PROGNOSTIC FACTORS OF DIABETIC RETINOPATHY AMONG ADULT PATIENTS WITH TYPE II DIABETES MELLITUS IN KELANTAN FROM 2013 TO 2017

MUHAMMAD ZA'IM BIN MOHD SAMSURI

UNIVERSITI SAINS MALAYSIA

2024

PROGNOSTIC FACTORS OF DIABETIC RETINOPATHY AMONG ADULT PATIENTS WITH TYPE II DIABETES MELLITUS IN KELANTAN FROM 2013 TO 2017

by

MUHAMMAD ZA'IM BIN MOHD SAMSURI

Research Project Report submitted in partial fulfilment of the requirements for the degree of Master of Public Health

JUNE 2024

ACKNOWLEDGEMENTS

بِسْمِ اللهِ الرَّحْمٰنِ الرَّحِيْمِ

I would like to express my deepest gratitude to my supervisor, Associate Professor Dr. Azriani binti Ab Rahman, for her exceptional dedication and unwavering support during the creation of this thesis. Her commitment to academic excellence was both captivating and inspiring.

I am also deeply thankful to my co-researchers, Dr. Noor Hashimah binti Abdullah from the Non-Communicable Diseases unit of the Kelantan State Health Department and Dr. Suhaily binti Mohd Hairon from the Department of Community Medicine at the School of Medical Sciences, Health Campus, Universiti Sains Malaysia. Additionally, my sincere appreciation goes out to all the lecturers in the Department of Community Medicine at the School of Medical Sciences, Universiti Sains Malaysia. I am grateful to my encouraging classmates in the Master of Public Health 2023/2024 program for their unwavering support and inspiration throughout this journey.

Finally, I want to thank my loving and understanding wife, Norsafirah Omar, as well as my children, Iman Medina, Iman Ameena, and Iman Khadeeja. I am also deeply grateful to my kind-hearted parents, Mohd Samsuri and Wan Zaidah and in-laws for their patience, resilience, and enduring support. Their prayers and encouragement have been instrumental in my success.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

*	Asterisk
>	More than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to
$\bar{x}$	Mean
β	Beta (regression coefficient)
p	p-value (probability value in hypothesis testing)
n	Sample size
R^2	R-squared (coefficient of determination)
α	Alpha (significance level in hypothesis testing)
~	Approximate
%	Percentage
Zα	The Z-score associated with the level of significance
P	Reference population according to literature
m1	Median time among non-prognostic group (by literature)
m2	Median time among Prognostic group (by literature)
d	Detectable differences relative precision
A	Accrual time
F	Additional follow up time

LIST OF ABBREVIATIONS

Adj. HR	Adjusted hazard ratio
AGEs	Advanced glycation end products
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
CeVD	Cerebrovascular disease
DR	Diabetic retinopathy
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated haemoglobin
HR	Hazard ratio
HTG	Hypertriglyceridemia
HDL-C	High-density lipoproteins cholesterol
LDL-C	Low-density lipoproteins cholesterol
MOH	Ministry of Health
NCD	Non-communicable disease
NDR	National Diabetic Registry
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical coherence tomography
OHA	Oral hypoglycaemic agents
PDR	Proliferative diabetic retinopathy
SD	Standard deviation
T1DM	Type I diabetes mellitus

T2DM	Type II diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
TyG	Triglyceride-glucose
VEGF	Vascular endothelial growth factor

LIST OF APPENDICES

FAKTOR-FAKTOR PROGNOSTIK DIABETIK RETINOPATI DALAM KALANGAN PESAKIT DEWASA DENGAN DIABETES MELLITUS JENIS II DI KELANTAN DARI TAHUN 2013-2017

ABSTRAK

Pengenalan: Diabetik Retinopati (DR) merupakan komplikasi penyakit diabetes yang biasa berlaku dan kesannya sangat teruk dan menjadi penyebab utama kepada kebutaan dan secara jelas mempengaruhi kualiti hidup. Di Kelantan, prevalen diabetes yang tinggi dan peratusan yang ketara daripada kalangan pesakit menghidap DR telah memberikan suatu cabaran yang besar kepada sektor kesihatan awam. Kajian ini bertujuan untuk menentukan kebarangkalian kejadian DR dan mengenal pasti faktor-faktor prognostik di kalangan pesakit dewasa dengan diabetes mellitus jenis II (T2DM) di Kelantan dari tahun 2013-2017.

Metodologi: Satu kajian kohort retrospektif telah dijalankan di Kelantan di kalangan pesakit dewasa yang menghidap penyakit diabetes mellitus jenis II (T2DM) yang berdaftar dalam Sistem Pendaftaran Diabetes Kebangsaan (NDR) dari 1 Januari 2013 hingga 31 Disember 2017. Pensampelan rawak mudah digunakan untuk memilih kes. Analisis kemandirian digunakan untuk mengkaji masa kepada diabetik retinopati. Model Regresi Cox Risiko Proporsional digunakan untuk menganalisis faktor prognostik.

