Received: 15 February 2021 | Revised: 9 April 2021 | Accepted: 17 April 2021

DOI: 10.1111/iwj.13607

ORIGINAL ARTICLE

IWJ WILEY

Outcomes in patients with chronic leg wounds in Denmark: A nationwide register-based cohort study

Ulla Riis Madsen[1,2] | **Nana Hyldig**[3] | **Knud Juel**[4]

[1]Department of Orthopedic Surgery, Holbaek Hospital, Holbaek, Denmark

[2]REHPA, Danish Knowledge Centre for Rehabilitation and Palliative Care, University of Southern Denmark, Odense, Denmark

[3]OPEN, Open Patient data Explorative Network, Odense University Hospital, Region of Southern Denmark, Odense, Denmark

[4]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

Correspondence
Ulla Riis Madsen, PhD, MPH, RN, Department of Orthopedic Surgery, Holbaek Hospital, Holbaek, Denmark, and REHPA, Danish Knowledge Centre for Rehabilitation and Palliative Care, University of Southern Denmark, Smedelundsgade 60, 4300 Holbaek, Denmark.
Email: urm@regionsjaelland.dk

Funding information
Novo Nordisk Fonden, Grant/Award Number: NNF18OC0051995

Abstract

This study aimed to investigate incidence and predictors of wound healing, relapse, major amputation, and/or death among patients with chronic leg wounds who were referred to specialist treatment at hospital for their condition. A nationwide register-based cohort study design was applied with 5 years of follow-up. All patients with diagnoses of chronic leg wounds in Denmark between 2007 and 2012 were included (n = 8394). Clinical, social, and demographic individual-level linked data from several Danish national registries were retrieved. Incidence rate per 1000 person-years (PY) was calculated. Predictors were investigated using Cox proportional hazards regression analysis. Incidence rates of having a healed wound was 236 per 1000 PY. For relapse, the incidence rate was 75 per 1000 PY, for amputation 16 per 1000 PY, and for death 100 per 1000 PY. Diabetes, peripheral arteria disease, or other comorbidities were associated with decreased chance of wound healing and increased risk of relapse, major amputation, and death. Regional differences in all four outcomes were detected. Basic or vocational education independently predicted risk of amputation and death. This study provides epidemiological data that may help identify patients at particular risk of poor outcomes. It also elucidates social inequality in outcomes.

KEYWORDS

chronic wounds, foot ulcer, major amputation, mortality, relapse

1 | BACKGROUND

Chronic leg ulceration, defined as a wound on leg or foot that does not progress through the healing process in a timely manner,[1] is both a major challenge in healthcare and burdensome to affected individuals.[2] This is especially true when wound treatment continues for extended periods of time and still ends in relapse, amputation, or death. Reliable epidemiological data on incidence and outcomes in patients with chronic leg ulceration is underreported,[3,4] which hampers efficient resource allocation, planning, and improvement of wound care for the most affected patients.

Globally, it has been estimated that approximately 1.5 per 1000 people in the general population have a chronic leg wound (>3 weeks, all aetiologies).[4] It has also been suggested that 15% to 25% of the diabetic population will have a foot wound at some point[5,6] with an annual

incidence of 2%.[7] Although diabetic foot ulcers without complications generally heal within 6 weeks, this is not a realistic outcome for the majority of diabetic patients as only 45% of patients presenting with an initial diabetic foot ulcer will become both ulcer free without experiencing amputation and alive at 12 months.[8] There are several reasons why leg wounds do not heal spontaneously with the most common being infection, venous insufficiency, and ischaemia. These conditions are often found in combination.[1,9] Critical limb threatening ischaemia has been suggested as a contributing factor for the absence of wound healing in 30% to 40% of cases[10] and is a strong predictor of amputation and early death.[10] In the western world, most amputations (>90%) are necessitated by complications associated with vascular disease. The majority of these patients have a history of chronic wounds.[11]

The aim of this study was to investigate incidence and predictors of wound healing, relapse, major amputations, and/or death among patients referred to specialist treatment at hospital for chronic leg wounds.

Key Messages

- high incidence of death among patients with chronic leg wounds highlights the need to incorporate a palliative approach to chronic wound care in order to address palliative care needs among the most affected
- this nationwide register-based cohort study investigates incidence and predictors of wound healing, relapse, major amputations, and/or death among patients referred to specialist treatment at hospital for chronic leg wounds, with 5 years of follow-up
- having peripheral arteria disease is the strongest predictor of major amputation. However, risk of major amputation and death when having chronic leg wound is independently predicted by lower educational level, and higher risk of relapse wound and death is associated with living alone

2 | METHODS

The study was designed as an observational register-based cohort study based on nationwide individual-level linked data from several Danish national registries with 5 years of follow-up.

The study is reported in concordance with the Reporting of Studies Conducted and uses the Observational Routinely-Collected Data (RECORD) statement (an extension of the existing STROBE guidelines).[12]

2.1 | Study population

The Danish healthcare system is government funded, which ensures free access to health care at hospitals, general practitioners, and homecare for all residents.[13] Patients with complicated leg wounds are referred to specialist treatment at hospital wound clinics while less complicated cases are treated in primary care. For this study, patients aged ≥18 years were included on their first referral to hospital for leg wounds within a 5-year period (wounds on leg or foot, all aetiologies). Patients were included if a wound required more than 6 weeks of treatment (admissions and/or outpatient visits) during the 6-year period from 1 January 2007 to 31 December 2012 (n = 8705). The index date was the date of admission/first outpatient visit plus 6 weeks. Disease-related risk factors were identified from ICD-10 codes on primary or secondary diagnoses 5 years prior to index date. Follow-up was 5 years after date of admission or until death.

