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ARTICLE

Increased risk of acute pancreatitis in persons with spinal cord injury: a population-based, propensity score-matched longitudinal follow-up study

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Abstract

Study design Retrospective cohort study.

Objective To evaluate the risk of acute pancreatitis (AP) in persons with spinal cord injury (SCI) based on a nationally representative sample.

Setting A retrospective cohort study using Taiwan's National Health Insurance Research Database.

Methods Drawing on Taiwan's Longitudinal Health Insurance Database 2005, the researchers created an SCI group consisting of 2280 persons with SCI aged 20–74 years. Propensity-score matching was then used to generate a non-SCI group of 9120 participants with similar baseline characteristics to the SCI group. These two groups' respective cumulative incidence of AP was compared, and the effect of SCI on AP risk was then assessed using stratified Cox proportional-hazards regression.

Results For the SCI and non-SCI groups, the respective incidence rates of AP were 1.34 per 1000 person-years (95% confidence interval [CI], 0.83–2.05) and 0.79 per 1000 person-years (95% CI, 0.61–1.01). Compared with the non-SCI group, the hazard ratio of AP for the SCI group was 1.96 (95% CI 1.19–3.25, $p = 0.0088$); and the SCI group's cumulative incidence of AP was significantly higher than that of the non-SCI group ($p = 0.0227$).

Conclusion This population-based longitudinal follow-up study indicates that there is an increased long-term risk of AP in persons with SCI.

Introduction

Previous studies have suggested that persons with spinal cord injury (SCI) are prone to gastrointestinal complications [1]. However, due to sensory impairments, SCI persons' gastrointestinal symptoms may be atypical or even absent [2]. Acute pancreatitis (AP) is a life-threatening gastrointestinal disease [3, 4]. Previous research has pointed out that clinical recognition of AP in persons with SCI can be hampered by impairment of their visceral sensory functions [5]. Therefore, understanding the AP risk it poses to persons with SCI is an important aspect of their clinical care. The first study of this topic, a six-case series from 1977, reported that AP with hyperamylasemia and fever was occasionally seen in persons with SCI [6]. A later retrospective case study that reviewed 338 cases of SCI found that 3% of these persons ($n = 10$) had experienced at least one episode of AP [5]. However, these previous studies were nonlongitudinal and lacked follow-up, meaning that the long-term risk of AP after SCI have not hitherto been evaluated. In addition, since most prior studies of this topic were designed as case series and lacked control groups, differences in the risk of AP across individuals with and without SCI has never been systematically assessed. We therefore carried out the present population-based, longitudinal follow-up study to evaluate the relative risk of AP in SCI persons and individuals without SCI.

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Methods

Data sources

Taiwan's National Health Insurance (NHI) system, established in 1995, is a mandatory social system for all 22 million of the country's citizens, and in practice, its coverage rate is around 99%. The present study used the Longitudinal Health Insurance Database 2005 (LHID2005), which consists of one million insurance claimants randomly sampled from the complete NHI claims database. LHID2005 has been verified as representative of the original NHI database (https://nhird.nhri.org.tw/en/Data_Subsets.html#S3). Prior to data analysis, personally identifiable information in this data was encrypted to protect the participants' privacy. This study was approved by the National Taiwan University Hospital Research Ethics Committee.

Study participants and design

The present study used a retrospective cohort study design to analyze the risk of AP in individuals with and without SCI. Propensity-score matching (PSM) was used to generate matched SCI and non-SCI groups with similar baseline demographic and clinical characteristics: a technique that allows researchers to minimize potential confounding factors or selection bias arising from imbalances in such baseline characteristics across groups [7].

The enrollment processes for both the present study's groups, as illustrated in Fig. 1, are as follows. The inclusion criteria for the initial SCI group were (1) having received a diagnosis of SCI (International Classification of Disease, 9th Revision, Clinical Modification [ICD-9-CM] code 806 or 952) at least two ambulatory medical care visits between January 1, 2002 and December 31, 2006, with the date of the first SCI diagnosis for each participant during that period being deemed his/her index date; (2) being aged 20–74 years old as of the index date. These inclusion criteria resulted in 2687 participants being selected for the initial SCI group. Then, the following exclusion criteria were applied to that group: (1) having had any diagnosis of AP (ICD-9-CM code 577.0) within 1 year prior to the index date; (2) having had any diagnosis of SCI (ICD-9-CM codes 806 or 952) within one year prior to the index date, so as to include as high a proportion as possible of newly diagnosed SCI cases. In all, 400 participants were eliminated from the initial SCI group due to one or both of the above exclusion criteria (Fig. 1).

