

# The Platelet-to-Lymphocyte Ratio Predicts Diabetic Retinopathy in Type 2 Diabetes Mellitus

Jing Zeng (✉ [zengjing2109@163.com](mailto:zengjing2109@163.com))

cheng du shi di wu ren min yi yuan

Min Chen

cheng du shi di wu ren min yi yuan

Qiu Feng

cheng du shi di wu ren min yi yuan

Haiyan Wan

cheng du shi di wu ren min yi yuan

Jianbo Wang

cheng du shi di wu ren min yi yuan

Fan Yang

cheng du shi di wu ren min yi yuan

Hongyi Cao

cheng du shi di wu ren min yi yuan

---

## Research

**Keywords:** Diabetic retinopathy, Type 2 diabetes mellitus, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Monocyte-to-lymphocyte ratios

**Posted Date:** March 26th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-342566/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

## Introduction:

Diabetic retinopathy (DR), as a serious and specific neurovascular complication of DM, remains the leading cause of vision loss and preventable blindness in adults aged 20–74 years. Several studies have indicated that chronic inflammation plays an important role in DR. Emerging evidence suggests that the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) are novel potential markers of inflammatory responses. However, only a few articles have evaluated the association between these factors and DR.

## Patients and Methods:

The study included 133 patients diagnosed with type 2 diabetes mellitus (T2DM). Retinopathy was graded using the International Clinical Diabetic Retinopathy Disease Severity Scale.

## Results:

The mean NLR, PLR and MLR were significantly higher in patients with DR than in patients without DR ( $p < 0.001$ ,  $p = 0.002$ , and  $p = 0.003$ , respectively). In the post hoc analysis, the PDR group had the highest NLR and MLR values among the three groups. Multiple logistic regression showed that the PLR was an independent risk factor for DR (odds ratio [OR]: 1.022, 95% confidence interval [CI]: 1.005–1.040  $p = 0.013$ ). Based on the receiver operating characteristic (ROC) curve, the cutoff value of PLR as an indicator for DR diagnosis was projected to be 78.70 and yielded a sensitivity and specificity of 80.7% and 48.9%, respectively, with an area under the curve of 0.669 (95% CI: 0.572–0.765,  $P = 0.002$ ).

## Conclusions:

Our results suggest that PLR may be an independent risk factor for evaluating DR in patients with type 2 diabetes.

# Introduction

Diabetes mellitus (DM) is a systemic metabolic disorder. Chronic hyperglycemia can lead to a variety of long-term micro- and macrovascular complications<sup>[1]</sup>. Diabetic retinopathy (DR) is the most common complication of DM, with an overall prevalence of approximately 35% in diabetic patients<sup>[2, 3]</sup>. DR, as a serious and specific neurovascular complication of DM, remains the leading cause of vision loss and preventable blindness in adults aged 20–74 years<sup>[4–6]</sup>. Many studies have implicated that chronic inflammation plays an important role in insulin resistance and DM development<sup>[1, 7, 8]</sup>. Moreover, accumulated evidence has shown that inflammation also plays a key part in the development and progression of DR<sup>[9–11]</sup>.

Accumulating evidence suggests that the white blood cell (WBC) count and its subtypes, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR), are potential novel indicators of systemic inflammation in various diseases<sup>[12–18]</sup>. Interestingly, increasing evidence has shown that they are also prognostic factors for DM and related complications<sup>[19–21]</sup>. However, only a few articles have evaluated the association between these factors and DR. Based on this background, the present study aimed to evaluate the relationships between DR and the NLR, PLR, and MLR.

## Materials And Methods

### Patients and data collection

This study was conducted between January 2018 and February 2020 in the Department of Endocrinology and Metabolism of Chengdu Fifth People's Hospital in Chengdu. Patients who were diagnosed with T2DM were enrolled in this study. The diagnosis of type 2 diabetes was made according to the 1999 World Health Organization criteria<sup>[22]</sup>. Patients were excluded if they were younger than 18 years old or had type 1 diabetes mellitus, pregnancy, any acute inflammation, active infection, glaucoma, malignant tumors, recent surgery, chronic liver or heart diseases, connective tissue diseases, or inflammatory bowel diseases. The study was approved by the Ethics Committee of Chengdu Fifth People's Hospital.

The following clinical data were collected from all participants: age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), smoking, history of hypertension and dietary compliance. Laboratory variables included glycosylated hemoglobin A1c (HbA1c), total bilirubin (TBL), albumin, serum creatinine (Scr), blood urea nitrogen (BUN), uric acid (UA), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL). Mean platelet volume (MPV), plateletcrit (PCT) and platelet distribution width (PDW) levels were gathered from patients' complete blood counts.

