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Original Article

Risk factors of diabetic foot ulcer in patients with type 2 diabetes: a retrospective cohort study

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Abstract: The aim of this study is to investigate the risk factors of diabetic foot ulcer (DFU) in patients with Type 2 diabetes. Baseline characteristics of DFU-free patients with Type 2 diabetes were retrospectively collected and DFU was identified during the follow-up. Incidence of DFU was calculated and cumulative incidence was estimated by Kaplan-Meier method. Cox regression model was used to explore factors associated with DFU. A total of 980 patients were included with a median follow-up time of 28.7 months. 259 (26.4%) patients developed DFU with an incidence rate of 11.3 per 100 person-years. The cumulative incidences of DFU at 1 year and 2 years during the follow-up were 5.4% (95% CI 3.9-6.9%) and 14.1% (95% CI 11.7-16.5%), respectively. Cox regression analysis indicated that factors associated with developing DFU included age (hazard ratio (HR)=1.06, 95% CI 1.05-1.07, per 1-year increase), body mass index (HR=1.05, 95% CI 1.02-1.07), higher level of education (HR=0.77, 95% CI 0.60-0.98), hypertension (HR=1.90, 95% CI 1.47-2.45), hyperlipidemia (HR=2.63, 95% CI 2.02-3.43), coronary heart disease (HR=2.88, 95% CI 2.22-3.75), heart failure (HR=2.47, 95% CI 1.91-3.20), stroke (HR=2.44, 95% CI 1.86-3.19), diabetic retinopathy (HR=1.86, 95% CI 1.40-2.48), diabetic kidney disease (HR=1.89, 95% CI 1.41-2.53), diabetic neuropathy (HR=1.73, 95% CI 1.31-2.30), poor glycemic control (HR=1.13, 95% CI 1.07-1.19, per 1% glycosylated hemoglobin increase), and course of diabetes (HR=1.01, 95% CI 1.00-1.01, per 1-month increase). The results showed a relatively high incidence of DFU, and revealed several baseline characteristics identified as risk factors of developing DFU.

Keywords: Diabetes mellitus, diabetic foot ulcer, incidence, risk factors, cohort studies

Introduction

Foot ulceration is a rather common complication of diabetes that affects the lower extremities [1]. It is estimated that about 34% patients with diabetes (either Type 1 or Type 2) develop foot ulcer in their lifetime [2]. As a major cause of morbidity, it is reported that about two-thirds of all nontraumatic amputations performed in the United States were due to diabetic foot ulcer (DFU), and about 25% hospitalizations among patients with diabetes were related to infected or ischemic DFU [3, 4]. At the same time, diabetic patients with DFU also have poor prognosis, which is associated with a 2.5-fold risk of death compared with those without DFU [5]. Recent report indicates that the 1-, 2-, and 5-year survival of patients with DFU was 81%, 69%, and 29%, respectively [6].

Although considerable advances were made over the past two decades [7] and there are several relevant national and international guidances [8, 9], DFU still remains a major health care problem [10, 11], and one of the reasons is that DFU is widely unappreciated. Based on current grading schemes, the more severe the ulcers, the worse the prognosis [12-14]. The severity of ulcer is found to be associated with the time to first expert assessment, suggesting that the longer the elapsed time to expert assessment, the more severe the ulcers and the worse the clinical outcomes [15]. Investigations indicate that delayed diagnosis

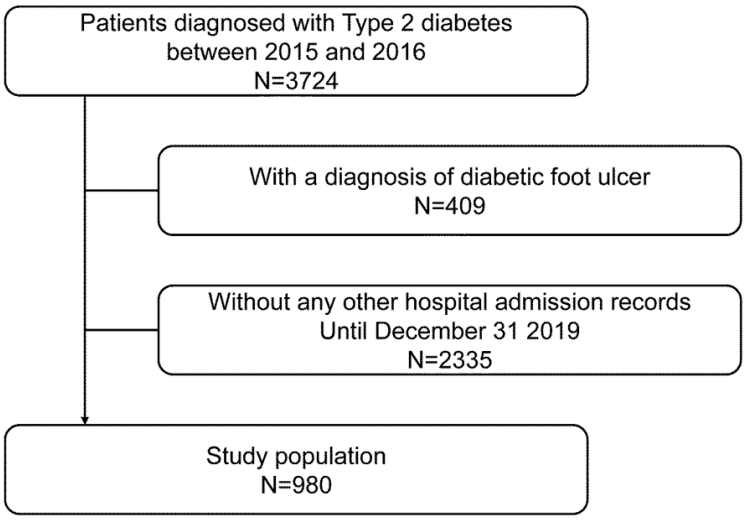

Figure 1. Inclusion of the study population.

