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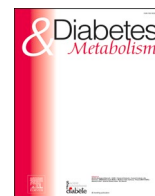
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Original article

Incidence of death and amputation in patients with a first diabetic foot ulcer: results from the CODIA cohort



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ABSTRACT

Aim: - To investigate the incidences of death and lower limb amputation (LLA) among patients hospitalized with a first diabetic foot ulcer and to identify the associated risk factors.

Methods: - We leveraged medical records from 08/2017 to 10/2023 in the clinical data warehouse of the Greater Paris Hospitals. The primary outcome was the cumulative incidence of death estimated at 12 months. We used Kaplan-Meier and Aalen-Johansen estimators to assess the incidence of death and LLA (identified through ICD-10 codes). We used multivariate Cox regression and Fine and Gray models to estimate risk factors (clinical/biological data, medications, and comorbidities at baseline) for death and LLA, accounting for death as a competing event.

Results: - 3102 patients were included; the median age was 70.66 years and there were 67.64% males. The cumulative incidence of death at 12 months was 21.64% [95%CI 20.11;23.26]. Mortality risk was associated with older age, chronic cardiac, hepatic, or renal diseases, cancer history, and systemic inflammation, whereas being overweight was linked to lower mortality. The cumulative incidence of LLA at 12 months was 24.15% [22.54;25.79]. Risk factors for LLA included male sex, history of peripheral artery disease, emergency admission, and systemic inflammation markers, while dementia was associated with a lower risk.

Conclusion: - Cumulative incidences of all-cause mortality and LLA during the months following hospitalization with a first diabetic foot ulcer were alarmingly high. Mortality risk was primarily associated with patient comorbidities, while amputation risk was closely associated with systemic inflammation and history of peripheral artery disease.

Introduction

Diabetic foot ulcers (DFUs) are one of the most severe complications of diabetes, affecting millions of individuals worldwide [1]. These chronic wounds often lead to significant morbidity and are associated with heightened risks of lower limb amputation (LLA) and mortality [2–5]. Despite advances in medical care, DFUs remain a critical concern, accounting for a large proportion of hospitalizations and healthcare

costs related to diabetes [6,7]. For example, in the USA in 2017, one-third of the \$237 billion spent due to diabetes was for DFUs — more than the direct costs associated with cancer in the USA in 2015 [8]. The complexity of these wounds, driven by neuropathy, ischemia, and infection, underscores the need for a deeper identification of the factors associated with poor outcomes, such as death and limb loss [9].

The risks of LLA and all-cause mortality among patients with DFUs are multifactorial. Peripheral artery disease (PAD), infection severity,

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and delayed wound healing have been described as the strongest predictors of amputation [10–15]. Risk of mortality in this population is also influenced by systemic factors such as cardiovascular disease, renal impairment, and advanced age [9,16], which often coexist in patients with DFUs. These complications are compounded by the fact that DFUs frequently recur [4,17], further exacerbating the long-term risk of poor outcomes [4].

In recent years, electronic health records (EHRs) have emerged as powerful tools for producing large datasets. Unlike traditional research approaches, which are often constrained by limited sample sizes or patient selection, EHRs provide access to real-life, longitudinal patient data collected across diverse healthcare services. This allows researchers to examine rare events, and generate insights that are more reflective of clinical realities. Furthermore, the integration of various data sources within EHRs systems, from medical records and laboratory to medication data, enables a comprehensive exploration of both outcomes and their associated risk factors [18–22].

Using the clinical data warehouse of the Greater Paris Hospitals (AP-HP CDW), we investigated the real-life cumulative incidences of all-cause mortality and LLA among patients with DFUs, and also searched to identify the associated risk factors.

At one-year follow-up, we found that one-fifth of patients were dead and one-fourth of patients had LLA.

Methods

Study design

This retrospective cohort study was conducted in the CODIA cohort (COHort DIAbetes) using data from the AP-HP CDW. Briefly, the CODIA cohort includes all presumed patients living N with diabetes, see **Supplementary Method 1 (see supplementary materials associated with this article on line)** for inclusion criteria. In the study reported here, we included all adult diabetic patients of the CODIA cohort hospitalized with a first episode of DFU. The inclusion period spanned from March 1st, 2020, to April 1st, 2023, and the observation period ended on October 1st, 2023, to allow a potential 6-month follow-up for all patients. We have used data since the launch of the AP-HP CDW, August 2017, for covariate creation.

We estimated the cumulative incidence of all-cause mortality and LLA (accounting for the competing risk of death) from the date of hospital admission over a 36-month period, as well as the risk factors associated with death and LLA. The index date for analyses was defined as 48 h after hospital admission with a code for DFU to ensure enough time for covariates identification and avoid immortal time bias as coinciding with eligibility assessment and start of follow-up.

Patients were followed from the index date until outcome of interest, death (if outcome was LLA), loss to follow-up (LTFU), or October 1st, 2023, whichever occurred first (**Supplementary Figure 1; see supplementary materials associated with this article on line**).

The reporting of the study follows the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) [23], available in **Supplementary Method 2 (see supplementary materials associated with this article on line)**.

Data sources

CODIA includes all subjects living with diabetes in the AP-HP CDW [24], which hosts data from more than 19 million patients across 38 university hospitals in the Greater Paris area, collected since 2017.

The data are structured in OMOP format tables, and contain the following variables: demographic data, diagnostic codes (main, associated, and related diagnostics, using the International Classification of Diseases, 10th edition, ICD-10), procedure codes (*Classification Commune des Actes Médicaux*, CCAM), in-hospital structured biological results, consultation and hospitalization dates. Additional information

was present as unstructured data from medical reports text: biological results, drug regimen, body mass index (BMI), tobacco and alcohol consumption. This information was extracted from medical notes using natural language processing (NLP) algorithms to identify and qualify entities [25,26], we then mapped them to referential (**Supplementary Method 3; see supplementary materials associated with this article on line**). Further variable preprocessing, such as aggregation and normalization rules, are provided in **Supplementary Method 4 (see supplementary materials associated with this article on line)**.

