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Predictors of lower extremity fracture-related amputation in persons with traumatic spinal cord injury: a case–control study

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STUDY DESIGN: This is a retrospective case–control study.
OBJECTIVES: To identify predictors of lower extremity (LE) long bone fracture-related amputation in persons with traumatic spinal cord injury (tSCI).
SETTING: US Veterans Health Administration facilities (2005–2015).
METHODS: Fracture-amputation sets in Veterans with tSCI were considered for inclusion if medical coding indicated a LE amputation within 365 days following an incident LE fracture. The authors adjudicated each fracture-amputation set by electronic health record review. Controls with incident LE fracture and no subsequent amputation were matched 1:1 with fracture-amputation sets on site and date of fracture (±30 days). Multivariable conditional logistic regression determined odds ratios (OR) and 95% confidence intervals (CI) for potential predictors (motor-complete injury; diabetes mellitus (DM); peripheral vascular disease (PVD); smoking; primary (within 30 days) nonsurgical fracture management; pressure injury and/or infection), controlling for age and race.
RESULTS: Forty fracture-amputation sets from 37 Veterans with LE amputations and 40 unique controls were identified. DM (OR = 26; 95% CI, 1.7–382), PVD (OR = 30; 95% CI, 2.5–371), and primary nonsurgical management (OR = 40; 95% CI, 1.5–1,116) were independent predictors of LE fracture-related amputation.
CONCLUSIONS: Early and aggressive strategies to prevent DM and PVD in tSCI are needed, as these comorbidities are associated with increased odds of LE fracture-related amputation. Nonsurgical fracture management increased the odds of LE amputation by at least 50%. Further large, prospective studies of fracture management in tSCI are needed to confirm our findings. Physicians and patients should consider the potential increased risk of amputation associated with non-operative management of LE fractures in shared decision making.

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INTRODUCTION

Lower extremity (LE) fractures secondary to low-impact or non-traumatic causes are common in persons with spinal cord injury/disorder (SCID) [1–6]. In persons with chronic SCID, these fragility fractures of the LE long bones, excluding the feet, are overwhelmingly attributable to sublesional osteoporosis [7]. In male Veterans with SCID of at least 2 years duration, there is a 14% 5-year incidence of LE fractures [8]. As many as 50% of persons with SCID and a LE fracture suffer a fracture-related complication [1, 2]. Fracture-related complications include hospitalization [1, 3, 6], pressure injury [1, 2, 4, 6, 8, 9], delayed union [1, 2, 4], nonunion [1, 4, 6, 10], persistent pain [1, 4], autonomic dysreflexia [1], infection [3, 4, 6, 11–13], functional impairment [14], LE amputation [4, 6, 15, 16] and mortality [17, 18]. In one study utilizing Veterans Affairs (VA) administrative data, an amputation or disarticulation occurred within 1 year following an incident fracture in 1.3% of LE fractures in Veterans with chronic SCID [16]. In chronic SCID, LE amputation is associated with equipment modification [15], loss of functional capacity [15] and mortality [18, 19]. However, there are no controlled studies identifying predictors of LE amputation secondary to LE fracture in SCID.

Medical comorbidities, including diabetes mellitus (DM) [20], peripheral vascular disease (PVD) [21], and peripheral neuropathy [21], as well as smoking [22], are known to increase the risk of LE amputation in the able-bodied population. While these comorbidities are common in persons with chronic SCID who require LE amputation [15, 23], the possible role of each in predicting amputation following LE fracture has not been evaluated in persons with SCID. While risk factors in the general population for LE fracture-related amputation often reflect the severity of the trauma (i.e., vascular injury, fasciotomy, concomitant fractures) [24], it is unknown if these factors will translate to predicting LE amputation in the SCID population in light of the propensity for

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low-impact or non-traumatic LE fractures in persons with chronic SCID [3, 5, 6, 10, 12, 14]. Svircev et al. [15] report there are often multiple simultaneous indications for a LE amputation performed on a person with chronic SCID, including fracture itself in 11.5%, as well as fracture-related complications: pressure injury, osteomyelitis, and pain. However, it remains unknown if the development of these or other complications following the fracture can predict a future LE amputation.

The purpose of this study was to determine factors that predict fracture-related LE amputation in persons with traumatic spinal cord injury (tSCI) following fracture of a LE long bone (excluding feet). We hypothesized, based on existing literature and clinical suspicion, that the following six features will be associated with higher odds of having a LE fracture-related amputation after controlling for age and race in persons with tSCI: motor-complete spinal cord injury (SCI) (i.e., American Spinal Injury Association Impairment Scale [25] Grade A or B), DM, PVD, current or former smoking (versus never smoking), primary nonsurgical fracture management, and pressure injury and/or infection following the fracture.

METHODS

Study design

A retrospective case–control study was conducted to identify predictors of fracture-related amputation in persons with tSCI. The Veterans Affairs Institutional Review Boards at the Charlie Norwood VA Hospital, Augusta, Georgia, and the Hines VA Hospital, Hines, Illinois approved the study.

