable to investigate the role of potentially important variables like self-care practices, physical activities, and smoking status in T2DM patients.

Abbreviations

AHR	Adjusted Hazard Ratio
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CBD	Cerebrovascular disease
CHD	Coronary Heart disease
CI	Confidence Interval
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DFU	Diabetic foot ulcer
DM	Diabetes mellitus
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HDL-C	High density lipoprotein cholesterol
HTN	Hypertension
IDF	International diabetes federation
JMUC	Jimma University Medical center
LDL-C	Low density; lipoprotein cholesterol
LMIC	Low and middle income countries
MVC	Macrovascular complication
NCD	Non-communicable disease
OHD	Oral antidiabetic drug
OHA	Oral hypoglycemic agent
PAD	Peripheral artery disease
QUALI	Quality-Adjusted Life Year
T2DM	Type 2 diabetes mellitus

T1DM Type 1 diabetes mellitus
WHO World Health Organization

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Authors' contributions
Abera Feyisa Adare: contributed to data collection, the conceptualization of the article, the article draft, design of the analysis and critical drafting for significant intellectual interaction. Firew Tiruneh Teyare: conceptualization of the article, the critical drafting for significant intellectual interaction and advised the paper. Buzuneh Tasfa Marine: conceptualization of the article, the article draft, design of the analysis, the thorough writing of the article, the critical drafting for significant intellectual interaction and the submission of the work. The final manuscript was read and approved by all authors.

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Data availability
The datasets used and or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by Jimma University institutional review board (IRB),Institute of Health with reference number (Ref.No. JU/IH/IRB/416/23). Formal support and ethical letters were obtained from Jimma University's IRB and given to the Jimma University Medical Center, which then wrote a permission letter to the DM clinic. Informed written consent was obtained from study participant. Jimma University institutional review board (IRB), Institute of Health was approved the written informed consent of study participants. The information gathered from the patient file will be handled with confidence. The programming of data extraction tools avoids the display of names and other private information. The Declaration of Helsinki's guiding principles were followed during the study's execution.

Consent for publication
Not applicable. No individual person's personal details, images, or videos are being used in this study.

Competing interests
The authors declare no competing interests.

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