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Diabetic foot ulcer severity predicts mortality among veterans with type 2 diabetes

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ABSTRACT

Aim: Diabetic foot ulcers are associated with an increased risk of death. We evaluated whether ulcer severity at presentation predicts mortality.

Methods: Patients from a national, retrospective, cohort of veterans with type 2 diabetes who developed incident diabetic foot ulcers between January 1, 2006 and September 1, 2010, were followed until death or the end of the study period, January 1, 2012. Ulcers were characterized as early stage, osteomyelitis, or gangrene at presentation. Cox proportional hazard regression identified independent predictors of death, controlling for comorbidities, laboratory parameters, and healthcare utilization.

Results: 66,323 veterans were included in the cohort and followed for a mean of 27.7 months: 1-, 2-, and 5-year survival rates were 80.80%, 69.01% and 28.64%, respectively. Compared to early stage ulcers, gangrene was associated with an increased risk of mortality (HR 1.70, 95% CI 1.57–1.83, $p < 0.001$). The magnitude of this effect was greater than diagnosed vascular disease, i.e., coronary artery disease, peripheral arterial disease, or stroke.

Conclusion: Initial diabetic foot ulcer severity is a more significant predictor of subsequent mortality than coronary artery disease, peripheral arterial disease, or stroke. Unrecognized or under-estimated vascular disease and/or sepsis secondary to gangrene should be explored as possible causal explanations.

1. Introduction

Half of patients who develop a diabetic foot ulcer will die within five years (Boyko, Ahroni, Smith, & Davignon, 1996; Martins-Mendes et al., 2014; Walsh, Hoffstad, Sullivan, & Margolis, 2015). Most often, they succumb to vascular complications, namely heart attacks and strokes (Boyko et al., 1996; Morbach et al., 2012; Moulik, Mtonga, & Gill, 2003). However, recent cohort studies concluded that foot ulcers alone remain a significant independent predictor of mortality, even after adjusting for known vascular disease and other comorbidities (Martins-Mendes et al., 2014; Walsh et al., 2015). We hypothesized that the subgroup of patients with severe diabetic foot ulcers, namely those complicated by osteomyelitis or gangrene, would have the highest associated mortality among patients with diabetic foot ulcers. This was based upon the finding that severe ulcers are associated with increased morbidity, especially major (above ankle) amputation (Helmer et al., 2011; Peters et al., 2001; Prompers, Schaper, et al., 2008). Therefore, our aim was to determine whether the severity of incident diabetic foot ulcers at presentation predicts subsequent mortality.

2. Subjects, Materials and Methods

2.1. Study Design and Subjects

We constructed a retrospective, rolling cohort of all patients with type 2 diabetes and incident diabetic foot ulcers receiving care through the U.S. Department of Veterans Affairs (VA) national healthcare system. It included data from the VA National Patient Care Database, the VA Decision Support System Pharmacy Datasets, and the Centers for Medicare and Medicaid Services Medicare claims files, including Part D Event files, available through the VA Information Resources Center. International Statistical Classification of Disease and Related Health Problems, version 9, codes (ICD-9 codes) used to generate variables are listed in the Appendix A. Patients were identified as having diabetes if they received at least one prescription for a diabetes medication in 2004 or if two or more ICD-9 codes for diabetes were present in VA in-patient or out-patient visits in 2004 or 2005, the two-year baseline period (Miller, Safford, & Pogach, 2004). To further increase specificity by

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excluding patients likely to have type 1 diabetes, those younger than 40 years or on insulin monotherapy were not included. Those with stage 5 chronic kidney disease (estimated glomerular filtration rate [eGFR] <15) were excluded because it falsely lowers hemoglobin A1C and cholesterol values. Finally, to ensure that the cohort was limited to patients with incident diabetic foot ulcers, we excluded patients with a foot ulcer diagnosis during the baseline period (Fig. 1; Finke, Miller, & Turpin, 2010; Sohn, Budiman-Mak, Stuck, Siddiqui, & Lee, 2010; Dubský et al., 2013).

Patients entered the cohort at the time of incident foot ulcer diagnosis, beginning January 1, 2006, and ending September 1, 2010. Patients were followed until death or the end of the study period, January 1, 2012 (Fig. 1). This study was approved by the institutional review boards of the Edward J. Hines Jr. and William S. Middleton Memorial Veterans Hospitals.

