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Analysis of risk factors for foot ulcers in diabetes patients with neurovascular complications

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Abstract

Background Diabetic foot ulcers (DFU), characterized by open sores or wounds primarily occurring on the feet of diabetes patients, are a serious and highly morbid complication of long-standing diabetes, accounting for significant morbidity and mortality. These ulcers develop when diabetes damages both nerves and blood vessels, a combination known as neurovascular complications. Neurovascular disease is a well-established risk factor. While studies have extensively examined risk factors for DFU, few have specifically focused on patients with diabetic neurovascular disease. Therefore, we assess the prevalence and risk factors for DFU in diabetic patients with established neurovascular complications.

Methods This study analyzed data from 6722 patients with diabetic neurovascular disease aged over 18 years old from the Southern Medical University Nanfang Hospital (SMUNFH) database (2018–2023) and 2689 patients with the same condition and age range from the National Institutes of Health (NIH) Integrated Surveillance System (NIS) database (2017–2019). The incidence of DFU was determined using information from the NIS database and SMUNFH databases. A binary logistic regression model was employed to explore the risk factors for DFU.

Results The incidence of DFU among neurovascular disease patients was 13.4% at SMUNH and 25.9% in the NIS Asian population. Multiple regression analysis identified several factors associated with DFU in the SMUNH database, including diabetic retinopathy, diabetic nephropathy, osteomyelitis, coronary heart disease, tinea pedis (fungal foot infection), sepsis, ability to sense a 128 Hz tuning fork (both left and right sides), C-reactive protein (CRP) levels, and urinary albumin-to-creatinine ratio (ACR). Analysis of NIS data revealed that in the broader Asian population, peripheral vascular disorders and osteomyelitis were associated with DFU.

Conclusion The prevalence of DFU is higher in Asia than in China. Focusing on peripheral vascular disorders and osteomyelitis can effectively reduce the prevalence of DFU in the Asian population while addressing diabetic retinopathy, diabetic nephropathy, osteomyelitis, coronary heart disease, tinea pedis, ability to sense a 128 Hz tuning fork, CRP levels, and urinary ACR can be effective in China.

Keywords Neurovascular disease, Diabetes mellitus, Diabetes foot ulcer, Risk factors

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Introduction

Diabetic Foot Ulcer (DFU) is a common and highly morbid consequence of long-standing, poorly managed diabetes. Of the estimated 537 million people with diabetes worldwide, 19% to 34% will develop a DFU in their lifetime [1], with approximately 18.6 million new cases diagnosed annually [2]. China has the world's largest population of diabetic patients, estimated at 157 million [3]. DFU is a major precursor to Lower Extremity Amputation (LEA) and increases mortality risk [4]. Approximately 20% of DFU patients require LEA (major or minor), and 10% will die within the first year of diagnosis [5]. The 5-year mortality rate for DFU patients is 30%, rising to over 70% for those with above-foot amputations [6]. A meta-analysis demonstrated a crude death rate of 231 per 1000 person-years in patients with DFU, compared to 182 per 1000 person-years in those without [7]. Additionally, the incidence of new ulcers within a year is 8.1%, with a 31.6% recurrence rate within a year of healing [8].

In diabetic patients, consistently high blood sugar levels can damage both nerves (causing neuropathy) and blood vessels (causing vasculopathy), leading to multiple forms of neuropathy affecting foot health. Sensory neuropathy results in a loss of temperature sensation, pain, and proprioception (collectively referred to as a loss of protective sensation), while motor neuropathy causes muscle wasting, foot deformities, and abnormal gait, resulting in abnormal pressure distribution and a tendency to develop new pressure point ulcers [9]. Vasculopathy impairs healing by reducing blood flow to the feet, with current evidence suggests that approximately 50% of DFU patients have lower extremity peripheral artery disease [10], and 90% of DFUs are associated with diabetes-related neuroischemic abnormalities [11]. The lifetime prevalence of DPN in adults is estimated to be at least 50%, and the risk of developing DFU is approximately sevenfold for those with any type of neuropathy. Peripheral artery disease (PAD) is a causative factor in 50%-70% of DFUs [12]. Therefore, recognition of risk factors and implementation of preventive measures are essential for DFU management. The enormous burden of DFU also poses a challenge to the world's health economy [13]. The direct expense of treating DFU in the United States is estimated to range between $9 billion and $13 billion annually [14].

Early detection and multidisciplinary treatment are essential to reduce the morbidity associated with diabetic foot ulcers [5]. Analyzing the risk factors of DFU patients with neurovascular lesions is key to preventing DFU development [15]. To address this, identifying various risk factors is crucial for creating effective preventive strategies. We gathered clinical data on Asian diabetic patients with neurovascular disease from the Nationwide Inpatient Sample (NIS) database (2017–2019) and the Southern Medical University Nanfang Hospital (SMUNH) database (2018–2023). This analysis of DFU risk factors provides evidence to improve rehabilitation outcomes and reduce DFU incidence.

Methods

Data

Data were extracted from the NIS and Southern Medical University Nanfang Hospital (SMUNH) databases. The NIS database is a 20% sample of all hospitalized patients in the United States. Its design is intended to represent the operation of the entire healthcare system, making it an ideal choice for conducting descriptive research, obtaining national estimates, researching costs, studying rare diseases, and understanding long-term trends. The SMUNH database collects information, including basic patient demographic information, such as age, gender, race, and basic hospital information, as well as some related comorbidities (Tables 1 and 2; Figs. 1 and 2).

Population

The clinical data of 3312 Asian patients with diabetes and neurovascular disease were collected from the NIS

Table 1 Variables used in binary logistic regression analysis (SUMDNF Database)

Variables Categories	Specific Variables
Patient demographics	Age (≤ 64 years and ≥ 65 years), sex (male and female), race (Han, Korean, Zhuang, Zang or, Manchu, Tujia ethnic group, Mongolian ethnic group, the Hui nationality, the Yao nationality and Other), BMI, Type of diabetes (Type I diabetes, Type 2 diabetes, Secondary diabetes, Gestational diabetes, Adult latent autoimmune diabetes/Adult delayed autoimmune diabetes, Hormone related diabetes and other), Course of disease
Inspection indicators	Fasting blood glucose, Sensing 128 Hz tuning fork (Left and Right), ABI (Left and Right), GLU2h oral glucose tolerance test, HbA1C, Urinary ACR, TG, CHOL, Serum HDL cholesterol, Serum LDL cholesterol, CRP, HCY, WBC, PCT
Comorbidities	Obesity, Alcohol abuse, Smoke, Diabetic retinopathy, Diabetic nephropathy, Ischemic stroke, Dementia, Diabetic ketoacidosis, Osteomyelitis, Hypertension, Coronary heart disease, Tinea pedis, Onychomycosis, Sepsis

