• Clinical Research •

Assessment of pan-immune-inflammation value as a novel marker of proliferative diabetic retinopathy stage

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Received: 2025-03-05 Accepted: 2025-09-26

Abstract

• **AIM:** To evaluate the predictive value of pan-immune-inflammation value (PIV) in the diagnosis of proliferative diabetic retinopathy (PDR) and its association with the stage of PDR.

• **METHODS:** This observational case-control study included participants who underwent routine complete blood count testing. Inflammation-related indices, including neutrophil-to-lymphocyte ratio, systemic immune-inflammation index (SII), and PIV, were derived and analyzed. Receiver operating characteristic curve (ROC) analysis was applied to assess the diagnostic performance of these indices in distinguishing patients with PDR, with sensitivity, specificity, area under ROC, and optimal threshold values calculated. In addition, binary logistic regression analysis was performed to evaluate the association between inflammatory indices and PDR stage.

• **RESULTS:** This study included 205 patients: 60 with diabetes without retinopathy (mean age: 61.81±10.76y), 80 with PDR (mean age: 61.63±10.03y) and 65 healthy controls (mean age: 59.52±5.88y). The PDR group had significantly higher white blood cell (WBC, P<0.001), monocyte (MONO, P=0.009) and neutrophil (NEU) counts (P<0.001). SII and PIV had the highest sensitivity and area under ROC for predicting patients with PDR (0.822, 0.846, respectively). The optimal cut-off values for discriminating patients with PDR were determined to be >527.12 and >299.08 for SII and PIV, respectively. The logistic regression analysis demonstrated that a decrease in lymphocyte (LYM) count and an increase in platelet count (PLT), glycated haemoglobin (HbA1c), SII, and PIV were all significantly associated with the development of high-risk PDR (all P<0.05). PIV was more stable than independent MONO, LYM, PLT and NEU levels in predicting both the diagnosis and stage of PDR. The optimal cut-off value for PIV to discriminate patients with high-risk PDR was found to be >345.87 area under ROC=0.871, with sensitivity of 0.827 and specificity of 0.812.

• **CONCLUSION:** PIV is a reliable, valuable, and inexpensive blood index that can be used for early detection and staging of PDR. PIV may therefore be essential to be used for the follow-up of diabetic patients.

• **KEYWORDS:** pan-immune-inflammation value; proliferative diabetic retinopathy; systemic immune-inflammation index; monocyte-related inflammation; systemic inflammation

DOI:10.18240/ijo.2026.03.12

Citation: Candan O, Orman G, Ünlü N, Uney G. Assessment of pan-immune-inflammation value as a novel marker of proliferative diabetic retinopathy stage. *Int J Ophthalmol* 2026;19(3):517-525

INTRODUCTION

Proliferative diabetic retinopathy (PDR) represents the most advanced and vision-threatening stage of diabetic retinal disease. Its development is driven by progressive microvascular damage, ultimately leading to retinal ischemia and pathological neovascularisation. These fragile new vessels markedly increase the risk of vitreous haemorrhage and tractional retinal detachment, which remain major causes of irreversible visual loss in affected patients[1-3]. Retinal ischemia and neovascular activity are commonly assessed using fundus fluorescein angiography; however, the invasive nature of this technique and the potential for serious adverse reactions restrict its suitability for widespread screening and longitudinal monitoring. As a result, there is growing interest in identifying non-invasive, inexpensive, and easily accessible biomarkers that could assist in risk stratification and disease assessment in PDR. Beyond angiogenesis, systemic inflammation has emerged as a key contributor to diabetes-related microvascular complications. Inflammatory pathways interact closely with vascular dysfunction in diabetic retinopathy (DR), promoting endothelial injury, capillary occlusion, and disease progression.

