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ORIGINAL RESEARCH

Relationship Between Chronic Inflammatory Indicators and Diabetic Peripheral Neuropathy in Hospitalized Elderly Patients with Type 2 Diabetes

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Purpose: Investigate the correlation between chronic inflammatory indicators and DPN in hospitalized elderly patients with Type 2 diabetes mellitus (T2DM), and to build a prediction model to provide scientific basis for early identification of high-risk groups.

Patients and Methods: Clinical data of 270 elderly T2DM patients hospitalized in the People's Hospital of Ningxia Hui Autonomous Region from January 2021 to December 2024 were selected and classified into a diabetic peripheral neuropathy group (DPN, n=163) and a non-diabetic peripheral neuropathy group (NDPN, n=107) depending on the presence of DPN. Clinical features, biochemical indicators and peripheral blood inflammatory indicators (PLR, NLR, MLR, SII, SIRI) of patients were collected, and a predictive model was constructed by logistic regression analysis.

Results: The age, duration of diabetes, retinopathy, HbA1c, fasting blood glucose (FBG) and 2hPPG in DPN group were all higher than those in nonDPN group (P<0.05). In addition, the levels of PLR, NLR, MLR, SII and SIRI in DPN group were significantly higher than those in NDPN group (P<0.05). Multivariate Logistic regression analysis showed that the duration of diabetes, accompanying retinopathy, HbA1c and NLR were independent risk factors for DPN. The area under ROC curve (AUC) of the combined predictor constructed based on these factors was 0.802, which showed good prediction efficiency.

Conclusion: Chronic inflammatory indicators such as PLR, NLR, MLR, SII and SIRI are closely related to elderly T2DM patients with DPN. Comprehensive evaluation of these indicators and key factors such as diabetes course can effectively predict the risk of elderly T2DM patients with DPN, which is conducive to early intervention and management, thereby improving patient prognosis. Reduce hospitalization rates and medical costs. This study provides a new perspective for understanding the role of chronic inflammation in DPN and lays the foundation for further research.

Keywords: diabetic peripheral neuropathy, Elderly type 2 diabetes mellitus, chronic inflammatory indicators

Introduction

The number of people with diabetes mellitus (DM) has been rising since the turn of the twenty-first century, and by 2050,[1] it is predicted that there will be 1.31 billion DM sufferers worldwide. In China, type 2 diabetes is the most common chronic metabolic condition. About 30% of DM patients are elderly, making them more vulnerable to the disease. DPN, one of the most prevalent chronic complications of DM in the elderly, is a major cause of falls and fractures, can result in foot ulcers and nontraumatic amputations, and has a significant negative impact on patients' quality of life, hospitalization rates, and financial burden. The risk of dying from any cause is significantly increased when DPN is present.[2] The financial toll that diabetes and DPN take is also significant; in 2015, the worldwide cost of diabetes care was US$1.3 trillion, or 1.8% of the world's gross domestic product (GDP). If current trends continue, it is anticipated that by 2030, the entire cost of diabetes care will reach US$2.48 trillion, or 2.2% of world GDP.[2] DM

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complications, such as DPN, are significantly more expensive to treat than DM itself.[3] In addition to being a major contributing factor to the cost of hospitalization for elderly patients with DPN complications, DPN is also a major factor in the hospitalization of elderly patients with T2DM.[4] This study represents the first attempt to integrate clinical features and pathophysiological indicators in identifying early risk factors associated with hospitalization among elderly patients with DPN. The primary objective is to mitigate the likelihood of DPN-related hospitalizations in individuals with DM, thereby reducing the associated healthcare and management costs.

Recent studies indicate that chronic inflammatory processes contribute to the onset and progression of DM, with inflammatory markers in peripheral blood serving as independent risk factors. Inflammation and metabolic response pathways are closely integrated and mutually dependent, playing a crucial role in the development of DPN. Kellogg et al reported elevated levels of the inflammatory marker tumor necrosis factor-α (TNF-α) in the peripheral nerves of diabetic *rats* compared to those in normal controls.[5] In patients with diabetic peripheral neuropathy, increased expression levels of inflammatory factors such as platelet-derived growth factor AA/BB (PDGF AA/BB), granulocyte colony-stimulating factor (G-CSF), C-reactive protein (CRP), and TNF-α have been observed relative to healthy controls.[6] Furthermore, in patients with advanced diabetic peripheral neuropathy, upregulation of cytokines, chemokines, and specific genes such as DBKRB2 and ADORA3 has been identified, suggesting an intensified inflammatory response and dysregulated immune defense, which may be linked to severe nerve damage.[7] There is also existing literature suggesting that inflammatory responses play a critical role in the progression of neurodegeneration.[8] Compared with the aforementioned inflammatory markers, the inflammatory indicators examined in this study are more accessible in clinical settings and offer greater cost-effectiveness. Previous studies have found that the ratio of neutrophil count to lymphocyte count (NLR), monocyte count to lymphocyte count (MLR), and platelet count to lymphocyte count (PLR) are correlated with the incidence of DPN, the PLR and NLR levels in patients with DPN are significantly higher compared to those in patients without DPN.[9–13] However, there are few studies on the correlation between DPN and inflammatory indicators in the elderly. SII is a marker of chronic low-grade inflammation based on neutrophil, lymphocyte count, and platelet count, which is more comprehensive than NLR, MLR, and PLR. Systemic Immune-Inflammation Index(SII) and Systemic Inflammatory Response Index (SIRI) are inflammatory biomarkers derived from the counts of monocytes, neutrophils, and lymphocytes. SII is defined as (neutrophil count (N) × platelet count (Plt)) / lymphocyte count (L), while SIRI is defined as (neutrophil count (N) × monocyte count (M)) / lymphocyte count (L). Research has demonstrated that elevated levels of SII are associated with an increased risk of malignant tumors, cognitive dysfunction, depression, cardiopulmonary diseases, rheumatic disorders, and metabolic conditions.[14–18] Although existing studies have identified a correlation between SIRI is limited evidence regarding its association with DPN.[19] This study represents the first investigation focusing on inflammatory factors PLR, NLR, MLR, SII, SIRI and type 2 diabetes mellitus in elderly patients with peripheral neuropathy. By analyzing the clinical characteristics of elderly patients with T2DM, this study examines the link between chronic inflammatory markers and DPN, develops a predictive model for identifying high-risk factors, and provides a scientific basis for early prevention of DPN progression, aiming to reduce hospitalization rates in this population.

