TIME TO DEVELOPMENT OF MACROVASCULAR COMPLICATIONS AND ITS PREDICTORS AMONG TYPE 2 DIABETES MELLITUS PATIENTS IN JIMMA MEDICAL CENTER, JIMMA, SOUTHWEST ETHIOPIA, 2023. A RETROSPECTIVE FOLLOW UP STUDY.

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A RESEARCH SUBMITTED TO THE DEPARTMENT OF EPIDEMIOLOGY, FACULTY OF PUBLIC HEALTH, INSTITUTE OF HEALTH SCIENCES, JIMMA UNIVERSITY; IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR A DEGREE OF MASTERS OF PUBLIC HEALTH IN EPIDEMIOLOGY.

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JIMMA, ETHIOPIA.

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Abstract

Background: Type 2 diabetes mellitus is a serious metabolic disease that is often associated with vascular complications. One of the most feared and common complications of diabetes and primary cause of death in diabetic patients are macrovascular complications.

Objective: The 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 medical center from 2018–2022.

Methods: An institutional-based retrospective follow-up study was conducted in Jimma Medical Center among newly diagnosed T2DM patient from 2018, to 2022. A systematic sampling technique was used to recruit 440 records of T2DM patient. The data were coded and entered into Epi-Data version 4.6 and transferred to STATA version 17.0. The Kaplan-Meier curve and the log-rank tests were used to determine the time to macrovascular complications, and evaluate the significant difference in survival probability among predictors respectively. Bivariable and multivariable cox-proportional hazard regression had used to identify the possible association between the variable and survival time.

Results: The incidence rate of macrovascular complications was 22.4 cases/1000 person months of observation. The median time to development of macrovascular complications was 24 months. Urban residence (AHR: 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), HDL-C levels < 40 mg/dl (AHR: 2.11; 1.16, 3.81), triglycerides > 150 mg/dl (AHR: 1.48; 95% CI: 1.02, 2.13), HgbA1C level >7%(AHR: 1.49; 95% CI: 1.04, 2.14), and OHA + insulin (AHR: 2.73; 95% CI: 1.81, 4.09) were the significant predictors for the time to development of macrovascular complications.

Conclusion: - Findings in this study indicated that the incidence of macrovascular complications was high among type 2 diabetes mellitus patients' and remains a public health problem in the Jimma Medical Center. Baseline age category in years, residence, presence of hypertension at baseline, presence of dyslipidemia at baseline, HDL-cholesterol level <40mg/dl at baseline, triglyceride >150mg/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. Targeted intervention for T2DM patients with hypertension and dyslipidemia comorbidities should be in place to promote good survival time and reduce the death of T2DM patients.

Key words: - Type 2 diabetes mellitus, time to macrovascular complications, predictor,

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ABBREVIATION AND ACRONYMS

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

JMC Jimma Medical center

LDL-C Low density lipoprotein cholesterol

LMIC Low and middle income countries

MVC Macrovascular complication

NCD Non-communicable disease

OAD Oral antidiabetic drug

OHA Oral hypoglycemic agent

PAD Peripheral artery disease

T2DM Type 2 diabetes mellitus

T1DM Type 1 diabetes mellitus

WHO World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 Background

Type 2 Diabetes Mellitus (T2DM), is caused by a combination of two primary factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond appropriately to insulin(1). T2DM, one of the most common metabolic disorders, is characterized by chronically elevated blood glucose (hyperglycemia) and elevated blood insulin (hyperinsulinemia)(2). It is a serious health condition that occurs when blood glucose, or blood sugar, levels are too high as the body is unable to use insulin correctly(3).

Over time, having high blood sugar levels can seriously damage blood vessels, leading to serious health complications that affect the entire body(3). T2DM is the most common in adults and accounts for 90-95% of those with DM(4). The common major symptoms of T2DM are frequent urination, increased thirst, fatigue, sudden weight loss, slow healing cuts or wounds, and blurred vision(5, 6). The main consequences, in the long term, of uncontrolled T2DM, are Macrovascular complications(6).

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. It can have long-term effects on different parts of the body(7). Macrovascular complications mainly refer to atherosclerotic cardiovascular disease, represented by coronary artery disease (CAD), Peripheral artery disease (PAD), and cerebrovascular disease (CBD)(8).

Time to development of Macrovascular complication is the time span between the diagnosis of T2DM and the incidence (development) of Macrovascular complication. The median time to developments of Macrovascular complications was ranged from 3.0 to 5.5 years(9, 10).

Due to complex biochemical pathways involving hyperglycemia and insulin resistance, patients with diabetes are more likely to experience macrovascular complications(11). Typically, T2DM and accelerated atherosclerosis are not identified until late in the course of cardiovascular disease (CVD). As a result, many individuals experience difficulties at the time of diagnosis or soon after(12). Vascular complications results in serious physical damages which may lead to the death of Type 2 diabetes mellitus patients(13).

Being the most common cause of mortality in diabetic patients, CVD mortality accounts for 50.3% of all deaths in T2DM(14). This resulted in diabetes being proclaimed as a vascular

disease and it is the leading cause of cardiovascular death worldwide(15). Macrovascular complications are one of the most feared and common complications of DMs and the primary cause of death in diabetic patients(16).

In 2017, there were approximately 462 million people worldwide who had T2DM, or 6.28% of the population. Diabetes alone is accountable for almost 1 million death annually, ranking as ninth largest cause of death(17). In Ethiopia, there are 1.92 million people living with DMs and it is found to be the ninth leading cause of death related to its complications(18).

The mean direct and indirect cost of diabetic mellitus per patient per month was US$ 28.73 and US$ 9.50 respectively in Ethiopia(19). T2DM, together with its vascular complications, has a considerable negative influence on people's quality of life and healthcare delivery and raises diabetic mortality(20, 21). The incidence of vascular complications among T2DM patients remains a significant public health problem(22).

The Global Diabetes Compact was introduced by WHO, which is a bold new initiative. The aims of the Global Diabetes Compact is to mobilize global efforts to both reduce the risk of diabetes and ensure that every person who has been diagnosed with that as well has access to equitable, all-inclusive, cost-effective, and high-quality care(23). The National Diabetes Prevention Program is the new direction working to prevent or delay T2DM and participate in evidence-based, affordable, and high-quality lifestyle change programs to reduce their risk of T2DM and improve their overall health(22).

Despite the fact that the prevalence of T2DM and its associated vascular complications is increasing, there is no current updated information on the survival time to development of macrovascular complications in Ethiopia, including the study area.

In fact, this study gathered data on the onset of macrovascular complications and their predictors in T2DM patients. It is crucial to avoid and delay the development of macrovascular complications as well as disability and death due to macrovascular complications. Knowing the time to the development of macrovascular complications and its predictors among T2DM patients can help save lives.

1.2 Statement of the problem

Non-communicable diseases (NCDs) have been established as a clear threat not only to human health, but also to development and economic growth(24). Globally, NCDs kills 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(25). About 32.2% of people with T2DM worldwide are affected by CVD. CVD is a major cause of mortality among people with T2DM (14). T2DM patients have a 2- to 4- fold increased risk of CVD(16, 26).

According to the International Diabetes Federation (IDF), 10.5% (536.6 million people) of all people in the world would have diabetes by 2021, and that number would increase to 12.2% (783.2 million) by 2045. Diabetes prevalence was comparable between genders and was highest in people aged 75 to 79. In 2021, the prevalence was predicted to be higher in urban (12.1%) than rural (8.3%) locations and in high-income (11.1%) than low-income (5.5%) countries(27).

In 2019, the global age-standardized point prevalence for T2DM was 5282.9 which is an increase of 49%, since 1990(28). The prevalence of macrovascular complications among T2DM was 12.7% overall and was greatest in Europe (26.7%) and lowest in South-East Asia 4.0%. The crude prevalence was 8.2% for CAD, 3.3% for heart failure, 2.2% for stroke, and 1.2% for PADs respectively(29). In LMIC, the estimated prevalence of macrovascular complication among T2DM is ranging between 1%-40% for peripheral arterial disease, 5%-10% for myocardial infarction, and 1%-27% ischemic heart disease (28).

