

Prognostic nutritional index as a novel marker for diabetic retinopathy in individuals with type 2 diabetes mellitus

Bengi E. Kurtul¹, Suleyman Koca², Muge O. Yilmaz³

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Abstract:

PURPOSE: In recent years, the prognostic nutritional index (PNI), an easily obtainable nutritional inflammatory marker, has been introduced as an independent prognostic indicator for various types of cancers and cardiovascular diseases. However, its clinical importance in the area of ophthalmology is not well known yet. We aimed to elucidate the association between the PNI and the occurrence of diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM).

METHODS: In this cross-sectional study, the PNI was applied to 128 consecutive patients with T2DM. The relationship between the PNI and the occurrence of DR was examined. PNI was calculated as $10 \times (\text{serum albumin}) + 0.005 \times (\text{total lymphocyte count})$. The risk factors for DR were evaluated using multivariate logistic regression analysis. A receiver operating characteristic (ROC) curve analysis of PNI for predicting DR was performed.

RESULTS: Patients with DR had significantly lower levels of PNI than those without DR (41.20 ± 4.81 and 44.49 ± 3.10 , respectively, $P < 0.001$). Multivariate regression analysis indicated that PNI, together with the duration of diabetes and creatinine, was an independent factor for DR occurrence (odds ratio, 0.885; 95% confidence interval: 0.735–0.971; $P = 0.017$). ROC curve analysis revealed that the best cutoff value of PNI was 43 (area under the curve: 0.713; sensitivity: 74%; specificity: 64%).

CONCLUSION: A lower PNI value is common among T2DM patients with DR and is strongly associated with the occurrence of DR. The PNI might be a useful biomarker for identifying DR to improve the risk stratification and management of T2DM patients.

Keywords:

Albumin, biomarker, diabetic retinopathy, lymphocyte, prognostic nutritional index, type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is one of the greatest global health issues of the 21st century, representing a huge burden to today's health-care systems.^[1] It is always involved in the injury of many organs and tissues, leading to various micro- and macrovascular complications. Diabetic retinopathy (DR) is one of the most common microvascular complications in patients with type 2 DM (T2DM) and it is the leading cause of preventable visual loss in working-age adults, affecting more than 35% of diabetic patients.^[2] The duration of DM, gene polymorphism, abnormal blood lipid levels, hyperglycemia, obesity, hypertension,

anemia, and smoking which through a series of pathological processes, contribute to the development and progression of DR.^[3-5] DR pathogenesis is complicated and related to many factors, but during recent decades, accumulating evidence has indicated that both oxidative stress and chronic inflammation are important in the development of DR.^[6-8] Early detection and treatment of DR largely contribute to preventing DM-associated visual impairment or loss.^[9]

Serum albumin and lymphocytes are well-known acute-phase reactants and have been used as inflammatory biomarkers for predicting prognosis in many diseases.^[10,11] Both serum albumin and lymphocyte levels decrease during inflammation. There is a significant association between serum albumin and retinopathy severity

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¹Department of Ophthalmology, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Hatay, ²Department of Ophthalmology, Nevsehir State Hospital, Nevsehir, ³Department of Endocrinology, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Hatay, Turkey

Address for correspondence: Dr. Bengi E. Kurtul, Mustafa Kemal Üniversitesi Tayfur Ata Sökmen Tıp Fakültesi Alahan, Hatay 31060, Turkey. E-mail: becekurtul@gmail.com

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in T2DM.^[12] The prognostic nutritional index (PNI) is calculated using serum albumin concentration and lymphocyte count and it has been introduced as an easily measurable systemic inflammatory index that has become popular in recent years. It is believed to be a more reliable predictor of inflammatory status than serum albumin or lymphocyte alone. The PNI has originally developed a prognostic marker for various types of cancers.^[13,14] It is also an independent prognostic factor in patients with many cardiovascular diseases.^[15-17] However, the clinical significance of the PNI in the ophthalmology area remains unclear. The aim of the present study was to investigate the significance of the PNI for predicting DR in patients with T2DM.

METHODS

Study population

Between March 2020 and September 2020, a total of 128 patients with T2DM were consecutively recruited in the Outpatient Clinic of the Department of Endocrinology and Metabolism of a University Hospital. The patients were sent to our ophthalmology outpatient clinic as part of the screening of DR. Hypertension was settled by the intake of antihypertensive agents or blood pressure $\geq 140/90$ mmHg. At the admission visit, the clinical data, which include hypoglycemic medication, diabetes duration, and other possible factors, were gathered from standardized inquiries.

