Mortality of Hospitalised Han Chinese Patients with Type 2 Diabetic Foot Ulcers in Kaifeng, China: A Retrospective Cohort Study

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ABSTRACT

Aim: To determine the rate and predictors of mortality in patients with type 2 diabetic foot ulcer (T2DFU) followed-up as inpatients in a grade 3A hospital.

Methods: This retrospective cohort study included Han Chinese inpatients aged at least 20 years who were diagnosed with T2DFU between September 2009 and November 2019. Of 431 eligible patients, 309 (168 men; 141 women) were included and completed the study (response rate: 71.7%).

Results: Of the 309 patients followed-up for a total of 948.7 person-years, 147 died, resulting in a mortality rate of 15.5 per 100 person-years. The cumulative mortality rate was 47.6% over a median follow-up period of 2.7 years (25th-75th percentile=1.2-4.4 years). Advanced age (adjusted hazard ration [HR]=1.80, 95% confidence Interval [CI]=1.28-2.54; P=0.001), Wagner grade ≥ 4 (adjusted HR=2.56, 95% CI=1.81-3.63; P<0.001), cardiovascular disease (CVD; adjusted HR=1.92, 95% CI=1.33-2.77; P=0.001), and diabetic nephropathy (adjusted HR=1.68, 95% CI=1.18-2.39; P=0.004) were identified as positive independent predictors of mortality.

Conclusion: Patients with T2DFU had a high mortality rate. Age, Wagner grade, CVD, and diabetic nephropathy, but not peripheral neuropathy, were associated with an increased risk of early death; these results should be considered in efforts to reduce the mortality rate associated with T2DFU.

Keywords: Mortality rate; Diabetic foot ulcer; Type 2 diabetes; Survival; Han Chinese

INTRODUCTION

Diabetic Foot Ulcer (DFU) is one of the most common, expensive, and severe complications of diabetes, and in 2019, it affected 40-60 million people with diabetes globally [1]. Health expenditures are 5 times higher in people with DFU than in people with diabetes mellitus without DFU and the recurrence rate of DFU is as high as 60% [1-3].

The 5-year relative mortality rate of DFU is as high as 48% in the United Kingdom [4]. This is clearly higher than those of most cancers (such as lung cancer, breast cancer, and lymphoma). A study in Germany showed that after the first sign of DFU in diabetes patients, the cumulative mortality rates at 1, 3, 5, and 10 years were 15.4%, 33.1%, 45.8%, and 70.4%, respectively [5]. Generally, patients with DFU have a more than two-fold higher risk of mortality at the 5 or 10-year follow-up than diabetes patients without DFU [4]. The risk factors associated with early

death in patients with DFU include age, active smoking, complications, and comorbidities [6-8].

Globally, owing to differences in economy, culture, religion, and the level of medical care available across different regions and countries, the incidence and prognosis of DFU vary greatly [1]. In the Western Pacific region, China had the largest population of diabetes patients aged between 20 and 79 years in 2019, with 116.4 million patients. This number is expected to increase to 140.5 million by 2030 [1]. In China, Han Chinese individuals account for more than 95% of the total population, and more than 95% of the patients with diabetes have type 2 diabetes [9]. Almost 85% of the Chinese population live in third or lower-tier cities and villages.

Along with increasing longevity in China, DFU has rapidly become the leading cause of chronic cutaneous wounds, as well as a major cause of amputations [10]. This study aimed to evaluate the mortality rate and predictors of early death in a population of Han Chinese patients with T2DFU who lived in the fourth-tier city of Kaifeng, China.

SUBJECTS, MATERIALS AND METHODS

Study Design and Subjects

We performed a retrospective cohort study at the Huaihe Hospital of Henan University, which is a grade 3A hospital located in Kaifeng, a fourth-tier city in China (the scale of urbanisation, economic and social development levels, and transportation are relatively ordinary). The case records of all Han Chinese patients with T2DFU admitted to the Huaihe Hospital of Henan University from 26 September 2009 to 19 November 2019 were analysed. During their stay in the hospital, all patients underwent comprehensive clinical examinations and treatment. Patients' files are securely stored in the hospital's electronic archives, and they contained the phone contacts for patients and at least one of their relatives.

