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ORIGINAL ARTICLE

Risk factors for osteoporotic fractures in persons with spinal cord injuries and disorders

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Abstract
Summary Clinical risk factors for fracture were explored among Veterans with a spinal cord injury. At the end of 11 years of follow-up, the absolute risk of fracture was approximately 20 %. Among the clinical and SCI-related factors explored, a prior history of fracture was strongly associated with incident fracture.
Introduction Few studies to date have comprehensively addressed clinical risk factors for fracture in persons with spinal cord injury (SCI). The purpose of this study was to identify risk factors for incident osteoporotic fractures in persons with a SCI that can be easily determined at the point of care.
Methods The Veteran's Affairs Spinal Cord Dysfunction Registry, a national database of persons with a SCI, was used to examine clinical and SCI-related risk factors for fracture. Incident fractures were identified in a cohort of persons with chronic SCI, defined as SCI present for at least 2 years. Cox regression models were used to estimate the risk of incident fractures.
Results There were 22,516 persons with chronic SCI included in the cohort with 3365 incident fractures. The mean observational follow-up time for the overall sample was 6.2 years (median 6.0, IQR 2.9–11.0). The mean observational follow-up time for the fracture group was 3.9 years (median 3.3, IQR 1.4–6.1) and 6.7 years (median 6.7, IQR 3.1–11.0) for the nonfracture group. By the end of the study, which included predominantly older Veterans with a SCI observed for a relatively short period of time, the absolute (i.e., cumulative hazard) for incident fractures was 0.17 (95%CI 0.14–0.21). In multivariable analysis, factors associated with an increased risk of fracture included White race, traumatic etiology of SCI, paraplegia, complete extent of SCI, longer duration of SCI, use of anticonvulsants and opioids, prevalent fractures, and higher Charlson Comorbidity Indices. Women aged 50 and older were also at higher risk of sustaining an incident fracture at any time during the 11-year follow-up period.
Conclusions There are multiple clinical and SCI-related risk factors which can be used to predict fracture in persons with a

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SCI. Clinicians should be particularly concerned about incident fracture risk in persons with a SCI who have had a previous fracture.

Keywords Clinical · Comorbidities · Fractures · SCI-related · Spinal cord injury

Introduction

In the USA, between 225,000 and 296,000 persons are living with a Spinal Cord Injury/Disorder (SCI/D), and more than 25,000 receive their care within the Veterans Affairs health care system [1, 2]. Osteoporosis-related fractures are a serious problem for these persons, as they are associated with substantial morbidity [3] and increased mortality [4]. A major focus of SCI research [5–10] and clinical care [11] is on the prevention and management of these fractures.

Clinical risk factors for osteoporotic fractures have been well described for the general population of older women and men without SCI [12]. However, since the pathophysiology of bone loss following spinal cord injury differs markedly from that of age-related, postmenopausal, or even simple disuse osteoporosis [13], it is uncertain whether risk factors for fracture would be similar in these populations. Moreover, in persons with a SCI, there are likely additional risk factors for osteoporotic fracture related to the spinal lesion itself, such as the severity of neurological dysfunction. However, to date, there are very few studies which examine risk for fracture in persons with a SCI, and these reports are limited to small sample sizes [14–17], examine only a few potential risk factors for fracture [18–20], include cross-sectional or retrospective data only [14], and do not exam the risk for site-specific fractures [14, 15, 21].

Therefore, the purpose of this study was to identify risk factors for incident osteoporotic fractures in persons with a SCI. By study design, the risk factors assessed were ones that would be easily available to clinicians at point of care services for persons with a SCI.

Materials and methods

Participants

All persons included in the VA Spinal Cord Dysfunction (SCD) Registry from Fiscal Year (FY) 2002–2012 with a SCI of at least 2 years duration were eligible for the analyses. A duration of SCI of at least 2 years was chosen to define chronic SCI. However, there is continued loss of cortical bone of the lower extremities that occurs for years following the initial injury [15, 22, 23].

The SCD Registry is a clinical administrative database maintained by SCI/D Services at individual VA medical centers to track the population of Veterans with traumatic and nontraumatic SCI/D followed by each center, and these data are aggregated at a national level [2]. The date of onset of SCI was obtained from SCD Registry data; of those with date of onset missing, those with at least 2 years of documented SCI care were included. Those who had received a medication for osteoporosis including bisphosphonates, selective estrogen receptor modulators (SERMS), hormonal replacement therapy (estrogen or estrogen/progesterone), teriparatide, calcitonin, or denosumab ($n = 33$) during the time period of the study were excluded.