Exclusion criteria were other retinal pathology (including hard drusen or signs of chronic systemic hypertension), uveitis, refractive error of 6 or more diopters, ocular hypertension and/or glaucoma, history of ocular surgery (including intravitreal injections and cataract surgery), and history of ocular/orbital trauma, and smoking. Patients also were excluded from the study if they had any acute/chronic inflammation, severe renal dysfunction (serum creatinine >2.5 mg/dL), active infection, cancer, or chronic liver diseases.

This study was performed in accordance with the tenets of the Declaration of Helsinki and approved by the ethics committee of a University Hospital (05/03/2020, authorization number 2020/48). Written informed consent was obtained from all the participants.

Clinical examination

A complete ophthalmologic examination, including visual acuity with Snellen chart, anterior segment observation, tonometry, and fundoscopic examination, was made by the same ophthalmologist. Following dilation of the pupils with one drop of phenylephrine (2.5%) and tropicamide (1%) in both eyes, a biomicroscopic fundus examination was carried out with a 90 diopter lens to assess DR. The study patients were divided into three groups: non-DR, nonproliferative DR (NPDR), and proliferative DR (PDR). Both these last groups were considered DR. The DR grade for each eye was determined, and an individual's classification was based on the worse eye. DR was evaluated according to the International Clinical DR Disease Severity Scale.^[18]

Biochemical analysis

Venous blood samples were obtained from antecubital veins after an overnight fast. Complete blood count test, fasting blood glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol, serum creatinine, high-density lipoprotein cholesterol, glycosylated hemoglobinA1c (HbA1c), C-reactive protein, and serum albumin levels were measured. The PNI was calculated using the following formula: $10 \times \text{serum albumin value (g/dL)} + 0.005 \times \text{total lymphocyte count in the peripheral blood (per mm}^3\text{)}$.^[19]

Statistical analysis

All statistical analyses were performed by SPSS software (version 21.0, Inc., Armonk, NY, USA). Kolmogorov–Smirnov test was used to evaluate the normality test for the numeric variables. Normally distributed continuous data were presented as means and standard deviations ($\pm$) and nonnormally distributed data were presented as median (interquartile range). Categorical variables were presented as numbers and percentages. Independent samples *t*-test was used to compare the means of quantitative traits and the Chi-square test was used for qualitative traits. A $P < 0.05$ was considered to represent statistical significance. Receiver operating characteristic (ROC) curve analysis was carried out to determine the optimal cutoff value of PNI for predicting DR. The multivariate logistic regression model with a forward procedure was performed to find out independent predictors of DR. Multiple logistic regression analysis was conducted for DR using age, duration of diabetes, hemoglobin, creatinine, PNI, hypertension, platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) as explanatory variables. Variables achieving univariate $P < 0.10$ were included in multivariate logistic regression analysis. The ROC curve analysis was carried out to determine the optimal cutoff values of PNI, NLR, and PLR. The areas under the curve (AUC) values were also calculated. A $P < 0.05$ was accepted as statistically significant.

RESULTS

The mean age was 59.3 ± 9.5 years and 76.6% of the patients were female in DR (+) patients ($n = 34$, 34.4% of all patients). In the DR (–) patients ($n = 84$, 65.6% of all patients), the mean age was 55.1 ± 8.6 years and 51.2% of the participants were female. The mean age was significantly higher in DR (+) patients ($P = 0.014$). The gender was similar between the DR (+) and DR (–) patients. Serum lipid parameters, fasting blood glucose, and body mass index levels were also comparable between the groups. Patients with DR had a higher prevalence of hypertension and insulin use, and a longer duration of diabetes, NLR, PLR, and creatinine levels than those without DR. Patients with DR were associated with lower levels of serum albumin and hemoglobin levels than those without DR [Table 1]. The mean PNI values were significantly lower in DR (+) patients than in DR (–) ones (41.20 ± 4.81 vs. 44.49 ± 3.10 , respectively, $P < 0.001$) [Figure 1, Panel A].

