WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

SJIF Impact Factor: 5.464

ISSN: 2457-0400
Volume: 6.
Issue: 9
Page N. 34-40
Year: 2022

Original Article

www.wjahr.com

PREDICTIVE VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN DIABETIC PERIPHERAL NEUROPATHY PATIENTS TYPE 2 DIABETES

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Received date: 13 July 2022 **Revised date:** 03 August 2022 **Accepted date:** 23 August 2022

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ABSTRACT

Background: Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes mellitus (DM). Further development of DPN can lead to diabetic foot, ulcers, amputation, seriously affecting patient life quality. Therefore, searching for a reliable indicator of DPN early diagnosis is of most significance. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte (PLR) have a close relationship with cancer, cardiovascular diseases, and diabetic microvascular concurrency diseases. We aimed to investigate the relation between NLR, PLR and DPN. **Methods:** A total of 129 newly diagnosed type 2 diabetes mellitus (T2DM) patients were recruited, including 43 patients without complication (DM group) as well as 86 patients complicated with DPN (DPN group). Student t test, Mann-Whiney U test, or x^2 test was applied to the data of the 2 groups. **Results:** NLR and PLR values were remarkably higher in DPN group compared to those of DM group (2,43±1,05 vs 1,31±0,19, P<0,001), (141.26± 63.36 vs 104.93± 44.89, p<0.001) consecutively. The values of glucose, urea, white blood cells count (WBC) and neutrophils count were higher in DPN group, whereas the lymphocyte count and hemoglobin of DPN group were lower than that of DM group (P<0,05). The ROC curve analysis confirmed that the optimal cut–off point, specificity, and sensitivity in diagnosing DPN by NLR and PLR were (1.69, 97.6%, 90.7%), (88.49, 80.2%, 53.5%) consecutively. **Conclusion:** We showed that NLR and PLR are significantly correlated with DPN, which suggested that NLR and PLR could be an independent risk factors of DPN.

KEYWORDS: Diabetic peripheral neuropathy, Neutrophil to lymphocyte ratio, platelet to lymphocyte, Type 2 diabetes mellitus.

1- INTRODUCTION

Diabetes is a major public health problem that is approaching epidemic proportions globally. It is increasing at an alarming rate worldwide. According to International Diabetes Federation statistics, approximately 415 million people are infected, or 8.8% of population is suffering from diabetes, and the number is expected to reach 642 million persons in 2040.[1] Diabetes is one of the most important ten causes of death according to World Health Organization, as it is the seventh place according to its report in 2017. Diabetes causes chronic vascular complications, including diseases affecting small and large blood vessels.[2] It is a major cause of mortality and disease prevalence.[3-4] Chronic high values in glucose results in inflammatory events leading to the release of various cytokines that play a central role in attracting neutrophils, whose activation leads to the release of peroxidase and reactive oxygen species, deepening thus metabolic disorders, accelerating microangiopathy, and increasing the risk of nerve injury with ischemic and metabolic damage.[5]

Diabetic peripheral neuropathy is one of the most common chronic complications of T2DM, as 35% of type 2 diabetics have peripheral neuropathy, while 50% are asymptomatic.[6-7] The development of diabetic peripheral neuropathy can lead to diabetic foot Ulcers, infection and amputation, which greatly affect patient

life.[7] The diagnosis of DPN patients depends on clinical examination and nerve conduction NCS study, but by electrical means it is only possible to detect the injury of a large number of damaged nerve fibers, which creates difficulties for early detection and diagnosis of DPN.[8-9] So the research of reliable indicator of clinical examination and early diagnosis of diabetic peripheral neuropathy is essential. Recently, the neutrophil-to-lymphocyte ratio and platelet to lymphocyte ratio have received attention because of its close association with cancer, heart disease, and microvascular disease caused by diabetes.[10,11] NLR also constitutes an independent risk factor for cerebral hemorrhage in patients with type 2 diabetes.[12] In comparison with other indicators of leukocytes, the stability of NLR is less affected by physiological, physical and pathological factors.[13-14] NLR and PLR are novel, available, and inexpensive marker of Inflammatory status. We aimed to study the association between DPN occurrence and NLR and PLR in T2DM patients, and patients without DPN were followed up to investigate the predictive value of these indicators on newly diagnosed DPN.

