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Comorbid status in patients with osteomyelitis is associated with long-term incidence of extremity amputation

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ABSTRACT

Introduction Osteomyelitis is associated with significant morbidity, including amputation. There are limited data on long-term amputation rates following an osteomyelitis diagnosis. We sought to determine the incidence of amputation in patients with osteomyelitis over 2 years.

Research design and methods Observational cohort study of 1186 inpatients with osteomyelitis between 2004 and 2015 and stratified by osteomyelitis location status to evaluate the impact on amputation, mortality rates, readmission data, and inpatient days.

Results Persons with diabetes had 3.65 times greater probability of lower extremity amputation (p<0.001), readmission (p<0.001), and longer inpatient stay (p<0.001) and had higher 2-year mortality (relative risk (RR) 1.23, p=0.0027), adjusting for risk factors. Male gender (RR 1.57, p<0.001), black race (RR 1.41, p<0.05), former smoking status (RR 1.38, p<0.01), myocardial infarction (RR 1.72, p<0.001), congestive heart failure (RR 1.56, p<0.001), peripheral vascular disease (RR 2.25, p<0.001) and renal disease (RR 1.756, p<0.001) were independently associated with amputation. Male gender (RR 1.39, p<0.01), black race (RR 1.27, p<0.05), diabetes (RR 2.77, p<0.001) and peripheral vascular disease (RR 1.59, p<0.001) had increased risk of lower, not upper, extremity amputation.

Conclusions Patients with osteomyelitis have higher rates of amputation and hospitalization. Clinicians must incorporate demographic and comorbid risk factors to protect against amputation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Persons with osteomyelitis are at risk of extremity amputation and the risk is amplified by a diagnosis of diabetes.

WHAT THIS STUDY ADDS

⇒ Patient race, gender, and select comorbid conditions at the time of osteomyelitis diagnosis are independently associated with amputation.

⇒ These findings indicate an association between increasing comorbidity burden and long-term lower extremity amputation rates.

⇒ Both type 1 diabetes mellitus and type 2 diabetes mellitus were associated with a significantly higher amputation risk in both our bivariable and regression analyses.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The ability to predict long-term outcomes following a diagnosis of osteomyelitis makes the clinical implications of these findings highly relevant and should inform clinical-patient discussions to set expectations in this population.

INTRODUCTION

Osteomyelitis is a highly morbid condition commonly associated with diabetes mellitus (DM).[1 2] Osteomyelitis is difficult to eradicate, expensive to treat, and has a significant social burden, consuming millions of dollars in healthcare resources regardless of whether an amputation is required.[3–7] The treatment of osteomyelitis is complex and requires close coordination among multidisciplinary teams that comprised individuals from surgery, infectious diseases, endocrinology, podiatry, among others.[1] Patients who develop osteomyelitis have additional medical comorbidities which complicate their care. Given the increasing incidence and prevalence of both osteomyelitis and DM across the world,[5 8–12] many physicians are likely to encounter patients with bone infections.

It is imperative for providers to gauge how osteomyelitis outcomes are complicated by a patient's comorbid status. Yet, there is currently little understanding of the impact of a patient's comorbidity burden on the incidence of non-traumatic amputation (hereafter referred to as 'amputation') following an osteomyelitis diagnosis. Current evidence-based guidelines on osteomyelitis management do not address the relationship between comorbidity burden and risk of amputation.[1] Several studies have examined the risk factors for initial *occurrence* of osteomyelitis.[13 14] For instance, osteomyelitis is now commonly

associated with diabetic foot ulcer infection.[1] However, there has not been a comprehensive evaluation of the risk factors for *outcomes* (eg, chronic osteomyelitis, amputation, or disability). We aimed to provide such an evaluation specifically for the outcome of amputation.

The objective of our investigation was to provide a comprehensive risk assessment, for patients with and without DM, of the comorbidities and risk factors associated with a long-term amputation risk following an initial diagnosis of osteomyelitis. We hypothesized an increasing number of comorbidities at the time of diagnosis were associated with an increased incidence of amputation in patients with osteomyelitis.

RESEARCH METHODS AND DESIGN

Data source

We performed a cohort study of all adult patients who had diagnosis codes for acute extremity osteomyelitis (online supplemental table 1) associated with admission at a large Michigan academic center between 2004 and 2015. We chose to use a single-institution dataset instead of national datasets. Available national datasets lack sufficient long-term follow-up or followed only on a demographically limited subset of the population (eg, Medicare patients greater than 65 years old). Furthermore, use of a single-center database enabled us to manually verify all diagnoses and demographics, thereby ensuring greater accuracy.

We queried the University of Michigan (UM) Data Warehouse, which stores patient demographics and International Classification of Diseases, Ninth Revision and Tenth Revision Clinical Modification (ICD-9/ICD-10-CM) billing codes. Following manual curation to confirm accuracy of demographic, comorbid and outcome variables, the data were deidentified.

