

The Prevalence and Risk Factors of Diabetic Retinopathy: Screening and Prophylaxis Project in 6 Provinces of China

Jiang Liu^{1,2,*}, Hao Hu^{1,3,*}, Shanhu Qiu⁴, Duolao Wang⁵, Jianing Liu¹, Ziwei Du¹, Zilin Sun¹

¹Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Nanjing, 210009, People's Republic of China; ²Department of Endocrinology, The Third Hospital of Nanchang, Nanchang, Jiangxi, People's Republic of China; ³Department of Endocrinology, The First People's Hospital of Xuzhou, Xuzhou, Jiangsu, People's Republic of China; ⁴Department of General Practice, Zhongda Hospital; Institute of Diabetes, School of Medicine, Southeast University, Nanjing, People's Republic of China; ⁵Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

*These authors contributed equally to this work

Correspondence: Zilin Sun, Department of Endocrinology, Zhongda Hospital, Institute of Diabetes, School of Medicine, Southeast University, Nanjing, 210009, People's Republic of China, Tel +8613951749490, Fax +862583262609, Email sunzilin1963@126.com

Purpose: To investigate the prevalence and associated factors of diabetic retinopathy (DR) and advanced DR in Chinese adults with diabetes mellitus (DM).

Patients and Methods: A cross-sectional study was performed on 4831 diabetic patients from 24 hospitals from April 2018 to July 2020. Non-mydratiac fundus of patients were interpreted by an artificial intelligence (AI) system. Fundus photos that were unsuitable for AI interpretation were interpreted by two ophthalmologists trained by one expert ophthalmologist at Beijing Tongren Hospital. Medical history, height, weight, body mass index (BMI), glycosylated hemoglobin (HbA1c), blood pressure, and laboratory examinations were recorded.

Results: A total of 4831 DM patients were included in this study. The prevalence of DR and advanced DR in the diabetic population was 31.8% and 6.6%, respectively. In multiple logistic regression analysis, male (odds ratio [OR], 1.39), duration of diabetes (OR, 1.05), HbA1c (OR, 1.11), farmer (OR, 1.39), insulin treatment (OR, 1.61), region (northern, OR, 1.78; rural, OR, 6.96), and presence of other diabetic complications (OR: 2.03) were associated with increased odds of DR. The factors associated with increased odds of advanced DR included poor glycemic control (HbA1c >7.0%) (OR, 2.58), insulin treatment (OR, 1.73), longer duration of diabetes (OR, 3.66), rural region (OR, 4.84), and presence of other diabetic complications (OR, 2.36), but overweight (BMI > 25 kg/m²) (OR, 0.61) was associated with reduced odds of advanced DR.

Conclusion: This study shows that the prevalence of DR is very high in Chinese adults with DM, highlighting the necessity of early diabetic retinal screening.

Keywords: diabetes mellitus, screening, artificial intelligence, glycemic control, rural region

Introduction

As the prevalence of diabetes mellitus (DM) continues to increase, 11.2% of adults worldwide and around half of Chinese adults are estimated to have pre-diabetes.¹ The total number of people with DM in China is projected to rise from 171 million in 2000 to 366 million by 2030.² Diabetic retinopathy (DR) remains the leading cause of preventable blindness in the working-age population.³ In particular, the age-standardized global prevalence for blindness resulting from diabetic eye disease has increased by 14.9% to 18.5% from 1990 to 2020.⁴ The number of patients with DR will increase to 191 million worldwide in 2030, and the condition in developing countries such as China and India will be more severe.^{5,6} More than one-third of people with diabetes show signs of irreversible blindness, which is the main reason for blindness in developed countries.⁷ Apart from its effects on vision, the presence of DR also signifies a heightened risk of life-threatening systemic vascular complications.⁸ Long-term hyperglycemia damages various organs

and tissues, including the eyes, kidneys, heart, nerves, and blood vessels.^{9,10} Several studies have shown that hyperglycemia and hypertension play an important role in the development of DR.¹¹ Several known mechanisms contribute to the development of DR, including the accumulation of sorbitol and advanced glycation end products, oxidative stress, inflammation, vascular endothelial growth factor, and genetic factors.¹²

Early DR is controllable. The International Diabetes Federation and International Council of Ophthalmology believe that early screening and regular follow-up are important to the prevention and management of DR. DR patients with moderate non-proliferative diabetic retinopathy (NPDR) and above should be referred and treated timely.¹³ The DR screening and prophylaxis project is a national artificial intelligence (AI) incubation process sponsored by the China Society for Microcirculation and the National Anti-blindness Technology Steering Group, China Microcirculation Society, Diabetes and Microcirculation Specialized Committee, and Beijing Shang Gong Medical Science and Technology Company. The project was implemented in primary hospitals of more than 100 cities from May 2016. In this study, we aim to report the prevalence and associated risk factors of DR in adult patients with diabetes based on this screening system. Especially in high-risk populations, research on risk factors of DR patients is important for evaluating and revising public health policies and strategies for the prevention and treatment of DR.

