Outcomes After Severe Distal Tibia, Ankle, and/or Foot Trauma: Comparison of Limb Salvage Versus Transtibial Amputation (OUTLET)

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Summary: Severe foot and ankle injuries are complex and challenging to treat, often requiring multiple operations to salvage the limb contributing to a prolonged healing period. There is some evidence to suggest that early amputation for some patients may result in better long-term outcomes than limb salvage. The challenge is to identify the regional injury burden for an individual that would suggest a better outcome with an amputation. The OUTLET study is a prospective, multicenter observational study comparing 18-month outcomes after limb salvage versus early amputation among patients aged 18–60 years with severe distal tibia, ankle, and foot injuries. This study aims to build upon the previous work of the Lower Extremity Assessment Project by identifying the injury and patient characteristics that help define a subgroup of salvage patients who will have better outcomes had they undergone a transtibial amputation.

Key Words: limb salvage, amputation, severe foot and ankle injuries

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BACKGROUND AND RATIONALE

High-energy open fractures and crush injuries to the distal tibia, ankle, hind foot, and midfoot are challenging to manage clinically as they often involve severe comminution and soft tissue damage and include concomitant fractures and dislocations of the talus, midfoot, and metatarsals.[1–6] Attempted limb salvage often requires arthrodesis, free tissue transfer, and/or skin grafts, frequently leaving the residual limb partially or fully insensate with chronic wound problems.[2,4,6] Some studies have reported significant disability after limb salvage of these injuries. Patients report high levels of pain with walking, difficulty returning to work, and in some cases, permanent disability.[3–5,7] Although the reconstruction of severe foot injuries might be feasible with current surgical capabilities, it might not be advisable. Treatment with a transtibial amputation may provide better long-term outcomes compared with limb salvage for some injury combinations. Patients receiving an early amputation may have a faster return to function by avoiding the sequelae associated with limb salvage including reoperations for complications and a long healing period. However, there are currently no established guidelines to inform treatment decisions, and it is unclear who benefits the most from an early amputation versus attempted limb salvage.

Several scoring systems such as the Mangled Extremity Severity Score have been developed to aid in determining when to amputate versus salvage, but none has been well validated in either military or civilian trauma populations.[8–11] Indicators that may signal amputation as a better treatment option include severe structural damage to the foot, unrepairable vascular injury, comminuted fractures of the foot, major joint dislocations, degloving of the mid to hind foot, and need for free tissue transfer for coverage. The challenge is to identify the regional injury burden for an individual that would suggest a better outcome with an amputation. Yet, few studies have been comprehensive enough to address this challenge. A substudy of 182 Lower Extremity Assessment Project (LEAP) participants with open hind foot or ankle injuries reported worse outcomes 2 years after injury among those who received limb salvage involving a free flap and/or arthrodesis (n = 38) compared with those receiving a standard below the knee amputation (n = 58).[5] On average, scores on both the physical and psychosocial components of the Sickness Illness Profile[12] were significantly higher

(worse outcome) for limb salvage patients with a free flap and/or arthrodesis compared with amputees. In addition, this subgroup of salvage patients had significantly more hospital readmissions for complications and longer times to full weight bearing. Although not statistically significant, fewer salvage patients with free tissue transfer and/or arthrodesis returned to work compared with amputees (56% vs. 70%).[5] While the number of patients in this analysis was small, the results suggest that for some patients with severe distal tibia and hindfoot injuries, transtibial amputation may provide a better outcome than limb salvage. Further studies are needed to determine the injury burden that better defines these patients so that appropriate treatment guidelines can be developed.

The purpose of the OUTLET study is to build upon the LEAP substudy cited above and compare 18-month outcomes of patients undergoing salvage versus early amputation (within 6 weeks of injury) after severe distal tibia, ankle, and/or foot injuries in a large prospective, multicenter observational cohort study. It is hypothesized that on average, there will be no difference between patients receiving limb salvage versus an early amputation on measures of self-reported function, physical performance, return to usual major activities, or participation in vigorous sports and recreational activities. However, it is anticipated that there will be a subgroup of salvage patients who would have had better outcomes had they undergone a transtibial amputation. An important aim of the study is to identify the injury and patient characteristics that help define this subgroup.