2- MATERIAL AND METHODS

2-1-Subjects

This study was conducted between June 2020 and June 2021 at Tishreen University in Lattakia, Syria. After screening, 129 newly diagnosed T2DM patients were recruited in this study. After further search for DPN, there were 43 T2DM patients (DM group) (18 males, 25 females) with an average age of 58.9±9.61 years and 160 T2DM patients complicated with DPN (DPN group) (40 males, 46 females) with an average age of 61.9±9.4 years. The diagnosis of T2DM was according to the 1998 World Health Organization consulting criteria.[15] and DPN was based on the 2006 American Diabetes Association criteria.[2] Patients with myocardial infarction, heart failure, active infection; severe tissue damage, acute massive hemorrhage, acute poisoning, cancer, blood diseases that affect neutrophils, lymphocytes and platelet (e.g, myeloproliferative disease and leukemia) were excluded from the study. All the patients had signed a written informed consent.

2-2-Research methods

All study subjects received a uniform questionnaire survey and physical examination, including measurement of height, weight, body mass index (BMI), fasting plasma glucose (Glu), triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), creatinine (Cr), urea, uric acid (UA), C-reactive protein (CRP), and whole blood count (CBC). Status of smoking was also included.

2-3-Statistical methods

Statistical analyses were performed using SPSS 25 software. Continuous variables were presented as mean±SD values, and categorical variables were expressed as percentages. Student T test was used for continuous variables with normal distribution, and Mann Whitney U test were used for continuous variables without normal distribution. The x^2 test was used for categorical variables. Pearson correlation analysis was used to assess the relationship between DPN and the other data. Those factors showed significance in univariate logistic regression analysis and were pooled in multivariate analysis to identify independent risk factors of DPN. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of NLR and PLR (at which sensitivity and specificity would be maximal) for the prediction of DPN. P values of less than 0.05 were considered to indicate statistical significance.

3-RESULTS

The sample included 129 patients, 58 males (55%) and 71 females (5%), they were divided into two groups:

1- Control group (DM), T2DM without DPN, 43 patients, 18 males (42%) and 25 females (58%).
2- (DPN) group, 86 patients, 40 males (46.5%) and 46 females (53.5%).

3-1- Social characteristics and laboratory results of patients

The difference in age, sex, body mass index, smoking, mean values of CRP, CREA, uric acid, cholesterol, triglycerides, low and high density lipoprotein, and platelet counts between the DM group and DPN group has no statistical significance (P>0.05). The mean values of NLR and PLR in DPN group were significantly higher compared with control group (2.43±1.56, 1.31±0.19), respectively; PLR (141.26±63.36, 104.93±44.89), respectively, Figures (1 and 2). The mean values of leukocytes, neutrophils, blood urea and glucose were significantly elevated in DPN group while the mean values of lymphocytes and hemoglobin were low compared with control group (P<0.05) Table (1).

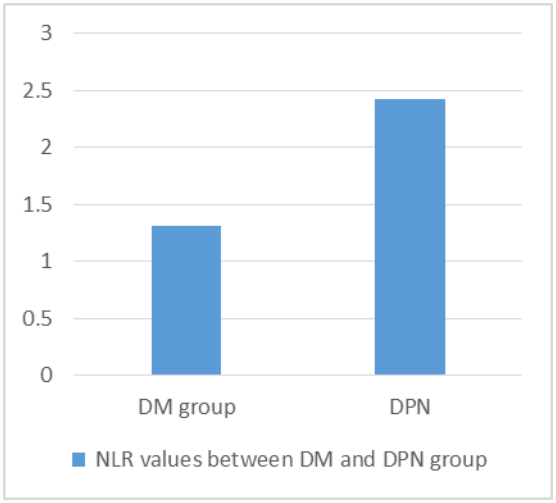

Figure 1: Shows NLR values between controls (DM) and patients (DPN).