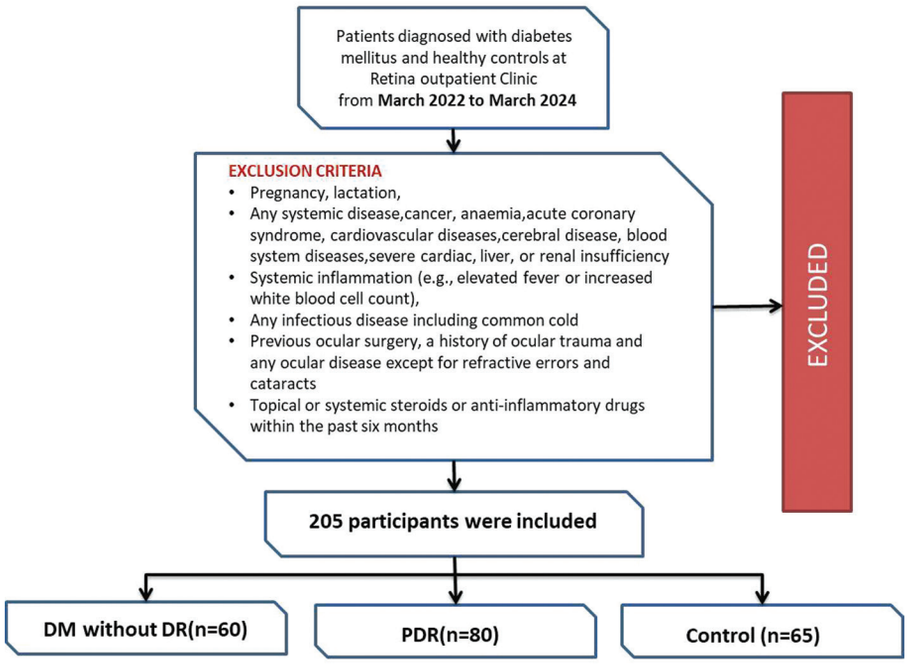

Figure 1 Study design flowchart DM: Diabetes mellitus; DR: Diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

Circulating immune cells, including neutrophils (NEU), monocytes (MONO), platelets (PLT), and lymphocytes (LYM), have all been implicated in these processes[4-5]. Genetic evidence further supports the inflammatory basis of proliferative disease. Mendelian randomisation analyses have demonstrated associations between PDR and elevated stem cell growth factor-β and interleukin-8 levels[6]. In recent years, composite indices derived from routine complete blood count parameters have been proposed as practical markers of systemic inflammatory burden. Measures such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and systemic immune-inflammation index (SII) have shown potential clinical utility in a range of inflammatory conditions and have also been explored in diabetic ocular disease, including diabetic macular edema (OME)[7-10]. Nevertheless, the diagnostic performance of these indices has been variable, and their ability to capture the full spectrum of inflammatory activity remains limited.

The pan-immune-inflammation value (PIV) integrates NEU, PLT, MONO, and LYM counts, thereby providing a broader representation of systemic immune activation. Experimental and clinical studies have demonstrated that both NEU-driven and MONO-mediated inflammatory mechanisms contribute to the pathogenesis of diabetic retinopathy and its progression to proliferative stages[10-14]. By incorporating MONO counts in addition to other leukocyte subtypes, PIV may offer a more comprehensive reflection of the inflammatory milieu underlying PDR.

Collectively, these observations suggest that PIV may reflect the systemic inflammatory burden associated with PDR. However, its clinical relevance in this setting has not yet been clearly defined. In this study, we explored its association with disease presence and stage.

PARTICIPANTS AND METHODS

Ethical Approval The study was conducted retrospectively after approval was obtained from the Ethics Committee of Ankara Education and Research Hospital, Ankara, Türkiye (approval number: E-24-148). Ethical principles consistent with the Declaration of Helsinki were followed throughout the study, and all participants provided informed consent prior to enrollment.

Participants A retrospective case-control study was conducted using clinical data collected from patients diagnosed with diabetes mellitus (DM) and healthy controls at Ankara Training and Research Hospital between March 2022 and March 2024. Participants aged 18y or older were enrolled and categorised into three cohorts. These comprised individuals with type 2 DM without DR, patients diagnosed with PDR, and an age- and sex-matched healthy control group. Individuals were excluded if they were pregnant or breastfeeding, had any concomitant systemic illness, showed evidence of active systemic inflammation (such as fever or leukocytosis), had a recent or ongoing infectious condition, or had a history of ocular trauma or previous ocular surgery. Additionally, participants with a history of topical or systemic corticosteroid or other anti-inflammatory medication use within the past six months were excluded from the study (Figure 1).

Data Collection Baseline demographic and clinical data, including age, sex, duration of DM, and glycated haemoglobin (HbA1c) levels, were collected for all participants. A

comprehensive ophthalmic assessment was performed for all participants. This included biomicroscopy and measurement of intraocular pressure, followed by evaluation of best-corrected visual acuity using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart with logMAR conversion. Medical and family histories were reviewed, and posterior segment examination was completed after pharmacological pupil dilation using a 90-dioptre lens. Structural retinal assessment was performed using optical coherence tomography (OCT; Heidelberg Engineering, Franklin, MA, USA). Fluorescein fundus angiography (Topcon TRC-50DX, Tokyo, Japan) was performed in patients with PDR for the assessment of retinal neovascular activity. In patients with bilateral PDR, analyses were limited to the eye exhibiting more advanced disease.

The classification of PDR was conducted in accordance with ETDRS criteria. The presence of high-risk PDR was defined by the presence of one of the following criteria: disc neovascularisation greater than ETDRS standard photograph 10A (approximately 1/3 of the disc area); neovascularisation of any size with vitreous haemorrhage; or new vessels elsewhere greater than 1/2 of the disc area with vitreous haemorrhage. Mild-moderate PDR was defined as the presence of new vessels on the disc neovascularisation or new vessels elsewhere that did not meet the high risk criteria.