Clinical risk factors

The clinical risk factors selected a priori for consideration of their association with incident fractures were chosen based on prior reports of their association with osteoporotic fractures in (1) the general population, or (2) the SCI population, and (3) the availability of these factors through administrative datasets that could also be easily assessed at point of care practice. Accordingly, the following fracture predictors were examined: history of prevalent fractures (fractures that existed prior to study start) [24] including all upper extremity fractures (ICD-9 810–819), all lower extremity fractures (ICD-9 808, 820–828), and hip fractures (ICD-9 code 820); gender [25, 26]; age [27]; and race [28]. Any medication use including mineralocorticoids [29], oral glucocorticoids [30], proton pump inhibitors (PPIs) [31], antidepressants [32, 33], thiazolidinediones (TZDs) [34], anticonvulsants [35], opioids [36], benzodiazepines (BZDs) [37], thiazides [38], and thyroid replacement medication [39] was determined from the VA Managerial Cost Accounting (MCA, formally known as the Decision Support System) pharmacy data files. SCI-specific factors including duration, level (tetraplegia vs. paraplegia), extent (complete vs. incomplete), American Spinal Injury Association Impairment Scale (AIS), and etiology of injury (traumatic vs. nontraumatic) were included from VA SCD Registry Data, the Spinal Cord Injury and Disorders Outcomes Database (SCIDO), and the SAS Medical Datasets. Traumatic injury was defined by a previously reported algorithm [40]. Etiology of the SCI was examined as a potential risk factor for fracture based on a prior report that those with a traumatic SCI are at increased risk for fracture compared to those with multiple sclerosis [18].

All potential predictors except prevalent fractures, medication use, and variables contained in the Charlson Comorbidity Index were collected from FY2002 or at entry into the VA SCD Registry. Prevalent fractures were obtained from fiscal year 1998 (first date these were available from the databases) to study start. Medication use was collected as a time-

dependent covariate. The Charlson Comorbidity Index score [41] was calculated 1 year prior to study start.

Age [42] and gender [43] differences in clinical risk factors for some fractures exist in the general population without a SCI; therefore, interactions with age and gender on fracture risk were also explored.

Fracture definitions

Fractures were defined using *International Statistical Classification of Diseases*, *Clinical Modification*, *9th Revision* (ICD-9) codes for fractures of the upper (ICD-9 808, 810–819) and lower extremity (ICD-9 820–828); E-coded fractures [44] were also included. Fracture codes were obtained from the Corporate Data Warehouse (CDW) MedSAS datasets and included outpatient, inpatient, extended care, and fee for care services. The CDW obtains its information on patient care directly from VistA, the VA's electronic health record. There has been no comprehensive review of the accuracy of VA administrative databases for ascertainment of incident fractures in spinal cord-injured patients. However, using previous data [45], the authors determined that in only 6 of 163 (3.6 %) cases was fracture status misclassified by VA administrative records compared to the gold standard of chart reviews.

A fracture was considered incident (i.e., a new fracture that occurred during the study period) if there were no encounters with the same three-digit ICD-9 codes within a 120-day time period prior to the identified fracture. This definition of incident fracture was derived from a prior report which included over 7000 Veterans from the SCD Registry including those with traumatic and nontraumatic injury in which the authors determined that this 120-day time period defined incident fractures based on chart reviews, clinical knowledge of fracture healing, and general clinical follow-up patterns [18]. If there was more than one fracture during the study period, the first fracture was included in the primary assessment of clinical risk factors for osteoporotic fractures. If there was more than one fracture that occurred on the same day, that person was not included in the analyses. In the general population without a SCI, risk factors for fracture differ by site of fracture [46]; thus, fractures were stratified by location (upper vs. lower extremity). Finally, since lower extremity fractures of the femur, tibia/fibula, and hip are the most common fracture sites in persons with a SCI [47], risk fractures for these site-specific fracture sites were also determined.

Statistical analyses

Bivariate analyses of baseline characteristics for persons with and without an incident fracture were performed using chi-square tests (or Fisher's exact test) for categorical variables and ANOVA for continuous variables. Since injury severity (completeness) and AIS have interrelated definitions and are expected to be highly correlated, both were not included in the multivariable fracture prediction models. Completeness of injury and not AIS score was included because there was less missing data for extent of injury compared with AIS (17.5 vs. 59.4 %). Medication use was defined as a time-dependent covariate in 3-month intervals indicating whether the individual at any time during the 3 months was on the particular medication or not (1 = yes, 0 = no). Cox regression models were used to estimate the hazard ratio of incident fracture based on the potential predictors outlined above. The primary model estimated included separate indicators for preexisting hip fracture and preexisting nonhip fracture. A separate model was estimated post hoc which just included an indicator for any preexisting fracture and excluded indicators for preexisting hip fracture and preexisting nonhip fracture. Additionally, separate multivariable models were constructed for upper and lower extremity fractures and site-specific fractures of hip, femur, and tibia/fibula as there are differences in the epidemiology and treatment modalities based on fracture site [47]. All covariates were included in multivariable models regardless of statistical significance in univariate analysis because a priori all were thought to be of clinical significance. Data was missing for etiology of injury in 20.8 %, level of injury in 8.7 %, and extent of injury in 17.5 %. Multiple imputations were done for missing data on etiology of injury. For other missing data, a case-wise deletion was performed such that observations with missing data for a given attribute were not included in the analyses. The proportional hazards assumption was verified using Schoenfeld residuals for the model for each of the variables and their correlation with time, log (time), and time squared. The model outcome was time of first incident fracture, and censoring events were either initiation of osteoporotic pharmacologic therapy, death, or end of FY 2012, whichever came first. Interactions between age (less than 50 vs. 50 or older) and gender were explored.