Methods

Subjects

A total of 270 elderly patients with T2DM (n = 107 without DPN and n = 163 with diagnosed DPN) who admitted to our inpatient clinic between January 2021 and December 2024 were enrolled. In accordance with the criteria of the Declaration of Helsinki, the Ethics Committee of the People's Hospital of Ningxia Hui Autonomous Region approved the study before it began.

Inclusion criteria: 1. The patient being conscious and having no significant communication impairment. 2. Age over 60 years; 3. Diagnosis of T2DM according to established clinical guidelines;[20] 4. Clinical or subclinical diagnosis of DPN), defined as follows: - Clinical diagnosis requires fulfillment of all four criteria (①–④); - Subclinical diagnosis requires fulfillment of three criteria (①, ②, ④, and ⑤): ① A clear history of diabetes mellitus; ② Onset or progression of neuropathy after the diagnosis of diabetes; ③ Presence of symptoms such as pain, numbness, or paresthesia, along

with abnormalities in at least one of the following neurological assessments: ankle reflex, pinprick sensation, vibration sensation, pressure sensation, or temperature sensation; ④Exclusion of other potential causes of neuropathy, including neurotoxic drug exposure (eg, chemotherapy), vitamin B12 deficiency, cervical or lumbar spine disorders (eg, compression, stenosis, degeneration), cerebral infarction, chronic inflammatory demyelinating neuropathy, hereditary neuropathy, vasculitis, acquired immunodeficiency syndrome, and renal insufficiency-induced nerve damage due to metabolic toxins; ⑤ In the absence of typical symptoms or signs, abnormal nerve conduction findings on neurophysiological testing. Exclusion criteria: Type 1 diabetes mellitus, type 2 diabetes mellitus with acute complications, pregnant patients, severe liver and kidney damage, acute and chronic infection, tumor, trauma, stress state (such as trauma, surgery), mental illness. Clinical data are incomplete.

Data Collection and Laboratory Analysis

General Information and Blood Samples Examination

The patient's gender, age, height, weight, blood pressure, duration of diabetes, smoking history, alcohol consumption history, and presence of chronic microvascular complications (including diabetic kidney disease (DKD) and diabetic retinopathy (DR), either previously diagnosed or diagnosed during hospitalization were recorded. Additionally, coexisting macrovascular complications such as diabetic vascular disease, hypertension and coronary atherosclerotic heart disease were documented. Blood samples were collected early in the morning of the following day after 8–10 hours of fasting after admission to the hospital, neutrophil count (N), lymphocyte count (L), monocyte count (M), platelet count (P), fasting blood glucose (FBG), 2hPPG after meals, glycated hemoglobin (HbAlc), fasting insulin (FINS), fasting C-peptide (FCP), 2h-INS after meals, and 2h-CP after meals. Aspartate aminotransferase (AST), serum alanine aminotransferase (ALT). Uric acid (UA), serum creatinine (Scr), urea nitrogen (BUN), cystatin C (CysC). 25-hydroxyvitamin D (25(OH)D) and other indexes were measured. Urinary microalbumin (MALB) was detected by collecting urine samples after early morning cleaning. Using flow cytometry to detect routine blood indexes, using automatic biochemical analyzer to detect biochemical indexes, using high-performance liquid-contrast cation-exchange chromatography to determine the glycated hemoglobin, and electrochemiluminescence to determine INS and C-peptide.

Neurophysiological Examination

Neuroelectrophysiological examination by a professional (machine model Dantec Keypoint4), The conduction velocity, evoked potential amplitude and distal latency of the motor branches of the median nerve, ulnar nerve, radial nerve, tibial nerve and common peroneal nerve, as well as the conduction velocity and evoked potential amplitude of the sensory branches of the median nerve, radial nerve, ulnar nerve and sural nerve were detected respectively.

Calculation Formula

Glomerular Filtration Rate (GFR) refers to the following formula (scr: blood creatinine value)

$GFR=175*Scr(mg/dl)^{-1.234}*Age(year)^{-0.179}(women*0.79)$

PLR=Platelet count (Plt)/Lymphocyte count (L)

NLR=neutrophil count (N)/lymphocyte count (L)

MLR=monocyte count (M)/lymphocyte count (L)

SII=neutrophil count (N)*platelet count (Plt)/lymphocyte count (L)

SIRI=neutrophil count (N)*monocyte count (M)/lymphocyte count (L)

Statistical Methods

SPSS24.0 was used for data statistics. The measurement data conforming to normal distribution were expressed by mean ± standard deviation, and comparison between the two groups was performed by *t*-test. The measurement data that did not conform to the normal distribution were represented by the median (interquartile distance), and the rank sum test was used between the two groups. Categorical variables were represented by %, and Chi-square test was used to compare rates. The correlation between blood cell ratio and DPN in elderly patients was evaluated and the optimal cut-off value

was determined using receiver operating curve (ROC). The logistic regression model was used to carry out multi-factor regression analysis, and the prediction model was constructed.

Results

Comparison of General Data and Laboratory-Related Indicators in All

The study subjects were divided into DPN and non-DPN groups according to the presence or absence of comorbid peripheral neuropathy. The proportion of elderly people and the duration of diabetes mellitus in the DPN group was higher than that in the NDPN group ($P < 0.05$), and the proportions of comorbid retinopathy and diabetic nephropathy were higher than that in the NDPN group ($P < 0.05$). Gender, smoking ratio, alcohol consumption ratio, body mass index, systolic and diastolic blood pressure were similar between the two groups ($P > 0.05$), and the proportions of coronary artery disease, hypertension, diabetic vasculopathy, and dyslipidemia were similar ($P > 0.05$).(Table 1) The levels of fasting blood glucose, postprandial 2-hour glucose, glycosylated hemoglobin, fasting insulin, urinary microalbumin, and urea nitrogen in the DPN group were significantly higher than those in the NDPN group ($P < 0.05$), 2-hour postprandial C-peptide, glutamic oxaloacetic transaminase, and glutamic alanine transaminase levels were significantly lower than those in the NDPN group ($P < 0.05$). Fasting C-peptide, insulin, cholesterol, triglycerides, HDL, LDL, total protein, albumin, 25-OH vitamin D, cystatin C, uric acid, and glomerular filtration rate levels were similar between the two groups ($P > 0.05$) (Table 2).

