A study of prognostic factors in Chinese patients with diabetic foot ulcers

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Objective: Few studies have identified factors as predictors of clinical prognosis of patients with diabetic foot ulcers (DFUs), especially of Chinese patients. In this study, we assessed the prognostic factors of Chinese patients with DFUs.

Methods and materials: This was a retrospective study (January 2009–January 2011) of 194 DFUs conducted in an inpatient population at PLA 454 Hospital in Nanjing, China, to determine the prognostic influential factors of DFUs in Chinese patients. All of the studied patients were grouped into an amputation group, a non-healing group, and a cured group, according to the clinical prognosis. Patient parameters, including gender, age, smoking habits, education level, family history of diabetes mellitus, medical history, duration of foot lesions and complications, ankle-brachial index (ABI), transcutaneous oxygen pressure (TcPO2), urinary albumin/creatinine ratio (Alb/Cr), fundus oculi, electrocardiogram, DFU characteristics, bacterial nature, and neuropathy, were cross-studied among the three groups.

Results: Compared with the other two groups, the amputation group showed a higher number of males, older in age, lower ABI and TcPO2 levels, higher Wagner wound grading and size, and significantly higher urinary Alb/Cr ratio, blood urea nitrogen, serum creatinine, white blood cell count, and erythrocyte sedimentation rate. Compared to the cured group (162 patients), more patients with an older age, smoking, family history of diabetes mellitus, medical history of foot ulcerations, lower ABI and TcPO2 levels, higher urine Alb/Cr ratio, and serum creatinine were found in the non-healing group. Regression analysis was used to study the correlation between various factors and clinical prognosis, and the results were as follows: age, Wagner wound classification, and heel ulcerations were negatively correlated to the DFU prognosis, whereas the female population, ABI, and TcPO2 were positively correlated with DFU prognosis.

Conclusion: In this retrospective study, we conclude that the DFU prognosis may be related to age, gender, wound location (heel), Wagner wound classification, ABI, and TcPO2 levels in the Chinese population.

Keywords: *Chinese*; *diabetic foot ulcers*; *prognosis*; *ankle brachial index*; *Wagner wound classification*

It is well known that the risk of non-traumatic amputations is higher in the diabetic population than in those patients without diabetes and that amputation itself could present as a major factor of disability among patients with diabetes mellitus. In addition, identifying the prognostic factors for diabetic foot ulcers (DFUs) and thereby reducing the risk of amputation in the diabetic population presents with an inevitable challenge for physicians and surgeons treating diabetic foot-related complications. In one study, Hämäläinen et al. (1) presumed that males, medical history of foot ulcers, glycated hemoglobin A1c, proteinuria, duration of diabetes mellitus, and smoking were the risk factors of amputation (1), while another study showed that the tendency for amputation was more obvious in the right lower limb (2). However, few clinical research data were related to prognostic factors of DFUs in Chinese patients.

Methods and materials

Diabetic patients with foot ulcers hospitalized between January 2009 and January 2011 were followed up for 1 year. According to the clinical prognosis, the patients with DFUs were divided into three groups: the amputation Group (above the ankle amputation), the non-healing

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group (DFU did not heal for at least 1 year, but no need for amputation), and the cured group (continuous live epithelial covering all previous wounds) (3).

All three groups of patients were interviewed for the following factors: gender, age, educational level, biochemical indicators, foot ulcer severity, and so on. Wagner grading was adopted to assess the DFU severity; American Image J-ij133-jdk15 software was used to calculate the DFU area; DFU was classified by the ulcer area site [front foot (toe tips to the metatarsal head), midfoot (metatarsal head to Chopart's joint), and hindfoot (the area closest to the Chopart's joint)] (4); English Huntleigh MD2 diabetes screening and diagnosis box was applied to vessel evaluation; transcutaneous oxygen pressure (TcPO2) was tested by multi-channel TcPO2 analyzer TCM400 from radiometer company; neuropathy condition was assessed with the World Health Organization criteria (four tests: pain, touch, vibratory sense, and Achilles tendon reflexes; no less than three abnormal was defined as positive); education level was defined as: 0 – illiterate, 1 – primary school, 2 – middle schools, and 3 – undergraduate and above. Comprehensive treatment program included glycemic control, antibiotic therapy, surgical debridement, microcirculation improvement, neurotropic therapy, and support treatment.