In analyses predicting the time to (1) upper extremity, lower extremity and (2) hip, femur, tibia/fibula, Bonferonni corrections were applied to account for multiple testing. For these, a p value ≤ 0.025 (0.05/2) and 0.017 (0.05/3), respectively, was considered statistically significant. All analyses were done using SAS v9.3 and SAS Enterprise Guide v6.1.

Results

The study included 22,516 persons. The mean observational follow-up time for the overall sample was 6.2 years (median 6.0, IQR 2.9–11.0). The mean observational follow-up time for the fracture group was 3.9 (median 3.3, IQR 1.4–6.1) and 6.7 years (median 6.7, IQR 3.1–11.0) for the nonfracture group. The absolute (i.e., cumulative hazard) fracture risk at 1 year was 0.03 (95%CI 0.02–0.03), 5 years 0.09 (95%CI

0.07–0.16), 10 years 0.16 (95%CI 0.13–0.20), and at 11 years (end of study) was 0.17 (95%CI 0.14–.21).

Women were excluded from the analyses more frequently than men due to the use of osteoporosis medications (27.1 % of women vs. 10.3 % of men, $p < 0.01$). Of the persons included in the study, 15 % ($n = 3365$) had an incident fracture (Fig. 1). E-coded fractures represented 23.7 % of all fractures ($n = 796$). The sites of incident fracture are shown in Table 1. The majority of fractures were in the lower extremity ($n = 2696$, 80.1 %). The three most common sites of fracture included the tibia/fibula ($n = 867$, 25.8 %), femur ($n = 607$, 18.0 %), and the hip ($n = 421$, 12.5 %) (Table 1).

Baseline demographic and clinical characteristics of the study population by fracture status are presented in Table 2. Data was missing on etiology of injury in 20.8 %, level of injury in 8.7 %, extent of injury in 17.5 %, and AIS in 59.4 %. There were significant differences in fracture status by age, race, etiology, level, severity (completeness and AIS classification), duration of SCI, Charlson Comorbidity Index, and history of prevalent fracture. There was no significant difference in fracture status based on gender (Table 2). Approximately half of the cohort had a duration of year less than 10 years (44.43 %) and approximately one third were younger than age 50 (31.38 %).

Table 3 depicts univariate and multivariate predictors of incident fractures. In multivariable analysis, the factors that were associated with an increased risk of fracture at any given point in time included White race (HR 1.18, 95%CI [1.08, 1.29]); traumatic etiology of SCI (HR 1.16, 95%CI [1.04, 1.30]); paraplegia (HR 1.09, 95%CI [1.02,1.18])]; complete SCI (HR 1.34, 95%CI [1.24,1.45]); duration of injury (HR 1.01 (1.01,1.01), Charlson Comorbidity Index (HR 1.12, 95%CI [1.10, 1.14]); and use of anticonvulsants (HR 1.17, 95%CI [1.06, 1.28]) or opioids (HR 1.36, 95%CI [1.24, 1.49]). A history of a prevalent hip fracture 1 year prior (HR 4.08, 95%CI [1.54, 10.77]) or a prevalent nonhip fracture 1 year prior (HR 4.01, 95%CI [2.54, 6.33]) were highly predictive of incident fractures, particularly prevalent fractures occurring in closer temporal proximity to the incident fracture (Table 3). Alone, age and gender were not predictive of incident fracture; however, an interaction between gender and dichotomous age (≤50 years old) revealed that women age 50 and older were at significantly increased risk of incident fractures (HR 1.56, 95%CI [1.18, 2.06]) compared with older men.

Multivariable predictors of incident upper and lower extremity fractures are shown in Table 4. Positive predictors of both incident upper and lower extremity fractures included White race, history of prevalent fractures, higher Charlson Comorbidity Index, and use of opioids. Traumatic etiology of SCI, paraplegia, and complete SCI was associated with an increased risk of lower extremity fractures but a decreased risk of upper extremity fractures. Anticonvulsants increased the risk of lower, but not upper extremity fractures; hydrochlorothiazide decreased the risk of lower extremity fractures only. Longer duration of SCI was significantly associated with lower, but not upper extremity fractures. Age and gender were not associated with risk of upper extremity fractures; however, women aged 50 or older were at increased risk of lower extremity fractures.

