Epidemiology of Major Lower Extremity Amputations in Individuals With Diabetes in Austria, 2014-2017: A Retrospective Analysis of Health Insurance Database

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Abstract

Background: Previous data show a high incidence of major lower extremity amputations (LEA) in Austria. Moreover, recent data on the epidemiology of major LEA are sparse in the Country. This study estimated the incidence and mortality rates of major LEA and assessed risk factors of post major LEA mortality in individuals with diabetes.

Methods: A retrospective cohort analysis of 507,180 individuals with diabetes enrolled in the Austrian Health Insurance between 2014 and 2017 was performed. Crude and age-standardized rates of major LEA (hip, femur, knee, lower leg) were estimated by extracting their procedure codes from the database. Short- (30-day, 90-day) and long-term (1-year, 5-year) all-cause cumulative mortality after major LEA was estimated from the date of amputation till the date of death. Poisson regression was performed to compare rates by characteristics and assess the annual trend. The Cox-regression was performed to identify significant risk factors of all-cause mortality after major LEA.

Results: A total of 2,165 individuals with diabetes underwent major LEA between 2014 and 2017. The mean age was amputees was 73.0 ±11.3 years, 62.7% were males, and 87.3% had a peripheral vascular disease (PVD).

The overall age-standardized rate was 6.44 per 100,000 population. The rate increased with age ($p<0.001$) and was higher ($p<0.001$) in males (9.38) than females (5.66). The rate was 5.71 in 2014, 6.86 in 2015, 6.71 in 2016, and 6.66 in 2017, with an insignificant annual change of 3% ($p=0.825$). The cumulative 30-day mortality was 13.5%, 90-day was 22.0%, 1-year was 34.4%, and 5-year was 66.7%. Age, male sex, above-knee amputation, Charlson index, and heart failure were significantly associated with both short- and long-term mortality. Cancer, dementia, heart failure, PVD, and renal disease were only associated with long-term mortality.

Conclusions: The rate of major LEA remained stable between 2014 and 2017 in Austria. Short and long-term mortality rates were considerably high after major LEA. Old age, male sex, above-knee amputations, heart failure, and Charlson Index were significant predictors of both short- and long-term mortality, whereas, comorbidities such as cancer, dementia, PVD, and renal disease were significant predictors of long-term mortality only.

Background

Lower extremity amputation (LEA) is a debilitating procedure that contributes to significant healthcare costs, loss of mobility, reduced quality of life, and mortality [1–4]. An estimated 75% of the total LEA are performed in individuals with diabetes. The risk of undergoing LEA is 15–45 times higher in individuals with diabetes than those without diabetes [5, 6]. Approximately 85% of LEA occur as a complication of the unhealed diabetic foot, which is mainly caused by inadequate glucose control, peripheral artery disease, and infection management [7, 8].

Evidence shows that a significant proportion of LEA in individuals with diabetes can be prevented by implementing effective multidisciplinary and multisectoral diabetes care programs [9]. Therefore, a reduction in the incidence of major LEA is a major health priority and considered a core indicator of the long-term quality of diabetes care worldwide [10]. Data from national audits in many countries and the Organization for Economic Cooperation and Development (OECD) have demonstrated a significant reduction in the incidence of diabetes-related major LEA over years owing to diabetic foot ulcer prevention and care programs [9–12]. Nevertheless, studies have reported up to a 20-fold variation in the rate of major LEA among countries [13, 14]. Furthermore, as per OECD estimates of 2017, Austria had a high age-sex standardized rate of major LEA (13.20 per 100,000 population) in individuals with diabetes amongst European Countries [10]. However, studies have argued that variation in LEA rates among countries could be attributed to differences in case definitions, coding systems, data acquisition methods, and estimation methods of LEA [13–16].

The observed variability in the incidence of major LEA in individuals with diabetes among countries, its high rate in Austria, and being the core quality indicator of diabetes care necessitates the need for more epidemiological research on major LEA. Moreover, there are no published countrywide data on the epidemiology of major LEA in Austria other than the OECD to evaluate the standard of diabetes care in the Country. Therefore, this study was undertaken to estimate the rate of major LEA and mortality rates after major LEA, analyze the trend of major LEA from 2014 to 2017, and evaluate the impact of characteristics and comorbidities on the risk of short- and long-term mortality after major LEA in individuals with diabetes.

Methods

Study Design

It was a retrospective analysis of the Austrian Health Insurance (AHI) database. The AHI database collects and stores data from 13 health insurances, which is supplied by participating hospitals throughout Austria. The AHI database covers 99% of the Austrian population and contains pseudo-anonymized information on demographic characteristics (sex, date of birth, states), primary and secondary medical diagnosis recorded as *International Classification of Disease* (ICD) codes along with discharge dates from hospitals, prescribed medications coded as *Anatomical Therapeutic Classification* (ATC) system introduced by the *World Health Organization* (WHO), along with their dosage, volume, start dates, and end dates, medical procedures recorded as MEL codes along with dates of procedures and dates of discharge after procedures, and all-cause mortality along with the date of death.

Ethical Considerations

This study was submitted to the ethics committee of the Medical University of Graz (application number: 1302/2020). This study fully conformed to principles of 1964 declaration of Helsinki and guidelines of the International Conference on Harmonization for Good Clinical Practice (ICH GCP E6 guidelines).

Data Extraction and Study Variables

This study analyzed the subset of AHI data of 507,180 individuals with established type 1 or type 2 diabetes who were hospitalized to undergo major LEA between January 1st, 2014 and December 31st, 2017. Type 1 and Type 2 diabetes were diagnosed using the ICD-10 and ATC codes of anti-diabetes medicines available in the database.

Major Lower extremity amputations

The procedure (MEL) codes of various levels of major LEA that include hip disarticulation (NZ080), femur amputation (NZ090), knee disarticulation (NZ100), and lower leg amputation (NZ110) along with their dates were extracted from the database. Major LEA was further classified as above-knee amputation (AKA), knee disarticulation (KD), and below-knee amputation (BKA). Multiple entries of major LEA of the same and/or different levels were documented for each patient in the database. However, it could not be determined from the codes whether those amputations were bilateral, contralateral, or records of the previous amputations. Therefore, only the first procedure of major LEA during the study period for each individual was included in the analysis, whereas, the subsequent amputations were excluded.

All-cause mortality

All-cause mortality was defined as short- (30-day, 90-day) and long-term (1-year, 5-year) mortality after LEA. Person-time to death was calculated both in days and years from the date of first major LEA till the date of death or the last date of contact (31st December 2018) with the hospital.