Statistical analysis: Statistical Product and Service Solutions (SPSS) 16.0 software was adopted for quantitative analysis purposes. One way ANOVA and two-tailed Student t-tests were used in our statistical analysis; $P < 0.05$ was considered statistically significant; frequency data were examined by X^2 test; continuity data were analyzed with multiple linear stepwise regression, to determine the statistically significant factors of DFUs prognosis among all potentially relevant factors being tested; multiple regression variables inclusion criteria were $P < 0.1$, where exclusion criteria were $P > 0.15$.

Results

Of the 194 patients with DFUs who were recruited in this study, the average age was 67.00 ± 12.26 years, where 110 patients were male and 84 were female. Twelve

patients were classified in the amputation group, making up 6.19% of all studied patients, all male with an average age of 78.00 ± 8.74 years. Results for the other two groups were as follows: the non-healing group (20 patients, 10.31% of all studied patients, 60% males, mean age 71.10 ± 9.28 years) and the cured group (162 patients, 83.5% of all studied patients, 48.15% males, mean age 65.63 ± 12.37 years). There were no differences among all three groups in terms of the education level or diabetes duration. Although the cured group had fewer patients with family history of diabetes and lower smoking rate, there were no statistically significant differences as shown in Table 1.

The amputation group was distinctive for having shorter diabetic foot disease duration, more common DFU history, higher Wagner classification level, larger ulcer area, more common heel ulcers, lower ankle-brachial index (ABI) and acrotarsium TcPO2, and a higher proportion of positive bacteria (but no significant differences from the non-healing group). Compared to the cured group, the non-healing group had a more common history of DFU, lower ABI and acrotarsium TcPO2, but no significant differences in terms of Wagner classification, ulcer area or site as shown in Table 2. However, the urine albumin/creatinine ratio (Alb/Cr), blood urea nitrogen, serum creatinine, white blood cell count, and erythrocyte sedimentation rates were significantly different among the three groups as shown in Table 3.

After adjusting (for prognosis), we used the multiple linear stepwise regression analysis to determine the factors that contribute to the prognosis. The results suggested that age [OR = −0.269, CI = (−0.021)–(−0.003), $P < 0.01$], Wagner classification [OR = −0.262, CI = (−0.261)–(−0.037), $P < 0.01$], and heel ulcers [OR = −0.210, CI = (−0.301)–(−0.008), $P < 0.05$] were negatively correlated to DFUs prognosis; female (OR = 0.319, CI = 0.142–0.579, $P < 0.01$), ABI (OR = 0.424, CI = 0.467–1.188, $P < 0.01$), and the acrotarsium TcPO2 (OR = 0.357, CI = 0.004–0.014, $P < 0.01$) were positively correlated with DFU prognosis.

Table 1. Demographic, behavioral, and family history of diabetic foot patients

	Major amputation	Non-healing	Healing	Total	P
Number (%)	12 (6.19%)	20 (10.21%)	162 (83.60%)[##]	194 (100%)	0.005
Male (no.)	12 (100%)	12 (60%)	78 (48.15%)[*###]	102 (52.58%)	0.003
Age (mean [SD] years)	78.00 ± 8.74	71.10 ± 9.28	65.63 ± 12.37[*#]	67.00 ± 12.26	0.029
Smoker (%)	50.00	40.00	20.99[#]	24.74	0.053
Education (mean [SD])	2.00 ± 1.27	1.70 ± 1.01	1.54 ± 1.11	2.00 ± 1.11	0.579
Duration of diabetes (mean [SD] years)	6.00 ± 3.85	9.22 ± 2.92	9.99 ± 6.55	9.78 ± 6.75	0.364
Family history of diabetes (%)	50.00	60.00	27.16[#]	31.96	0.069

Major amputation compared with others, *$P < 0.05$, non-healing compared with healing, #$P < 0.05$, ##$P < 0.01$.

