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Assessing the importance of risk factors for diabetic retinopathy in patients with type 2 diabetes mellitus: Results from the classification and regression tree models

Ziyang Zhang, Deliang Lv, Yueyue You, Zhiguang Zhao, Wei Hu, Fengzhu Xie, Yali Lin, Wei Xie, Xiaobing Wu

Abstract:

BACKGROUND: Diabetic retinopathy (DR) is one of the serious complications of diabetes mellitus (DM). Many studies have identified the risk factors associated with DR, but there is not much evidence on the importance of these factors for DR. This study aimed to investigate the associated factors for patients with type 2 DM (T2DM) and calculate the importance of the identified factors.

MATERIALS AND METHODS: Using probability proportionate to size sampling method in this community-based cross-sectional study, 22 community health service centers were selected from 10 administrative districts in Shenzhen, China. Approximately 60 T2DM patients were recruited from each center. The participants completed a structural questionnaire, had their venous blood collected, and underwent medical examinations and fundus photography. Logistic regression models were used to identify the risk factors of DR. The classification and regression tree (CART) model was used to calculate the importance of the identified risk factors.

RESULTS: This study recruited 1097 T2DM patients, 266 of whom were identified as having DR, yielding a prevalence rate of 24.3% (95% confidence interval [CI]: 21.7%–26.9%). Results showed that a longer duration of DM, indoor-type lifestyle, and higher levels of hemoglobin A1c (HbA1c) or urea increased the risk of DR. Patients with HbA1c values ≥7% were about 2.45 times (odds ratio: 2.45; 95% CI: 1.83–3.29) more likely to have DR than their counterparts. The CART model found that the values of variable importance for HbA1c, DM duration, lifestyle (i.e., indoor type), and urea were 48%, 37%, 10%, and 4%, respectively.

CONCLUSION: The prevalence of DR is high for T2DM patients who receive DM health management services from the primary healthcare system. HbA1c is the most important risk factor for DR. Integration of DR screening and HbA1c testing into the healthcare services for T2DM to reduce vision impairment and blindness is urgently warranted.

Keywords:

Classification and regression tree, diabetes mellitus, diabetic retinopathy, hemoglobin A1c, risk factors

Department of Cardio-Cerebrovascular and Diabetes Prevention and Control, Shenzhen Center for Chronic Disease Control, Shenzhen, Guangdong, China

Address for correspondence:
Dr. Xiaobing Wu, No. 2021, Buxin Road, Luohu District, Shenzhen 518001, Guangdong Province, China.
E-mail: bingfsh@126.com

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Introduction

Diabetes mellitus (DM) is a common chronic disease that occurs as a result of increased blood levels of glucose from impaired insulin secretion.[1] Type 2 DM (T2DM) accounts for the vast majority of DM,[2] and diabetic retinopathy (DR) is one of the serious complications of DM.[3] DR not only impacts DM patients' health-related quality of life but also predicts vascular

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and all-cause mortality.[4,5] An analysis of 35 studies worldwide reports that almost 33% of DM patients develop DR, and more than 10% of patients develop vision-threatening DR.[6] Although early screening and prompt treatment of DM patients can effectively prevent the occurrence and development of DR, it is still a serious public health problem in view of the dramatic rise in the prevalence of DM worldwide.[7]

Many studies have identified the risk factors associated with DR, such as poor blood pressure and glycemic control, and longer DM duration.[8-10] Higher levels of hemoglobin A1c (HbA1c) are associated with the progression of DR, and intensive glycemic control can reduce the incidence and deterioration of DR.[11] Other factors included smoking, higher body mass index (BMI), and diabetic nephropathy (DN).[12,13] In addition, healthy lifestyle (e.g., sufficient physical activity), which may involve glycemic control, is the protective factor of DR.[14,15] However, how important these factors are and which is the most important for DR are seldom reported. The method of classification and regression tree (CART) model is increasingly being used in some health research to identify the risk factors and calculate the importance of the identified factors.[16,17] A recent study used CART models to identify the risk factors for DN, finding that HbA1c, hypertension, and fasting blood glucose (FBG) had the strongest associations with the condition.[18]

To fill the research gaps mentioned above, this study's aim was to assess the risk factors of DR and use the CART models to calculate the importance of identified factors based on the data from the Shenzhen Diabetic Eye Disease Program.

