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RESEARCH ARTICLE

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Correlation between the platelet-to-lymphocyte ratio and diabetic foot ulcer in patients with type 2 diabetes mellitus

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Abstract

Objective: To investigate the correlation between the platelet-to-lymphocyte ratio (PLR) and diabetic foot ulcer (DFU) in patients with type 2 diabetes mellitus (T2DM).

Method: From January 2018 to August 2019, 206 patients with T2DM admitted to the Central Hospital of Wuhan, China, were enrolled in this study, including 104 patients with DFU (DFU group) and 102 patients without DFU (T2DM group). During the same period, 90 healthy subjects were randomly screened as normal controls (NC group). The correlation between PLR and DFU in patients with T2DM was explored by comparing the PLR of the subjects in the three groups.

Results: The PLRs of the DFU and T2DM groups were higher than that of the NC group, whereas the PLR of the DFU group was higher than that of the T2DM group ($p < 0.05$). PLR was positively correlated with the Wagner DFU grade ($p < 0.001$). Based on logistic regression analysis, PLR was found to be an independent risk factor for DFU (OR =1.029, 95% CI: 1.019 ~ 1.039, $p < 0.001$). The receiver operating characteristic curve analysis of the PLR showed that the area under the curve of the PLR for predicting diabetic foot ulcer was 0.776 ($p < 0.001$), and the analysis determined that the optimal critical value of the PLR for predicting DFU was 147.6.

Conclusion: The PLR is significantly elevated in patients with DFU and positively correlated with the Wagner DFU grade, which might be a valuable marker for early diagnosis and assessment of severity of DFU.

KEYWORDS
diabetic foot ulcer, risk factor, the platelet to lymphocyte ratio, type 2 diabetes mellitus

1 | INTRODUCTION

Diabetic foot is a common and severe chronic diabetic complication and has become a public health issue,[1] with the global prevalence of diabetic foot ulcer (DFU) being 6.3%.[2] Around 25% of patients with diabetes develop a foot ulcer in their lifetime,[3] and compared to nondiabetic patients, those with DFU have higher amputation rates and increased mortality.[4] Peripheral arterial disease, diabetic peripheral neuropathy, deformity, previous amputation, and infection are the main factors contributing to the development of DFU.[5] Hence, early identification of risk factors for the diabetic foot is especially important for its prevention and treatment.

Kuanxin Zhang and Sheng Ding contributed equally to this work.

The pathogenesis of DFU has not been fully elucidated yet; however, the role of the inflammatory response in DFU has received increasing attention. The platelet-to-lymphocyte ratio (PLR) is a new type of systemic inflammatory response marker that can reflect the inflammatory state of the body and can be easily determined using peripheral blood. In this study, we analyzed the PLR of patients with type 2 diabetes mellitus (T2DM), T2DM plus DFU, and healthy individuals to explore the correlation between PLR and DFU.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was approved by the Ethics Committee of the Central Hospital of Wuhan, China, and was conducted in accordance with the principles of the 1964 Helsinki Declaration and its later amendments. From January 2018 to August 2019, 206 patients with T2DM who were admitted to the Department of Endocrinology, the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology were enrolled in this study. Adult patients were included if they suffered from T2DM alone (T2DM group) or had an additional DFU (DFU group). During the same period, healthy subjects were randomly screened as normal controls (NC group). Patients were excluded if they suffered from acute inflammation or infectious diseases such as pulmonary infection, urinary tract infection, severe liver function, renal function, cardiopulmonary failure, thyroid diseases, autoimmune diseases, malignant tumors, and other diseases affecting platelet and lymphocyte counts.

2.2 | Study methods

General clinical data of the subjects were collected, including gender, age, smoking status, duration of T2DM, body mass index (BMI), and Wagner DFU grade.[6] Fasting venous blood was obtained, and blood routine related parameters including white blood cell count (WBC), platelet count (PLT), and lymphocyte count (LYM) were measured using a Sysmex XN-10 analyzer (Sysmex). The PLR was calculated as the platelet-to-lymphocyte ratio. Triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting blood glucose (FPG) were measured using an Olympus AU5421 analyzer (Olympus), and glycated hemoglobin (HbA1c) was measured using a Bio-Rad D10 analyzer (Bio-Rad).

