RISK OF LOWER EXTREMITY AMPUTATION REVISION IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE ADJUSTING FOR A COMPETING RISK OF DEATH

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Objectives: The aims of this study are to estimate the cumulative incidence of lower extremity amputation (LEA) revision and reamputation adjusting for a competing risk of death, estimate the one-year event-free mortality rates for patients with peripheral vascular disease undergoing LEA, and develop predictive models for LEA revision and reamputation adjusting for a competing risk of death.

Methods: This was a retrospective review of the prospectively collected Vascular Quality Initiative (VQI) registry between 2013 and 2018. Adults undergoing unilateral LEA were included. Demographics, comorbidities, medications, smoking status, history of vascular procedures and revascularization attempts, and procedure urgency were considered. Models to predict LEA revision and reamputation were developed using multivariable regression on the interval-censored competing risks data using semiparametric regression on the cumulative incidence function.

Results: The cumulative incidences of LEA revision and revision-free mortality within one year of index amputation are 14.9% and 15.5% respectively. Patient BMI, smoking status, aspirin use, history of revascularization, and level of planned LEA are significantly associated with the odds of LEA revision. Age, amputation urgency, dialysis, and level of planned LEA are associated with the one-year odds of revision-free mortality. A patient receiving an index above knee amputation (AKA) has 61% lower odds of LEA revision ($p < 0.0001$) but 51% higher odds of revision-free mortality following LEA ($p < 0.0001$). Previous revascularization procedures increase the odds of revision by 23% ($p < 0.0001$).

The cumulative incidences of reamputation and one-year reamputation-free mortality following LEA are 11.5% and 16.9% respectively. Urgency of the procedure, history of revascularization procedures, and level of planned LEA are statistically associated with the odds of reamputation when adjusting for the competing risk of death. Patients receiving index AKA have 62% lower odds of reamputation ($p < 0.0001$) compared to BKA. Dialysis is the strongest predictor of one-year mortality (OR 2.576, $p < 0.0001$).

Conclusions: Patients with appropriately managed PVD, which still progresses to amputation have higher odds of LEA revision and reamputation. Revision risk can be predicted and compared on the basis of patient factors and the planned index amputation.

Giorgos Bakoyannis, PhD, Chair

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LIST OF ABBREVIATIONS

AIC – Akaike Information Criterion

AKA – Above Knee Amputation

BKA – Below Knee Amputation

BMI – Body Mass Index

CIF – Cumulative Incidence Function

ESRD – End Stage Renal Disease

IQR – Interquartile Range

LEA- Lower Extremity Amputation

OR – Odds Ratio

PSO – Patient Safety Organization

PVD – Peripheral Vascular Disease

PVI – Percutaneous Vascular Intervention

SSDI – Social Security Death Index

SVS – Society for Vascular Surgery

TMA – Transmetatarsal Amputation

VQI – Vascular Quality Initiative

INTRODUCTION

There are an estimated 185,000 limb amputations performed in the United States every year at a cost of more than $4 billion annually (1, 2). Estimates for the proportion of limb loss related to peripheral vascular disease (PVD) range from 38% to 82% (2-4). There has also been a positive trend noted in the number of these amputations performed for vascular disease (2). Lower extremity amputation (LEA) is a particularly morbid operation with the incidence of post-operative wound complications reported as high as 10% following below knee amputation (BKA) and 7.2% following above knee amputation (AKA) (5, 6). The incidence of reamputation to a more proximal anatomic level due to failure of the initial LEA is estimated to be between 8% and 26% depending on the study and the exact patient population considered (1, 7, 8).

Patient factors such as concomitant sepsis, emergent amputation, obesity, active tobacco use, preoperative functional status, insulin-dependent diabetes, and end stage renal disease (ESRD) are significant risk factors for amputation revision or reamputation following LEA (5, 6, 9, 10). Previous revascularization attempts have been shown to increase a patient's risk of amputation revision but not the risk of reamputation to a more proximal anatomic level (11). The level of index LEA is also related to the risk of revision and reamputation. Patients who undergo a foot or ankle level amputation have a higher frequency of reamputation compared to patients who undergo a higher index amputation (1). In addition to the higher rate of wound complications, patients receiving an index BKA have significantly higher risk of subsequent hospital readmission compared to those receiving index AKA. On the contrary, patients receiving an index AKA have a higher mortality rate and worse functional outcomes (5, 8, 12, 13).

If the morbidity associated with LEA wasn't enough, the all-cause mortality rate following LEA is astounding. In a 2017 meta-analysis of mortality following LEA, the composite one-year mortality rate was 47.9% (14). Diabetes, coronary artery disease, cerebrovascular disease, chronic renal disease, and non-ambulatory status were all common comorbid conditions in the patient population with PVD and were closely associated with death in this patient

population (14). The high population-specific mortality rate raises the issue of a competing risk of death when attempting to accurately estimate the incidence of LEA revision or reamputation. A competing risk can be defined as any alternative outcome of clinical significance, which may alter the probability of observing the event of interest (15, 16). In this case, it is reasonable to consider that some patients are likely to die of comorbid conditions before progressing to LEA revision or reamputation despite actually having wound complications or worsening underlying PVD which may have otherwise lead to reoperation had they survived long enough. An entirely separate group of patients will either be lost to follow-up or "censored" at the close of the study time. In other words, we hypothesized that by adjusting for a competing risk of death, we can differentiate between those who die and those who are lost to follow-up, and therefore, more accurately estimate the incidence of LEA revision or reamputation.

The first aim of this study was to estimate the cumulative incidence of amputation revision and reamputation in the first year following LEA adjusting for a competing risk of death. The second aim was to estimate the one-year event-free mortality rate following LEA in the patient population with PVD. The final aim of the study was to develop two separate prognostic models to preoperatively predict the one-year risk of LEA revision and reamputation also adjusting for a competing risk of death.

METHODS

Study Design

This was a retrospective analysis of the prospectively collected Vascular Quality Initiative (VQI) registry maintained by the Society for Vascular Surgery - Patient Safety Organization (SVS-PSO). The VQI represents a collaborative effort of more than 500 centers across the United States who voluntarily contribute patient and procedure details (17). Participating centers are required to provide details for all procedures performed. Clinical data managers and professionals at each center enter data regarding initial procedures and follow-up information using patient medical charts and uniform variable definitions provided by the VQI data dictionary. Data are audited for completeness and accuracy annually using comparison with claims data (17). Mortality data are obtained from a combination of medical charts and the Social Security Death Index (SSDI). The maximum number of days survived following a procedure is defined by either the SSDI-confirmed date of death of the patient or the last known follow-up date in the medical records and VQI.

The VQI Amputation Module was queried from January 2013 to September 2018 for adult patients over the age of 18 years with PVD who underwent unilateral LEA. Patients undergoing bilateral LEA, defined as either part of the same operative procedure or contralateral amputation within 30 days of index LEA, and those undergoing a planned staged amputation were excluded from the study. LEA revision was defined as any return to the operating room for wound management or reoperation related to the index LEA. Reamputation was defined as reoperation with LEA to a higher defined anatomical level. For patients undergoing multiple revisions of the same index LEA, only the first revision was considered, and for patients undergoing contralateral LEA more than 30 days after the index LEA, only the first index LEA was considered in order to avoid the statistical issue of repeated measures on the same individual.