Materials and Methods

This cross-sectional study was conducted between December 30, 2018, and April 29, 2019. A research panel involving ophthalmologists, general practitioners, and epidemiologists was formed to design the study, write the survey methods and analytic guidelines, confirm the grade of DR, and complete the report. Brief information (e.g., name, initiated year of service, and number of T2DM patients on the roll) of each community health service center (CHSC) in Shenzhen's primary healthcare system was collected. The candidate survey sites were centers that had been in service for at least 1 year and provided T2DM health management services (THMSs) for more than 100 T2DM patients. The number of candidate centers in each district was then calculated. Using the probability proportionate to size sampling method, 22 centers were selected from 10 administrative districts. Specifically, in Shenzhen (city name), we have 10 administrative districts, 6 with larger populations (sample size: 1.63 million, 1.03 million, 1.49 million, 3.25 million, 2.38 million, and 1.67 million), and 4 with relatively smaller populations (0.24 million, 0.44 million, 0.63 million, and 0.15 million). For those six administration districts, each one randomly selected three centers ($6 \times 3 = 18$ centers); for the four districts, each one randomly selected 1 center ($4 \times 1 = 4$ centers). A total of 22 centers were selected [Table 1]. The sample size was calculated using the formula $n = Z^2 \times (P \times [1 - P])/E^2$; considering population proportion 25%, $\alpha = 0.05$, relative error = 10%, and nonresponse = 10%, the calculated sample size was 1320. Ethical approval was obtained from the Institutional Review Board Vide Letter No. SZCCC-2018001 dated 19/10/2018, and informed written consent was taken from all participants in the study.

Each selected center recruited 60 T2DM patients who fulfilled the following criteria: (1) diagnosed with T2DM according to the World Health Organization criteria (1999), (2) aged 35 years or older, (3) having visited CHSCs for any DM-related health service in the last 12 months, and (4) voluntary participation in this study. Patients who were incapable of completing all examinations or questionnaires, had a serious mental illness, had drug abuse, or had any nondiabetic eye disease (e.g., cataract, glaucoma, and acute inflammation) that might affect DR assessment were excluded from the study. This study recruited a total of 1320 participants, but 223 individuals were excluded for refusal to participate ($n = 11$), lack of fundus photographs ($n = 123$), unwillingness to undergo blood collection ($n = 56$), or inability to complete the questionnaire ($n = 33$). The final number of T2DM individuals included in the study was 1097.

Trained medical staff from selected CHSCs contacted the eligible participants through telephone or WeChat, briefed them about the purpose, content, and benefits of the study, and invited them to participate. The staff reminded the patients 1 or 2 days before the survey was conducted. The nonmydriatic fundus cameras were transported to the CHSCs, and their accuracy and clarity were corrected. At the beginning of the survey, the staff clarified the content and the process of the study and distributed the structural questionnaires to participants.

The survey was in three parts: completion of the questionnaire (i.e., demographic information, socioeconomic status, and lifestyle behaviors), venous blood collection, and medical examination. Anthropometric measurements were taken to obtain height, weight, waist circumference, heart rate, and blood pressure according to the health industry standard of the People's Republic of China (WS/T 424-2013). A basic ophthalmic examination was performed to assess the participants' ocular history and uncorrected/corrected

Table 1: The population size of each of the 10 administrative districts and the number of centers selected from each district

District	Population (10,000 people)	Community health center	Number of diabetes patients managed
Fu tian	163.37	Xiang mi	330
		Yi tian	412
		Jing mi	362
Luo hu	103.99	Huang beiling	284
		Cao puxi	370
		Hu jing	293
Nan shan	149.36	Nan you	287
		Shen zhen wan	310
		Feng jing	277
Long gang	238.64	Ke yuan	396
		An liang	368
		Shan sha	267
Long hua	167.28	Niu hu	312
		Shi jing	333
		Jing shi	301
Bao an	325.78	Xing wei	402
		An le	340
		Hong xing	407
Ping shan	44.63	Bi ling	324
Guang ming	62.50	He shuikou	276
Yan tian	24.29	Yang ang	256
Da peng	15.30	Wang mu	277