METHODS: TRIAL DESIGN AND PATIENT SELECTION

Overview

The study was initiated at 32 US trauma centers participating in the Major Extremity Research Trauma Consortium (METRC); centers are listed at Appendix 1. The study protocol, including the written informed consent form, was approved by the Johns Hopkins Bloomberg School of Public Health (location of the METRC Coordinating Center), the Department of Defense Human Research Protection Office (DoD HRPO) (study sponsor), and the local institutional review board at each participating center. Furthermore, each site was required to obtain DoD HRPO approval of local institutional review board documents and certification by the Coordinating Center to ensure proper training on study procedures and data collection before initiation of the study.

The study population consisted of patients aged 18–60 years with severe injuries to the distal tibia, ankle, or foot (Fig. 1). Eligible patients who provided informed consent were treated according to standard of care at the discretion of the treating surgeon. Enrolled patients were followed at 3, 6, 12, and 18 months after injury.

Patient Selection

Participants meeting the study criteria described in Table 1 were approached for informed consent while in the hospital for initial treatment of their injury. METRC has adopted

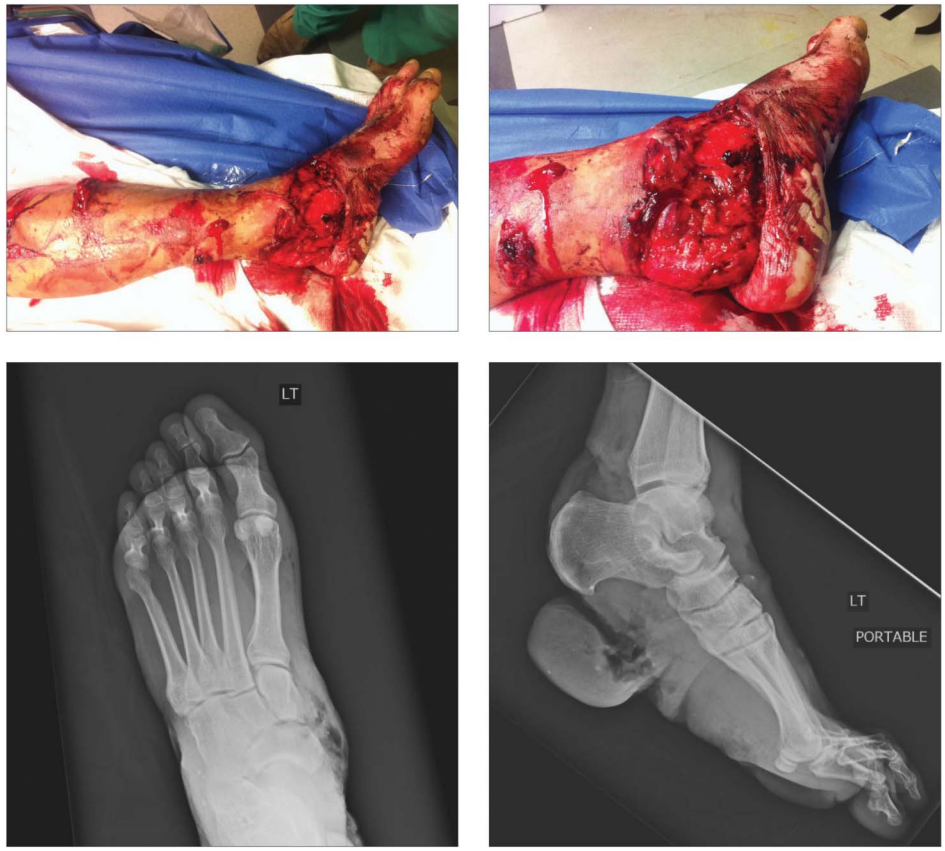

FIGURE 1. Injury eligible for the OUTLET study.

a comprehensive informed consent process for all of its studies that involves an orthopaedic trauma surgeon, the clinical site research coordinator, and material and resources for patients and family members to facilitate informed decision making about participation (see **Figure**, **Supplemental Digital Content Figure 1**, http://links.lww.com/BOT/A879). A legally authorized representative was permitted to consent on behalf of patients who were unable to do so during the initial hospitalization.