Patient demographics, body mass index (BMI), medical comorbidities (diabetes, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, ESRD, dialysis

requirement, and hypertension), pre-operative smoking status, pre-operative use of aspirin, other antiplatelet medications, anticoagulants, beta-blockers, statins, and ACE-inhibitors, and history of previous vascular surgery procedures were considered. These variables were dichotomized into binary indicators of a comorbidity or regular medication use. Any previous amputation, arterial bypass, carotid stenting or endarterectomy, or aneurysm repair were noted. Patients were defined as having had an ipsilateral revascularization procedure if they reported having a history of inflow arterial bypass or endovascular stenting or lower extremity arterial bypass or stenting to the same leg subsequently requiring amputation. Given that the known date of last contact or death for each patient is constant within the database, the time between index LEA and revision or reamputation was determined using comparison of the number of days survived post-procedure for each operation. For example, if a patient was known to survive for 30 days after index LEA but only 10 days after revision, the time between LEA and revision was defined as 20 days and considered accurate to within a 24-hour period.

Given the de-identification of the data, this work is exempt from approval by the Indiana University Institutional Review Board. The SVS-PSO National Research Advisory Committee approved the proposal for this project.

Statistical Analysis

Patients were first grouped based on whether or not they required any LEA revision or reamputation within one year of index LEA. Demographic information, disease characteristics, comorbidity information, procedure details, and outcomes were calculated as raw descriptive statistics and incidences for the entire patient population. Two separate prognostic models were then pursued to predict any LEA revision (Model 1) and reamputation (Model 2). Each patient was defined as experiencing the first of either revision/reamputation or death within 365 days of index LEA. Death was considered a mutually exclusive competing risk as observation of death precludes observation of amputation revision or reamputation. Patients were considered lost to follow-up or right-censored at the minimum of either 365 days or their last known follow-up visit

time if they had neither a recorded revision/reamputation nor a confirmed date of death within the registry (Equation 1).

$$C_{Model\ 1} = \begin{cases} 0 = Right\ Censored \\ 1 = Revision \\ 2 = Death \end{cases} \quad and \quad C_{Model\ 2} = \begin{cases} 0 = Right\ Censored \\ 1 = Reamputation \\ 2 = Death \end{cases}$$

[Equation 1]

where $C_{Model\ 1}$ and $C_{Model\ 2}$ represent the event indicators for Model 1 and Model 2 respectively.

For patients with complete records and a Social Security Number reported to the VQI, the time from index LEA to revision or reamputation could be determined to within a 24 hour period. However, for patients without the aid of the SSDI to determine the number of days survived after index LEA, the day of revision or reamputation was not precisely known and could only be determined to within a 60-day window. Therefore, all data on timing of revision or reamputation were considered interval-censored in order to minimize the bias introduced by measurement error. The cause-specific cumulative incidence function (CIF) is of most interest given the study goal of prognostication and can be shown to be as follows for the situation including two competing risks in Equation 2 (18, 19).

$$F_j(t) = \Pr(T \le t,\ C = j) = \int_0^t \lambda_j(u) \exp\left[-\int_0^u \sum_{c=1}^{2} \lambda_c(w) dw \right] du, \qquad j = 1, 2$$

[Equation 2]

where $\lambda_j(u)$ is the cause-specific hazard function and T is the failure time for the specific cause of failure, C. Regression analysis on the CIF using the traditional semiparametric proportional subdistribution hazards model (Fine-Gray Model) does not account for interval-censored data. Parametric likelihood approaches were avoided in order to avoid imposing strict assumptions for the possible causes of failure (20). Multivariable regression on the interval-censored competing

risks data was performed using semiparametric regression on the CIF in which each baseline "risk" function for the j^{th} failure cause indicator is estimated non-parametrically using a B-spline based sieve maximum likelihood approach (21). This approach does not impose distributional assumptions on the CIFs. The overall model estimated was a semiparametric transformation model using the logit link function called the proportional odds model and is given by the model equation (Equation 3) below.

$$logit\left[F_j(t; Z, \theta_i)\right] = \phi_j(t) + \beta_j' Z$$

[Equation 3]

where β_j is the vector of parameter estimates and Z is the patient-specific covariate vector of interest. This implies that given a set of covariates, the cause-specific CIF for a specific individual at any time point, t, can be calculated using Equation 4 as follows.

$$F_j\left(t; Z, \phi_j, \beta_j\right) = \frac{\exp[\phi_j(t) + \beta_j' Z]}{1 + \exp[\phi_j(t) + \beta_j' Z]}$$

[Equation 4]

The baseline "risk" function, $\phi_j(t)$, is considered an infinite dimensional parameter as it can take on an infinite number of values over the continuous variable for time. This leads to a difficult and extremely computationally burdensome process to attempt maximization of the likelihood function. This can be remedied using the B-spline approach in order to maximize the likelihood over a sieve, which is a sequence of finite-dimensional parameter spaces that approximates the infinite-dimensional parameter space of ϕ (22). The B-spline can be thought of as a complex polynomial with the number of internal knots and order of the polynomial defined as N_j and m_j respectively. It was used to non-parametrically estimate the baseline risk of LEA revision and reamputation without consideration of covariates as shown in Equation 5 where γ_j represent the unknown control points of the polynomial of the B-spline to be estimated (21, 22).

$$\Theta_{j,n} = \left\{ \begin{array}{c} \phi_j : \phi_j(t) = \sum_{s=1}^{N_j+m_j} \gamma_{j,s} B_{s,m_j}(t), t \in [a,b], \\ \gamma_j \in \mathbb{R}^{N_j+m_j}, \gamma_{j,1} < \cdots < \gamma_{j,N_j+m_j} \end{array} \right\}$$

[Equation 5]

For the interval-censored data with the event time bounded by the lower bound, *V*, and the upper time bound, *U*, the likelihood function consists of the portion contributed by those patients experiencing either amputation revision or reamputation within the interval [*V, U*] as well as the portion contributed by those who are right censored and lost to follow-up (21). Maximizing the likelihood function shown below (Equation 6) using the B-spline approach then leads to consistent and asymptotically normally distributed estimators. These estimators can then easily be used for further inference regarding amputation revision or reamputation (21). It should also be noted that maximization and determination of the cause-specific CIF must be done under the restriction that the sum of all cause-specific CIF functions at the maximum follow up time cannot exceed one (21). This leads to a constrained maximization problem.

$$L(\theta, D) \propto \prod_{i=1}^{n} \left(\left\{ \prod_{j=1}^{2} \left[F_j(U_i;\, Z_i, \theta_j) - F_j(V_i;\, Z_i, \theta_j) \right]^{\delta_{ij}} \right\} \left[1 - \sum_{j=1}^{2} F_j(V_i;\, Z_i, \theta_j) \right]^{1-\delta_i} \right)$$

$$\theta_j = (\phi_j, \beta_j')'$$

[Equation 6]

where δ_{ij} is the indicator that the *i*th patient experienced the *j*th cause of failure.