Mortality data come from in-hospital mortality data and national vital status data [27]. National mortality data are linked to the AP-HP CDW using deterministic matching.

Study population

Inclusion criteria

Eligible patients were adult patients (aged 18 years or older) with diabetes hospitalized with a first episode of DFU at AP-HP (index hospitalization) and alive 48 h after admission. Diabetes and foot ulcer diagnoses were identified using ICD-10 codes (**Supplementary Method 5; see supplementary materials associated with this article on line**), which reflect both the diversity of lesion types and locations and the variability in coding practices across hospital departments. Patients were included if they had at least one DFU ICD-10 code as a principal diagnosis code for hospitalization but also if DFU codes were labeled as associated or related codes to hospitalization since the principal code does not always reflect the reason for hospitalization in the French system. “First DFU” was defined as the first occurrence of an ICD-10 code related to DFU identified since 2017. To validate this definition, 100 hospital discharge summaries from 100 different patients were randomly selected from the initial cohort and reviewed by an experienced diabetologist, who did not identify any prior history of DFU in the clinical text that had been missed by the ICD-10 code-based approach.

The index date was defined as 48 h after hospital admission, which allowed to collect information at inclusion while mitigating immortality bias. Clinically, this approach also helped exclude moribund patients and those admitted solely for the amputation procedure but followed or hospitalized outside of the AP-HP system.

Exclusion criteria

We excluded patients with a history of LLA before index hospitalization, in palliative care or who had a foot stump before index hospitalization. See *Outcome measures* section for LLA definition.

Outcome measures

The primary outcome was the cumulative incidence of death (all-cause mortality) estimated at 12 months from the index date.

Secondary outcomes were the cumulative incidence of death over the 36 months from the index date, with incidence rates reported at different times of interest, namely at 1 and 2 weeks, and at 1, 2, 3, 6, 9, 18, 24, 30 and 36 months.

Other secondary outcomes were the cumulative incidence of LLA (accounting for the competing risk of death) over the 36 months following index date, with incidence rates reported at 1 and 2 weeks, and at 1, 2, 3, 6, 9, 12, 18, 24, 30 and 36 months.

LLA was identified using specific CCAM procedure codes for amputations, including toe amputation, ankle or hindfoot amputation, transtibial amputation, transfemoral amputation, and partial foot amputations such as disarticulation of several toes, as well as medial or forefoot amputation with or without hindfoot stabilization. More details on the definition of exclusion codes can be found in **Supplementary Method 5 (see supplementary materials associated with this article on line)**.

Minor amputations were defined as removal of toes or parts of the foot up to the ankle, whereas major amputations referred to those

occurring above the ankle. The corresponding CCAM procedure codes are listed in **Supplementary Method 5 (see supplementary materials associated with this article on line)**.

Definition of baseline characteristics

Biological results (Supplementary Method 4; see supplementary materials associated with this article on line)

A three-month look-back period from the index date was used to extract data regarding HbA1c. We considered the last available HbA1c per patient up to the first 48 h of hospitalization. The maximum HbA1c per patient up to one year from the index date was also considered. Structured data and unstructured ones from medical notes were used.

All other laboratory data considered were those available during the first 48 h of hospitalization.

Medication (Supplementary Method 4; see supplementary materials associated with this article on line)

The history of treatments was extracted from the entire available medical history (up to August 2017) and up to the first 48 h of hospitalization. Treatments were extracted using NLP in medical notes.

Medical history (Supplementary Method 4; see supplementary materials associated with this article on line)

The history of comorbidities was extracted from the entire available medical history and up to the first 48 h of hospitalization. Comorbidities were identified using ICD-10 codes. Alcohol and tobacco usage were extracted using NLP in medical notes. We assumed that if we did not retrieve information about a condition, the patient did not have it.

Others (Supplementary Method 4; see supplementary materials associated with this article on line)

A one-year look-back period from the start of the inclusion period, up to the first 48 h of hospitalization was used to extract data regarding BMI using NLP in medical notes, and then categorized as “overweight or obese” ($> 25 \text{ kg/m}^2$) or not.

Statistical analyses

Categorical variables are presented as the number of participants with the corresponding percentage. Continuous variables are expressed as median (IQR). To avoid excluding patients from the analysis due to incomplete biological results, and considering missingness is informative (not missing at random), a categorical approach was chosen, with one of the categories being “missing data”. For example, for monocytes, three categories were defined: “missing data”, “ $< 0.5 \text{ G/l}$ ”, and “ $\geq 0.5 \text{ G/l}$ ”. More detail can be found in (**Supplementary Method 4; see supplementary materials associated with this article on line**).

The index date was 48 h after hospitalization admission with a first episode of DFU.

The Kaplan-Meier estimator was used to estimate the cumulative incidence of death. The Aalen-Johansen estimator was used to estimate the cumulative incidence of LLA, accounting for the competing risk of death.

Risk factors associated with death were identified with a multivariate Cox proportional hazards model, based on demographics, biological results at inclusion, medication, clinical history.

Risk factors associated with LLA were identified with a multivariate Fine and Gray regression model. We also reported risk factors for LLA identified with a cause-specific (accounting for the competing risk of death) multivariate Cox proportional hazards model, see (**Table S1; see supplementary materials associated with this article on line**).

The complete list of covariates used in the models can be found in **Supplementary Method 4 (see supplementary materials associated with this article on line)**. Repartition of categories for biological results and BMI can be found in (**Table S2; see supplementary materials associated with this article on line**). We verified the proportional hazards assumption using Schoenfeld residuals.