Materials and Methods

Study Participants

Based on the China DR screening and prophylaxis project, the study was conducted in 24 hospitals in six provinces (Jiangsu, Henan, Hebei, Ningxia, Hunan, Gansu province). The inclusion criteria were diabetic patients 18 years of age or older who received care in the outpatient or inpatient department. Patients were excluded if they could not undergo retinal imaging owing to cognitive or physical impairment or if they had undergone a documented retinal examination within the past 6 months. All diagnosed subjects with DM were invited to participate in the project. A total of 4947 patients who received treatment for diabetes (from April 2018 to July 2020) were enrolled. Every diabetic patient accepted fundus screening. With incomplete, abnormal, and duplicate values eliminated by data cleaning, 4831 adult DM patients were finally included for analysis.

DR Screening Methods

Fundus photography was performed with a 45° non-mydratic retinal imaging system that patients need not dilation for fundus imaging (model: Canon camera Cr-2AF, image size: 20 million pixels). Photographic fields were taken from each eye of diabetes patients centered on the fovea, and one photograph was taken for each eye. The images were transmitted to the computer terminal in real time for AI interpretation using the DR screening system, which is an ophthalmic image intelligent recognition software (SG-DR) designed and produced by Zhuhai Shang Gong Company of China (Guangdong Registration Certificate for Medical Device No. 20,172,700,901). In our previous study, in diabetes patients, the sensitive of this AI system for any DR was 91.6% (95% CI: 86.3–95.3) and the specificity was 89.0% (95% CI: 87.0–90.7).⁴⁹ The resolution of the upload image for AI system was at least 1000×1000 pixels. Photos that were unsuitable for AI system interpretation were analyzed by two ophthalmologists trained by one expert ophthalmologist at Beijing Tongren Hospital. The classification and definition of DR were conducted as follows: Stage 1 (mild NPDR): only microangioma; Stage 2 (moderate NPDR): between mild and severe, may be combined with retinal hemorrhage, hard exudate, and cotton wool spots; Stage 3 (severe NPDR): any of the following changes but no signs of proliferative DR: A. There were more than 20 intraretinal hemorrhages in each of the four quadrants; B. Vein beading changes in more than two quadrants; C. Significant microvascular abnormalities in more than one quadrant of the retina; D. Cotton-like soft exudation; Stage 4 (early PDR): neovascularization; Stage 5 (middle PDR): fibroplasia membrane, or preretinal or vitreous hemorrhage; Stage 6 (late PDR): fibroplasia membrane and retinal detachment. The patients were categorized as advanced DR (having stage 3–6 DR and/or macular edema and requiring referral to ophthalmology) and DR without referral (without DR or with mild NPDR in one or both eyes). A questionnaire survey was conducted to obtain basic information including height; weight; duration of diabetes; age; personal history of smoking; personal history of alcohol

consumption; treatment of DM; systolic blood pressure (SBP); diastolic blood pressure (DBP); and histories of hypertension, hyperlipidemia, or other diabetic complications.

Statistical Analysis

All statistical analysis was performed with the SPSS 23.0 software for Windows (SPSS Inc., Chicago, IL, USA). Non-normal numeric variables were expressed as median and interquartile range. Categorical variables were expressed as frequency (n) and percentage (%). Baseline characteristics of the study participants with and without DR were compared using chi-square test for proportions or Mann–Whitney *U*-test for means. Binary logistic regression models were applied to assess the associations between DR and the other parameters evaluated after adjusting for age gender and other confounding factors, and also applied to assess the association factors with advanced DR. Continuous data were transformed into categorical data for logistic regression: (1) age was divided into less than 30 years old, 30–50 years old, 50–70 years old and more than 70 years old; (2) HbA1c was divided into HbA1c $\leq 7.0\%$ and HbA1c $> 7.0\%$; (3) the duration of DM was divided into five groups: less than 5 years, 5–10 years, 10–15 years, 15–20 years and more than 20 years; The odds ratio (OR) and 95% confidence interval (CI) were calculated. Statistical significance was considered at $P < 0.05$.

Results

Characteristics of the Study Population

Among patients with DM, there were 2580 males and 2251 females. The mean age of patients was 56.7 ± 13.1 years. The mean disease duration was 8.6 ± 6.9 years, and the mean body mass index (BMI) was 25.3 ± 3.6 kg/m². Among all subjects, 737 patients originated from the rural region, and 4094 originated from the urban region. A total of 3123 patients originated from the northern region, and 1708 patients originated from the southern region. A total of 1965 fundus photos of patients were classified manually by ophthalmologists (accounting for 40.7%).

Estimated Prevalence and Characteristics Between Patients with DR and Those Without DR

There were 1536 patients with DR, and the estimated prevalence of DR was 31.8%. The prevalence of DR showed no significant difference in males and females (31.9% versus 31.7%, $P = 0.87$). The duration of DM, SBP, DBP, fasting plasma glucose (FPG), 2 h postprandial plasma glucose (2hPG), hemoglobin A1c (HbA1c), and triglycerides (TG) were higher in the DR group than in the non-DR group, whereas the BMI and high-density lipoprotein (HDL) were lower in the DR group than in the non-DR group ($P < 0.05$). There were 338 patients with DR in the rural region (54.1%) and 1198 patients with DR in the urban region (29.3%). The DR group had higher percentages of history of hypertension, presence of other diabetic complications, and insulin treatment compared with the non-DR group (Table 1).

