

## Evaluation of Predictors for the Development and Progression of Diabetic Retinopathy among Diabetes Mellitus Type 2 Patients

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### ABSTRACT

*Diabetic retinopathy is one of the microvascular complications caused by prolonged uncontrolled diabetes. It is believed that diabetic retinopathy correlates with certain predictors and risk factors that might worsen the disease, eventually causing visual loss and blindness among diabetes patients. There are some predictors and risk factors that attribute to the development and progression of diabetic retinopathy, such as the duration of diabetes and HbA1c trends. This study aims to evaluate the predictors and risk factors associated with the development and/or progression of diabetic retinopathy. Retrospective data were collected from a single healthcare facility in the northwest of Peninsular Malaysia. Patients included in this study were those with type 2 diabetes mellitus diagnosed with diabetic retinopathy. The total number of patients involved in this study were 197, where 161 of them were newly diagnosed or with progressive diabetic retinopathy. The characteristics of diabetes patients with complication of diabetic retinopathy were described through descriptive statistics. Characteristics include demographics data such as age, gender, race and clinical data such as HbA1c readings HbA1c, estimated glomerular filtration rate (eGFR), urea and haemoglobin concentration (Hb). The results show that 7 predictors and risk factors are significant to the development and progression of diabetic retinopathy among diabetes patients. By using multinomial logistic regression, this study offers better understanding of the significant predictors and risk factors related to diabetic retinopathy.*

**Keywords:** diabetic retinopathy, predictors, multinomial logistic regression

## 1 INTRODUCTION

Diabetic retinopathy is a microvascular complication caused by prolonged uncontrolled diabetes mellitus which may cause significant disability including blindness. The prevalence of diabetic retinopathy worldwide ranges from 6.8% to 44.4% in patients with diabetes mellitus. Globally, the number of people with diabetic retinopathy were estimated to grow from 126.6 million in 2010 to 191.0 million by 2030 if remedial action is not taken [1], [2]. However, in Malaysia the prevalence of diabetic retinopathy has been reported to increase from 44.1% to 48.6% [3]. The prevalence of diabetic retinopathy in Malaysia is comprised of 12.3% of type 1 and another 22.3% of type 2 diabetes mellitus. Diabetic retinopathy refers to all the vascular changes in the retina occurring from the disease detected from ophthalmologic evaluation, risking visual impairment

and blindness among patients with diabetes [4]. According to the International Clinical Diabetic Retinopathy, diabetic retinopathy is categorized by six stages; (i) no retinopathy, (ii) mild non-proliferative diabetic retinopathy (NPDR), (iii) moderate NPDR, (iv) severe NPDR, (v) proliferative diabetic retinopathy (PDR) and (vi) advanced diabetic eye disease (ADED)[5].

From past studies, predictors and risk factors that are commonly associated to the progression of diabetic retinopathy includes the duration of diabetes, age, gender, HbA1c and hypertension [3],[6],[7],[8],[9]. In addition, there are clinical predictors which can be significant to the development of diabetic retinopathy. Common clinical predictors that may affect the progression of diabetic retinopathy are glycosylated haemoglobin trends (HbA1c), systolic and diastolic blood pressure, serum creatinine and urea [10]. Synonymously, [11], [12], [13] agreed that blood glucose control as measured by HbA1c, insulin treatment, glucose levels and serum creatinine could also impact the progression of diabetic retinopathy. However, the testing on the significance of these predictors varied from one study to another.

Diabetes patients with diabetic retinopathy can be divided into three groups. Group 1 include diabetes patients who were diagnosed with diabetes without obvious clinical findings of diabetic retinopathy (show development). Unfortunately, some of them may have developed occult signs of early diabetic retinopathy. While Group 2 consists of diabetes patients who were diagnosed with diabetic retinopathy and remain in the same stage for a certain period of time until the current follow-up, and Group 3 involves diabetes patients who were diagnosed with diabetic retinopathy at certain stage for a period of time but progressively worsen over time during the current follow-up (show progression). Thus, the purpose of this study is to evaluate the predictors and risk factors associated to the development or progression of diabetic retinopathy among Group 1 and Group 3. However, for the descriptive statistics, analysis will involve all the three groups.