A national group of wound specialists selected a comprehensive list of ICD-10 codes (supplementary appendix), which identified eligible cases of leg wounds. Other wound specialist in seven hospitals then confirmed this list. Comprehensiveness of the list was further validated by comparing codes used at two hospitals for patients with known leg wounds without more codes being identified. Pressure ulcers and cancer-related wounds were excluded as the ICD-10 codes could not definitively define whether these wounds were situated on a foot or leg. Patients were excluded if they had had major amputation within 5 years before study start (n = 243), died within 6 weeks of 1 January 2007 (n = 38) or emigrated during the study period (n = 30). The final sample for analysis consisted of 8394 patients.

2.2 | Data sources

In Denmark, all residents are provided with a unique personal identification number,[13] which is used as the key identifier in all Danish health and social care registers. Data from the following national registers were used to identify the study population and to extract data on baseline characteristics, risk factors, and outcomes:

- The Danish Civil Registration System (all persons living in Denmark).[13]

- The Danish National Patient Register (all somatic inpatient admissions and outpatient visits including diagnosis codes).[14]
- The Danish National Prescription Registry (individual data on all dispensed prescription pharmaceuticals sold in Danish community pharmacies. Data consist of information on ATC codes, price, reimbursement, and so on, at patient level).[15]
- The Danish Population Education Register (information on completed education).[16]
- Different socio-economic registers from Statistics Denmark (population-level demographic data).

2.3 | Variables

2.3.1 | Outcomes

Four outcome variables were chosen for analysis: wound healing, relapse of wound, amputation, and death. *Wound healing* was defined as end of contact with hospital as patients are normally monitored at hospital until wound healing is achieved (wound is completely epithelised). Patients with major amputation who continued hospital contact with a wound diagnosis were not considered healed until end of contact. *Relapse wound* was defined as new contact with one of the abovementioned diagnoses more than 2 weeks after end of first hospital contact. Index date was last day of first hospital contact. *Major amputation* was defined as amputation above the ankle. *Death* was defined as death by all causes; see supplementary appendix for more details.

2.3.2 | Explanatory variables

The following explanatory variables were chosen based on the potential influence on extended wound healing and risk of amputation[1,3,9,17]:

- Age (20-year intervals [eg, 40–59])
- Sex (male/female)
- Cohabitation (cohabiting [married or residing with partner]/living alone).
- Educational level basic (primary school)/vocational (vocational or lower secondary)/higher. For each patient, the highest completed level at day of admission was selected.
- Place of residence (five regions). This variable controls for local variability in health care.
- Diabetes (yes/no). Individuals with diabetes were identified with the ICD-10 code for diabetes type 1 or 2 (E10-11) and/or having picked up prescribed antidiabetic medication from pharmacies more than once in 5 years before inclusion. To identify patients diagnosed with diabetes when they presented with a wound, individuals who had the diagnosis or had picked up prescribed antidiabetic medication from pharmacies at least once from day of admission until index date were classified as having diabetes.
- Peripheral arteria disease (PAD) (yes/no). Individuals with at least one ICD-10 code for PAD or arteriosclerosis within 5 years prior to inclusion were considered.
- Comorbidity (categorised in Charlson comorbidity index 0, 1-2, and 3+ where higher score predicted increased risk of death[18]). In the hazard ratio (HR) models, diagnoses of diabetes and PAD were not included in the Charlson comorbidity calculation. This was to avoid controlling for the same diagnosis multiple times as diabetes and PAD were included as separated variables in the models.

All variables were used at date of admission unless otherwise stated. More details, including diagnostic codes, are available in the supplementary appendix.

2.3.3 | Statistics

Incidence of wound healing, relapse, major amputation, and mortality were calculated as 5 years cumulated incidence among patients with chronic leg wounds (patients referred to specialist treatment at hospital for >6 weeks) and as incidence rate per 1000 person-years (PY) for both each outcome and among patients with diabetes or PAD. Characteristics of individuals are presented for all outcomes using numbers and percentages.

Cox proportional hazards regression analysis was used to estimate the effects (HRs) of covariates on the four outcomes. Results are presented as crude values and HR adjusted according to the distribution of the other covariates, 95% confidence intervals (CIs) and P values. The proportional hazard assumption was tested using Schoenfeld residuals.[19] For variables that did not meet the proportional hazard assumption (cut-off value $P < .01$), time splitting was performed, and HR was calculated the first year and from start of years 2 to 5. All analyses were performed using Stata version 16 (StataCorp, College Station, Texas).

3 | RESULTS

The characteristics of patients referred to specialist treatment at hospital for chronic leg wounds in Denmark from 2007 to 2012 are presented in Table 1. Most patients

(76%) had basic or vocational levels of education. Within the study population, 17% had diabetes and 62% had a Charlson comorbidity index score[18] of 0.

Of patients with chronic leg wounds, n = 7659 (91%) fulfilled the criteria for having a healed wound, and n = 91 (1%) were still in treatment for leg wounds after 5 years (Table 2). Almost one fourth of those who healed had a relapse wound. In total, n = 514 (7%) had a major amputation with 310 of these amputations happening after primary healing. Thirty-nine percent (n = 3240) died during follow-up and 630 of these died with the wound. The largest proportions of deaths occurred among the oldest and those with the most comorbidities. It is worth noting that 29% of those without registered comorbidities also died within 5 years of follow-up.

TABLE 1 Characteristics of patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012

	n (%)
Total	8394 (100)
Mean age (SD)	68.2 (17.7)
18 to 39	612 (7)
40 to 59	1669 (20)
60 to 79	3593 (43)
80+	2520 (30)
Sex	
Male	4002 (48)
Female	4392 (52)
Cohabitation	
Cohabiting	3839 (46)
Living alone	4527 (54)
Missing	28 (0)
Educational level	
Basic	3525 (42)
Vocational	2820 (34)
Higher	1204 (14)
Missing	845 (10)
Place of residence (region)	
Capital	2928 (35)
Zealand	1148 (14)
Southern Denmark	1881 (22)
Central Denmark	1743 (21)
North Denmark	666 (8)
Missing	28 (0)
Diabetes	1436 (17)
Peripheral arteria disease (PAD)	1902 (23)
Comorbidity (Charlson index)	
0	5227 (62)
1 to 2	2395 (29)
≥3	772 (9)
Comorbidity (Charlson modified)[a]	
0	5774 (69)
1 to 2	1958 (23)
≥3	662 (8)

[a]Diagnosis of diabetes and peripheral arterial disease (PAD) not included in Charlson comorbidity calculation.