Table 1 Baseline Demographic, Clinical of Study Population According to Presence of Neuropathy

Variant	DPN Group (n=163)	NDPN Group (n=107)	t/Z/X^2	P-value
Age (years)	67 (63,70)	65 (62, 69)	−2.896	0.004
Genders			0.315	0.575
Male	94 (57.7%)	58 (54.2%)		
Female	69 (42.3%)	49 (45.8%)		
Smoking history (%)			2.644	0.104
Yes	47 (28.8%)	41 (38.3%)		
No	116 (71.2%)	66 (61.7%)		
Drinking history (%)			1.029	0.310
Yes	34 (20.9%)	28 (26.2%)		
No	129 (79.1%)	79 (73.8%)		
Duration of diabetes (months)	**144 (96, 240)**	**72 (12, 144)**	**−5.617**	**<0.001**
BMI (kg/m^2)	24.23±3.21	24.58±2.72	0.944	0.346
Systolic blood pressure (mmHg)	126 (118, 136)	125 (118, 134)	−0.561	0.575
Diastolic blood pressure (mmHg)	80 (70,85)	80 (70,85)	−0.299	0.765
Coronary heart disease (%)			0.362	0.548
Yes	37 (22.7%)	21 (19.6%)		
No	126 (77.3%)	86 (80.4%)		
Hypertension (%)			0.337	0.561
Yes	79 (48.5%)	48 (44.9%)		
No	84 (51.5%)	59 (55.1%)		
DR (%)			**17.807**	**<0.001**
Yes	**34 (20.9%)**	**3 (2.8%)**		
No	**129 (79.1%)**	**104 (97.2%)**		
DKD (%)			**8.636**	**0.003**
Yes	**16 (9.8%)**	**1 (0.9%)**		
No	**147 (90.2%)**	**106 (99.1%)**		

Notes: Significance at a P value of <0.05, the significantly different findings be marked with bold letters to increase the understanding.
Abbreviations: BMI, weight (kg)/height (m); DR, diabetic retinopathy; DKD, diabetic kidney disease.

Table 2 Baseline Laboratory Characteristics of Study Population According to Presence of Neuropathy

Variant	DPN Group (n=163)	NDPN Group (n=107)	t/Z	P-value
FPG (mmol/L)	**8.30 (6.80,10.20)**	**7.4 (6.20,8.90)**	**−3.088**	**0.003**
2hPBG (mmol/L)	14.10 (10.90,17.00)	12.40 (10.20,15.90)	−2.013	0.044
HbA1c (%)	**8.80 (7.50, 10.40)**	**7.40 (6.50, 9.20)**	**−4.618**	**<0.001**
FINS (mU/L)	**11.00 (6.00, 24.00)**	**9.70 (5.10,14.70)**	**−2.059**	**0.040**
FCP (nmol/L)	**0.41 (0.22,0.62)**	**0.48 (0.30,0.66)**	**−1.853**	**0.064**
2hINS (mU/L)	35.40 (22.5, 62.1)	44.2 (29.471.7)	−1.744	0.081
2hCP (nmol/L)	**0.93 (0.57, 1.51)**	**1.53 (0.88,2.03)**	**−4.695**	**<0.001**
ALT (U/L)	18.60 (13.80, 24.00)	24.08 (14, 1.75)	−2.067	0.039
AST (U/L)	18.00 (15.00,22.00)	21.00 (14.00,32.00)	−2.217	0.027
25(OH)D (ng/mL)	19.03 (13.72,28.60)	17.83 (12.27, 25.55)	−1.198	0.231
MALB (mg/L)	11.70 (4.50, 38.20)	8.2 (4.60,16.00)	−2.256	0.024
Cr (μmol/L)	63.00 (53.00,73.00)	62.00 (50.00,73.00)	−0.742	0.469
BUN (mmol/L)	6.15 (5.20, 7.20)	5.93 (4.74,6.89)	−1.974	0.048
CysC (mg/L)	0.83 (0.72, 0.99)	0.84 (0.76,0.95)	−0.069	0.945
UA (μmol/L)	290.00 (233.00, 345.70)	293.00 (236.00, 350.00)	0.480	0.631
GFR (mL/min/1.73m^2)	**114.87 (95.76, 138.01)**	**118.72 (104.11, 137.59)**	**−0.755**	**0.450**

Notes: Significance at a P value of <0.05, the significantly different findings be marked with bold letters to increase the understanding.
Abbreviations: FPG, fasting blood glucose; 2hPBG, 2-hour postprandial blood glucose; HbA1c, glycated hemoglobin; FINS, fasting insulin; 2hINS, 2-hour postprandial insulin; FCP, fasting C-peptide; 2hCP, 2-hour postprandial C-peptide; ALT, alanine aminotransferase; AST, aminotransferase; 25(OH)D, 25 hydroxyvitamin D; MALB, urinary microalbumin; Cr, creatinine; BUN, urea nitrogen; CysC, cystatin C; UA, uric acid; GFR, glomerular filtration rate.

Comparison of Peripheral Blood Inflammation Indexes Between the Two Groups of Patients

Comparison of peripheral blood inflammation indexes between the two groups of patients, PLR, NLR, MLR, SII, SIRI in the DPN group were significantly higher than those in the NDPN group (P<0.05). (Table 3, Figure 1) Predictive value of peripheral blood inflammation indexes for DPN. NLR, MLR, SII and SIRI are all valuable in the diagnosis of type 2 diabetes mellitus combined with peripheral neuropathy in the elderly (Figure 2, Table 4).