Multivariable predictors of incident fracture were also examined for the three most frequent fracture sites (hip, femur, and tibia/fibula) and are shown in Table 5. A history of prevalent fractures, complete SCI, Charlson Comorbidity Index scores, and opioid use were all associated with an increased risk of incident fracture at each of these fracture sites. Traumatic etiology of SCI was associated with an increased risk of femur and tibia/fibula fractures, but not hip fractures. Factors associated with an increased risk of hip fractures included White race and use of BZDs. Paraplegia was

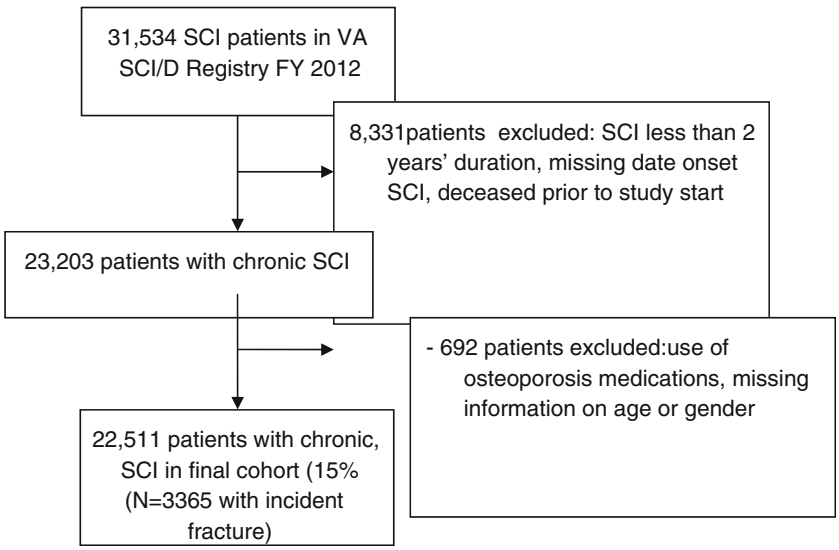

Fig. 1 Study population

Table 1 Sites of incident fractures

Fracture site	*n* (%)
Upper extremity	668 (19.8)
Scapula	13 (0.4)
Clavicle	80 (2.4)
Humerus	183 (5.4)
Forearm	115 (3.4)
Carpal	72 (2.1)
Metacarpal	84 (2.5)
Phalanges of Hand	115 (3.4)
Multiple Hand	5 (0.2)
Lower extremity	2697 (80.2)
Pelvis	73 (2.2)
Hip	421 (12.5)
Femur	607 (18.0)
Patella	29 (0.9)
Tibia/Fibula	868 (25.8)
Ankle	348 (10.3)
Tarsal/Metatarsal	203 (6.0)
Phalanges of Foot	148 (4.4)
All fractures	3365 (100.0)

associated with an increased risk for femur fractures. Women age 50 and older were at increased risk of tibia/fibula fractures, but the risk of hip and femur fractures was not elevated in women, regardless of age. Although hydrochlorothiazide was associated with a decreased risk of lower extremity fractures, when examining site-specific fractures, none of the associations met statistical significance. Longer duration of injury was associated with an increased risk for tibia/fibula and femur fractures, but not hip fractures.

Discussion

In persons with a SCI, multiple clinical and SCI-related factors easily elucidated at point of care including White race, more comorbidities, longer duration of injury, prior history of fractures, etiology (traumatic), level (paraplegia), and completeness of injury predicted incident fractures. Additionally, the use of anticonvulsants, opioids, and BZDs increased the risk for incident fractures, while the use of hydrochlorothiazide was protective against fractures of the lower extremity. Although clinical and SCI-related risk factors for fracture differed for upper and lower extremity fractures, and also among lower extremity fractures of the hip, femur, and tibia/fibula, a higher Charlson Comorbidity Index and the presence of prevalent fractures were common factors for all fractures.

Higher Charlson Comorbidity Indices and a history of a prevalent fracture were associated with increased risks for incident fracture at any of the locations examined (upper and lower extremity, hip, femur, and tibia/fibula). This is particularly important information for persons with a SCI, since higher Charlson Comorbidity Indices are also associated with increased mortality following fracture [4]. These findings are also in accord with previous reports suggesting a positive association between Charlson Comorbidity Index and fracture risk in persons without a SCI [48, 49]. Prevalent fractures, especially those occurring in temporal proximity to the incident fracture, were the strongest predictors of incident fracture in this cohort and were associated with an increased fracture risk at all fracture sites examined. This is in agreement with a previous study from the non-SCI population indicating that past fractures place persons at higher risk of future fractures [50]. It is noteworthy that, among prevalent hip fractures, the upper limit of the hazard ratio was as high as 10.8, suggesting that history of a prior hip fracture could be a particularly important predictor of future incident fractures in this population.

