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Analysis of 5-year Mortality following Lower Extremity Amputation due to Vascular Disease

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Background: Mortality rates following major lower extremity amputations (LEAs) 30 days–365 days postoperative have decreased, but 5-year rates remain high at 40.4%–70%. These data may not reflect recent advances in peripheral arterial disease (PAD) care, and comorbidities of chronic PAD may lead to mortality more frequently than the amputation itself. Mortality rates between diabetic and nondiabetic patients were also analyzed.

Methods: The California Office of Statewide Health Planning and Development hospital database was queried for patients admitted January 1, 2007–December 31, 2018. ICD-9-CM codes identified patients with vascular disease and an amputation procedure.

Results: There were 26,669 patients. The 30-day, 90-day, 1-year, and 5-year major LEA mortality rates were 4.82%, 8.62%, 12.47%, and 18.11%, respectively. Weighted averages of 30-day, 90-day, 1-year, and 5-year major LEA mortality rates in the literature are 13%, 15.40%, 47.93%, and 60.60%, respectively. Mortality risk associated with vascular disease after amputation (hazard ratio = 22.07) was 11 times greater than risk associated with amputation-specific complications from impaired mobility (hazard ratio = 1.90; $P < 0.01$). Having diabetes was associated with lower mortality at 30 days, 90 days, and 1 year ($P < 0.01$) but not at 5 years ($P = 0.22$).

Conclusions: This study suggests that people may be living longer after their major LEA than was previously thought. This study suggests that patients' PAD may play a bigger role in contributing to their mortality than complications from loss of mobility postamputation. Although having diabetes was associated with lower postamputation mortality, the difference was no longer significant by 5 years. *(Plast Reconstr Surg Glob Open 2023; 11:e4727; doi: 10.1097/GOX.0000000000004727; Published online 11 January 2023.)*

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INTRODUCTION

Thirty-day mortality rates following major lower extremity amputations (LEAs) have declined from 22% in the late 1990s and early 2000s[1,2] to less than 7% by 2007.[3–5] Yet reported 5-year mortality rates in the literature have remained high, ranging from 40.4%[6] to 70%,[7] and major LEA, particularly above the knee amputation (AKA), continues to be cited as a significant predictor of mortality.[2,8] However, the majority of the literature supporting these rates is relatively old and may not reflect recent advances in medical disease management, perioperative and postoperative support, and advanced rehabilitative care. In older literature, the leading causes of death were pulmonary embolism and sepsis, suggesting that lack of mobility and postoperative complications were the major contributors to high mortality rates.[9] More recently, common

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causes of mortality include cardiac disease, stroke, malignancy, renal complications,[10,11] and diabetes,[6] indicating comorbidities of chronic disease put patients at a higher risk of death than the amputation itself.

The authors suspected that 5-year mortality rates following LEA have decreased due to recent advances in medical management of peripheral arterial disease (PAD), including the increased use of statins[12] and other cardiovascular risk modifiers, which decrease mortality.[13] Based on evidence presented by Thorud et al,[8] the authors also hypothesized that comorbidities of chronic PAD led to mortality more frequently than the amputation itself. The aim of this study was to analyze short- (30 days) and long-term (5 years) mortality following major LEA for PAD to determine the rates and causes of death following major LEA to assess the current mortality in the context of historical rates.

Takeaways

Question: Are patients living longer postamputation than was previously thought?

Findings: Retrospective analysis of 26,669 patients using a statewide hospital database showed decline in postamputation 5-year mortality compared with weighted averages of rates reported in the literature. Overall, the 30-day, 90-day, 1-year, and 5-year major lower extremity amputation mortality rates were 4.82%, 8.62%, 12.47%, and 18.11%, respectively. Corresponding weighted averages from mortality rates reported in the literature are 13%, 15.40%, 47.93%, and 60.60%, respectively.

Meaning: People may be living longer after their major lower extremity amputation than was previously thought.

METHODS

The California Office of Statewide Health Planning and Development (OSHPD) patient discharge database was queried for patients admitted between January 1, 2007 and December 31, 2018. Patients who enter a California hospital are assigned an OSHPD Record Linkage Number, which is specific to each patient and is used to link episodes of care over time and across healthcare facilities in California. Due to the deidentified nature of patient information in the database, IRB approval was waived.

