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Risk of adverse cardiovascular events following spinal cord injury in patients with osteoporosis: Real-world evidence

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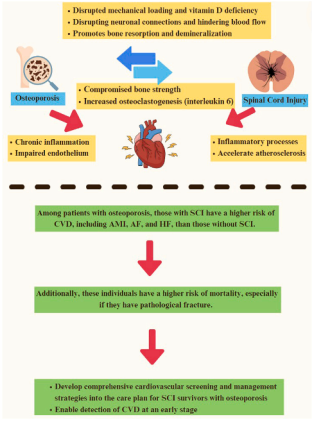
GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: Spinal cord injury (SCI) is associated with increased cardiovascular risks, and cardiovascular disease (CVD) remains a leading cause of death for individuals with SCI. Osteoporosis, a condition associated with SCI, has been linked to CVD. However, the cardiovascular risk profile of individuals with SCI with osteoporosis remains unclear.

Methods: We conducted a retrospective cohort study by using data from the TriNetX Research Network. We included adults with osteoporosis with or without a diagnosis of SCI between 2015 and 2020: case (SCI group, $N = 7{,}308$) and control (non-SCI group, $N = 843{,}235$) cohorts. Propensity score matching was performed to balance baseline characteristics between the cohorts ($N = 7{,}296$ in each group). A Cox regression model was

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employed to estimate the hazard ratio (HR) for the primary outcomes: the development of acute myocardial infarction (AMI), atrial fibrillation (AF), or heart failure (HF).
Results: Individuals with SCI with osteoporosis have a significantly higher risk of cardiovascular events (HR: 1.15, 95 % confidence interval [CI]: 1.08–1.22)—including AMI (HR: 1.17 95 % CI: 1.02–1.33), AF (HR: 1.14, 95 % CI: 1.04–1.24), and HF (HR: 1.14, 95 % CI: 1.05–1.24)—than do those without SCI. Furthermore, mortality risk is higher in individuals with SCI, particularly those with pathological fracture. Subgroup analyses based on sex and age supported these findings.
Conclusion: The complex interplay between SCI, osteoporosis, and cardiovascular health underscores the requirement for comprehensive management strategies for individuals with SCI who also have osteoporosis.

1. Introduction

Spinal cord injury (SCI) is a complex condition with lasting functional, psychological, and socioeconomic effects [1]. Although notable advancements have been made in the prompt management of conditions such as renal failure and pneumonia following SCI, cardiovascular complications remain a leading cause of mortality for individuals with SCI [2]. Several studies have demonstrated that cardiovascular morbidities, particularly coronary artery disease, are prevalent in individuals with SCI, in whom they also manifest earlier and progress more rapidly than in the general population [3–5]. In addition, a recent large-scale database study conducted in Korea by Yoo et al. revealed that SCI survivors face significantly elevated risks of acute myocardial infarction (AMI), heart failure (HF), and atrial fibrillation (AF) [6].

The heightened cardiovascular risks in chronic SCI stem from metabolic disturbances like insulin resistance, dyslipidemia, and hypertension, which create an atherogenic profile [7]. SCI-induced changes in body composition, such as reduced muscle mass and increased fat, along with immobilization, worsen these issues and promote cardiovascular disease (CVD) [8]. Autonomic dysfunction in chronic SCI patients further raises risks by impairing blood pressure and heart rate regulation, leading to hypertension and cardiovascular events [9,10]. Yoo et al. reported that severely disabled SCI patients face significantly higher risks—3.74 times for AMI, 3.96 times for HF, and 3.32 times for AF [6]—highlighting how reduced physical activity impairs vascular and endothelial function, key factors in atherosclerosis. Moreover, immobility-related osteoporosis[11], hormonal imbalances of hypogonadism and low circulating levels of insulin-like growth factor 1 [12,13], and thyroid dysfunction [14,15] in chronic SCI patients might exacerbate these risks.

Beyond the aforementioned factors, individuals with SCI experience accelerated bone loss compared to those without, which is characterized by compromised bone strength and increased fracture risk [16,17]. Post-injury, patients exhibit significant bone mass reduction, especially below the injury site, with the iliac bones and metaphyseal regions of long bones being particularly vulnerable. Approximately six weeks after injury, a notable increase in urinary calcium and hydroxyproline levels indicates heightened bone resorption. This accelerated bone loss may be attributed to paraplegia-induced localized expansion of bone marrow progenitors capable of forming osteoclast-like cells, potentially driven by elevated interleukin 6 production below the injury level [18,19]. SCI also affects the sympathetic nervous system, disrupting neuronal connections and hindering blood flow, which promotes bone resorption and demineralization [20]. Furthermore, several studies have established a connection between osteoporosis and coronary artery disease [21–23].

Patients with osteoporosis, especially those at high risk for fragility fractures, face significantly higher rates of major adverse cardiovascular events (MACE), including AMI and CVD-related mortality. A UK study found fragility fractures greatly increase MACE risk compared to osteoporosis alone or anti-osteoporosis treatment [24]. Similarly, U.S. data from the National Health and Nutrition Examination Survey shows an inverse relationship between femoral bone mineral density and CVD risk, with osteoporosis doubling the risk compared to normal bone mass [25]. In postmenopausal women, osteoporosis severity is strongly linked to cardiovascular risk, with a 3.9-fold higher risk of events, while vertebral fractures triple this risk [26]. In both osteoporosis and CVD conditions, endothelial dysfunction serves as a precursor, worsened by elevated levels of non-inflammatory and inflammatory factors and by high concentrations of nitric oxide, which adversely affect bone metabolism [20]. Additionally, chronic inflammation may be responsible for age-related bone loss and CVD [27–29].

These findings highlight the need to understand the shared mechanisms between osteoporosis and SCI to develop effective prevention and treatment strategies. However, the specific cardiovascular risk profile of individuals with SCI who also have osteoporosis remains poorly understood. Using a large real-world dataset, the present study investigated the risk of AMI, AF, and HF in individuals with osteoporosis with SCI compared with matched controls without SCI to provide insights into the cardiovascular health of individuals with SCI and osteoporosis.