## **2 STUDY DESIGN**

This is a retrospective study involving patients with diabetes mellitus type 2 (T2DM) from a single healthcare centre located in the northwest of Peninsular Malaysia. A total of 197 diabetes patients were included in this study. The characteristics of patients selected in this study were; diabetes patients who were diagnosed with diabetic retinopathy, on follow-up treatment in the respective healthcare centre from their first clinic visit, up to the year 2020. Predictors and risk factors evaluated in this study are age, gender, ethnicity, duration of T2DM, duration of diabetic retinopathy, diabetic nephropathy, hypertension, dyslipidaemia, HbA1c, estimated glomerular filtration rate (eGFR), urea and haemoglobin concentration (Hb). The details and clinical data for every patient were obtained from their medical card, which was recorded by trained and credentialed personnel, with prior review by experienced ophthalmologists at the Ophthalmologist Clinic.

## **3 STATISTICAL ANALYSIS**

Evaluation for significant predictors and risk factors for this study was implemented by modelling the multinomial logistic regression model using the predictors and risk factors involved in the study. Multinomial logistic regression is an extension of binary logistic regression that allows more than two categories of dependent variable. Commonly, multinomial logistic regression model is applied for classification in medical, education, transportation, physiological, mathematical finance and engineering area. Multinomial logistic is also known as the polytomous

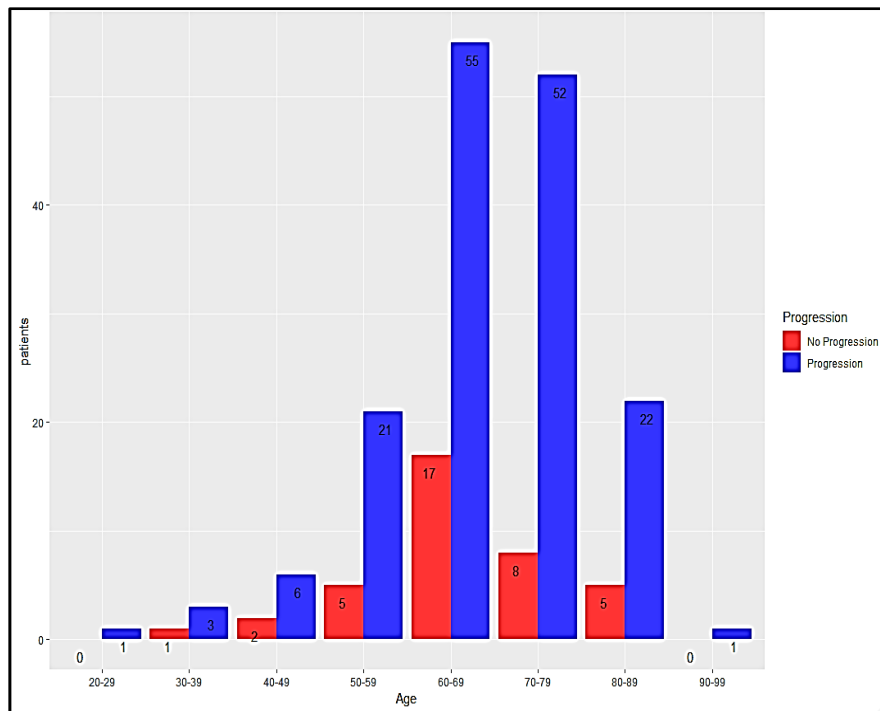
or multiclass logistic regression method. In order to make sure valid results are obtained from the model, all the six assumptions of the model including, (i) the dependent variable i.e. stages of diabetic retinopathy should be measured at the nominal level, (ii) the model has one or more independent variables i.e. predictors and risk factors that are continuous, ordinal or nominal, (iii) the model has independence of observations and the stages of diabetic retinopathy should have mutually exclusive and exhaustive categories, (iv) there should be no multicollinearity among the predictors and risk factors, (v) there needs to be a linear relationship between any continuous predictors and risk factors, and the logit transformation of the stages of diabetic retinopathy, and (vi) there should be no outliers for the scale or continuous variables. Multinomial logistic regression model is presented as:

$$\text{logit}(Y_{DR}) = \ln \left[ \frac{P(Y_{DR} = j | X)}{P(Y_{DR} = J | X)} \right] = \beta_{j0} + \beta_{j1}X_1 + \beta_{j2}X_2 + \dots + \beta_{jk}X_k \quad (1)$$

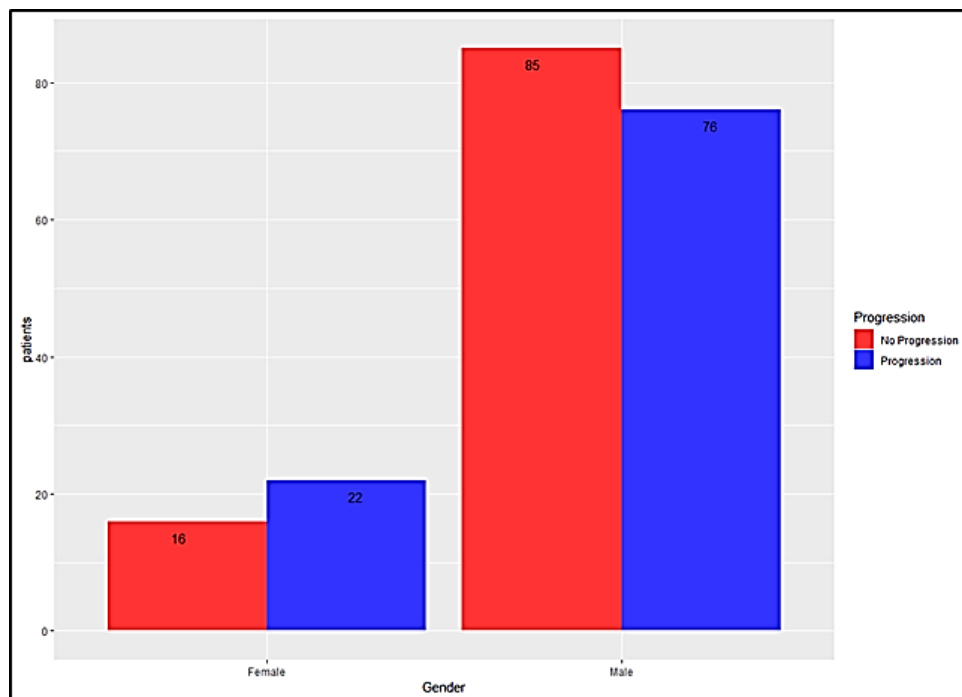
where  $j = 1, 2, \dots, J - 1$  is a logit equation and  $J$  represents the categories of the reference outcome.  $Y_{DR}$  includes the categorical predictors which represent the stages of diabetic retinopathy (no diabetic retinopathy (stage 0), mild NPDR (stage 1), moderate NPDR (stage 2), severe NPDR (stage 3), PDR (stage 4) and ADED (stage 5);  $Y = 0, 1, 2, 3, 4, 5$ ).  $X$  refers to the predictors and risk factors associated with diabetic retinopathy, while  $k$  denotes the number of predictors and risk factors for diabetic retinopathy, where  $X_1, X_2, \dots, X_k$  can either be continuous or categorical predictors (replaced by dummy variables) and risk factors. Predictors and risk factors in this study include age, gender, ethnicity, duration of T2DM, duration of diabetic retinopathy, diabetic nephropathy, hypertension, dyslipidaemia, HbA1c, eGFR, Urea and Hb.  $\beta_{jk}$  is the logit coefficient providing information on how great a change in the logit is made by a one-unit increase of the value of  $k$ -th predictors. This study used R Studio Packages to perform the respective statistical analyses.

