

Predictors of Mortality following Incident Diabetic Foot Ulcers

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BACKGROUND

- 25% of patients with diabetes will develop a diabetic foot ulcer during their lifetime.^{1,2}
 - Half of the patients who develop a diabetic foot ulcer will die within the next 5 years, most commonly from heart attacks and stroke.^{3,4}
 - We do not know whether ulcer severity or common mediators of vascular disease, such as statin use, are associated with mortality.
- AIM**
- To identify predictors of mortality for patients with an incident diabetic foot ulcer

METHODS

•Study design: Retrospective, rolling cohort constructed from national US Veterans Affairs healthcare datasets

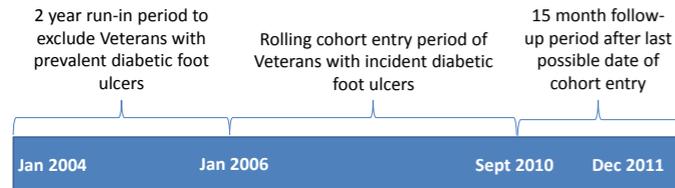


FIGURE 1. TIMELINE OF RETROSPECTIVE, ROLLING COHORT

- Inclusion criteria: Veterans with type 2 diabetes who developed an incident diabetic foot ulcer between January 1, 2006 and September 1, 2010.
- Exclusion criteria: Veterans receiving renal replacement therapy or with stage 5 chronic kidney disease, patients younger than 40 years, or on insulin monotherapy.
- Follow-up: Veterans were followed until death or the end of the study period, January 1, 2011.
- Independent variables: Ulcer severity was categorized at the time of cohort entry (diagnosis) as early stage, osteomyelitis, or gangrene. Comorbidities, hemoglobin A1C, cholesterol, systolic blood pressure, statin use, and healthcare utilization were determined in the 12 month baseline period preceding ulceration.
- Dependent variable: time from diagnosing an incident diabetic foot ulcer to death.

•Statistics: Kaplan Meier survival curves stratified by ulcer severity were used to compare unadjusted differences in survival. Stepwise Cox proportional hazard models were constructed using forward selection with a $p \leq 0.25$ level for entry and $p > 0.15$ level for exclusion. To model both stringent and lax control being associated with mortality, total cholesterol, LDL-c, hemoglobin A1C and systolic blood pressure were allowed into the model with the possibility of a squared term.⁵

RESULTS

TABLE 1. PATIENT CHARACTERISTICS

Characteristic	Count or Mean Value	% or SD
Age, years	69	10.38
Male	65,280	98.43
Race		
White	52,837	79.67
Black	8,904	13.43
Other	4,582	6.91
Hispanic	4,107	6.19
Married	41,305	62.28
Comorbidities		
Peripheral neuropathy	9,937	14.98
Coronary artery disease	31,998	48.25
Peripheral arterial disease	10,300	15.53
History of stroke	4,817	7.26
History of vascular procedure	508	0.77
History of eye disease	16,775	25.29
Foot deformity	1,445	2.18
CKD stage 1	9,033	15.31
CKD stage 2	28,161	47.72
CKD stage 3	19,908	33.73
CKD stage 4	1,916	3.25
Healthcare utilization		
Outpatient visits	18.01	15.73
Emergency room visits	1.49	2.46
Hospitalizations	0.71	1.27
Statin use	46,322	69.84
Systolic blood pressure, mmHg	134	15.38
Hemoglobin A1C, %	7.60	1.60
Total cholesterol, mg/dL	159	36.36
LDL cholesterol, mg/dL	86	29.76
Ulcer severity at the time of diagnosis		
Early stage	61,383	92.55
Osteomyelitis	2,930	4.42
Gangrene	2,010	3.03
Died during follow-up	33,554	50.59

•Of the 66,323 Veterans included in the cohort, 33,554 died during the study period (50.59%, Table 1). The mean follow-up time was 27.7 months.

•Compared to early stage ulcers, gangrene was associated with an increased risk of mortality (HR 1.70, Table 2, Figure 2). The magnitude of this effect was greater than estimates for the following established risk factors of death from vascular disease: diagnosed coronary artery disease, peripheral arterial disease, and stroke.

•70% of the cohort was prescribed a statin in the year prior to ulceration, which was protective (HR 0.89, Table 2).

•23% of patients presenting with gangrene were previously diagnosed with peripheral arterial disease.

•Compared to those presenting with early stage ulcers or osteomyelitis, those with gangrene had a higher proportion of missing values critical for appropriate management of vascular disease despite similar numbers of outpatient visits.

