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Peripheral Arterial Disease and Spinal Cord Injury

A Retrospective Nationwide Cohort Study

Ta-Wei Su, MD, Tzu-Yi Chou, MD, Herng-Jeng Jou, MD, Pei-Yu Yang, MD, Cheng-Li Lin, MSc, Fung-Chang Sung, PhD, Chung-Y. Hsu, MD, PhD, and Chia-Hung Kao, MD

Abstract: The aim of this study was to elucidate the relationship between spinal cord injury (SCI) and the risk of peripheral arterial disease (PAD) in a cohort study with a large representative sample.

The National Health Insurance Database was used to select patients who were diagnosed from 2000 to 2010. Patients with a history of PAD were excluded. The SCI group comprised 42,673 patients diagnosed with SCI, and we enrolled 170,389 matched controls (non-SCI group). We used a Cox proportional hazards regression model to analyze the adjusted risk of PAD between the case and control patients.

Patients with SCI exhibited a significantly higher risk (hazard ratio [HR] = 1.37; 95% confidence interval [CI] = 1.22–1.53) of PAD than patients without SCI. Patients with diabetes were at the highest risk of developing PAD (adjusted HR = 3.11, 95% CI = 2.80–3.44). Among patients without comorbidity, SCI patients exhibited a significantly higher risk of PAD than non-SCI patients. Furthermore, lumbar, sacral, or coccygeal spine, and multiple spine SCI were significantly associated with an increased risk of PAD (HR = 1.56, 95% CI = 1.33–1.84, HR = 2.11, 95% CI = 1.59–2.79, respectively).

SCI is associated with an increased risk of PAD. Future studies should focus on modifying risk factors to reduce PAD risk among patients with SCI.

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Abbreviations: CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, C-spine = cervical spine, CVD = cardiovascular disease, DM = diabetes mellitus, HR = hazard ratio, HTN = hypertension, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IR = incidence ratio, L-S-Co spine = lumbar, sacral, or coccygeal spine, NHIRD = National Health Insurance Research Database, PAD = peripheral arterial disease, SCI = spinal cord injury, T-spine = thoracic spine.

INTRODUCTION

Spinal cord injury (SCI) impairs a patient's motor, sensory, or autonomic system, and SCI-related costs incurred by health care systems often burden society.[1,2] Respiratory failure, cardiovascular dysfunction, thromboembolism, and autonomic dysreflexia are the common complications of SCI.[3,4] Furthermore, recent studies have reported a higher risk of developing insulin resistance, glucose intolerance, and lipid abnormalities in SCI patients than in able-bodied people.[5–7] Supporting a patient severely affected by SCI can cost up to US$1 million in the first year.[1] During the past decades, the outcome and survival rate of SCI have improved. Up to 250,000 people worldwide sustain a SCI every year,[6] and their life expectancy continues to increase.[8]

Peripheral arterial disease (PAD) is one of the most lethal diseases but is frequently neglected.[9,10] Even without previous ischemic stroke or myocardial infarction, patients with PAD are at an equal risk of death as are patients with cardiovascular disease (CVD) or previous coronary or cerebrovascular disease.[11–13] A meta-analysis[14] suggested that PAD affects more than 202 million people worldwide. Resting pain, claudication, and atypical leg discomfort are the symptoms of PAD; however, up to 50% of patients with PAD are asymptomatic.[10] The confirmed risk factors of PAD include diabetes mellitus (DM), smoking, hypertension (HTN), and dyslipidemia.[9,11]

Patients with SCI are at a greater risk of CVD and a relevant higher risk of death than able-bodied persons.[14] Recent studies have advocated CVD as the leading cause of mortality in patients with SCI.[15–17] Several studies have proposed subclinical atherosclerotic markers for patients with SCI including the carotid intima-media thickness[18] and ankle-brachial index.[16] The relationship between SCI and PAD requires further large-scale investigation because PAD is an atherosclerotic process affecting the noncoronary arterial system. Our retrospective

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From the Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan (TWS); Department of Physical Medicine and Rehabilitation, China Medical University Hospital (TYC, PYY); Department of Orthopedic Surgery, Kuang Tien General Hospital (HJJ); Department of Nursing, Hungkuang University (HJJ); School of Medicine, China Medical University (PYY, CLL); Management Office for Health Data, China Medical University Hospital (CLL, FCS); Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University (FCS, CYH, CHK); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (CHK).