### Definitions Of Terms

The NLR, PLR, and MLR were calculated as the ratios of the absolute peripheral neutrophils, platelets, and monocytes to lymphocytes, respectively. All counts were obtained from the same automated blood sample measurement collected at the time of admission to the study. DR was evaluated according to the International Clinical Diabetic Retinopathy Disease Severity Scale<sup>[23]</sup>.

### Statistical analysis

All statistical analyses were performed using SPSS version 23.0 and GraphPad Prism 6. All data are expressed as the mean (SD, standard deviation) for normally distributed numerical variables and median (IQR, interquartile range) for nonnormally distributed numerical variables. Categorical variables are presented as numbers (percentages). The Kolmogorov–Smirnov test was used to evaluate the

distribution of variables. We performed Student's t-tests and one-way ANOVA for continuous variables with normal distribution, the Mann–Whitney U or Kruskal-Wallis H test for continuous variables without normal distribution, and the chi-square test for categorical variables. Multivariable logistic regression analysis was conducted to assess the independent risk factors for DR. Receiver operating curve (ROC) analysis was used to calculate cutoff values. Significance was defined as a two-sided *P*-value of < 0.05.

## Results

Finally, a total of 133 patients were enrolled in the study. They were divided into three groups: 45 control subjects with T2DM, 75 diabetic subjects with nonproliferative diabetic retinopathy (NPDR), and 13 patients with proliferative diabetic retinopathy (PDR). The baseline demographic and clinical characteristics of all 133 subjects are described in Table 1 and Table 2. The groups were similar in terms of sex, BMI, smoking, SBP, DBP, UA, TC, LDL-C, WBCs, monocytes, MPV, and PDW ( $P > 0.05$ ). Compared with the patients without DR, DR patients were older; had a longer diabetes duration; had higher levels of Scr, BUN, HDL-C, neutrophils, and PLT; and had a higher proportion of hypertension. However, the levels of TBL, TG, and Hgb were lower in DR patients ( $P < 0.05$ ).

Table 1  
Patients' baseline and clinical characteristics.

Variable	DM (n = 45)	DR (n = 88)	P
Age (years)	47.76 ± 11.48	59.58 ± 10.38	< 0.001
Male sex (%)	29(64.4)	44(50.0)	0.113
Duration of DM (years),range	3(1–14)	10.5(1–25)	< 0.001
BMI (kg/m <sup>2</sup> )	24.77 ± 3.76	24.11 ± 3.21	0.382
Smoking (%)	17(37.8)	27(30.7)	0.411
Hypertension (%)	15(33.3)	46(52.3)	0.038
SBP (mmHg)	126(121–135)	130(124–143)	0.051
DBP (mmHg)	79(74–85)	80(75–85)	0.858
HbA1c (%)	8.98 ± 2.06	9.45 ± 2.24	0.246
TBL(mmol/L)	10.20 (7.35–14.75)	8.20 (5.75–11.20)	0.032
Albumin (g/dL)	43.56 ± 3.35	41.28 ± 4.86	0.002
Scr (umol/L)	56.10 (49.30–65.10)	65.60 (51.75–81.75)	0.006
BUN (mg/dL)	5.66 (4.44–6.73)	7.04 (5.85–8.63)	< 0.001
UA (umol/L)	299.00 (258.00–383.00)	334.50 (253.00–406.00)	0.208
TG (mmol/L)	2.56 (1.30–3.77)	1.75 (1.15–2.48)	0.016
TC (mmol/L)	4.78 (4.32–5.38)	4.68 (4.12–5.55)	0.816
HDL-C (mmol/L)	0.99 (0.88–1.29)	1.18 (0.97–1.38)	0.025
LDL-C (mmol/L)	2.47 ± 0.65	2.56 ± 0.90	0.485
WBCs (10 <sup>9</sup> /L)	6.14 ± 1.11	6.32 ± 1.56	0.438
Neutrophils (10 <sup>9</sup> /L)	4.11 ± 0.80	4.55 ± 1.11	0.019
Lymphocytes (10 <sup>9</sup> /L)	1.97 ± 0.34	1.81 ± 0.38	0.026

Data are expressed as mean ± SD, median (inter-quartile range), or percentage; n, number of patients; DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TBL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; Hgb, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio;