Considering the pre-operatively available patient variables listed above, model selection was done on the basis of a pseudo-Akaike Information Criterion (pseudo-AIC) calculated as shown (Equation 7) considering a penalty for the number of parameter coefficients estimated for

each possible model. While it is certainly possible that other covariates may show an association with LEA revision or reamputation if included, only those that added to the model fit and predictive value without contributing undue complexity to the model were included. Additionally, keeping a relatively small number of predictors is more practical for clinical use of the prediction model.

$$Pseudo\ AIC = -2 * \log likelihood + 3 * (\#\ parameters\ estimated)$$

[Equation 7]

The final models were those with the best predictive value as evidenced by the lowest pseudo AIC value. They were then run using 50 bootstrapped repetitions in order to estimate the variance of the parameter estimates and allow for calculation of confidence intervals and statistical inference. This model selection procedure is preferable over traditional variable selection approaches, such as backwards selection, as it does not utilize hypothesis testing, unlike the traditional approaches, and, therefore, does not lead to an abuse of type I error due to multiple comparisons. Also, it has been proven mathematically to lead to consistent model selection in simpler statistical models such as linear regression models (23). Statistical significance was defined as a Type I Error rate (α) < 0.05. The regression analysis was accomplished using the "intccr" package available in R version 3.5.3 (24). Data management and descriptive statistics were accomplished using SAS 9,4 (Cary, NC).

RESULTS

Out of the 12,068 total entries in the VQI registry Amputation Module, 8,156 individual patients with a single qualifying LEA were identified and included in the study. Index LEA level was transmetatarsal amputation (TMA) (20%), BKA (43%), AKA (34%), and other (3%). Of these, 885 (10.9%) were noted to have undergone any amputation revision, and 600 of those required reamputation to a higher anatomic level within one year of follow-up (Figure 1). The raw one-year mortality rate in the patient population was 1,140 deaths/8,156 patients (14%) (Figure 1). The most common conversion was BKA to AKA (n = 282) followed by TMA to BKA (n = 223) and TMA directly to AKA (n = 50). In the total included patient population, the mean age was 65.3 years, 2,164 (26.6%) were active smokers at the time of index LEA, 5,613 (68.9%) had diabetes, and 1,496 (18.4%) were currently receiving dialysis (Table 1). The most common previous revascularization procedure to the ipsilateral leg was extremity percutaneous vascular intervention (PVI) in 15.2% (n = 1,239) of patients followed by extremity arterial bypass in 10.4% (n = 851). Prior extremity PVI was noted in 20.9% (n = 185) of patients undergoing LEA revision and in 21.8% (n = 131) of patients who required reamputation to a higher level. Full details of patient demographics, comorbidities, and history can be found in Table 1.

The most common indications for index LEA were ischemic tissue loss in 4,044 (49.6%) patients and uncontrolled infection in 2,564 (31.4%) patients. Less than 10% of index LEAs (n = 760) were considered emergent. Only 29.8% (n = 2,427) of patients were discharged directly to home following hospitalization for their index LEA while 68% (n = 5,215) of patients required discharge to either a rehabilitation or skilled nursing facility (Table 2). The median maximum follow-up time for all patients included in the study was 384 days (IQR 306-509). Procedure and discharge details can be seen in full in Table 2.

Model 1- Any LEA Revision

When the baseline "risk" is estimated, the cumulative incidence of LEA revision at one-year follow-up from index LEA was 14.9% while the cumulative incidence of revision-free death

was 15.5% (Figure 2a). The model to predict LEA revision (Model 1) includes the patient variables age, gender, BMI, urgency of amputation, smoking status, ESRD requiring dialysis, preoperative aspirin use, history of ipsilateral revascularization procedures, and the anatomic level of the planned index LEA. The model demonstrates that, of these, BMI, smoking status, preoperative aspirin use, history of ipsilateral vascular procedures, and level of the planned amputation are all statistically significantly associated with odds of LEA revision within one year of index LEA. Modeled simultaneously, patient age, amputation urgency, dialysis, and level of the planned amputation are all statistically significantly associated with the odds of revision-free death. The indication for index LEA, race, and other comorbidities, including diabetes, did not contribute adequately to the predictive value of the model and were excluded. The details of the final Model 1 selected can be seen in Table 3a. It should be noted that odds ratios (OR) provided represent the increase or decrease in odds of revision or death for a one-unit increase in the variable of interest. When a 10 kg/m^2 difference in patient BMI is considered, a patient with a BMI of 35 kg/m^2 has a 17% lower odds of revision ($p = 0.0008$) compared to an otherwise equivalent patient with a BMI of 25 kg/m^2. A more proximal anatomic level of index LEA is protective against LEA revision but predictive of revision-free mortality within one year of index LEA. A patient receiving an index AKA has 61% lower odds ($p < 0.0001$) of LEA revision but 51% higher odds ($p < 0.0001$) of revision-free mortality within one year compared to a patient who receives an index BKA (Table 3a). Patients who have had their PVD previously medically managed with aspirin or undergone revascularization procedures but have still progressed to index LEA have 33% ($p = 0.0011$) and 23% ($p < 0.0001$) higher odds of LEA revision within one year respectively when compared to counterparts without a history of these interventions (Table 3a). Additionally, revascularization procedures are additive. A patient with a history of any two ipsilateral revascularization procedures has an OR of 1.52 (95% CI 1.39- 1.66) indicating an additional 28.7% increase in the odds of LEA revision compared to a patient with a history of

only one revascularization procedure. The most dramatic predictor of revision-free mortality is ESRD requiring dialysis (OR 2.818, $p < 0.0001$).

Model 2- Reamputation

When only reamputation to a higher level was considered the event of interest, the baseline cumulative incidence of reamputation at one-year follow up was 11.5% while the cumulative incidence of reamputation-free death was 16.9% (Figure 2b). The details of the final Model 2 selected can be seen in Table 3b. The model to predict reamputation to a more proximal anatomic level (Model 2) includes the same covariates listed in Model 1. Index LEA level, urgency of the procedure, and history of prior revascularization procedures are statistically significantly associated with the risk of reamputation. Age, index LEA level, urgency of the procedure, ESRD requiring dialysis, and history of prior revascularization procedures are associated with the risk of reamputation-free mortality within one year of index LEA. A 10-year increase in age increases the odds of mortality by 43% ($p < 0.0001$). When considering only major reamputation, patient BMI is no longer significantly associated with reamputation ($p = 0.0968$) or mortality ($p = 0.5808$). Patients receiving an index AKA have 62% lower odds of reamputation ($p < 0.0001$) and 53% higher odds of reamputation-free mortality ($p < 0.0001$) within one year of index LEA compared to patients undergoing index BKA. Patients undergoing an elective index LEA have 29% lower odds of reamputation ($p = 0.0045$) but 39% higher odds of mortality ($p = 0.0033$) compared to those that require emergent index LEA (Table 3b). Similar to Model 1, the most dramatic predictor of reamputation-free mortality remains ESRD requiring dialysis (OR 2.576, $p < 0.0001$).

DISCUSSION

Our data demonstrate a cumulative incidence of 14.9% for LEA revision, 11.5% for reamputation, and 15.5% to 16.9% for event-free mortality in the year following LEA. The estimated cumulative incidences of revision and reamputation are comparable to current literature. There is a very wide range of estimates reported likely due at least in part to the relatively small sample size of many available studies. Kelly et.al. demonstrated that between 2000 and 2012, the proportion of patients requiring LEA reamputation to a higher level has decreased substantially from 11.5% to 7.2% (25). A cohort study by Schmiegelow et.al. reported that of 180 amputations, 21.6% required reamputation within 90 days of index LEA (26). When follow-up is extended to 3 years, Kono et.al. found a 49.1% incidence of reamputation among 116 patients with PVD (10). In a larger study by Dillingham et.al. in 2005, 3565 patients with PVD who underwent LEA were included, and 26% ultimately required an additional amputation procedure within one year following index LEA (1). More closely related to our chosen analysis, in 2014 Rosen et.al. completed a study of 188 patients who underwent LEA for ischemic or infectious reasons (27). The authors used survival analysis with a Cox proportional hazards model to assess mortality following BKA vs. AKA and were able to support the finding that mortality is higher following AKA. Interestingly, they were also able to demonstrate that the bulk of reoperations following index LEA occur within the first year post-operatively (27). This is in direct agreement with the findings of our study which also suggest that early LEA revision and reamputation are much more common early than late with a steep upslope in the cumulative incidences between 0 and 100 days following index LEA.