Incidence rates of a healed wound were 1812 per 1000 PY, decreasing to 1100 and 1485 PY among patients with diabetes or PAD, respectively. For relapse, the incidence rate was 75 per 1000 PY, which increased to 112 and 107 per 1000 PY among patients with diabetes or PAD, respectively. The incidence rate of amputation was 16 per 1000 PY, which increased to 27 and 66 per 1000 PY among patients with diabetes or PAD, respectively. The mortality rate was 100 per 1000 PY in the total population increasing to 104 and 184 per 1000 PY among patients with diabetes and PAD, respectively.

All four variables were found to be negatively associated with wound healing (place of residence, PAD, diabetes, and Charlson index >0) (Table 3). Place of residence and PAD did not fit the model conditions for Cox regression analysis, and time splitting was performed. It was found that place of residence (living in the Capital or Zealand regions) and PAD decreased the chance of wound healing the first year. Sex, cohabitation, and educational level did not influence chance of wound healing. A sensitivity test was performed with amputation before wound healing being put in the model as competing risk factors with only one significant change in result: older age became a predictor of lower chance of wound healing (age 80+, HR adjusted 0.89 CI 0.81–0.98, *P* .01).

Six variables were found to increase the risk of relapse: older age, living alone, diabetes, PAD, and Charlson index >0 (Table 4). Age, place of residence, and diabetes did not fit the model conditions for Cox regression analysis, and time splitting was performed. Higher age and diabetes were found to increase risk of relapse independent of time splitting. Living in all regions outside the Capital region increased risk of relapse the first year. Sex and educational level did not influence risk of relapse.

All but one variable (cohabitation) was associated with major amputation within 5 years (Table 5). Time splitting was performed in three variables (sex, PAD, and Charlson index). Younger age and living in the Capital, Zealand, or Southern Denmark regions were associated with lower risk as was being female (first year only). Lower educational levels, diabetes, and particularly having PAD was associated with increased risk.

TABLE 2 Five years cumulated incidence of wound healing, relapse, major amputation, and death among patients referred to specialist treatment at hospital for chronic leg wounds in Denmark from 2007 to 2012

	Total n (%)[a]	Wound healing n (%)[b]	Relapse n (%)[b]	Major amputation n (%)[b]	Death n (%)[b]
Total	8394 (100)	7659 (91)[c]	2012 (24)	514 (7)	3240 (39)
Age					
18 to 59	2281 (27)	2195 (96)	473 (21)	48 (2)	218 (10)
60 to 79	3593 (43)	3298 (92)	923 (26)	254 (7)	1291 (36)
80+	2520 (30)	2166 (86)	616 (24)	212 (8)	1731 (69)
Sex					
Male	4002 (48)	3647 (91)	979 (24)	270 (7)	1427 (36)
Female	4392 (52)	4012 (91)	1033 (24)	244 (6)	1813 (41)
Cohabitation					
Cohabiting	3839 (46)	3554 (93)	870 (23)	209 (5)	1126 (29)
Living alone	4527 (54)	4077 (90)	1135 (25)	304 (7)	2111 (47)
Missing	28	28	7	1	3
Educational level					
Basic	3525 (42)	3216 (91)	916 (26)	257 (7)	1447 (41)
Vocational	2820 (34)	2605 (92)	661 (23)	159 (6)	883 (31)
Higher	1204 (14)	1129 (94)	268 (22)	43 (4)	317 (26)
Missing	845	709	167	55	593
Place of residence (region)					
Capital	2928 (35)	2654 (91)	647 (22)	150 (5)	1159 (40)
Zealand	1148 (14)	1013 (88)	245 (21)	74 (6)	414 (36)
Southern Denmark	1881 (22)	1724 (92)	498 (26)	94 (5)	758 (40)
Central Denmark	1743 (21)	1603 (92)	414 (24)	139 (8)	622 (36)
North Denmark	666 (8)	637 (96)	201 (31)	56 (8)	284 (45)
Missing	28	28	7	1	3
Diabetes					
Yes	1436 (17)	1244 (87)	463 (32)	139 (10)	576 (40)
Peripheral arteria disease (PAD)					
Yes	1902 (23)	1625 (85)	513 (27)	352 (19)	1114 (59)
Charlson index					
0	5227 (62)	4959 (95)	1152 (22)	249 (5)	1496 (29)
1 to 2	2395 (29)	2093 (87)	685 (29)	195 (8)	1199 (50)
≥3	772 (9)	607 (79)	175 (23)	70 (9)	545 (71)
Charlson index modified)[c,d]					
0	5774 (69)	5432 (94)	1349 (23)	298 (5)	1663 (29)
1 to 2	1958 (23)	1706 (87)	516 (26)	162 (8)	1094 (56)
≥3	662 (8)	521 (79)	147 (22)	54 (8)	483 (73)

[a]Column%.
[b]Row%.
[c]Including n = 190 who had a major amputation before healing and continued their hospital contact with a diagnosis of wound, n = 310 who had a major amputation after primary wound healing, and n = 2600 who died after primary healing.
[d]Diagnosis of diabetes and peripheral arterial disease not included in Charlson comorbidity calculation

TABLE 3 Cox regression analysis for predicting wound healing among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 with 5 years of follow-up