Keputusan: Dalam analisis akhir terhadap 1372 pesakit diabetes mellitus jenis II dewasa (T2DM), didapati sebanyak 11.9% menghidap penyakit diabetik retinopati (DR) sepanjang tempoh kajian, dengan pola peningkatan selama lima tahun (mencapai 9.5% pada tahun kelima). Faktor prognostik yang signifikan untuk DR adalah usia,

hipertensi, nefropati, tahap HbA1c, dan tahap trigliserida (TG). Pesakit berusia 60 tahun atau lebih menunjukkan kebarangkalian yang lebih tinggi untuk mendapat DR berbanding mereka yang berusia di bawah 60 tahun (Adj. HR: 1.85; 95% CI: 1.30, 2.62). Mereka yang mempunyai penyakit nefropati mempunyai kebarangkalian yang jauh lebih tinggi untuk mendapat DR berbanding mereka yang tidak mengalami nefropati (Adj. HR: 3.46; 95% CI: 2.41, 4.97). Pesakit dengan tahap HbA1c 6.5 dan ke atas, lebih cenderung untuk mendapat DR berbanding mereka dengan tahap di bawah 6.5 (Adj. HR: 1.42; 95% CI: 1.01, 2.02). Peningkatan tahap trigliserida dikaitkan dengan kebarangkalian yang lebih tinggi untuk mendapat DR (Adj. HR: 1.18; 95% CI: 1.03, 1.34). Mereka yang mempunyai hipertensi mempunyai kebarangkalian yang lebih rendah untuk mendapat DR berbanding mereka yang tidak mempunyai hipertensi (Adj. HR: 0.33; 95% CI: 0.24, 0.47).

Kesimpulan: Kajian kami mendapati peningkatan yang ketara dalam prevalen diabetik retinopati dengan tempoh diabetes mellitus yang lebih lama. Kami mengenal pasti usia yang lebih tua, nefropati, HbA1c yang tinggi, dan tahap trigliserida (TG) yang tinggi sebagai faktor prognostik untuk DR dalam pesakit diabetes mellitus jenis II (T2DM), manakala, dengan tidak disangka, hipertensi menunjukkan kesan perlindungan. Penemuan ini menekankan kepentingan pengenalpastian faktor risiko untuk strategi pencegahan bersasar yang berpotensi meningkatkan pengurusan pesakit dan kualiti hidup dengan mengurangkan insiden dan keterukan DR dalam T2DM.

Kata kunci: Diabetik Retinopati, Kebarangkalian kejadian, Komplikasi diabetes, Faktor prognostik

PROGNOSTIC FACTORS OF DIABETIC RETINOPATHY AMONG ADULT PATIENTS WITH TYPE II DIABETES MELLITUS IN KELANTAN FROM 2013 TO 2017

ABSTRACT

***Introduction*:** Diabetic Retinopathy (DR), a common and severe complication of diabetes, is a leading cause of blindness and significantly affects quality of life. In Kelantan, the high prevalence of diabetes and the substantial proportion of patients with DR highlight a critical public health challenge. This study aims to determine the event probability of DR and identify its prognostic factors among adult patients with type II diabetes mellitus (T2DM) in Kelantan from 2013-2017.

***Methodology*:** A retrospective cohort study was conducted in Kelantan among adult patients with type II diabetes mellitus (T2DM) registered in the National Diabetic Registry (NDR) from 1st January 2013 to 31st December 2017. Simple random sampling was used to select the cases. Survival analysis was used to examine time to diabetic retinopathy. The Cox Proportional-Hazards Regression Model is used to analyse prognostic factors.

***Results*:** In the final analysis of 1372 adult patients with T2DM, 11.9% developed DR over the study duration, with an increasing trend over five years (reaching 9.5% by the fifth year). Significant prognostic factors for DR progression were age, hypertension, nephropathy, HbA1c levels, and triglyceride (TG) levels. Patients aged 60 or older exhibited a significantly higher hazard of developing DR compared to those under 60 years old (Adj. HR: 1.85; 95% CI:1.30, 2.62). Those with nephropathy were at a

substantially increased hazard of DR compared to those without nephropathy (Adj. HR: 3.46; 95% CI: 2.41, 4.97). Patients with HbA1c levels of 6.5 and above were more likely to develop DR than those with levels below 6.5 (Adj. HR: 1.42; 95% CI: 1.01, 2.02). An increase in TG levels was associated with a higher hazard of progression to DR (Adj. HR: 1.18; 95% CI: 1.03, 1.34). Those with hypertension had a decreased hazard of developing DR compared to those without hypertension (Adj. HR: 0.33; 95% CI: 0.24, 0.47).

***Conclusion*:** Our study reveals a significant increase in DR prevalence with longer durations of diabetes mellitus. We identified older age, nephropathy, elevated HbA1c, and high TG levels as prognostic factors for DR in T2DM patients, while hypertension surprisingly showed a protective effect. These findings highlight the importance of risk factor identification for targeted prevention strategies, potentially improving patient management and quality of life by mitigating DR incidence and severity in T2DM.

***Keywords*:** Diabetic retinopathy, Event probability, Diabetes complication, Prognostic factor

CHAPTER 1

INTRODUCTION

1.1 Introduction

1.1.1 Diabetes Mellitus

Diabetes Mellitus constitutes a significant worldwide public health issue, shaped by various factors such as the aging population, urbanization, and an increasing prevalence of overweight and obesity. Projections by the International Diabetes Federation (IDF) in 2021 anticipate that by 2045, roughly 783 million adults, or 1 in 8 people, will be affected by diabetes globally (IDF, 2021). According to the National Health and Morbidity Survey (NHMS) 2023, approximately one in six adult Malaysians are living with diabetes (IPH, 2024). The survey showed an upward trend in diabetes prevalence in Malaysia from 2011 to 2023, with cases rising from 11.2% to 15.6% (IPH, 2020; IPH, 2024).

