• Clinical Research •

Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in patients with type 2 diabetes at different stages of diabetic retinopathy

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Abstract

● **AIM:** To investigate systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) levels in patients with type 2 diabetes at different stages of diabetic retinopathy (DR).

● **METHODS:** This retrospective study included 141 patients with type 2 diabetes mellitus (DM): 45 without diabetic retinopathy (NDR), 47 with non-proliferative diabetic retinopathy (NPDR), and 49 with proliferative diabetic retinopathy (PDR). Complete blood counts were obtained, and NLR, PLR, and SII were calculated. The study analysed the ability of inflammatory markers to predict DR using receiver operating characteristic (ROC) curves. The relationships between DR stages and SII, PLR, and NLP were assessed using multivariate logistic regression.

● **RESULTS:** The average NLR, PLR, and SII were higher in the PDR group than in the NPDR group (P=0.011, 0.043, 0.009, respectively); higher in the NPDR group than in the NDR group (P<0.001 for all); and higher in the PDR group than in the NDR group (P<0.001 for all). In the ROC curve analysis, the NLR, PLR, and SII were significant predictors of DR (P<0.001 for all). The highest area under the curve (AUC) was for the PLR (0.929 for PLR, 0.925 for SII, and 0.821 for NLR). Multivariate regression analysis indicated that NLR, PLR, and SII were statistically significantly positive and independent predictors for the DR stages in patients with DM [odds ratio (OR)=1.122, 95% confidence interval (CI): 0.200-2.043, P<0.05; OR=0.038, 95%CI: 0.018-0.058, P<0.05; OR=0.007, 95%CI: 0.001-0.01, P<0.05, respectively).

● **CONCLUSION:** The NLR, PLR, and SII may be used as predictors of DR.

● **KEYWORDS:** diabetic retinopathy; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; systemic immune-inflammation index

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INTRODUCTION

Diabetic retinopathy (DR) is one of the most prevalent causes of blindness globally[1]. Patients with DR undergo repeated visits, receive medication, undergo laser therapy, and surgery, and require lifelong follow-up. This seriously affects their quality of life[2-4]. In the previous study,

DR can be divided into two phases: non-proliferative DR (NPDR), and proliferative DR (PDR)[5]. DR involves multiple pathogenesis mechanisms, including vascular, immune, and neural pathways.

In recent years, there are already some drugs that have been widely used as a promising treatment for PDR and diabetic macular edema (DME), such as anti-vascular endothelial growth factor (anti-VEGF) drugs. However, anti-VEGF drugs are ineffective in approximately 30% of patients[6], indicating that DR is a multifactorial disease. Inflammation mediates the structural and molecular changes associated with DR. The levels of inflammation-related chemokines and cytokines are reportedly increased in various tissues of patients with DR, including serum, vitreous, aqueous humor, and retina[7]. Various cytokines, such as tumor necrosis factor-α, interleukin-6, and interleukin-1β, have been found to promote the development of inflammation, which can change during DR progression[8-9]. In the pathogenesis of DR, endothelial cells and pericytes are activated to secrete pro-inflammatory factors that recruit white blood cells (WBCs) adhering to the vascular endothelium, causing leukocyte stasis and subsequent capillary hypoperfusion[10]. The retina undergoes a series of cellular abnormalities and tissue injuries caused by the low-grade inflammation[11]. The inflammatory processes involved in DR are receiving increasing attention, particularly in the early stages of DR.

Recently, the complete blood count is an accessible and affordable test, and subtypes of WBCs are thought to be biomarkers of inflammatory responses because they are caused by activation synthesis of inflammatory cytokines, such as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII; platelet×neutrophil/lymphocyte). One study suggested that the circulating WBC subtypes may exert a beneficial effect in the pathogenesis of patients with DME[12]. Yalinbas Yeter *et al*[13] argued that NLR was a simple and cost-effective biomarker to predict DME. Elbeyli *et al*[14] found that SII could be a diagnostic biomarker for identification of DME, which could improve risk stratification and management in patients with NPDR. In addition, these indicators have been reported to have a significant relationship with other ocular diseases, such as central retinal artery occlusion[15], idiopathic epiretinal membrane[16], and no-narteritic anterior ischemic optic neuropathy[17].