The Veterans Health Administration (VHA) Allocation Resource Center (ARC) is a cumulative list of Veterans who have ever received healthcare in the VHA. Persons with a SCID were identified from the 2016 VHA ARC list based on International Classification of Diseases, Ninth Revision (ICD-9) codes for a SCID and treatment in either a SCID bed section and/or SCID outpatient clinic [26]. Data for this SCID cohort were then linked to the VHA's Corporate Data Warehouse (a system-wide national data infrastructure maintained by the VHA) to ascertain participant demographics, inpatient, outpatient and pharmacy data. The cohort was further linked with the VA Spinal Cord Dysfunction Registry and/or the SCID Outcomes Database, historical databases aggregated at a national level and containing information about SCID etiology, date of onset, level of injury, completeness of injury and the Veteran's healthcare [26]. The cohort was then restricted to Veterans with SCI of traumatic etiology without a history of malignant neoplasm and/or Paget's disease of bone to form the study tSCI cohort.

Incident LE fractures were identified within the tSCI cohort using ICD-9 LE fracture codes (820–829, 733.10, 733.14–16, and 733.19) recorded from the fiscal years 2005 to 2015, inclusive, from national VA administrative utilization and diagnosis data. As VA administrative data adopted International Classification of Diseases, Tenth Revision (ICD-10) coding in 2016, we stopped our study in 2015 to avoid introducing bias from coding system changes mid-study while collecting sufficiently recent fracture data to generalize to current clinical practice. All electronic health record (eHR) encounters within a 120-day time frame with the same ICD-9 fracture code recorded were considered to be the same fracture; the date of the first encounter with the ICD-9 code of interest within this 120-day window was considered the date of the incident fracture [27]. Amputations were identified by an ICD-9 code for amputation of the LE (84.11-19) within 365 days following an incident LE fracture. A 365-day time window between incident fracture and LE amputation was selected in order to enrich the group of fractures undergoing eHR review with fractures related to subsequent amputation and avoid fractures unrelated to subsequent amputation, while achieving a reasonable sample size to conduct these analyses.

Fracture-amputations sets

The authors reviewed the eHR of fracture-amputation sets from Veterans with tSCI identified from administrative data. Sets from Veterans without tSCI, with active malignancy or with Paget's disease of the bone were excluded. If no fracture could be identified, the fracture occurred prior to or at the time of the SCI, or the amputation was not related to the fracture (i.e., contralateral LE), the fracture-amputation set was excluded. Fracture-amputation sets were then restricted to fracture-amputation sets with fractures of LE long bones, excluding the foot (i.e. femur, tibia and/or fibula), and amputations that occurred within 365 days of the incident fracture based on actual fracture date from eHR review (Fig. 1). Timing and site of amputation were identified for each fracture-amputation set.

Controls

For each fracture-amputation set, one matched control was initially selected from administrative data. Controls were randomly selected from Veterans with tSCI and an incident LE fracture (by ICD-9 codes) with no subsequent ICD-9 code for a LE amputation. Controls were matched with fracture-amputation sets on site (hip, femur, or tibia/fibula) and date of fracture (ICD-9 fracture code within ±30 days of actual fracture date of the fracture-amputation set from eHR review [in contrast to date of ICD-9 coding for the fracture]). Candidate controls underwent retrospective eHR review for the presence of any exclusion criteria. Exclusion criteria included Veteran without tSCI, with active malignancy, with Paget's disease of bone, or with any LE amputation any time before the Veteran's death or date eHR review was performed (whichever occurred first); fracture occurred prior to or at time of SCI; and fracture site was not the same fracture site as the correlate fracture-amputation set. If the candidate control was excluded, that control was randomly replaced with a new unique candidate control that underwent eHR review until one unique matched control was identified for each fracture-amputation set (Fig. 1).

Clinical characteristics

Standardized data were collected by eHR review uniformly for fracture-amputation sets and controls. Demographics (age, race, ethnicity, sex, and body mass index [BMI]), SCI-related characteristics (duration, level, and extent of injury), comorbidities (DM, PVD), lifestyle factors (tobacco smoking status, e-cigarette smoking status, chewing tobacco status, alcohol abuse, substance use), and medication use (corticosteroids, non-steroidal anti-inflammatory drugs) were collected at the time of incident fracture or most recent time prior to fracture that this data was available. Lifestyle factors of current, former or never smoking, alcohol abuse, and substance use were ascertained by eHR review of documentation including but not limited to primary care, psychiatry, and Domiciliary Care Program notes. Fracture-related data on mechanism (high-impact, low-impact, or no/unknown trauma), fracture site, type (open or closed, displaced or non-displaced, comminuted or non-comminuted), time from fracture to clinical recognition and presence of associated complications (additional fracture(s), vascular injury, limb ischemia [pulselessness, paresthesia, slow capillary refill], compartment syndrome, persistent hypotension) were collected. Low-impact trauma was defined as the equivalent of a fall from standing position, such as a fall from a wheelchair or fall during transfer.

