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Epidemiology and the Medical Burden of Diabetic Foot Ulcers Especially in Patients With Infection—A Population-Based Analysis From Germany

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ABSTRACT

Due to limited data on the epidemiology of diabetic foot ulcers (DFU) in Germany, especially for those infected, the study determined the prevalence and incidence of DFU and the associated medical burden. Anonymised claims data of 3.3 million insured lives were sourced from a statutory health insurance fund. Patients with DFU between 04/01/2016 and 12/31/2019 were selected ($n = 7764$) and divided into patients with/without infection/with prophylactic use of antibiotics. Outcome variables were described categorically. Two-sided *t*-tests and chi-squared tests ($p < 0.05$) were performed. The prevalence and incidence in patients with DFU was 4.6% and 2.1%, respectively. The mean Charlson Comorbidity Index was 7.9, significantly higher in those infected than in those uninfected (8.1% vs. 7.2%, $p < 0.0001$). Amputations occurred significantly more often in DFU patients with infection than in those without (minor 25.4% vs. 3.0%, $p < 0.0001$; major 6.7% vs. 1.2%, $p < 0.0001$). The 5-year mortality rate was significantly higher in patients with infection than in those without (64.0% vs. 51.3%, $p < 0.0001$). The occurrence of comorbidities and complications associated with DFU, in particular the high overall medical burden and mortality rate—especially in DFU patients with infections—underscores the importance of prevention and early, appropriate treatment.

1 | Introduction

Diabetic foot ulcer (DFU) is one of the most common complications of Type 1 and Type 2 diabetes mellitus worldwide. 19%–34% of people with diabetes will develop DFU during their lifetime. The annual incidence of DFU is 2%–6% [1]. Among people with diabetes in Germany, studies report a prevalence of DFU between 6.1% and 9.4% [2, 3].

The DFU is subordinate to the diabetic foot syndrome (DFS), which includes "all pathological changes in the foot of a person with diabetes mellitus" [4]. DFU's are defined by the International Working Group on the Diabetic Foot (IWGDF) as "a break of the skin of the foot that involves as a minimum of the epidermis and part of the dermis" in patients with diabetes [5]. The extended nature of the disease is associated with a reduced quality of life and higher mortality [6, 7]. Khunkaew et al. conducted a meta-analysis of health-related quality of life in people with DFU. They reported that people with DFU had a significantly lower health-related quality of life than people without DFU [6]. According to a meta-analysis by Walsh et al., diabetics with DFU had a three times higher risk of death than diabetics without DFU. The 5-year mortality rate of patients with DFU was 42.2% [7].

Summary

- Skin breaks on the foot of a diabetic patient are defined as diabetic foot ulcers (DFU). DFU is a common complication of diabetes and can lead to serious complications such as amputation.
- Anonymised claims data from 3.3 million insured lives in Germany were used to assess the prevalence and incidence of diabetic foot ulcer in patients with diabetes and to describe its epidemiology, as well as the medical burden of DFU measured by comorbidities, complications, DFU recurrence and mortality. In addition, the number of patients with infected DFUs and their associated burden of disease were determined.
- The prevalence and incidence of DFU in patients with diabetes was 4.6% and 2.1%, respectively. The most common comorbidities were neuropathy, peripheral artery disease (PAD), their combination, nephropathy and renal insufficiency, which were more common in patients with infection than in those without. The high mean Charlson Comorbidity Index (CCI) was 7.9. Amputations were more common in DFUs with infection than in DFUs without infection. Twenty-five percent of DFUs with infection had a minor amputation and 6% had a major amputation. The high 5-year mortality rate was 60% in DFU patients and 64% in patients with infection. Both mean CCI, amputation rates and mortality were higher in patients with infection, highlighting the high burden of DFU and the importance of prevention and early and appropriate treatment.

A delayed or ineffective treatment of DFU can lead to further complications such as infections, which can result in amputations [8, 9]. Around 50%–60% of patients with DFU develop a diabetic food infection (DFI) within a year [1, 10] and about 20% of these patients with DFI had undergone an amputation [11]. Therefore, infection is considered as a severe complication of DFU and an ultimately speed-determining step for amputation [12]. Infection should therefore be avoided [13] and infection control and thus also antibiotic therapy are of particular importance in acute treatment. Thus, out of uncertainty of a relevant infection, in some cases, harmful prophylactic in other cases delayed antibiotic therapy is used.

Current figures on DFI and resulting amputations for a representative population in Germany are not yet known. Regarding amputations in Germany, it is known that patients with a diagnosis of diabetes mellitus accounted for 63.7% of major amputations and 85.6% of minor amputations performed in 2014 [14]. Bohn et al. conducted an observational study of diabetic patients with DFU. Minor amputations occurred in 25.9% of patients and major amputations in 11.3% of patients from 452 specialist diabetes centres [3].

To stop the fast deterioration and complications and to avoid amputations caused by infection, systemic infections or sepsis, diabetic foot infections are treated with antibiotic therapy. However, the IWGDF does not recommend prophylactic antibiotic therapy to prevent infection or promote ulcer healing [9]. They concluded that no strong evidence supporting the benefit of prophylactic antibiotic use for clinically uninfected diabetic foot ulcers, and the potential harms of such therapy outweigh any theoretical benefits. To avoid the development of antibiotic resistance, the German Diabetes Association's practice recommendation for DFS refers to the Antibiotic Stewardship (ABS) criteria, which state that antibiotics should be administered when indicated and require culture-controlled administration [4]. In line with this, the German Society for Wound Healing and Wound Treatment's guideline for local therapy of difficult to heal and/or chronic wounds with peripheral arterial disease (PAD), diabetes mellitus or chronic venous insufficiency recommends that if there is evidence of a pathogen-related infectious disease in the wound area, the pathogens should be identified and the sensitivity to antimicrobial substances determined before antibiotic therapy is initiated [15]. But a reliable diagnosis of a relevant tissue infection can ultimately only be made by microbial analysis of deep tissue samples. However, this is only carried out in the rarest of cases. Usually only a swab is taken, often only superficially. The purely clinical assessment of an infection is based on the classic features of local swelling, erythema (>0.5 but <2 cm), pain, local increased warmth, purulent discharge [13]. These characteristics are often only present to a limited extent in DFS due to neuropathy and PAD. Therefore, antibiotic therapy is often started too late but on the other hand often too early prophylactically, despite the lack of convincing data. Serena et al. analysed antimicrobial prescribing practices for chronic wounds within a study of 350 chronic wounds across 20 clinicians in USA and concluded that the reliance on clinical signs and symptoms for the diagnosis of bacterial burden in chronic wounds leads to the arbitrary use of antimicrobial agents. It was identified that in 23.2% of patients without clinical signs and symptoms of infection oral antibiotics were prescribed [16]. Even though evidence on prophylactic use is very limited, it can be assumed that antibiotics are still used prophylactically in patients with DFU even if this is not recommended [16]. Additionally, also Abbas et al. pointed out that there is no evidence to support the prophylactic use of antibiotics and underline that antibiotics should be used to treat infections, not to promote the healing of uninfected wounds or to prevent infections. Therefore, due to the financial and social aspects (antibiotic resistance), prophylactic prescribing is not appropriate [17].

