• Clinical Research •

Pan-immune-inflammation value as a novel biomarker for diabetic retinopathy severity

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Abstract

● **AIM:** To investigate the association between peripheral blood immune-inflammatory biomarkers (PBIBs), including the pan-immune-inflammation value (PIV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) of diabetic retinopathy (DR), to identify novel biomarkers and therapeutic targets.

● **METHODS:** This nested case-control study enrolled 228 patients with type 2 diabetes mellitus (T2DM). Based on the staging criteria outlined in the American Diabetes Association's Position Statement on DR, patients were classified into three groups: diabetes without DR (diabetes mellitus, DM; *n*=75), non-proliferative DR (NPDR, *n*=80), and proliferative DR groups (PDR, *n*=73). Comprehensive clinical data, including fasting blood tests and biochemical profiles, were collected for all subjects. PIV and other PBIBs were calculated based on hematological parameters, specifically the absolute counts of neutrophils, platelets, and monocytes, along with their respective ratios to lymphocytes. Kendall's tau-b analysis assessed the correlation between research indicators and DR severity, while Spearman analysis evaluated the associations with baseline characteristics. Ordinal logistic regression was used to evaluate the predictive performance of peripheral blood molecular markers for DR severity.

● **RESULTS:** The study included 75 patients in the DM group (41 males), aged 60.00y (interquartile range, IQR 56.00, 66.00), 80 patients in the NPDR group (44 males), aged 60.50y (IQR 57.00, 66.00), and 73 patients in the PDR group (43 males) aged 61.00y (IQR 56.50, 68.00). PBIBs, most notably PIV, showed significant intergroup differences and demonstrated positive correlations with the severity of DR (all $P<0.05$). PIV was also significantly positively correlated with age, duration of diabetes and hypertension, fasting blood glucose and glycated hemoglobin. Multivariable ordinal logistic regression analysis revealed that the standardized PIV had the highest odds ratio (OR) [OR=7.76, 95% confidence interval (CI): 3.92–15.36, $P<0.001$]. Compared to the PIV, SIRI (OR=5.07, 95%CI: 2.83–9.07, $P<0.001$), SII (OR=2.00, 95%CI: 1.33–3.00, $P<0.001$), NLR (OR=1.59, 95%CI: 1.08–2.35, $P=0.019$), and PLR (OR=2.11, 95%CI: 1.37–3.25, $P<0.001$) had lower predictive role in comparison with PIV.

● **CONCLUSION:** PIV has higher predictive value than other PBIBs, and is an independent risk factor for DR severity, serving as a novel peripheral blood molecular biomarker for assessing DR progression.

● **KEYWORDS:** diabetic retinopathy; pan-immune inflammation value; peripheral blood immune-inflammatory biomarkers

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INTRODUCTION

Diabetic retinopathy (DR) is the most severe ocular complication of diabetes mellitus (DM) and is the leading cause of blindness among the working-age population[1]. DR is characterized by a range of pathological changes resulting from abnormal glucose metabolism, which ultimately leads to retinal microvascular damage and neuronal degeneration. Beyond established pathological mechanisms, including enhanced oxidative stress, protein kinase C activation, increased polyol pathway flux, and advanced glycation end product accumulation and the four major metabolic pathway abnormalities, immune inflammation recently emerged as a potential pathogenic factor in the development and progression of DR.

Previous research has shown that chronic hyperglycemia-induced retinal ischemia and hypoxia lead to the release of various damage-associated factors, triggering defensive responses and inducing immune inflammation in retinal tissue[2]. Peripheral blood parameters such as platelets, neutrophils, lymphocytes, and monocytes are routinely accessible and function as indicators of systemic immune inflammation, suggesting their potential predictive value in patients with DR. Both clinical studies and animal experiments have confirmed that neutrophils, platelets, and monocytes are abnormally elevated in the peripheral blood of both DR patients and animal models[3-4]. Furthermore, composite immune-inflammatory indices derived from these cellular counts, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV), have demonstrated established prognostic and predictive utility in a range of conditions, including malignancies and cardiovascular diseases[5-6]. However, their relevance in DR is limited.