Haematological Analysis After a 12-hour fasting period, blood samples were collected from the antecubital vein by an experienced phlebotomist between 8:30 *a.m.* and 10:30 *a.m*. The samples were analysed using an automated haematology analyser, the Sysmex XN 3000, manufactured in Kobe, Japan. The analysis was conducted within three hours of collection at room temperature (23°C±2°C). Absolute counts of white blood cells (WBC), LYM, NEU, PLT, and MONO were obtained from complete blood count analyses. Based on these parameters, inflammation-related indices were derived. The NLR was calculated as NEU/LYM. The SII was defined as PLT×(NEU/LYM). PIV was calculated using the formula (NEU×PLT×MONO)/LYM.

The main endpoint of the study was to establish the diagnostic performance of PIV for PDR, including cut-off values, sensitivity, and specificity. A subsequent objective was to assess the relationship between inflammatory blood markers and the severity of PDR.

Statistical Analysis Statistical computations were carried out in IBM SPSS Statistics, version 25.0, and data normality was examined using the Kolmogorov-Smirnov method. In order to determine the differences between the three groups, the Kruskal-Wallis test was used. To address the issue of false-positive risks associated with multiple comparisons, a post hoc analysis with Bonferroni corrections was conducted. Continuous variables were summarised as mean±standard deviation or median with minimum-maximum values, as appropriate, while categorical variables were presented as frequencies and percentages. The discriminatory performance of three inflammatory indices (NLR, SII, and PIV) for identifying PDR was assessed using receiver operating characteristic (ROC) analysis, with comparisons made against patients with DM without retinopathy and healthy controls. Sensitivity, specificity, area under the curve (AUC), and optimal cut-off values were determined accordingly. Furthermore, following the implementation of ROC analysis, cut-off values of blood markers with high sensitivity and specificity were also calculated to differentiate between patients with mild to moderate risk of PDR and patients with high risk of PDR. Binary logistic regression models were used for further analysis to evaluate the relationship between PDR stage and DM duration, HbA1c, age, sex, WBC, LYM, NEU, PLT, MONO, NLR, SII, and PIV. In the model, the dependent variable was the PDR stage (the presence of mild-moderate PDR was defined as "1", and the presence of high-risk PDR was defined as "2"). The independent variables encompassed the baseline clinical findings and blood markers. A multivariable model adjusted for age, gender, and HbA1c was used to assess independent associations. In the baseline model (model 1), DM duration, HbA1c, age, sex, LYM, NEU, WBC, MONO, and PLT were included as independent variables to assess the relationship with PDR stage. The effect of adding SII and PIV to the logistic regression model on PDR stage was also tested. All analyses were conducted using two-sided statistical tests, with statistical significance defined as a P value <0.05.

RESULTS

A total of 205 participants were included in the analysis. The mean values for the WBC, NEU and MONO count were significantly higher in patients with PDR than in patients without DR or in the control group (P<0.001, <0.001, 0.009, respectively). There were no significant differences in the other hematological parameters between the groups. A significant increase in the levels of NLR, SII and PIV was observed in patients with PDR when compared to the other groups (P<0.001, <0.001, <0.001, respectively). Baseline characteristics of the study population and the outcomes of intergroup comparisons are presented in Tables 1 and 2 and Figure 2.

ROC analysis demonstrated that SII and PIV provided better predictive performance for PDR than other haematological indices, showing higher sensitivity and AUC (0.786 and 0.795, respectively). The optimal cut-off values for discriminating between patients with PDR were determined to be be >527.12 and >299.08 for SII and PIV, respectively. Moreover, the optimal cut-off values for discriminating patients with high-

Table 1 Baseline demographic and clinical characteristics of the study groups

Parameters	Group 1 (DM)	Group 2 (PDR)	Control	*P*
Patients (*n*)	60	80	65	
Age (y)	61.81±10.76	61.63±10.03	59.52±5.88	0.267[a]
Gender (M/F)	29/31	44/36	32/33	0.167[b]
BCVA (logMAR)	0.00	0.3±0.12	0.00	<0.001[a]
Duration of DM (y)	7.91±5.10	12.25±6.88	-	-
HbA1c (%)	7.70±1.66	9.33±2.58	-	-
WBC (10^9/L)	7.65±1.75	8.63±2.07	7.19±1.42	<0.001[a]
NEU (10^9/L)	4.62±1.3	5.69±1.45	4.35±1.19	<0.001[a]
LYM (10^9/L)	2.28±0.63	2.1±0.72	2.21±0.61	0.129[a]
MONO (10^9/L)	0.62±0.37	0.63±0.21	0.53±0.13	0.009[a]
PLT (10^9/L)	271.6±64.76	286.6±71.18	274.63±55.19	0.438[a]
NLR	2.14±0.77	2.97±1.13	2.06±0.66	<0.001[a]
SII	584.55±302.8	853.75±411.84	574.98±238.53	<0.001[a]
PIV	352.21±232.56	524.64±269.11	303±150.05	<0.001[a]

