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Rates and Timing of Subsequent Amputation After Initial Minor Amputation

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Abstract

Objectives: Studies evaluating major amputation after initial minor amputation are few with rates of subsequent major amputation ranging from 14 to 35% with limited understanding of associated comorbidities and time to limb loss. The aim of this study is to determine the major amputation rates for patients who had already undergone an initial minor amputation and determine which factors are associated with need for subsequent major amputation.

Methods: Using statewide data between 2005 and 2013, patients with peripheral arterial disease (PAD), diabetes mellitus (DM), and combined PAD/DM who had a lower extremity ulcer and who had also undergone a minor amputation were identified. These patients were evaluated for the rate of subsequent major amputation and competing risk Cox Proportional Hazards modeling was used to study which factors were associated with the risk of subsequent limb loss.

Results: The cohort consisted of 11,597 patients (DM = 4254, PAD = 2142, PAD/DM = 5201) with lower extremity ulcers who underwent an initial minor amputation. The rate of any subsequent amputation was highest in patients with PAD/DM (23% vs DM = 17%, PAD = 17%, p = not statistically significant (NS)). The rate of subsequent minor amputation was 16% in the PAD/DM vs 15.2% in PAD and 12.2% in DM patients (p<.001). Patients with PAD/DM had the highest rate of subsequent major amputation (6.3% vs DM = 5.2%, PAD = 2.1%, p<.001). There was no statistically significant difference in the median time to major amputation among the three groups (PAD/DM = 13 months, DM = 14 months, PAD = 8.6 months, p = NS). Patients who were revascularized before a repeat minor amputation had a decreased risk of a major amputation compared to those who were intervened on after a repeat minor amputation (Hazards Ratio (HR) = .002, 95% Confidence Interval (CI): 0-.22). Patients treated completely in the outpatient setting were also less likely to undergo subsequent major amputation (HR = .7, 95% CI: .5-.98) compared to those who required hospitalization or presented to the emergency room.

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Conclusions: Patients with ulcers and combined PAD and diabetes have a higher risk for secondary major and minor amputation than patients with either disease alone with half of the limb loss occurring at approximately one year after the initial minor amputation. Additionally, early diagnosis and appropriate referral may result in decreased limb loss for these patients.

Table of Contents Summary

In this retrospective study of an administrative database patients with combined peripheral artery disease and diabetes were at highest risk and underwent major amputation approximately one year after minor amputation. The data also suggests that early diagnosis and intervention may limit limb loss.

Introduction:

Major amputation is a significant concern for patients who have undergone a minor amputation due to diabetes and/or peripheral artery disease (PAD). In a recent study of 461 patients with foot ulcers and other foot pathology, Wukich et al. found patients were more likely to fear a major amputation than they were to fear death.[1] There is a significant loss of mobility and independence with major amputation. Only 55% of below knee amputation patients and 45% of above knee amputation patients report a "good" functional outcome.[2] The rate of major amputation after initial minor amputation varies in the literature from 14% to 35% depending on the cohort.[3, 4]

Renal failure and the sequelae of diabetes mellitus (DM) have both been implicated as factors that increase the risk of subsequent major amputation.[5] The challenge is understanding the true rates within the overlapping populations of patients that vascular providers see. These include patients with diabetes mellitus, PAD, and those with combined PAD/DM. These patients each have unique amputation risk and prior studies have shown that patients with combined PAD/DM have a markedly higher amputation rate that those with PAD or DM alone.[6, 7] Furthermore, limited data exists on when patients may ultimately require major amputation after having an initial minor amputation. Skoutas et al. found that patients with DM are at the highest risk for major amputation 6 months after their initial minor amputation but the cumulative major amputation rate for these patients continues to climb up to 10 years after the initial minor amputation.[8, 9] This study used an all-payer database encompassing all non-federal hospitals in California, providing the ability to capture patients missed with Medicare or VA administrative datasets. The goal of this study is to identify the patient population with an increased risk for subsequent major amputation, the time to major and repeat minor amputation, and other associated factors such as the setting of the patient's initial evaluation and if timing of revascularization was associated with limb loss.