Table 2. The clinical characteristics of diabetic foot ulcers (DFUs)

	Major amputation	Non-healing	Healing	Total	P
Duration of DFU (mean [SD] weeks)	5.67±3.03	34.20±12.08**	15.08±11.79*#	16.36±6.74	0.046
History of DFU (%)	66.67	60	27.16*#	32.99	0.021
Wagner grade	3.67±1.36	2.50±1.08*	2.73±0.90*	2.76±0.97	0.046
Area of ulcers (mean [SD] cm^2)	33.65±24.21	13.70±4.49**	12.98±8.97**	14.34±10.16	0.510
Sites of foot ulcers					0.105
Fore (no.)	4	10	102		
Mid (no.)	2	6	42		
Hind (no.)	6	6	18*		
ABI (mean [SD])	0.45±0.25	0.73±0.19*	0.91±0.26**#	0.86±0.28	0.000
TcPO2 (mean [SD] mmHg)	32.83±18.30	46.50±18.06*	61.11±21.16**#	57.86±21.97	0.002
Gram-Positive bacteria (%)	66.67	50.00	39.51*	42.27	0.073

Major amputation compared with others, *P <0.05, **P <0.01; non-healing compared with healing, #P <0.05, ##P <0.01.

Discussion

In 2011, Chinese Diabetes Society studies have shown that Chinese diabetic foot disease accounted for 12.4% of the hospitalized patients with diabetes in 2010 with a high amputation rate of 7.3%, where amputation rates caused by diabetes accounted for 28.2% of all amputations and 41.5% of non-traumatic amputations, which stands first on the non-traumatic amputation list (5). Diabetic foot complications have become the main reason for amputation among diabetic patients (6). Our paper analyzes the factors that may be related to the Chinese DFUs patient prognosis.

Age and its relation to DFU patient prognosis

This study showed that the DFUs patient prognosis worsened with age (P = 0.029). Age was the risk factor of amputation, the risk factor of systemic atherosclerosis (ASO), and also the risk factor of peripheral vascular disease (PVD) among diabetic patients (7, 8). About 3% of diabetic patients in their 60s had PVD, whereas the percentage was >20% for patients older than 75 (9). The role of age in lower extremity vascular disease is not yet clear, but it is highly possible that vascular biological dynamics change is related to the passage of time, low-density lipoprotein cholesterol, blood pressure, smoking,

Table 3. The clinical features of diabetic foot patients

	Major amputation	Non-healing	Healing	Total	P
Electrocardiogram (1+) (%)	83.33	60.00	62.96	63.95	0.591
Retinopathy (1+) (%)	66.67	40.00	46.68	46.39	0.565
Neuropathy (1+) (%)	66.67	60.00	53.09	54.64	0.812
Systolic blood pressure (mean [SD] mmHg)	135.83±17.44	139.50±26.51	134.10±18.45	135.9±19.20	0.700
Diastolic blood pressure (mean [SD] mmHg)	75.83±11.14	79.90±11.21	76.53±10.49	77.05±10.54	0.621
Fasting glucose (mean [SD] mmHg)	8.25±4.12	10.01±4.79	8.51±4.08	8.65±4.14	0.547
HbAlc (mean [SD] (%)	10.10±2.21	9.48±1.46	9.87±2.50	9.80±2.38	0.857
Urine Alb/cr (mean [SD] mmol/L)	291.83±194.79	159.20±106.50**	64.40±42.00**##	88.24±53.23	0.000
BUN (mean [SD] mmol/L)	14.33±8.04	7.22±2.70**	6.80±3.00**	8.65±4.14	0.000
Cr (mean[SD] mmol/L)	279.83±206.50	198.10±122.59	109.03±68.00**##	129.03±98.64	0.000
TP (mean [SD] mmol/L)	55.42±8.09	61.92±4.42	63.18±6.67**	62.57±6.78	0.023
ALB (mean [SD] mmol/L)	33.22±5.14	35.46±7.35	35.02±5.13	34.95±5.35	0.698
TG (mean [SD] mmol/L)	1.27±0.76	1.19±0.33	1.16±0.63	1.21±0.72	0.913
TCH (mean [SD] mmol/L)	4.58±1.49	4.38±0.71	4.02±1.09	4.10±1.09	0.318
WBC (×10^9)	11.83±7.17	9.10±3.43	7.81±3.41*	8.19±1.08	0.030
N (mean [SD] (%)	66.37±6.69	64.93±14.35	66.06±13.38	65.96±13.07	0.965
Hb (mean [SD] g)	90.33±19.47	110.70±27.89	110.92±22.62	109.62±23.32	0.112
ESR (mean [SD] mm/h)	79.00±28.54	38.20±23.69*	35.23±19.88*	38.25±23.15	0.000

Major amputation compared with others, *P <0.05, **P <0.01; non-healing compared with healing, #P <0.05, ##P <0.01.

and blood glucose that has sustained damage on blood vessels, which will eventually lead to vascular ASO (10).

