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Clinical characteristics and risk factors of diabetic foot ulcers with PAD

G.-L. TAO[1], L.-S. ZHENG[2], Z.-Y. WANG[1], Y.-P. XU[1], X.-G. ZHONG[1], H. WANG[3], X.-S. ZHANG[4]

[1]Department of Wound Repairment, The Second Affiliated Hospital of Dalian Medical University, Ganjingzi District, Dalian City, Liaoning Province, China
[2]Department of Neurology, The First Affiliated Hospital of Dalian Medical University, Dalian Development Zone, Liaoning Province, China
[3]Department of Laboratory, The Second Affiliated Hospital of Dalian Medical University, Ganjingzi District, Dalian City, Liaoning Province, China
[4]Department of Intervention, The Second Affiliated Hospital of Dalian Medical University, Ganjingzi District, Dalian City, Liaoning Province, China

Guilu Tao and Lisha Zheng are equal contributors

Abstract. – OBJECTIVE: This study aimed to analyze the clinical characteristics of patients with diabetic foot ulcers combined with peripheral arterial disease (PAD) and the risk factors.

PATIENTS AND METHODS: A retrospective study was conducted on 120 patients with diabetic foot ulcers in the Second Affiliated Hospital of Dalian Medical University from October 2018 to February 2021. The patients were divided into uncombined with the PAD group (42 cases) and combined with the PAD group (78 cases). The baseline information and clinical indicators were measured from two groups. Univariate and binary logistic regression was used to analyze the risk factors of PAD in patients with diabetic foot ulcers.

RESULTS: The proportion of patients with age ≥ 60 years, Wagner grade 4-5 and smoking history in the combined group was higher than that in the uncombined group ($p < 0.05$). The diastolic blood pressure (DBP) of the combined group was lower than that of the uncombined group, while the C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and glycated hemoglobin (HbA1c) levels of the combined group were higher than those of the uncombined group ($p < 0.05$). Binary logistic regression analysis showed that age ≥ 60 years, high Wagner grade, smoking, elevated CRP, NLR and HbA1c levels were risk factors for patients with diabetic foot ulcer combined with PAD (OR > 1, $p < 0.05$). An elevated DBP level was the protective factor for PAD in patients with diabetic foot ulcer (OR < 1, $p < 0.05$).

CONCLUSIONS: Patients with diabetic foot ulcer combined with PAD have the clinical characteristics of poor blood pressure control, long course of disease, and low ABI value. Age ≥ 60 years, high Wagner grade, smoking history, elevated CRP, NLR and HbA1c levels are the risk factors of PAD in patients with diabetic foot ulcer. Increased DBP is protective for PAD in patients with diabetic foot ulcer.

Key Words:
Diabetic foot ulcer, Lower extremity arterial disease, Smoking, Blood pressure, C reactive protein.

Introduction

A diabetic foot ulcer is a common complication of diabetes, which is mainly caused by long-term hyperglycemia leading to functional damage of large blood vessels, cranium, nerves, and other systems. It can lead to ischemic rest pain and intermittent claudication. If not treated in time, gangrene and ulcers will occur, seriously affecting the quality of life of patients[1]. Once a diabetic foot ulcer forms, the wound will be difficult to heal, taking an average of 6-14 weeks. Many factors, such as lower extremity artery disease, have an influence on this disease[2]. Peripheral arterial disease (PAD) is one of the most serious complications of diabetes, caused by the deposition of advanced glycation end products[3]. PAD can prolong the healing time of patients with diabetic foot ulcers and increase the risk of infection, which can lead to amputation and even death[4]. It can be concluded that reducing the incidence of PAD in patients with diabetic foot ulcers is critical to improve the quality of life of patients and save their lives. Recent studies in literature mainly focus on the analysis of the clinical characteristics and risk factors of patients with diabetic foot ulcers, but

Corresponding Authors: Huan Wang, MD; e-mail: whuan525@sina.com; Xuesong Zhang, MD; e-mail: zhangxuesongdy2y@163.com

lack of evidence-based support on patients with diabetic foot ulcers combined with PAD. Therefore, this study retrospectively analyzed the clinical information of 120 patients with diabetic foot ulcers; univariate and binary logistic regression was performed to analyze risk factors of diabetic foot ulcers combined with PAD. The aim of this study is to provide evidence for the early clinical prevention and treatment of this disease.