In persons with a SCI, among the demographic factors explored, only race (White) was associated with an increased risk of incident fracture. This is consistent with a previous report of fracture risk for femur fractures by race in persons without a SCI [51]. The lack of an overall age association with fracture risk is in agreement with other reports that older age is not a significant risk factor for fractures in persons with a SCI [18, 52]. In contrast, in a prior small study of men ($n=120$) with mostly traumatic SCI (91 %), fracture incidence increased in successively older age groups [53]. Our study differs from the previous report [53] in the larger sample size and fewer persons with a traumatic etiology of SCI. In our study, however, there was a significant interaction of age with gender, such that older women were at increased risk for fractures. Our findings suggest that although both younger and older individuals with a SCI are at risk for fracture, older women are at particular risk. In agreement with other reports, [16, 18], longer duration of injury was a significant risk factor for fracture. Although gender did not predict incident fracture risk, women aged 50 and older had an increased risk of incident fracture, particularly for the tibia/fibula site. Prior studies have found mixed results for gender and fracture risk in SCI [48–50, 54]. Surprisingly, female gender was not associated with an increased risk of hip fracture, regardless of age. This is in contrast to hip fracture risk in persons without a SCI, in which there is a strong female predisposition [55]. Substantially more women were excluded from the current analyses because of medication use for osteoporosis, which may have removed the women at highest risk of hip fracture. This also suggests that clinicians may already perceive women with a SCI to be at higher risk for fracture.

A number of SCI-related factors predicted incident fractures including traumatic etiology of the SCI, complete extent of SCI and paraplegia. That traumatic etiology of SCI is an important predictor of incident lower extremity fractures is in accord with a previous report [18] but extends these findings

Table 2 Baseline characteristics of persons by fracture status

Characteristic		Fracture status		
	Total ($n = 22,516$)	Incident fracture ($n = 3365$)	No incident fracture ($n = 19,151$)	p value[a]
Age (years), mean ± SD		54.0 ± 12.3	56.2 ± 13.1	<0.0001
Gender, *n* (%)				0.61
Male	21,758 (96.6)	3246 (14.9)	18,512 (85.1)	
Female	758 (3.4)	119 (15.7)	639 (84.3)	
Race, *n* (%)				<0.0001
White	17,347 (77.0)	2701 (15.6)	14,646 (84.4)	
Black	4550 (20.2)	578 (12.7)	3972 (87.3)	
Other	619 (2.7)	86 (13.9)	533 (86.1)	
Etiology of injury, *n* (%)				<0.0001
Traumatic	13,848 (61.5)	2214 (16.0)	11,634 (84.0)	
Nontraumatic	3979 (17.7)	417 (10.5)	3562 (89.5)	
Missing	4689 (20.8)	734 (15.6)	3955 (84.3)	
Level of injury, *n* (%)				<0.0001
Paraplegia	9530 (42.3)	1264 (13.3)	8266 (86.7)	
Tetraplegia	11,027 (49.0)	1857 (16.8)	9170 (83.2)	
Missing	1959 (8.7)	244 (12.5)	1715 (87.5)	
Extent of injury, *n* (%)				<0.0001
Complete	7446 (33.1)	1421 (19.1)	6025 (80.9)	
Incomplete	11,138 (49.5)	1521 (13.7)	9617 (86.3)	
Missing	3932 (17.5)	423 (10.8)	3509 (89.2)	
AIS scale, *n* (%)				<0.0001
A	3653 (16.2)	793 (21.7)	2860 (78.3)	
B	1039 (4.6)	164 (15.8)	875 (84.2)	
C	1306 (5.8)	199 (15.2)	1107 (84.8)	
D	3131 (13.9)	409 (13.1)	2722 (86.9)	
Missing	13,387 (59.4)	1800 (13.4)	11,587 (86.5)	
Duration of injury (years), mean ± SD		18.4 ± 13.9	15.6 ± 14.3	<0.0001
Charlson Comorbidity Index,[b] mean ± SD		0.76 ± 1.35	0.82 ± 1.51	0.02
History of prevalent Fx, *n* (%)				<0.0001
Yes	1263 (5.6)	412 (12.2)	851 (4.4)	
No	21,253 (94.4)	2953 (87.8)	18,300 (95.6)	

[a] ANOVA for continuous variables, chi-square/Fisher's exact test for categorical variables

[b] Does not include index component for paraplegia/tetraplegia

to suggest that among lower extremity fractures, traumatic etiology of SCI is a predictor for femur and tibia/fibula fractures but not hip fractures. In accord with a previous study, traumatic etiology of SCI did not predict upper extremity fractures [18]. Similarly, complete SCI was associated with an increased risk of lower extremity fractures, including site-specific fractures of the hip, femur, and tibia/fibula, supporting several prior studies [16, 18, 56]. The association between paraplegia and increased risk of incident lower extremity fractures [14, 21, 57] with a higher risk for upper extremity fractures in those with tetraplegia [58] is in accord with prior studies. The reasons for the decreased risk for upper extremity fractures in persons with paraplegia are not known; however, this is not likely secondary to higher BMD from differences in physical activity between those with paraplegia and tetraplegia. In support of this in a study including eight pairs of identical twins, discordant for chronic SCI, it was the lower extremities and the pelvis and not the upper extremities that had significantly lower BMD in the twin with SCI, suggesting that BMD is not increased due to upper body weight-bearing exercise [59]. In agreement with several prior reports [15, 52], longer