International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes were evaluated to identify admissions of patients with vascular disease and an amputation procedure. Vascular disease was defined as a diagnosis code for atherosclerosis (440) and/or peripheral vascular disease (443). Procedure codes used to identify below-the-knee amputation (BKA) were 84.14 and 84.15. AKA was identified with procedure code 84.17. Amputation to unspecified limbs was identified with procedure codes 84.10 and 84.91. Traumatic amputations were excluded using the diagnosis codes listed in the Appendix. The initial admission of a patient who carried a diagnosis code for vascular disease and who had an amputation procedure performed was defined as the index visit for the study. Subsequent admissions for each patient following the index admission were added to the dataset to assess postdischarge health status.

The primary comorbidity exposures of interest included myocardial infarction (401), acute ischemic heart disease (411), chronic ischemic heart disease (414), cardiomyopathy (425), dysrhythmia (427), heart failure (428), other heart disease (429), occlusion and stenosis of precerebral arteries (433, 434), cerebral ischemia (435), cardiovascular disease (436, 437), and late effects of cardiovascular disease (438). The primary postamputation complication exposures of interest included deep vein thrombosis (453.4), pneumonia (480, 481, 482, 483, 484, 485, 486), ulcers (707), sepsis (995.91), and pulmonary embolism (415.1). These exposures were selected to address whether patients died from complications due to impaired mobility after their amputation or complications of the chronic disease associated with the amputation. A subanalysis of patients with diabetes was also performed to investigate the association of diabetes and mortality after LEA.

The outcomes of interest were hospital readmission and mortality occurring within 5 years of the index visit. For the analysis on readmissions, follow-up time was calculated as the difference between the date of their subsequent admission and their index discharge date when the amputation was performed. Patients who were not readmitted were censored on December 31, 2018. Hospital discharge disposition was evaluated at each subsequent admission for mortality. Deaths that occurred at any in-state accredited care facility, such as hospitals, rehabilitation centers, and skilled nursing facilities, were captured. Follow-up time for mortality was calculated as the difference between the final discharge disposition date and the date of the amputation during the index admission. Patients who did not show evidence of dying during the study period were censored at their most recent discharge date. Postdischarge evaluation of mortality was assessed at 30 days, 90 days, 1 year, and 5 years.

Data were managed and analyzed using Stata MP, version 13.1 (StataCorp LLP, College Station, Tex.). Descriptive statistics were calculated using *t* tests, rank-sum tests, or chi-square tests, and displayed as means (standard deviation), medians (interquartile range), or proportions, as appropriate. Survival analyses were used to evaluate the risk for each outcome based on the presence of each exposure. Kaplan-Meier survival curves were subsequently evaluated, and the Wilcoxon method used to assess statistical difference in risk for each outcome. These methods were subsequently replicated for each timeframe for postdischarge mortality. Cox proportional hazards models were constructed to evaluate the adjusted association between each exposure and each outcome, adjusting for relevant covariates. Results from these adjusted models are shown as hazard ratios (SHR) with 95% confidence intervals (95% CIs) and their resultant *P* value. A *P* value less than 0.05 was used to define statistical significance.

To calculate weighted averages of historical LEA mortality rates, PubMed database was searched for the following key terms: above knee amputation, mortality, and

peripheral artery disease. A data range filter was set to include articles published 1979–2020. Articles were filtered for human subjects and those written in English. This search criteria yielded 76 results, including two review articles specifically investigating long-term mortality rates after LEA by Thorud et al[8] and Stern et al.[14] Citations from these articles were added to the literature review. Studies were examined for the presence of major LEA associated with PAD and overall combined mortality reported at 30 days, 90 days, 1 year, or 5 years. For this study, "major" amputation was defined as transtibial and anything more proximal.