Patients and Methods

Clinical Characteristics

A total of 120 patients with diabetic foot ulcers were admitted to the Second Affiliated Hospital of Dalian Medical University from October 2018 to February 2021. The retrospective study involved 61 males and 59 females. The average age was 62.50 ± 3.74 years (ranging from 51 to 74 years). The mean BMI was 24.50 ± 0.95 kg/m^2 (ranging from 22 to 28 kg/m^2). The average duration of diabetes was 6.50 ± 1.45 years (ranging from 2 to 11 years). The sites of diabetic foot ulcers included toes in 64 cases, soles in 35 cases, and others in 21 cases. According to Wagner's classification of diabetic foot[5], all patients were divided into 32 cases of grade 1, 27 cases of grade 2, 36 cases of grade 3, 21 cases of grade 4, and 4 cases of grade 5. There were complications, including hypertension in 46 cases and coronary heart disease in 30 cases. In addition, there were 69 cases with smoking history and 62 cases with drinking history.

Patients with diabetic foot ulcers were followed up regularly, once every 3 months, by telephone or outpatient service. PAD was confirmed by imaging. Foot imaging was systematically reviewed by a senior radiologist. Abnormalities for diagnosing CF included (sub-)luxations, fragmentations, dislocations of the foot and/or the ankle joint found on radiographs, magnetic resonance imaging and/or CT-scan. Patients with PAD were included in the combined group, and patients without PAD were included in the uncombined group.

Inclusion criteria: (1) The diabetic foot ulcer met the diagnostic criteria in the guidelines of the Infectious Diseases Society of America[6] and was confirmed by imaging examination and clinical indicators; (2) Single foot disease; (3) Wagner grade ≥1; (4) Patients had normal daily activities and no communication barriers; (5) Complete clinical data.

Exclusion criteria: (1) Complicated with malignant tumor; (2) Foot lesions caused by other reasons; (3) Patients with cognitive dysfunction; (4) Co-infected patients; (5) Accompanied by autoimmune diseases, such as systemic lupus erythematosus, vasculitis, etc.; (6) Patients with severe anemia, gastrointestinal bleeding, organ dysfunction, tumor, cerebrovascular accident, or other neurological diseases. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University.

Therapies

Patients with diabetic foot ulcers were carried out the debridement. Patients with abscesses or deep wounds were cut openly to expand the wound and drain. According to the size and shape of the patient's wound, the Furcone polyurethane foam dressing (Huibo Medical Device Co., LTD, Zhengzhou City, Henan, China; approval number: 20183640111) was trimmed, the wound was fitted, the combined drainage tube (Omega Chi Medical Device Co., LTD, Shanghai, China; approval number: 20152660497) was selected, and the side hole and tube end of the drainage tube were placed inside the dressing and connected with the three-way tube. The low negative pressure aspirator (Keling Medical Device Co., LTD, Jiangsu, China; approval number: 20152141382) was connected, and the mode of negative pressure intermittent was chosen. The parameters were set as positive pressure for 5 min, negative pressure for 2 min, and negative pressure between -80 mmHg and -125 mmHg. The dressing and drainage tube were replaced once a week, and the treatment was continued until the wound healed.