To ensure consistency in the application of inclusion criteria and in the classification of foot injuries, all closed foot crush and blast injures were prospectively evaluated an adjudication committee. Injury x-rays, photographs, and a detailed description of the injury obtained after informed consent were independently evaluated by the 3-member committee. Patients with injuries that were adjudicated ineligible by most of the committee were withdrawn from the study. Once study enrollment was complete, the adjudication committee retrospectively reviewed all other injuries to verify eligibility. Data for patients considered ineligible will not be included in the final analysis.

METHODS: DATA COLLECTION AND OUTCOME MEASURES

Baseline Assessment and Frequency of Follow-up Assessments

Data collected at baseline (during the index hospitalization for initial treatment of the injury) are summarized in **Supplement Digital Content Table 1** (see **Table**, http://links.lww.com/BOT/A883) and include patient characteristics and preinjury health, classification of study and nonstudy injuries, and treatment parameters including details regarding fixation, soft tissue coverage, and amputation.

Participants return for follow-up study visits at 3, 6, 12, and 18 months after injury. Study visits involve a clinical examination to evaluate residual limb function, complications and healing, and a patient interview to measure patient-reported physical function, general health, and well-being. At the final study visit, participants are asked to complete a series of physical performance tests and given a StepWatch[13] Activity Monitor to wear at home.

TABLE 1. Inclusion and Exclusion Criteria for the OUTLET Study

Inclusion Criteria	Exclusion Criteria
1. 18–60 years of age 2. Admitted to the hospital before definitive wound closure with an injury meeting at least one of the following criteria Gustilo type III pilon fractures (43B1.3, 43B2-B3, or 43C) Gustilo type III B or III C ankle fractures Gustilo type III mid and/or hind foot fractures (81B2-B3, 82B, or 82C) Open foot crush or blast injuries from high-energy mechanism involving the mid and/or hind foot with significant soft tissue damage or Other severe foot injuries including closed foot crush or blast injuries*	1. Glasgow Coma Scale (GCS) motor score of 0–4 or a GCS motor score of 5 with a significant traumatic brain injury defined as an Abbreviated Injury Score (AIS) code of 5 or 6 2. Nonambulatory due to an associated complete spinal cord injury 3. Previous leg of foot amputation or nonambulatory preinjury 4. Third degree burns on more than 10% total surface area affecting the study limb 5. Speaks neither English nor Spanish 6. Diagnosed with a severe psychiatric condition 7. Lives outside the hospital catchment area or plans to follow-up at another medical center 8. Severe problems with maintaining follow-up (eg, planned incarceration, homeless, cognitively challenged with no family support)

*Foot crush or blast injuries were considered eligible if they were at significant risk for impaired outcome with moderate to severe disability according to the treating surgeon. These injuries typically include one of the following associated injuries: ankle, subtalar, or Chopart dislocation; extruded talus; multiple midfoot dislocations; 3 or more metatarsal fractures; heel pad/plantar degloving; or extensive muscle necrosis, ischemia, or foot compartment syndrome. Patients were not excluded based on co-occurring injuries.

Primary Outcome

The main study outcome is patient-reported function as measured by the Short Musculoskeletal Functional Assessment (SMFA), a validated 46-item questionnaire consisting of 2 main indices. The dysfunction index includes 34 items assessing function in 4 domains: daily activities, arm and hand function, mobility, and emotional status. The bother index includes 12 items designed to detect how much patients are bothered by functional deficits.[14]

Secondary Outcomes

Secondary outcomes of interest include clinical and patient-reported outcomes, collected according to the data standards adopted by the consortium.[15] The timing of data collection is summarized in **Supplement Digital Content Table 1** (see **Table**, http://links.lww.com/BOT/A883).