Correspondence: Chia-Hung Kao, MD, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No.2, Yuh-Der Road, Taichung City 404, Taiwan (e-mail: d10040@mail.cmuh.org.tw).

Fung-Chang Sung and Chia-Hung Kao contributed equally to this work.

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nationwide cohort study investigated the relationship between SCI and PAD by using data from a national health insurance database. We hypothesized that SCI is associated with an increased risk of PAD.

METHODS

Data used in this study were obtained from the Taiwan National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program is a government-run, single-payer insurance system that was established in 1995 in Taiwan. This NHI program covers over 99% of the 23.74 million residents of Taiwan (http://www.nhi.gov.tw). The National Health Research Institute (NHRI) audits and releases the NHIRD data for use in health service studies. In accordance with the Personal Information Protection Act, all patient reimbursement data are deidentified and linked to a patient identification number before being released for academic research. For this study, we used a subset of the NHIRD containing health care data including files of inpatient claims and the Registry of Beneficiaries. All clinical diagnoses were recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes. In our National Health Insurance (NHI) program, all insurance claims are under scrutiny of medical reimbursement specialists and anonymous peer reviews. The definition of SCI and PAD was based on ICD-9-CM codes determined by clinical physicians after strict inspections in the reimbursement process based on laboratory, imaging, and pathological data. Moreover, there are even severe penalties for physicians if inappropriate ICD-9-CM codes were documented in clinical records. Therefore, the diagnoses or definition of SCI, and PAD are accurate and reliable. The study was exempted from full review by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-105).

SAMPLED PARTICIPANTS

We selected adult patients with a first diagnosis of SCI (ICD-9-CM codes 806 and 952) from 2000 to 2010 as the SCI cohort. We classified SCI patients into 4 subgroups: 1. cervical spine (C-spine) (ICD-9-CM codes 806.0, 806.1, 952.0, 952.00, 952.01, 952.02, 952.03, 952.04, 952.05, 952.06, 952.07, 952.08, and 952.09); 2. thoracic spine (T-spine) (ICD-9-CM codes 806.2, 806.21, 806.26, 806.3, 952.1, 952.11, and 952.16); 3. lumbar, sacral, or coccygeal spine (L-S-Co spine) (ICD-9-CM codes 806.4, 806.5, 806.6, 806.7, 806.8, 806.9, 952.2, 952.3, 952.4, 952.8, and 952.9); 4. multiple spine SCI (any 2 or more than 2 lesions in the C-spine, T-spine, and L-S-Co spine). The date of admission and diagnosis of SCI was defined as the index date. The exclusion criteria were an age younger than 20 years, incomplete age or sex information, and a history of PAD (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9) at the baseline. A non-SCI cohort was randomly selected from the NHI beneficiaries aged 20 years and older and frequency-matched for age (every 5 years), sex, index year, and comorbidities, including diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), heart failure, obesity, CAD, stroke, and asthma with the SCI cohort at a 4:1 ratio, and was subjected to the same exclusion criteria.

OUTCOME AND COMORBIDITIES

The main outcome was based on the admission claims data of PAD diagnoses during follow-up. Each patient was followed up from the index date to the date of PAD occurrence, withdrawal from the NHI, or December 31, 2011.

Baseline comorbidities including DM (ICD-9-CM codes 250), HTN (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM codes 272), COPD (ICD-9-CM codes 491, 492, and 496), heart failure (ICD-9-CM codes 428), obesity (ICD-9-CM code 278), coronary artery disease (CAD) (ICD-9-CM codes 410–414), stroke (ICD-9-CM codes 430–438), and asthma (ICD-9-CM code 493) were identified according to diagnoses in hospitalization records before the index date.