The inclusion criteria were as follows:

- Admission to the Huaihe Hospital of Henan University from 26 September 2009 to 19 November 2019

- Diagnosis of type 2 diabetes mellitus

- At least one foot ulcer located at or below the ankle (Wagner classification: Grade 1-5) or a high risk of DFU but without any ulcer (Wagner classification: Grade 0)

- Hospital files with all the required information and a valid phone number

- Contact could be established with the patient directly or through their relatives *via* telephone from 1 May 2020 to 22 December 2020

- Han Chinese nationality

The exclusion criteria were as follows:

- Contact could not be established with the patient after a maximum of four telephone calls

- Lack of consent to participate in the study

- Non-Han nationality

- No confirmed diagnosis of type 2 diabetes mellitus

- Missing medical information required for data analysis

Data Collection

All collected data were entered into a structured dataset. Sociodemographic and clinical data were retrieved from hospital electronic records. Sociodemographic variables included age (20-96 years), sex (male, female), occupation (employee, non-employee), marital status (married, single/widow), and residence (urban, non-urban). Clinical variables included Wagner grade (≤ 3, ≥ 4), amputation (no, yes), hypertension (no, yes), CVD (no, yes), cerebrovascular disease (CBD; no, yes), peripheral neuropathy (PN; no, yes), diabetic retinopathy (DR; no, yes), and diabetic neuropathy (DN; no, yes).

First, we contacted the patient to ascertain whether or not the patient was alive. In case the patient was dead, we expressed our condolences and determined when and where the patient had died. For patients who died at the Huaihe Hospital of Henan University, the time of death and the department in which they died were further confirmed from hospital records.

Operational Definitions

Type 2 Diabetes Mellitus (T2DM): Any patient diagnosed with T2DM, and confirmation of the diagnosis by at least one attending doctor in accordance with the American Diabetes Association guidelines at inclusion [11].

Type 2 Diabetic Foot Ulcer (T2DFU): Any T2DM patient with diagnosed DFU at inclusion as per medical records. In our hospital, T2DFU lesions were classified according to the Wagner classification [12].

Hypertension: Patients with a history of hypertension or systolic blood pressure ≥ 140 mm Hg and or diastolic blood pressure ≥ 90 mm Hg, confirmed by the attending doctor at inclusion.

Peripheral Neuropathy (PN): Patients with a history of PN or those meeting one or more of the following criteria at inclusion: Light sensory abnormalities, diagnosed with the Semmes-Weinstein 5·07 g/10 g monofilament test and deep paraesthesia, diagnosed based on the final measured value on 128-Hz tuning fork tests [1,2,13,14].

Diabetic Nephropathy (DN): Patients with a history of DN at inclusion or a urinary albumin excretion rate>30 mg/24 h, tested using a 24-hour urine radioimmunoassay.

Diabetic Retinopathy (DR): Patients with a history of DR or diagnosed with DR on the basis of fundus photographs reviewed by an ophthalmologist at inclusion. In the end, after excluding 122 ineligible subjects from a total of 431, 309 (168 men and 141 women) Han Chinese patients who were diagnosed with T2DFU were included in the study (**Figure 1**). Follow-up periods differed on a case-by-case basis because the admission and end dates varied.

Statistical Analysis

Categorical variables were presented as the number of cases (percentage), and person-years (non-normally distributed variable) were presented as medians (25th-75th percentile). Mortality rate was expressed as deaths per 100 person-years, and