According to the actual situation, we randomly selected three social health regions with a population of>1 million, one social health region with a population of <1 million as the survey point, and 60 diabetic patients managed by social health at each survey site as the survey object

visual acuity. Retinal images of both eyes were taken using a nonmydriatic fundus camera, and the fundus photographs were sent to three ophthalmologists for reading and grading. A free breakfast was provided for each participant after the survey.

Blood samples were transferred to the Shenzhen Center for Chronic Disease Control, a city-level prevention and control center for hypertension and DM. The results of the blood sample included FBG, HbA1c, serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), serum creatinine (SCr), and urea. All testing results were sent back to the CHSCs 7 days after receipt of the samples.

The results of the medical examinations and blood sample tests, along with health recommendations, were integrated into a health examination report. The reports were provided to the participants four weeks after the survey concluded. Participants with DR were referred to an eye specialist clinic or hospital for further examination or treatment.

DR was defined as the presence of any characteristic lesion, as described by the International Clinical DR Disease Severity Scale.[19] Its severity was classified into five categories as follows: (1) no apparent retinopathy; (2) mild nonproliferative DR (NPDR), that is, microaneurysms only; (3) moderate NPDR, more than just microaneurysms but less than severe NPDR; (4) severe NPDR, more than 20 intraretinal hemorrhages in each of the four quadrants, definite venous beading in at least two quadrants, or prominent intraretinal microvascular abnormalities in at least one quadrant but no signs of proliferative DR (PDR); and (5) PDR, neovascularization, and vitreous/preretinal hemorrhage.

Three ophthalmologists read the fundus photographs and independently assessed the DR categories according to the above scale. The assessment results for each participant were sent back to the research panel. The category was confirmed if all three ophthalmologists reported the same grade. Discrepancies were resolved, and the category was determined in a discussion by members of the research panel.

Demographic information, socioeconomic status, lifestyle behaviors, medical examination results, and laboratory test results were considered candidate risk factors based on previous studies.[7,20] Current smokers and current drinkers were defined as those currently smoking or drinking occasionally, often, or every day. Lifestyle was categorized into three groups according to participants' self-reported working and living status: indoor type (i.e., sedentary work and lifestyle), outdoor type (i.e., physical work and lifestyle), and mixed type (i.e., both sedentary and physical). The duration

of DM was calculated as the interval between the year of diagnosis and the year of enrollment in the study. The cutoff for defining high FPG was ≥7.0 mmol/L, HbA1c ≥7%, TC ≥4.5 mmol/L, TG ≥1.7 mmol/L, and LDL-C ≥ 2.6 mmol/L. Low HDL-C was defined as ≤1.0 mmol/L for men or ≤ 1.3 mmol/L for women. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg. High waist circumference was defined as waist circumference ≥90 cm for men and ≥85 cm for women. BMI was categorized as normal (<24.0 kg/m^2), overweight (24.0–27.9 kg/m^2), and obesity (≥28.0 kg/m^2). The values for SCr and urea were classified into three high, normal, and low according to the Health Industry Standard of the People's Republic of China (WS/T 404.5-2015).

The primary outcome of interest was the prevalence of DR in T2DM patients and the constitution of varied categories of DR. Prevalence was calculated as the number of participants with DR in one or both eyes divided by the total number of T2DM participants. The 95% confidence interval (CI) of the prevalence was calculated using the direct standardization method. The Shapiro–Wilk test was used to examine the distribution of continuous variables, such as BMI, HbA1c, SBP, and DBP. For normally distributed variables, the mean value, and its standard deviation were calculated, and Student's *t*-test was used to compare the differences between NDR and DR. For those with skewed distribution, the median value and its interquartile range (IQR) were calculated, and Mann–Whitney *U*-test was used for comparisons between NDR and DR.