Age-adjusted Charlson Comorbidity Index

A validated weighted summary score called the age-adjusted *Charlson Comorbidity Index* (ACCI) was generated using the ICD-9 and ICD-10 codes of various comorbidities in the AHI database. These comorbidities were myocardial infarction, congestive heart failure (CHF), peripheral vascular disease (PVD), stroke, dementia, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, peptic ulcer disease, liver disease, diabetes, hemiplegia, renal disease, cancer, acquired immune deficiency syndrome (AIDS), and age categories (< 50 years, 50–59 years, 60–69 years, 70–79 years, 80 + years) [17]. The ACCI score was further categorized into 0–2, 3–5, and 6 + scores. Cardiovascular disease (CVD) was defined as a composite of myocardial infarction, stroke, CHF, or PVD.

Demographic characteristics

Other variables were the age of individuals calculated from the date of birth until the date of amputation, gender, and year of major LEA.

Statistical Analysis

All Statistical analyses were carried out in Stata version 16.0 (StataCorp LLC). The characteristics of individuals with major LEA were tabulated as mean ± standard deviation (± SD) or frequencies and

percentages (%) as appropriate. The rate of major LEA was calculated by dividing the total number of individuals with diabetes who underwent amputations between 2014 and 2017 with the total population of Austria aged 20 years and above during that period (provided by the AHI) and multiplied by 100,000 population. Age-standardized rates were estimated using the direct method and the European standard population of 2013 [18]. The 95% confidence intervals (CI) for rates were derived from the Poisson distribution. Simple and multiple negative binomial regressions were performed to compare the rate between characteristics. The temporal trend was assessed in terms of the average annual percentage change (AAPC). The results of regression were reported as rate ratios (RR) and adjusted rate ratios (aRR) with corresponding 95% CIs and p-values. The all-cause mortality rate was estimated by dividing the total number of individuals who underwent major LEA with the person-time and compared between characteristics, individual comorbidities, and the ACCI categories by applying chi-square tests. Cumulative mortality rates were estimated for 30-days, 90-days, 1-year, and 5-years and log-rank tests were applied to compare the rate at each time-point between characteristics, levels of amputations, individual comorbidities, and the ACCI categories. Cumulative mortality curves were presented as Kaplan-Meier plots and compared between variables using log-rank tests. The Cox proportional hazard regression was performed to investigate the association of characteristics, levels of amputations, individual comorbidities (model I), and the ACCI score (model II) with all-cause mortality at 30-days, 90-days, 1-year, and 5-years each. In the model I, both stepwise backward elimination (variables with $p < 0.20$) and Least Absolute Shrinkage and Selection Operator (LASSO) techniques were applied to select significant predictors (excluding the ACCI) of mortality at each time-point. In the model II, the association of the ACCI score with mortality at each time-point was adjusted for sex, types of diabetes, and levels of amputations. The results of Cox regression were reported as adjusted hazard rates (aHR) with corresponding 95% CI and p-values (< 0.05 considered as statistically significant).

Results

A total of 2165 individuals with diabetes underwent major LEA between 2014 and 2017. Of the total major LEA, 56.5% (1,223) were BKA and 42.5% (921) were AKA. The mean age of amputees was 73.0 ± 11.3 years, 62.9% were males, and 83.3% had type 2 diabetes. The most prevalent comorbidities were PVD (87.3%), renal disease (38.5%), CHF (28.8%), and stroke (27.2%). The mean ACCI score was 6.1 ± 2.4 (See Table 1).

The overall crude rate of major LEA was 7.85 (7.53–8.19) and the age-standardized rate was 6.44 (6.17–6.71) per 100,000 population. In males, the crude rate was 10.19 (9.65–10.74) and the age-standardized rate was 9.38 (8.88–9.88). In females, the crude rate was 5.66 (5.28–6.07) and the age-standardized rate was 4.00 (3.72–4.28). The regression analysis showed that the rate increased significantly ($p < 0.001$) with age and was 2.53 times higher ($p < 0.001$) in males than females. The rate was not significantly different through the investigated years (See Table 2).

Table 1
Characteristics of participants who underwent major lower extremity amputations (N = 2165)

Variable	Freq.	%
Age at major LEA – Mean ± SD	73.0	± 11.3
Age categories		
< 60 years	270	12.5
60–69 years	522	24.1
70–79 years	697	32.2
≥ 80 years	676	31.2
Sex		
Female	804	37.1
Male	1361	62.9
Year of major LEA		
2014	478	22.1
2015	543	25.1
2016	566	26.1
2017	578	26.7
Levels of amputations		
AKA	921	42.5
KD	21	1.0
BKA	1223	56.5
Type of diabetes		
Type 1	362	16.7
Type 2	1803	83.3
Comorbidities		
CVD*	1960	90.5
Myocardial infarction	178	8.2
Stroke	588	27.2
CHF	624	28.8
PVD	1819	87.3

Variable	Freq.	%
Renal Disease	833	38.5
Liver Disease	233	10.8
Cancer	206	9.5
Dementia	293	13.5
ACCI score, mean ± SD	6.1	± 2.4
ACCI categories		
0–2	134	6.2
3–5	804	37.1
6+	1227	56.7

ACCI: Age-adjusted Charlson Comorbidity Index, AKA: Above Knee Amputation, BKA: Below Knee Amputation, CVD: Cardiovascular Disease, CHF: Congestive Heart Failure, KD: Knee Disarticulation, LEA: Lower Extremity Amputation, Freq: Frequency, PVD: Peripheral Vascular Disease, SD: Standard Deviation

*Composite of myocardial infarction, stroke, congestive heart failure, or peripheral vascular disease

Table 2
Crude amputation rates and negative binomial regression of major lower extremity amputations with age, sex, and years

Variables	Amputation Rate (100,000 population)		Unadjusted NB Regression		Adjusted NB Regression	
	Individuals with major LEA	Crude AR (95% CI)	RR (95% CI)	P-Value	aRR (95% CI)	P-Value
Overall	2165	7.85 (7.53–8.19)				
Age						
< 50 years	48	0.34 (0.25–0.45)	Reference		Reference	
50–59 years	222	4.29 (3.74–4.89)	12.69 (7.09–22.71)	< 0.001	12.09 (8.35–17.54)	< 0.001
60–69 years	522	14.35 (13.15–15.64)	43.65 (24.60-77.44)	< 0.001	41.35 (28.97–59.03)	< 0.001
70–79 years	697	24.20 (22.43–26.06)	75.13 (42.42-133.08)	< 0.001	75.05 (52.72-106.84)	< 0.001
80 + years	676	38.03 (35.23–41.02)	117.55 (66.33-208.34)	< 0.001	134.14 (94.02-191.37)	< 0.001
Sex						
Female	804	5.66 (5.28–6.07)	Reference		Reference	
Male	1361	10.19 (9.65–10.74)	2.02 (0.93–4.37)	0.074	2.53 (2.15–2.99)	< 0.001
Year						
2014	478	6.99 (6.38–7.64)	Reference		Reference	
2015	543	8.04 (7.38–8.75)	1.13 (0.37–3.48)	0.825	1.12 (0.89–1.40)	0.325
2016	566	8.21 (7.55–8.91)	1.14 (0.37–3.50)	0.815	1.14 (0.91–1.42)	0.263
2017	578	8.17 (7.52–8.86)	1.16 (0.38–3.55)	0.798	1.12 (0.89–1.39)	0.329