Although there are studies describing the epidemiology of DFU in Germany, the data are not up to date or representative of the general German population. In addition, there is a lack of recent data on the impact of infection in DFU in Germany based on a representative study population. Therefore, it is hard to depict the public health impact, or derive any management recommendations, based on them. To overcome this limitation, this study aims to provide insight into the current number of incident DFU patients, incident DFU patients with and without infections and incident DFU patients with prophylactic treatment of antibiotics, all sourced from a large dataset. In addition, the study aims to describe patient characteristics (e.g., age, gender) and the medical burden of DFU, particularly in patients with infections.

2 | Methods

2.1 | Study Design and Data Source

This population-based observational study used a longitudinal design and was based on an anonymised claims dataset containing data on people covered by statutory health insurance

(SHI) over a 6-year period (01/01/2016–12/31/2021), divided into quarters as it is typical in German claims recording.

The database contained 3 323 506 insured lives of a company health insurance fund (Betriebskrankenkasse, BKK), covering about 4% of the German population. Approximately 90% of the German population are enrolled in the SHI system, and all the individual health insurance funds offer similar levels of benefits and reimbursement. The database is adjusted for age, sex and co-morbidities in order to make representative and generalisable statements about routine medical care [18].

Besides demographics such as age and gender, the database included information on inpatient and outpatient resource use. The German Modification of the International Statistical Classification of Diseases, 10th Revision (ICD-10-GM) is used to code diagnoses in both sectors (Appendix A).

Outpatient medical treatments and procedures are identified using the panel physician's fee schedule "EBM". The German adaptation of the International Classification of Procedures in Medicine (ICPM) was used for the coding of inpatient treatments. The description of drug treatments was based on the Anatomical Therapeutic Chemical (ATC) codes.

Enrolled individuals could be identified in the database by means of an anonymised unique identification number. This information allowed for longitudinal analyses as well as observations across different sectors of the healthcare system. Patients could not opt out of the analysis, as only a change of insurance company or death could lead to a patient dropout.

2.2 | Study Population

2.2.1 | Selection of the Study Population and Observation Period

Patients with a diagnosis of diabetes mellitus (E10–E14) and incident DFU (E10.74, E10.75, E11.74, E11.75, E12.74, E12.75, E13.74, E13.75, E14.74 and E13.75) in the database between 04/01/2016 and 12/31/2019 were selected if they were aged 18 years or older. These patients represented the study population. The period from 01/04/2016 to 31/12/2019 was thus defined as the overall index period, in which each patient had an individual index quarter. The individual index quarter was the quarter of a newly diagnosed DFU.

Patients were defined as having DFU if they had:

a. an outpatient diagnosis of DFU confirmed by a general practitioner, diabetologist, surgeon or dermatologist and a prescription for dressings/bandage shoe in the same quarter as the outpatient diagnosis, or

b. a confirmed outpatient diagnosis of DFU from a general practitioner and a confirmed outpatient diagnosis of DFU from a diabetologist or dermatologist or surgeon or dermatologist, or

c. a primary or secondary inpatient diagnosis of DFU.

A DFU patient is considered as newly diagnosed or incident if there was no diagnosis of DFU before the index quarter.

As it is possible for a patient to develop DFU more than once over time, the individual DFU episodes that occurred during the index period were also tracked. Each DFU diagnosis (according to the above criteria) occurring during the index period without a DFU diagnosis in the previous month was counted as a single DFU episode.

After defining the study population and the DFU episodes, the latter were further stratified into episodes with and without infection, and the latter further subdivided into episodes with prophylactic antibiotic prescription to prevent infection.

For this purpose, all incident DFU episodes were monitored for a period of 1 year for the development of an infection in the DFU. Subgrouping was then performed as follows (criteria are summarised in Table 1):

a. As there is no claim for DFI in Germany, DFU patients who had (a) an inpatient ICD-10 diagnosis of an infection in the index quarter or within three quarters after the index quarter at the same time as the diagnosis of DFU or (b) a fee code for a DFU swab and an antibiotic prescription in the same quarter of the fee code "swab" or the presence of an antibiotic prescription and a subsequent antibiotic prescription within a maximum of 30 days after the date of the first antibiotic prescription in the outpatient sector, were considered to be "with infection".

b. DFU episodes that did not develop an infection within 1 year were defined as incident DFU episodes "without infection".

c. In order to obtain at least a rough estimate of prophylactic antibiotic administration from the insured person data we chose the following definition: if episodes without infection had no fee coding for a swab of the DFU, but an initial antibiotic prescription without, however, any subsequent antibiotic prescription within the following 30 days from the date of the initial antibiotic prescription, they were defined as incident DFU episodes "with prophylactic antibiotic prescription" and represented a subset of DFU patients without infection.

2.2.2 | Observation Period and Variables of Interest

To describe the outcome parameters, all DFU episodes were followed up for 1 year was chosen as the median DFU healing time is 3 months [19]. Due to differences in the definition of the subgroups, the groups were followed up from different points in time. DFU episodes with infection were followed for 1 year from the date of the first antibiotic prescription or the admission date of the inpatient diagnosis of an infection. The follow-up period for DFU episodes without infection started from the index quarter for 1 year. For incident DFU episodes with prophylactic antibiotic prescriptions, the follow-up started at the date of the first antibiotic prescription.

TABLE 1 | Selection criteria of incident DFU patients with and without infection, and patients without infection but prophylactic antibiotics.

Group	Criteria	Detailed description of criteria
Group 1: With infection		
Criteria 1 or	Inpatient ICD-10 code infection	Inpatient ICD-10 code of an infection in the index quarter or within three quarters after (at the same time of the DFU diagnosis)
Criteria 2 or	DFU swab and antibiotic prescription	Fee code for DFU swab and antibiotic prescription (both in the same quarter)
Criteria 3	Two antibiotic prescriptions within 30 days	Presence of an antibiotic prescription and a subsequent antibiotic prescription within a maximum of 30 days after the date of the first antibiotic prescription in the outpatient sector
Group 2: Without infection		
Criteria 1	Residual size	All incident DFU cases minus DFU cases with infection
Group 2a: With prophylactic antibiotic prescription		
Criteria 1	Only 1 antibiotic prescription	No inpatient ICD-10 code of an infection, no fee code for DFU swab, antibiotic prescription without a second prescription within 30 days after the first antibiotic prescription

In addition to the 1-year follow-up, all patients were followed until December 31, 2021 to describe long-term outcomes such as mortality and recurrence rates.

