• Investigation •

Prevalence and risk factors of diabetic retinopathy in patients with type 2 diabetes in Shanghai

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Abstract

● **AIM:** To investigate the prevalence of diabetic retinopathy (DR) in residents of Shanghai and analyze the risk factors of DR.

● **METHODS:** This study involved 7233 patients with diabetes in 2016. The demographic data of the participants were collected using a questionnaire survey. Physical examination, laboratory tests, and ophthalmological examinations were conducted. Two professional ophthalmologists diagnosed and graded DR by fundus examination and then combined the results with fundus images. The unconditional multivariate Logistic regression analysis was used to determine the risk factors.

● **RESULTS:** In total, 6978 patients with type 2 diabetes in Shanghai with a mean age of 68.33±8.40y were recruited, including 2975 males (42.6%) and 4003 females (57.4%). Overall, 1184 patients were diagnosed with DR, with a prevalence rate of 16.97%. Regression analysis showed that duration of diabetes (OR 1.061, 95%CI 1.049-1.073), high systolic blood pressure (SBP; OR 1.071, 95%CI 1.037-1.106), increased glycosylated hemoglobin level (OR 1.234, 95%CI 1.162-1.311), high blood glucose level (OR 1.061, 95%CI 1.023-1.099), increased neutrophil-to-lymphocyte ratio (NLR; OR 1.132, 95%CI 1.053-1.217) and mean platelet volume (MPV; OR 1.077, 95%CI 1.016-1.142) were risk factors of DR. Conversely, hematocrit (HCT; OR 0.971, 95%CI 0.954-0.988) and mean corpuscular volume (MCV; OR 0.980, 95%CI 0.965-0.994) were protective factors.

● **CONCLUSION:** The prevalence rate of DR in Shanghai is 16.97%. The duration of diabetes, high SBP, increased glycosylated hemoglobin, NLR, and MPV were determined as risk factors of DR.

● **KEYWORDS:** type 2 diabetes; diabetic retinopathy; prevalence; neutrophil-to-lymphocyte ratio

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INTRODUCTION

The incidence and mortality rates of diabetes mellitus (DM) have been increasing in recent decades, especially in low and middle-income countries. According to the World Health Organization, the number of diabetes cases will increase from 171 million in 2000 to 366 million in 2030[1]. In 2013, among Shanghai residents aged 35 years and above, the overall prevalence rate of diabetes was 17.6%. The prevalence rates were 19.1%, 15.4%, and 16.1% among urban, suburban, and rural residents[2]. DM is a metabolic disease characterized by chronic hyperglycemia, which can lead to various microvascular complications, mainly manifested as diabetic retinopathy (DR) in the eyes. DR is diagnosed based on clinical manifestations of vascular abnormalities in the retina. Clinically, DR is divided into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR, which represents the early stage of DR, is characterized by retinal pathologies such as microaneurysms, hemorrhages, and hard exudates. PDR, a more advanced stage of DR, is characterized by neovascularization[3].

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age≥35y	Age<35y
Able to cooperate with the examination and questionnaire	Unable to cooperate with the examination and questionnaire
Willing to undergo full physical examination	Experienced acute metabolic complications such as diabetic ketoacidosis and had fundus images that could not be examined
Willing to sign an informed consent form	

DR is the leading cause of visual impairment (VI) and blindness in working-age Europeans[4]. Thus, an increase in the number of patients with DM will lead to an increase in the number of patients with DR, which is estimated to increase to 191 million by 2030[5]. The study showed that the prevalence rate of DR with type 2 DM was 21.7% in 2015 in Shanghai[6]. Therefore, early detection and prevention can delay the occurrence of DR and, consequently, reduce blindness caused by DR. The risk factors of DR can be divided into modifiable and non-modifiable factors. Non-modifiable factors include the duration of diabetes, genetic factors, *etc*. Modifiable factors include blood glucose, blood lipid, blood pressure, and obesity. This study is a part of the Shanghai Cohort Study of Diabetic Eye Disease study (SCODE). SCODE was a community-based prospective cohort study performed over 3 consecutive years, *i.e.*, from 2016 to 2018. Individuals with diabetes aged ≥35y were recruited from community health service centers (CHSCs) using stratified random sampling. A total of 7233 adults with diabetes (34.7% enrollment rate, 20 844 eligible) from eight CHSCs in four districts were recruited and participated in the study.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethics Committee of Shanghai General Hospital, Affiliated to Shanghai Jiao Tong University School of Medicine (No.2013KY023). This study followed the principles of the Declaration of Helsinki; all patients understood the purpose and significance of the study and provided informed consent.