AR: Amputation Rate, CI: Confidence Interval, LEA: Lower Extremity Amputation, NB: Negative Binomial, RR: Rate Ratio, aRR: adjusted Rate Ratio

AAPC: Average Annual Percentage Change

The median survival after major LEA was 36 months and overall mortality rate was 27.3 (25.8–29.1) per 100 person-years. The mortality rate significantly increased with age ($p < 0.001$) and the ACCI score ($p < 0.001$). The rate was significantly higher in females (32.0% vs 24.9%, $p < 0.001$) than males and individuals with AKA (40.7% vs 20.1%, $p < 0.001$) than BKA. Individuals with comorbidities like PVD (29.3% vs 16.4%, $p < 0.001$), CHD (41.3% vs 22.9%, $p < 0.001$), stroke (30.6% vs 26.2%, $p = 0.019$), renal disease (35.4% vs 23.1%, $p < 0.001$), dementia (57.6% vs 24.3%, $p < 0.001$), and cancer (34.1% vs 26.7%, $p = 0.008$) had significantly higher mortality rates compared to those without these comorbidities (Table 3).

Overall 30-day mortality after major LEA was 13.5% (12.2–15.1%), 90-day mortality was 22.0% (20.3–23.8%), 1-year mortality was 34.4% (32.4–36.4%), and 5-year mortality was 66.7% (64.4–68.9%). Thirty-day mortality significantly increased with age ($p < 0.001$) and the ACCI score ($p < 0.001$). It was significantly higher in individuals with AKA ($p < 0.001$), type 2 diabetes ($p = 0.027$), CHD ($p = 0.06$), and dementia ($p < 0.001$) compared to those with BKA, type 1 diabetes and without CHD and dementia. Ninety-day mortality was significantly higher in females than males ($p = 0.036$), older than younger individuals ($p < 0.001$), those with higher ACCI score ($p < 0.001$), AKA than BKA ($p < 0.001$) and individuals with CHF ($p < 0.001$), renal disease ($p = 0.019$), and dementia ($p < 0.001$) than those without these diseases. One-year and 5-year mortality rates were significantly higher in older versus younger individuals ($p < 0.001$ for both), females than males ($p = 0.038$, $p < 0.001$), those with higher ACCI score (< 0.001), and individuals with AKA than BKA ($p < 0.001$ for both), PVD ($p = 0.002$, $p < 0.001$), CHF ($p < 0.001$ for both), renal disease ($p < 0.001$ for both), and dementia ($p < 0.001$ for both). See Table 3 and Fig. 2.

T1DM: Type 1 Diabetes, T2DM: Type 2 Diabetes, PVD: Peripheral Vascular Disease, CHF: Congestive Heart Disease, ACCI: Age-adjusted Charlson Comorbidity Index, BKA: Below Knee Amputation, AKA: Above Knee Amputation

Table 3
Mortality rate and short-term and long-term cumulative all-cause mortality after major lower extremity amputations, overall, by characteristics, comorbidities, and Charlson Index

Variable	Mortality Rate per 100 PY				Cumulative Mortality			
	n	PY	Rate (95%CI)		30-day	90-day	1-year	5-year
	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)				
Overall	1067	3901	27.3 (25.8–29.1)		13.5 (12.2–15.1)	22.0 (20.3–23.8)	34.4 (32.4–36.4)	66.7 (64.4–68.9)
Age								
< 60 years	68	652	10.4 (8.2–13.2)		5.9 (3.7–9.5)	10.7 (7.6–15.1)	17.8 (13.7–22.9)	41.5 (34.6–49.3)
60–69 years	174	1133	15.3 (13.2–17.8)		8.2 (6.2–10.9)	14.2 (11.5–17.5)	21.3 (18.0–25.0)	51.1 (46.0-56.4)
70–79 years	353	1249	28.3 (25.5–31.4)		12.3 (10.1–15.0)	19.9 (17.2–23.1)	33.3 (29.9–36.9)	67.5 (63.5–71.5)
≥ 80 years	472	866	54.5 (49.8–59.7)		21.9 (19.0-25.2)	34.8 (31.3–38.5)	52.2 (48.5–56.0)	82.8 (79.7–85.8)
P-value			< 0.001		< 0.001	< 0.001	< 0.001	< 0.001
Sex								
Male	629	2531	24.9 (23.0-26.9)		13.4 (11.7–15.3)	20.7 (18.6–22.9)	32.8 (30.3–35.3)	63.9 (61.0-66.9)
Female	438	1347	32.0 (29.1–35.1)		13.8 (11.6–16.4)	24.4 (21.6–27.5)	37.1 (33.8–40.5)	71.1 (67.5–74.6)
P-value			< 0.001		0.631	0.035	0.038	< 0.001
Amputations								

Multiple Cox regression analysis (Table 4) shows that age, male sex, a higher level of major LEA, and the ACCI score were significantly associated with both short-term and long-term mortality. In unadjusted analysis, the hazard of mortality was higher in females than males. However, adjusting for age resulted in reversing the association because of the confounding effect of age on gender and all-cause mortality. Among comorbidities, only CHF was a significant risk factor of both short-term and long-term mortality, while PVD, renal disease, dementia, cancer, and a composite CVD were significant risk factors of long-term (1-year and 5-year) mortality only.