#### 4 RESULT AND DISCUSSION

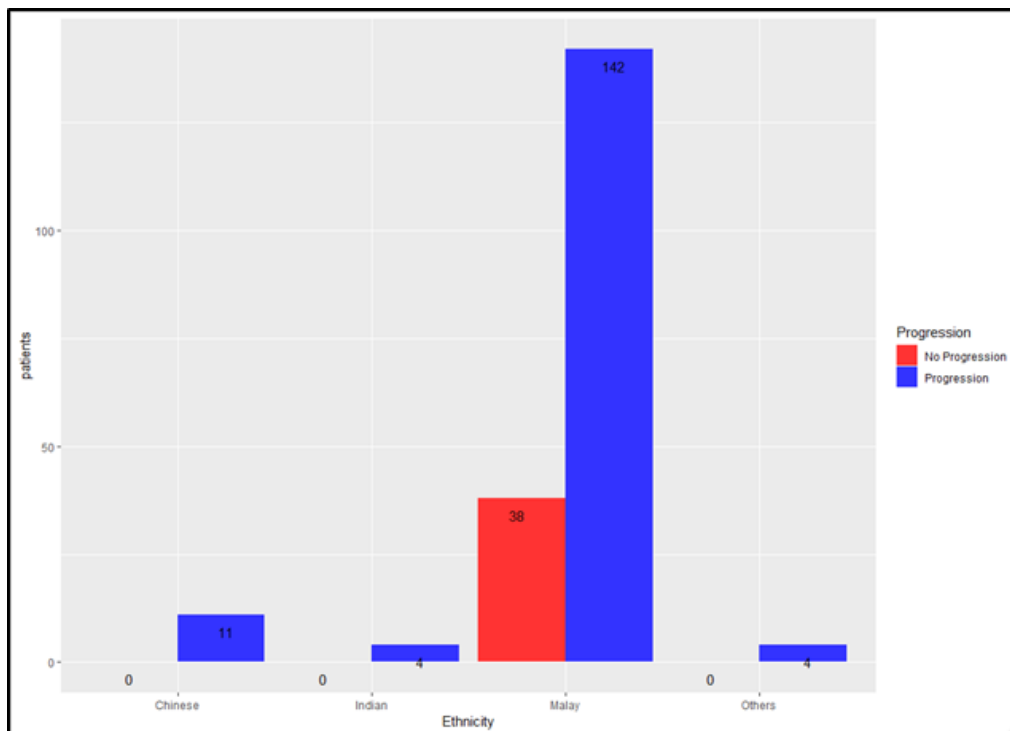
For this study, progression of diabetic retinopathy refers to diabetes patients in Group 1 and Group 3, while diabetes patients in Group 2 shows no progression. Figure 1 shows the composition of diabetes patients according to the age group. Among diabetes patients in Group 1 and 3, the blue bars indicate that most number of patients with the age group from 50 to 89 years are among those who have higher potential of showing diabetic retinopathy progression. Compared to the red bars that reflect diabetes patients in Group 2, the number of patients with age 60 to 69 shows no progression in diabetic retinopathy. While Figure 2 illustrates that the number of male and female diabetes patients are similar regardless whether patients are in Group 1, 2 or 3.



**Figure 1.** Comparison between diabetes patients with no progression and with progression status according to patients' age group.



**Figure 2.** Comparison between no progression and with progression status according to gender.



**Figure 3.** Comparison between no progression and with progression status according to ethnicity

Figure 3 demonstrates the ethnicity of diabetes patients involved in the study. Malay diabetes patients show the highest number of patients experiencing progressive diabetic retinopathy. Similar observation was also noted for diabetes patients with no progression. Based on the data, mostly Malay patients are among the majority who come for follow up at the Ophthalmologist Clinic.