2. Materials and methods

2.1. Study design and database

The present study adopted a retrospective cohort design. Data were obtained from the US Collaborative Network of the TriNetX Research Network, a database comprising 64 health-care organizations with deidentified electronic health records on over 73 million patients [11]. This network offers a diverse dataset, including demographic information, diagnostic codes from the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), procedure codes from the *International Classification of Diseases, Tenth Revision, Procedure Coding System* (*ICD-10-PCS*), Current Procedural Terminology medication codes from the Veterans' Affairs National Formulary (VA), laboratory tests from the Logical Observation Identifiers Names and Codes and TriNetX Curated values (TNX Curated), genetic data from the Human Genome Variation Society, and health-care utilization details. The health-care organizations in the network range from hospitals to primary care and specialty clinics and provide data from insured and uninsured patients. Additional information regarding TriNetX is available at (https://trinetx.com). The data used in this study were collected on December 18th, 2024.

2.2. Statement of ethics

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable laws and regulations for non-interventional and observational studies. Data de-identification is formally attested as per section §164.514(b)(1) of the Health Insurance Portability and Accountability Act Privacy Rule. The requirement for informed consent was waived because of the anonymized nature of the data and the retrospective nature of this study. Additionally, the use of TriNetX in the current study was approved by the Institutional Review Board of the Shin Kong Wu Ho-Su Memorial Hospital (IRB: 20240904R).

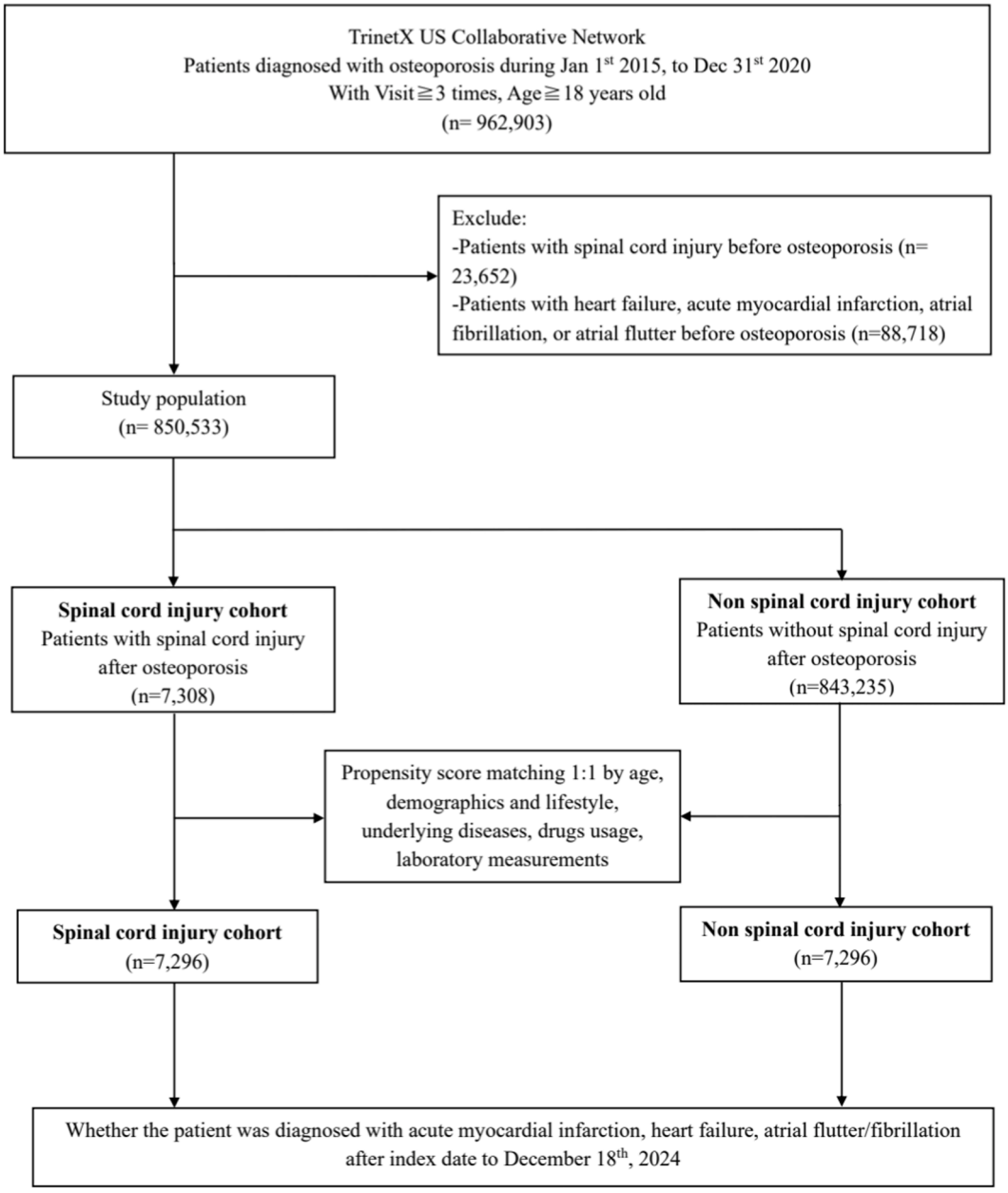

Fig. 1. Flowchart of cohort construction.

2.3. Study design and population

Fig. 1 illustrates the study design. Adult patients (≥18 years old) with at least three healthcare visits who were diagnosed with osteoporosis between January 1, 2015, and December 31, 2020, were included in the study (N = 962,903). Patients with spinal cord injury (SCI) before osteoporosis diagnosis (N = 23,652) or with heart failure (HF), acute myocardial infarction (AMI), atrial fibrillation (AF), or atrial flutter before osteoporosis diagnosis (N = 88,718) were excluded, resulting in a study population of 850,533 patients.