PIV, calculated as the ratio of neutrophil, platelet, and monocyte counts divided by lymphocyte count, is a multidimensional biomarker that reflects systemic immune-inflammatory status[7-9] in peripheral blood. It serves as a biomarker for both immune activation and a prognosis indicator, emerging as a novel hematological indicator for patients with diabetes, obesity, and metabolic syndrome[10]. However, the role of PIV as a comprehensive indicator of immune response in the pathogenesis of DR has not yet been fully elucidated.

To address this research gap, our study aims to investigate the association of PIV and other peripheral blood immune-inflammatory biomarkers (PBIBs) with DR, identifying novel PBIBs for the early detection of DR.

PARTICIPANTS AND METHODS

Ethical Approval The study protocol was approved by Ethics Committee of Beijing Tongren Hospital in 2016 (TRECKY-2016-054-XZ-1) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Participants This nested case-control study, conducted from 2018 to 2022, included 228 type 2 diabetes mellitus (T2DM) patients who visited Beijing Tongren Hospital, affiliated with Capital Medical University, based on the diagnostic criteria of the 2018 American Diabetes Association (ADA) "Standards of Medical Care in Diabetes"[11]. Diagnosis and staging of DR were based on the 2018 DR position statement[12]. A total of 228 participants of T2DM were stratified into three groups: 75 participants were assigned into the DM group as control; 80 patients were in the non-proliferative DR (NPDR group) and 73 patients were in the proliferative DR (PDR group). Relevant clinical data, such as age, sex, duration of diabetes and high blood pressure (HBP), were documented for subsequent analysis.

Inclusion and Exclusion Criteria The inclusion criteria were as following: patients without neovascularization in either eye were assigned into NPDR group; patients were diagnosed PDR (PDR group) if optic disc and/or retinal neovascularization with or without iris/angle neovascularization was found in at least one eye [neovascularization was confirmed by slit-lamp, fundus photography and optical coherence tomography angiography (OCTA)][12]. Moreover, patients with DM without DR in both eyes were assigned into the DM group[11].

The exclusion criteria were: 1) patients with coexisting ocular diseases including age-related macular degeneration, retinal vein occlusion, macular hole, or glaucoma; 2) patients received intravitreal injections, anti-vascular endothelial growth factor (VEGF) therapy, anterior or posterior segment surgery within 6mo; 3) individuals with ocular media opacity or those unable to tolerate examination due to severe systemic organic diseases; 4) patients with systemic conditions including inflammatory disorders, cardiovascular/cerebrovascular diseases, or immune system abnormalities; 5) patients presenting with other diabetic microvascular complications (*e.g.*, nephropathy and neuropathy).

Biochemical Analysis Fasting blood samples (4 mL) were obtained from the median cubital vein. Glycated hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) levels were measured using an automated biochemical analyzer (XN-9000, Sysmex Corporation, Japan). Complete blood count parameters were analyzed, including platelet distribution width (PDW), platelet count (PLT), mean platelet volume (MPV), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), and absolute monocyte count (AMC).

Definition of PBIBs According to the 2008 Clinical and Laboratory Standards Institute (CLSI) guidelines[13-14], we calculated the following composite hematological indices: the PIV was derived as (neutrophils×platelets×monocytes)/lymphocytes; NLR as neutrophils/lymphocytes; PLR as platelets/lymphocytes; LMR as lymphocytes/monocytes; MLR as monocytes/lymphocytes; SII as (platelets×neutrophils)/lymphocytes; and SIRI as (neutrophils×monocytes)/lymphocytes.

