Postprint of a Case-Control Study on Risk Factors for Recurrence of Diabetic Foot Ulcers After Healing

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Abstract

Background: Diabetic foot ulcer (DFU) is a serious complication of diabetes mellitus with a high recurrence rate after healing. Numerous risk factors affect recurrence, yet systematic evidence-based research remains lacking.

Objective: To investigate the risk factors for recurrence after DFU healing and to provide additional evidence for DFU prevention and treatment.

Methods: An unmatched case-control study design was employed. Patients diagnosed with DFU for the first time during hospitalization at the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine from January 1, 2016 to February 1, 2019 were selected as the source population. They were divided into case and control groups based on whether recurrence occurred within 3 years after healing. Baseline characteristics, main exposure factors, and other relevant data were collected for both groups. Count data were compared using 2 test, and unconditional Logistic regression analysis was used to screen risk factors for DFU recurrence. The relationship between DFU recurrence and the number of risk factors and time was further analyzed.

Results: The overall recurrence rate within 3 years after DFU healing was 45.3% (86/190). Logistic regression analysis showed that age >60 years (OR=1.88, 95% CI 1.06-3.76, P=0.04), HbA1c >7.5% (OR=5.04, 95% CI 2.02-11.8, P<0.001), PAD (OR=2.56, 95% CI 1.46-4.84, P=0.008), osteomyelitis (OR=2.22, 95% CI 1.25-4.18, P=0.01), callus (OR=3.01, 95% CI 1.65-5.20, P=0.002), ABI<0.9 (OR=2.98, 95% CI 1.42-5.66, P=0.022), plantar ulcer (OR=5.88, 95% CI 2.24-8.99, P<0.001), and Wagner grade $ $3 (OR=4.66, 95% CI 2.01-9.42, P<0.001) were risk factors for DFU recurrence. The number of combined risk factors in the case group was concentrated between 5 and 9, while most patients in the control group had 2 to 5 risk factors. In the case group, 35 patients recurred in

year 1, 28 in year 2, and 23 in year 3, with cumulative recurrence rates of 18.4% (35/190) in year 1, 33.2% (63/190) in year 2, and 45.3% (86/190) in year 3.

Conclusion: The recurrence rate of DFU is relatively high, which may be associated with risk factors such as age >60 years, HbA1c >7.5%, PAD, osteomyelitis, callus, ABI<0.9, plantar ulcer, and Wagner grade $ $3. The number of combined risk factors is positively correlated with the recurrence rate.

Full Text

A Case-Control Study of Risk Factors for Recurrence of Diabetic Foot Ulcers

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Abstract

Background: Diabetic foot ulcer (DFU) is a serious complication of diabetes with a high recurrence rate after healing. Numerous risk factors influence recurrence, yet systematic evidence-based research remains lacking.

Objective: To investigate risk factors for DFU recurrence after healing and provide evidence for DFU prevention and treatment.

Methods: We conducted a non-matched case-control study. Patients hospitalized for first-time DFU diagnosis at the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine from January 1, 2016, to February 1, 2019, were selected as the source population. Participants were divided into case and control groups based on recurrence within 3 years post-healing. Baseline characteristics and major exposure factors were collected for both groups. Categorical data were compared using ^{2} tests, and unconditional logistic regression was used to screen risk factors for DFU recurrence. The relationship between recurrence and both the number of risk factors and timing was further analyzed.

Results: The overall recurrence rate within 3 years of DFU healing was 45.3% (86/190). Logistic regression analysis identified the following risk factors: age >60 years (OR=1.88, 95% CI 1.06-3.76, P=0.04), HbA1c >7.5% (OR=5.04, 95% CI 2.02-11.8, P<0.001), peripheral arterial disease (PAD) (OR=2.56, 95% CI 1.46-4.84, P=0.008), osteomyelitis (OR=2.22, 95% CI 1.25-4.18, P=0.01), callus (OR=3.01, 95% CI 1.65-5.20, P=0.002), ABI <0.9 (OR=2.98, 95% CI 1.42-5.66, P=0.022), plantar ulcers (OR=5.88, 95% CI 2.24-8.99, P<0.001), and Wagner classification ≥grade 3 (OR=4.66, 95% CI 2.01-9.42, P<0.001). The number of comorbid risk factors in the case group was concentrated between 5 and 9,

while most patients in the control group had 2 to 5 risk factors. The case group had 35 recurrences in year 1, 28 in year 2, and 23 in year 3, with cumulative recurrence rates of 18.4% (35/190) in year 1, 33.2% (63/190) in year 2, and 45.3% (86/190) in year 3.

