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Correlation of neutrophil - to - lymphocyte ratio, platelet- to - lymphocyte ratio and type 2 diabetic retinopathy

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中性粒细胞及血小板与淋巴细胞比值与2型糖尿病视网膜病变相关性

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摘要

目的:探讨中性粒细胞与淋巴细胞比值(NLR)、血小板与淋巴细胞比值(PLR)与2型糖尿病视网膜病变(DR)的相关性。

方法:选择2型糖尿病(DM)患者200例,按眼底检查结果分为眼底正常组(n=100)、非增殖期视网膜病变组(NPDR, n=62)和增殖期视网膜病变组(PDR, n=38)。同时选取100例健康体检者作为正常对照(n=100)组;测定中性粒细胞、淋巴细胞及血小板计数等相关指标。

结果:PDR组患者NLR值(2.54)高于对照组(1.81)、DM组(1.76)及NPDR组(1.85),差异有统计学意义(P<0.05),PDR组患者PLR值(126.18)高于DM组(111.64),差异有统计学意义(P<0.05)。Logistic回归分析显示,年龄(β=-0.047)是糖尿病视网膜病变的保护因素(P<0.05),病程(β=0.071)和收缩压(β=0.024)是危险因素(P<0.05),而NLR、PLR在回归分析中无统计学意义。

结论:NLR、PLR值在PDR组升高,但并非糖尿病视网膜病变发生的独立危险因素。

关键词:2型糖尿病;糖尿病视网膜病变;中性粒细胞与淋巴细胞比值;血小板与淋巴细胞比值

Abstract

• AIM: To investigate the relationship between neutrophil-to - lymphocyte ratio (NLR), platelet - to - lymphocyte ratio (PLR) and type 2 diabetic retinopathy (DR).

• METHODS: A total of 200 cases with type 2 diabetes mellitus were involved. All patients were divided into three groups according to the fundus examination: diabetes mellitus (DM, n = 100), non - proliferative diabetic retinopathy (NPDR, n = 62) and proliferative diabetic retinopathy (PDR, n = 38). 100 healthy persons were selected as the normal control group (NCG, n = 100). The related indicators, such as neutrophil count, lymphocyte count and platelet count were measured.

• RESULTS: The value of NLR was significantly higher in PDR group patients than in NC group (1.81), DM group (1.76) and NPDR group (1.85) (P<0.05). The value of PLR was significantly higher in PDR group patients (126.18) than in DM group (111.64) (P<0.05). Logistic regression analysis showed that age (β = -0.047) was protective factor, course of diabetes (β = 0.071) and systolic blood pressure (β = 0.024) were risk factors for diabetic retinopathy (P<0.05), but the value of NLR and PLR was not statistically significant in the Logistic regression analysis.

• CONCLUSION: The value of NLR and PLR increased in the PDR group, but it is not independent risk factor for diabetic retinopathy.

• KEYWORDS: type 2 diabetes mellitus; diabetic retinopathy; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio

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INTRODUCTION

Diabetic retinopathy (DR) is a common severe microvascular complication of diabetes mellitus (DM) and is the most easily neglected disease among working-age people. According to statistics, China had about 98 million diabetic patients in 2013, making it the country with the largest number of diabetic patients in the world[1], among which the prevalence rate of DR was 24.7%-37.5%[2]. The pathogenesis of DR is complex and has not been fully elucidated. However, in recent years, it has been found that inflammation has a considerable impact on the occurrence and development of DR[3]. Neutrophil / lymphocyte ratio and platelet / lymphocyte ratio are emerging inflammatory markers in recent years, which have important predictive value for assessing the severity of acute coronary syndrome[4-5] and the prognosis of various malignant tumors[6-7]. For that reason, numerous literatures have reported their relationship with diabetic retinopathy[8-10]. The purpose of this study was to explore the relationship between NLR and PLR and diabetic retinopathy by analyzing and comparing the hematological parameters of type 2 DM.

SUBJECTS AND METHODS

Clinical Data

Inclusion criteria 1) Type 2 diabetes is in line with the diagnostic criteria established by WHO in 1999; 2) Diabetic retinopathy meets the diagnostic and staging criteria set by the Ophthalmology Group of the Ophthalmological Society of the Chinese Medical Association in 2014; 3) Healthy subjects undergoing physical examination at the same time.