2.2. Independent Variables

Ulcer severity at the time of diagnosis was categorized as early stage, osteomyelitis, or gangrene based on validated ICD-9 codes (Finke et al., 2010; Sohn et al., 2010). Early stage ulcers were defined as uncomplicated or those with a diagnosis of infection limited to the skin and soft tissue, such as cellulitis. We chose not to separate skin and soft tissue infections into their own disease severity category due to concerns that this level of infection may be difficult to distinguish from non-infected wounds that were associated with bacterial colonization or dependent rubor in the outpatient setting. The following demographics, comorbidities, and healthcare utilization measures were assessed during the baseline period: age, sex, race, marital status, peripheral neuropathy, coronary artery disease, peripheral arterial disease and any previous vascular procedures, stroke, chronic kidney disease, eye disease, foot deformity, number of out-patient and emergency room visits, and number of hospitalizations (Newton et al., 1999). Hemoglobin A1C, total cholesterol, low density lipoprotein cholesterol (LDL-c) and out-patient systolic blood pressures were averaged over the 12-month period preceding the initial ulceration. Statin use, defined as possession of at least a 30-day supply, was also assessed in the 12-month period preceding the ulceration.

2.3. Dependent Variable

Time to death was measured as the number of days from incident diabetic foot ulcer to death (Sohn, Arnold, Maynard, & Hynes, 2006).

2.4. Statistical Analysis

Kaplan–Meier survival curves, stratified by ulcer severity, were used to compare unadjusted differences in survival. Differences in survival curves were assessed using the log rank test. To identify the most parsimonious model for predicting survival, stepwise Cox proportional hazard models were constructed using forward selection with a $p \le 0.25$ level for entry into the model 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 (Kontopantelis et al., 2015). A post-hoc sensitivity analysis was conducted, excluding 13,639 patients identified by ICD-9 codes 707.9 (chronic skin ulcer NOS) and 707.10 (lower limb ulcer, unspecified) due to concerns these codes may identify patient with calf ulcers rather than diabetic foot ulcers. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used.

3. Results

We identified 66,323 patients with type 2 diabetes and an incident foot ulcer. At the time of diagnosis, osteomyelitis and gangrene complicated 4.42% and 3.03% of the wounds. Nearly half the cohort had known coronary artery disease, and 15.33% were diagnosed with peripheral arterial disease. Ulcerated patients were followed from initial diagnosis for a mean of 27.72 months (Table 1). The 1-, 2-, and 5-year survival rates were as follows: 80.80%, 69.01%, and 28.94%.

Compared to the entire cohort, patients presenting with gangrene had a higher frequency of diagnosed peripheral arterial disease (15.53% versus 23.83%) and prior vascular procedures (0.77% versus 2.29%; Table 1). This subset also included a larger proportion of minorities. They were engaged in the healthcare system, with similar mean numbers of out-patient visits and slightly higher rates of emergency room utilization and hospitalizations. Despite healthcare engagement and similar proportions of statin use, a larger percentage of this subset had missing values for systolic blood pressures and laboratory parameters than the entire cohort (Table 1 footnote).

Of the 2010 patients presenting with gangrene, the 1-, 2-, and 5-year survival rates were 62.67%, 48.95%, and 18.82%, respectively. The Kaplan–Meier survival curve for those presenting with gangrene was significantly steeper than for those with early stage ulcers or osteomyelitis (log rank $p < 0.001$; Fig. 2). This was particularly true for the first year following ulceration, after which the lines ran relatively parallel to one another.

In a multivariate stepwise Cox proportional hazard model, the hazard ratio for death among patients with gangrene was 1.70 (95% CI 1.57–1.83, $p < 0.001$; Table 2) compared to those with early stage ulcers. This effect was higher than that for known coronary artery disease, stroke, or peripheral arterial disease (Table 2). The hazard ratio for osteomyelitis was also elevated at 1.09 (95% CI 1.02–1.17, $p = 0.014$) compared to early stage ulcers. Seventy percent of the cohort used statins in the year prior to ulceration, which was protective (HR 0.89, 95% CI 0.86–0.92, $p < 0.001$). Neither total cholesterol nor LDL-c were included in the final model after eliminating variables. Hemoglobin A1C and systolic blood pressure were adjusted for in the final analysis and modeled with a U-shaped curve, although their associations with death were not statistically significant (Table 2 footnote). In the sensitivity analysis, the hazard ratio for death among patients with gangrene

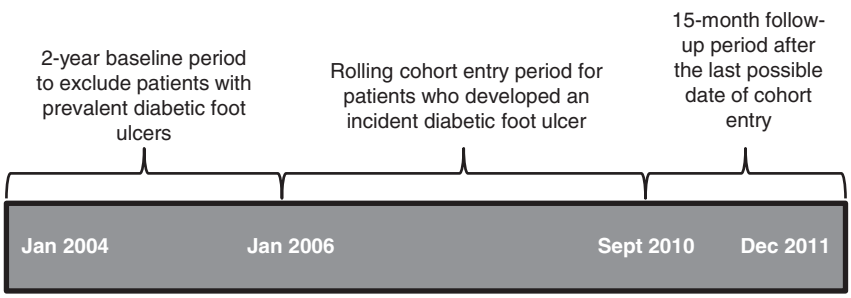

Fig. 1. Timeline depicting rolling cohort study design.