The remaining patients were divided into two cohorts. Patients who developed SCI after osteoporosis diagnosis were classified as the SCI cohort (N = 7308), and patients who did not develop SCI after osteoporosis diagnosis were classified as the non-SCI cohort (N = 843,235).

Propensity score matching was performed in a 1:1 ratio based on age, demographics, lifestyle factors, underlying diseases, drug usage, and laboratory measurements, resulting in two matched cohorts of 7296 patients each. The cohort creation process is illustrated in **eMethod** in the supplementary file.

2.4. Covariates

Baseline characteristics before the index date were assessed. We adjusted for the covariates of age, sex, race (white, African American, Hispanic, and Asian), tobacco usage, alcohol usage, underlying conditions, drug usage, and laboratory measurements. The underlying conditions examined were hypertensive diseases; hyperlipidemia; type 2 diabetes mellitus; chronic kidney disease; depressive episodes; fracture of thoracic vertebra; fracture of lumbar vertebra; fracture of cervical vertebra; fracture of hip; gastro-esophageal reflux disease; urinary tract infection; pneumonia; disorders of the thyroid gland; acute embolism and thrombosis of deep veins; pressure ulcer; cirrhosis of liver; and neurogenic bowel.

Also assessed was the use of blood glucose regulation agents, insulin, antiarrhythmics, anticoagulants, thrombolytics, platelet aggregation inhibitors, beta blockers, diuretics, calcium channel blockers, agents

Table 1
Baseline characteristics of study subjects before and after propensity score matching.

	Before matching			After matching		
	Patients with SCI after Osteoporosis (N = 7,308)	Patients without SCI after Osteoporosis (N = 804,923)	SMD	Patients with SCI after Osteoporosis (N = 7,296)	Patients without SCI after Osteoporosis (N = 7,296)	SMD
Age at index (Mean ± SD)	67.30 ± 10.74	66.53 ± 10.40	0.07	67.32 ± 10.72	67.40 ± 10.86	0.01
Demographics and lifestyle, *n* (%)						
Female	5,448 (74.6)	669,946 (83.2)	0.21	5,444 (74.6)	5,453 (74.7)	0.01
Male	1,443 (19.8)	82,826 (10.3)	0.27	1,435 (19.7)	1,418 (19.4)	0.01
White	5,311 (72.7)	578,477 (71.9)	0.02	5,301 (72.7)	5,317 (72.9)	0.00
African American	708 (9.7)	54,221 (6.7)	0.11	706 (9.7)	681 (9.3)	0.01
Hispanic or Latino	422 (5.8)	45,251 (5.6)	0.01	422 (5.8)	439 (6.0)	0.01
Asian	191 (2.6)	30,287 (3.8)	0.07	191 (2.6)	182 (2.5)	0.01
Tobacco use	506 (6.9)	16,812 (2.1)	0.23	501 (6.9)	437 (6.0)	0.04
Alcohol use	82 (1.1)	2,503 (<0.1)	0.10	82 (1.1)	86 (1.2)	0.01
Underlying disease, *n* (%)						
Hypertensive diseases	4,909 (67.2)	308,908 (38.4)	0.60	4,899 (67.2)	5,032 (69.0)	0.04
Hyperlipidemia	3,692 (50.5)	236,079 (29.3)	0.44	3,685 (50.5)	3,770 (51.7)	0.02
Diabetes mellitus	1,936 (26.5)	109,494 (13.6)	0.33	1,931 (26.5)	2,001 (27.4)	0.02
Chronic kidney disease	1,084 (14.8)	45,069 (5.6)	0.31	1,081 (14.8)	1,090 (14.9)	0.00
Depressive episode	2,714 (37.1)	113,450 (14.1)	0.55	2,703 (37.1)	2,762 (37.9)	0.02
Liver cirrhosis	191 (2.6)	9,885 (1.2)	0.10	190 (2.6)	199 (2.7)	0.01
Urinary retention	816 (11.2)	16,040 (2.0)	0.38	809 (11.1)	739 (10.1)	0.03
Urinary tract infection	2,242 (30.7)	102,270 (12.7)	0.45	2,233 (30.6)	2,211 (30.3)	0.01
Deep vein thrombosis	414 (5.7)	11,712 (1.5)	0.23	409 (5.6)	372 (5.1)	0.02
Pressure ulcer	356 (4.9)	5,332 (0.7)	0.26	348 (4.8)	302 (4.1)	0.03
Neurogenic bowel	199 (2.7)	1,117 (0.1)	0.22	190 (2.6)	140 (1.9)	0.05
Gastro-esophageal reflux disease	3,534 (48.4)	181,695 (22.6)	0.56	3,528 (48.4)	3,548 (48.6)	0.01
Disorders of thyroid gland	2,637 (36.1)	174,931 (21.7)	0.32	2,633 (36.1)	2,772 (38.0)	0.04
Hip fracture	500 (6.8)	18,952 (2.4)	0.22	500 (6.9)	463 (6.4)	0.02
Cervical vertebrae fracture	633 (8.7)	13,665 (1.7)	0.32	625 (8.6)	613 (8.4)	0.01
Thoracic vertebrae fracture	792 (10.8)	14,831 (1.8)	0.38	783 (10.7)	737 (10.1)	0.02
Lumbar vertebrae fracture	797 (10.9)	16,088 (2.0)	0.37	788 (10.8)	754 (10.3)	0.02
Drugs usage, *n* (%)						
Blood glucose regulation agents	2,790 (38.2)	133,009 (16.5)	0.50	2,781 (38.1)	2,828 (38.8)	0.01
Insulin	1,386 (19.0)	51,533 (6.4)	0.38	1,381 (18.9)	1,401 (19.2)	0.01
Antiarrhythmics	4,508 (61.7)	201,372 (25.0)	0.80	4,496 (61.6)	4,559 (62.5)	0.02
Anticoagulants	3,424 (46.9)	131,091 (16.3)	0.70	3,412 (46.8)	3,430 (47.0)	0.00
Thrombolytics	361 (4.9)	7,274 (0.9)	0.24	358 (4.9)	317 (4.4)	0.03
Platelet aggregation inhibitors	2,884 (39.5)	152,179 (18.9)	0.46	2,876 (39.4)	2,944 (40.4)	0.02
ACEI/ARB	2,840 (38.9)	169,955 (21.1)	0.39	2,836 (38.9)	2,903 (39.8)	0.02
Beta blockers/related	3,095 (42.4)	156,133 (19.4)	0.51	3,085 (42.3)	3,134 (43.0)	0.01
Calcium channel blockers	2,126 (29.1)	109,697 (13.6)	0.38	2,122 (29.1)	2,174 (29.8)	0.02
Diuretics	2,888 (39.5)	154,928 (19.3)	0.46	2,878 (39.4)	2,906 (39.8)	0.01
Calcium	3,896 (53.3)	198,969 (24.7)	0.61	3,884 (53.2)	3,941 (54.0)	0.02
Lipid modifying agents	3,310 (45.3)	214,678 (26.7)	0.40	3,304 (45.3)	3,400 (46.6)	0.03
NSAID	2,014 (27.6)	104,263 (13.0)	0.37	2,008 (27.5)	2,039 (28.0)	0.01
Alendronate	1,451 (19.9)	82,376 (10.2)	0.27	1,446 (19.8)	1,418 (19.4)	0.01
Romosozumab	10 (0.1)	24 (<0.1)	0.05	10 (0.1)	10 (0.1)	0.00
Denosumab	590 (8.1)	13,792 (1.7)	0.30	584 (8.0)	554 (7.6)	0.02
Vitamin D	3,313 (45.3)	178,141 (22.1)	0.51	3,304 (45.3)	3,330 (45.6)	0.01
Glucocorticoids	5,285 (72.3)	301,420 (37.4)	0.75	5,273 (72.3)	5,417 (74.2)	0.05
Laboratory Measurements, Mean ± SD						
Hemoglobin (g/dL)	12.42 ± 1.96	12.96 ± 1.61	0.30	12.42 ± 1.96	12.65 ± 1.82	0.12
Creatinine (mg/dL)	0.91 ± 1.00	0.86 ± 1.53	0.04	0.91 ± 1.00	0.96 ± 1.93	0.03
Aspartate aminotransferase (U/L)	25.15 ± 18.75	24.75 ± 29.21	0.02	25.14 ± 18.72	25.93 ± 31.29	0.03
Alanine aminotransferase (U/L)	22.57 ± 21.43	23.13 ± 28.23	0.02	22.56 ± 21.43	23.25 ± 22.28	0.03
Alkaline phosphatase (U/L)	88.99 ± 63.51	81.80 ± 52.37	0.12	88.99 ± 63.56	86.59 ± 54.79	0.04
Diastolic blood pressure (mmHg)	72.77 ± 11.63	73.39 ± 10.90	0.06	72.78 ± 11.63	72.94 ± 11.01	0.01
Systolic blood pressure (mmHg)	128.73 ± 19.98	128.11 ± 18.81	0.03	128.76 ± 19.97	128.63 ± 19.29	0.01
C-reactive protein (mg/dL)	22.37 ± 43.51	15.88 ± 36.65	0.16	22.20 ± 43.34	20.43 ± 42.22	0.04
Total cholesterol (mg/dL)	183.22 ± 46.72	190.99 ± 44.86	0.17	183.24 ± 46.74	183.53 ± 46.19	0.01