To describe the medical burden of DFU comorbidities, complications, recurrence of DFU and mortality were used. Comorbidities include neuropathy, PAD, tumour diseases, kidney and eye diseases as well as heart attacks, strokes, dementia and depression. In addition, the Charlson Comorbidity Index (CCI), which is a weighted index of predefined morbidities [20], was analysed.

The complications investigated were osteomyelitis, wound infections, Charcot foot, sepsis, amputations and infections with methicillin-resistant *Staphylococcus aureus* (MRSA). For a more detailed description of the infections in DFU patients with infection, the mean time to infection was recorded and the number of patients with one or more secondary infection was determined. Time to infection was defined as the number of days from the first day of the index quarter to the day of either the inpatient diagnosis of "infection" or to the day of the first (outpatient) antibiotic prescription made in the same quarter as the swab test.

Individual DFU episodes in the index quarter were analysed for the classification according to Wagner. Therefore, the diagnosis of decubitus ulcers was used, as the severity of DFUs are coded in the German healthcare system under decubitus ulcers. To describe the severity of the DFU, the most widely used Wagner classification was applied (0 = pre- or post-ulcerative lesion, 1 = superficial lesion, 2 = lesion up to tendon or capsule level, 3 = wound down to bone and joint level) [21].

A recurrence of DFU was deemed present if the first DFU episode was followed by at least one other DFU episode. Recurrences of DFU episodes were only recorded for the total population of patients with incident DFU.

The study design was prepared according to the recommendations of the German Society for Epidemiology [22].

2.3 | Statistical Analysis

Absolute and relative frequencies are reported for the number of patients in the study population and subgroups during the index period. Based on these frequencies, prevalence and incidence estimates are expressed as percentages and referred to the index period (04/01/2016–12/31/2019 = 45 months). The 95% confidence intervals (CI) for incidence and prevalence estimates were calculated using the Wilson CI with OpenEpi version 3 [23]. Information on the patient characteristics age and gender refers to the index quarter.

The analysis of comorbidities and complications was based on the respective number of episodes with incident DFU and included the index quarter and the respective follow-up year per episode. Ulcer description according to Wagner classification referred to the respective episodes during the index quarter. The calculation of the mean time to infection related to the individual DFU episodes and included the index quarter as well as the respective subsequent year per episode.

The respective rates for recurrence of DFU and mortality are given cumulatively for each follow-up year. The analysis was based on the number of incident DFU patients.

All outcome measures were reported descriptively as relative and absolute frequencies, minimum, maximum, mean, standard deviation, median and interquartile range (Q25, Q75). Two-tailed *t*-tests or chi-squared tests were used for group comparisons at a significance level of $p < 0.05$. SAS 9.3 was used for these group comparisons.

2.4 | Ethical Approval

There was no ethical committee consultation as the work is based on secondary data. This is in line with the Guideline of Good Practice of Secondary Data Analysis [24].

3 | Results

3.1 | Study Population

3.1.1 | Patient Flow

The database comprised 3 323 506 insured people who were continuously observable between 04/01/2016 and 12/31/2019. During the index period, 393 245 insured persons had a diabetes diagnosis and were aged 18 or older. DFU was present in 18 139 patients with diabetes, of whom 7764 had an incident DFU. These 7764 incident DFU patients had a total of 9021 DFU episodes.

Of the incident DFU patients, 5218 had an infection, corresponding to 6025 DFU episodes. Conversely, 2546 incident DFU patients did not have an infection, corresponding to 2996 episodes. Of the patients without an infection, 922 were prescribed prophylactic antibiotics, representing 1046 episodes.

The patient flow is shown in Figure 1.

3.1.2 | Prevalence and Incidence

In the index period, the prevalence of diabetes mellitus was 11.8% (95% CI 11.80%–11.87%). A total of 4.6% of patients with diabetes were diagnosed with DFU, representing the prevalent DFU patients (95% CI 4.55%–4.68%). The incidence of DFU in patients with diabetes in the database was 2.1% (95% CI 2.03%–2.12).

3.2 | Results of the Total Population of Incident DFU Patients

The mean age of patients with incident DFU was 74.9 years (SD: 11.6). 59.8% of incident DFU patients were male.

Among DFU episodes a classification defined by Wagner or unspecified in the index-quarter occurred in 22%. 40.3% of DFU episodes with Wagner classification were classified as severe (Wagner 2 or 3) and 37.4% were classified as mild (Wagner 0 or 1). In 22.3% of cases, the DFU was not further specified.

The most common comorbidities in incident DFU episodes were neuropathy (75.9%), PAD (54.3%) and its combination (45.3%), renal insufficiency (61.7%) and nephropathy (41.2%).

The mean CCI of incident DFU episodes was 7.9 (SD: 3.0).

Amputations (major: 18.3%; minor 5.1%), osteomyelitis (11.3%) and sepsis (10.9%) were the most common complications in incident DFU episodes. An MRSA infection was diagnosed in 6.5% of the DFU episodes.

In the first year after the first DFU, 10.0% developed a recurrence. After 2 years, the recurrence rate was 22.5% and after 3 years, 42.5%. After 5 years, more than half of patients (53.9%) had a recurrence of DFU.

Eighty-five percent of DFU patients were admitted to hospital within 1 year, staying for 15 days on average. 20.6% of DFU