Variable	DM (n = 45)	DR (n = 88)	P
Monocytes (10 <sup>9</sup> /L)	0.38 ± 0.51	0.34 ± 0.11	0.079
Platelets (10 <sup>9</sup> /L)	162.67 ± 43.51	186.76 ± 51.22	0.005
Hgb (g/dL)	141.71 ± 17.87	128.62 ± 19.93	< 0.001
MPV (fL)	12.63 ± 1.61	12.41 ± 1.75	0.361
PCT (%)	0.21 ± 0.05	0.21 ± 0.05	0.990
PDW (fL)	16.60 (16.50–16.70)	16.50 (16.30–16.70)	0.132
NLR	2.15 ± 0.53	2.60 ± 0.76	< 0.001
PLR	85.77 ± 29.76	108.38 ± 40.96	0.002
MLR	0.16 ± 0.06	0.20 ± 0.06	0.003
<p>Data are expressed as mean ± SD, median (inter-quartile range), or percentage; n, number of patients; DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TBL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; Hgb, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio;</p>			

Table 2

Comparison of clinical characteristics and hematological parameters in patients with and without retinopathy and its severity

Variable	DM (n = 45)	NPDR (n = 73)	PDR (n = 15)	P
Age (years)	47.76 ± 11.48 <sup>*,#</sup>	60.63 ± 10.05 <sup>*,†</sup>	54.47 ± 10.80 <sup>#,†</sup>	< 0.001
Male sex (%)	29(64.4)	38(52.1)	6(40.0)	0.198
Duration of DM (years),range	3(1–14) <sup>*,#</sup>	11(1–25) <sup>*</sup>	12(5–23) <sup>#</sup>	< 0.001
BMI (kg/m <sup>2</sup> )	24.77 ± 3.76	23.94 ± 2.88	25.60 ± 4.37	0.156
Smoking (%)	17(37.8)	23(31.5)	4(26.7)	0.667
Hypertension (%)	15(33.3) <sup>*</sup>	41(56.2) <sup>*</sup>	5(33.3)	0.032
SBP (mmHg)	126(121–135)	130(125–143)	125(123–142)	0.098
DBP (mmHg)	79(74–85)	80(75–85)	80(69–87)	0.932
HbA1c (%)	8.98 ± 2.06 <sup>#</sup>	9.26 ± 2.12 <sup>†</sup>	10.84 ± 2.24 <sup>#,†</sup>	0.009
TBL(mmol/L)	10.20 (7.35–14.75)	8.50 (6.05–11.50)	6.90 (4.60–10.10)	0.074
Albumin (g/dL)	43.56 ± 3.35 <sup>*,#</sup>	41.84 ± 4.72 <sup>*,†</sup>	38.57 ± 4.75 <sup>#,†</sup>	0.001
Scr (umol/L)	56.10 (49.30–65.10) <sup>*,#</sup>	66.30 (51.70–77.40) <sup>*</sup>	61.30 (54.10–82.50) <sup>#</sup>	0.022
BUN (mg/dL)	5.66 (4.44–6.73) <sup>*,#</sup>	7.16 (5.88–8.53) <sup>*</sup>	6.71 (5.77–6.94) <sup>#</sup>	< 0.001
UA (umol/L)	299.00 (258.00–383.00)	333.00 (245.00–396.00)	367.00 (279.00–424.00)	0.267
TG (mmol/L)	2.56 (1.30–3.77) <sup>*</sup>	1.70 (1.08–2.45) <sup>*</sup>	2.12 (1.59–3.76)	0.013
TC (mmol/L)	4.78 (4.32–5.38)	4.70 (4.17–5.34)	4.66 (3.94–6.64)	0.851
HDL-C (mmol/L)	0.99 (0.88–1.29)	1.18 (0.96–1.41)	1.15 (0.98–1.26)	0.079
LDL-C (mmol/L)	2.47 ± 0.65	2.54 ± 0.86	2.66 ± 1.10	0.933

Data are expressed as mean ± SD, median (inter-quartile range), or percentage; n, number of patients; DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TBL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; Hgb, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; \*Significant difference between DM and NPDR. # Significant difference between DM and PDR; † Significant difference between PDR and NPDR;