Eye Examinations All participants underwent a comprehensive ophthalmic evaluation. Best-corrected visual acuity (BCVA) was measured using the international standard visual acuity chart. Intraocular pressure was assessed with non-contact tonometry (TX20, Santen, Japan). Anterior segment examination was conducted with a slit-lamp microscope

(SL-IE, Topcon, Japan). Color fundus photographs, centered on the optic disc and macula, were captured bilaterally using a non-mydriatic fundus camera (CR-1, Canon, Japan). Swept-source optical coherence tomography (SS-OCT) imaging was performed with either the DRI OCT1 (Topcon, Japan) or Plex Elite 9000 (Zeiss, Germany) systems, employing a 9 mm×9 mm scanning model to obtain 12 high-resolution B-scans through the foveal center. OCTA images were obtained using a 6 mm×6 mm macular scanning pattern. A single ophthalmologist (Zhang XY) determined DR severity stages according to established international classification standards.

Sample Size Calculation Power Analysis and Sample Size software (PASS15, 202, NCSS LLC, Utah, USA) were used to determine the sample size previously described[15]. With the significance level (α) set at 0.05, statistical power (1-β) at 0.9, a 95% confidence interval (CI), and a permissible error of ±5%[16], based on preliminary PIV data (DM group: 118.30±59.91; NPDR group: 188.62±83.43; PDR group: 336.23±122.93), the calculation indicated a minimum requirement of 25 participants per group. Considering the individual variability and fluctuations inherent and to enhance the statistical robustness, we ultimately increased the sample size to over 50 participants per group.

Statistical Analysis Statistical analysis was conducted using SPSS software (IBM SPSS Statistics version 25.0, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess data distribution. Normally distributed measurement data are presented as mean±standard deviation, while non-normally distributed measurement data are described as median (interquartile range). Intergroup comparisons were conducted using the Chi-square test, one-way analysis of variance (one-way ANOVA), or the Kruskal-Wallis test. Kendall's tau-b correlation analysis was applied to evaluate the relationship between PIV and other research indicators with DR severity. Spearman correlation analysis was used to assess the correlations between the above indicators and age, DM duration, duration of HBP, HbA1c, and FBG. Univariate ordinal logistic regression analysis was used to preliminarily screen potential influencing factors for DR severity, using odds ratio (OR) and 95%CI. A multivariable ordinal logistic regression model was constructed to adjust for confounding factors such as age, gender, duration of DM and HBP, HbA1c, and FBG. The proportional odds assumption (parallel lines assumption) was tested using both global and variable-specific tests to evaluate whether the model satisfied the proportional odds assumption. To compare the relative predictive performance of different PBIBs, these continuous variables were treated as independent variables and standardized using *Z*-score. Standardization was performed using the formula $Z=(x-\mu)/\sigma$, where each original value was centered by subtracting the mean (μ) and scaled by dividing by the standard deviation (σ). By comparing the standardized ORs of each marker, their independent effects on DR severity and their relative predictive capabilities were objectively evaluated. $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics and Intergroup Comparisons The study enrolled 75 patients (75 eyes) in the DM group, 80 patients (80 eyes) in the NPDR group, and 73 patients (73 eyes) in the PDR group, as detailed in Table 1. No significant differences were observed in age or gender distribution among the three groups. However, significant intergroup differences were identified in the duration of DM and HBP, HbA1c, and FBG (all $P<0.001$). Additionally, the levels of several PBIBs, such as PDW, PLT, ANC, PLR, NLR, SII, SIRI, and PIV increased significantly with DR ($P_{PDW}<0.001$, $P_{PLT}<0.001$, $P_{ANC}=0.007$, $P_{PLR}<0.001$, $P_{NLR}<0.001$, $P_{SII}<0.001$, $P_{SIRI}<0.001$, $P_{PIV}<0.001$).

Correlations Between PBIBs and DR Severity with Systemic Factors Kendall's tau-b rank correlation analysis revealed significant positive correlations between PIV, PLR, NLR, SII, and SIRI and DR severity (PIV: $r=0.558$, $P<0.001$; PLR: $r=0.353$, $P<0.001$; NLR: $r=0.302$, $P<0.001$; SII: $r=0.341$, $P<0.001$; SIRI: $r=0.546$, $P<0.001$; Figure 1A).

