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MAJOR ARTICLE

Recurrence of Diabetic Foot Complications: A Domino Effect Leading to Lethal Consequences—Insights From a National Longitudinal Study

Chun-Chien Hsu,[1] Hsi-Yu Lai,[1,2] Hung-Yu Lin,[1] Sung-Ching Pan,[3] Nai-Chen Cheng,[4] Liang-Kung Chen,[5,6,7] Fei-Yuan Hsiao,[1,8,9] and Shu-Wen Lin[1,8,10]

[1]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [2]Health Data Research Center, National Taiwan University, Taipei, Taiwan, [3]Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan, [4]Division of Plastic Surgery, Department of Surgery, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan, [5]Center for Healthy Longevity and Aging Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan, [6]Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan, [7]Taipei Municipal Gan-Dau Hospital, Taipei, Taiwan, [8]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan, [9]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan, and [10]Department of Pharmacy, National Taiwan University Cancer Center, Taipei, Taiwan

Background. Foot complications are common in people with diabetes mellitus (DM), leading to increased health care utilization, heightened mortality risk, and notable recurrence rates even after treatment. This retrospective cohort study aimed to investigate the impact of repeated occurrence of DM-related foot complications on the risk of all-cause mortality and to identify the potential risk factors associated with repeated events.

Methods. People with DM admitted with foot complications (ulcer, skin and soft tissue infection, or osteomyelitis) from 2012 to 2014 were identified from Taiwan's National Health Insurance Research Database, with a 3-year follow-up for repeated events. We categorized the study subjects based on their cumulative number of hospital admissions with foot complications. Logistic regression was conducted to explore the potential risk factors associated with repeated diabetic foot events. Kaplan-Meier curves and Cox proportional hazard models were used to examine the associations between repeated diabetic foot events and all-cause mortality.

Results. In this study, 28 754 eligible individuals were enrolled and classified into 3 groups: no repeated diabetic foot events (76.1%), 1 repeated event (16.0%), and 2 or more repeated events (7.9%). Logistic regression revealed that advanced age, male sex, congestive heart failure, dyslipidemia, hypertension, nephropathy, retinopathy, neuropathy, peripheral vascular disease, diabetes-related preventable hospitalizations, and outpatient visits due to diabetic foot were significantly associated with repeated events of diabetic foot complications. Compared with those with no repeated events, the adjusted hazard ratios for all-cause mortality were 1.26 (95% CI, 1.19–1.34) for 1 repeated event and 1.36 (95% CI, 1.26–1.47) for 2 or more repeated events.

Conclusions. The significant association between repeated diabetic foot and elevated mortality risk highlights the critical necessity for proactive and targeted patient care within clinical practice. More research to delve into the predictive factors related to the repeated occurrence of diabetic foot is needed to provide additional insights for prevention strategies.

Keywords. diabetes foot; repeated event; landmark analysis; mortality; risk factor.

Diabetic foot, in light of the rising prevalence and incidence of diabetes mellitus (DM), presents a considerable global medical and societal conundrum [1]. The prevalence of foot ulcers is 6.3% in the global population with DM and varies from 1% in Europe and North America to >11% in African countries [1, 2]. Approximately 19% to 34% of people with DM develop foot ulcers throughout their lifetime, with over half of these ulcers possibly becoming infected [3]. Foot infections, depending on their severity, may progress from soft tissue infections to deeper tissue involvement, leading to osteomyelitis [4]. Ultimately, up to 20% of severely affected individuals require lower extremity amputation to manage foot ulcer and infection issues [3]. It is noteworthy that the disease course with increased risk of infection and amputation can persist in the case of recurrent diabetic foot ulcers [5]. A previous study has indicated that compared with other ambulatory clinical cases, diabetic foot ulcers or infections have a higher demand for emergency and inpatient medical resources [6]. Moreover, patients with these conditions also exhibit a higher risk of mortality, with a 2.5-fold increased risk within 5 years and a 1.5-fold increased risk within 10 years [7–9].

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Correspondence: Shu-Wen Lin, PharmD, MS, Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, No. 33, Linsen S. Rd, Taipei 10050, Taiwan (shuwenlin@ntu.edu.tw); or Fei-Yuan Hsiao, PhD, Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, No. 33, Linsen S. Rd, Taipei 10050, Taiwan (fyshsiao@ntu.edu.tw).

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The resolution of diabetic foot is not always achieved after 1 treatment course, and there is a high probability of recurrence even after wound healing [3]. An estimation from the existing literature has shown that around 60% of patients with diabetic foot ulcers experience recurrence within 3 years after healing of the ulcers [3]. Another meta-analysis reported a global recurrence rate of 22.1% per person-year in diabetic foot ulcers [10]. Given the high mortality risk and the nature of recurrence of diabetic foot, it is imperative to clarify the epidemiology and cumulative impact of diabetic foot based on the status of recurrent events. However, the body of research addressing this issue is comparatively limited, and the extant studies are potentially influenced by certain biases attributable to their research design or insufficient sample size [11, 12].