Variable	Mortality Rate per 100 PY			Cumulative Mortality			
	n	PY	Rate (95%CI)	30-day	90-day	1-year	5-year
AKA	553	1357	40.7 (37.5–44.3)	19.5 (17.1–22.3)	31.2 (28.3–34.3)	45.6 (42.5–48.9)	75.9 (72.7–78.9)
BKA	503	2502	20.1 (18.4–21.9)	8.9 (7.4–10.7)	15.0 (13.1–17.2)	25.8 (23.5–28.4)	58.7 (55.5–62.0)
P-value			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
diabetes							
Type 1	176	685	25.7 (22.1–29.8)	9.7 (7.0-13.2)	19.6 (15.9–24.1)	31.8 (27.2–36.8)	65.7 (60.0-71.3)
Type 2	891	3215	27.7 (25.9–29.6)	14.3 (12.8–16.0)	22.5 (20.7–24.5)	34.9 (32.7–37.1)	66.9 (64.3–69.4)
P-value			0.289	0.027	0.283	0.257	0.443
Comorbidities							
CVD*							
No	56	471	11.9 (9.1–15.5)	11.7 (8.0–17.0)	16.1 (11.7–21.9)	19.5 (14.7–25.6)	44.7 (36.7–53.6)
Yes	1011	3430	29.5 (27.7–31.3)	13.7 (12.3–15.3)	22.7 (20.9–24.6)	35.9 (33.8–38.1)	68.6 (66.3–70.9)
P-value			< 0.001	0.247	0.019	< 0.001	< 0.001
MI							
No	974	3609	27.0 (25.3–28.7)	13.5 (12.1–15.1)	22.2 (20.4–24.1)	34.3 (32.3–36.5)	66.3 (63.9–68.7)

Multiple Cox regression analysis (Table 4) shows that age, male sex, a higher level of major LEA, and the ACCI score were significantly associated with both short-term and long-term mortality. In unadjusted analysis, the hazard of mortality was higher in females than males. However, adjusting for age resulted in reversing the association because of the confounding effect of age on gender and all-cause mortality. Among comorbidities, only CHF was a significant risk factor of both short-term and long-term mortality, while PVD, renal disease, dementia, cancer, and a composite CVD were significant risk factors of long-term (1-year and 5-year) mortality only.

Variable	Mortality Rate per 100 PY			Cumulative Mortality			
	n	PY	Rate (95%CI)	30-day	90-day	1-year	5-year
Yes	93	292	31.9 (26.0-39.1)	14.0 (9.7–20.1)	20.2 (15.0-26.9)	34.8 (28.3–42.3)	70.5 (62.8–77.9)
P-value			0.065	0.750	0.340	0.821	0.261
Stroke							
No	753	2875	26.2 (24.4–28.1)	13.8 (12.1–15.6)	21.9 (20.0-24.1)	33.7 (31.4–36.1)	65.2 (62.5–68.0)
Yes	314	1026	30.6 (27.4–34.2)	12.9 (10.5–15.9)	22.3 (19.1–25.9)	36.2 (32.5–40.3)	70.3 (66.1–74.5)
P-value			0.019	0.530	0.953	0.370	0.047
CHF							
No	675	2952	22.9 (21.2–24.7)	12.5 (10.9–14.2)	20.2 (18.3–22.3)	31.8 (29.5–34.2)	61.7 (58.9–64.6)
Yes	392	949	41.3 (37.4–45.6)	16.2 (13.5–19.3)	26.6 (23.3–30.3)	40.7 (37.0-44.7)	77.5 (73.8–81.1)
P-value			< 0.001	0.006	< 0.001	< 0.001	< 0.001
PVD							
No	96	587	16.4 (13.4–20.0)	13.5 (10.0-18.1)	18.6 (14.5–23.7)	25.9 (21.1–31.5)	53.5 (46.5–60.8)
Yes	971	3314	29.3 (27.5–31.2)	13.5 (12.1–15.2)	22.5 (20.7–24.5)	35.6 (33.5–37.8)	68.4 (66.0-70.8)
P-value			< 0.001	0.691	0.128	0.002	< 0.001
Renal disease							

Multiple Cox regression analysis (Table 4) shows that age, male sex, a higher level of major LEA, and the ACCI score were significantly associated with both short-term and long-term mortality. In unadjusted analysis, the hazard of mortality was higher in females than males. However, adjusting for age resulted in reversing the association because of the confounding effect of age on gender and all-cause mortality. Among comorbidities, only CHF was a significant risk factor of both short-term and long-term mortality, while PVD, renal disease, dementia, cancer, and a composite CVD were significant risk factors of long-term (1-year and 5-year) mortality only.

Variable	Mortality Rate per 100 PY			Cumulative Mortality			
	n	PY	Rate (95%CI)	30-day	90-day	1-year	5-year
No	586	2542	23.1 (21.3–25.0)	13.0 (11.3–14.9)	20.4 (18.3–22.7)	30.8 (28.4–33.3)	61.8 (58.7–64.9)
Yes	481	1359	35.4 (32.4–38.7)	14.4 (12.2–17.0)	24.6 (21.8–27.7)	40.1 (50.9–57.2)	73.8 (70.4–77.1)
P-value			< 0.001	0.299	0.019	< 0.001	< 0.001
Liver disease							
No	954	3472	27.5 (25.8–29.3)	13.3 (11.9–14.9)	21.9 (20.1–23.8)	34.1 (32.0-36.3)	66.6 (64.2–69.0)
Yes	113	428	26.4 (21.9–31.7)	15.5 (11.4–20.8)	23.2 (18.3–29.1)	36.5 (30.7–43.0)	67.2 (60.3–74.1)
P-value			0.927	0.860	0.914	0.799	0.796
Cancer							
No	941	3532	26.7 (25.0-28.4)	13.9 (12.5–15.5)	22.4 (20.6–24.3)	34.1 (32.1–36.2)	65.5 (63.1–68.0)
Yes	126	369	34.1 (28.7–40.6)	9.7 (6.4–14.6)	18.9 (14.2–25.0)	36.9 (30.7–43.9)	76.7 (70.0-82.7)
P-value			0.008	0.066	0.201	0.650	0.013
Dementia							
No	858	3538	24.3 (22.7–25.9)	12.9 (11.4–14.5)	20.4 (18.6–22.3)	31.5 (29.4–33.6)	63.6 (61.0-66.1)
Yes	209	363	57.6 (50.3–65.9)	17.7 (13.8–22.6)	32.4 (27.4–38.1)	52.9 (47.3–58.7)	83.5 (78.7–87.8)

Multiple Cox regression analysis (Table 4) shows that age, male sex, a higher level of major LEA, and the ACCI score were significantly associated with both short-term and long-term mortality. In unadjusted analysis, the hazard of mortality was higher in females than males. However, adjusting for age resulted in reversing the association because of the confounding effect of age on gender and all-cause mortality. Among comorbidities, only CHF was a significant risk factor of both short-term and long-term mortality, while PVD, renal disease, dementia, cancer, and a composite CVD were significant risk factors of long-term (1-year and 5-year) mortality only.