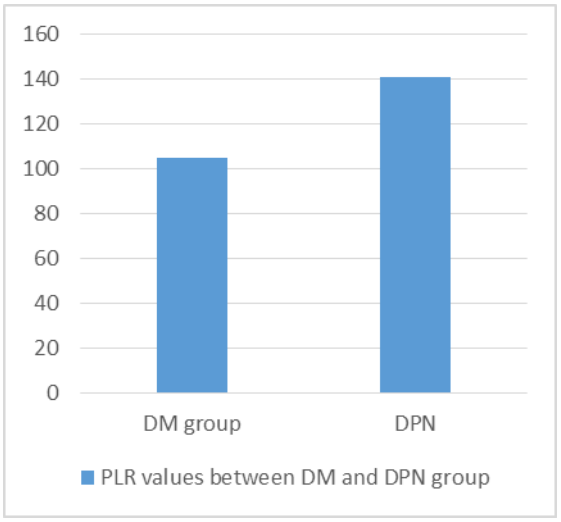

Figure 2: Shows of PLR values between controls (DM) and patients (DPN).

3-2-Relationship between DPN and other indexes

3-2-1-According to Pearson's analysis

There is a positive association between DPN and duration of type 2 diabetes (r=0.363, P<0.001) blood glucose values (r=0.249, p=0.004), blood urea (r=0.203, p=0.021), WBC (r=0.348, p<0.001), neutrophils (r=0.519, p<0.001) and lymphocytes (r=-0.297, p<0.001)), platelets (r = 0.183, p = 0.038), hemoglobin (r = -0.261, p = 0.003), NLR (r= 0.522, p < 0.001) and PLR (r = 0.286, p = 0.001).

3-2-2-According to a multivariate logistic regression analysis

Results showed that NLR (OR=3.7, CI=95%), and PLR (OR=1.6, CI=95%), are independent risk factors for type 2 diabetic peripheral neuropathy (P<0.001).

3-2-3-Sensitivity, specificity analysis, and ROC

The importance of any studied parameter based on its ability to separate patient with DPN from patient without DPN. To determine this ability, ROC Receiver operator charectatisctcs curve was performed, which represents the relationship between sensitivity and 1-specificity. The parameter to be studied is evaluated by the area under the curve. Figure (3) represents ROC curve of NLR for prediction of DPN, Area under the curve 0.982, p-value < 0.05, CI: 0.963–1,000.

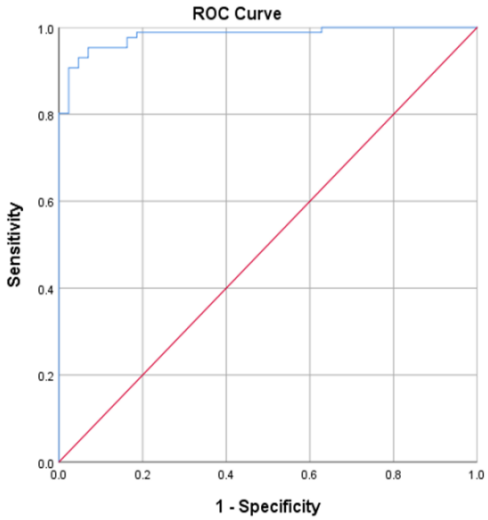

Figure 3: ROC curve of NLR for prediction of DPN.

The curve enables the determination of the threshold value, at which the sensitivity and specificity are at the maximum value, by relying on the Youden parameter, which is equal to sensitivity – (1 - specifity). NLR cut-off value is 1.69, with a sensitivity 90.7% and a specificity 97.6%.

Figure (4) represents ROC curve of PLR for prediction of DPN, area under the curve 0.962, p-value < 0.05, CI: 0,597-0.788.