Univariate Analysis of the Risk Factors of DR Among Patients with Diabetes

In univariate logistic regression analysis, DR was associated with rural region ($P < 0.001$), northern region ($P = 0.17$), duration of DM ($P < 0.001$), older age ($P < 0.001$), occupation ($P < 0.001$), insulin treatment ($P < 0.001$), DBP ($P < 0.001$), SBP ($P < 0.001$), BMI ($P = 0.003$), overweight ($P = 0.03$), history of hypertension ($P < 0.001$), presence of other diabetic complications ($P < 0.001$), TG ($P = 0.014$), HDL ($P = 0.022$), HbA1c ($P < 0.001$), FPG ($P < 0.001$), 2hPG ($P < 0.001$), and number of presence of other diabetic complications ($P < 0.001$). The associations of other parameters with the presence of DR were not statistically significant (Table 2).

Multivariate Analysis of the Risk Factors of DR Between the DR Group and Non-DR Group

The risk factors for DR in patients with diabetes were analyzed. Multivariate analysis showed that gender (male compared with female) (OR, 1.35; 95% CI 1.06 to 1.75), rural region (OR, 5.93; 95% CI 3.10 to 11.35), longer duration of DM (OR, 1.05; 95% CI 1.02 to 1.07), presence of other diabetic complications (OR, 2.03; 95% CI 1.32 to 3.06),

Table 1 Comparison of the Characteristics Between Subjects with or Without DR

Variable	DR Group (n=1536)	Non-DR Group (n=3925)	P value
Age (years) ^b	57 (50, 65)	57 (48, 66)	0.931
Age subgroup			
<30 years ^a	25 (1.6)	165 (5.0)	<0.001
30–50 years ^a	366 (23.8)	827 (25.1)	
50–70 years ^a	979 (63.7)	1797 (54.5)	
>70 years ^a	166 (10.8)	506 (15.4)	
Duration of diabetes (years) ^b			
<5 years ^a	472 (31.3)	1456 (45.8)	<0.001
5–10 years ^a	340 (22.5)	742 (23.3)	
10–15 years ^a	379 (25.1)	513 (16.1)	
15–20 years ^a	187 (12.4)	254 (8.0)	
>20 years ^a	130 (8.6)	213 (6.7)	
Sex			
Male ^a	823 (53.6)	1757 (53.3)	0.867
Female ^a	713 (46.4)	1538 (46.7)	
Residence			
Rural ^a	338 (22.0)	399 (12.1)	<0.001
Urban ^a	1198 (78.0)	2896 (87.9)	
Region			
Northern ^a	1014 (66.0)	2109 (64.0)	0.174
Southern ^a	522 (34.0)	1186 (36.0)	
Occupation			
Worker ^a	423 (27.5)	1194 (36.2)	<0.001
Farmer ^a	624 (40.6)	1061 (32.2)	
Business \service\housework ^a	306 (19.9)	479 (14.5)	
Scientific\ military\civil servants \ public institutions ^a	183 (11.9)	561 (17.0)	
Lifestyle			
Past and current smoking ^a	519 (33.8)	1046 (31.7)	0.157
Past and current drinking ^a	494 (32.2)	987 (30.0)	0.121
Comorbidities			
Self – reported hypertension ^a	414 (27)	676 (20.5)	<0.001
Presence of other complications of diabetes mellitus ^a	362 (30.8)	457 (22.5)	<0.001
Insulin treatment ^a	835 (54.4)	1512 (45.9)	<0.001
Anthropometry			
Weight (kg) ^b	69 (60, 76)	70 (61, 79)	0.001
Height (cm) ^b	165 (160, 172)	166 (160, 173)	0.045
BMI (kg/m ²) ^a	24.8 (22.8, 27.2)	25.1 (23.0, 27.7)	0.005
BMI subgroup			0.021

(Continued)

Table 1 (Continued).

Variable	DR Group (n=1536)	Non-DR Group (n=3925)	P value
BMI < 25kg/m ²	807 (52.5)	1614 (49.0)	
BMI ≥ 25kg/m ²	729 (47.5)	1681 (51.0)	
SBP (mmHg) ^b	130 (122, 146)	130 (120, 140)	<0.001
DBP (mmHg) ^b	80 (78, 90)	80 (75, 86)	<0.001
FPG (mmol/L) ^b	9.0 (7.0, 12.0)	8.4 (7.0, 11.0)	<0.001
2hPG (mmol/L) ^b	12.7 (10.0, 16.1)	12 (9.7, 15.4)	<0.001
HbA1c (%) ^b	8.8 (7.4, 10.2)	8.2 (6.9, 10.0)	<0.001
HbA1c subgroup			<0.001
HbA1c ≤ 7.0% ^a	154 (21.2)	432 (28.8)	
HbA1c > 7.0% ^a	432 (78.8)	1067 (71.2)	
TC (mmol/L) ^b	4.6 (3.9, 5.3)	4.6 (3.9, 5.4)	0.241
TG (mmol/L) ^b	1.6 (1.0, 2.4)	1.7 (1.1, 2.6)	0.024
LDL (mmol/L) ^b	2.7 (2.0, 3.2)	2.7 (2.1, 3.3)	0.076
HDL (mmol/L) ^b	1.0 (0.9, 1.2)	1.0 (0.9, 1.3)	0.037
Hyperlipidemia ^a	528 (76.1)	1121 (79.1)	0.11

Notes: ^aNo (%); ^bMedian (25th percentile-75th percentile); DR group: the diabetic patients who was diagnosed as DR; Non-DR group: the diabetic patients who cannot be diagnosed as DR.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, Fasting plasma glucose; 2hPG, 2 h postprandial plasma glucose; HbA1c, hemoglobin A1c; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Univariate and Multivariate Analyses of Factors Associated with DR in Patients with Diabetes