Analyses were performed with Python 3.7 using package lifelines

version 0.27.8, EDS-NLP [28] version 0.12.3 and EDS-Scikit [29] version 0.1.7. Fine and Gray was implemented using R version 4.3.1 and package cmprsk version 2.2.12.

Institutional review board approval

Our study was reviewed and approved by the institutional review board of AP-HP (IRB00011591, decision CSE 21–37). French regulation does not require the patient’s written consent for this kind of research, but in accordance with the European General Data Protection Regulation, the patients were informed of the secondary use of their data for research and those who opposed were not included in the study. Data were pseudonymized by replacing names and places of residence by aliases [30].

Results

Study population

A total of 3102 patients met the eligibility criteria between March 2020 and April 2023 with a first DFU and were included (as detailed in the flowchart presented in **Figure S2 (see supplementary materials associated with this article on line)**). This cohort comprised a majority of men (67.64 %), with a median age of 70.66 years; 8.79 % had type 1 diabetes and 91.21 % type 2 diabetes. Other baseline characteristics are presented in **Table I**. The total follow-up duration was 2639.57 patient-years and the median follow-up was 486 days. Within the first 48 h of hospitalization, 20 of these 3102 patients passed away, and 172 underwent amputation.

The median duration of hospitalization was 12.90 days, with 11.17 days [Q1-Q3: 5.15–20.96 days] for patients without LLA during hospitalization ($n = 2560$, 82.53 %) and 23.09 days [Q1-Q3: 12.77–38.82 days] for patients with LLA during hospitalization ($n = 542$, 17.47 %) (**Figure S3; see supplementary materials associated with this article on line**). During the index hospitalization, minor amputation occurred for 437 (14.09 %) patients and major amputation for 70 (2.26 %) patients, accounting for amputations in the first 48 h.

The majority (58.76 %) of patients were discharged home, while other discharge modalities included follow-up care and rehabilitation (22.85 %), transfer to another unit (11.66 %), and death during hospitalization (6.70 %). Among patients who did not undergo amputation, the majority were discharged home (61.41 %) compared to those who underwent amputation (46.31 %). Conversely, a higher proportion of amputated patients were discharged to follow-up care and rehabilitation services (35.61 %) compared to non-amputated patients (20.16 %) (**Figure S4; see supplementary materials associated with this article on line**).

Cumulative incidences

The cumulative incidence curves for mortality and LLA are presented in **Figs. 1A and 1B**. At 1 month, 6 months, and 12 months, the cumulative incidence of death was 6.05 %, 16.50 %, and 21.64 %, respectively. The cumulative incidence of LLA was 15.37 % at 1 month, 21.61 % at 6 months, and 24.15 % at 12 months. Additional time points and details are available in (**Table S3; see supplementary materials associated with this article on line**).

Risk factors for mortality and for LLA

In our cohort, risk factors for mortality were older age (HR 1.04 [95 %CI 1.03;1.05]), a history of chronic diseases such as cardiac (HR 1.79 [1.52;2.12]), hepatic (HR 1.99 [1.59;2.51]), or renal disease defined as baseline eGFR below $30 \text{ ml/min/1.73m}^2$ (HR 1.63 [1.26;2.10]). A history of neoplasia, including metastatic cancer (HR 2.02 [1.42;2.86]) or lymphoma (HR 1.96 [1.23;3.13]), as well as baseline biological markers

Table I
Baseline characteristics of patients in the analysis of death.

Characteristic	Population for the analysis of mortality	Completeness (% patients)
Demographics		
	n = 3072	
Age - median [IQR]	70.66 [60.59 - 80.20]	100.0
Male sex - no. (%)	2078 (67.64)	100.0
Type 1 diabetes - no. (%)	270 (8.79)	-
BMI, kg/m ² - median (IQR)	27.30 [23.90 - 31.90]	50.81
Emergency admission - no. (%)	1139 (37.08)	-
Tobacco consumption		
Current smoker - no. (%)	1045 (34.02)	-
Past smoker - no. (%)	461 (15.01)	-
Non smoker - no. (%)	1566 (50.98)	-
Alcohol consumption		
Current drinker - no. (%)	685 (22.30)	-
Past drinker - no. (%)	97 (3.16)	-
Non drinker - no. (%)	2290 (74.54)	-
Overweight or obese - no. (%)	1393.0 (45.35)	-
Diabetic Foot Ulcer characteristics*		
Ulcer of lower limb - no. (%)	1332 (43.36)	-
Necrotizing fasciitis - no. (%)	13 (0.42)	-
Arthritis and polyarthritis - no. (%)	60 (1.95)	-
Osteomyelitis - no. (%)	447 (14.55)	-
Osteonecrosis - no. (%)	5 (0.16)	-
Pyoderma - no. (%)	134 (4.36)	-
Atherosclerosis of the distal arteries, with gangrene - no. (%)	736 (23.96)	-
Cutaneous abscess, furuncle and carbuncle of limb - no. (%)	331 (10.77)	-
Gas gangrene - no. (%)	14 (0.46)	-
Medical history		
Cardiac disease - no. (%)	1407 (45.80)	-
Peripheral artery disease - no. (%)	1443 (46.97)	-
Metastatic cancer - no. (%)	74 (2.41)	-
Lymphoma - no. (%)	44 (1.43)	-
Chronic liver disease - no. (%)	286 (9.31)	-
Dementia - no. (%)	109 (3.55)	-
Biological results		
Max HbA1c over past year, % - median (IQR)	8.34 [7.00 - 10.20]	63.93
Most recent HbA1c, % - median (IQR)	7.91 [6.81 - 9.60]	56.64
CRP, mg/l - median (IQR)	46.0 [11.68 - 121.82]	67.15
Leukocytes, G/l - median (IQR)	9.07 [7.00 - 12.00]	73.34
Neutrophils, G/l - median (IQR)	6.41 [4.49 - 9.15]	69.82
Lymphocytes, G/l - median (IQR)	1.47 [0.99 - 2.05]	69.69
Monocytes, G/l - median (IQR)	0.73 [0.56 - 0.97]	69.40
eGFR, ml/min per 1,73m ² - median (IQR)	68.44 [36.00 - 94.00]	45.61
Urinary albumin concentration, mg/l - median (IQR)	50.95 [12.98 - 247.50]	17.06
HDL, mmol/l - median (IQR)	0.95 [0.78 - 1.19]	28.16
LDL, mmol/l - median (IQR)	1.84 [1.34 - 2.52]	27.80
ASAT, U/l - median (IQR)	23.00 [17.00 - 34.00]	57.13
ALAT, U/l - median (IQR)	20.00 [13.00 - 31.00]	58.14
Fibrinogen, g/l - median (IQR)	5.74 [4.50 - 7.22]	33.92
Albuminemia, g/l - median (IQR)	30.70 [26.00 - 35.00]	52.57
Medication		
Insulin - no. (%)	1851 (60.25)	-
Metformin - no. (%)	1773 (57.71)	-
SGLT2i - no. (%)	205 (6.67)	-
GLP1 RA - no. (%)	445 (14.49)	-
DPP4i - no. (%)	623 (20.28)	-
Sulfonylureas - no. (%)	866 (28.19)	-
Glinides - no. (%)	434 (14.13)	-

