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Characteristics and clinical significance of blood inflammatory markers in patients with diabetic retinopathy

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糖尿病视网膜病变患者血液炎症标志物的特征及临床意义

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摘要

目的:评估全身炎症反应和高凝状态在糖尿病视网膜病变(DR)及其威胁视力的并发症[糖尿病性黄斑水肿(DME)和新生血管性青光眼(NVG)]发病机制中的临床意义,并探讨常规及新型血液学指标对 DR 早期检出与风险分层的诊断效能。

方法:本研究为横断面研究,收集于我院行体格检查的 DR 患者及健康对照者。所有参与者均接受外周血常规检测。计算并比较两组间常规血液学参数及新型复合指标,包括平均血小板体积/淋巴细胞计数(PMLR)和平均血小板体积×中性粒细胞计数/淋巴细胞计数(PMNLR)。在 DR 队列中进行亚组分析,比较单纯 DR 患者与合并 DME 或 NVG 的患者。采用 Logistic 回归分析与 DR 及其并发症相关的危险因素。应用受试者工作特征(ROC)曲线评估单一及联合血液学标志物的诊断效能,并计算最佳截断值、敏感度、特异度、曲线下面积(AUC)及 95%置信区间(*CI*)。

结果:共纳入 497 例 DR 患者(男 243 例,女 254 例,平均年龄 58.01±11.13 岁)和 858 例健康对照者(男 473 例,女 385 例,平均年龄 58.05±12.14 岁)。与健康组相比,DR 组白细胞计数、中性粒细胞计数(NEU)、中性粒细胞与淋巴细胞比值(NLR)及全身免疫炎症指数(SII)显著升高,血小板计数显著降低,而平均血小板体积升高(均 $P<0.05$)。在 DR 患者中,不同亚组的炎症及血小板相关指标存在差异:DME 组 NEU、NLR 及 PMNLR 高于单纯 DR 组,NVG 组 NEU、NLR、SII 及 PMNLR 高于单纯 DR 组(均 $P<0.05$),提示不同 DR 并发症具有不同的血液学特征。多因素 Logistic 回归显示 NEU、单核细胞计数(MONO)、PMLR 及 SII 是 DR 发生的危险因素(均 $OR>1$),淋巴细胞计数(LYM)是 DR 发生的保护因素($OR=0.326$)。ROC 曲线分析显示,NLR、NEU 和 PMNLR 对 DR 诊断具有较好的敏感度和特异度,联合多标志物模型(NLR+NEU+PMNLR)可获得更高的诊断准确性(AUC=0.743,95%*CI*:0.716-0.770)。

结论:炎症反应和高凝状态在 DR 及其并发症的发生发展中发挥关键作用。NLR、NEU、SII、PMLR 和 PMNLR 等血液标志物可作为 DR 早期诊断和风险分层的有效工具。未来研究应聚焦于疾病进展过程中上述标志物的纵向监测,并通过多中心研究在不同人群中验证其临床应用价值。

关键词:糖尿病视网膜病变;糖尿病性黄斑水肿;新生血管性青光眼;炎症标志物;血小板相关指标;Logistic 回归;受试者工作特征曲线

Abstract

• AIM: To evaluate the clinical significance of systemic inflammatory responses and hypercoagulability in the pathogenesis of diabetic retinopathy (DR) and its vision-threatening complications including diabetic macular edema (DME) and neovascular glaucoma (NVG), and to explore the diagnostic efficacy of routine and novel hematological indices for early DR detection and risk stratification.

• METHODS: DR patients and healthy control participants who underwent physical examinations in our hospital were enrolled in this cross-sectional study. All

participants underwent routine peripheral blood tests. Conventional hematological parameters and novel composite indices, including mean platelet volume-to-lymphocyte count ratio (PMLR) and mean platelet volume×neutrophil count/lymphocyte count (PMNLR), were calculated and compared between groups. Subgroup analyses were conducted within the DR cohort to compare patients with uncomplicated DR versus those with DME or NVG. Logistic regression analysis was used to identify risk factors associated with DR and its complications. Receiver operating characteristic (ROC) curves were applied to evaluate the diagnostic efficacy of single and combined hematological markers, with optimal cut-off values, sensitivity, specificity, area under the curve (AUC) and 95% confidence interval (*CI*) calculated.