PIV: Pan-immune-inflammation value; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; PLT: Platelet counts; DM: Diabetes mellitus; PDR: Proliferative diabetic retinopathy; BCVA: Best-corrected visual acuity. Group 1 included patients with diabetes mellitus without diabetic retinopathy. [a]The Kruskal-Wallis test with Bonferroni adjustment was used for multiple group comparisons; [b]Pearson's Chi-square test was applied for categorical variables. Statistical significance was defined as $P<0.05$.

Table 2 Subgroup comparison of characteristics in patients with PDR

Variables	PDR stage (subgroups of group 2)		
	Mild-moderate	High-risk	*P*
Patients (*n*)	35	45	
Age (y)	61.4±9.96	61.82±10.21	0.892
Gender (M/F)	18/17	26/19	0.571[b]
BCVA (logMAR)	0.26±0.07	0.34±0.09	0.041[a]
Duration of DM (y)	10.97±4.78	13.24±8.07	0.494
HbA1c (%)	8.74±2.02	9.79±2.89	0.114
WBC (10^9/L)	8.11±2.17	9.04±1.9	0.051
NEU (10^9/L)	5.2±1.39	6.07±1.4	0.009[a]
LYM (10^9/L)	2.21±0.81	2.01±0.64	0.401
MONO (10^9/L)	0.6±0.19	0.65±0.22	0.32
PLT (10^9/L)	253.51±67.12	312.33±63.77	<0.001[a]
NLR	2.57±0.91	3.27±1.19	0.004[a]
SII	644.99±285.77	1016.12±424.02	<0.001[a]
PIV	386.24±215.05	632.29±259.23	<0.001[a]

PIV: Pan-immune-inflammation value; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; PLT: Platelet counts; DM: Diabetes mellitus; PDR: Proliferative diabetic retinopathy; BCVA: Best-corrected visual acuity. Group comparisons were performed using the Mann-Whitney *U* test[a] or Pearson's Chi-square test[b] as appropriate. Statistical significance was defined as $P<0.05$.

risk PDR were determined to be >666.96 and >345.87 for SII and PIV, respectively. The sensitivity and specificity were found to be 86.7% and 65.7% for SII and 88.9% and 68.9% for PIV, respectively (Table 3).

Subsequent analysis of the data using binary logistic regression indicated a correlation between clinical and blood parameters and the severity of PDR. In Model 1, when the mild to moderate PDR was set as the reference, the development of high-risk PDR was found to be associated with elevated levels of HbA1c ($P=0.028$) and PLT ($P=0.004$), but decreased levels of LYM count ($P=0.038$). The AUC was 0.788 (0.682–0.893), with a sensitivity of 0.689 and a specificity of 0.686. After adjustment for SII, increased levels of HbA1c ($P=0.039$) and SII ($P=0.001$) were found to be significantly associated with an increased risk of developing high-risk PDR. The AUC was 0.828 (0.733, 0.922), with a sensitivity of 0.8 and a specificity of 0.771. After the adjustment for PIV, elevated levels of HbA1c ($P=0.028$) and PIV ($P=0.001$) were found to be significantly associated with an increased risk of developing high-risk PDR. The AUC was 0.871 (0.793, 0.949), with a sensitivity of 0.827 and a specificity of 0.812 (Figures 3 and 4).

DISCUSSION

This study was the first to assess the importance of PIV in the occurrence of PDR, and it also demonstrated that PIV can be used in the staging of PDR. The current study definitively established that HbA1c level, PIV and SII be an important factor in the development of high-risk PDR.