Care for individuals with diabetic foot diseases is a complex endeavor, requiring the collaboration of multidisciplinary teams [13]. Hence, a thorough comprehension of the risk factors for the recurrence of diabetic foot holds immense significance for health care professionals. This knowledge may facilitate tailoring precise and efficient care, optimizing health care efforts. While the 2023 prevention guidelines of the International Working Group on the Diabetic Foot (IWGDF) primarily focused on preventing diabetic foot episodes by early detection of the at-risk foot, there is insufficient elaboration on other person-level factors [14]. Although several published studies have investigated the risk factors associated with diabetic foot recurrence, some limitations exist, including confinement to specific geographical areas and single health care institutions, small sample sizes, and inconsistencies in results across studies [15–19]. Therefore, the aims of the present study were to analyze the association between repeated occurrence of diabetic foot complications and the risk of all-cause mortality, and then explore the potential risk factors associated with repeated diabetic foot using population-based data.

METHODS

Data Source

This is a retrospective cohort study using data derived from National Health Insurance Research Database (NHIRD) in Taiwan. The NHIRD records all claims submitted under the National Health Insurance (NHI), a single-payer mandatory health insurance program covering >99% of the population in Taiwan (~23 million) [20]. NHIRD data comprise demographic characteristics, medical resource utilization (ambulatory care, inpatient, and emergency department visits), service costs, prescribed medications, and diagnostic codes based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM), or 10th Revision (ICD-10 CM). Mortality data from Taiwan's National Death Registry, validated in prior studies, were employed to estimate all-cause mortality based on ICD-10-CM coding [21].

Patient Consent

All potentially identifying data in the NHIRD were encrypted to protect anonymity, and thus informed consent of individual patients was waived. The Institutional Review Board of National Taiwan University Hospital approved the protocol (No. 202102015RIND).

Study Population

We identified individuals with diabetes (ICD-9-CM code 250) who were admitted with any of the following diagnoses of foot complications between January 1, 2012, and December 31, 2014: ulcer, skin and soft tissue infection (SSTI), or osteomyelitis (Supplementary Table 1). These foot complications were based on the Infectious Diseases Society of America (IDSA) classification for diabetic foot infections [22]. The date of the first admission with foot complications (index event) during this period was defined as the index date. People with an unknown date of birth or gender and those under the age of 20 years were excluded from the analysis. In addition, no history of hospitalization with any foot complication diagnoses within 3 years before the index date was required to ensure that the index events were new onset. Under a landmark analysis approach, individuals who died within 3 years after the index date (landmark time) were excluded to ensure complete information collection and to avoid biases due to different follow-up times.

Study Design and Measurements

Figure 1 shows the study design. To investigate the association between repeated diabetic foot events and subsequent risk of mortality, we employed a landmark analysis design, necessitating the establishment of a landmark period for the participants. The landmark period spanned 3 years from the index date. The decision to set up a 3-year landmark time was made after thorough deliberation for 2 reasons. First, previous studies have reported that within 3 years over half of patients (60%) exhibit recurrence of foot ulcers [3]. Second, our preliminary analyses revealed that the average interval between repeated diabetic foot complication events is ~1.2 years. A 3-year landmark time thus provides sufficient duration to observe at least 2 repeated events.

During the landmark period, the study subjects were followed up to observe the occurrence of subsequently repeated diabetic foot events. Repeated events were defined as admissions with any of the diagnoses of foot complications; these repeated events had to occur at least 30 days after the previous event. Individuals were categorized into 1 of the 3 groups according to the number of repeated events in those who survived for 3 years after the index admission: "no repeated events," "1 repeated event," or "2 or more repeated events." The follow-up period for capturing mortality was from the end of the landmark period until death or end of study (December 31,

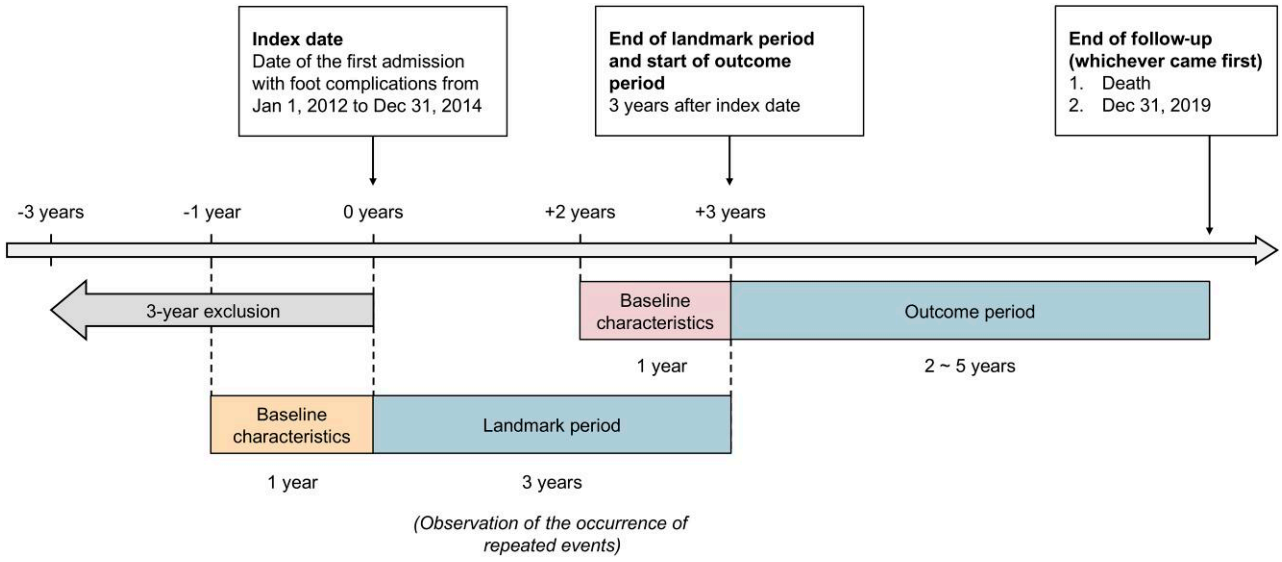

Figure 1. Study design and timeline.