PSM for this study included baseline demographic variables, comorbidities, and socioeconomic factors. The selected comorbid conditions were diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM code 401–405), dyslipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (ICD-9-CM code is 496), stroke (ICD-9-CM code 430–438), cardiovascular disease (ICD-9-CM code 410–414), and alcohol dependence syndrome (ICD-9-CM code 303). Information about these pre-existing comorbidities, defined as at least two ambulatory-visit records or at least one discharge record that included the relevant diagnosis code(s), was obtained from LHID2005 data from a 1-year period immediately prior to each participant's index date. The socioeconomic status factors included the general geographic location of the participant's primary residence (i.e., northern, central, eastern, or southern Taiwan); the urbanization level of his/her local area; and his/her monthly income [8]. The researchers initially adopted the National Institutes of Health system for stratifying all Taiwanese townships into seven urbanization levels, with Level 1 denoting the highest urbanization level, and Level 7 the lowest [9], but because relatively few participants lived in Level 5, 6, or 7 communities, these three levels were combined under the label of Level 5 for the purposes of the present study. The participants' monthly incomes in New Taiwan Dollars (NT$), as represented by their payroll data transmitted to the NHI for insurance purposes, were divided into four levels: (1) NT$0, (2) NT$1–NT$15,840, (3) NT$15,841–NT$25,000, and (4) ≥NT $25,001. NT$15,840 was chosen as the first cutoff level because this amount was Taiwan's minimum monthly wage for full-time employees announced by government in 2000. Seven SCI participants with missing socioeconomic status information were excluded. Therefore, a total of 407 participants were excluded from the initial SCI group, leaving 2280 participants in the final SCI group (Fig. 1).

The inclusion criteria for the non-SCI group were (1) never having been diagnosed with SCI during ambulatory visits between January 1, 2002 and December 31, 2006, with the participant's first such visit during that period being defined as his/her index date; and (2) being 20–74 years old as of the index date. This led initially to 654,446 participants being included. The exclusion criteria for the non-SCI group were as same as those for the SCI group. AP and SCI diagnoses within one year prior to the index date led to 1512 exclusions, and missing socioeconomic status information to 952 more. Thus, a total of 651,982 participants without SCI remained for PSM.

The PSM process utilized a logistic-regression model that included age, sex, pre-existing comorbidities, and socioeconomic status as covariates to estimate each participant's propensity score, i.e., the predicted probability of being diagnosed with SCI. A greedy matching algorithm was then used to identify four propensity score-matched non-SCI participants from the control pool for each SCI person, resulting in final sizes of 2280 for the SCI group and 9120 for the non-SCI group.

Outcomes

The primary outcome was the first diagnosis of AP during follow-up. Each participant was tracked from the index date