Regression Analysis of Influencing Factors Associated with Peripheral Neuropathy in Patients with Type 2 Diabetes Mellitus with Complications

The presence or absence of DPN was included as the dependent variable, and age, duration of diabetes, concomitant diabetic retinopathy, concomitant diabetic nephropathy, fasting glucose, 2-hour postprandial glucose, glycosylated hemoglobin, fasting insulin, 2-hour postprandial C-peptide, ghrelin, urea nitrogen, urinary microalbumin, glomerular filtration rate, PLR, NLR, MLR, SII, and SIRI were included as independent variables. Duration of diabetes, concomitant retinopathy, glycosylated hemoglobin, glomerular filtration rate, and NLR were risk factors for DPN (Table 5).

Table 3 Inflammatory Indicators Between the Two Groups of Patients

Variant	DPN Group (n=163)	NDPN Group (n=107)	t/Z	P-value
PLR	112.19 (83.94, 127.10)	95.79 (80.89, 118.14)	−2.129	0.033
NLR	1.99 (1.52, 2.34)	1.45 (1.16,1.91)	−4.870	<0.001
MLR	0.22 (0.17,0.25)	0.19 (0.14, 0.24)	−2.205	0.027
SII	396.65 (273.96, 451.26)	304.14 (220.76, 389.85)	−2.776	0.006
SIRI	0.80 (0.51,0.96)	0.50 (0.40,0.82)	−3.083	0.002

Note: Significance at a P value of <0.05.
Abbreviations: PLR, Platelet count (Plt)/Lymphocyte count (L); NLR, neutrophil count (N)/lymphocyte count (L); MLR, monocyte count (M)/lymphocyte count (L); SII, neutrophil count (N)*platelet count (Plt)/lymphocyte count (L); IRI, neutrophil count (N)*monocyte count (M)/lymphocyte count (L).

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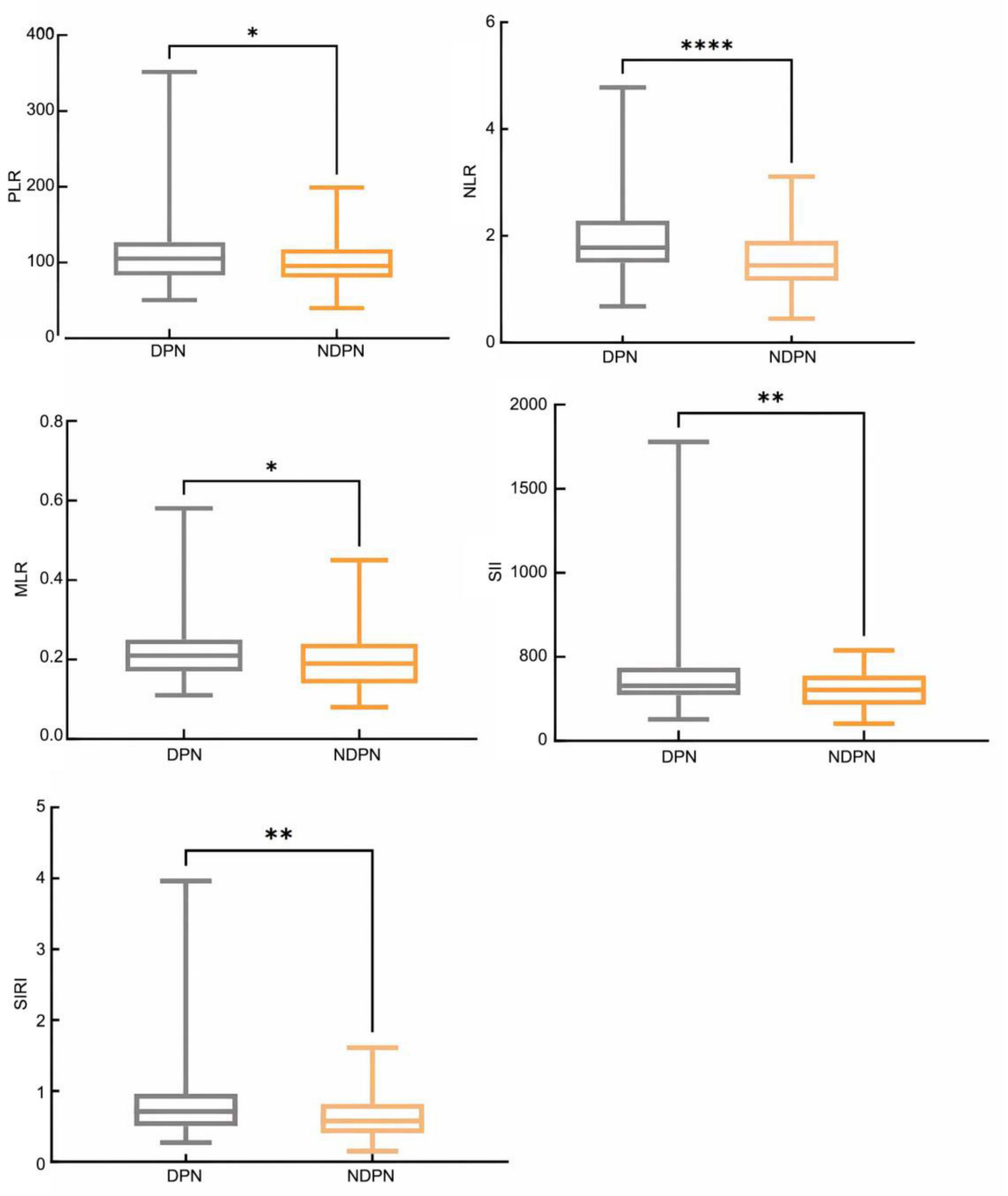

Figure 1 PLR, NLR, MLR, SII, SIRI in two groups of patients. *P <0.05, **P <0.01 and ****P <0.001.

Abbreviations: PLR, Platelet count (Plt)/Lymphocyte count (L); NLR, neutrophil count (N)/lymphocyte count (L); MLR, monocyte count (M)/lymphocyte count (L); SII, neutrophil count (N)*platelet count (Plt)/lymphocyte count (L); SIRI, neutrophil count (N)*monocyte count (M)/lymphocyte count (L).