Variable	DR Group (n)	Non-DR Group (n)	Crude Model		Adjust Model	
			OR (95% CI)	P value	OR (95% CI)	P value
Gender (male)	823	1757	1.01 (0.90, 1.14)	0.87	1.35 (1.06, 1.75)	0.015
Age <30 years	25	165	Ref		Ref	
30–50 years	366	827	2.92 (1.88, 4.53)	<0.001	3.20 (1.32, 7.70)	0.01
50–70 years	979	1797	3.60 (2.34, 5.52)	<0.001	2.86 (1.20, 6.87)	0.018
>70 years	166	506	2.17 (1.37, 3.42)	<0.001	1.02 (0.39, 270)	0.96
SBP			1.01 (1.00, 1.01)	<0.001	1.01 (0.99, 1.01)	0.36
DBP			1.01 (1.00, 1.02)	<0.001	1.01 (0.99, 1.02)	0.54
Rural region	338	399	2.05 (1.75, 2.40)	<0.001	5.93 (3.10, 11.35)	<0.001
Northern region	1014	2109	2.29 (1.85, 2.83)	<0.001	1.78 (1.20, 2.66)	0.005
Self – reported hypertension	1122	2619	1.42 (1.23, 1.63)	<0.001	0.85 (0.61, 1.19)	0.36
Presence of other diabetic complications	362	467	1.54 (1.31, 1.81)	<0.001	2.01 (1.32, 3.06)	0.001

(Continued)

Table 2 (Continued).

Variable	DR Group (n)	Non-DR Group (n)	Crude Model		Adjust Model	
			OR (95% CI)	P value	OR (95% CI)	P value
Workers	423	1197	Ref		Ref	
Farmer	624	1061	1.66 (1.43, 1.93)	<0.001	1.39 (1.00, 1.92)	0.049
Business\service\housework	306	479	1.33 (1.50, 2.16)	<0.001	1.32 (0.91, 1.91)	0.14
Scientific\military\civil servants\public institutions	183	561	0.92 (0.75, 1.13)	0.42	1.04 (0.70, 1.55)	0.85
Not treating with insulin	701	1783	Ref		Ref	
Insulin treatment	835	1512	1.41 (1.24, 1.59)	<0.001	1.61 (1.25, 2.06)	<0.001
FPG			1.05 (1.03, 1.07)	<0.001	1.04 (1.00, 1.09)	0.059
HbA1c			1.08 (1.04, 1.13)	<0.001	1.11 (1.04, 1.18)	0.002
HbA1c ≤ 7.0%	154	432	Ref		Ref	
HbA1c > 7.0%	572	1067	1.50 (1.22, 1.86)	<0.001	1.61 (1.17, 2.22)	0.003
BMI			0.98 (0.96, 0.99)	0.003	0.99 (0.96, 1.03)	0.84
BMI < 25 kg/m ²	807	1614	Ref		Ref	
BMI ≥ 25 kg/m ²	729	1681	0.87 (0.77, 0.98)	0.021	0.88 (0.73, 1.06)	0.23
Duration of diabetes (years)			1.04 (1.03, 1.05)	<0.001	1.05 (1.02, 1.07)	0.001
< 5 years	472	1456	Ref		Ref	
5 ≤ duration < 10	340	742	1.41 (1.20, 1.67)	<0.001	1.37 (0.99, 1.88)	0.054
10 ≤ duration < 15	379	513	2.28 (1.93, 2.70)	<0.001	2.29 (1.63, 3.21)	<0.001
15 ≤ duration < 20	187	254	2.27 (1.83, 2.82)	<0.001	1.60 (1.01, 2.53)	0.044
Duration ≥ 20	130	213	1.88 (1.48, 2.40)	<0.001	2.07 (1.24, 3.48)	0.006
Number of other complications comdiabetic complications			1.20 (1.11, 1.31)	<0.001	0.94 (0.76, 1.16)	0.54

Notes: Crude model: adjusted no factors. Adjust-Model: adjustment for gender, SBP, DBP, FPG, 2hPG, TG, HDL, HbA1c, age, duration of diabetes, BMI, history of hypertension, insulin treatment, presence of other diabetic complications, number of other diabetic complications, region (rural, urban), occupation.

farmer (OR, 1.39; 95% CI 1.00 to 1.92), FPG (OR, 1.04; 95% CI 1.00 to 1.09), HbA1c (OR, 1.11; 95% CI 1.04 to 1.18), insulin treatment (OR, 1.61; 95% CI 1.25 to 2.06), and northern region (OR, 1.78; 95% CI 1.20 to 2.66) were independently associated with DR.

Multivariate Analysis of the Risk Factors of DR Within Subgroups

Further analysis of the risk of DR in DM patients was performed based on disease duration and age stratification. Compared with age less than 30 years old, 30–50 years old (OR, 3.20; 95% CI 1.32 to 7.70) and 50–70 years old (OR, 2.86; 95% CI 1.20 to 6.87) were independently associated with increased odds of DR. Compared with less than 5 years DM duration, 5–10 years (OR, 1.37; 95% CI 0.99 to 1.88), 10–15 years (OR, 2.29; 95% CI 1.63 to 3.21), 15–20 years (OR, 1.60; 95% CI 1.01 to 2.53), and >20 years DM duration (OR, 2.07; 95% CI 1.24 to 3.48) and poor glycemic control (HbA1c >7.0%) (OR, 1.61; 95% CI 1.17 to 2.22) were associated with increased odds of DR (Table 2).