Baseline Information

Baseline information of the patients includes gender (male and female), age (≥ 60 years, < 60 years), body mass index (BMI) value (≥ 24 kg/m^2, < 24 kg/m^2), duration of diabetes (≥ 5 years, < 5 years), location of diabetic foot ulcer (toe, plantar, others), Wagner grade (0-1, 2-3, 4-5), ankle-brachial index (ABI) value (> 0.9, ≤ 0.9)[7], complicated with hypertension (systolic blood pressure ≥ 120 mmHg and/or diastolic blood pressure ≥ 90 mmHg), complicated with coronary heart disease (confirmed by coronary angiography examination), smoking history (≥ 1 cigarette once a day, and persistent smoking for 1 year), drinking history (alcohol intake > 25 g/day, and persistent drinking for 1 year).

Clinical Indexes

A series of clinical indexes were collected from patients, including systolic blood pressure (SBP), diastolic blood pressure (DBP), C-reactive protein

(CRP), neutrophil-to-lymphocyte ratio (NLR), glycated hemoglobin (HbA1c), fasting blood glucose (FBG), 2 h postprandial blood glucose (2 h BG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) levels. SBP and DBP levels were detected at the time of admission using the medical electronic blood pressure meter YXY-61 (Donghuayuan Medical Device Co., LTD, Beijing, China; approval number: 20202070084). CRP levels were detected using dry fluorescence immunochromatography, and NLR levels were detected using the flow cytometer FACSVia (BD Medical Device Co., LTD, Franklin Lakes, NJ, USA; approval number: 20172402482), and HbA1c, FBG, 2h BG, TC, TG, HDL-C, and LDL-C levels were measured using blood glucose and lipid monitor LipidPro (OSANG Healthcare Co., Ltd., Gyeonggi-do, Republic of Korea; approval number: 20152222771).

Statistical Analysis

All measurement data was analyzed by SPSS 25.0 software (IBM Corp., Armonk, NY, USA). Independent sample *t*-test was used for inter-group measurement data, which was represented by $\bar{x}$+s, and χ^2 test was used to represent count data by percentage. Binary logistic regression analysis was used to analyze the risk factors of patients with diabetic foot ulcers combined with PAD. GraphPad Prism 8.0 software (La Jolla, CA, USA) was used to draw the forest map of the risk factors of this disease. $p < 0.05$ was considered statistically significant.

Results

Comparison of Baseline Information Between the Two Groups

The proportion of patients with age ≥ 60 years old, Wagner grade 4-5, and smoking history in the combined group was higher than that in the uncombined group ($p < 0.05$; Table I).

Comparison of Clinical Indexes Between the Two Groups

As shown in Figure 1, the DBP level of the combined group was lower than that of the uncombined group, while the CRP, NLR and HbA1c levels of the combined group were higher than those of the uncombined group ($p < 0.05$). There was no difference in other indexes between the two groups ($p > 0.05$).

Table I. Comparison of baseline information between the two groups.

Information		Combined group (n=78)	Uncombined group (n=42)		
		n (%)	n (%)	χ^2	p
Gender	Male	43 (55.13)	18 (42.86)	1.645	0.200
	Female	35 (44.87)	24 (57.14)		
Age	≥ 60 years	51 (65.38)	19 (45.24)	4.559	0.033
	< 60 years	27 (34.62)	23 (54.76)		
BMI	≥ 24 mg/m^2	48 (61.54)	24 (57.14)	0.220	0.639
	< 24 mg/m^2	30 (38.46)	18 (42.85)		
Duration of diabetes	< 5 years	17 (21.79)	11 (26.19)	0.295	0.587
	≥ 5 years	61 (78.21)	31 (73.81)		
Sites of diabetic foot ulcer	Toes	43 (55.13)	21 (50.00)	0.294	0.863
	Soles	22 (28.21)	13 (30.95)		
	Others	13 (16.67)	8 (19.05)		
Wagner grade	0-1	16 (20.51)	16 (38.10)	7.132	0.028
	2-3	41 (52.56)	22 (52.38)		
	4-5	21 (26.92)	4 (9.52)		
ABI	> 0.9	27 (34.62)	17 (40.48)	0.404	0.525
	≤ 0.9	51 (65.38)	25 (59.52)		
Complicated with hypertension	Yes	31 (39.74)	15 (35.71)	0.187	0.665
	No	47 (60.26)	27 (64.29)		
Complicated with coronary heart disease	Yes	19 (24.36)	11 (26.19)	0.049	0.825
	No	59 (75.64)	31 (73.81)		
Smoking history	Yes	49 (62.82)	20 (47.62)	2.582	0.108
	No	29 (37.18)	22 (52.38)		
Drinking history	Yes	43 (55.13)	19 (45.24)	1.069	0.301
	No	35 (44.87)	23 (54.76)		