Figure 4(a) refers to the stages for diabetes patients when first diagnosed with diabetic retinopathy, while Figure 4(b) refers to the same diabetes patients when diagnosed with diabetic retinopathy during the current follow up. Based on Figure 4(a), diabetes patients with stage 0 are those who have higher potential to develop diabetic retinopathy. This means that if a patient in Group 1 have not yet diagnosed with diabetic retinopathy, he/she may develop to other stage of diabetic retinopathy after certain period of time. For example, a patient could present with no diabetic retinopathy initially, however may progressed directly to stage 2 (mild NPDR) or stage 3 (moderate NPDR). Figure 4(b) shows the increasing number of diabetes patients who have shown some stage progression. For example, about 118 diabetes patients who were first diagnosed with stage 0 have shown progression to stage 1, 10 patients have developed to stage 2, 11 patients developed to stage 3, and 15 patients developed to stage 4. Also, from Figure 4(b) one patients has shown progression from stage 4 to 5. Compared with no progression case for stages at diagnosis during the current follow up, the number of patients with no progression is higher for stage 2 (mild NPDR) and onwards.

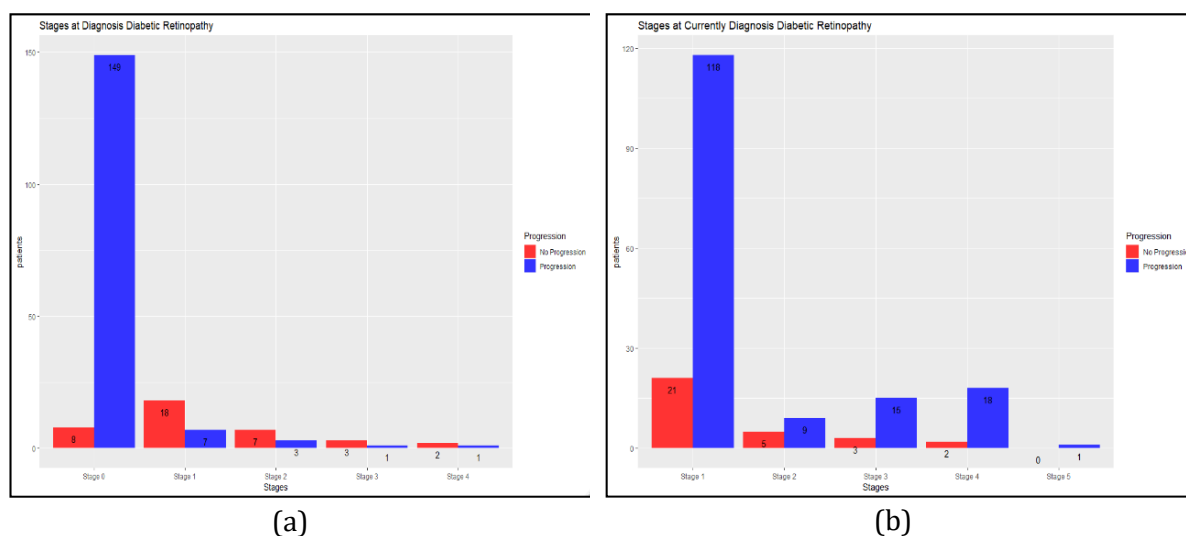


Figure 4: Comparison between the (a) developed stages at diagnosis of diabetic retinopathy and (b) stages diabetic retinopathy at current follow up.

#### 4.1 Comparison of Demographic and Clinical Data between Patients with and without Development or Progression of Diabetic Retinopathy

As mentioned earlier, this study includes three groups of patients; Group 1 includes diabetes patients who were diagnosed with diabetes but not yet diagnosed with diabetic retinopathy (show development), Group 2 refers to diabetes patients who were diagnosed with diabetic retinopathy and remain in the same stage for a certain period of time until the current follow-up, and Group 3 involves diabetes patients who were diagnosed with diabetic retinopathy at certain stage for a period of time but worsen to other stage during the current follow-up (show progression). A total of 197 patients with diabetes, 81.7% were patients from Group 1 and 3, while 18.3% from Group 2. From Table 1, the mean age for both groups is similar (67 years). However, the duration of diabetes, HbA1c, eGFR, urea and HB readings baseline for patients in Group 1 and 3 is higher than the readings for Group 3.