• RESULTS: A total of 497 DR patients (243 males and 254 females; mean age 58.01±11.13 y) and 858 healthy controls (473 males and 385 females; mean age 58.05±12.14 y) were enrolled. The DR group exhibited significantly higher levels of white blood cell count, neutrophil count (NEU), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII), and mean platelet volume, along with significantly lower platelet counts, compared to the healthy group (all $P<0.05$). Among DR patients, hematological profiles differed across subgroups: the DME group had higher NEU, NLR, and PMNLR than the simple DR group, while the NVG group had higher NEU, NLR, SII, and PMNLR than the simple DR group (all $P<0.05$), suggesting distinct hematological profiles among DR subgroups. Multivariate logistic regression showed that NEU, monocyte count (MONO), PMLR, and SII were risk factors for DR (all $OR>1$) and lymphocyte count (LYM) was protective factor for DR ($OR=0.326$). ROC curve analysis revealed that NLR, NEU, and PMNLR exhibited favorable sensitivity and specificity for DR diagnosis, with a combined multi-marker model (NLR+NEU+PMNLR) yielding improved diagnostic accuracy (AUC=0.743, 95%*CI*: 0.716-0.770).

• CONCLUSION: Inflammation and hypercoagulability play critical roles in the development of DR and its complications. Blood markers such as NLR, NEU, SII, PMLR, and PMNLR may serve as valuable tools for early diagnosis and risk stratification of DR. Future research should focus on longitudinal monitoring of these markers during disease progression and validate their clinical utility across diverse populations through multi-center studies.

• KEYWORDS: diabetic retinopathy; diabetic macular edema; neovascular glaucoma; inflammatory markers; platelet-related indices; logistic regression; receiver operating characteristic curves

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INTRODUCTION

Diabetes mellitus is a global public health crisis affecting 537 million adults worldwide, with prevalence projected to reach 783 million by 2045[1-7]. Diabetic retinopathy (DR), the most common microvascular complication of diabetes, remains the leading cause of preventable blindness in working-age adults globally. The development of DR is long-term hyperglycemia-induced metabolic disorders[8-9], which cause retinal endothelial damage, basement membrane thickening, and increased vascular permeability. These changes trigger retinal ischemia and hypoxia, and prompt the formation of neovascularization[10-12]. These fragile neovessels rupture easily, leading to vitreous hemorrhage, fibrous proliferation, and ultimately retinal detachment and irreversible visual impairment[13-16]. A critical unmet clinical need is that about 30% of patients develop progressive DR despite optimal glycemic control, a phenomenon termed "metabolic memory"[17-19]. Camacho *et al*[20] recently demonstrated that differential DNA methyltransferase expression correlates with heterogeneous anti-vascular endothelial growth factor (anti-VEGF) responses in refractory diabetic macular edema (DME), proving that systemic inflammatory and epigenetic alterations precede clinically detectable retinal structural changes. This underscores the urgent need for accessible early biomarkers to enable timely intervention. In recent years, hematological indicators have attracted increasing attention due to their low cost, minimal invasiveness, high reproducibility, and ability to reflect systemic pathophysiological status[21-25]. However, most existing DR studies have focused on conventional single markers [*e.g.*, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR)], neglecting composite indices that integrate the interconnected "inflammation-coagulation" axis central to DR pathogenesis. Furthermore, data comparing marker performance across the full DR severity spectrum, including both DME and neovascular glaucoma (NVG), remain limited.

In this study, we analyzed a comprehensive panel of hematological parameters in 497 DR patients and 858 healthy controls. We evaluated two novel composite indices: mean platelet volume-to-lymphocyte count ratio (PMLR) and mean platelet volume×neutrophil count/lymphocyte count (PMNLR), which were designed to capture both platelet activation and inflammatory cell imbalance. We aimed to identify superior biomarkers for early DR detection and complication risk stratification.

PARTICIPANTS AND METHODS

Ethical Approval The requirement for informed consent was waived by the Ethics Committee of of Shanxi Eye Hospital (Approval No. SXYYLL20230705), due to the retrospective nature of the study and the use of anonymized data. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the

Declaration of Helsinki.

Participants This was a single-center cross-sectional study conducted at Shanxi Eye Hospital between January 2023 and December 2025.

Selection of the Healthy Group The healthy group comprised 858 individuals from the Department of Plastic Surgery and Strabismus. Inclusion criteria: no history of diabetes; normal oral glucose tolerance test (OGTT) results (fasting blood glucose <6.1 mmol/L, 2-hour postprandial blood glucose <7.8 mmol/L); no history of hypertension, cardiovascular disease, or liver/kidney dysfunction; normal fundus examination. Exclusion criteria: any systemic disease affecting hematological parameters; recent use of medications interfering with test results.

Selection of the Diabetic Retinopathy Group Inclusion criteria for the DR group: All patients met the diagnostic criteria for diabetes mellitus formulated by the World Health Organization (WHO) in 1999, *i.e.*, presence of typical diabetic symptoms (polydipsia, polyphagia, polyuria, weight loss) with random blood glucose ≥11.1 mmol/L, or fasting blood glucose ≥7.0 mmol/L, or 2-hour OGTT blood glucose ≥11.1 mmol/L. The duration of confirmed diabetes was ≥5 y. DR was confirmed by dilated fundus examination, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT). Exclusion criteria: presence of severe dysfunction of important organs such as the heart, liver, and kidneys; presence of hematological diseases or use of drugs affecting hematological indicators (*e.g.*, anticoagulants, immunosuppressants); presence of stress events such as infection, surgery, or trauma within the past 3 mo. Finally, 497 DR patients were included as research subjects.