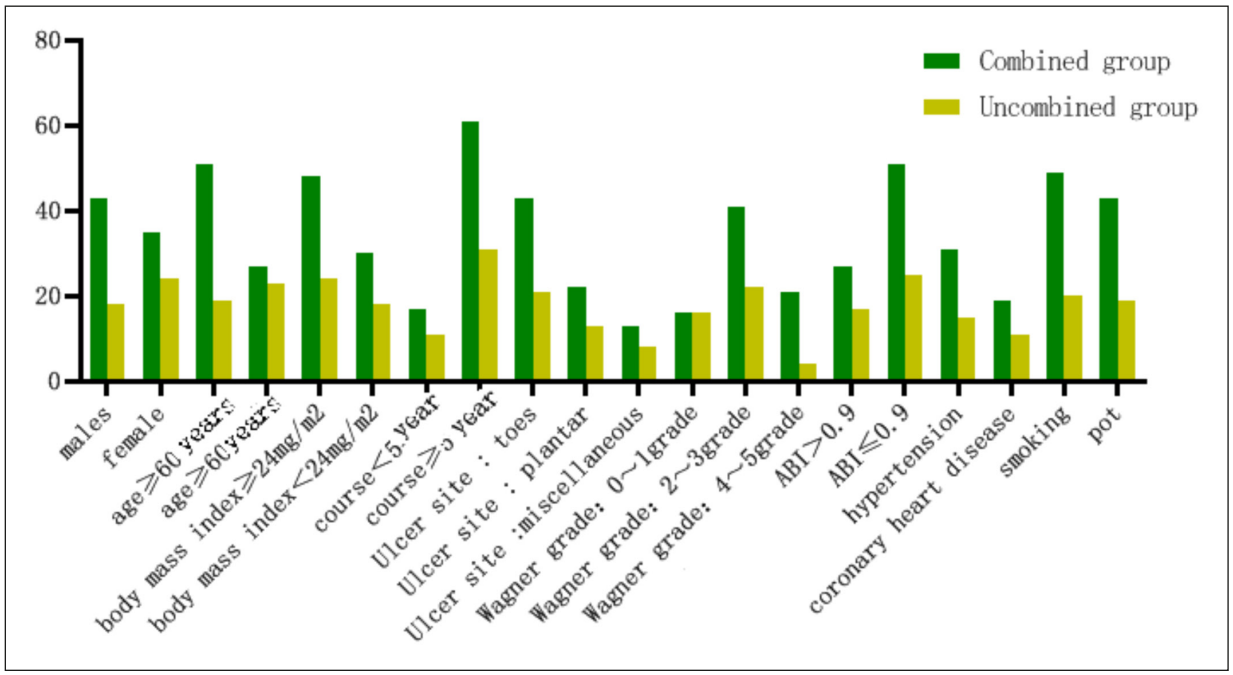

Figure 1. Baseline information between groups.

Binary Logistics Regression Analysis

The occurrence of PAD in patients with diabetic foot ulcer was taken as the dependent variable ("0"= not combined, "1"= combined), and the variables (age, Wagner grade, smoking history, DBP, CRP, NLR, HbA1c) with statistically significant differences (Table II and Figure 2) were taken as the independent variables (Table III for the values assignment). After the single logistics regression analysis, the *p*-value was expanded to < 0.1, and eligible factors were included. As shown in Table IV and Figure 3, the results of binary logistics regression analysis showed that age ≥ 60 years, high Wagner grade, smoking history, elevated CRP, NLR, and HbA1c were risk factors for patients with diabetic foot ulcer combined with PAD (OR > 1, $p < 0.05$). Elevated DBP was the protective factor for patients with diabetic foot ulcer combined with PAD (OR < 1, $p < 0.05$).