Methods Inclusion and exclusion criteria were shown in Table 1. Type 2 DM was diagnosed according to the definitions of the World Health Organization[7]. The diagnosis and classification of DR were performed in accordance with international standards[8]. In case of conflicting diagnoses, the senior ophthalmologist reviewed the diagnoses. After exclusion of ineligible participants, 7233 participants who underwent eye examinations were recruited, but only 6978 of them had complete data.

Data Collection

Questionnaire Before the beginning of the examination, a face-to-face questionnaire survey was conducted for each patient. Each questionnaire included the following aspects: name, age, sex, education level, occupation, income level, marital status, type of diabetes, course of diabetes (calculated from the date of diagnosis in internal medicine), history of hypertension, other diabetes complications, drug use history, family history (emphasizing the family history of diabetes), history of cataract surgery, history of tobacco and alcohol use, and exercise habits, the realizing of the ocular complications of diabetes.

Physical examination and laboratory tests The patients' height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP), waist circumference, abdominal circumference, and heart rate were measured by a trained clinician, and the body mass index (BMI) was calculated.

The laboratory tests included the following examinations: 1) Routing blood examinations: red blood cell (RBC) count, mean corpuscular volume (MCV), hematocrit (HCT), mean RBC hemoglobin (MCH), mean RBC hemoglobin concentration, RBC distribution width (RDW), platelet (PLT) count, mean PLT volume (MPV), PLT distribution width (PDW), PLT-large cell ratio (P-LCR), white blood cell (WBC) count, neutrophil count (N), lymphocyte count (L), lymphocyte percentage (L%), neutrophil percentage (N%), monocytes, eosinophils, and basophils; 2) Renal function tests included blood urea levels, blood creatinine levels, glomerular filtration rate, and serum bilirubin levels; 3) Liver function tests included alkaline phosphatase levels, alanine transaminase levels, aspartate transaminase (AST) levels, total protein, albumin, globulin, C-reactive protein (CRP), fasting blood glucose level (FBG), and glycosylated hemoglobin (HbA1c) level; 4) Lipid profile included triglycerides (TG), total cholesterol (TP), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum lipoprotein A, apolipoprotein AI, and apolipoprotein B; 5) Urine analyses included urine creatinine (UCR), urine sugar (GLU), urea (UREA), urine microalbumin (mALB), and urine albumin-to-creatinine ratio.

Fasting venous blood samples were collected from 8:00 to 9:30 a.m. Blood was sampled with the patient in a sitting position after fasting overnight to avoid potential confusion due to time and posture.

Eye examinations Ophthalmologists conducted the following eye examinations: refractive degree using automatic optometry machine (KR-8900, TOPCON, Japan), and the international standardized logMAR chart was used to determine best-

Table 2 Demographic information and disease characteristics mean±SD

Variable	DR (*n*=1184)	No DR (*n*=5794)	t/χ^2 value	*P*
Age (y)	68.33±8.40	68.10±8.47	0.875	0.381
Gender, *n* (%)			0.276	0.603
Male	366 (40.53)	1623 (41.48)		
Female	537 (59.47)	2290 (58.52)		
Waist, cm	87.08±10.02	87.06±14.32	0.029	0.977
BMI, kg/m^2	24.84±3.21	25.06±3.43	-2.016	0.035
Smoking, *n* (%)			5.020	0.170
Smoking daily	118 (9.97)	616 (10.63)		
Smoking irregularly	31 (2.62)	102 (1.76)		
Former smoking	83 (7.01)	451 (7.78)		
Nonsmoking	952 (80.40)	3052 (78.83)		
Alcohol drinking, *n* (%)			0.971	0.808
Daily drinking	54 (4.56)	278 (4.80)		
Drinking ≥3 times/wk	21 (1.78)	84 (1.44)		
Drinking <3 times/wk	117 (9.88)	596 (10.29)		
Nondrinking	992 (83.78)	4836 (83.47)		
Family history, *n* (%)			0.773	0.379
Yes	342 (28.89)	1748 (30.17)		
No	842 (71.11)	4046 (69.83)		
Duration of diabetes (y)	14.41±5.82	11.65±5.50	15.567	<0.001

DR: Diabetic retinopathy; BMI: Body mass index.

corrected visual acuity. Slit-lamp biomicroscopy (SL130, Zeiss, Germany) was used to examine the eyelids, conjunctivae, cornea, anterior chambers, iris, pupils, and lenses, and a 90-D non-contact lens (90 D, Ocular, US) was used to examine the fundus of the retina. Digital fundus photography without mydriasis (AFC-210, NIDEK, Tokyo, Japan), was used to obtain two 45° digital retinal images centered on the macula and optic disc for each eye. Intraocular pressure and tonometry (NT-530p, Nidek, Tokyo, Japan) were assessed. IOL master (500, Carl Zeiss meditec, Dublin, CA, USA) was used to measure the axial length, anterior chamber depth, corneal thickness, corneal diameter, and lens thickness. Swept-source optical coherence tomography angiography (Triton, TOPCON, Tokyo, Japan) was used to examine the macular retina.