Physical performance and overall activity are objectively evaluated using measures of performance in tests of agility (using the Four Square Step Test and the Illinois Agility Test), strength/power (using the Sit to Stand and Timed Stair Ascent Tests), speed (using self-selected walking speed and the 10-m shuttle run), and postural stability (using the Single Leg Stance test) (see **Figure**, **Supplement Digital Content Figure 2**, http://links.lww.com/BOT/A880). The performance tests were selected by an expert panel of physical therapists and orthopaedic surgeons and include those which can easily be conducted in a standard orthopaedic outpatient office by a trained Research Coordinator. Tests were also selected based on their ability to measure performance at different levels of difficulty to evaluate both low and high functioning individuals. Daily activity is assessed using the StepWatch activity monitor, worn by participants for 2 weeks after the 18-month study visit.[13]

Participation in sports and leisure activities is measured using the Paffenbarger Activity Scale, which asks patients to report the frequency and duration of their participation in recreational and sport activities in the past week.[16] Return to usual major activities is assessed by asking patients what they were doing most of the time during the week before the visit.

Monitoring and Quality Assurance

Details of the METRC-wide standard operating procedures for monitoring can be found in the online supplement material (see **Figure**, **Supplemental Digital Content Figure 3**, http://links.lww.com/BOT/A881). The monitoring plan is

designed to verify site compliance with the protocol and with study-specific standard operating procedures on data collection and procedures. The plan facilitates compliance with good clinical practice guidelines (5.18.1). The chair of the Data Safety and Monitoring Board serves as the Medical Monitor who reviews each serious adverse event as it is reported in real time.

METHODS: DATA MANAGEMENT AND ANALYSIS

Data Management

Data are collected by site Research Coordinators and clinical investigators using paper case report forms designed specifically for this study and then entered into REDCap,[17] the web-based distributed data collection system used for all METRC studies (see **Figure**, **Supplemental Digital Content Figure 4**, http://links.lww.com/BOT/A882).

Data Analysis

The main aims of the study involve the comparison of outcomes for salvage patients at 18 months to the outcomes these patients would have had, had they undergone amputation within 6 weeks of their injury. For each salvage patient, the outcome under both salvage and amputation is conceptualized; for an amputee, only the latter outcome is conceptualized. For this causal analysis, it is assumed that, after accounting for baseline patient characteristics (e.g., age, co-morbidities, pre-injury function, education), and characteristics of the non-study injury (contralateral injuries and injuries to other body systems), there are no additional factors (measured or unmeasured) that are associated with both an individual's outcome after amputation and the decision to amputate. To estimate the causal effects of interest the following approach will be used:

1. Predict (using baseline patient and non-study injury characteristics) the outcomes that salvages would have had under amputation.
2. For salvages, the distribution of the observed outcomes will then be compared with the distribution of the predicted outcomes.
3. Using regression techniques, subgroups of salvage patients (based on factors such as Gustilo type of open study injuries, contamination, heel pad degloving, ipsilateral injuries, and nonstudy leg injuries) who would do better under amputation (based on the causal analysis) will be identified.

For all analyses, estimates of the causal effects, standard errors, and confidence intervals will be reported. Standard errors and confidence intervals will be constructed using bootstrapping procedures. Multiple imputation methods will be used to handle missing baseline covariates, but missing outcomes will not be imputed. In addition, sensitivity analyses will be conducted to evaluate the robustness of the study results to various untestable assumptions about the missing data mechanism.

Adequacy of the Sample Size

The initial sample size projection for the study (n = 441 enrolled) was based on the assumption that 32% of patients enrolled would receive a transtibial amputation within 6 weeks of injury, resulting in 300 limb salvage and 141 amputation patients. However, the rate of amputation was lower (15%) than suggested by previous studies.[5,18] To partially address this limitation, the enrollment period was extended, bringing the number of amputees to 88. In addition, data from patients enrolled in the Transtibial Amputation Outcomes Study (TAOS), a randomized trial comparing the Ertl versus Burgess amputation procedures (see article in this Supplement), will be used to increase the final analytic sample. Given the similarity in data collection across the 2 studies and the assumption that injury characteristics at or below the level of the amputation are not associated with outcomes under amputation, data from the TAOS study can be used to supplement the analysis without introducing bias.