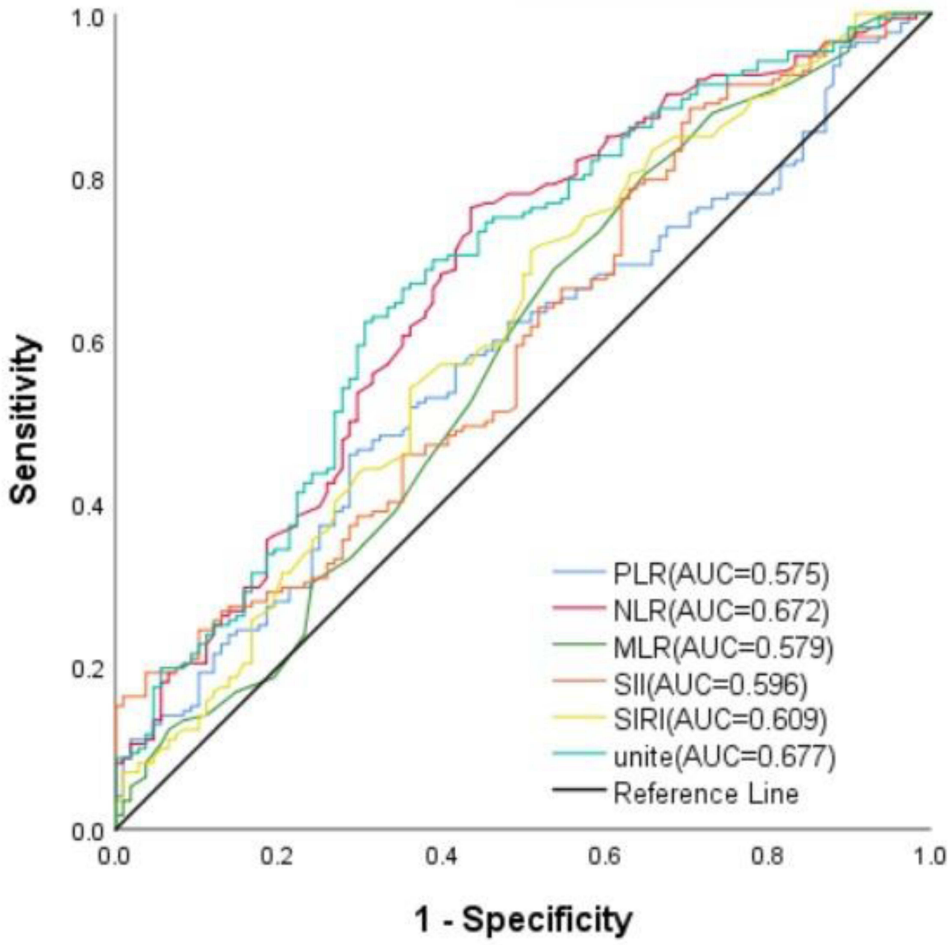

Figure 2 ROC curves of PLR, NLR, MLR, SII, SIRI regarding DPN in elderly type 2 diabetes mellitus.
Abbreviations: PLR, Platelet count (Plt)/Lymphocyte count (L); NLR, neutrophil count (N)/lymphocyte count (L); MLR, monocyte count (M)/lymphocyte count (L); SII, neutrophil count (N)*platelet count (Plt)/lymphocyte count (L); IRI, neutrophil count (N)*monocyte count (M)/lymphocyte count (L).

Constructing the Joint Predictor of Peripheral Neuropathy in Patients with Type 2 Diabetes Mellitus

Combining the results of multifactorial analysis, the joint predictor was constructed according to the regression coefficients of diabetes duration, whether or not diabetic retinopathy was combined, glycated hemoglobin, glomerular

Table 4 Area Under the ROC Curve for PLR, NLR, MLR, SII, SIRI

Variant	AUC	P-value	95% CI	Truncation Value	Sensitivity	Specificity
PLR	0.575	0.035	0.507~0.642	110.035	0.459	0.713
NLR	0.672	<0.001	0.606~0.737	1.485	0.762	0.565
MLR	0.579	0.026	0.509~0.649	0.165	0.802	0.352
SII	0.596	0.007	0.528~0.664	226.53	0.884	0.296
SIRI	0.609	0.002	0.54~0.678	0.545	0.709	0.491
Unite	0.677	<0.001	0.612~0.742	0.60	0.622	0.694

Note: Significance at a P value of <0.05.
Abbreviations: PLR, Platelet count (Plt)/Lymphocyte count (L); NLR, neutrophil count (N)/lymphocyte count (L); MLR, monocyte count (M)/lymphocyte count (L); SII, neutrophil count (N)*platelet count (Plt)/lymphocyte count (L); SIRI, neutrophil count (N) *monocyte count (M)/lymphocyte count (L).

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Table 5 Logistic Regression Analysis of Patients with and without Diabetic Combined Neuropathy

Considerations	B	SE	Wald	P-value	OR	95% CI
DM course	0.008	0.002	21.813	<0.001	1.008	1.005–1.012
DR	1.358	0.65	4.360	0.037	3.888	1.087–13.906
HbA1c	0.34	0.079	18.545	<0.001	1.405	1.203–1.640
NLR	0.888	0.252	12.389	<0.001	2.430	1.482–3.984
Constant	−1.925	1.295	2.208	0.137	0.146	

Note: Significance at a P value of <0.05.
Abbreviations: DR, diabetic retinopathy; HbA1c, glycosylated hemoglobin; NLR, ratio of neutrophil count to lymphocyte count.