Subgroup Division of Diabetic Retinopathy Patients in the DR group who developed DME were divided into the DME subgroup. DME was diagnosed primarily by spectral-domain OCT (gold standard), defined as central subfield thickness >300 μm in the absence of other causes of macular edema. FFA was used as an adjunct to assess vascular leakage in equivocal cases. A total of 12 cases (10.3%) were diagnosed based on FFA alone due to poor OCT image quality, which may introduce minor selection bias. Patients who developed NVG were divided into the NVG subgroup. The diagnostic criteria were elevated intraocular pressure (>21 mmHg), presence of neovascularization on the anterior chamber angle and iris surface, accompanied by symptoms such as eye pain and a sharp decline in visual acuity. Through detailed ophthalmic examinations and diagnosis, a total of 116 patients were classified into the DME subgroup and 136 patients into the NVG subgroup.

Experimental Methods

Collection of blood samples All subjects fasted overnight, and 5 mL of elbow venous blood was collected in the early morning. The collection site was disinfected routinely, and under strict aseptic conditions to avoid specimen contamination. The collected blood was injected into vacuum blood collection tubes containing ethylenediaminetetraacetic acid dipotassium (EDTA-K2) anticoagulant, and gently inverted and mixed 8-10 times to ensure sufficient mixing of blood and anticoagulant and prevent blood coagulation. The blood samples were sent for testing within 2 h after collection, and severe vibration was avoided to maintain the stability of the specimens.

Detection methods of indicators White blood cell count (WBC) and platelet count (PLT) were detected using a fully automatic hematology analyzer (Model: XN-1000i), based on the principles of electrical impedance and laser scattering principles. The instrument was calibrated and quality-controlled daily according to standard operating procedures. Mean platelet volume (MPV) was directly measured by the fully automatic hematology analyzer. NLR, PLR, and monocyte-to-lymphocyte ratio (MLR) were calculated from the results of WBC, PLT, and lymphocyte count (LYM). The formula for the Systemic Immune-Inflammation Index (SII) is: SII = PLT × neutrophil count (NEU)/LYM. The formulas for the novel indicators PMLR and PMNLR are: PMLR = MPV/LYM, and PMNLR = MPV × NEU/LYM. These composite indices were selected because they integrate information on both inflammatory cell activation and platelet function, which are key components of the "inflammation-coagulation" axis implicated in DR pathogenesis. All detections were performed by trained technicians.

Statistical Analysis R 4.5.2 statistical software was used for data analysis. For a normal distribution measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Independent samples t-test was used for comparison between the healthy group and the DR group; one-way analysis of variance (ANOVA) was used for comparison between each subgroup of the simple DR, DME, and NVG subgroups. If the ANOVA result was statistically significant, Tukey's honestly significant difference (HSD) test was performed for pairwise comparison. For non-normally distributed measurement data, Mann-Whitney U test or Kruskal-Wallis H were used. Enumeration data were expressed as the number of cases or rate, and the Chi-square test was used for inter-group comparison. A P-value <0.05 was considered statistically significant.

Pearson correlation analysis was used for linear correlations between normally distributed variables; Spearman rank correlation analysis was used for non-normally distributed variables. Multivariate logistic regression analysis was performed to identify independent risk factors for DR and its complications, with odds ratios (OR) and 95% confidence intervals (CI) calculated. Receiver operating characteristic (ROC) curves were plotted to evaluate thediagnostic performance of each hematological indicator. The area under the curve (AUC) was calculated, and optimal cut-off values were determined by the maximum Youden index.

RESULTS

Indicator Differences Between the Healthy Group and the

Diabetic Retinopathy Group Comparison of hematological indicators between the healthy group and the DR group revealed significant differences in multiple indicators (all $P<0.05$). The DR group exhibited significantly higher levels in indicators including WBC, NEU, monocyte count (MONO), NLR, MLR, SII, PMLR, PMNLR, and MPV compared with the healthy group. In contrast, the DR group had significantly lower PLT and LYM than the healthy group, whereas the PLR did not differ significantly between the two groups (Table 1). These findings confirm the presence of systemic inflammation and hematological dysregulation in DR patients, with elevated inflammatory markers closely linked to disease development.