	Wound healing				
Variable	**Person-years**	**HR crude (95% CI)**	***P***	**HR adjust (95% CI)[a]**	***P***
Number of subjects		7431			
Age			.001		>.10
18 to 39	282	1 (Ref.)		1 (Ref.)	
40 to 59	950	0.88 (0.80–0.97)		1.00 (0.91–1.11)	
60 to 79	1940	0.84 (0.77–0.92)		1.01 (0.92–1.10)	
80+	1054	0.90 (0.82–0.99)		1.05 (0.95–1.16)	
Sex			.003		>.10
Male	2152	1 (Ref.)		1 (Ref.)	
Female	2074	1.07 (1.02–1.12)		0.99 (0.94–1.04)	
Cohabitation			>.10		>.10
Cohabiting	2014	1.01 (0.97–1.06)		1.00 (0.95–1.05)	
Living alone	2194	1 (Ref.)		1 (Ref.)	
Educational level			.01		>.10
Basic	1684	1.08 (1.01–1.16)		1.04 (0.97–1.11)	
Vocational	1523	1.01 (0.94–1.08)		1.01 (0.94–1.09)	
Higher	668	1 (Ref.)		1 (Ref.)	
Place of residence (region)		Year 1[c]	<.001	Year 1[c]	<.001
Capital	1828	1 (Ref.)		1 (Ref.)	
Zealand	769	1.02 (0.94–1.10)		1.05 (0.96–1.14)	
Southern Denmark	669	1.49 (1.39–1.59)		1.47 (1.37–1.58)	
Central Denmark	737	1.41 (1.32–1.50)		1.40 (1.30–1.50)	
North Denmark	206	1.90 (1.73–2.08)		1.88 (1.70–2.07)	
Place of residence (region)		Years 2 to 5[c]	<.001	Years 2 to 5[c]	.02
Capital		1 (Ref.)		1 (Ref.)	
Zealand		0.75 (0.60–0.89)		0.81 (0.65–0.97)	
Southern Denmark		1.26 (1.00–1.52)		1.22 (0.96–1.48)	
Central Denmark		1.03 (0.83–1.23)		1.09 (0.88–1.31)	
North Denmark		0.98 (0.62–1.34)		0.96 (0.59–1.33)	
Diabetes			<.001		<.001
No	3095	1 (Ref.)		1 (Ref.)	
Yes	1131	0.67 (0.63–0.71)		0.67 (0.63–0.72)	
PAD		Year 1[c]	<.001	Year 1[c]	<.001
No	3132	1 (Ref.)		1 (Ref.)	
Yes	1094	0.73 (0.69–0.78)		0.71 (0.67–0.76)	
PAD		Years 2 to 5[c]	.01	Years 2 to 5[c]	.05
No		1 (Ref.)		1 (Ref.)	
Yes		1.24 (1.06–1.42)		1.19 (1.00–1.37)	
Charlson index modified[b]			<.001		.01
0	2924	1 (Ref.)		Ref.	
1 to 2	973	0.93 (0.88–0.99)		0.94 (0.89–1.00)	
≥3	330	0.85 (0.77–0.93)		0.88 (0.80–0.97)	

Abbreviation: PAD, peripheral arteria disease.

[a]All HR adjusted for the listed covariates.

[b]Charlson index excluding diabetes and peripheral arterial disease.

[c]Timesplitting, HR the first year and from start of year 2 until end of year 5.

TABLE 4 Cox regression analysis for predicting relapse, among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 within 5 years of follow-up

	Relapse				
Variable	**Person-years**	**HR crude (95% CI)**	***P***	**HR adjust (95% CI)[a]**	***P***
Number of subjects		7441			
Age		Year 1[c]	<.001	Year 1[c]	<.001
18 to 39	2757	0.42 (0.30–0.61)		0.51 (0.35–0.74)	
40 to 59	6422	0.71 (0.58–0.87)		0.81 (0.65–1.00)	
60 to 79	11 843	0.83 (0.71–0.98)		0.83 (0.70–0.99)	
80+	5984	1 (Ref.)		1 (Ref.)	
Age		Years 2 to 5[c]	<.001	Years 2 to 5[c]	<.001
18 to 39		0.09 (0.06–0.11)		0.29 (0.19–0.39)	
40 to 59		0.62 (0.52–0.72)		0.69 (0.56–0.81)	
60 to 79		0.78 (0.67–0.88)		0.78 (0.66–0.90)	
80+		1 (Ref.)		1 (Ref.)	
Sex			>.10		>.10
Male	13 022	1 (Ref.)		1 (Ref.)	
Female	13 985	0.98 (0.89–1.07)		0.93 (0.84–1.03)	
Cohabitation			<.001		<.001
Cohabiting	13 320	0.81 (0.74–0.88)		0.84 (0.76–0.92)	
Living alone	13 581	1 (Ref.)		1 (Ref.)	
Educational level			<.001		>.10
Basic	10 947	1.33 (1.16–1.53)		1.12 (0.98–1.29)	
Vocational	9697	1.10 (0.96–1.27)		1.05 (0.91–1.21)	
Higher	4380	1 (Ref.)		1 (Ref.)	
Place of residence (region)		Year 1[c]	<.001	Year 1[c]	<.001
Capital	9655	1 (Ref.)		1 (Ref.)	
Zealand	3698	1.37 (1.07–1.75)		1.38 (1.06–1.78)	
Southern Denmark	5868	2.11 (1.75–2.55)		2.27 (1.86–2.78)	
Central Denmark	5699	1.69 (1.38–2.07))		1.77 (1.43–2.20)	
North Denmark	1980	2.50 (1.96–3.18)		2.43 (1.87–3.16)	
Place of residence (region)		Years 2 to 5[c]	.05	Years 2 to 5[c]	>.10
Capital		1 (Ref.)		1 (Ref.)	
Zealand		0.84 (0.69–1.00)		0.84 (0.68–1.00)	
Southern Denmark		0.91 (0.77–1.05)		0.94 (0.79–1.09)	
Central Denmark		0.85 (0.72–0.99)		0.90 (0.75–1.04)	
North Denmark		1.09 (0.85–1.32)		1.07 (0.83–1.32)	
Diabetes		Year 1[c]	<.001	Year 1[c]	<.001
No	22 879	1 (Ref.)		1 (Ref.)	
Yes	4128	1.37 (1.16–1.62)		1.39 (1.17–1.66)	
Diabetes		Years 2 to 5[d]	<.001	Years 2 to 5[d]	<.001
No		1 (Ref.)		1 (Ref.)	
Yes		1.81 (1.57–2.05)		1.74 (1.49–1.98)	
PAD			<.001		<.001
No	22 201	1 (Ref.)		1 (Ref.)	