Therefore, this study investigated whether NLR, PLR, and SII were associated with the development and progression of DR at different stages in patients with type 2 diabetes mellitus (DM).

SUBJECTS AND METHODS

Ethical Approval This study was carried out by the Helsinki Declaration principles and was approved from our hospital ethics committee, Medical School, Nanjing University (approval number 2021JLHDWLS-007). Informed consent was obtained from all individual participants included in the study.

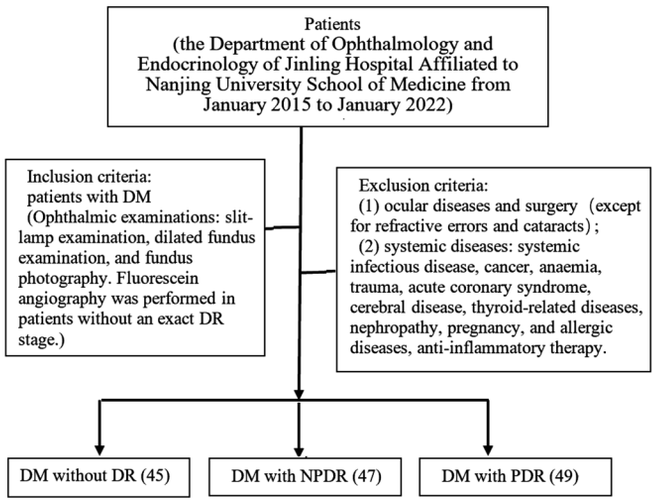

Figure 1 Study flow chart DM: Diabetes mellitus; DR: Diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy.

Inclusion and Exclusion Criteria This was a retrospective comparative study performed at the Ophthalmology and Endocrinology Departments of the Affiliated Jinling Hospital, Medical School, Nanjing University, from January 2015 to January 2022. The cohort included 141 patients with type 2 DM, 45 without diabetic retinopathy (NDR), 47 with NPDR, and 49 with PDR. Patients with ocular diseases (except for refractive errors and cataracts) were excluded. Patients with a history of ocular or general surgery were also excluded. Additional exclusion criteria included systemic diseases, such as systemic infectious disease, cancer, anaemia, trauma, acute coronary syndrome, cerebral disease, thyroid-related diseases, nephropathy, pregnancy, and allergic diseases. Furthermore, patients who received anti-inflammatory therapy were also excluded (Figure 1).

Examinations Ophthalmic examinations included slit-lamp, dilated fundus examination, and fundus photography. Patients without an exact stage of DR underwent evaluation with fluorescein angiography. Venous blood samples were collected from the antecubital veins after overnight fasting. Complete blood counts, including leukocyte, lymphocyte, neutrophil, monocyte, and platelet counts, were measured using an automatic hematology analyzer (Sysmex XE-5000; Sysmex, Kobe, Japan). Statistics for blood cell-related indicators, such as NLR, PLR and SII.

Statistical Analysis Statistical analysis was performed using SPSS software (version 21.0; IBM, Armonk, NY, USA). The descriptive data were assessed using the mean and standard deviation (SD). Comparison of normality distributed data was

Table 1 Clinical characteristics and complete blood counts

Parameters	NDR group (*n*=45)	NPDR group (*n*=47)	PDR group (*n*=49)	*P*
Age, y	53.78±1.88	51.72±1.64	53.00±1.52	0.687[a]
Gender (M/F)	21/24	30/17	27/22	0.254[b]
Hypertension, *n* (%)	25 (50.6)	33 (70.2)	24 (49.0)	0.099[b]
Leukocyte (10^9/L)	5.75±0.10	5.78±0.17	6.19±0.23	0.776[c]
Lymphocyte (10^9/L)	2.57±0.08	2.05±0.07	1.93±0.08	0.000[c]
Neutrophil (10^9/L)	2.92±0.09	3.35±0.14	3.64±0.15	0.001[c]
Monocyte (10^9/L)	0.24±0.01	0.27±0.02	0.39±0.02	0.000[c]
Platelet (10^9/L)	155.67±3.29	189.06±6.44	199.02±8.31	0.000[c]
NLR	1.20±0.06	1.67±0.07	1.99±0.09	0.000[c]
PLR	62.54±1.83	94.53±3.09	107.09±4.56	0.000[c]
SII	183.19±7.97	305.71±10.51	385.73±21.12	0.000[c]
HDLc (mmol/L)	1.01±0.22	1.08±0.43	1.07±0.37	0.565[c]
LDLc (mmol/L)	2.78±0.11	2.95±0.25	2.45±0.13	0.084[c]
TC (mmol/L)	5.10±0.10	5.14±0.14	5.13±0.16	0.852[c]
TG (mmol/L)	2.28±0.17	2.13±0.16	2.16±0.24	0.076[c]
HbA1c (%)	6.90±0.19	7.64±1.18	7.73±0.24	0.008[c]
FBG (mmol/L)	7.54±0.17	8.28±0.27	6.46±0.42	0.000[c]