BMI Body mass index, *ABI* Ankle brachial index, *HbA1C* Glycosylated hemoglobin, *ACR* Albumin to creatinine ratio, *TG* Serum triglycerides, *CHOL* Serum total cholesterol, *CRP* C-Reactive Protein, *HCY* Homo-cysteine, *WBC* White blood cell count, *PCT* Procalcitonin

Table 2 Variables used in binary logistic regression analysis (NIS Database)

Variables Categories	Specific Variables
Patient demographics	Age (≤ 64 years and ≥ 65 years), sex (male and female),
Hospital characteristics	Type of admission (non-elective, elective), bed size of hospital (small, medium, large), teaching status of hospital (nonteaching, teaching), location of hospital (rural, urban), type of insurance (Medicare, Medicaid, private insurance, self-pay, no charge, other), location of the hospital (northeast, Midwest or north central, south, west)
Comorbidities	AIDS, alcohol abuse, deficiency anemia, rheumatoid diseases, chronic blood loss anemia, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, neurological disorders, obesity, paralysis, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, solid tumor without metastasis, peptic ulcer disease, valvular disease and weight loss, diabetic retinopathy, diabetic nephropathy, diabetic ketoacidosis, osteomyelitis, Osteomyelitis, sepsis, coronary heart disease, dementia, ischemic stroke, Tinea pedis

AIDS Acquired immunodeficiency syndrome

database (January 1, 2017, to December 31, 2019) and the SMUNH database (January 1, 2018, to December 31, 2023). After excluding 623 individuals with missing data, we included 2689 diabetic patients with neurovascular disease from the NIS database. Similarly, we extracted 6722 records from the SMUNH database, excluded 2402 individuals with missing data, and included 4320 diabetic patients with neurovascular disease. This resulted in a total study population of 7009 diabetic patients with neurovascular disease (Figs. 3, 4 and 5). Patients were eligible for inclusion if they had documented diagnoses of both diabetes and coexisting neuropathy and vascular disease, as defined by the International Statistical Classification of Diseases, 10th Revision (ICD-10). We then investigated potential risk factors for DFU by comparing patient demographic and clinical characteristics between the DFU group and the non-DFU group, aiming to analyze the factors contributing to the development of DFU.

Definitions

Diabetic peripheral neuropathy (DPN) is a diverse clinical entity characterized by signs or symptoms of peripheral nerve dysfunction without a clear alternative cause, presumed to be a result of metabolic and vascular complications of chronic hyperglycemia [16]. DPN typically manifests as a symmetrical polyneuropathy, characterized by pain, paresthesia, or, in up to 50% of cases, no symptoms. It can affect sensory, motor, and autonomic functions. Peripheral artery disease [12, 16], on the other hand, is a complication arising from narrowed or obstructed blood vessels in the extremities, typically the lower limbs. This narrowing reduces blood flow to the affected area. Diabetes is a strong contributor to the development and progression of PAD, leading to a distinct PAD phenotype in diabetic patients [17]. Studies indicate that the lifetime prevalence of PAD in individuals with diabetes ranges from 20 to 50% [10]. PAD has been recognized as a significant risk factor for delayed wound healing, infection, amputation (including both minor and major lower limb amputations), and increased mortality in diabetic populations [18–20].

Statistical analysis

Statistical analysis was performed using IBM SPSS 26.0 software (IBM Corp., 2019). The study population was divided into two groups in each database: DFU group ($n=578$, 13.4%) and non-DFU group ($n=3742$, 86.6%) in the SMUNH database, and DFU group ($n=696$, 25.9%) and non-DFU group ($n=1993$, 74.1%) in the NIS database. Categorical variables were compared using chi-square tests, while continuous variables were analyzed with unpaired Student's t-tests. Descriptive statistics were presented as frequencies and percentages for categorical variables and as mean ± standard deviation (SD) for continuous variables. Logistic regression models were used to identify factors associated with diabetic foot ulcers. Univariate analysis was conducted first to identify significant variables, followed by multivariate analysis using variables with p-values < 0.05 from the univariate analysis as covariates. Statistically significant differences were reported with p-values less than 0.05 ($P<0.05$).

Results

Among 4320 SMUNH patients, DFU patients averaged 65 years versus 56 years in non-DFU patients (Table 3). Most patients were male (60.4%, $n=2609$, Table 3) and had type 2 diabetes (93.7%). We divided patients into groups with DFU ($n=578$; 13.4%) and without DFU ($n=3742$; 86.6%). DFU patients were predominantly male (64.2%), a difference with statistical significance compared to the non-DFU group. Similarly, we collected overall demographic data for 2689 Asian patients in the NIS database between 2017 and 2019 (Table 4). The mean ages for patients with and without DFU were 64 and 71, respectively, and female (64.3%, $n=1728$) predominance was observed (Table 4). Patients were divided into groups with DFU ($n=696$; 25.9%) and without DFU ($n=1993$; 74.1%). In contrast to the