Table 3 Univariate and multivariable predictors of incident fractures (statistically significant HRs in bold)

Characteristic	Hazard ratios (95%CI)	
	Univariate model	Multivariable model[a]
Age (years)	1.00 (1.00,1.00)	1.00 (0.99,1.00)
Gender		
Women	Referent	Referent
Men	0.92 (0.77,1.10)	0.87 (0.72,1.05)
Race		
Black	Referent	Referent
White	**1.24 (1.13,1.35)**	**1.18 (1.08,1.29)**
Other	1.08 (0.86,1.35)	1.11 (0.88,1.39)
History of prevalent fx		
Within 365 days of study start	**4.54 (2.96,6.97)**	**4.51 (2.93,6.92)**
Within 730 days of study start	**3.73 (3.04,4.57)**	**3.49 (2.85,4.29)**
Within 1095 days of study start	**3.06 (2.71,3.45)**	**2.70 (2.39,3.05)**
History of prevalent hip fx		
Within 365 days of study start	**4.24 (1.61,11.20)**	**4.08 (1.54,10.77)**
Within 730 days of study start	**2.98 (1.87,4.75)**	**2.92 (1.83,4.66)**
Within 1095 days of study start	**2.10 (1.61,2.73)**	**2.09 (1.61,2.72)**
History of prevalent nonhip fx		
Within 365 days of study start	**4.24 (2.70,6.69)**	**4.01 (2.54,6.33)**
Within 730 days of study start	**3.45 (2.78,4.28)**	**3.17 (2.55,3.94)**
Within 1095 days of study start	**2.80 (2.46,3.19)**	**2.51 (2.20,2.86)**
Etiology of injury		
Nontraumatic	Referent	Referent
Traumatic	**1.30 (1.17,1.45)**	**1.16 (1.04,1.30)**
Missing	**1.24 (1.10,1.40)**	**1.33 (1.17,1.51)**
Level of injury		
Tetraplegia	Referent	Referent
Paraplegia	**1.20 (1.12,1.29)**	**1.09 (1.02,1.18)**
Missing	**0.86 (0.75,0.99)**	0.97 (0.83,1.12)
Extent of injury		
Incomplete	Referent	Referent
Complete	**1.39 (1.30,1.50)**	**1.34 (1.24,1.45)**
Missing	**0.83 (0.75,0.93)**	**0.82 (0.73,0.92)**
Duration of injury (years)	**1.01 (1.01,1.01)**	**1.01 (1.01,1.01)**
Charlson Comorbidity Index Scores	**1.12 (1.10,1.14)**	**1.12 (1.10,1.14)**
Medication use		
PPI	**1.31 (1.20,1.44)**	1.11 (1.00,1.22)
Glucocorticoids	1.04 (0.80,1.37)	0.82 (0.63,1.08)
Mineralocorticoids	1.06 (0.71,1.57)	0.91 (0.61,1.36)
Hydrochlorothiazide	1.06 (0.97,1.17)	0.90 (0.81,1.00)
Thiazolidinediones	1.01 (0.69,1.46)	0.82 (0.56,1.19)
Thyroid medications	1.17 (0.98,1.40)	1.03 (0.86,1.24)
Anticonvulsants	**1.29 (1.18,1.40)**	**1.17 (1.06,1.28)**
Opioids	**1.51 (1.39,1.63)**	**1.36 (1.24,1.49)**
Benzodiazepines	**1.32 (1.20,1.45)**	1.06 (0.96,1.17)
TCA	**1.24 (1.09,1.41)**	1.08 (0.94,1.23)
SNRI	**1.20 (1.05,1.37)**	0.99 (0.86,1.14)
SSRI	**1.24 (1.12,1.37)**	1.06 (0.95,1.18)

[a] Adjusted for age, gender, race, etiology, level, extent and duration of injury, Charlson Comorbidity Index, medication use and prevalent hip, and prevalent nonhip fracture (hazard ratio estimates for any prevalent fracture obtained from a separate model excluding prevalent hip and prevalent nonhip fracture)

duration of SCI was associated with an increased risk of fracture.

Similar to previous reports, in this cohort, medications including anticonvulsants [60], opioids [19], and BZDs [37] were associated with an increased rate of fracture, while hydrochlorothiazide was associated with a decreased rate of lower extremity fracture [38]. Use of antidepressants [32, 33], PPIs [31], TZDs [34], and thyroid replacement medications [39], while shown to affect fracture risk in persons without a SCI, does not appear to significantly alter fracture risk in the SCI population.

This study has several strengths. First, this is largest and most comprehensive examination of clinical risk factors for fractures in the SCI population to date, including over 22,000 persons. Second, risk factors for upper and lower extremity fractures, as well as site-specific fractures of the lower extremity (hip, femur, and tibia/fibula), were explored.

