Risk factors of proliferative diabetic retinopathy in Chinese Patients with Type 2 Diabetes

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Abstract

Background: To investigate the relationship between systemic parameters and proliferative diabetic retinopathy(PDR) in Type 2 diabetes mellitus(T2DM).

Methods: This was a cross-sectional study. Based on retinal examination findings, diabetic patients were classified into three groups: non-diabetic retinopathy (non-DR), non-proliferative diabetic retinopathy (NPDR), and PDR. The comprehensive medical data was used for analysis. Odds ratios(OR) from multinomial logistic regression models were calculated to obtain the risk factors of PDR, and a prediction model was built whose predictive ability was assessed by the area under the receiver operating characteristic curves (AUROC).

Results: The study comprised 801 patients with non-DR, 330 patients with NPDR, and 99 patients with PDR. The systemic factors associated with PDR were: duration of diabetes($P < 0.000$), Haemoglobin A1c ($P = 0.015$) , fasting plasma glucose ($P = 0.001$), total cholesterol($P = 0.007$), estimated glomerular filtration rate ($P = 0.024$), and MPV($P = 0.005$). The mean platelet volume (MPV) demonstrated an increasing trend with the severity of DR, whose differences were statistically significant among the three groups($P = 0.045$). The prediction model which was based on multi-factors showed stronger predictive power for PDR (AUROC=0.790) than these risk factors of PDR.

Conclusions: Some systemic factors including MPV are independently associated with PDR in T2DM. The prediction model might be a beneficial prognostic marker of PDR in patients with T2DM.

1. Background

Type 2 diabetes mellitus (T2DM), which can lead to micro- and macrovascular complications, has become a serious threat to global human health. Diabetic retinopathy (DR) might develop to proliferative diabetic retinopathy (PDR), which is the main cause of impaired vision and even blindness in diabetics[1]. The increasing evidence which even established risk factors of DR including hyperglycemia, hypertension, dyslipidemia, and duration of diabetes, can only explain a limited proportion of the developing risk[2, 3].

Although the pathogenesis of DR is not clear, microthrombus formation caused by microcirculation changes is a pathogenic factor, in which platelet plays an important role[4, 5]. Mean platelet volume (MPV) is a simple and reliable index of platelet size which correlates well with their activation[6]. Larger platelets produce higher amounts of the prothrombotic factor thromboxane A2, increasing a propensity to thrombosis[7]. Platelets with hyper-reactivity in T2DM may play a pivotal role in the prothrombotic state and prompt the development of diabetic microvascular complications[5, 8].

The aims of the present study were to: 1) measure the systemic parameters in difference DR stages and find their correlation with PDR; 2) establish a prediction model for PDR and evaluate the diagnostic accuracy of the prediction model and independent risk factors for PDR.

2. Methods

2.1 Study Participants

This was a retrospective cross-sectional study that focused on the clinical risk factors of PDR. The medical records of patients with T2DM who admitted to Yiwu Central Hospital, Zhejiang Province, China, between 2018 and 2020 were reviewed. Individuals who was diagnosed with diabetes by an endocrinologist or took glucose lowering medicines were identified as known cases of diabetes. Exclusion criteria included: (1) data of blood and urine tests were not available; (2) systemic diseases that could affect platelets; (3) patients using antiplatelet agents or receiving chemotherapy; (4) patients who have undergone surgery or retinal photocoagulation.

The study protocol had been approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University and conformed to the Declaration of Helsinki.

2.2. Clinical Data Collections

Clinical demographics(age, gender), medical history (hypertension, hyperlipidemia, and duration of diabetes), and laboratory variables(fasting blood glucose, glycated hemoglobin A1c; total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein cholesterol, serum creatinine, blood urea nitrogen, estimated glomerular filtration rate, mean platelet volume and platelets count) were collected. The calculation of body mass index (BMI) was body weight in kilograms divided by the square of height in meters. The plasma glucose and HbA1c levels were not used for diabetes diagnosis.

2.3. Dr Diagnosis And Grades

The diagnosis of DR was made by an experienced retinal ophthalmologist after a dilated fundus examination. The presence and severity of DR were graded based on the guidelines of the International Council of Ophthalmology[1,9]. NPDR was defined as microaneurysms, intraretinal hemorrhage, hard exudates, cotton-wool spots, or macular edema but no evidence of retinal or iris neovascularization. PDR was defined as neovascularization on the optic disc, retina, or iris, with or without vitreous hemorrhage or prior pan-retinal photocoagulation. The more severe eye was employed to determine the presence and grade of DR when the two eyes in one patient had different DR severity.