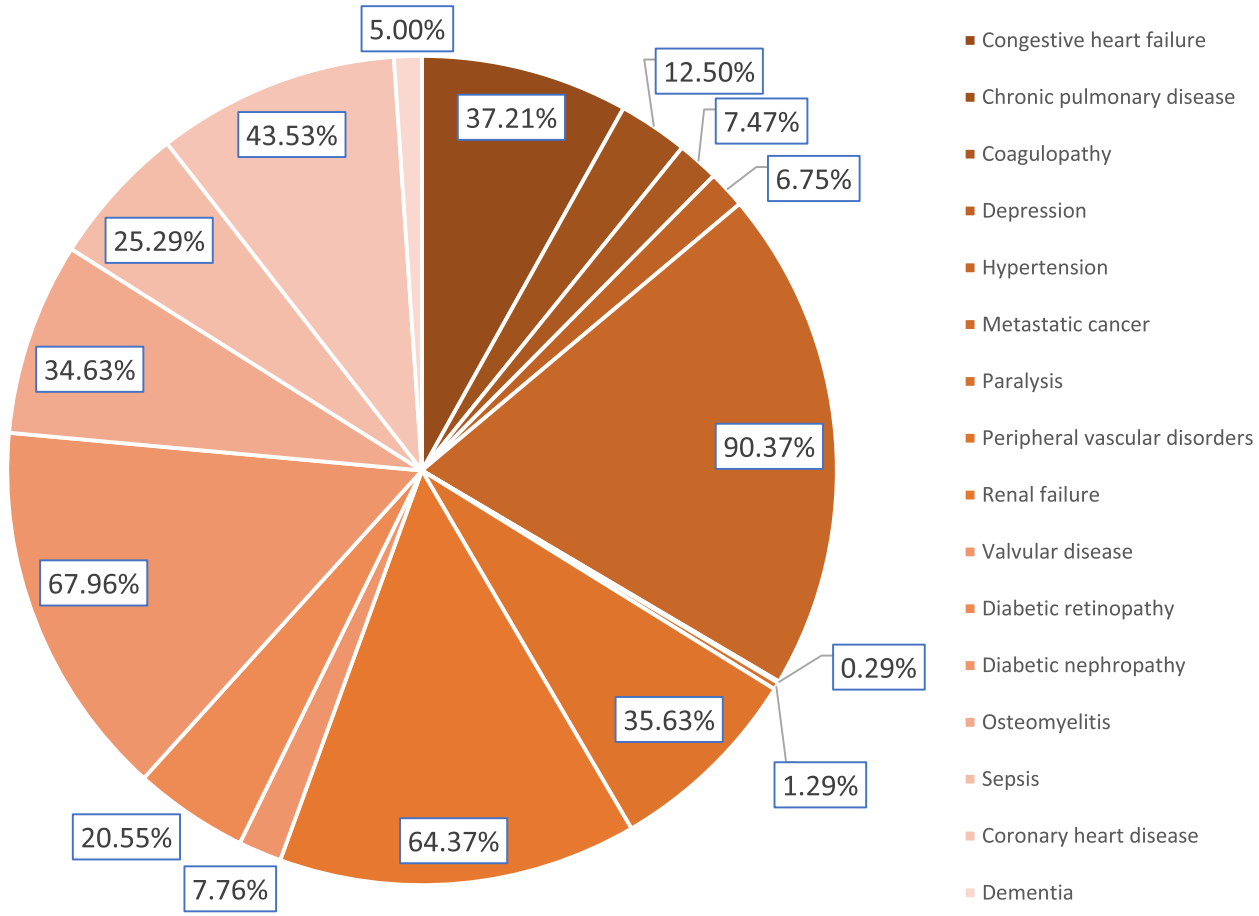

Fig. 1 Incidence of DFU related comorbidities in the NIS

non-DFU group, the majority of DFU patients in the NIS database were female (71.00%), and this difference was statistically significant.

Based on the demographic analysis results from SMUNH, multiple regression analysis was conducted on the relevant variables. The results showed that age (OR, 1.03; 95% CI, 1.01–1.04, $P=0.003$), fasting blood glucose (OR, 1.05; 95% CI, 0.99–1.11, $P=0.030$) and course of disease (OR, 1.03; 95% CI, 1.00–1.05, $P=0.041$) were significantly correlated with DFU (Table 5).

Our study of DFU in the SMUNH database revealed a correlation between DFU and various comorbidities and complications ($P<0.05$). Multiple regression analysis identified the following independent risk factors for DFU: diabetic retinopathy (DR) (OR, 1.74; 95% CI, 1.36–2.23; $P<0.001$), diabetic nephropathy(DN) (OR, 1.49; 95% CI, 1.16–1.92; $P=0.002$), osteomyelitis (OR, 37.57; 95% CI, 7.66–184.28; $P<0.001$), coronary heart disease (CHD) (OR, 1.58; 95% CI, 1.17–2.15; $P=0.003$), tinea pedis (TP) (OR, 5.31; 95% CI, 1.37–20.53; $P=0.016$), sepsis (OR, 28.13; 95% CI, 2.92–271.30; $P=0.004$), sensing 128 Hz tuning fork (left) (OR, 2.00; 95% CI, 1.34–2.97; $P=0.001$), sensing 128 Hz tuning fork (right) (OR, 3.51; 95% CI, 2.30–5.38; $P<0.001$), C-reactive protein (CRP) (OR, 1.01; 95% CI, 1.01–1.02; $P<0.001$), and urinary albumin creatinine ratio (UACR) (OR, 1.06; 95% CI, 1.04–1.09; $P<0.001$).

For DFU patients in the Asian NIS cohort with comorbidities and complications, univariate analysis demonstrated significant associations with the factors listed above ($P<0.05$) (Table 6). This suggests a significant association between DFU and these comorbidities. Subsequent multiple regression analysis identified two independent risk factors for DFU: peripheral vascular disorders (OR: 1.86; 95% CI: 1.48–2.28; $P<0.001$) and osteomyelitis (OR: 7.55; 95% CI: 5.80–9.83; $P<0.001$).Furthermore, an analysis of patient outcomes revealed that among diabetic patients with neuropathy, the DFU group experienced longer hospitalization times and higher total costs compared to the non-DFU group (Tables 7 and 8).