In Africa, there are an estimated 24 million adults who have diabetes, and by 2045, that number is predicted to increase by 129% to 55 million (29). In Middle East Africa the crude prevalence of macrovascular complications were 10.7%. Coronary artery disease was the numeral prevalent complications in all countries range from 2.7% to 11.6 %(30). In Sub-Saharan countries the prevalence of DMs in those aged 20-79 years has increased rapidly in the last quarter of a century with varying rates of 2.0% in the Gambia,6.3% in the Congo,9.3% in south Africa, and as high as 14.8% in Mauritius(31). In Ethiopia a total of 42.5% of T2DM patients had CVD, composed of hypertensive heart diseases (38.99%), heart failure (6.83%), and stroke (2.20%) (19).

Global deaths due to diabetes increased from 0.61 million in 1990 to 1.37 million in 2017, with a 125.5% increase. In 2019 T2DM the disability-adjusted life-years (DALY) rate was

801.5 per 100,000 people(28). 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(30). The death rate from CVD among T2DM patients in Ethiopia was 32% (26, 30). The average monthly direct and indirect costs of diabetes per patient were US$28.73 and US$9.50, respectively(19).

T2DM is determines a significant expenditure of the health system and substantial health losses. The expected QALY of a recently diagnosed T2DMs patient were 12.44 QALYs(31). The commonly 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(32).

Some retrospective and cross-sectional research on the occurrence, prevalence, determinants, and predictors of T2DM and its vascular complications has been done in Ethiopia. Even though many cross-sectional studies have been done, their level of predictability is low and they can't identify which came first. A little study has been conducted on estimating the survival time to the development of micro vascular complications in T2DM patients and its predictor factors.

A retrospective cohort study was conducted among a total of 159 T2DM patients enrolled between December 2011 and December 2012 at Felege Hiwot Referral Hospital. This has an inadequate patient sample and a short follow-up period. Because of the natural history (requiring long-term periods) of the diseases being studied, the study's two-year time frame is too short for this particular topic. So, inadequate a sample size and too short a follow-up period create bias, which affects the validity of the research. Despite the fact that the prevalence of type 2 diabetes mellitus 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.

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, triglyceride level, HgA1C level, protein urea and medication regimens which were contributed to an increased likelihood of macrovascular complications in people with T2DM (20, 26, 33). 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 JMC from 2018–2022, Jimma, southwest Ethiopia.

This study will be proposed to fill the listed gaps by increasing the sample size and follow-up period. In fact, this study generates evidence about the development time of macrovascular complications and identifies its predictors among T2DM patients. It is crucial to avoid and delay macrovascular complications development, as well as disability and death due to macrovascular complications among T2DM patients. Knowing the time to the development of macrovascular complications and identifying its predictors among T2DM patients can help to save lives.

1.3 Significance of the Study

The global burden of macrovascular complications due to T2DM is high in terms of morbidity and mortality. A different study revealed that the burden due to T2DM is higher than that of other chronic illnesses due to the cost of treating and managing its complications. To proceed with prevention, it is preferable to first understand the time to development and predictors of macrovascular complications.

The findings of this study have a significant contribution to different stakeholders, first for JMC, other health institutions, and 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.

Second, it is hoped that this study should help health care providers in local settings and other parts of the country to know the hazards and the major factors contributing to T2DM macrovascular complications development and enhance evidence-based practice implementation to reduce T2DM macrovascular complications mortality. Third, this study was used as baseline data by other researchers for further investigation.

CHAPTER TWO: LITERATURE REVIEW

2.1. Macrovascular complications

Macrovascular complications occur due to damage of large blood vessels and it is the disease that affects these blood vessels, including the coronary arteries, the aorta, and the large arteries in the brain and limbs(7). In LMIC, the estimated prevalence of macrovascular complication among T2DM is ranging between 1%-40% for peripheral arterial disease, 5%-10% for myocardial infarction, and 1%-27% ischemic heart disease (28). A study revealed that the Patients with T2DM are at a higher risk of developing coronary artery disease (CAD) than are non-T2DM patients(34).

In Ethiopia the studies revealed that the crude prevalence was 8.2% for coronary artery diseases, 3.3% for heart failure, 2.2% for stroke, 1.2% for peripheral artery disease (35). The risk of stroke in diabetic patient is 1.34 times higher than those without diabetes(36).

One of the most prominent macrovascular complications of diabetes mellitus, peripheral arterial diseases (PAD), is linked to cardiovascular mortality and a high rate of impairment after the amputation of an extremity in diabetic patients. The study was conducted on 280 T2DM patients the prevalence of PAD was 30.7% among these, 37 (43%) were symptomatic. Study has shown that there is a 28% increase in the risk of atherosclerotic PAD for each incremental 1% increase in glycosylated hemoglobin(37).

Similar study indicated that the prevalence of DFU among T2DM was 21.1%. the risk of increased diabetes ulcers who were starting treatment with insulin 4.43 times, obesity 27.76, delay to start follow-up 2.22, history of infection 3.50, and hypertension 3.99 respectively(38).

2.2 Time to Macrovascular complications development among T2DM

The median time to incidence of a T2DM complication ranged from 3.0 to 5.2 years, according to an observational retrospective cohort study on the prevalence and incidence of micro vascular and macrovascular complications over 15 years among patients with incident T2DM conducted at Kaiser Permanente Southern California. The high incidence rate of T2DM macrovascular complications was 11.9 per 1000 person year (39).

A 3-year, prospective observational study program conducted across 38 countries showed that the cumulative probability of developing vascular complications among type 2 DM patients

who were free of any complications at the start of treatment increased as the duration of diabetes increased during the follow up period(29). Similar studies revealed that the crude prevalence was 8.2% for CAD, 3.3% for heart failure, 2.2% for stroke, 1.2% for PAD(35).

A retrospective cohort study conducted on Predictors of vascular complications among T2DM in University of Gondar Referral Hospital revealed that the incidence of vascular complications was found to be 40.6 cases per 1000 person year observation. From the incidence of Macrovascular complications included stroke was 17.0, CHD was 16.7 and PAD was 15.1 cases per 1000 persons per year of observation. At a median follow-up duration of 6.8 years, the overall incidents of vascular complications during the study period were 28%(20).

A similar study conducted at Felege Hiwot referral Hospital at Bahir Dar, Northwest Ethiopia showed that a total of 387 patients were followed retrospectively for a median follow-up time of 95 months. With an incidence rate of 4 cases per 100 person-years of observation, 66 (17.05%) individuals out of the total developed DFU(40). Another retrospective cohort study conducted among type 2 diabetes mellitus patients at Felege Hiwot referral Hospital showed that the incidences of stroke, CHD, and PAD were 5.4, 8.1, and 13.5 cases per 100-person year of observation respectively. The overall mean and median estimated survival time of patients under the study were 24.77 and 20 months respectively(13).

2.3 Predictors of Macrovascular complication among T2DM

For effective prevention of Macrovascular complications development in T2DM patients, identifying factors that have an influence on the development of Macrovascular complication is very important. According to different studies conducted in different parts of the world, the common possible factors associated with Macrovascular complications development in T2DM patients were socio-demographic factors (baseline age in years, sex of the patient, and place of residence, clinical factors (duration of DM, anti-DM taken, total cholesterol level, LDL cholesterol level, HDL cholesterol level, Protein urea), presence of comorbidities at baseline (presence of dyslipidemia and HTN), and anthropometric (baseline weight and height, BMI).

2.3.1 Socio-demographic factors for macro vascular complication among T2DM

Factors in this group are age, sex, and place of residence of the patients. A retrospective data based study conducted on the prevalence and associated predictors of vascular complications

in inpatient T2DM at a tertiary care department; Ningbo, China indicated that the hazards of Macrovascular complications increased with aged greater than 60years among T2DM patient (18–39 years: 1; 40–59 years: 6.54; and >60 years: 15.98 respectively) and lower in women than in men (0.65)(41).