2019). All-cause mortality, the primary outcome, was identified using Taiwan's National Death Registry.

Demographic characteristics of the participants including their age, gender, comorbidities, and outpatient visits due to diabetic foot were collected for 1 year preceding the landmark period and the outcome period. We calculated the scores using the Charlson Comorbidity Index (CCI) [23] and the adapted Diabetes Complications Severity Index (aDCSI) [24, 25] during the same period (Supplementary Tables 2 and 3). The aDCSI consists of 7 categories of complications: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic disease. Each category is assigned a score (0, 1, 2) based on different diagnoses, resulting in a total score that ranges from 0 to 13. The aDCSI had been validated in several health insurance databases including the Taiwan NHIRD, demonstrating its reliability in measuring diabetes severity [24–26]. As all our study participants are diabetic patients and we also adopted the aDCSI to capture their diabetic complications, the diagnosis of diabetes (with or without chronic complications) was not included when calculating the CCI.

We further investigated potential clinical factors associated with developing repeated diabetic foot events using the same study design described earlier. During the previously mentioned landmark period, the participants were categorized into 2 groups based on whether they experienced repeated events: "without repeated events" and "with repeated events." Demographics collected from the year preceding the index date were analyzed, encompassing age, gender, comorbidities, and outpatient visits due to diabetic foot. Additionally, diabetes-related preventable hospitalization (DRPH), as an indicator of the adequacy and quality of primary diabetes care, was also included in this analysis. DRPH was assessed using the Prevention Quality Indicators (PQIs) proposed by the Agency for Healthcare Research and Quality (AHRQ) in the United States [27]. Our study adopted 3 of the PQIs within the diabetes composite: diabetes short-term complications (PQI 1), diabetes long-term complications (PQI 3), and uncontrolled diabetes without complications (PQI 14) (Supplementary Table 4).

Statistical Analysis

Descriptive analyses were used to summarize the characteristics of the study cohort, presenting categorical variables as numbers and percentages and continuous variables as means with standard deviations. To compare the differences in characteristics between the study groups, we utilized chi-square tests for categorical variables and analysis of variance tests for continuous variables.

Univariable and multivariable logistic regression models were performed to identify independent risk factors for developing repeated diabetic foot events. The multivariable model selected variables from the univariable models with statistical significance, incorporating appropriate clinically meaningful variables and then identifying the final significant risk factors. The odds ratios (ORs) and 95% CIs were reported.

The associations between repeated diabetic foot events and all-cause mortality were examined using Kaplan-Meier survival curves with log-rank tests and Cox proportional hazard models and were presented as hazard ratios (HRs) with 95% CIs. A univariable model was fitted first; then the demographics and comorbidities were adjusted incrementally in different multivariable models. The first model included adjustment for age and gender. The second model included further adjustment for CCI and aDCSI.