RESULTS

There were 26,669 patients identified, average age at time of amputation was 70.5 (±15.2) years, 35% were women, 67% had BKA, and 33% had AKA. Of the patients who had originally received a BKA, 6.63% received a subsequent AKA. The prevalence of diabetes was 45.2%. The average age at time of surgery was 67 years old for BKA and 74 years old for AKA. Cohort demographics are summarized in Table 1. Overall, the 30-day, 90-day, 1-year, and 5-year major LEA mortality rates were 4.82%, 8.62%, 12.47%, and 18.11%, respectively (Fig. 1). Weighted averages of 30-day, 90-day, 1-year and 5-year major LEA mortality rates reported in the literature are 13%, 15.40%, 47.93%, and 60.60%, respectively. Methods for deriving these weighted averages are shown in **figure, Supplemental Digital Content 1**, which shows the weighted averages of major LEA (**http://links.lww.com/PRSGO/C326**). Twenty-eight articles met inclusion criteria to contribute to the weighted average. The included studies were published from 1993 to 2018, the smallest cohort was 41 patients, and the largest cohort was 1,86,338 patients. Articles published in 2001, 2013, 2016, and 2018 had the largest cohorts.

When broken down by amputation site, the 30-day, 90-day, 1-year, and 5-year AKA mortality rates were 9.27%, 14.73%, 19.40%, and 24.49%, respectively. The 30-day, 90-day, 1-year, and 5-year BKA mortality rates were 4.18%, 7.50%, 10.88%, and 16.67%, respectively. AKA had a higher mortality risk than BKA with an HR of 1.29 (CI, 1.22–1.37; $P < 0.01$). For 5-year mortality, the difference between AKA and BKA is robust to adjustment for age and comorbidities (Fig. 2).

The most common comorbidities present during initial admission were heart failure (23.88%), dysrhythmias (20.35%), and sepsis (7.81%). Of the patients who died, those with AKA were more likely to have had myocardial infarctions (SHR = 3.44; $P < 0.01$), chronic ischemic heart disease (SHR = 2.19; $P < 0.01$), cardiomyopathy (SHR = 2.02; $P < 0.01$), dysrhythmia (SHR = 1.91; $P < 0.01$), heart failure (SHR = 2.35; $P < 0.01$), late effects of cerebrovascular disease (SHR = 5.05; $P < 0.01$), and deep venous thrombosis (SHR = 3.53; $P < 0.01$) compared with BKA. Patients with an AKA who died were also more likely to have had pneumonia (SHR = 3.29; $P < 0.01$), pressure ulcers (SHR = 2.20; $P < 0.01$), and sepsis (SHR = 2.13; $P < 0.01$) compared with those with a BKA who died. These results are summarized in Table 2. Mortality risk associated with vascular disease after amputation was 11 times greater than the risk associated with amputation-specific complications resulting from impaired mobility, such as deep venous thrombosis, sepsis, pneumonia, ulcer, or pulmonary embolism. These findings are summarized in Table 3.

Table 1. Cohort Demographics

	Lived, n (%)	Died, n (%)	*P*
Gender			
Female	7733 (79.26)	2024 (20.74)	<0.01
Male	13,850 (81.89)	3062 (18.11)	
Level of amputation			
Below knee	15,015 (83.33)	3003 (16.67)	<0.01
Above knee	6814 (75.51)	2210 (24.49)	
Presence of diabetes	17,613 (80.85)	4171 (19.15)	0.22
Average age	68.98	71.41	<0.01

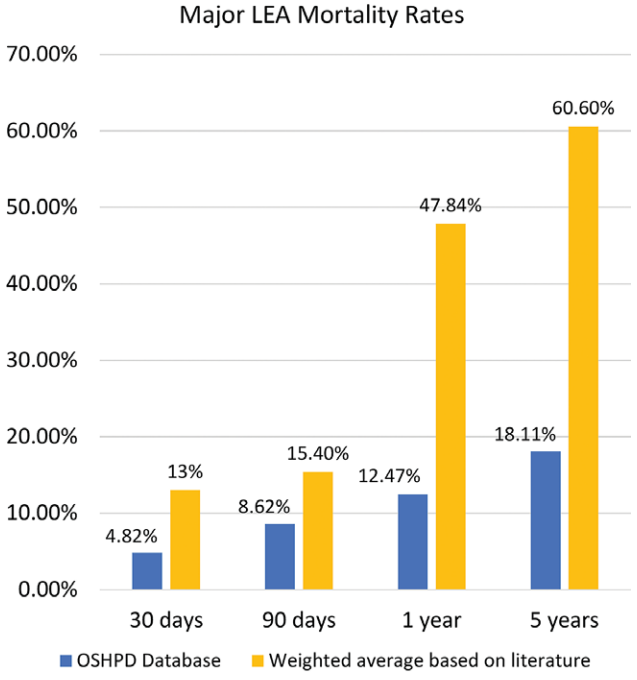

Fig. 1. Major lower extremity amputation mortality rates as reported in the literature vs data from the OSHPD database.[1–7,13,16–18,20–21,23,27,32–44]