Previous studies have demonstrated a strong association between chronic systemic inflammation and the development of DR, DME, and PDR. Moreover, WBC subtypes have been reported to play an important role in the inflammatory mechanisms underlying DR[4,14-16]. The presence of elevated NEU has been identified as a significant factor in the

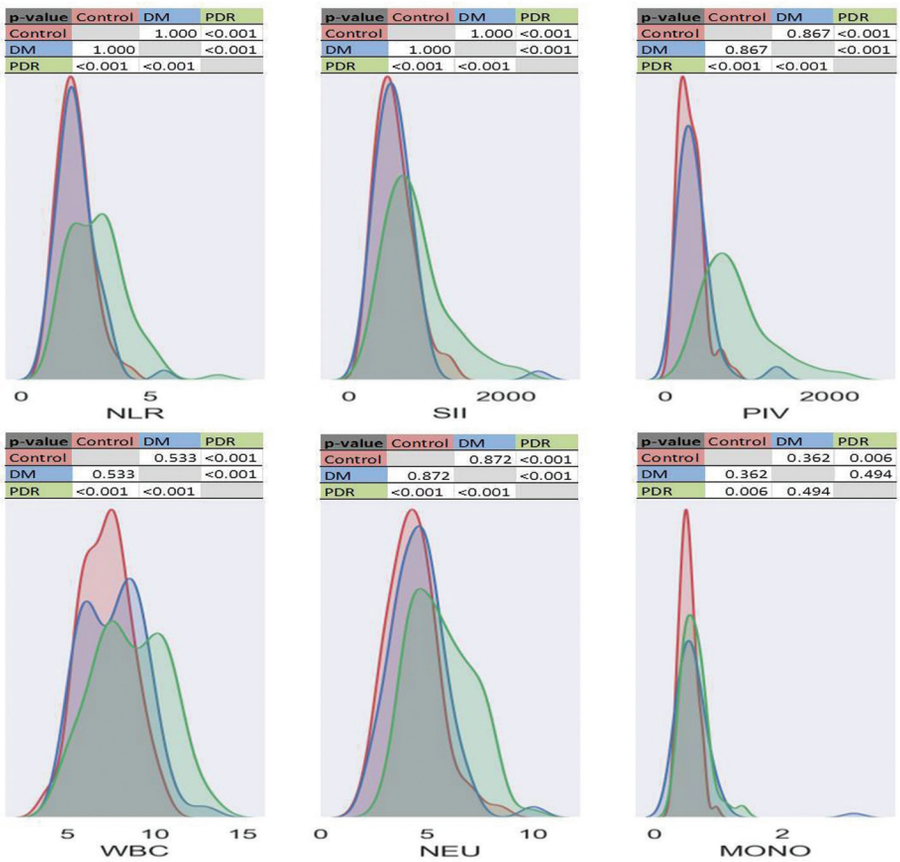

Figure 2 Density distributions of inflammatory indices and haematological parameters showing statistically significant differences among study groups PIV: Pan-immune-inflammation value; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; PLT: Platelet counts; DM: Diabetes mellitus; PDR: Proliferative diabetic retinopathy. All *P*-values corrected using Bonferroni correction.

	Beta Coefficient	P	OR	95% C.I. for OR Lower	Upper
MODEL 1 (Mild-moderate PDR was set as reference)					
Age	-0,0173	0,6831	0,9828	0,9045	1,0680
Duration Of DM	0,0791	0,2636	1,0824	0,9421	1,2434
Gender (Reference Female)	1,3825	0,0720	3,9849	0,8839	17,9653
HbA1c	0,3472	**0,0282**	1,4151	1,0190	1,9651
WBC	0,4037	0,4851	1,4973	0,4820	4,6510
PLT	0,0194	**0,0035**	1,0196	1,0064	1,0330
NEU	0,2230	0,7104	1,2498	0,3852	4,0549
LYM	-1,6463	**0,0383**	0,1928	0,0406	0,9149
MONO	1,4792	0,5202	4,3893	0,0484	398,3580
MODEL 2 (Mild-moderate PDR was set as reference)					
Age	-0,0092	0,7862	0,9908	0,9272	1,0589
Duration Of DM	0,0569	0,3198	1,0585	0,9463	1,1841
Gender (Reference Female)	0,8670	0,1767	2,3797	0,6765	8,3704
HbA1c	0,2721	**0,0385**	1,3127	1,0017	1,7201
WBC	0,0247	0,8832	1,0250	0,7374	1,4247
SII	0,5053	**0,0014**	1,6574	1,0020	1,0086
MODEL 3 (Mild-moderate PDR was set as reference)					
Age	-0,0304	0,4151	0,9701	0,9018	1,0436
Duration Of DM	0,0908	0,1179	1,0950	0,9772	1,2270
Gender (Reference Female)	1,1652	0,0833	3,2065	0,8577	11,9871
HbA1c	0,2608	**0,0281**	1,2979	0,9911	1,6998
WBC	0,2386	0,1162	1,2695	0,9426	1,7097
PIV	0,6036	**0,0007**	1,8286	1,0015	1,0057

Figure 3 Results of the analysis of binary logistic regression for PDR stage PIV: Pan-immune-inflammation value; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; MONO: Monocyte; PLT: Platelet counts; DM: Diabetes mellitus; PDR: Proliferative diabetic retinopathy; OR: Odds ratio; HbA1c: Glycated hemoglobin A1c.