Primary management for the fracture was considered surgical if eHR review identified a surgical intervention (other than amputation) performed within 30 days of the incident fracture. Timing and type of surgery were recorded. Initial and subsequent nonsurgical management strategies in chronological order (cast, splint, orthotic, external fixator, soft dressing only, traction, non-weight bearing only, none, secondary surgery) for fractures with primary nonsurgical management and complications (hospital admission and length of stay; delayed union, nonunion, or malunion; pressure injury and location; infection [osteomyelitis, soft tissue] with causal organism(s)) for all fractures were identified by eHR review until amputation in fracture-amputation sets (up to 365 days) and in the first 12 months following fracture in controls. Pressure injury and/or infection was marked as present if there was (i) a pressure injury (with or without associated infection), (ii) osteomyelitis, or (iii) a soft tissue infection other than osteomyelitis. A fracture was recorded to be complicated by a delayed union, nonunion, or malunion if the documentation available on eHR review from either the orthopedic surgeon or the radiologist stated explicitly that one of any of these three complications was present.

The time to amputation after fracture was recorded in days and then categorized as early (<90 days after fracture) versus delayed (90–365 days after fracture). We chose 90 days to designate early versus late amputation because previous large cohort studies in the general population have shown statistically different outcomes related to early versus late amputation using a similar time frame [28]. The location of the amputation was also ascertained.

Statistical analyses

Descriptive statistics summarized demographic and clinical features in fracture-amputation sets and controls. Conditional logistic regression analysis controlling for age and race was used to test the primary