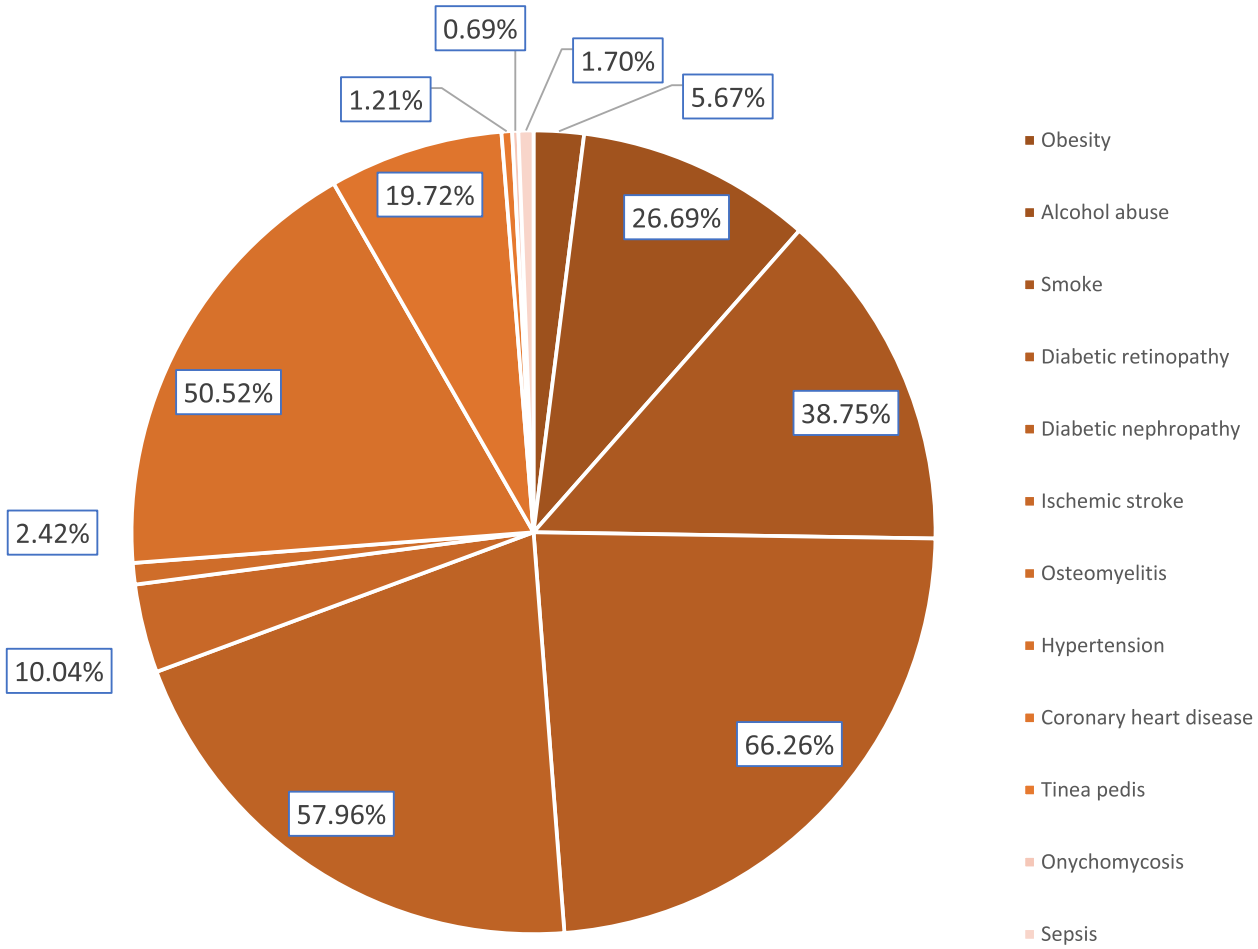

Fig. 2 Incidence of DFU patients related comorbidities in SMUNFH

In addition, we collected the Wagner scores of patients and conducted correlation analysis with their complications. The results showed that neurovascular complications such as diabetic retinopathy, diabetic neuropathy, and ischemic stroke were closely related to the occurrence and development of DFU (Table 9).

Discussion

DFU prevalence was higher among US Asians (NIS database: 25.9%) compared to SMUNH patients (13.4%), the prevalence in both groups remained lower than the rates reported in Ethiopia (31.1%) and Nigeria (41.1%) [21, 22]. This discrepancy may be due to variations in sample size, geographic location, and social or cultural differences among participants. Our study identified several risk factors for DFU: age, course of disease, fasting blood glucose, diabetic retinopathy, diabetic nephropathy, osteomyelitis, coronary heart disease, tinea pedis, sepsis, ability to sense a 128 Hz tuning fork (both left and right sides), CRP, and UACR in SMUNH patients. In the NIS database, peripheral vascular disorders and osteomyelitis were found to be independent risk factors for DFU in Asian populations (Tables 10 and 11).

Data from all patients and various risk factors for DFU were evaluated. Consistent with previous research by Tong T, Zhang P, Boyko EJ, and Rossboth S et al. [23–26], our analysis demonstrated that older age, longer disease duration, and elevated fasting blood glucose levels were significant risk factors for diabetic foot ulcers. Furthermore, the mean age in our study was higher than that reported by Hokkam et al. This discrepancy could be attributed to known differences in life expectancy between the studied populations, with individuals in Europe and the United States generally living longer than those in other regions [27].

Our study also found that patients with diabetic retinopathy had a 1.74 times higher risk of DFU compared to those without DR. Both DR and DFU are well-established microvascular complications of diabetes mellitus. Existing research supports a positive correlation between DFU