Exclusion criteria 1) Acute complications of diabetes; 2) Acute and chronic infection of the whole body; 3) Combined with other eye diseases.

Packet data 1) Totally 200 patients with T2 DM were randomly selected from January 2016 to December 2017 in Affiliated Haikou Hospital of Xiangya Medical College, Central South University, and all underwent fundus examination, including fundoscopy, fundus photography or fundus angiography without mydriasis. The patients were divided into DR group (100 cases) that was further divided into non-proliferative retinopathy (NPDR) group (62 cases) and proliferative retinopathy (PDR) group (38 cases), and DM group (100 cases); 2) At the same time, 100 healthy subjects in our hospital were selected as normal control group (NCG). We obtained informed consent from all subjects. The study protocol was approved by the Ethics Committee of Affiliated Haikou Hospital of Xiangya Medical College, Central South University.

Methods

General index collection All participants were inquired about their medical histories, and their ages, genders, courses of diabetes and systemic disease were recorded, followed by the measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was at rest.

Blood index determination All subjects were fasted for 12h, and the elbow vein blood samples were collected afterward in the early morning. The fasting plasma glucose (FPG), creatinine (Cr), blood urea nitrogen (BUN), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL) were measured by automatic biochemical analyzer (Uni Cel DxC 800, Beckman Coulter, USA). High-density lipoprotein (HDL), low-density lipoprotein (LDL), and glycosylated hemoglobin A1c (HbA1c) was measured by a glycosylated hemoglobin analyzer (Piemier Hb9210, Trinity Biotech, Ireland). Besides, No. XT-2000i from Sysmex Company of Japan was applied not only to measure neutrophils, lymphocytes, platelets (PLT), but also calculate neutrophil count / lymphocyte count (NLR) and platelet count/lymphocyte count (PLR).

Statistical processing In this study, SPSS 23.0 statistical software was used to analyze the data, and Shapiro-Wilk test was used to evaluate the normality. The measurements of normal distribution were expressed as mean ± SD deviation. After logarithmic transformation, the non-normal distribution data were still expressed as median and quartile spacing. In addition, several tests and analyses were used in this study, including Levene test, Variance analysis for comparison between groups which conformed to normal distribution and homogeneity of variance, LSD test for comparison between two groups, Kruskal-Wallis test for comparison between groups which did not conform to normal distribution and heterogeneity of variance, Chi-square test for comparison between the two groups, and Logistic regression analysis for analyzing the risk factors of retinopathy. Enumeration data were expressed by rate, and the significant level was taken by $\alpha = 0.05$ and $P < 0.05$, indicating a statistically significant difference.

RESULTS

Comparison of General Information in Each Group There was no significant difference in sex, age, SBP, DBP among each group ($P>0.05$). The duration of DM of NPDR group was significantly longer than that of DM group ($P < 0.05$). There was no significant difference in the duration of DM between DM group and PDR group, NPDR group and PDR group ($P>0.05$). The results are shown in Table 1.

Comparison of Biochemical Indicators in Each Group The BUN, TG, LDL, FPG and HbA1c were significantly lower in NCG group than in other groups ($P<0.05$). The BUN of DM group was significantly lower than that of PDR group ($P<0.05$). The Cr of NCG group was significantly higher than that of DM and NPDR group ($P<0.05$). The HDL was significantly higher in NCG group than in other groups ($P<0.05$). There was no significant difference in TC among each group ($P>0.05$). The results are shown in Table 2.