Cohort selection

We queried the UM Data Warehouse using ICD-9/ICD-10-CM diagnosis codes to identify any adult patients with a new diagnosis of osteomyelitis during an inpatient stay between 2004 and 2015. Additionally, we evaluated any adult patients who were diagnosed with osteomyelitis in the outpatient setting (ie, clinical encounters) for initial exposure comparison. Our query excluded any patients with pre-existing osteomyelitis, as well as those with fewer than 2 years of follow-up after osteomyelitis diagnosis and those with traumatic amputation. A total of 1281 patients met automated inclusion and exclusion criteria. Initial diagnoses, comorbidities and outcomes of these patients were then manually verified by TPKB and AMH through chart review using the Electronic Medical Record Search Engine.[15] Due to the complex process of osteomyelitis diagnosis,[1] we excluded patients whose osteomyelitis could not be definitely verified from imaging and/or pathology reports. Ninety-five patients were excluded during this verification for a final sample size of 1186. This suggests a specificity of 92.6% when determining osteomyelitis status based on ICD-9-CM and ICD-10-CM codes using advanced data mining tools. This represents a level of specificity in the higher end of that achieved in previous studies.[16 17]

Outcomes

The primary exposure was any diagnosis of type 1 DM (T1DM) or T2DM prior to acute osteomyelitis diagnosis (online supplemental table 2). The primary outcome was incidence of extremity amputation within 2 years of extremity osteomyelitis diagnosis. We chose a 2-year follow-up to balance losses to follow-up, longitudinal nature of outcomes and ability to attribute amputation to initial osteomyelitis diagnosis. Select comorbidities from the Charlson Comorbidity Index (CCI) were chosen as confounders. The CCI is a repeatedly validated measure of patient morbidity and mortality.[18–21] We excluded three CCI comorbidities that we decided were non-germane to osteomyelitis outcomes (cerebrovascular accident, dementia, and HIV/AIDS). Peripheral vascular disease (PVD) status was assessed by Ankle-Brachial Index (ABI) including absolute pressures (in mm Hg) on the affected limb. Patients with palpable pulses and/or an ABI between 0.9 and 1.3 demonstrated no evidence of PVD, and those with an ABI<0.9 were demonstrative of the presence of PVD.[22] Anatomical location(s) of initial osteomyelitis diagnosis was a further covariable. Demographic variables constituted the remaining confounders. Specifically, age, sex, race, body mass index (BMI) and smoking history were abstracted. Outcomes included 2-year incidence of amputation, 30-day and 2-year mortality, initial length of stay, as well as total number of all-cause readmissions and total inpatient days during the 2-year follow-up period.

Statistical analysis

All statistical analyses were performed in STATA V.15 (College Station, Texas). In cohorts of patients with osteomyelitis with and without DM, we described the study sample using median, range, mean, SD, frequencies, and percentages of sociodemographic characteristics, comorbidities, and outcomes. Differences in sociodemographic characteristics, comorbidities and outcomes were determined using t-test and χ^2 test.

We performed a relative risk (RR) regression using the modified Poisson approach to test the bivariate association of each independent variable with mortality and amputation, and report the RR of mortality and amputation with the presence of each risk factor.[23] We then performed two separate multivariable RR regressions[23] to determine the differential risk of mortality and amputation in patients with and without DM, controlling for sociodemographic characteristics and comorbid conditions. We used pairwise comparison of marginal effects to determine if the outcomes were significantly different based on the type of DM diagnosis. The area under the receiver operating characteristic curve was used to measure the discriminating power of the variables in the logistic regression models.

A negative binomial regression tested the bivariate association of each individual independent variable with total number of inpatient days and total number of readmissions. We performed two separate multivariable negative binomial regressions to determine the differences in the total number of inpatient days and total number of readmissions, again controlling for sociodemographic characteristics and comorbid conditions. We used pairwise comparison of marginal effects to determine if the outcomes were significantly different, depending on the type of DM diagnosis. An a priori alpha level was set at 5% for all statistical significance testing.

RESULTS

Study population

A total of 2029 patients were diagnosed with osteomyelitis during the study period. A total of 843 and 1186 patients were diagnosed with acute osteomyelitis in the outpatient setting and inpatient setting, respectively. Seventy-eight patients in the outpatient cohort were not adults and were excluded, resulting in a total cohort of 743 individuals. When compared with the inpatient cohort of patients with osteomyelitis exposure, patients in the outpatient setting were younger (51.9 vs 56.6 years, p<0.05) and were less frequently reported to be of African American race (9.1% vs 14.6%, p<0.05). Patient demographics and comorbid status such as sex, BMI, chronic kidney disease, coronary artery disease, DM (% type 1), liver disease, cancer history, congestive heart failure (CHF), history of myocardial infraction, and PVD did not differ significantly between settings.

The inpatient cohort was used to assess longitudinal outcomes given comparable demographic and comorbid status with outpatients with osteomyelitis. Six hundred and ten patients with DM and 576 patients without DM who met inclusion and exclusion criteria were identified. The DM cohort was older than the non-DM cohort, and more likely to be African American, obese and has a history of smoking (table 1). Furthermore, patients with DM were more likely to have some of comorbidities that were measured. Patients with DM were significantly more likely to have osteomyelitis of the midfoot and hindfoot (10.8% vs 3.6%, p<0.0001) and also of the anatomic forefoot (50.5% vs 11.8%, p<0.0001). Patients without DM were more likely to have osteomyelitis of the skull (6.6% vs 1.0%, p<0.0001), vertebrae (19.3% vs 11.1%, p=0.0001), hip and pelvis (17.5% vs 5.4%, p<0.0001), and sacrum (13.0% vs 5.6%, p<0.0001).