Table 6 AUC Under ROC Curve of Joint Predictor

Variable	AUC	SE	P-value	95% CI	Truncation Value	Sensitivity	Specificity
Co-predictors	0.802	0.026	<0.001	0.751～0.854	0.5523815	0.755	0.701

Note: Significance at a P value of <0.05.
Abbreviations: AUC, area under the curve; SE, standard error; Co-predictors, diabetes duration, diabetic retinopathy, glycosylated hemoglobin, NLR.

filtration rate, and NLR, and the joint predictor=−4.735+0.008*(diabetes duration)+1.477*(whether or not diabetic retinopathy was combined)+0.296*(glycated hemoglobin)+0.861*(NLR), the cutoff point of the joint predictor was calculated to be 0.5523815, and the area under the ROC curve was 0.802 (95% CI 0.751 to 0.854) (Table 6, Figure 3).

Discussion

The etiology and pathogenesis of DPN are complex and have not been fully elucidated. Currently, it is believed that DPN is related to age, diabetes course, gender, body mass index, smoking or not, education level, hyperglycemia, hyperlipidemia, insulin resistance, oxidative stress, chronic systemic inflammation, nerve growth factor, etc. In recent years, many studies have suggested that chronic inflammation plays an important role in the occurrence and development of DPN.[21,22] Inflammation refers to the process in which the body makes a series of responses to restore homeostasis after a destructive stimulus, and if this state persists or does not subside, it will cause chronic low-grade inflammation. At present, the main triggers for chronic low-grade inflammation are Westernized eating habits, low physical activity, lack of sleep and environmental pollution.[23] Chronic low-grade inflammation is closely related to the occurrence and development of chronic diseases, including cardiovascular diseases, diabetes, obesity, and tumors.[23] In people with DM, this chronic low-grade inflammation can lead to microvascular dysfunction, including vascular endothelial cell damage, increased vascular permeability, increased blood flow resistance, and platelet aggregation, leading to diabetic microvascular complications.[24,25] DPN is one of the common chronic microvascular complications of T2DM and a major cause of lower limb amputation and disabling neuropathic pain. Zheng et al found in a prospective cohort study that baseline plasma levels of tumor necrosis factor-α (TNF-α), IL-6, and intercellular adhesion molecule-1 (ICAM-1) were higher in DPN (P<0.05).[26] In a multivariate model, plasma TNF-α levels increased after adjusting for known DPN risk factors (OR= 8.74; 95% CI: 1.05–72.68; P<0.05) and ICAM-1(OR= 23.74; 95% CI: 1.47–383.81; P<0.05) were associated with new DPN.[26] Increased levels of plasma pro-inflammatory factors (especially TNF-α and ICAM-1) can predict the incidence of DPN in Chinese DM patients within 5 years.[26] Herder et al, in a population-based study of older adults of European descent, showed that TNF-α and IL-6 are predictors of the development of distal sensorimotor polyneuropathy, while the interleukin-1 receptor antagonist IL-1RA and ICAM-1 are associated with the progression of the regulation of known DPN risk factors.[27] The peripheral blood cells included in this study (neutrophil count, lymphocyte count, monocyte count, and platelet count) play a key role in the inflammatory response and immune system. Neutrophils are an essential part of the innate immune system and are a major effector of acute inflammatory

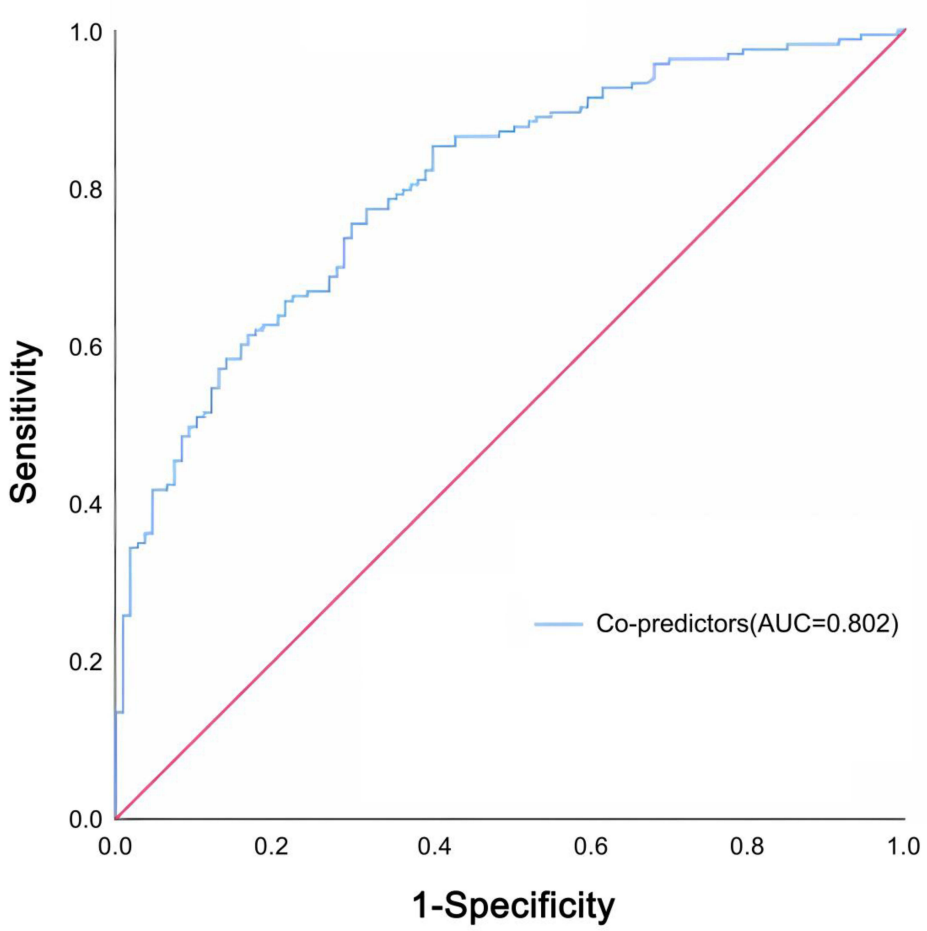

Figure 3 ROC curves of joint predictors regarding peripheral neuropathy in type 2 diabetes mellitus.
Notes: Co-predictors: including diabetes duration, diabetic retinopathy, glycosylated hemoglobin and NLR.
Abbreviation: NLR, neutrophil count (N)/lymphocyte count (L).