HbA1c was categorized into two subgroups (HbA1c <7.0% and HbA1c ≥7.0%). DR was significantly associated with rural region, 10–15 years DM duration, and insulin treatment in multivariate analysis after adjusting for potential confounders in the HbA1c <7.0% subgroup. In the HbA1c ≥7.0% subgroup, DR was also significantly associated with rural region, 10–15 years and 15–20 years of DM duration, insulin treatment, and presence of other diabetic complications. However, compared with normal weight, overweight (BMI ≥25 kg/m²) was associated with a lower odds of DR after full-adjustment (OR, 0.76; 95% CI 0.60 to 0.89) (Table 3).

Categorizes HbA1c into two subgroups (HbA1c <7.0% and HbA1c ≥7.0%), DR was significantly associated with the rural region, duration between 10 and 15 years of DM, treat with insulin in multivariate analysis after adjustment for potential confounders in the HbA1c <7.0% subgroup. In the HbA1c ≥7.0% subgroup, DR was also significantly associated with the rural region, duration between 10–15 years and 15–20 years of diabetes, treat with insulin, presence of other diabetic complications. But compared with normal weight, overweight (BMI≥25kg/m²) was associated with a lower odds of DR after full-adjustment, the OR (95% CI) was 0.76 (0.60 to 0.89) (Table 3).

BMI as a continuous variable was also associated with a lower odds of DR in crude mode (OR, 0.98; 95% CI 0.96 to 0.99). Meanwhile, if BMI was a categorical variable, overweight was also associated with a reduced odds of DR in all patients in the crude model (OR, 0.87; 95% CI 0.77 to 0.98). After adjusting for all potential confounders, higher BMI levels and overweight were associated with a lower risk of DR, but without statistical significance (Table 2).

The Characteristics Between Patients with Diabetes Who Require Referral to the Ophthalmologist and Patients Without Requiring Referral

A total of 319 diabetes patients require referral for ophthalmology. In the univariate analysis, the advanced DR patients who require for referral to ophthalmology (Referral group) was significantly associated with older age, longer duration of DM, the higher lever of SBP, DBP, FPG, 2hPG, HbA1c, the higher percentage of past and current smoking, treated with

Table 3 Multivariate Analyses of Factors Associated with DR in Subgroup According to HbA1c Level

Variable	Adjust-Model	
	OR (95% CI)	P value
HbA1c<7.0%		
BMI<25 kg/m ²	Ref	
BMI≥25 kg/m ²	1.28 (0.75, 2.16)	0.36
Urban region	Ref	
Rural region	12.53 (4.65, 33.75)	<0.001
Not treating with insulin	Ref	
Treating with insulin	2.34 (1.37, 3.98)	0.002
No other diabetic complication	Ref	
Presence of other diabetic complication	1.36 (0.77, 2.39)	0.34
Duration<5 years	Ref	
5 ≤ Duration < 10 years	1.31 (0.66, 2.60)	0.45
10 ≤ Duration <15 years	2.98 (1.46, 6.06)	0.003
15 ≤ Duration < 20 years	1.20 (0.40, 3.61)	0.75
Duration ≥ 20 years	2.58 (0.92, 7.22)	0.07

(Continued)

Table 3 (Continued).

Variable	Adjust-Model	
	OR (95% CI)	P value
HbA1c \geq 7.0%		
BMI < 25 kg/m ²	Ref	
BMI \geq 25 kg/m ²	0.76 (0.59, 0.99)	0.04
Urban region	Ref	
Rural region	3.49 (1.53, 7.96)	0.003
Not treating with insulin	Ref	
Insulin treatment	1.47 (1.13, 1.91)	0.004
No other diabetic complication	Ref	
Presence of other diabetic complication	2.19 (1.66, 2.88)	<0.001
Duration < 5 years	Ref	
5 \leq Duration < 10 years	1.45 (1.03, 2.05)	0.32
10 \leq Duration < 15 years	2.05 (1.43, 2.94)	<0.001
15 \leq Duration < 20 years	1.89 (1.19, 2.98)	0.007
Duration \geq 20 years	1.63 (0.97, 2.74)	0.063

Notes: Adjust-Model: adjustment for gender, age, SBP, TG, HDL, BMI (<25kg/m², \geq 25kg/m²), duration of diabetes (less than 5 years, 5–10 years, 10–15 years, 15–20 years and more than 20 years), insulin treatment (insulin treatment alone or combine with oral drugs, not treating with insulin), history of hypertension, presence of other diabetic complication (yes, no), region (rural, urban).

insulin, farmer, rural region, hypertension, and presence of other diabetic complications but associated with lower BMI level compare to patients without the referral (Table 4).