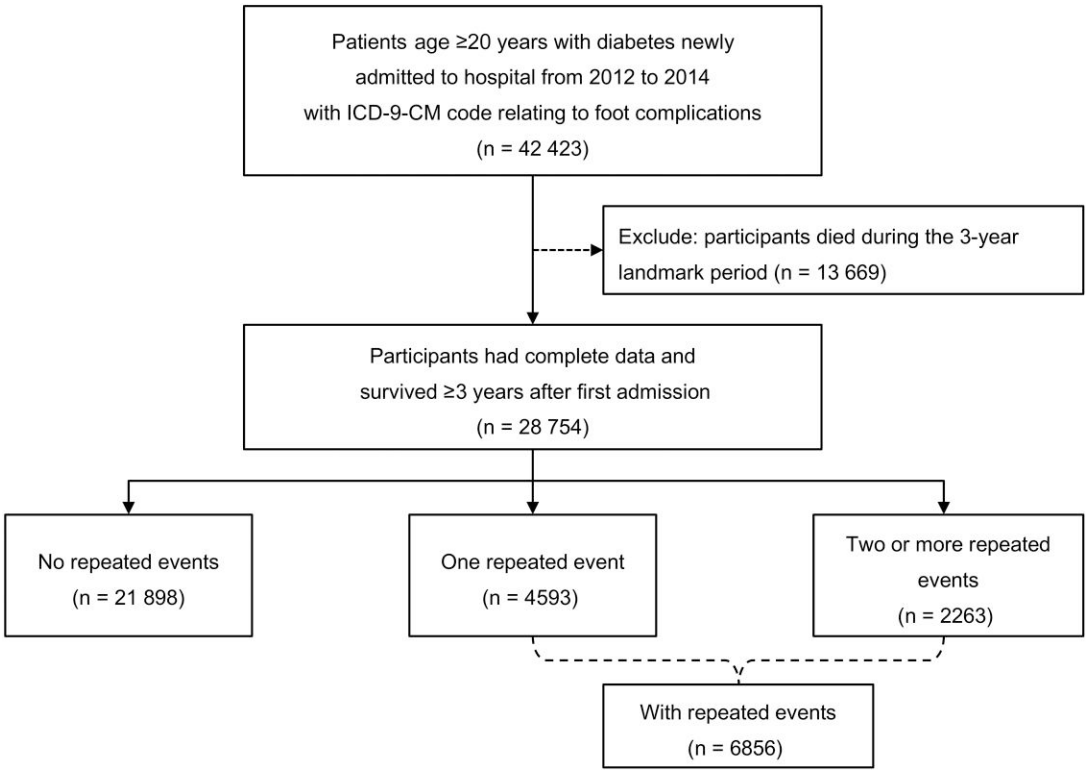

Figure 2. Study population selection. Abbreviation: ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). In all cases, a 2-tailed P value <.05 was considered statistically significant.

RESULTS

Study Cohort

Our study identified a total of 42 423 adults with DM who were admitted with any new-onset foot complications between January 1, 2012, and December 31, 2014. After excluding 13 669 (32.2%) individuals who died during the 3-year landmark period, the remaining 28 754 (67.8%) patients comprised the final cohort. According to the number of repeated events that occurred, the participants were divided into 3 groups: no repeated events (21 898 [76.1%] of 28 754), 1 repeated event (4593 [16.0%]), and 2 or more repeated events (2263 [7.9%]). The last 2 groups could be combined into a single group, representing a total of 6856 individuals with repeated events (Figure 2).

Baseline Characteristics

The highest mean age of participants was in the no repeated events group (63.6 ± 13.7 years), followed by the 1 repeated event group (63.0 ± 13.6 years) and the 2 or more repeated events group (60.5 ± 13.6 years). As for gender, a higher proportion of males was observed in all 3 groups, with the 2 or more repeated events group having the highest proportion (1427 [63.1%] of 2263). At the start of the landmark period, the lowest to highest CCI scores were in the no repeated events group (mean 1.1 (IQR 0-2)), the 1 repeated event group (1.3 (0-2)), and the 2 or more repeated events group (1.4 (0-2)). The aDCSI score showed the same pattern. Both the CCI and aDCSI scores before the follow-up period increased in each group, except the aDCSI score in the no repeated events group (decreased from 1.7 to 1.5). More pronounced increases were seen in the groups with more repeated events. In addition, most of the comorbidities investigated, including ischemic heart disease, congestive heart failure, hypertension, and diabetes-related complications (nephropathy, retinopathy, neuropathy, and peripheral vascular disease) presented differences between groups, with the proportions being highest in the 2 or more repeated events group (Table 1).

Risk Factors of Recurrence of Diabetic Foot Complications

In the multivariable logistic regression model, the reported significant potential risk factors for developing repeated events of diabetic foot complications were male gender, congestive heart failure, hypertension, nephropathy, retinopathy, neuropathy, peripheral vascular disease, diabetes-related preventable hospitalization, and outpatient visits due to diabetic foot. In contrast, advanced age (65 years and older) and dyslipidemia were

Table 1. Demographics of the Study Population, Stratified by Repeated Events (A) Before the Landmark Period and (B) Before the Outcome Period

A

	No Repeated Events (n = 21 898)	One Repeated Event (n = 4593)	Two or More Repeated Events (n = 2263)	*P* Value
Age, mean ± SD, y	63.6 ± 13.7	63.0 ± 13.6	60.5 ± 13.6	<.0001
Male, No. (%)	12 578 (57.4)	2697 (58.7)	1427 (63.1)	<.0001
CCI, mean (IQR)	1.1 (0–2)	1.3 (0–2)	1.4 (0–2)	<.0001
aDCSI, mean ± SD	1.7 ± 1.8	2.1 ± 2.0	2.5 ± 2.1	<.0001
Comorbidities, No. (%)				
Cerebrovascular disease	3168 (14.5)	700 (15.2)	305 (13.5)	.1368
Ischemic heart disease	3877 (17.7)	891 (19.4)	467 (20.6)	.0002
Congestive heart failure	2010 (9.2)	563 (12.3)	268 (11.8)	<.0001
Dyslipidemia	8046 (36.7)	1562 (34.0)	818 (36.2)	.0021
Hypertension	15 137 (69.1)	3308 (72.0)	1574 (69.6)	.0005
Depression	886 (4.1)	179 (3.9)	97 (4.3)	.7417
Nephropathy	5566 (25.4)	1468 (32.0)	845 (37.3)	<.0001
Retinopathy	2058 (9.4)	584 (12.7)	319 (14.1)	<.0001
Neuropathy	2750 (12.6)	733 (16.0)	427 (18.9)	<.0001
Peripheral vascular disease	3458 (15.9)	1076 (23.4)	650 (28.7)	<.0001
Callus, ingrown or thickened toenail, and dermatophytosis	1242 (5.7)	260 (5.7)	115 (5.1)	.5067
Past diabetic foot outpatient visit, No. (%)	1898 (8.7)	608 (13.2)	332 (14.7)	<.0001