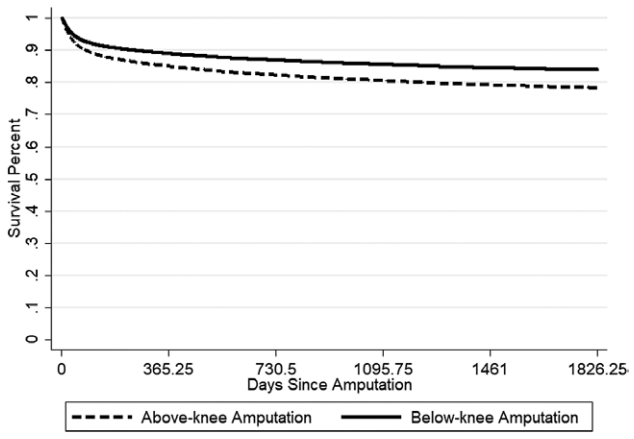

Fig. 2. Kaplan-Meier survival curve for above-the-knee versus below-the-knee amputation.

Table 2. Comorbidities by Amputation Level

Comorbidity	Amputation Level	Sub-HR	*P*	95% CI
Myocardial infarction	Above knee	3.44	<0.01	2.19–5.39
Chronic ischemic heart disease	Above knee	2.19	<0.01	1.60–3.00
Cardiomyopathy	Above knee	2.02	<0.01	1.21–3.37
Dysrhythmia	Above knee	1.91	<0.01	1.48–2.45
Heart failure	Above knee	2.35	<0.01	1.77–3.13
Late effects of cerebrovascular disease	Above knee	5.05	<0.01	2.45–10.43
Deep vein thrombosis	Above knee	3.53	<0.01	1.57–7.97
Pneumonia	Above knee	3.29	<0.01	2.33–4.64
Pressure ulcer	Above knee	2.20	<0.01	1.70–2.85
Sepsis	Above knee	2.13	<0.01	1.31–3.49

Patients with a BKA were used as the comparison group for all comorbidity analyses.

Among patients with diabetes, postamputation mortality rates at 30 days, 90 days, 1 year, and 5 years were 4.93%, 8.84%, 12.93%, and 19.15%, respectively. Postamputation mortality rates for patients without diabetes at 30 days, 90 days, 1 year, and 5 years were 9.80%, 14.36%, 17.04%, and 18.16%, respectively. Diabetes was associated with lower mortality at 30 days, 90 days, and 1 year ($P < 0.01$) but at 5 years, the difference was no longer statistically significant ($P = 0.22$). The results are displayed in Fig. 3.

DISCUSSION

The results of this study suggest that patients undergoing amputation for chronic PAD complications may live longer after their amputation than was previously thought. While the 30-day major LEA mortality rates are similar to rates reported in recent literature,[3–5] there is a dramatic decrease in 5-year mortality (Fig. 1). This difference is sustained across small and large cohort studies of patients with PAD in the presence or absence of diabetes.

Gök et al[7] observed 140 patients with major LEAs done 2001–2011 with a 5-year mortality rate of 70%, despite having a lower average age at time of amputation (66.5 years) to this study (70.4 years) and similar gender breakdown—60% men[7] versus 65% men. In contrast, 45.2% of patients in this study had diabetes, whereas Gok et al[7] focused exclusively on patients with diabetes. In another small cohort study, Fortington et al[1] followed the outcomes of 299 major LEAs done in 2003–2004, average age 74.1 years, and found an overall 5-year mortality of 77%. The 5-year mortality for the 101 patients who received an AKA was also 77%.[1] Although the overall age of the cohort in the study by Fortington et al[1] was higher than the overall age of this study, it is identical to the average age of specifically AKA patients from this study so the discrepancy in overall cohort age does not fully explain the drastically higher 5-year overall mortality rate as well as the higher mortality rate for the AKA cohort. The cohorts were also similar in terms of gender (60% men[1] versus 65% men) and rates of diabetes (50%[1] versus 45.2%).