A univariate logistic regression model was applied to examine the relationships between each potential risk factor and the occurrence of DR. Significant factors in the univariate analyses (i.e., those with $P < 0.10$) were then entered into a multivariate logistic regression model with a stepwise selection procedure to identify independent risk factors. The odds ratio (OR) and its 95% CI were calculated. Using the CART model, the importance of factors identified in the multivariate logistic regression was determined. The value of the Gini impurity was calculated, and the variable with the smallest Gini impurity was selected as the node. The importance of each variable was calculated and presented in proportion. All analyses were performed using R 3.6.1 (R Project for Statistical Computing, https://www.r-project.org/) software. Statistical significance was set at $P < 0.05$.

The differences between the included and excluded groups on several factors were compared using Chi-square tests. No differences were found in sex, DM duration, BMI, and severity of DR. The excluded group was older than the included group [Table 2].

Results

This study recruited a total of 1320 participants, but 223 participants were excluded for refusal to participate ($n = 11$), lack of fundus photographs ($n = 123$), unwillingness to undergo blood collection ($n = 56$), or inability to complete the questionnaire ($n = 33$). In the end, 1097 T2DM individuals with an average age of 57.8 ± 10.5 years were included in the analysis. Of them, 56.2% were male, 45.6% had an education level of senior high school or above, and 68.7% had an indoor-type lifestyle. The median duration of DM was 7.0 years, and 61.4% had been diagnosed for more than 5 years [Table 2].

Overall, 266 individuals were identified as having DR, yielding a prevalence rate of 24.3% (95% CI: 21.7%–26.9%). Of them, 186, 47, 26, and 7 participants had mild NPDR, moderate NPDR, severe NPDR, and PDR, respectively. The corresponding prevalence rates were 17.0% (95% CI: 14.8%–19.3%), 4.3% (95% CI: 3.2%–5.7%), 2.4% (95% CI: 1.6%–3.5%), and 0.6% (95% CI: 0.3%–1.3%), respectively. A total of 177 (16.1%) participants had DR in both eyes, and 89 (8.1%) participants had DR in the left or right eye only [Table 3].

Findings from the univariate logistic regression model showed that the prevalence of DR varied in different subgroups of lifestyle, DM duration, BMI, SBP, DBP, FBG, HbA1c, and urea [Table 4]. In the multivariate logistic regression model, participants who had a longer duration of DM were more likely to have DR than their counterparts.Specifically, compared to diabetic patients with a duration of 5 years or less, those diagnosed for 6–9 years and more than 10 years had 1.67 and 2.48 times the likelihood of having DR, respectively. Participants with a higher HbA1c (OR: 2.45, 95% CI: 1.83–3.29) or urea (OR: 3.28, 95% CI: 1.59–6.83) were more likely to have DR than their counterparts. Those with an indoor-type lifestyle (OR: 1.54, 95% CI: 1.03–2.35) were more likely to have DR than those with outdoor-type lifestyle [Table 5].

Based on the results of Table 5, we used the variables of HbA1c, DM duration, lifestyle, and urea to develop a CART model. The model created 10 nodes with a complexity parameter of 0.005. HbA1c was the first split factor related to DR prevalence, with a Gini impurity of 0.350. DM duration (≤5-year group vs. 6–9-year and ≥10-year groups) was the second split factor, with a Gini impurity of 0.433. Lifestyle (indoor type vs. outdoor type and mixed type), urea (high group vs. normal and low groups), and DM duration (6–9-year group vs. ≥10-year groups) were also split, with a Gini impurity of 0.479, 0.425, and 0.488, respectively [Figure 1]. The values