Amputation outcomes

Two-year incidence of amputation was nearly fourfold higher for the DM cohort (43.1% vs 12.3%, RR 3.50, 95% CI 2.76 to 4.43, p<0.001). Incidence of lower extremity (LE) amputation was 41.8% vs 11.5% (RR 3.65, 95% CI 2.85 to 4.66, p<0.001), while there was no difference in upper extremity amputation (2.6% vs 1.2%, p>0.05). In terms of DM influencing location-dependent incidence of amputation, patients with DM were at higher risk with initial diagnosis location of the sacrum (14.7% vs 1.3%, RR 11.03, 95% CI 1.34 to 90.83, p=0.0046), fingers (RR 2.06, 95% CI 1.07 to 3.97, p=0.0366) and tibia/fibula (RR 3.98, 95% CI 1.90 to 8.36, p=0.0002) (online supplemental table 3).

Depending on comorbidity burden, incidence of LE amputation was as low as 7.2% in patients without DM without any comorbidities. It was 36.1% in patients with DM and no comorbidities and as high as 75.0% in patients with a burden of DM, CHF and PVD (figure 1). These findings indicate an association between increasing comorbidity burden and long-term LE amputation rates.

Bivariable analysis

T1DM (RR 4.31, 95% CI 3.15 to 5.91) and T2DM (RR 3.54, 95% CI 2.76 to 4.55) were independently associated with increased risk of LE amputation (both p<0.001). Among baseline characteristics, male gender (RR 1.57, 95% CI 1.26 to 1.95, p<0.001), African American race (RR 1.41, 95% CI 1.07 to 1.86, p<0.05), increasing BMI (RR 1.02, 95% CI 1.01 to 1.03, p<0.01) and former smoking status (RR 1.38, 95% CI 1.12 to 1.70, p<0.01) were associated with increased risk of amputation. Among comorbidities, history of myocardial infarction (MI; RR 1.72, 95% CI 1.38 to 2.15), CHF (RR 1.56, 95% CI 1.26 to 1.93), PVD (RR 2.25, 95% CI 1.84 to 2.75), renal disease (RR 1.76, 95% CI 1.46 to 2.11) and prior LE amputation (RR 2.41, 95% CI 2.02 to 2.87) were associated with increased risk (all p<0.001). Rheumatic disease (RR 0.47, 95% CI 0.25 to 0.91) and any malignancy (RR 0.63, 95% CI 0.42 to 0.94), both p<0.05, as well as hemiparaplegia (RR 0.33, 95% CI 0.18 to 0.60, p<0.001) were associated with decreased risk of LE amputation (table 2).

Multivariable regression model

In our multivariable model for LE amputation, T2DM (RR 2.77, 95% CI 1.97 to 3.90) had a greater RR than T1DM (RR 2.60, 95% CI 1.97 to 3.45, both p<0.001). Among demographics, male gender (RR 1.39, 95% CI 1.13 to 1.71, p<0.01) and African American race (RR 1.27, 95% CI 1.04 to 1.56, p<0.05) remained statistically significant for increased incidence of LE amputation (table 3). For comorbidities, PVD (RR 1.59, 95% CI 1.29 to 1.96, p<0.001) and past LE amputation (RR 1.64, 95% CI 1.36 to 1.97, p<0.001) were associated with increased LE amputation risk, while hemiparaplegia (RR 0.51, 95% CI 0.28 to 0.93, p<0.05) was associated with lower risk (table 3). Several demographics and comorbidities were therefore associated with LE amputation in both the bivariable and multivariable models.

Mortality

Bivariable analysis

There was no difference in 30-day mortality between cohorts. Crude 2-year mortality in the DM group was higher than the non-DM cohort (22.3% vs 15.4%, RR 1.23, 95% CI 1.08 to 1.39, p<0.01). T2DM was independently