Spearman correlation analysis further revealed significant positive associations between PIV and systemic parameters. Specifically, PIV correlated with age ($r=0.134$, $P=0.044$), duration of DM ($r=0.552$, $P<0.001$), duration of HBP ($r=0.469$, $P<0.001$), HbA1c ($r=0.516$, $P<0.001$), and FBG ($r=0.401$, $P<0.001$), as shown in Figure 1B.

Predictive Value of PIV and Other PBIBs for DR Severity As shown in Table 2, using DR severity as the dependent variable and the DM group as the reference, univariate ordinal logistic regression analysis demonstrated that PIV (OR=1.02, 95%CI: 1.01–1.02, $P<0.001$), PLR (OR=1.03, 95%CI: 1.02–1.04, $P<0.001$), NLR (OR=2.29, 95%CI: 2.15–3.96, $P<0.001$), SII (OR=1.01, 95%CI: 1.00–1.01, $P<0.001$), and SIRI (OR=4.17, 95%CI: 1.89–9.19, $P<0.001$) were all risk factors for DR severity. Additionally, established risk factors including age (OR=1.05, 95%CI: 1.02–1.08, $P<0.001$), duration of DM (OR=1.52, 95%CI: 1.40–1.65, $P<0.001$), duration of HBP (OR=1.21, 95%CI: 1.15–1.27, $P<0.001$), HbA1c (OR=5.39, 95%CI: 3.84–7.56, $P<0.001$), and FBG (OR=1.88, 95%CI: 1.61–2.21, $P<0.001$) were also associated with increased DR severity.

To further assess the independent predictive value of PBIBs for DR development and compare their relative predictive efficacy, we established multivariable ordinal logistic regression models, and verified the proportional odds

Table 1 Comparison of baseline demographic characteristics across the DM, NPDR, and PDR groups

Variables	DM	NPDR	PDR	$H/\chi^2/F$	*P*
Number	75	80	73	-	-
Age, y	60.00 (56.00, 66.00)	60.50 (57.00, 66.00)	61.00 (56.50, 68.00)	1.98[b]	0.372
Gender (male/female)	41/34	44/36	43/30	0.34[c]	0.846
Duration of DM, y	6.00 (4.00, 8.00)	12.00 (10.00, 15.00)	15.00 (12.00, 20.00)	133.99[b]	<0.001[d]
Duration of HBP, y	1.00 (0, 5.00)	4.00 (0, 10.00)	10.00 (8.00, 11.50)	73.33[b]	<0.001[d]
HbA1c, %	6.20 (5.90, 6.60)	7.40 (6.80, 8.30)	8.50 (7.95, 9.60)	134.51[b]	<0.001[d]
FBG, mmol/L	6.20 (5.80, 6.80)	7.53 (6.32, 8.96)	9.13 (7.99, 10.83)	85.41[b]	<0.001[d]
PDW, fL	12.20 (10.30, 13.90)	16.00 (11.45, 16.50)	15.30 (11.85, 16.45)	14.68[b]	<0.001[d]
PLT, 10^9/L	214.24±33.75	224.83±39.96	241.97±46.20	8.94[a]	<0.001[d]
MPV, fL	9.90 (9.10, 10.80)	9.50 (8.70, 10.98)	10.10 (9.10, 10.90)	2.13[b]	0.344
ALC, 10^9/L	2.21 (1.90, 3.00)	2.00 (1.80, 2.13)	1.88 (1.60, 2.15)	25.51[b]	<0.001[d]
ANC, 10^9/L	3.91 (3.35, 4.70)	4.13 (3.49, 4.98)	4.40 (3.77, 5.31)	9.90[b]	0.007[d]
AMC, 10^9/L	0.30 (0.23, 0.37)	0.40 (0.30, 0.49)	0.58 (0.50, 0.60)	118.82[b]	<0.001[d]
LMR	8.48 (5.97,10.33)	5.08 (4.07, 6.70)	3.42 (2.77, 4.13)	115.23[b]	<0.001[d]
MLR	0.12 (0.10, 0.17)	0.20 (0.15, 0.25)	0.29 (0.24, 0.36)	115.23[b]	<0.001[d]
PLR	91.36 (69.66, 118.09)	115.76 (95.54, 130.11)	132.45 (107.93, 157.06)	44.89[b]	<0.001[d]
NLR	1.79±0.66	2.12±0.64	2.50±0.78	20.06[a]	<0.001[d]
SII	374.57 (255.30, 487.23)	477.32 (373.93, 550.37)	587.39 (450.16, 764.13)	41.54[b]	<0.001[d]
SIRI	0.48 (0.35, 0.69)	0.82 (0.60, 1.07)	1.36 (0.99, 1.77)	106.00[b]	<0.001[d]
PIV	102.12 (73.52, 152.89)	181.82 (142.62, 238.78)	320.39 (236.45, 441.10)	108.70[b]	<0.001[d]