Table 2: Basic characteristics of inclusion and exclusion of samples

Variable	Include group (*n*=1097) *N* (%)	Exclude group (*n*=212) *N* (%)	*P*-value
Gender*			
Male	616 (56.2)	126 (59.4)	0.420
Female	481 (43.8)	86 (40.6)	
BMI (kg/m^2)*			
<24	414 (37.7)	89 (42.0)	0.246
24.0–27.9	473 (62.3)	92 (43.4)	
≥28	210 (19.0)	31 (14.6)	
Age (years)*			
<40	43 (3.9)	6 (2.8)	<0.001
40–49	194 (17.7)	27 (12.7)	
50–59	385 (35.1)	46 (21.7)	
60–69	323 (29.3)	59 (27.8)	
≥70	152 (13.9)	74 (34.9)	
DM duration (years)*			
≤5	423 (38.6)	66 (31.1)	0.077
5–9	274 (25.0)	49 (23.1)	
≥10	400 (36.4)	97 (45.8)	
Severity of DR*			
No apparent retinopathy	831 (75.8)	78 (86.7)	0.152
Mild NPDR	186 (17.0)	7 (7.8)	
Moderate NPDR	47 (4.3)	3 (3.3)	
Severe NPDR	26 (2.4)	1 (1.1)	
PDR	7 (0.6)	1 (1.1)	
DR*			
In both eyes	177 (16.1)	1 (1.1)	<0.05
Only in left or right eye	89 (8.1)	11 (12.2)	

**P*-values were calculated from Chi-square test. DR=Diabetic retinopathy, DM=Diabetes mellitus, NPDR=Nonproliferative DR, BMI=Body mass index

Table 3: Clinicodemographic characteristics of the participants

Variables	Total (*n*=1097)		NDR (*n*=831)		DR (n=266)*		*P*-value
	Median	IQR	Median	IQR	Median	IQR	
BMI (kg/m2)*	24.9	4.21	25.0	4.2	24.52	4.3	0.032
Waist circumference (cm)	89.0	12.5	89.0	12.1	88.0	11.5	0.470
SBP (mmHg)**	133.3	23.3	132.7	22.7	135.8	26.3	0.003
DBP (mmHg)*	78.3	13.3	78.0	13.0	80.2	13.9	0.025
FBG (mmol/L)***	7.4	2.7	7.2	2.3	8.2	3.8	<0.001
HbA1c (%)***	6.4	1.7	6.3	1.5	7.1	2.3	<0.001
TC (mmol/L)	5.1	1.6	5.0	1.6	5.1	1.6	0.649
TG (mmol/L)	1.5	1.1	1.5	1.1	1.5	1.2	0.466
HDL-C (mmol/L)	1.2	0.4	1.3	0.4	1.2	0.4	0.725
LDL-C (mmol/L)	3.4	1.2	3.4	1.1	3.5	1.2	0.534
Urea (mmol/L)*	5.0	1.8	5.0	1.7	5.2	2.0	0.023
SCr (μmol/L)	69.8	25.2	69.4	25.4	71.8	24.3	0.501

*P<0.05, **P<0.01, ***P<0.001. All the variables in this table were in positive-skewed distribution. Mann–Whitney U-testing was used to compare the difference between males and females. IQR=Interquartile range, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FBG=Fasting blood glucose, HbA1c=Hemoglobin A1c, TC=Serum total cholesterol, TG=Triglyceride, HDL-C=High-density lipoprotein-cholesterol, LDL-C=Low-density lipoprotein-cholesterol, SCr=Serum creatinine

for variable importance of HbA1c, DM duration, lifestyle, and urea were 48%, 37%, 10%, and 4%, respectively.

Discussion

The aim of this study was to identify the associated factors for T2DM patients and calculate the importance of the identified factors. The results showed that a longer duration of DM, indoor-type lifestyle, and higher levels of HbA1c or urea increased the risk of DR. In addition, the results of the CART model showed that the variable importance of the values for HbA1c, DM duration, lifestyle, and urea was 48%, 37%, 10%, and 4%, respectively.