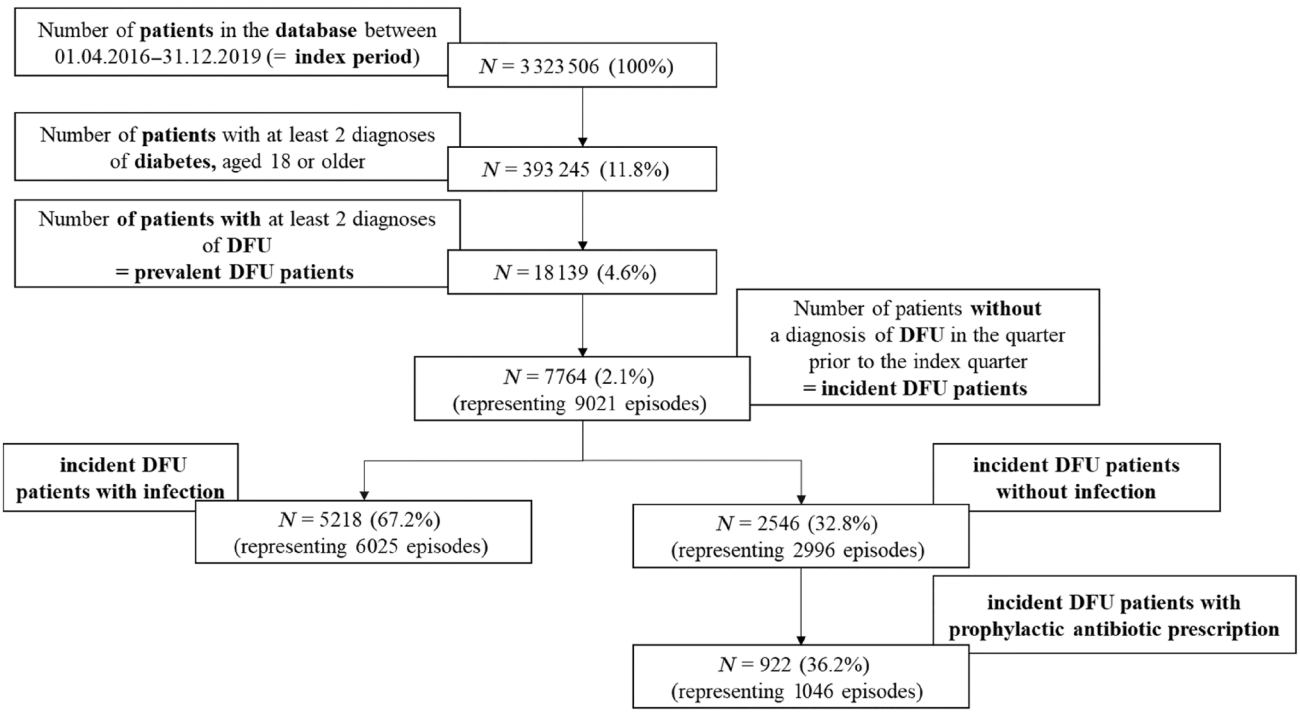


FIGURE 1 | Patient flow.

patients died within 1 year and 60.0% of patients had died within 5 years of follow-up.

3.3 | Results of Incident DFU Patients With and Without Infection

Incident DFU patients with infection were aged 74.8 (SD: 11.3) years on average and did not differ from incident DFU patients without infection (75.2 years, SD: 12.1, $p = 0.153$).

The proportion of male patients was significantly higher in the patients with infection than in the patients without infection (62.3% vs. 55.0%, $p < 0.0001$).

Table 2 summarises the patient characteristics in terms of age and gender.

A differentiated analysis of DFU episodes with diabetic foot ulcer diagnosis according to the Wagner classification was performed more frequently in episodes with infection (25%) compared to episodes without infection (16%) ($p < 0.0001$). The analysis showed that severe courses (Wagner 2 and 3) were significantly more frequently diagnosed in episodes with infection (42.9%) than in episodes without infection (24.5%, $p < 0.0001$). Accordingly, milder courses (Wagner 0 and 1) were significantly more frequently classified in episodes without infection than in episodes with infection (48.5% vs. 36.9%, $p < 0.0001$). In 20% of DFU patients with infection and 27% of patients without infection, unspecified diagnoses of DFUs were identified.

Neuropathy was the most common comorbidity in episodes with incident DFU with or without an infection, with a significantly higher incidence in episodes with an infection than in episodes without an infection (78.7% vs. 68.2%, $p < 0.0001$). There was also a significant difference in the frequency of PAD between DFU episodes with and without infection. PAD was present in 63.1% of DFU episodes with infection and 35.1% of episodes without infection (63.1% vs. 35.1%, $p < 0.0001$). The combined occurrence of neuropathy and PAD was twice as common in DFU episodes with infection than in those without (53.2% vs. 27.6%, $p < 0.0001$). The results are given in Figure 2.

In addition, renal insufficiency and nephropathy were also significantly more common in the infected than in the uninfected DFU episodes (66.9% vs. 50.5%, $p < 0.0001$; 45.2% vs. 31.6%, $p < 0.0001$).

The proportion of episodes with strokes was significantly higher in episodes with infection (20.9%) than in episodes without infection (18.8%; $p = 0.022$). Heart attacks were less frequent compared to the aforementioned comorbidities, but a significant difference was observed between DFU episodes with and without infection (9.1% vs. 7.2%, $p = 0.003$).

The frequencies of comorbidities shown in Figure 3 indicate that there are no significant differences between DFU episodes with and without infection for retinopathy, tumour disease, depression and dementia.

The occurrence of each specific comorbidity is shown in Figure 3.

The mean CCI in DFU episodes with infection was 8.1 (SD: 2.9), significantly higher than the CCI of 7.2 (SD: 3) in episodes without infection ($p < 0.0001$).

Regarding the DFU complications, the differentiation of amputations into minor and major amputations showed that both were performed at significantly higher rates in episodes with infection than in episodes without infection. Minor amputations were

TABLE 2 | Patient characteristics in the index quarter.

	Incident DFU patients		With infection		Without infection		With prophylactic antibiotics	
	N	%	*N*	%	*N*	%	*N*	%
	7764	**100**	**5218**	**100**	**2546**	**100**	**922**	**100**
Age								
18 to < 35	28	0.4	15	0.3	13	0.5	5	0.5
35 to < 50	180	2.3	123	2.4	57	2.2	46	5.0
50 to < 65	1191	15.3	798	15.3	385	15.1	210	22.8
65 to < 80	3290	42.4	2268	43.5	1019	40.0	430	46.6
≥ 80	3075	39.6	2014	38.6	1072	42.1	231	25.1
Ø (SD)	74.9 (11.6)		74.8 (11.3)		75.2 (12.1)		75.2 (12.7)	
Median (IQR)	77 (68–83)		77 (68–83)		78 (68–84)		78 (68–84)	
Gender								
Female	3124	40.2	1970	37.8	1146	45.0	449	48.8
Male	4640	59.8	3448	62.2	1400	55.0	473	51.2

Note: Rounding errors may occur.