TABLE 4 (Continued)

	Relapse				
Variable	**Person-years**	**HR crude (95% CI)**	***P***	**HR adjust (95% CI)[a]**	***P***
Yes	4806	1.51 (1.36–1.67)		1.32 (1.18–1.47)	
Charlson index modified[b]			<.001		<.001
0	20 407	1 (Ref.)		1 (Ref.)	
1 to2	5235	1.42 (1.28–1.57)		1.34 (1.21–1.49)	
≥3	1365	1.50 (1.26–1.77)		1.30 (1.09–1.56)	

Abbreviation: PAD, peripheral arteria disease.
[a]All HRs are adjusted for the listed covariates.
[b]Charlson index modified with diagnosis of diabetes and peripheral arterial disease not included in calculation.
[c]Timesplitting, HR the first year and from start of year 2 until end of year 5.

TABLE 5 Cox regression analysis for predicting amputations among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 within 5 years of follow-up

	Major amputation				
Variable	**Person-years**	**HR crude (95% CI)**	***P***	**HR adjust (95% CI)[a]**	***P***
Number of subjects		7528			
Age			<.001		<.001
18 to 39	3021	0.03 (0.01–0.11)		0.04 (0.01–0.29)	
40 to 59	7666	0.24 (0.18–0.34)		0.42 (0.29–0.60)	
60 to 79	13 816	0.70 (0.58–0.84)		0.76 (0.62–0.93)	
80+	6901	1 (Ref.)		1 (Ref.)	
Sex		Year 1[c]	.02	Year 1[c]	.04
Male	15 233	1 (Ref.)		1 (Ref.)	
Female	16 171	0.73 (0.58–0.90)		0.73 (0.57–0.93)	
Sex		Years 2 to 5[c]	>.1	Years 2 to 5[c]	>.1
Male		1 (Ref.)		1 (Ref.)	
Female		1.03 (0.74–1.32)		1.03 (0.71–1.34)	
Cohabitation			.002		.06
Cohabiting	15 476	0.76 (0.63–0.90)		0.83 (0.68–1.01)	
Living alone	15 800	1 (Ref.)		1 (Ref.)	
Educational level			<.001		.05
Basic	12 869	2.20 (1.59–3.04)		1.50 (1.08–2.09)	
Vocational	11 262	1.63 (1.16–2.28)		1.40 (0.99–1.96)	
Higher	5061	1 (Ref.)		1 (Ref.)	
Place of residence (region)			<.001		.008
Capital	10 996	1 (Ref.)		1 (Ref.)	
Zealand	4308	1.27 (0.96–1.68)		1.13 (0.84–1.52)	
Southern Denmark	7004	0.97 (0.75–1.26)		1.02 (0.77–1.34)	
Central Denmark	6581	1.55 (1.23–1.96)		1.52 (1.19–1.95)	
North Denmark	2386	1.67 (1.22–2.27)		1.31 (0.94–1.85)	
Diabetes			<.001		<.001
No	26 165	1 (Ref.)		1 (Ref.)	

(Continues)

TABLE 5 (Continued)

Variable	Major amputation				
	Person-years	HR crude (95% CI)	*P*	HR adjust (95% CI)[a]	*P*
Yes	5240	1.80 (1.48–2.19)		1.72 (1.39–2.13)	
PAD		Year 1[c]	<.001	Year 1[c]	<.001
No	26 104	1 (Ref.)		1 (Ref.)	
Yes	5301	13.35 (10.27–17.36)		10.13 (7.62–13.48)	
PAD		Years 2 to 5[c]	<.001	Years 2 to 5[c]	<.001
No		1 (Ref.)		1 (Ref.)	
Yes		5.77 (4.12–7.41)		4.43 (3.09–5.76)	
Charlson index modified[b]		Year 1[c]	.001	Year 1[c]	.001
0	23 654	1 (Ref.)		1 (Ref.)	
1 to 2	6167	1.75 (1.37–2.23)		1.32 (1.02–1.71)	
≥3	1584	2.16 (1.53–3.05)		1.38 (0.95–2.00)	
Charlson index modified[b]		Years 2 to 5[c]	.003	Years 2 to 5[c]	.02
0		1 (Ref.)		1 (Ref.)	
1 to 2		2.04 (1.40–2.67)		1.80 (1.21–2.38)	
≥3		2.12 (0.98–3.26)		1.66 (0.75–2.56)	

Abbreviation: PAD, peripheral arteria disease.
[a]All HRs are adjusted for the listed covariates.
[b]Charlson index modified with diagnosis of diabetes and peripheral arterial disease not included in calculation.
[c]Timesplitting, HR the first year and from start of year 2 until end of year 5.