Methods:

This is a retrospective cohort study using all-payer statewide data from the California Office of Statewide Health Planning and Development (OSHPD) between the years of 2005 and 2013. The Institutional Review Boards for the California Health and Welfare Agency

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(Committee for the Protection of Human Subjects) approved this study and waived consent given the retrospective nature of the study.

Database

The California OSHPD database captures all non-federal inpatient hospitalizations as part of the Patient Discharge Database (PDD). Additionally, OSHPD also collects data from all emergency departments as a part of the Emergency Department Database (EDD) visits and from eligible ambulatory surgery centers as a part of the Ambulatory Surgery Database (ASD) within California. Non-federal hospitals account for 96% of the hospitals in California. Records for each patient in the OSHPD database are linked through an encrypted Social Security Number called the Record Linkage Number.[10, 11] For each PDD, EDD, and ASD visit, the collected data include demographic information, insurance status, a principal diagnosis code with up to 24 secondary diagnoses codes, and a principal procedure code with up to 20 additional secondary procedure codes. Within the PDD and EDD, medical diagnoses and procedures were coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). All patients admitted to the hospital are captured as part of the PDD and had their therapy administered on an inpatient basis. Emergency classification indicates the patient was first evaluated in the emergency department and discharged. Patients that initially presented to the emergency room are part of the EDD. Patients who were admitted after their emergency department visit had their encounter combined with the inpatient data as part of the PDD. Procedure data in the ASD indicate patients who were initially evaluated and had their treatment done completely on an outpatient basis. The ASD procedures are coded using Current Procedural Terminology codes. In and out of hospital deaths in California and states with a reciprocal reporting relationship with California are tracked through linkage of the OSHPD data to the California Death Statistic Master File.[12]

Patient Cohort and Endpoints

The index patient cohort was created by searching the PDD, EDD, and ASD for principal and secondary ICD-9-CM diagnosis codes indicating the presence of a lower extremity ulcer including those with gangrene, and a corresponding diagnosis of PAD, DM, or combination of PAD/DM. If a patient were coded as having PAD but had a secondary ICD-9-CM code for DM, the patient was classified into the combined PAD/DM disease group. Once the disease cohort was identified, only patients who had PAD, DM, or combined disease who also underwent a minor amputation after their initial diagnosis were included. Additionally, a 5-year look back from their index diagnosis was performed to ensure that only patients with a lower extremity ulcer and previous minor amputation without prior revascularization were included. Minor amputation was defined using ICD-9-CM codes 84.11 (amputation of toe) and 84.12 (amputation though the foot). Records with ICD-9-CM codes indicating an acquired arteriovenous fistula, rheumatic disease, or thromboangitis obliterans as the underlying arterial condition were excluded (Figure 1).

The primary end point was major amputation; defined as a below knee or an above knee amputation and was identified by ICD-9-CM codes. The secondary endpoints include time to major amputation, repeat minor amputation, time to repeat minor amputation, overall

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mortality, time to death, and the combined outcome of amputation or death. Additional analysis was performed to examine how timing of revascularization and location of initial presentation were associated with risk of subsequent major amputation.

Comorbidity Data

The Elixhauser comorbidity software was used to define comorbidities; DM and PAD were excluded from the list of co-morbidities specified in this manner.[13] Additional co-morbid conditions were captured using data provided by the secondary diagnosis codes; such as coronary artery disease (CAD), congestive heart failure (CHF), renal failure, and tobacco use.