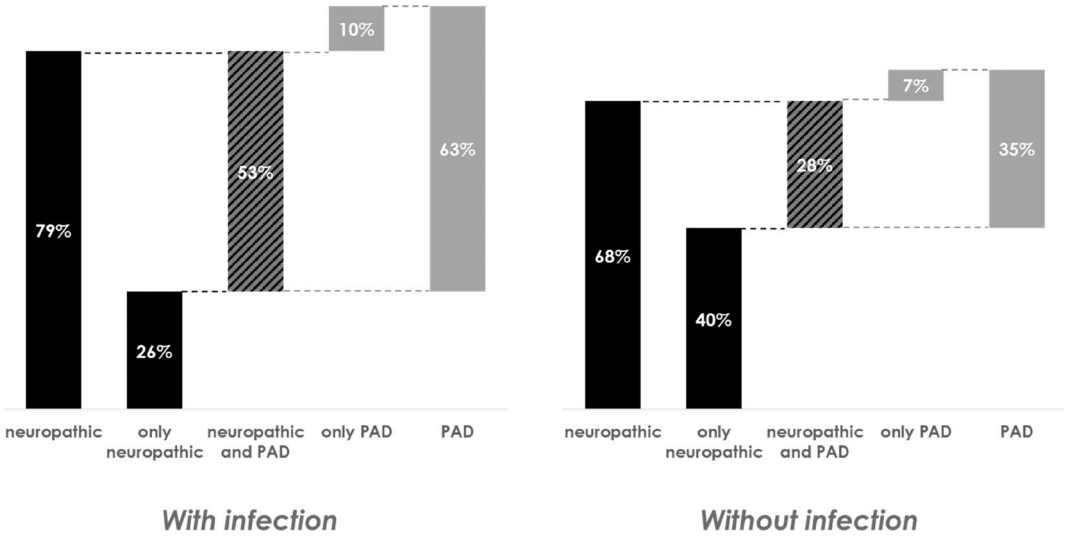
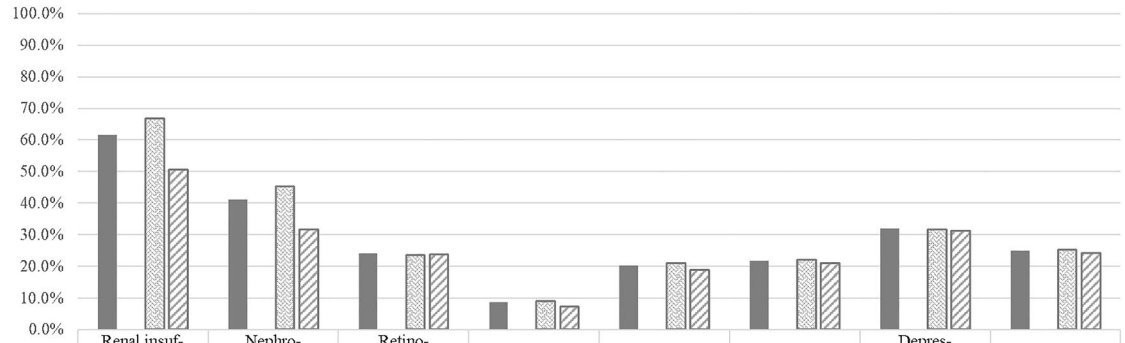


FIGURE 2 | PAD and neuropathy at index quarter and 1-year follow-up.



	Renal insuf-ficiency	Nephro-pathy	Retino-pathy	Heart attack	Stroke	Tumour disease	Depres-sion	Dementia
Incident DFU episodes ($N = 9021$)	61.7%	41.2%	24.1%	8.7%	20.3%	21.8%	31.9%	24.9%
with infection ($N = 6025$)	66.9%	45.2%	23.6%	9.1%	20.9%	22.1%	31.7%	25.2%
without infection ($N = 2996$)	50.5% ***	31.6% ***	23.8%	7.2% **	18.8% *	21.0%	31.2%	24.2%

Chi²-Test for comparison of incident DFS patients with and without infection
*$p < 0.05$; **$p < 0.01$, ***$p < 0.001$

FIGURE 3 | Comorbidities at index quarter and 1-year follow-up.

performed in 25.4% of episodes with infection and in 3.0% of episodes without infection ($p < 0.0001$). Major amputations were performed less frequently in both groups (6.7% of episodes with infection and 1.2% of episodes without infection, $p < 0.0001$).

In the DFU episodes with infection the most common three complications within 1-year follow-up were minor amputations (25.4%), osteomyelitis (16.0%) and sepsis (15.6%). An MRSA infection was diagnosed in 9.2% of the DFU episodes with infection. DFU episodes without infections most often suffered from minor amputations (3.0%), Charcot foot (1.8%) and sepsis/post-traumatic wound infection (both 1.4%). An MRSA infection was diagnosed in 0.9% of the DFU episodes without infection.

Figure 4 displays the occurrence of the analysed complications.

In patients with incident DFU with infection, 38.9% had a second infection, the mean time to infection in episodes with infections being 37.9 days (SD: 25.9).

Ninety-three percent of the incident DFU patients with infection were admitted to hospital within the observation period compared to 67% of the incident DFU patients without infection. DFU patients with infection stayed on average for 16 days compared to 10 days in patients without infection. In incident DFU patients with infection, 25.0% died within the first year and 64.0% within 5 years of follow-up. The number of deaths within both 1 year and within 5 years was significantly higher in patients with infection compared to patients without infection (first year 25.0% vs. 13.7%, $p < 0.0001$; fifth year 64.0% vs. 51.3%, $p < 0.0001$).

3.4 | Results of Incident DFU Patients Without Infection and With Prophylactic Antibiotic Prescription

Patients without an infection and a prophylactic antibiotic prescription represent a subgroup of patients without an

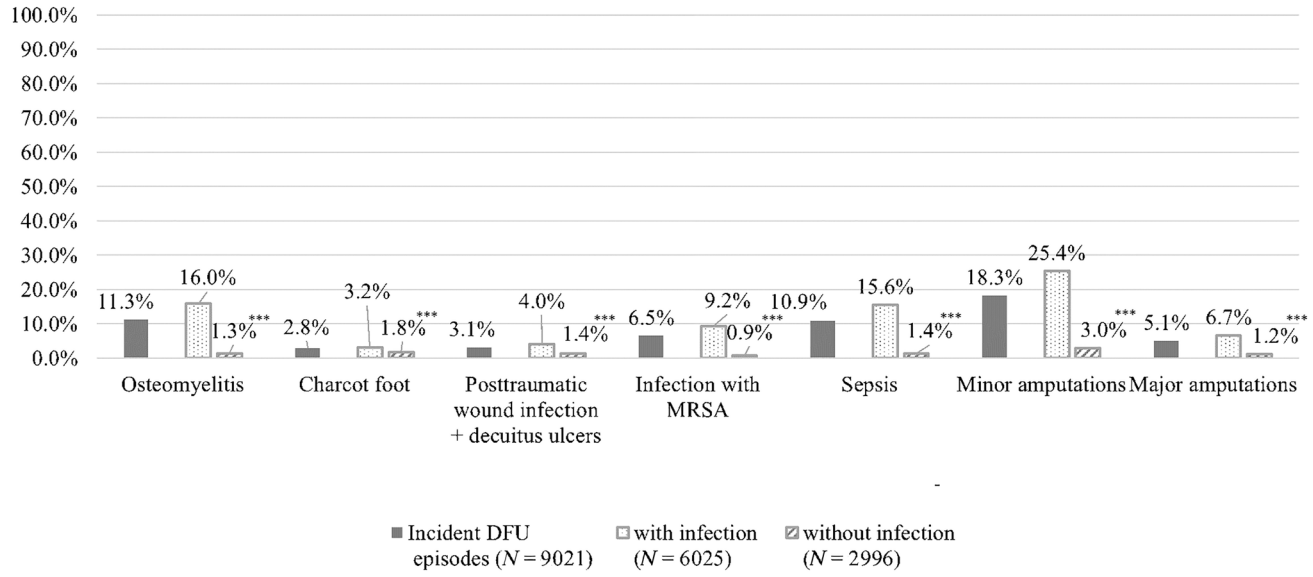


FIGURE 4 | Complications at index quarter and 1-year follow-up.

infection. 36.2% (922 of 2546) of incident DFU patients without infection received prophylactic antibiotics. The mean age of DFU patients with prophylactic antibiotics was 75.2 (SD: 12.1) years, and the proportion of men was 51%. Although the proportion of male patients was higher than in DFU patients without infection (proportion of men 55%), the difference was not significant ($p = 0.051$).