Hematological Differences Between Simple DR and Complicated DR Subgroups Within the DR cohort, comparison of hematological indices among the simple DR, DME, and NVG subgroups revealed significant differences in WBC, PLT, MONO, NEU, NLR, MLR, SII, and PMNLR (all $P<0.05$; PLR $P=0.055$; Table 2). The DME group had significantly higher WBC, MONO, NEU, NLR, MLR, and PMNLR levels than the simple DR group . The NVG group

Table 1 Comparison of blood indicators between the healthy group and the DR group

Indicators	Healthy control group ($n=858$)	DR group ($n=497$)	P
Gender(n)			0.051
Male	473	243	
Female	385	254	
Age ($\bar{x}\pm s$, y)	58.05±12.14	58.01±11.13	0.961
Hematological indicators ($\bar{x}\pm s$)			
WBC ($\times10^9$/L)	6.35±1.58	7.38±1.79	<0.001
PLT ($\times10^9$/L)	253.83±63.36	237.90±69.58	<0.001
MPV (fL)	10.21±0.99	10.42±1.11	<0.001
MONO ($\times10^9$/L)	0.44±0.14	0.49±0.14	<0.001
LYM ($\times10^9$/L)	2.29±0.80	2.03±0.61	<0.001
NEU ($\times10^9$/L)	3.64±1.19	4.68±1.44	<0.001
Inflammatory index ratios ($\bar{x}\pm s$)			
NLR	1.78±0.88	2.49±1.05	<0.001
SII	447.26±243.76	593.73±313.95	<0.001
PLR	123.97±54.25	126.42±51.76	0.409
MLR	0.22±0.11	0.26±0.12	<0.001
PMLR	5.04±2.01	5.70±2.29	<0.001
PMNLR	18.15±9.28	26.02±11.47	<0.001

DR: Diabetic retinopathy; WBC: White blood cell count; PLT: Platelet count; MPV: Mean platelet volume; MONO: Monocyte count; LYM: Lymphocyte count; NEU: Neutrophil count; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PMLR: Mean platelet volume-to-lymphocyte count ratio; PMNLR: Mean platelet volume×neutrophil count/lymphocyte count.

Table 2 Comparison of blood indices among different subgroups in the DR group $\bar{x}\pm s$

Index	Simple DR group	DME group	NVG group	P
WBC ($\times10^9$/L)	6.16±1.50	6.99±1.70	7.33±2.05	<0.001
PLT ($\times10^9$/L)	235.92±52.27	224.17±55.18	249.88±65.13	0.002
MPV (fL)	10.36±0.88	10.31±1.00	10.30±1.03	0.871
MONO ($\times10^9$/L)	0.42±0.12	0.46±0.12	0.48±0.17	0.002
LYM ($\times10^9$/L)	2.05±0.49	2.08±0.72	2.05±0.66	0.909
NEU ($\times10^9$/L)	3.49±1.00	4.24±1.25	4.60±1.79	<0.001
NLR	1.79±0.64	2.21±0.88	2.46±1.29	<0.001
PLR	122.36±43.18	118.29±45.79	131.72±46.67	0.055
MLR	0.21±0.07	0.24±0.09	0.25±0.09	0.002
SII	422.34±178.86	496.80±261.48	607.96±332.85	<0.001
PMLR	5.37±1.53	5.50±1.89	5.58±2.01	0.673
PMNLR	18.56±6.80	22.75±9.30	25.35±13.51	<0.001

WBC: White blood cell count; PLT: Platelet count; MPV: Mean platelet volume; MONO: Monocyte count; LYM: Lymphocyte count; NEU: Neutrophil count; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PMLR: Mean platelet volume-to-lymphocyte count ratio; PMNLR: Mean platelet volume×neutrophil count/lymphocyte count; DR: Diabetic retinopathy; DME: Diabetic macular edema; NVG: Neovascular glaucoma.

showed the highest WBC, MONO, NEU, NLR, SII, and PMNLR levels, all significantly higher than the simple DR group, and its PLT and SII were significantly higher than those in the DME group. No significant differences among the three groups were found in MPV, LYM, PLR, or PMLR. These findings indicate distinct hematological profiles across DR subtypes, with the simple DR group showing the lowest inflammatory burden and the NVG group the highest.

Pairwise Comparisons Among Diabetic Retinopathy Subgroups Pairwise comparisons among the simple DR, DME, and NVG subgroups revealed significant differences in multiple hematological indices (Table 3). NEU, NLR and PMNLR were significantly higher in the DME group than in the simple DR group, and NEU, NLR, SII, and PMNLR were significantly higher in the NVG group than in the simple DR group. PLT and SII were also significantly higher in the NVG group than in the DME group. These findings demonstrate distinct hematological profiles across DR subtypes, with the simple DR group showing the lowest inflammatory burden and the NVG group showing the highest. Notably, the novel index PMNLR, first proposed by our team, was significantly higher in both the DME and NVG groups than in the simple DR group, supporting its potential value for DR progression assessment.