2.3 | Statistical analysis

Statistical analysis was performed using SPSS version 22.0 statistical software (SPSS Inc.). The distribution of the continuous variables was evaluated using the Kolmogorov-Smirnov test. Normal distribution measurement data were expressed as means ±standard deviation (SD), and comparison among multiple groups is conducted using one-way ANOVA. Non-normally distributed data were expressed as medians (Q1 to Q3), and comparison among multiple groups was conducted using the Kruskal-Wallis test. Count data were expressed as frequency and percentage (%), and the chi-square test was used for comparison between groups. The correlation between PLR and Wagner DFU grade was analyzed using Spearman's correlation. The influencing factors of DFU were analyzed using logistic regression. The area under the receiver operating characteristic (ROC) curve was calculated based on the diagnosis of DFU as a positive result, and the PLR cutoff point with the highest sensitivity and specificity was obtained. The difference was statistically significant at $p < 0.05$.

3 | RESULTS

3.1 | Comparison of general data and laboratory indicators

A total of 296 study participants were enrolled, of which 90 served as healthy controls (NC group), 104 had DFU (DFU group), and 102 patients presented with T2DM only (T2DM group). Compared to that in the NC group, the smoking rates and the levels of BMI, HbA1c, FBG, and PLR were higher in the T2DM and DFU groups (all $p < 0.05$) and the levels of HDL and LYM were lower (all $p < 0.05$). Compared to that in the T2DM group, the smoking rate and HbA1c, WBC, PLT, and PLR levels were higher in the DFU group (all $p < 0.05$) and the levels of TC and LYM were lower (all $p < 0.05$) (see Table 1).

3.2 | Comparison of PLR in patients with different Wagner DFU grades

The PLR of patients with different Wagner DFU grades revealed a statistically significant difference ($p < 0.001$), and the PLR displayed an increasing trend with an increase of the Wagner DFU grade (see Table 2).

3.3 | Correlation between Wagner DFU grade and laboratory parameters

Spearman's correlation analysis showed that the WBC, PLT, PLR, and HbA1c levels positively correlated with the Wagner DFU grade with statistical significance (all $p < 0.05$), whereas the LYM and TC levels negatively correlated with the Wagner DFU grade with statistical significance (all $p < 0.05$). The PLR showed the highest correlation with the Wagner DFU grade ($r = 0.504$, $p < 0.001$) (see Table 3).

3.4 | Logistic regression analysis of influencing factors of DFU

Binary logistic regression analysis with PLR, smoking status, HbA1c, TG, TC, HDL, LDL, FPG, WBC, PLT, and LYM as independent variables in all patients with T2DM showed that PLR, smoking status,

TABLE 1 Participant characteristics and laboratory parameters in each group

Characteristics	NC	T2DM	DFU
n (M/F)	90 (50/40)	102 (58/44)	104 (63/41)
Age (years)	52.0 ± 8.1	51.3 ± 8.7	52.1 ± 9.3
Duration of T2DM (years)	—	9.87 ± 7.94	11.35 ± 7.63
Smoking Rate (%)	29 (32.22)	40 (39.21)*	61 (58.65)***
BMI (kg/m^2)	22.31 ± 6.83	25.38 ± 5.21*	26.16 ± 4.62*
HbA1c (%)	5.51 ± 0.50	8.10 ± 1.75*	9.58 ± 2.64***
TG (mmol/L)	1.36 (1.07 to 1.86)	1.55 (1.03 to 2.22)*	1.45 (1.14 to 2.08)
TC (mmol/L)	4.31 (3.57 to 5.10)	4.75 (3.34 to 5.34)	4.00 (3.40 to 4.72)**
HDL (mmol/L)	1.31 ± 0.39	1.10 ± 0.24*	1.03 ± 0.40*
LDL (mmol/L)	2.56 ± 0.73	2.92 ± 1.03	2.54 ± 0.92
FPG (mmol/L)	5.35 ± 0.46	9.28 ± 3.48*	9.36 ± 2.06*
WBC (×10^9/L)	5.29 (4.69 to 6.12)	6.09 (5.32 to 7.04)*	6.99 (5.55 to 8.64)***
PLT (×10^{12}/L)	197.29 ± 45.45	213.06 ± 43.64	230.96 ± 68.09***
LYM (×10^9/L)	1.96 (1.72 to 2.32)	1.78 (1.53 to 2.16)*	1.34 (1.03 to 1.72)***
PLR	99.98 ± 20.36	119.35 ± 33.84*	171.19 ± 60.73***

Abbreviations: BMI, body mass index; FPG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LYM, lymphocyte count; *n* (M/F), number of study participants (Male/Female); PLR, platelet-to-lymphocyte ratio; PLT, platelet count; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WBC, white blood cell count.

* vs NC group, $p < 0.05$.