Furthermore, the mean PNI values gradually decreased from non-DR to PDR [Figure 1, Panel B]. The mean outcomes of laboratory characteristics of patients according to the severity of DR subgroups are shown in Table 2. Multivariate logistic regression analysis demonstrated that PNI (odds ratio [OR] = 0.845, 95% confidence interval [CI] = 0.735–0.971, $P = 0.017$), duration of diabetes (OR = 1.135, 95% CI = 1.051–1.226, $P = 0.001$), and creatinine (OR = 8.468, 95% CI = 1.773–40.454, $P = 0.007$) were statistically significant and independent risk factors for DR in patients with T2DM [Table 3]. In ROC curve analysis, the sensitivity of PNI was 74% and specificity was 64% for predicting DR; and the cutoff value was 43, $P < 0.001$ [Figure 2]. The AUC

values for PNI were relatively high compared with NLR and PLR (0.713, 0.607, and 0.582, respectively).

DISCUSSION

This study demonstrates an independent association of PNI levels with DR in patients with T2DM, which may become a potential biomarker or provide novel therapeutic targets for DR. First of all, we verified that the PNI was inversely associated with the presence of DR and levels of PNI were lower in the DR group. Furthermore, according to our multivariate analysis, the PNI was an independent variable for DR, after adjustment for traditional risk factors, including A1C, duration of diabetes, and hypertension. We also demonstrated that serum creatinine and duration of diabetes were other independent risk factors for DR.

During recent decades, accumulating evidence has indicated that chronic inflammation is important in the development of T2DM and its chronic complications, including DR.^[20] Yue *et al.*^[21] demonstrated that the PLR and NLR were significantly increased in the setting of DR, but after correcting for possible confounding factors, the monocyte-to-lymphocyte ratio was found to be a risk factor for DR. Recently, Wang *et al.*^[22] reported that systemic inflammatory response indexes NLR and PLR were associated with the presence of DR among T2DM patients. In this study, we demonstrated that the PNI, which was calculated according to serum albumin levels and peripheral lymphocyte counts, reflects both the nutritional and inflammatory status and was inversely associated with the occurrence of DR in T2DM.

A second mechanism that may be relevant in the initiation of DR in T2DM is oxidative stress. It is well accepted that in the development of different eye diseases such as cataract, age-related macular degeneration, glaucoma or DR (NPDR or PDR), and oxidative stress is involved.^[23] Oxidative stress reduces nitric oxide levels, promotes leukocyte adhesion to the endothelium, decreases barrier function of endothelial cells, and damages cellular proteins.^[24] In addition to primary retinal damage by the inflammatory process, induction of

Table 1: Clinical and laboratory data of the patients

Variable	DR (+) (n=44)	DR (-) (n=84)	P
Age (years)	59.3±9.5	55.1±8.6	0.014
Female (sex), n (%)	27 (61.4)	43 (51.2)	0.272
Duration of diabetes (years)	15 (6.5-20)	6 (2.5-10.5)	<0.001
Body mass index (kg/m ²)	30.1±5.4	32.2±7.6	0.115
Hypertension, n (%)	26 (59.1)	34 (40.5)	0.045
Fasting blood glucose (mg/dL)	165.5 (105-236)	155 (117-235)	0.706
Hemoglobin A1c (%)	9.12±2.40	8.86±2.20	0.549
Creatinine (mg/dL)	0.99±0.46	0.79±0.23	0.002
Hemoglobin (g/dL)	12.8±1.8	13.6±1.6	0.009
Total cholesterol (mg/dL)	192.4±57	180.5±40.4	0.316
Low-density lipoprotein (mg/dL)	120.1±38.1	115.7±35.2	0.525
High-density lipoprotein (mg/dL)	41.8±10.4	39.6±9.0	0.341
Triglyceride (mg/dL)	170 (107-269)	170.5 (129-238)	0.946
Albumin (g/dL)	4.11±0.48	4.44±0.31	<0.001
CRP (mg/L)	4.99 (3.11-8.58)	3.58 (3.11-7.99)	0.937
Neutrophil-to-lymphocyte ratio	2.51±1.25	2.08±0.84	0.024
Platelet-to-lymphocyte ratio	131.9±54.2	113.9±37.5	0.030
Prognostic nutritional index	41.20±4.81	44.49±3.10	<0.001
Hypoglycemic medications, n (%)			
Oral hypoglycemic only	38 (86.4)	76 (90.5)	0.479
Insulin only	28 (63.6)	22 (26.2)	<0.001
Oral hypoglycemic + insulin	22 (50.0)	15 (17.9)	<0.001