According to Clinical Practice Guidelines Management of Type II Diabetes Mellitus 6th edition (2020), type II diabetes mellitus (T2DM) stands as the predominant form of diabetes in Malaysia, encompassing over 90% of adult-onset cases (MOH, 2020). It frequently coexists with other non-communicable diseases like hypertension, dyslipidemia, and obesity. With its prevalence surging globally and locally, T2DM poses a significant socioeconomic burden due to heightened morbidity from vascular complications and premature mortality (Khan *et al.*, 2020; Ong *et al.*, 2023).

Type II Diabetes Mellitus (T2DM) manifests through a progressive decline in beta-cell function and increased insulin resistance in muscle and fat tissue (Solis-Herrera *et al.*, 2021). This resistance leads to increased glucose production by the liver and reduced glucose utilization by organs, resulting in fasting and postprandial hyperglycemia. Additionally, impaired secretion of intestinal incretins disrupts meal-related insulin release and glucagon suppression, further exacerbating postprandial hyperglycemia (Nauck and Meier, 2018). Excessive renal tubular reabsorption of glucose also contributes to elevated blood glucose levels (Vallon and Thomson, 2020).

Type II Diabetes Mellitus (T2DM) is a critical risk factor for cardiovascular disease (CVD) and various microvascular complications, such as retinopathy, nephropathy, and neuropathy (Zakir *et al.*, 2023). Furthermore, the rate of undiagnosed cases remains high at 5.9% (IPH, 2024), leading many individuals to become aware of their diabetes only upon the onset of complications (Ogurtsova *et al.*, 2022).

1.1.2 Diabetic Retinopathy

As the number of people diagnosed with T2DM increases globally, the incidence of complications associated with the disease such as diabetic retinopathy (DR) also increase. In a study on diabetes control and complications in private primary health care in Malaysia. In 2020, approximately 103 million adults globally were affected by diabetic retinopathy (DR), representing about 22.7% of all diabetes patients (Teo *et al.*, 2021). This prevalence is projected to increase significantly, with an estimated 161 million people expected to be affected by DR by 2045 (Kropp *et al.*, 2023). DR was also the fifth leading cause of blindness and significant vision impairment worldwide (Teo *et al.*, 2021). This increase in DR incidence, particularly among younger patients,

is a growing concern (Romero-Aroca *et al.*, 2016). Affecting 30%-50% of all individuals diagnosed with diabetes, DR is the leading cause of legal blindness among people aged 20-74 in developed nations such as the USA and Singapore (Lee *et al.*, 2015). In Malaysia, 11.12% of diabetes patients had DR in 2023 (MOH, 2023). This condition is also correlates with significant psychological morbidity, contributing to elevated levels of anxiety, depression, and a reduced quality of life for affected individuals (Deswal *et al.*, 2020).

Diabetic retinopathy (DR) is a serious condition that affects the blood vessels in the retina, leading to vision impairment or even blindness (Mounirou *et al.*, 2022; Kropp *et al.*, 2023). It is caused by prolonged high blood sugar levels and is more common in individuals who have had diabetes for a long time. Elevated blood sugar levels lead to the production of advanced glycation end products (AGEs) and activation of protein kinase C, resulting in significant damage to the retinal capillaries (Seewoodhary, 2020). Additionally, elevated serum VEGF levels are strongly linked with DR and stimulate the formation of new blood vessels on the retinal surface (Sayin *et al.*, 2015; Ahuja *et al.*, 2019). These new vessels are fragile and prone to bleeding, leading to scar tissue formation, which can exacerbate tractional retinal detachment and further contribute to vision loss (Xu *et al.*, 2018). Moreover, lipid deposits manifest as yellow exudates, and macular edema can develop, posing additional threats to vision (Seewoodhary, 2020).

Diabetic Retinopathy (DR) can be categorized into two types: non-proliferative and proliferative. Non-proliferative diabetic retinopathy (NPDR), which represents the initial stage of DR, is further categorized as mild, moderate, or severe. This stage presents the best opportunity for intervention to improve diabetes control before the

condition progresses to proliferative diabetic retinopathy (PDR) (Naserrudin et al., 2022). PDR is diagnosed when neovascularization is present (Huda *et al.*, 2023). Patients often remain unaware of the progression of their retinopathy due to the typically asymptomatic nature of early retinal damage (Nwanyanwu et al., 2021). Early detection and treatment can help prevent or delay the progression of DR, making it crucial for individuals with diabetes to have regular eye examinations (MOH, 2017).

In Malaysia, the screening and management of DR follow a structured protocol to detect and address sight-threatening conditions promptly. Individuals who were diagnosed with T2DM should undergo screening at the time of diagnosis. Follow-up schedules vary by the stage of retinopathy, with intervals ranging from 3 to 24 months. Conditions necessitating immediate referral to an ophthalmologist comprise any stage of diabetic maculopathy, severe NPDR, any level of PDR, unexplained visual loss, or if the screening examination cannot be performed, including ungradable fundus photos. Emergency referrals are necessary in cases of abrupt and severe vision loss or indications of acute retinal detachment. Referrals within a week are recommended for the emergence of retinal neovascularization, preretinal or vitreous haemorrhages, and rubeosis iridis. Referrals within four weeks are necessary for unexplained drops in visual acuity, any form of maculopathy, severe NPDR, or worsening retinopathy. This holistic strategy was designed to identify sight-threatening DR early and facilitate prompt intervention to prevent vision loss (MOH, 2017).