Gender and its relation to DFU patient prognosis

This study demonstrated that the male DFU patient prognosis was worse ($P = 0.003$). It is worth mentioning that all six cases in the amputation group were males. The latest research also showed that the average age of amputated male patients was 10 years earlier than that for their female counterparts; moreover, infection and repeated amputation were also more severe for men (11). Previous smoking habits, height, and increased weight, leading to foot over-pressure, were also possible factors (12). Moreover, wounds found in females may have healed better due to the existence of estrogen receptor β, while male androgen was considered harmful for wound healing (13).

Wagner classification and its relation to DFU patient prognosis

This study showed that in the amputation group, Wagner classification was significantly higher than the cured group, with an average higher grading of three levels. This finding supported that severe foot infections in the amputation group was one of the risk factors that caused amputation (14). A recent Indian study surveyed 94 patients with diabetic foot disease during September 2009 and December 2010. The survey showed that among 32 cases, 34% had amputations (including major and minor amputations) and 93.8% of them had a Wagner classification of no less than level 3 (15).

Heel ulcer and its relation to DFU patient prognosis

This study found that heel ulcers were cumulative to 6 of 12 cases, which accounted for 50% of the major amputees, and significantly higher than that of the cured patients. Among all DFU patients, heel ulcer was one of the most serious and common risk factors that led to amputation (16). Some of the possible reasons were attributed to the relatively fixed structure, the existence of diabetic neuropathy, heel structure deformity, formation of peripheral ASO, which led to arterial ischemia, and local and systemic treatment requirement that caused treatment difficulties, resulting in the recovery rate being only about 40% (17).

ABI and acrotarsium TcPO2 and its relation to DFU patient prognosis

This study showed that ABI (0.45 ± 0.25) and TcPO2 (32.83 ± 18.30) in the amputation group were significantly lower than that in the other two groups. Multiple regression analysis suggested that ABI and dorsum TcPO2 were positively correlated to DFUs prognosis.

Macroangiopathy and high ASO rates were common among diabetic foot patients; however, only possible vascular disease caused by multiple stenoses ASO, which resulted in no neovascularization, was a risk factor of amputation, where ASO patients whose peripheral outflow tract was reserved, could avoid high amputation rates via vascular bypass operation or percutaneous transluminal angioplasty (PTA) (17). Armstrong et al. found that the amputation rate in patients with ischemic infection was 90 times higher than that of non-ischemic infected wound patients. Blood flow problems caused by PVDs form the basis of determining the anti-infection effect and the ultimate cure of the diabetic foot (18).

In this study, we indirectly illustrated that for diabetic foot patients, if vascular occlusion in lower extremities existed without enough collateral formation, it may eventually lead to reduction in foot tissue oxygen supply, which then causes wound infection control difficulty and poor wound healing. In this study, the one-way ANOVA analysis revealed that patients in the amputation group generally had low total protein levels, high blood urea nitrogen, high creatinine levels, high white blood cell count, and high erythrocyte sedimentation rate. The cured group manifested a low smoking rate, less previous podiatric and family history of diabetes, smaller ulcer area, and a tendency of low blood urea nitrogen and creatinine levels. However, multiple regression analysis indicated that there was no significant correlation between these factors and the prognosis. The regression results also suggested that gram-positive bacteria invasion was not related to prognosis, but in the amputation group it was significantly different from that of the cured group (66.67% vs. 39.51%, $P < 0.05$).

In conclusion, the Chinese DFUs patient prognosis was related to age, gender, Wagner wound classification, presence of heel ulcers, ABI, and the acrotarsium TcPO2. In clinical practice, medical personnel should pay high attention to and actively evaluate these indexes, which may contribute to better and standardized treatment in DFUs.

Conflict of interest and funding

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