and treatment of DFU is not rare in real practice [16, 17]. In addition, researches on DFU are also limited compared to other diabetes complications. Given these, to increase early diagnosis and treatment might be the currently most practical way to improve prognosis of DFU.

Several risk factors were identified for DFU, such as peripheral neuropathy, diabetic retinopathy, and diabetic nephropathy [18]. For some factors, such as hypertension, however, controversial findings were reported between studies [19, 20], suggesting that more researches are necessary. To provide additional evidence about risk factors for developing DFU, the study aimed to investigate the risk factors of DFU in a cohort of patients with Type 2 diabetes.

Methods

Patients

The study included DFU-free patients with Type 2 diabetes. We used the following inclusive and exclusive criteria. Inclusive criteria: (1) patients who once visited the diabetic clinic of Wuhan University People's Hospital (Hanchuan People's Hospital) between January 1 2015 and December 31 2016; (2) patients with a diagnosis record of Type 2 diabetes (identified by screening hospitalization records in the diabetic clinic); (3) the first available hospitalization record for patients who had more than 1 hospitalization record between January 1 2015 and December 31 2016. Exclusive criteria: (1) patients who had any diagnosis records of DFU in the hospitalization records within 30 days after the baseline hospitalization; (2) patients who did not have any other hospital admission records after the baseline hospitalization until December 31 2019. The inclusion of the study population was shown in **Figure 1**. The study received approval from the Institutional review board of Wuhan University People's Hospital (Hanchuan People's Hospital) and informed consent was waived.

Baseline characteristics

We collected the below baseline characteristics by screening the record of the baseline hospitalization: age, sex, body mass index (BMI), education (lower, or equal to or higher than high school), comorbid hypertension, hyperlipidemia, coronary heart disease, heart failure, stroke, diabetic retinopathy, diabetic kidney disease, diabetic neuropathy, admission hemoglobin A1C, course of diabetes, and type of treatment (oral hypoglycemic drugs, insulin, or both). All the baseline characteristics were retrieved directly from the recorded data via free text.

Clinical outcome

DFU was the clinical outcome of the study, which was identified by screening data retrieved from electronic health records of Wuhan University People's Hospital (Hanchuan People's Hospital) up to December 31 2019 via free text. If a patient had DFU diagnosis record(s) in hospitalization records, the admission date of the first hospitalization would be considered as the date of diagnosis of DFU. If no DFU diagnosis record was found until December 31 2019, the patient will be censored at the date of admission of the last hospitalization.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median and inter

Table 1. Baseline characteristic of the study population

Variable	Statistics
Age (years)	61.49±12.38
Sex	
Male	514 (52.45%)
Female	466 (47.55%)
BMI (kg/m^2)	25.06±5.69
Education	
Lower than High school	384 (39.18%)
High school or above	596 (60.82%)
Calendar year	
2015	502 (51.22%)
2016	478 (48.78%)
Comorbidities	
Hypertension	484 (49.39%)
Hyperlipidemia	471 (48.06%)
Coronary heart disease	429 (43.78%)
Heart failure	437 (44.59%)
Stroke	142 (14.49%)
Diabetic retinopathy	150 (15.31%)
Diabetic kidney disease	133 (13.57%)
Diabetic neuropathy	149 (15.20%)
Hemoglobin A1C (%)	7.97±2.35
Course of diabetes (months)	139 (60-238)
Type of treatment	
Oral hypoglycemic drugs	370 (37.76%)
Insulin	272 (27.76%)
Combination	338 (34.49%)

Abbreviation: BMI, body mass index.

quartile range; categorical variables were presented as frequency and percentages. Comparisons between two groups were examined by student *t* test or *Kruskal-Wallis* H test for continuous variables, and *Chi*-squared test or *fisher's* exact test for categorical variables. The incidence rate of DFU was calculated by dividing the total number of cases to the total observation time. Cumulative incidence of DFU for the entire cohort was estimated by *Kaplan-Meier* method. Univariable *Cox* regression analysis was used to explore factors associated with DFU. A *P* value <0.05 was declared to be statistical significance.