BMI: Body Mass Index; CRP: C-Reactive Protein; SGLT2i: SGLT2 Inhibitors; GLP1RA: Glucagon-Like Peptide-1 Receptor Agonists.

*according to ICD-10 codes.

of systemic inflammation such as elevated CRP above 50 mg/l (HR 1.45 [1.16;1.80]), were also associated with increased mortality risk. In contrast, being overweight or obese was associated with a lower risk of mortality (Table II).

Risk factors for LLA were male sex (HR 1.43 [1.19;1.71]), PAD (HR 3.06 [2.57;3.63]), admission through the emergency department (HR 1.24 [1.05;1.47]), and baseline systemic inflammation markers, including elevated neutrophil count above 7 G/l (HR 1.38 [1.13;1.69]), monocyte count above 0.5 G/l (HR 1.54 [1.17;2.04]), and CRP levels above 50 mg/l (HR 1.51 [1.23;1.86]). Conversely, patients with dementia (HR 0.37 [0.19;0.71]) had a lower risk of amputation (Table III). The cause-specific Cox proportional hazards produced consistent associations (Table S1; see supplementary materials associated with this article on line).

Subgroup analyses

No difference in mortality since discharge (index date for this subgroup analysis) was observed between patients who underwent LLA during hospitalization and those who did not (logrank p-value = 0.7785). Similarly, there was no difference in mortality based on whether the amputation was major or minor (logrank P-value = 0.7785) or whether it occurred within the first week of hospitalization or later (logrank P-value = 0.863) (Fig. 2).

We also analyzed the cumulative incidence of death at 12 months in patients included with a DFU code labeled as a primary diagnosis (n = 1652), who showed lower mortality (16.96 % [15.10 - 19.04] at 12 months vs 21.64 % [20.11 - 23.26]) in the overall DFU population (logrank P-value < 0.0001) (Fig. 3).

Discussion

This retrospective cohort study, conducted using data from the AP-HP CDW, included 3102 adult diabetic patients hospitalized with a first DFU between March 2020 and April 2023. The study estimated the cumulative incidence over a 36-month period of all-cause mortality and LLA accounting for the competing risk of death. Key findings include a very high cumulative incidence of death at 12 months of 21.64 %, while the cumulative incidence of LLA at 12 months was 24.15 %. Risk factors for mortality included older age, chronic diseases (cardiac, hepatic, renal), neoplasia, and elevated inflammatory markers at admission. Risk factors for LLA included male sex, PAD, emergency department admission, and elevated inflammatory markers at admission.

Risk factors associated with mortality

These results are consistent with the increased mortality risk associated with DFU (RR 2.45 [1.85-2.85]) observed in the meta-analysis by Saluja et al. [31], but our analysis shows even more severe outcomes than those reported in the existing literature. A 2020 study involving a cohort of 347 patients with diabetes reported a one-year mortality rate of 10 % [7.3-13.8] [32], which is half the rate observed in our study; although these patients came from the same area as ours, they were slightly younger (65 vs 70 years old) and they were managed in a specialized center for diabetic foot wound care, which may account for the lower mortality. Moreover, our cohort included patients admitted through emergency departments or vascular surgery units, reflecting a potentially more severe clinical profile. This is further supported by the inclusion of cases where DFU was coded as a secondary diagnosis, with primary diagnoses likely corresponding to acute and severe conditions occurring during hospitalization (e.g., septic shock, severe infection, or critical ischemia). Such profiles likely contributed to the higher early mortality observed in our study. In their 2022 meta-analysis, Lihong Chen et al. [5] included 124,376 patients from 34 studies and described a 1-year mortality rate of 13.10 % [8.5-17.4], which is 10 % lower than in our analysis (24.10 %), but closer to our subgroup analysis restricted