(*continued on next page*)

Table 1 (*continued*)

	Before matching			After matching		
	Patients with SCI after Osteoporosis (N = 7,308)	Patients without SCI after Osteoporosis (N = 804,923)	SMD	Patients with SCI after Osteoporosis (N = 7,296)	Patients without SCI after Osteoporosis (N = 7,296)	SMD
LDL (mg/dL)	100.56 ± 36.61	106.26 ± 36.55	0.16	100.57 ± 36.63	100.80 ± 37.23	0.01
HDL (mg/dL)	58.36 ± 21.35	60.62 ± 21.83	0.11	58.37 ± 21.36	57.40 ± 20.85	0.05
Triglyceride (mg/dL)	125.45 ± 76.69	117.75 ± 75.55	0.10	125.41 ± 76.66	127.85 ± 81.68	0.03
Troponin I (ng/mL)	0.20 ± 2.07	0.22 ± 4.44	0.01	0.20 ± 2.07	0.09 ± 0.58	0.07
Creatine kinase, MB (ng/mL)	3.57 ± 8.69	3.20 ± 9.89	0.04	3.58 ± 8.72	4.23 ± 15.80	0.05
Creatine kinase (ng/mL)	147.83 ± 337.70	133.38 ± 567.62	0.03	146.49 ± 335.93	188.73 ± 1987.12	0.03
Calcium (mg/dL)	9.34 ± 0.64	9.40 ± 0.58	0.10	9.34 ± 0.64	9.33 ± 0.63	0.01
Phosphate (mg/dL)	3.40 ± 0.77	3.43 ± 0.85	0.03	3.40 ± 0.77	3.41 ± 0.76	0.01
Calcidol (ng/mL)	37.07 ± 16.20	36.02 ± 15.27	0.07	37.08 ± 16.20	35.65 ± 16.21	0.09
Albumin (g/dL)	3.92 ± 0.57	4.06 ± 0.47	0.28	3.92 ± 0.56	3.96 ± 0.52	0.07

Abbreviations: SCI: spinal cord injury; SD: standard deviation, CI: confidence interval; SMD: standardized mean difference; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor antagonist, NSAID: non-steroidal anti-inflammatory analgesics; LDL: low-density lipoprotein; HDL: high-density lipoprotein

acting on the renin-angiotensin system, lipid-modifying agents, nonsteroidal anti-inflammatory analgesics, glucocorticoids, vitamin D, calcium supplements, as well as osteoporosis treatments such as alendronate, denosumab, and romosozumab. Laboratory measurements comprised hemoglobin, creatinine, diastolic blood pressure, systolic blood pressure, C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, troponin I, creatine kinase, creatine kinase-MB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), calcium, phosphate, and calcidiol.