Statistical Analysis

The Chi-squared test was used to examine and compare the distributions of the categorical variables of the SCI and the non-SCI cohort. The Student's *t* test was used to examine the mean ages and mean follow-up times of the cohorts. We estimated the cumulative incidence by using the Kaplan–Meier method, and the log-rank test was used to compare the cumulative incidence curves of the SCI and non-SCI cohorts. The overall sex-, age-, and comorbidity-specific incidence densities of PAD were measured for each cohort. Univariable and multivariable Cox proportional hazards regression models were used to examine the association between SCI and the risk of PAD, which is expressed as a hazard ratio (HR) with a 95% confidence interval (CI). The multivariable model was adjusted for age, sex, and comorbidities. We selected the comorbidities as variables in multivariable analysis because they were statistically significant in the univariable model. We further tested the interaction between sex and SCI, age and SCI, and between comorbidity and SCI by including a cross-product term in the model. We used the scaled Schoenfeld residuals for testing the proportional hazard model assumption. Because the proportional hazard model assumption was violated ($P = 0.005$), we stratified the follow-up duration to deal with the violation of proportional hazard assumption. Further analysis was performed to assess the variations in the association of PAD at different levels of SCI. Data management and descriptive analyses were performed using the SAS 9.2 statistical package (SAS Institute Inc., Cary, NC). We adopted a 2-tailed *P* value lower than 0.05 as the statistical significance level.

RESULTS

This study included 42,673 with SCI and 170,389 patients without SCI. In our study, men constituted the majority (63.2% versus 36.8%), and almost 71.7% of the patients were more than 50 years old. The mean age of the SCI cohort was 52.4 ± 18.2 years and that of the non-SCI cohort was 52.1 ± 18.4 years. The SCI cohort and non- SCI cohort were well matched for comorbidities, except for obesity.

During the mean follow-up of 5.66 years for the SCI cohort and 6.03 years for the non-SCI cohort, the cumulative incidence of PAD was significantly higher for patients in the SCI cohort than for those in the non-SCI cohort (log-rank test $P < 0.001$) (Figure 1). The overall incidence of PAD was 29% higher in the SCI cohort than in the non-SCI cohort (1.68 versus 1.30 per 1000 person-years) with an adjusted HR of 1.37 (95% CI = 1.22–1.53) (Table 1). The sex-specific adjusted HR of PAD for the SCI and non-SCI cohorts was significant for women (HR = 1.29, 95% CI = 1.07–1.53) and men (HR = 1.42, 95% CI = 1.23–1.65). The PAD incidence increased with age in both cohorts. However, the age-specific relative risk of PAD was the greatest for the youngest age group among the SCI and non-SCI cohorts (≤50 years, adjusted

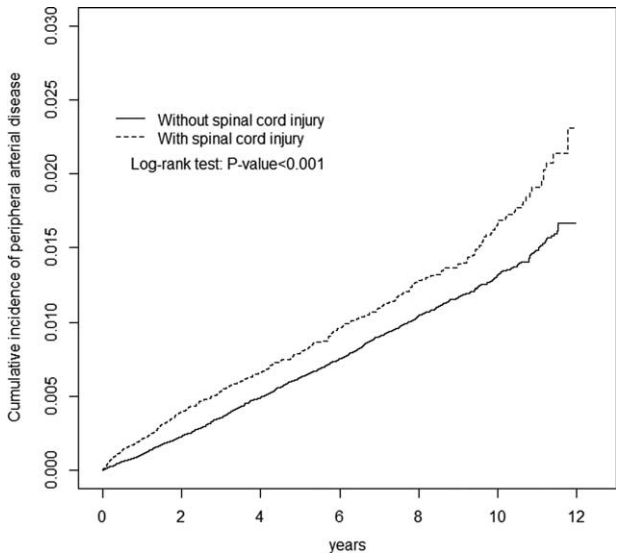

FIGURE 1. Kaplan–Meier curve for the cumulative incidence of PAD in the SCI and non-SCI cohorts during the 12-year follow-up.