1.2 Problem Statement and Rationale of study

The surge in the incidence of DR by more than 25% in the last decade highlights an emerging public health challenge that is expected to place further demands on already overstretched healthcare systems (Tan and Wong, 2022). In Kelantan, the prevalence of diabetes mellitus was 19.5% (IPH, 2020), underscoring the magnitude of this challenge. This underscores the condition's significance as a health concern within specific communities.

Public health initiatives have often overlooked the morbidity associated with DR, an issue that necessitates immediate attention and policy reform (Teo *et al.*, 2021). The condition not only impairs vision but also significantly affects daily functioning, independence, and mental health, which may complicate diabetes management and elevate the risk of social isolation, depression, and anxiety (MOH, 2017). Economically, DR poses significant challenges, contributing to rising healthcare expenditures, reduced labour productivity, and an escalated need for caregiver support (Dar *et al*., 2023).

Furthermore, the likelihood of developing DR is also directly correlated with the duration of diabetes, marking it as a leading cause of blindness among adults in developed nations (MOH, 2020). In response to these growing challenges, there is a pressing need to shift the focus towards a more proactive approach in managing diabetic retinopathy. Healthcare providers and policymakers should prioritize early detection and intervention to prevent the progression of DR. This includes implementing comprehensive screening programs, educating patients on the

importance of regular eye examinations, and providing better support systems for those at risk.

By understanding the event probability and identifying key prognostic factors of diabetic retinopathy (DR) in Kelantan, we aim to tailor interventions that not only prevent the onset of this debilitating condition but also empower patients to manage their diabetes more effectively. This approach is designed to enhance patients' quality of life, reduce the emotional and financial burden on families, and ease the strain on healthcare systems. Our research specifically targets these objectives by addressing existing gaps in prevention and management strategies for DR. By improving these strategies, we anticipate significant support for the Kelantan State Health Department and healthcare practitioners. Ultimately, our findings could lead to enhanced health outcomes and quality of life for people with diabetes through more efficient allocation of medical resources, fostering a healthier community where individuals can lead full, independent lives without the looming threat of vision loss from diabetic retinopathy.

1.3 Research Questions

1. What is the event probability of diabetic retinopathy among adult patients with type II diabetes mellitus in Kelantan from 2013-2017?

2. What are the prognostic factors of diabetic retinopathy among adult patients with type II diabetes mellitus in Kelantan from 2013-2017?

1.4 Research Objectives

1.4.1 General Objective

To determine the event probability of diabetic retinopathy and its prognostic factors among adult patients with type II diabetes mellitus in Kelantan from 2013-2017.

1.4.2 Specific Objectives

1. To determine the event probability of diabetic retinopathy among adult patients with type II diabetes mellitus in Kelantan from 2013-2017

2. To determine the prognostic factors of diabetic retinopathy among adult patients with type II diabetes mellitus in Kelantan from 2013-2017

1.5 Research Hypothesis

Null Hypothesis (Ho): There are no significant prognostic factor of diabetic retinopathy among adult patients with type II diabetes mellitus in Kelantan from 2013-2017

CHAPTER 2

LITERATURE REVIEW

The literature review was conducted using a comprehensive approach, leveraging multiple online search engines including PubMed, Scopus, and EBSCOhost, in addition to university-subscribed databases, to gather a diverse range of relevant literature. The search was focused on publications from 2014 to 2024 to ensure recent and up-to-date studies were included. However, a few older studies were also incorporated due to their significant relevance. Throughout this process, a variety of searching strategies were employed, incorporating advanced techniques such as Boolean operators (AND, OR, NOT) to effectively combine key terms and refine the search results. This methodical approach aimed to capture a comprehensive scope of literature pertinent to the research topic, enhancing the depth and breadth of the literature review analysis. The keywords that apply during the search are diabetic retinopathy, type II diabetes mellitus, event probability, survival analysis, and prognostic factor.

2.1 Median time to development of Diabetic Retinopathy

The risk of retinopathy rises significantly with the prolonged duration of diabetes (Adj.HR: 2.86; 95% CI: 1.41, 5.31) (Gelcho and Gari, 2022). To establish appropriate follow-up intervals for patients, a literature review was conducted on the median time to development of DR. This helped estimate the optimal intervals for additional patient monitoring. Reports on the onset of DR vary globally, with medians ranging from 41 months in Jimma, Southwest Ethiopia to 150 months in South Korea (Kim *et al.*, 2014; Gurmessa Nugussu Gelcho, 2022). Other findings include 138 months in Skaraborg,

Sweden, (Garberg *et al.*, 2015), 74 months in Addis Ababa, Ethiopia, (Azeze *et al.*, 2018), 104 months in Northwest Ethiopia, (Takele *et al.*, 2022), and 76 months in Germany, (Hermann *et al.*, 2014). This range of approximately 3.5 to 12.5 years highlights the impact of local factors on disease progression and underscores the need for tailored screening intervals based on demographic and regional health data. The variation in DR onset is influenced by factors such as the prevalence of undiagnosed diabetes mellitus (DM), differences in healthcare infrastructure, accessibility to and frequency of screening programs, and socio-economic conditions. In regions where diabetes often goes undiagnosed or is diagnosed late, as seen in parts of Ethiopia, the onset of DR may occur earlier due to prolonged periods of uncontrolled hyperglycaemia (Takele *et al.*, 2022). Conversely, in areas with well-developed healthcare systems, like South Korea, early detection and management of diabetes can delay DR onset (Kim *et al.*, 2014).