Table 4 Multivariable predictors of incident upper and lower extremity fractures

Characteristic	Hazard ratios (95%CI)	
	Upper extremity($n = 668$)	Lower extremity ($n = 2697$)
Gender (age < 50)		
Men	Referent	Referent
Women	1.01 (0.62,1.64)	0.93 (0.70,1.24)
Gender (age ≥ 50)		
Men	Referent	Referent
Women	1.68 (0.94,2.99)	**1.54 (1.12,2.11)**
Race (*n*)		
Black	Referent	Referent
White	**1.23 (1.00,1.50)**	**1.17 (1.06,1.30)**
Other	1.51 (0.96,2.39)	1.03 (0.79,1.34)
History of prevalent fx		
Within 365 days of study start	**6.50 (2.79,15.19)**	**4.06 (2.47,6.69)**
Within 730 days of study start	**4.09 (2.75,6.08)**	**3.32 (2.61,4.22)**
Within 1095 days of study start	**2.58 (1.91,3.48)**	**2.71 (2.38,3.10)**
Etiology of injury		
Nontraumatic	Referent	Referent
Traumatic	1.03 (0.82,1.30)	**1.22 (1.07,1.39)**
Missing	**1.33 (1.03,1.73)**	**1.35 (1.17,1.56)**
Level of injury		
Tetraplegia	Referent	Referent
Paraplegia	**0.68 (0.58,0.80)**	**1.23 (1.13,1.34)**
Missing	0.91 (0.68,1.20)	0.97 (0.81,1.15)
Extent of injury		
Incomplete	Referent	Referent
Complete	**0.73 (0.61,0.89)**	**1.52 (1.40,1.66)**
Missing	0.87 (0.68,1.10)	**0.80 (0.70,0.92)**
Duration of injury (years)	1.00 (0.99,1.01)	**1.01 (1.01,1.01)**
Charlson Comorbidity Index	**1.12 (1.08,1.17)**	**1.12 (1.10,1.14)**
Medication use		
PPI	1.19 (0.95,1.49)	1.08 (0.97,1.21)
Glucocorticoids	0.71 (0.38,1.33)	0.87 (0.64,1.18)
Mineralocorticoids	1.21 (0.57,2.56)	0.83 (0.52,1.32)
Hydrochlorothiazide	0.96 (0.76,1.21)	**0.88 (0.78,0.99)**
Thiazolidinediones	0.74 (0.31,1.81)	0.83 (0.55,1.25)
Thyroid medications	1.08 (0.73,1.60)	1.00 (0.82,1.24)
Anticonvulsants	1.11 (0.90,1.37)	**1.18 (1.06,1.31)**
Opioids	**1.52 (1.23,1.87)**	**1.32 (1.18,1.46)**
Benzodiazepines	0.85 (0.67,1.07)	**1.12 (1.00,1.25)**
TCA	1.08 (0.81,1.45)	1.08 (0.93,1.26)
SNRI	1.06 (0.79,1.42)	0.97 (0.83,1.13)
SSRI	1.10 (0.87,1.38)	1.05 (0.93,1.18)

Values in bold were statistically significant

There are also several limitations to this study. The SCD Registry has limitations. As designed, patients were to be entered into the Registry when they began receiving care for SCI at the VA, and this information was supposed to be updated with changes for the registrants. However, this did not uniformly happen, particularly if patients were not seen at a VA SCI Center. As it exists, it is a registry list of persons who have SCI/D in the VA [2]. The analyses were restricted to factors which

Table 5 Multivariable predictors of incident hip, femur, and tibia/fibula fractures