NDR: No diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; HDLc: High-density lipoprotein; LDLc: Low-density lipoprotein cholesterol; TG: Triglycerides; TC: Total cholesterol; FBG: Fasting blood glucose. [a]One-way ANOVA test; [b]Chi-squared test; [c]Kruskal-wallis test.

Table 2 Receiver operator characteristic analysis results of NLR, PLR, and SII

Parameters	Cut off	Sensitivity (%)	Specificity (%)	AUC	95%CI	*P*
NLR	>1.25	86.46	64.44	0.821	0.747-0.880	<0.001
PLR	>70.07	90.62	84.44	0.929	0.873-0.965	<0.001
SII	>260.65	73.96	95.56	0.925	0.868-0.962	<0.001

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; AUC: Area under curve; CI: Confidence interval.

performed using one-way analysis of variance (ANOVA) and the Kruskal-Wallis test for non-normality distributed data. Group differences in categorical variables were determined using the Chi-squared test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive ability of systemic inflammatory indicators to distinguish NPDR and PDR from NDR. Their predictive value was calculated by comparing the area under the curve (AUC). SII, PLR, and NLP were used as explanatory variables in a multivariable ordered logistic regression analysis to identify independent predictors of DR stage. A *P*-value <0.05 indicated significance.

RESULTS

Totally 141 patients were included: 45, 47, and 49 in the NDR, NPDR, and PDR groups, respectively. The clinical characteristics and complete blood count data of the three groups are shown in Table 1. The specific distribution and statistical differences in the indicators of systemic inflammatory status are shown in Figure 2.

The ROC curve analysis concluded that NLR, PLR, and SII were significant predictors of DR (all *P*<0.001). The AUCs of the NLR, PLR, and SII were 0.821, 0.929, and 0.925, respectively. The optimal cutoff values of NLR, PLR, and SII for predicting DR were >1.25, >70.07, and >260.65 (Table 2, Figure 3).

The multivariate ordinal logistic regression analysis revealed that NLR, PLR and SII were statistically significant and independent predictors for the stage of DR in patients with DM [odds ratio (OR)=1.122, 95% confidence interval (CI): 0.200–2.043, *P*=0.028; OR=0.038, 95%CI: 0.018–0.058, *P*<0.05; OR=0.007, 95%CI: 0.001–0.01, *P*=0.028 respectively; Table 3].

DISCUSSION

This study investigated the correlation between systemic inflammation markers and different stages of DR in patients with type 2 DM. The present study showed evidence that patients with PDR had higher NLR, PLR, and SII than patients with NPDR and in patients with NPDR than NDR. The DR stage was significantly positively associated with NLR, PLR,