Statistical analysis

Rates were determined by the number of patients who underwent major amputation divided by the number of patients in each disease category and reported as a percentage. Means and standard deviations were used to describe normally distributed continuous variables. Medians and interquartile range (IQR) were used to describe skewed continuous data. Frequencies and percentages were used for categorical variables. For categorical variables, the three distinct disease groups were compared using the χ^2 test. For continuous variables, the groups were compared using a pairwise t-test with Bonferroni adjustment. Competing risk Cox Proportional Hazards analysis was used to evaluate for risk factors associated with major amputation. All analyses were performed using "R" Programming for Statistical Analysis. A p value of <.05 was considered statistically significant.

Results:

Baseline characteristics varied significantly between the three disease groups (Table I). Patients in the combined PAD/DM group had more co-morbidities with a higher prevalence of CAD, CHF, and renal failure. The patients with DM alone tended to be younger with an average age of 62 ± 13 years old, while there were more smokers (PAD = 20%, DM = 10%, PAD/DM = 10%, p<.001) and white patients (PAD = 52% DM = 40%, PAD/DM = 35%, p<.001) in the PAD only group. Furthermore, the groups differed in their treatment patterns as well. Patients with DM alone were the least likely to undergo any revascularization procedure during the study period (DM = 75% no revascularization, PAD = 64%, PAD/DM = 63%, p<.001).

Rate of subsequent amputation

The overall rate of major amputation in the cohort was 5.1% (n = 594) and the rate of repeat minor amputation was 14.5% (n = 1676). Patients with combined PAD/DM were more likely to undergo major amputation (n = 327, 6.3%) compared to patients with DM (n = 223, 5.2%) or PAD alone (n = 44, 2.1%, p<.001). Patients in the PAD/DM group were also more likely to require a second minor amputation as well (PAD/DM = 16%, DM = 12.2%, PAD = 15.2%, p<.001, Table II).

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Time to subsequent amputation

The median time to a second minor amputation was 4.9 months (IQR = 1.8–14.7). Patients with DM had a longer time between the initial minor amputation and the second minor amputation (5.9 months, IQR = 2.1–17 months, p<.01), while patients with PAD and PAD/DM were more likely to require a second minor amputation sooner, with both groups having a median time of 4.5 months (PAD IQR = 1.5–15, PAD/DM IQR = 1.8–13). The median time to major amputation for all patients was 12.9 months (IQR = 5.4–27.6 months). There was no statistically significant difference in time to major amputation between patients in the three groups, but patients with PAD only had a median time to major amputation of 8.6 months (IQR = 4.2–23.4 months) compared to patients with DM at 14.1 (IQR = 5.6–33.1) and PAD/DM at 13.3 months (IQR = 5.5–25.3, Table II).

Mortality

The overall mortality for the entire cohort was high at 46.7% (Figure 2). Patients in the DM only group had the lowest mortality at 41% compared to 52% in the PAD only group and 49% in the combined PAD/DM group. As shown in Table II, the median time to death for patients in the DM only group was longest at 17.6 months (1.5 years, IQR = 7.1–35.3 months). Patients with PAD had the shortest time to death at 10 months (.8 years, IQR = 4.4–25.4 months). The median time to death for patients with combined PAD/DM was 13.3 months (1.1 years, IQR = 5.3–32.6 months, p<.001).

Revascularization

In 63% of patients with known PAD and 64% of patients with PAD/DM, no revascularization was attempted before subsequent major amputation was performed. After adjusting for age, race, sex, payer status, and associated co-morbid conditions, there was a significant association between timing of revascularization and risk of major amputation. Patients who underwent revascularization before a repeat minor amputation had a lower risk (HR = .002, 95% CI: 0-.22) of subsequent major amputation compared to patients who underwent a revascularization procedure after their second minor amputation (Table III).