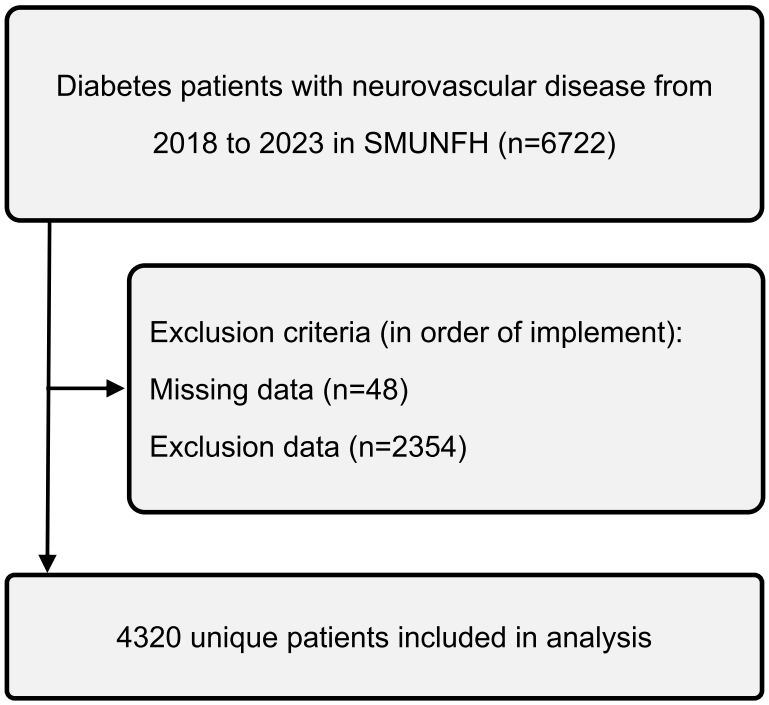

Fig. 3 Procedures for patient inclusion and exclusion of the SMUNFH

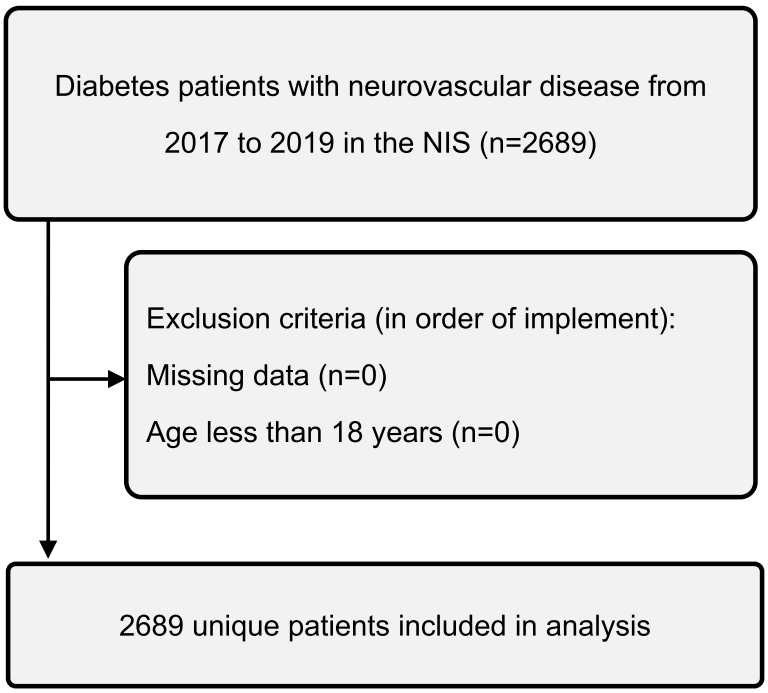

Fig. 4 Procedures for patient inclusion and exclusion of the NIS

incidence and DR [28, 29], which aligns with our findings. It is well-established that DR affects the small blood vessels [30] in the lower limbs and impairs wound healing [31]. At the same time, unhealed DFU may accelerate the progression of DR due to the presence of chronic inflammation and associated infections [32].

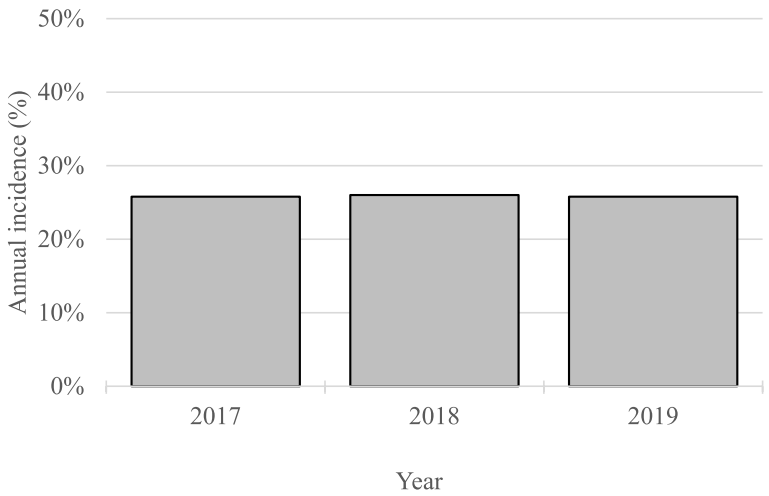

Fig. 5 Incidence rate of foot ulcers in diabetes patients with neurovascular disease and diabetes in the NIS

Table 3 Patient characteristics and outcomes with neurovascular disease and diabetes (SUMDNF Database from 2018–2023)

Characteristics	DFU	No DFU	*P*
Total (n = count)	578	3742	
Total incidence (%)	13.4		
Age (median, years)	64 (55,71.25)	55 (46, 64)	< 0.001
Gender (%)			
Male	64.20	59.80	0.043
Female	35.80	40.20	
Race (%)			
Han	93.30	95.70	0.060
Korean	6.20	3.60	
Zhuang	0.20	0.30	
Zang	0.00	0.00	
Manchu	0.00	0.20	
Tujia ethnic group	0.00	0.00	
Mongolian ethnic group	0.00	0.10	
the Hui nationality	0.30	0.10	
the Yao nationality	0.00	0.10	
Other	0.00	0.10	
BMI (median)	23.23 (21.50,25.29)	24.10 (21.50,26.28)	< 0.001
Type of diabetes (%)			
Type I diabetes	1.60	4.30	< 0.001
Type 2 diabetes	98.40	93.00	
Secondary diabetes	0.00	0.70	
Gestational diabetes	0.00	0.90	
Adult latent autoimmune diabetes/Adult delayed autoimmune diabetes	0.00	1.00	
Hormone related diabetes	0.00	0.10	
Other	0.00	0.00	
Course of disease (median, years)	10.00 (5.13,15.00)	5.63 (1.00,12.00)	< 0.001

Table 4 Patient characteristics and outcomes with neurovascular disease and diabetes in Asia (NIS Database from 2017–2019)

Characteristics	DFU	No DFU	*P*
Total (*n* = count)	696	1993	
Total incidence (%)	25.9		
Age (median, years)	64 (55,73)	71 (62, 79)	< 0.001
Age group (%)			
18–44	8.30	3.60	< 0.001
45–64	43.70	26.80	
65–74	26.10	31.50	
≥ 75	21.80	38.00	
Gender (%)			
Male	29.00	38.10	< 0.001
Female	71.00	61.90	
Number of Comorbidity (%)			
0	1.30	0.70	< 0.001
1	7.30	4.00	
2	17.10	9.90	
≥ 3	74.30	85,40	
Type of insure (%)			
Medicare	56.20	75.70	< 0.001
Medicaid	18.70	11.10	
Private insurance	21.00	11.30	
Self-pay	3.20	1.00	
No charge	0.00	0.10	
Other	1.00	0.80	
Bed size of hospital (%)			
Small	18.70	15.40	0.008
Medium	25.30	31.00	
Large	56.00	53.60	
Elective admission (%)	90.80	88.70	0.116
Type of hospital (teaching, %)	79.90	78.30	0.386
Location of hospital (urban, %)	98.1	98.3	0.710
Region of hospital (%)			
Northeast	11.10	9.20	0.547
Midwest or North Central	9.50	9.20	
South	11.60	12.00	
West	67.80	69.60	

Table 5 Related risk factors of diabetes patients with neurovascular disease and diabetic foot ulcers (SUMDNF Database from 2018–2023)

Variable	Multivariate Logistic Regression		
	OR	95% CI	*P*
Age	1.025	1.01–1.04	0.003
Female	0.762	0.58–1.00	0.762
BMI	0.936	0.89–0.99	0.021
Type of diabetes	0.786	0.55–1.13	0.194
Course of disease	1.025	1.00–1.05	0.041

OR Odds ratio, *CI* Confidence interval

Table 6 Related risk factors of diabetes in Asian patients with neurovascular disease and diabetic foot ulcers (NIS Database from 2017–2019)