Previous studies on HbA1c and DR suggested that HbA1c was a risk factor for DR.[8,21,22] For example, the results of investigation by Song *et al*.,[23] of the risk factors of DR in the systematic review and meta-analysis showed that a higher level of HbA1c was associated with a higher prevalence of DR in people with DM (OR: 1.15; 95% CI: 1.09–1.20). Our findings support this finding, and we also found that HbA1c value of 7% or above was an independent risk factor for DR. Specifically, patients with HbA1c ≥7% were 2.45 times more likely to have DR than their counterparts. In addition, our study added the evidence of the importance of HbA1c on the risk factors of DR using the CART model. The findings from the CART model indicated that HbA1c was much more

Table 4: Logistic regression analysis: Risk factors for diabetic retinopathy

Variables	Total	*N* (%)	OR (95% CI)	*P*-value
Sex				
Male	616	159 (25.8)	1.00	
Female	481	107 (22.3)	0.82 (0.62–1.09)	0.172
Age (years)				
<40	43	10 (23.3)	1.00	
40–49	194	59 (30.4)	1.44 (0.69–3.26)	0.352
50–59	385	103 (26.8)	1.21 (0.59–2.66)	0.622
60–69	323	74 (22.9)	0.98 (0.48–2.18)	0.960
≥70	152	20 (13.2)	0.50 (0.22–1.21)	0.110
Education level				
Elementary school or below	262	67 (25.6)	1.00	
Junior middle school	335	86 (25.7)	1.01 (0.70–1.46)	0.978
Senior high school	284	71 (25.0)	0.97 (0.66–1.43)	0.878
Junior college and above	216	42 (19.4)	0.70 (0.45–1.08)	0.113
Lifestyle				
Outdoor type	189	38 (20.1)	1.00	
Indoor type	754	198 (26.3)	1.42 (0.97–2.12)	0.082
Mixed type	154	30 (19.5)	0.96 (0.56–1.64)	0.885
Current smoker				
No	900	212 (23.6)	1.00	
Yes	197	54 (27.4)	1.23 (0.86–1.73)	0.253
Current drinker				
No	796	188 (23.6)	1.00	
Yes	301	78 (25.9)	1.13 (0.83–1.53)	0.429
DM duration (years)				
≤5	423	63 (14.9)	1.00	
6–9	274	66 (24.1)	1.81 (1.23–2.67)	0.002
≥10	400	137 (34.3)	2.98 (2.13–4.19)	<0.001
BMI				
<24	414	115 (27.8)	1.00	
24–27.9	473	104 (22.0)	0.73 (0.54–0.99)	0.046
≥28	210	47 (22.4)	0.75 (0.51–1.10)	0.147
Waist circumference				
Normal	606	147 (24.3)	1.00	
High	491	119 (24.2)	1.00 (0.76–1.32)	0.994
SBP				
Normal	700	152 (21.7)	1.00	
High	397	114 (28.7)	1.45 (1.09–1.92)	0.095
DBP				
Normal	930	217 (23.3)	1.00	
High	167	49 (29.3)	1.36 (0.94–1.96)	0.096
FBG				
Normal	450	79 (17.6)	1.00	
High	647	187 (28.9)	1.91 (1.42–2.58)	<0.001
HbA1c				
Normal	695	119 (17.1)	1.00	
High	402	147 (36.6)	2.79 (2.10–3.71)	<0.001
TC				
Normal	331	77 (23.3)	1.00	
High	766	189 (24.7)	1.08 (0.80–1.47)	0.617
TG				
Normal	656	151 (23.0)	1.00	
High	441	115 (26.1)	1.18 (0.89–1.56)	0.247
HDL-C				
Normal	756	185 (24.5)	1.00	
Lower	341	81 (23.8)	0.96 (0.71–1.29)	0.798
LDL-C				
Normal	185	42 (22.7)	1.00	
High	912	224 (24.6)	1.11 (0.77–1.63)	0.591
Urea				
Normal	1038	242 (23.3)	1.00	
Low	24	5 (20.8)	0.87 (0.29–2.18)	0.776
High	35	19 (54.3)	3.91 (1.98–7.81)	<0.001
SCr				
Normal	962	224 (23.3)	1.00	
Low	36	12 (33.3)	1.65 (0.79–3.28)	0.168
High	99	30 (30.3)	1.43 (0.90–2.24)	0.121

OR=Odds ratio, CI=Confidential interval, DM=Diabetes mellitus, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FBG=Fasting blood glucose, HbA1c=Hemoglobin A1c, TC=Serum total cholesterol, TG=Triglyceride, HDL-C=High-density lipoprotein-cholesterol, LDL-C=Low-density lipoprotein-cholesterol, SCr=Serum creatinine