2.4. Statistical Analysis

Statistical package for Social Sciences (SPSS version 23) was used for data analysis and Microsoft Excel to generate graphs. Continuous variables were expressed as a mean ± standard deviation (SD), while categorical variables were expressed as percentages. The student's test (t-test), univariate chi-square analysis, and multiple logistic regression test were performed

for statistical analysis. According to the results of multiple logistic regression, a prediction model was built. The predictive ability of the risk factors and prediction model was evaluated using AUROC analysis, which could be compared using the method developed by Hanley and Mc Neil [10]. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics of Participants

The study included 1230 patients with T2DM who had complete electronic medical records. The prevalence of DR was 34.88% (429/1230) and the prevalence of PDR was 8.05% (99/1230) among the T2DM patients. The mean (SD) age of the patients was 59.41 (12.85) years in Non-DR group, 60.51 (11.51) years in NPDR group, 58.74(10.70) years in PDR group, which had no difference among the three groups (P > 0.05) (Table 1).

Table 1. Characteristics of the patients with T2DM by the severity of DR (*n* = 1230)

	Non-DR (n = 801)	NPDR (n = 330)	PDR (n = 99)	*P*-value*
Age(years)	59.41±12.85	60.51±11.51	58.74±10.70	0.294
Male (%)	57.80	49.09	53.54	**0.026**
Duration of diabetes(years)	8.41±6.47	12.09±6.31	13.74±7.60	**0.000**
BMI (kg/m 2)	24.11±3.50	24.96±3.43	25.73±8.01	0.806
HbA1c, %	8.76±2.32	9.40±2.18	9.95±2.25	**0.002**
Fasting blood glucose (mg/dl)	7.69±2.72	8.45±3.24	9.30±3.82	**0.000**
Total cholesterol (mmol/L)	4.12±1.19	4.05±1.14	4.54±1.44	**0.001**
Triglyceride (mmol/L)	1.78±1.44	1.74±1.30	2.14±2.29	0.057
HDL-C (mmol/L)	0.97±0.27	0.98±0.28	1.03±0.31	0.211
LDL-C (mmol/L)	2.25±0.88	2.18±0.84	2.37±0.95	0.140
Hypertension (%)	48.31	49.70	54.55	0.493
SCr (μmol/L)	68.48±24.10	70.58±30.72	80.90±36.36	**0.000**
BUN (mmol/L)	5.69±1.86	6.09±2.01	6.63±2.19	**0.000**
eGFR	121.32±34.22	118.25±37.72	102.74±36.01	**0.000**
MPV(fl)	10.26±1.18	10.37±1.19	10.55±1.10	**0.045**
Plt count/cm2	193.56±58.71	187.26±53.73	182.94±58.04	0.084

Continuous values are expressed as mean ± SD. P <0.05 is indicated in bold.

Abbreviations: Non-DR: non-diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy; BMI, body mass index; HbA1c, glycated hemoglobin a1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SCr: serum creatinine; BUN: blood urea nitrogen; eGFR, estimated glomerular filtration rate; MPV: mean platelet volume; Plt: platelets.

3.2. Changes in Systemic Parameters among different DR Groups

Univariate analysis on clinical and laboratory data of the participants was summarized in Table 1. Characteristics of patients among the three groups significantly differed in gender, duration of diabetes, HaemoglobinA1c(HbA1c), fasting plasma glucose(FPG), total cholesterol, serum creatinine(SCr), blood urea nitrogen (BUN), estimated glomerular filtration rate(eGFR) , and MPV (all P < 0.05). There was no significant difference in age, body mass index (BMI), hypertension, triglycerides, high-density lipoprotein

cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and platelet count among the three groups (all P > 0.05).

MPV was 10.26±1.18fL in non-DR group, 10.37±1.19fL in NPDR group, and 10.55±1.10fL in PDR group. Figure 1 showed that the MPV was highest in the PDR group and the association was statistically significant (P = 0.045).