A cross-sectional multi-stage survey conducted on the prevalence of micro vascular and macro vascular complications and their risk factors in T2DM in Saudi Arabian Population revealed that age is the significant predictors of macro vascular complications among T2DM Population. For each year increase in age, the probability of developing Macrovascular complications in diabetic patients increased by 1.05 times(42). A Hospital based cross-sectional study conducted on prevalence of vascular complications among T2DM patients in South India indicated that females had lower risk of associated diabetic foot than males(15).

A retrospective cohort study conducted on the factors of vascular complication among T2DM patients at University of Gondar Referral Hospital revealed that the risk of developing vascular complications is decreased by 50% among male T2DM patients than female patients(20). The hospital-based retrospective data review was conducted in Harari Region, Eastern Ethiopia revealed that age older than 60 years T2DM patient were more than 3 times higher to develop Macrovascular complication than their counter parts (26).

A prospective observational study was done on people with diabetes attending the ambulatory clinic of Mettu Karl Referral Hospital showed that Urban residents were 1.94 times more likely develop Macrovascular complication than rural residents(43).

2.3.2 Clinical factors for Macrovascular complication among T2DM.

Several studies demonstrated that duration of diabetes as risk factors for the development Macrovascular complication among T2DM patients. A literature review for the predictors associated with T2DM complication conducted in George Town, Malaysia revealed that longer duration of diabetes increases the risk of CVD complication in T2DM. This may suggest early prevention of diabetes itself may play an important role in reducing the risk of Macrovascular complications(44).

A retrospective data based study conducted on the prevalence and associated factors of vascular complications among inpatient T2DM at a tertiary care department; Ningbo, China revealed that the hazards of patients having T2DM for >10 years were 2.75 higher to develop Macrovascular complication than patients having T2DM ≤1 year. The hazards of patients on

lifestyle modification + oral antidiabetic drug (OAD) + insulin were 1.57 times higher than patients on lifestyle modification alone (41).

A cross-sectional study conducted in Morocco indicate that a large proportion of the diabetic participants (62.5%) had a family history of diabetes, and 37.8% had T2DM for ten years or more, and also Half of the patients (49.9%) were treated only with oral hypoglycemic agents (OHA), 73.4% of them had HbA1c values > 7%(45).

According to a retrospective follow-up study on predictors of vascular complications in T2DM patients at University of Gondar Referral Hospital, positive protein urea at the beginning of diabetes treatment increased the risk of vascular complications by 69% in comparison to negative protein urea. In comparison to HDL-C levels below 40mg/dl at the beginning of anti-diabetic medication, HDL-C levels above 40mg/dl reduced the chance of vascular complications by 57%. Compared to patients with baseline LDL-C less than 100mg/dl, those with baseline LDL-C greater than 100mg/dl had a 3.05 times greater risk of having cardiovascular disease. In comparison to triglyceride levels below 150 mg/dl, triglyceride levels above 150 mg/dl at the start of anti-diabetic medication raised the risk of vascular problems by 2.74 times(20).

A prospective observational study was done on people with diabetes attending the ambulatory clinic of Mettu Karl Referral Hospital showed that the risk of Macrovascular complications were 2.05 times higher in durations of diabetes ≥10 years than durations of diabetes ≤10 years(43).

2.3.3 Comorbidity factors for development of Macrovascular complication

A retrospective data based study conducted on the prevalence and associated factors of vascular complications among inpatient T2DM at a tertiary care department; Ningbo, China indicated that the risk of Macrovascular complication in diabetic patients were 1.47 times higher in hypertensive diabetic patients than no hypertensive diabetic patients(41). In South India's rural health center, a hospital-based cross-sectional study on the prevalence of vascular problems among T2DM patients found that hypertension and longer diabetes duration were associated with an increased risk of cerebrovascular diseases(15).

According to a cross-sectional multi-stage survey on the prevalence of macro and micro vascular complications and their risk factors in the Saudi Arabian Population, the development of macrovascular complications among T2DM patients was positively correlated

with hypertension. Macro vascular complications were 2.71 times more likely to occur in diabetics with hypertension than in diabetics without hypertension(42). A similar study carried out in the United Arab Emirates revealed that dyslipidemia and hypertension are prominent co-morbidities in type 2 diabetic patients. Type 2 diabetes comorbidities of dyslipidemia (93.43%) and hypertension (83.40%) were prevalent(46, 47).

A prospective observational study conducted on the prevalence, patterns and predictors of chronic complications of Diabetes mellitus at a large referrer Hospital in Ethiopia revealed that duration of diabetes greater than 10 years and having hypertension comorbidity increase the risk chronic vascular complication. Chronic diabetes complications were 4.19 times more likely among participants who had hypertension when compared to participants who had no hypertension(43).

According to systematic reviews and meta-analyses conducted in Ethiopia, the overall magnitude of modified risk factors hypertension and dyslipidemia among stroke patients were 49% and 20.99% respectively(48). According to a retrospective cohort study on the predictors of vascular complications among T2DM patients in University of Gondar Referral Hospital, patients who had hypertension at baseline had a 3.99-times higher risk of vascular complications than those who did not. This showed a considerable positive correlation between the development of macrovascular complications and hypertension in T2DM patients(20).

According to a retrospective study carried out in the Harari Region of Ethiopia, T2DM patients with hypertension had a 2.41-times higher risk of developing macrovascular complications than those with non-hypertensive T2DM. The development of macrovascular complications in T2DM and hypertension are strongly correlated(26). A prospective observational study was done on people with diabetes attending the ambulatory clinic of Mettu Karl Referral Hospital showed that the risk of Macrovascular complications were 4.15 times higher in hypertensive patients than patients without hypertension(43).

2.3.4 Anthropometric Factors for macro vascular complication among T2DM.

There is a association between BMI and heart failure, according to a systematic literature analysis on the frequency of cardiovascular illness in T2DM patients worldwide between 2007 and 2017. The prevalence rate of heart failure was 38.7% in patients with a BMI ≥ 30 kg/m^2 and 23.4% in those with a BMI < 30 kg/m^2, which represents a 65% increase due to obesity (14). A cross-sectional study conducted in Morocco indicate that a large

majority of the population studied were in the overweight or obesity range with 50.4% of cases in obesity(45).A retrospective study conducted in Harari Region, Ethiopia revealed that the odds having body mass index >24.9 kg/m^2 T2DM patient were 1.81 times higher to develop Macrovascular complication than patient having body mass index <24.9 kg/m^2)(26).

2.3 Conceptual frame work

To address the associated factors of time to development of macrovascular complications, a conceptual frame work was developed based on review of different literatures (7, 13, 26, 28, 29, 34-47). The influence of socio-demographic, comorbidity, clinical and anthropometric factors on time to development of macrovascular complications is depicted in the following figure 1.