However, our study did not evaluate the median time. Establishing such follow-up intervals was not feasible due to the insufficient number of patients reaching the 50% threshold required for reliable median time estimation. Additionally, a longer follow-up period is needed, as this study only included a 5-years follow-up, which is inadequate to capture the full progression timeline for many patients.

2.2 Event probability of Diabetic Retinopathy

A review of the literature on the event probability of DR in individuals with T2DM illustrates that the risk of developing this condition escalates as the duration of the disease extends. Notably, the study by Klein *et al.* (1984), which is extensively cited,

indicated that the event probability in Wisconsin, USA, grew from 25% at 5 years to 80% at 15 years post-diagnosis of diabetes. Further detail is provided by the work of Romero-Aroca *et al.* (2017) in Spain, which documented an ascending event probability for diabetic retinopathy, starting at 14.7% after 5 years, rising to 41.9% at 10 years, advancing to 54.4% at 15 years, and reaching 66.7% at 20 years. When these probabilities are compared with cumulative incidence rates from other regions, they revealed a significant variation: an 18.2% event probability within 3 years in Kinmen, Taiwan, (Tung *et al.*, 2005), 36% within 4 years in Wales, (Thomas *et al.*, 2012), 38.3% within 8 years in Japan, (Kawasaki *et al.*, 2011) and 50.6% within 15 years in Bangladesh, (Ahmed *et al.*, 2012). These discrepancies suggest that the event probability for DR not only increases with the progression of diabetes but also varies according to different regional and potentially other factors, such as the time from disease onset to diagnosis and differences in healthcare services. Understanding these variations is crucial for the objective of this research. Klein *et al.* (1984) work continues to be a benchmark for understanding the timeline of risk increment, which is crucial for the objective of this research.

2.3 Prognostic factors of Diabetic Retinopathy

2.3.1 Sociodemographic characteristics

Studies have yielded disparate findings regarding gender's role in DR risk. While a Taiwanese study by Lee *et al.* (2021) suggests a marginal increase in risk for males (Adj. HR: 1.13; 95% CI: 1.00, 1.27), a U.S. study by Harris Nwanyanwu *et al.* (2013) found no significant effect (Adj. HR: 1.11; 95% CI: 0.88, 1.40). These disparate

findings highlight the complexity of DR risk factors and suggest that gender may play a variable role depending on the population studied.

In the context of age as a prognostic factor for DR, the study from Spain identified older age at diagnosis as a risk factor (Adj. HR: 1.34 ; 95% CI:1.29, 1.66) (Romero-Aroca *et al.*, 2017). Similarly, a study from Ethiopia by Gurmessa Nugussu Gelcho (2022) found that elder age was significantly associated with the development of DR (Adj. HR: 3.17; 95% CI: 1.53, 6.58).

The impact of ethnicity on DR progression has also been explored, particularly concerning Black individuals. Though not statistically conclusive, Harris Nwanyanwu *et al.* (2013) suggest that Black individuals may have a higher likelihood of their NPDR progressing to PDR (Adj. HR: 1.29; 95% CI: 0.92, 1.82).

2.3.2 Clinical characteristics

Research by Hietala *et al.* (2010) indicates that an increased BMI has a minimal impact on the risk of developing DR (Adj. HR: 1.02; 95% CI: 0.99, 1.05). T2DM stands out as a considerably stronger risk factor for DR compared to T1DM. Individuals with T2DM face a higher likelihood of complications and a shorter time to onset of retinopathy (Adj. HR: 4.01; 95% CI: 1.34, 12.00) (Azeze *et al.*, 2018). This underscores the importance of early detection and tailored management strategies for T2DM patients to mitigate DR risks. The risk of retinopathy increases significantly with the duration of diabetes (Adj. HR: 2.86; 95% CI: 1.41, 5.31) (Gurmessa Nugussu Gelcho, 2022).

While smoking may potentially elevate the risk of DR, the association lacks statistical conclusiveness (Adj. HR: 1.62; 95% CI: 0.53, 5.01) (Lim *et al.*, 2017). Additionally, kidney disease (nephropathy) is a powerful predictor of worsening retinopathy, with a strong correlation marked (Adj. HR: 5.01; 95%CI: 4.68, 5.37) (Jeng *et al.*, 2016). In Taiwan, studies have highlighted the impact of various cardiovascular conditions on the progression of diabetic retinopathy. Hyperlipidaemia was shown to increase the risk for both NPDR and PDR, (Adj. HR: 1.21; 95% CI: 1.12, 1.31) (Lee *et al.*, 2021), and hypertension was associated with an elevated risk for progressing to PDR (Adj. HR: 1.08; 95% CI: 0.96, 1.22) (Lee *et al.*, 2021). Additionally, heart disease was not found to be a statistically significant factor in the progression of DR (Adj. HR: 1.07; 95% CI: 0.94, 1.23) (Lee *et al.*, 2021), while stroke was significantly associated with the progression of this condition (Adj. HR: 1.11; 95% CI: 1.10, 1.37) (Jeng *et al.*, 2016).