Discussion

The diabetic foot is one of the most serious complications of diabetes, which is characterized by a long duration, high disability, and high mortality rate. It leads to muscle atrophy in the extremities of patients, develops blistering infections, forming

Table II. Comparison of laboratory indicators between the two groups (±s).

Group	SBP/mmHg	DBP/mmHg	CRP/(mg/L)	NLR/%	HbA1c/%
Combined group (n=78)	137.07±20.58	71.19±10.28	5.17±1.87	5.28±1.72	9.76±2.17
Uncombined group (n=42)	139.63±20.87	79.62±9.94	2.27±0.87	2.18±0.84	6.29±1.82
t	0.647	4.334	9.498	10.981	8.822
P	0.519	<0.001	<0.001	<0.001	<0.001

Continue to Table II (±s, mmol/L).

Group	FPG	2hPG	TC	TG	LDL-C	HDL-C
Combined group (n=78)	12.68±4.06	13.78±3.11	6.06±1.32	2.06±0.83	3.02±1.02	1.01±0.41
Uncombined group (n=42)	11.85±3.57	12.89±2.91	5.92±1.18	1.94±0.77	2.91±0.87	1.14±0.43
t	1.113	1.529	0.575	0.774	0.592	1.629
P	0.268	0.129	0.567	0.440	0.555	0.106