Comparison of Peripheral Blood Cell Indices in Each Group Overall, there was no significant difference in the lymphocytes value among each group. However, the PLT value of the control group and PDR group was significantly higher than

Table 1 Comparison of general information in each group

Variables	NCG (n=100)	DM (n=100)	NPDR (n=62)	PDR (n=38)	Statistic	P
Sex						
M	53 (53.0%)	60 (60.0%)	33 (53.2%)	19 (50.0%)	χ^2=1.634	0.652
F	47 (47.0%)	40 (40.0%)	29 (46.8%)	19 (50.0%)		
Age (a)	57.50 (49.00,65.00)	59.00 (49.00,65.75)	57.00 (51.75,62.25)	53.50 (48.00,62.00)	χ^2=2.821	0.420
Duration of DM (a)	-	7.50 (3.25,12.00)[a]	10.00 (8.00,15.00)	9.50 (5.00,16.00)	χ^2=9.718	0.008
SBP (mmHg)	132.75±16.25	133.93±19.37	139.45±19.41	140.89±23.65	χ^2=7.746	0.052
DBP (mmHg)	81.00±11.48	79.53±10.24	80.40±11.14	81.26±11.77	F=0.382	0.766

[a]Significantly different from NPDR, P<0.05. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NGG: Normal control group; DM: Diabetes Mellitus.

Table 2 Comparison of biochemical indicators in each group

Variables	NCG (n=100)	DM (n=100)	NPDR (n=62)	PDR (n=38)	Statistic	P
BUN (mmol/L)	3.24 (1.41)	3.79 (3.11, 5.00)[a,b]	4.73 (3.54, 5.72)[a]	5.50 (3.95, 7.55)[a]	χ^2=54.837	<0.001
Cr (umol/L)	93.50 (81.25,105.75)	87.00 (75.00,97.75)[a]	82.50(71.75, 103.00)[a]	95.50 (71.50, 103.00)	χ^2=11.354	0.010
TC (mmol/L)	5.06 (4.46, 55.77)	5.04 (4.22, 5.86)	4.73 (4.07, 5.98)	5.18 (3.87, 6.40)	χ^2=0.987	0.804
TG (mmol/L)	1.19 (0.86, 5.77)	1.55 (1.04, 2.85)[a]	1.53 (1.11, 2.12)[a]	1.60 (1.08, 2.05)[a]	χ^2=16.316	0.001
HDL (mmol/L)	1.55 (1.29, 1.90)	1.30 (1.15, 1.52)[a]	1.27 (1.07, 1.51)[a]	1.26 (1.09, 1.45)[a]	χ^2=33.156	<0.001
LDL (mmol/L)	2.33 (1.94, 2.84)	2.70 (2.29, 3.34)[a]	2.63 (2.23, 3.53)[a]	2.93 (2.06, 3.85)[a]	χ^2=19.291	<0.001
FPG (mmol/L)	5.59 (5.16, 6.14)	8.46 (6.58, 10.69)[a]	7.81 (6.24, 10.58)[a]	9.35 (6.66, 15.68)[a]	χ^2=90.387	<0.001
HbA1c (%)	5.50(5.30, 5.80)	8.55 (7.02, 9.98)[a]	8.40 (7.25, 10.4)[a]	8.75 (6.98, 10.75)[a]	χ^2=159.953	<0.001

[a]Significantly different from NCG, P<0.05; [b]Significantly different from PDR, P<0.05. BUN: Blood urea nitrogen; Cr: Creatinine; TC: Total cholesterol; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin A1c; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NGG: Normal control group; DM: Diabetes Mellitus.

Table 3 Comparison of peripheral blood cell indices in each group

Variables	NCG (n=100)	DM (n=100)	NPDR (n=62)	PDR (n=38)	Statistic	P
Neutrophils ($\times10^9$/L)	3.46 (2.93, 4.14)[b]	3.96 (2.97, 4.75)[b]	3.52 (2.76, 4.31)[b]	4.67 (3.83, 5.63)	χ^2=22.129	<0.001
Lymphocytes ($\times10^9$/L)	2.02(1.69, 2.48)	2.17 (1.81, 2.56)	1.9 (1.56, 2.48)	1.85 (1.48, 2.31)	χ^2=5.256	0.154
PLT($\times10^9$/L)	261 (222.25, 320.0)	229 (205.25, 273.00)[a,b]	223.5 (178.50, 272.50)[a,b]	265.5 (223.25, 309.75)	χ^2=16.774	0.001
NLR	1.81 (1.29, 2.28)[b]	1.76 (1.29, 2.42)[b]	1.85 (1.25, 2.29)[b]	2.54 (1.74, 3.65)	χ^2=14.017	0.003
PLR	129.88 (100.66, 156.65)	111.64 (86.16, 133.28)[a,b]	115.45 (81.65, 133.28)[a,b]	126.18 (103.27, 197.53)	χ^2=13.287	0.004

[a]Significantly different from NCG, P<0.05; [b]Significantly different from PDR, P<0.05. PLT: Platelets; NLR: Neutrophil count / lymphocyte count; PLR: Platelet count/lymphocyte count; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NGG: Normal control group; DM: Diabetes Mellitus.