the cumulative mortality rate was expressed as deaths per 100 T2DFU patients. Cox proportional hazards regression analysis was used to calculate the Hazards Ratio (HR) and 95% confidence Interval (CI). To select variables for the final multivariate cox proportional hazards regression model, the associations between independent variables and death were first analysed using a univariate cox proportional hazards model. The candidate independent variables (P<0.25) were then analysed in a multivariate Cox proportional hazards regression model. Significant independent variables were retained in the final multivariate Cox proportional hazards model. The total viable count (TVC) test was used to verify the proportionality of the final model, and the fit of the final model was evaluated using Cox-Snell residuals. Finally, we generated cumulative Kaplan-Meier survival curves for the entire study population as well as groups stratified by age (>70 vs. ≤ 70 years), Wagner grade (≥ 4 vs. ≤ 3), CVD (yes vs. no), DN (yes vs. no), and PN (yes vs. no). All participants included in the data analysis had no missing data for any specific analysis. Data were analysed using Stata software, version 14 (Stata Corporation, College Station, TX, USA). Two-tailed tests were used. P-value less than 0.05 was considered statistically significant.
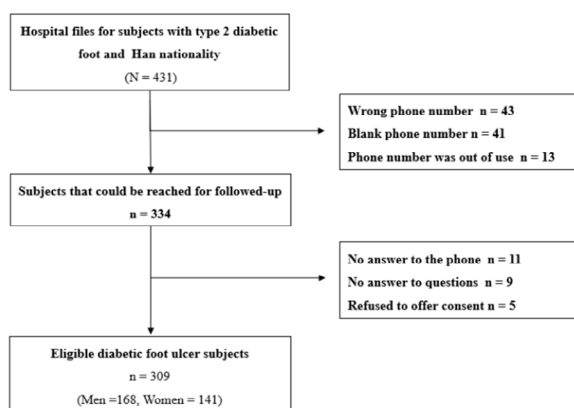
Figure 1: Schematic diagram of patient enrollment in the present study

Patient and Public Involvement

We collected data from the database of the Huaihe Hospital of Henan University. Patients and or the public were not involved directly in the setting of the research question or outcome measures. During the follow-up period, if a patient died, their relatives would provide the time and place of the patient's death.

Ethical Approval and Consent to Participate

The present study was approved by the Ethics Committee of the Huaihe Hospital of Henan University. All participants or their relatives provided verbal consent to participate in the study.
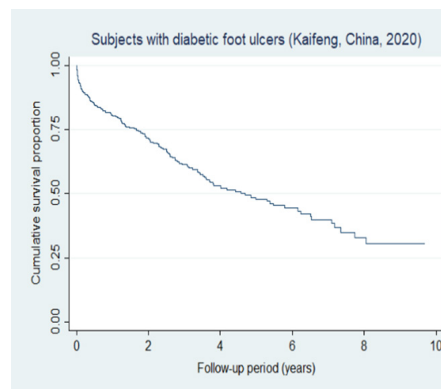
RESULTS

General Characteristics of the Participants

Of the 309 patients with T2DFU, 168 were male (54.4%); 122 were aged above 70 years (39.5%). Amputations were noted in 6.2% of cases; CVD, 52.4%; CBD, 48.9%; PN, 57.3%; DR, 46.9%; and DN, 48.5%. Statistical analysis showed that the distributions of occupation (P=0.011) and residence (P=0.022) differed between men and women (**Table 1**).

Mortality

During a total of 948.7 person-years of follow-up for the 309 patients, 147 died, resulting in a mortality rate of 15.5 per 100 person-years and a cumulative mortality rate of 47.6% over a median follow-up period of 2.7 years (**Figure 2**). The cumulative survival of all patients with T2DFU is illustrated in **Table 2**.

Figure 2: Cumulative survival of total subjects with type 2 diabetic foot ulcer (n=309)

Table 1: Demographic data and comorbidities of the study population

Variables	Total (n=309)	Men (n=168)	Women (n=141)	P-value*
Age>70 years	122 (39.5)	65 (38.7)	57 (40.4)	0.756
Non-Employee	285 (92.2)	149 (88.7)	136 (96.5)	0.011
Married	277 (89.6)	155 (92.3)	122 (86.5)	0.099
Non-urban	136 (44.0)	64 (38.1)	72 (51.1)	0.022
Wagner grade≥4	82 (26.5)	48 (28.6)	34 (24.1)	0.377
Amputated	19 (6.2)	9 (5.4)	10 (7.1)	0.527
Hypertension	231 (74.8)	127 (75.6)	104 (73.8)	0.711
CVD	162 (52.4)	83 (49.4)	79 (56.0)	0.246
CBD	151 (48.9)	86 (51.2)	65 (46.1)	0.373
Peripheral neuropathy	177 (57.3)	102 (60.7)	75 (53.2)	0.183
Diabetic retinopathy	145 (46.9)	72 (42.9)	73 (51.8)	0.118
Diabetic nephropathy	150 (48.5)	87 (51.8)	63 (44.7)	0.213
Death	147 (47.6)	78 (46.4)	69 (48.9)	0.66
Person-years	2.7 (1.2-4.4)	2.5 (1.0-4.1)	2.8 (1.4-4.7)	0.085

Note: Data are presented as number of cases (percentage) for categorical variables and median (25th-75th percentile) for person-years (not normally distributed). *P-value for comparison between men and women (Chi square test for categorical data; Wilcoxon rank-sum (Mann-Whitney) test for person-years. CVD, cardiovascular diseases; CBD, cerebrovascular disease.