A differentiated analysis of DFU episodes with diabetic foot ulcer diagnosis according to the Wagner classification occurred in 12% of the episodes with a prophylactic antibiotic prescription. The proportion of DFU episodes with a classification according to Wagner 0 and 1 was 48.6% for episodes with a prophylactic antibiotic prescription and 16.2% according to Wagner 2 and 3. The DFU diagnosis was not further specified in 35.2% of episodes with prophylactic antibiotic use. In comparison, the proportion of DFU episodes with a classification with a mild course (Wagner 0 and 1) in the group of episodes without infection was 48.5% ($p = 0.983$) and the proportion of severe cases (Wagner 2 and 3) was 24.5%, significantly higher than in the group receiving prophylactic antibiotics ($p = 0.035$).

No significant differences in the occurrence of comorbidities were found between the episodes without infection and the subgroup with prophylactic antibiotic prescription. As most frequent comorbidities, 65.9% of patients with antibiotic prophylaxis had neuropathy and 34.9% had PAD, compared with 68.2% and 35.1%, respectively, in the group of episodes without infection (neuropathy $p = 0.168$, PAD $p = 0.898$). Renal insufficiency was present in 52.2% of patients with a prophylactic antibiotic prescription, compared to 50.5% of DFU patients without infection ($p = 0.177$).

Similarly, the occurrence of complications was comparable. Minor amputation was performed in 2.5% of DFU episodes with a prophylactic antibiotic prescription, which did not differ significantly from the comparison group of patients without infection (3.04%, $p = 0.361$). As fewer than five episodes with prophylactic antibiotic prescription resulted in a major amputation, it is not possible to give an exact number for reasons of anonymity, nor can it be compared with episodes without infection. Sepsis was documented in 1.7% of episodes with prophylactic antibiotic therapy, osteomyelitis in 2.2% and MRSA infection in 1.0%. There were no significant differences compared with episodes without infection in general (sepsis 1.7% vs. 1.4%, $p = 0.417$; osteomyelitis 2.2% vs. 1.3%, $p = 0.054$; MRSA infection 1.0% vs. 0.9%, $p = 0.790$).

Sixty-four percent of incident DFU patients without infection but prophylactic antibiotic prescription were admitted to hospital within 1 year, staying for 10 days on average. Mortality was higher in patients with prophylactic antibiotic prescriptions than in patients without infection at 1 and 5 years, although no significant difference was found (1-year follow-up 18.1% vs. 13.7%, $p = 0.112$; 5 year follow-up 52.7% vs. 51.5%, $p = 0.725$).

4 | Discussion

4.1 | Summary

This study was designed to determine the number of incident DFU patients and defined subgroups and to describe their patient characteristics as well as the medical burden of DFU. Based on data from 3.3 million insured patients in Germany, our analysis revealed a prevalence of DFU of 4.6% and an incidence of 2.1% among patients with diabetes mellitus. DFU showed a high medical burden, represented by a high CCI, occurrence of comorbidities and complications, particularly high rates of amputations, osteomyelitis, sepsis and a high mortality. Comorbidities

and complications are more common in DFU patients with infection than in those without, as demonstrated by higher CCI and mortality.

4.2 | Comparison With Other Studies

At 4.6%, the prevalence of DFU among patients with diabetes in the data study was lower than the prevalence of 6.6% in a study based on insurance data from all SHI funds of Germany in 2013 [2]. Bohn et al. showed a prevalence of DFU of 9.4% in patients with diabetes using data from a "standardised multicentre diabetes follow-up register (DPV)", which includes specialised diabetes centres in Germany, Austria, Switzerland and Luxembourg [3]. To assess the epidemiology of DFU worldwide, Zhang et al. conducted a meta-analysis. They reported a global prevalence of 6.3% (95% CI: 5.4%–7.3%) and a European prevalence of 5.1 (95% CI: 4.1%–6.0%) [25]. Compared with the studies cited, the prevalence in this data study is the lowest, but comparable with national (German) and international findings. The differences in prevalence rates between the studies mentioned could be due to the different settings of the studies. Therefore, the prevalence of specialised centres and the DPV register [3] is expected to be higher.

A total of 67% (5128 out of 7764) of DFU patients had an infection. Comparable current data based on a large, representative population as in this study are not known for Germany. Internationally, it is assumed that 50%–60% of patients with DFU will develop an infection [1, 10, 26], which is slightly lower proportion in comparison with our results. Additionally, a coding or specification of the diagnosis DFU into infected and non-infected is not always intended or available in the documentation structures of healthcare systems.

36.2% of the DFU patients without an infection had a prescription for prophylactic antibiotics. Current guidelines, as the IWGDF/IDSA Guidelines (2023) [13], do not recommend the use of prophylactic antibiotics in uninfected foot ulcers. Given our data, about one-third of all patients without an infection had a prescription for prophylactic antibiotics, this shows that the current guidelines [4, 9, 13] are not being implemented in clinical practice in the outpatient setting. In parallel, a study by Serena et al. revealed that 23.2% of patients with chronic wounds received oral antibiotics despite the absence of clinical infection symptoms or signs [16]. To tackle the pressing challenge of antimicrobial resistance and enhance patient outcomes, it is imperative to conduct further research assessing the utility of prophylactic antibiotics. Principles of antibiotic stewardship—a strategy for a thoughtful antibiotic use—in persons with infection should be raise more awareness to avoid the risk of developing resistance to common pathogens. Additionally, prioritising education, fostering awareness and implementation of guidelines are essential [16, 17].

In terms of comorbidities, the occurrence of PAD (54.3%) in this data study is consistent with the literature. Azhar et al. conducted a prospective cross-sectional study to investigate the prevalence of PAD in patients with DFU and showed comparable results. Among the 392 DFU patients included in the study, 43.9% had PAD [27]. Bohn et al. reported a prevalence of neuropathy of 59.4% in patients with Type 2 diabetes [3] which is lower than the prevalence of 75.9% in the data study. The different settings of the studies may explain this difference, as the study by Bohn et al. includes specialised diabetes centres that may treat more severe cases with a higher rate of comorbidities. As neuropathy with associated loss of protective sensitivity and PAD are risk factors for foot ulcers, the IWGDF recommends regular foot screening and early and appropriate treatment to prevent progression and complications. In addition, the IWGF recommends that patients be educated about foot care and encouraged to check their feet regularly [8]. The high rate of patients with neuropathy or PAD underlines these risk factors and highlights the importance of prevention.