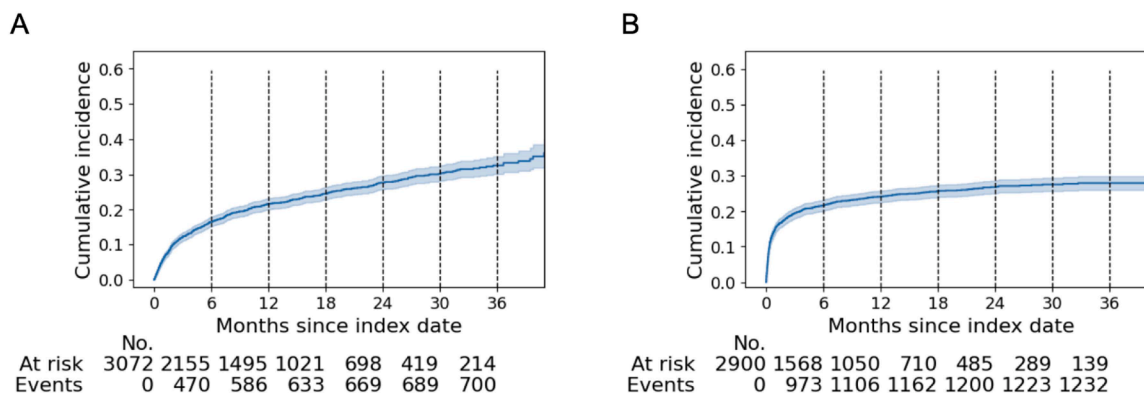


Fig. 1. Cumulative incidence with 95 % confidence intervals of death (A) and of LLA accounting for the competing risk of death (B). Reporting of cumulative incidences with 95 % confidence intervals available in Table S1 (see supplementary materials associated with this article on line).

to DFU coded as the primary diagnosis, for which the 1-year mortality was 16.96 %. This difference may be explained by the inclusion criteria of our study, which focused on hospitalized patients — across all types of departments, not just diabetology units — and did not include those managed solely on an outpatient basis, who are likely less severe. In contrast, at 3 years, our mortality rate is similar, as we found 32.57 % mortality incidence compared to 33.10 % reported by Lihong Chen et al. [5]. This can be explained by the fact that our study included patients who were hospitalized for acute events (such as infections or ischemia), leading to higher early mortality. In studies reported by Lihong Chen et al. [5], patients may have had 1 or 2 years of outpatient follow-up or recurrences that eventually led to hospitalizations for acute events, resulting in comparable mortality rates over a 3-year period.

In our cohort, several key risk factors for mortality were identified among patients hospitalized for the first time with a DFU. These included older age, comorbidities such as cardiac, hepatic, or renal disease (i.e. low eGFR), which are consistent with the results of Lihong Chen et al.'s meta-analysis [5]. Additionally, we identified cancers (metastatic and lymphomas) and dementia —none of which were evaluated in the studies included in Lihong Chen et al.'s meta-analysis— as comorbidities associated with a higher risk of death, which was expected. More innovatively, our study highlights that baseline inflammation markers (CRP, neutrophil count, monocyte count) —likely indicators of tissue infection— are associated with an increased risk of mortality. It should nevertheless be noted that in Lihong Chen meta-analysis [5], infections (sepsis, respiratory infection, and foot infection) were the second most common cause of death, with a pooled proportion of 24.80 % [95 %CI 16.00;33.50]. However, we did not find that amputation (of any type) during hospitalization was associated with an increased risk of death among those alive at discharge, suggesting that while amputation is an indicator of the severity of the ulcer, it is also likely a part of the treatment for this condition. Additionally, it is possible that the frailest patients were not selected for surgery, which may have influenced this association.

Interestingly, in our study, overweight and obesity were associated with lower in-hospital mortality among patients admitted for a first DFU. This observation is consistent with the so-called *obesity paradox*, described in various chronic and acute conditions [33]. While hypotheses such as greater metabolic reserve or earlier care have been proposed, this paradox remains debated. It may reflect confounding factors such as frailty, unintentional weight loss, or underlying under-nutrition—factors that we could not fully characterize in our data—suggesting that either the obesity paradox is at play or that nutritional deficiency, rather than excess weight, is the true risk factor.

Risk factors associated with LLA

For LLA, the cumulative incidence in our cohort was 15.37 % at 1

month, 21.61 % at 6 months, and 24.15 % at 12 months. In their meta-analysis, Rodrigues et al. [3] reported a prevalence of LLA among patients with DFU of 8.70 % at 1 year and 12.50 % at 3 years, which is lower than the rates observed in our cohort. This discrepancy may be attributed to differences in patient selection criteria, selecting more severe foot ulcers compared to most retrospective studies in this meta-analysis.

A more recent analysis based on data from 133,791 patients in the French National Health Data System also reported a lower one-year amputation rate than in our study, at 9.2 % [34]. However, this study only considered major amputations, whereas our analysis accounted for both major and minor amputations. Moreover, our cohort consisted of patients hospitalized in tertiary care centers, likely managing more severe cases—for example, the prevalence of peripheral arterial disease (PAD) was 47 % in our study compared to 23 % in theirs.

In our cohort, classical metabolic and lifestyle variables such as age, BMI, smoking status, and HbA1c were not significantly associated with LLA. Instead, male sex, emergency admission, insulin or sulfonylurea treatment, a history of PAD, and elevated markers of inflammation (CRP, monocytes, and neutrophils) were independent risk factors. Dementia or cardiovascular disease appeared to be protective—potentially reflecting a contraindication, where patients with significant frailty or comorbidities are less likely to undergo major surgical interventions.

These findings partially contrast with the meta-analysis of Rodrigues et al. [3], which identified age, low BMI, renal impairment, and high inflammatory markers as frequent risk factors, while also reporting heterogeneity in the role of smoking—sometimes even suggesting a protective effect.

Furthermore, the recent study by Vanherwegen et al. [35] reinforces the importance of sex differences in DFU presentation and outcomes. In their large Belgian cohort, male patients presented with more severe ulcers—deeper, more frequently infected, and with more frequent systemic involvement—despite no delay in presentation compared to women. Their adjusted analysis also confirmed that female sex was independently associated with better healing outcomes without major amputation. These observations align closely with our findings, underscoring male sex as a robust risk factor for poorer outcomes in DFU, potentially mediated by more severe clinical presentation and comorbidity patterns.