Table 1 Sociodemographic and comorbid status of inpatient cohort

Sociodemographics	No diabetes (n=576)		Diabetes (n=610)		Total (n=1186)
Age (mean±SD)	53.1±18.2		59.9±13		
Gender					
Male	351	60.9%	398	65.2%	749 (63.1)
Female	225	39.1%	212	34.8%	437 (36.9)
Race					
White	490	85.1%	487	79.8%	977 (82.3)
African American	71	12.3%	102	16.7%	173 (14.6)
Other	15	2.6%	21	3.4%	36 (3.0)
BMI (mean±SD)	26.6±6.78		31.1±8.35		
Smoking history					
Never smoker	249	43.2%	218	35.7%	467 (39.4)
Former smoker	185	32.1%	295	48.4%	480 (40.5)
Current smoker	142	24.7%	97	15.9%	239 (20.1)
Type 1 diabetes	N/A		83	13.6%	
Specific comorbidities					
Myocardial infarction	25	4.3%	107	17.5%	132 (11.1)
Congestive heart failure	42	7.3%	135	22.1%	177 (14.9)
Peripheral vascular disease	30	5.2%	76	12.5%	106 (8.9)
COPD	74	12.8%	105	17.2%	179 (15.1)
Rheumatic disease	40	6.9%	21	3.4%	61 (5.1)
Liver disease	24	4.2%	20	3.3%	44 (3.7)
Hemiparaplegia	86	14.9%	20	3.3%	106 (8.9)
Renal disease	59	10.2%	236	38.7%	295 (24.9)
Any malignancy	57	9.9%	38	6.2%	95 (8.0)
Prior upper extremity amputation	9	1.6%	12	2.0%	21 (1.8)
Prior lower extremity amputation	48	8.3%	149	24.4%	197 (16.6)
Number of comorbidities					
No major comorbidities	221	38.4%	119	19.5%	340 (28.7)
1 comorbidity	220	38.2%	189	31.0%	409 (34.5)
2 comorbidities	81	14.1%	157	25.7%	238 (20.0)
3 or more comorbidities	54	9.4%	145	23.8%	199 (16.8)
Initial osteomyelitis location					
Non-extremity*	343	59.5%	167	27.4%	510 (43)
Skull	38	6.6%	6	1.0%	44 (3.7)
Vertebrae	111	19.3%	68	11.1%	179 (15.1)
Hip/pelvis	101	17.5%	33	5.4%	134 (11.3)
Sacrum	75	13.0%	34	5.6%	109 (9.2)
Any upper extremity*	39	6.8%	24	3.9%	63 (5.3)
Shoulder	2	0.3%	2	0.3%	4 (0.3)
Humerus	4	0.7%	2	0.3%	6 (0.5)
Elbow	10	1.7%	3	0.5%	13 (1.0)
Radius/ulna	4	0.7%	0	0.0%	4 (0.3)
Hand/wrist	4	0.7%	7	1.1%	11 (0.9)
Finger(s)	18	3.1%	10	1.6%	28 (2.4)

Continued

Table 1 Continued

Sociodemographics	No diabetes (n=576)		Diabetes (n=610)		Total (n=1186)
Any lower extremity*	205	35.6%	431	70.7%	636 (53.6)
Femur	40	6.9%	17	2.8%	57 (4.8)
Knee	12	2.1%	11	1.8%	23 (1.9)
Tibia/fibula	51	8.9%	16	2.6%	67 (5.6)
Ankle	16	2.8%	18	3.0%	34 (2.9)
Midfoot and hindfoot	21	3.6%	66	10.8%	87 (7.3)
Forefoot	68	11.8%	308	50.5%	376 (31.7)

*findings are significant
BMI, body mass index; COPD, chronic obstructive pulmonary disease.

associated with increased risk of death (RR 1.47, 95% CI 1.15 to 1.89, p<0.01), whereas T1DM was not (RR 1.25, 95% CI 0.77 to 2.02, p>0.05).

Age (RR 1.03, 95% CI 1.02 to 1.04, p<0.001) and African American race (RR 1.42, 95% CI 1.02 to 1.98, p<0.05) were associated with increased 2-year mortality. Other race (neither Caucasian nor African American) decreased the mortality risk (RR 0.68, 95% CI 0.52 to 0.89, p<0.01). Lower BMI (RR 0.98, 95% CI 0.96 to 0.99, p<0.05) also contributed to a decreased mortality risk. Among comorbidities, CHF (RR 1.51, 95% CI 1.14 to 1.99, p<0.01), chronic obstructive pulmonary disease (COPD) (RR 1.45, 95% CI 1.09 to 1.92, p<0.05), liver disease (RR 2.12, 95% CI 1.43 to 3.14, p<0.001), renal disease (RR 1.80, 95% CI 1.42 to 2.28, p<0.001) and any malignancy (RR 2.55, 95% CI 1.98 to 3.29, p<0.001) were all associated with increased 2-year mortality (table 2). Among specific diagnostic locations for initial osteomyelitis diagnosis, only osteomyelitis of the forefoot was independently associated with increased mortality (RR 1.27, 95% CI 1.05 to 1.53, p<0.05). There was no association between LE amputation and mortality (RR 1.09, 95% CI 0.85 to 1.42, p>0.05).

Multivariable regression model

On multivariable analysis, neither T1DM nor T2DM remained significantly associated with increased mortality (table 3). Age (RR 1.03, 95% CI 1.02 to 1.04, p<0.001), other race (RR 0.68, 95% CI 0.52 to 0.89, p<0.01), and BMI (RR 0.97, 95% CI 0.95 to 0.99, p<0.01) positively associated with mortality, as did COPD (RR 1.48, 95% CI 1.11 to 1.97, p<0.01), liver disease (RR 2.05, 95% CI 1.35 to 3.11, p<0.001), renal disease (RR 1.42, 95% CI 1.09 to 1.84, p<0.01) and any malignancy (RR 1.81, 95% CI 1.31 to 2.52, p<0.001) (table 3). In both multivariable regression models, there was not a significant association between LE amputation and 2-year mortality.