Results of Regression Analysis We performed multivariate logistic regression analysis to identify independent risk factors for DR. The dependent variable was the presence or absence of DR, and the independent variables were hematological indices with statistical differences (Table 4). Univariate analysis identified significant associations between DR risk and multiple hematological indices, including NEO, LYM, PLR, PMLR, MONO, SII, and NLR. The standardized regression equation derived from the regression analysis is: $\text{logit}(P) = 0.047 + 0.512 \times \text{NEU} - 1.120 \times \text{LYM} - 0.029 \times \text{PLR} + 0.389 \times \text{PMLR} + 1.545 \times \text{MONO} + 0.005 \times \text{SII} - 1.031 \times \text{NLR}$. After adjusting for confounding factors, NEU, MONO, PMLR, and SII remained positively associated with DR ($OR>1$), whereas LYM was negatively associated. In the univariate analysis, all inflammatory markers including NEU, NLR, MONO, SII, PMNLR, and PMLR were significantly elevated in DR, consistent with the ROC findings.

To further identify risk factors specific to the development of vision-threatening DR complications, we performed separate multivariate logistic regression analyses for DME and NVG, with the presence of each complication as the dependent variable (Tables 5 and 6). In the DME prediction model, PMNLR and MONO were independently associated with DME. In the NVG prediction model, SII and MONO were independently associated with NVG. These findings suggest that platelet-related indices may play a role in the progression to NVG, the most severe vision-threatening complication.

Results of ROC Curve Analysis This study evaluated the performance of multiple hematological indices in the diagnosis of DR using ROC curves (Table 7). The results indicated that NLR, NEU, and PMNLR all had diagnostic value (all $P<0.001$). Among single markers, the novel composite index

Table 3 Pairwise comparison of blood indices among DR subgroups

Dependent variable	(I) Group	(J) Group	Mean difference (I-J)	Significance	95%*CI* (lower bound)	95%*CI* (upper bound)
PLT	NVG	DME	25.71[a]	0.002	8.36	43.06
NEU	DME	Simple DR	0.74[a]	<0.001	0.30	1.19
NLR	NVG	Simple DR	1.11[a]	<0.001	0.68	1.54
SII	NVG	Simple DR	185.62[a]	<0.001	103.66	267.58
	NVG	DME	111.15[a]	0.004	30.58	191.73
PMNLR	DME	Simple DR	4.19[a]	0.008	0.89	7.49
	NVG	Simple DR	6.79[a]	<0.001	3.61	9.97

[a]Statistically significant difference between the groups. PLT: Platelet count; NEU: Neutrophil count; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; PMNLR: Mean platelet volume × neutrophil count/lymphocyte count; NVG: Neovascular glaucoma; DR: Diabetic retinopathy; DME: Diabetic macular edema; CI: Confidence interval.

Table 4 Logistic regression analysis results for DR occurrence

Variable	Regression coefficient (β)	z	P	OR	95%*CI*
NEU	0.512	3.337	<0.001	1.669	1.235, 2.255
LYM	-1.120	-5.138	<0.001	0.326	0.213, 0.500
PLR	-0.029	-5.180	<0.001	0.972	0.961, 0.982
PMLR	0.389	4.458	<0.001	1.476	1.244, 1.751
MONO	1.545	3.333	<0.001	4.686	1.889, 11.621
SII	0.005	3.875	<0.001	1.005	1.003, 1.008
NLR	-1.031	-3.595	<0.001	0.357	0.203, 0.626

DR: Diabetic retinopathy; NEU: Neutrophil count; LYM: Lymphocyte count; PLR: Platelet-to-lymphocyte ratio; PMLR: Mean platelet volume-to-lymphocyte count ratio; MONO: Monocyte count; SII: Systemic immune-inflammation index; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; CI: Confidence interval.

PMNLR showed the highest AUC at 0.733 (95%*CI*: 0.706-0.760). NLR had an AUC of 0.727 (95% *CI*: 0.700-0.754), while NEU had an AUC of 0.716 (95%*CI*: 0.688-0.743). The combination of NLR + NEU + PMNLR (NNP model) achieved the highest accuracy with an AUC of 0.743 (95%*CI*: 0.716-0.770), outperforming all single markers. For the diagnosis of DR - related vision - threatening complications, different hematological indices exhibited distinct diagnostic profiles (Tables 8 and 9).

For DME, PMNLR showed the highest sensitivity (78.4%, AUC = 0.667), while NEU had the highest specificity (66.2%, AUC = 0.639). NLR had an AUC of 0.663 with a sensitivity of 75.9%.

For NVG, NEU again had the highest sensitivity (69.9%, AUC = 0.681), while SII showed the highest specificity (61.9%, AUC = 0.665). In summary, hematological indices exhibit moderate sensitivity and specificity in the diagnosis of DR and its complications. NEU is suitable for large-scale screening due to its relatively highsensitivity, while composite indices like PMNLR and SII provide better specificity for confirmation. The ROC curves of all indices were shown in Figure 1, which allows for intuitive comparison of their diagnostic efficacy and provides a more visual reference for clinical application.