B

	No Repeated Events (n = 21 898)	One Repeated Event (n = 4593)	Two or More Repeated Event (n = 2263)	*P* value
CCI, mean (IQR)	1.3 (0–2)	1.7 (0–3)	2.0 (0–3)	<.0001
aDCSI, mean ± SD	1.5 ± 1.6	2.2 ± 2.0	2.9 ± 2.2	<.0001
Comorbidities, No. (%)				
Cerebrovascular disease	3197 (14.6)	729 (15.9)	340 (15.0)	.0848
Ischemic heart disease	3833 (17.5)	947 (20.6)	581 (25.7)	<.0001
Congestive heart failure	2211 (10.1)	654 (14.2)	373 (16.5)	<.0001
Dyslipidemia	8195 (37.4)	1558 (33.9)	809 (35.8)	<.0001
Hypertension	13 874 (63.4)	3147 (68.5)	1617 (71.5)	<.0001
Depression	956 (4.4)	217 (4.7)	104 (4.6)	.5245
Nephropathy	7554 (34.5)	2055 (44.7)	1227 (54.2)	<.0001
Retinopathy	2140 (9.8)	650 (13.2)	358 (15.8)	<.0001
Neuropathy	2374 (10.8)	639 (13.9)	369 (16.3)	<.0001
Peripheral vascular disease	1611 (7.4)	880 (19.2)	746 (33.0)	<.0001
Callus, ingrown or thickened toenail, and dermatophytosis	418 (1.9)	176 (3.8)	112 (5.0)	<.0001
Past diabetic foot outpatient visit, No. (%)	922 (4.2)	738 (16.1)	699 (30.9)	<.0001

Abbreviations: aDCSI, adapted Diabetes Complications Severity Index; CCI, Charlson Comorbidity Index; IQR, interquartile range.

significantly associated with lower risk of developing repeated events (Table 2).

Mortality

During 84 770 person-years of follow-up, 7835 (27.2%) of the 28 754 patients in the study cohort had all-cause mortality events. The mortality rate per 100 person-years was 8.4 in the no repeated events group, 11.7 in the 1 repeated event group, and 13.1 in the 2 or more repeated events group. (Supplementary Table 5). Kaplan-Meier curves showed the reduced probabilities of survival among the 2 groups with repeated events compared with the group with no repeated events. The 5-year cumulative survival probabilities during the follow-up period were 66.2% in the no repeated events group, 56.6% in the 1 repeated event group, and 53.3% in the 2 or more repeated events group (Figure 3).

Adjusted for age, gender, CCI, and aDCSI, the HRs of all-cause mortality for the 1 repeated event group and the 2 or more repeated events group were 1.26 (95% CI, 1.19–1.34) and 1.36 (95% CI, 1.26–1.47), respectively, compared with the no repeated events group (Figure 4).

DISCUSSION

The study involved 28 754 adults with DM and related foot complications. They were categorized based on repeated events: none (76.1%), 1 (16.0%), and 2 or more (7.9%). Risk factors of recurrence of diabetic foot complications included male

Table 2. Logistic Regression of Factors Associated With Developing Repeated Diabetic Foot Events

	Without Repeated Event (n = 21 898)	With Repeated Events (n = 6856)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age, No. (%)				
<65 y	11 409 (52.1)	3938 (57.4)	Ref	Ref
≥65 y	10 489 (47.9)	2918 (42.6)	0.81 (0.76–0.85)*	0.77 (0.72–0.81)*
Gender, No. (%)				
Female	9320 (42.6)	2732 (39.9)	Ref	Ref
Male	12 578 (57.4)	4124 (60.2)	1.12 (1.06–1.18)*	1.08 (1.02–1.14)*
Comorbidities, No. (%)				
Cerebrovascular disease				
No	18 730 (85.5)	5851 (85.3)	Ref	
Yes	3168 (14.5)	1005 (14.7)	1.02 (0.94–1.10)	
Ischemic heart disease				
No	18 021 (82.3)	5498 (80.2)	Ref	Ref
Yes	3877 (17.7)	1358 (19.8)	1.15 (1.07–1.23)*	1.06 (0.99–1.14)
Congestive heart failure				
No	19 888 (90.8)	6025 (87.9)	Ref	Ref
Yes	2010 (9.2)	831 (12.1)	1.37 (1.25–1.49)*	1.31 (1.19–1.43)*
Dyslipidemia				
No	13 852 (63.3)	4476 (65.3)	Ref	Ref
Yes	8046 (36.7)	2380 (34.7)	0.92 (0.87–0.97)*	0.88 (0.83–0.93)*
Hypertension				
No	6761 (30.9)	1974 (28.8)	Ref	Ref
Yes	15 137 (69.1)	4882 (71.2)	1.11 (1.04–1.17)*	1.10 (1.03–1.17)*
Depression				
No	21 012 (96.0)	6580 (96.0)	Ref	
Yes	886 (4.0)	276 (4.0)	1.00 (0.87–1.14)	
Nephropathy				
No	16 332 (74.6)	4543 (66.3)	Ref	Ref
Yes	5566 (25.4)	2313 (33.7)	1.49 (1.41–1.58)*	1.32 (1.24–1.41)*
Retinopathy				
No	19 840 (90.6)	5954 (86.8)	Ref	Ref
Yes	2058 (9.4)	902 (13.2)	1.46 (1.34–1.59)*	1.14 (1.04–1.24)*
Neuropathy				
No	19 148 (87.4)	5696 (83.1)	Ref	Ref
Yes	2750 (12.6)	1160 (16.9)	1.42 (1.32–1.53)*	1.24 (1.15–1.34)*
Peripheral vascular disease				
No	18 413 (84.1)	5130 (74.8)	Ref	Ref
Yes	3485 (15.9)	1726 (25.2)	1.78 (1.67–1.90)*	1.50 (1.40–1.60)*
Callus, ingrown or thickened toenail, and dermatophytosis				
No	20 656 (94.3)	6481 (94.5)	Ref	
Yes	1242 (5.7)	375 (5.5)	0.96 (0.86–1.08)	
Diabetes-related preventable hospitalization, No. (%)				
No	18 774 (85.7)	5259 (76.7)	Ref	Ref
Yes	3124 (14.3)	1597 (23.3)	1.83 (1.71–1.95)*	1.48 (1.38–1.59)*
Diabetic foot outpatient visit, No. (%)				
No	20 000 (91.3)	5916 (86.3)	Ref	Ref
Yes	1898 (8.7)	940 (13.7)	1.68 (1.54–1.82)*	1.48 (1.36–1.62)*