In our study, unlike the 2018 meta-analysis by Li et al. [36], the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors was not identified as a risk factor for lower limb amputation. However, it is worth noting that in the meta-analysis, the increased risk was specifically associated with canagliflozin, whereas during the study period in our analysis, only empagliflozin and dapagliflozin were available in France. Moreover, only 205 patients in our cohort were treated with SGLT2 inhibitors, which limits the statistical power to detect a potential association.

Table II

Risk factors associated with death identified with a multivariate Cox proportional hazards model.

Covariate	HR [95 %CI]	P-value
Clinical data at inclusion		
Age at inclusion	1.04 [1.03–1.05]	< 0.0001
Male	1.02 [0.86–1.20]	0.85
Type 1 diabetes	1.12 [0.85–1.47]	0.44
BMI below 25 kg/m ²	Ref	
BMI above 25 kg/m ²	0.75 [0.60–0.93]	< 0.01
BMI missing	0.86 [0.70–1.07]	0.18
Emergency admission	1.00 [0.85–1.17]	0.98
Ever smoker	0.87 [0.73–1.04]	0.14
Ever drinker	1.12 [0.93–1.36]	0.32
Amputated during first 48 after admission	0.89 [0.63–1.26]	0.50
Medication		
Insulin	1.16 [0.97–1.38]	0.10
Metformin	0.99 [0.84–1.18]	0.94
SGLT2i	1.11 [0.80–1.54]	0.53
Sulfonylureas	0.91 [0.75–1.10]	0.33
Glinides	1.24 [1.01–1.52]	0.04
DPP4i	0.89 [0.74–1.08]	0.25
GLP1 RA	0.80 [0.61–1.04]	0.10
Comorbidities at inclusion		
Cardiac disease	1.79 [1.52–2.12]	< 0.0001
Peripheral artery disease	1.08 [0.93–1.27]	0.31
Chronic liver disease	1.99 [1.59–2.51]	< 0.0001
Metastatic cancer	2.02 [1.42–2.86]	< 0.0001
Lymphoma	1.96 [1.23–3.13]	< 0.01
Dementia	1.26 [0.91–1.73]	0.16
Biological results at inclusion		
HbA1c below 10 %	Ref	
HbA1c above 10 %	0.94 [0.70–1.26]	0.68
HbA1c missing	0.98 [0.82–1.16]	0.80
Urinary albumin concentration below 20 mg/l	Ref	
Urinary albumin concentration 20 to 200 mg/l	1.11 [0.62–1.99]	0.71
Urinary albumin concentration above 200 mg/l	1.24 [0.68–2.26]	0.48
Urinary albumin concentration missing	1.54 [0.95–2.48]	0.08
Albuminemia below 40 g/l	Ref	
Albuminemia above 40 g/l	0.49 [0.27–0.88]	0.02
Albuminemia missing	0.75 [0.62–0.92]	< 0.01
Monocytes below 0.5 G/l	Ref	
Monocytes above 0.5 G/l	0.80 [0.63–1.01]	0.06
Monocytes missing	0.58 [0.19–1.79]	0.34
Neutrophils below 7 G/l	Ref	
Neutrophils above 7 G/l	1.30 [1.06–1.60]	0.01
Neutrophils missing	3.48 [0.76–15.98]	0.11
Lymphocytes below 4 G/l	Ref	
Lymphocytes above 4 G/l	1.89 [0.77–4.64]	0.16
Lymphocytes missing	0.39 [0.06–2.40]	0.31
CRP below 50 mg/l	Ref	
CRP above 50 mg/l	1.45 [1.16–1.81]	< 0.001
CRP missing	2.03 [1.52–2.69]	< 0.0001
eGFR above 30 ml/min/1.73m ²	Ref	
eGFR below 30 ml/min/1.73m ²	1.63 [1.26–2.10]	< 0.001
eGFR missing	1.04 [0.86–1.26]	0.70

BMI: Body Mass Index; CRP: C-Reactive Protein; SGLT2i: SGLT2 Inhibitors; GLP1RA: Glucagon-Like Peptide-1 Receptor Agonists; eGFR: estimated Glomerular Filtration Rate. Significant associations shown in bold.

Use of a CDW

This study relies on real-world data from a hospital CDW, enabling inclusion of a large patient population with a wider range of disease severity than typically observed in randomized clinical trials or in protocolized cohort study in expert centers. Nevertheless, since the cohort is drawn from a hospital setting, it does not necessarily reflect the broader general population, rather it represents individuals with more severe forms of the condition requiring hospitalization. Despite this, the large sample size allows for comprehensive adjustment for numerous covariates, improving control of potential confounding factors.

There is growing support in the literature for the use of real-world data from CDWs in research, given their capacity to expand the

Table III

Risk factors associated with LLA identified with a multivariate Fine and Gray model, accounting for the competing risk of death.