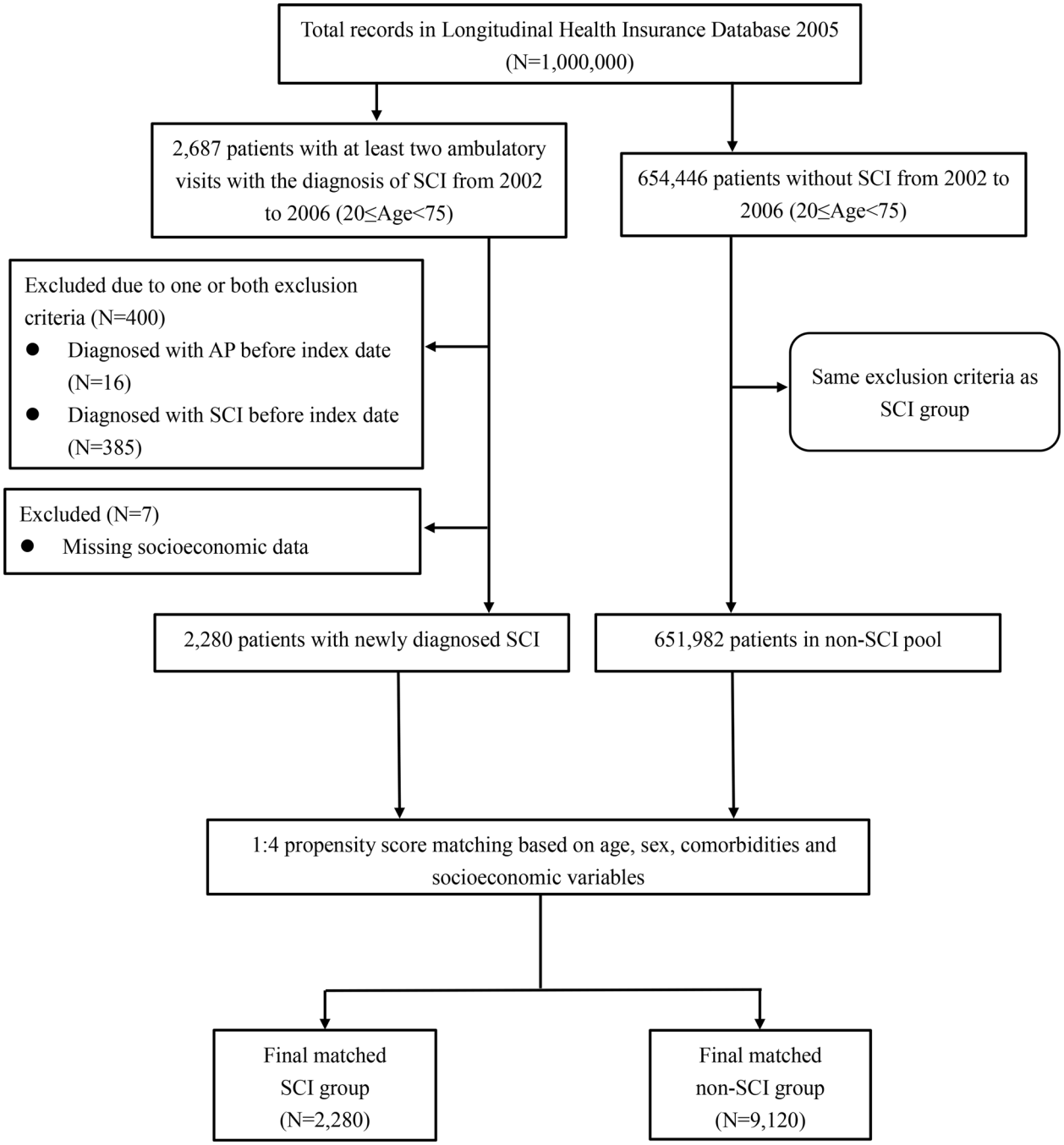

Fig. 1 Enrollment processes of the propensity score-matched SCI and non-SCI groups. SCI spinal cord injury.

until the earliest of (1) the known occurrence of AP (based on at least one discharge record or at least two ambulatory-visit records including a diagnosis of AP); (2) his/her death (as indicated from withdrawal from the NHI system); or (3) the end of 2011. Our proxy for the cause of death was the principal diagnosis code recorded in connection with discharges and/or ambulatory visits within three months before the participant's death [10].

Statistical analysis

Intergroup differences in baseline characteristics were evaluated using the standardized-difference method [11], which is independent of sample size and therefore preferred over hypothesis-testing methods. An absolute standardized difference of less than 0.1 for a given variable indicates a negligible between-group imbalance for that variable [12].

Table 1 Demographic and clinical characteristics of the matched spinal cord injury (SCI) and non-SCI groups after propensity-score matching.

Variable	SCI group ($N = 2280$)	Non-SCI group ($N = 9120$)	Standardized difference
Sex (female)	1260 (55.3)	4659 (51.1)	−0.08379
Age (year)	50.2 ± 15.7	50.2 ± 15.4	−0.00329
Diabetes (yes)	287 (12.6)	1155 (12.7)	−0.00231
Hypertension (yes)	488 (21.4)	1997 (21.9)	−0.01198
Dyslipidemia (yes)	213 (9.3)	830 (9.1)	0.00834
Cardiovascular disease (yes)	128 (5.6)	481 (5.3)	0.01498
Chronic obstructive pulmonary disease (yes)	47 (2.1)	171 (1.9)	0.01342
Stroke (yes)	127 (5.6)	538 (5.9)	−0.01415
Alcohol dependence syndrome (yes)	4 (0.2)	13 (0.1)	0.00826
Monthly income			0.05029
NT$0	525 (23.0)	2,111 (23.2)	
NT$1–NT $15,840	473 (20.8)	1949 (21.4)	
NT$15,841–NT $25,000	867 (38.0)	3570 (39.1)	
≧ NT$25,001	415 (18.2)	1490 (16.3)	
Urbanization level			0.03829
1 (most urbanized)	959 (42.1)	3707 (40.6)	
2	662 (29.0)	2796 (30.7)	
3	215 (9.4)	864 (9.5)	
4	248 (10.9)	995 (10.9)	
5 (least urbanized)	196 (8.6)	758 (8.3)	
Geographic location			0.02330
Northern	1086 (47.6)	4301 (47.2)	
Central	551 (24.2)	2161 (23.7)	
Southern	597 (26.2)	2480 (27.2)	
Eastern	46 (2.0)	178 (1.9)	

Data are expressed as Numbers (%) or mean ± Standard Deviation.