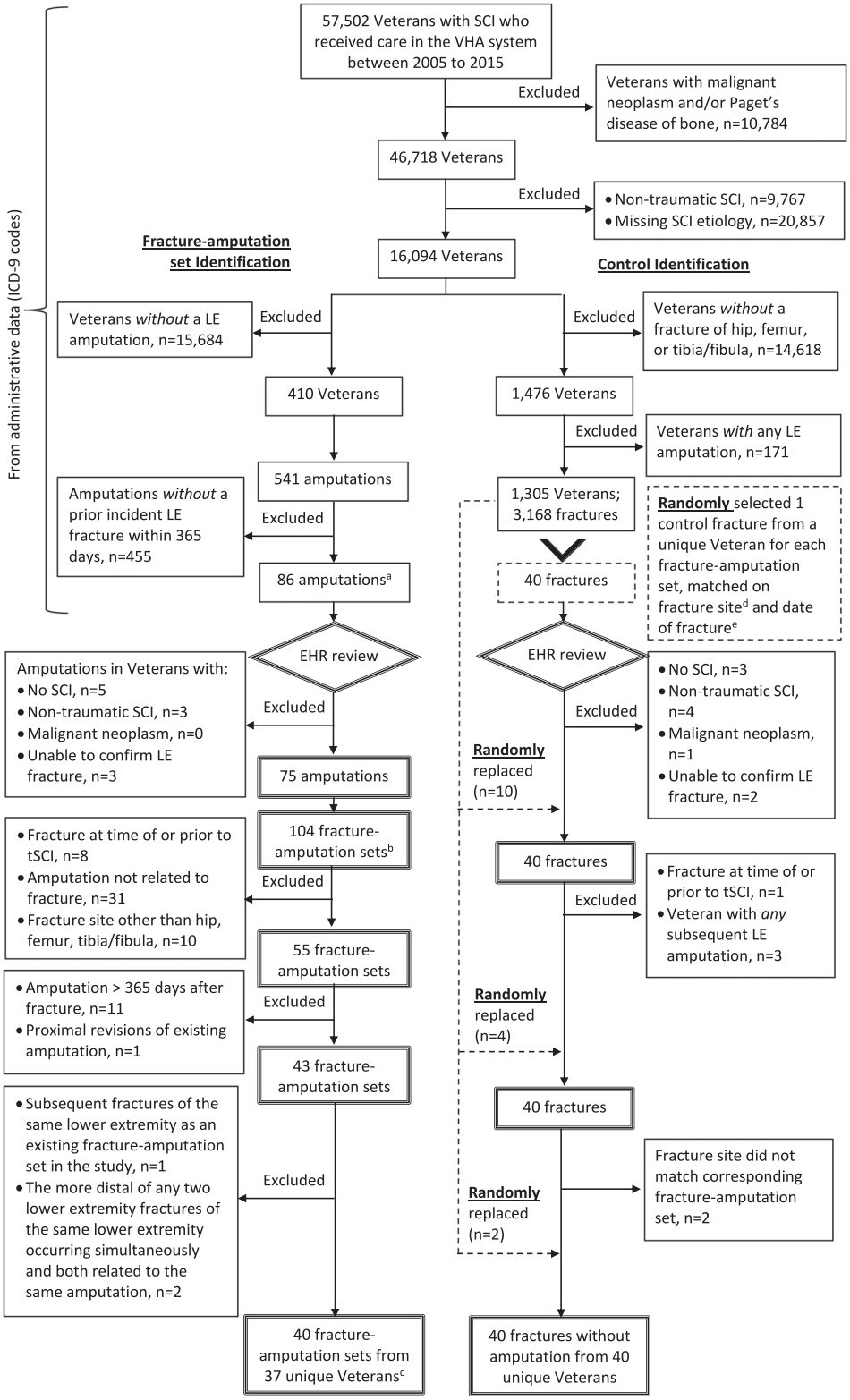

Fig. 1 Diagram of fracture-amputation set and control identification. SCI spinal cord injury, VHA Veterans Health Administration, LE lower extremity, ICD-9 International Classification of Diseases, Ninth Revision. ICD-9 codes considered for LE fracture included: 820–829, 733.10, 733.14–16, and 733.19. [a]86 amputations from Veterans with tSCI, and incident LE fracture, and subsequent LE amputation within 365 days by administrative data. [b]The electronic health record of each Veteran with an amputation considered for inclusion was examined for any prior lower extremity fracture and any possible subsequent associated lower extremity amputation. Of the 75 amputations, 23 Veterans had more than one incident lower extremity fracture (up to 4) and 13 Veterans had more than one lower extremity amputation (up to 3). Therefore, the number of fracture-amputation sets considered for inclusion exceeds the number of Veterans. [c]Three Veterans contributed two fracture-amputation sets each. Each of these Veterans had a fracture and fracture-related amputation in both of their extremities. [d]Lower extremity fracture sites for matching categorized as hip, femur, tibia and/or fibula. [e]Based on the actual date of the fracture and the amputation from electronic health record review, in contrast to the date of the International Classification of Diseases, Ninth Revisions (ICD-9) code date from initial screening.

Table 1. Baseline characteristics of study population by amputation status.

	Lower extremity fractures with resultant amputation ($n = 40$)[a]	Lower extremity fractures without resultant amputation ($n = 40$)[b]
Age (years), mean (SD)	60 (8)	57 (12)
Race, *n* (%)		
White	27 (68)	36 (90)
Black	12 (30)	3 (8)
Pacific Islander	0 (0)	1 (3)
Biracial	1 (3)	0 (0)
Hispanic/Latino, *n* (%)	0 (0)	5 (13)
Female, *n* (%)	1 (3)	1 (3)
BMI (kg/m^2), mean (SD)	25 (5)	27 (4)
Level of injury, *n* (%)		
Paraplegia	30 (75)	27 (68)
Tetraplegia	10 (25)	13 (33)
AIS Grade, *n* (%)		
A	35 (88)	28 (70)
B	3 (8)	4 (10)
C	0 (0)	3 (8)
D	2 (5)	5 (13)
Motor-complete SCI, *n* (%)[c]	38 (95)	32 (80)
Duration of tSCI (years), mean (SD)	28 (14)	23 (18)
Diabetes mellitus, *n* (%)	9 (23)	3 (8)
HbA1c, median [IQR]	7 (6–8)	5 (5,6)
Duration of DM (years), median [IQR]	8 (5–15)	7 (3–10)
Diabetic management, *n* (%)		
Non-pharmacologic	0 (0)	1 (33)
Non-insulin medications	6 (67)	1 (33)
Insulin	3 (33)	1 (33)
Peripheral vascular disease, *n* (%)	19 (48)	2 (5)
Smoking history		
Tobacco smoking status, *n* (%)		
Current	13 (33)	10 (25)
Former	15 (38)	18 (45)
Never	12 (30)	12 (30)
Pack-years tobacco, mean (SD)	31 (19)	20 (19)
E-cigarette smoking status, *n* (%)		
Current	1 (3)	0 (0)
Former	0 (0)	0 (0)
Never	39 (98)	40 (100)
Chewing tobacco use, *n* (%)		
Current	2 (5)	1 (3)
Former	0 (0)	1 (3)
Never	38 (95)	38 (95)
Chewing tobacco years, median [IQR]	46 (46)	10 (9–12)
Alcohol abuse, *n* (%)		
Current	7 (18)	1 (3)
Former	11 (30)	8 (20)
Never	22 (55)	31 (78)
Substance use, *n* (%)		
Current	8 (20)	7 (18)
Former	9 (23)	5 (13)
Never	23 (58)	28 (70)
Prescription medication use, *n* (%)		
Corticosteroids	0 (0)	0 (0)
NSAIDs	9 (23)	12 (30)

SD standard deviation, *BMI* body mass index, *AIS* American Spinal Injury Association Impairment Scale, *tSCI* traumatic spinal cord injury, *IQR* interquartile range, *DM* diabetes mellitus, *E-cigarette* electronic cigarette.
[a]*n* represents the number of distinct fracture-amputation sets.
[b]*n* represents the number of distinct controls, each of which is a unique lower extremity fracture from a distinct Veteran with traumatic spinal cord injury and no subsequent lower extremity amputation.
[c]Motor-complete SCI presents if AIS Grade is A or B.

hypothesis, i.e., to determine if there is an association between a pre-specified predictor set (motor-complete tSCI, DM, PVD, tobacco (cigarette or cigar) smoking status, primary fracture management, and a composite variable of pressure injury and/or infection) and fracture-related LE amputation. The conditional logistic regression analysis was conducted with specified clustered standard errors for individual Veterans who contributed multiple fracture-amputation sets to allow for intragroup correlation. These associations were summarized as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were performed using Stata version 12.1 (StataCorp LLC, College Station, TX, USA). Existing Stata commands for conditional logistic regression ("clogit") and its built-in options to set the variance-covariance matrix to "cluster" were used to perform the primary analysis, where clusters were specified as the individual unique Veterans (who may contribute up to two fracture-amputation sets, one for each LE). The assumptions for conditional logistic regression were met. We confirmed there was no multicollinearity among predictors, there were no extreme outliners, and there was a linear relationship between the continuous predictor variable and the logit of the response variable.