DISCUSSION

Analysis of Index Differences Between the Healthy Group and DR Group Comparison of hematological indices between DR patients and healthy controls revealed significant changes in multiple inflammation- and coagulation-related parameters. This suggests that systemic immune-inflammatory

Table 5 Logistic regression analysis results for DME occurrence

Variable	Regression coefficient (β)	*z*	*P*	*OR*	95%*CI*
PMNLR	0.066	3.450	<0.001	1.069	1.031, 1.111
MONO	2.938	2.468	0.014	18.880	1.941, 211.160

DME: Diabetic macular edema; PMNLR: Mean platelet volume×neutrophil count/lymphocyte count; MONO: Monocyte count; OR: Odds ratio; CI: Confidence interval.

Table 6 Logistic regression analysis results for NVG occurrence

Variable	Regression coefficient (β)	*z*	*P*	*OR*	95%*CI*
SII	0.003	4.702	<0.001	1.003	1.002, 1.005
MONO	3.419	3.118	0.002	30.535	3.969, 292.502

NVG: Neovascular glaucoma; SII: Systemic immune-inflammation index; MONO: Monocyte count; OR: Odds ratio; CI: Confidence interval.

Table 7 ROC curve analysis results for DR diagnosis

Variable	Area (AUC)	Sig.	95%*CI*	Optimal cut-off value	Sensitivity	Specificity
NEU	0.716	<0.001	0.688, 0.743	3.78	0.742	0.608
NLR	0.727	<0.001	0.700, 0.754	1.81	0.726	0.615
PMNLR	0.733	<0.001	0.706, 0.760	19.07	0.716	0.643
Combined index NNP (NLR+NEU+PMNLR)	0.743	<0.001	0.716, 0.770	-	0.731	0.66
Combined index NN (NLR+NEU)	0.737	0.001	0.711, 0.764	-	0.727	0.645
Combined index NEUP (NEU+PMNLR)	0.743	0.001	0.716, 0.769	-	0.709	0.643
Combined index NRP (NLR+PMNLR)	0.733	0.001	0.707, 0.760	-	0.705	0.656

ROC: Receiver operating characteristic; DR: Diabetic retinopathy; NEU: Neutrophil count; NLR: Neutrophil-to-lymphocyte ratio; PMNLR: Mean platelet volume×neutrophil count/lymphocyte count; NNP: NLR+NEO+PMNLR; NN: NLR+NEU; NEUP: NEU+PMNLR; NRP: NLR+PMNLR; AUC: Area under the curve; CI: Confidence interval.

Table 8 ROC curve analysis results for DME diagnosis

Variable	Area (AUC)	Sig.	95%*CI*	Optimal cut-off value	Sensitivity	Specificity
NEU	0.639	<0.001	0.587, 0.691	3.96	0.569	0.662
NLR	0.663	<0.001	0.616, 0.711	1.63	0.759	0.508
PMNLR	0.667	<0.001	0.619, 0.714	16.25	0.784	0.491

ROC: Receiver operating characteristic; DME: Diabetic macular edema; NEU: Neutrophil count; NLR: Neutrophil-to-lymphocyte ratio; PMNLR: Mean platelet volume×neutrophil count/lymphocyte count; AUC: Area under the curve; CI: Confidence interval.

Table 9 ROC curve analysis results for NVG diagnosis

Variable	Area (AUC)	Sig.	95%*CI*	Optimal cut-off value	Sensitivity	Specificity
NEU	0.681	<0.001	0.633, 0.729	3.70	0.699	0.580
SII	0.665	<0.001	0.617, 0.713	471.37	0.654	0.619

ROC: Receiver operating characteristic; NVG: Neovascular glaucoma; NEU: Neutrophil; SII: Systemic immune-inflammation index; AUC: Area under the curve; CI: Confidence interval.