Results

Baseline characteristics

A total of 980 patients were included retrospectively with a median follow-up time of 28.7 (15.2-41.1) months. The average age was 61.49±12.38 years and 47.55% were female. The average BMI was 25.06±5.69 kg/m^2 and 60.82% had an education level of high school or above. Hypertension (49.39%) and hyperlipidemia (48.06%) were the most two frequent comorbidities. The patients had an average Hemoglobin A1C of 7.97±2.35% and a median course of diabetes of 139 (60-238) months, and oral hypoglycemic drugs (37.76%) was the most frequent treatment (**Table 1**). Compared with patients with a course of diabetes less than 10 years, patients with a course of diabetes ≥10 years had a higher average age (64.81±10.50 versus 57.34±13.28 years, *P*< 0.001), and more comorbidities (**Table 2**).

Occurrence of DFU during the follow-up

259 (26.4%) patients developed DFU with an incidence rate of 11.3 per 100 person-years. The cumulative incidences of DFU at 6 months, 1 year, and 2 years during the follow-up were 2.2% (95% CI 1.3-3.1%), 5.4% (95% CI 3.9-6.9%), and 14.1% (95% CI 11.7-16.5%), respectively, which were estimated by *Kaplan-Meier* curves (**Figure 2**).

Risk factors associated with DFU

Cox regression analysis (**Table 3**) indicated that factors associated with developing DFU included elderly (hazard ratio (HR)=1.06, 95% CI 1.05-1.07, per 1-year increase), body mass index (HR=1.05, 95% CI 1.02-1.07, per 1-kg/m^2 increase), higher level of education (HR 0.77, 95% CI 0.60-0.98), hypertension (HR 1.90, 95% CI 1.47-2.45), hyperlipidemia (HR 2.63, 95% CI 2.02-3.43), coronary heart disease (HR 2.88, 95% CI 2.22-3.75), heart failure (HR 2.47, 95% CI 1.91-3.20), stroke (HR 2.44, 95% CI 1.86-3.19), diabetic retinopathy (HR 1.86, 95% CI 1.40-2.48), diabetic kidney disease (HR 1.89, 95% CI 1.41-2.53), diabetic neuropathy (HR 1.73, 95% CI 1.31-2.30), poor glycemic control (HR 1.13, 95% CI 1.07-1.19, per 1% glycosylated hemoglobin increase), and course of diabetes (HR 1.01, 95% CI 1.00-1.01, per 1-month increase).

Discussion

This study investigated the incidence of DFU and risk factors associated with DFU among a cohort of patients with prevalent Type 2 diabetes. In this study, among 980 individual Type 2

Table 2. Baseline characteristic of the study population stratified by course of diabetes

