Peripheral Arterial Disease and Spinal Cord Injury
A Retrospective Nationwide Cohort Study
Ta-Wei Su, MD, Tzu-Yi Chou, MD, Herring-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.

(Medicine 94(41):e1655)

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.3,5 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-analysis14 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.15 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 thickness18 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
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. The definition of SCI includes a cross-product term in the model. 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 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 9% 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 = 1.23–1.53) 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
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 = 1.94–2.81), 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

| 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        |       |      |       |       |      |       |                   |                        |
| 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        |       |      |       |       |      |       |                   |                        |
| 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        |       |      |       |       |      |       |                   |                        |
| 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.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.
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 carbohydrate5,22 and dyslipidemia.6,7,22 Lee et al23 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 metabolism.

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

| Variable                  | Crude HR (95% CI) | Adjusted 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.

$P < 0.05, \ P < 0.001.$

**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 | 1.02  | 0.78 (0.65–1.27)  | 1.09 (0.91–1.31)     |
| C-spine SCI               | 127   | 125,016 |       | 2.42              | 1.87 (1.46–2.39)     |
| T-spine SCI               | 67    | 27,673  |       | 2.29              | 1.75 (1.49–2.07)     |
| L-S-Co-spine SCI          | 161   | 70,424 |       | 2.73              | 2.10 (1.58–2.79)     |
| Multiple spine SCI        | 50    | 18,298 |       | 2.73              | 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.

$P < 0.0001.$
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.

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

| Variable                  | No N = 170,389 | Yes N = 42,673 | P    |
|---------------------------|---------------|---------------|------|
| Sex                       |               |               |      |
| 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              |               |               |      |
| ≤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.

REFERENCES

1. Cannon B. Sensation and loss. Nature. 2013;503:S2–S3.
2. May M. The spine. Nature. 2013;503:S1.
3. Hagen EM. Acute complications of spinal cord injuries. World J Orthop. 2015;6:17–23.
4. Sezer N, Akkuş S, Uğurlu FG. Chronic complications of spinal cord injury. World J Orthop. 2015;6:24–33.
5. Gorgey AS, Dolbow DR, Dolbow JD, et al. Effects of spinal cord injury on body composition and metabolic profile: part I. J Spinal Cord Med. 2014;37:693–702.
6. Schmid A, Halle M, Stützle C, et al. Lipoproteins and free plasma catecholamines in spinal cord injured men with different injury levels. Clin Physiol. 2000;20:304–310.
7. Gilbert O, Crofoot JR, Taylor AJ, et al. Serum lipid concentrations among persons with spinal cord injury: a systematic review and meta-analysis of the literature. Atherosclerosis. 2014;232:305–312.
8. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? Spinal Cord. 2006;44:523–529.
9. Hirsch AT, Duval S. The global pandemic of peripheral artery disease. Lancet. 2013;382:1312–1314.
10. Olin JW, Sealove BA. Peripheral artery disease: current insight into the disease and its diagnosis and management. Mayo Clin Proc. 2010;85:678–692.
11. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med. 2001;344:1608–1621.
12. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 1999;19:538–545.
13. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348:1329–1339.
14. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382:1329–1340.
15. Garshack E, Kelley A, Cohen SA, et al. A prospective assessment of mortality in chronic spinal cord injury. Spinal Cord. 2005;43:408–416.
16. Bell JW, Chen D, Bahls M, et al. Evidence for greater burden of peripheral arterial disease in lower extremity arteries of spinal cord-injured individuals. Am J Physiol Heart Circ Physiol. 2011;301:H766–H772.
17. West CR, Alyahya A, Laher I, et al. Peripheral vascular function in spinal cord injury: a systematic review. Spinal Cord. 2013;51:10–19.
18. Matos-Souza JR, Pithon KR, Ozahata TM, et al. Subclinical atherosclerosis is related to injury level but not to inflammatory parameters in spinal cord injury subjects. Spinal Cord. 2010;48:740–744.
19. Chen YJ, Lin MS, Hsu KY, et al. Prevalence of asymptomatic peripheral arterial disease and related risk factors in younger and elderly patients in Taiwan. Angiology. 2014;65:396–401.
20. Chen SC, Su HM, Chang JM, et al. Increasing prevalence of peripheral artery occlusive disease in hemodialysis patients: a 2-year follow-up. Am J Med Sci. 2012;343:440–445.
21. Groah SL, Weitzenkamp D, Sett P, et al. The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. Spinal Cord. 2001;39:310–317.
22. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. Am J Phys Med Rehabil. 2007;86:142–152.
23. Lee MY, Myers J, Hayes A, et al. C-reactive protein, metabolic syndrome, and insulin resistance in individuals with spinal cord injury. *J Spinal Cord Med.* 2005;28:20–25.

24. Olive JL, McCully KK, Dudley GA. Blood flow response in individuals with incomplete spinal cord injuries. *Spinal Cord.* 2002;40:639–645.

25. Olive JL, Dudley GA, McCully KK. Vascular remodeling after spinal cord injury. *Med Sci Sports Exerc.* 2003;35:901–907.

26. McDonald CM, Abresch-Meyer AL, Nelson MD, et al. Body mass index and body composition measures by dual x-ray absorptiometry in patients aged 10 to 21 years with spinal cord injury. *J Spinal Cord Med.* 2007;30:S97–S104.