[a]One-way analysis of variance (ANOVA); [b]Non-parametric Kruskal-Wallis test; [c]Chi-square test; [d]*P*<0.05. DM: Diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; HBP: High blood pressure; HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; PDW: Platelet distribution width; PLT: Platelet count; MPV: Mean platelet volume; ALC: Absolute lymphocyte count; ANC: Absolute neutrophil count; AMC: Absolute monocyte count; LMR: Lymphocyte-to-monocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; PIV: Pan-immune-inflammation value.

assumption, as shown in Figure 2. We used the proportional odds assumption test to evaluate whether the model satisfied the parallel lines assumption. The results showed no significant difference in the overall test or the variable-by-variable test (*P*>0.05), suggesting that the model met the proportional odds assumption and supported the use of the ordinal logistic regression model for analysis. The study used the standardized PBIBs as independent variables, and the DR severity classification as the dependent variable. After adjusting for age, gender, duration of DM and HBP, HbA1c, and FBG, the analysis revealed that standardized PIV, SII, SIRI, PLR, and NLR all remained independent risk factors for DR progression. However, their predictive efficacy of these indices for DR progression differed. Among all model, the standardized PIV showed the highest OR (OR=7.76, 95%CI: 3.92–15.36, *P*<0.001), far exceeding those of other indices: standardized SIRI (OR=5.07, 95%CI: 2.83–9.07, *P*<0.001), standardized SII (OR=2.00, 95%CI: 1.33–3.00, *P*<0.001), standardized NLR (OR=1.59, 95%CI: 1.08–2.35, *P*=0.019), and standardized PLR (OR=2.11, 95%CI: 1.37–3.25, *P*<0.001). This suggests that each standard deviation increase in PIV multiplies the odds of DR severity progression by 7.76-fold.

DISCUSSION

Elevated PIV levels were significantly positively correlated with DR severity. Multivariable ordinal logistic regression analysis, after adjusting for traditional DR risk factors, confirmed PIV as an independent risk factor for DR progression. The standardized PIV exhibited the strongest association with DR severity progression, suggesting that PIV possesses the highest predictive capability among other inflammatory indices. Together, these findings establish PIV as a promising PBIB for assessing DR severity, providing a valuable tool for clinical screening and stratification of DR patients.

PIV is a comprehensive peripheral blood molecular biomarker that integrate neutrophil, platelet, monocyte, and lymphocyte counts[7-9,17]. Previous studies have documented significantly elevated PIV levels in metabolic disorders including diabetes