All power calculations assume 20% missing outcome data at 18 months and are based on the assumption that the decision to amputate does not depend on the outcome under amputation. Based on enrolling 133 amputees (88 from OUTLET and 45 from TAOS) and 511 salvages, complete outcome data are expected for 106 amputees and 409 salvages. The primary equivalence hypothesis is that the mean SMFA score for salvage patients at 18 months will be within $\pm$ 6 points of the mean SMFA score had these patients undergone early amputation. Assuming a common SMFA SD of 15 for salvages and amputees, there is a 95% chance that a 90% confidence interval for the mean difference in SMFA between salvages and early amputees will fall wholly within the interval $(-6, 6)$ when the true mean difference is zero. A key secondary equivalence hypothesis is that the odds of returning to major usual activity by 18 months for salvages will be between one-half and twice the odds had these patients undergone amputation. Assuming that the probability of returning to usual major activity is 70%, there is an 80% chance that a 90% confidence interval for the odds ratio will fall wholly within the interval (0.5, 2) when the true odds ratio is 1.

STUDY RECRUITMENT AND BASELINE CHARACTERISTICS

Figure 2 summarizes the screening and enrollment of patients into the study. A total of 1400 patients were screened for eligibility of whom 779 (56%) were eligible. A total of 621 patients were ineligible; 537 patients did not meet the inclusion criteria and 84 patients had injuries that were determined to be ineligible by the adjudication committee. Among the 779 patients who were eligible, 599 patients provided consent and were enrolled into the study (511 treated with limb salvage and 88 patients received an amputation within 6 weeks of injury). A total of 45 patients enrolled in TAOS who received a transtibial amputation within 6 weeks of injury will be included in the final study analyses and are included in the baseline data presented in Table 2.

Principal Study Injury

For analysis, the principal study injury will be defined as the most severe injury at greatest risk for poor outcomes according to the treating surgeon. Among patients treated with limb salvage, 41% had open pilon or ankle fractures; 22% had an open talus or calcaneus fracture and 37% had a severe foot injury, which included open or closed foot crush and blast injuries with significant soft tissue damage. Approximately 20% of patients had more than one study-eligible injury. Among the 88 OUTLET amputees, 26% had an open pilon or ankle fracture; 15% had an open foot or calcaneus fracture, 51% had a severe foot injury, and 8 were traumatic amputations.

Demographics

There were few significant differences in demographic characteristics between those undergoing amputation and limb salvage. However, patients receiving limb salvage were slightly younger than patients receiving amputation (45% are less than 35 years old among salvages vs. 38% among amputees; $P = 0.05$), more likely to be women (36% among salvages vs. 18% among amputees; $P < 0.001$) and more likely to have at least some college education (49% among salvages vs. 41% among amputees; $P = 0.05$). Most of the patients across both groups (78%) were working or on active duty before their injury and 20% of patients had no health insurance. Over two-thirds (68%) of patients reported always having some emotional support from family and friends. Before their injury, 64% of patients reported very good or excellent health. Approximately 21% of patients were morbidly obese, 42% had 1 or more pre-existing conditions, and 41% were current tobacco users.

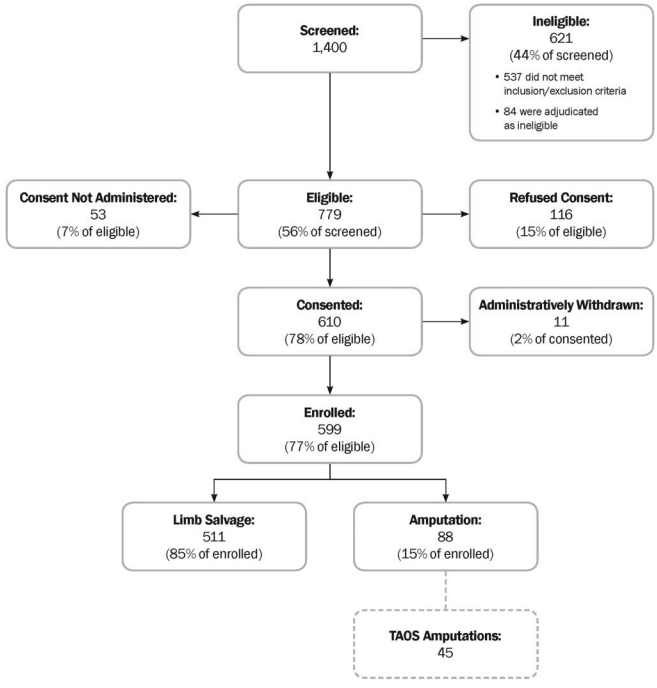

FIGURE 2. OUTLET enrollment summary.