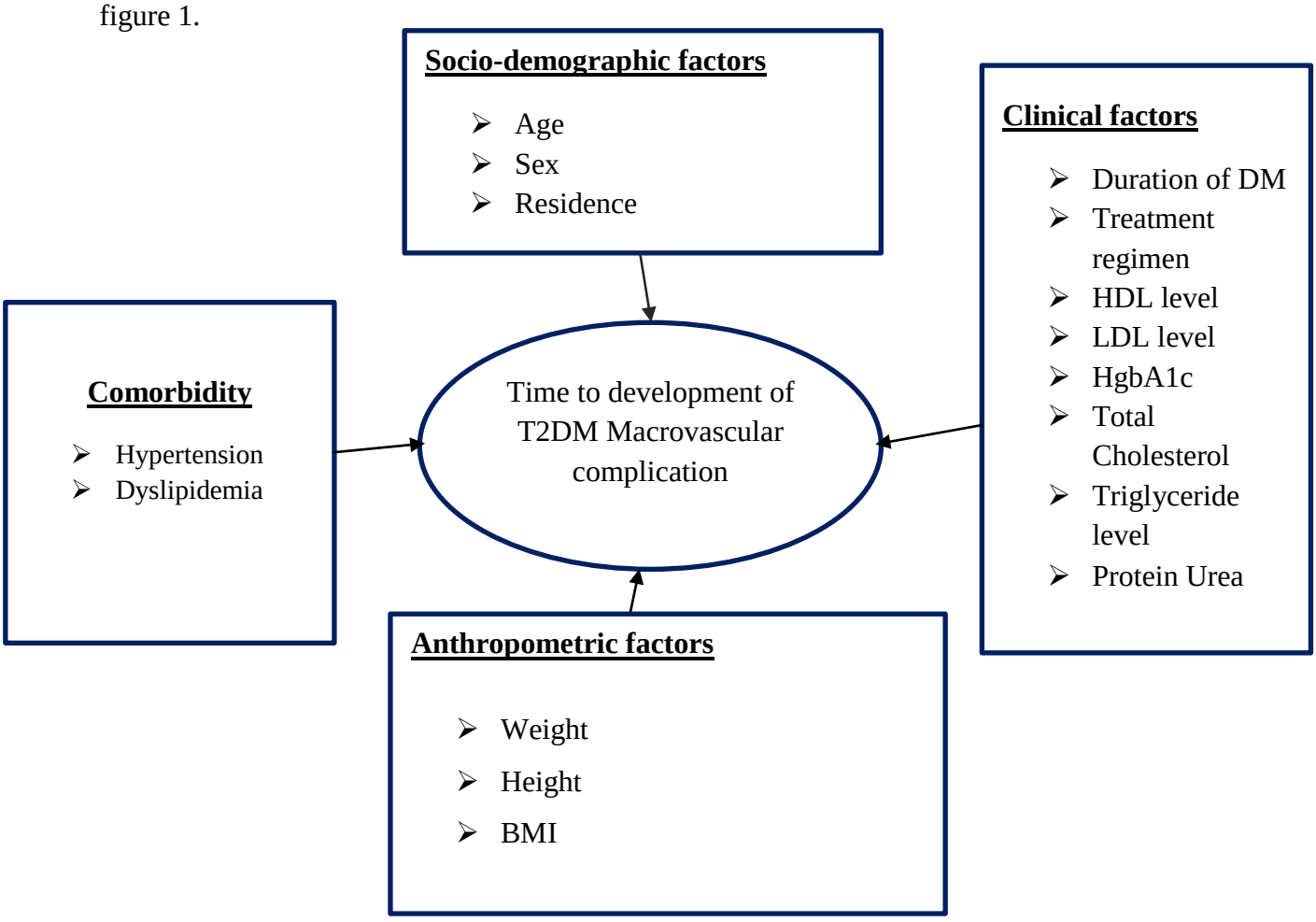

Figure 1.A conceptual framework of time to development of macrovascular complications and its predictors among T2DM patients (Developed after reviewing different kinds of related literature).

CHAPTER 3: OBJECTIVES

3.1 General Objective

- ✓ To assess the time to development of macrovascular complications and identify its predictors among type 2 diabetes mellitus patients in Jimma Medical Center from 2018–2022, G.C, Jimma, southwest Ethiopia.

3.2 Specific Objectives

- ✓ To determine the time to development of macrovascular complications among type 2 diabetes mellitus patients in Jimma Medical Center from 2018–2022, G.C, Jimma, southwest Ethiopia.
- ✓ To identify the predictors of time to development of macrovascular complications among type 2 diabetes mellitus patients in Jimma Medical Center from 2018–2022, G.C, Jimma, southwest Ethiopia.

CHAPTER 4: METHODS AND MATERIALS

4.1: Study area and period

The study was conducted in the Jimma Medical Center, Jimma Town, South west Ethiopia. Jimma town is located 357 kilometers 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.

4.2 Study Design

Institutional-based retrospective cohort study was conducted.

4.3 *Populations*

4.3.1 Source Population

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.

4.3.2 Study population

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.

4.3.3 Study unit

T2DM patient record was the study unit.

4.4 Eligibility Criteria

4.4.1 Inclusion criteria

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.

4.4.2 Exclusion criteria

T2DM patient records with incomplete date of diagnosis/ treatment initiation and date of outcomes occurred were excluded from the study.

4.5 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(49, 50).

$E = (z\alpha + z\beta)2 \ / (\ln \text{HR})^2 \text{PQ}$

Where:-

E: the number of events required to be observed

P: the proportion of exposed (4.06% or 0.0406 from the previous study)(20).

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)(43). 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 =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=404

By inserting all the values in the formula the result is 404. By adding 10% missing data/incomplete data the total sample size has become 440.

4.6 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 440 records of T2DM patient from a total of 1,141 eligible T2DM records. The interval used to select the T2DM Patient record for data collection was determined depending on the number of total T2DM records as K=N/n, K = 1141/440, and K = 3. Where N is the total number of T2DM patient records and n is the sample size. The first T2DM Patient record was selected by lottery, and then every third T2DM Patient record was sampled. Then the medical record numbers of the sampled T2DM records were reviewed.

4.7 Data collection procedures

A structured data extraction checklist was prepared and pretested to extract routinely recorded data of T2DM patient's from January 1, 2018 to December 31, 2022 G.C. The medical registration or record number was used to identify the records that were reviewed. Every time the study participant had a follow-up appointment in the hospital, all of the macrovascular complications were assessed. The patient's registration records and charts were used to assess all baseline characteristics at the beginning of anti-diabetic treatment.

The checklist also comprises general information, socio-demographics factors, comorbidity factors, clinical factors and anthropometric factors, laboratory related factors and treatment related factors of T2DM patients. Data were collected by trained health professionals (a two nurse working in a DM clinic) by reviewing the records of all clients ever enrolled. Those records of T2DM patients that did not fulfill the inclusion criteria were excluded.

4.7.1 Data collection techniques

The data were collected by identifying the medical record number on the registration log book. After getting the medical record number of T2DM patients, the chart was obtained from the medical record room. Then the chart that fulfilled the inclusion criteria was checked and the necessary data were extracted using a data extraction format. The primary outcome was having any macrovascular complications, such as cerebrovascular disease (stroke), Peripheral arterial disease and Coronary artery disease. Those complications were determined based on

the clinical decision of the physician. All baseline characteristics at the beginning of anti-diabetic treatment were assessed from the patient's records, which were included in the study.

4.8 Study variables

4.8.1 Dependent Variable

Time to development of Macrovascular complication

4.8.2 Independent Variables

Socio-demographic variables

- Sex
- Age
- Residence

Clinical variables

- Duration of DM
- Family history of CVD
- Types of Treatment regimen
- HDL Cholesterol level
- LDL Cholesterol level
- Total cholesterol level
- Triglyceride level
- HgbA1C level
- Protein urea

Comorbidity

- Hypertensions
- Diabetic ketoacidosis
- Dyslipidemia

Anthropometric

- Initial Weight
- Height
- BMI

4.9 Operational definitions

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

Coronary artery disease: - diagnosed as coronary artery 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 macrovascular complication is the time between newly diagnosed T2DM until the development macrovascular complications (in months).

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

4.10. Data quality control

To ensure the quality of the data, the data extraction tool was properly designed, and a pretest was done on 5% of the total study population in Shenen Gibe General Hospital to ensure the consistency of understanding the data extraction tools and the completeness of the data items. Any error found after doing the pretest was corrected, and modifications were made to the final format of the data abstraction tools. Training was given to the data collectors and their supervisors. To make sure the data was accurate and consistent, supervision and checking were done. All collected data were examined for completeness and consistency during data extraction on a daily basis by the supervisor. The data was thoroughly examined during the data entering process, which included double data entry verification and the data was properly analyzed.

4.11. 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.

4.12 Ethical Consideration

The proposal was approved by advisors and the Jimma University institutional review board (IRB). 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. The data collectors and supervisors were assured of the confidentiality of patients' recorded data.

4.13 Dissemination Plan

The findings of this study were presented to the Jimma University Department of Epidemiology and then disseminated to the Jimma University Epidemiology Department, the Jimma Medical Center, and other concerned governmental and nongovernmental organizations working on NCDs. Conditions were adjusted as much as possible to present it in various seminars and workshops and for publication in a peer-reviewed, reputable journal.