Variable	DM (n = 45)	NPDR (n = 73)	PDR (n = 15)	P
WBCs (10 <sup>9</sup> /L)	6.14 ± 1.11	6.30 ± 1.55	6.4 ± 1.65	0.763
Neutrophils (10 <sup>9</sup> /L)	4.11 ± 0.80	4.52 ± 1.10	4.68 ± 1.29	0.054
Lymphocytes (10 <sup>9</sup> /L)	1.97 ± 0.34 <sup>#</sup>	1.86 ± 0.32 <sup>†</sup>	1.53 ± 0.52 <sup>#,†</sup>	0.003
Monocytes (10 <sup>9</sup> /L)	0.38 ± 0.51	0.35 ± 0.11	0.33 ± 0.06	0.215
Platelets (10 <sup>9</sup> /L)	162.67 ± 43.51 <sup>*,#</sup>	185.03 ± 50.71 <sup>*</sup>	195.20 ± 54.69 <sup>#</sup>	0.023
Hgb (g/dL)	141.71 ± 17.87 <sup>*,#</sup>	130.43 ± 19.37 <sup>*</sup>	125.83 ± 20.98 <sup>#</sup>	< 0.001
MPV (fL)	12.63 ± 1.61	12.28 ± 1.24	13.01 ± 1.08	0.155
PCT (%)	0.21 ± 0.05 <sup>#</sup>	0.21 ± 0.05 <sup>†</sup>	0.17 ± 0.05 <sup>#,†</sup>	0.021
PDW (fL)	16.60 (16.50–16.70)	16.50 (16.30–16.70)	16.50 (16.20–16.70)	0.100
NLR	2.15 ± 0.53 <sup>*,#</sup>	2.47 ± 0.69 <sup>*,†</sup>	3.21 ± 0.81 <sup>#,†</sup>	< 0.001
PLR	85.77 ± 29.76 <sup>*,#</sup>	101.97 ± 33.32 <sup>*</sup>	139.55 ± 58.83 <sup>#</sup>	0.001
MLR	0.16 ± 0.06 <sup>*,#</sup>	0.19 ± 0.06 <sup>*,†</sup>	0.23 ± 0.07 <sup>#,†</sup>	0.001
<p>Data are expressed as mean ± SD, median (inter-quartile range), or percentage; n, number of patients; DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TBL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; Hgb, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; *Significant difference between DM and NPDR. # Significant difference between DM and PDR; † Significant difference between PDR and NPDR;</p>				

The mean HbA1c (%) values was higher and significantly different in the PDR group compared to the other two study groups (10.84 ± 2.24 in PDR group, 9.26 ± 2.12 in NPDR group, and 8.98 ± 2.06 in controls, P = 0.006 in PDR versus NPDR, and P = 0.003 in PDR versus control). There was no significant difference between the NPDR and control groups (P = 0.510). The albumin level in the control group (43.56 ± 3.35) was higher than that in the NPDR (41.84 ± 4.72) and PDR groups (38.57 ± 4.75, P = 0.037, and P < 0.001, respectively). When comparing the NPDR and PDR groups, the NPDR group was significantly higher than the PDR group (P = 0.008). There was a significant difference in lymphocyte values between the DR group and the control group (1.81 ± 0.38 versus 1.97 ± 0.34, P = 0.026). The PDR group had the lowest lymphocyte values among the groups (1.53 ± 0.52 in the PDR group, 1.86 ± 0.32 in the NPDR group, and 1.97 ± 0.34 in controls, P = 0.024 in PDR versus NPDR, and P = 0.002 in PDR versus control). There was no

significant difference between the NPDR and control groups ( $P = 0.417$ ). The PDR group had lower levels of PCT (%) than the other two study groups ( $0.17 \pm 0.05$  in the PDR group,  $0.21 \pm 0.05$  in the NPDR group, and  $0.21 \pm 0.05$  in the controls,  $P = 0.005$  and  $P = 0.027$ , respectively), but there was no significant difference between the NPDR and control groups ( $P = 0.480$ ).