Univariate and Multivariate Analysis of DR Requiring Referral to Ophthalmology

In univariate analysis, referral to ophthalmology was significantly associated with categorical data such as longer duration of DM, older age, FPG, SBP, DBP, rural/urban region, overweight, farmer, poor glycemic control, history of hypertension, insulin treatment, and past and current smoking. When the multivariate analysis was carried out, the presence of advanced DR was significantly associated with rural region (OR: 4.84, 95% CI: 2.53 to 9.24, $P < 0.001$), presence of other diabetic complications (OR: 2.36, 95% CI: 1.55 to 3.61, $P < 0.001$), poor glycemic control (OR: 2.58, 95% CI: 1.38 to 4.55, $P = 0.003$), longer duration of DM (15–20 years and more than 20 years versus less than 5 years) (OR: 3.12, 95% CI: 1.66 to 5.85, $P < 0.001$; OR: 3.66, 95% CI: 1.80 to 7.44, $P < 0.001$), insulin treatment (OR: 1.73, 95% CI: 1.13 to 2.65, $P < 0.001$), and overweight (OR: 0.61, 95% CI: 0.41 to 0.92, $P = 0.017$) (Table 5).

Comparison of the Fundus Features Between the Referral and Non-Referral Group Within DR Patients

In the non-referral DR group, the main characteristics of the fundus included microaneurysm (39.5%) and spot hemorrhage (65.0%), which were significantly higher than those in the referral DR group ($P < 0.001$). The percentages of microaneurysms and spot hemorrhage in the referral DR group were 20.4% and 30.4%, respectively. In the referral DR group, except for microaneurysms and spot hemorrhage, the main characteristics of the fundus included flaky

Table 4 Comparison of the Characteristics Between Referral Group and Non-Referral Group

Variable	Referral Group (n=319)	Non-Referral Group (n=4512)	P value
Age (years)	60 (53, 67)	57 (49, 66)	<0.001
Age subgroup			
<30 years ^a	2 (0.6)	188 (4.2)	<0.001
30–50 years ^a	57 (17.9)	1136 (25.2)	
50–70 years ^a	214 (67.1)	2562 (56.8)	
>70 years ^a	46 (14.4)	626 (13.9)	
Duration of diabetes (years)	11 (6, 18)	8.5 (2, 12)	<0.001
Duration subgroup			<0.001
<5 years ^a	69 (21.9)	1859 (42.5)	
5–10 years ^a	64 (20.3)	1018 (23.3)	
10–15 years ^a	69 (21.9)	823 (18.8)	
15–20 years ^a	65 (20.6)	376 (8.6)	
>20 years ^a	48 (15.2)	295 (6.7)	
Male ^a	138 (43.3)	2399 (53.2)	0.22
Rural (versus urban) ^a	82 (25.7)	655 (14.5)	<0.001
Occupation			<0.001
Worker ^a	76 (34.2)	1541 (34.2)	
Farmer ^a	146 (45.8)	1539 (34.1)	
Business/service/housework ^a	66 (20.7)	719 (15.9)	
Scientific /military/civil servants/public institutions ^a	66 (20.7)	713 (15.8)	
Past and current smoking ^a	122 (38.2)	1443 (32.0)	0.02
Past and current drinking ^a	108 (33.9)	1373 (30.4)	0.20
Self – reported hypertension ^a	120 (37.6)	970 (21.5)	<0.001
Self – reported other complications of diabetes mellitus ^a	159 (61.4)	719 (24.4)	<0.001
Insulin treatment ^a	201 (63.0)	2146 (47.6)	<0.001
BMI (kg/m ²)	24.4 (22.1, 26.5)	25.0 (22.9, 27.6)	<0.001
BMI subgroup			0.002
BMI < 25kg/m ²	187 (58.6)	2234 (49.5)	
BMI ≥ 25kg/m ²	132 (41.4)	2278 (50.5)	
SBP (mmHg) ^b	140 (129, 154)	130 (120, 140)	<0.001
DBP (mmHg) ^b	80 (78, 90)	80 (75, 87)	0.003
FPG (mmol/L) ^b	9.7 (7.5, 12.5)	8.5 (7.0, 11.1)	<0.001

(Continued)

Table 4 (Continued).

Variable	Referral Group (n=319)	Non-Referral Group (n=4512)	P value
2hPG (mmol/L) ^b	13.0 (10.7, 16.8)	12.0 (9.8, 15.8)	0.004
HbA1c (%) ^b	9.3 (8.1, 10.7)	8.3 (7.0, 10.0)	<0.001
HbA1c subgroup			<0.001
HbA1c ≤ 7.0% ^a	16 (11.3)	570 (27.4)	
HbA1c > 7.0% ^a	126 (88.7)	1513 (72.6)	
TC (mmol/L) ^b	4.8 (3.9, 5.4)	4.6 (3.9, 5.4)	0.375
TG (mmol/L) ^b	1.6 (1.1, 2.1)	1.7 (1.1, 2.6)	0.104
LDL (mmol/L) ^b	2.8 (2.1, 3.3)	2.7 (2.1, 3.3)	0.415
HDL (mmol/L) ^b	1.1 (0.9, 1.4)	1.0 (0.9, 1.2)	0.398

Notes: ^aNo (%); ^bMedian (25th percentile-75th percentile); Referral group: DR need for referral to ophthalmology. Non-Referral group: No DR or DR without need for referral to ophthalmology.