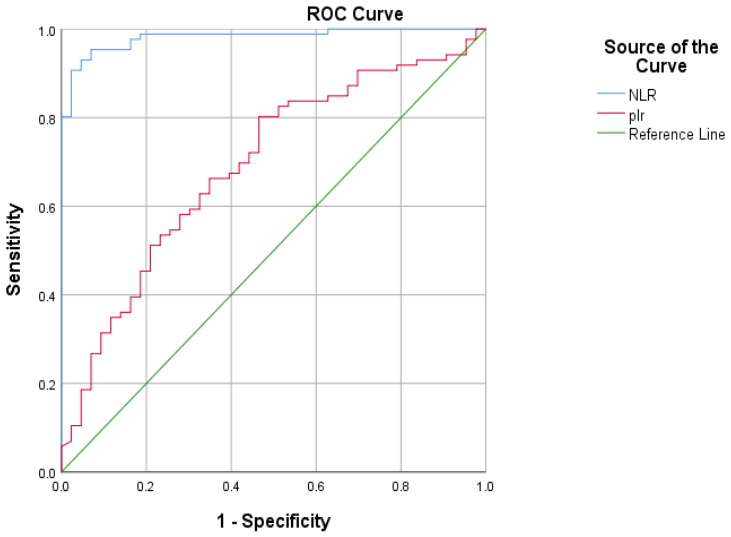

Figure 4: ROC curve of PLR for prediction of DPN.

PLR cut-off value is 88.49, with a sensitivity 80.2% and a specificity 53.5%.

Table 1: Characteristics and laboratory data of the groups.

Variable		(n = 43) DM	(n = 86) DPN	P- Value
Age, Y		58.93±9.66	61.92±9.4	0.095
Male	Sex	(%41) 18	(%53)46	0.708
Fmale		(%59)25	(%47)40	
BMI kg/m^2		29.57±5.18	29.87±4.94	0.746
Yes	Smoking	21	41	1
No		22	45	
duration of diabetes, Y		7.81±4.97	14.12±8.7	< 0,001*
Glu, mg/dl		134.76±42.2	167.6±86.1	0.012*
CRP,mg/l		2.26±1.71	2.76±1.82	0.111
Crea, mg/dl		0.97±0.19	1.05±0.37	0.646
Urea, mg/dl		26.94±7.25	33.64±18.07	0.023*
U.A, mg/dl		5.01±1.19	5.16±1.42	0.052
CHOL, mg/dl		181±73.62	177±45.62	0.67
T.G, mg/dl		209.36±107.9	216.3±124.2	0.79
HDL, mg/dl		44.45±8.59	43.58±10.6	0.64
LDL, mg/dl		87.7±20.98	90.1±30.08	0.43
WBC, (×10^3/ul)		6.55±1.74	7.91±1.73	<0,001*
Neutrophil (×10^3/ul)		3.31±9.09	4.91±1.39	<0,001*
Lymphocyte (×10^3/ul)		2.56±7.55	2.14±5.76	<0.001
Platelets (×10^3/ul)		246±63	280±95	0.08
Hg g/dl		12.2±1.4	11.4±1.6	*0.003
NLR		1.31±0.19	2.43±1.05	<0,001*
PLR		104.9±44.8	141.26±63.4	<0,001*

All parameters are expressed as mean ± standard deviation, unless otherwise stated. Significance level was set at P < .05. BMI=body mass index, Cr=creatinine, Glu=plasma glucose, HDL=high density lipoprotein, CRP= C-reactive protein, LDL=low density lipoprotein, NLR=neutrophil-to-lymphocyte ratio, TC=total cholesterol, TG=triglycerides, WBC=white blood cell. ∗ Data are expressed as number (%).

4-DISCUSSION

Diabetic peripheral neuropathy is the most common complication in diabetic patients. Its onset is subtle and its progression is slow. In the early stages, symmetrical numbness, pain, and confusion in sensory function can occur or be asymptomatic. In late stages, ulcers and gangrene can occur in feet.[15] Therefore, precautions and early diagnosis of DPN are of great importance in improving patients life quality. Research has shown that diabetes mellitus is an inflammatory disease and immune system dysfunction. This chronic inflammation contributes to the complications of this disease.[16-17]