The mean NLR values were  $3.21 \pm 0.81$  in the PDR group,  $2.47 \pm 0.69$  in the NPDR group, and  $2.15 \pm 0.53$  in the controls. The NLR value in the DR group was significantly higher than that in the control group ( $P < 0.001$ ), and the PDR group had the highest NLR values among the groups ( $P = 0.009$  in the NPDR group versus controls,  $P < 0.001$  in the PDR group versus controls, and  $P < 0.001$  in the PDR group versus the NPDR group). The mean PLR was  $85.77 \pm 29.76$  in the control group,  $101.97 \pm 33.32$  in the NPDR group, and  $139.55 \pm 58.83$  in the PDR group. There was a significant difference between the three groups regarding the PLR ( $P = 0.001$ ). In the post hoc analysis, the values of the NPDR and PDR groups were significantly higher than those of the control group ( $P = 0.037$  in the NPDR group versus controls, and  $P = 0.001$  in the PDR group versus controls), yet there was an insignificant difference between the NPDR and PDR groups ( $P = 0.080$ ). There was a significant difference among the 3 groups with regard to the MLR ( $P = 0.001$ ). The mean MLR values were  $0.23 \pm 0.07$  in the PDR group,  $0.19 \pm 0.06$  in the NPDR group, and  $0.16 \pm 0.06$  in the controls. The PDR group had the highest MLR values among the groups ( $P = 0.020$  in the NPDR group versus controls,  $P < 0.001$  in the PDR group versus controls, and  $P = 0.022$  in the PDR group versus the NPDR group).

The multiple logistic regression analysis revealed that independent risk factors for DR were age ( $P = 0.023$ ), DM duration ( $P < 0.001$ ), BUN ( $P = 0.005$ ), and PLR ( $P = 0.013$ ), as shown in Table 3.

Table 3  
multivariate analysis of DR in patients with T2DM

Characteristics	OR	95%CI	P
Age (years)	1.071	1.010–1.036	0.023
Duration of DM (years)	1.293	1.143–1.461	0.000
BUN (mg/dL)	1.615	1.153–2.261	0.005
PLR	1.022	1.005–1.040	0.013
DR, diabetic retinopathy; T2DM, type 2 diabetes mellitus; BUN, blood urea nitrogen; PLR, platelet-to-lymphocyte ratio; 95% CI, 95% Confidence interval; OR, Odds Ratio;			

Figure 1 shows that as an independent risk factor for DR, the cutoff value of the PLR was 78.70, and the sensitivity and specificity of the PLR for DR diagnosis were 80.7% and 48.9%, respectively, with an area under the curve of 0.669 (95% CI: 0.572–0.765,  $P = 0.002$ ).

## Discussion

By 2015, more than 415 million people worldwide had been diagnosed with diabetes, and its incidence was gradually increasing<sup>[5]</sup>. Diabetes can lead to a range of macrovascular and microvascular complications, such as cardiovascular disease, stroke, kidney disease and retinopathy<sup>[24]</sup>. Diabetic retinopathy is the most severe ocular diabetes mellitus and is also the main cause of blindness in middle-aged and elderly people. Several stages of diabetic retinopathy include mild nonproliferative abnormalities characterized by increased vascular permeability, moderate and severe nonproliferative diabetic retinopathy (NPDR) characterized by vascular occlusion, and proliferative diabetic retinopathy (PDR) characterized by neovascularization of the retina and posterior vitreous surface<sup>[6]</sup>. Early changes in diabetic retinopathy are usually asymptomatic, and the condition of many patients has already progressed to irreversible before treatment. Therefore, early detection and timely treatment for primary prevention will help to reduce the risk of vision loss<sup>[25]</sup>.

The risk factors for diabetic retinopathy include the duration of disease, glycemic control, hypertension, diabetic nephropathy, puberty, pregnancy, obesity, and anemia <sup>[26–28]</sup>. Chronic inflammation plays a vital role in the occurrence and development of diabetes and further accelerates the deterioration of microvascular disease and macrovascular disease in diabetic patients. Increasing evidence indicates that inflammation plays an important role in the early and progressive stages of DR. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) are potential new indicators of systemic inflammation, and there is growing evidence that they are related to the progression of DM and its related complications.

Our results suggest that DM patients with DR had significantly higher NLR levels than those without DR, and the NLR was correlated with DR grades. This is in accordance with the findings of Ulu et al<sup>[29]</sup>. In addition, our research found that the MLR and PLR levels of DR patients were also higher than those of patients without DR, which was similar to the results of Yue et al<sup>[30]</sup>. Their study also found a significant increase in the NLR, PLR and MLR in DR patients. In their research, the MLR was considered to be a risk factor for DR. However, in our study, we found that the PLR rather than the MLR was an independent risk factor for DR. Recently, in a study by Wang et al <sup>[31]</sup>, the NLR and PLR levels were found to be significantly higher among DR patients without an associated family history than among NDR patients, and after fully adjusting for confounding factors, they found that the NLR remained an independent risk factor for DR. Interestingly, a meta-analysis of the prognostic value of blood cell-associated inflammation in 31 studies revealed that increased NLR and PLR values could be recommended as biomarkers for the diagnosis of DR<sup>[20]</sup>. This difference may be due to different sample sizes, heterogeneity of the subjects and differences in lifestyle.