3.3. Risk Factors and prediction model of PDR

Multiple logistic regression analysis was performed to find variables having independent association with PDR (Table 2, n =1230). Compared with Non-DR, MPV showed significant relation with PDR (OR=1.304, 95% CI, 1.084-1.567). Other variables showing independent association with PDR were duration of diabetes (OR=1.118, 95% CI, 1.082-1.155), HbA1c (OR=1.142, 95% CI, 1.027-1.271), FPG (OR=1.131, 95% CI, 1.049-1.219), total cholesterol (OR=1.253, 95% CI, 1.063-1.476) and eGFR (OR=0.987, 95% CI, 0.976-0.998). Based on these variables, the prediction model of PDR was logit(P)=(-8.434)+0.112×duration of diabetes +0.133×HbA1c+0.123×FPG +0.225×total cholesterol -0.013×eGFR +0.265×MPV

We performed the ROC analysis to assess the predictive power of the prediction model and these variables which had independent correlation with PDR on multivariate analysis. As shown in Figure 2, the prediction model provided a more excellent forecast for PDR (AUROC = 0.790) than any risk factor. Among the risk factors, duration of diabetes was the strongest predictive factor for PDR (AUROC =0.707), followed by FPG (AUROC =0.620) and HbA1c (AUROC =0.619). And meanwhile, total cholesterol and MPV provided relatively poor prediction for PDR(AUROC =0.579, 0.573).

Table 2. Multiple Logistic Regression Analysis Showing the Parameters with Significant Association with PDR (*n* = 1230).

	Variable	B	Adjusted OR	95% CI	*P*-value*
PDR	intercept	-8.434			
	Male (%)	0.121	1.128	0.671-1.897	0.649
	Duration of diabetes(years)	0.112	1.118	1.082-1.155	**0.000**
	HbA1c, %	0.133	1.142	1.027-1.271	**0.015**
	Fasting plasma glucose (mg/dl)	0.123	1.131	1.049-1.219	**0.001**
	Total cholesterol (mmol/L)	0.225	1.253	1.063-1.476	**0.007**
	SCr (μmol/L)	0.000	1.000	0.987-1.014	0.978
	BUN (mmol/L)	0.075	1.078	0.939-1.238	0.286
	eGFR	-0.013	0.987	0.976-0.998	**0.024**
	MPV(fl)	0.265	1.304	1.084-1.567	**0.005**

P <0.05 is indicated in bold. The prediction model of PDR was logit(P)=(-8.434)+0.112×duration of diabetes +0.133×HbA1c+0.123×random blood glucose +0.225×total cholesterol -0.013×eGFR +0.265×MPV.

Abbreviations: NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy; BMI, body mass index; HbA1c, glycated hemoglobin; SCr: serum creatinine; BUN: blood urea nitrogen; eGFR, estimated glomerular filtration rate; MPV: mean platelet volume.

4. Discussion

Diabetic retinopathy(DR), which begins with asymptomatic retinal abnormalities, might progress to PDR characterized by neovascularization. The evidence put forward in previous studies suggests that systemic risk factors may contribute to the development of sight-threatening PDR[11,12,13]. Progression to PDR is related to capillary occlusion in the retinal periphery, which may be associated with a prothrombotic state and increased thrombocyte aggregation[1,14].

Platelets are activated in DM[15]and may participate in the development of DR by thrombogenesis in microvascular lesions[16]. MPV which reflects the average size of platelets is a marker indicating subclinical platelet activation in the blood sample[17]. The larger MPV with more likely formation of thrombosis may be associated with the incident of PDR[18] and may reflect the severity of DR[16]. There is a significant difference of MPV values among DR stages in our study (P < 0.05), in accordance with a previous study[19]. Compared to Non-DR, MPV shows independently significant association with PDR

(OR=1.304, 95% CI, 1.084-1.567), which proposes that MPV is a risk factor for retinal neovascularization[16].

Duration of diabetes is an independent risk factor for the severity of DR[12,20,21]. In the study of Voigt et al.[22], T2DM individuals have the low prevalence and the infrequent progression of DR within the first 10 years of diabetes duration. And more, most patients have a non-proliferative form which can be reversible and rarely requires intervention. In our study, T2DM patients who are suffering from more serious DR have longer diabetes duration, in accordance with previous study[14]. Compared to non-DR, the longer diabetes duration shows an independent significant association with PDR.

Poor glycemic control is an independent risk factor for the development of DR[23]. The increasing risk of developing PDR with increasing HbA1c underlines that the progression to sight-threatening DR is accelerated by poor glycemic control[24,25]. Both FPG and HbA1c are significantly related to PDR in our study, and meanwhile have almost the same predictive ability for detecting DR[26]. However, there is another study indicating the superiority of HbA1c to FPG for the diagnosis of DR[27]. Therefore, maintaining HbA1c levels within the normal range should be advised to slow the progression of DR.

Clinical evidence for the relation between total cholesterol and DR is controversial[28,29,30,31].

The study of Tan GS et al. showed that the higher total cholesterol was associated with lower odds of DR incidence[28, 29],and might protect against DR[32]. However, another conclusion showed that the total cholesterol level was not significantly associated with DR[33]. Other studies showed that the total cholesterol was significantly higher in the NPDR and PDR group than that in the NDR group[34]. Our study revealed that the higher total cholesterol level was associated with an increased hazard of progression to PDR, and then contributed to the accumulating evidence which high total cholesterol might be implicated in PDR.