2.3.3 Blood parameters

The progression to PDR has been closely linked to HbA1c levels as a prognostic factor in multiple studies. In Taiwan, Lee *et al.* (2021) reported that HbA1c levels increased the likelihood of PDR progression, (Adj. HR: 1.11; 95% CI: 1.05, 1.17). In Spain, Romero-Aroca *et al.* (2017) specifically highlighted high HbA1c levels as a significant prognostic factor for PDR progression (Adj. HR: 2.21; 95% CI: 1.73, 6.87). Additionally, in the USA, Harris Nwanyanwu *et al.* (2013) found that HbA1c levels were associated with the progression to DR (Adj. HR: 1.14; 95% CI: 1.07, 1.21). Additionally, serum creatinine levels serve as a prognostic indicator for PDR, with

elevated levels suggesting a heightened risk (Adj. HR: 1.02; 95% CI: 0.96, 1.07) (Lee *et al.*, 2021).

Lipid profiles also have prognostic value. HDL-C levels impact the timing of DR onset (Adj. HR: 1.13; 95% CI :0.89, 1.43) (Ahmed *et al.*, 2012). Furthermore, elevated TG levels have been significantly associated with the occurrence of DR. In Ethiopia, Azeze *et al.* (2018) reported an increase in hazard ratio (Adj. HR: 2.59; 95% CI: 1.31, 4.97) , while Takele *et al.* (2022) found that TG levels greater than 150 mg/dL, compared to levels below 150 mg/dL, were increased hazard ratio (Adj. HR: 2.59; 95% CI:1.31, 4.97).

2.3.4 Treatment

In the U.S., being on insulin was linked with a modestly increased risk (Adj. HR: 1.45; 95% CI: 0.94, 2.24) (Harris Nwanyanwu *et al.*, 2013). However, the study from Ethiopia reported a much stronger association, with insulin therapy alone being a significant prognostic factor for the development of DR (Adj. HR: 3.91; 95% CI: 1.36, 7.94) (Gurmessa Nugussu Gelcho, 2022). On the other hand, oral hypoglycaemic agents (OHAs) did not show a significant prognostic effect on DR development in the U.S. study (Adj. HR: 1.04; 95% CI: 0.68,1.59) (Harris Nwanyanwu *et al.*, 2013). Furthermore, statin use was identified as a prognostic factor associated with an increased risk of both non-proliferative and proliferative forms of DR in Taiwan (Adj. HR: 1.17; 95% CI:1.08, 1.27) (Jeng *et al.*, 2016).

2.4 Conceptual framework

The literature review highlights several significant factors influencing the progression to DR among patients with T2DM. The factors are categorized into four main groups: socio-demographic characteristics, clinical characteristics, blood parameters, and treatment factors. Socio-demographic factors include age, sex, and ethnicity. Clinical factors comprise duration of DM, body mass index (BMI), and comorbidities like hypertension, heart disease, nephropathy, and stroke. Blood parameters include HbA1c level, TC, HDL-C, LDL-C, and total TG. Creatinine level was excluded because it was already represented by the status of nephropathy. Socioeconomic status and smoking status were not included due to incomplete secondary data in the National Diabetes Registry (NDR) line listing. Treatment factors were not considered due to limitations in capturing historical treatment data prior to the development of diabetic retinopathy. The primary outcome of interest in this survival study is time-to-event or progression time, defined as the duration in months from the diagnosis of T2DM to the diagnosis of DR during the study period. Figure 2.1 shows Conceptual Framework on Prognostic Factors of Diabetic Retinopathy Among Adult Patients with T2DM.