Compared with inflammatory cytokines such as interleukin-6, interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ , the calculation methods of the NLR, PLR and LMR are very simple because they can be obtained by peripheral blood examination, which is inexpensive, convenient and easy to explain. In addition, as novel markers to predict DR, the NLR, PLR and LMR show better stability than neutrophil, lymphocyte, and total leukocyte counts when physiological, pathological, and physical factors of the WBC count vary.

We admit that some limitations still exist in our study. First, the present study is a single-center retrospective study. Additionally, due to the lack of follow-up, we were unable to verify the predictive value of the factors in clinical practice. Hence, further research is still required to investigate the role of the PLR in predicting DR among diabetic patients.

## **Conclusions**

In conclusion, the NLR, PLR and MLR are significantly increased in the setting of DR. Our results suggest that the PLR may be an independent risk factor when evaluating type 2 diabetes patients in terms of DR. However, large-scale prospective studies are warranted to further validate these results.

## **Declarations**

### **Acknowledgments**

Not applicable.

### **Authors' contributions**

Hongyi Cao had full access to the data used in this manuscript and is the guarantor of this work. Jing Zeng and Fan Yang wrote the first draft of the manuscript. Min Chen and Qiu Feng performed statistical analyses and edited the manuscript. Haiyan Wan and Jianbo Wang researched data, contributed to discussion. All authors contributed to the study design, data interpretation, and editing of the manuscript for intellectual content and gave final approval for this version to be published.

### **Funding**

This study was supported by the Scientific Research Project of the Health and Family Planning Commission of Sichuan Province [Grant No. 18PJ352] and the Scientific Research Project of the Health and Family Planning Commission of Chengdu Municipal [Grant Nos. 2018094 and 2018090].

### **Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### **Ethics approval and consent to participate**

The study was approved by the Ethics Committee of Chengdu Fifth People's Hospital.

### **Consent for publication**

Not applicable.

## Competing interests

The authors declare that they have no competing interests

## Abbreviations

DM, diabetes mellitus; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TBL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; Hgb, hemoglobin; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio;

## References

- [1] ZHANG Y, SUN X, ICLI B, et al. Emerging Roles for MicroRNAs in Diabetic Microvascular Disease: Novel Targets for Therapy[J]. *Endocrine reviews*, 2017, 38(2): 145-168.
- [2] COLE J, FLOREZ J. Genetics of diabetes mellitus and diabetes complications[J]. *Nature reviews. Nephrology*, 2020, 16(7): 377-390.
- [3] SOLOMON S, CHEW E, DUH E, et al. Diabetic Retinopathy: A Position Statement by the American Diabetes Association[J]. *Diabetes care*, 2017, 40(3): 412-418.
- [4] VUJOSEVIC S, ALDINGTON S, SILVA P, et al. Screening for diabetic retinopathy: new perspectives and challenges[J]. *The lancet. Diabetes & endocrinology*, 2020, 8(4): 337-347.
- [5] SABANAYAGAM C, BANU R, CHEE M, et al. Incidence and progression of diabetic retinopathy: a systematic review[J]. *The lancet. Diabetes & endocrinology*, 2019, 7(2): 140-149.
- [6] FONG D, AIELLO L, GARDNER T, et al. Retinopathy in diabetes[J]. *Diabetes care*, 2004, : S84-87.
- [7] BRENNAN E, MOHAN M, ANDREWS D, et al. Specialized pro-resolving mediators in diabetes: novel therapeutic strategies[J]. *Clinical science (London, England : 1979)*, 2019, 133(21): 2121-2141.
- [8] PITSAVOS C, TAMPOURLOU M, PANAGIOTAKOS D, et al. Association Between Low-Grade Systemic Inflammation and Type 2 Diabetes Mellitus Among Men and Women from the ATTICA Study[J]. *The review of diabetic studies : RDS*, 2007, 4(2): 98-104.
- [9] R BSAM A, PARIKH S, FORT P. Role of Inflammation in Diabetic Retinopathy[J]. *International journal of molecular sciences*, 2018, 19(4).