Table 5: Logistic regression analysis final model: Risk factors for diabetic retinopathy

Variables	B	SE	OR (95% CI)	*P*-value
DM duration (years)				
≤5			1.00	
6–9	0.51	0.20	1.67 (1.12–2.48)	0.011
≥10	0.91	0.18	2.48 (1.75–3.53)	<0.001
Lifestyle				
Outdoor type			1.00	
Indoor type	0.43	0.21	1.54 (1.03–2.35)	0.039
Mixed type	–0.10	0.29	0.90 (0.51–1.58)	0.719
HbA1c				
Normal			1.00	
High	0.90	0.15	2.46 (1.83–3.30)	<0.001
Urea				
Normal			1.00	
Low	–0.21	0.52	0.82 (0.26–2.12)	0.700
High	1.22	0.37	3.40 (1.66–7.08)	<0.001

A multivariate logistic regression model with a stepwise selection procedure was performed by entering significant variables in univariate analyses (i.e., with $P<0.10$). BMI, SBP, DBP, and FBG levels were not retained in the final model. SE=Standard error, OR=Odds ratio, CI=Confidential interval, DM=Diabetes mellitus, HbA1c=Hemoglobin A1c, BMI=Body mass index, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, FBG=Fasting blood glucose

important than DM duration, lifestyle, and urea, which further underlines the importance of glycemic control for the occurrence and development of DR. The American Diabetes Association recommends that the HbA1c level should be under 7%.[24] China also sets HbA1c levels below 7% as a goal in the integrated control targets for T2DM.[25] However, HbA1c has not been widely used in THMS or even primary healthcare system in China because of the lack of technicians and funds. Therefore, income policies should be implemented to ensure the equitable distribution of resources and to provide more

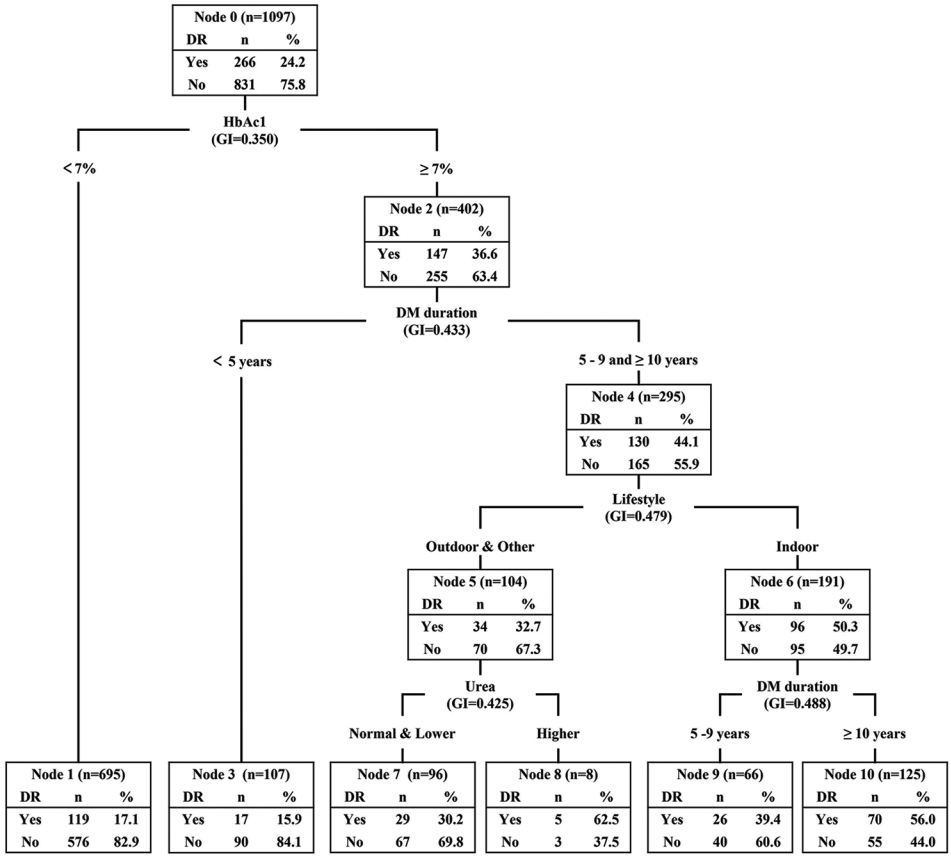

Figure 1: Classification and regression tree models of risk factors for diabetic retinopathy. DR = Diabetic retinopathy

technical support for primary healthcare staff for HbA1c testing.