2.5. Outcomes

The primary outcome of the present study was new diagnosis of cardiovascular-related events, specifically AMI, AF, and HF. Mortality was the secondary outcome. The codes for outcomes can be found in eMethod in supplementary file. The study monitored the outcomes of interest from the time of the index event, continuing through until December 18th, 2024. The final available date of data and the end of study were considered as the censor date.

2.6. Sensitivity test

To ensure the reliability of our findings, we performed two distinct sensitivity analyses aimed at addressing potential limitations and verifying the consistency of our results. First, we applied different statistical models that were carefully adjusted for multiple confounders to reduce bias and better isolate the effects of the variables under study. Second, we established a reference group of individuals without osteoporosis or SCI and compared event rates among those with osteoporosis only, SCI only, both conditions, and neither to evaluate their incremental impact on CVD and mortality.

2.7. Statistical analysis

Statistical analysis was performed *in situ* within the TriNetX platform. Continuous variables are presented as means ± standard deviations, whereas categorical variables are presented as numbers and percentages. The baseline characteristics of patients with SCI and osteoporosis were compared with those of patients with osteoporosis but without SCI by using a *t*-test for continuous variables and the chi-squared test for categorical variables. We also conducted subgroup analyses stratified by age, sex, and the presence of pathological fractures. To ensure the reliability of our results, we conducted further analysis comparing cardiovascular event rates between patients with SCI and osteoporosis and those with SCI but without osteoporosis.

Propensity score matching at a 1:1 ratio was employed to balance baseline characteristics. The built-in propensity score matching function of the TriNetX dataset was used for this purpose, with the type of function being greedy nearest-neighbor matching based on factors such as age, sex, ethnicity, comorbidities, medication, and laboratory data. The balance of baseline characteristics was assessed using standardized differences, with a standardized difference of less than 0.1 indicating a small difference [30]. Event-free survival curves were estimated using the Kaplan–Meier method and tested through the log-rank test. Moreover, hazard ratios (HRs) were calculated to quantify the relative risks of cardiac events through time-to-event analysis. Cox proportional-hazard models were used to calculate HRs and associated 95 % confidence intervals (CIs). The proportional-hazard assumption was tested using the generalized Schoenfeld approach included in the TriNetX platform.

Statistical significance for all tests was set at a two-sided P value of < 0.05. The figures presented in this manuscript were created using R software version 4.3.0, provided by the Free Software Foundation Inc. with ggplot2 and forestploter packages.

3. Results

3.1. Baseline participant characteristics

Using propensity score matching, this study identified 7296 patients who received a diagnosis of SCI following a diagnosis of osteoporosis and an equal number of patients who did not receive a diagnosis of SCI following a diagnosis of osteoporosis. The selection process is illustrated in Fig. 1. The demographic characteristics, comorbidities, and laboratory measurements of the groups before and after propensity score matching are presented in Table 1. The mean age of the patients in the SCI cohort was 67.32 ± 10.72 years at the index date after matching. A total of 74.6 % of the SCI cohort were women, and the majority were white people (72.7 %). The two groups were well-matched regarding the distribution of demographic variables, comorbidities, drug usage, and laboratory data (standardized differences < 0.1).

3.2. Spinal cord injury as a risk for cardiovascular events and mortality in the patients with osteoporosis

The Kaplan–Meier curves of all cardiac event outcomes (Fig. 2A) and mortality (Fig. 2B) revealed a significant difference between the two cohorts (all log-rank test, $P < 0.001$). A further analysis of cardiovascular events, including AMI, AF, and HF, across two groups also showed significant difference. (all log-rank tests, $P < 0.001$, eFig. 1 in supplementary file)

Table 2 presents evidence that patients who received an SCI diagnosis after a diagnosis of osteoporosis had a significantly higher risk of any type of cardiovascular-related events (HR: 1.15, 95 % CI: 1.08–1.22, $P < 0.001$). The risks of individual cardiac events—AMI (HR: 1.17, 95 % CI: 1.02–1.33, $p = 0.022$), HF (HR: 1.14, 95 % CI: 1.05–1.24, $p = 0.001$),