Multiple factors contribute to DPN including endothelial damage, microvascular impairment, metabolic disturbance, oxidative stress, cytokines and inflammatory factors. Chronic hyperglycemia leads to a series of pathological changes in blood vessels, where endothelial cells growth increases, which leads to narrowing of the lumen of blood vessels and consequently reduced blood flow and hypoxia of nerves, thus stimulating the production of cytokines and exacerbating the damage. In addition, chronic hyperglycemia contributes to activate the polyol pathway and increase the end products of glycine, protein kinase C and nitric oxide, and these biochemical processes can form inflammatory and oxidative mediators that increase tissue damage.[18-19]

NF-Kb can be stimulated by hyperglycemia and oxidative stress. Activation of this factor will induce inflammatory event by increasing expression of ICAM-1, pre-inflammatory cytokines and chemokines,[20] resulting in overexpression of ICAM-1 on all inflammatory cells releasing large amount of cytokines to recruit more inflammatory cells,[21] myeloperoxidase and reactive oxygen are released during increased neutrophil activation leading to increased oxidative stress and persistent inflammation. Its complications, in many studies,[22-23] can be attributed to increased oxidative damage, DNA damage and programmed cell death of peripheral blood lymphocytes.[24]

NLR represents a mixture of two main components: neutrophils, which are closely associated with the inflammatory response, and lymphocytes, which reflect immune regulatory pathways, and this ratio can reflect the functional state of the immune system in the chronic inflammatory process.[25] as well as the innate immunity

response by neutrophils and adaptive immunity response by lymphocytes. Compared with other leukocyte markers, this ratio is more stable and less influenced by physical, physiological and pathological factors.[13-14] The non-specific inflammatory response resulting from hyperglycemia may lead to changes in Peripheral blood cell levels which may explain abnormal NLR values, where high neutrophil values are a sign of persistent non-specific inflammatory process and low lymphocyte values indicate inadequate immune system regulation,[26] on the other hand, this ratio was observed to be an independent risk factor in DPN-related pathogenesis affecting nutritional support of neuron and Schwann cell and thus neuronal dysfunction and neuropathy.[27-28]

PLR is reported to be a prognostic marker of inflammation for many types of cardiovascular disease, including peripheral arterial disease (PAD) and hypertension [29-30]. PLR is also reported to have predictive effect about diabetes mellitus and diabetic complications in recent years. A cross-sectional study from Japan demonstrated that PLR can be a marker for high risk diabetic foot and diabetic foot ulcer in patients with type 2 diabetes.[31] Besides, Duan et al's study demonstrated that the PLR was associated with proteinuria and prognosis in diabetic kidney disease (DKD) patients.[32]

Our study showed that the neutrophil values in DPN group were significantly higher in comparison with DM group (3308.02 $\pm$ 909.37, 4905.26 $\pm$ 1387.63; P<0.001) while the lymphocyte values were lower in patients group compared with control group (2563.86 $\pm$ 755.72, 2143.62 $\pm$ 576.02; P<0,001). These results could indicate a different inflammation degrees between the two groups.

The values of NLR in DPN group were significantly higher compared to control group (1.31 $\pm$ 0.19, 2.43 $\pm$ 1.05; P<0.001), and logistic regression analysis showed that this ratio is an independent risk factor for DPN occurrence ~~0.001)~~ (P<0.001,OR=3,7, CI=95%). We extracted ROC curve to determine the optimal cut-off point for NLR, which was 1.69, with 90.7% sensitivity and 97.6% specificity.

Our study is consistent with a study conducted by XU and colleagues in China in 2017 to determine the relationship between NLR and DPN, neutrophil values of DPN group were higher than that of DM group, with statistically significant difference (3.80$\pm$1.23, 4.04$\pm$1.05, P=0.02), and lymphocyte values were lower in DPN group compared with DM group (1.84$\pm$0.75, 1.61 $\pm$ 0.47, P<0.001). NLR was high in DPN group compared with control group (2.18 $\pm$ 0.61, 2.58 $\pm$0.5, P<0.001), the logistic regression analysis in this study showed that this ratio is a risk factor for Diabetic peripheral neuropathy (P=0.002, OR=4.96,CI=95%). The optimal cut-off value was 2.13 with a sensitivity of 81.3% and specificity of 48.1%.[33]