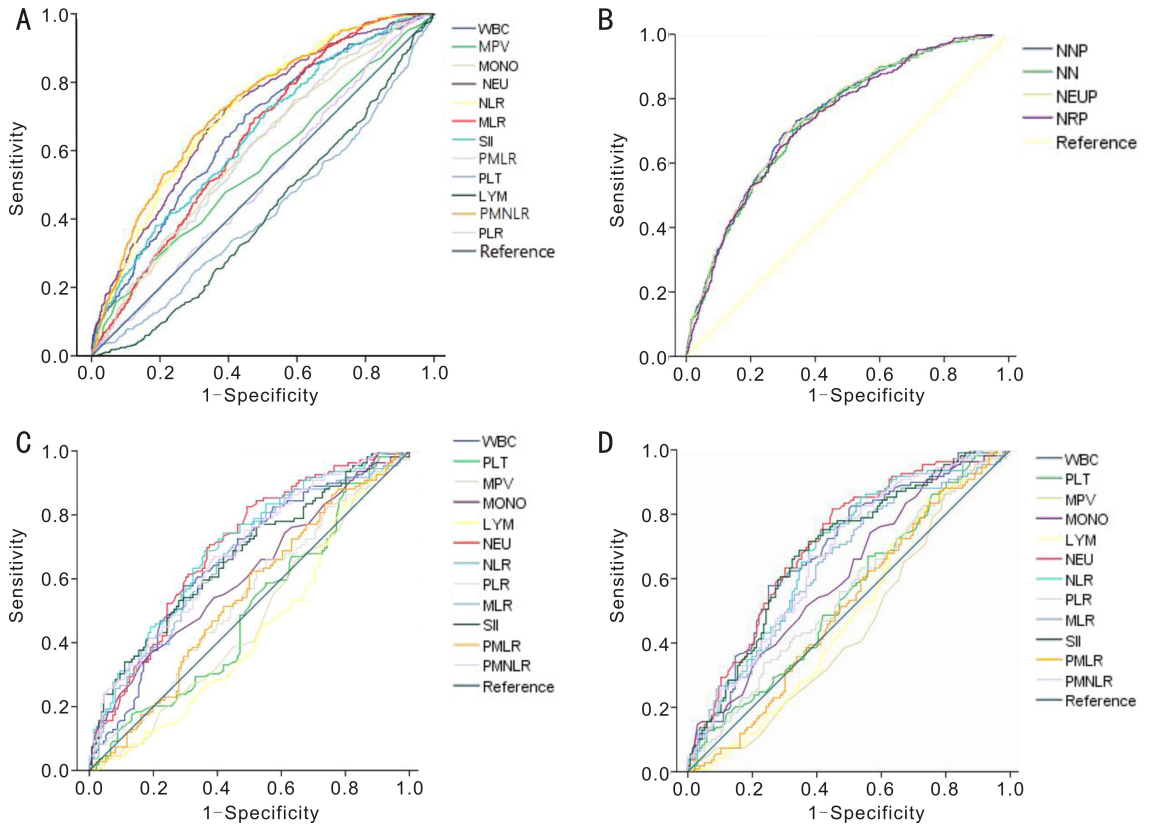


Figure 1 **ROC curve analysis results for DR diagnosis and its complications** A: ROC curve analysis results for DR diagnosis; B: ROC curve analysis results of combined index analysis for DR diagnosis; C: ROC curve analysis results for DME diagnosis; D: ROC curve analysis results for NVG diagnosis. ROC: Receiver operating characteristic; WBC: White blood cell count; PLT: Platelet count; MPV: Mean platelet volume; MONO: Monocyte count; LYM: Lymphocyte count; NEU: Neutrophil count; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PMLR: Mean platelet volume-to-lymphocyte count ratio; PMNLR: Mean platelet volume×neutrophil count/lymphocyte count; NNP: NLR+NEU+PMNLR; NN: NLR+NEU; NEUP: NEU+PMNLR; NRP: NLR+PMNLR.

responses and a hypercoagulable state play crucial roles in the pathogenesis of DR. DR patients showed a general increase in indices such as WBC, NEU, MONO, NLR, MLR, SII, PMLR, PMNLR, and MPV, accompanied by decreases in PLT and LYM. These changes collectively reflect persistent chronic inflammation and abnormal platelet function in DR patients. In a hyperglycemic environment, inflammatory cells are activated and release factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). which further exacerbate leukocyte proliferation and endothelial damage, promoting retinal microvascular leakage and ischemic changes[26-28]. Changes in platelet-related indices are particularly prominent: decreased PLT with increased PMLR/PMNLR indicate enhanced platelet activation and consumption, leading to hypercoagulability. Increased large platelets exacerbate microthrombosis and retinal ischemia, driving DR progression.

Analysis of Index Differences Among Different Patients Within the DR Group Significant differences in inflammatory and platelet-related indices were observed among the simple DR, DME, and NVG subgroups, reflecting distinct pathophysiological processes. The DME group had significantly higher NEU, NLR, MLR, and PMNLR levels than the simple DR group. The NVG group showed the highest NEU, NLR, SII, and PMNLR, and its PLT and SII were significantly higher than those in the DME group. No significant differences in MPV, LYM, PLR, or PMLR were observed among the three groups. These changes are underpinned by distinct pathological mechanisms: increased inflammatory factors enhance vascular permeability causing DME, while driving pathological retinal neovascularization leading to NVG. Concurrently, decreased platelets and increased activation indices elevate microthrombosis risk, worsening retinal ischemia and accelerating complication progression. Notably, these findings have important clinical implications for refractory DME management. Patients with persistently elevated PMLR or PMNLR despite anti-VEGF therapy may benefit from adjunctive corticosteroid treatment, which targets both inflammatory and angiogenic pathways. Dynamic monitoring of these indices facilitates early identification of high-risk patients and guide personalized treatment strategies.