CRP: C-reactive protein, DR: Diabetic retinopathy

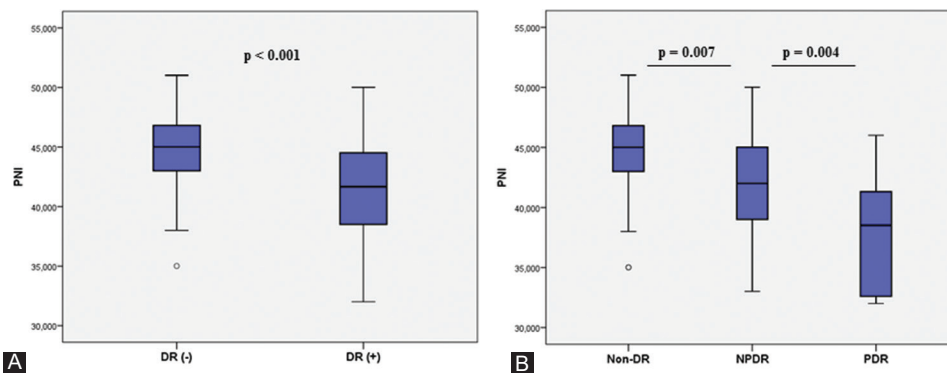


Figure 1: Panel A: Comparison of PNI levels between DR (+) and DR (-) patients. Panel B: PNI levels among T2DM patients with non-DR, NPDR, and PDR. PNI = Prognostic nutritional index, DR = Diabetic retinopathy, PDR: Proliferative DR, NPDR: Non-PDR

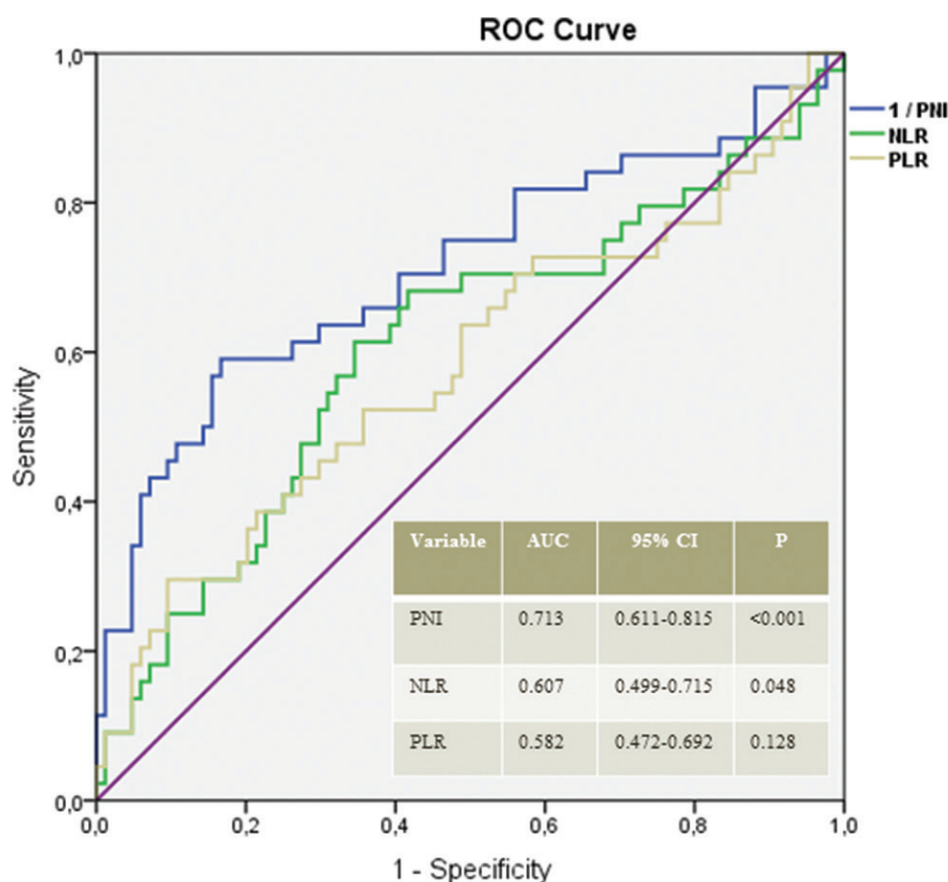


Figure 2: Receiver operating characteristic (ROC) curves of the PNI, NLR, and PLR for predicting DR. PNI = prognostic nutritional index, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, DR = diabetic retinopathy, AUC = area under the curve, CI = confidence interval