Variable	Mortality Rate per 100 PY			Cumulative Mortality			
	n	PY	Rate (95%CI)	30-day	90-day	1-year	5-year
P-value			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
ACCI							
0–2	15	352	4.3 (2.6–7.1)	2.2 (0.7–6.8)	6.0 (3.0-11.6)	9.0 (5.2–15.2)	23.5 (15.5–34.7)
3–5	321	1589	20.2 (18.1–22.5)	13.3 (11.1–15.9)	20.4 (17.8–23.3)	28.5 (25.5–31.7)	57.7 (53.7–61.7)
6+	731	1959	37.3 (34.7–40.1)	14.9 (13.0–17.0)	24.9 (22.5–27.4)	41.0 (38.3–43.8)	75.2 (72.4–77.8)
P-value			< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

ACCI: Age-adjusted Charlson Comorbidity Index, AKA: Above Knee Amputation, BKA: Below Knee Amputation, CVD: Cardiovascular Disease, CHF: Congestive Heart Failure, KD: Knee Disarticulation, LEA: Lower Extremity Amputation, Freq: Frequency, PVD: Peripheral Vascular Disease, PY: Person-Year, SD: Standard Deviation

*Composite of myocardial infarction, stroke, congestive heart failure, or peripheral vascular disease

Multiple Cox regression analysis (Table 4) shows that age, male sex, a higher level of major LEA, and the ACCI score were significantly associated with both short-term and long-term mortality. In unadjusted analysis, the hazard of mortality was higher in females than males. However, adjusting for age resulted in reversing the association because of the confounding effect of age on gender and all-cause mortality. Among comorbidities, only CHF was a significant risk factor of both short-term and long-term mortality, while PVD, renal disease, dementia, cancer, and a composite CVD were significant risk factors of long-term (1-year and 5-year) mortality only.

Table 4
Multiple Cox-regression analysis of 30-day, 90-day, 1-year, and 5-year all-cause mortality after major lower extremity amputations with significant predictors.

Variable	aHR (95% CI)	P-value
30-day mortality		
Age at major LEA	1.06 (1.04–1.07)	< 0.001
Male/Female	1.56 (1.20–2.02)	0.001
AKA/BKA	1.97 (1.53–2.52)	< 0.001
Cancer, +/-	0.66 (0.41–1.07)	0.089
ACCI score	1.06 (1.01–1.11)	0.029
90-day mortality		
Age at major LEA	1.05 (1.04–1.06)	< 0.001
Male/Female	1.26 (1.03–1.53)	0.025
AKA/BKA	1.91 (1.57–2.31)	< 0.001
CHF, +/-	1.22 (1.01–1.48)	0.042
ACCI score	1.07 (1.03–1.11)	0.001
1-year mortality		
Age at major LEA	1.05 (1.04–1.06)	< 0.001
Male/Female	1.32 (1.13–1.55)	0.001
AKA/BKA	1.71 (1.47–1.99)	< 0.001
CVD, +/-	1.50 (1.08–2.10)	0.017
Renal Disease, +/-	1.26 (1.09–1.46)	0.002
Dementia, +/-	1.25 (1.04.-1.51)	0.019
ACCI score	1.11 (1.07–1.14)	< 0.001
5-year mortality		
Age at major LEA	1.05 (1.04–1.06)	< 0.001
Male/Female	1.23 (1.08–1.40)	0.003
AKA/BKA	1.53 (1.35–1.73)	< 0.001
CVD	1.59 (1.21–2.09)	0.001
CHF, +/-	1.27 (1.12–1.46)	< 0.001

Variable	aHR (95% CI)	P-value
PVD, +/-	1.26 (1.02–1.56)	0.034
Renal Disease, +/-	1.26 (1.11–1.43)	< 0.001
Cancer, +/-	1.28 (1.06–1.54)	0.010
Dementia, +/-	1.29 (1.10–1.51)	0.002
ACCI score	1.14 (1.11–1.17)	< 0.001

ACCI: Age-adjusted Charlson Comorbidity Index, aHR: Adjusted Hazard Ratio, CI: Confidence Interval, LEA: Lower Extremity Amputation, AKA: Above Knee Amputation, BKA: Below Knee Amputation, CVD: Cardiovascular Disease, CHF: Congestive Heart Failure, PVD: Peripheral Vascular Disease

Discussion

This is the first study delineating the epidemiology of major LEA in individuals with diabetes in Austria using the nationally representative health insurance database. The analysis showed that the overall age-standardized rate of major LEA was 6.44 per 100,000 population, which remained unchanged from 2014 to 2017, increased with age, and was 2.53-fold higher in males compared to females. Individuals who underwent major LEA were predominantly elderly and males with a high burden of PVD, and other comorbidities including stroke, CHF, and renal disease. Both short- and long-term all-cause mortality rates were high after major LEA. Age, being a male, levels of amputation, CHF, and the ACCI score were significant risk factors of both short-term and long-term mortality after major LEA, while cancer, dementia, PVD, and renal disease were significant risk factors of long-term mortality only.

According to our analysis, the age-standardized rate of major LEA was 6.44 per 100,000 population, which is half of 13.20 per 100,000 population reported by the OECD in 2017 [10]. This drastic difference in the rates may be explained by the discrepancy in the case definition of LEA used by these studies. Our case definition included only the number of individuals with diabetes who underwent their first major LEA during the study period, while subsequent amputations were excluded. Whereas, two different case definitions of LEA have been documented by the OECD. According to the first definition, all LEA except toe amputations were considered; which could have included multiple amputations per individual as well. While the second definition included only the number of diabetes patients who underwent LEA, which is reasonably similar to our case definition [13, 19]. The above-mentioned rate of 13.20 in Austria is based on the first definition of the OECD, which might explain the difference in rates between these two data to some extent. Unfortunately, rates of LEA as per second definition of the OECD are not available for Austria to compare with our results. While comparison with other European countries indicates that our rate is meeting the OECD average, as it is similar to Spain (6.20), Lithuania (6.44), and Latvia (6.60), lower than Estonia (7.20), Finland (8.70), and Portugal (10.30), but higher than Italy (3.70), France (3.70), and the Netherlands (4.10) during the same time [19]. However, these comparisons should be taken with caution due to differences in case definitions, denominator population, and estimation methods of LEA

[14, 16]. These issues accentuate the need for adopting a unified case definition and estimation method for LEA to allow better comparison of this important health quality indicator among countries.