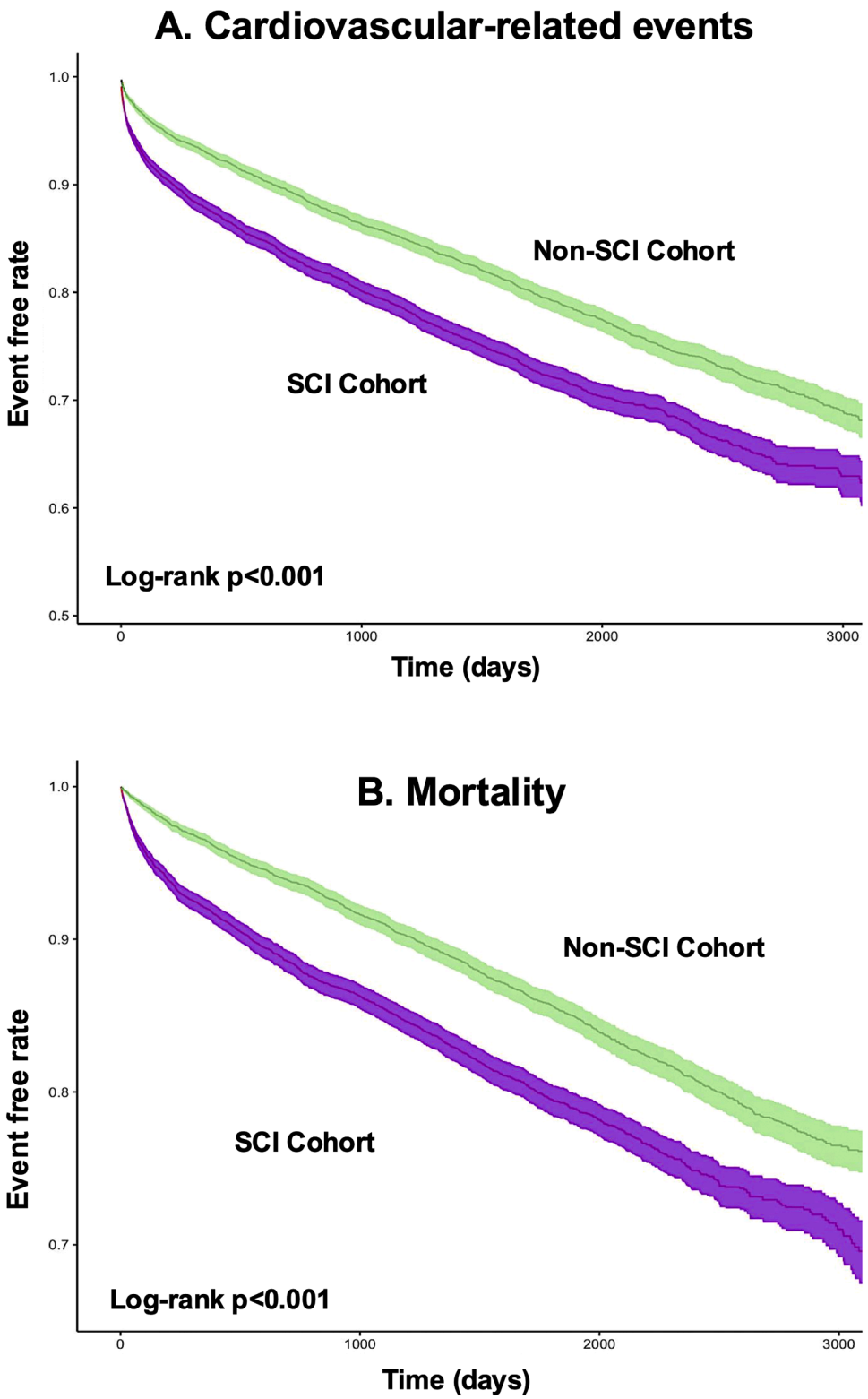

Fig. 2. Kaplan–Meier curves. Cardiovascular-related events (A) and mortality (B) between osteoporosis patients with/without spinal cord injury (SCI). Shaded areas indicate 95 % confidence intervals. The figures of the KM plots were truncated at 3000 days.

AF (HR: 1.14, 95 % CI: 1.04–1.24, $p = 0.004$), and mortality (HR: 1.19, 95 % CI: 1.11–1.28, $P < 0.001$)—were also higher in the SCI cohort.

3.3. Subgroup analyses

We examined the risk of cardiovascular events and mortality in subgroups based on pathological fracture status, gender, and age (Fig. 3). Osteoporosis patients with SCI consistently exhibited significantly higher risks of atrial fibrillation, heart failure, and mortality across most subgroups. Notably, the increased risks were more pronounced in females, younger individuals, and those without pathological fractures. For acute myocardial infarction, significant associations

Table 2
Risk analysis of clinical outcomes in osteoporosis with and without spinal cord injury.

Outcomes	The patients with osteoporosis			
	With SCI (N = 7,296)	Without SCI (N = 7,296)	Hazard Ratio (95% CI)	p-value
CV-related events, *n* (%)	1,840 (25.2)	1,603 (22.0)	1.15 (1.08–1.22)	<0.001
Acute myocardial infarction, *n* (%)	457 (6.3)	392 (5.4)	1.17 (1.02–1.33)	0.022
Atrial flutter/ fibrillation, *n* (%)	974 (13.4)	857 (11.7)	1.14 (1.04–1.24)	0.004
Heart failure, *n* (%)	1,123 (15.4)	984 (13.5)	1.14 (1.05–1.24)	0.001
Deceased, *n* (%)	1,449 (19.9)	1,215 (16.7)	1.19 (1.11–1.28)	<0.001

Abbreviations: CV, cardiovascular; SCI, spinal cord injury; CI, confidence interval.

were observed in older individuals, males, and patients without pathological fractures, while no significant difference was found in those with fractures or younger individuals. Similarly, heart failure risk was not significantly elevated in patients with pathological fractures. These results underscore the varied impact of SCI on cardiovascular and mortality risks, depending on demographic and clinical factors.

3.4. Osteoporosis as a risk for cardiovascular events in patients with SCI

A further comparison was conducted between patients with both SCI and osteoporosis and those with SCI alone. As shown in eTable 1 in the supplementary file, patients with SCI and osteoporosis had a higher incidence of CV-related events (HR: 1.24, 95 % CI: 1.08–1.42, $p = 0.002$). The risks for atrial flutter/fibrillation (HR: 1.27, 95 % CI: 1.04–1.55, $p = 0.019$) and heart failure (HR: 1.32, 95 % CI: 1.11–1.56, $p = 0.001$) were significantly higher in the SCI with osteoporosis group. The SCI with osteoporosis group exhibited a higher mortality rate compared to the SCI without osteoporosis group (HR: 1.41, 95 % CI: 1.25–1.59, $P < 0.001$). Propensity score matching was performed based on baseline covariates outlined in the eMethod section of the supplementary file.

3.5. Sensitivity test

The results remained consistent across different models after adjusting for multiple confounders (eTable 2 in supplementary file). Finally, further analysis shows that patients with both conditions faced the highest risks of cardiovascular events and mortality, indicating an amplified cumulative effect of the two illnesses (eTable 3 in supplementary file).