To complement the exploration of such physical comorbidities, a systematic review by Westby et al. examined behavioural and psychological factors associated with the development and healing of foot ulcers. They concluded that the presence of depression can increase the risk of foot ulcers [28]. The high prevalence of depression in the data study, which was 31.9%, underlines the importance of depression in patients with DFU and is in line with the literature. Jiang et al. conducted a meta-analysis of the prevalence of depression in people with DFU and reported a prevalence of 37% (95% CI: 23%–51%) in Europe [29]. To address the risk factor of depression as a significant barrier to diabetes self-management, patients with DFU should be screened for depression to support self-management [30].

In addition to the defined comorbidities, the CCI was calculated as a weighted index of morbidity, which averaged 7.9 for the DFU episodes. This is in line with the literature. In a study based on individual DFU episodes, Petersen et al. analysed data from the Medicare Limited Data Set between 2013 and 2019. They reported that the CCI at the beginning of a first DFU episode was 6.0, while the CCI at the end of a first DFU episode increased to 7.3 [31]. The importance of comorbidities in patients with DFU is evident when compared to patients with diabetes in general. Lopez et al. calculated the CCI for patients with diabetes Type 2 using data from the 2012 US National Health and Wellness Survey (NHWS). A mean CCI of 1.8 was calculated for patients with Type 2 diabetes aged 65–74 years and for patients aged 75 years and older [32]. A comparison with lung cancer, a serious disease that is most common in the elderly with multiple comorbidities, further highlights the level of comorbidity in patients with DFU. Bossert et al. determined a mean CCI of 6.7 for incident lung cancer patients based on German SHI claims data from 2013 to 2017 [33] which is comparable with the CCI of DFU.

In addition to the high frequency of comorbidities, the occurrence of complications demonstrates the high burden of DFU. Amputations were the most common complication of DFU episodes in the data study (minor 18.3%, major 5.1%). They were more common in patients with infection (minor 25.4%, major 6.7%) compared to patients without an infection (minor 3.0%, major 1.2%).

This distinction between infected and non-infected DFU, made for the first time in Germany based on a large, representative dataset, suggests that infections are associated with subsequent amputations. Additionally, Jeong et al. showed that a significant predictor of lower extremity amputation in hospitalised patients

with DFU was comorbid infection. This significantly increases the odds of amputation (OR 11.39, 95% CI: 2.55%–50.93%) [34] and may explain the difference in amputation rates between incident DFU episodes with and without infection in the study population. Musuuza et al. showed in a systematic review that multidisciplinary teams providing timely, coordinated and appropriate glycaemic control, wound care and infection control can reduce major amputations in patients with DFU [35].

If infections occur and are not treated appropriately, there is a risk that the infection will spread and lead to osteomyelitis or sepsis. As 16% of DFUs with infection developed osteomyelitis and 16% developed sepsis, this suggests that a significant proportion of patients had an advanced course of DFU that was likely to end in amputation [9, 36]. Nine percent of infected DFUs had MRSA infection, which is also associated with poorer healing and a higher likelihood of amputation [37, 38]. This underlines the importance of appropriate therapy to avoid complications such as infection and amputations.

Interestingly, osteomyelitis, sepsis and MRSA infection also occurred in the group of DFU episodes without infection, which by definition should not be expected. The presence of neuropathy and PAD can mask the clinical signs and symptoms of infection [36, 39, 40]. Therefore, this data indicates that infections have gone undetected and point out the difficulties in a correct diagnosis of infection. However, we cannot rule out that also other complications might have caused the sepsis.

The 5-year all-cause mortality of patients with incident DFU in the study population was 60%, comparable to the findings of Chen et al. They conducted a meta-analysis to determine the 5-year mortality of patients with DFU, which was 50%, with patients with amputations having a higher risk of mortality [41]. As infections are a major risk factor for amputation [12], the higher mortality risk associated with amputation highlights the importance of preventing or treating infections early.

Comparing the mortality rate of patients with DFUs with that of patients with diabetes but without ulcers, the impact of DFUs on mortality is evident. According to a meta-analysis by Saluja et al., DFUs were associated with a twofold increased risk of all-cause mortality compared with diabetic patients without ulcers [42]. A comparison with the 5-year mortality rate of the German reference population also illustrates the impact of DFU on mortality. This was 17.2% for the German male population at an average age of 72 years [43].

4.3 | Strengths and Limitations

This study's robustness stems from a large and representative data pool of 3.3 million insured patients, providing a comprehensive overview of DFU patients and their medical burden. Stratification of patients with incident DFU into those with and without infection and those taking prophylactic antibiotics or not allows differentiation, which is important for designing individualised healthcare interventions.

In addition to these strengths, there are also limitations. The main limitation of these data is that they are retrospective and may be subject to administrative and reporting bias. In addition, coding restrictions or data entry errors are possible, which could lead to misclassification and miscoding. First, there is no code for an infected DFU. Clinical symptoms that indicate an infection (local swelling, erythema (>0.5 but <2 cm), pain, local increased warmth, purulent discharge)—that are also used for the clinical diagnosis of an infection regarding the IWGDF/IDSA guidelines [13]—are not available in the claims database as they are not relevant for reimbursement. Second, classification within the outpatient sector is limited to Wagner classification, which not contains a distinguishment between infected and non-infected DFUs as other classification systems, for example, Wagner–Armstrong. Furthermore, the patients without infection and the subgroup with a prophylactic antibiotic prescription may include low-grade infections that were not medically proper documented and required microbiological cultures prior to antibiotic treatment were not conducted. Reasons could include limited time and lack of knowledge. Therefore, the subgroup with prophylactic antibiotic prescription needs to be carefully considered and might present also low-grade infections. Additionally, we cannot rule out the possibility that antibiotics were required for managing other medical conditions. Consequently, these cases might also be included in the group without infection. We also do not have any reasons given in the database why patients are treated with prophylactic antibiotic prescriptions. Furthermore, only billable services are recognised, which can lead to an undervaluation of unbilled services. Due to the reimbursement system in Germany, only antibiotic prescriptions from the outpatient sector were included, patients with antibiotics given in the hospital sector could therefore not be included in the group "with prophylactic antibiotics".

Comparability of study results with existing literature may be confounded by differences in setting, length of observation period, duration and severity of illness and different definitions of comorbidities and complications. As there was no demographic information on diabetes duration or quality of diabetes adjustment, education, income, lifestyle or adherence to medical instructions in the data, these covariates were not included in the analysis (unmeasured confounding). Finally, prevailing systemic factors and incentives, such as absolute and relative remuneration—for example, of "efficient" amputations compared to lengthy wound management episodes—may play a role in real-world outcomes, which our study could not account for.