Table 2: Univariate analysis of risk factors for death in patients with type 2 diabetic foot ulcers

Variables	Categories	Person-years	No. of death	Death rate (%)	Univariate HR	95% CI	P-value*
Total		948.7	147	15.5			
Sex	Man	479.3	78	16.3	1		
	Women	469.4	69	14.7	0.93	0.67-1.28	0.649
Age, years	≤ 70	580.2	61	10.5	1		
	>70	368.4	86	23.3	2.4	1.72-3.33	<0.001
Occupation	Employee	85.1	5	5.9	1		
	Non-employee	863.6	142	16.4	2.73	1.12-6.65	0.028
Marriage	Married	858.8	126	14.7	1		
	Single/Widow	89.9	21	23.4	1.57	0.99-2.49	0.057
Residence	Urban	517.4	84	16.2	1		
	Non-urban	431.3	63	14.6	0.9	0.65-1.25	0.538
Wagner grade	< =3	749.3	88	11.7	1		
	> =4	199.4	59	29.6	2.53	1.82-3.52	<0.001
Amputation	No	867	129	14.9	1		
	Yes	81.7	18	22	1.61	0.98-2.64	0.06
Hypertension	No	266.2	31	11.6	1		
	Yes	682.4	116	17	1.41	0.94-2.09	0.093
CVD	No	512.8	50	9.8	1		
	Yes	435.8	97	22.3	2.2	1.56-3.10	<0.001
CBD	No	511.3	60	11.7	1		
	Yes	437.3	87	19.9	1.66	1.20-2.31	0.002
Peripheral neuropathy	No	367	75	20.4	1		
	Yes	581.7	72	12.4	0.62	0.45-0.86	0.004
Diabetic retinopathy	No	457.2	84	18.4	1		
	Yes	491.5	63	12.8	0.72	0.52-1.00	0.047
Diabetic nephropathy	No	508.2	61	12	1		
	Yes	440.4	86	19.5	1.62	1.16-2.24	0.004

Note: A for univariate analysis, Cox proportional-hazards model included outcomes (survival and death) and one of the following variables: Sex, age, occupation, marriage, residence, Wagner grade, amputation, hypertension, CVD, CBD, peripheral neuropathy, diabetic retinopathy, or diabetic nephropathy. HR, hazard ratio; CI, confidence interval; CBD, cerebrovascular disease; CVD, cardiovascular diseases.

Predictors of Death

Univariate Cox proportional hazards regression analysis demonstrated that age, occupation, Wagner grade, and CVD were positively associated with mortality risk, while PN and DR were negatively associated with mortality risk.

In the final multivariate Cox proportional regression model, age, Wagner grade, CVD, and PN were independently and proportionally (TVC test, P>0.05) associated with mortality risk. Briefly, patients aged above 70 years had a higher risk of mortality than those aged ≤ 70 years (adjusted HR=1.80, 95% CI=1.28-2.54; P=0.001). Compared with Wagner grade ≤ 3, Wagner grade ≥ 4 was associated with a higher risk of mortality (adjusted HR=2.56, 95% CI=1.81-3.63; P<0.001). Both CVD (adjusted HR=1.92, 95% CI=1.33-2.77; P=0.001) and DN (adjusted HR=1.68, 95% CI=1.18-2.39; P=0.004) were associated with a higher risk of mortality. However, patients with PN had a lower risk of mortality (HR=0.67, 95% CI=0.47-0.94, P=0.020) (**Table 3**).