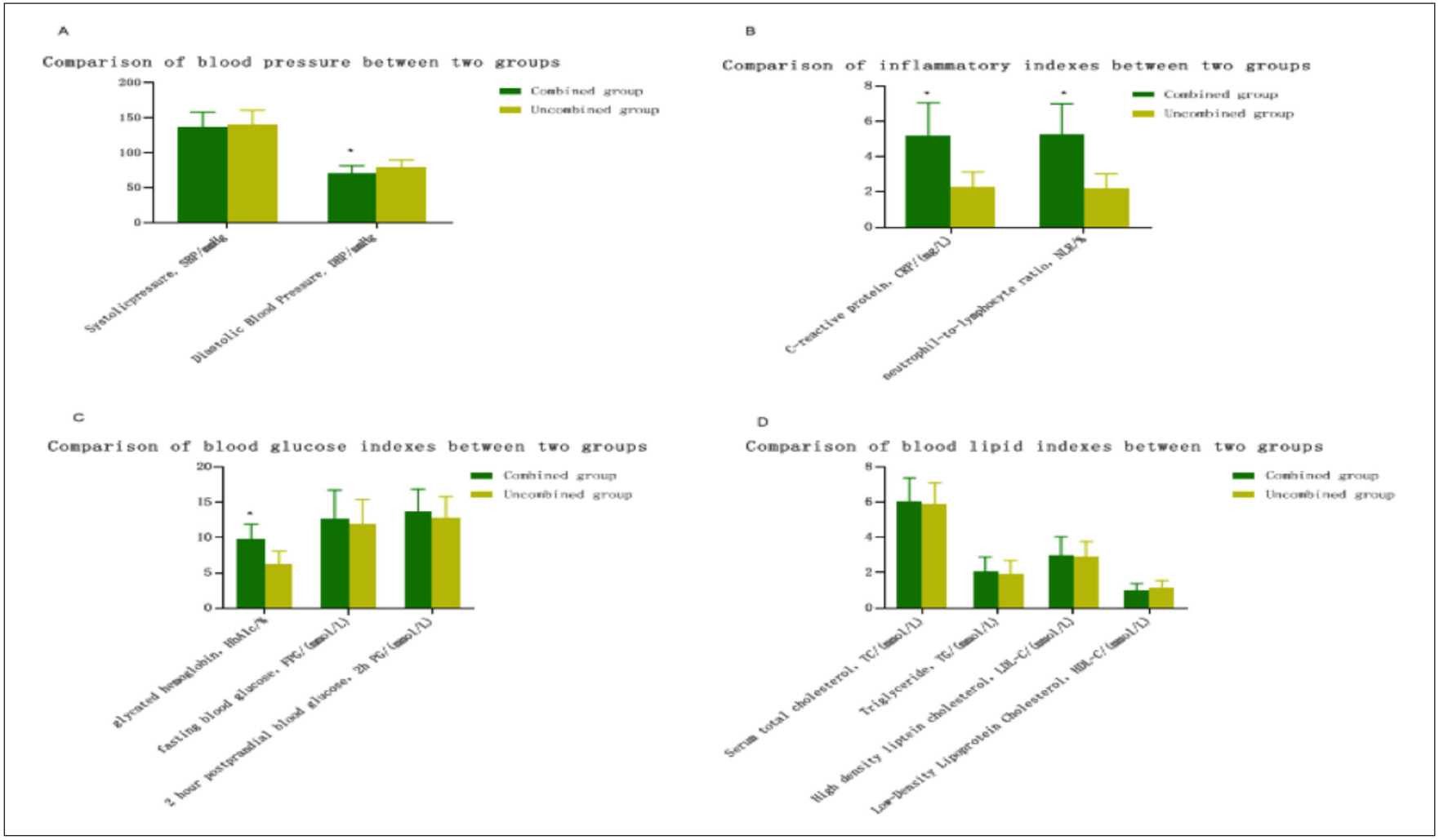

Figure 2. Bar chart of blood pressure levels (**A**), inflammatory indexes (**B**), blood glucose levels (**C**), and blood lipid indexes (**D**) between groups. *p<0.05

Table III. Details for independent variables.

Variables	Types	Details
Age	Categorical variables	"1"=Phase II-III, "0"= Phase I
Wagner grade	Categorical variables	"2" = Grade 4-5, "1" = Grade 2-3, "0" = Grade 0-1
Smoking history	Categorical variables	"1"= Yes, "0"= No
DBP	Continuous variables	-
CRP	Continuous variables	-
NLR	Continuous variables	-
HbA1c	Continuous variables	-

Table IV. Binary Logistics regression analysis of PAD in diabetic foot ulcer patients.

Variables	B	SE	Wald	P	OR	95% confidence interval
Intercept	-17.038	9.285	3.367	0.067	-	-
Age	2.053	1.475	1.938	0.016	21.956	1.475-100.870
Wagner classification	-1.047	1.194	0.769	0.038	6.111	1.025-150.805
Smoking	1.174	1.425	0.679	0.041	6.192	2.171-224.659
DBP	-0.052	0.079	0.679	0.048	0.708	0.500-0.979
CRP	0.981	0.482	4.144	0.042	3.042	1.181-7.836
NLR	1.546	0.542	8.145	0.004	5.469	1.334-22.412
HbA1c	1.490	0.678	4.702	0.030	6.486	4.250-150.805