Abbreviations: OR, odds ratio; Ref, reference group.

*$P < .05$.

gender, heart failure, hypertension, nephropathy, retinopathy, neuropathy, peripheral vascular disease, and diabetes-related hospitalization. Advanced age and dyslipidemia were associated with lower risk. The mortality rate increased with the number of repeated events. After adjustments, the hazard ratios for mortality were 1.26 and 1.36 for the 1 and 2 or more repeated events groups, respectively. To the best of our understanding, this represents the first study that employs national longitudinal data to examine the correlation between recurrent diabetic foot incidents and mortality risk, while concurrently investigating potential contributory factors to the recurrence of such events. Our findings underscored the significance of secondary

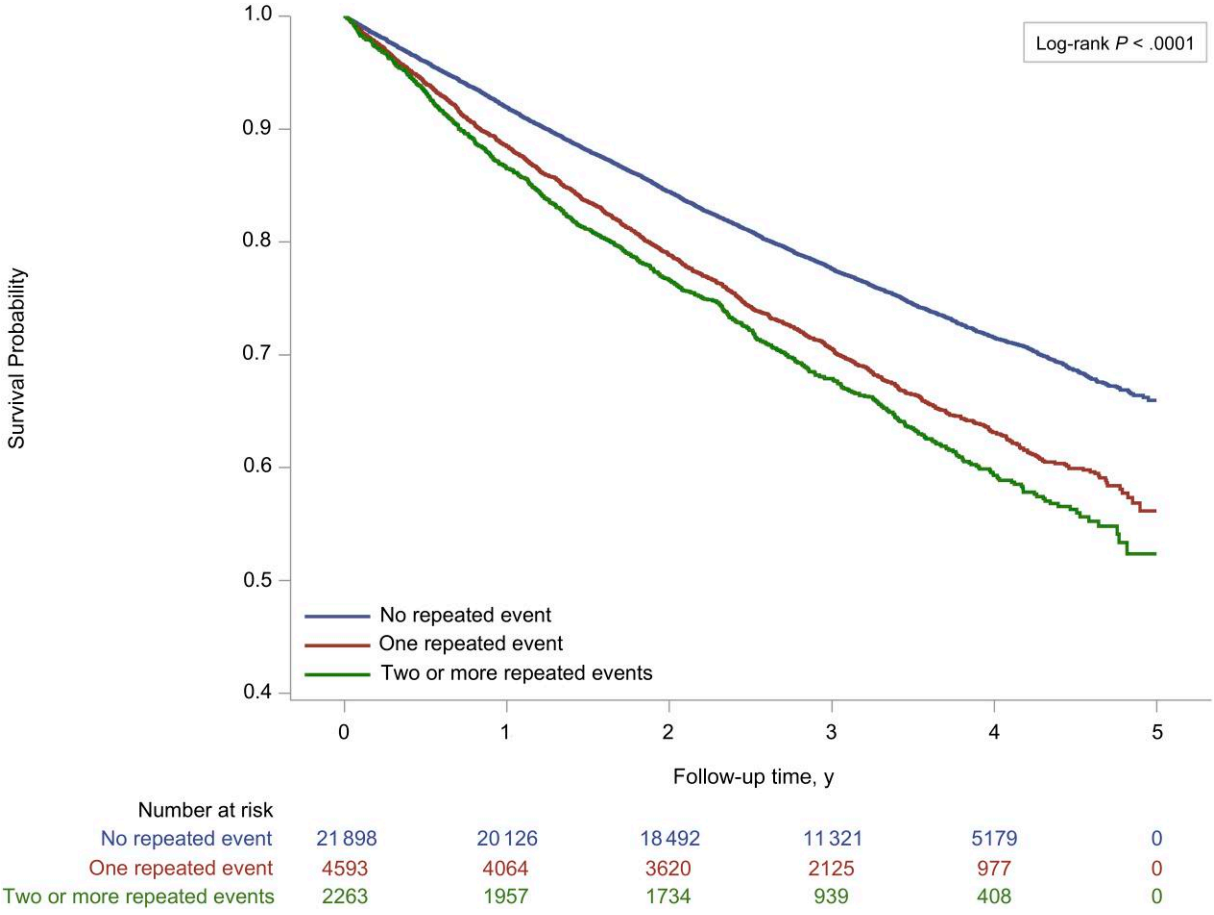

Figure 3. Kaplan-Meier survival curves of diabetic patients with different repeated event statuses during the follow-up period.