Setting of initial presentation

Table IV illustrates how the setting of initial presentation is related to amputation free survival compared to risk of major amputation. After adjusting for age, race, sex, payer status, and associated co-morbid conditions, there was no difference in the risk of amputation or death when patients were treated on an inpatient basis compared to those who presented in the emergency room or were treated on a completely outpatient basis. However, after analysis using a competing risk model for death, the data demonstrate that patients who were evaluated and treated completely in the ambulatory setting had a lower risk of subsequent major amputation (HR = .7, 95% CI: .5-.98) than patients who had their initial evaluation in the emergency room or who were treated on an inpatient basis.

Discussion:

This study offers an insight into the rates and timing of subsequent major and minor amputations in California among three distinct groups of patients and has shown that

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patients with combined PAD/DM incur additional risks beyond those patients with diabetes or PAD alone. The majority of the work up to this point have analyzed patients based on the conditions of either diabetes mellitus or PAD, but has not reported those with combined disease as a third separate group.[3–5, 14–16] Understanding which patients are at higher risk for and the timing of subsequent major amputation is not only important for counseling patients but also important for directing resources and educational efforts. The work here illustrated that the overall rate of subsequent major amputation in the cohort was 5.1% and the overall rate of subsequent minor amputation was 14.5%. Importantly, the data here show that the patients who had any form of diabetes had a higher risk of subsequent major amputation than patients without diabetes. Not unexpectedly, patients with combined PAD/DM had the highest risk of subsequent limb loss. The data did not demonstrate a significant difference among the three groups regarding the timing of the subsequent major amputation with the majority of amputations occurring approximately one year after the initial minor amputation. Finally, the patients who underwent revascularization before a second minor amputation and those who were able to be evaluated and treated entirely as an outpatient, had a lower risk of major amputation.

The reported rate of limb loss has varied widely across different studies. Glaser et al. conducted a single institution retrospective review showing the rate of subsequent major and minor amputations to be 14.2% and 19.9% respectively.[3] However, one smaller study by Griffin et al. had demonstrated the rate of subsequent major amputation to be as high as 35%.[4] Additionally, a meta-analysis evaluating the rate of major amputation after initial trans-metatarsal amputation, using a random-effects model, estimated the rate of limb loss to be approximately 30.16%.[14] The OSHPD data indicate that while the overall subsequent minor amputation rate in this study is comparable to previously reported rates, the rate of subsequent major amputation is lower. This finding may be due to the differences in study methodology and cohort selection. Prior work had focused largely on single institution outcomes from groups that see the most at-risk patients, while this study concentrates on population-based outcomes. The dataset used in this work includes patients with varying levels of disease severity and offers a broader view. This potentially allows for a truer estimate of the rate of limb loss after initial minor amputation and not just in the extreme risk patients.

In addition to the rate, the timing of subsequent amputation is important to patients and clinicians. Prior data on timing of subsequent major amputation is limited but overall largely congruent. In this study, the median time to subsequent major amputation was about 12 months and time to repeat minor amputation was about 5 months. This finding is consistent with previously reported data demonstrating that the majority of any re-amputation, major or minor, happened by about 6 months after the initial minor amputation.[8, 9] Nerone et al. found that patients with severe PAD had an average time to major amputation after minor amputation of approximately 18 months.[16] The fact that the timing of repeat amputation is on the order of months stresses the potential importance of continued follow-up and evaluation of the limb and its perfusion in the period after initial minor amputation. Moreover, the data also demonstrate that revascularization before a repeat minor amputation decreases the risk of future major amputation, again underscoring the value of close follow up care.

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One striking point revealed by this dataset is the large number of the patients with PAD or PAD/DM and wounds on their lower extremity, 63% and 64% respectively, who did not undergo any revascularization procedure. While there is a select group of patients who are not candidates for revascularization either due to anatomy, co-morbidities, or disease severity, there are certainly patients in this group who could have benefited from revascularization. A study conducted by Goodney et al. using Medicare data examined how factors besides patient-level characteristics affected amputation rates on a regional level. The authors found that there was an inverse association between the intensity of vascular care and a region's amputation rate, suggesting that increased care does decrease amputation rates.[17] The large number of patients with PAD without revascularization found in this study may represent important opportunities to decrease the major amputation rate.