Variable	<10 years (n=436)	≥10 years (n=544)	*P* value
Age (years)	57.34±13.28	64.81±10.50	<0.001
Sex			0.284
Male	237 (54.36%)	277 (50.92%)	
Female	199 (45.64%)	267 (49.08%)	
BMI (kg/m^2)	25.06±5.76	25.05±5.65	0.990
Education			0.302
Lower than High school	163 (37.39%)	221 (40.62%)	
High school or above	273 (62.61%)	323 (59.38%)	
Calendar year			0.113
2015	211 (48.39%)	291 (53.49%)	
2016	225 (51.61%)	253 (46.51%)	
Comorbidities			
Hypertension	206 (47.25%)	278 (51.10%)	0.230
Hyperlipidemia	185 (42.43%)	286 (52.57%)	0.002
Coronary heart disease	169 (38.76%)	260 (47.79%)	0.005
Heart failure	158 (36.24%)	279 (51.29%)	<0.001
Stroke	41 (9.40%)	101 (18.57%)	<0.001
Diabetic retinopathy	39 (8.94%)	111 (20.40%)	<0.001
Diabetic kidney disease	48 (11.01%)	85 (15.62%)	0.036
Diabetic neuropathy	32 (7.34%)	117 (21.51%)	<0.001
Hemoglobin A1C (%)	7.99±2.31	7.95±2.38	0.795
Course of diabetes (months)	52.50 (26.00-86.00)	226.50 (170.00-280.25)	<0.001
Type of treatment			<0.001
Oral hypoglycemic drugs	208 (47.71%)	162 (29.78%)	
Insulin	139 (31.88%)	133 (24.45%)	
Combination	89 (20.41%)	249 (45.77%)	

Abbreviation: BMI, body mass index.

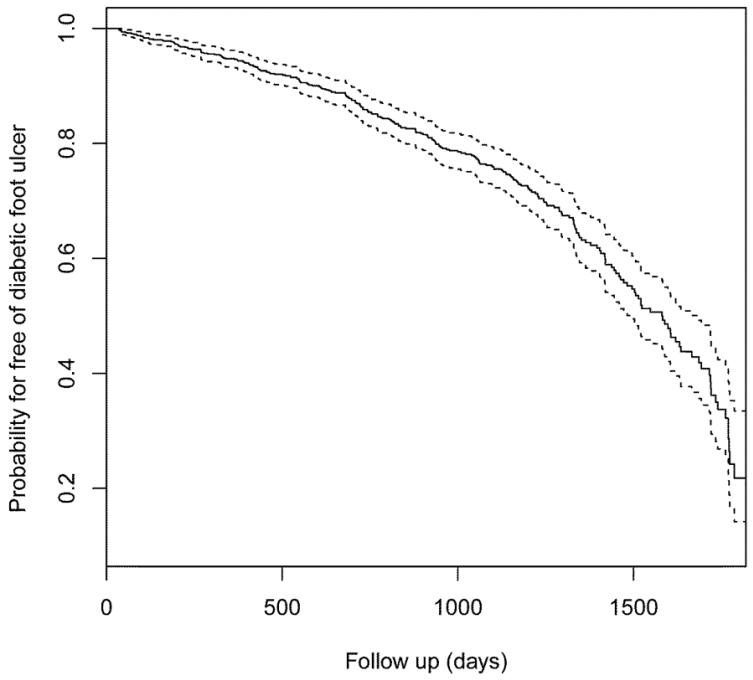

Figure 2. Kaplan-Meier curves displaying the estimated probability for free of diabetic foot ulcer. The dashed lines indicated the 95% confidence interval.

diabetic patients, 259 (26.4%) developed DFU during the follow-up with an incidence rate of 11.3 per 100 person-years. Several baseline characteristics including an older age, a higher BMI, lower level of education, poor glycemic control evaluated by Hemoglobin A1C, and various comorbidities were found to be associated with an increased risk of developing DFU. These findings might further raise clinicians' awareness of DFU and help to promote its early diagnosis.

Table 3. Factors associated with DFU

Variable	Hazard ratio	95% confidence interval	*P* value
Age (years)	1.06	1.05-1.07	<0.001
Sex			
Male	Reference		
Female	1.18	0.93-1.51	0.175
BMI (kg/m^2)	1.05	1.02-1.07	<0.001
Education			
Lower than High school	Reference		
High school or above	0.77	0.60-0.98	0.036
Hypertension			
No	Reference		
Yes	1.90	1.47-2.45	<0.001
Hyperlipidemia			
No	Reference		
Yes	2.63	2.02-3.43	<0.001
Coronary heart disease			
No	Reference		
Yes	2.88	2.22-3.75	<0.001
Heart failure			
No	Reference		
Yes	2.47	1.91-3.20	<0.001
Stroke			
No	Reference		
Yes	2.44	1.86-3.19	<0.001
Diabetic retinopathy			
No	Reference		
Yes	1.86	1.40-2.48	<0.001
Diabetic kidney disease			
No	Reference		
Yes	1.89	1.41-2.53	<0.001
Diabetic neuropathy			
No	Reference		
Yes	1.73	1.31-2.30	0.001
Hemoglobin A1C (%)	1.13	1.07-1.19	<0.001
Course of diabetes (months)	1.01	1.00-1.01	<0.001
Type of treatment			
Oral hypoglycemic drugs	Reference		
Insulin	0.84	0.60-1.16	0.280
Combination	1.27	0.96-1.67	0.095

Abbreviation: BMI, body mass index.