HR = 4.02; 95% CI = 2.22–7.26). The corresponding adjusted HR decreased to 1.23 (95% CI, 1.08–1.42) for the oldest age group (>65 years), although this group had the highest incidence of PAD. The PAD incidence rate was greater in patients with comorbidities than in patients without comorbidity in both the cohorts. A significantly higher risk of PAD was observed in SCI patients without comorbidities (HR = 1.87; 95% CI = 1.50–2.33) than in the non-SCI patients without comorbidities, respectively. In the first year of follow-up, the SCI cohort had a higher risk of PAD than the non-SCI cohort (adjusted HR = 1.98, 95% CI = 1.53–2.57). Moreover, the risk of PAD in the SCI cohort was still significantly higher than that in the non-SCI cohort after 5 years of follow-up (adjusted HR = 1.36, 95% CI = 1.12–1.65).

The results of the univariable and multivariable Cox proportional hazards regression models for analyzing the risk of variables contributing to PAD are summarized in Table 2. The adjusted HR of PAD was increased 1.42-fold for men relative to women (95% CI = 1.29–1.73) and increased 1.06-fold (95% CI = 1.06–1.07) with age (every year). The risk of PAD was greater in patients with comorbidities, namely DM (adjusted HR = 3.11, 95% CI = 2.80–3.44), HTN (adjusted HR = 1.50, 95% CI = 1.34–1.68), hyperlipidemia (adjusted HR = 1.49, 95% CI = 1.29–1.73), heart failure (adjusted HR = 1.81, 95% CI = 1.54–2.12), obesity (adjusted HR = 2.33, 95% CI = 1.04–5.21), CAD (adjusted HR = 1.16, 95% CI = 1.02–1.31), and stroke (adjusted HR = 1.57, 95% CI = 1.35–1.82).

Table 3 lists the relative risk and HR of PAD associated with different levels of SCI lesion. Compared with the non-SCI cohort, patients with L-S-Co-spine injury were at a 56% (adjusted HR = 1.56, 95% CI = 1.33–1.84) higher risk of PAD, respectively. Patients with multiple SCI lesions had a

TABLE 1. Incidence Ratio and HR of PAD According to SCI Status Stratified by Demographic Factors and Comorbidities

	SCI							
		No		Yes			SCI to Non-SCI	
Variable	**Event**	**PY**	**Rate****	**Event**	**PY**	**Rate****	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
All	1334	1,026,888	1.30	405	241,463	1.68	1.29 (1.16–1.44)§	1.37 (1.22–1.53)§
Sex								
Female	568	381,584	1.49	173	91,813	1.88	1.27 (1.07–1.50)§	1.29 (1.09–1.53)‡
Male	766	645,304	1.19	232	149,651	1.55	1.31 (1.13–1.51)§	1.42 (1.23–1.65)§
P for interaction								0.79
Stratify age								
≤50	22	319,412	0.07	22	79,469	0.28	4.01 (2.22–7.25)§	4.02 (2.22–7.26)§
50–65	358	454,842	0.79	127	107,218	1.18	1.51 (1.24–1.85)§	1.50 (1.23–1.84)§
65+	954	252,634	3.78	256	54,777	4.67	1.25 (1.08–1.43)‡	1.23 (1.08–1.42)‡
P for interaction								<0.001
Comorbidity***								
No	276	745,346	0.37	113	177,432	0.64	1.72 (1.38–2.14)§	1.87 (1.50– 2.33)§
Yes	1058	281,541	3.76	292	64,032	4.56	1.22 (1.07–1.39)‡	1.25(1.10–1.42)§
P for interaction								0.008
Follow time, years								
≤1	179	167,583	1.07	84	40,267	2.09	1.95 (1.50–2.53)§	1.98 (1.53–2.57)§
2–4	685	326,236	2.10	185	77,187	2.40	1.13 (0.96–1.33)§	1.15 (0.97–1.35)
>5	470	333,234	1.41	136	77,460	1.76	1.25 (1.03–1.51)†	1.36 (1.12–1.65)‡

CI, confidence interval; crude HR, crude hazard ratio; PY, person-years; SCI, spinal cord injury.

*Adjusted HR: multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, obesity, CAD, stroke, and asthma.