A large study by Sandnes et al[15] retrospectively reviewed 4075 patients, average age 75 years, who had an AKA during 1987–2000 to determine if AKA 5-year mortality improved over time. While Sandnes et al[15] reported a statistically significant decline in 5-year AKA mortality from 68.7% in the "early era" (1987–1989) to 55.6% in the "recent era" (1995–2000), the recent era 5-year AKA mortality of 55.6% still far exceeds the 24.49% 5-year AKA mortality of this study despite both cohorts having a similar average age of 75 years[15] versus 74 years. The cohorts were also similar in terms of gender (58.5% men[15] versus 65% men) but differed in the rate of diabetes (61.3%[15] versus 45.2%). The same observation is also true for BKA. Sandnes et al[15] examined 5298 patients with BKA amputations and found a 40% 5-year mortality rate among the recent era cohort, which is much higher than the 16.67% 5-year mortality rate observed in this study. Again, the demographics between the two studies are strikingly similar—average age of 68 years[15] versus 67 years, and 61% men[15] versus 65% men.

The influence of diabetes on post-LEA mortality has mixed results. Some studies found no difference in mortality between those with diabetes and those without,[1,16,17] while others found that diabetes is a mortality risk factor.[18,19] This study showed an association between lower mortality rates and having diabetes. Other studies also found lower mortality rates associated with diabetes,[20,21] possibly because these patients tend to have more distal amputations,[1,22] which is associated with lower mortality.[2,8,23] However, the mortality difference between those with diabetes and those without was no longer significant at 5 years post-amputation. This finding is consistent with results from Mayfield et al[20] and Icks et al,[21] which also showed an association between a lower mortality rate and having diabetes, although the mortality curves crossed at 5 years post-amputation and 2–3 years post-amputation, respectively. This observed shift

Table 3. Mortality Risk

	Crude			Fully Adjusted		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Amputation location	1.00	—	—	1.00	—	—
Below knee	1.49	1.41–1.58	<0.01	1.30	1.22–1.38	<0.01
Above knee	2.90	1.38–6.10	<0.01	2.60	1.24–5.47	0.01
Unspecified						
Age at most recent admission	1.01	1.01–1.02	<0.01	1.01	1.01–1.01	<0.01
Chronic disease-associated mortality risk	41.57	37.05–46.64	<0.01	22.07	16.27–29.95	<0.01
Postoperative complication-associated mortality risk	36.51	32.41–41.11	<0.01	1.90	1.39–2.60	<0.01

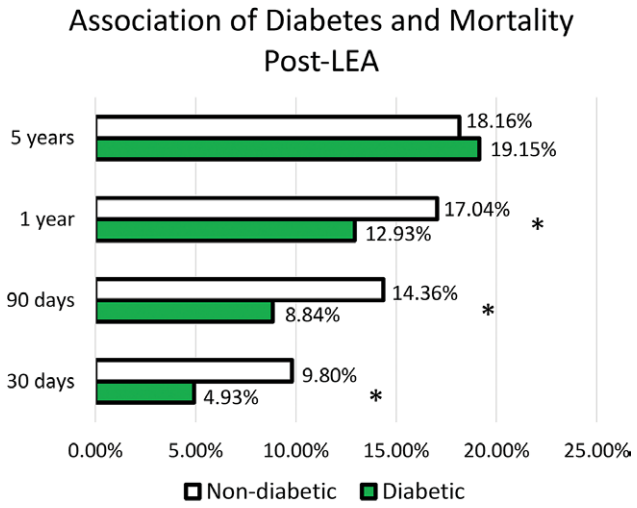

Fig. 3. Association of diabetes and mortality post lower extremity amputation; (*) indicates a statistically significant difference ($P < 0.01$) in mortality rate.

is likely due to advancing complications of diabetes over time, as diabetes has been reported as the leading cause of death in patients with LEAs.[11] Additionally, Dillingham et al[24] found patients with diabetes were more likely to progress to a higher amputation level, which is associated with higher mortality.[2,8,23] With this evidence, differences in rates of diabetes between this study and the literature do not clearly account for the significantly reduced 5-year mortality observed in this study.