5 | Conclusion

In summary, the study provided current data on the prevalence and incidence of DFU patients with and without infections and with prophylactic antibiotic prescription. The high incidence of comorbidities and complications, as well as the high mortality rate in patients with DFU in general and with infections in particular, indicate a high medical burden of the DFU. The data indicate that prophylactic use of antibiotics, while not guideline-compliant, is still practiced and should be replaced by early-onset prevention strategies. To slow the progression of DFU and prevent serious complications such as amputations, patient education, early alert systems, bespoke prevention strategies are essential to improve patient health and avoid rather impactful and costly complications or even premature death. Particular,

the higher rates of complications of infected DFU ulcer compared to non-infected DFU emphasise an early and appropriate treatment of DFU to prevent infection and the accompanying burden. On a system level, prevailing incentive structures need to be monitored carefully to encourage interventions in the best interest of the patient.

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Conflicts of Interest

T.V. is owner and employee; and M.K. is an employee of LinkCare GmbH, which receive consulting honoraria BSN medical GmbH (Essity Group). Y.Z. has served as a paid consultant to BSN medical in the past. J.W. received consulting fees for the support of the data analysis from BSN medical GmbH (Essity Group). O.E. and B.S. are employees of BSN medical GmbH (Essity Group).

Data Availability Statement

Research data are not shared.

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Appendix.

Important details.

1. Relevant ICD codes for selection of study population

Classification	ICD-code
Diabetes mellitus	E10, E11, E12, E13, E14
Diabetic foot syndrome	E10.74, E10.75, E11.74, E11.75, E12.74, E12.75, E13.74, E13.75, E14.74, E13.75

2. Relevant codes for the selection of incident DFU with infection

Classification	ICD-code
Infection	A49.9, T79.3, B95, B96, B99, L02, L03, L04, L08, U80–U85, U80.00, A40, A41, Z29.28, A46, M86, T87.4
	Codes of office-based medical treatments and procedures
MRSA swab	30940, 30950, 32726, 32727
Microbial examination	32151, 32750, 32775, 32774, 32760, 32761, 32762, 32763, 32707, 32759

3. Relevant ATC codes for selecting patients with DFU for prophylactic antibiotics

Classification	ICD-code
Antibiotics	J01A, J01B, J01C, J01D, J01E, J01F, J01G, J01M, J01R, J01X, J02A

4. Relevant ICD codes to select population with DFU classification according to Wagner

Classification	ICD-code
Decubitus (Wagner 0)	L89.07, L89.08
Decubitus (Wagner 1)	L89.17, L89.18
Decubitus (Wagner 2)	L89.27, L89.28
Decubitus (Wagner 3)	L89.37, L89.38
Decubitus (not further defined)	L89.98, L89.99

5.Relevant ICD codes for selection of defined comorbidities

Classification	ICD-code
PAD	I70.2
Neuropathy	G60, G61, G62, G63, G64
Renal insufficiency	N17, N18, N19
Nephropathy	N07, N08.3, I12
Retinopathy	H35.0, H35.1, H35.2, H36.0, H36.8, H31.0
Heart attack	I21, I22
Stroke	I63, I64, I69.3, I69.4
Tumour disease	B21, C00–C97
Depression	F32, F33, F06
Dementia	F00, F01, F03

6.Relevant ICD-codes for determining the Charlson Comorbidity Index

Classification	ICD-code
Heart attack	I21*, I22*, I25.2*
Heart failure	I43*, I50*, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8*, I42.9, P29.0
Peripheral vascular diseases	I70*, I71*, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8*, K55.9, Z95.8*, Z95.9
Cerebrovascular diseases	G45*, G46*, I60*, I61*, I62*, I63*, I64*, I65*, I66*, I67*, I68*, I69*, H34.0
Dementia	F00*, F01*, F02*, F03, F05.1, G30*, G31.1
Chronic obstructive pulmonary disease	J40, J41*, J42, J43*, J44*, J45*, J46, J47, J60, J61, J62*, J63*, J64, J65, J66*, J67*, I27.8, I27.9, J68.4, J70.1, J70.3
Rheumatic diseases	M05*, M06*, M31.5, M32*, M33*, M34*, M35.1*, M35.3, M36.0
Diseases of the stomach and duodenum	K25*, K26*, K27*, K28*
Mild liver disease	B18*, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73*, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4
Diabetes without complications	E10.0*, E10.1*, E10.6*, E10.8*, E10.9*, E11.0*, E11.1*, E11.6*, E11.8*, E11.9*, E12.0*, E12.1*, E12.6*, E12.8*, E12.9*, E13.0*, E13.1*, E13.6*, E13.8*, E13.9*, E14.0*, E14.1*, E14.6*, E14.8*, E14.9*
Diabetes with complications	E10.2*, E10.3*, E10.4*, E10.5*, E10.7*, E11.2*, E11.3*, E11.4*, E11.5*, E11.7*, E12.2*, E12.3*, E12.4*, E12.5*, E12.7*, E13.2*, E13.3*, E13.4*, E13.5*, E13.7*, E14.2*, E14.3*, E14.4*, E14.5*, E14.7*
Hemiparesis and hemiplegia	G81*, G82*, G04.1, G11.4, G80.1, G80.2, G83.0, G83.1, G83.2, G83.3, G83.4*, G83.9
Renal insufficiency	N18*, N19*, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N25.0, I12.0, I13.1, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2
Cancer	C00*–C26*, C30*–C34*, C37*–C41*, C43*, C45*-C58*, C60*–C76*, C81*, C82*, C83*, C84*, C85*, C88*, C90*, C91*, C92*, C93*, C94*, C95*, C96*, C97*

Classification	ICD-code
Moderate to severe liver disease	K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7, I85.0, I85.9, I86.4, I98.2
Metastasising carcinoma	C77*, C78*, C79*, C80*
AIDS/HIV	B20, B21, B22, B24

7.Relevant codes for selection of defined complications

Classification	ICD-codes
Osteomyelitis	M86
Posttraumatic wound infection and ± decubitus	T79.3 and L89
Charcot foot	M14.6
Sepsis	A40, A41
Classification	**ICPM-codes**
Infection MRSA	8-987
Minor amputations	5-865.0, 5-865.1, 5-865.2, 5-865.3, 5-865.4, 5-865.5, 5-865.6, 5-865.7, 5-865.8. 5-865.9, 5-865.x, 5-865.y
Major amputations	5-864.0, 5-864.1, 5-864.2, 5-864.3, 5-864.4, 5-864.5, 5-864.6, 5-864.7, 5-864.8, 5-864.9, 5-864.a, 5-864.x, 5-864.y, 5-869.0