Table 3: Final model of predictors of death for patients with type 2 diabetic foot ulcers

Predictors		Multivariatea	Multivariatea HR	Multivariatea 95% CI	P-value
Total		309			
Age, years	≤ 70	187	1		
	>70	122	1.8	1.28-2.54	0.001
Wagner grade	≤ 3	227	1		
	≥ 4	82	2.56	1.81-3.63	<0.001
CVD	No	147	1		
	Yes	162	1.92	1.33-2.77	0.001
Peripheral neuropathy	No	132	1		
	Yes	177	0.67	0.47-0.94	0.02

Diabetic nephropathy	No	159	1		
	Yes	150	1.68	1.18-2.39	0.004

Note: A the final Cox proportional-hazards model included outcomes (survival and death), age, Wagner grade, CVD, peripheral neuropathy, and diabetic nephropathy. HR, Hazard Ratio; CI, Confidence Interval; CVD, Cardiovascular Diseases.

Graphical presentations for age, Wagner grade, CVD, PN, and DN using stratified Kaplan-Meier survival plots are shown in **Figure 3**.
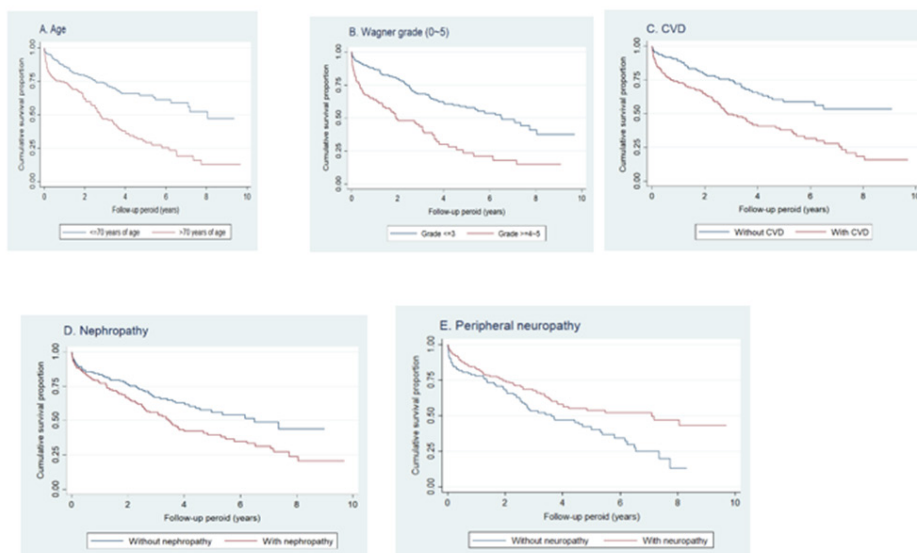
Figure 3: Cumulative survival of subjects with type 2 diabetic foot ulcers in subgroups A) Subjects with advanced age exhibited a poorer overall survival (OS) compared with younger age (log-rank test, χ2=30.31; P<0.0001), B) Subjects with higher Wagner grade of diabetic foot ulcers exhibited a poorer OS compared with lower grade (log-rank test, χ2=32.32; P<0.0001), C) Subjects with CVD exhibited a poorer OS compared with those without CVD (log-rank test, χ2=21.52; P<0.0001), D) Subjects with diabetic nephropathy exhibited a marginal poorer OS compared with those without diabetic nephropathy (log-rank test, χ2=8.37; P=0.0038), E) Subjects with diabetic neuropathy exhibited a better OS compared with those without diabetic neuropathy (log-rank test, χ2=8.38; P=0.0038)

DISCUSSION

Our study showed a mortality rate of 15.5 per 100 person-years and a cumulative mortality rate of 47.6% over a median follow-up period of 2.7 years in patients with T2DFU presenting to a grade 3A hospital in Kaifeng, China. We identified that advanced age, higher Wagner grade, CVD, and DN were independently associated with an increased risk of early mortality.

Iwase reported a cumulative mortality rate of 12.3% after 5 years of follow-up in Japan [15]. Al-Rubeaan et al. reported a mortality rate of 4.25 per 100 person-years after 6 years of follow-up in a study including 840 patients diagnosed with DFU in Saudi Arabia [16]. Additionally, Anderson et al. reported a mortality rate of 4.16 per 100 person-years over a median follow-up period of 10.5 years in the UK [6]. The mortality rate in our study was obviously higher than those in the above-described studies. A possible explanation might be that patients in the abovementioned studies were supported by a better health care system, easier access to qualified healthcare providers, a better foot screening system, and preventive measures for ulceration.