Table 3 Results of ROC curve analysis for discriminating patients with PDR and high-risk PDR

Hematological indices	AUC (95%CI)	Cut-off	*P*	Sensitivity (%)	Specificity (%)
Results of ROC curve analysis for discriminating patients with PDR					
PIV	0.795 (0.69–0.86)	299.08	<0.001	78.8	46.7
SII	0.786 (0.673–0.839)	527.12	<0.001	76.3	46.7
Results of ROC curve analysis for discriminating high-risk PDR patients from mild-moderate PDR patients					
PIV	0.846 (0.744–0.947)	345.87	<0.001	88.9	68.9
SII	0.822 (0.73–0.934)	666.96	<0.001	86.7	65.7

ROC: Receiver operating characteristic curve; AUC: Area under the curve; PDR: Proliferative diabetic retinopathy; PIV: Pan-immune-inflammation value; SII: Systemic immune-inflammation index.

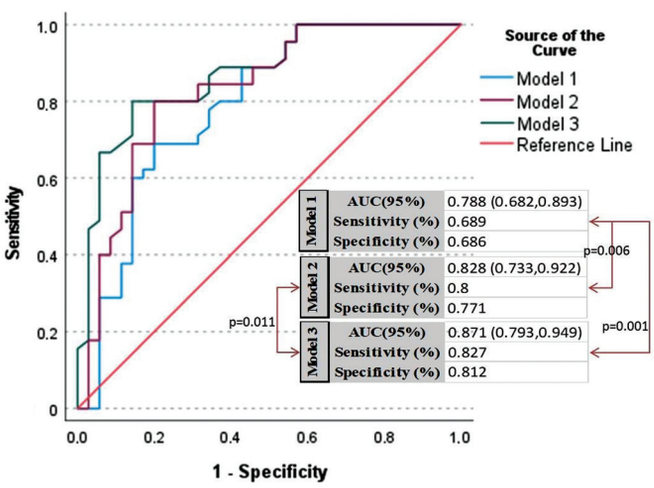

Figure 4 Results of the ROC analysis for regression models ROC: Receiver operating characteristic curve; AUC: Area under the curve. DeLong's test was used to detect differences between ROC curves of models.

pathogenesis of DR. Previous studies have demonstrated the importance of NEU-mediated inflammation in the development of DR. In accordance with the existing literature, this study found that NEU counts were higher in patients with PDR. This study provides evidence supporting the involvement of NEU-mediated inflammatory mechanisms in the development of PDR[6,17]. MONO has been widely investigated for their role in the pathogenesis of diabetes and DR[4,14,18]. The present study demonstrated that patients diagnosed with PDR exhibited a substantial increase in WBC and MONO counts when compared to diabetic patients without DR. This finding suggests that not only NEU-mediated but also MONO-mediated inflammatory mechanisms may be involved in the development of PDR.

Previous investigations have explored the role of systemic inflammatory indices, including NLR, SII, and PLR, in the context of DR and DME, suggesting their potential utility for disease assessment and staging[10-12,15-16]. However, the reported diagnostic performance of these indices has been inconsistent. For example, Özata *et al*[11] evaluated inflammatory marker profiles in patients with serous macular detachment secondary to DME and reported cut-off values for NLR and SII (above 1.75 for NLR and above 388.95 for SII). Despite these findings, both indices showed limited diagnostic performance, with sensitivity values of approximately 60% and specificity ranging between 55% and 60%. Similarly, Zhou *et al*[12] analysed treatment-naïve patients with centre-involving DME and observed associations between hyperreflective retinal foci on OCT and several systemic inflammatory indices, particularly SII. Their study, conducted in 82 patients with DME, demonstrated correlations between OCT-derived hyperreflective retinal foci and inflammatory indices (notably SII), but lacked a control group and predefined cut-off values. In the study by Wang *et al*[15], they analysed a total of 500 individuals, including 256 patients without DR and 244 patients diagnosed with DR, to assess the diagnostic performance of the systemic inflammatory response index (SIRI) and SII. Their analysis focused on the presence of DR rather than disease staging. An SII threshold exceeding 419.57 was proposed; however, both indices demonstrated only moderate discriminative ability, with sensitivity and specificity values ranging from approximately 65% to 75%. In a further study, Chen *et al*[16] investigated the correlation between OCT-based grading of DME and systemic inflammatory indices. The authors classified DME into four stages: early, advanced, severe, and atrophic, according to OCT findings. They reported that NLR, PLR, MLR, and SII were associated with different stages of DME. However, the researchers did not evaluate the predictive capacity of the indices in DME staging and did not calculate a cut-off value. The aforementioned studies determined the cut-off values, sensitivity and specificity of the SII, NLR and SIRI. Some of these studies contained a single group, while others did not include a control group. In addition, the sensitivity and specificity of the SII cut-off values calculated in these studies were lower than in our study. Our study demonstrated higher levels of inflammatory blood indices in patients with PDR than in diabetic patients without retinopathy and controls. However, the novel inflammatory indices, PIV and SII, were found to exhibit higher sensitivity and specificity for the diagnosis of PDR than NLR. The