This study also found that a longer duration of DM indicated a higher prevalence of DR, which is consistent with previous studies.[26,27] For example, one study conducted in the United Kingdom showed that the 5-year cumulative incidence of DR was 4%, but this increased to 16.4% after 10 years of follow-up in T2DM patients.[27] In addition, according to the results of the CART model, the importance of DM duration in these risk factors was 37%. However, since there is no prior study on this issue for reference, we recommend more future studies on this.

In addition, our results showed that indoor-type lifestyle is a risk factor for the occurrence of DR. A possible explanation may be that indoor-type lifestyle usually involves more sedentary time and fewer physical activities, which are well-established risk factors for macrovascular diseases as well as changes in microvascular structure.[28-31] In addition, indoor-type lifestyle is usually accompanied by a longer time spent looking at screens, which has a potentially adverse effect on retinal microvascular structure. The time spent watching TV every day is positively correlated with the magnitude of arteriolar narrowing.[32,33] Since indoor-type lifestyle is a modifiable risk factor for patients with diabetes, more interventions or guidelines should be given to them to prevent DM-related complications.

Results from regression models showed that serum urea was associated with the occurrence of DR. Previous studies reported that higher levels of serum urea were not only associated with a higher risk of DR but also with the severity of DR.[34,35] DR and DN share a common pathophysiological mechanism, in which prolonged high blood glucose triggers excessive oxidative stress, leading to inflammation and microvascular endothelial dysfunction.[36] The increase in blood urea nitrogen level is positively correlated with thinning of the retinal nerve fiber layer, suggesting that serum urea levels may also affect the damage process of retinal neural tissue, leading to the occurrence of DR.[35] Notably, although higher levels of urea increased the risk of DR, the CART model showed the lowest variable importance. This may be due to the small number of participants with higher levels of urea (35 individuals, accounting for 3.19% of all participants). In addition, SCr was not associated with DR in this study, a finding that is inconsistent with previous studies.[35,37] A possible explanation may be the small sample size; therefore, we recommend conducting future studies with more participants.

A major strength of this study was that it was the first study to use the CART model to identify the associated factors for T2DM patients and calculate the importance of the identified factors. Nevertheless, some limitations should be considered. First, this study was a cross-sectional design, and thus, we could not confirm the causality between the identified factors and the outcome. Second, more than 200 patients were excluded because of a lack of fundus photographs, unwillingness to collect blood, or inability to complete the questionnaire. However, nonresponse analyses were conducted, and the results showed that there were no significant differences between included and excluded groups in basic characteristics (e.g., sex, BMI, diabetes duration, and severity of DR), which indicated that our sample size has a relevant low nonresponse bias. Third, this study focused on the prevalence and risk factors of DR and did not collect data on diabetic macular edema (DME). Further studies that include DME assessment are needed. Finally, other risk factors such as diet and physical activity were not investigated in this study.

Conclusion

This study used community-based data to estimate the prevalence of DR in T2DM patients in an urban area of southern China. Patients

with longer DM duration, a higher level of HbA1c, having indoor-type lifestyle, and a higher serum urea were more likely to have DR than their counterparts. HbA1c was the most important variable for the development of DR. The high prevalence of DR and the importance of HbA1c point toward the need to raise awareness of DR and its risk factors. The integration of diabetic retinopathy screening and HbA1c testing into telemedicine health management systems or even primary healthcare services is urgently warranted to reduce vision impairment and blindness.

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Conflicts of interest

There are no conflicts of interest.

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