So why is this newest reported rate so much lower? Many studies assessing 5-year mortality for LEA had cohorts recruited in the 1990s and early 2000s. There was also a history of undertreatment of PAD when it comes to aggressive statin therapy[12,13,25,26] despite evidence that high-intensity or medium-intensity statins offered a mortality benefit.[13] In recognition of this care gap, statin use has been on the rise.[12,27] Reynolds et al[12] reported that the proportion of patients with PAD on high-intensity statins increased from 7.3% in 2002 to 41.9% in 2015, including an increase from 7.2% to 39.4% in those with critical limb ischemia. This rise in statin use may promote the observed decline in postamputation mortality.

Advances in wound management may also play a role in improving mortality rates following major LEA. The TIME-H tool, used as a way of prognosticating wound healing by evaluating tissue, inflammation/infection, moisture, edge/epithelialization, and healing time, offers a way to predict healing rates for chronic wounds.[28] This prognostic tool may have prevented progression of amputation level for some individuals by guiding more conservative wound management. Improvements in orthoplastic approaches may also prevent progression of amputation level by offering multidisciplinary wound management strategies, including pressure offloading with external fixators, tendon release, and exostectomy, and flaps for soft tissue coverage, such as the keystone perforator island flap, which has been successful in treating chronic wounds.[29,30]

In this study, a small percentage of patients (6.63%) who originally received a BKA received a subsequent AKA. The rate of subsequent amputation was highest at 30 days and remained stable across all time periods. Because ICD-9 codes do not specify laterality, it is not possible to confirm whether these subsequent AKAs occurred on the same leg as the original BKA or the opposite leg. However, due to the short interval between the first and second amputations, it is likely that these subsequent amputations were revisions of the original BKA rather than a sign of significant progression of PAD or development of chronic wound complications at previous surgical sites.

The 5-year mortality difference between AKA (24.49%) and BKA (16.67%) was robust to adjustment for age and comorbidities (Fig. 2). The correlation between increased amputation level and increased mortality is consistent with the literature[7,8,22] and may be due to more advanced vascular disease at the time of amputation. Postamputation mortality risk associated with vascular disease was 11 times greater than the risk associated with amputation-specific complications. These results are consistent with other studies such as the nationwide population-based cohort study by Mao et al[11] in which the leading cause of death was diabetes mellitus and PAD-related complications, comprising 17.2% of the patients who died. Similarly, Morbach et al,[10] Inderbitzi et al,[31] and Chin et al,[32] cited cardiovascular disease as the leading cause of death among patients who received major LEAs.

It is important to note that the OSHPD database describes diseases the patient died with rather than what they died from, so this study is only claiming the diagnoses a patient had during the hospital admission in which they died tended to be those associated with vascular disease complications rather than amputation-specific complications, such as sepsis, pulmonary embolism, deep vein thrombosis, pneumonia, and ulcers. This study also evaluated all-cause mortality, so the significance of the index event is expected to decrease with time. An additional limitation of this study is the weighted averages calculated based on LEA mortality rates reported in previous studies. Many studies did not differentiate between the first and the second amputation when reporting mortality rates or how amputation level may have changed. Also, rates of comorbidities and reason for amputation differed across studies, which may influence mortality rates. Therefore, the studies that made up the weighted average may not be directly comparable. Additionally, any deaths that occurred outside of a state-accredited care facility, such as deaths at home, were not captured so the number of deaths reported in this study may be an underestimate. Despite these limitations, this study remains relevant because it is one of the largest cohort studies to evaluate 5-year mortality following a major LEA.

CONCLUSIONS

This study suggests that people may be living longer after their major LEA than was previously thought, with a reduction in the 5-year mortality rate of approximately

70% compared with historical rates. This mortality rate reduction is likely multifactorial and may be due in part to an increase in statin use, allowing for more aggressive medical management of PAD. Furthermore, this study suggests that patients' chronic PAD may play a bigger role in contributing to mortality than complications related to loss of mobility post-amputation. Therefore, major LEA seems to be a marker for chronic disease severity rather than directly causing earlier mortality. These results are important because they will enhance the conversations between physicians and patients about prognosis and mortality risk regarding major LEAs due to chronic PAD.