prevention in patients with diabetic foot and aid in pinpointing individuals possessing relevant risk factors.

In this study, there was statistical evidence that people with repeated diabetic foot events had higher mortality risk compared with those without repeated events. Moreover, those who experienced multiple repeated events exhibited the highest risk of mortality, indicating an exposure–response relationship. However, these findings are inconsistent with those of the previous studies. Winkley and colleagues [11] found that diabetic patients with recurrent foot ulceration had lower mortality risk (HR, 0.23; 95% CI, 0.1–0.53) than those without recurrence via univariable analysis. Similarly, Rubio and colleagues [12] also reported a lower 5-year mortality risk in patients who suffered re-ulceration (HR, 0.58; 95% CI, 0.37–0.92), but this association did not remain significant after adjusting for potential confounding factors (adjusted HR, 0.72; 95% CI, 0.43–1.19). Unlike the abovementioned studies, which started following mortality outcomes from the time of entry into the study, ours utilized the landmark method to mitigate the influence of immortal time bias, offering a plausible explanation for the differing results. Nevertheless, it is worth noting that our findings align more closely with clinical expectations. Another reason for the differences could be our definition of diabetic foot events as hospitalizations, that is, a more severe form of diabetic foot. Therefore, it is reasonable to assume that multiple hospitalizations have a greater impact on mortality.

Another merit of this study is that we have taken into account CCI and aDCSI scores, serving as proxies for health status, and adjusted them in the analytical models assessing the association between repeated diabetic foot and all-cause mortality. Both of the scores in this study were lowest in the no repeated events group and highest in the 2 or more repeated events group, reflecting that the burden of comorbidities and diabetes severity is, to some extent, correlated with repeated events. We continued to observe significant associations even after adjustments, thereby validating the robustness of our results. The findings in our survival analyses accentuated that the repeated occurrence of foot complications does not merely lead to a burden of the disease itself but is also associated with severe adverse outcomes such as death. In addition, while several unmeasured covariates such as chronic glycemic control,

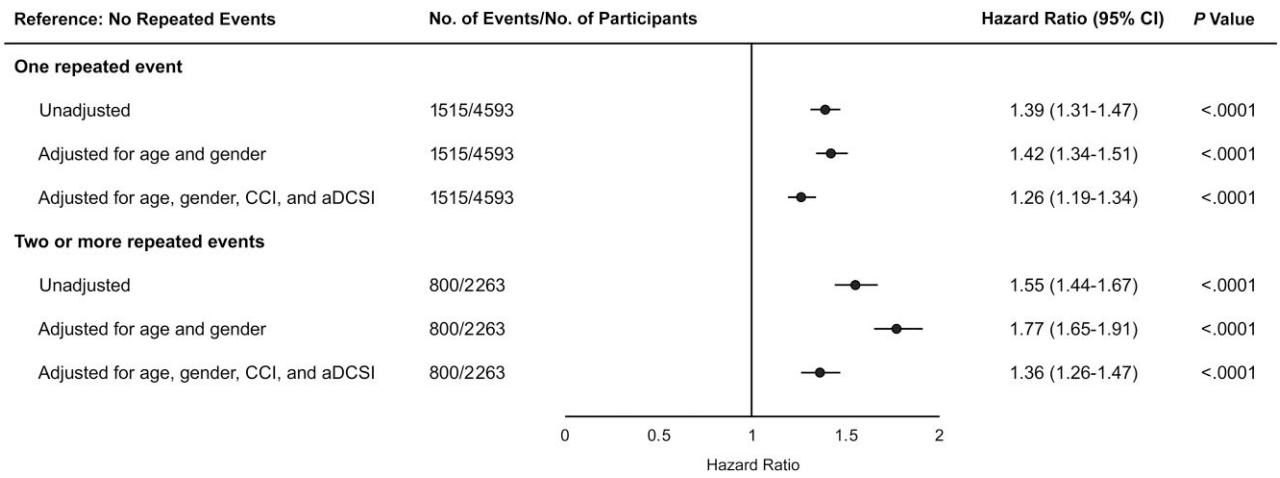

Figure 4. Hazard ratios for all-cause mortality in diabetic patients with different repeated event statuses during the follow-up period. Abbreviations: aDCSI, adapted Diabetes Complications Severity Index; CCI, Charlson Comorbidity Index.

treatment adherence, and socioeconomic status may concurrently increase both the risk of foot complications and the risk of mortality among diabetic patients, diabetic foot is not merely as an isolated condition but a manifestation or signal of these underlying issues [9, 28]. This underscores the paramount significance of comprehensive diabetes management strategies. Thus, apart from treatment and monitoring for each instance of foot complications, the provision of integrated care covering all underlying comorbid conditions after such events is crucial to reducing the possibility of recurrence and improving the long-term prognosis for DM management.