Statistical Analysis All statistical analyses were performed with SAS version 9.4 (SAS Company, USA). Continuous variables were described as mean±standard deviation (SD); skewed distribution as median (lower and upper quartiles), and categorical variables as frequency (percentage). For comparison between the groups, we used Chi-square tests for categorical variables and independent *t*-test for continuous variables; Mann-Whitney Wilcoxon test was used for skewed distribution variables. Multivariate Logistic regression analysis was used to analyze the risk factors. A two tailed values of $P<0.05$ were considered to be statistically significant.

RESULTS

Baseline Characteristics In this study, more than 7247 patients with type 2 DM were recruited in 2016. Among them, 6978 patients aged 68.33±8.40y had completed data including 2975 males (42.6%) and 4003 females (57.4%). In total, 1184 patients with DR were diagnosed, with a prevalence rate of 16.97%. The proportion of patients with PDR was 0.85% and 4.99% of patients had DR.

Differences of age, sex, smoking and drinking status, and family history between patients with DR and without DR were not significant ($P>0.05$). The duration of diabetes in patients with DR was significantly higher than that in no DR ($P<0.001$), as shown in Table 2.

Univariate Analysis of Blood Lipid, Blood Glucose Levels, and Blood Pressure The results of univariate analysis showed that there were significant differences in SBP, HbA1c, and fasting blood glucose levels between patients with DR and no DR ($P<0.05$; Table 3).

Univariate Analysis of Blood Routine Tests There were significant differences in serum albumin levels, PLT count, MPV, P-LCR, PDW, HCT, RDW, hemoglobin levels, MCV, WBC count, L%, L, neutrophil-to-lymphocyte ratio (NLR), N%, N, and globulin levels between the DR and no DR groups ($P<0.05$; Table 4).

Multivariate Logistic Regression Analysis of Diabetic Retinopathy The duration of diabetes, SBP, HbA1c, NLR, fasting blood glucose level and PLT count had independent effects on DR after adjusting for other factors. Among them, the duration of diabetes, SBP, HbA1c, glucose level, NLR, and

Table 3 Comparison of blood lipid, blood glucose levels, and blood pressure mean±SD

Variable	DR (*n*=1184)	No DR (*n*=5794)	*t*/*Z*	*P*
SBP, ×10 mm Hg	14.46±2.01	14.10±2.00	5.529	<0.001
DBP, ×10 mm Hg	7.91±1.27	7.90±1.20	0.108	0.914
HbA1c, %	8.00±1.76	7.10±1.42	16.497	<0.001
LDL, mmol/L	2.96±1.00	2.92±0.95	1.275	0.203
HDL, mmol/L	1.34±0.37	1.34±0.37	0.350	0.727
TG, mmol/L	1.71±1.60	1.70±1.33	0.226	0.822
FBG, mmol/L	8.56±30.2	7.18±2.28	17.831	<0.001
Serum lipoprotein A, median (Q_l, Q_u)	8.70 (4.20, 22.00)	8.4 (4.00, 21.5)	0.004	0.997
Apolipoprotein AI	148.23±28.21	149.21±27.64	-0.958	0.338
Apolipoprotein B	99.57±27.90	99.02±26.25	0.649	0.519

DR: Diabetic retinopathy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycosylated hemoglobin; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; FBG: Fasting blood glucose; Q_l, Q_u: Lower and upper quartiles.