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APPENDIX

Diagnosis codes used to identify traumatic amputations: (codes 808.00, 820.00, 821.00, 822.00, 823.00, 824.00, 825.00, 826.00, 827.00, 828.00, 829.00, 835.00, 836.00, 837.00, 838.00, 895.00 896.00, 897.00, 904.00, 926.00, 928.00, 945.00).[20]

REFERENCES

1. Fortington LV, Geertzen JH, van Netten JJ, et al. Short and long term mortality rates after a lower limb amputation. *Eur J Vasc Endovasc Surg.* 2013;46:124–131.
2. Remes L, Isoaho R, Vahlberg T, et al. Major lower extremity amputation in elderly patients with peripheral arterial disease: incidence and survival rates. *Aging Clin Exp Res.* 2008;20:385–393.
3. Yamada K, Yasunaga H, Kadono Y, et al. Postoperative outcomes of major lower extremity amputations in patients with diabetes and peripheral artery disease: analysis using the Diagnosis Procedure Combination database in Japan. *Am J Surg.* 2016;212:446–450.
4. Morisaki K, Yamaoka T, Iwasa K. Risk factors for wound complications and 30-day mortality after major lower limb amputations in patients with peripheral arterial disease. *Vascular.* 2018;26:12–17.
5. Gabel J, Jabo B, Patel S, et al; Vascular Quality Initiative. Vascular quality initiative. Analysis of patients undergoing major lower extremity amputation in the vascular quality initiative. *Ann Vasc Surg.* 2018;46:75–82.
6. Lee JS, Lu M, Lee VS, et al. Lower-extremity amputation. Incidence, risk factors, and mortality in the Oklahoma Indian Diabetes Study. *Diabetes.* 1993;42:876–882.
7. Gök U, Selek O, Selek A, et al. Survival evaluation of the patients with diabetic major lower-extremity amputations. *Musculoskelet Surg.* 2016;100:145–148.
8. Thorud JC, Plemmons B, Buckley CJ, et al. Mortality after nontraumatic major amputation among patients with diabetes and peripheral vascular disease: a systematic review. *J Foot Ankle Surg.* 2016;55:591–599.
9. Colt JD, Lee PY. Mortality rate of above-the-knee amputation for arteriosclerotic gangrene: a critical evaluation. *Angiology.* 1972;23:205–210.
10. Morbach S, Furchert H, Gröblinghoff U, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. *Diabetes Care.* 2012;35:2021–2027.
11. Mao CT, Tsai ML, Wang CY, et al. Outcomes and characteristics of patients undergoing percutaneous angioplasty followed by below-knee or above-knee amputation for peripheral artery disease. *PLoS One.* 2014;9:e111130.
12. Reynolds K, Mues KE, Harrison TN, et al. Trends in statin utilization among adults with severe peripheral artery disease including critical limb ischemia in an integrated healthcare delivery system. *Vasc Med.* 2020;25:3–12.
13. DeCarlo C, Scher L, Shariff S, et al. Statin use and other factors associated with mortality after major lower extremity amputation. *J Vasc Surg.* 2017;66:216–225.
14. Stern JR, Wong CK, Yerovinkina M, et al. A Meta-analysis of long-term mortality and associated risk factors following lower extremity amputation. *Ann Vasc Surg.* 2017;42:322–327.
15. Sandnes DK, Sobel M, Flum DR. Survival after lower-extremity amputation. *J Am Coll Surg.* 2004;199:394–402.
16. Shah SK, Bena JF, Allemang MT, et al. Lower extremity amputations: factors associated with mortality or contralateral amputation. *Vasc Endovascular Surg.* 2013;47:608–613.
17. Tentolouris N, Al-Sabbagh S, Walker MG, et al. Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study. *Diabetes Care.* 2004;27:1598–1604.
18. Kulkarni J, Pande S, Morris J. Survival rates in dysvascular lower limb amputees. *Int J Surg.* 2006;4:217–221.
19. Schofield CJ, Libby G, Brennan GM, et al; DARTS/MEMO Collaboration. DARTS/MEMO Collaboration. Mortality and hospitalization in patients after amputation: a comparison between patients with and without diabetes. *Diabetes Care.* 2006;29:2252–2256.
20. Mayfield JA, Reiber GE, Maynard C, et al. Survival following lower-limb amputation in a veteran population. *J Rehabil Res Dev.* 2001;38:341–345.
21. Icks A, Scheer M, Morbach S, et al. Time-dependent impact of diabetes on mortality in patients after major lower extremity amputation: survival in a population-based 5-year cohort in Germany. *Diabetes Care.* 2011;34:1350–1354.
22. Kihn RB, Warren R, Beebe GW. The "geriatric" amputee. *Ann Surg.* 1972;176:305–314.
23. Jones WS, Patel MR, Dai D, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J.* 2013;165:809–815.e1.
24. Dillingham TR, Pezzin LE, Shore AD. Reamputation, mortality, and health care costs among persons with dysvascular lower-limb amputations. *Arch Phys Med Rehabil.* 2005;86:480–486.
25. Colantonio LD, Hubbard D, Monda KL, et al. Atherosclerotic risk and statin use among patients with peripheral artery disease. *J Am Coll Cardiol.* 2020;76:251–264.
26. Mahtta D, Ahmed ST, Ramsey DJ, et al. Statin prescription rates, adherence, and associated clinical outcomes among women with PAD and ICVD. *Cardiovasc Drugs Ther.* 2020;34:745–754.
27. Harrison TN, Scott RD, Cheetham TC, et al. Trends in statin use 2009-2015 in a large integrated health system: pre- and post-2013 ACC/AHA Guideline on treatment of blood cholesterol. *Cardiovasc Drugs Ther.* 2018;32:397–404.
28. Guarro G, Cozzani F, Rossini M, et al. The modified TIME-H scoring system, a versatile tool in wound management practice: a preliminary report. *Acta Biomed.* 2021;92:e2021226.
29. Al-Mousawi A, Sanese G, Baljer B, et al. Use of the keystone perforator island flap in the treatment of chronic lower extremity wounds complicated by osteomyelitis. *Injury.* 2020;51:744–749.
30. Bibbo C, Mayer BE, Michetti LA. Foot and ankle surgery for chronic nonhealing wounds. *Surg Clin North Am.* 2020;100:707–725.