In a study performed by Wajaidah,[34] and her colleagues in Egypt in 2022,–neutrophil values were high while lymphocyte values were low in DPN group compared with control group (2440±1250, 1920±900, P<0.001), (1750±1190, 2140±1390, P<0.001), respectively; NLR ratio was also significantly elevated in patient group compared to control group with a statistically significant difference (2.44 $\pm$ 1.5, 1.92 $\pm$ 1.21, P < 0.001), repectively, cut-off value was 1.58 with 100% sensitivity and 40% specificity.

Our study showed no statistically significant difference for age between two groups. Pearson's Correlation Coefficient showed no association between DPN and age (r = 0.17, P = 0.9), this is relatively due to the fact that T2DM begins after the age of 40, as well as rapprochement of two age ranges to these two groups, and this is consistent with the study conducted by XU and colleagues.[33] in China and differs with HICKS and colleagues study.[35] and with Hopkin and colleagues study,[36] which showed that DPN increases with age, reaching 44.2% with 70-79 years age.

Our study also showed statistically significant difference for duration of T2DM between the two groups, and positive correlation according to Pearson's coefficient between duration of T2DM and the incidence of DPN (r=0.363, P<0.001). and increasing neurological damage over time.[25-26] and this is consistent with the study of Young and colleagues.[36] which showed increased incidence of morbidity with injury duration, reaching 5% with diabetes duration of $\leq$ 5 years and 36.8% with diabetes duration of of $\geq$10 years, and it differs with a study in Egypt where there was no difference between the two groups.

Our study showed difference between the two groups in terms of blood glucose values and a positive correlation between blood glucose values and the incidence of morbidity (r = 0.249, p = 0.004), as uncontrolled diabetes mellitus contributes to the development of microvascular disease, this was supported by many studies including the previous mentioned studies.

Hemoglobin values were low in DPN group compared to DM group, and there was a negative correlation between them (r=-0.261, p=0.003), this is consistent with Young and colleagues study.[36] in China in 2017, their study concluded that low hemoglobin levels are associated with DPN (P<0.001), as low hemoglobin levels contribute to hypoxia during nerve perfusion, which contributes to development of DPN.

For platelets count values, no statistically significant difference was observed, in contrast to the platelets to lymphocytes ratio, PLR, whose differences between the two groups were statistically significant and positively associated with DPN (r = 0.286, p = 0.001). This explains that in diabetic patients, abnormal insulin action may lead to increased platelet adhesion. At the same

time, hyperglycemia also accelerate platelet metabolism and production, exacerbating the imbalance between coagulation and anticoagulation in vivo. This process may play an important role in atherogenesis, thrombosis and microcirculation disturbance. This is consistent with Youyou and colleagues study.[98] in China in 2021, their study concluded that PLR may be a predictive indicator of DPN and an auxiliary test.[37]

In contrast to previous studies, smoking or body mass index were not a risk factor, as no significant difference was observed between the two groups (P>0.05). This difference may be due to the small number of patients in our study compared to other studies.

Our study is a case-control study and the sample size is small compared to the other precedent studies, so we need cohort studies and a larger sample size to evaluate the prognostic value of NLR and PLR in DPN patients, which will increase the accuracy in setting the alarm and will prove the diagnostic value of NLR and PLR in DPN, so that they can be included in the diagnostic program for early detection of this disorder.

5-CONCLUSIONS

Patients with T2DM with elevated NLR and PLR values are more likely to develop DPN. High values of NLR and PLR in DPN patients compared with controls indicate the existence of a potential diagnostic value for this laboratory scale that allows it to be included in the criteria for early diagnosis of this disorder. The cut-off value of the NLR was extracted to help predicting DPN, which was 1.69, with 90.7% sensitivity and 97.6% specificity. The cut-off value of PLR was 88.42, with 80,2% sensitivity and 53.5% specificity.

ACKNOWLEDGEMENTS

We would like to thank all doctors in the Department of laboratory and Internal Medicine for assistance.

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