RESULTS

A total of 86 candidate fracture-amputation sets from Veterans with at least one incident LE fracture and a LE amputation within 365 days of fracture were identified for eHR review for possible inclusion. After eHR review, 75 amputations were confirmed from Veterans with tSCI and an incident LE fracture. Twenty-three Veterans had multiple incident LE fractures (up to 4) and 13 had multiple LE amputations (up to 3, including a proximal ipsilateral amputation following a more distal amputation), yielding 104 possible fracture-amputation sets for further eHR review. After considering the exclusion criteria, 40 fracture-amputation sets from 37 unique Veterans were included in this study (Fig. 1). Thirty-four Veterans contributed a single fracture-amputation set. Three Veterans contributed two fracture-amputation sets each. Each of these three Veterans had a fracture and fracture-related amputation in both of their lower extremities. For each fracture-amputation set, one matched control was identified following eHR review where 16 candidate controls were excluded and randomly replaced (Fig. 1).

Baseline characteristics of the study population are outlined in Table 1. The majority of the study population was White, but more

Table 2. Fracture characteristics and fracture complications by amputation status.

	Lower extremity fractures with resultant amputation ($n = 40$)[a]	Lower extremity fractures without resultant amputation ($n = 40$)[b]
Fracture-related characteristics		
Open, *n* (%)	2 (5)	0 (0)
Displaced, *n* (%)	38 (95)	29 (76)
Comminuted, *n* (%)	24 (60)	25 (64)
Mechanism of fracture, *n* (%)		
High-impact trauma	1 (3)	3 (7)
Low-impact trauma[c]	29 (73)	26 (67)
No or unknown trauma[d]	10 (25)	10 (26)
Fracture site[e]		
Hip	0 (0)	0 (0)
Femur	23 (56)	23 (56)
Tibia and/or fibula	17 (43)	17 (43)
No. of simultaneous fractures, *n* (%)		
Isolated fracture	33 (83)	31 (79)
2	4 (10)	6 (15)
3	2 (5)	2 (5)
4	1 (3)	0 (0)
Simultaneous fracture site, if present, *n* (%)		
Ipsilateral lower extremity	4 (43)	7 (88)
Contralateral lower extremity	3 (38)	4 (57)
Upper extremity	0 (0)	0 (0)
Axial skeleton	0 (0)	0 (0)
Time from fracture to clinical recognition (days), median [IQR]	1 [0–3]	2 [0–4]
Associated injury present at time of fracture diagnosis, *n* (%)		
Vascular injury	1 (3)	0 (0)
Limb ischemia[f]	2 (5)	0 (0)
Persistent hypotension	2 (6)	0 (0)
Limb ischemia for >6 h	1 (3)	0 (0)
Compartment syndrome	0 (0)	0 (0)
Primary fracture management, *n* (%)[g]		
Surgical	3 (8)	8 (20)
Time from diagnosis of fracture to primary surgery (days), median [IQR]	1 (1–15)	2 [0–11]
Hospital admission for fracture, *n* (%)	27 (71)	18 (48)
Length of stay (days), if hospitalized for fracture, median [IQR]	21 (8–121)	12 (4–53)
Fracture delayed union, nonunion or malunion, *n* (%)	26 (65)	18 (45)
Pressure injury related to fracture, *n* (%)	26 (65)	21 (53)
Location of pressure injury, *n* (%)		
At the fracture site	5 (19)	2 (10)
Both at and away from fracture site	14 (54)	4 (19)
Not at fracture site	7 (27)	15 (71)
Osteomyelitis, *n* (%)	19 (48)	2 (5)
Cause of osteomyelitis, *n* (%)		
Polymicrobial	4 (21)	0 (0)
Single organism	6 (32)	1 (50)
Unknown etiologic organism	9 (47)	1 (50)
Soft tissue infection, *n* (%)[h]	5 (13)	2 (5)
Cause of soft tissue infection, *n* (%)		
Polymicrobial	0 (0)	0 (0)
Single organism	2 (40)	2 (100)
Unknown etiologic organism	3 (60)	0 (0)
Pressure injury and/or infection, *n* (%)[i]	30 (75)	22 (55)