DISCUSSION

Results from the LEAP study suggest that limb salvage is advisable for most patients with severe lower extremity injuries.[18] However, a subset of the data showed that patients with bad foot and ankle injuries may have better long-term outcomes with an amputation.[5] The OUTLET study aims to build upon these results to further explore the injury characteristics that identify patients who would benefit from an amputation early in their care. Defining the regional injury burden associated with poor outcomes will provide the surgeon and the patient with information that can be used to guide the initial treatment decision regarding limb salvage or amputation for these injuries.

Strengths of the study include its multicenter approach involving 32 trauma centers from around the country and the adjudication of both eligibility criteria and classification of severe foot injuries. A potential limitation of the study involves heterogeneity of the treatments and injury severity across sites and between the 2 treatments of interest. Because randomization was not feasible, the study will use a state-of-the-art causal inference technique to understand how salvage patients would have done had they been amputated. The idea of conceptualizing counterfactuals, as planned here, has been previously used in orthopaedic trauma research.[19–21] However, the approach depends on the ability to build a reasonable prediction model of the outcomes that salvages would have had under amputation.

In addition to providing clinical information that can be used to inform treatment decisions for this complicated group of injuries, OUTLET builds upon the LEAP study in several important ways. First, the OUTLET study includes objective measures of physical performance to supplement self-reported function. Although both measure similar aspects of function, performance measures offer advantages over self-report in terms of their applicability across different patient populations and their ability to characterize higher levels of function. This is particularly relevant to military patients who tend to be higher functioning and for whom return to active duty depends on tests of physical performance. Having both self-reported and performance based assessments of function will enhance our understanding of the recovery process for patients with these injuries. It will also provide normative data on performance, which can be used as a reference for future trials.

OUTLET also employs the use of a StepWatch activity monitor to measure daily activity 18 months after injury. These data will provide another dimension of function that will help elucidate our understanding of recovery from these types of injuries after limb salvage versus amputation. Activity monitors have been used extensively in research on stroke, chronic obstructive pulmonary disease, cerebral palsy, cancer, joint replacement, orthotics, and spinal cord injury (https://modushealth.com/publications/). Their utility in orthopaedic trauma patients has not been widely studied.

Treatment decisions related to the care of severe distal tibia, ankle, and/or foot injuries remain challenging. Data from the OUTLET study have the potential to help inform patients and clinicians when considering the difficult decision of limb