Characteristic	Hazard ratios (95%CI)		
	Hip ($n = 421$)	Femur ($n = 607$)	Tibia/fibula ($n = 868$)
Gender (age < 50)			
Men	Referent		
Women	0.39 (0.12,1.24)	0.82 (0.42,1.60)	1.04 (0.63,1.73)
Gender (age ≥ 50)			
Men	Referent		
Women	0.41 (0.10,1.66)	1.43 (0.67,3.03)	**2.09 (1.25,3.51)**
Race			
Black	Referent		
White	**1.34 (1.03,1.76)**	1.15 (0.93,1.44)	1.09 (0.91,1.30)
Other	1.72 (0.96,3.07)	0.71 (0.37,1.36)	0.94 (0.59,1.50)
History of prevalent fx			
Within 365 days of incident fx	3.28 (0.95,11.28)	**7.11 (2.47,20.43)**	**2.37 (0.89,6.35)**
Within 730 days of incident fx	**3.11 (1.71,5.64)**	**4.70 (2.81,7.85)**	**2.67 (1.65,4.31)**
Within 1095 days of incident fx	**2.95 (2.11,4.12)**	**3.11 (2.41,3.99)**	**3.00 (2.41,3.73)**
Etiology of injury			
Nontraumatic	Referent		
Traumatic	0.82 (0.62,1.09)	**1.54 (1.14,2.10)**	**1.58 (1.23,2.04)**
Missing	1.09 (0.79,1.50)	1.37 (0.96,1.95)	**1.71 (1.28,2.28)**
Level of injury			
Tetraplegia	Referent		
Paraplegia	1.22 (0.98,1.51)	**1.42 (1.19,1.70)**	1.08 (0.94,1.25)
Missing	1.25 (0.85,1.85)	0.77 (0.50,1.20)	**0.58 (0.40,0.84)**
Extent of injury			
Incomplete	Referent		
Complete	**1.34 (1.07,1.67)**	**2.35 (1.95,2.84)**	**2.03 (1.75,2.37)**
Missing	0.86 (0.62,1.19)	1.07 (0.79,1.46)	0.85 (0.66,1.11)
Duration of injury (years)	1.01 (1.00,1.02)	**1.01 (1.00,1.02)**	**1.01 (1.01,1.02)**
Charlson Comorbidity Index	**1.21 (1.16,1.26)**	**1.09 (1.04,1.14)**	**1.08 (1.03,1.12)**
Medication use			
PPI	0.91 (0.68,1.22)	1.24 (0.97,1.58)	1.11 (0.91,1.35)
Glucocorticoids	0.85 (0.42,1.72)	0.88 (0.45,1.72)	0.59 (0.31,1.15)
Mineralocorticoids	1.18 (0.48,2.87)	0.71 (0.23,2.23)	0.78 (0.32,1.88)
Hydrochlorothiazide	0.94 (0.71,1.25)	0.77 (0.59,1.00)	0.90 (0.73,1.11)
Thiazolidinediones	0.19 (0.03,1.36)	0.88 (0.36,2.14)	0.59 (0.24,1.42)
Thyroid medications	1.00 (0.60,1.67)	1.12 (0.72,1.75)	1.00 (0.68,1.46)
Anticonvulsants	0.97 (0.74,1.28)	1.05 (0.82,1.34)	1.15 (0.94,1.39)
Opioids	**1.50 (1.16,1.95)**	**1.50 (1.19,1.88)**	**1.28 (1.06,1.54)**
Benzodiazepines	**1.40 (1.07,1.83)**	1.09 (0.86,1.38)	1.07 (0.88,1.29)
TCA	1.25 (0.87,1.79)	1.21 (0.88,1.66)	0.81 (0.60,1.10)
SNRI	0.67 (0.43,1.04)	1.01 (0.72,1.42)	1.17 (0.90,1.53)
SSRI	1.10 (0.82,1.48)	1.09 (0.84,1.42)	1.03 (0.83,1.28)

Values in bold were statistically significant

were collected in the databases; therefore, all clinical risk factors for fracture could not be examined. This limitation may be of particular concern for women, as age at menopause is a putative risk factor for osteoporosis and was not available in these datasets [61]. Other potential important risk factors including height, weight, body mass index, and lifestyle factors such as smoking and alcohol use [62], and vitamin D levels [63] were not available in these datasets. Doses of medications were

not examined. Additionally, data was missing for etiology of injury in 20.8 % of persons, level of injury in 8.7 %, and extent of injury in 17.5 %. The one variable that may not have been missing at random is etiology of injury (traumatic vs. nontraumatic) since Veterans with a traumatic SCI may have been more likely to receive care from a SCI Center than those with a nontraumatic SCI. The SCI/D System of Care is a "Hub and Spoke" system. Comprehensive care for patients with a SCI is provided at SCI Centers (Hubs) that have interdisciplinary SCI care teams and are most often located within large VA medical centers. SCI Spokes are located at other VA medical centers that have dedicated SCI primary care teams [64]. However, to overcome this limitation, we imputed those with a "missing etiology of injury" as traumatic and then nontraumatic and this did not significantly change the findings. AIS information was also missing in 59.4 % of persons as the SCD Registry did not systematically collect AIS scores, and therefore and was not included in the analyses. In the new SCIDO Registry, AIS scores are being collected and will be useful in further analyses. Radiographic confirmation of all fractures was not available. The study included only 763 females. Vertebral fractures were not examined, and risk factors for these fractures may be different than those for appendicular fractures [46]. Detailed studies of the epidemiology of vertebral fractures in SCI are lacking although it appears that DXA measurements may overestimate BMD in persons with a SCI [65]. Fracture etiology was unknown and all fractures were included. E-coded fractures for falls were particularly common, accounting for 25 % of the E-coded fractures. Fracture sites including, for example, the femur did not include details on specific locations within that site (i. distal, vs. midshaft area) which have different proportions of cortical vs. trabecular bone. This is important because the efficacy of pharmacological treatments for osteoporosis in persons with a SCI may differ for sites enriched in cortical vs. trabecular bone. Radiographic verification of ICD-9 codes for fractures was not done. Finally, more than one third of Veterans with a SCI utilizing VA services are also recipients of services under Medicare and/or Medicaid [66], and Medicare and Medicaid data were not included.

In conclusion, there are multiple and easily ascertained clinical and SCI-related risk factors that predict fractures in persons with a SCI. In particular, clinicians should be aware of the pivotal role of prior fractures as a key determinant of future fractures in persons with a SCI.

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Compliance with ethical standards

Conflicts of interest No disclosures.

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