The retina and kidney share similar microvascular complications in DM[35, 36]. Wu et al.[37] showed that decreased eGFR significantly correlated with DR, even after adjusting for age, gender, and albuminuria. AJin Cho et al.[38] found that a ≥20% decline in eGFR was independently associated with the progression to PDR in NPDR patients. Our study also revealed that decreased eGFR was indepently related to PDR, compared to Non-DR. Declining renal function, which increased the risk of progression to PDR might play a good role in predicting the occurrence of PDR[39].

To reduce the progression to PDR, preventive measures and prompt treatments are needed for high-risk patients in the early DR stage. It is vital to estimate the individual risk of DR development and determine an appropriate screening interval for T2DM individuals. To our knowledge, this is the first study that build a model to predict the risk of PDR based on multi-factors. Our prediction model for PDR, which consists of independent risk factors, results in higher predictive ability than any risk factor. Among the independent risk factors, the duration of diabetes is the strongest prognostic factor, followed by HbA1c and FPG. MPV in itself has limited value as a predictive marker, but we believe that its independent

association with PDR might be a part of the pathogenic mechanism and a possible therapeutic target. Although our findings should be interpreted with caution, the results suggested that the prediction model might be used for monitoring T2DM individuals and could enable physicians to timely refer to the ophthalmologist for prompt management.

There are several limitations in our study. First, because of the nature of cross-sectional studies, we cannot define the causal relationship between risk factors and PDR. Further longitudinal studies should be performed to validate the risk factors as clinical markers for the progression of DR and to identify MPV as a potential player in its pathogenesis. Second, not all potential risk factors are included in the design of this study. And so, the prediction model might change with more included systematic factors. Finally, this study is based on patients from one single hospital of China, limiting the generalizability of our study findings. Future multicenter cohort studies are needed to validate our conclusions. Despite these limitations, we believe our study is valuable in that we have shown many accessible clinical and laboratory parameters including MPV are independent risk factors for PDR and in that we have explored a prediction model for PDR.

5. Conclusions

In conclusion, our study revealed that systemic risk factors such as glycemic regulation, diabetes duration, total cholesterol, eGFR, and MPV showed independent association with PDR. MPV increased significantly with the progression of DR and elevated MPV might take part in the pathogenesis of advance-stage PDR. The prediction model including MPV and traditional risk factors might play a valuable role in predicting the probabilities of PDR.

Abbreviations

PDR: proliferative diabetic retinopathy; T2DM: Type 2 diabetes mellitus; non-DR: non-diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy; OR: Odds ratios; AUROC: the area under the receiver operating characteristic curves; MPV: mean platelet volume; BMI: body mass index; SD: standard deviation; HbA1c: hemoglobin a1c; HDL-C: high-density lipoprotein cholesterol; LDL-C; low-density lipoprotein cholesterol; SCr: serum creatinine; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; Plt: platelets; FPG: fasting plasma glucose.

Declarations

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Ethics approval and consent to participate

The study protocol had been approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Informed consent was obtained from all subjects.

Consent for publication

Not applicable.

Availability of data and material

Some or all data generated or used during the study are available from the corresponding author by request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Lili Zhu analyzed the data and wrote the main manuscript text.

Xiaojin Fu facilitated patient recruitment and provided clinical inputs.

Jianyong Wang conceived this study and revised the manuscript.