Age and Wagner grade have been largely reported as independent predictors of early death in previous studies on T2DFU [8,17,18]. These two risk factors were also confirmed in our T2DFU population.

CVD has been suggested to be a leading cause of early mortality in most long-term follow-up studies on DFU, and in patients with DFU, mortality might be decreased by aggressive cardiovascular risk management [5,8,19,20]. A study by Young showed that aggressive cardiovascular risk management can reduce the 5-year mortality rate from 48.0% to 26.8% in individuals with DFU [21]. CVD could be used as an indicator of systemic vascular damage [22]. Several reports have suggested that diabetes patients with foot ulcers were more likely to experience complications of cardiac disease and had a higher incidence of new cardiac events than those without foot ulcers [20,23]. Patients with a history of DFU are at much greater risk of infection, inflammatory reactions, and abnormal coagulation function, resulting in extreme cardiovascular risk [20,24].

DN was another independent risk factor for mortality in our T2DFU population. Previous studies have reported that DFU patients with DN have a greater risk of complications, serious delays in wound healing,[22,25,26] and an increased risk of major amputations [27-29]. Many patients with renal dysfunction require early dialysis, and medical priorities are diverted to the dialysis itself at the dialysis stage of DN [30]. Monge demonstrated that the risk of death in patients undergoing dialysis who have undergone minor and major amputations is 10-times higher than that in patients who have not undergone dialysis [31]. Chronic Kidney Disease (CKD) may be a surrogate marker for microvascular damage, which in turn indicates a higher risk of neuropathy and vascular insufficiency, both of which are associated with poor survival in patients with DN [32]. The

UK Prospective Diabetes Study demonstrated that progression of DN led to a progressive increase in cardiovascular mortality, particularly in those who required renal replacement therapy [33]. Our data showed that the longer the survival of T2DFU patients, the poorer the survival for those with DN (**Figure 3**).

Several studies have shown that PN is a risk factor for mortality in patients with DFU [31-34]; however, the role of PN may be more complicated, and PN may act as a protector from early death in some situations [5]. In our population, PN was negatively associated with the risk of death in T2DFU patients. The first explanation for this is that the development of PN might have alerted the patients and potentially delayed the progression of T2DFU, leading to prolonged survival. The second explanation is that both patients and attending doctors paid more attention to PN at the early stages of T2DFU but paid more attention to vital complications at the later stage of T2DFU. The third explanation is that lack of cooperation between clinical departments could have result in a selection bias for PN.

Sex, marital status, occupation, amputation, CBD, hypertension, and DR were not included in the final model. A few studies have demonstrated that socioeconomic disadvantages independently increased mortality in people with DFU and amputation has been widely reported as a predictor of death [6,35-38]. However, the sample size of both employees (7.8%) and amputees (6.2%) may have discounted their role in the survival analysis in the present T2DFU population.

We are cognizant of the limitations of the present study. First, data were restricted to Han Chinese patients with T2DFU enrolled from a single hospital, which did not allow for robust extrapolation to other Han Chinese T2DFU or DFU subpopulations. Second, the diagnosis of T2DFU was made by attending doctors from different clinical departments, and some observational bias would be difficult to avoid. Third, mortality data were collected *via* telephone interviews, and the exact cause of death was not identified, which might have restricted further exploration of the clinical factors associated with early death.

Nevertheless, the present study demonstrated the prognosis of T2DFU in Han Chinese patients from a grade 3A university hospital located in a fourth-tier city; in China, most patients with T2DFU live in such regions, making the findings of this study extremely important.

CONCLUSION

In conclusion, the mortality rate was high in patients with T2DFU in our hospital. Age, Wagner grade, CVD, and DN, but not PN, were associated with an increased risk of early death in our study population. We strongly recommend that healthcare providers actively screen for complications of diabetes mellitus and provide timely and systematic care for patients with T2DFU in the Han Chinese population to reduce T2DFU-related mortality.

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DECLARATION OF INTEREST

None.

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DATA AVAILABILITY STATEMENT

The datasets used and or analysed during the current study are available from the corresponding author on reasonable request.

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