- 18% of the total cohort did not have a hemoglobin A1C. Missing values for those with early stage ulcers, osteomyelitis, and gangrene, respectively: 17%, 16%, 25%.
- 22% of the total cohort did not have a low density lipoprotein (LDL) cholesterol. Missing values for those with early stage ulcers, osteomyelitis and gangrene, respectively: 22%, 22%, 30%.

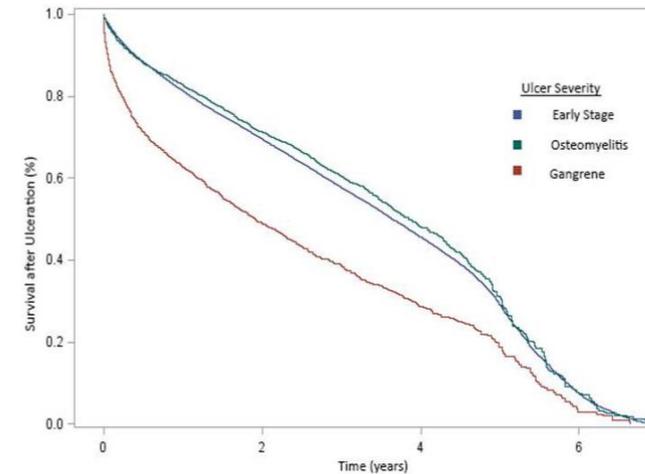


FIGURE 2. KAPLAN MEIER SURVIVAL CURVE FOLLOWING INCIDENT DIABETIC FOOT ULCER DIAGNOSIS, STRATIFIED BY ULCER SEVERITY

TABLE 2. ADJUSTED HAZARD RATIOS FOR DEATH FOLLOWING INCIDENT DIABETIC FOOT ULCERS, MODELED USING STEPWISE COX PROPORTIONAL HAZARDS*

Characteristic	Hazard Ratio	95% CI	p-value
Foot ulcer severity (references = early stage ulcer)			
Osteomyelitis	1.09	1.02 – 1.17	0.014
Gangrene	1.70	1.57 – 1.83	<0.0001
Covariates			
Additional year of age	1.04	1.04 – 1.04	<0.0001
Male	1.45	1.26 – 1.66	<0.0001
Black (ref = White)	0.97	0.92 – 1.01	0.150
Other race (ref = White)	0.92	0.87 – 0.97	0.003
Married	0.98	0.97 – 0.99	0.004
Peripheral neuropathy	0.94	0.91 – 0.98	0.002
Coronary artery disease	1.14	1.11 – 1.18	<0.0001
Peripheral arterial disease	1.09	1.05 – 1.13	<0.0001
History of stroke	1.14	1.09 – 1.20	<0.0001
Foot deformity	0.87	0.79 – 0.95	0.003
1 mL/min increase in estimated glomerular filtration rate	0.99	0.99 – 0.99	<0.0001
Additional outpatient visit	1.01	1.01 – 1.01	<0.0001
Additional emergency room visit	1.02	1.02 – 1.03	<0.0001
Additional hospitalization	1.12	1.11 – 1.14	<0.0001
Statin use	0.89	0.86 – 0.92	<0.0001

*The hazard ratios are also adjusted for average systolic blood pressure (SBP) and hemoglobin A1C (A1C). The mathematical equations for each are listed below:

$$(HR_{SBP}) = -0.000106(SBP - 144) + 0.0002577(SBP - 144)^2$$

$$(HR_{A1C}) = -0.00167(A1C - 5.9) + 0.00935(A1C - 5.9)^2$$

CONCLUSIONS

- Diabetic foot ulcers are common and portend a high risk of death.
 - They should be considered a “red flag,” identifying patients at high risk of death from heart attacks and strokes.^{3,4}
- Gangrene is a strong, independent predictor of subsequent mortality, out-performing diagnosed vascular disease.
 - Vascular disease may be underestimated or under diagnosed.
 - Patients presenting with gangrene are missing quality metrics of care for diabetes and vascular disease.
 - This gap cannot be entirely explained by a lack of healthcare utilization; they were engaging with the VA healthcare system about 20 times a year.
 - Reasons for this discrepancy need to be explored.
- Statin use in this population may be particularly beneficial.
 - Initiating statins should be further explored as a means of lowering the mortality associated with diabetic foot ulcers.

•Next steps:
 •We are using this database to investigate whether statin use is associated with changes in mortality. In this population with a high risk of impending death, improving classic mediators after ulceration may or may not have enough time to impact the associated mortality.^{6,7}

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