CHAPTER FIVE: RESULTS

5.1. 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 (SD ±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.Socio-demographic characteristics of T2DM patients in JMC, Jimma, Southwest Ethiopia, from January 1, 2018–December 31, 2022 (n = 434).

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%)

5.2. 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 (SD±33.65) and 399.54 (SD±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 40mg/dl, whereas more than half (55.3%) of the patients had triglycerides levels less than or equal to 150 mg/dl.

At baseline, 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 oral hypoglycemic agents together to manage their diabetes.

Table 2.Comorbidity, clinical, and Anthropometric characteristics of T2DM patients in Jimma 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(SD ±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 (SD ±18.60)			
DBP	Mean(SD): 84.64 (SD ±11.04)			
FBS	Mean(SD): 185.10 (SD ±33.65)			

RBS	Mean(SD): 399.54 (SD ±89.16)			
Total cholesterol	≤200mg/dl	44(17.5%)	207(82.5%)	251(57.8%)
	>200mg/dl	133(72.7%)	50(27.3%)	183(42.2%)
HDL-cholesterol	≥ 40mg/dl	42(16.6%)	211(83.4%)	253(58.3%)
	<40mg/dl	135(74.6%)	46(25.6%)	181(41.7%)
LDL-cholesterol	≤100mg/dl	64(24.0 %%)	202(76.0%)	266(61.3%)
	>100mg/dl	113(67.3%)	55(32.7%)	168(38.7%)
Triglyceride	≤150mg/dl	64(26.7%)	176(73.3%)	240(55.3%)
	>150mg/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%)

5.5. 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 time to develop macrovascular complications was 24 months (Fig.2).

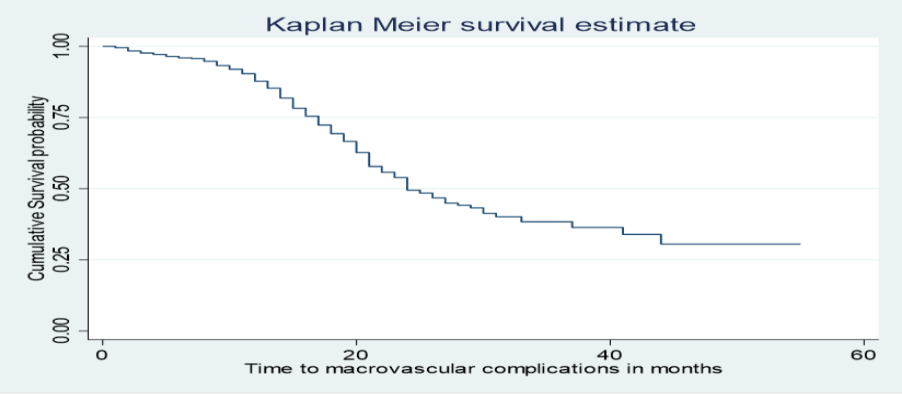

Figure 2.Kaplan Meier graph for overall Survival functions for time to development of macrovascular complications among T2DM patients in JMC, Jimma, Southwest Ethiopia from January 1, 2018 to December 31, 2022 G.C.(n=434).

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 estimates 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 40mg/dl (4.33 cases; 95% CI: 3.6, 5.1) per 100 persons-months observations, and triglycerides greater than 150mg/dl (3.3 cases, 95% CI: 2.7, 4.0) per 100 persons-months observations.

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%) death; and thirty-seven (8.53%) were lost to follow-up (Fig.3).

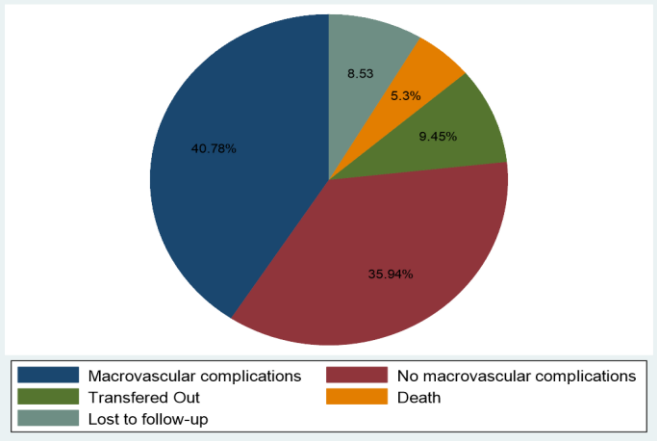

Figure 3.Overall outcomes of adult Type 2 DM patients in JMC, Jimma, and southwest Ethiopia from January 1, 2018 to December 31, 2022 G.C.

5.5.1. 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 were 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 *(Fig. 4).*

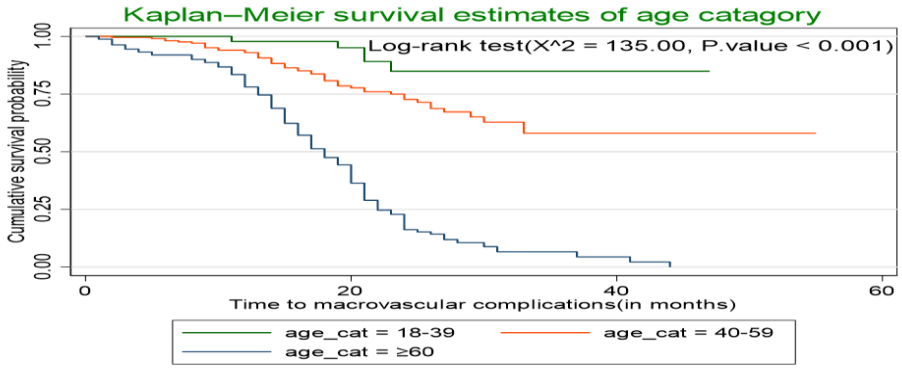

Figure 4.Kaplan Meier and log rang survival estimated graph of time to development of macrovascular complications among T2DM patients by age category in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

The median survival time for the development of macrovascular complications among urban residents was 21 months, whereas rural residents had no median survival time. The urban residence had a shorter survival time than the rural residence. This was a statistically significant difference, with the test statistics X^2 = 53.85 and P.Value < 0.001 (Fig. 5).

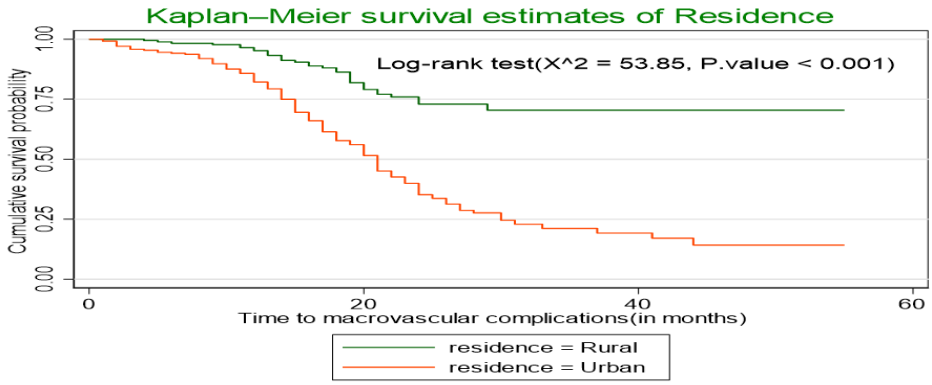

Figure 5.Kaplan Meier and log rang survival estimated graph of time to development of macrovascular complications among T2DM patients by residence in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

The median survival time to the development of macrovascular complications among hypertensive T2DM patients at the beginning of DM treatment was 20 months, whereas the median survival time of non-hypertensive patients was 41 months.

This indicated that hypertensive T2DM patients had a shorter survival time than non-hypertensive patients. This was a statistically significant difference, with test statistics X^2 = 41.88 and P.Value <0.001 (Fig. 6).