Furthermore, it is also worth noting that there was an association between a lower risk of subsequent major amputation and the ability of the patient to receive their evaluation and revascularization completely as an outpatient. Although it can be argued that this group of patients may have had less severe disease, the thesis is that this difference could potentially be due to earlier recognition of their disease, better access to care, and/or better-timed treatment. Additionally, as previously discussed, the data show that patients who underwent revascularization before a repeat minor amputation had a lower risk of subsequent major amputation when compared to patients who underwent revascularization after having a repeat minor amputation. Intuitively, patients requiring a repeat minor amputation are at higher risk of further amputations. In this higher risk group, the finding that revascularization prior to repeat minor amputation is protective against major amputation is compelling and corroborates the point that earlier recognition of vascular disease can improve outcomes. The mechanism of this finding cannot be elucidated with the present dataset but the hypothesis is that it could possibly be due to closer follow-up and disease specific care; as other authors have suggested that early referral and involvement of vascular specialists may delay or prevent amputation.[16, 18]

The selection criteria used in this study includes a large number of patients with critical limb ischemia and these patients often have significant comorbidities. It has been observed that the mortality rate of patients with critical limb ischemia can be upwards of 20% at 6 months and be greater than 50% at 5 years.[19] The mortality of this cohort over the study period was similarly high at 46.7% with the highest mortality seen in patients with combined PAD/DM. The median time to death after initial minor amputation was between 10 to 17 months. Among the three groups, the median time to subsequent limb loss was 8 to 14 months suggesting that many of these patients are dying shortly after or around the time of their major amputation. There is congruence between the timing of amputation and death likely due to the fact that requiring an amputation in this setting serves a marker of severe systemic atherosclerotic disease burden.[20, 21] Further, the true subsequent major amputation rate has the potential to even be higher, but because many of these patients die, they never progress to limb loss. The high mortality in this cohort further underscores the tenuous health of these patients and the importance of preventative and interventional care.

This study has several limitations. The OSHPD database is an administrative database and the results of this study are dependent on accurate ICD-9-CM coding. Despite using specific

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diagnosis and procedural codes to create the cohort of interest, it is still possible to incorporate inappropriate patients as well as exclude patients of interest. Furthermore, the OSHPD database represents patients seen in non-federal hospitals in California, thus potentially limiting its generalizability to other populations. However, other than the distribution of race where California is more diverse with larger populations of Asians and Hispanics, California's demographic is similar to the rest of the United States. Additionally, because this work is based on an administrative database using ICD-9-CM codes, the dataset precludes certain patient level data such as vascular disease severity, anatomy, wound severity, limb laterality, or indication for procedure. Lastly, we can only comment on the rates of amputation and mortality during the study period as these are captured in inpatient and procedural data. We cannot make conclusions regarding the follow up time as the OSHPD database does not include outpatient clinic follow up data.

Conclusion:

Despite these limitations, the data illustrate that patients with lower extremity wounds who require any amputation have multiple comorbidities and have a high mortality rate. A number of these patients, especially those with combined PAD and DM, will require a subsequent major amputation in approximately one year after their initial minor amputation. Furthermore, the lower risk of subsequent limb loss in patients who were revascularized before another minor amputation and those who were evaluated and treated entirely on an outpatient basis, suggest that there is benefit in early diagnosis and therapy and future work should aim to evaluate the effect of time to treatment on patient outcomes.

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Article Highlights

Type of Research:

Retrospective cohort study using an administrative database.

Key Findings:

Patients with combined peripheral artery disease and diabetes had the highest rate of subsequent major (6.3%) and minor (16%) amputation. Revascularization before initial minor amputation (HR = .002, 95% CI: 0-.22) along with outpatient evaluation and treatment decreased the risk of limb loss (HR = .7, 95% CI: .5-.98).