Table 4 Logistic regression analysis

Variables	β	SE	Wald	OR	95% *CI*		P
					Lower	Upper	
Age	−0.047	0.019	5.727	0.955	0.919	0.992	0.017
Duration of DM (a)	0.069	0.028	6.138	1.071	1.014	1.131	0.013
SBP	0.024	0.012	4.117	1.025	1.001	1.047	0.042

DM: Diabetes Mellitus.

that of DM group and NPDR group (P<0.05). Furthermore, both neutrophils value and NLR value in PDR group were considerably higher than those in control group, DM group and NPDR group (P<0.05), although the NLR value in NPDR group was higher than that in DM group, the difference was not statistically significant (P>0.05). The PLR value of the control group and PDR group was significantly higher than that of DM group and NPDR group (P<0.05), and the PLR value in NPDR group was higher than that in DM group, but the difference was not statistically significant (P>0.05). The results are shown in Table 3.

Logistic Regression Analysis of Risk Factors for DR in Patients With and Without Diabetes All patients were grouped according to whether they had DR or not. The binary Logistic regression analysis was performed with gender, age, course of disease, SBP, DBP, BUN, Cr, TC, TG, HDL, LDL, FPG, HbA1c, Neutrophils, Lymphocytes, PLT, NLR and PLR as covariates. The results showed that the regression coefficients of age, course of disease and SBP were −0.047, 0.071 and 0.071, respectively, and the P values were 0.017, 0.013 and 0.042 respectively, which were all less than 0.05,

Table 5 Logistic regression analysis

Variables	β	SE	Wald	OR	95% *CI*		*P*
					Lower	Upper	
NLR	0.241	0.109	4.900	1.273	1.028	1.577	0.027
PLR	0.001	0.002	0.497	1.001	0.998	1.005	0.481

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelte-to-lymphocyte ratio.

indicating statistical significance. Accordingly, age is a protective factor for DR, while duration and SBP are risk factors for DR patients (Table 4).

Logistic Analysis Using the DR as the Dependent Variable and the NLR, PLR as the Independent Variables A Logistic regression analysis was performed, using DR as the dependent variable and the NLR, PLR as the independent variable, to determine the association of NLR, PLR with DR. We could observe DR showed a significant association with NLR ($P<0.05$), while DR showed no significant association with PLR ($P>0.05$) (Table 5).

DISCUSSION

DR is one of the most common severe microangiopathy in DM, whose occurrence and development involves a great number of pathogenic factors, but the specific pathogenesis has not been fully clarified. Recent studies have shown that diabetic retinopathy is closely related to inflammation, since the expression of inflammatory cytokines such as IL-6[11-13], IL-1beta[14] and TNF-alpha[15-17] in the vitreous fluid and serum of patients with diabetic retinopathy is significantly with the correlated severity of the disease. Joussen *et al*[18] identified an important role for TNF-alpha in the pathogenesis of signature diabetic retinopathy pathologies and demonstrated that etanercept (TNF-alpha antagonist) can inhibit diabetic rat retinal cell death. Wu *et al*[19] found that inocycline decreased the exprssion of IL-1beta, which could protect the retinal vessels. As a result, these studies suggest that inflammation has a significant influence on the pathogenesis of DR.