** vs T2DM group, $p < 0.05$.

***(* #) means DFU group vs NC group $p < 0.05$ and DFU group vs T2DM group $p < 0.05$.

TABLE 2 Comparison of PLR in patients with different Wagner DFU grades

Wagner DFU grade	*n*	PLR	F	*p*
1	15	126.51 ± 27.37	15.007	<0.001
2	41	154.03 ± 39.53		
3	35	179.08 ± 52.52		
4	11	246.10 ± 76.93		
5	2	308.08 ± 102.57		

Abbreviations: 1, Wagner DFU grade 1; 2, Wagner DFU grade 2; 3, Wagner DFU grade 3; 4, Wagner DFU grade 4; 5, Wagner DFU grade 5; DFU, diabetic foot ulcer; PLR, platelet-to-lymphocyte ratio.

and HbA1c were independent risk factors for DFU (all $p < 0.05$) (see Table 4).

3.5 | Predictive value of PLR for DFU

The ROC curve analysis of the PLR showed that the area under the curve (AUC) of the PLR predicting DFU was 0.776, $p < 0.001$. The analysis determined that the optimal threshold value of the PLR for predicting DFU was 147.6, with a sensitivity of 65.4% and a specificity of 80.4% (see Figure 1).

4 | DISCUSSION

As a simple and economical experimental index, the PLR has been confirmed to be closely related to T2DM and its chronic complications, cardiovascular disease, peripheral arterial disease, and tumors.[7-17] We found that the PLR was significantly elevated in patients with DFU and it was identified as an independent risk factor for DFU. The results of the ROC curve further showed that the PLR could be used as a simple clinical indicator for the clinical diagnosis of DFU, which was consistent with the findings of a previous study.[18] As previously reported, the PLR was significantly

TABLE 3 Spearman's correlation analysis between Wagner DFU grade and laboratory parameters

	Wagner DFU grade	
Variable	***p***	***r***
Duration of T2DM	0.130	0.150
WBC	0.001***	0.313
PLT	0.001***	0.315
LYM	0.018**	−0.232
PLR	<0.001***	0.504*
HbA1c	0.008**	0.260
TG	0.122	−0.153
TC	0.025**	−0.220
HDL	0.102	−0.161
LDL	0.079	−0.173

Abbreviations: DFU, diabetic foot ulcer; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LYM, lymphocyte count; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WBC, white blood cell count.

*$r > 0.5$.

**$p < 0.05$.

***$p < 0.005$.

higher in osteomyelitis and it had a predictive value in predicting amputation in diabetic foot infection.[19] In this cross-sectional study, we additionally analyzed statistical the PLR of patients with different Wagner DFU grades and found that the PLR of DFU patients increased gradually with the increase of Wagner grade and the PLR was positively correlated with the Wagner grade. The PLR may be helpful to evaluate the severity of DFU.

The PLR may be related to glycemic control levels and could be useful to predict peripheral arterial disease and diabetic peripheral neuropathy leading to assess the risk of DFU in patients with T2DM. This study found that the PLR of the T2DM and DFU groups was higher than that of the NC group. Atak et al. also found that the PLR of patients with T2DM was higher than that of the healthy subjects, and there was a positive correlation between PLR and HbA1c.[20] These results suggested that the PLR may be helpful in predicting the development and level of glycemic control. An elevated PLR in patients with T2DM may reflect the underlying inflammatory burden of diabetes mellitus, with inflammation markers, including PLR, being elevated due to poor glycemic control and exacerbated underlying chronic low-grade inflammation. The PLR has also been reported to be associated with vascular disease of the lower extremities in T2DM patients.[14] Gary et al. found that the PLR can be used to assess peripheral arterial occlusive disease with critical limb ischemia (CLI). Patients with a PLR >150 have an increased risk of CLI.[21] Platelet-induced inflammatory response plays an important role in the development of atherosclerosis in diabetic patients. The mitotic substances and inflammatory mediators released by activated platelets recruit more platelets and white blood cells to the site of inflammation.[22] This inflammatory response releases several inflammatory mediators, which may result in a decrease in lymphocytes and thus inhibit the normal immune functions of the body. In this study, we found that the PLT count of patients in the DFU group was higher than that of the patients in the T2DM group, and the LYM count was lower than that in the T2DM group. Spearman's correlation analysis indicated that the PLT count was positively correlated and the LYM count was negatively correlated with the Wagner DFU grade. Many clinical studies have found that patients with T2DM having complications, such as diabetic peripheral neuropathy and peripheral arterial disease, have a similar decrease in LYM count,[23-25] which may be attributed to increased DNA damage and apoptosis of lymphocytes in diabetes mellitus caused by increased reactive oxygen species.[26] The high PLR detected in this study may be attributed to the elevated PLT level and the opposite effect of inflammation on lymphocytes. The elevated PLT count reflects the high inflammatory state and thrombotic risk, and the decreased LYM count reflects the relative insufficiency of immune regulation. The PLR is the combination of these two indicators that can better reflect the correlation with DFU. However, its specific mechanism remains to be further investigated. In addition, the PLR may be an effective monitoring parameter for anti-inflammatory therapy.