NT$ New Taiwan dollar, *SCI* spinal cord injury.

US $1 = NT $33 in 2002.

The incidence rate was calculated as the number of AP cases divided by the sum of AP-free follow-up time (per 1000 person-years). The cumulative incidence rates of AP among the SCI and non-SCI groups were estimated using Kaplan–Meier curves, and compared with log-rank tests. We used stratified Cox proportional-hazards regression to estimate the effect of SCI on the risk of developing AP. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC), with the significance level set to alpha = 0.05.

Results

Table 1 presents the demographic and clinical characteristics of the matched SCI and non-SCI groups. The mean age of the SCI group was 50.2 (standard deviation [SD] = 15.7), and the mean age of the non-SCI group was the same (SD = 15.4). After PSM, the absolute standardized differences were less than 0.1 for all variables listed in Table 1, indicating that intergroup differences in all baseline characteristics were negligible.

The two matched groups' numbers of AP cases and their hazard ratios are shown in Table 2. Among the 2280 SCI persons, 21 cases of AP occurred over 15,636.6 person-years, an incidence rate of 1.34 per 1000 person-years (95% confidence interval [CI], 0.83–2.05). Among the 9120 participants without SCI, 65 cases of AP occurred over 81,982.0 person-years, an incidence rate of 0.79 per 1000 person-years (95% CI, 0.61–1.01). Compared with the non-SCI group, the AP hazard ratio for the SCI group was 1.96 (95% CI, 1.19–3.25, $p = 0.0088$). The cumulative incidence of AP in the SCI group was higher than that in the non-SCI group (Fig. 2, $p = 0.0227$). The 30-day mortality rates for patients with AP in the SCI and non-SCI groups were 4.8% (1/21) and 3.1% (2/65), respectively. There is lack of significant difference in the mortality of AP between the SCI and non-SCI groups ($p = 0.57$).

Discussion

The present work is the first population-based longitudinal follow-up study to evaluate the long-term risk of AP in persons with SCI. We found that such persons were at higher risk of AP (HR = 1.96, 95% CI, 1.19–3.25). SCI may be followed by severe gastrointestinal complications, among which, AP is one of the most likely to be fatal [13, 14]. Because the typical symptoms of AP (notably, sharp and devastating upper abdominal pain, radiating to left side of the back, tachycardia, nausea, and vomiting) may be effaced in SCI persons [2], it is very important for clinicians to recognize the risk of AP in persons with SCI.

Prior studies have suggested that among SCI persons, autonomic failure may lead to a combination of sphincter of Oddi dysfunction (i.e., the inability of this sphincter to open and relax in a normal fashion), as well as to increased secretion of pancreatic cells [15, 16]. Sphincter of Oddi dysfunction may also obstruct the outflow of pancreatic juice [16, 17]. The results of one animal study indicated that sphincter of Oddi dysfunction coupled with overstimulated pancreatic secretion might cause AP [16]. In human studies, sphincter of Oddi dysfunction has also been linked to higher risk of AP [17]. SCI persons often have imbalances in their sympathetic-parasympathetic systems, and neurohormonal studies have suggested that such imbalances can cause

Table 2 Number of acute pancreatitis cases and hazard ratio of acute pancreatitis for the matched spinal cord injury (SCI) and non-SCI groups.

Variable	SCI group ($N = 2280$)	Non-SCI group ($N = 9120$)
Acute pancreatitis cases, *N*	21	65
Risk per 1000 person-year (95% CI)	1.34 (0.83–2.05)	0.79 (0.61–1.01)
Hazard ratio (95% CI)	1.96 (1.19–3.25)[a]	1.00

CI confidence interval.

[a]$p = 0.0088$.

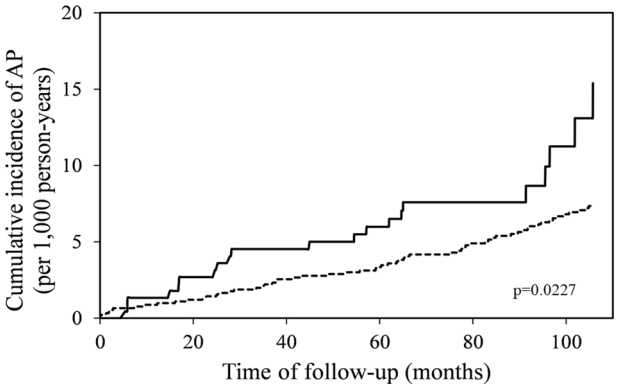

Fig. 2 Cumulative incidence of AP for the propensity score-matched SCI and non-SCI groups. The solid line represents the SCI group and the dotted line represents the non-SCI group. AP acute pancreatitis, SCI spinal cord injury.

sphincter of Oddi dysfunction and overstimulation of pancreatic cells [18]. Thus, the above mechanisms may predispose SCI persons to a higher risk in developing AP. Moreover, one case report has suggested that early papillotomy was helpful in treating AP in SCI persons, lending further support to the idea that sphincter of Oddi dysfunction may be a pathophysiological mechanism that can account for the higher risk of AP in such persons [5, 17].