Table 4 Comparison of blood and urine routine tests mean±SD

Variable	DR (*n*=1184)	No DR (*n*=5794)	*t*/*Z*	*P*
Serum albumin, g/L	46.02±3.62	45.68±3.77	-3.029	0.003
Platelet count, $\times10^{10}$/L	20.13±5.78	19.61±5.80	2.845	0.004
Mean platelet volume, fL	10.84±1.98	10.71±1.16	3.377	0.001
P-LCR, %	31.94±9.47	31.02±9.41	3.450	0.001
Platelet distribution width, fL	13.19±2.39	12.90±2.32	4.024	<0.001
Hematocrit, %	40.88±4.32	41.23±3.97	2.729	0.006
RBC distribution width, %	40.73±4.15	41.31±4.07	-4.445	<0.001
RBC, $\times10^{12}$/L	4.54±0.53	4.54±0.48	-0.030	0.976
Hemoglobin, g/L	136.79±15.45	137.85±14.50	-2.247	0.025
MCV, fL	90.15±5.40	90.97±5.78	4.720	<0.001
Mean RBC hemoglobin, pg	30.15±2.10	30.40±52.04	-3.732	<0.001
MCHC, g/L	333.91±16.97	333.77±14.76	0.307	0.759
White blood cell, $\times10^9$/L	6.51±1.63	6.40±1.77	2.141	0.032
Lymphocyte percentage, %	31.40±7.71	32.64 ±7.75	4.982	<0.001
Lymphocyte count, $\times10^9$/L	2.02±0.70	2.06±0.64	-2.155	0.031
Neutrophil-to-lymphocyte ratio	2.15±0.92	2.01±0.83	4.990	<0.001
Neutrophil percentage, %	61.29±8.54	59.97±8.54	4.852	<0.001
Neutrophil count, $\times10^9$/L	4.03±1.35	3.87±1.26	3.905	<0.001
GLB, g/L	29.24±4.59	29.07±4.36	1.158	0.247
uCRE, median (Q_l, Q_u)	6520 (4130, 9870)	7060 (4400, 11030)	-3.910	<0.001
Microalbuminuria, median (Q_l, Q_u)	14.00 (3.50, 52.90)	7.50 (2.50, 26.00)	9.638	<0.001
ACR, median (Q_l, Q_u)	1.06 (0.43, 3.54)	1.04 (0.44, 3.69)	-0.515	0.606

P-LCR: Large percentage of cells in platelets; RBC: Red blood cell; MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin contentration; GLB: Globulin; uCRE: Urine creatinine; ACR: Urinary trace albumin/urinary creatinine; Q_l, Q_u: Lower and upper quartiles.

MPV were risk factors of DR. The risk of occurrence increased by 6.1%, 7.1%, 23.4%, 6.1%, 13.2%, and 7.7% for each additional unit, respectively. For each unit increase in HCT and MCV, the risk decreased by 2.9% and 2.0% respectively, as shown in Table 5.

DISCUSSION

The results of this cross-sectional study showed that the prevalence of DR in patients with diabetes in Shanghai was 16.97%. Due to different races, economic development levels, study designs, and sample populations, the prevalence of DR varies in different countries. In European countries such as Sweden, Denmark and Italy, the prevalence of DR varied from 30% to 40%[4]. The “Lifeline Rapid Diabetic Retinopathy Screening Program” in China reported that the prevalence of

Table 5 Multivariate Logistic regression analysis of DR

Variable	β	SE	Wald	OR	95% upper	95% lower	*P*
Disease course	0.059	0.006	102.432	1.061	1.049	1.073	<0.001
SBP	0.069	0.017	17.320	1.071	1.037	1.106	<0.001
HbA1c	0.211	0.031	46.443	1.234	1.162	1.311	<0.001
Blood glucose	0.059	0.018	10.260	1.061	1.023	1.099	0.001
Neutrophil-to-lymphocyte ratio	0.124	0.037	11.342	1.132	1.053	1.217	0.001
Mean platelet volume	0.074	0.030	6.202	1.077	1.016	1.142	0.013
Hematocrit	-0.030	0.009	11.360	0.971	0.954	0.988	0.001
Mean corpuscular volume	-0.021	0.007	7.644	0.980	0.965	0.994	0.006

DR: Diabetic retinopathy; SBP: Systolic blood pressure; HbA1c: Glycosylated hemoglobin.

DR range from 23.1% to 47.2%[9]. These studies all targeted hospital population. A Beijing-based study on the recruitment of patients with diabetes in the community was similar to our research population. Literature reports that the DR prevalence of patients with type 2 diabetes in the Beijing community in 2009 was 24.7%[10]. At the same time, our research in Shanghai 10y ago reported that the prevalence of DR was about 25%[11]. In recent years (with the combined efforts of Shanghai Chronic Metabolic Disease Management Center and DRDR's eye remote health system[11] and other modes), the prevalence of DR in Shanghai has decreased. It was lower compared to other cities, meaning patients with diabetes had a significant effect from the education and management of the eye health in Shanghai. Furthermore, Shanghai is located in the southeast of China and belongs to an economically developed southern city. This is consistent with findings that the prevalence of southern China is significantly lower than in the north[9,12].