In conclusion, the PLR is significantly elevated in patients with DFU and positively correlated with the Wagner DFU grade, which might be a valuable marker for early diagnosis and assessment of severity of DFU. The PLR can be determined using inexpensive methods and can easily be calculated from the peripheral hemogram, thereby providing a new diagnostic perspective for the prevention of DFU. There are several shortcomings in this study. This study is a cross-sectional study and did not evaluate the time-dependent changes of the PLR. There are many possible factors affecting the peripheral blood PLT and LYM counts, which need to be further expanded and verified by evaluating a larger study population.

TABLE 4 Logistic regression analysis of DFU risk factors

Variable	*β*	SE	Wald	*p*	OR (95%CI)
Smoking	0.704	0.353	3.990	0.046	2.022 (1.013 ~ 4.036)
HbA1c	0.308	0.089	12.077	0.001	1.336 (1.144 ~ 1.620)
PLR	0.028	0.005	33.398	<0.001	1.029 (1.019 ~ 1.039)

Abbreviations: DFU, diabetic foot ulcer; HbA1c, glycated hemoglobin; PLR, platelet-to-lymphocyte ratio.

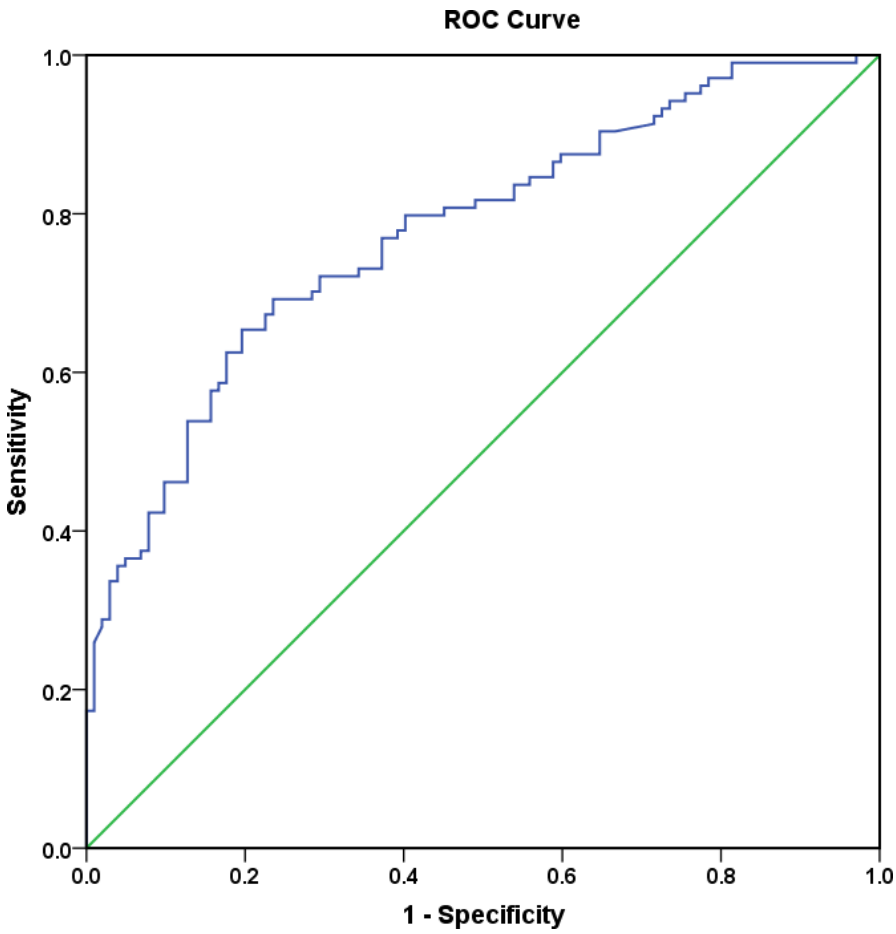

FIGURE 1 ROC curve analysis of the PLR. PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic

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CONFLICT OF INTEREST

The authors disclose no conflicts of interest.

AUTHOR CONTRIBUTIONS

KX Zhang, S Ding, and ZJ Wang conceived and designed the study. KX Zhang and S Ding analyzed the data and generated the tables and figures. XY Lyu and Q Tan collected and recorded the data. KX Zhang wrote the study. All authors have read and approved the final study. KX Zhang and S Ding contributed equally to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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