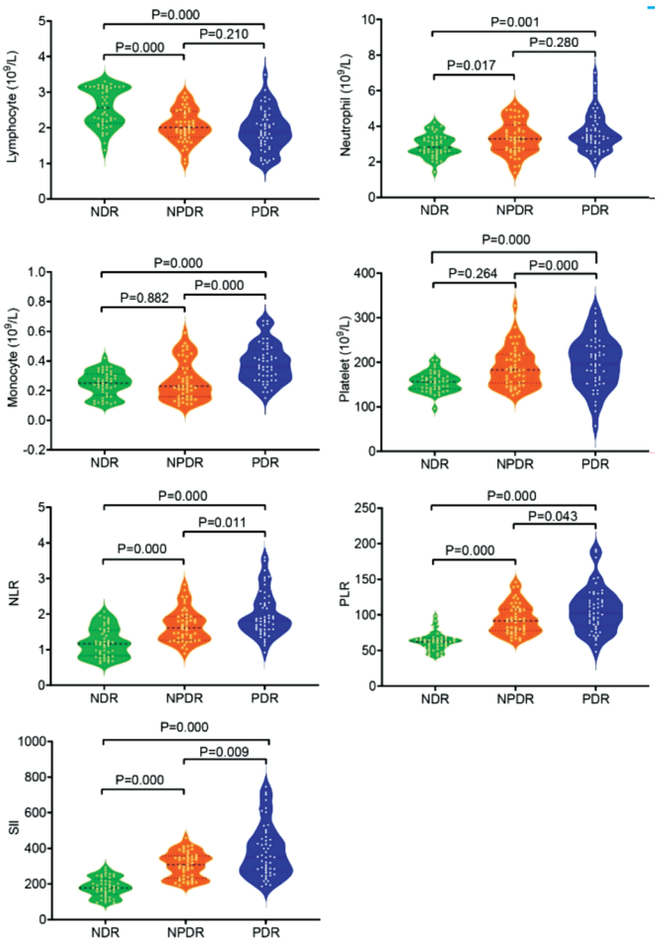

Figure 2 Specific distribution and statistical differences in lymphocyte, neutrophil, monocyte, platelet counts, NLR, PLR, and SII among the NDR, NPDR, and PDR groups NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; NDR: No diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

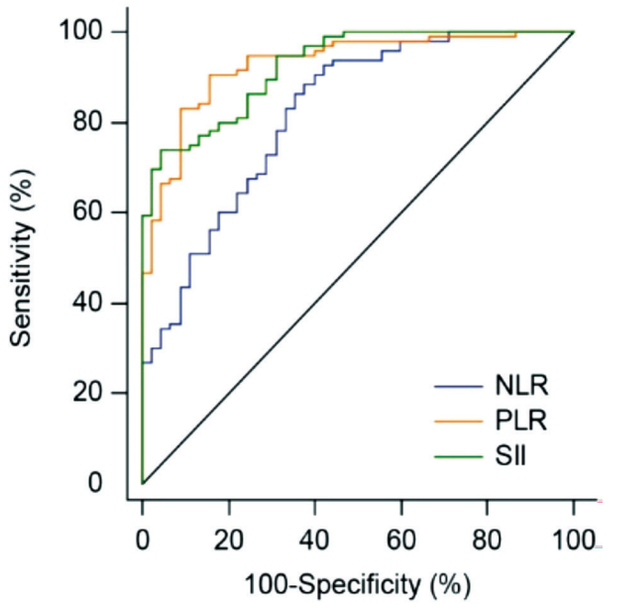

Figure 3 Receiver operating characteristic curves of NLR, PLR, and SII to distinguish NPDR and PDR from NDR NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NDR: No diabetic retinopathy.

Table 3 NLR, PLR, and SII in multivariate ordinal logistic regression analysis with the stage of DR as the dependent variable

Independent variable	OR	95%CI	*P*
NLR	1.122	0.200–2.043	0.028
PLR	0.038	0.018–0.058	0.000
SII	0.007	0.001–0.01	0.028

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; DR: Diabetic retinopathy; OR: Odds ratio; CI: Confidence interval.

and SII, as determined by multivariate logistic regression analysis.

In recent years, the counts and ratios of lymphocytes, neutrophils, platelets, and monocytes, which may easily be obtained from complete blood counts, have been recognized as predictors of systemic inflammation. The indicators of systemic inflammatory status in various systemic or ocular diseases can be obtained using NLR, PLR, and SII. In this study, these were used as prognostic markers to assess the inflammatory and immune status of patients with DR.