In addition, Table 1 shows the descriptive statistics and the significant predictors and risk factors for diabetes patients in Group 1 and 3 based on the evaluation using multinomial logistic regression model. These significant predictors and risk factors were tested based on the small p-value ( $<0.001$ ). From 11 predictors evaluated, 7 predictors were found significant. Age, gender, duration of T2DM, duration diabetic retinopathy, HbA1c, eGFR, and urea are significant predictors for the development and progression of diabetic retinopathy. Some of these findings were found to be similar with the previous studies. Many studies have shown that duration of diabetes and gender are significant [8], [14], [15], [16]. While for the clinical data (HbA1c, eGFR and urea) some of studies agreed that HbA1c greatly influenced the progression of diabetic retinopathy [8], [14], [17]. This study highlights that eGFR and urea as new significant predictors to the progression of diabetic retinopathy among Group 1 and 3. This new finding are less discussed in the previous studies may be due to its effect to diabetic retinopathy.

**Table 1** Characteristics of diabetic patients according to development or progression of diabetic retinopathy or without development or progression of diabetic retinopathy. (Group 1 - diabetes patients who were diagnosed with diabetes without obvious clinical findings of diabetic retinopathy (show development), Group 2 - diabetes patients who were diagnosed with diabetic retinopathy and remain in the same stage for a certain period of time until the current follow-up and Group 3 - diabetes patients who were diagnosed with diabetic retinopathy at certain stage for a period of time but progressively worsen over time during the current follow-up (show progression)). Values are proportions and means (standard deviations).

Characteristics	All Patients (n=197)	Group 1 & 3 Patients with Development/Progression of Diabetic Retinopathy (n=161)	Group 2 Patients without Development/Progression of Diabetic Retinopathy (n=36)	P-value
Age	67.33 (10.99)	67.68 (11.02)	67.78 (11.02)	<0.001
Gender				<0.001
Male	0.52	0.53	0.42	
Female	0.48	0.47	0.58	
Ethnicity				0.9636
Malay	0.89	0.88	1.00	
Chinese	0.05	0.07		
India	0.03	0.01		
Others	0.02	0.01		
Duration of T2DM	12.66 (5.03)	13.31 (5.00)	12.52 (5.05)	<0.001
Duration Diabetic Retinopathy	6.02 (3.45)	6.79 (3.99)	5.96 (3.38)	<0.001
Diabetic Nephropathy	1.00	0.82	0.18	0.4392
Hypertension	0.99	0.82	0.18	0.576
Dyslipidaemia	0.89	0.91	0.20	0.6231
HbA1c	8.64 (2.47)	9.41 (2.50)	8.54 (2.47)	<0.001
eGFR	59.45 (25.34)	59.78 (25.37)	54.54 (23.47)	<0.001
Urea	7.04 (3.77)	7.82 (3.93)	7.44 (3.94)	<0.001
Hb	11.46 (2.01)	11.34 (2.00)	11.89 (1.97)	0.8069

## 5 CONCLUSION

This study found that age, gender, duration of T2DM, duration of diabetic retinopathy, HbA1c, eGFR and urea are significant to the progression of diabetic retinopathy. Overall, this results suggest that for high risk diabetic retinopathy patients, these predictors could potentially influence to the development of severe stage of diabetic retinopathy. Therefore, to avoid rapid progression of stages in diabetic retinopathy among diabetes patients, these significant predictors and risk factors need to be given attention to prevent serious microvascular complications.

## ETHICAL CLEARANCE

This study was registered with the National Medical Research Register of the Ministry of Health, Malaysia (NMRR-19-3896-47105) and received ethical clearance from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (KKM/NIHSEC/P20-376).

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