responses, while studies have also found that neutrophils can cause chronic inflammation and adaptive immune responses.[28,29] Lymphocytes are mainly involved in immune regulatory pathways and chronic inflammatory response processes, adaptive immunity involving CD4+T cells is crucial for the regulation of chronic inflammation, and helper T cells 17 (Th17) and regulatory T cells (Treg) are crucial for maintaining immune homeostasis.[30] monocytes are innate immune cells that develop in the bone marrow and play an active role in endogenous inflammation. Monocytes are highly plastic and can migrate from the blood to different tissues to differentiate into various monocyte derived cells, which are involved in inflammation and immune regulation.[31] Platelets not only participate in the process of thrombosis and hemostasis, but also play a key role in the regulation of chronic inflammatory response. Studies have found that platelet-derived extracellular vesicles can carry specific lipids and metabolites in the inflammatory response, regulating the severity of inflammation.[32] PLR, NLR, MLR, SII and SIRI are the integration indicators of the above peripheral blood cells. Compared with the number of individual blood cells, the integration indicators can more stably reflect the inflammatory state of the body. PLR is the ratio of platelet count to lymphocyte count and is an inflammatory marker commonly used to evaluate many inflammatory diseases, tumors, and cardiovascular diseases.[33,34] NLR is a dynamic reflection between neutrophils and lymphocytes in disease states, and is an immune response marker for various infectious and non-infectious triggers. It has been widely used in recent years, and can provide a good early warning of infection, inflammation, arteriosclerosis, tumor and psychiatric diseases.[35] MLR is the ratio of monocyte count to lymphocyte count, and is also an inflammatory marker used to assess the risk of cancer, kidney disease, cardiovascular disease, depression, and vascular disease.[36–42] SII is a more comprehensive marker of chronic low-grade inflammation

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based on neutrophils, lymphocyte counts, and platelet counts, and studies have found that elevated SII is associated with an increased risk of malignancies, cognitive dysfunction, depression, cardiopulmonary, rheumatic, and metabolic diseases.[14–18] SIRI is an inflammatory indicator based on monocyte count, neutrophil count and lymphocyte count. Studies have found that SIRI has important diagnostic value in the identification of T2DM complicated DR, and may be used as an early screening indicator for DR.[19] However, there are few studies in DPN field. In cardiovascular diseases, cerebrovascular diseases, malignant tumors, neuropsychiatric diseases, new inflammatory indicators have been confirmed to be related to the risk of disease, diagnosis and prognosis. At present, there are few studies on the correlation between PLR, NLR, MLR, SII, SIRI level and elderly T2DM combined DPN at home and abroad. In this study, the levels of PLR, NLR, MLR, SII and SIRI in the elderly T2DM group combined with DPN were higher than those in the group without DPN, the essence of which was increased neutrophil count, monocyte count and platelet count in peripheral blood, decreased lymphocytes and high levels of chronic inflammation. Previous studies have reported that,[11] PLR, NLR, and SII were all identified as independent risk factors for DPN ($P < 0.05$). Among these biomarkers, NLR demonstrated superior predictive value for DPN compared with PLR and SII. Furthermore, the combined use of these three indicators showed higher predictive efficiency than any single indicator alone (all $P < 0.05$). The results of this study revealed that the area under the ROC curve (AUC) for PLR, NLR, MLR, SII, and SIRI in predicting DPN was 0.575, 0.672, 0.579, 0.596, and 0.609, respectively — all exceeding 0.5. The corresponding specificity values were 71.3%, 56.5%, 35.2%, 29.6%, and 49.1%, while the sensitivity values were 45.9%, 76.2%, 80.2%, 88.4%, and 70.9%, respectively. The optimal cut-off values were determined to be 110.035 for PLR, 1.485 for NLR, 0.165 for MLR, 226.53 for SII, and 0.545 for SIRI. These findings suggest that PLR, NLR, MLR, SII, and SIRI have potential clinical utility in the diagnosis of DPN among elderly patients. Li et al found that peripheral blood SII level in T2DM patients complicated with DPN was higher than that in T2DM patients.[43] The multivariate logistic regression analysis of this study demonstrated that a history of DR (OR = 3.888, 95% CI:1.087–13.906, $p < 0.05$), elevated NLR (OR = 2.430, 95% CI:1.482–3.984, $p < 0.01$), and GFR (OR = 0.967, 95% CI: 0.944–0.990, $p < 0.01$) were independent risk factors for DPN. Li et al showed that NLR is a more effective potential inflammatory marker to identify the risk of T2DM patients with DKD, albuminuria, and low glomerular filtration rate in the United States.[44] These are consistent with the results of this study, PLR, NLR, SII, and SIRI as indicators of chronic inflammation, and the elevated levels suggest that inflammatory responses are closely related to diabetic microvascular complications.

Furthermore, microvascular disease is an important pathological basis for the occurrence and development of DPN. Aging will affect the vascular microenvironment of patients, resulting in decreased blood flow velocity, endothelial cell damage, endothelial dysfunction, vascular remodeling, and vascular sclerosis.[45] Blood vessel stenosis and slow blood flow lead to microcirculation ischemia and hypoxia. Microvascular ischemia and hypoxia of the nervous system can lead to neuron cell damage and long-term neuronal cell necrosis, resulting in impaired nerve function and decreased nerve conduction speed in the body. One study found that age was an independent risk factor for DPN in Chinese T2DM patients (OR=1.036, 95% CI1.018–1.054, P<0.01).[46] This is consistent with the conclusions reached in this study. The incidence of DPN is higher in men than in women, which may be related to estrogen levels in women, which studies have shown prevents beta cell failure in most diabetic rodent models.[47] In postmenopausal women, estrogen levels in the body decrease and the prevalence of DM is similar to that of men. On the one hand, the decrease of estrogen level increases the blood viscosity, on the other hand, it can lead to the increase of oxidative stress level leading to the damage of nerve cells, and the estrogen level in postmenopausal women decreases. Therefore, the prevalence of DPN in postmenopausal women is similar to that in men. This study found that DPN patients with diabetic microangiopathopathy had a higher proportion of DR And DKD than NDPN patients, which was consistent with previous studies.[48–50] Furthermore, the findings of this study demonstrated that an extended duration of diabetes (OR = 1.008, 95% CI: 1.005–1.012, $p < 0.01$) was independently associated with a higher risk of DPN. Which is consistent with the results of Yueyue Fu et al.[51] There may be the following reasons: On the one hand, the disease course of DM is prolonged, and the body is in the state of hyperglycemia for a longer time. Hyperglycemia causes damage to the nervous system by activating multiple metabolic pathways in the body. For example, the polyol pathway is activated, resulting in the conversion of excess glucose to sorbitol via aldose reductase, an increase in sorbitol, resulting in an imbalance in cell osmosis, resulting in metabolic exodulation of inositol, and a decrease in inositol leading to impaired normal neurophysiological function.[52] On the other