Number of readmissions and inpatient days

Patients with DM had significantly more all-cause hospital readmissions (mean 2.7 vs 1.8, median 2.0 vs 1.0, p<0.0001) and a higher number of total inpatient days

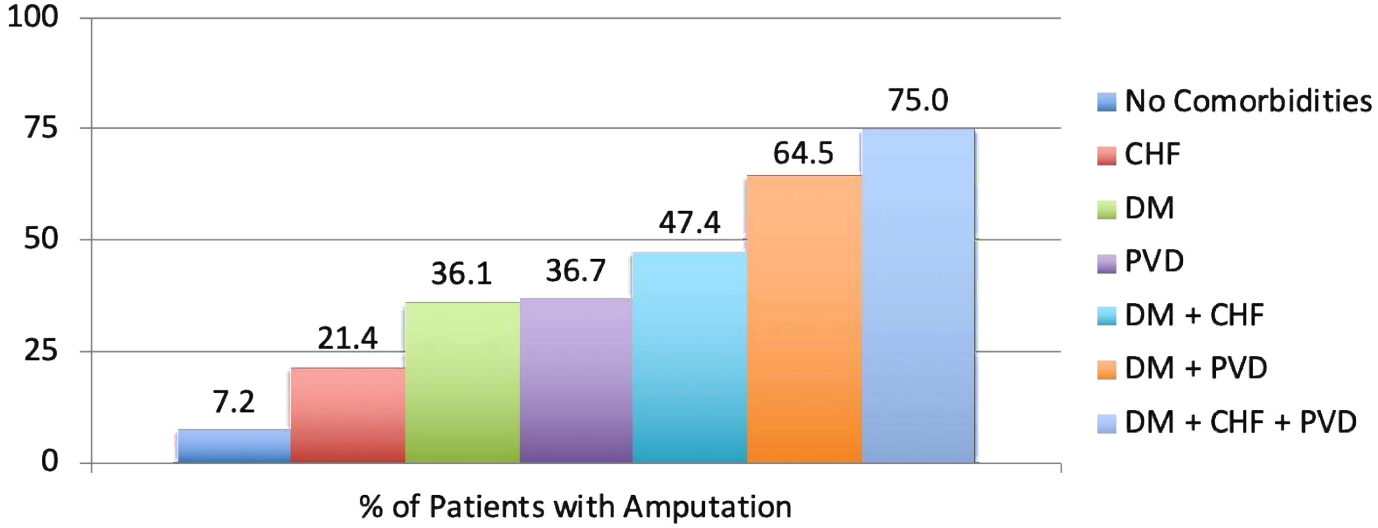

Figure 1 Incidence of lower extremity (LE) amputation based on cumulative comorbidity burden. CHF, congestive heart failure; DM, diabetes mellitus; PVD, peripheral vascular disease.

Table 2 Bivariable associations of independent variables to outcomes among patients with osteomyelitis

	Any LE amputation†		Death within 2 years†		Readmission count within 2 years‡		Total inpatient days within 2 years‡	
	RR	95% CI	RR	95% CI	IRR	95% CI	IRR	95% CI
Age	1.005	(1.000, 1.01)	1.027***	(1.020, 1.03)	0.999	(0.994, 1.00)	0.996	(0.990, 1.002)
Male gender	1.569***	(1.264, 1.94)	0.875	(0.689, 1.11)	0.907	(0.786, 1.04)	0.885	(0.722, 1.085)
Caucasian	Reference		Reference		Reference		Reference	
African American	1.412*	(1.071, 1.86)	1.420*	(1.016, 1.98)	1.376**	(1.137, 1.66)	1.214	(0.919, 1.605)
Other race	0.781*	(0.627, 0.97)	0.677**	(0.519, 0.88)	0.752**	(0.630, 0.89)	0.852	(0.658, 1.102)
No diabetes	Reference		Reference		Reference		Reference	
Type 1 diabetes	4.311***	(3.147, 5.90)	1.248	(0.772, 2.01)	1.580***	(1.206, 2.07)	1.557*	(1.050, 2.309)
Type 2 diabetes	3.544***	(2.761, 4.54)	1.474**	(1.151, 1.88)	1.440***	(1.248, 1.66)	1.554***	(1.269, 1.903)
BMI	1.017**	(1.007, 1.02)	0.981*	(0.963, 0.99)	1.004	(0.995, 1.01)	1.001	(0.989, 1.015)
Never smoker	Reference		Reference		Reference		Reference	
Former smoker	1.380**	(1.120, 1.69)	1.193	(0.894, 1.59)	1.063	(0.910, 1.24)	1.087	(0.872, 1.354)
Current smoker	0.977	(0.736, 1.29)	0.884	(0.603, 1.29)	0.962	(0.794, 1.16)	0.810	(0.619, 1.061)
No major comorbidities	Reference		Reference		Reference		Reference	
Myocardial infarction	1.724***	(1.381, 2.15)	1.276	(0.914, 1.78)	1.253*	(1.010, 1.555)	1.301	(0.953, 1.778)
Congestive heart failure	1.561***	(1.261, 1.93)	1.505**	(1.139, 1.99)	1.264*	(1.045, 1.530)	1.306	(0.992, 1.720)
Peripheral vascular disease	2.247***	(1.835, 2.75)	1.274	(0.884, 1.83)	1.23	(0.969, 1.561)	1.322	(0.937, 1.864)
COPD	1.013	(0.782, 1.31)	1.446*	(1.090, 1.91)	1.137	(0.938, 1.377)	1.017	(0.772, 1.338)
Rheumatic disease	0.471*	(0.245, 0.90)	0.948	(0.548, 1.64)	1.038	(0.759, 1.421)	1.062	(0.680, 1.657)
Liver disease	0.663	(0.352, 1.25)	2.121***	(1.433, 3.14)	1.311	(0.919, 1.871)	1.308	(0.778, 2.198)
Hemiparaplegia	0.328***	(0.180, 0.59)	0.625	(0.370, 1.05)	0.978	(0.766, 1.249)	0.894	(0.633, 1.263)
Renal disease	1.756***	(1.459, 2.11)	1.799***	(1.421, 2.27)	1.329***	(1.136, 1.556)	1.367**	(1.090, 1.714)
Any malignancy	0.625*	(0.415, 0.94)	2.550***	(1.978, 3.28)	0.786	(0.616, 1.003)	0.667*	(0.478, 0.932)
Past LE amputation	2.406***	(2.016, 2.87)	1.152	(0.855, 1.55)	1.224*	(1.019, 1.470)	1.298	(0.997, 1.689)
n	1186		1186		1186		1186	