Take home Message:

Patients with combined peripheral artery disease and diabetes are at the highest risk of subsequent limb loss. Early diagnosis and treatment may prevent major amputation.

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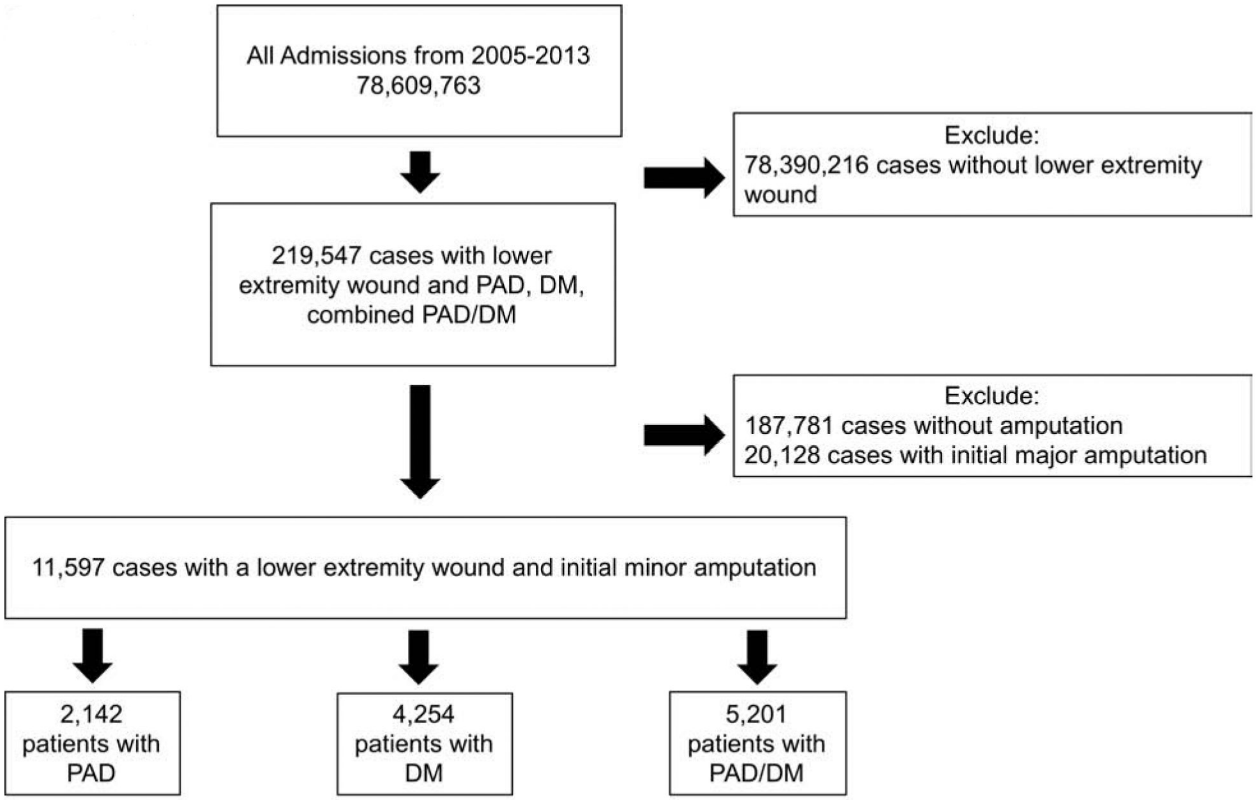

Figure 1.
Flow diagram of cohort selection.