**Rate, incidence rate, per 1000 person-years.

***Comorbidity: Patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, COPD, heart failure, obesity, CAD, stroke, and asthma were classified as the comorbidity group.

†$P < 0.05$, ‡$P < 0.01$, §$P < 0.001$.

TABLE 2. HR of PAD in Association With Sex, Age, and Comorbidities in Univariable and Multivariable Cox Regression Models

	Crude		Adjusted*	
Variable	**HR**	**(95% CI)**	**HR**	**(95% CI)**
Sex (women versus men)	1.25	(1.13–1.37)§	1.42	(1.29–1.73)§
Age, years	1.08	(1.07–1.08)§	1.06	(1.06–1.07)§
Baseline comorbidities (no versus yes)				
SCI	1.29	(1.16–1.44)§	1.37	(1.22–1.53)§
Diabetes	7.05	(6.41–7.76)§	3.11	(2.80–3.44)§
Hypertension	5.93	(5.40–6.52)§	1.50	(1.34–1.68)§
Hyperlipidemia	4.06	(3.55–4.65)§	1.49	(1.29–1.73)§
Heart failure	7.30	(6.31–8.44)§	1.81	(1.54–2.12)§
Obesity	1.78	(0.80–3.98)	2.33	(1.04–5.21)†
COPD	4.19	(3.65–4.81)§	1.00	(0.86–1.17)
CAD	5.09	(4.57–5.67)§	1.16	(1.02–1.31)†
Stroke	5.06	(4.52–5.66)§	1.57	(1.35–1.82)§
Asthma	3.47	(2.95–4.08)§	1.04	(0.87–1.24)

CI, confidence interval; crude HR, relative hazard ratio.
*Adjusted HR: multivariable analysis including age, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, obesity, CAD, stroke, and asthma.
†$P < 0.05$, §$P < 0.001$.

2.11-fold higher risk of PAD than the non-SCI cohort (95% CI = 1.59–2.79).

DISCUSSION

This study was conducted in a region with a high prevalence of PAD.[19,20] In our study, comorbidities were significantly more prevalent in the SCI group than in the non-SCI group. After adjustment for sex, age, and the aforementioned comorbidities, the SCI group exhibited a 1.37-fold higher risk of PAD than the non-SCI group. The overall incidence of PAD was 29% higher in the SCI cohort than in the non-SCI cohort. During the 12-year follow-up, a significantly higher risk of PAD was noted within the first year.

In our study, L-S-Co-spine and multiple spine SCI were significantly associated with an increased risk of PAD. A historical prospective study among patients surviving at least 20 years with SCI stated that the risk of all CVD increased with severity of SCI. The CVD in this study defined by ICD/9 codes 390 to 448; thus, PAD was included. But this study did not examine the isolated risk estimates for PAD.[21] Furthermore, the number of patients with PAD in our study might have been underestimated because PAD is commonly underdiagnosed.[10] Hence, the true impact of SCI on PAD might be stronger than that reported here.

Several possible factors may compound the risk of PAD in SCI patients. First, the patients with SCI in our study had a significantly higher incidence of comorbidities than did the non-SCI patients (Table 4). Moreover, HTN, DM, and hyperlipidemia were observed to be the major risk factors for PAD.[11] Thus, patients with these comorbidities possibly exhibited a higher risk of PAD than did patients without comorbidities. Second, previous research has reported a susceptibility of patients with SCI to metabolic disorders including carbohydrate[5,22] and dyslipidemia.[6,7,22] Lee et al[23] reported that a quarter of the SCI population presented with metabolic syndromes and insulin resistance. The impact of SCI on the metabolism provides evidence of the association between SCI and subsequent

TABLE 3. Incidence and HR of PAD Among Patients With Different Levels of SCI

Variable	Event	PY	Rate*	Crude HR (95% CI)	Adjusted HR (95% CI)
Non-SCI	1334	1,026,941	1.30	1.00	1.00
C-spine SCI	127	125,016	1.02	0.78 (0.65–1.27)	1.09 (0.91–1.31)
T-spine SCI	67	27,673	2.42	1.87 (1.46–2.39)§	1.25 (0.97–1.60)
L-S-Co-spine SCI	161	70,424	2.29	1.75 (1.49–2.07)§	1.56 (1.33–1.84)§
Multiple spine SCI	50	18,298	2.73	2.10 (1.58–2.79)§	2.11 (1.59–2.79)§