Conclusion: DFU recurrence is common and may be associated with risk factors including age >60 years, HbA1c >7.5%, PAD, osteomyelitis, callus, ABI <0.9, plantar ulcers, and Wagner classification ≥grade 3. The number of comorbid risk factors showed a positive correlation with recurrence rate.

Keywords: Diabetic foot ulcer; Recurrence; Case-control study; Risk factor

Introduction

Diabetic foot is a common and complex complication in diabetic patients, with outcomes primarily including ulceration, amputation, and death. The lifetime risk of developing diabetic foot ulcer (DFU) in diabetic patients can reach 34% [1], and DFU accounts for 84% of diabetes-related lower extremity amputations [2]. DFU has a high recurrence rate after healing, with studies reporting recurrence rates of approximately 40% within 1 year, about 60% within 3 years, and up to 65% within 5 years after healing [1]. This high recurrence rate increases disability and mortality rates as well as treatment costs, significantly impacting patients' quality of life [3]. Reducing DFU recurrence represents a major challenge in diabetic foot care. However, current research on DFU recurrence is limited, with most reports not investigating recurrence as an epidemiological characteristic [4]. Some domestic retrospective studies have reported risk factors for DFU recurrence [5][6][7], but they lack standardized research design and accurate exposure factor definitions. To further understand factors influencing DFU recurrence and provide evidence for optimized prevention and treatment strategies, this study analyzed 3-year clinical data from DFU patients at the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine using a non-matched case-control design to explore characteristics and risk factors for DFU recurrence.

Methods

1.1 Study Population

Patients hospitalized for first-time DFU diagnosis at the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine from January 1, 2016, to February 1, 2019, were selected as the source population. Inclusion criteria: (1) Met diabetes diagnostic criteria [8] (1999 WHO standards); (2) Met Wagner grade 1-5 criteria for diabetic foot ulcer [9]; (3) Ulcer healed at discharge. Exclusion criteria: (1) Foot ulcers caused by non-diabetic reasons; (2) Incomplete medical records or refusal to participate in follow-up; (3) Malignant tumors or critical illness. Participants were divided into case and control groups based on

recurrence within 3 years post-healing. This study was approved by the Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine [Approval No.: 2019KL-020].

1.2 Data Collection

Data for both groups were extracted through medical record system searches combined with telephone follow-up. Collected information included: (1) Basic information: sex, age, body mass index (BMI), personal history, past medical history, and family history; (2) Diabetes-related information: diabetes duration, insulin use, glycated hemoglobin (HbA1c); (3) DFU-related factors: peripheral arterial disease (PAD), osteomyelitis, callus, ankle-brachial index (ABI), Charcot foot, ulcer duration, ulcer area, ulcer location (plantar, dorsal, toe), and Wagner grade. All data were first recorded on paper forms, double-checked, and then entered into a computerized clinical research database.

1.3 Definition of Exposure Factors

BMI >24 kg/m^2 was defined as overweight; smoking history: >1 cigarette per day for >1 year; alcohol consumption: >50g daily alcohol intake for >1 year; end-stage renal disease defined as requiring dialysis; HbA1c >7.5% defined as poor glycemic control; PAD defined as ABI <0.9 or inability to palpate pedal pulses [10]; osteomyelitis diagnosed by clinical features and X-ray findings; Charcot foot diagnosed by skin temperature difference >2°C between feet plus X-ray and/or radionuclide bone scan; C-reactive protein (CRP) >5 mg/L indicated DFU infection [11]; callus diagnosed by clinical examination identifying localized hyperkeratotic thickening; ulcer location categorized as plantar (covering forefoot, midfoot, or heel) or dorsal/toe; multidrug resistance defined as resistance to $ $3 antibiotic classes in ulcer secretion culture; Wagner grade $ $3 used as severity cutoff.

1.4 Statistical Analysis

SPSS 22.0 was used for statistical analysis. Categorical data were expressed as percentages and compared between groups using ^{2} tests. Unconditional logistic regression was used for multivariate analysis to screen risk factors for DFU recurrence and calculate odds ratios (OR) and 95% confidence intervals (95% CI). P<0.05 was considered statistically significant.

Results

From the medical record system, 256 patients with first-time DFU diagnosis were identified. Among them, 210 had healed ulcers, 12 had unhealed ulcers, 20 died, and 14 underwent amputation. Of the 210 healed patients, 12 were lost to follow-up and 8 were excluded due to incomplete data, leaving 190 healed DFU patients for analysis. Eighty-six patients experienced recurrence within 3 years

(case group) and 104 did not (control group). The case screening flow chart is shown in Figure 1 [Figure 1: see original paper].