Table 2: Laboratory characteristics of patients according to the severity of diabetic retinopathy

Variable	Non-DR (n=84)	NPDR (n=34)	PDR (n=10)	P
Prognostic nutritional index	44.49±3.10	42.18±4.24	37.86±5.36	<0.001
Neutrophil-to-lymphocyte ratio	2.08±0.84	2.33±1.29	3.09±0.92	0.008
Platelet-to-lymphocyte ratio	114±38	127±53	149±58	0.037
Creatinine (mg/dL)	0.79±0.23	0.94±0.40	1.21±0.64	0.001
Hemoglobin (g/dL)	13.69±1.64	13.37±1.70	11.12±0.77	<0.001

DR: Diabetic retinopathy, PDR: Proliferative DR, NPDR: Non-PDR

Table 3: Multivariate logistic regression analysis showing independent predictors of diabetic retinopathy

Variable	Multivariate analysis	
	OR (95% CI)	P
Age	1.029 (0.967-1.095)	0.366
Duration of diabetes	1.135 (1.051-1.226)	0.001
Hypertension	1.022 (0.356-2.935)	0.967
Creatinine	8.468 (1.773-40.454)	0.007
Hemoglobin	0.904 (0.668-1.222)	0.511
Prognostic nutritional index	0.845 (0.735-0.971)	0.017
Platelet-to-lymphocyte ratio	1.009 (0.991-1.027)	0.340
Neutrophil-to-lymphocyte ratio	1.383 (0.468-4.082)	0.557

OR: Odds ratio, CI: Confidence interval

toxic effects on retinal pericytes due to oxidative stress may result in apoptosis culminating in full-blown DR.^[25] Serum albumin is synthesized in the liver and has many physiological functions. Serum albumin provides important protection against oxidative stress. Iwasaki *et al.*^[12] reported a significant association of serum albumin with the severity of retinopathy in T2DM. Recently, it has been found that serum albumin is independently associated with diabetic chronic vascular complications.^[26] In the present study, lymphocyte counts were not statistically significant between the groups. However, serum albumin levels were found to be significantly lower in patients with DR, which leads us to suggest that in this group lower PNI values are mainly driven by decreased albumin levels. This implies that lower serum albumin might contribute to the development of DR due to its diminished antioxidant and anti-inflammatory effects.

On the other hand, a wide array of nutrients, by their natural physiological, biochemical, and molecular action, can preserve retinal structure and functions by interfering with the various pathological steps prompting DR incidence. Nutrients can also play a central role in DR patients. Nutrition-based approaches have a high potential to be developed as an adjunct therapy for arresting the occurrence or progression of DR and subsequent

loss of vision in the early stages.^[27] The PNI is as an easily measurable index of nutrition status. Herein, in light of our study findings, we can speculate that lower PNI levels in patients with DR may also reflect underlying malnutrition in these patients.

Finally, several studies have shown associations between serum creatinine and DR.^[28-30] In line with these previous studies, in the current study we also demonstrated that serum creatinine was another independent risk factor for the presence of DR.

This study has several potential limitations. First, the single-center design and relatively small sample size of the study are the main limitations. Second, since this study is cross-sectional, we could not refer to causal relationships. Third, given that the PNI as the nutritional evaluation was conducted only at a single time point, we did not investigate the changes in nutritional status over time and its relationship with DR outcomes. Finally, the sensitivity and specificity of PNI levels to predict DR is not very high, which may be related to the small sample size. We hope to expand the number of enrolled patients in our further investigation.

CONCLUSION

The present study revealed that PNI was inversely and independently associated with the presence of DR. The assessment of inflammatory-nutritional status with PNI could allow clinicians to identify patients with T2DM at elevated risk for DR. Further, clinical trials are needed to prospectively evaluate the efficacy of nutritional interventions on DR development and progression in patients with T2DM.

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Conflicts of interest

There are no conflicts of interest.

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