The incidences of DFU have been reported in various studies. Adem et al [21] reported that the incidence of DFU was 4 cases per 100 person-years of observation in a cohort of patients with newly diagnosed diabetes from a hospital in Ethiopia. Iwase et al [22] investigate patients with type 2 diabetes attending an outpatient diabetes clinic in Japan and report a DFU incidence rate of 0.29/100 person-years. Abbott et al [23] reported an average annual incidence of 2.2% in a community-based patient cohort from United Kingdom. Compared with these reported incidences, the incidence in our study (11.3 per 100 person-years) was much higher. This could be related to the different study population in our study, where prevalent Type 2 diabetic patients from a hospital with a median course of diabetes of about 10 years were studied. In our study, when the courses of diabetes were counted into observation time, the incidence of DFU was about 3.5 cases per 100 person-years (data not shown above), which was quite close to the incidences reported by Adem et al [21]. In addition, differences in diabetic care between countries might also explain the differences in the reported incidences [24].

Several baseline characteristics were found to be associated with an increased risk of developing DFU. We found the risk of DFU was increased with the increase of age, which was consistent with the findings from other studies [25, 26], but since our study only investigated prevalent diabetic patients, we were unable to study the association between the age of the onset of diabetes and DFU. We found there was no significant association between sex and DFU, and this was consistent with the study from Dinh et al [27], which suggests that women has the same risk of developing DFU as men when they have neuropathy or other risk factors. Increased BMI was associated with increased risk of DFU, which was also reported by other studies [21, 28, 29], with the hypothesis that obesity might increase atherosclerosis and decrease blood supply to lower extremities [21]. We found patients with higher level of education might have lower risk of DFU com-

pared with patients with lower level of education. This variable was rarely investigated in similar studies, but the mechanism behind it could be that patients with higher level of education might receive diabetic education better which is proved to be associated with lower risk of DFU [30]. The several comorbidities we studied were all associated with increased risk of developing DFU, including hypertension, hyperlipidemia, coronary heart disease, heart failure, stroke, diabetic retinopathy, diabetic kidney disease, and diabetic neuropathy. In the study from Yazdanpanah et al [31], dyslipidemia was also reported as a risk factor for developing DFU. The mechanisms could be that these comorbidities shared some of pathogenesis of DFU [32]. Poor glycemic control evaluated by Hemoglobin A1C and longer course of diabetes are also reported as risk factors of DFU in other studies [33, 34]. Insulin consumption is found as a risk factor for DFU [35], while the association was not statistically significant in our study. This might be due to the categorization of types of treatment in our study, since it could be observed that the combination of oral hypoglycemic drugs and insulin showed a hazard ratio of 1.27 which though not significant, was toward the direction of a risk factor.

The study had some limitations. First, the study used retrospectively collected data mainly based on free text, which might raise concerns about the validity of the diagnosis of DFU and several comorbidities studied. Second, the follow-up for the study outcome was based on hospitalization records, which meant we might include a study population with worse health status. Third, we only studied the baseline characteristics as potential risk factors of DFU, but some of the characteristics might change with time such as Hemoglobin A1C. Last, some other variables were not included in the study, which could also be risk factors of DFU, such as foot deformity.

In conclusion, the study observed relatively high incidences of DFU in a cohort of hospitalized patients with type 2 diabetes, and identified several baseline characteristics as risk factors of developing DFU. It provided information for health care providers, but further studies were still needed to reveal the mechanisms about the associations.

Disclosure of conflict of interest

None.

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