Covariate	sub-HR [95 % CI]	P-value
Clinical data at inclusion		
Age at inclusion	1.00 [0.99–1.00]	0.31
Male	1.43 [1.19–1.71]	< 0.001
Type 1 diabetes	1.01 [0.76–1.34]	0.95
BMI below 25 kg/m ²	Ref	
BMI above 25 kg/m ²	0.98 [0.78–1.23]	0.86
BMI missing	1.03 [0.83–1.28]	0.79
Emergency admission	1.24 [1.05–1.47]	0.01
Ever smoker	0.87 [0.72–1.04]	0.12
Ever drinker	1.00 [0.82–1.21]	0.98
Medication		
Insulin	1.20 [1.01–1.43]	0.04
Metformin	0.97 [0.81–1.16]	0.71
SGLT2i	1.10 [0.81–1.50]	0.52
Sulfonylureas	1.21 [1.01–1.47]	0.04
Glinides	0.85 [0.68–1.07]	0.17
DPP4i	0.88 [0.71–1.08]	0.22
GLP1 RA	0.86 [0.68–1.08]	0.19
Comorbidities at inclusion		
Cardiac disease	0.74 [0.63–0.88]	< 0.001
Peripheral artery disease	3.06 [2.57–3.63]	< 0.0001
Chronic liver disease	0.78 [0.58–1.06]	0.11
Metastatic cancer	0.66 [0.36–1.21]	0.18
Lymphoma	0.86 [0.41–1.80]	0.68
Dementia	0.37 [0.19–0.71]	< 0.01
Biological results at inclusion		
HbA1c below 10 %	Ref	
HbA1c above 10 %	1.19 [0.94–1.52]	0.16
HbA1c missing	1.02 [0.85–1.22]	0.82
Urinary albumin concentration below 20 mg/l	Ref	
Urinary albumin concentration 20 to 200 mg/l	1.27 [0.86–1.87]	0.23
Urinary albumin concentration above 200 mg/l	1.00 [0.65–1.52]	0.98
Urinary albumin concentration missing	0.63 [0.45–0.89]	< 0.01
Albuminemia below 40 g/l	Ref	
Albuminemia above 40 g/l	0.81 [0.54–1.20]	0.29
Albuminemia missing	0.98 [0.81–1.18]	0.82
Monocytes below 0.5 G/l	Ref	
Monocytes above 0.5 G/l	1.54 [1.17–2.04]	< 0.01
Monocytes missing	2.87 [1.08–7.58]	0.03
Neutrophils below 7 G/l	Ref	
Neutrophils above 7 G/l	1.38 [1.13–1.69]	< 0.01
Neutrophils missing	4.89 [1.46–16.44]	0.01
Lymphocytes below 4 G/l	Ref	
Lymphocytes above 4 G/l	1.20 [0.58–2.49]	0.62
Lymphocytes missing	0.13 [0.03–0.53]	< 0.01
CRP below 50 mg/l	Ref	
CRP above 50 mg/l	1.51 [1.23–1.86]	< 0.001
CRP missing	1.08 [0.82–1.42]	0.58
eGFR above 30 ml/min/1.73m ²	Ref	
eGFR below 30 ml/min/1.73m ²	1.09 [0.82–1.46]	0.54
eGFR missing	1.21 [1.00–1.46]	0.05

BMI: Body Mass Index; CRP: C-Reactive Protein; SGLT2i: SGLT2 Inhibitors; GLP1RA: Glucagon-Like Peptide-1 Receptor Agonists; eGFR: estimated Glomerular Filtration Rate. Significant associations shown in bold.

relevance and scope of evidence. Martins and Rangel [37] highlighted how these infrastructures enable rapid analysis of large datasets, supporting timely and robust results. Ho et al. [38] showed that EHRs from large academic centers provide granular data for complex assessments, while in France, Karakachoff et al. [39] demonstrated that biomedical data warehouses in university hospitals foster large-scale, multidisciplinary research through access to rich, standardized clinical data. However, the heterogeneity of these data—both structured and especially unstructured, not initially collected for research—requires extensive and complex data curation. Successfully replicating known associations in such data, as achieved here, represents an important validation step. Furthermore, the large sample size and comprehensive

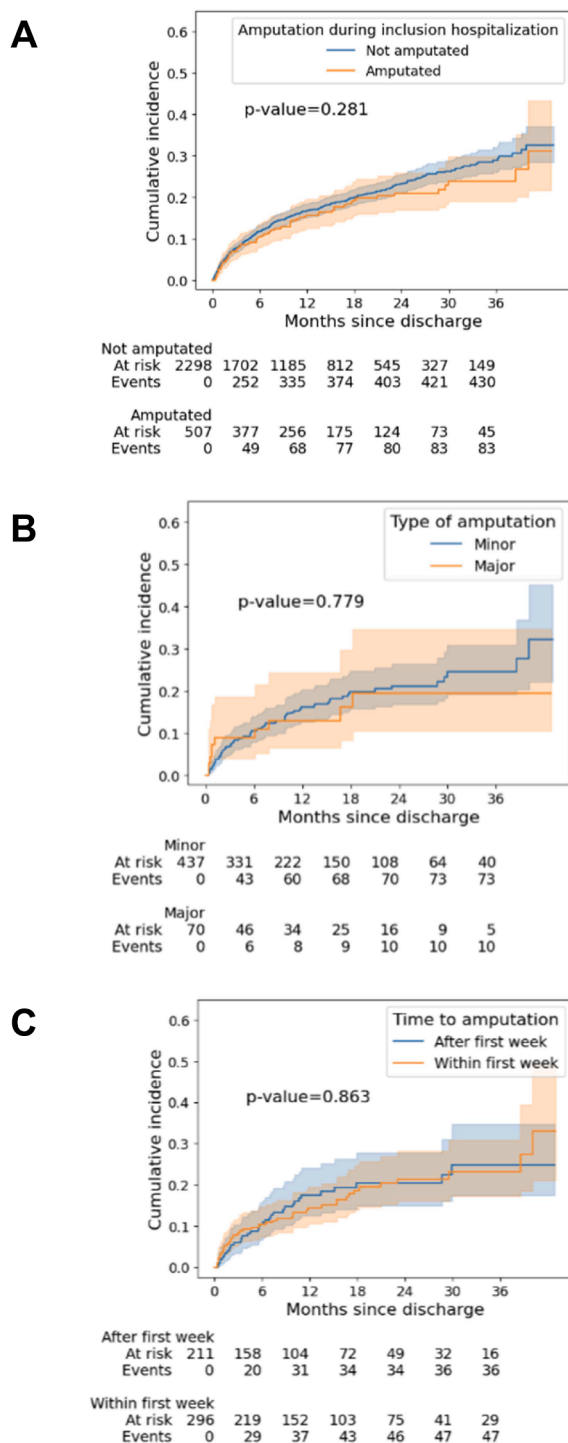


Fig. 2. Cumulative incidence of death since discharge according to (A) amputation status during index hospitalization among all patients, (B) type of amputation among patients amputated during index hospitalization, (C) time to amputation among patients amputated during index hospitalization. P-value corresponds to the logrank test.

set of covariates in our study enabled the identification of novel associations, such as those involving inflammatory markers.