TABLE 6 Cox regression analysis for predicting death among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 within 5 years of follow-up

Variable	Death				
	Person-years	HR crude (95% CI)	*P*	HR adjust (95% CI)[a]	*P*
Number of subjects		7534			
Age			<.001		<.001
18 to 39	3026	0.01 (0.01–0.03)		0.02 (0.01–0.05)	
40 to 59	7782	0.11 (0.10–0.13)		0.17 (0.14–0.20)	
60 to 79	14 382	0.38 (0.36–0.41)		0.46 (0.42–0.50)	
80+	7262	1 (Ref.)		1 (Ref.)	
Sex			<.001		<.001
Male	15 804	1 (Ref.)		1 (Ref.)	
Female	16 648	1.20 (1.12–1.29)		0.77 (0.71–0.83)	
Cohabitation			<.001		<.001
Cohabiting	15 906	0.56 (0.52–0.60)		0.77 (0.71–0.84)	
Living alone	16 415	1 (Ref.)		1 (Ref.)	
Educational level			<.001		.01
Basic	13 410	1.74 (1.54–1.96)		1.20 (1.06–1.36)	
Vocational	11 600	1.23 (1.08–1.40)		1.12 (0.99–1.28)	
Higher	5145	1 (Ref.)		1 (Ref.)	
Place of residence (region)		Year 1[c]	.006	Year 1[c]	.002

TABLE 6 (Continued)

	Death				
Variable	**Person-years**	**HR crude (95% CI)**	***P***	**HR adjust (95% CI)[a]**	***P***
Capital	11 302	1 (Ref.)		1 (Ref.)	
Zealand	4458	1.07 (0.89–1.30)		1.24 (1.00–1.54)	
Southern Denmark	7197	1.03 (0.88–1.22)		1.24 (1.03–1.49)	
Central Denmark	6859	1.00 (0.84–1.18)		1.05 (0.86–1.28)	
North Denmark	2504	1.12 (0.89–1.41)		1.29 (1.00–1.68)	
Place of residence (region)		Years 2 to 5[c]	<.001	Years 2 to 5[c]	.006
Capital		1 (Ref.)		1 (Ref.)	
Zealand		0.83 (0.72–0.95)		0.91 (0.77–1.05)	
Southern Denmark		1.02 (0.91–1.14)		1.14 (1.00–1.28)	
Central Denmark		0.84 (0.74–0.94))		0.92 (0.80–1.04)	
North Denmark		1.10 (0.92–1.27)		1.17 (0.96–1.37)	
Diabetes			>.10		.02
No	26 924	1 (Ref.)		1 (Ref.)	
Yes	5527	1.05 (0.96–1.15)		1.13 (1.02–1.25)	
PAD			<.001		<.001
No	26 406	1 (Ref.)		1 (Ref.)	
Yes	6046	2.24 (2.08–2.41)		1.63 (1.50–1.76)	
Charlson index modified[b]		Year 1[c]	<.001	Year 1[c]	<.001
0	24 350	1 (Ref.)		1 (Ref.)	
1 to 2	6450	2.80 (2.45–3.20)		2.51 (2.15–2.94)	
≥3	1651	5.01 (4.26–5.89)		4.70 (3.92–5.64)	
Charlson index modified[b]		Years 2 to 5[c]	<.001	Years 2 to 5[c]	<.001
0		1 (Ref.)		1 (Ref.)	
1 to 2		2.29 (2.08–2.50)		2.00 (1.80–2.21)	
≥3		3.65 (3.16–4.13)		3.16 (2.71–3.61)	

Abbreviation: PAD, peripheral arteria disease.

[a]All HRs are adjusted for the listed covariates.

[b]Charlson index modified with diagnosis of diabetes and peripheral arterial disease not included in calculation.

[c]Timesplitting, HR the first year and from start of year 2 until end of year 5.

Two variables needed time splitting to fit the assumptions for Cox regression analysis on risk of death (place of residence and Charlson index) (Table 6). Younger age, female, living with someone, and residing in the Capital or Central Denmark (first year) were protective factors from death. Lower educational level, diabetes, PAD, and especially more comorbidities (Charlson index > 0) increased risk of dying within 5 years from presenting with a leg wound that was not healed within 6 weeks.

4 | DISCUSSION

This study identified patients with chronic leg wounds at risk of delayed wound healing, relapse, major amputation, and death. It confirms that PAD is a strong predictor of amputation and death[10] as are diabetes and having more comorbidities (Charlson index > 0). The finding of significant differences in all outcomes associated with place of residence and the higher risk of major amputations and death associated with lower educational level and living alone is surprising.

4.1 | Wound healing

Comparable to other wound healing studies,[20,21] 91% of patients experienced a healed wound during follow-up. However, 1% still had an unhealed wound after 5 years, and diabetes was particularly associated with decreased

chance of wound healing. A list of factors is known to predict healing in chronic wounds. This list includes renal disease, wound aetiology, and malnutrition among others.[22] Although highly relevant,[23] detailed data on more predicting factors are not routinely registered and was therefore not available for this study. Future benchmarking efforts that implement clinical wound care data registries in Denmark would be beneficial.

Patients whose wounds do not heal or for whom healing would pose an undue medical or social burden should be involved in shared decision-making processes[24,25] regarding whether they prefer a palliative approach to wound care[26,27] that reduces the complexity of care and minimises risk of infection and hospitalisation, or if they prefer a major amputation.[25,28]

4.2 | Relapse

The cumulative incidence for relapse was 24% in the total population of patients with chronic leg wounds. This increased to 32% and 27% among patients with diabetes or PAD, respectively. A European recurrence rate of diabetic foot ulcers of 24.9% per PY was calculated in a recent systematic review and meta-analysis of 49 studies (9670.6 PY of follow-up).[29] Relapse has been estimated to occur in 65% of cases among patients with diabetic foot ulcers within 5 years.[26] This number was 17% to 20% within 12 months among patients with venous leg ulcers.[30] These studies did not include only patients with chronic leg wounds as ours did, and our rates of relapse could be underestimated if the relapse wound did not warrant hospital contact. Patient education and access to appropriate footwear combined with other preventive interventions tailored to the needs of patients most at risk[31] are crucial for preventing recurrent leg wounds regardless of aetiology.[26,32,33] The regional differences we observed could indicate differences in access to these preventive interventions. It is important to note that differences in study design and populations make comparisons difficult.