*P<0.05, **p<0.01, ***p<0.001.
Exponentiated coefficients; 95% CIs in parenthesis.
†Bivariate associations of each individual independent variable to dichotomous outcomes of any lower extremity amputation and death within 2 years was estimated using simple logistic regression.
‡Bivariate associations of each individual independent variable to number of readmissions and total number of inpatient days within 2 years was estimated using simple negative binomial regression due to overdispersion of outcomes in both cases.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; LE, lower extremity; RR, relative risk.

Table 3 Associations of independent variables to outcomes among patients with osteomyelitis using multiple regression, adjusted

	Any LE amputation†		Death within 2 years†		Readmission count within 2 years‡		Total inpatient days within 2 years‡	
	RR	95% CI	RR	95% CI	IRR	95% CI	IRR	95% CI
Age	0.996	(0.989, 1.004)	1.026***	(1.017, 1.035)	0.994**	(0.990, 0.998)	0.996	(0.991, 1.001)
Male gender	1.392**	(1.134, 1.708)	0.834	(0.654, 1.065)	0.898	(0.784, 1.028)	0.999	(0.861, 1.158)
Caucasian	Reference		Reference		Reference		Reference	
African American	1.273*	(1.037, 1.563)	1.327	(0.999, 1.764)	1.272**	(1.071, 1.511)	1.096	(0.848, 1.415)
Other race	0.842	(0.681, 1.041)	0.679**	(0.516, 0.893)	0.826*	(0.701, 0.974)	1.166	(0.967, 1.406)
No diabetes	Reference		Reference		Reference		Reference	
Type 1 diabetes	2.604***	(1.966, 3.451)	1.222	(0.932, 1.603)	1.292**	(1.106, 1.511)	1.043	(0.883, 1.233)
Type 2 diabetes	2.771***	(1.969, 3.899)	1.528	(0.935, 2.496)	1.333*	(1.023, 1.737)	0.791	(0.587, 1.067)
BMI	1.001	(0.991, 1.012)	0.974**	(0.954, 0.994)	0.998	(0.989, 1.006)	0.995	(0.986, 1.004)
Never smoker	Reference		Reference		Reference		Reference	
Former smoker	1.06	(0.871, 1.290)	1.051	(0.813, 1.358)	0.997	(0.862, 1.152)	1.095	(0.933, 1.286)
Current smoker	0.956	(0.735, 1.244)	1.037	(0.725, 1.482)	1.03	(0.861, 1.232)	0.865	(0.709, 1.056)
No major comorbidities	Reference		Reference		Reference		Reference	
Myocardial infarction	1.242	(0.998, 1.544)	1.043	(0.735, 1.481)	1.144	(0.935, 1.399)	1.033	(0.823, 1.297)
Congestive heart failure	1.141	(0.917, 1.421)	0.99	(0.723, 1.355)	1.172	(0.974, 1.410)	1.122	(0.908, 1.388)
Peripheral vascular disease	1.588***	(1.287, 1.958)	0.935	(0.656, 1.334)	0.978	(0.784, 1.220)	1.004	(0.784, 1.286)
COPD	0.944	(0.739, 1.205)	1.475**	(1.105, 1.967)	1.186	(0.995, 1.415)	0.897	(0.738, 1.091)
Rheumatic disease	0.697	(0.374, 1.299)	0.976	(0.576, 1.653)	1.036	(0.774, 1.386)	1.192	(0.868, 1.635)
Liver disease	0.769	(0.421, 1.405)	2.048***	(1.347, 3.113)	1.143	(0.829, 1.576)	0.81	(0.560, 1.173)
Hemiparaplegia	0.509*	(0.279, 0.926)	0.971	(0.592, 1.593)	1.136	(0.902, 1.430)	1.05	(0.815, 1.353)
Renal disease	1.022	(0.845, 1.236)	1.418**	(1.094, 1.838)	1.1	(0.940, 1.289)	0.975	(0.816, 1.165)
Any malignancy	0.862	(0.585, 1.270)	1.813***	(1.305, 2.520)	0.784	(0.613, 1.002)	0.761*	(0.584, 0.991)
Past LE amputation	1.639***	(1.361, 1.972)	1.262	(0.936, 1.703)	1.13	(0.949, 1.345)	1.031	(0.851, 1.249)
n	1186		1186		1186		1186	