The temporal trend of major LEA reflects the performance of the primary healthcare system regarding the long-term care of diabetes. As mentioned earlier, the reduction in the incidence of major LEA in individuals with diabetes has been witnessed worldwide [12, 13], however, an interesting temporal trend for LEA has been observed in Austria as per OECD estimates. The rate remained stable at 21.00 per 100,000 population from 2002 to 2006, dropped to 15.90 in 2008, peaked to 26.00 in 2009, declined again from 24 to 13 between 2010 and 2014, and stayed at 13.00 till 2017 [19]. In our study, the observed overall and sex-specific age-standardized rate of major LEA remained constant at around 6.00 during the period of 2014 and 2017, which is similar to the trend noted in the OECD data during the same period, however, at a significantly lower level. Despite the increasing burden of diabetes and high rate of diabetes-related admission rate (266 per 100,000 population in 2015) in Austria [20], the stagnation of major LEA rates in the diabetes population reported by these two data sources indicates improvement or at least sustainability in the quality of diabetes care in the country. Given that there are no reliable prevalence data on diabetes in Austria, we can only speculate on the trend of people affected. However, if we assume an increase in the prevalence as observed worldwide, a sustainable number of amputations related to the total population can be regarded as an improvement in diabetes care.

In our study, the overall and yearly age-standardized rate of major LEA was significantly higher in males than females. Similar to our results, the analysis of national data of Germany noted higher amputation rates in males compared to females between 2005 and 2015 [12]. Another study from Germany reported significantly higher rates of amputations in males with and without diabetes compared to females that were independent of healthcare-related factors [21]. Likewise, a literature review of 27 studies published from 1985 to 2010 found that males were more likely to undergo amputations than females relatively at a younger age, but there was no contribution of healthcare-related factors [22]. However, evidence suggests that biological factors like diabetic foot ulcer, PVD, and peripheral neuropathy may contribute to sex-related differences in amputation rates [22, 23]. Our stratified analysis also found that males were younger (72.5 years) on average than females (77.5 years) at the time of major LEA, however, the prevalence of PVD (male = 87.1%, female = 87.7%), and other comorbidities was not significantly different by gender. These findings suggest the need for exploring sex-related differences regarding major LEA in Austria.

Peripheral vascular disease is an established underlying risk factor of both major and minor LEA, which is known to increase with age and in the presence of comorbidities like diabetes, chronic renal disease, and CVD [24]. Previous studies have reported that PVD contributed up to 80% of LEA and increased its odds and risk by and 63- and 13-fold, respectively [5, 12, 25, 26]. In line with other studies, 87.3% of individuals in our cohort had a PVD and were older (73.6 versus 69.0 years, $p < 0.001$) with a significantly higher burden of comorbidities such as renal disease (40.6% versus 23.7%, $p < 0.001$), CHF (31.1% versus 13.1%, $p < 0.001$), stroke (28.9% versus 15.0%, $p < 0.001$), and the mean ACCI score (6.3 versus 4.1, $p < 0.001$) than those without PVD. In agreement with our results, a study found a high proportion of ischemic heart

disease (46.0%), CHF (31.6%), stroke (27.7%), and chronic kidney disease (25.0%) among patients with arteriopathy [27]. Research has also shown a strong association between the accumulating burden of comorbidities and the risk of LEA. In this regard, a study has demonstrated a 12-fold increase in the risk of major LEA due to the increasing burden of comorbidities, as measured by the ACCI [26]. These factors altogether explain the high proportion of PVD in our cohort of major LEA and suggest that the ACCI could be a useful clinical tool to assess the risk of LEA.

Despite the advancements in surgical and medical management, patients with major LEA represent a patient population with high short- and long-term mortality [28]. However, significant disparities have been noted in both short- and long-term mortality rates of major LEA worldwide due to various patient- and healthcare-related factors. In our cohort, 30-day mortality was 13.5%, 90-day mortality was 22.0%, 1-year mortality was 34.4%, and 5-year mortality was 66.7% after major LEA. While other countries revealed lower 30-day mortality rates of 1.0% and 12.4% in the United Kingdom [4, 28], 6.4% in Japan [24], and 11.0% in New Zealand [29]. Likewise, a slightly lower 90-day mortality (18.0%) was reported in New Zealand [29]. In contrast to our study, a study in the Netherlands showed a much higher 30-day mortality of 21.0% [30]. Comparison of long-term mortality showed a significantly lower 1-year mortality of 10% and 5-year mortality of 27.0% after total LEA in the United Kingdom [4], whereas, higher mortality rates of 41.0% and 77.0% for 1-year and 5-year, respectively in the Netherlands [30]. Similarly, a meta-analysis of 21 cohort studies published between 2005 and 2015 reported the weighted mortality of 47.9% at 1-year and 62.2% at 5-year after LEA in individuals with and without diabetes [31]. It is worth noting that the majority of the previous studies were published within the first decade of 2000, while our data is comparatively recent. Again, these figures highlight the difficulties in comparing data across countries due to different age distribution, the burden of PVD, diabetes, and associated comorbidities, the proportion of individuals with severe amputations, and the stage at which the amputation was performed [30]. Yet, high rates of short- and long-term mortality observed in our cohort are important and its underlying and modifiable factors need to be investigated.

Although major LEA confers high mortality, the differential risk in mortality has been demonstrated with respect to various factors. Age was identified as a strong predictor of short- and long-term mortality in our study, as it has been shown previously [28, 29]. Interestingly, the risk of both short- and long-term mortality was significantly higher in males than females in our analysis, even after the adjustment for age and co-morbidities. Consistent with our results, another study demonstrated 25% higher odds of 30-day mortality in males compared to females [24]. On the contrary, most studies found no significant difference in the risk of mortality by sex [29, 32, 33]. The level of amputation was another significant predictor of mortality, which had a stronger association with the short-term mortality (91–97%) compared to the long-term mortality (50–71%). In support of our results, a meta-analysis showed that a higher level of amputation increased the risk of mortality by 140–220% than lower levels of amputations [31].

Our analysis revealed that except CHF, comorbidities including PVD, renal disease, dementia, and cancer were only associated with long-term mortality after major LEA. The evidence regarding the relationship between individual comorbidities and short-term mortality after LEA is inconsistent. According to one

study, among comorbidities, stroke was identified as a significant predictor of 30-day mortality [30], while other recent studies did not report the association of any comorbidity with 30-day mortality [28, 29, 34]. Conversely, higher odds of 30-days mortality were shown in patients with chronic renal disease (188%), cancer (46%), and cardiac disease (63%) compared to those without these comorbidities [24]. While research is consistent regarding the impact comorbidities on the long-term mortality after major LEA. In agreement with our study, a meta-analysis also reported peripheral artery disease (134%), coronary artery disease (101–133%), stroke (150–155%), end-stage renal disease (112–435%), dementia (102–177%) as strong predictors of long-term mortality [31].