- [10] DEHDASHTIAN E, MEHRZADI S, YOUSEFI B, et al. Diabetic retinopathy pathogenesis and the ameliorating effects of melatonin; involvement of autophagy, inflammation and oxidative stress[J]. *Life sciences*, 2018, 193: 20-33.
- [11] SPENCER B, ESTEVEZ J, LIU E, et al. Pericytes, inflammation, and diabetic retinopathy[J]. *Inflammopharmacology*, 2020, 28(3): 697-709.
- [12] CORBEAU I, THEZENAS S, MARAN-GONZALEZ A, et al. Inflammatory Blood Markers as Prognostic and Predictive Factors in Early Breast Cancer Patients Receiving Neoadjuvant Chemotherapy[J]. *Cancers*, 2020, 12(9).
- [13] BILEN M, MARTINI D, LIU Y, et al. The prognostic and predictive impact of inflammatory biomarkers in patients who have advanced-stage cancer treated with immunotherapy[J]. *Cancer*, 2019, 125(1): 127-134.
- [14] AVCIL S. Evaluation of the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as inflammatory markers in children with attention-deficit hyperactivity disorder[J]. *Psychiatry and clinical neurosciences*, 2018, 72(7): 522-530.
- [15] KIM H, CHOI H, LEE M, et al. Systemic Inflammatory Response Markers and CA-125 Levels in Ovarian Clear Cell Carcinoma: A Two Center Cohort Study[J]. *Cancer research and treatment*, 2016, 48(1): 250-258.
- [16] CHOI Y, LEE J, LEE S, et al. A High Monocyte-to-Lymphocyte Ratio Predicts Poor Prognosis in Patients with Advanced Gallbladder Cancer Receiving Chemotherapy[J]. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 2019, 28(6): 1045-1051.
- [17] HUANG Y, DENG W, ZHENG S, et al. Relationship between monocytes to lymphocytes ratio and axial spondyloarthritis[J]. *International immunopharmacology*, 2018, 57: 43-46.
- [18] JIN Y, XIE M, YANG C, et al. Prognostic value of peripheral blood markers in patients with myositis-associated interstitial lung diseases[J]. *Scandinavian journal of rheumatology*, 2021, : 1-9.
- [19] LIU J, LIU X, LI Y, et al. The association of neutrophil to lymphocyte ratio, mean platelet volume, and platelet distribution width with diabetic retinopathy and nephropathy: a meta-analysis[J]. *Bioscience reports*, 2018, 38(3).
- [20] LUO W, ZHANG W. The relationship of blood cell-associated inflammatory indices and diabetic retinopathy: a Meta-analysis and systematic review[J]. *International journal of ophthalmology*, 2019, 12(2): 312-323.
- [21] VERDOIA M, SCHAFFER A, BARBIERI L, et al. Impact of diabetes on neutrophil-to-lymphocyte ratio and its relationship to coronary artery disease[J]. *Diabetes & metabolism*, 2015, 41(4): 304-311.

- [22] PUAVILAI G, CHANPRASERTYOTIN S, SRIPHRAPRADAENG A. Diagnostic criteria for diabetes mellitus and other categories of glucose intolerance: 1997 criteria by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (ADA), 1998 WHO consultation criteria, and 1985 WHO criteria. World Health Organization[J]. Diabetes Res Clin Pract, 1999, 44(1): 21-26.
- [23] WILKINSON C, FERRIS F, KLEIN R, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales[J]. Ophthalmology, 2003, 110(9): 1677-1682.
- [24] DEFRONZO R, FERRANNINI E, GROOP L, et al. Type 2 diabetes mellitus[J]. Nature reviews. Disease primers, 2015, 1: 15019.
- [25] OCKRIM Z, YORSTON D. Managing diabetic retinopathy[J]. BMJ (Clinical research ed.), 2010, 341: c5400.
- [26] SCHORR S, HAMMES H, MILLER U, et al. The Prevention and Treatment of Retinal Complications in Diabetes[J]. Deutsches Arzteblatt international, 2016, 113(48): 816-823.
- [27] AHLQVIST E, VAN ZUYDAM N, GROOP L, et al. The genetics of diabetic complications[J]. Nature reviews. Nephrology, 2015, 11(5): 277-287.
- [28] WONG T Y, CHEUNG C M G, LARSEN M, et al. diabetic retinopathy[J]. Nature Reviews Disease Primers, 2016, 2: 16030.
- [29] ULU S, DOGAN M, AHSEN A, et al. Neutrophil-to-lymphocyte ratio as a quick and reliable predictive marker to diagnose the severity of diabetic retinopathy[J]. Diabetes technology & therapeutics, 2013, 15(11): 942-947.
- [30] YUE S, ZHANG J, WU J, et al. Use of the Monocyte-to-Lymphocyte Ratio to Predict Diabetic Retinopathy[J]. International journal of environmental research and public health, 2015, 12(8): 10009-10019.
- [31] WANG J, CHEN Z, YANG K, et al. Association between neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and diabetic retinopathy among diabetic patients without a related family history[J]. Diabetology & metabolic syndrome, 2020, 12: 55.