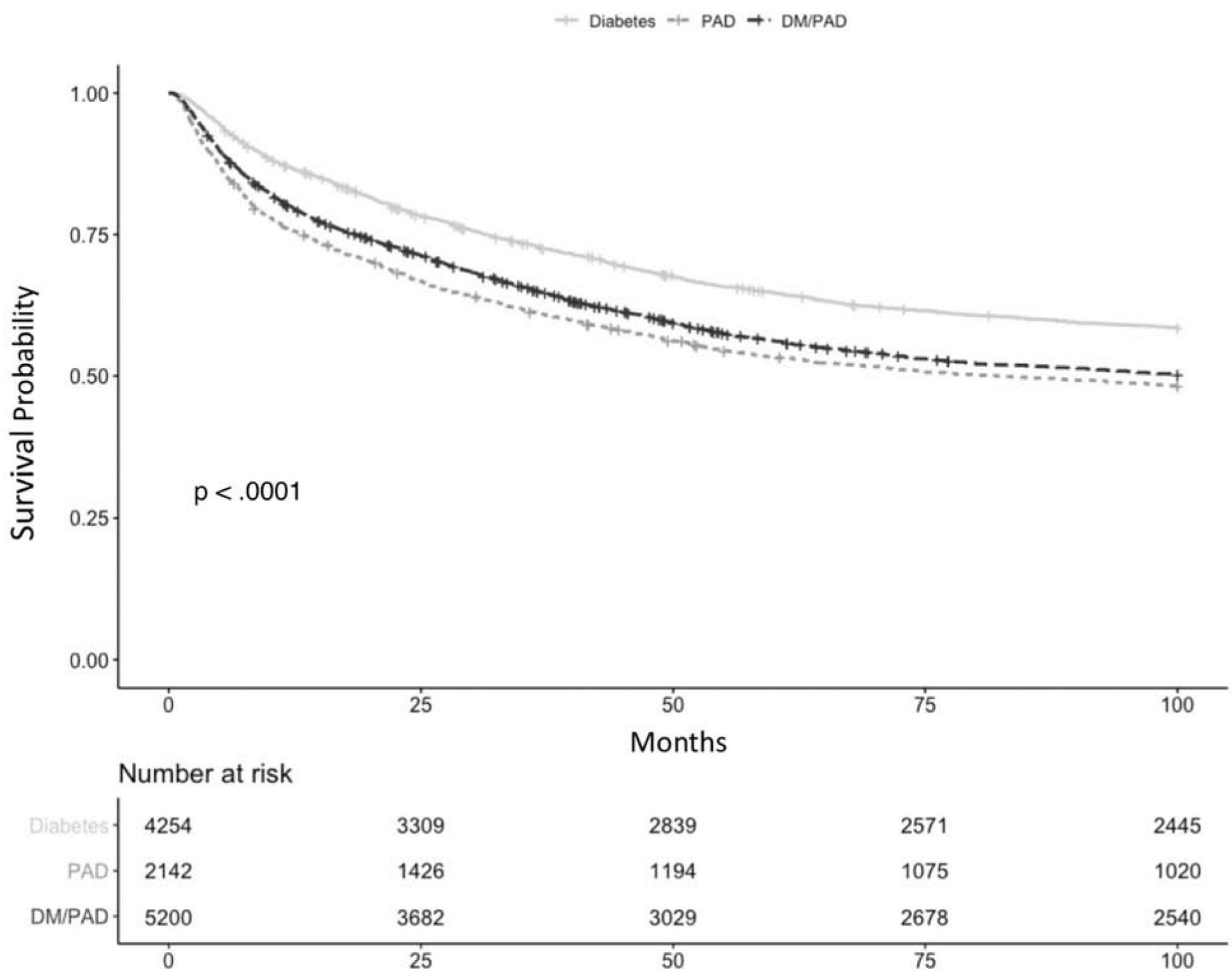

Figure 2.

Kaplan-Meier Survival Curve illustrating mortality in the three disease groups. Adjusted for race, sex, payer status, and comorbidities.

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Table I.

Patient characteristics by disease group. P-value <.05 is considered statistically significant.