The ACCI has been demonstrated as a valid tool for predicting the mortality outcomes in various diseases. Studies have also applied this tool to predict mortality after amputations. However, previous studies that have utilized it either did not generate it as a summary tool or had small sample sizes to achieve valid results [3, 34, 35]. Whilst other studies have shown its association with either short- or long-term mortality after major LEA [4, 29, 36, 37]. Adding to the existing evidence, our study has shown ACCI to be a significant predictor of both short-term and long-term mortality after major LEA even after adjusting for sex, age, levels of amputations, and type of diabetes. These findings suggest that comorbidities significantly influence the risk of short- and long-term mortality in individuals undergoing major LEA and the ACCI is a useful tool to summarize and quantify their impact on mortality outcomes. Additionally, it can be utilized in clinical settings to identify and thereafter manage high-risk individuals undergoing major amputations. However, more studies are recommended to use this index in larger and diverse cohorts to establish its predictive performance in this population.

Limitations

This study has several limitations related to data acquisition. First, the analysis included only index cases of major LEA due to the lack of availability of reliable data on repeated amputations for each individual, which might lead to an underestimation of the overall major LEA rates in Austria. As major amputations are less likely to be repeated, we assume that this approach has not a major impact on the estimates. Second, the rate of major LEA has been estimated by using the total population of Austria as a denominator, because the estimates of the total population living with diabetes according to age strata are not available. Although the approach adopted by us has been commonly reported in the literature, the estimates using the diabetes population would have allowed us to compare our rates with studies that have adopted this approach. With increasing diabetes prevalence, a sustainable amputation rate per 100,000 population suggests a decrease in individuals with manifest diabetes. Furthermore, the AHI database does not collect information about important factors such as ethnic background, social index, patient and healthcare factors, duration of diabetes, indications for amputations, and clinical and laboratory parameters. Last, the data on amputations in individuals without diabetes were not available to compare the risk and mortality of major LEA between groups.

Strengths

This study was based on a countrywide health insurance database, which captured 99% of the individuals who underwent major amputations. Therefore, our results are applicable to the entire Country. Also, this is the first study exploring the epidemiology of major LEA in the Austrian diabetes population and its findings carry significant importance for clinicians, policymakers, and stakeholders of the healthcare system in Austria. Another strength was the completeness of data collected by the AHI, which ensures the validity of the findings of this study. Last, unlike most population-based studies that used hospital discharge dates to capture amputations, actual dates of amputations were recorded in the AHI database, which allowed us to accurately calculate person-time to mortality.

Conclusions

The age-standardized rate of major LEA in the Austrian diabetes population estimated by this study is remarkably different from that reported previously, which needs further research. The overall and sex-specific age-standardized rate remained stable between 2014 and 2017 in Austria, which is promising given the increasing burden of diabetes and the high rate of diabetes-related hospital admission rates in the Country. Both short and long-term mortality rates after major LEA are comparatively high in our study cohort and research addressing its responsible factors might help in reducing the mortality in this vulnerable population. Old age, male sex, higher levels of amputations, peripheral vascular disease, and the presence of comorbid conditions such as CHF, cancer, dementia, and renal disease were significant risk factors of mortality after undergoing major LEAs. In addition to individual comorbidities, the accumulation of comorbidities summarized as the Charlson Comorbidity Index was identified as a strong predictor of both short- and long-term mortality. This can be a useful tool for clinicians to identify high-risk individuals who are undergoing major LEA. However, more research evidence is needed to validate the clinical usefulness of this tool in this patient population.

Abbreviations

ACCI
Age-adjusted Charlson Comorbidity Index; AHI:Austrian Health Insurance; AIDS:Acquired Immune Deficiency Syndrome; aHR:adjusted Hazard Ratio; AKA:Above-knee amputation; AAPC:Annual Percentage Change; aRR:adjusted Rate Ratio; ATC:Anatomical Therapeutic Classification; BKA:Below-knee amputation; CHF:Congestive Heart Failure; COPD:Chronic Obstructive Pulmonary Disease; CI:Confidence Interval; CVD:Cardiovascular Disease; HR:Hazard Ratio; ICD:International Classification of Disease; KD:Knee disarticulation; LASSO:Least Absolute Shrinkage and Selection Operator; LEA:Lower Extemity Amputations; OECD:Organization for Economic Cooperation and Development; PVD:Peripheral Vascular Disease; RR:Rate Ratio; SD:Standard Deviation; WHO:World Health Organization

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical University of Graz (application number: 1302/2020). Consent of participants was not required as it was a pseudonymized data obtained from the Austrian Health Insurance database.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing interests

The authors have no competing interests related to this work.

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Authors' contributions

HS and FA designed the study, FA performed the statistical analysis and wrote the first draft of the manuscript. HS and FA are the guarantors of the work and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and approved the final version of the manuscript.