Variable	Multivariate Logistic Regression		
	OR	95% CI	*P*
Age ≥ 65 years old	0.570	0.452–0.719	< 0.001
Female	0.737	0.596–0.911	0.005
Number of Comorbidity			
1	0.968	0.331–2.827	0.953
2	0.985	0.346–2.807	0.978
≥ 3	0.720	0.249–2.078	0.544
Type of insurance			
Medicare	1.254	0.924–1.701	0.147
Medicaid	1.394	1.042–1.866	0.025
Private insurance	2.551	1.272–5.116	0.008
Self-pay	0.000	0.000	0.999
No charge	1.302	0.476–3.564	0.607
Other	Ref	——	——

OR Odds ratio, *CI* Confidence interval

Besides, our results showed that the risk of DFU in patients with DN was 1.49 times higher than in those without DN (OR, 1.49; 95% CI, 1.16–1.92; $P = 0.002$). The risk of DFU patients with abnormal UACR was 1.06 times higher than that in patients with normal UACR (OR, 1.06; 95% CI, 1.04–1.09; $P < 0.001$). UACR reflects the severity of DN and plays an important role in the occurrence and development of diabetic foot ulcers [33]. UACR is also a marker of kidney injury, which can be used for the diagnosis and staging of chronic kidney disease [34], and diabetic nephropathy. Furthermore, elevated UACR levels are associated with an increased risk of all-cause mortality, major adverse cardiovascular events, and composite outcomes [35]. DN is the most common microvascular complication in diabetic patients and can lead to impaired renal function. One study found that mildly decreased renal function (eGFR 30–60 mL/min/1.73 m^2) was associated with increased risk of DFU and amputation [36].

Among DM patients with coronary heart disease, the risk of DFU was 1.58 times higher than in those without CHD (OR, 1.58; 95% CI, 1.17–2.15; $P = 0.003$). Diabetes patients with osteomyelitis had a 5.31-fold higher DFU risk than those without osteomyelitis (OR, 37.57; 95% CI, 7.66–184.28; $P < 0.001$). This association is supported by evidence demonstrating a strong link between

Table 7 Prognosis and results of patients with neurovascular diseases and diabetes (NIS Database from 2017–2019)

Characteristics	DFU	No DFU	*P*
LOS (median, d)	7.00 (4.00, 11.00)	5.00 (3.00, 8.00)	< 0.001
TOTCHG (median, $)	63,749.50 (34,876.25, 115,224.50)	48,023.50 (26,183.50, 91,938.00)	< 0.001
Died (%)	1.40	2.70	< 0.001

LOS Length of stay, *TOTCHE* Total charge

Table 8 Prognosis and outcomes in Asian patients with neurovascular disease and diabetes (2017–2019)

Characteristics	DFU	No DFU	*P*
LOS (median, d)	6.00 (4.00, 11.00)	5.00 (3.00, 8.00)	< 0.001
TOTCHG (median, $)	75,036.00 (41,128.25, 137,829.25)	60,960.00 (32,898.50, 117,516.50)	< 0.001
Died (%)	4.20	3.00	0.177

LOS Length of stay, *TOTCHE* Total charge

diabetes, cardiovascular disease, and the increased risk of both acute and chronic osteomyelitis [37]. Cardiovascular disease, including coronary artery disease, stroke, and congestive heart failure [38], affects up to 30% of diabetic patients worldwide and is the leading cause of death in DFU patients [39]. Active management of cardiovascular risk factors is crucial in multidisciplinary diabetes care, as it has been shown to reduce both DFU risk and mortality in DFU patients [40]. Several studies support the bidirectional relationship between DFU and osteomyelitis. Lavery et al. found that the presence of osteomyelitis negatively impacts diabetic foot infection outcomes, potentially promoting DFU development [41]. Furthermore, Yesil et al. [42] emphasized the significance of osteomyelitis as a risk factor for major amputation among DFU patients, extending its impact beyond DFU occurrence.

Our results also demonstrated that diabetes patients with tinea pedis had a 5.31-fold higher DFU risk than those without (OR, 5.31; 95% CI, 1.37–20.53; $P=0.016$). This aligns with research by Akkus et al., who reported a significantly higher prevalence of fungal infections between the toes, soles, and toenails in patients with DFU compared to those without [43]. They further highlighted that poor blood glucose control and peripheral vascular disease in diabetic patients increased susceptibility to fungal infections, potentially contributing to DFU development.

Sepsis (OR, 28.13; 95% CI, 2.92–271.30; $P=0.004$) poses a severe complication in vulnerable DFU patients, elevating the risk of non-traumatic amputation, multiorgan failure, and even death [44]. Diabetics with abnormal C-reactive protein had a 1.01 times greater risk of developing DFU than diabetics with normal CRP (OR, 1.01; 95% ci, 1.01–1.02; $P<0.001$). CRP, an acute phase response protein, is considered the most valuable biomarker for diabetic foot ulcer infection [45]. A study demonstrates differences in serum CRP levels and diabetic foot ulcer infections across continents globally [46], with Asia leading the way. As the epicenter of the diabetes epidemic, Asia accounts for about 60% of the global total [47]. Geographic location, economic level, and lifestyle factors may account for these observed disparities.

The NIS Asian patient study demonstrated that individuals with peripheral vascular disorders (PVD) had a 1.86-fold increased risk of DFU compared to those without PVD (OR, 1.86; 95% CI, 1.48–2.28; $P<0.001$). PVD encompasses arterial and venous system diseases, and its complex nature often leads to asymptomatic diabetic foot ulcers in the early stages, progressing to chronic nonhealing ulcers with prominent tissue loss in later stages. The impact of peripheral arterial disease, which involves the narrowing or blockage of arteries in the lower limbs, leading to reduced blood flow [48], is well-documented. It has been reported that PAD contributes to 50–70% of DFU cases and is a significant risk factor for delayed wound healing, infection, amputation, and mortality in both type 1 and type 2 diabetes [1].