Our raw overall mortality rate estimate of 14% is relatively low when compared to rates previously reported in the literature. A meta-analysis by Stern et.al. looking specifically at mortality included 16 separate studies reporting a range of mortality rates from 9.1% to 53% with a composite mortality rate calculated to be 47.9% one year after index LEA (14). It is important to keep in mind that our reported event-free mortality rate does not include those patients who

died within one year of index LEA *after* requiring revision or reamputation. Patients are not considered further after requiring revision. Thus, caution should be used when comparing our event-free mortality rate of 15.5% to 16.9% with overall mortality rates reported in the literature.

Insulin-dependent diabetes, ESRD, BMI, resistant bacterial infections, gangrene present at the time of index LEA, history of prior revascularization attempts, active tobacco use, and need for emergency operation are significant risk factors for reoperation in the existing literature (1, 6, 9-11, 27). Both Model 1 and Model 2 detailed by our analysis are generally in agreement with these findings and support the importance of patient BMI, ESRD requiring dialysis, smoking, and previous revascularization attempts. O'Brien et.al. demonstrated an adjusted 215% higher odds of early amputation failure within 30 days of index LEA when the procedure is done emergently. This is in direct comparison to the 20-30% increased odds of revision or reamputation for an emergent versus elective procedure found in our study (6). Wu et.al. calculated an OR of 3.85 for reamputation from BKA to AKA associated with ESRD (9). The statistically insignificant p-values in our models (Tables 3a and 3b) should not be interpreted to say that ESRD is not a risk factor for revision. Rather, it is meant to be interpreted as one simultaneous model suggesting that ESRD requiring dialysis increases the risk of mortality so dramatically that it precludes the observance of any increased risk of LEA revision or reamputation related to ESRD.

Studies have consistently supported a lower risk of amputation failure for higher anatomic levels of index LEA (1, 6, 10, 27). When comparing BKA and AKA, Rosen et.al. noted reamputation to a higher level in 15.8% and 3.6% of patients respectively ($p = 0.018$) (27). Dillingham et.al. noted the highest percentage of progression to a higher level of amputation among those undergoing foot amputation (1). Looking specifically at anatomic levels within foot amputation, Kono et.al. were able to demonstrate higher proportions of reamputation for patients undergoing metatarsal and toe amputations compared to those undergoing midfoot or hindfoot amputations (10).

Finally, our models both demonstrate a statistically significant association between previous revascularization attempts, whether PVI or open bypass, and the odds of LEA revision or reamputation ($p < 0.0001$ and $p = 0.0003$ respectively). In Model 2, previous ipsilateral revascularization procedures were also statistically significantly associated with one-year reamputation-free mortality ($p = 0.0001$). A previous study by Barnes et.al. matched patients based on comorbidities and demographics and found that those undergoing amputation after a previous revascularization attempt were significantly more likely to require revision surgery ($p = 0.027$) but *not* reamputation ($p = 0.341$). They also found no increased risk of mortality ($p = 0.782$) based on Kaplan-Meier survival analysis (11). The association between previous revascularization procedures and mortality in our results may be simply due to a tendency to offer revascularization to patients with fewer comorbidities and less severe PVD overall.

While the preceding discussion demonstrates the compatibility of our results with existing literature, the crux of this analysis rests on the consideration of death as a competing risk to revision and reamputation. The importance of this consideration is outlined here. In 2016, Serizawa et. al. specifically investigated the mortality and amputation-free survival of patients on dialysis undergoing major LEA using a Kaplan-Meier analysis (28). The group was able to demonstrate a 56% survival rate and 39% amputation-free survival rate following the patient's first major LEA, but while these results illustrate the dramatic mortality rate in this subpopulation of patients with PVD, it did not directly control for the competing risk of death (28). In traditional survival analysis using a Kaplan-Meier estimate to calculate the cumulative incidence of the event of interest, patients who die and those who are lost to follow-up are both considered right-censored despite being quite different in reality (15). Patients considered right-censored are included in the total "at risk" population for revision or reamputation for the full yearlong duration of the study. This is appropriate for those patients lost to follow-up and presumed to be alive and thus truly at risk of reoperation, but it is not appropriate for patients who have died. Grouping these patients together in the Kaplan-Meier analysis has been shown to lead to

overestimation of the incidence of the event of interest (15). The accuracy of our models to predict the incidence of LEA revision or reamputation is improved by considering the cause-specific CIF which accounts for the competing risk of death (16). The estimates provided by the competing risk analysis represent the probability of LEA revision or reamputation given that a patient is free of revision and has survived up to the time point of interest (15, 16).

For instance, when the traditional Kaplan-Meier survival analysis is done for LEA revision in our dataset simply considering those who die to be right censored at the time of death, the incidence of revision is 15.9% compared to the 14.9% estimated using the competing risk analysis on interval-censored data. While comparing 15.9% to 14.9% (a 6.3% bias or overestimation) does not appear dramatic, we must consider also that this overestimation is sensitive to the mortality rate in the population. In a simulation by Berry et.al. arguing in favor of competing risk analysis for elderly patients, they demonstrated that this bias increase from 9.5% to 47.6% as mortality increased from 10% to 85% (15). It follows also that as the number of patients remaining alive and able to experience the event of interest decreases over time, this bias towards overestimation will become more pronounced as patients are followed out further in time. In our patient population with PVD, the fact that the revision-free mortality rate of 15.5% to 16.9% and interest in only one-year post-amputation outcomes produces a measurable bias suggests that the competing risk analysis is imperative for evaluation of any long-term outcomes or complications in these patients.

Previous literature has supported the use of a competing risk analysis in both aging patient populations as well as those with high risk of premature death (15, 18, 19). A study by Jacqmin-Gadda et.al. to predict the 10-year risk of dementia in elderly patients developed a predictive model adjusting for the competing risk of death before diagnosis of dementia (29). The authors were able to demonstrate the improved predictive value of their model based on ROC analysis for a patient population shown to have a raw 10-year mortality rate of 36%. Assessing a patient population clinically more similar to the patient population of interest in our study, in

2012, Grams et.al. established the importance of considering a competing risk analysis for patients with ESRD and peripheral vascular disease. The authors compared analyses done without and then with the competing risk adjustment and found a 66% to 51% drop and 51% to 29% drop for the incidence of ESRD and death prior to diagnosis with ESRD, respectively when death is considered a competing risk (30). The staggering mortality rates following LEA undeniably place patients with PVD requiring amputation into the high-risk category for premature death. These findings are also in agreement with the results of our study demonstrating more than a 200% increased odds of mortality for patients with PVD on dialysis before ever progressing to LEA revision or reamputation (Tables 3a and 3b).