Variable	DM	PAD	PAD/DM	P-value
Number of Patients (%)	4254 (37)	2142 (18)	5201 (45)	
Male (%)	2732 (64)	1112 (52)	3280 (63)	<.001
Age (Mean ± SD)	62±13	75±13	69±12	<.001
Smoker (%)	406 (10)	428 (20)	528 (10)	<.001
Payer Category (%)				
-Medicare	2019 (47)	1592 (74)	3412 (66)	<.001
-Medicaid	746 (18)	168 (8)	611 (12)	<.001
-Private	1077 (25)	321 (15)	957 (18)	<.001
-Self Pay	231 (5)	36 (2)	103 (2)	<.001
-Indigent	14 (0.3)	11 (0.5)	23 (0.4)	.51
-Government	167 (4)	14 (0.7)	95 (1.8)	<.001
Race (%)				
-White	1712 (40)	1119 (52)	1835 (35)	<.001
-Hispanic	1307 (31)	281 (13)	1600 (31)	<.001
-Black	633 (15)	374 (17)	811 (16)	.08
-Asian	128 (3)	70 (3)	262 (5)	<.001
-Other/Unknown	473 (11)	291 (14)	693 (13)	<.006
Coronary Artery Disease (%)	787 (19)	528 (25)	1775 (34)	<.001
Congestive Heart Failure (%)	718 (17)	426 (20)	1178 (23)	<.001
Renal Failure (%)	1295 (30)	428 (20)	2130 (41)	<.001
No Attempt at Revascularization (%)	3174 (75)	1357 (64)	3302 (63)	<.001

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Table II.

Rate of major and repeat minor amputations by disease group. Median time to amputation and mortality data by disease group. NS = not statistically significant.

	DM	PAD	PAD/DM	P-value
Number of Patients	4254 (37%)	2142 (18%)	5201 (45%)	
No Subsequent Amputation	3516 (82.6%)	1772 (82.7%)	4040 (77.7%)	NS
Major Amputation Rate	223 (5.2%)	44 (2.1%)	327 (6.3%)	<.001
Median Time to Major Amputation (months, IQR)	14.1 (5.6 – 33.1)	8.6 (4.3 – 23.4)	13.3 (5.5 – 25.3)	NS
Minor Amputation Rate	516 (12.2%)	326 (15.2%)	834 (16%)	<.001
Median Time to Minor Amputation (months, IQR)	5.9 (2.1 – 17)	4.5 (1.5 – 15)	4.5 (1.8 – 13)	<.01
Mortality	1752 (41%)	1104 (52%)	2563 (49%)	<.001
Median Time to Death (months, IQR)	17.5 (7.1 – 35.3)	10 (4.4 – 25.4)	13.3 (5.3 – 32.6)	<.001

Table III.

Amputation risk (analysis completed with competing death risk). Adjusted for race, sex, payer status, and comorbidities.

	Major Amputation	
Variable	**Hazards Ratio**	**95% Confidence Interval**
Female	.19	.04 – .86
Race		
-Black	1.02	.79 – 1.33
-Hispanic	1.32	1.08 – 1.59
-Asian	.83	.51 – 1.35
-Other	.86	.45 – 1.65
Timing of Revascularization		
30–60 Days Before Minor Amputation	.25	.18 – .78
>60 Days Before Minor Amputation	.002	0 – .22
Within 30 days AFTER Minor Amputation	1.22	.64 – 1.79

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Table IV.

Amputation free survival and amputation risk by location of initial presentation (analysis completed with competing death risk). Adjusted for age, sex, race, comorbidities, and payer status.

	Amputation or Death		Amputation	
	Hazards Ratio	**95% Confidence Interval**	**Hazards Ratio**	**95% Confidence Interval**
Location of Initial Presentation				
Inpatient Admission	Reference		Reference	
Emergency Department	1.08	.97 – 1.2	.93	.7 – 1.26
Outpatient Setting	1.12	1.0 – 1.2	.7	.5 – .98