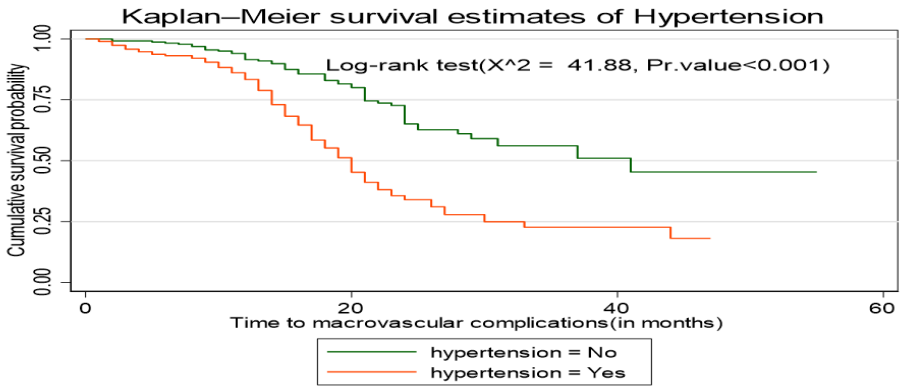

Figure 6.Kaplan Meier and log rang survival estimated graph of time to development of macrovascular complications among T2DM patients by hypertension comorbidity in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

In this study, the median survival time to the development of macrovascular complications among T2DM patients with dyslipidemia at the beginning of antidiabetic treatment was 16 months, whereas the median survival time of T2DM patients without dyslipidemia was 26 months. This showed that T2DM patients with dyslipidemia at the beginning of antidiabetic treatment had a shorter survival time than T2DM patients without dyslipidemia. This was a statistically significant difference with test statistics X^2 = 34.18 and a P value <0.001(Fig.7).

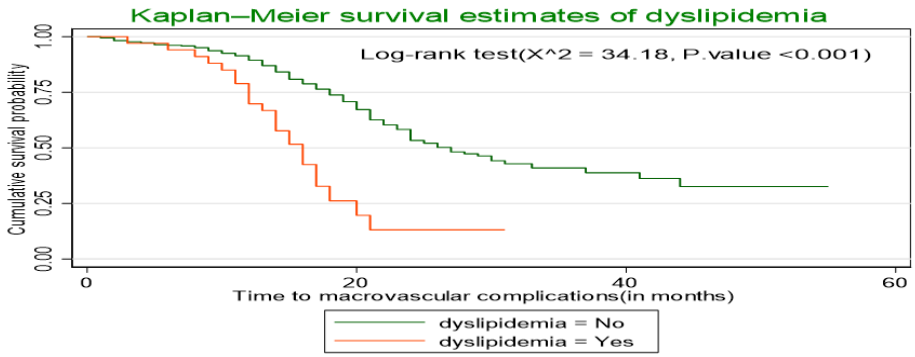

Figure 7.Kaplan Meier and log rang survival estimated graph of time to development of macrovascular complications among T2DM patients by dyslipidemia comorbidity in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

In this study, the median survival time to the development of MVCs among T2DM patients with HDL-C <40 mg/dl at the start of antidiabetic treatment was 19 months, whereas T2DM patients with HDL-C ≥ 40 mg/dl had no median survival time. The patients with HDL-C ≥ 40 mg/dl at the beginning of antidiabetic treatment had a longer survival time than T2DM patients with HDL-C <40 mg/dl. This was a statistically significant difference, with test statistics X^2 = 111.47 and a P value <0.001 (Fig. 8).

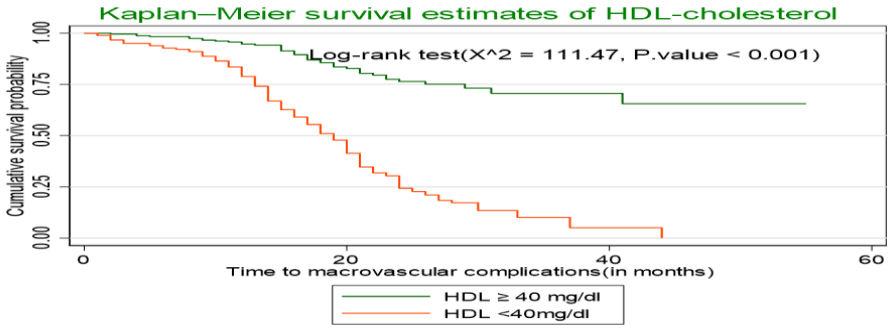

Figure 8.Kaplan Meier and log rang survival estimated graph of time to development of macrovascular complications among T2DM patients by HDL levels in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

In this study, the median survival time to the development of MVCs among T2DM patients with triglyceride >150 mg/dl at the beginning of antidiabetic treatment was 21 months, whereas the median survival time of patients with triglyceride ≤150 mg/dl was 44 months. The patients with triglycerides >150 mg/dl at the beginning of diabetic treatment had a shorter survival time than T2DM patients with triglycerides ≤150 mg/dl. This was a statistically significant difference with test statistics X^2 = 35.37 and a P value< 0.001 (Fig. 9).

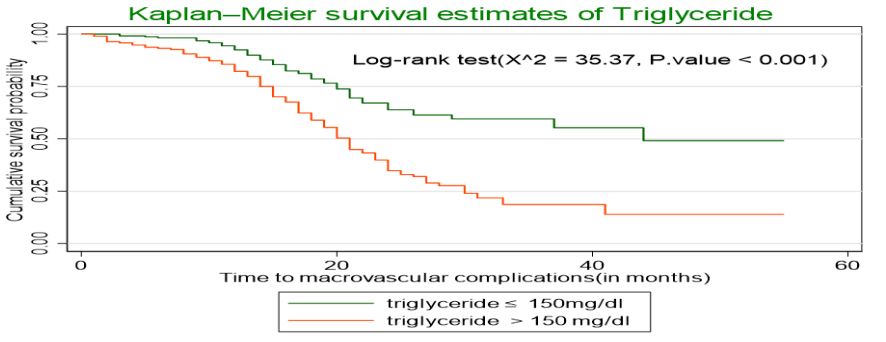

Figure 9.Kaplan Meier and log rang survival estimated graph of time to development of MVCs among T2DM patients by triglycerides levels in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

The median survival time to the development of macrovascular complications among T2DM patients with HgbA1c >7% at the beginning of antidiabetic treatment was shorter than the median survival time of T2DM patients with HgbA1c ≤7%. This was a statistically significant difference, with test statistics X^2 = 46.45 and a P value <0.001(Fig. 10).

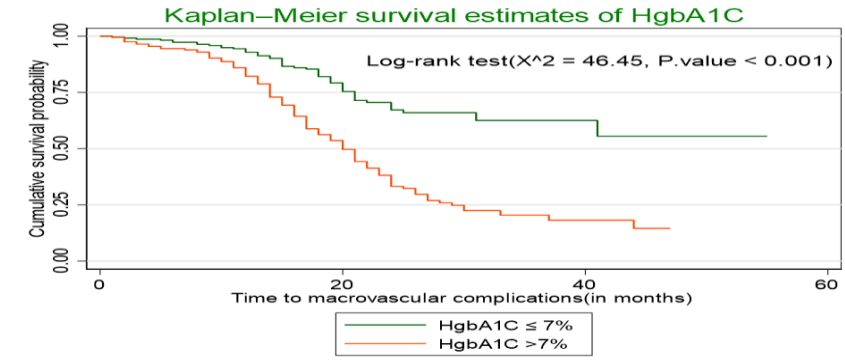

Figure 10.Kaplan Meier and log rang survival estimated graph of time to development of macrovascular complications among T2DM patients by HgbA1C levels in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

The median survival time to the development of macrovascular complications among T2DM patients who received both OHA and insulin was 17 months, whereas the median survival time of T2DM patients who received only OHA was 41 months. T2DM patients who received both OHA and insulin had a shorter survival time than T2DM patients who received only OHA. This was a statistically significant difference with test statistics X^2 = 109.13 and a P value <0.001 (Fig. 11).