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Figures

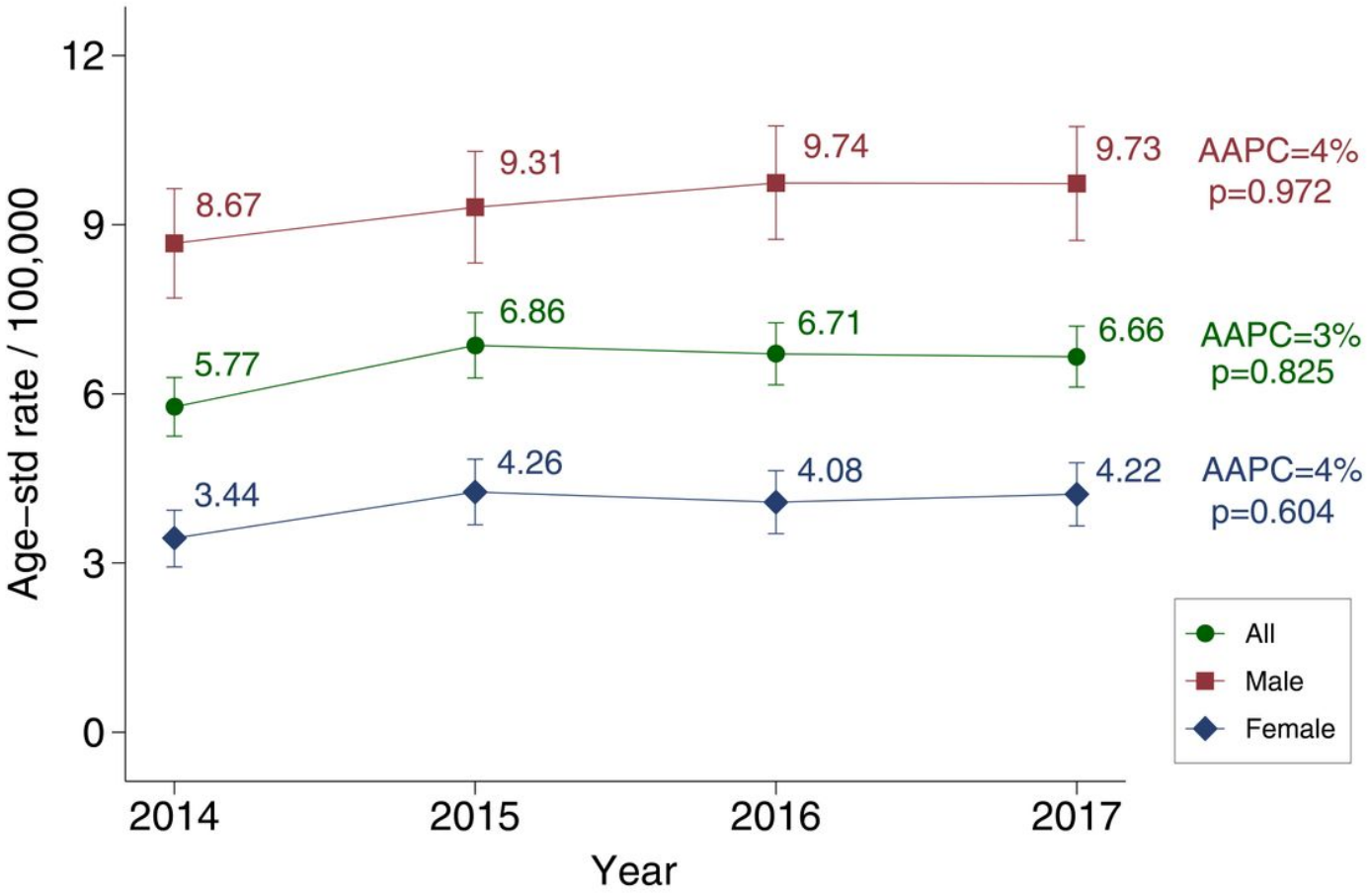

Figure 1

Age-standardized rates of major lower extremity amputation per 100,000 population, overall and by gender, between 2014 and 2017.

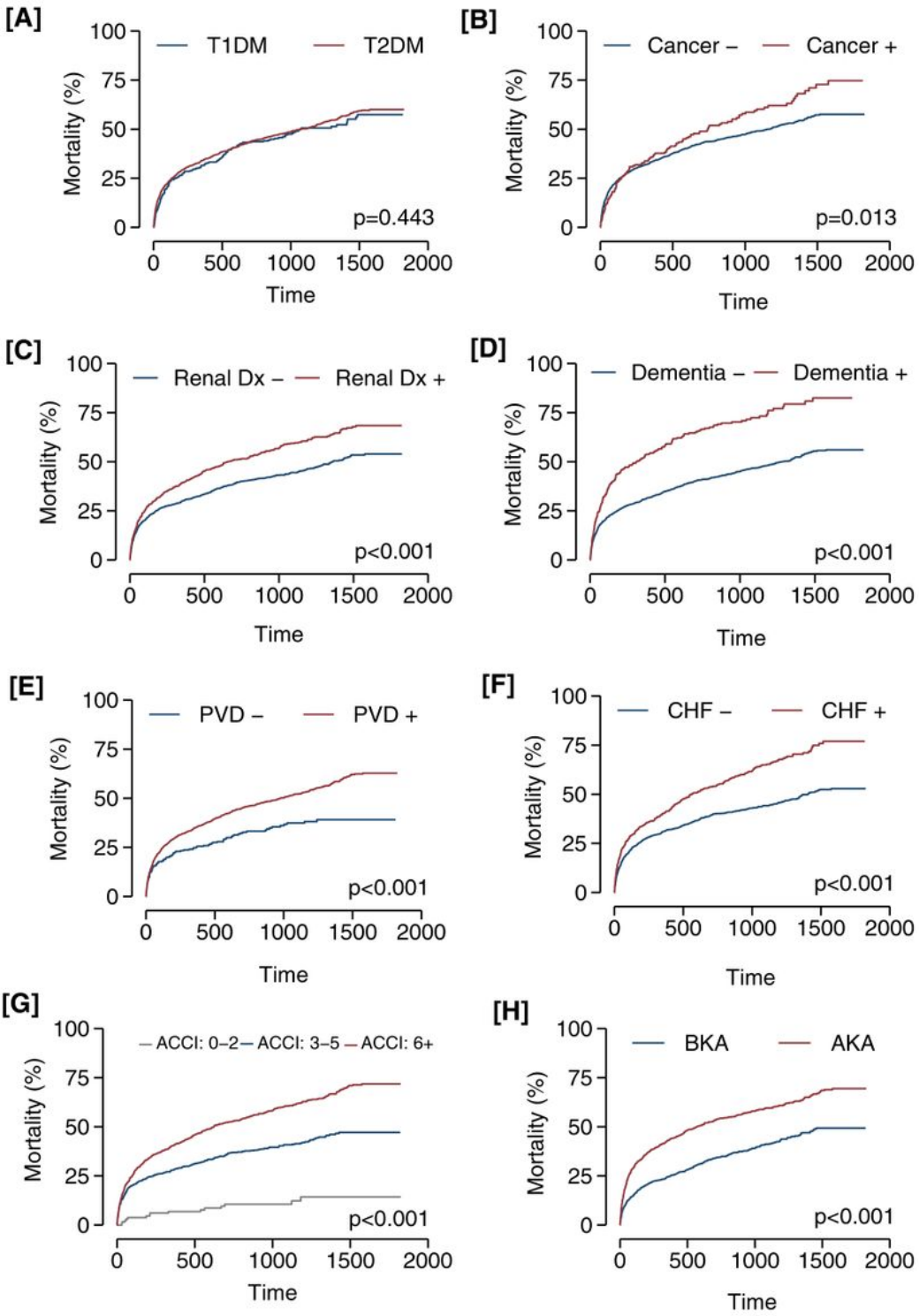

Figure 2

Kaplan-Meier plots of cumulative all-cause mortality after major lower extremity amputations: [A] types of diabetes, [B] Cancer, [C] Renal disease, [D] Dementia, [E] PVD, [F] CHF, [G] ACCI, and [H] types of amputations.

Supplementary Files

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