Interval censoring is a common phenomenon in medicine as medical providers are frequently unable to pinpoint an exact time of disease onset. Two options traditionally used to deal with this uncertainty using single imputation include right imputation, which assumes the onset occurred at the time of the most recent medical encounter and midpoint imputation, which assumes the onset of disease occurred at the midpoint between medical encounters (31). Both of these options introduce measurement error which in turn leads to biased regression parameter estimates (31). A third option for dealing with interval censoring in medical studies is to use multiple imputation, but this method has been shown to lead to potential bias due to misspecification of the imputation model used to impute the missing failure time data (32, 33). By considering the full interval during which we are certain the failure or censoring occurred, we avoid these biases in estimation of the CIF and regression parameter estimates in our models.

Despite the use of a prospectively collected and maintained registry, this study is limited by the retrospective nature of the analysis. It is also subject to the limitations of the VQI database including the lack of several desirable data points. For instance, the VQI database provides information on whether a patient has diabetes and what treatment regimen they are on to manage their diabetes, but it does not include preoperative or post-operative hemoglobin A1C values to indicate adequacy of blood glucose management. Including diabetes as a control variable in our

models did not add to their predictive value despite previous studies demonstrating worse outcomes following LEA for patients with diabetes (1, 10). Additionally, with 50.3% of preoperative ankle-brachial index (ABI) values missing for the included patient population in the VQI registry, the decision was made to exclude this variable from model consideration despite its potential clinical importance. It is unclear how much of the missing data for ABI is related to reporting and how much is due to an actual lack of testing. Finally, while the VQI provides a large sample size, the registry is composed of voluntarily participating centers only and may not be perfectly representative of the greater patient population with PVD.

The next step for this project is to build a user-friendly tool to allow clinical implementation of these models in practice. By including only variables that should be readily available to the surgeon preoperatively, our vision is to incorporate the model into an interface capable of quickly calculating the cumulative incidences based on user entry of covariate values. We also plan to pursue validation of the predictive ability of our models using a new data set, which will allow determination of the sensitivity and specificity of the models.

CONCLUSIONS

Our models provide a means to predict any LEA revision (Model 1) or reamputation to a higher anatomic level while adjusting for and simultaneously modeling the cumulative incidence of death within one year following index LEA. Patients who have been appropriately medically managed with aspirin and have had previous revascularization procedures as well as those actively smoking have higher odds of LEA revision or reamputation. Adding the planned level of index LEA into the model not only improves the predictive value but also will allow clinicians to compare and contrast the revision and reamputation risk based on the index operation offered to the patient. Our hope is that these models may help guide preoperative conversations and shared decision-making when planning the level of index LEA.

APPENDICES

Appendix A- Tables

Table 1: Patient characteristics, preoperative health status, and history of vascular procedures for the total patient population and the subgroups that required any amputation revision or reamputation to a more proximal anatomic level within one year of initial lower extremity amputation.

	Total Population (n = 8156)	**No Revision Group (n = 7271)**	**Revision Group (n = 885)**	**Reamputation Group (n = 600)**
Age (years), mean (SD)	65.3 (13.0)	63.4 (12.4)	63.4 (13.1)	64.5 (12.1)
Gender, n (%) male	5282 (64.8)	4672 (64.3)	610 (68.9)	407 (67.8)
Race, n (%)				
White	4770 (58.5)	4248 (58.4)	522 (59.0)	356 (59.3)
Black	2862 (35.1)	2541 (34.9)	321 (36.3)	217 (36.1)
Other	524 (6.4)	482 (6.6)	42 (4.7)	27 (4.6)
Primary Insurer, n (%)				
Medicare	4648 (57.0)	4179 (57.5)	469 (53.0)	325 (54.2)
Medicaid	883 (10.8)	764 (10.5)	119 (13.5)	75 (12.5)
Private	2213 (27.2)	1965 (27.0)	248 (28.0)	167 (27.8)
Military	88 (1.1)	79 (1.1)	9 (1.0)	8 (1.3)
None	305 (3.7)	278 (3.8)	40 (4.5)	25 (4.2)
BMI (kg/m^2)	27.9 (7.7)	27.8 (7.3)	27.9 (7.7)	27.7 (7.4)
Pre-op Smoking Status, n (%) active smoker	2164 (26.6)	2905 (40.0)	352 (39.8)	180 (30.1)
Pre-op Comorbidities, n (%)				
Hypertension	7199 (88.3)	6400 (88.0)	799 (90.4)	546 (91.2)
Diabetes	5613 (68.9)	4975 (68.4)	638 (72.1)	432 (72.1)
CAD	2545 (31.2)	2268 (31.2)	277 (31.3)	192 (32.1)
CHF	2307 (28.3)	2097 (28.8)	210 (23.7)	146 (24.5)
COPD	1902 (23.3)	1725 (23.7)	177 (20.0)	125 (20.9)
Dialysis	1496 (18.4)	1322 (18.2)	174 (19.7)	129 (21.5)
Pre-op Hemoglobin (gm/dL)	9.9 (2.2)	10.1 (2.0)	9.9 (2.2)	10.1 (2.0)
Pre-op Ambulation, n (%)				
Ambulatory	3263 (40.2)	2852 (39.2)	411 (46.7)	264 (44.2)

Assistance	2846 (35.0)	2513 (34.6)	333 (37.8)	238 (39.9)
Wheelchair	1627 (20.0)	1504 (20.7)	123 (14.0)	87 (14.6)
Pre-op ASA Class, n (%)				
I	6 (0.1)	5 (0.07)	1 (0.1)	0 (0)
II	154 (1.9)	136 (1.9)	18 (2.0)	14 (2.3)
III	4747 (58.4)	4188 (57.6)	559 (63.4)	378 (63.2)
IV	3170 (39.0)	2868 (39.4)	302 (34.2)	204 (34.1)
V	46 (0.57)	44 (0.6)	2 (0.2)	2 (0.3)
Pre-op Medications, n (%)				
Aspirin	4915 (60.3)	4325 (59.5)	590 (66.7)	393 (65.5)
P2Y12 Antagonist	2271 (27.8)	1966 (27.0)	305 (34.5)	215 (35.9)
Statin	5263 (64.6)	4666 (64.2)	597 (67.5)	404 (67.3)
Beta Blocker	4592 (56.3)	4078 (56.1)	514 (58.1)	346 (57.8)
ACE/ARB	3299 (40.5)	2896 (39.8)	403 (45.6	270 (45.0)
Anticoagulant	1806 (22.1)	1610 (22.1)	196 (22.1)	143 (24.0)
Previous Vascular Procedures, n (%)				
Arterial Bypass	2184 (26.8)	1902 (26.1)	282 (31.9)	205 (34.2)
CEA/CAS	352 (4.3)	304 (4.2)	48 (5.4)	30 (5.0)
Aneurysm Repair	157 (1.9)	145 (2.0)	12 (1.4)	6 (1.0)
PVI	3089 (37.9)	2671 (36.7)	418 (47.2)	292 (48.7)
Any Amputation	3795 (46.6)	3359 (46.2)	436 (49.3)	288 (48.1)
Previous Ipsilateral Vascular Procedures, n (%)				
Inflow Bypass	272 (3.3)	244 (3.4)	28 (3.2)	19 (3.2)
Inflow PVI	396 (4.8)	347 (4.8)	49 (5.5)	32 (5.3)
Extremity Bypass	851 (10.4)	731 (10.1)	120 (13.6)	86 (14.3)
Extremity PVI	1239 (15.2)	1054 (14.5)	185 (20.9)	131 (21.8)
Amputation	2937 (36.0)	2588 (35.6)	349 (39.4)	228 (38.0)

ASA = preoperative anesthesia physical status classification
ACE = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
CEA = carotid endarterectomy
CAS = carotid artery stent
PVI = percutaneous vascular intervention (any non-cardiac endovascular intervention)

Table 2: Details of initial amputation, discharge from the hospital, and follow-up for the total patient population and the subgroups that required amputation revision or reamputation to a more proximal anatomic level within one year of initial lower extremity amputation.