On the other hand, our study reaffirms previous findings and unveils new insights into the risk factors associated with the development of repeated diabetic foot events. We identified male gender as a risk factor for repeated diabetic foot, which is in line with the findings from Engberg and colleagues [16]. This association, however, may require further investigation as prior studies have yet to establish such a relationship. On the other hand, those of advanced age (65 years and older) were found to be less likely to experience repeated events. Hicks and colleagues [17] also demonstrated a significant association between younger age and ulcer recurrence. This finding is potentially attributable to the better walking ability of the younger population. Increased frequency of physical activity could lead to elevated pressure on the feet, resulting in repetitive injuries. Consequently, the use of therapeutic footwear to relieve plantar pressure has consistently been recommended by the international guidelines for preventing recurrent diabetic foot issues [1, 14].

Congestive heart failure was a risk factor for repeated events in our study, while ischemic heart disease showed no association. In previous research, Gazzaruso and colleagues [18] found a significant relationship between history of cardiovascular disease (CVD) and recurrence, but they did not clearly define CVD. Xu and colleagues [29] conducted a study to follow hospitalized patients with diabetic foot ulcers and found that patients with concurrent heart failure had a higher rate of ulcer recurrence, consistent with the findings in our study. The mechanism through which heart failure affects diabetic foot prognosis remains unclear and may involve factors such as peripheral ischemia, increased oxygen transport distance to the ulcer site due to edema, and renal insufficiency leading to vascular calcification and impaired immune function [30]. Conversely, it is not unexpected as the burden of CVD tends to accumulate, contributing to complexity in disease management.

We also identified hypertension as a risk factor for repeated events. While existing research has limited discussion on the relationship between hypertension and recurrent diabetic foot, some studies have indicated that hypertension is associated with an increased risk of incident foot ulcers, subsequent amputations, and mortality [9, 31]. This link may be due to the effects of hypertension on vascular stiffness and inflammation and its impact on lower limb blood supply [32]. Additional research is required to explore this relationship. Nonetheless, it remains essential for people with DM to maintain blood pressure within an optimal range through lifestyle modifications or medication. Interestingly, individuals with hyperlipidemia were associated with a lower risk of repeated events. This finding is likely related in part to the use of lipid-lowering medications such as statins. Statins may enhance lower limb perfusion by reducing plaque formation, increasing vasodilation, and attenuating inflammation [33, 34]. However, more studies are required to investigate the effectiveness of lipid-lowering therapy on repeated diabetic foot complications.

Several existing studies have investigated the associations of DM-related microvascular diseases and peripheral vascular disease with ulcer recurrence [15–19, 35]. Though previous

findings lacked consistency, ours yielded positive associations. The disparities in findings may stem from variations in study population, variable definitions, and treatment approaches across different studies. However, all these conditions signify diabetes severity and are often implicated in the etiology of foot complications, emphasizing the need for attentive care in clinical practice before novel therapeutics are available to change the scenario [36]. Our study also highlights the important link between DM-related preventable hospitalization (DRPH) and repeated diabetic foot complications. Diabetes demands long-term continuous outpatient care for stable blood sugar control to prevent complications and reduce hospitalizations. Hence, DRPH represents potentially suboptimal disease control and access to health care resources. Existing research has also reported an association between poor glycemic control and ulcer recurrence [15, 35]. By judiciously allocating health care resources, improving routine diabetes care, and enhancing treatment adherence, not only can the repeated occurrence of diabetic foot events be mitigated, but there is also the potential to reduce the burden of preventable hospitalizations.

Despite all the efforts that went into our study, this work has several limitations. First, as with all studies using a claims database, some variables, such as laboratory test data, social history, and nutritional status, are not routinely captured in the NHIRD. However, we adopted the aDCSI as a proxy to capture the severity of diabetes. Second, the landmark method requires participants to survive during the landmark period. While this may result in a certain loss of study participants, this approach helps avoid immortal time bias, which may have existed in previous studies. Third, the definition of foot complications was based on ICD codes, making it challenging to ensure that infection was actually present; nonetheless, we focused exclusively on hospitalized patients to enhance the accuracy of the definition while also concentrating on a more extensive disease burden. Fourth, we presented our results as composite diabetic foot complications. Considering the potential variations between different types of diabetic foot, we further categorized the index event into different types for survival analysis. However, due to smaller sample sizes after subdivision, distinguishing between single and multiple repeated events in the ulcer and osteomyelitis groups was challenging. Nevertheless, all groups with repeated events exhibited poorer survival outcomes compared with those without (Supplementary Figure 1).

CONCLUSIONS

This study demonstrated a significant association between repeated diabetic foot events and mortality, indicating their considerable impact on adverse outcomes. Therefore, health care providers can play a crucial role in raising patient awareness and promoting compliance to reduce repeated diabetic foot complications and alleviate such burdens. The identification of relevant risk factors in this study will aid in targeting high-risk patients more effectively and improve patient care overall.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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