In this study, multivariate regression analysis was used to analyze the risk factors of DR. The results showed that prolonged diabetes, increased glycated hemoglobin levels, high fasting blood glucose, and high SBP, were risk factors of DR. This is consistent with the findings from other scholars in the past[1,10,13-14]. However, no correlation between the prevalence of DR and hyperlipidemia was found. This result is consistent with the multi-ethnic study of atherosclerosis and the Singapore-Indian Eye Study report[15-16].

WBC count, lymphocyte count, and lymphocyte percentage were significantly different between DR and non-DR groups. Multivariate analysis found that NLR was an independent risk factor for DR. In recent years, studies have shown that NLR, a new inflammatory marker has a significant relationship with traditional inflammatory markers. NLR is positively correlated with serum IL-6 and CRP[17-18]. Compared to neutrophils, NLR is less affected by various physiological and pathological conditions and can reflect the balance between peripheral blood neutrophils and lymphocytes better. NLR is associated to ocular inflammation and vascular diseases, such as DR, age-related macular degeneration, retinal vein occlusion, glaucoma, and dry eye disease[19-22]. DR is a pathology of retinal micro vessels caused by diabetes. Some of its pathological processes include inflammation, ischemia, and progressive retinal pigment epithelium cell degeneration. Various systemic and local (vitreous and aqueous) inflammatory factors play important roles in the development of DR[23-25]. Currently, there are controversies about the link between NLR and DR. Some studies show a correlation between NLR and DR[26], but some scholars believe that the two are not directly related[27]. Our study is a large-scale community-based study, and the results are consistent with most recent studies. We believe that DR is related to NLR, and NLR is economically accessible. In a large-scale epidemiological survey, NLR can be used as a monitoring indicator for DR prevalence in patients with diabetes. However, the mechanism of NLR as a marker of inflammatory response in DR is not clear and needs further research.

Platelets are one of the causes of diminished (or no) perfusion in patients with diabetes. The nature of platelets and platelet activation in patients with diabetes has been reported, which is closely related to insulin resistance, hyperglycemia and abnormal blood lipids[28-29]. Some studies indicate that platelets participate in DR development as microvascular thrombi[30]. The increased platelet activation plays an important role in the occurrence of abnormal coagulation and thromboembolic events in patients with diabetes[31]. Our results showed that PLT count, MPV, P-LCR, and platelet distribution width were significantly different between the DR groups. However, further analysis showed that only MPV was an independent risk factor for DR. This is because they were closely related and affect each other. Physiologically, the MPV reflects the average size of platelets in a person's blood sample. Platelets with higher MPV values have more metabolism and enzyme activity than platelets with lower MPV values[32]. Large platelets are metabolically and enzymatically more active and have the potential to increase thrombosis[33]. MPV is positively correlated with platelet adhesion and aggregation. At its higher levels, platelet adhesion and aggregation rate are higher and the

function is stronger. DR microvascular disease is characterized by thickening of the basement membrane of the capillary. Platelet dysfunction has an important impact on the occurrence of microvascular complications. In recent years, several studies have elucidated the correlation between MPV and DR[30,34].

Our results showed that the hematocrit, standard deviation of RBC distribution width, hemoglobin measurement, MCV, and MCH were significantly different between the groups. Previous studies suggested that anemia may be an independent risk factor for the occurrence of DR[35]. Some scholars reported that parameters of RBC were related to the development of DR[36]. In our study multivariate analysis showed that HCT and MCV were risk factors of DR. MCV referred to the average volume of each red blood cell. MCV is an important indicator in the diagnosis of anemia. The capillary diameter is between 2 and 10 μm, and the average diameter of red blood cells is 75 μm. The deformability of red blood cells allows red blood cells to pass through the small blood vessels in the circulation, in order to ensure the supply and support of micro vessels. In the state of high blood sugar, the degenerative ability of red blood cells is weak[37], and oxygen cannot be transported through small blood vessels. This leads to an abnormal blood oxygen supply to the retina, and consequently the development of DR.

There are shortcomings in this study. First, the proportion of patients in the proliferative phase in our study was very low, thus no further discussion about the classification of patients with DR occurred. Second, due to the large number of elderly participants, limited information regarding daily medications was recorded. Thus, the situation and impact of medications in this study was poorly studied.

In our study, the prevalence of DR in Shanghai patients with diabetes was 16.7%, slightly lower than other studies. As in previous studies, it was proved that the course of diabetes, HbA1c, FBG, and increased SBP were all risk factors for the incidence of DR. MPV as an indicator of platelet activation; MCV as a parameter of erythrocyte volume is also closely related to the occurrence of DR. However, this study did not find any correlation between blood lipids and DR in patients with diabetes.

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