4.3 | Major amputation

Our observation of regional differences confirms variations in amputation rates, which has been seen in studies between and within countries (ie, some countries have shown larger rates than others).[9,34] It is important to acknowledge that amputation is not a measure of the natural history of disease but simply a treatment and that the selection of treatment varies according to healthcare provider, medical necessity, medical need, and patient preference.[34]

4.4 | Risk of death

This study emphasises that patients with chronic leg wounds are in the latter part of their lives. In total, 39% of all cases died within 5 years. The proportion of those with PAD was 59% and as high as 73% among the patients with multiple comorbidities (Charlson comorbidity index ≥3). In comparison, 4-year mortality rates of 19% to 64% have been reported among patients with PAD depending on severity and whether or not they have wounds.[9,35,36] Additionally, 5-year mortality rates of 46% have been reported among patients with diabetic foot ulcers who are treated in specialist diabetes centres.[37] Although it has been shown that having diabetes and foot ulcer increases risk of death,[38] this study identified no literature describing the same association in patients with leg wounds and other comorbidities. This could be a topic for future research. For patients with a Charlson index of 0 (equal to no comorbidities), risk of death within 5 years was almost one-third. These high mortality rates in patients with chronic leg wounds highlight the need to incorporate a palliative approach to chronic wound care to address palliative care needs including advanced care planning.[39]

4.5 | Inequality in health

Our findings point at more areas of inequalities in health among patients with chronic leg wounds. Current evidence supports an association between socioeconomic inequalities and non-communicable diseases globally.[40] Although evidence is incomplete and limited,[40] this has become even more evident during the Covid-19 pandemic.[41] Even though Denmark is a small country with free health care available to all residents, studies have found that the country has socioeconomic inequalities in health that are among the highest of the Nordic countries and that these inequalities have increased over time.[42,43]

Lower education has recently been associated with both higher morbidity[44] and inadequate health literacy.[31] Lower educational level and living alone, for example, have been associated with lower adherence to evidence-based practice in heart failure care.[45] Regional differences in outcomes could indicate local differences in care provided. This may translate into differences in access to vascular surgery[9] and underuse of evidence-based practices in wound care, which was seen in another study.[46]

4.6 | Strengths and limitations

To our knowledge, this is the first study to investigate incidence and predictors of wound healing, relapse,

major amputations, and/or death among patients with chronic leg wounds who are referred to specialist treatment at hospital with 5 years of follow up and is based on nationwide register data. The major strength of the study is the nationwide comprehensive prospectively collected data of a list of clinically relevant factors with potential influence on outcomes in patients with chronic wounds. These factors included reliable data on diabetes and social characteristics. Another strength of this study is that there is little missing data and relatively long follow-up period.

This study is limited by the fact that available wound diagnoses did not make it possible to differentiate patients into individuals with venous, arterial, or diabetic ulcers. This lack of classification makes it difficult to compare our findings with other studies in this particular stratification. We report outcomes for all patients with chronic leg wounds who have a number of epidemiological characteristics, which have a clear impact on outcomes. Our results may help identify patients at particular risk of poor outcomes independent of wound aetiology. Even though this study is based on nationwide data, it does not represent all patients with chronic wounds in Denmark as there may be patients who were not referred to hospital for wound management. By defining wound healing as end of contact with the hospital, we might overestimate healing rates as some patients might be released from hospital before wound healing occurs.

5 | CONCLUSION

This study provides reliable epidemiological data on four clinically important outcomes and is based on a group of patients who were seeking medical care, which is by definition the group of patients health care can treat. Our estimates are directly applicable to patients with chronic leg wounds who are receiving care at specialist wound care facilities and for whom new treatments and preventive, rehabilitative, and palliative strategies can be introduced.

ACKNOWLEDGEMENTS

We thank Inge Petersen, Odense University Hospital and Department of Clinical Research, University of Southern Denmark, for help with statistics. This work was supported by the Novo Nordisk Foundation (NNF18OC0051995 in the call "Postdoc Fellowships in Nursing Research").

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article. Raw data cannot be shared for privacy reasons. Programming codes will be shared on reasonable request to the corresponding author.

ETHICS STATEMENT

The study was approved by the Danish Data Protection Agency, J.nr. 19/10332. When conducting registry-based research in Denmark, no further approval is required.

ORCID

Ulla Riis Madsen https://orcid.org/0000-0001-9436-6887

Nana Hyldig https://orcid.org/0000-0001-6758-6294

REFERENCES

1. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle)*. 2015;4(9):560-582.
2. Olsson M, Jaarbrink K, Divakar U, et al. The humanistic and economic burden of chronic wounds: a systematic review. *Wound Rep Reg*. 2019;27(1):114-125.
3. Gould L, Abadir P, Brem H, et al. Chronic wound repair and healing in older adults: current status and future research. *J Am Geriatr Soc*. 2015;63(3):427-438. https://doi.org/10.1111/jgs.13332.
4. Martinengo L, Olsson M, Bajpai R, et al. Prevalence of chronic wounds in the general population: systematic review and meta-analysis of observational studies. *Ann Epidemiol*. 2019;29:8-15. https://doi.org/10.1016/j.annepidem.2018.10.005.
5. Singh NA, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA*. 2005;293(2):217-228.
6. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. *Lancet*. 2003;361(9368):1545-1551.
7. CAH A, Carrington AL, Ashe H, et al. The north-west diabetes foot care study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med*. 2002;19(5):377-384.
8. Jeffcoate WJ, Chipchase SY, Ince P, Game FL. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. *Diabetes Care*. 2006;29(8):1784-1787.
9. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58(1S):S1-S109.e33.
10. Davies MG. Criticial limb ischemia: epidemiology. *Methodist Debakey Cardiovasc J*. 2012;8(4):10-14.
11. Global Lower Extremity Amputation Study Group. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. *Br J Surg*. 2000;87(3):328-337.
12. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg*. 2014;12(12):1500-1524.
13. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591.
14. Lynge EM, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health*. 2011;39(7 Suppl):30-33.

15. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017 Jun 1;46(3):798-798f.
16. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health*. 2011;39(7 Suppl):91-94.
17. Brownrigg JR, Hinchliffe RJ, Apelqvist J, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):128-135.
18. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*. 2004;57 (12):1288-1294.
19. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81: 515-526.
20. Fife CE, Eckert KA, Carter MJ. Publicly reported wound healing rates: the fantasy and the reality. *Adv Wound Care (New Rochelle)*. 2018;7(3):77-94.
21. Ennis WJ, Meneses P. Clinical evaluation: outcomes, benchmarking, introspection, and quality improvement. *Ostomy Wound Manage*. 1996;42(10A Suppl):40S-47S.
22. Horn SD, Fife CE, Smout RJ, Barrett RS, Thomson B. Development of a wound healing index for patients with chronic wounds. *Wound Repair Regen*. 2013;21(6):823-832.
23. Fife CE, Walker D, Eckert KA. Qualified clinical data registries: how wound care practitioners can make the Most out of the merit-based incentive payment system. *Adv Wound Care (New Rochelle)*. 2018;7(11):387-395.
24. Dillon MP, Anderson SP, Duke EJ, Ozturk HE, Stuckey R. The lived experience of sequential partial foot and transtibial amputation. *Disabil Rehabil*. 2019;22:1-9.
25. Rassin M, Tzevlin VF, Malul EF, Harel SF, Shakhar H. Retrospective study of emerging themes in the decision-making process of patients considering amputation. *J Vasc Nurs*. 2012 Jun; 30(2):54-60.
26. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367-2375.
27. Verdin C, Rao N. Exploring the value of a podiatric consult in palliative wound care. *J Palliat Med*. 2017;20(1):6.
28. Wang SY, FAU LJ, FAU HY, Chang YY. The diabetic foot amputation decision-making process. *Adv Skin Wound Care*. 2018;31(9):413-420.
29. Fu XL, Ding H, Miao WW, Mao CX, Zhan MQ, Chen HL. Global recurrence rates in diabetic foot ulcers: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2019;35(6):e3160.
30. McCosker L, Tulleners R, Cheng Q, et al. Chronic wounds in Australia: a systematic review of key epidemiological and clinical parameters. *Int Wound J*. 2019;16(1):84-95.
31. Svendsen MT, Bak CK, Sørensen K, et al. Associations of health literacy with socioeconomic position, health risk behavior, and health status: a large national population-based survey among Danish adults. *BMC Public Health*. 2020;20(1):565.
32. Jorgetto JV, Gamba MA, Kusahara DM. Evaluation of the use of therapeutic footwear in people with diabetes mellitus—a scoping review. *J Diabetes Metab Disord*. 2019;18(2):613-624.
33. Nelson EA, Adderley U. Venous leg ulcers. *BMJ Clin Evid*. 2016;2016:1902.
34. Margolis DJ, Jeffcoate W. Epidemiology of foot ulceration and amputation: can global variation be explained? *Med Clin North Am*. 2013;97(5):791-805.
35. Game F. Choosing life or limb. Improving survival in the multi-complex diabetic foot patient. *Diabetes Metab Res Rev*. 2012;28(Suppl 1):97-100.
36. Reinecke H, Unrath M, Freisinger E, et al. Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. *Eur Heart J*. 2015;36(15):932-938.
37. Morbach S, Furchert H, Gröblinghoff U, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. *Diabetes Care*. 2013;36(4):e48.
38. Iversen MM, Tell GS, Riise T, et al. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trøndelag Health Study, Norway. *Diabetes Care*. 2009;32(12):2193-2199.
39. WHO Definition of Palliative Care. http://www.who.int/cancer/palliative/definition/en/
40. Sommer I, Griebler U, Mahlknecht P, et al. Socioeconomic inequalities in non-communicable diseases and their risk factors: an overview of systematic reviews. *BMC Public Health*. 2015;15:914.
41. Bambra C, Riordan R, Ford J, Matthews F. The COVID-19 pandemic and health inequalities. *Scand J Public Health*. 2021;49 (1):14-16.
42. Brønnum-Hansen H, Baadsgaard M. Increase in social inequality in health expectancy in Denmark. *Scand J Public Health*. 2008;36(1):44-51.
43. Christiansen T, Lauridsen JT, Kifmann M, Lyttkens CH, Ólafsdóttir T, Valtonen H. Healthcare, health and inequality in health in the Nordic countries. *Nord J Health Econ*. 2018;6(2): 10-28.
44. Møller SP, Laursen B, Johannesen CK, Tolstrup JS, Schramm S. Patterns of multimorbidity and demographic profile of latent classes in a Danish population—a register-based study. *PLoS One*. 2020;15(8):e0237375.
45. Schjødt I, Johnsen SP, Strömberg A, Valentin JB, Løgstrup BB. Inequalities in heart failure care in a tax-financed universal healthcare system: a nationwide population-based cohort study. *ESC Heart Fail*. 2020 Oct;7(5):3095-3108.
46. Gray TA, Rhodes S, Atkinson RA, et al. Opportunities for better value wound care: a multiservice, cross-sectional survey of complex wounds and their care in a UK community population. *BMJ Open*. 2018 Mar;22:8(3).

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Madsen UR, Hyldig N, Juel K. Outcomes in patients with chronic leg wounds in Denmark: A nationwide register-based cohort study. *Int Wound J*. 2022;19:156–168. https://doi.org/10.1111/iwj.13607