4. Discussion

The present study indicates that among patients with osteoporosis, those with SCI have a higher risk of CVD, including AMI, AF, and HF, than do individuals without SCI. Further analysis reinforces our primary findings, suggesting that the presence of osteoporosis in patients with SCI exacerbates the risk of cardiovascular events and mortality. This underscores the complex interaction between the two conditions, emphasizing how their coexistence significantly amplifies the risk of cardiovascular diseases. This study suggests that health-care providers should closely monitor the cardiovascular health of patients with osteoporosis who also have SCI. Incorporating comprehensive cardiovascular screening and management strategies into the care plan for SCI survivors with osteoporosis may enable detection of CVD at an early stage and potentially reduce the risk of mortality.

The uncoupling of bone formation and resorption accelerates the process of osteoporosis in individuals with SCI [31]. Additionally, the osteoporotic process in individuals with SCI differs from other forms of osteoporosis due to unique mechanisms, such as increased osteoclastogenesis stimulated by interleukin 6 [18,19]. Moreover, mechanical loading, crucial for bone remodeling, is disrupted in SCI, impairing osteocyte modulation of bone cell activity and dysregulating pathways such as Wnt and receptor activator of nuclear factor kappa-B ligand/receptor activator of nuclear factor kappa-B/osteoprotegerin [32,33]. Vitamin D (25-hydroxyvitamin D) deficiency is prevalent in individuals with chronic SCI and is known to raise osteoporosis risk [34]. Finally, studies conducted in France and Sweden found that lower bone mineral density and higher levels of bone resorption markers are associated with a higher risk of cardiovascular events, including myocardial infarction [35,36]. Consistent with these findings, the present study discovered that among patients with osteoporosis, those with SCI had a higher risk of CVD.

SCI not only exacerbates the osteoporotic process and is associated with a higher risk of CVD but also substantially increases the risk of myocardial infarction and HF in individuals with SCI without comorbidities such as hypertension, type 2 diabetes, and dyslipidemia [37,38]. This finding suggests that SCI itself may predispose individuals to cardiovascular complications, independent of traditional risk factors. In a large-scale database study conducted in Korea, Yoo et al. demonstrated that SCI survivors had higher risks of myocardial infarction (aHR: 2.41; 95 % CI: 1.93–3.00), HF (aHR: 2.24; 95 % CI: 1.95–2.56), and AF (aHR: 1.84; 95 % CI: 1.49–2.28) than did individuals without SCI, highlighting the danger of heart disease in individuals with SCI [6]. Several studies have indicated strong associations between CVD and SCI. One such study demonstrated that SCI-related inflammatory processes can accelerate atherosclerosis, increasing the risks of conditions such as AMI and HF and predicting increased risk of AF [39]. An elevated level of CRP, an inflammatory indicator, is common in acute and chronic SCI and is associated with other CVD risk factors [40]. Studies have demonstrated that SCI often leads to cardiovascular abnormalities—such as orthostatic hypotension, autonomic dysreflexia, and cardiac arrest—due to autonomic dysfunction stemming from the loss of vasomotor control; these autonomic dysfunctional complications occur across all levels of SCI [41–44]. A further study indicated that SCI can disrupt cardiac vagal modulation, impairing cardiac vagal control even when parasympathetic activity is preserved [10]. Finally, several studies have concluded that physical inactivity after SCI contributes to a sedentary lifestyle, lower energy expenditure, reduced cardiorespiratory fitness, unfavorable body composition changes, and alterations of metabolic profile, all of which exacerbate the cardiometabolic disease risk profile of individuals with SCI [12,37,45–47].

The present study discovered that individuals with SCI with osteoporosis have a significant risk of mortality, especially those with concurrent pathological fracture. Other studies have revealed that pathological fracture, particularly in load-bearing parts of the skeleton below the level of injury, contributes to early and acute bone demineralization in patients with SCI [48,49]. This type of fracture often occurs years after injury, with the median time to the first fragility fracture being 8.5 years [50]. Pathological fracture can cause various systemic and infectious complications, including lengthy immobilization and pressure sores [51]. In the present study's subgroup analysis, individuals with SCI and osteoporosis with concurrent pathological fracture had a higher risk of mortality than those without concurrent pathological fracture. This association may have been due to faster progression or earlier onset of systemic or infectious complications. Although neurological osteoporosis is a common chronic complication of SCI, therapies to manage the condition often have unsatisfactory results. Thus, further studies of neurological osteoporosis are warranted to optimize treatments for individuals with SCI.