LE lower extremity, *No.* number.
[a]*n* represents the number of distinct fracture-amputation sets.
[b]*n* represents the number of distinct controls, each of which is a unique lower extremity fracture from a distinct Veteran with traumatic spinal cord injury and no subsequent lower extremity amputation.
[c]Equivalent of a fracture due to a fall from a standing position, including a fall from a wheelchair that is not moving, or a fall during transfers.
[d]Veteran cannot identify any precipitating event or the activity associated with the fracture is equivalent to an activity of daily living that is non-traumatic (i.e., rolling over in bed).
[e]Lower extremity fracture sites for matching categorized as hip, femur, tibia and/or fibula; a simultaneous fracture of the tibia and fibula is considered a single fracture for purposes of this study.
[f]Limb ischemia defined as pulselessness, paresthesia, slow capillary refill.
[g]Defined as management of fracture within 30 days of incident fracture diagnosis.
[h]Soft tissue infection other than pressure-injury-related infection.
[i]Composite variable that is present if fracture complicated by a pressure injury, osteomyelitis or soft tissue infection and absent if none of these occurred.

persons of Black race had LE fractures with resultant amputation than controls (30% versus 8%). Participants most commonly had motor-complete paraplegia. Fracture-amputation sets had a higher proportion of PVD than controls without LE amputation (48% versus 5%).

Fracture-related data, including primary fracture management, is displayed in Table 2. Among fracture-amputation sets and their controls, fractures were largely closed, displaced and secondary to low-impact trauma. The most common fracture site was the femur (56%) followed by the tibia and/or fibula (43%). There were no hip fractures in our cohort. Nonsurgical primary fracture management was common in both fracture-amputation sets (92%) and controls (80%). Types of nonsurgical and surgical primary management are detailed in Supplementary Tables S1 and S2, respectively. There was one fracture-amputation set with a delayed union, nonunion, or malunion after primary surgical management. Nonsurgical management strategies in chronological order for fractures complicated by a delayed union, nonunion, or malunion in both fracture-amputation sets and controls are shown in Supplementary Table S3. Fracture complications are shown in Table 2. Fracture-amputations sets more commonly developed incident osteomyelitis (48% versus 5%) and soft tissue infection other pressure-injury-associated infection (13% versus 5%) than fractures without a fracture-related amputation.

Table 3. Characteristics of amputations within 365 days of lower extremity fracture in fracture-amputation sets from Veterans with traumatic spinal cord injury.

	Lower extremity fractures with resultant amputation ($n = 40$)[a]
Time to amputation after fracture (days), mean (SD)	123 (96)
Timing of amputation, *n* (%)	
Early (<90 days after fracture)	20 (50)
Delayed (90–365 days after fracture)	20 (50)
Location of amputation, *n* (%)	
Below the knee	7 (18)
Disarticulation of the knee	5 (13)
Above the knee	27 (68)
Disarticulation of the hip	1 (3)

[a]*n* represents the number of distinct fracture-amputation sets.

Among fracture-amputation sets, LE amputation was equally likely to occur early (<90 days after fracture) or delayed (90–365 days after fracture) (50%) (Table 3). Most amputations were above the knee amputations (68%) (Table 3). Indications contributing to the decision for amputation in some persons involved factors that are not captured in Table 2, including elective for improved functional status or quality of life ($n = 12$; 30%), anticipatory medical indication such as high risk for infection, high risk for nonunion, or social situation precludes caring for pressure injury at home ($n = 3$; 8%), and critical limb ischemia ($n = 1$; 3%). Key fracture complications and amputation-related features among fracture-amputation sets, stratified by level of injury, are shown in Supplementary Table S4.

Multivariate conditional logistic regression showed DM (OR = 26; 95% CI, 1.7–382), PVD (OR = 30; 95% CI, 2.5–371), and nonsurgical primary fracture management (OR = 40; 95% CI, 1.5–1,116) were predictors of LE fracture-related amputation (Table 4). In multivariate conditional logistic regression, motor-complete SCI, current or former smoking (versus never smoking), and pressure injury and/or infection following fracture were not associated with increased odds of LE amputation.

Table 4. Univariate and multivariate conditional logistic regression models for lower extremity amputation within 365 days following a lower extremity long bone fracture (excluding feet) in Veterans with traumatic spinal cord injury.

	Univariate model	Multivariate model[a]
	OR (95% CI)	OR (95% CI)
Age	1.0 (0.99–1.1)	1.09 (0.94–1.3)
Non-white race[b]	5.5 (1.2–26)	16 (0.39–663)
Motor-complete SCI	4.0 (0.83–19)	2.8 (0.09–89)
Diabetes mellitus	3.0 (0.80–11)	26 (1.7–382)
Peripheral vascular disease	18 (2.3–139)	30 (2.5–371)
Tobacco smoking status		
Current	1.4 (0.39–4.8)	29 (0.16–5,519)
Former	0.86 (0.30–2.4)	1.6 (0.26–9.4)
Never	Reference	Reference
Primary management: nonsurgical[c]	3.5 (0.71–17)	40 (1.5–1,116)
Pressure injury and/or infection[d]	2.6 (0.91–7.4)	0.87 (0.21–3.7)