Gallstones are a common cause of AP in the general population [19]. Previous studies have shown that the ejection fraction of gallbladder was lower in individuals with SCI than in those without SCI, and that this might lead to cholestasis and make gallstone formation more likely [20, 21]. And SCI persons have been found to have a higher prevalence of cholelithiasis than non-SCI persons do [22], which could also lead to a higher risk of AP after SCI.

While hypercalcemia is uncommon in the general population, its estimated prevalence among SCI persons is between 10 and 24% [23, 24]. Because such persons are usually immobilized due to motor paralysis, this high prevalence may be attributable to physical inactivity in such persons [23], which can accelerate bone resorption and calcium release. Since hypercalcemia is a potential cause of AP, the higher prevalence of hypercalcemia in SCI persons is another plausible potential explanation for the observed link between AP and SCI.

Previous population-based epidemiological studies have reported that case-fatality rates for AP range from 2 to 6% in recent years [25–27]. In our study, the 30-day mortality rates of AP were 4.8% for the SCI group and 3.1% for the non-SCI group. There is lack of significant difference in the mortality rates of AP between the SCI and non-SCI groups ($p = 0.57$).

As noted above, SCI persons' AP signs and symptoms may be atypical or absent [1, 5, 6] because of interruption of the sensory afferent [6], making timely diagnosis of AP in such individuals difficult. For persons with high-level SCI, the initial symptom of AP may be autonomic dysreflexia [2, 28], which typically occurs in people with neurologic injury levels above T6, and presents symptoms such as paradoxical high blood pressure, pounding headache, and flushed face [29]. The presence of autonomic dysreflexia may therefore help clinicians to make early diagnoses of AP or other acute abdominal problems in SCI persons.

Crucially, our adoption of a longitudinal design and data from a nationwide healthcare system enabled us to assess the long-term risk of AP in SCI persons. However, this study has some limitations. First, its data on diagnoses of SCI, AP, and comorbid conditions rely on the ICD-9-CM codes from the LHID2005, a subset of the NHI database, which could provoke disquiet about such diagnoses' precision. Nevertheless, the medical records in LHID2005 have been periodically sampled and reviewed by the NHI Bureau's specialist committees, to ensure the accuracy of its diagnosis information as well as to assess the quality of care. There are differences in the sensitivity and positive predictive value of diagnosis across multiple conditions from the NHI database [30]. Shen et al. evaluated the validity of AP diagnosis in the NHI database by using chart review, and reported the positive predictive value of the AP diagnosis in the NHI database was 90.0% [25], which may indicate acceptable diagnostic accuracy of AP in LHID2005. Second, the LHID2005 lacks information about lifestyles and habits, including alcohol drinking and smoking, and this absence might cause residual confounding to our conclusions about the association between SCI and AP. Previous studies have suggested that higher alcohol consumption is correlated with an increased risk of AP [31]. Therefore, we used alcohol dependence syndrome (ICD-9-CM code 305) as a proxy for drinking habits during PSM. Likewise, because smoking can increase the risk of AP [32, 33], we used chronic obstructive pulmonary disease (ICD-9-CM code 496) as a surrogate indicator for smoking, as there is a strong association between the two [34, 35].

In summary, the present population-based longitudinal study has shown that persons with SCI have an increased risk of AP. Clinicians should bear this increased risk in mind, as doing so will help them to make timely diagnoses of AP in the SCI population. However, further research on the mechanisms underlying the linkage between these two conditions is needed.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available due to person's health information privacy but are available from the corresponding author on reasonable request.

Author contributions WTH participated in conception and design, drafting the article, analysis and interpretation of data, and revising the text critically for major intellectual content and final approval. KCY participated in acquisition, analysis, and interpretation of data. SLP participated in conception and design, analysis and interpretation of data, revising the text critically for major intellectual content and final approval, and taking responsibility for the integrity of the work.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics statement This study was approved by the National Taiwan University Hospital Research Ethics Committee. (Reference number: 201912207RIND).

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