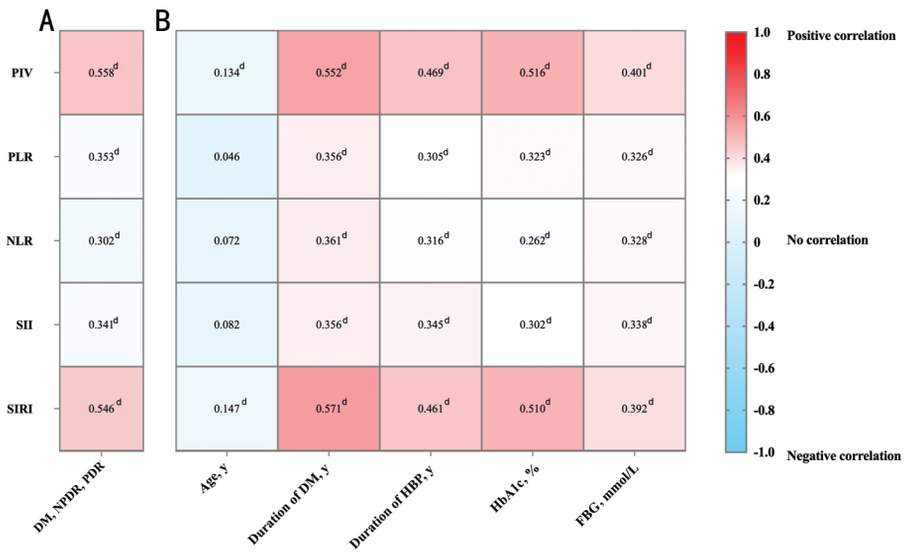


Figure 1 Correlation of PBIBs with DR severity and traditional risk factors A: Kendall's tau-b analysis shows positive correlations between PIV, PLR, NLR, SII, SIRI, and DR severity; B: Spearman analysis shows that PIV and other PBIBs have positive correlations with age, DM duration, HBP duration, HbA1c, and FBG. $^{d}P<0.05$. Values in the grids represent the correlation coefficient (*r*). PIV: Pan-immune-inflammation value; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; DM: Diabetes mellitus; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; HBP: High blood pressure; HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; PBIBs: Peripheral blood immune-inflammatory biomarkers; DR: Diabetic retinopathy.

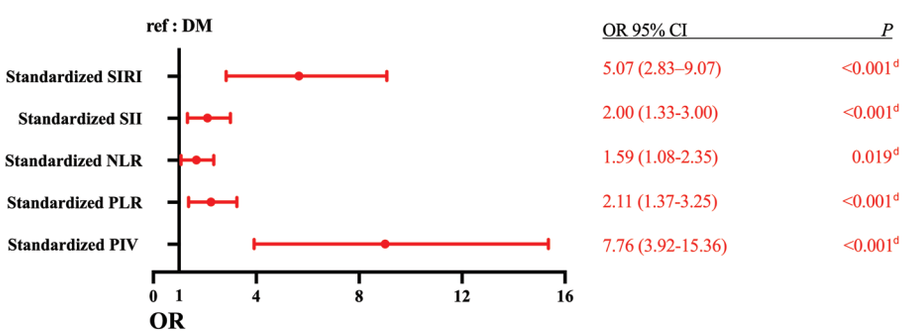


Figure 2 Multivariable ordinal logistic regression analysis identifies PBIBs as independent risk factors for DR All models were adjusted for age, sex, DM duration, HBP duration, FBG, and HbA1c. The analysis confirms that the PIV, PLR, NLR, SII, and SIRI are independent risk factors for DR severity. The OR for PIV was significantly higher than that of other PBIBs. $^{d}P<0.05$. DM: Diabetes mellitus; HBP: High blood pressure; SIRI: Systemic inflammation response index; SII: Systemic immune-inflammation index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PIV: Pan-immune-inflammation value; ref: Reference; OR: Odds ratio; CI: Confidence interval; PBIBs: Peripheral blood immune-inflammatory biomarkers; DR: Diabetic retinopathy; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c.

and obesity, where it correlates positively with insulin resistance[10]. Our current findings further identified PIV as both an independent risk factor and a reliable biomarker for DR severity.

Our results align with those of Bulu and Keser[18], who reported PIV as a predictor of DR progression. However, their intergroup comparisons (DM, NPDR, PDR) did not adjust for confounders. We addressed this by performing correlation and univariate ordinal logistic regression, and further applying *Z*-score transformation to all indicators in a multivariate model adjusting for DM duration, HBP duration, HbA1c, and FBG. This approach enabled unbiased estimation of PIV's independent effect on DR grading. Moreover, while Candan *et al*[19] proposed PIV for early PDR detection, we extend their work by using *Z*-score standardization to provide a more objective statistical basis.