The overall recurrence rate within 3 years was 45.3% (86/190). Patients >60 years accounted for 80.2% (69/86) in the case group, significantly higher than the 65.4% (68/104) in the control group (P=0.023). No significant differences were found between groups in sex, smoking history, alcohol consumption, coronary heart disease (CHD), hypertension, hyperlipidemia, diabetes duration, insulin use, multidrug-resistant bacterial infection, or ulcer duration >3 months (P>0.05). The case group had significantly higher proportions of HbA1c >7.5%, osteomyelitis, callus, ABI <0.9, CRP >5 mg/L, plantar ulcers, ulcer area >5 cm^2, and Wagner grade $ $3 (P<0.05). The control group had higher proportions of dorsal and toe ulcers (P<0.05). Baseline characteristics are shown in Table 1 .

Logistic regression analysis of potential risk factors for DFU recurrence was performed, with OR values and 95% CIs calculated (Table 2). Univariate analysis indicated that age >60 years, HbA1c >7.5%, PAD, osteomyelitis, callus, ABI <0.9, CRP >5 mg/L, plantar ulcers, ulcer area >5 cm^2, and Wagner grade $ $3 were risk factors, while smoking, dorsal ulcers, and toe ulcers appeared protective. Multivariate logistic regression confirmed age >60 years (OR=1.88, 95% CI 1.06-3.76, P=0.04), HbA1c >7.5% (OR=5.04, 95% CI 2.02-11.8, P<0.001), PAD (OR=2.56, 95% CI 1.46-4.84, P=0.008), osteomyelitis (OR=2.22, 95% CI 1.25-4.18, P=0.01), callus (OR=3.01, 95% CI 1.65-5.20, P=0.002), ABI <0.9 (OR=2.98, 95% CI 1.42-5.66, P=0.022), plantar ulcers (OR=5.88, 95% CI 2.24-8.99, P<0.001), and Wagner grade $ 3($OR = 4.66, 95^{2} $ (OR=1.68, 95% CI 0.84-3.01, P=0.95), and CRP >5 mg/L (OR=2.14, 95% CI 0.96-4.67, P=0.059) showed no significant association.

Eight potential risk factors for DFU recurrence were identified (Figure 2 [Figure 2: see original paper]). The case group had a minimum of 3 risk factors (4 patients), with most patients having 5 (15 patients), 6 (22 patients), or 7 (26 patients) risk factors, and 9 patients had 8 risk factors. In contrast, most control group patients had 2-5 risk factors (Figure 3 [Figure 3: see original paper]). Regarding recurrence timing, 35 patients recurred in year 1, 28 in year 2, and 23 in year 3, with cumulative recurrence rates of 18.4% (35/190) in year 1, 33.2% (63/190) in year 2, and 45.3% (86/190) in year 3 (Figure 4 [Figure 4: see original paper]).

Discussion

DFU can result from multiple factors causing skin breakdown, including peripheral neuropathy, PAD, foot deformities, limited joint mobility, hyperkeratosis, foot edema, and ill-fitting shoes [12]. In diabetic populations, the annual risk of DFU is approximately 2% [13], but for patients with prior DFU, the 3-year recurrence risk increases to 17-60% [14]. A prospective German-Czech study of 321 DFU patients with 15-year follow-up reported a cumulative recurrence rate

of 70% [15], with most recurrences concentrated in the first 3 years post-healing and few after 10 years, possibly due to severe complications and comorbidities reducing the at-risk population through high mortality [15]. Recurrent DFU patients experience slow healing, deteriorating physical condition, increased medical costs, reduced quality of life, and higher amputation and mortality rates [16][17]. Due to high recurrence rates, the International Working Group on the Diabetic Foot [18] recommends high-risk patients undergo specialist foot examination every 1-3 months after initial healing, while low-risk patients do not require such intensive monitoring.

However, research on DFU recurrence risk factors is limited, with few known predictive factors [4][18][19]. Further analysis of these risk factors to develop prevention strategies would greatly benefit DFU management [20].