This study has several strengths. First, we utilized data from the

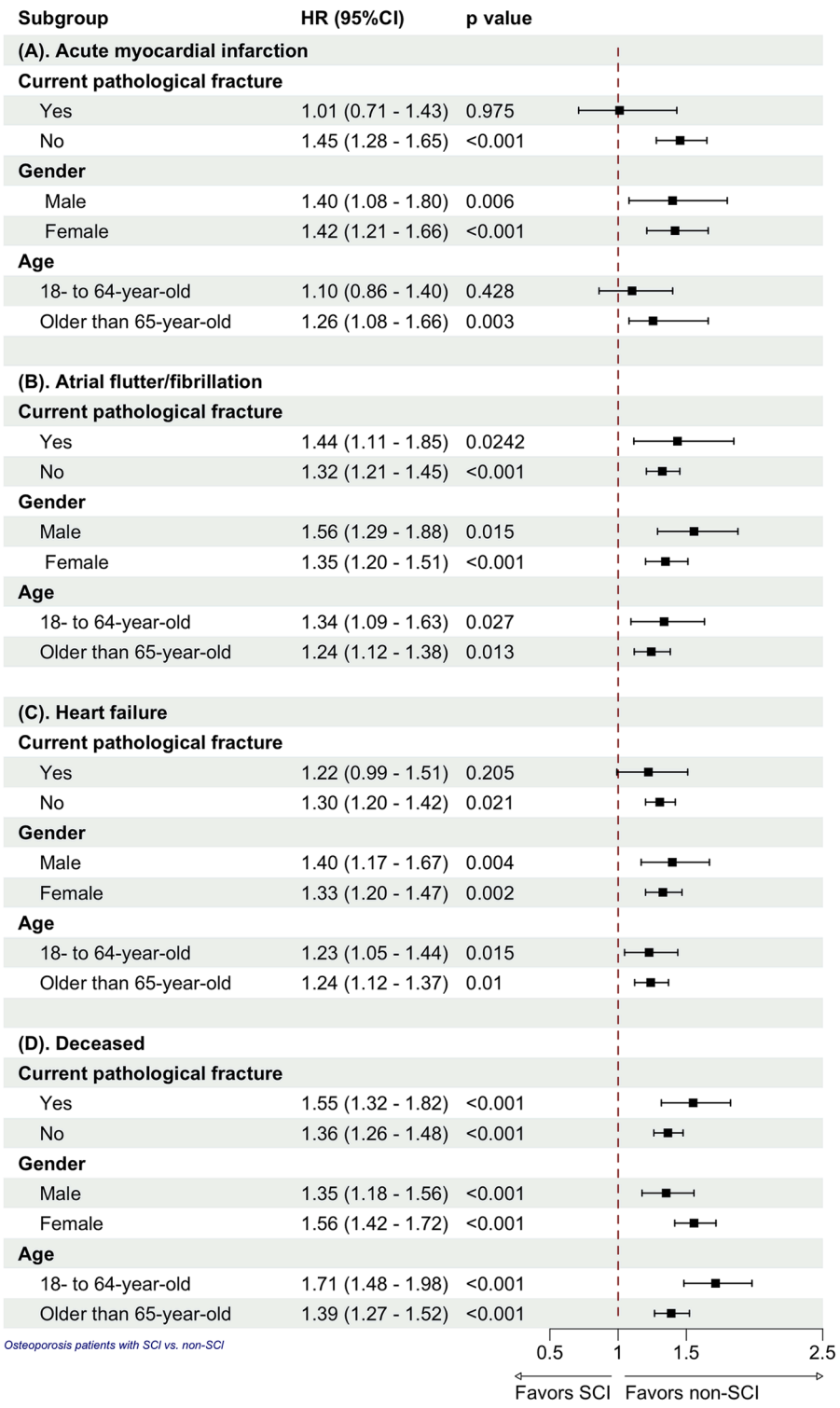

Fig. 3. Subgroup analysis. Forest plots of hazard ratios (HRs) for the osteoporosis patients with spinal cord injury (SCI) on acute myocardial infarction (A), atrial flutter/fibrillation (B), heart failure (C), and deceased (D) compared those without SCI. The propensity score matching by baseline covariates as Table 1 was adopted to reach a baseline balance between groups. The vertical line shows an HR of 1.00. When the lower limits of 95 % confidence intervals (CIs) are greater than 1.00, it signifies a notably higher risk.

TriNetX Research Network, which includes electronic health records from patients across diverse health-care organizations, providing a robust and comprehensive dataset. This extensive dataset ensures the generalizability and reliability of the findings. Second, propensity score matching was used to effectively balance the baseline characteristics between the SCI and non-SCI cohorts, strengthening the validity of our comparisons and minimizing the influence of confounding variables. Third, we examined a range of cardiovascular outcomes—AMI, AF, HF, and mortality—to obtain a holistic understanding of the cardiovascular risk profile of individuals with SCI with osteoporosis. Finally, the study addresses a gap in the literature by directly investigating the cardiovascular risk profile of these individuals. These strengths underscore the

validity of the study's findings and the necessity of monitoring the cardiovascular health of individuals with SCI.

Our study also has several limitations. First, the data were obtained from the TriNetX Research Network, which, while robust, was not specifically designed to collect detailed clinical information on osteoporosis or SCI. We lacked access to diagnostic criteria, dual-energy X-ray absorptiometry scans, fragility fractures, or disease severity data. Key metrics like Fracture Risk Assessment Tool scores, linking fracture risk to CVD, were unavailable. These gaps may have caused bias, highlighting the need for prospective studies with better data. Second, while *ICD-10-CM* codes are widely used in large database analyses and have shown reasonable reliability in identifying these cardiovascular conditions [52–54], there may be variations in diagnostic practices and coding accuracy across different healthcare settings. For example, the diagnosis of HF, which includes both systolic and diastolic forms, was based on *ICD-10-CM* code I50, but we cannot confirm whether transthoracic echocardiography was consistently used to establish this diagnosis. In addition, individuals with SCI may have impaired perception of chest pain in ischemic heart disease, potentially leading to underestimation of CVD cases during follow-up. Finally, the follow-up duration varied; individuals receiving a diagnosis of SCI between 2015 and 2020 were followed until 2024. Long-term follow-up studies are warranted to validate the present study's findings, which must be interpreted with caution.

5. Conclusion

The present study highlights the increased risk of CVD in individuals with osteoporosis who also have SCI. We emphasize the complex interplay between SCI, osteoporosis, and cardiovascular health and indicate that comprehensive management strategies are required to treat these conditions. Future studies should adopt a prospective design with a longer follow-up period to elucidate the cardiovascular risk in this population.

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None.

Statement of ethics

This study was conducted following the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable legislations for noninterventional and observational studies. Data de-identification is formally attested as per section §164.514(b)(1) of the Health Insurance Portability and Accountability Act Privacy Rule. The requirement for informed consent was waived because of the anonymized nature of the data and the retrospective nature of this study. Additionally, the use of TriNetX in the current study was approved by the Institutional Review Board of the Shin Kong Wu Ho-Su Memorial Hospital (IRB: 20240904R).

CRediT authorship contribution statement

Shih-Kai Kao: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Yu-Ting Yu:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Ming-Hsien Tsai:** Writing – review & editing, Supervision, Resources, Project administration, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.100938.

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