Limitations

While this study provides valuable insights into the mortality and amputation rates associated with DFU, it has several limitations.

First, the definition of DFU was based on ICD-10 codes, which may lack the granularity required to accurately capture the complexity and severity of DFUs, especially since there is no specific ICD-10 code for DFU. In addition, the use of ICD-10 codes is service-dependent and influenced by local coding practices and habits, which may further affect consistency and completeness. Furthermore, the distinction between primary and secondary (or associated) diagnoses may lead to disparities in epidemiological descriptive results and subsequently affect the interpretation of outcomes, including mortality rates.

Second, the focus on hospitalized patients, more likely to present more severe DFUs compared to those managed in outpatient settings. This urban-centric cohort may not be representative of the broader population, limiting the generalizability of the results to other regions or healthcare context.

Third, the study period includes 2020, during which the Covid-19 pandemic significantly disrupted healthcare systems worldwide. The pandemic led to delays in routine care especially in DFU care, reallocation of medical resources, and increased mortality rates [40–42], all of which could have influenced patient outcomes and the study’s findings.

Additionally, as a retrospective analysis, the study is subject to missing data inherent in real-world clinical settings, and some risk factors such as infection severity and delayed wound healing are unavailable.

Furthermore, the use of large datasets increases statistical power and enables the detection of associations that may go unnoticed in smaller cohorts, including those with small effect sizes. This raises the question of their actual clinical relevance. However, in our study, with the exception of age at baseline, all observed hazard ratios (HRs) were either greater than 1.1 (up to 2.03) or less than 0.9 (down to 0.49), suggesting that the associations identified are not only statistically significant but also potentially clinically meaningful.

Finally, the use of NLP techniques to extract information from unstructured clinical notes may introduce biases due to variability in language use and documentation practices among healthcare providers. While NLP offers valuable insights, for example regarding information on treatments, smoking status, and BMI, its accuracy depends on the quality of the source data and the algorithms employed. Furthermore, the current NLP algorithms were not able to extract individual-level information on diabetes duration.

Conclusion

In conclusion, the findings of this study highlight the significant risks of mortality and amputation associated with DFUs, reinforcing existing literature. Risk factors such as advanced age, chronic diseases, and inflammatory markers show important association with death and LLA. The integration of data from EHRs presents a substantial opportunity to deepen our understanding of long-term outcomes for these conditions and enhance clinical interventions.

Declaration of generative AI in scientific writing

During the preparation of this work the authors used ChatGPT in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data sharing

Access to the CDW raw data can be granted following the process described on its website: eds.aphp.fr. A prior validation of the access by the local IRB is required. In the case of non-AP-HP researchers, the signature of a collaboration contract is also mandatory.

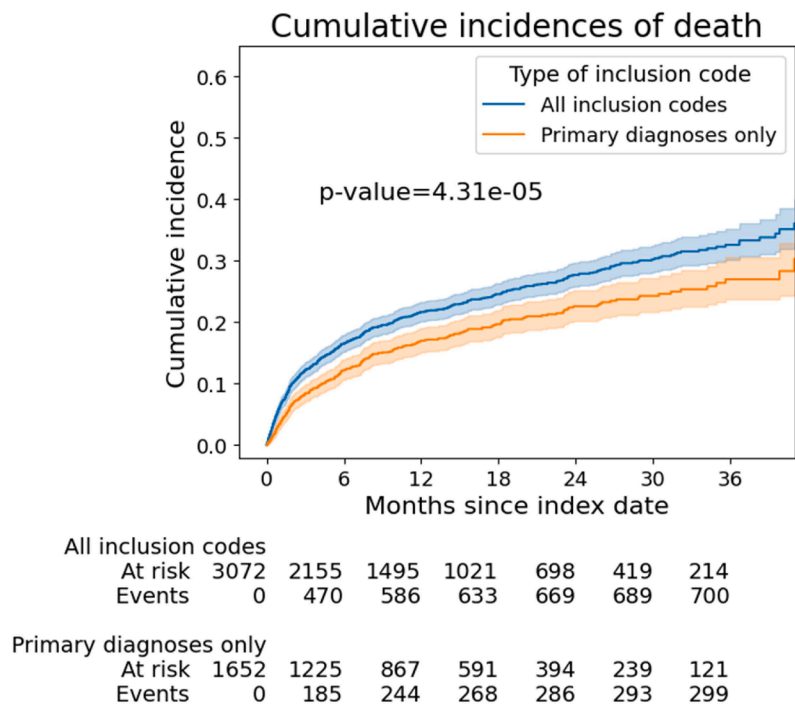


Fig. 3. Cumulative incidence of death stratified by whether the DFU inclusion code was the primary diagnosis. P-value corresponds to the logrank test.

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CRediT authorship contribution statement

Jean-Baptiste Julla: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization. **Théo Jolivet:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Candice Estellat:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Gaël Varoquaux:** Validation, Methodology, Funding acquisition, Conceptualization. **Aurélié Carlier:** Writing – review & editing, Visualization, Methodology. **Jean-François Gautier:** Writing – review & editing, Visualization. **Julie Alberge:** Writing – review & editing, Methodology, Conceptualization. **Yawa Abouleka:** Writing – review & editing, Visualization, Validation, Methodology, Investigation. **Audrey Bergès:** Writing – review & editing, Software, Data curation. **Elise Liu:** Writing – review & editing, Software, Data curation. **Judith Abecassis:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Florence Tubach:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Louis Potier:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.diabet.2025.101700](https://doi.org/10.1016/j.diabet.2025.101700).

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