Adjusted HR: Adjusted hazard ratio, multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, obesity, CAD, stroke, and asthma. C-spine SCI: ICD-9-CM 06.0, 806.1, 952.0, 952.00, 952.01, 952.02, 952.03, 952.04, 952.05, 952.06, 952.07, 952.08, 952.09. T-spine SCI: ICD-9-CM 806.2, 806.21, 806.26, 806.3, 952.1, 952.11, 952.16. L-S-Co-spine SCI: ICD-9-CM 806.4, 806.5, 806.6, 806.7, 806.8, 806.9, 952.2, 952.3, 952.4, 952.8, and 952.9. C, cervical; CI, confidence interval; L-S-Co, lumbar, sacral, and coccygeal; PY, person-years; SCI, spinal cord injury; T, thoracic.
*Rate, incidence rate, per 1000 person-years.
§$P < 0.0001$.

TABLE 4. Demographic Characteristics and Comorbidities in Study Patients According to SCI Status

	Spinal Cord Injury		
Variable	**No N = 170,389**	**Yes N = 42,673**	***P***
Sex	n (%)	n (%)	0.91
Female	62,588 (36.7)	15,687 (36.8)	
Male	107,801 (63.3)	26,986 (63.2)	
Age, mean (SD)	52.1 (18.4)	52.4 (18.2)	0.001*
Stratify age			0.99
≤50	48,197 (28.3)	12,056 (28.3)	
50–65	733,240 (43.0)	18,343 (43.0)	
65+	48,952 (28.7)	12,274 (28.8)	
Comorbidity			
Diabetes	20,964 (12.3)	5284 (12.4)	0.66
Hypertension	32,924 (19.3)	8270 (19.4)	0.79
Hyperlipidemia	7772 (4.56)	1975 (4.62)	0.55
Heart failure	4987 (2.93)	1284 (3.01)	0.37
Obesity	287 (0.17)	102 (0.12)	0.002
Smoking-related diseases			
COPD	8784 (5.16)	2236 (5.24)	0.48
CAD	13,951 (8.19)	3532 (8.28)	0.55
Stroke	12,628 (7.41)	3192 (7.48)	0.63
Asthma	6165 (3.62)	1583 (3.71)	0.37

Chi-square test. SCI = spinal cord injury.
*Two-sample *t* test.

PAD. Third, impaired control of vessels[24] and altered vascular reactivity[25] in patients with SCI possibly contribute to atherosclerosis in the lower extremities. Fourth, a sedentary lifestyle and subsequent loss of lean body mass,[26] and fluctuations in the blood pressure[17] are possible mechanisms underlying PAD observed in SCI patients.

The strengths of this study are that it is the first cohort study focusing on PAD in SCI patients with uniform data collection and a sufficiently large sample size to enable meaningful analyses. Nevertheless, some limitations must be noted. First, the diagnoses recorded in the NHIRD are not validated for academic purposes. Moreover, the NHIRD diagnoses were documented using ICD-9-CM codes, and data on environmental risk factors influencing PAD such as smoking habits and family history could not be obtained. Second, despite the controls and adjustment for interfering factors, we probably did not completely control for the confounding effects of preexisting comorbidities of PAD, potentially leading to an inaccurate estimation of the relationship between SCI and PAD risk. Third, details of severity of PAD could not be obtained; thus, further survey in our study was limited. Fourth, we have tried to minimize the basic difference between the SCI and non-SCI cohorts; however, the confounding variables of smoking, blood pressure, and cholesterol level were not available in our database. Thus, the effect of residual confounding could not be completely excluded.

In conclusion, patients with SCI are associated with an increased risk of PAD, regardless of preexisting comorbidities. Our findings improve physicians' awareness of the risk of PAD in patients with SCI and facilitate developing strategies to prevent, detect, and manage PAD in patients with SCI.

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