Table 5 The Association Between the Prevalence of Advanced DR in Subjects with Diabetes Mellitus

Variable	Crude-Model		Adjust-Model	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender (male versus female)	1.16 (0.92, 1.45)	0.21	0.51 (0.73, 1.97)	0.47
Age subgroup				
< 30 years	Ref		Ref	
30–50 years	4.72 (1.14, 19.48)	0.032	1.86 (0.42, 8.32)	0.42
50–70 years	7.85 (1.93, 31.85)	0.004	1.21 (0.27, 5.37)	0.80
> 70 years	6.91 (1.66, 28.72)	0.008	0.64 (0.13, 3.23)	0.59
FPG	1.06 (1.03, 1.09)	<0.001	1.03 (0.98, 1.09)	0.24
SBP	1.02 (1.01, 1.03)	<0.001	1.00 (0.99, 1.02)	0.81
DBP	1.02 (1.01, 1.03)	<0.001	1.00 (0.98, 1.03)	0.70
Past and current smoking (vs no smoking)	1.32 (1.04, 1.67)	0.021	1.11 (0.68, 1.82)	0.68
Hypertension (yes versus no)	2.20 (1.74, 2.79)	<0.001	1.40 (0.84, 2.33)	0.19
HbA1c (≥7.0% versus < 7.0%)	2.97 (1.75, 5.04)	<0.001	2.58 (1.38, 4.85)	0.003
Occupation				
Worker	Ref		Ref	
Farmer	1.92 (1.45, 2.56)	<0.001	1.16 (0.70, 1.93)	0.57
Business/service/housework	1.86 (1.32, 2.62)	<0.001	0.73 (0.40, 1.33)	0.30
Scientific/military/civil servants/public institutions	0.88 (0.58, 1.35)	0.56	0.66 (0.33, 1.33)	0.25

(Continued)

Table 5 (Continued).

Variable	Crude-Model		Adjust-Model	
	OR (95% CI)	P value	OR (95% CI)	P value
Duration subgroup				
< 5 years	Ref		Ref	
5–10 years	1.69 (1.20, 2.40)	0.003	1.25 (0.70, 2.24)	0.46
10–15 years	2.26 (1.60, 3.19)	<0.001	1.32 (0.72, 2.42)	0.36
15–20 years	4.66 (3.26, 6.65)	<0.001	3.12 (1.66, 5.85)	<0.001
> 20 years	4.38 (2.97, 6.46)	<0.001	3.66 (1.80, 7.44)	<0.001
Rural region (versus urban)	2.00 (1.70, 2.35)	<0.001	4.84 (2.53, 9.24)	<0.001
Insulin treatment (yes versus no)	1.35 (1.20, 1.53)	<0.001	1.73 (1.13, 2.65)	0.012
BMI \geq 25kg/m ² (versus BMI < 25kg/m ²)	0.88 (0.78, 0.99)	0.043	0.61 (0.41, 0.92)	0.017
Presence of other diabetic complication (yes versus no)	1.49 (1.27, 1.76)	<0.001	2.36 (1.55, 3.61)	<0.001

Notes: Crude model: adjusted no factors. Adjust-Model: adjustment for gender, age (<30 years, 30–50 years, 50–70 years, >70 years), SBP, DBP, BMI (<25kg/m², \geq 25kg/m²), FPG, HbA1c (\geq 7.0%, <7.0%), duration of diabetes (<5 years, 5–10 years, 10–15 years, 15–20 years, >20 years), personal history of smoking, history of hypertension, region (rural, urban), occupation, insulin treatment, presence of other diabetic complication.

hemorrhage (26.6%), hard exudates (22.9%), macular edema (16.0%), cotton wool spots (7.8%), vitreous hemorrhage (0.6%), fibroplasia membrane (10.0%), and other microvascular abnormalities (6.3%), which were significantly higher than those in the non-referral DR group ($P < 0.01$) (Table 6).

Table 6 Comparison of the Fundus Features Between Referral and Non-Referral Group Within DR Patients

Fundus Features	Referral DR n=319	Non-Referral DR n=1217	
Microaneurysm ^a	65 (20.4)	481 (39.5)	<0.001
Spot hemorrhage ^a	97 (30.4)	791 (65.0)	<0.001
Flaky hemorrhage ^a	85 (26.6)	0 (0)	<0.001
Vitreous hemorrhage ^a	2 (0.6)	0 (0)	0.006
Preretinal hemorrhage ^a	10 (3.1)	0 (0)	<0.001
Hard exudates ^a	73 (22.9)	60 (4.9)	<0.001
Cotton wool spots ^a	25 (7.8)	31 (2.5)	<0.001
Macular edema ^a	51 (16.0)	0 (0)	<0.001
Other proliferative manifestations	32 (10.0)	0 (0)	<0.001
Other microvascular abnormalities ^a	20 (6.3)	0 (0)	<0.001

Notes: ^aNo (%); Other proliferative manifestations: including fibroplasia membrane, vitreous hemorrhage, anterior retinal membrane, epimacular membrane, patchy membrane; Other microvascular abnormalities: including microvascular abnormalities, neovascularization, vascular occlusion, venous beading.

Discussion

Using the screening method of AI combined with ophthalmologist in this DR screening and prophylaxis project in China, the prevalence of DR and advanced DR in the study population was 31.8% and 6.6%, respectively. The risk factors for DR were male, duration of DM, poor glycemic control (FPG, HbA1c), rural region, northern region, occupation (farmer), presence of other diabetic complications, and insulin treatment.