	Total Population (n = 8156)	**No Revision Group (n = 7271)**	**Revision Group (n = 885)**	**Reamputation Group (n = 600)**
Urgency, n (%)				
Elective	5418 (66.6)	4830 (66.4)	588 (66.7)	412 (690)
Urgent	1958 (24.1)	1737 (23.9)	221 (25.1)	140 (23.5)
Emergent	760 (9.3)	687 (9.4)	73 (8.3)	45 (7.5)
Indication for Initial Amputation, n (%)				
Ischemic Rest Pain	479 (5.9)	411 (5.7)	68 (7.7)	45 (7.5)
Ischemic Tissue Loss	4044 (49.6)	3598 (49.5)	446 (50.4)	338 (56.3)
Acute Ischemia	688 (8.4)	613 (8.4)	75 (8.5)	49 (8.2)
Uncontrolled Infection	2564 (31.4)	2303 (31.7)	261 (29.5)	148 (24.7)
Neuropathic Tissue Loss	232 (2.8)	207 (2.8)	25 (2.8)	15 (2.5)
Other	149 (1.8)	139 (1.9)	10 (1.1)	5 (0.8)
Transfusion required, n (%)	3091 (37.9)	2798 (38.5)	293 (33.1)	194 (32.6)
EBL (mL), mean (SD)	145.8 (177.9)	106.2 (123.2)	150.6 (182.8)	100.6 (110.8)
Discharge Ambulation, n (%)				
Ambulatory	325 (4.1)	267 (3.7)	58 (6.6)	35 (5.9)
Assistance	3167 (39.6)	2740 (37.7)	427 (48.6)	283 (47.5)
Wheelchair	3634 (45.4)	3285 (45.2)	349 (39.8)	250 (42.0)
Bedridden	882 (11.0)	838 (11.5)	44 (5.0)	28 (4.7)
Discharge Medications, n (%)				
Aspirin	5352 (66.4)	4693 (64.5)	659 (74.6)	443 (73.8)
P2Y12 Antagonist	2455 (30.1)	2126 (29.2)	329 (37.2)	227 (37.9)
Statin	5468 (67.8)	4839 (66.6)	629 (71.2)	429 (71.5)
Beta Blocker	4734 (58.7)	4192 (57.7)	542 (61.4)	361 (60.2)
ACE/ARB	3079 (38.2)	2711 (37.3)	368 (41.7)	246 (41.0)
Anticoagulant	2048 (25.1)	1815 (25.0)	233 (26.3)	172 (28.7)

Discharge Status, n (%)				
Home	2427 (29.8)	2118 (29.1)	309 (35.0)	197 (32.9)
Rehab Facility	3110 (38.2)	2759 (37.9)	351 (39.8)	239 (40.0)
Nursing Facility	2105 (25.8)	1913 (26.3)	192 (21.7)	145 (24.3)
Other Hospital	225 (2.8)	201 (2.8)	24 (2.7)	12 (2.0)
Dead (in hospital)	8 (0.1)	272 (3.7)	5 (0.6)	3 (0.5)
Median Max Follow-Up, median (IQR)	384 (306-509)	365 (296-475)	387 (308-514)	369 (289-477)

Table 3a: Model 1 showing the odds ratios (OR), 95% Confidence Intervals (CI) for the OR, and p-values for the risks of lower extremity amputation revision and death as competing risks modeled using a proportional odds model on interval-censored competing risks data.

	Revision			**Revision-Free Death**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Female Gender	0.950	(0.803- 1.123)	0.5454	1.075	(0.939- 1.231)	0.296
Age (years)	0.996	(0.990- 1.002)	0.1959	1.037	(1.029- 1.044)	**<0.0001**
BMI (kg/m^2)	0.982	(0.971- 0.992)	**0.0008**	0.993	(0.982- 1.005)	0.265
Amputation Level			**<0.0001**			**<0.0001**
AKA vs. BKA	0.398	(0.371- 0.428)		1.509	(1.379- 1.651)	
AKA vs. TMA	0.100	(0.084- 0.120)		2.797	(2.235- 3.501)	
BKA vs. TMA	0.251	(0.226- 0.280)		1.854	(1.620- 2.121)	
Urgency			0.0786			**0.0110**
Elective vs. Urgent	0.895	(0.790- 1.013)		1.171	(1.037- 1.322)	
Elective vs. Emergent	0.800	(0.625- 1.026)		1.371	(1.075- 1.748)	
Urgent vs. Emergent	0.895	(0.790- 1.013)		1.171	(1.037- 1.322)	
Smoking	1.269	(1.058- 1.523)	**0.0104**	0.975	(0.815- 1.166)	0.781
Dialysis	1.047	(0.871- 1.260)	0.6222	2.818	(2.343- 3.390)	**<0.0001**
Pre-op Aspirin	1.331	(1.121- 1.582)	**0.0011**	0.925	(0.802- 1.067)	0.286
History of Vascular Procedures (ipsilateral)	1.232	(1.124- 1.351)	**<0.0001**	0.933	(0.853- 1.021)	0.1310
*Bolded p-values are statistically significant at the 0.05 level						

Table 3b: Model 2 showing the odds ratios OR, 95% CI for the OR, and p-values for the risks of reamputation to a more proximal anatomic level and death as competing risks also modeled using a proportional odds model on interval-censored competing risks data.

	Reamputation			Reamputation-Free Death		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Female Gender	0.957	(0.810- 1.130)	0.6012	1.046	(0.918- 1.191)	0.5015
Age (years)	0.999	(0.990- 1.008)	0.8578	1.032	(1.025- 1.040)	**<0.0001**
BMI (kg/m^2)	0.989	(0.977- 1.002)	0.0968	0.997	(0.986- 1.008)	0.5808
Amputation Level			**<0.0001**			**<0.0001**
AKA vs. BKA	0.385	(0.350- 0.423)		1.532	(1.386- 1.694)	
AKA vs. TMA	0.092	(0.072- 0.116)		2.907	(2.262- 3.735)	
BKA vs. TMA	0.238	(0.207- 0.275)		1.897	(1.632- 2.205)	
Urgency			**0.0045**			**0.0033**
Elective vs. Urgent	0.844	(0.751- 0.949)		1.178	(1.056- 1.314)	
Elective vs. Emergent	0.712	(0.564- 0.900)		1.387	(1.115- 1.726)	
Urgent vs. Emergent	0.844	(0.751- 0.949)		1.178	1.056- 1.314)	
Smoking	1.147	(0.956- 1.377)	0.1406	0.915	(0.778- 1.078)	0.2881
Dialysis	1.011	(0.810- 1.261)	0.9261	2.576	(2.124- 3.123)	**<0.0001**
Pre-op Aspirin	1.160	(0.979- 1.376)	0.0866	0.907	(0.797- 1.032)	0.1391
History of Vascular Procedures (ipsilateral)	1.161	(1.071- 1.259)	**0.0003**	0.861	(0.799- 0.928)	**0.0001**
*Bolded p-values are statistically significant at the 0.05 level						