White blood cell counts and their subtypes are typical indicators of inflammation. Neutrophils play an important role in non-specific immunity, as they can secrete a variety of inflammatory mediators. Lymphocytes are mainly involved in specific immune responses. Platelets are derived from megakaryocytes. Besides participating in the pathophysiological processes of coagulation and thrombosis, activated platelets can release a large number of fine particles. Cytokines and chemokines regulate lymphocyte function, participate in inflammatory reaction and produce immune effects. Inflammatory reactions can increase the number of neutrophils, megakaryocytes and platelets, while the number of lymphocytes decreases. However, the absolute value of the above indicators is susceptible to physiological, pathological and physical environment changes, and their stability is poor. NLR and PLR are new and comprehensive inflammatory markers found in recent years, which can objectively reflect the imbalance of the proportion of cells in the body, and have high stability. Compared with other inflammatory markers, their detection methods are fast, simple and cheap.

In this study, the NLR value of PDR group was significantly higher than that of DM group and NPDR group ($P<0.05$), indicating that the inflammation of PDR group was more serious than that of DM group and NPDR group. At the same time, the NLR value of group NPDR was higher than that of group DM, but the difference was not statistically significant. The PLR value of PDR group was significantly higher than that of DM group and NPDR group ($P<0.05$), which also revealed a more severe inflammation of PDR group than that of DM group and NPDR group. Moreover, the results showed that the order of PLR size was PDR group > NPDR group > DM group, but no significant difference was obtained between the two groups. The NLR and PLR values of patients in group PDR were remarkably higher, suggesting that the occurrence and development of DR are closely related to inflammation.

The Logistic regression analysis of risk factors for DR in diabetic patients demonstrated that age was a protective factor for DR, duration of DM and SBP were risk factors for DR. Consistent with our research, Wong *et al*[20] reported the prevalence and risk factors of diabetic retinopathy in a multi-ethnic cohort in the US, which demonstrated that the age was a protective factor for DR. A study in USA[21] aimed at adults with diabetes aged 40 years and older showed that the longer duration of DM was an independent risk factor for DR. The UKPDS[22] reported that the higher systolic blood pressure was independently associated with diabetic retinopathy.

On the contrary, the Logistic regression analysis of risk factors for DR in diabetic patients demonstrated that no significant difference was found between NLR and PLR, indicating that NLR and PLR were not independent risk factors for DR in DM patients. Meanwhile, a Logistic regression analysis was performed, using DR as the dependent variable and the NLR, PLR as the independent variable, to determine the association of NLR, PLR with DR. We could observe DR showed a significant association with NLR ($P<0.05$), while DR showed no significant association with PLR ($P>0.05$), suggesting that the occurrence and development of DR are closely related to NLR. Yue *et al*[8] reported that the NLR and PLR ratios in DR group were significantly higher than those in DR group. Ulu *et al*[9] announced that the NLR values were closely related to the severity of DR, while Öztürk *et al*[23] considered the NLR values to be associated with diabetic microvascular complications and suggested that they could be used for early diagnosis of diabetic microangiopathy. Huang *et al*[24] used

logistic regression analysis to show that NLR was a risk factor for predicting DN and DR in type 2 diabetic patients. They also used ROC analysis to evaluate the predictive accuracy of NLR and other models to predict DR risk in patients. The auROC of the NLR was 0.669 (95% *CI*: 0.606-0.732). In the same dataset, WBCs had an auROC of 0.576 (95% *CI*: 0.512-0.641), a neutrophils of 0.635 (95% *CI*: 0.573-0.698), a lymphocytes of 0.585 (95% *CI*: 0.520-0.651), a creatinine of 0.555 (95% *CI*: 0.491-0.619), significantly lower than that of the NLR (all $P<0.001$). In the present study, DM patients have not yet unified hypoglycemic regimen, and there are considerable differences among long-term use of different drugs, different patients with compliance, diagnosis as well as treatment process. From a clinical point of view, they may be confounding factors, thus affecting NLR and PLR values, which can be further explored by a large sample correlation study of multiple factors. Considering that this study is cross-sectional and that neutrophils, lymphocytes and platelets have a short life span and a large number of fluctuations, reflecting only a specific time point, rather than a long-term state of the body, the impact of NLR and PLR on DR may not be sufficient to offset the impact of other risk factors at the current time point.

To sum up, NLR and PLR values in the PDR group increased, but the risk factors for DR did not. This study is a small sample of retrospective analysis, which still need to be further explored for the clinical treatment of DR to provide new ideas.

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