Neutrophils, a key cellular component integrated in the PIV calculation, show a significant positive correlation between their elevated absolute counts and the severity of DR. These cells contribute directly to vascular endothelial damage and blood-retinal barrier disruption through the release of reactive oxygen species[20], matrix metalloproteinase-9[21-22], and elastase[23], thereby accelerating DR progression. Furthermore, hyperglycemic conditions promote the formation of neutrophil

Table 2 Univariate ordinal logistic regression

Variables	OR (95%CI)	*P*
Age, y	1.05 (1.02–1.08)	<0.001[d]
Gender (ref: male)	0.88 (0.55–1.43)	0.610
Duration of DM, y	1.52 (1.40–1.65)	<0.001[d]
Duration of HBP, y	1.21 (1.15–1.27)	<0.001[d]
HbA1c, %	5.39 (3.84–7.56)	<0.001[d]
FBG, mmol/L	1.88 (1.61–2.21)	<0.001[d]
PIV	1.02 (1.01–1.02)	<0.001[d]
PLR	1.03 (1.02–1.04)	<0.001[d]
NLR	2.29 (2.15–3.96)	<0.001[d]
SII	1.01 (1.00–1.01)	<0.001[d]
SIRI	4.17 (1.89–9.19)	<0.001[d]

[d]*P*<0.05. Univariate logistic regression analysis identified several risk factors for DR progression when using the DM group as reference. These included duration of DM, duration of HBP, HbA1c, FBG, PIV, PLR, NLR, SII, SIRI. OR: Odds ratio; CI: Confidence interval; DM: Diabetes mellitus; HBP: High blood pressure; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; PIV: Pan-immune-inflammation value; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; DR: Diabetic retinopathy.

extracellular traps, which exacerbate retinal oxidative stress through the generation of superoxide[24-25]. Platelets contribute to DR pathogenesis through dual mechanisms. Under hyperglycemia conditions, increased secretion of platelet-derived growth factor induces retinal pericyte apoptosis and microvascular injury. Concurrently, elevated MPV in high-glucose environments facilitates microthrombus formation, thereby collectively exacerbating DR pathology[18].

Beyond neutrophils and platelets, monocytes and lymphocytes represent essential components of PIV. In DR patients, circulating monocytes release proinflammatory microparticles that exacerbate microvascular damage through procoagulant, adhesive, and oxidative stress pathways, thereby significantly contributing to disease progression[26-27]. In contrast, lymphocytes exert anti-inflammatory and endothelial-protective effects[28], playing a crucial role in adaptive immune regulation during DR[29]. By secreting anti-inflammatory cytokines including interleukin-10 and tumor necrosis factor (TNF)-β, lymphocytes help suppress excessive inflammation and limit retinal injury[29].Therefore, by comprehensively integrating the pathophysiological alterations of these four leukocyte subsets, PIV provides a systemic reflection of the inflammatory condition in DR, offering an objective tool for evaluating disease severity.

Emerging evidence further indicates that PIV demonstrates superior predictive performance compared to other inflammatory indices, including SII and SIRI, across various pathological conditions such as rheumatoid arthritis[30], myocardial infarction[9], and stroke[31]. This advantage may be attributed to the fact that PIV incorporates four distinct hematological parameters (platelets, neutrophils, monocytes, and lymphocytes), thereby providing a more complete reflection of the inflammatory state in DR progression. In contrast, SIRI and SII integrate only three cellular components, while PLR and NLR merely two parameters, thus constraining their ability to fully capture the complex inflammatory landscape. Collectively, through its multidimensional integration of key inflammatory cells, PIV exhibits enhanced comprehensiveness and greater clinical potential for evaluating inflammatory status and monitoring disease progression in DR.

We found that both the SII and SIRI were positively correlated with DR severity, establishing them as risk factors for disease progression. These findings are consistent with previous reports by Wang *et al*[32]. Both SII and SIRI have demonstrated close relationships with DM, with SII specifically showing utility in predicting and evaluating diabetic nephropathy[32]. Metabolic disturbances induced by hyperglycemia and insulin resistance has been shown to significantly impact the level of PBIBs[33], including the SII and SIRI. The hyperglycemic condition promotes metabolic abnormalities in circulating blood cells through enhanced glucose uptake, accelerated aerobic glycolysis, exacerbated oxidative stress, and metabolite accumulation, ultimately disrupting neutrophil and monocyte homeostasis[34].