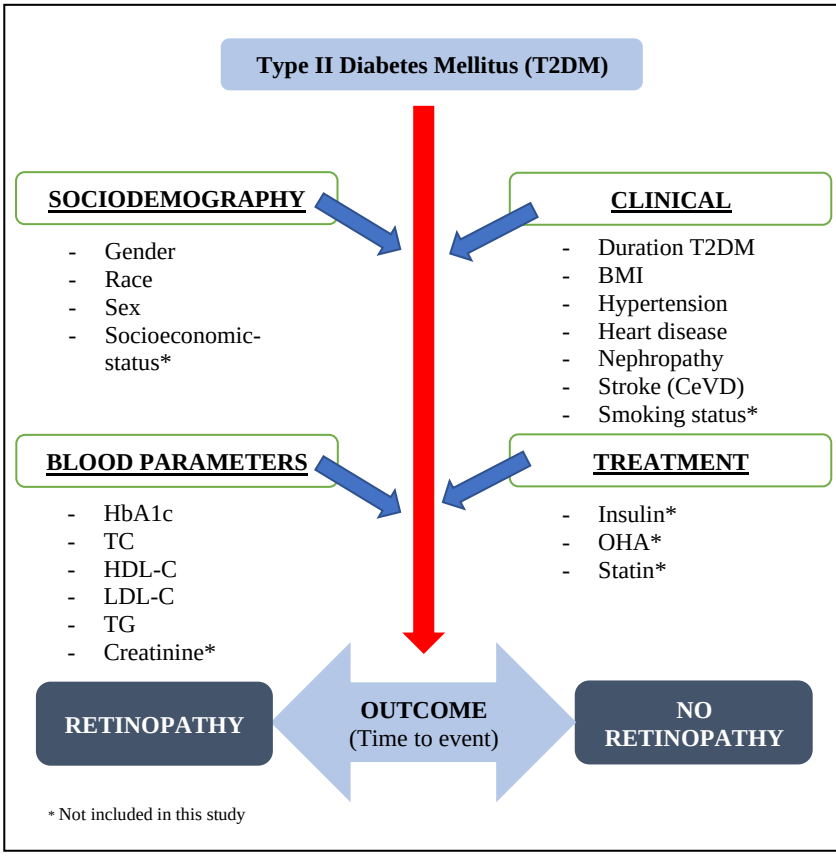

Figure 2.1: Conceptual framework on prognostic factors of diabetic retinopathy among adult patients with T2DM

CHAPTER 3

METHODOLOGY

3.1 Study Design

A retrospective cohort study was applied in this study.

3.2 Study Duration

This study was conducted between January 2024 till June 2024

3.3 Study Area

The research was carried out in Kelantan, a state situated in the north-eastern region of Peninsular Malaysia. Kelantan shares borders with Thailand to the north, the state of Terengganu to the east, the state of Perak to the west, the state of Pahang to the south, and the South China Sea to the northeast. Spanning roughly 15,040 square kilometres, it is divided into ten administrative districts: Kota Bharu, Bachok, Pasir Mas, Tumpat, Pasir Puteh, Tanah Merah, Machang, Kuala Krai, Gua Musang, and Jeli (DOSM, 2020).

According to the Department of Statistics Malaysia (DOSM, 2024b), the population of Kelantan is estimated to be approximately 1.89 million people in the first quarter of 2024 with a population density of approximately 119 persons per square kilometer. In Kelantan, approximately 95.5% of the population is Malay, followed by 2.4% Chinese, with the remainder consisting of Indians, Siamese, and other ethnic

groups, and the gender ratio is about 101 males to 100 females (DOSM, 2024a). Kelantan is served by 113 health clinics, 146 *klinik desa*, and 9 government hospitals (MOH, 2024).

Figure 3.1: Map of Kelantan State

3.4 Study Population

3.4.1 Reference Population

The reference population was all adult patients with T2DM in Kelantan.

3.4.2 Source Population

The source population for the study was all adult patients with T2DM registered in National Diabetic Registry in Kelantan from 1st January 2013 till 31st December 2017

3.4.3 Sampling Frame

The sampling frame for this study was all adult patients with T2DM registered in NDR from 1st January 2013 till 31st December 2017 who fulfilled the study criteria.

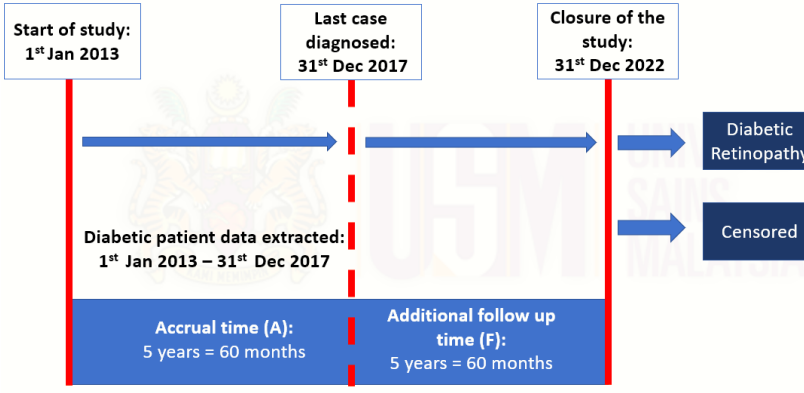

Figure 3.2: Timeline of study

3.5 Data Criteria

3.5.1 Inclusion Criteria

1. Data of patients who were registered in NDR (Clinical audit datasets Negeri Kelantan 2022)

2. Data of patients who were diagnosed with type II diabetes mellitus from 1/1/2013 till 31/12/2017

3. Data of Adult patients (≥18 years old)

3.5.2 Exclusion Criteria

Missing data of more than 30% of the interested variables from the database,

3.6 Sample Size Estimation

The calculation of the sample size was determined according to the study objectives as follow:

3.6.1 Objectives 1 : Using Single Proportion Formula

$$n = \left(\frac{Z_{\alpha/2}}{d} \right)^2 * P(1 - P)$$

σ = Population's standard deviation (from previous study)

α = Type 1 error

d = Margin of error estimating mean

Table 3.1: Formula for calculation using Single Proportion Formula

Variables	**Value**
Significance (α)	0.05
P Reference Population according to Literature (NDR report,2020)	0.12
d detectable differences relative Precision	0.01
Zα = normal deviates that reflects Type I error; (level of significance at 5%; 95% CI)	1.96
Total Sample Size calculated	1014
Sample Size with 20% drop out	1267