Appendix B- Figures

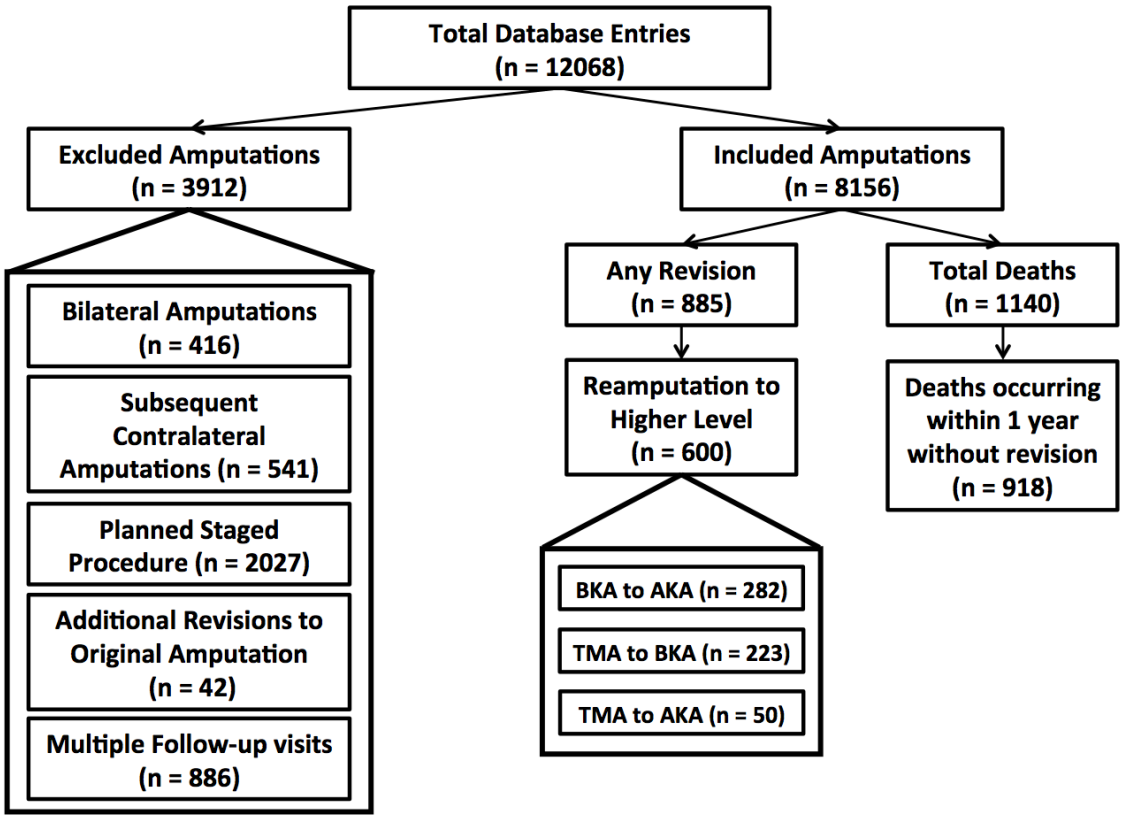
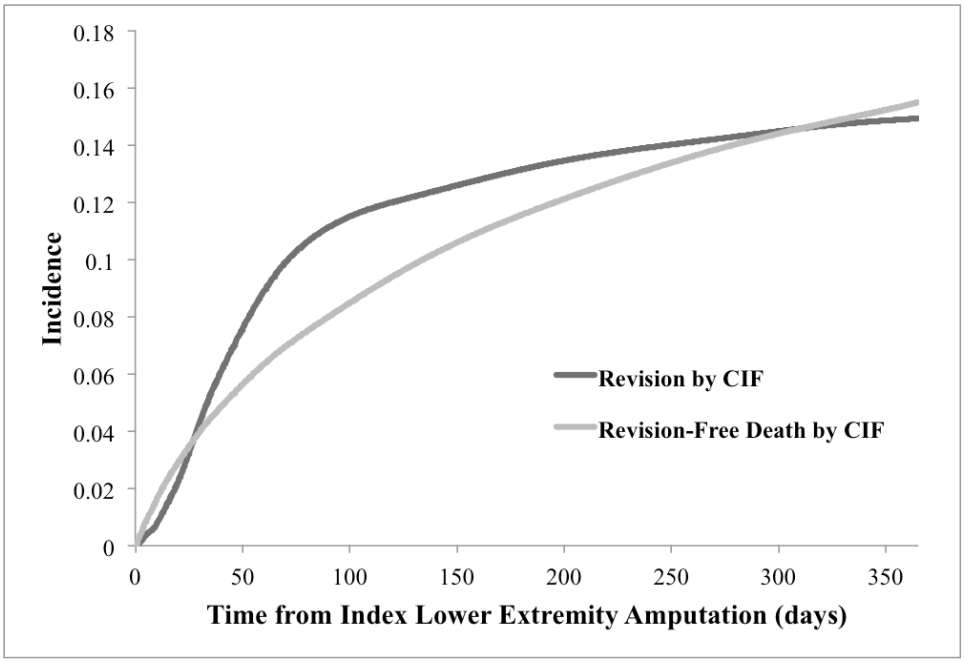


Figure 1: Decision tree demonstrating the inclusion and exclusion criteria for the study, the final number of patients included, and the number of patients experiencing the events of interest.

a.



b.

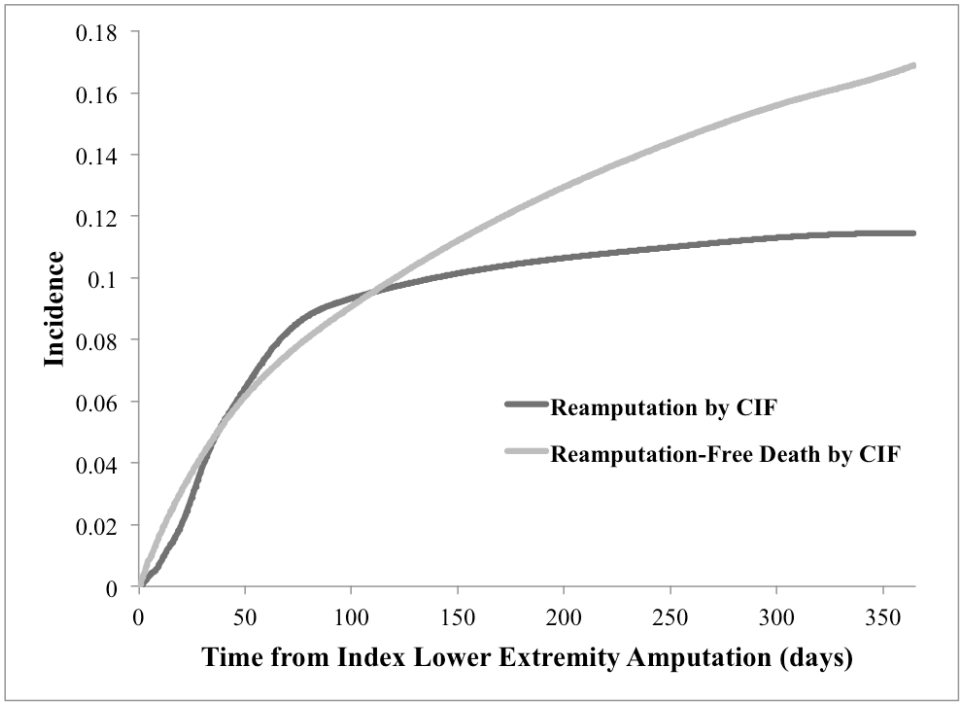


Figure 2: Non-parametrically estimated baseline "risk" of amputation revision adjusting for a competing risk of death (top) and reamputation to a more proximal anatomic level also adjusting for a competing risk of death (bottom) within the first year following index lower extremity amputation. Note that the estimated mortality in both instances is event-free mortality and NOT overall mortality.