OR odds ratio, *CI* confidence interval, *SCID* spinal cord injury/disorder.
[a]Conditional logistic regression model with specified clustered standard errors for individuals who contributed multiple fracture-amputation dyads to allow for intragroup correlation, adjusted for age, race (white versus non-white), motor-complete spinal cord injury, diabetes mellitus, peripheral vascular disease, tobacco smoking status (current, former, never), primary management (nonsurgical versus surgical) and presence of pressure injury or infection.
[b]Reference group: White race; Non-white consists of predominately blacks with 1 Pacific Islander and 1 Biracial person.
[c]Defined as management of fracture within 30 days of incident fracture; Reference group is surgical management (surgical management must be other than amputation).
[d]Composite variable that is present if fracture complicated by a pressure injury, osteomyelitis or soft tissue infection and absent if none of these occurred.

DISCUSSION

In Veterans with tSCI and incident LE fracture, DM, PVD, and primary nonsurgical fracture management were predictors of LE fracture-related amputation in multivariable analysis adjusted for a pre-specified predictor set. There are very few published reports addressing risk factors for fracture-related LE amputations in SCID [13–16]. Our study is the first, to our knowledge, to establish DM and PVD as predictors of LE fracture-related amputation in tSCI.

DM and PVD are known to be important risk factors for LE amputation in the general population and have a demonstrated negative synergistic effect in the general population [29]. DM and PVD each disproportionately affect persons with chronic SCID [30–33], and therefore, may pose a more significant burden in the chronic SCID population. Following SCID, drastic alterations occur in body composition including sarcopenia and accumulation of intramuscular fat within skeletal muscle [34]. One possible mechanism for the increased risk of DM in chronic SCID is this sarcopenia, which is associated with adverse glucose metabolism independent of obesity [35, 36]. Another consideration is the increased susceptibility of persons with SCID to metabolic disorders of carbohydrate and lipid metabolism, which in turn may contribute to elevated DM and PVD risk [37]. Several other possible factors may contribute to the increased risk of PVD in SCID: vascular remodeling with impaired blood vessel control [38], decreased vascular reactivity [39] and autonomic dysfunction resulting in abnormal fluctuations in blood pressure [40].

Svircev et al. reported in their retrospective 15-year study of 58 amputations among 52 individuals with chronic SCID that 42% of them had prevalent DM [15]. Bethel et al. reported amputations following LE fracture in chronic SCID were more common in Veterans with DM than non-diabetics (38% versus 15%) [16]. Persons with SCID and DM have three times the likelihood of any microvascular complication, including but not limited to amputation, compared to persons with SCID without DM [41]. Our study shows, among persons with tSCI, at least a 70% increased odds of a LE fracture resulting in amputation within 356 days if that person has DM compared to a person without DM. Our estimates are too imprecise to make any conclusions about the risk of amputation attributed to DM in the tSCI population versus its attributable risk in the general population. However, physical impairment has been demonstrated to predict the occurrence of diabetic foot ulcers, a central risk factor for LE amputation [42]. Furthermore, a study of persons with prevalent DM before AIS C SCID demonstrated increased wheelchair requirements and decreased ambulatory ability at one year after injury [43]. Therefore, the interaction between physical impairment and DM is a possible avenue by which persons with SCID and DM could be more at risk of LE

amputation than the general diabetic population, and this merits further study.

In the series by Svircev et al. of persons with chronic SCID who underwent LE amputation, almost half (48%) had PVD [15]. PVD is a common indication for LE amputation in chronic SCID irrespective of a prior LE fracture [15, 44]. Our study shows at least 2.5 times the odds of amputation within 365 following an LE fracture in a Veteran with tSCI and PVD than in a Veteran with tSCI and without PVD. As with DM, our estimates are too imprecise to make any conclusions about the risk of amputation conveyed by PVD in the tSCI population versus its attributable risk in the general population. However, there are possible considerations for how PVD may uniquely affect the person with SCID in predisposing to amputation. First, the communication between osteoblasts and endothelial cells is altered by the state of mechanical unloading, one of the multiple mechanisms of osteoporosis in chronic SCID [45]. In addition, typical symptoms of PVD, such as claudication, may not be detectable in persons with SCID who are insensate in the lower extremities, and this may delay the diagnosis and treatment of PVD in SCID compared to the general population [33]. Early and aggressive strategies to prevent DM and PVD in tSCI are needed to mitigate future amputation risk. Reducing PVD is of particular importance given its association with increased mortality following LE amputation in chronic SCID (post-amputation 5-year survival of 30% with PVD versus 70% without PVD) [15].