Limitations

Our research benefits from a large sample size and utilizes data from both the NIS database and the SMUNH database, enabling robust analysis of diabetic patients with neurovascular complications. However, several limitations warrant consideration. The retrospective design inherently constrains our ability to establish causal relationships between identified risk factors and foot ulcer development. Our analysis was necessarily limited to

Table 9 Correlation test of Wagner score in patients with neurovascular diseases and diabetes (SUMDNF database 2018–2023)

Classification	0	I	II	III	IV	V	*P*
Gender (%)							0.034
Male	59.80	57.30	6.00	65.70	67.30	60.00	
Female	40.20	42.70	35.70	34.30	32.7	40.00	
Race (%)							0.009
Han	95.70	95.10	91.80	92.90	94.30	85.00	
Korean	3.60	3.90	8.20	6.10	5.70	15.00	
Zhuang	0.30	0.00	0.00	0.50	0.00	0.00	
Zang	0.00	0.00	0.00	0.00	0.00	0.00	
Manchu	0.20	0.00	0.00	0.00	0.00	0.00	
Tujia ethnic group	0.00	0.00	0.00	0.00	0.00	0.00	
Mongolian ethnic group	0.00	0.00	0.00	0.00	0.00	0.00	
the Hui nationality	0.10	0.00	0.00	0.00	0.00	0.00	
the Yao nationality	0.10	0.00	0.00	0.00	0.00	0.00	
Other	0.10	0.00	0.00	0.00	0.00	0.00	
Obesity (%)	12.30	6.30	5.90	7.90	3.00	0.00	< 0.001
Alcohol abuse(%)	27.10	20.60	26.50	24.70	35.20	10.00	0.964
Smoke(%)	35.40	35.00	38.80	38.40	44.00	20.00	0.100
Diabetic retinopathy(%)	49.70	73.80	68.40	62.60	66.70	50.00	< 0.001
Diabetic nephropathy(%)	34.00	57.30	48.00	59.10	61.00	75.00	< 0.001
Ischemic stroke(%)	5.70	6.80	9.20	12.10	10.10	10.00	< 0.001
Dementia(%)	0.50	1.90	0.00	0.50	1.90	0.00	0.139
Diabetic ketoacidosis(%)	4.60	3.90	2.00	4.50	2.50	0.00	0.132
Osteomyelitis(%)	0.10	0.00	0.10	0.10	0.10	0.00	< 0.001
Hypertension(%)	40.60	50.50	54.10	48.50	49.70	60.00	< 0.001
Coronary heart disease(%)	10.50	22.30	18.40	18.20	18.90	35.00	< 0.001
Tinea pedis(%)	0.20	2.90	3.10	0.50	0.00	0.00	0.001
Onychomycosis(%)	0.10	1.00	1.00	0.50	0.60	0.00	< 0.001
Sepsis(%)	0.20	1.90	1.00	1.00	3.10	0.00	< 0.001

documented clinical parameters, precluding assessment of important variables such as patient adherence to preventive foot care protocols and detailed lifestyle factors. Furthermore, the variability in assessment and classification of neurovascular complications across healthcare settings may affect result comparability. The HCUP-NIS database's limitation in providing granular clinical data potentially impacts the depth of medical quality and outcome assessments. Despite these limitations, our findings have substantial clinical and public health implications. The data clearly demonstrate that patients with extended disease duration and suboptimal glycemic control require intensified screening protocols and preventive interventions. Based on these findings, we recommend: Implementation of risk-stratified monitoring programs, Development of targeted intervention strategies for patients with multiple high-risk characteristics and Regular reassessment of preventive care protocols based on patient risk profiles. These evidence-based recommendations provide healthcare providers with actionable frameworks for improving patient outcomes in this high-risk population.

Conclusion

DFU, a serious diabetic complication, significantly impacts patient quality of life and mortality. Research indicates a high prevalence of DFU among individuals with neurovascular disease. Understanding DFU pathophysiology and the rapid identification of risk factors is crucial. Factors correlated with DFU include diabetic retinopathy, diabetic nephropathy, osteomyelitis, peripheral vascular disease, coronary heart disease, tinea pedis, sepsis, elevated CRP, and urinary ACR. Targeted interventions addressing these risk factors can aid in preventing diabetic foot in patients with neurovascular disease. Further research is required to elucidate the reasons for disparities between affected groups and the underlying mechanisms influencing

Table 10 Relationship between diabetic foot ulcers and comorbidities (SUMDNF Database from 2018–2023)

Comorbidities and Inspection indicators	Univariate Analysis		Multivariate Logistic Regression			
	No DFU	DFU	*P*	OR	95% CI	*P*
Comorbidities						
Obesity	450 (0.4%)	221 (0.5%)	0.131	0.42	0.26–0.66	< 0.001
Alcohol abuse	224(6.0%)	58 (10.1%)	< 0.001	1.08	0.92–1.28	0.356
Smoke	1049 (28.0%)	162 (28.0%)	0.015	0.96	0.78–1.17	0.670
Diabetic retinopathy	1273 (34.0%)	335 (58.0%)	< 0.001	1.74	1.36–2.23	< 0.001
Diabetic nephropathy	1859 (49.7%)	383 (66.3%)	< 0.001	1.49	1.16–1.92	0.002
Ischemic stroke	214 (5.7%)	58 (6.3%)	< 0.001	0.95	0.75–1.22	0.706
Osteomyelitis	3 (0.1%)	14 (2.4%)	< 0.001	37.57	7.66–184.28	< 0.001
Hypertension	1520 (40.6%)	292 (50.5%)	< 0.001	1.01	0.79–1.28	0.960
Coronary heart disease	393 (10.5%)	114 (19.7%)	< 0.001	1.58	1.17–2.15	0.003
Tinea pedis	9 (0.2%)	7 (1.2%)	< 0.001	5.31	1.37–20.53	0.016
Onychomycosis	2 (0.1%)	4 (0.7%)	< 0.001	6.98	0.93–52.47	0.059
Sepsis	6 (0.2%)	10 (1.7%)	< 0.001	28.13	2.92–271.30	0.004
Inspection indicators: mean (SD)						
Fasting blood glucose (mmol/L)	10.97 (0.21)	10.78 (0.38)	< 0.001	1.05	0.99–1.11	0.030
Sensing 128 Hz tuning fork (left)	192 (5.9%)	161 (34.7%)	< 0.001	2.00	1.34–2.97	0.001
Sensing 128 Hz tuning fork (right)	169 (5.2%)	157 (33.3%)	< 0.001	3.51	2.30–5.38	< 0.001
ABI (Left)	1.09 (0.01)	0.98 (0.03)	< 0.001	0.19	0.04–0.78	0.022
ABI (Right)	1,13 (0.01)	1.01 (0.03)	< 0.001	0.21	0.54–0.84	0.027
GLU2h oral glucose tolerance test (mmol/L)	12.78 (0.31)	11.23 (0.42)	< 0.001	0.92	0.89–0.97	0.001
HbA1C (%)	9.88 (0.15)	9.25 (0.22)	< 0.001	0.91	0.84–1.00	0.043
TG (mmol/L)	2.44 (0.15)	1.51 (0.08)	< 0.001	0.73	0.60–0.90	0.003
CHOL (mmol/L)	4.69 (0.78)	4.30 (0.13)	< 0.001	1.05	0.74–1.50	0.791
Serum HDL cholesterol (mmol/L)	1.07 (0.03)	1.00 (0.06)	< 0.001	0.34	0.17–0.69	0.003
Serum LDL cholesterol (mmol/L)	2.91 (0.55)	2.76 (0.99)	< 0.001	0.96	0.64–1.45	0.85
CRP (mg/L)	24.70 (2.70)	42.34 (4.88)	< 0.001	1.01	1.01–1.02	< 0.001
HCY (mmol/L)	12.77 (0.450)	13.60 (0.63)	< 0.001	1.00	0.97–1.03	0.96
WBC ($\times 10^9$/L)	10.88 (2.65)	9.33(0.44)	< 0.001	1.00	0.99–1.01	0.88
Urinary ACR	5.85 (0.41)	9.20 (0.92)	< 0.001	1.06	1.04–1.09	< 0.001