*P<0.05, **p<0.01, ***p<0.001.
Exponentiated coefficients; 95% CIs in parenthesis.
†Bivariate associations of independent variable to dichotomous outcomes of any lower extremity amputation and death within 2 years was estimated using multiple logistic regression.
‡Bivariate associations of independent variables to number of readmissions and total number of inpatient days within 2 years was estimated using multiple negative binomial regression due to overdispersion of outcomes in both cases.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; LE, lower extremity; RR, relative risk.

(mean 20.7 vs 13.3, median 8.0 vs 5.0, p<0.0001) within 2 years of diagnosis.

Bivariable model

There was a positive association between total number of readmissions within the 2-year follow-up period and T1DM (RR 1.58, 95% CI 1.21 to 2.07) and T2DM (RR 1.44, 95% CI 1.25 to 1.66, both p<0.001). African American race was associated with increased number of readmissions (RR 1.38, 95% CI 1.14 to 1.67), whereas other race was associated with a decreased number (RR 0.75, 95% CI 0.63 to 0.90, both p<0.01). Among comorbidities, renal disease (RR 1.33, 95% CI 1.14 to 1.56, p<0.001) as well as MI (RR 1.25, 95% CI 1.01 to 1.56), CHF (RR 1.26, 95% CI 1.05 to 1.53) and past LE amputation (RR 1.22, 95% CI 1.02 to 1.47, all p<0.05) were all associated with increased total number of readmissions.

Both T1DM (RR 1.56, 95% CI 1.05 to 2.31, p<0.05) and T2DM (RR 1.55, 95% CI 1.27 to 1.90, p<0.001) were also associated with increased total number of inpatient days during follow-up. Among demographic and comorbidity variables, only renal disease (RR 1.37, 95% CI 1.09 to 1.71, p<0.01) and any malignancy (RR 0.67, 95% CI 0.48 to 0.93, p<0.05) significantly associated with total inpatient days.

Multivariable regression model

T1DM (RR 1.29, 95% CI 1.11 to 1.51, p<0.01) and T2DM (RR 1.33, 95% CI 1.02 to 1.74, p<0.05) both continued to have a significant effect on total number of readmissions; no other comorbidities did. Age (RR 0.99, 95% CI 0.990 to 0.998, p<0.01), African American race (RR 1.27, 95% CI 1.07 to 1.51, p<0.01) and other race (RR 0.83, 95% CI 0.70 to 0.97, p<0.05) were additional factors which affected the total number of readmission events in the regression model. Only malignancy had a significant effect on total inpatient days within 2 years of diagnosis (RR 0.76, 95% CI 0.58 to 0.99, p<0.05). Thus, DM led to increased hospital readmissions but not total number of inpatient days.

DISCUSSION

Osteomyelitis remains a diagnostic and therapeutic challenge and consensus guidelines to guide therapy are lacking. We included those patients diagnosed with osteomyelitis as inpatients. The inpatient diagnosis of acute osteomyelitis occurred 160% more frequently than as an outpatient (1186 vs 743) in our study period. Besides an older age with initial exposure (51.9 vs 56.6 years, p<0.05) and a higher proportion of individuals who identify as African American (14.6% vs 9.1%, p<0.05), the inpatient cohort with osteomyelitis exposure was similar to those patients with osteomyelitis exposure in the outpatient setting (p>0.05). Because we choose to analyze outcomes of inpatients with osteomyelitis, our sample selection may be biased towards sicker patients with greater likelihood of amputation and mortality than the general population. However, our research approach mimicked real-life practice in that most patients who suffer amputation are initially diagnosed in the inpatient setting. It is strengthened by analyzing a group of patients with similar demographics and comorbid status as those diagnosed in lower acuity settings.

In this cohort study of 1186 patients, T1DM, T2DM and certain other comorbidities increased a patient's risk of LE amputation. On bivariable analysis, we demonstrated common comorbidities such as prior MI, CHF, PVD and renal disease were associated with increased incidence of LE amputation in patients with LE osteomyelitis. Comorbidity burden had a significantly greater influence on incidence of amputation than previously demonstrated.[24–26] As described above, incidence of LE amputation can be as high as 75% in certain populations (figure 1). In addition, we find substantial 2-year incidence of LE amputation in otherwise healthy patients (7.2%). To our knowledge, this is the first investigation to comprehensively quantify and compare risk of LE amputation across a variety of comorbid and demographic covariables with high longitudinal follow-up.