When a fracture occurs, the goals of treatment strategy selection (primary surgical versus nonsurgical management) include restoration of pre-fracture function and avoidance of complications [46]. In the general population, while clinical practice guidelines do allow for consideration of non-operative LE fracture care in certain settings, the vast majority of LE fractures are managed surgically after consideration of risks and benefits [47]. In contrast, only 13 out of 88 (15%) fractures in our study of persons with tSCI underwent primary surgical management. Comparable rates of surgical management of LE fracture in chronic SCID are reported in other VA studies (7–37%) [9, 14, 16]. Primary surgical management may be more common in nonveteran SCID populations, 63% in one study [10]. Several factors may influence the decision to pursue nonsurgical management more often in SCID than in the general population: (1) delayed diagnosis of fractures due to absent protective sensation [46]; (2) historical concerns for high complication rates of surgical management [3]; (3) preexisting mobility limitations from the SCID itself, potentially allowing for restoration of the pre-fracture level of function without surgical intervention [3]; and osteoporosis and atrophic soft tissue envelop common in SCID complicating surgical fixation [46].

Nonsurgical primary fracture management increased the odds of LE fracture-related amputation by at least 50% in our study. This finding is in accord with existing retrospective series in chronic SCID. Cochran et al. [14] reported no amputations among 14 LE fractures treated with primary surgical management and two fracture-related amputations in 73 fractures treated with primary nonsurgical management. Cass and Sems [13] reported no amputations among 17 femur fractures managed operatively and three amputations in 12 femur fractures managed non-operatively, albeit only one of these amputations was deemed related to the fracture. Bethel et al. [16] reported 24 amputations following LE long bone fracture from administrative data, and only one was preceded by a surgical procedure (an open reduction internal fixation).

This study has important strengths. Foremost, to our knowledge, this is the first case–control study to examine predictors for amputation following LE fracture in SCID. By performing eHR review rather than employing only administrative data, a causal relationship between the fracture and subsequent amputation was confirmed and a more comprehensive list of potential predictors was explored.

There are also limitations to this study. Our small sample size led to wide confidence intervals. Despite the statistical adjustment, these results still might be confounded by differences between Veterans and fractures that were selected for surgery and those that were not. Our initial screening of Veterans to undergo eHR review relied on querying administrative data for fracture and amputation ICD-9 codes; therefore, lack of medical coding of these events may have led to missed opportunities for Veterans with tSCI to be included as fracture-amputation sets. While 63% of Veterans with SCID use the VA healthcare system exclusively, a substantial minority are multiple-system users [17]. Thus, fractures and/or amputations occurring outside the VA system may not be captured and other clinical data, including fracture treatment, may be incomplete, although we minimized these omissions through eHR review. However, we acknowledge there was no review of electronic health records in health systems outside of the VHA conducted as part of this analysis.

Misclassification of lifestyle factors (smoking, alcohol abuse, substance use) may exist due to incomplete eHR documentation. Fracture management practices and quality of care may vary from within versus outside the VA system, as well as within the VA system between SCI centers and non-SCI centers. We did not control for the clinical site of fracture care, which may have impacted our findings. We did not collect sufficient data in eHR review to reliably separate delayed union, nonunion, and malunion; furthermore, we did not systematically collect data on timing of nonsurgical management strategies with respect to the diagnosis of delayed union, nonunion, or malunion. We were unable to evaluate the fracture site as an independent predictor of amputation because the controls were matched on the fracture site. There are fewer women Veterans with SCID than in the general SCID population (3% versus 22%) [16, 48], and our findings may not generalize to women Veterans with SCID given the small sample size in our study. We studied U.S. Veterans with tSCI and results may not generalize to Veterans outside the U.S., nonveterans and those with other SCID etiologies. Our study was conducted from 2005 to 2015, and there is a possibility these results may not generalize to more recent clinical practices regarding fracture management in tSCI if there has been an appreciable change.

In conclusion, we have identified three key modifiable predictors of LE fracture-related amputation in persons with tSCI: DM, PVD, and primary nonsurgical fracture management. Nonsurgical fracture management increased odds of LE amputation by at least 50%. Further large, prospective studies of fracture management in tSCI are needed to confirm our findings. Physicians and patients should consider the potential increased risk of amputation associated with non-operative management of LE fractures in shared decision making.

DATA AVAILABILITY

The data that support the findings of this study are the property of the United States Government's Department of Veterans Affairs (VA) and are only available as part of VA-approved research activities pursuant to Veterans Health Administration (VHA) Directives 1200.05(2), VHA 1200.01, and/or VHA 1080.01.

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AUTHOR CONTRIBUTIONS

REE was responsible for conceiving and designing the work, extracting and analyzing data, interpreting results, drafting the manuscript, and approval of the final version. CER was responsible for extracting and analyzing the data, revising the manuscript, and approval of the final version. SM was responsible for extracting and analyzing the data and approval of the final version. FMW was responsible for conceiving and designing the work, interpreting results, revising the manuscript, and approval of the final version. BG was responsible for extracting and analyzing the data and approval of the final version. WO was responsible for conceiving and designing the work, interpreting results, revising the manuscript, and approval of the final version. LDC was responsible for conceiving and designing the work interpreting results, revising the manuscript, and approval of the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The Veterans Affairs (VA) Institutional Review Boards at the Charlie Norwood VA Hospital, Augusta, Georgia [reference number 975087] and the Hines VA Hospital, Hines, Illinois [reference number 1000753] approved this study.

ADDITIONAL INFORMATION

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