hand, the prolongation of the course of DM is associated with the aging process of the body. With the prolongation of the course of DM, the body is gradually aging, and the function of islet cells in DM patients is gradually weakened, the vascular elasticity is reduced, and the peripheral blood circulation function is weakened, which further accelerates the development of DPN. Poor glycemic control is a recognized risk factor for DPN.

In this study, it was found that the FBG, 2hPPG and HbA1c of elderly patients in the DPN group were significantly higher than those in the NDPN group, and the 2hCP level was lower than that in the NDPN group, which was consistent with the results of Yueyue Fu et al.[51] Elevated levels of HbA1c (OR = 1.405, 95% CI:1.203–1.640, $p < 0.01$) were identified as an independent risk factor for DPN. Chronic hyperglycemia can lead to an increase in the production of advanced glycation total products, and then promote the expression of pro-inflammatory transcription factors and the release of various inflammatory factors by activating intracellular signaling.[53–55] C peptide can promote the function of vascular endothelial cells, increase blood perfusion of nerve tissue, reduce the production of reactive oxygen species (ROS) and inflammatory factors, and protect nerve cells.[56,57] With the prolongation of the disease course of DM, the function of pancreatic β cells gradually declined, resulting in further reduction of C-peptide secretion and enhanced chronic inflammatory symptoms compared with NDPN. GFR is a key indicator for assessing renal function. A reduction in GFR results in the accumulation of urea nitrogen and creatinine in the body, which may trigger oxidative stress, inflammatory reactions, and neurological damage. Studies have indicated that early impairment of renal function in patients with T2DM may accelerate the onset and progression of DPN.[58,59] In the present study, univariate analysis revealed a statistically significant difference in GFR between the DPN group and the non-DPN group ($p < 0.05$). Furthermore, multivariate logistic regression analysis demonstrated that a decreased GFR was an independent risk factor for the development of DPN (OR = 0.967, 95% CI: 0.944–0.990, $p < 0.01$).

The findings of this study indicate that prolonged duration of diabetes, a history of DR, elevated HbA1c levels, an increased NLR, and GFR are independent risk factors associated with the development of DPN among elderly patients with type 2 diabetes. A combined predictive model was developed using logistic regression coefficients derived from these variables. ROC curve analysis demonstrated that the AUC was 0.802, a sensitivity was 75.5%, and a specificity was 70.1%. These results suggest that the proposed model exhibits strong discriminatory power and holds significant potential for clinical application. From the perspective of pathophysiological mechanisms, these indicators constitute a multidimensional network that contributes to the onset and progression of DPN. Among these factors, chronic inflammation serves as a central hub linking various metabolic disturbances with microvascular injury. The prolonged duration of diabetes and elevated HbA1c levels reflect sustained metabolic dysregulation resulting from long-term hyperglycemic exposure. This condition can activate the polyol pathway and the protein kinase C (PKC) pathway, as well as promote the accumulation of advanced glycation end products (AGEs), leading to increased oxidative stress and facilitating the development of localized chronic inflammatory responses.[60] Furthermore, DR as a major manifestation of diabetic microvascular complications, reflects widespread endothelial dysfunction and disturbances in microcirculation. This pathology not only compromises the blood supply to the retina but may also affect peripheral nerves, resulting in reduced neurotrophic support and hypoxic injury. Concurrently, a decrease in GFR indicates impaired renal function, which may further intensify systemic inflammation through the accumulation of metabolites such as methylglyoxal and symmetric dimethylarginine.[61] These substances can interfere with the metabolism of neurotrophic vitamins, including the B complex, thereby worsening structural and functional damage to neural tissues. NLR, as a biomarker of systemic inflammation, reflects an underlying state of immune dysregulation and chronic low-grade inflammation. This inflammatory milieu can directly impair neural tissue by activating glial cells and promoting the release of pro-inflammatory cytokines, while simultaneously hindering neural repair mechanisms, thus accelerating the progression of DPN. In summary, the interplay among systemic inflammatory responses, glycemic control, microvascular health, and renal function changes during the course of diabetes collectively contributes to the onset and progression of DPN.

This study has certain restriction. First, this study is a single-center retrospective cross-sectional study, making our observations susceptible to inherent bias and unable to establish causation. Therefore, prospective studies with larger sample sizes are still needed to clarify cause and effect. Secondly, the current regression model does not include work, treatment compliance, dietary habits, lifestyle, and medication history, such as hypoglycemic drugs, anti-hyperlipidemia drugs, and antihypertensive drugs, and we did not consider the influence of these factors on chronic low-grade

inflammation and metabolic levels. This is the deficiency of this paper, in the future work, as far as possible to eliminate the factors affecting the key indicators.

Conclusion

Compared with the old NDPN, chronic inflammation indexes of PLR, NLR, SII, SIRI is closely related to the elderly DPN. DM in DPN group had longer disease course, higher HbA1c level, higher NLR level, and higher probability of DR. In elderly TDM patients, the combination of NLR, DM duration, DRand HbA1c index can predict the occurrence of DPN.

Ethics Statement

The study followed the principles in the Declaration of Helsinki and was approved by Ningxia Hui Autonomous Region People's Hospital Ethical Committees (2024-LL-135). In addition, this study was a retrospective non-interventional study, and the patient's information was anonymous and confidential, so the signed informed consent was exempted.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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