Discussion on Regression Analysis Results Multivariate logistic regression identified independent risk factors for DR and its complications, confirming the central roles of systemic inflammation and hypercoagulability in disease progression. In the multivariate model, NEU ($OR=1.669$, 95%CI: 1.235-2.255, $P<0.001$), MONO ($OR=4.686$, 95%CI: 1.889-

11.621, $P<0.001$), PMLR ($OR=1.476$, 95%CI: 1.244-1.751, $P<0.001$), and SII ($OR=1.005$, 95%CI: 1.003-1.008, $P<0.001$) were positively associated with DR, whereas LYM was negatively associated ($OR=0.326$, 95%CI: 0.213-0.500, $P<0.001$). In the univariate analysis, all inflammatory markers including NEU, NLR, MONO, SII, PMNLR, and PMLR were significantly elevated in DR, confirming that chronic inflammation is a core pathophysiological mechanism. Elevated NEU and MONO reflect enhanced innate immune activation, while reduced LYM indicates impaired immunomodulation; together these damage the retinal vascular endothelium and increase vascular permeability. In the complication models, the MONO was independently and positively associated with both DME ($OR=18.880$, $P=0.014$) and NVG ($OR=30.535$, $P=0.002$), while the novel composite PMNLR was independently associated with DME ($OR=1.069$, $P<0.001$) and SII with NVG ($OR=1.003$, $P<0.001$). These findings indicate that monocyte-driven innate inflammation, together with the composite inflammatory indices, contributes to progression toward vision-threatening complications, consistent with the ROC results.

Discussion on ROC Curve Results ROC curve analysis confirmed the diagnostic value of these hematological indices for DR and its complications, with NEU, NLR, and PMNLR showing the best performance.Among single markers, PMNLR had the highest AUC (0.733), NEU had the highest sensitivity (74.2%), and PMNLR had the highest specificity (64.3%). This indicates that NEU is suitable for large-scale screening of high-risk patients, while PMNLR is useful for confirming diagnoses in suspected cases. Importantly, the combined model of multiple indices (*e.g.*, the NNP combination) achieved the highest comprehensive diagnostic performance (AUC=0.743). This reflects the multifactorial nature of DR pathogenesis, where combined indices better capture disease complexity and improve diagnostic accuracy. For complications, different indices showed distinct diagnostic profiles: for DME, PMNLR had the highest sensitivity (78.4%) and NEU the highest specificity (66.2%); for NVG, NEU had the highest sensitivity (69.9%) and SII the highest specificity (61.9%). As a composite index integrating platelet and immune cell data, SII better reflects the chronic inflammation and microthrombosis underlying neovascularization.

Significance and Value of New Indices (PMLR, PMNLR) A key innovation of this study is the introduction and validation of two novel composite indices, PMLR and PMNLR, which showed significant differences across all study groups. Unlike traditional single markers, these indices integrate platelet activity with inflammatory cell profiles, providing a new perspective on DR pathogenesis. PMLR reflects the comprehensive changes in platelet activity and count, while PMNLR embodies the synergistic effect of platelet activity and neutrophil activity. They more comprehensively reflect systemic hematological abnormalities in DR, improving early diagnostic sensitivity and specificity. Further investigation of these indices may reveal novel DR pathophysiological mechanisms and inform the development of targeted therapies.

Study Limitations This study has several limitations. First, it was a single-center cross-sectional study, which cannot establish causal relationships between hematological markers and DR progression. Second, the sample sizes of the complication subgroups (DME and NVG) were relatively modest compared with the main DR and healthy cohorts, and the wide confidence intervals for the monocyte odds ratios indicate limited precision, which may constrain the statistical power of the subgroup and multivariable analyses. Third, we did not perform longitudinal follow-up to assess the predictive value of these markers for disease progression. Finally, the potential confounding effects of medications such as statins and antiplatelet agents were not fully adjusted for in the regression analysis. Future multi-center prospective studies with larger sample sizes are needed to validate our findings.

In conclusion, systemic inflammation and hypercoagulability play critical roles in the development and progression of DR and its complications. Blood markers such as NLR, NEU, SII, and the novel indices PMLR and PMNLR may serve as valuable, cost-effective tools for early diagnosis and risk stratification of DR. These findings provide a basis for the development of personalized management strategies for DR patients.

Conflicts of Interest: Zhao DD, None; Kang YG, None.
Authors' Contributions: Zhao DD contributed to study design, data collection, laboratory testing, statistical analysis and manuscript writing; Kang YG contributed to study design supervision, manuscript review and revision, and correspondence. All authors have read and approved the final manuscript.

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