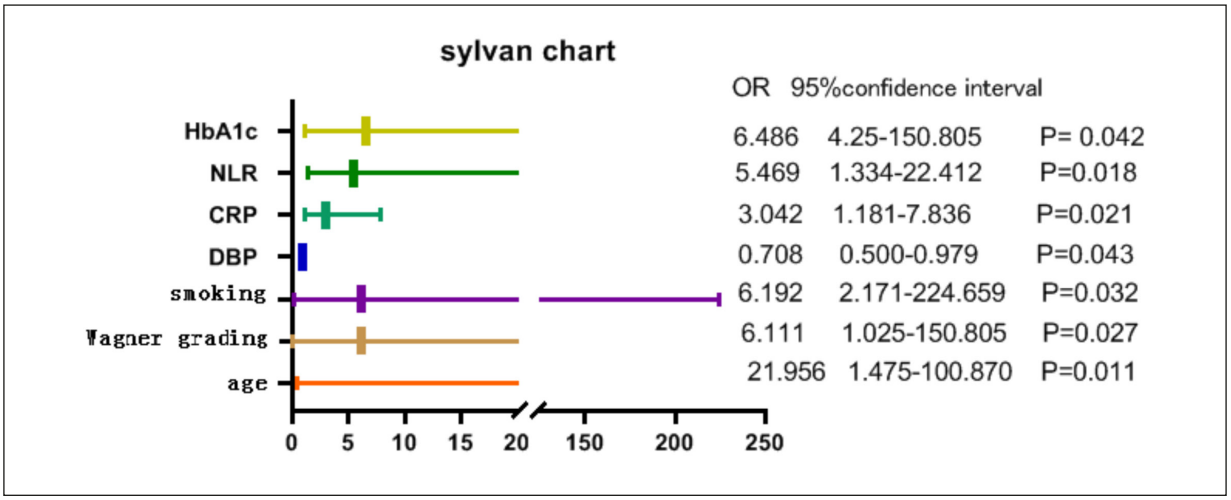

Figure 3. Forest map of influencing factors of PAD in patients with diabetic foot ulcer.

ulcers or gangrene, which can lead to amputation or death if left untreated[8]. In the meanwhile, the recovery of diabetic foot ulcers is closely related to lower extremity arterial disease (PAD). Shwaiki et al[9] found that up to 50% of patients with diabetic foot ulcers worldwide suffer from underlying PAD, which can lead to inadequate blood perfusion in the lower limbs, causing ischemia and hypoxia in the lower limbs, which is detrimental to healing, prolonging their hospital stay and increasing the risk of infection[10]. Therefore, reducing the risk of PAD in patients with diabetic foot ulcers is important for patient recovery.

The results of this study showed that the proportion of patients with a smoking history in the combined group was higher than that in the uncombined group, the DBP level of the combined group was lower than that in the uncombined group, and the CRP, NLR, and HbA1c levels of the combined group were higher than those of the combined group. Binary logistics regression analysis demonstrated that age ≥ 60 years, high

Wagner grade, smoking history, elevated CRP, NLR, and HbA1c levels are risk factors for PAD in patients with diabetic foot ulcers. Elevated DBP level is considered to be a protective factor for this disease. The reasons may be as follows:

(1) Smoking history: Smoking is an important factor to induce peripheral vascular lesions. Tobacco contains nicotine, tar, and other substances, which can affect vascular endothelial function and lead to the reduction of nitric oxide and prostacyclin levels in the body, thereby inducing vascular endothelial injury[11]. Vascular endothelial cells can coordinate vasodilation, maintain the balance between contractile factors, inhibit platelet adhesion and thrombosis, and protect blood vessels. However, when endothelial cells are damaged, they can promote the growth and proliferation of vascular smooth muscle cells, resulting in arterial thickening and stenosis and induce PAD. At the same time, endothelial cell injury can also cause abnormal vasomotor, resulting in increased vascular tension, decreased elasticity, and increased risks of PAD[12]. Therefore, we should encourage patients with a smoking history to quit smoking, inform them of the dangers of smoking, and instruct their families to supervise their smoking behaviors, which will help them develop good living habits and reduce the risk of PAD.

(2) Decreased DBP: DBP is the pressure generated when the elastic retraction of arterial vessels occurs during heart relaxation, which can reflect the arterial vascular elasticity of patients to some extent[13]. The decline of DBP indicates that the vascular elasticity of the patient decreases, and the excess blood flow cannot be stored in the blood vessels, which affects the arterial blood supply of the lower extremity and leads to the decrease of the terminal flow of the lower extremity. Long-term ischemia and hypoxia of the lower extremities can cause an insufficient supply of nutrients, aggravate the degree of vascular disease of the lower extremities, and induce PAD[14]. Therefore, it is necessary to pay close attention to the changes in the blood pressure level of patients in the combined group, especially the DBP level, and control the blood pressure level of patients through proper exercise and a healthy diet, so as to ensure the blood supply to the lower extremities of patients and reduce the risk of PAD.