superior predictive capability and sensitivity of PIV and SII, particularly of PIV, in the diagnosis of PDR may suggest that evaluating the combined effect of different leukocyte subtypes could be beneficial in predicting the progression of the patient's diabetes stage. However, the primary limitation of this study is the lack of consensus regarding reference values for these blood markers and the pathological thresholds at which they should be considered abnormal. In the literature, normal reference ranges have been reported as 1–2 for NLR, 260–675 for SII, a recently proposed hematological index, and 310–362 for PIV[15-16,19-22]. In ophthalmology, cut-off values of these indices are only recently being determined and no study has been conducted on the cut-off value of PIV. Notwithstanding the pioneering nature of the present study, a higher cut-off value than 527.12 for SII and 299.08 for PIV was identified as the most appropriate value for predicting patients with PDR. Furthermore, the present study evaluated the blood markers in order to differentiate between high-risk PDR and mild-to-moderate PDR in patients who developed PDR. SII and PIV, especially PIV, have been definitively shown to have superior predictive capacity for PDR staging when compared to other indices. Furthermore, elevated cut-off values for SII and PIV, exceeding 666.96 and 345.87, respectively, were identified as significant risk factors for the development of high-risk PDR. It is vital to determine sensitivity and specificity when setting cut-off values. Higher sensitivity can lead to lower specificity and false positive results. Our study identified patients who could develop PDR. We achieved high sensitivity (80%–85%) in differentiating PDR patients from controls and DM patients and in staging PDR. However, the specificity was relatively low (~60%). These blood indices have the potential to serve as a cost-effective and readily available screening test for the identification of PDR in patients with DM. This test can be used by an endocrinologist or a general practitioner before consultation with an ophthalmologist. The implementation of highly sensitive cut-off values can facilitate the early identification of patients at high risk of developing PDR, thereby preventing irreversible vision loss.

In the second phase of the study, the associations between systemic inflammatory indices and PDR stage were evaluated. A number of studies have been conducted on the use of systemic inflammatory indices in the staging of DR. These indices include NLR, PLR, SII, and SIRI. It is suggested that these can be used as potential biological indicators in both DM diagnosis and DR staging[15,23-24]. Wang *et al*[15] evaluated the diagnostic ability of SII and SIRI in relation to DR, without performing disease staging, and reported an optimal SII cut-off value greater than 419.57 for discriminating patients with DR; however, both sensitivity and specificity were relatively low (approximately 65%–75%). In the current study, the cut-off value for SII in differentiating patients with PDR was found to be 527.12, which is higher than that of Wang *et al*[15]. The higher cut-off value for SII in the present study may be due to the fact that the patient group consisted of patients diagnosed with PDR, whereas in their study, they only included patients with DR and did not perform DR staging. It is well known that both local and systemic inflammation are more severe in advanced stages of DR. In a further study, Deng *et al*[23] investigated the relationship between six serological inflammatory markers and different stages of type 2 DR. The study included three groups of patients: non-DR group (n=121), non-proliferative diabetic retinopathy (NPDR) group (n=77) and PDR group (n=199). The authors emphasised that SII and PLR have important roles in the development and progression of type 2 DR. However, they also stated that combining multiple indices improves predictive accuracy. The authors reported that the AUC value of each index was greater than 0.6 (0.66–0.69) and demonstrated diagnostic value for DR. They also noted that when all the indices were combined, AUC value was 0.69, with a sensitivity of 54% and a specificity of 75%. However, the authors did not calculate any cut-off value. The present study demonstrated that both AUC and the sensitivity and specificity values of PIV and SII in differentiating PDR patients were higher than in the study by Deng *et al*[23]. The AUC for SII was 0.786 with a sensitivity of 76.3% and a specificity of 46.7%, and for PIV was 0.795 with a sensitivity of 78.8% and a specificity of 46.7%. In a different study, Gao *et al*[24] analysed SII, NLR and PLR levels in patient groups similar to those of Deng *et al*[23], and reported that all three indices were predictors of inflammation in DR. The AUC and sensitivity and specificity values found in their study were comparatively higher than in our study (AUC for SII: 0.925, with a sensitivity of 73.96% and a specificity of 95.6%). However, Gao *et al*[24] calculated the cut-off value for SII to differentiate NPDR and PDR from NDR to be 260.65. This value was lower than the cut-off value (299.08) for identifying PDR patients in our study. This difference can be explained by the fact that the purpose of the cut-off value calculated by Gao *et al*[24] was to distinguish patients with DR from those without DR. The focus of their calculation was not to predict patients with PDR and NPDR. However, the prevailing studies have investigated the role of these indices in the presence of DR and in the differentiation of PDR and NPDR. Moreover, these studies have not focused on the relationship between PIV and DR, nor on the role of these indices in staging PDR. Logistic regression analysis in the present study revealed showed that LYM and PLT, the level of HbA1c, SII and PIV were significantly associated with the development of high-risk PDR. It has been previously established that PLT play a pivotal role in the process of microthrombus formation,