Recent studies found that the prevalence of DR in Mainland China in the past years showed large discrepancies, ranging from 8.1% to 43.1%.^{14,15} The discrepancy may be due to different study designs, grading standards, and populations sampled. The prevalence of DR in this study was slightly higher than those in a 2018 meta-analysis in Mainland China and the Beijing Eye Study 2006.^{6,17} However, it was lower than the worldwide prevalence,^{18,19} higher than the prevalence in Iceland and India,^{20–22} lower than the prevalence in Singapore,²³ and similar to the prevalence in Africa.²⁴ The prevalence of DR among diabetes patients was 37.7% in the Blue Mountains Eye Study,²⁵ 29.1% in the Visual Impairment Project of Australia,²⁶ and 26.2% in southern India.²⁷ Most patients in this study were older, which likely accounts for the higher prevalence of DR, and the difference in the prevalence of DR between rural and urban region (45.9% versus 29.3%) was significant, similar to the result of Beijing Eye study.¹⁸ This might be because the mean duration of DM, FPG, SBP, DBP were higher in rural patients than urban patients. But after adjusting for all potential confounding factors, the rural region also showed a 5.93-fold increased odds of DR when compared with subjects from the urban region.

In this study, farmer was significantly associated with DR compared with other occupations. It may be partly due to the lower economic development level, lower income, and restricted education in rural China. In the Chinese context, rural residents usually have lower awareness of DM, and the time to diagnose and treat DM was delayed. At the same time, rural residents may have difficulty in maintaining good glycemic control.^{28–30} In this study, the northern region was also associated with DR. There was no difference in HbA1c and FPG levels between the northern and southern regions, and the duration of diabetes and age was shorter and younger in the northern than southern region. In further multivariate analysis, the northern region was significantly associated with DR after adjusting for the duration of DM, age, occupation, and other confounding factors. Similar results were reported by Liu et al in a meta-analysis of DR prevalence in Mainland China.³¹ The result might be partly due to the different economy, social environments, and lifestyle in different regions.

In the Global Study, longer DM duration, higher HbA1c levels, and higher blood pressure have been recognized as key risk factors for DR in people with DM. Some studies showed that dyslipidemia; age of onset of diabetes; faster heart rate; higher blood urea nitrogen; elevated serum creatinine level, creatinine clearance rate, and uric acid; and long-term exposure to fine particulate matter (PM_{2.5}) were risk factors for DR.^{16,32–36} Other systemic and lifestyle factors, including obesity, alcohol consumption, markers of anemia, hypothyroidism, and inflammation or endothelial dysfunction are associated with the increased risk of DR among diabetic patients.^{37–41} This study confirmed that poor glycemic control and longer duration of DM are commonly accepted risk factors for DR. This study suggested that blood lipid was not associated with DR, which was supported by a previous study.⁴² Future investigations should focus on the reasons for the discrepancies between the studies cited and evaluate whether subtypes of lipids may have a better association with DR than lipid levels only.

This study also showed that there was a correlation between BMI and DR. Studies on the relationship between BMI and DR in type 2 diabetes patients are controversial. Earlier reports found that higher BMI increased DR risk.^{43,44} In this study, BMI (as continuous or categorical variables) was not associated with DR in the full-adjustment model, but overweight had a protective effect on DR in the HbA1c >7.0% subgroup in subgroup analysis. In the overall population, BMI as a continuous or categorical variable was associated with less risk of DR. However, the magnitudes of these correlations were weakened after full adjustment. The results were congruent with those of an Asian study that overweight and obesity decreased the 6-year risk of DR in Singapore.⁴⁵ Similarly, Rooney et al proved that overweight showed a protective effect against the development of any DR compared with normal and underweight in the Asian population.⁴⁶ This might be because the islet function is different in different BMI patients. Lu et al showed that overweight patients in China have lower DR prevalence than normal-weight individuals, which may be attributable to better islet beta-cell function in overweight patients.⁴⁷ In addition, in this study, insulin treatment and presence of other

diabetic complications were confirmed to be associated with DR and advanced DR in patients with DM. These results are congruent with those of the Los Angeles Latino Eye Study and Multi-Ethnic Study of Atherosclerosis in the US.⁴⁸ In this study, except for microaneurysms and spot hemorrhage, the main characteristics of the fundus in the referral group included flaky hemorrhage, hard exudates, cotton wool spots, vitreous hemorrhage, fibroplasia membrane, macular edema, and other microvascular abnormalities. The AI screening system uses a 156-layer convolutional neural network model for DR grading,⁴⁹ and this mechanism can strengthen the useful features and weaken the useless features for all hierarchical features. Although the AI system is less sensitive than optical coherence tomography in screening for diabetic macular edema, studies have shown that the AI system has high sensitivity and specificity for DR detection including diabetic macular edema.⁵⁰

Some limitations of this study should be mentioned. First, this study was a cross-sectional investigation, which does not allow conclusions on risk factors, but allows conclusions on associated risk factors for DR. Second, as a hospital-based study, the patients recruited in the study may not be representative of the overall population with diabetes. Third, this study was conducted in six provinces of China. It can show a tendency but cannot conclude for China in general. Fourth, other possible risk factors, such as family income, education, and psychosocial factors, were not included as variables in this study.

Conclusion

We report a high prevalence of DR in this population. Disease duration, treatment type, region, BMI, glycemic control, and presence of other diabetic complications were associated with DR.

Data Sharing Statement

All data included in this study are available upon request by contact with the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (No. 2016ZDSYLL092-P02). The written informed consent was obtained from each subject. The study was carried out in conformity to the Declaration of Helsinki (as revised in 2013).

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Disclosure

The authors report no conflicts of interest in this work.

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