Leukocyte subtypes include neutrophils, monocytes, lymphocytes, eosinophils, and basophils; together these make up the WBC count. In the early stages of DR, neutrophils and monocytes can lead to occlusion and non-perfusion, which are caused by the activation of the vascular endothelium and circulating myeloid cells[18]. Woo *et al*[19] found that the systemic neutrophil count was increased in the advanced stages of DR, and neutrophil-mediated inflammation might be important in the pathogenesis of DR. Lessieur *et al*[20] suggested that neutrophil-derived proteases are related to the onset of early DR. In patients with DR, the monocyte count was significantly higher compared to uncomplicated patients, while the lymphocyte count was significantly lower than in uncomplicated patients[21]. A study conducted by Tang *et al*[22] enrolled 607 patients with NDR and 164 patients with DR. The study showed that higher monocyte counts was observed in patients with DR. Our study findings were consistent with the above-mentioned studies. In another study[23], a correlation was found between decreased levels of peripheral blood monocytes and higher odds of diabetic retinopathy in diabetic adults after adjusting for potential confounders. Tetikoğlu *et al*[24] investigated the platelet count, mean platelet volume, plateletcrit, and platelet distribution width in healthy individuals, patients with DM without DR, patients with NPDR, and with PDR. They found that high mean platelet volumes might play a significant role in the development

of PDR and DME in patients with DR. In our study, the levels of neutrophil, monocyte, and platelet counts gradually increased across the NDR, NPDR, and PDR groups, except for lymphocyte counts. There were some inconsistencies in the results, which may be related to the varying sample sizes among the different studies.

In research by Elbeyli *et al*[14], patients with DME had significantly higher NLR, PLR, and SII values compared to those without it. Thus, they conclude that NPDR could enhance risk stratification and management of DME by detecting SII, a diagnostic biomarker of DME, and by demonstrating the significant role of inflammation in the pathophysiology of DME. Furthermore, Ilhan *et al*[25] demonstrated that NLR has high sensitivity and specificity in diagnosing DME, and PLR was similar between patients with and without DME. The results mentioned above for DME were largely consistent with our study. In a recent study[26], a retrospective analysis of 129 patients with type 2 DM was divided into three groups: NDR, NPDR, and PDR. The study found no statistical differences in any of the WBC inflammatory biomarkers between the NDR and NPDR groups. However, NLR and SII values were significantly higher in the PDR group than in the NDR and NPDR groups. PLR values increase with the severity of DR. There were differences in the values among the groups, but no significant differences. In the above study, the group of subjects was similar to ours; however, we focused on individuals with yellow skin tone, while they focused on Caucasian individuals. While WBC parameters have been suggested to depend on ethnicity, gender, geography, and other factors[27], our study was consistent with the aforementioned research. These studies support the idea that systemic inflammation is associated with DR, which is also key factors requiring further study.

Chronic inflammation is implicated in the development and complications of DR. Thus, targeting inflammation may improve DM and prevent its progression and complications[28-29]. Many factors contribute to the development of a whole-body proinflammatory environment. The retinal vasculature is damaged in NPDR. The damage to the retina-blood barrier may increase the adhesion of immune cells, exposing them to systemic inflammation. Inflammation is activated by the secretion of local cytokines and the infiltration of immune cells, which accelerate the course of DR.

This study has several limitations. First, the study was not multicenter study and had a relatively small sample size. Patients with DM without DR and those with DM and NPDR or PDR were included in this study; however, healthy controls were not included. Second, this was a retrospective study. Some information and parameters were incomplete, such as diabetes duration, blood glucose status, and retinal or choroidal related data, which should be investigated further. Meanwhile, the complete blood count of the patients used in this study was extracted from only one blood test, which would not check the blood parameters regularly to monitor the ongoing changes. Third, the study lacked additional examinations of blood or eye tissues for testing inflammatory markers such as cytokines and C-reactive protein.

In conclusion, our findings indicate that the average NLR, PLR, and SII were higher in the PDR group compared to the NPDR group. Additionally, these values were higher in the NPDR group than in the NDR group, and higher in the PDR group than in the NDR group. NLR, PLR, and SII are simple to calculate, easy to apply, and cost-effective. Higher values of NLR, PLR, and SII are significantly associated with PDR in patients with type 2 DM, making them reliable predictors of inflammation in DR. However, the precise role of inflammation in DR still requires more substantial evidence by further prospective, randomized controlled studies involving larger series of patients.

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