## Figures

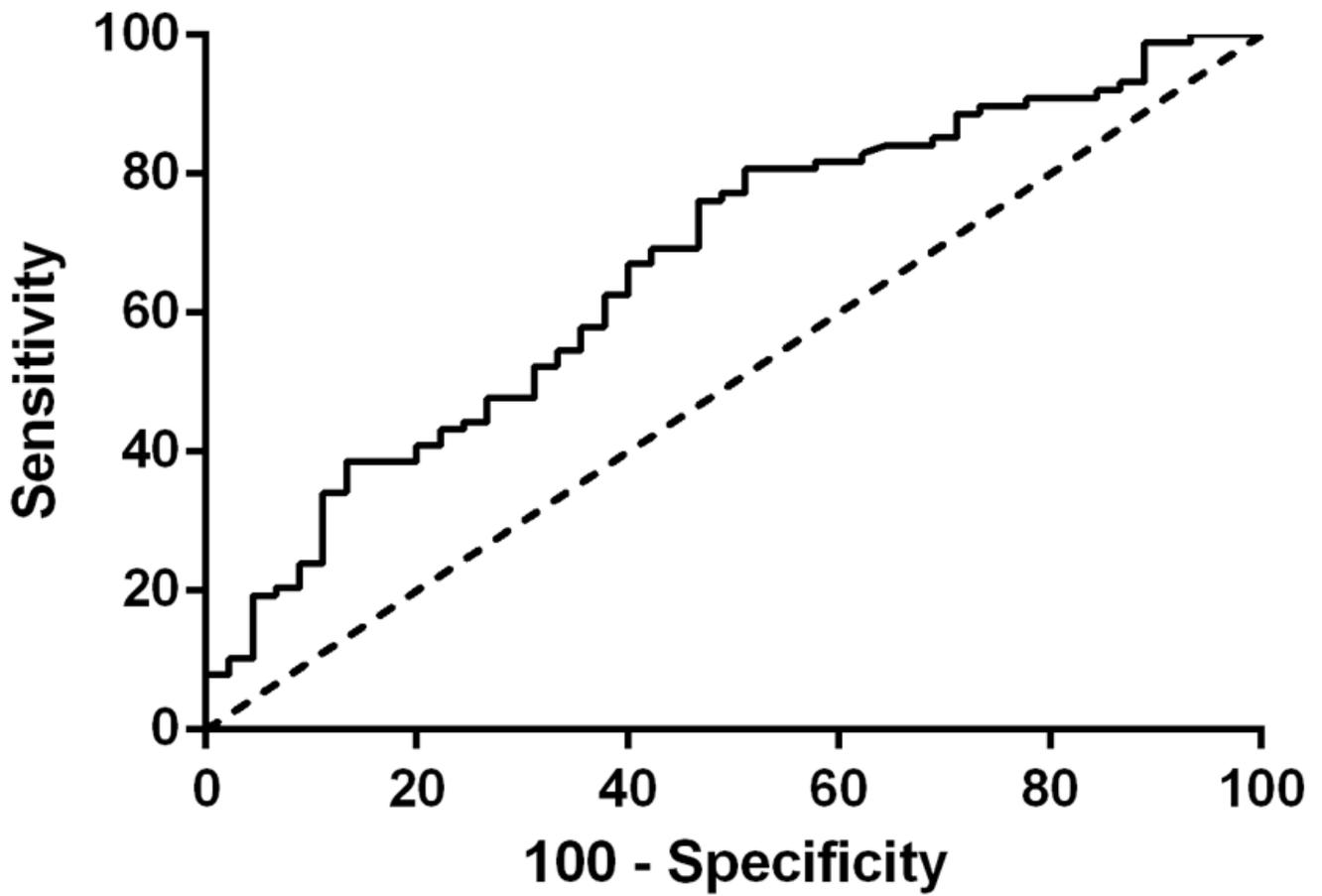


Figure 1

Figure 1 shows that as an independent risk factor for DR, the cutoff value of the PLR was 78.70, and the sensitivity and specificity of the PLR for DR diagnosis were 80.7% and 48.9%, respectively, with an area under the curve of 0.669 (95% CI: 0.572–0.765, P = 0.002).