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CURRICULUM VITAE

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EDUCATION AND TRAINING

Undergraduate

2007-2011	Vanderbilt University School of Engineering Nashville, Tennessee	BE (2011), Biomedical Engineering
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PUBLICATIONS AND PRESENTATIONS

Abstracts (Chronological order)

1. **Williams SE**, Heemskerk A, Welch EB, Damon BM*, Park JH*. 3271: The Quantitative Effects of Inclusion of Fat on Diffusion Tensor MRI (DT-MRI) of Human Thigh Muscles. Poster presentation at the International Society for Magnetic Resonance in Medicine 19th Annual Meeting 2011, Montreal, Quebec, Canada.
2. **Williams SE**, Su E, Zuccoli F, Fitz C, Maul T, Fink E. 715: Frequency and Outcomes of Neurological Abnormalities in Infants and Children Requiring Extracorporeal Membrane Oxygenation (ECMO). *Critical Care Medicine*. 40(12):1-328, December 2012. Poster presentation at the Society for Critical Care Medicine Annual Congress 2013, San Juan, Puerto Rico.
3. Su E, Maul T, Zuccoli G, **Williams SE**, Fink E. 526: Brain CT Gray:White Matter Ratio Association With Cerebral Edema in Children Requiring ECMO Post-Cardiac Arrest. *Critical Care Medicine*. 40(12):1-328. December 2012. Poster presentation (Eric Su, MD) at the Society for Critical Care Medicine Annual Congress 2013, San Juan, Puerto Rico.
4. **Severance S**, Zarzaur B, Obeng-Gyasi S, Thiruchelvam P, Fisher C. Decreasing rates but increasing complexity of axillary lymph node dissection for breast cancer. *Journal of the American College of Surgeons*. 227(4): S33. October 2018. Podium presentation at the American College of Surgeons Clinical Congress 2018, Boston, MA.
5. Carr B, Wooster M, Nemani L, **Severance S**, Hartwell J. Atrial Fibrillation and a Fall: Risk Scores Do Not Accurately Stratify for Stroke or Bleed In Elderly Fall Victims. *Journal of Trauma and Acute Care Surgery*. Podium presentation (Bryan Carr, MD) at the Eastern Association for the Surgery of Trauma Annual Scientific Assembly, January 2019.
6. Carr BW, **Severance SE**, Bell TM, Zarzaur BL. Preceived Loss of Social Support After Non-Neurologic Injury Negatively Impacts Recovery. *Journal of Trauma and Acute Care Surgery*. Podium presentation (Byran Carr, MD) at the Eastern Association for the Surgery of Trauma Annual Scientific Assembly 2019 as part of the Raymond H. Alexander, MD Resident Paper Competition, January 2019.
7. Obeng-Gyasi S, Timsina L, Bhattacharyya O, **Severance S**, Haggstrom D. Underinsurance and Healthcare Utilization among Working-Age Breast Cancer Patients. Podium presentation at the Academic Surgical Congress Annual Meeting in Houston, TX, February 2019.
8. **Severance SE**, Feizpour C, Coleman J, Zarzaur BL, Feliciano DV, Rozycki GS. Timing of Cholecystectomy After Emergent Endoscopic Retrograde Cholangio-pancreatography for Cholangitis. Podium presentation at Southeastern Surgical Conference in Charlotte, NC, February 2019.
9. Carr BW, **Severance SE**, Hill J, Savage SA, Zarzaur BL. The Geri-Rib Score: Predicting Adverse Outcomes with Readily Available Tools. *Journal of Trauma and Acute Care Surgery*. Podium presentation (Bryan Carr, MD) as part of the Earl Young Resident Paper Competition at the Western Trauma Association Annual Meeting in Snowmass, CO, March 2019.
10. Obeng-Gyasi, S, Bhattacharyya O, Timsina L, **Severance SE**, Fisher CS, Haggstrom DA. High Socioeconomic Status Associated with Increasing Statewide Mastectomy Trends. Accepted for podium presentation at the American College of Surgeons Clinical Congress 2019 in San Francisco, CA.

11. **Severance SE**, Bakoyannis G, Zarzaur BL, Lemmon GW. Risk of Lower Extremity Amputation Revision Adjusting for a Competing Risk of Death in Patients with Peripheral Vascular Disease. Submitted for consideration to the Midwestern Vascular Surgical Society Annual Meeting, Chicago, IL, September 2019.

Manuscripts (Chronological Order)

1. **Williams SE**, Heemskerk AM, Welch EB, Li K, Damon BM*, Park JH*. Quantitative effects of inclusion of fat on muscle diffusion tensor MRI measurements. *J Magn Reson Imaging*. 38(5):1292-1297. November 2013. *Co-senior authors. PMID: 23418124
2. Carr B, Wooster M, Nemani L, **Severance SE**, Hartwell J. Atrial Fibrillation and a Fall: Risk Scores Do Not Accurately Stratify for Stroke or Bleed In Elderly Fall Victims. Submitted for consideration to *Journal of Trauma and Acute Care Surgery*.
3. Carr BW, **Severance SE**, Bell TM, Zarzaur BL. Preceived Loss of Social Support After Non-Neurologic Injury Negatively Impacts Recovery. Submitted for consideration to *Journal of Trauma and Acute Care Surgery*.
4. Carr BW, **Severance SE**, Hill J, Savage SA, Zarzaur BL. The Geri-Rib Score: Predicting Adverse Outcomes with Readily Available Tools. Submitted for consideration to *Journal of Trauma and Acute Care Surgery*.
5. Murphy PB, **Severance SE**, Savage S, Obeng-Gyasi S, Timsina LR, Zarzaur BL. Financial Toxicity is Associated with Worse Physical and Emotional Long-term Outcomes After Traumatic Injury. Accepted for publication by *Journal of Trauma and Acute Care Surgery* on June 10, 2019.
6. **Severance SE**, Feizpour C, Coleman J, Zarzaur BL, Feliciano DV, Rozycki GS. Timing of Cholecystectomy After Emergent Endoscopic Retrograde Cholangio-pancreatography for Cholangitis. Accepted for publication in *American Surgeon* on April 12, 2019.

Other Presentations

1. **Williams SE**, Turner J, Sundermann M, Hodges SE, Maynord N*, Berutti T*. Hollow Waveguide UV Light Probe for Reduction of Ventilator Associated Pneumonia in Pediatric Patients. Senior Design Project presented for the Vanderbilt University School of Engineering Senior Design Day. Project description available at http://engineering.vanderbilt.edu/docs/pubs/2011-Senior-Design-Day-Brochure.pdf
   *Project mentors

PROFESSIONAL ACTIVITIES: RESEARCH ACTIVITIE**S**

2018 Thesis work towards a Master of Science in Biostatistics looking at factors predictive of reamputation following below knee amputation in patients with peripheral vascular disease. PI: Gary Lemmon, MD; Thesis Advisor and Committee Chair: Giorgios Bakoyannis, PhD

2010 Design of research protocol and exercise protocol aimed at causing a controlled amount of damage to human skeletal muscles measurable with diffusion weighted- MRI. PI: Bruce M. Damon, PhD, Vanderbilt University Institute of Imaging Science, Nashville, TN