3.6.2 Objectives 2 : Using Two Median Survival Time formula by PS Software

Table 3.2: Formula for calculation using Two Median Survival Time

Variables	**Value**
α	0.05
Power	80%
m1	Median time among non-prognostic group (by literature)
m2	Median time among Prognostic group (by literature/expert opinion)
m	Ratio of non-prognostic to prognostic group (from the population)
Accrual time (A)	60 months (2013-2017)
Additional Follow Up time (F)	60 months

Table 3.3: Calculation sample size using Two Median Survival Time

Prognostic Factor	**m1**	**m2**	**A**	**F**	**M**	**N**	**n+20%**	**Author , Year**
BMI <24.9 vs >30	76	61	60	60	1	1098	**1372**	(Gurmessa Nugussu Gelcho, 2022)
HbA1c <6.7 vs >8.2	48	28	60	60	1	136	170	(Lee *et al.*, 2021)

Single Proportion Formula was used for Objective 1 and a sample size of 1267 was obtained, whereas for Objective 2, Two Median Survival Time formula via PS Software yielded a sample of 1372; thus, larger sample of **1372** was chosen for this study.

3.7 Sampling Method and Subject Recruitment

The research process began with the collection of data from the Kelantan NDR Dataset of Non-Communicable Disease (NCD) unit in the Kelantan State Health Department, utilizing a proforma checklist to extract pertinent information while prioritizing patient confidentiality. Permission to access and use the data was obtained from the Director of the State Health Department, ensuring compliance with ethical guidelines. Initially, the dataset revealed 3032 cases of T2DM diagnosed between January 2013 and December 2017, which underwent rigorous data cleaning resulting in 2935 eligible cases for the study. Subsequently, a simple random sampling method was applied using the RAND() function in Microsoft Excel to select a representative sample of 1372 cases from the dataset. The selected sample was then transferred to SPSS 28 for comprehensive statistical analysis, encompassing descriptive and inferential analyses. Throughout the process, careful documentation ensured reproducibility and

transparency, with detailed records of the sampling methodology, data cleaning procedures, and statistical analyses. This methodological rigor and adherence to ethical standards bolstered the integrity and reliability of the research outcomes, supporting valid conclusions about the broader T2DM patient population in the region.

3.8 Research tools

3.8.1 National Diabetic Registry (NDR)

This study involves the collection of secondary data from the Clinical Audit Diabetes Database within the National Diabetic Registry (NDR) system managed by the Non-Communicable Disease Unit (NCD) of Kelantan Health State. The National Diabetic Registry (NDR) represents an innovation by the Ministry of Health (MOH) for diabetic surveillance. This web-based registry facilitates a systematic method for gathering data and monitoring the quality of care provided to patients with T2DM managed within MOH facilities(Chandran *et al.*, 2019). It consists of two main components: a patient registry and a clinical audit dataset. The clinical audit dataset, which is a subset of the patient registry, contains comprehensive information including clinical variables, medication usage, and care outcomes for audited patients. Each year, patients from the registry are randomly chosen for audit to ensure data accuracy and completeness. To maintain confidentiality, all study subjects were identified only by a unique code number within the dataset. This secondary data collection process provides valuable insights into diabetes management and treatment outcomes in the Kelantan Health State region.

3.8.2 Proforma checklist

Relevant information from audited patients was extracted using a structured proforma checklist, which includes the code number, date and duration of diabetes mellitus (DM), and whether diabetic retinopathy (DR) is present or absent, along with the date of DR diagnosis if applicable. The checklist also records demographic details such as age at diagnosis, gender, and ethnicity. Clinical factors are assessed through body mass index (BMI) categorized as normal, overweight, underweight, or obese, and measurements of height and waist circumference. Other comorbidities, including hypertension, nephropathy, hyperlipidaemia, and stroke, are noted, as well as smoking status. Blood parameters such as HbA1c, total triglycerides (TG), creatinine, cholesterol, and HDL levels are documented. Finally, the checklist includes information on treatments, specifying whether the patient is on insulin, statins, or oral hypoglycaemic agents (OHA).

3.9 Operational Definitions

1. Type II diabetes mellitus (T2DM): All type II diabetes mellitus that has been registered in the NDR system

2. Diabetic retinopathy: A condition with progressive retinal damage that occurs due to microvascular complication of diabetes mellitus was assessed through clinical examination and categorized as either present (yes) or absent (no) based on the charts.

3. Event: Diabetic retinopathy.

4. Time to event (diabetic retinopathy): Time from date of diagnosis of T2DM till date of diagnosis of DR.

5. Censored observation: Patient who did not experience diabetic retinopathy (event of interest) during the closure of study (31st December 2022) as this represents the most recent complete set of records available at the time of analysis

6. Blood Parameters: All blood results for cases of DR were taken within one year prior to the diagnosis of DR. For non-diabetic retinopathy cases, the blood results represent the latest data available in the system.

7. Old age: 60 years old and above (MyGovernment, 2024)

3.10 Data Collection Method

This research utilized secondary data obtained from the clinical audit diabetes database sourced from the Non-Communicable Disease Unit (NCD) within the Kelantan Health State, accessed via the NDR system. A structured proforma checklist was employed to extract all pertinent information. Each study participant was assigned a code number to protect their identity. The proforma served as a thorough checklist for data collection, ensuring confidentiality was upheld throughout. Subsequently, the data was