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Figures

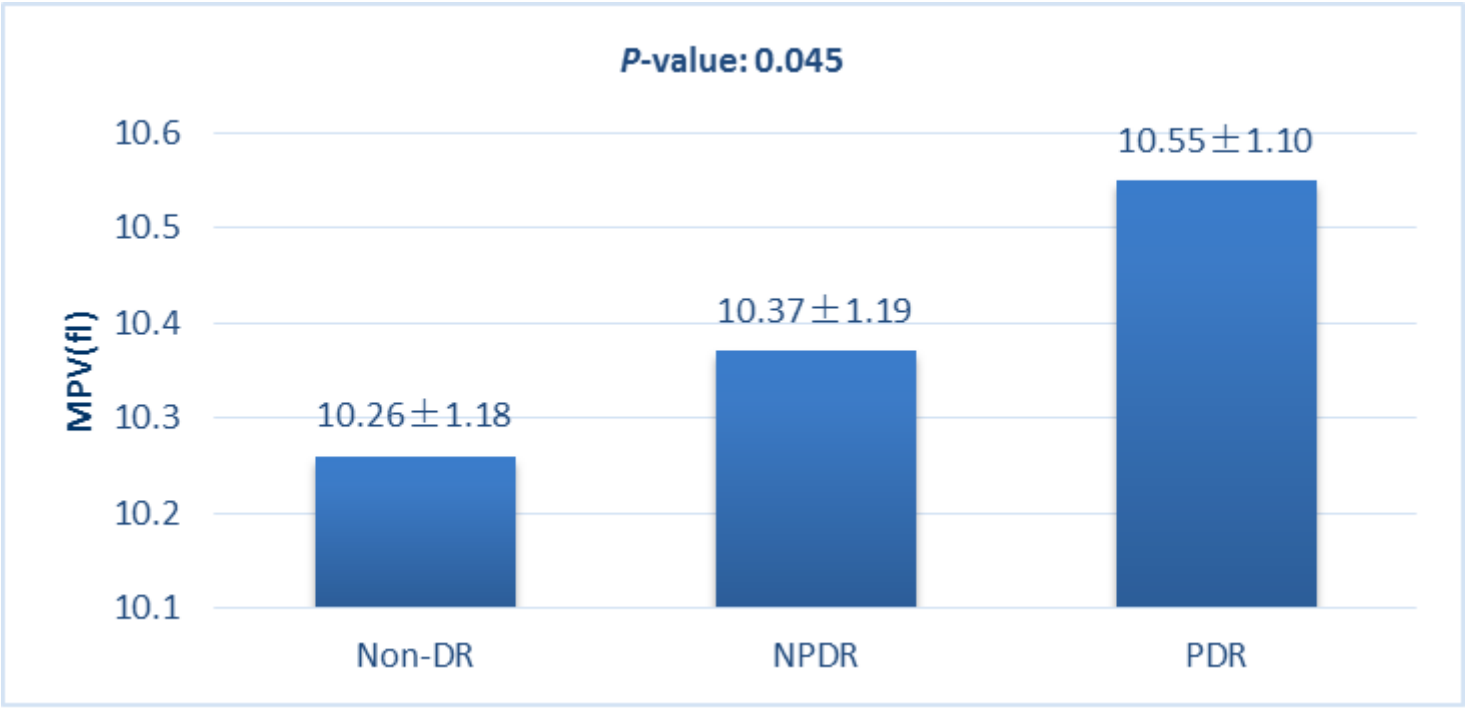

Figure 1

A simple histogram of association of mean MPV and severity of diabetic retinopathy

Abbreviations: Non-DR: non-diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy; MPV: mean platelet volume.

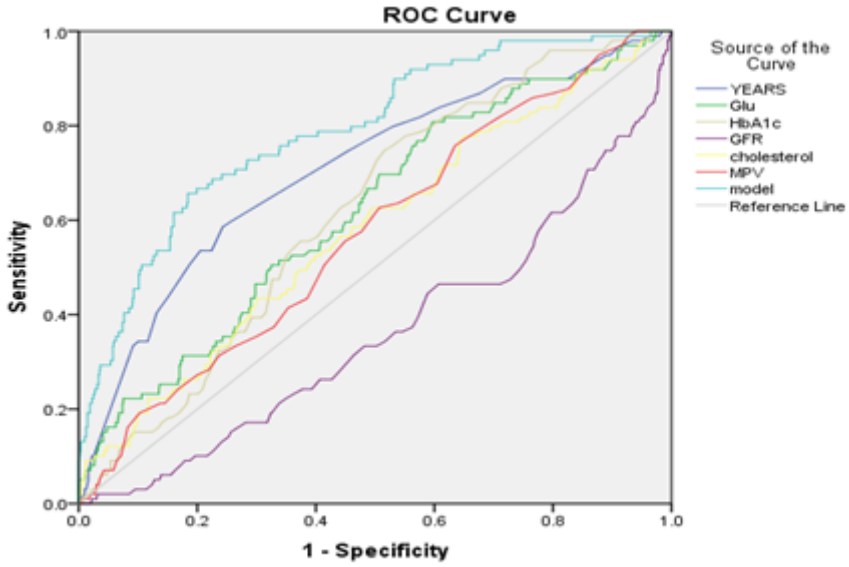

Figure 2

ROC curves of the prediction models(AUROC = 0.790) , duration of diabetes(years)(AUROC = 0.707), fasting blood glucose(AUROC = 0.620), HbA1c(AUROC = 0.619), cholesterol(AUROC = 0.579), MPV(AUROC = 0.573) and eGFR(AUROC = 0.361) for predicting PDR.