31. Inderbitzi R, Buettiker M, Enzler M. The long-term mobility and mortality of patients with peripheral arterial disease following bilateral amputation. *Eur J Vasc Endovasc Surg.* 2003;26:59–64.
32. Chin JW, Teague L, McLaren AM, et al. Non traumatic lower extremity amputations in younger patients: an 11-year retrospective study. *Int Wound J.* 2013;10:73–78.
33. Aulivola B, Hile CN, Hamdan AD, et al. Major lower extremity amputation: outcome of a modern series. *Arch Surg.* 2004;139:395–399.
34. Scott SW, Bowrey S, Clarke D, et al. Factors influencing short- and long-term mortality after lower limb amputation. *Anaesthesia.* 2014;69:249–258.
35. Corey MR, St Julien J, Miller C, et al. Patient education level affects functionality and long term mortality after major lower extremity amputation. *Am J Surg.* 2012;204:626–630.
36. Barnes R, Souroullas P, Lane RA, et al. The impact of previous surgery and revisions on outcome after major lower limb amputation. *Ann Vasc Surg.* 2014;28:1166–1171.
37. Ploeg AJ, Lardenoye JW, Vrancken Peeters MP, et al. Contemporary series of morbidity and mortality after lower limb amputation. *Eur J Vasc Endovasc Surg.* 2005;29:633–637.
38. Jindeel A, Narahara KA. Nontraumatic amputation: incidence and cost analysis. *Int J Low Extrem Wounds.* 2012;11:177–179.
39. Cruz CP, Eidt JF, Capps C, et al. Major lower extremity amputations at a Veterans affairs hospital. *Am J Surg.* 2003;186:449–454.
40. Feinglass J, Pearce WH, Martin GJ, et al. Postoperative and late survival outcomes after major amputation: findings from the Department of Veterans Affairs National Surgical Quality Improvement Program. *Surgery.* 2001;130:21–29.
41. Frykberg RG, Arora S, Pomposelli FB, Jr, et al. Functional outcome in the elderly following lower extremity amputation. *J Foot Ankle Surg.* 1998;37:181–185.
42. Luther M. The influence of arterial reconstructive surgery on the outcome of critical leg ischaemia. *Eur J Vasc Surg.* 1994;8:682–689.
43. McWhinnie DL, Gordon AC, Collin J, et al. Rehabilitation outcome 5 years after 100 lower-limb amputations. *Br J Surg.* 1994;81:1596–1599.
44. Carmona GA, Hoffmeyer P, Herrmann FR, et al. Major lower limb amputations in the elderly observed over ten years: the role of diabetes and peripheral arterial disease. *Diabetes Metab.* 2005;31:449–454.