(3) Increased C-reactive protein and NLR: Inflammatory reaction runs through the whole process of occurrence and development of arterial lesions. CRP is a protein that increases sharply when the body is infected or injured, which can activate complement and strengthen phagocytosis of phagocytes, and play an important role in the immune process of the body[15]. CRP can activate nuclear factor 2kB, induce the release of tumor necrosis factor-2α, promote the release of many inflammatory mediators, damage vascular endothelial function and arterial vessels, and then induce PAD[16]. CRP can directly inhibit the synthesis of endothelial nitric oxide, promote endothelial cell apoptosis, aggravate vascular endothelial dysfunction, and increase the risk of PAD. NLR is the ratio of neutrophils to lymphocytes, which is an important indicator of inflammation[17]. NLR can effectively reflect the level changes of both, in which neutrophils can secrete granulin, which activates or secretes metalloproteinases and oxidative metabolites in different mechanisms. It degrades basement membrane and extracellular matrix components and increases vascular fragility and the risk of PAD[18]. Moreover, Lee et al[19] showed that lymphocytes, including B lymphocytes and natural killer cells, play a bidirectional role in the formation and development of atherosclerosis. It can be concluded that NLR level is closely related to the occurrence of PAD. Therefore, for patients with high CRP expression, anti-inflammatory therapy can be given to improve the level of inflammation and reduce the damage to vascular endothelial cells, which reduces the risk of PAD.

(5) Increased HbA1c: HbA1c is the product of a non-enzymatic reaction of hemoglobin in red blood cells and carbohydrates in serum, which has the characteristics of continuous, slow, and irreversible. Therefore, the level of HbA1c can effectively reflect the long-term blood glucose changes in patients with diabetes. The increase in HbA1c indicates that the blood glucose level of patients in the past 8-12 weeks is high. Hyperglycemia can promote apoptosis of vascular endothelial cells and inhibit cell growth. A large amount of glycosylation end products can cause proliferation and stenosis of vascular wall, promote the formation of occlusive arteriosclerosis, and increase the risk of PAD[20]. Long-term elevated blood glucose can also lead to lipid metabolism disorders, increase blood viscosity, and put the body in a hypercoagulable state. It promotes the formation of lower limb atherosclerosis and thrombosis and threatens the life safety of patients[21]. Therefore, health education, including diabetes knowledge, should be provided to patients with elevated HbA1c. Their self-management ability should be improved. Regular and quantitative medication

and well-controlled blood glucose level are necessary for reducing the risk of PAD. Furthermore, the results in this study also showed that advanced age and high Wagner grade were risk factors for PAD, which have been widely confirmed[22-24]. Previous studies in literature mainly analyzed the basic conditions of patients, such as age and living habits, but this study included laboratory indicators on this basis. Compared with the basic conditions of patients, conventional indicators such as inflammation, blood sugar, and blood lipid are easy to investigate, and the survey results are more objective and specific, which is conducive to clinical assessment of the risk of diabetic foot ulcer based on patient indicators.

Conclusions

Patients with diabetic foot ulcers combined with lower extremity arterial diseases have clinical characteristics of poor blood pressure control, long course of disease, and low ABI value. Age $\geq$ 60 years, high Wagner grade, smoking history, elevated CRP, NLR and HbA1c levels are risk factors for PAD in patients with diabetic foot ulcer, while an elevated DBP level is the protective factor for this disease.

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Data Availability
All data generated and analyzed during this study are included in this article.

Ethics Approval
The study was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University.

Informed Consent
Due to the retrospective nature of this study, the research waived the need for informed consent.

Conflict of Interest
The authors have no conflict of interest to declare.

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