OR Odds ratio, *CI* Confidence interval

these factors. Such insights would contribute to effective policy-making, priority setting, and resource allocation within diabetes prevention and treatment. Accordingly, medical professionals should emphasize patient education and promotion of foot self-care practices to reduce foot infections and inflammation. Continued investigation of potential DFU risk factors is essential for prevention, ultimately aiming to reduce its prevalence.

Specific Comorbidities	Operaional Definitions
Acquired immune deficiency syndrome(AIDS)	AIDS is an acquired immunodeficiency syn-drome defined by a severe depletion of T cells and over 20conventional degenerative and neoplastic diseases
(Iron) Deficiency anemia(IDA)	IDA is classically described as a microcytic anemia and due to reduced or absent iron stores needed to make red blood cells
Hypertension	Hypertension can be defined as a rise in blood pressure of unknown cause that increases risk for cerebral, cardiac, and renal events
Obesity	Body mass index(BMI) of 30 kg/m2 or higher is used to identify individuals with obesity
Peripheral vascular Disorderse(PVD)	PVD is the presence of systemic atherosclerosis in arteries distal to the arch of the aorta. As a result of the atherosclerotic process, patients with PVD develop narrowing of these arteries. The most common symptom of PVD is intermittent claudication, which manifests as pain in the muscles of the legs with exercise. 5

Table 11 Relationship between diabetic foot ulcers and comorbidities (NIS Database from 2017–2019)

Comorbidities	Univariate Analysis			Multivariate Logistic Regression		
	No DFU	DFU	*P*	OR	95% CI	*P*
Comorbidities						
Congestive heart failure	996 (50.0%)	259 (37.2%)	< 0.001	0.994	0.794–1.244	0.957
Chronic pulmonary disease	470 (23.60%)	87 (12.5%)	< 0.001	0.701	0.553–0.922	0.011
Coagulopathy	241 (12.1%)	52 (7.5%)	0.001	0.823	0.582–1.166	0.273
Depression	200 (10.0%)	47 (6.8%)	0.010	0.721	0.499–1.041	0.081
Hypertension	1805 (90.6%)	629 (90.4%)	0.881	0.971	0.707–1.333	0.855
Metastatic cancer	36 (1.8%)	2 (0.3%)	0.003	0.200	0.046–0.865	0.031
Paralysis	86 (4.3%)	9 (1.3%)	< 0.001	0.340	0.165–0.700	0.003
Peripheral vascular disorders	565 (28.3%)	248 (35.6%)	< 0.001	1.863	1.481–2.277	< 0.001
Renal failure	1468 (73.7%)	448 (64.4%)	< 0.001	0.869	0.608–1.241	0.440
Valvular disease	226 (13.3%)	54 (7.8%)	< 0.001	0.871	0.618–1.228	0.431
Diabetic retinopathy	490 (24.6%)	143 (20.5%)	0.031	0.830	0.654–1.054	0.127
Diabetic nephropathy	1521 (76.3%)	473 (68.0%)	< 0.001	0.940	0.658–1.343	0.734
Osteomyelitis	107 (5.4%)	241 (34.6%)	< 0.001	7.552	5.801–9.831	< 0.001
Sepsis	398 (20.0%)	176 (25.3%)	0.003	1.263	1.000–1.596	0.050
Coronary heart disease	1113 (55.8%)	303 (43.5%)	< 0.001	0.789	0.642–0.970	0.024
Dementia	173 (8.7%)	35 (5.0%)	0.002	0.958	0.637–1.442	0.837

OR Odds ratio, *CI* Confidence interval

Specific Comorbidities	Operaional Definitions
Weight loss	
Osteomyelitis	Osteomyelitis is an inflammatory condition of bone secondary to infection; it may be acute or chronic. Symptoms of acute osteomyelitis include pain, fever, and edema of the affected site, and patients typically present without bone necrosis in days to weeks following initial infection. Chronic osteomyelitis develops after months to years of persistent infection and may be characterized by the presence of necrotic bone and fistulous tracts from skin to bone
Tinea pedis	Tinea pedis, which is a dermatophytic infection of the feet, can involve the interdigital web spaces or the sides of the feet and may be a chronic or recurring condition
Sepsis	Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

Supplementary Information

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Supplementary Material 1.

Authors' contributions

ZF: Principal investigator who analyzed clinical data, managed the research project, and led manuscript writing. YLiu: Responsible for patient data collection, statistical analysis, and visualization of clinical outcomes. HX: Oversaw research methodology, supervised clinical assessments, and performed statistical validation. QY: Conducted patient examinations, managed clinical data, and contributed to manuscript development. GZ: Performed clinical investigations, validated diagnostic findings, and assisted in data visualization. PZ: Supervised patient assessments, managed clinical protocols, and reviewed manuscript content. HD: Study conceptualization, funding procurement, and overall project supervision.

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Data availability

The datasets used and/or analyzed at Nanfang Hospital, Southern Medical University are from the Orthopedic Biomedical database and are available from the corresponding author (Ding Hong) upon reasonable request.

Declarations

Ethics approval and consent to participate

This study utilized the NIS database, which provides anonymous and retrospective information from 2017 to 2019. It was considered exempt from ethics review by the Ethics Committee of Nanfang Hospital, Southern Medical University, under ethical approval number NFEC-2024–149. The research was conducted in accordance with local legislation and institutional requirements, and the Ethics Committee waived the need for written informed consent from participants or their legal guardians, as all data were anonymized and did not involve patient privacy. Furthermore, this study adheres to the standards set forth by the Helsinki Declaration.

Consent for publication
All data used in this study were anonymized, and the patients were informed and gave consent for the study to be published.

Competing interest
The authors declare no competing interests.

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