In fact, our study provides the most comprehensive evidence, to date, that DM is an important independent marker for amputation risk. Both T1DM and T2DM were associated with a significantly higher amputation risk in both our bivariable and regression analyses. Our regression model also reaffirms the importance of PVD as a risk factor for amputation.[24 27]

Additionally, African Americans were disproportionately diagnosed with osteomyelitis, regardless of setting, and had a higher proportion of DM. It is well established African American populations have less access to glucose-lowering treatments and receive disproportionately higher rates of amputation[28 29] and may partly explain why inpatient African Americans have a higher risk (RR 1.41, p<0.05) of amputation when diagnosed with osteomyelitis in our cohort. Admittedly, further research is needed as this was not within the scope of our current research.

There are at least two notable challenges which remain in the osteomyelitis population. We currently lack an ability to predict long-term outcomes when an initial diagnosis (of osteomyelitis) is made. Poor prediction of outcome is based on a multitude of issues. The first issue is the sensitivity and specificity of probe-to-bone (PTB) testing, as well as plain radiographs for the diagnosis of osteomyelitis.[1 30 31] These are readily available tools used to assess osseous structures. While PTB testing has a reported sensitivity and specificity of ~90% in the inpatient setting, its sensitivity drops significantly, particularly in the outpatient setting,[32] because of associated changes in disease prevalence. Similarly, radiographic sensitivity may be lower due to delayed evidence of cortical changes.[33] As a result, there are limited data to automatically warrant more expensive (advanced) imaging in this patient population. The second challenge which exists is the lack of clinical data to guide clinicians in determining which demographic and comorbid factors are associated

with the greatest risk of amputation. Our study attempts to minimize this gap. Additionally, a related issue is the significant variation in treatment protocols. However, we argue that the ability to tailor treatment based on consistent risk profiles will provide the opportunity for greater standardization and lead to more uniform standard care practices for individuals with osteomyelitis.

We believe that the large number of comorbidities associated with amputation on bivariable analysis also bears further consideration, because these diseases often appear in combinations that may be synergistic or deleterious. These data were consistent with previous studies' single-variable associations with risk of LE amputation (eg, DM, age >60),[34–36] while finding several new finding associations (eg, MI, CHF). We expect that lack of statistical significance for variables such as MI and CHF on regression is largely a function of the size of our single-institution dataset. Neither type of DM carried a higher mortality risk in our regression model, whereas increased risk was seen with other variables that are commonly linked with mortality, such as age, malignancy, COPD and liver disease. Given the CIs (table 3), the lack of increased mortality with DM may again be due to small sample size. We posit that the effect of amputation itself on mortality remains inconclusive, as the effect of decreased functionality on mortality may take longer than 2-year timeframe of our study follow-up to manifest.

The ability to predict long-term outcomes following a diagnosis of osteomyelitis makes the clinical implications of these findings highly relevant. When evaluating patients with equivocal radiographs who are found to meet a certain threshold for risk of LE amputation based on phenotypic characteristics, clinicians will be justified to escalate to advanced modalities such as MRI or bone biopsy.[37] Additionally, there is significant benefit in the application of our findings to inform therapeutic intervention. For example, if a patient has a high risk of amputation (eg, 75% with the not uncommon clinical picture of DM, PVD and CHF), physicians may use this information to recommend more aggressive debridement or discuss amputation as a definitive treatment option. Further, it can help develop a clinical calculator to predict long-term LE amputation probability at the time of osteomyelitis diagnosis. In that context, it would be particularly appropriate to compare our findings to a national-level cohort. However, the use of a larger dataset must be weighed against concerns about accuracy of diagnosis codes, as well as the availability of long-term follow-up. These two concerns were strongly considered in our rationale to select a single-center cohort for the purposes of this observational study.

Our study is not without limitation. First, our study did not account for morbidity of LE osteomyelitis other than amputation. Prior reports have demonstrated patients with (chronic) osteomyelitis experience worse quality of life and greater activity restrictions versus those with long bone fracture non-union requiring amputation (ie, traumatic amputation).[7 38] By addressing the most drastic outcomes of osteomyelitis—amputation and mortality—we did not account for other significant morbidity that may be important in clinical decision-making (eg, chronic pain or non-ambulatory status). Our findings highlight the need to prospectively examine the complex morbidity of osteomyelitis, especially as it is related to disability and health-related quality of life measures. Furthermore, we excluded patients followed for fewer than 2 years, which may have underestimated the incidence of amputation. For instance, patients who had an amputation within 6 months of diagnosis and then had their last follow-up at 18 months would have been excluded. However, during the same period we have strong evidence demonstrating the impact of collaborative multidisciplinary teams to manage extremity osteomyelitis, particularly LE osteomyelitis, which resulted in a reduced count and proportion of amputations at our institution,[32 33] and thus minimizes this concern. Finally, the limitations typical of single-center observational studies, such as inability to determine causation, institution-specific measurement biases and patient selection bias at an academic tertiary care center, apply to our study. We manually abstracted the covariables of all included patients to minimize these limitations, but reviews were non-blinded.

In conclusion, increased risk of LE amputation is quantifiably associated with both T1DM and T2DM, as well as multiple demographic factors and comorbidities found in the CCI. There is a very high incidence of LE amputation in patients with DM, PVD and CHF, whom clinicians may commonly encounter in their practice. These findings indicate the need for further research of the long-term sequelae of osteomyelitis. Clinical risk tools to enable providers to better assess likelihood of amputation based on patient risk profile to inform clinical decision-making are urgently needed.

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