Elevated SII, which reflects systemic inflammation and immune dysregulation, may exacerbate DR progression by promoting microvascular dysfunction through endothelial damage, increased vascular permeability, heightened vascular resistance, and platelet aggregation. SIRI, a composite index balancing neutrophil, monocyte, and lymphocyte counts, is clinically useful for early detection, prognostic assessment, and treatment monitoring across various pathologies. By quantifying the balance between innate and adaptive immunity, SIRI serves as a valuable indicator of pathological processes in DR[35-39].

Elevated PLR was significantly positively correlated with DR severity, suggesting its potential as a risk factor for disease progression, consistent with Ghosh *et al*[40]. PLR integrates platelet and lymphocyte counts. Chronic hyperglycemia-driven oxidative stress has been shown to reduce lymphocyte populations[33], while DR patients simultaneously exhibit enhanced platelet activation that releases multiple inflammatory mediators contributing to vascular damage and inflammatory responses[40]. Therefore, as a biological biomarker reflecting platelets and lymphocytes, the abnormal elevation of PLR may be related to inflammation activation mediated by the

hyperglycemic environment and microvascular damage caused by platelets[32,41].

This study showed that elevated NLR was positively correlated with DR severity, establishing NLR was a risk factor for DR progression. This is consistent with previous studies by Ulu *et al*[42] and Wang *et al*[43], who similarly observed associations between NLR and DR severity. Furthermore, the study by Bulu and Keser[18] showed that NLR possesses high predictive performance for DR (detection sensitivity: 0.85). Although Liu *et al*[44] confirmed an association between NLR and the occurrence of DR, they found no clear correlation with specific DR severity stages. The predictive utility of NLR has been widely explored in various retinal diseases, including DR, diabetic macular edema, and retinal vein occlusion[45], highlighting its clinical relevance in evaluating ocular inflammatory conditions.

Spearman correlation analysis revealed significant positive correlations between the PIV and established DR risk factors, after controlling for age, duration of DM and HBP, HbA1c, and FBG levels. This finding aligns with studies by Ma *et al*[46] and Okyar Baş *et al*[47], which link elevated PIV to increasing age, supporting the concept that aging is a state of chronic inflammation that accelerates disease progression. Wu *et al*[48] further identified increased PIV as a predictor of all-cause and cardiovascular mortality in hypertensive patients, potentially mediated through elevated circulating inflammatory cytokines that exacerbate endothelial dysfunction, vascular remodeling, and arterial stiffness. Furthermore, Ramasamy *et al*[10] also documented significant variations in PIV across different metabolic states, with both diabetic and pre-diabetic individuals showing higher values than normoglycemic controls. Taken together, PIV's strong correlation with multiple traditional DR risk factors suggests its utility as a potential integrated biomarker, capable of comprehensively reflecting the systemic inflammatory status related to advanced age, metabolic dysfunction, and hypertension.

Several limitations warrant consideration when interpreting these findings. First, the single-center nested case-control design cannot provide the causative relationship between the PBIBs and DR. Future multi-center, large-sample prospective cohort studies are warranted to validate our results. Second, the lack of measurements for specific inflammatory mediators (*e.g.*, interleukins, TNF-α) limited a more detailed molecular investigation into the specific inflammatory pathways by which PIV drives DR progression. Integrating multi-omics technologies with functional experiments to fully elucidate the underlying pathways will be our future direction[49-50].

In conclusion, this study has shown that PIV as a reliable PBIBs associated with DR progression, identifying it as an independent risk factor. The significant positive correlation between PIV and traditional DR risk factors (age, duration of DM and HBP, HbA1c, and FBG) suggests that PIV may integrate inflammatory responses with these traditional factors synergistically promote disease progression. The combined application of PIV and these traditional biomarkers provide substantial promise for enhancing DR screening and diagnosis.

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