TABLE 2. Patient Demographics and Health History

	Overall (n = 644)	Salvage (n = 511)	Amputation (n = 133)	*P**
Age, yrs				
Mean (SD)	38.2 (12.3)	37.7 (12.2)	40 (12.7)	0.055
<25	117 (18)	97 (19)	20 (15)	
25–34	162 (25)	131 (26)	31 (23)	
35–44	137 (21)	108 (21)	29 (22)	
45–54	155 (24)	125 (24)	30 (23)	
>54	73 (11)	50 (10)	23 (17)	
Gender				
Male	434 (67)	325 (64)	109 (82)	
Female	210 (33)	186 (36)	24 (18)	<0.001
Race-ethnicity				
Hispanic	71 (11)	59 (12)	12 (9)	
Non-hispanic non-white	122 (19)	98 (19)	24 (18)	
Non-hispanic White	446 (69)	349 (68)	97 (73)	
Other	5 (1)	5 (1)	0 (0)	0.666
Education				
Less than high school	109 (17)	91 (18)	18 (14)	
High school or GED	221 (34)	162 (32)	59 (44)	
Some college or higher	303 (47)	248 (49)	55 (41)	
Ref/Unk	11 (2)	10 (2)	1 (1)	0.051
Usual major activity				
Working/active duty	500 (78)	392 (77)	108 (81)	
Laid off/looking for work	34 (5)	28 (5)	6 (5)	
Going to school	31 (5)	27 (5)	4 (3)	
Taking care of your house	39 (6)	30 (6)	9 (7)	
Something else	33 (5)	27 (5)	6 (5)	
Ref/Unk	7 (1)	7 (1)	0 (0)	0.717
Marital status				
Married (or cohabiting)	283 (44)	222 (43)	61 (46)	
Never married	225 (35)	187 (37)	38 (29)	
Widowed, divorced, or separated	125 (19)	93 (18)	32 (24)	
Ref/Unk	11 (2)	9 (2)	2 (2)	0.252
Social-emotional support				
Always	439 (68)	342 (67)	97 (73)	
Usually	102 (16)	84 (16)	18 (14)	
Sometimes	54 (8)	43 (8)	11 (8)	
Rarely	17 (3)	15 (3)	2 (2)	
Never	12 (2)	11 (2)	1 (1)	
Ref/Unk	20 (3)	16 (3)	4 (3)	0.79
Health insurance				
No insurance	132 (20)	108 (21)	24 (18)	
Medicaid	74 (11)	62 (12)	12 (9)	
Private	289 (45)	225 (44)	64 (48)	
Other	139 (22)	108 (21)	31 (23)	
Unknown	10 (2)	8 (2)	2 (2)	0.741
Self-assessed health status				
Excellent	190 (30)	150 (29)	40 (30)	
Very Good	219 (34)	166 (32)	53 (40)	
Good	158 (25)	132 (26)	26 (20)	
Fair	59 (9)	47 (9)	12 (9)	
Poor	9 (1)	7 (1)	2 (2)	
Missing	9 (1)	9 (2)	0 (0)	0.339

(*continued on next page*)

TABLE 2. (*Continued*) Patient Demographics and Health History

	Overall (n = 644)	Salvage (n = 511)	Amputation (n = 133)	*P**
BMI, kg/m^2				
Mean (SD)	30 (7.6)	30.1 (7.9)	29.7 (6.3)	0.757
<18.5	6 (1)	5 (1)	1 (1)	
18.5–25	182 (28)	148 (29)	34 (26)	
25–30	185 (29)	142 (28)	43 (32)	
30–35	133 (21)	105 (21)	28 (21)	
≥35	138 (21)	111 (22)	27 (20)	
Major comorbidity (count)				
0	371 (58)	293 (57)	78 (59)	
1	154 (24)	125 (24)	29 (22)	
≥2	119 (18)	93 (18)	26 (20)	0.806
Major comorbidity (by type)				
Any	273 (42)	218 (43)	55 (41)	0.844
Cardiac/vascular	136 (21)	100 (20)	36 (27)	0.074
Psychiatric	104 (16)	89 (17)	15 (11)	0.112
Diabetes	46 (7)	37 (7)	9 (7)	1
Other	125 (19)	96 (19)	29 (22)	0.461
Tobacco use				
Current tobacco use	261 (41)	196 (38)	65 (49)	
Former tobacco use	125 (19)	98 (19)	27 (20)	
No tobacco use	247 (38)	208 (41)	39 (29)	
Ref/Unk	11 (2)	9 (2)	2 (2)	0.079
Previous leg injury				
Yes	103 (16)	77 (15)	26 (20)	
No	524 (81)	419 (82)	105 (79)	
Ref/Unk	17 (3)	15 (3)	2 (2)	0.378

Data are presented as mean (SD)/n (%) unless otherwise specified.
*P values computed using Fischer's exact test for categorical variables and Wilcoxon rank sum tests for continuous variables.
BMI, body mass index; GED, general educational diploma; Ref/Unk, refused/unknown.

salvage versus amputation for these severe injuries and will also provide the basis for future trials designed to rigorously evaluate the advantages of one treatment over another in specific subgroups of patients.

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