This study found a 3-year recurrence rate of 45.3% among 190 patients, lower than four previous foreign studies [21][22][23][24] (60%, 60.5%, 60.9%, and 61% respectively). This may be attributed to the integrated Chinese-Western medicine approach used, including herbal foot baths and oral decoctions, which our previous research confirmed reduces DFU recurrence [25][26]. Recurrence timing showed the highest rate in year 1 (18.4%), decreasing in years 2 (14.7%) and 3 (12.1%), possibly due to gradual improvement in risk factors such as glycemic control, custom offloading footwear, and lower limb perfusion. Multivariate logistic regression identified age >60 years, HbA1c >7.5%, PAD, osteomyelitis, callus, ABI <0.9, plantar ulcers, and Wagner grade $ $3 as independent risk factors. By effect size (Figure 2 [Figure 2: see original paper]), the top three were plantar ulcers (OR=5.88, 95% CI 2.24-8.99), HbA1c >7.5% (OR=5.04, 95% CI 2.02-11.8), and Wagner grade $ $3 (OR=4.66, 95% CI 2.01-9.42). The case group had significantly more risk factors than the control group (Figure 3 [Figure 3: see original paper]). Ulcer size was not a risk factor, consistent with previous research [20][27]. CRP >5 mg/L and multidrug-resistant bacterial infection also showed no significant association, contrasting with Dubsky [21] and Jeandrot [28], who found CRP >5 mg/L predictive. In our cohort, 72.1% had CRP >5 mg/L, possibly reflecting non-specific inflammation rather than DFU infection severity, warranting future stratified analysis. Multidrug-resistant infection cases were few (9 in case group, 5 in control), potentially explaining the negative finding.

We found 80.2% (69/86) of recurrent ulcers were plantar, similar to Dubsky' s findings (75.3%) [21]. Plantar DFU may recur more frequently due to higher pressure and less detectable damage. Defining HbA1c >7.5% as poor glycemic control, we found it associated with recurrence (OR=5.04), consistent with international studies [21][29], reflecting both glycemic control and patient compliance with monitoring, medication, and education. Using Wagner grade $ $3 as a severity cutoff, we identified it as an independent risk factor, differing from Mo et al. [5] possibly because previous studies didn' t account for confounders like ischemia and infection. The 2019 Chinese Diabetic Foot Guidelines [30] indicate Wagner grade predicts prognosis and amputation risk, aiding early identification

and treatment adjustment.

Age >60 years correlated with recurrence (OR=1.88, 95% CI 1.06-3.76), differing from Engberg [31], possibly due to lower activity levels in Chinese versus Western populations. PAD represents diabetic macrovascular disease in lower limbs, with high prevalence in DFU patients. ABI <0.9 is an important PAD indicator, both reflecting lower limb perfusion and identified as recurrence risk factors, consistent with previous research [22][32].

Foot callus was identified as a risk factor (OR=3.01, 95% CI 1.65-5.20), a relationship not previously reported. As diabetic vasculopathy and neuropathy progress, increased plantar pressure causes hyperkeratosis and callus formation, increasing DFU risk [33]. Persistent callus after healing may increase pressure and recurrence risk, while callus removal can reduce plantar pressure by 53% [34], warranting encouragement for removal when feasible.

Despite no association with CRP, osteomyelitis was a risk factor (OR=2.22, 95% CI 1.25-4.18), possibly due to treatment difficulty and preference for conservative management over surgery. Aragon-Sanchez [35] reported 43% recurrence in 65 surgically treated osteomyelitis patients, indicating high risk even after surgery.

As a case-control study, bias control was crucial. We extracted data through medical record searches and telephone follow-up, strictly applied diagnostic criteria, and used double-checking to minimize information bias. Limitations include: (1) analysis limited to 3 years post-healing due to data constraints; (2) small, single-center sample with potential selection bias; (3) all 190 patients received integrated Chinese-Western medicine (oral decoctions, foot baths, acupuncture, negative pressure therapy, autologous platelet gel), but we didn' t analyze different treatment modalities' effects on recurrence; (4) incomplete post-discharge medication compliance data may represent unmeasured confounding.

Conclusion

DFU recurrence after healing is common and associated with risk factors including age >60 years, HbA1c >7.5%, PAD, osteomyelitis, callus, ABI <0.9, plantar ulcers, and Wagner grade $ $3, with risk factor burden positively correlating with recurrence rate. Identifying these factors helps clinicians better assess recurrence risk and develop targeted prevention strategies.

Author Contributions: Gang Wang conceived and designed the study, analyzed statistical results, and wrote the manuscript. Guangming Gong and Gang Wang implemented the study and collected data. Rensong Yue and Guangming Gong performed quality control, revised and approved the manuscript, and take overall responsibility.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.