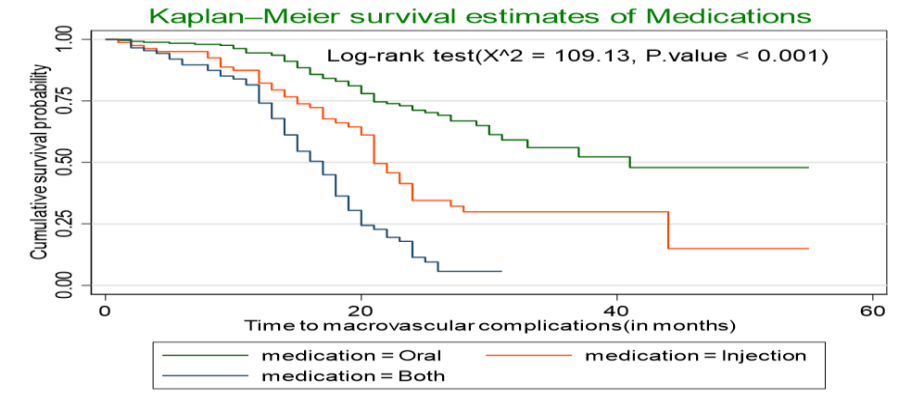

Figure 11.Kaplan Meier and log rang survival estimated graph of time to development of macrovascular complications among T2DM patients by medication regimen in JMC, January 1, 2018 to December 31, 2022 G.C.(n=434).

5.3. Test of Proportional assumption (Model diagnosis)

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) to confirmed the curve are roughly parallel, and the presence of a time-dependent covariate in the model to indicated the proportionality assumption of the cox-proportional hazard model. Martingale residuals and deviance residuals were 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. The plot of deviance was symmetric about zero and the scatter plot has the patterns. This indicated that the observations didn't have influential observations.

5.4. 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.

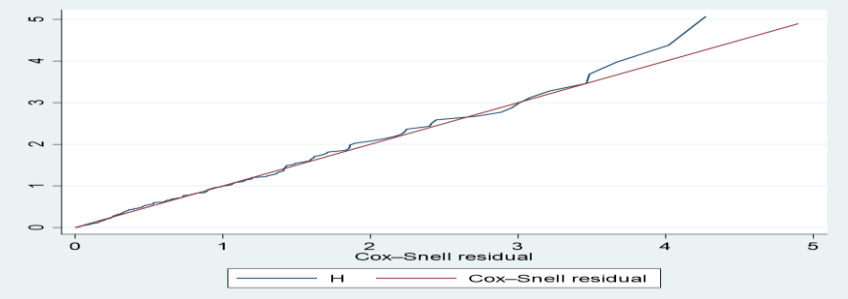

Figure 12.Cox-Snell residual graph, based on the Kaplan Meier estimated survivor function, to test the overall goodness of fit cox-proportional model of time to macrovascular complications among T2DM patients in JMC, January 1, 2018 to December 31, 2022 G.C.

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

The development of macrovascular complications was considered a failure, while the other outcomes were considered censored. Univariable Cox proportional hazard regression analyses were performed to select potential candidate variables for the multivariable analysis. In univariable analysis, a significant difference was observed between predictors. The multivariable analysis included variables with a p-value of less than 0.25 from the univariable analysis.

According to the results of the univariable analysis, gender, baseline age category, residence, comorbidity (hypertension, DKA, and dyslipidemia) at baseline, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, HgbA1C, protein urea, family history of CVD, and medication regimen were found to be associated with the development of macrovascular complications among T2DM patients.

According to the results of the multivariable analysis, baseline age ≥60yeares, residence, presence of baseline hypertension, baseline dyslipidemia, baseline HDL-cholesterol level <40mg/dl, baseline triglyceride level >150mg/dl, baseline HgbA1C >7%, and medication regimens were found to be significant independent predictors for the time to development of macrovascular complications among T2DM patients after controlling for the effect of other variables.

The hazard of developing macrovascular complications among T2DM patients aged ≥ 60 years at baseline of anti-diabetic treatment follow-up was 4.42 times higher than that of T2DM patients aged 18–39 years (AHR: 4.42; 95% CI: 1.72, 11.29). Also, the risk of developing macrovascular complications among T2DM patients with urban residence was 2.02 times higher than those with rural residence (AHR: 2.02; 95% CI: 1.33, 3.05).

Similar to this, T2DM patients with hypertension comorbidity at baseline had a 1.50-fold increased risk of developing macrovascular complications as compared to non-hypertensive T2DM patients (AHR: 1.50; 95% CI: 1.06, 2.13). The risk of developing macrovascular complications was 2.11 times higher among T2DM patients with baseline HDL-C <40mg/dl as compared to HDL-C ≥40mg/dl patients (AHR: 2.11; 95% CI: 1.16, 3.81). The hazard of developing macrovascular complications was 1.82 times higher among T2DM patients with baseline dyslipidemia comorbidity at the beginning of diabetic treatment follow-up as compared to T2DM patients without dyslipidemia (AHR: 1.82; 95% CI: 1.13, 2.93).

By controlling the other variables as constants, HgbA1C levels ≥ 7% at the beginning of anti-diabetic treatment increased the risk of developing macrovascular complications by 1.49 times higher as compared to HgbA1C levels< 7%. Triglycerides >150mg/dl at the initiation of diabetic treatment increased the hazard of macrovascular complications by 52% as compared to triglycerides ≤150mg/dl.

The hazards of patients on oral hypoglycemic agent (OHA) plus insulin were 2.73 times higher than those of patients on oral hypoglycemic agent alone (AHR: 2.73; 95% CI: 1.81, 4.09).

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			
Chronic kidney diseases	Yes	52	57	3.03(1.94,4.72)	0.000	1.19(0.69,2.04)	0.523
	No	125	200	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	>200mg/dl	133	50	4.73(3.36,6.67)	0.000	1.38(0.75,2.53)	0.300
	≤200mg/dl	44	207	1			
HDL-C	<40mg/dl	135	46	5.31(3.74,7.55)	0.000	2.11(1.16,3.81)	0.013
	≥40mg/dl	42	211	1			
LDL-C	>100mg/dl	113	55	3.14(2.30,4.27)	0.000	0.73(0.48,1.11)	0.144
	≤100mg/dl	64	202	1			
Triglyceride	>150mg/dl	113	81	2.43(1.78,3.31)	0.000	1.48(1.02,2.13)	0.037
	≤150mg/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			

CHAPTER SIX: DISCUSSION

This retrospective cohort study was aimed to assess the time to development of macrovascular complications and identifies its predictors among adult T2DM patients who were free at the beginning of antidiabetic treatment in JMC. Within this cohort, 434 patients were followed for 7,929 person-months observations. During the follow-up, 177 patients developed macrovascular complications, making the incidence and median survival time for development of macrovascular complications 22.4 cases (95% CI: 19.4, 26.0) per 1,000 person-month observations and 24 months, respectively.

Baseline age category in years, residence, presence of hypertension at the beginning, presence of dyslipidemia at baseline, HDL-cholesterol level <40mg/dl at baseline, triglyceride >150mg/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 was lower than that in a study done at Kaiser Permanente Southern California (3.0 to 5.2 years)(39), the University of Gondar Referral Hospital(6.8 years)(20), and Felege Hiwot Referral Hospital at Bahir Dar, Northwest Ethiopia(95 months)(40), respectively. This variation might be due to differences in the length of the follow-up. The length of follow-up in this study was shorter than that of the above study.

The findings in this study showed that the overall incidence rate of macrovascular complications among T2DM patients was 22.4 cases per 1000 person-months of observation. This finding was in discordance with the study done at Kaiser Permanente Southern California (11.9 cases per 1000 person-year observations)(39). The possible reason for this difference was that diabetic care in these countries and other developed countries might be better organized than in LMI countries like Ethiopia. Many factors, such as fragmentation of health care services, limited resource allocation, inadequate training among health-care professionals, and low health literacy among DM patients, contributed to the high incidence of macrovascular complications in this research.