thus causing alterations in microcirculation, and they are a potential pathogenic factor in the development of DR[25]. As shown in the current literature, a high MONO to lymphocyte ratio (MLR) in patients with PDR may indicate an increased inflammatory response and impaired immune function[14]. In the present study, a decrease in LYM levels was identified as a risk factor for the development of high-risk PDR, suggesting a potential link with immune function. Furthermore, the success of leukocyte subtypes in independently predicting the development of high-risk PDR was lower than that of the SII and PIV indices. The present study definitively demonstrated that SII and PIV, especially PIV, are more stable than independent MONO, LYM, PLT, and NEU levels in predicting both the diagnosis and stage of PDR. This is most likely due to the balance that results from using four leukocyte subtypes together in the calculation of PIV.

As previously emphasised, inflammation is a pivotal factor in the development of PDR. The use of blood indices to assess systemic inflammation in these patients is a cost-effective and practical approach. Although indices such as NLR, SII, and SIRI have been proposed for use in studies to monitor inflammation, a novel index, PIV, offers a more comprehensive and balanced monitoring strategy by encompassing four distinct cell types. Consequently, in clinical practice, PIV can be employed as a screening test within primary healthcare institutions, with the aim of identifying high-risk patient groups for PDR, thereby reducing the financial burden associated with treating complications due to PDR. The use of PIV in clinical practice may also be useful in the management of complications of PDR and in monitoring the effectiveness of treatment. Moreover, the assessment of PIV does not require active patient participation, a factor which may make them particularly valuable in assessing diabetic patients with mobility limitations or cognitive impairment for the development of PDR. However, in patients with impaired glycaemic control, the combined use of PIV and HbA1c may provide a useful approach for monitoring the development of PDR.

The present study is an evaluation of the connection between PIV and SII, two inflammatory markers that have recently been identified, and the development and stage of PDR. To the best of our knowledge, no previous studies have reported this relationship. It is crucial to acknowledge the limitations of this study. First, it is retrospective and conducted at a single centre, introducing potential biases and limitations in the generalisability of the findings. Second, in patients with PDR, bilateral disease was present in 45 cases, and analyses were restricted to the eye with more advanced involvement, a choice that may have introduced selection-related bias. In addition, the limited sample size constrains the generalisability of the findings and highlights the need for confirmation in larger, independent cohorts. Third, the study design is limited by the fact that it analyses the predictive capacity of PIV in patients with PDR in a single time interval. Longitudinal follow-up data, including repeated measurements of patients to evaluate how PIV changes over time in patients with PDR, are not available in the present study. Moreover, this study represents the first investigation to determine the cut-off value of PIV in ophthalmology using an independent group design. However, it should be noted that the cut-off values have yet to be validated in an independent data set. Finally, certain parameters, such as lipid levels [*e.g.,* high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels] and inflammatory markers (*e.g.*, C-reactive protein) were not available in this study. In addition, the study could not provide data on retinal or choroidal examination findings. These need to be studied thoroughly.

In conclusion, our results clearly demonstrate that PIV is a reliable, valuable and inexpensive blood index that can be used for early detection of PDR development and staging of PDR in diabetic patients. Furthermore, SII and PIV, especially PIV, are more stable than independent MONO, LYM, PLT, and NEU levels in predicting both the diagnosis and stage of PDR. Therefore, PIV can also be considered as an important component in the management of patients with DM during follow-up, as a precautionary measure to prevent potential complications. In patients with impaired glycaemic control, the combined use of PIV and HbA1c may be a valuable approach to monitoring the development of PDR. Further research is needed to evaluate the potential role of PIV in the management of PDR and to determine the optimal cut-off value.

ACKNOWLEDGEMENTS

Authors' Contributions: Conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results: Candan O, Orman G, Ünlü N; Drafted or revised the manuscript: Candan O, Ünlü N, and Uney G; Approved the final version: Candan O, Orman G, Ünlü N, and Uney G; Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Candan O, Orman G, Ünlü N, and Uney G.

Conflicts of Interest: Candan O, None; **Orman G,** None; **Unlü N,** None; **Uney G,** None.

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