In this study, baseline age greater than or equal to 60 years and urban residence increased the hazard of developing macrovascular complications among T2DM patients. This result is in line with the studies done at Ningbo, China(41), Harari Region, Eastern Ethiopia(26), and Mettu Karl Referral Hospital(43), that showed that baseline age greater than or equals to 60

years and urban residence increase the risk of developing macrovascular complications among T2DM patients. The possible reason was that aging can cause changes in the heart and blood vessels that may increase a person's risk of developing CVD. Moreover, there is a high prevalence of atherosclerosis and arteriosclerosis due to the progression of diabetes with advanced age(51). Urban dwellers are found to be a greater probability to have risk factors for type 2 diabetes mellitus complications, such as obesity, physical inactivity, and irregular eating patterns(43).

This study's findings also stated that T2DM patients who had a history of hypertension at the beginning of diabetic treatment had an increased risk of developing macrovascular complications. This result is in accordance with the studies done in Ningbo, China(41), South India(15), Saudi Arabia(42), Ethiopia(43), and the University of Gondar Referral Hospital(20), which indicated that a history of hypertension puts the patients at a higher risk for macrovascular complications. The possible reason could be the impact of hypertension on endothelial cell structure and function, which promotes increased growth and vasoconstriction. As a result of the endothelial alterations brought on by hypertension, arthrosclerosis develops, which ultimately exposes patients to vascular problems(52).

This study's findings also indicated that T2DM patients who had a history of dyslipidemia at the beginning of diabetic treatment had an increased risk of developing macrovascular complications. This result is in line with the study done in Jimma(53), which revealed that a history of dyslipidemia puts the patients at a higher risk for macrovascular complications. The possible reason is in T2DM patients, dyslipidemia is linked to an increase in free fatty acid flow as a result of insulin resistance(1).

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(20),which stated that patients with higher triglyceride and lower HDL cholesterol levels were increased the risk of developing macrovascular complications. This might be a result of the fact that the function of HDL-C is to transport fats (lipids) 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(54).

This study revealed that the risk of developing macrovascular complications increased with an elevated HgbA1C level > 7%. This outcome was consistent with findings from a different Moroccan study(44). The findings of the present study demonstrated an increased risk of macrovascular complications with the use of insulin and oral hypoglycemic agents (OHA). This study was comparable to studies conducted in Ningbo, China(41) and Morocco(44), respectively. A stepwise approach is recommended in the Ethiopian T2DM management guideline(55). The first step is lifestyle modification. With disease progression, OHAs and insulin are added. Therefore, the identified association is more likely to represent disease severity and chronicity than medication effects.

6.1 Strength of the study

This study discovered the incidence and time to macrovascular complications, and identified its predictors among T2DM patients in clinical settings, which may be the first to be in the country. Therefore, it may help to intervene in the existing problem. Additionally, the study's findings have coherence with the natural history (accepted facts about disease occurrence) of T2DM disease.

6.2 Limitation of the study

This 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. The start of follow-up was considered from the time of the diagnosis of T2DM to the development of macrovascular complications. This time does not reflect the true time for macrovascular complications to develop among T2DM patients. Additionally, the event of interest was assessed and measured by different criteria for various members of the cohort. Those criteria create measurement errors, which affect the precision and validity of the finding.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

In this retrospective cohort study, findings indicated that the incidence of macrovascular complications was high among T2DM patients' and remains a public health problem in the Jimma Medical Center. T2DM patients who had a significant factor at the base line had a shorter median survival time than their counterparts. 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.

7.1 Recommendations

Based on the above finding of this study the following recommendations are forwarded.

For Jimma university medical center

- ✓ Clinical experts should strengthen follow-up with T2DM patients, especially at early stages, to increase their survival time.
- ✓ Continuous training and programmed supportive supervision should be in place to reduce the incidence of macrovascular complications among T2DM patients.

For Jimma city and Jimma zone health bureau

- ✓ Continuous training and programmed supportive supervision should be in place to promote good survival time and reduce the death of T2DM patients.

For researchers

- ✓ A prospective cohort study will determine to reflect the true time from the onset of T2DM to the development of macrovascular complications.
- ✓ Potentially important variables like self-care practices, physical activities, and smoking status will be included in the study.
- ✓ The event of interest will be assessed using the same criteria for various members of the cohort to minimize the measurement error.

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Annex 1: - Data Extraction Checklist

Topics: - Survival Time to development of macro vascular complications and its predictors among Type 2 diabetic mellitus patients in Jimma Medical Center from January 1, 2018 – December 31, 2022, Jimma Zone, Southwest Ethiopia: 2023.

Instruction:-Dear data collector this is a data extraction form designed to collect data of the patients diagnosed to T2DM and started the treatment in Jimma Medical Center starting from January 1,2018-December 31,2022. Please fill all the requested fields that are prepared in the section of the data extraction form.

The form has five section:-

The 1st Section: - General Information

The 2nd Section: - Socio-demographic characteristics of the patients

The 3rd Section: - The clinical and Anthropometric characteristics of the patients

The 4th section: - laboratory of T2DM patient

The 5th Section: - Treatment characteristics of the patients.

Part I General information

001. Date: _____

002. Name of the health facility _____

003. Code given for the chart_____

004. Name of the data collector_____

005. Name of the supervisor_____

Part II Socio demographic characteristics of T2DM patient

Code	Characteristics	Coding classification
201	Gender	1.Male 2.Female
202	Age	_____Years
203	Place of residence	1.Urban 2.Rular

Part III Baseline clinical, comorbidity and Anthropometric characteristics of T2DM patients

301	Date of the patient confirmed as T2DM patient	dd/mm/yy//_____
302	Hypertension	0. No 1. Yes
303	Liver Disease	0. No 1. Yes
304	HIV AIDS	0. No 1. Yes
305	Chronic Kidney disease	0. No 1. Yes
306	Diabetic ketoacidosis	0. No 1. Yes
307	Dyslipidemia	0. No 1. Yes
308	Base line Systolic Blood Pressure	_____mmhg
309	Baseline Diastolic blood pressure	_____mmhg
310	Base line Wt. (Kg) _ Base line Ht. (m) ___ Base line BMI _____ kg/m^2	0. Normal weight 18.5–24.99 kg/m^2 1. Overweight 25–29.99 kg/m^2 2.Obese $\geq$ 30 kg/m^2 3.Underweight< 18.5 kg/m^2
311	Duration of follow up? Follow up times	_____month
312	Duration of DM (for how long the patient live as Type 2 diabetic patient)	_____month

Part IV Laboratory (Physiological) characteristics of T2DM patient

401	Base line Total cholesterol level (mg/dl)____	1. ≤ 200mg/dl 2. > 200mg/dl
402	Baseline HDL(mg/dl)_____	1. ≥40mg/dl 2. <40 mg/dl
403	Baseline LDL (mg/dl) _____	1. ≤100mg/dl 2. >100mg/dl
404	Baseline Triglyceride(mg/dl)	1. ≤ 150mg/dl 2. > 150 mg/dl
405	Baseline Protein urea	1. Negative 2. Positive
406	Baseline Fasting serum glucose (mg/dl)	_____mg/dl
407	Baseline Random blood glucose (mg/dl)	_____mg/dl
408	Base line Glycemic Control measured by hemoglobin A1c	1. ≤7% 2. ≥7%
409	Family History of CVD	1. No 2. Yes

Pat V Treatment- related factors and status of patients

501	Types of medication	1. Oral hypoglycemic agent 2. Injection/Insulin 3. Both
502	Status of patients at last contact	1.Censored 2. Macro-vascular complications
503	Coronary artery disease	0. No 1. Yes
504	Peripheral artery disease	0. No 1. Yes
505	Cerebrovascular disease	0. No 1. Yes
506	Combination of Coronary artery and peripheral artery diseases	0. No 1. Yes
507	Combination of coronary artery and Cerebrovascular diseases	0. No 1. Yes
508	Combination of Peripheral artery and cerebrovascular diseases	0. No 1. Yes
509	If last contact is “censored”	1. No macro-vascular complication 2. Transferred out 3. Death 4. Lost to follow up
510	If the answer to Q502 is macro-vascular complication date confirmed to the complication	dd/mm/yy_/ _____
511	Last contact/end date	dd/mm/yy_/ _____